Next Frontier in Stroke: Neuro-Rehabilitation and Neuro-Recovery

Timea Hodics, M.D.

9/21/2022

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Recent advances

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- Timing and dose matters (CPASS)
- Activity based advanced technologies:
  - Aphasia studies
  - robotics, e-stim devices,
  - BCI controlled hand robot (IpsiHand) FDA
  - telerehabilitation/home therapy options, domotics (home automation)
- Plasticity enhancing options:
  - Personalized stimulation approaches, spine and brain
  - Frequency-tuned ELF-EMF (BrainQ) FDA
  - VNS stimulation to enhance motor recovery (Vivistim) FDA
  - Cellular therapies
- Summary

Timeline of Post-Stroke Recovery

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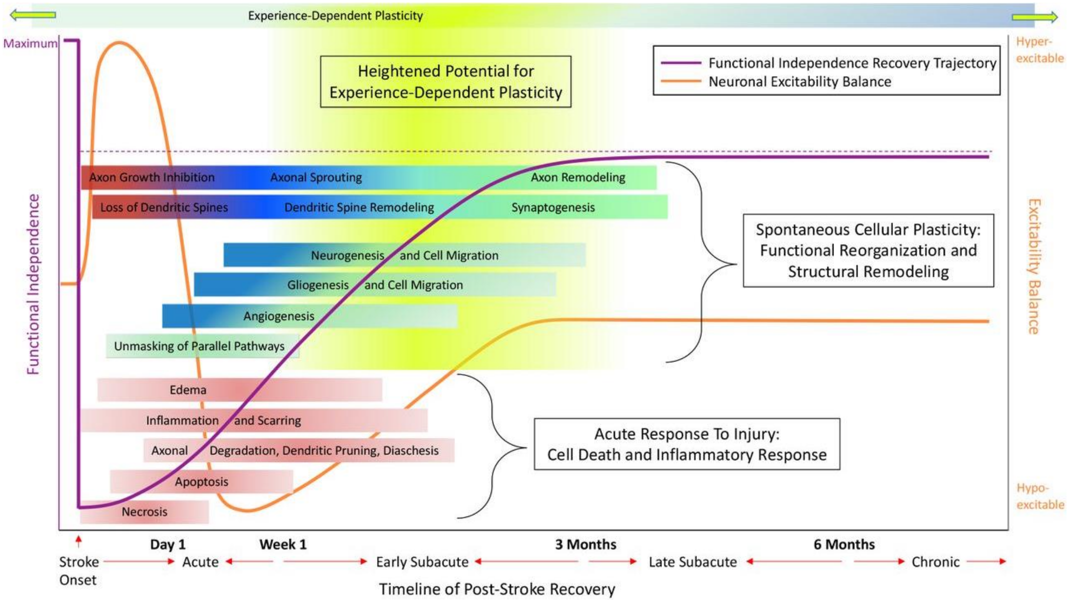

Da Silva et al. medRxiv 2021

Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans

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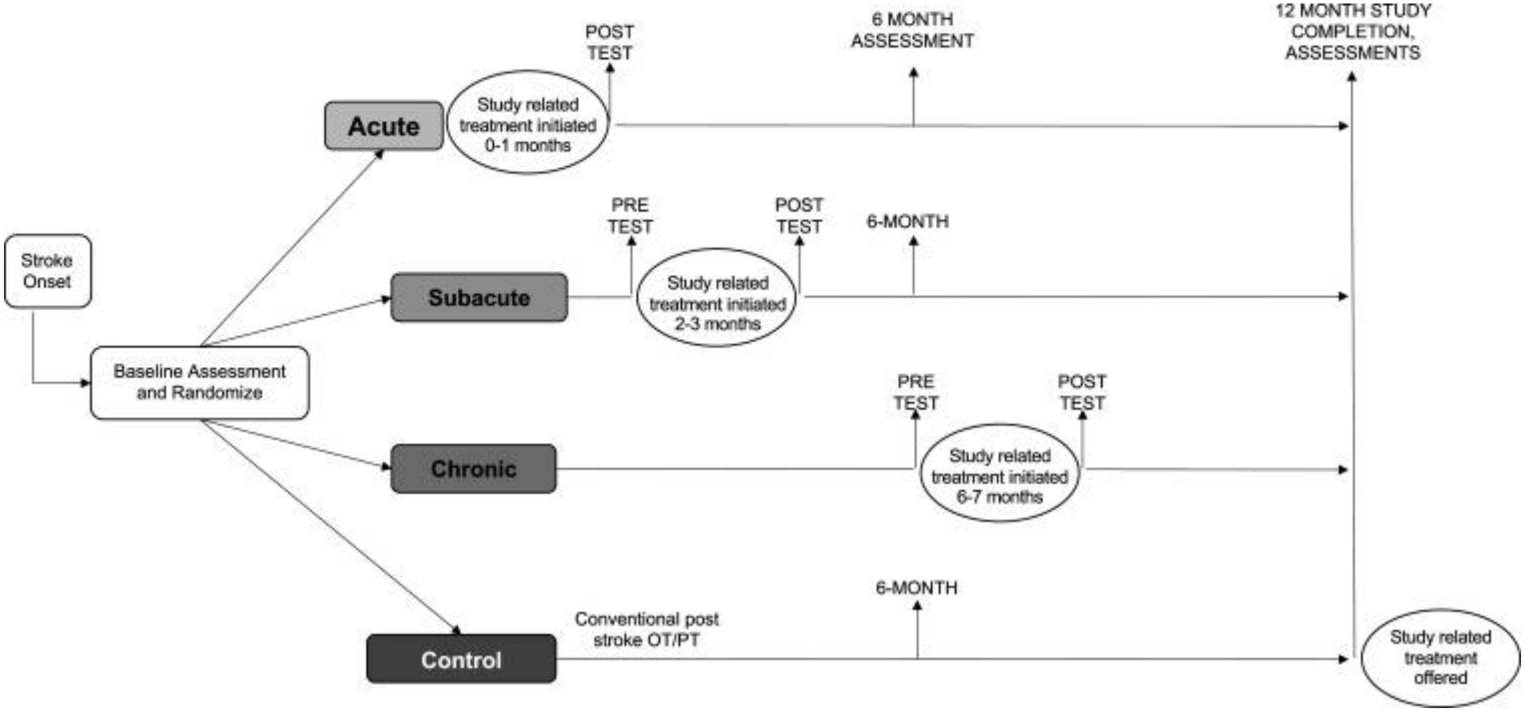
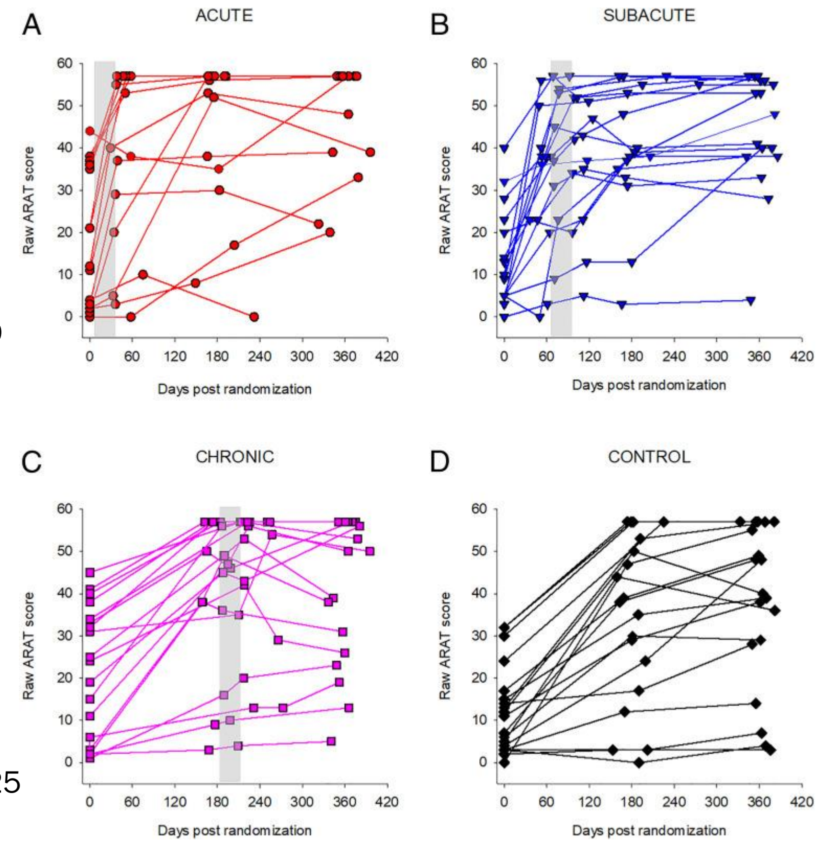


Dromerick et al. Proc Natl Acad Sci U S A. 2021 Sep 28;118(39):e2026676118.

Critical period after stroke in humans

+5.25±2.59

+6.87±2.63
(MCID=5.7 points)



+2.41±2.25

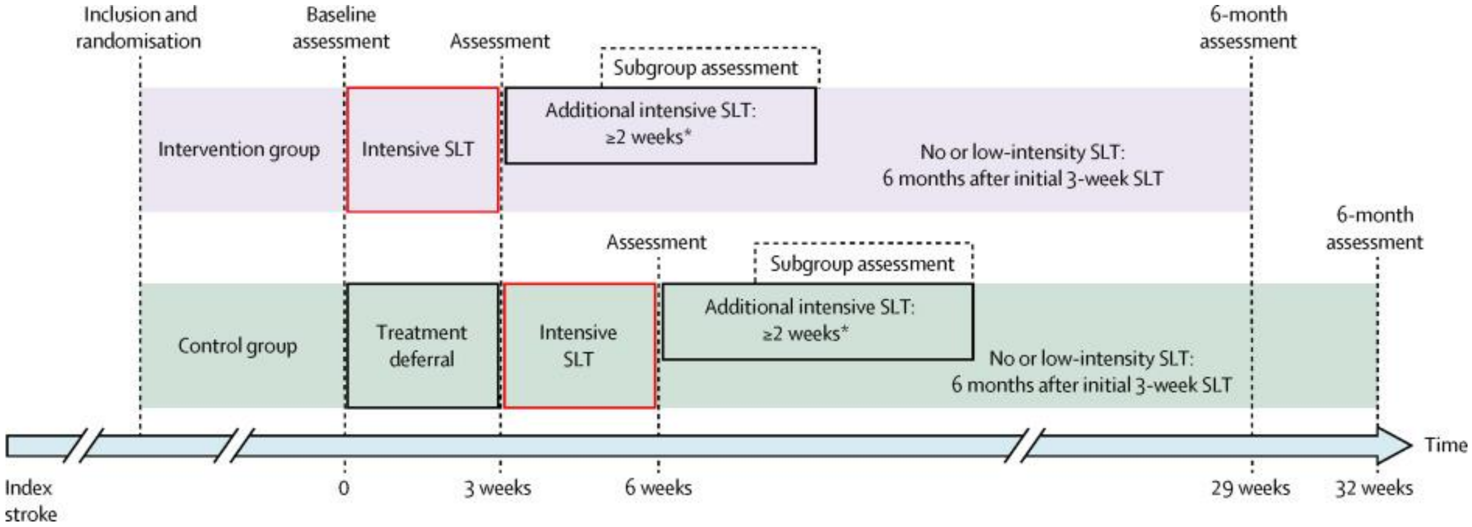
Aphasia treatment

- Cochrane review: treatment effects immediately after intervention for functional communication (SMD 0.28, 95% CI 0.06 to 0.49, p=0.01) when treatment was provided with sufficient intensity (5–10 hours per week), but not at 6 month follow-up (Brady et al 2016)
- Chronic trials: variability in participant treatment response, with stroke and aphasia severity

FCET2EC

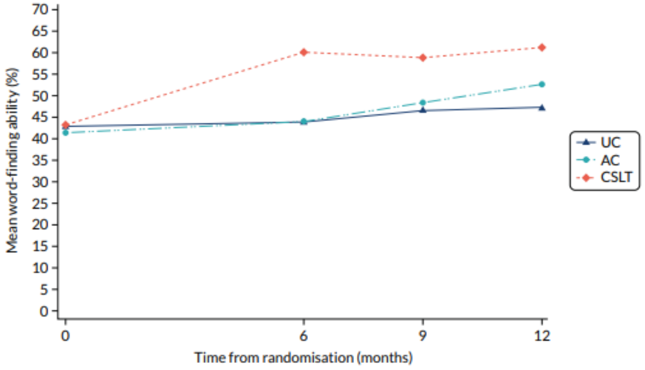
From controlled experimental trial to = 2 everyday communication

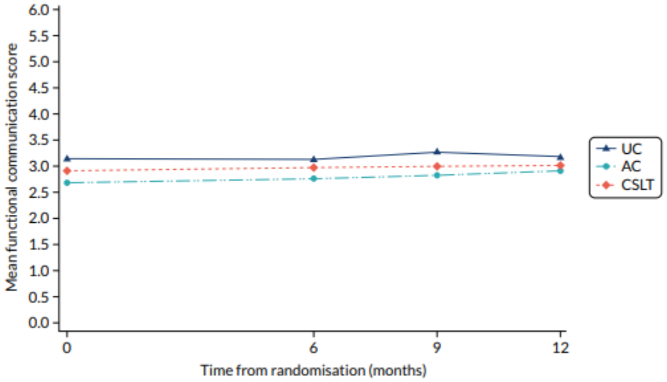
- mean of 46 hours of linguistic and pragmatically focused, clinician delivered, individual therapy showing significant effects (moderate ESs) on functional communication immediately post-intervention and at 6 month follow-up. (Breitenstein 2017)



Big CACTUS

- Big CACTUS used computer-based naming therapy and demonstrated significant effects (moderate ESs) on word finding for trained items but not functional communication in 240 subjects. (Palmer 2019, Palmer 2020)





Word-finding and functional communication: co-primary outcome measures

COMPARE trial

- Constraint-induced or Multimodality Aphasia Therapy compared with usual care in chronic post-stroke aphasia (Rose et al 2022)
  - 201 patients
  - CIAT-Plus and M-MAT were effective for word retrieval, functional communication, and quality of life, while usual care was not.
  - Word retrieval benefits were maintained at 12-week follow-up.
  - Future studies should explore predictive characteristics of responders and impacts of maintenance doses.

Robot-Assisted Training as Self-Training for Upper-Limb Hemiplegia in Chronic Stroke

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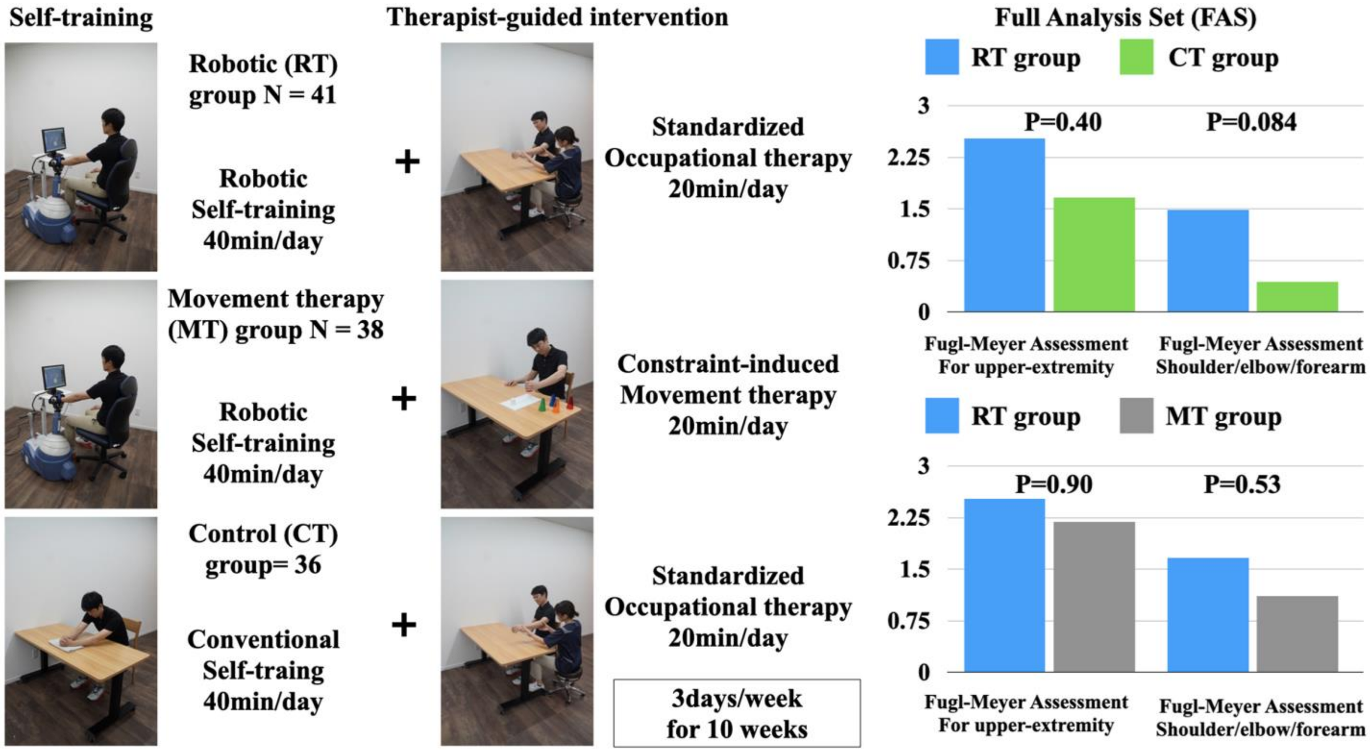

Takashi Takebayashi. Stroke. Robot-Assisted Training as Self-Training for Upper-Limb Hemiplegia in Chronic Stroke: A Randomized Controlled Trial, Volume: 53, Issue: 7, Pages: 2182-2191, DOI: (10.1161/STROKEAHA.121.037260)

BCI controlled hand robot as home therapy (IpsiHand)

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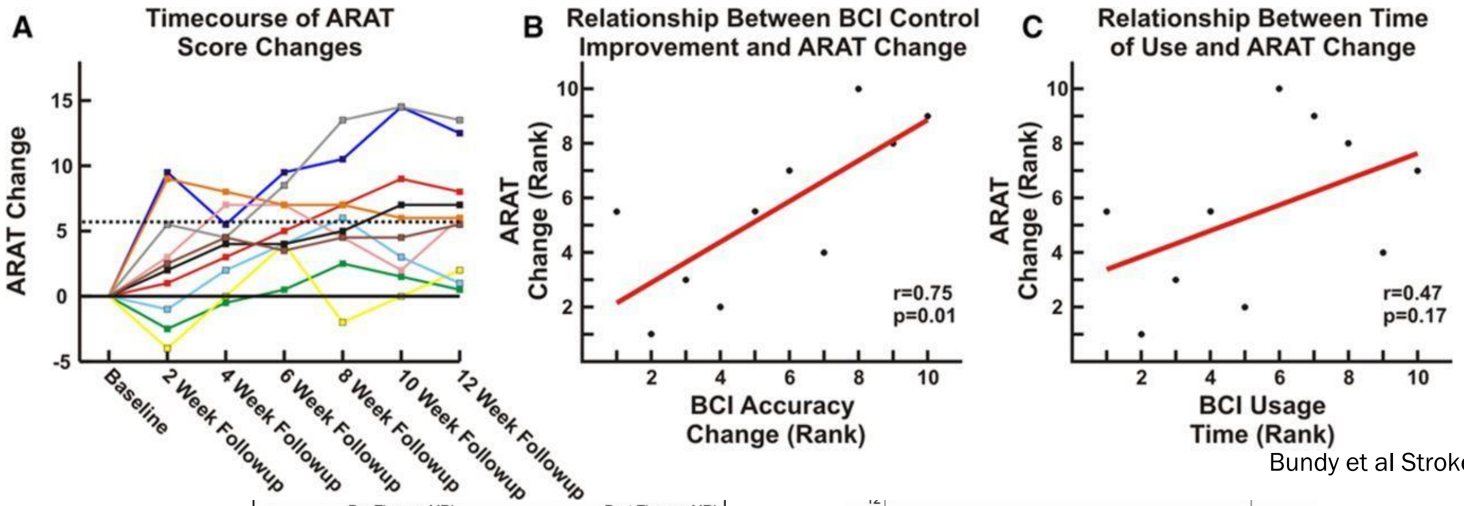
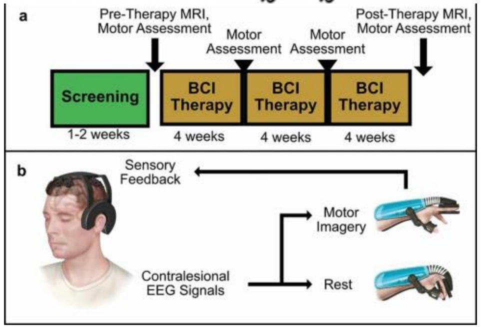
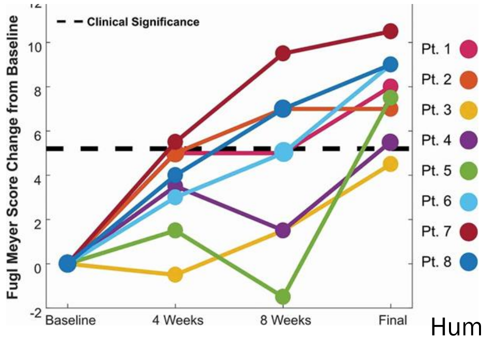


Bundy et al Stroke 26 May 2017





Humphries et al Stroke 01 July 2022

Telerehabilitation/home therapy

- Gamified home therapy improved adherence, improved mental health measures, alleviates burden for caregivers
- Training duration correlates with arm functional improvements
- Equivalent to in-clinic therapy
- Lower depression scores
- Active peripheral nerve stimulation with motor training led to long lasting improvement in arm performance
- Clinical team support at home, community-based therapy motivates patient to continue with therapy and prevents psychological deterioration.
- Daily reminders (smartwatch) are motivational

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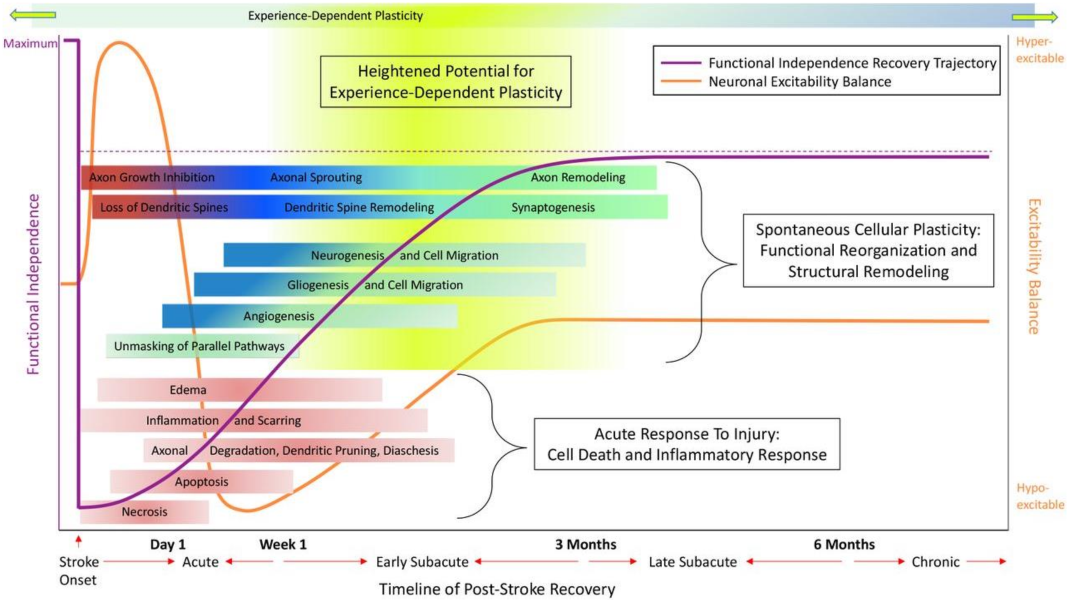
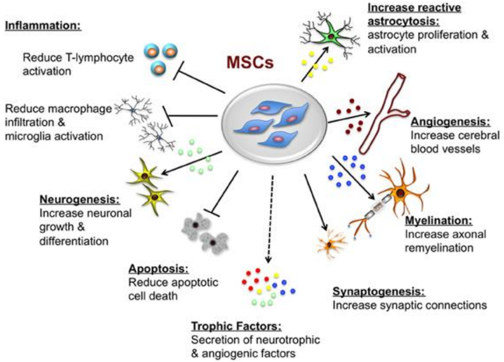


Da Silva et al. medRxiv 2021

Plasticity enhancing options



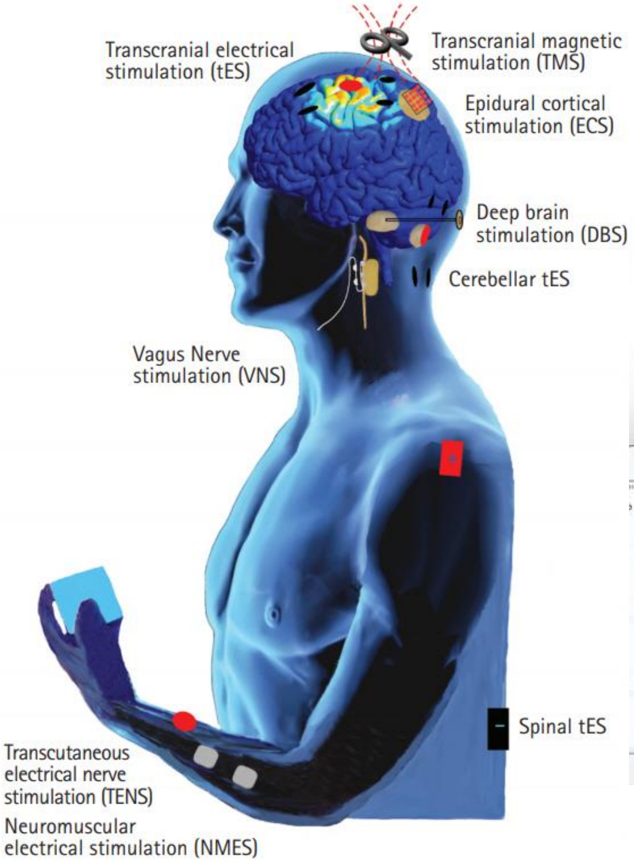


Image Source: frontiersin.org

Noninvasive Stimulation

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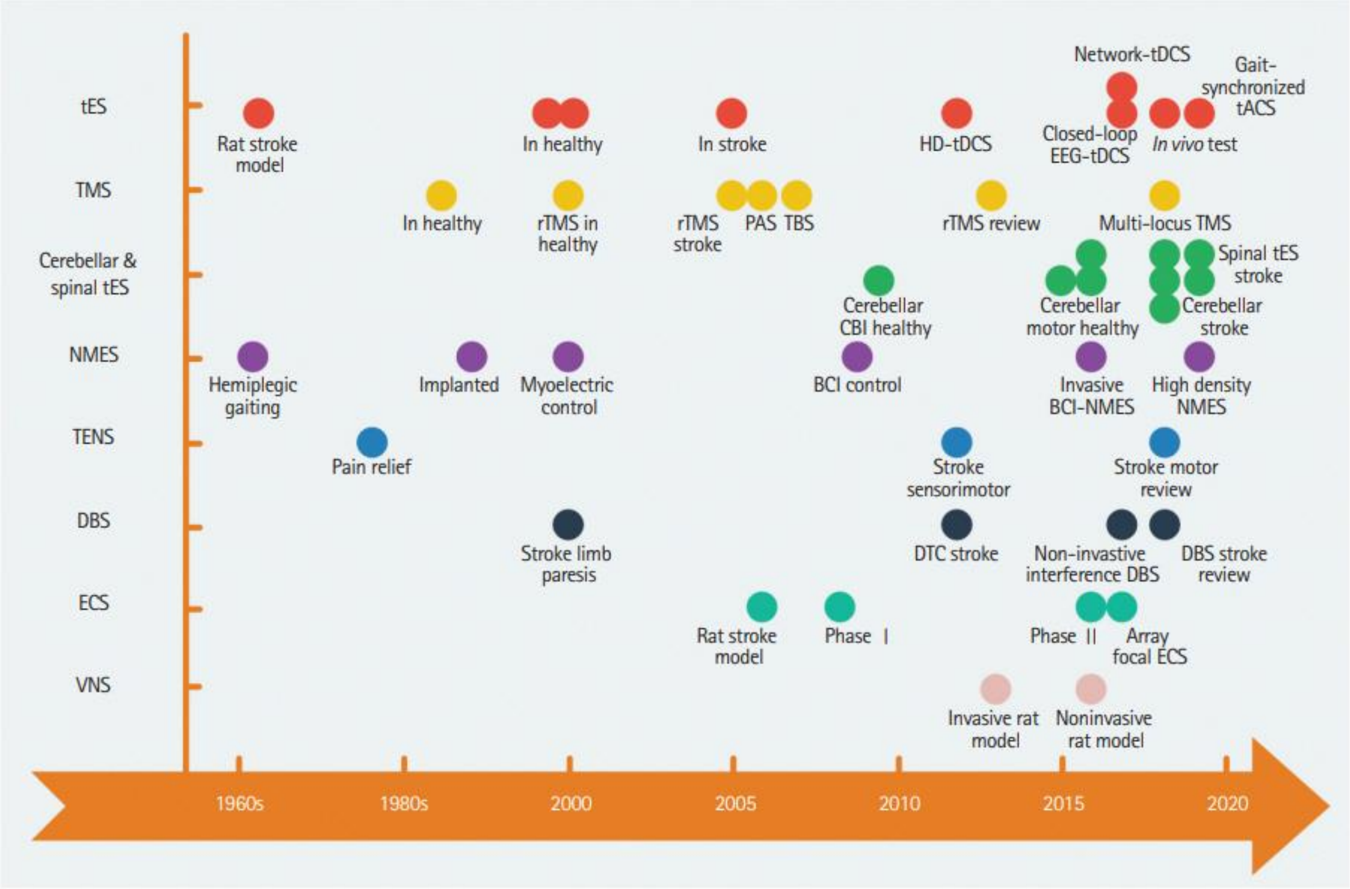
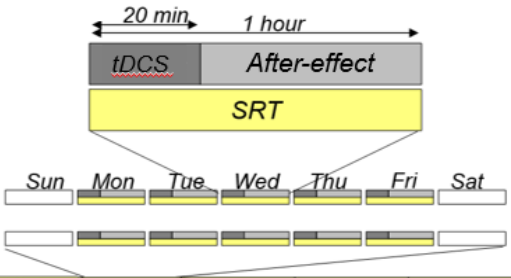


TDCS enhanced stroke recovery

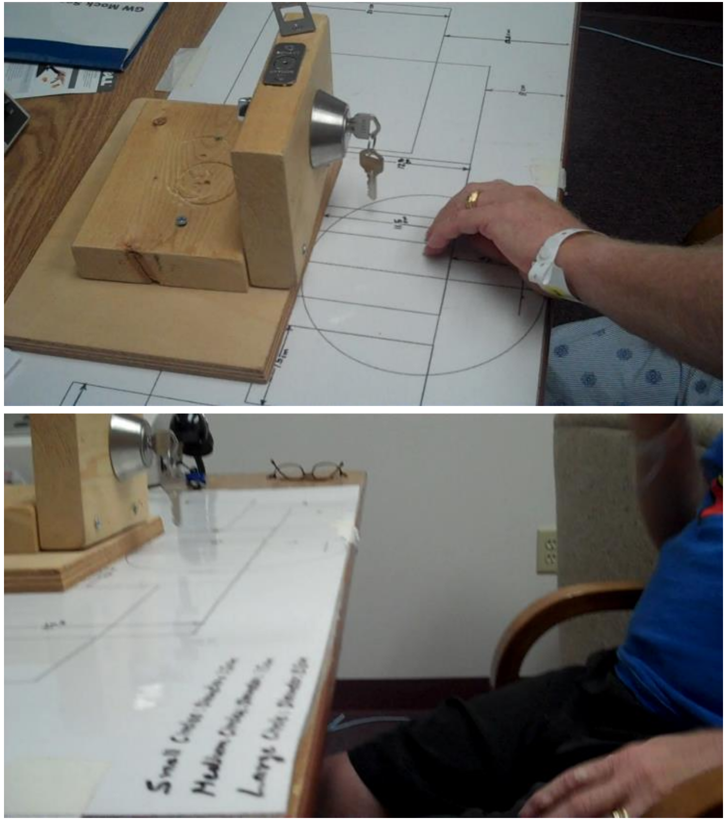


Timing	Day of Admission	Rehabilitation Day 2	Monday to Friday (5 times a week)	At discharge (over two days)	3 Months Follow-up	12 Months Follow-up
Event	Screening, enrollment, informed consent (1 hour)	Initial evaluation, test scales (1.5 hours)	TDCS/sham+ PT (total of 10)	Evaluation test scales (1.5hours)	Evaluation test scales (1.5hours)	Evaluation test scales (1.5hours)

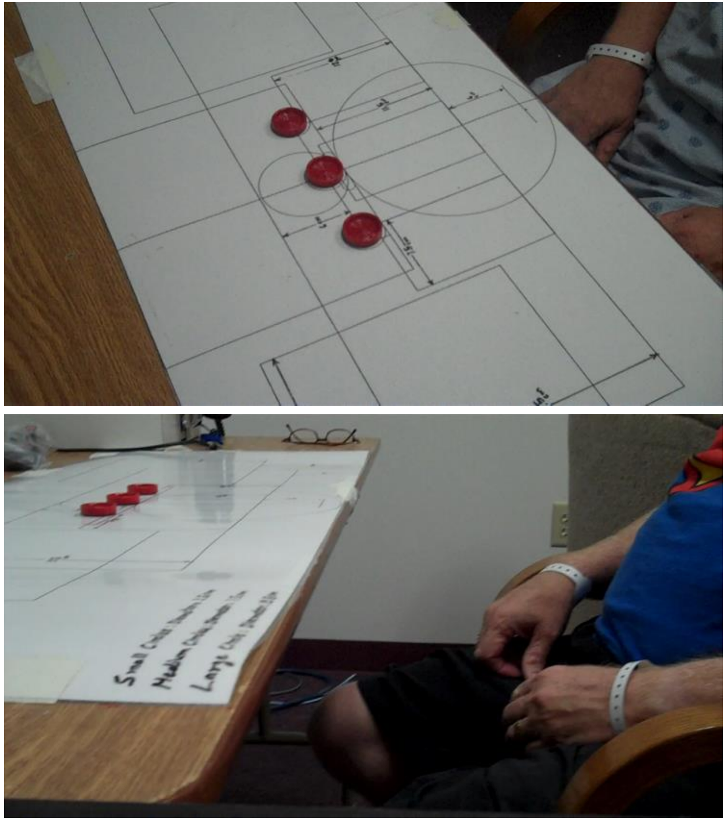
Hodics et al. AAN 2022

Wolf motor function test

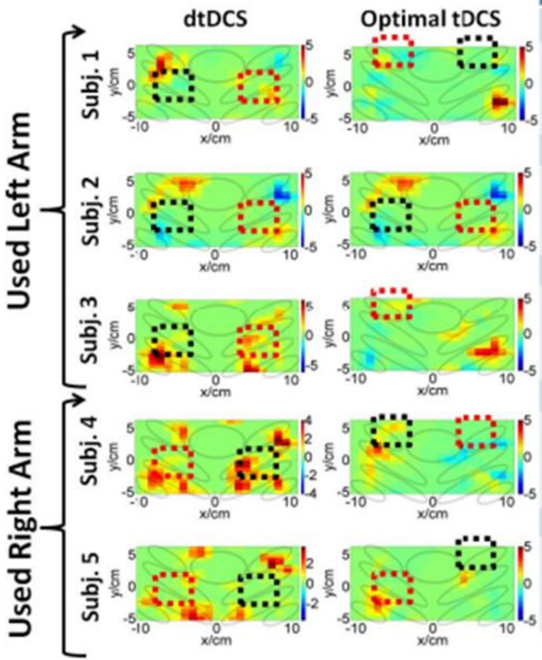
Turning a key



Stacking checkers



Personalized tDCS montage



	RT		Error		Error x RT	
	dtDCS	Optimal	dtDCS	Optimal	dtDCS	Optimal
Subj. 1	↓ 37.32 %	↓ 38.43 %	↓ 37.19 %	↓ 52.63 %	↓ 10.47 %	↓ 93.69 %
Subj. 2	↓ 50.12 %	↓ 50.12 %	↓ 1.72 %	↓ 1.72 %	↓ 51.78 %	↓ 51.78 %
Subj. 3	↑ 12.84 %	↓ 55.62%	↓ 13.02 %	↓ 73.92 %	↓ 8.95 %	↓ 83.14 %
Subj. 4	↑ 38.31 %	↑ 12.55%	↓ 1.51 %	↓ 96.92 %	↓ 15.82 %	↓ 79.55 %
Subj. 5	↑ 12.84 %	↑ 12.62%	↓ 13.02 %	↓ 66.92 %	↓ 10.95 %	↓ 53.69 %

Transcranial rotating magnet stimulation

- 30 chronic ischemic stroke patients
- Bilateral stimulation 20x40min over 4 weeks well tolerated
- Increased MRI BOLD active voxels x8.8 vs sham
- Not powered for clinical endpoints
- Dr. David Chiu is assembling a multicenter clinical trial

Chiu et al. J Stroke Cerebrovasc Dis.2020

Non-invasive spinal neuromodulation and robotic exoskeleton to recover upper limb function after stroke

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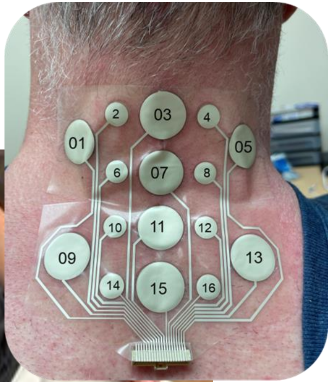
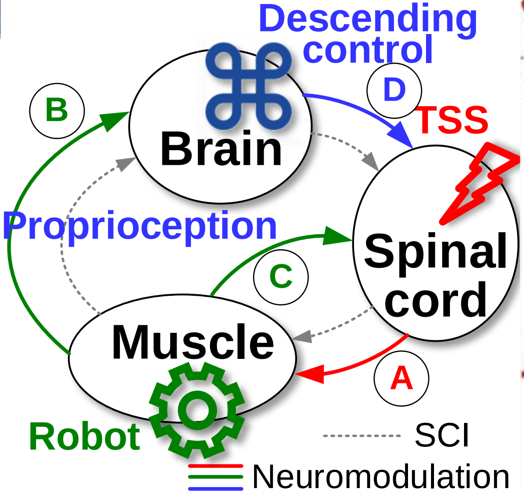
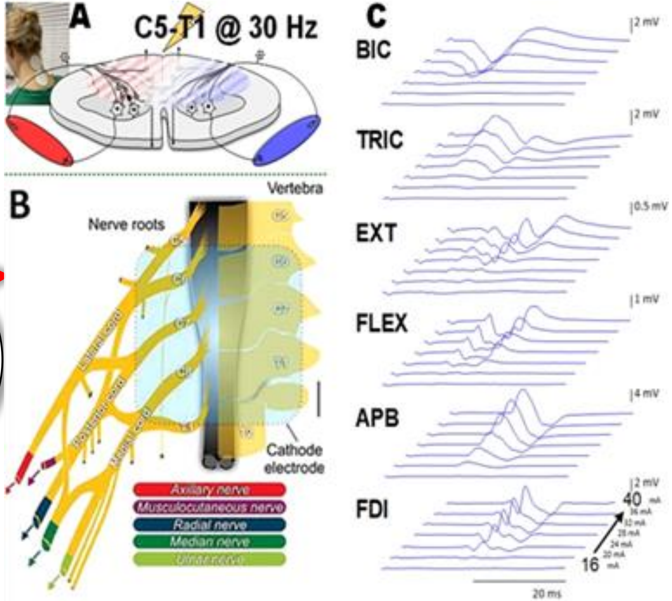


Custom electrode array
(Aneuvo™, CA)





Extremely-low-intensity and low-frequency, frequency-tuned electromagnetic fields

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- Rats recovered forepaw function with 3.93 Hz and 15.72 Hz, and increased progenitor cell markers and WM tract integrity (Segal et al. 2016)
- 25 patients <21days from stroke 40 minutes of ELI-LFEMF treatment (active or sham) 5 days/week, for 8 weeks, in conjunction with 10(?) minutes of physical therapy
- BQ uses AI algorithms to extract motor related spectral features in EEG for use as treatment frequency
- FMA-UE improved 23 vs 10 at 4 weeks and 31 vs 23 at 8 weeks, mRS 2.5 vs 1.3 at week 9 (Weisinger et al. Abstract at AHA ISC 2021)
- Frequency selected networks

"EMAGINE" study

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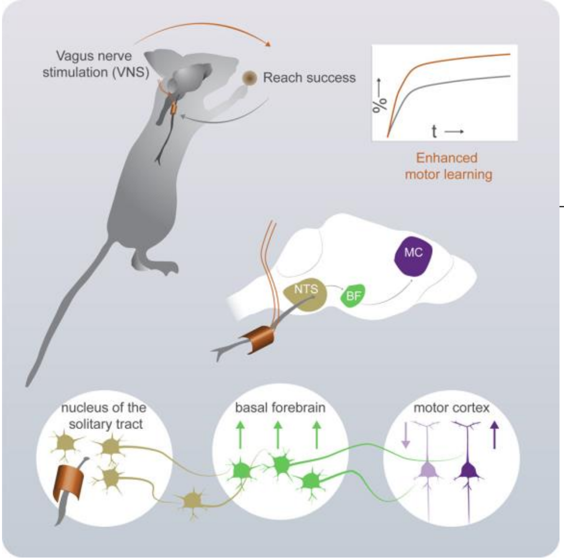
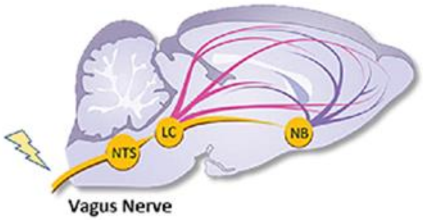
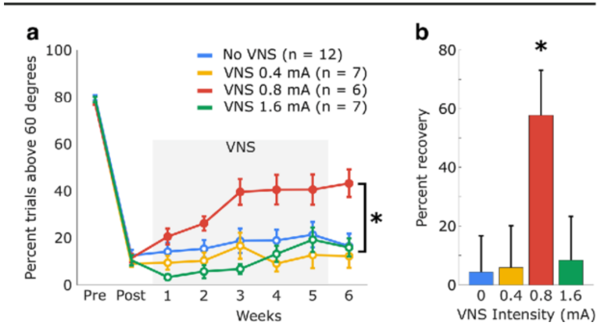
The Efficacy of a Frequency-tuned Electromagnetic Field Treatment in Facilitating the Recovery of Subacute Ischemic Stroke Patients - a Pivotal Study) (BQ5) ongoing pivotal multicenter study

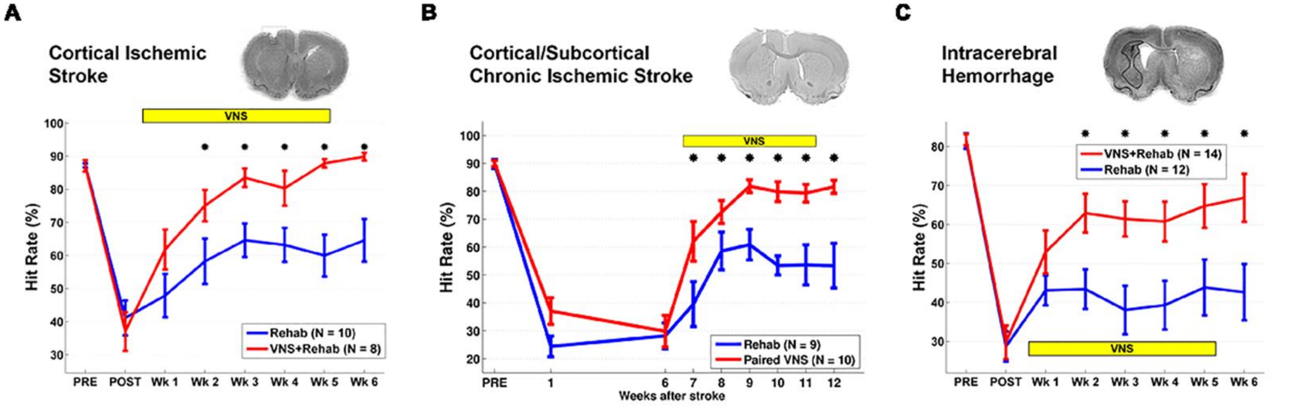
- 150 patients <21 days from ischemic stroke 45 minutes of BQ treatment (active or sham) 5 days/week, for 9 weeks, in conjunction with 60 minutes of OT/PT
- Enrolling patients with mRS 3-4, (pre mRS 0-1) UFM 10-45
- Primary outcome change mRS at 90 day,
- PI Jeffry Saver and Pamela Duncan

Brain Stimulation-VNS



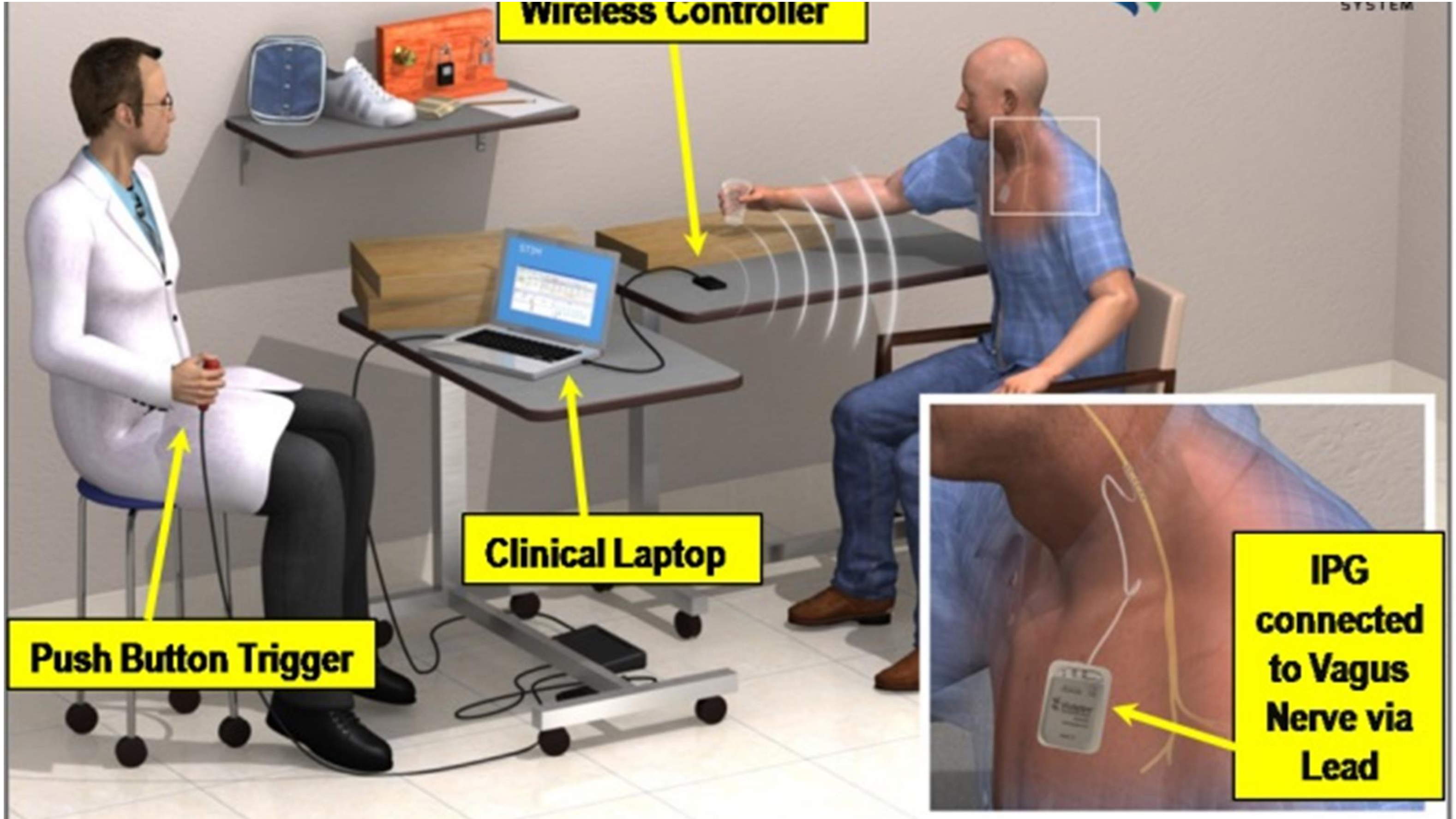






Engineer et al. . Front. Neurosci., 29 March 2019, Bowles et al. Neuron, 7 September 2022

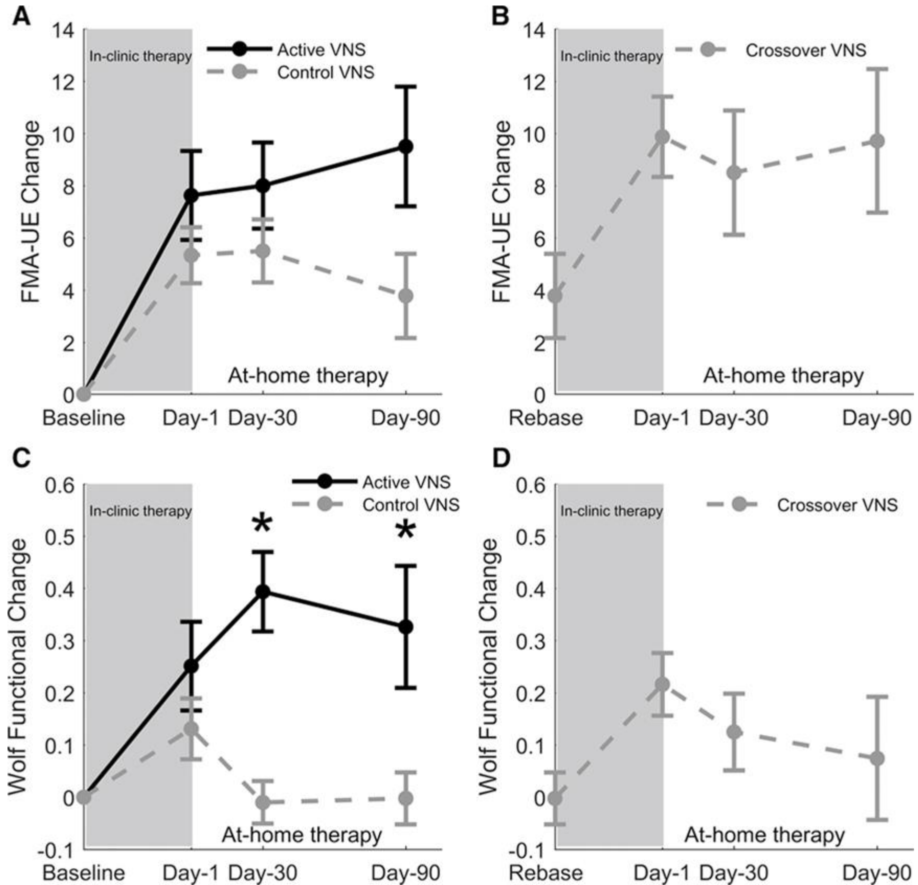
OT paired with VNS



Clinical trial results- VNS

Study	VNS/control N	FMA-UE (p)	Time frame	Resp/nonresp	comment
Dawson et al 2015 (assessor masked)	9/11	+8.7/+3.0 (0.064)	>6mo	67%/36%	Per protocol +9.6/+3 p =0.038,
Kimberly et al. 2018	8/9	+7.6/+5.3 (0.2)	4mo- 5y	75%/33%	At day 90 +9.5/+3.8 P=0.055
VNS-REHAB 2021	53/55	+5.0/+2.4 (0.0014)	9mo- 10y	47%/24%	At day 90 +5.8/+2.8

At home therapy, VNS crossover



Cellular therapies

- Heterogeneity: autologous bone marrow mesenchymal stem cell, mononuclear stem cells; multipotent adult progenitor cells; peripheral blood stem cells
- Human studies vary in design, overall safe and well tolerated.
- Optimal time frame administration route, sensitive endpoint measures need to be determined
- May benefit older patients more
- NIHSS and mRS did not differ for acute/subacute stroke, however, a significant improvement was noted in case of chronic stroke
- Lower mortality (Kumar et al 2022)

Iv MSC in chronic stroke

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Stroke
Volume 50, Issue 10, October 2019; Pages 2835-2841
https://doi.org/10.1161/STROKEAHA.119.026318

American Heart Association.

CLINICAL SCIENCES

Phase I/II Study of Safety and Preliminary Efficacy of Intravenous Allogeneic Mesenchymal Stem Cells in Chronic Stroke

Michael L. Levy, MD, PhD, John R. Crawford, MD, Nabil Dib, MD, Lev Verkh, PhD, Nikolai Tankovich, MD, PhD, and Steven C. Cramer, MD

-3 doses of iv allogenic ischemia tolerant MSC in 36 chronic stroke patients
-BI increased by 11 points,
-excellent BI increased from 11.4% at baseline to 35.5 at 12 mo

ISIS-HERMES

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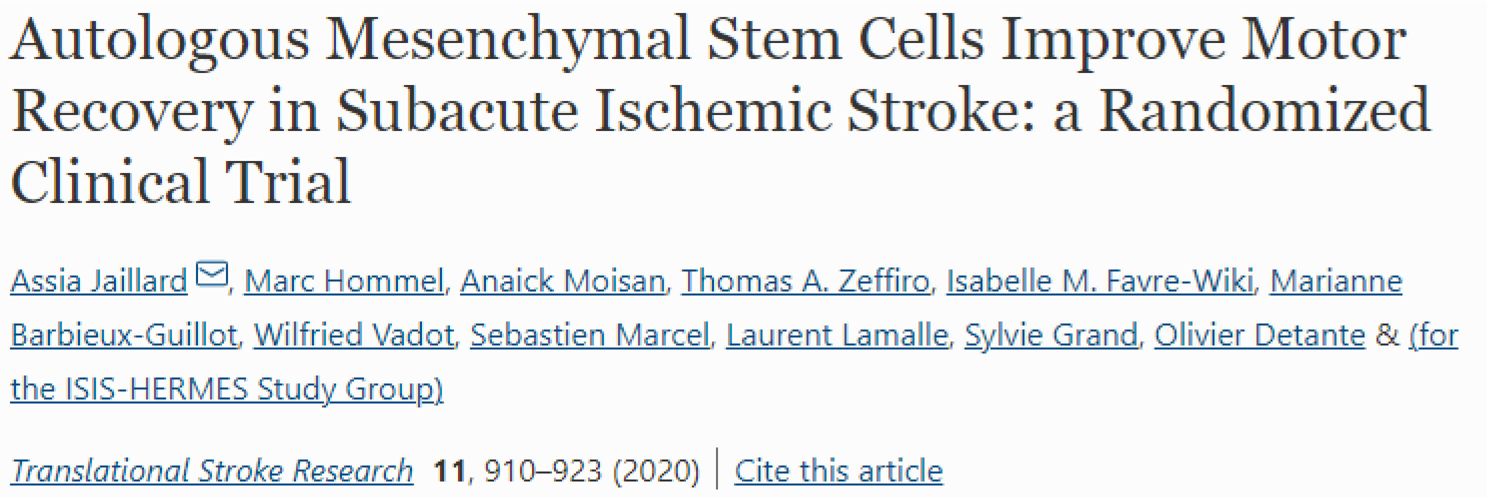
Autologous Mesenchymal Stem Cells Improve Motor Recovery in Subacute Ischemic Stroke: a Randomized Clinical Trial

Assia Jaillard, Marc Hommel, Anaick Moisan, Thomas A. Zeffiro, Isabelle M. Favre-Wiki, Marianne Barbieux-Guillot, Wilfried Vadot, Sebastien Marcel, Laurent Lamalle, Sylvie Grand, Olivier Detante & (for the ISIS-HERMES Study Group)

Translational Stroke Research **11**, 910–923 (2020) | Cite this article

Open-label RCT stroke pts enrolled within 2 weeks of mod/severe ischemic carotid stroke 2-year follow-up
Safe and feasible, motor performance improved through sensory-motor plasticity

RECOVER-Stroke trial

- Study of ALD-401 via Intracarotid Infusion in Ischemic Stroke Subjects) in 48 patients averaging 16 days poststroke,
- There was no difference in 90-day mRS between those receiving an intracarotid infusion of autologous aldehyde dehydrogenase-bright (ALD-401 stem cells), a marrow-based cell with high aldehyde dehydrogenase expression and controls.

Savitz et al. Circulation 2019

PISCES-2

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- Pilot Investigation of Stem Cells in Stroke Phase II Efficacy
- Only 1/23 patients with severe arm motor deficits a median of 7 months poststroke receiving intracerebral implantation of allogeneic human neural stems (CTX0E03) met responder criteria for arm functional gains 3 months post-implantation.
- In secondary analyses at 12 months, 3/20 did, and 7/20 showed an improved mRS.

Muir et al. J Neurol Neurosurg Psychiatry. 2020

STARTING-2: MSCs not effective, safe

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Efficacy and Safety of Intravenous Mesenchymal Stem Cells for Ischemic Stroke

Jong-Won Chung, MD, PhD, Won Hyuk Chang, MD, PhD, Oh Young Bang, MD, PhD, Gyeong Joon Moon, PhD, Suk Jae Kim, MD, MSc, Soo-Kyoung Kim, MD, PhD, Jin Soo Lee, MD, PhD, Sung-Il Sohn, MD, PhD, and Yun-Hee Kim, MD, PhD, for the STARTING-2 Collaborators

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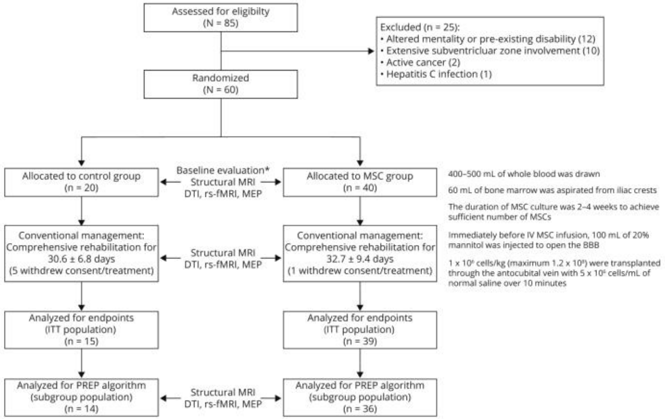
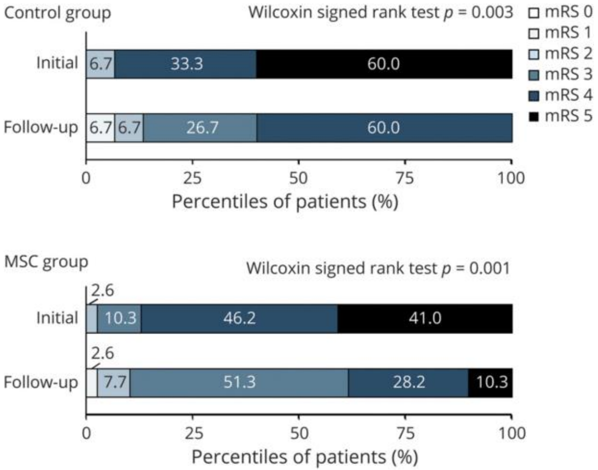
Neurology® 2021;96:e1012-e1023. doi:10.1212/WNL.0000000000011440





Good Responder Rate

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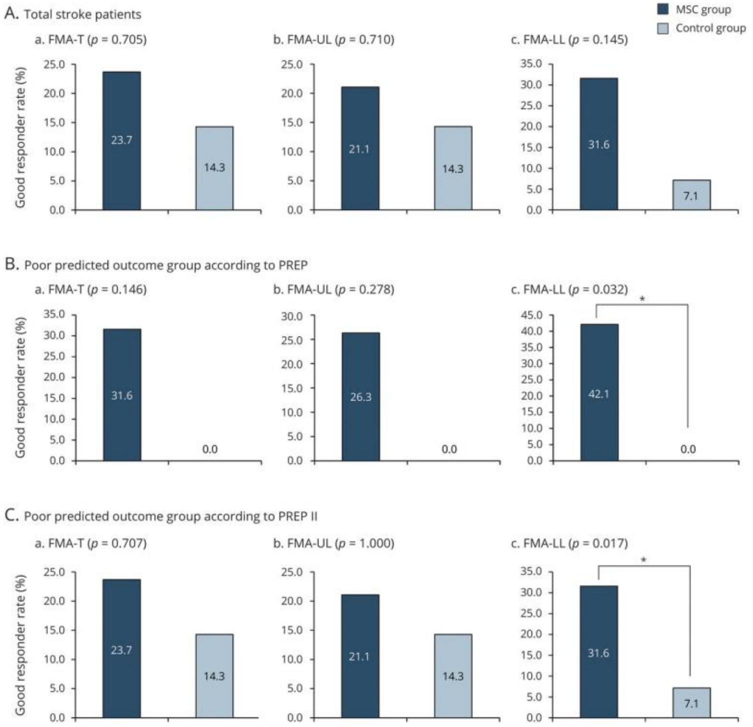

AMASCIS

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- Allogeneic Adipose Tissue-Derived Mesenchymal Stem Cells in Acute Ischemic Stroke (AMASCIS): A Phase II, Randomized, Double-Blind, Placebo-Controlled, Single-Center, Pilot Clinical Trial (Cekis-Ruiz 2022)
- 13 patients within 2 weeks of moderate to severe stroke,
- safe

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