UCSF
University of California
San Francisco

Technology in Stroke Rehabilitation

Gary M. Abrams, M.D.
Professor of Neurology
Medical Director of Rehabilitation,
UCSF Medical Center and San Francisco VAMC

10/13/2017

Disclosure of Financial Relationships

Gary M. Abrams M.D.

Has disclosed the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Disclosures:
Research: Halo Neuroscience – Medical Advisor
MIndMaze – Research grant

Resolution of Potential Conflicts of Interest:
-Video clip of virtual reality kindly provided by MindMaze

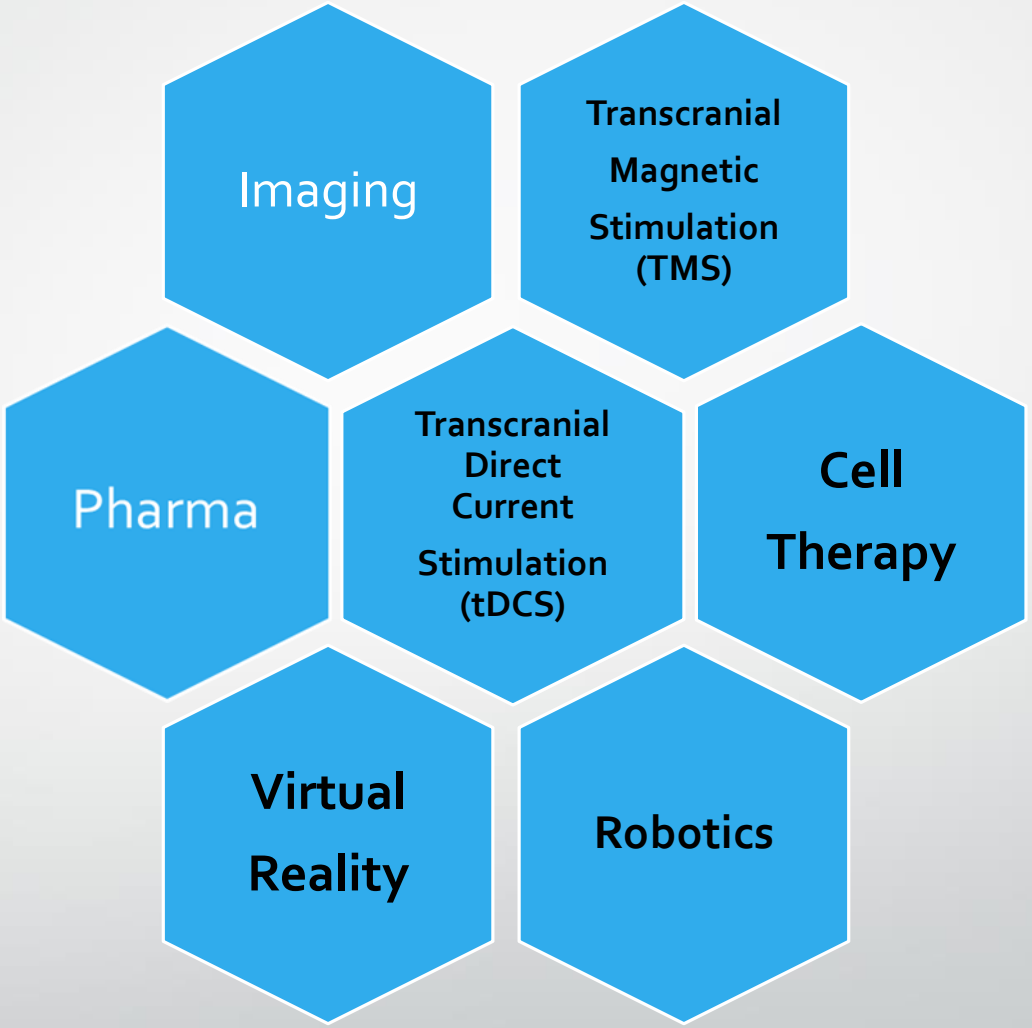
‘Neurotechnology’

Neurotechnology is any technology that has a fundamental influence on how people understand the brain…….

It includes technologies designed to improve and repair brain function and allow researchers and clinicians to visualize the brain

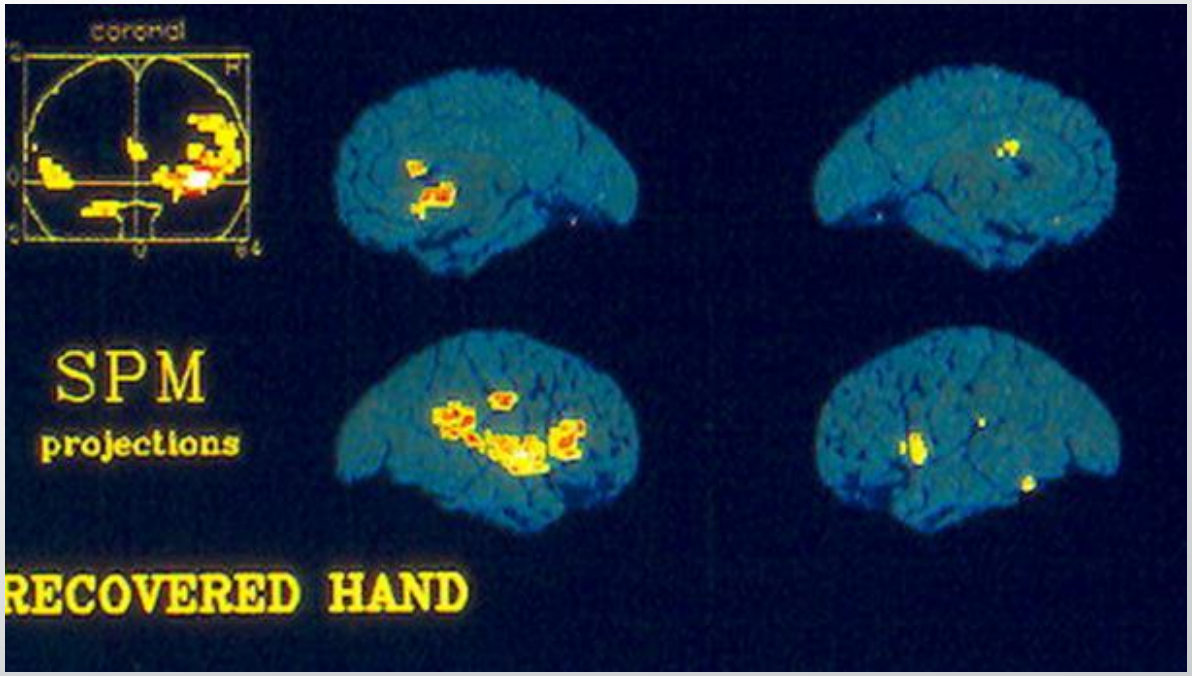
Neurotechnology

Stroke Rehabilitation



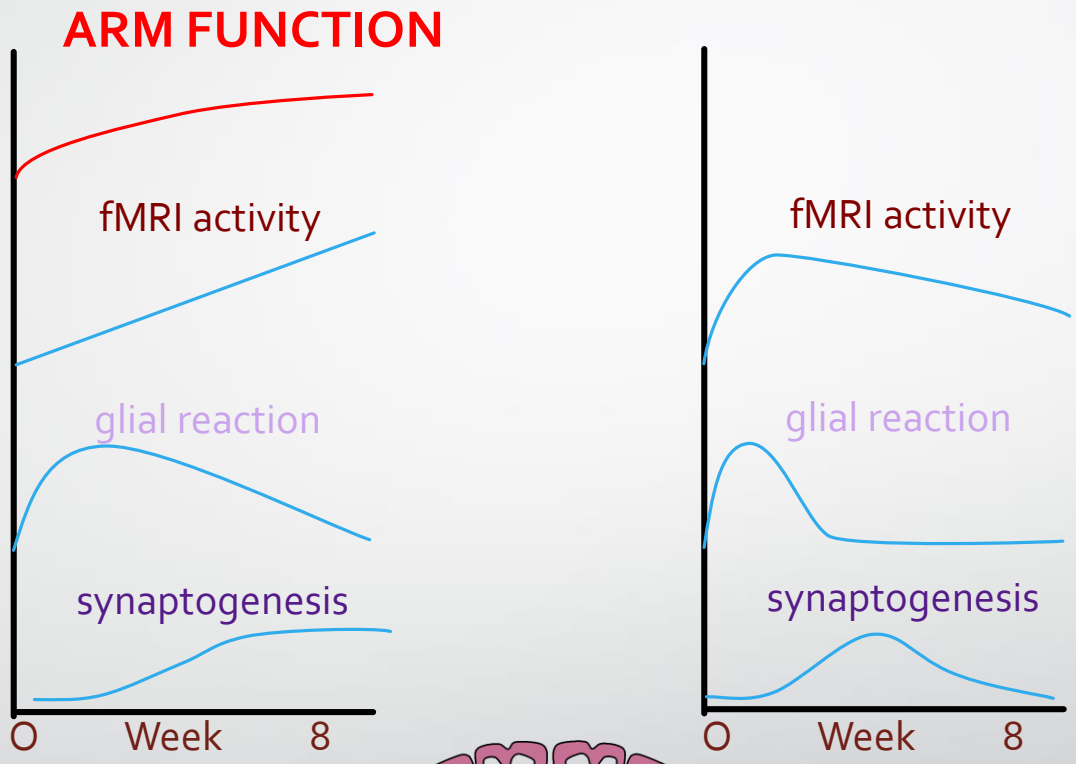
Theories of Brain Recovery after Stroke

- Restoring homeostasis and intrinsic repair
- Reversal of diaschisis
- Neural reorganization

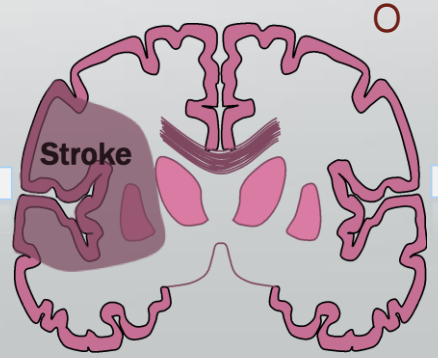


Brain Repair and Reorganization
A Tale of Two Hemispheres

REPAIR MECHANISMS
- Growth factors
- GABA receptor
- Angiogenesis
- Inflammation
- Dendritic branching
- Axonal Sprouting
- Cell-cycle proteins
- Excitability



Ipsilesional Hemisphere



Contralesional Hemisphere

Adapted from Cramer, *Ann Neurol, 2008*

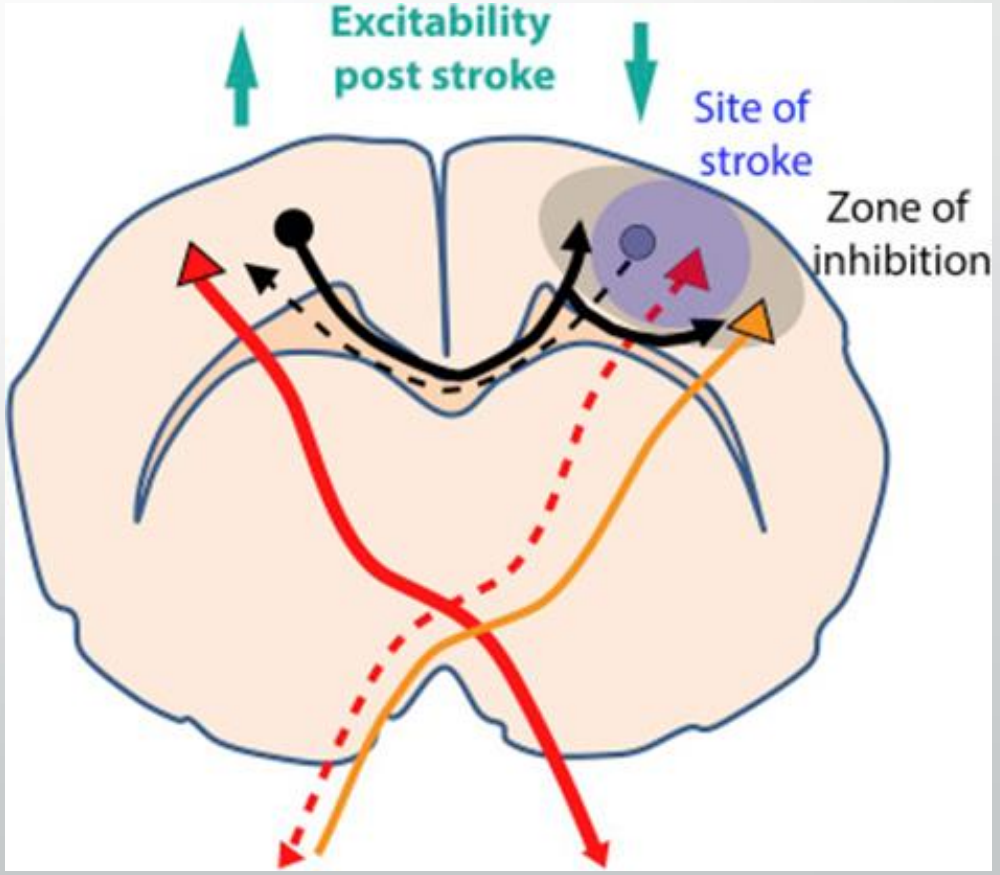
Cerebral Hemispheres Working Together

Hemispheres **inhibit** each other via neural circuitry across the corpus callosum

Stroke causes ***loss*** of inhibition of the non-lesioned hemisphere

---------->

The disinhibited, non-lesioned hemisphere then provides ***excessive*** inhibition of the lesioned hemisphere



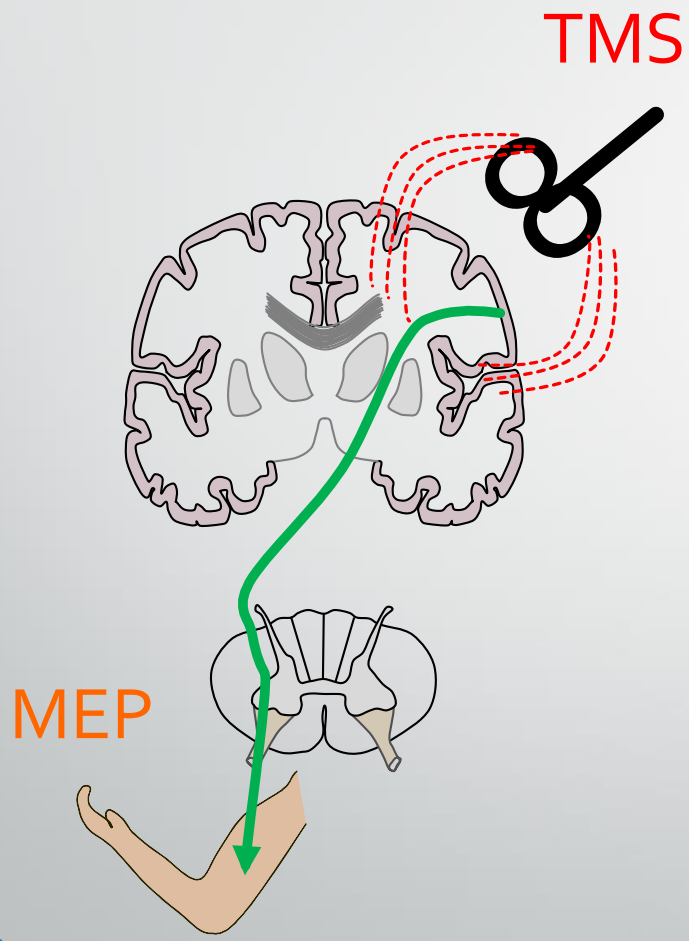
Restoring Hemispheric Balance is Associated with Improved Function

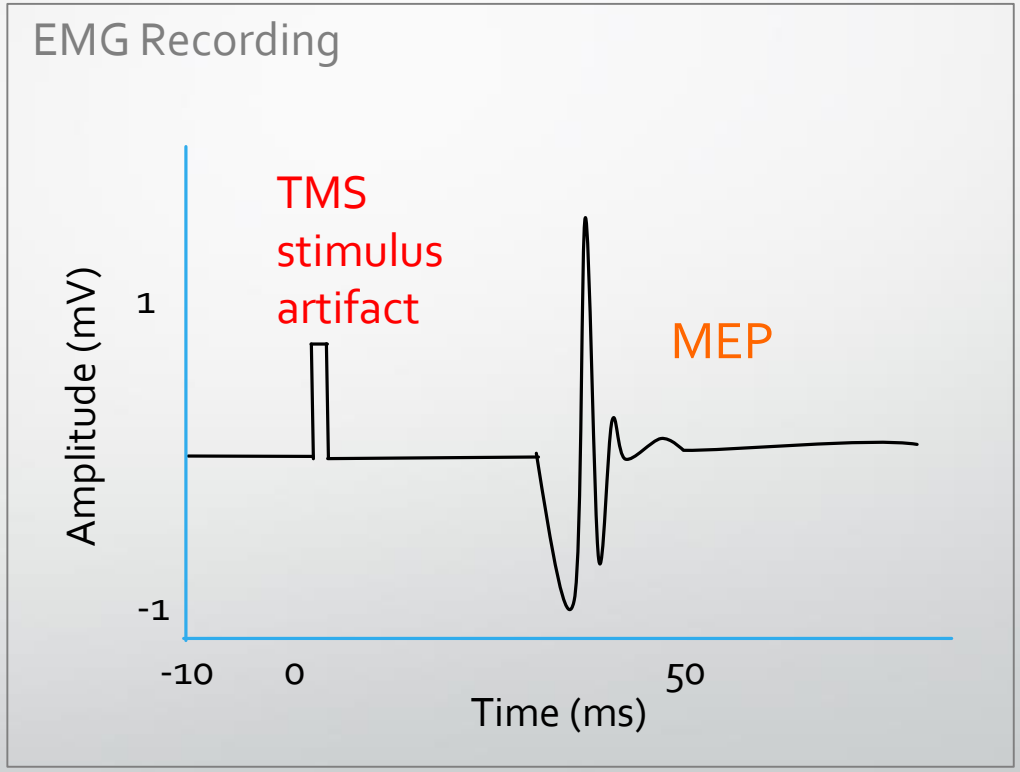
Non-invasive Brain Stimulation (NIBS)

Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

Transcranial magnetic stimulation TMS

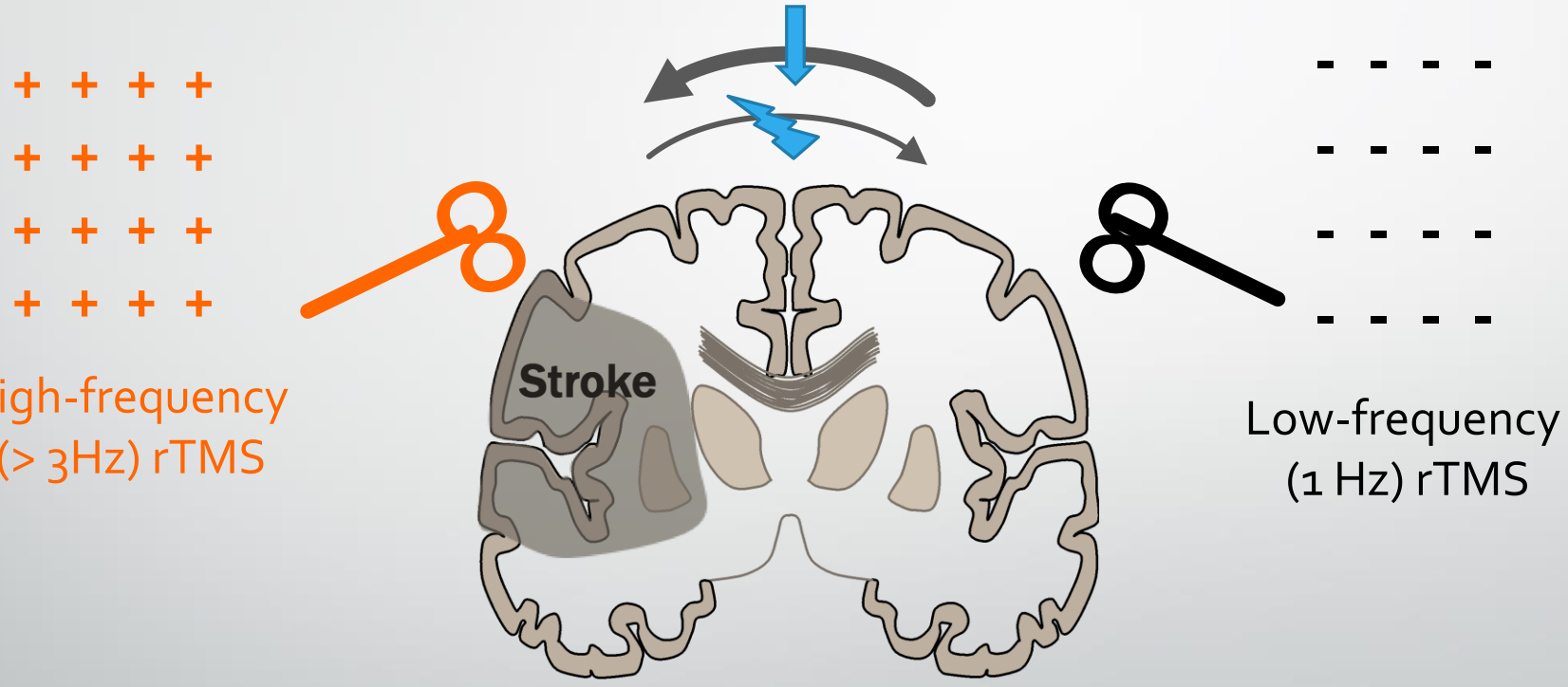




TMS = Transcranial Magnetic Stimulation
MEP = Motor Evoked Potential

Non-Invasive Repetitive TMS (rTMS)

Restoring balance to inter-hemispheric inhibition



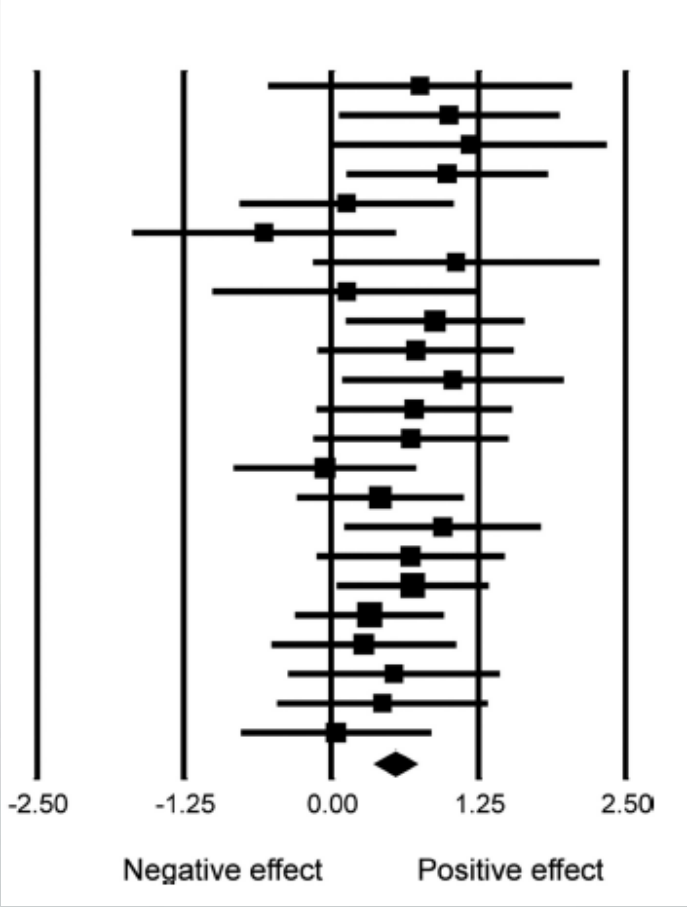
High-frequency
(> 3Hz) rTMS

Low-frequency
(1 Hz) rTMS

Hummel et al., 2008; Wessel et al., 2015

Meta-Analysis of TMS trials in Stroke

- 23 studies with ~10 patients/study from 2005-2012
- Many were randomized, double blind
- Lo freq rTMS over non-lesioned hemisphere ***or*** Hi freq rTMS to lesioned hemisphere
- Outcomes - (simple) e.g. reaction time → (complex) e.g. Wolf Motor Function Test



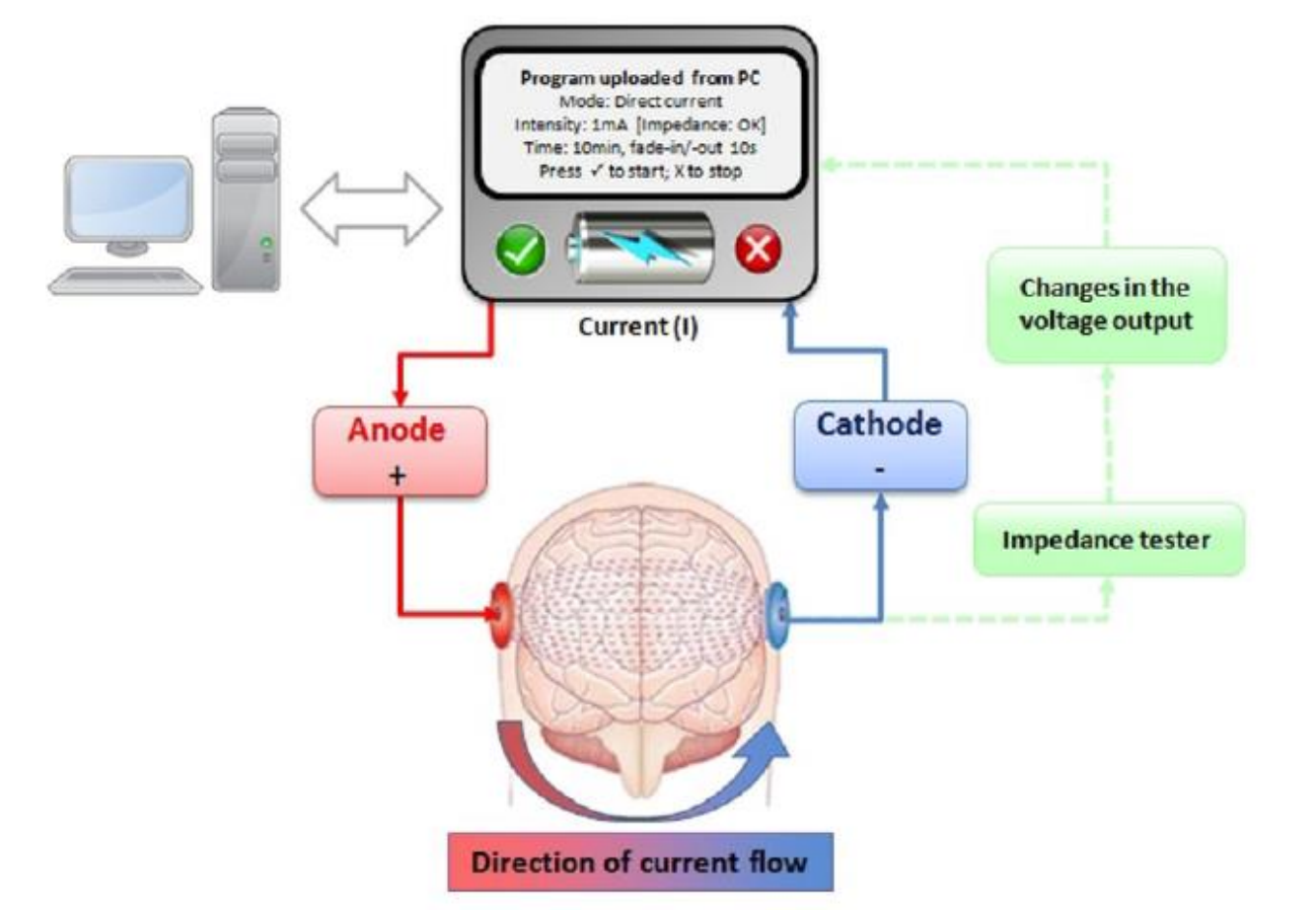
Hsu et al., Stroke 2012

Cochrane Library of Evidence-Based Medicine rTMS Stroke

(2012)

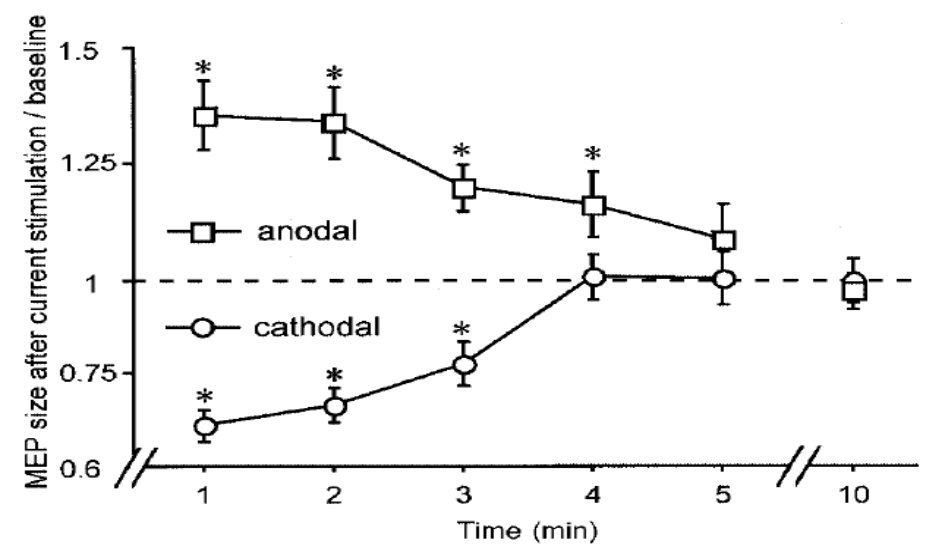
- Review of 19 trials involving 588 participants.
- No effect on motor function or ADLS
- Current evidence does not support the routine use of rTMS for the treatment of stroke.
- Larger trials are needed to determine a suitable rTMS protocol and the long-term functional outcomes

Transcranial Direct Current Stimulation (tDCS)



Fertonani and Miniussi, 2016

Motor cortex excitability after 5 minutes of 1 mA stimulation

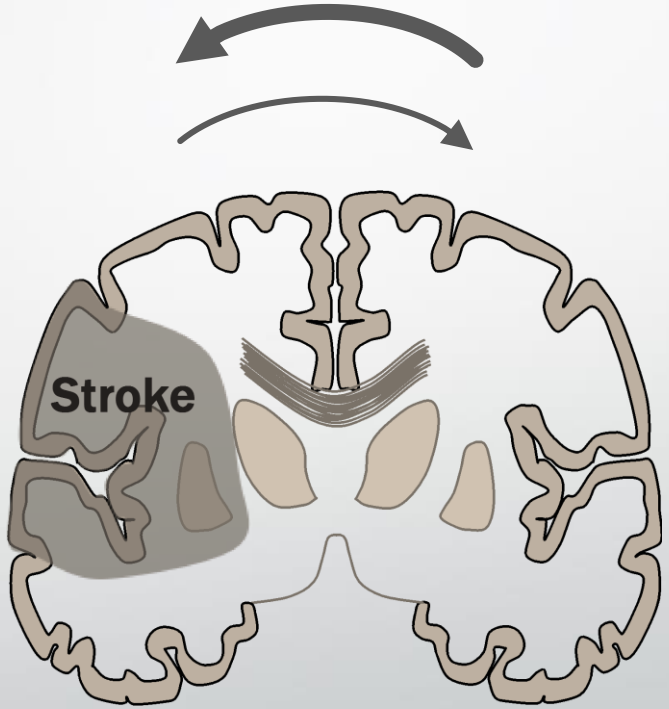


Nitsche & Paulus, 2000

Transcranial Direct Current Stimulation

Restoring balance to inter-hemispheric inhibition

"Anodal"



"Cathodal"

Hummel et al., 2008; Wessel et al., 2015

Challenges to Studying tDCS (or rTMS) Stroke

- Heterogeneous populations
  - Time after stroke
    - Level of impairment
      - # of treatment sessions
        - Pairing with tasks
          - Electrode placement (tDCS)
            - Monocephalic v. bihemispheric stimulation (tDCS)

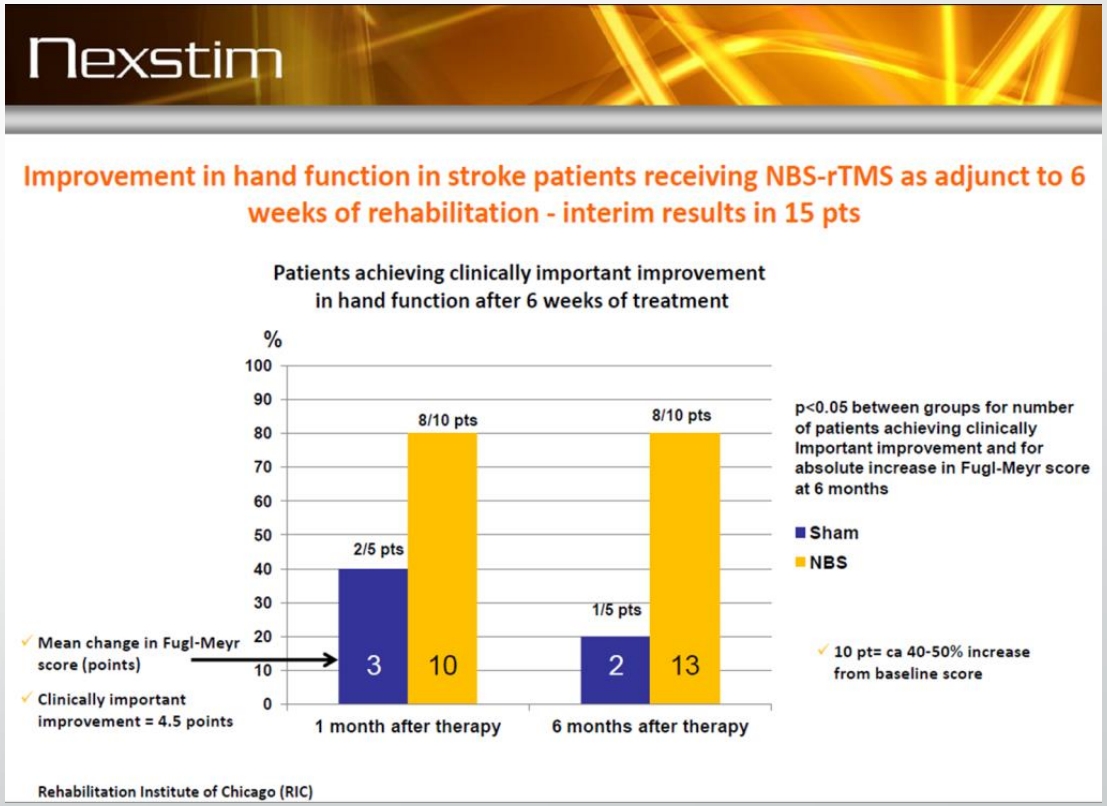
Cochrane Library of Evidence-Based Medicine tDCS Stroke

(2016)

- 32 studies with 748 participants
- Variable modes of stimulation; dosages, etc.
- ….tDCS might enhance ADLs, but it is still uncertain if arm and leg function, muscle strength and cognitive abilities may be improved.

Non-invasive Brain Stimulation Future Directions

- rTMS and tDCS are promising technologies to help promote recovery
- Need better optimization and consistency in designing trials
- 1 Large-scale Phase III trial (NICHE)
  - UE rehab therapy + rTMS was safe
  - Both rTMS arm and sham TMS arm outcomes were the same
- Characteristics of responders versus non-responders?



Virtual Reality

Virtual Reality (VR)

- An artificial environment experienced through sensory stimuli provided by a computer and in which one's actions partially determine what happens in the environment
- VR has been used to train pilots and surgeons.
- VR has been adapted for rehabilitation

Virtual Reality - Why Stroke Rehabilitation?

- Repetitive task training has been shown to be effective in some aspects of stroke rehabilitation (AHA Stroke CPG)
  - Improves walking distance and speed (French 2007) Class 1; Level A evidence
  - Improves upper limb function (Verbeek 2014) Class 1; Level A evidence
- VR can offers enjoyable goal-oriented tasks - motivates more engagement therapy
  - Clinician has ability to grade tasks, challenge the user, provide real-time feedback; train in unsafe situations (crossing street)
  - Can train without therapist

Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial

Gustavo Saposnik, Leonardo G Cohen, Muhammad Mamdani, et al , Lancet Neurol, 2016

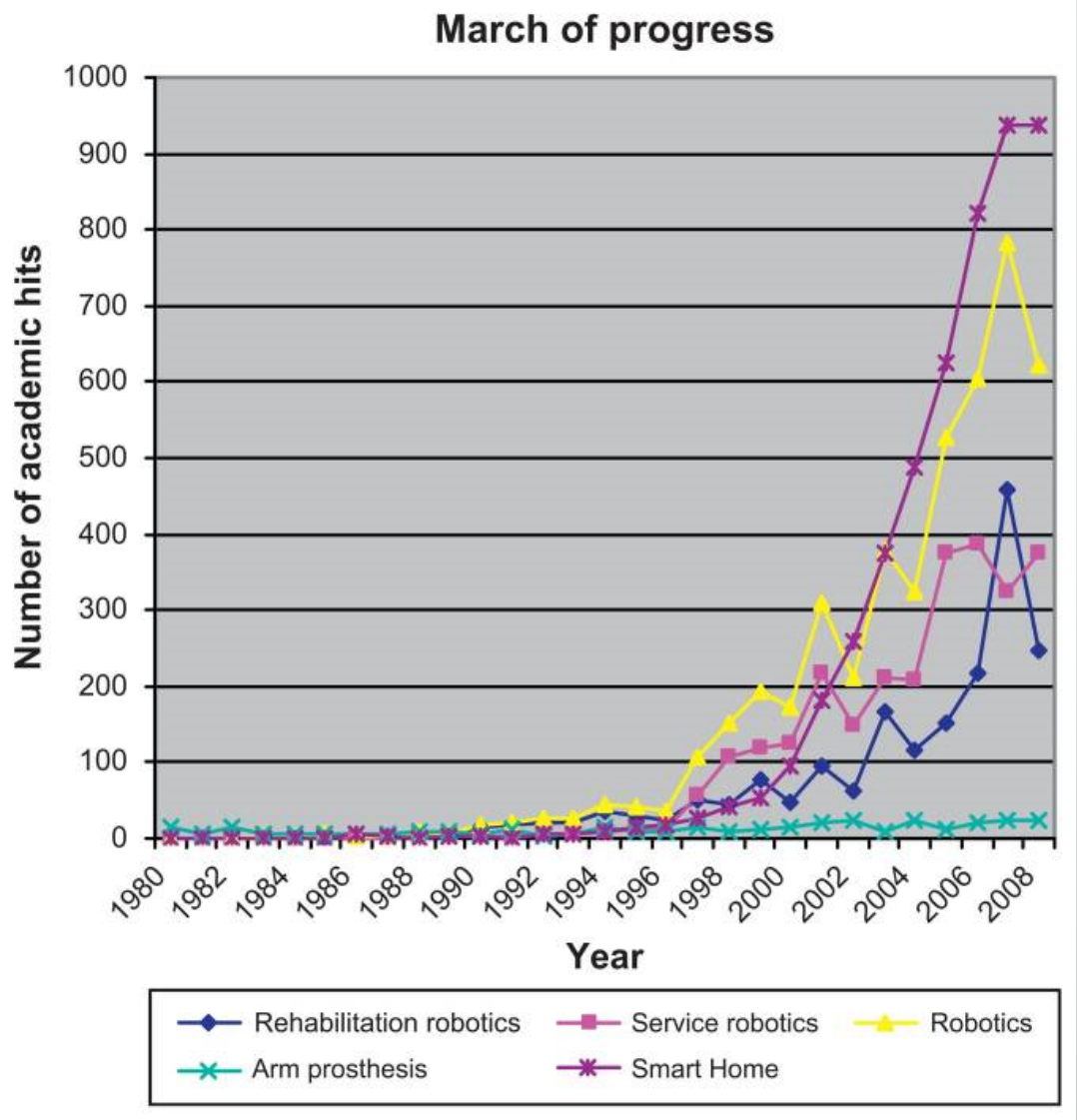
- Single-blinded trial (N=142)
- Subjects were within 3 months of stroke – mild/moderate deficits
- 71 received VR with Nintendo Wii; 70 received rec therapy; equal amounts of conventional rehabilitation
- Both groups improved; No difference between groups

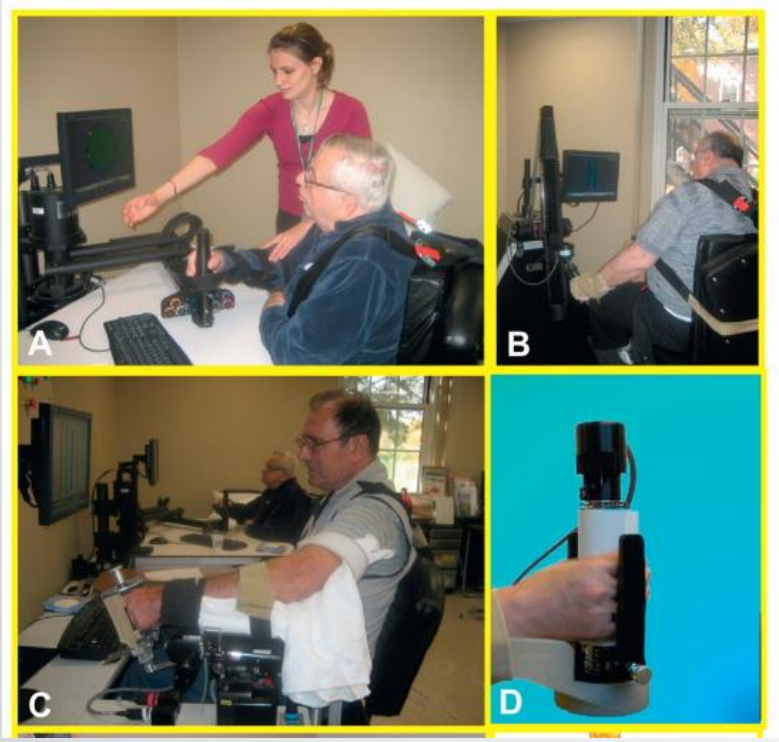
VR Training for Arm

Cochrane Library of Evidence-Based Medicine Virtual Reality (2015)

- Virtual reality and interactive video gaming may be beneficial in improving upper limb function and ADL function
  - an adjunct to usual care (to increase overall therapy time)
  - when compared with the same dose of conventional therapy.
- Insufficient evidence to reach conclusions about the effect of VR or video gaming on grip strength, gait speed or global motor function.
- It is unclear which characteristics of virtual reality are most important
- It is unknown whether effects are sustained in the longer term.

Robotics


March of progress
Number of academic hits
1000
900
800
700
600
500
400
300
200
100
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
Rehabilitation robotics
Service robotics
Robotics
Arm prosthesis
Smart Home



Lo AC, Guarino PD, Richards LG et al, N Engl J Med 2010

Byl, Abrams, Pitsch et al, J Hand Ther 2013

Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke

Lo AC, Guarino PD, Richards LG et al, N Engl J Med 2010;362:1772-83

- Multicenter trial – 127 patients with moderate-to-severe arm impairment > 6 months post-stroke
- Robot therapy vs intensive arm therapy vs. usual care
- Therapy – 36, 1 hour session over 12 weeks: primary outcome – Fugl-Meyer
- Robot therapy not better than usual care or intensive therapy
- Secondary analysis - robot therapy better than usual care at 36 weeks

Cochrane Library of Evidence-Based Medicine
Arm/Hand Robots

(2015)

- 34 trials with 1160 participants
- Varying types of robots
  - Electromechanical and robot-assisted arm/hand training improved ADLs in people after stroke and
  - Function and muscle strength of the affected arm.
- Safety unclear; how and when to use uncertain
- Low quality of evidence

Cochrane Library of Evidence-Based Medicine – **Robotic Gait Trainers**

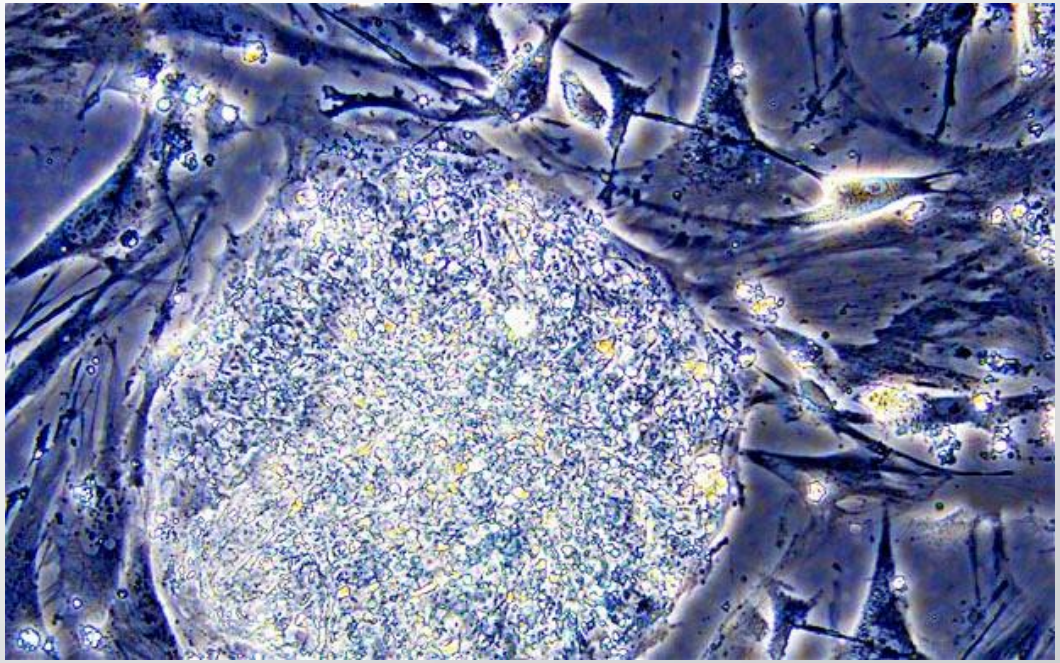
(2017)

- 36 trials involving 1472 participants.
- Electromechanical-assisted gait training coupled with PT after stroke is more likely to achieve independent walking than PT alone
- 7 patients need to be treated to prevent 1 dependent walker
- Most benefit is seen by -
  - People in the first 3 months after stroke
  - Those who are not able to walk
- Best type of device is not clear, nor is the most effective training regimen and how long any benefit may last.

Stem Cells

Stem Cells

- Pilot trials have shown acceptable safety and maybe benefit using different types of stem cells
  - Transformed teratocarcinoma cells
  - Immature neural cells
  - Immature hematopoietic cells



Why Stem Cells for Stroke?

- Secrete bioactive molecules such as growth factors, cytokines and chemokines
  - May attenuate immune responses and reduce inflammation
  - Promote neurogenesis
  - Promote angiogenesis
- Probably not working via tissue replacement

Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

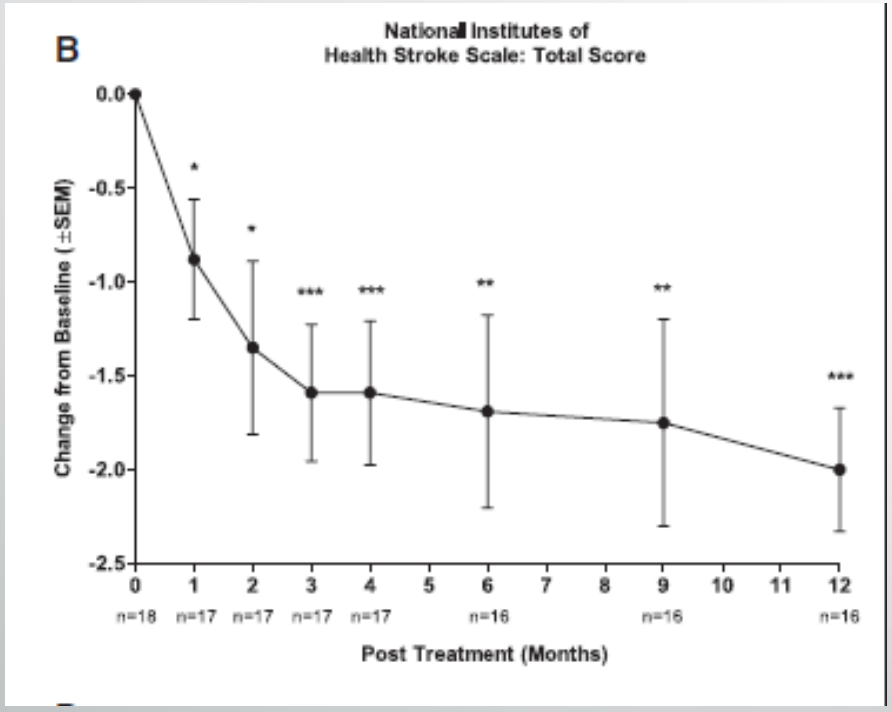
Steinberg et al, Stroke, 2016

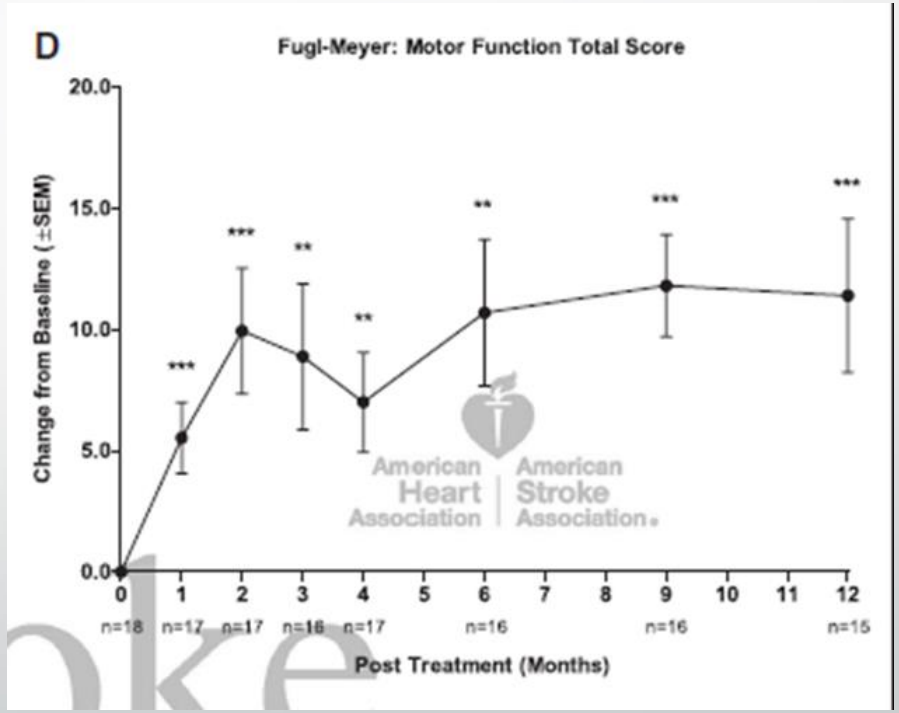
- Enrolled 18 patients between 6 and 60 months post-ischemic stroke
- Modified bone-marrow-derived mesenchymal stem cells implanted stereotactically around the stroke – one burr hole; 3 cannula tracts
- 3 cohorts (6) – 2.5×10^6; 5.0×10^6; 10×10^6 cells
- Baseline mean NIH Stroke Scale (NIHSS) – 9.4; Fugl-Meyer Motor Score (FMMS) -30.4

12 Month Outcomes

Steinberg et al, Stroke, 2016

Fairly safe – 6 serious AE with 1 seizure and 1 asymptomatic subdural hygroma related to procedure





NIHSS mean decrease of 2 points.

FMMS mean increase of 11.4 points


Allen
Martin
Elizabeth
Cook
6:00 PM
5
CBSSF.COM

Neurotechnology in Stroke Rehabilitation

- Many different options have shown promise
  - NIBS
  - Virtual Reality
  - Robotics
  - Stem Cells
- Many questions remain about the optimal way to employ these techniques
- Some tech -
  - May be more effective than current practices
  - May enhance or supplement current practice
  - May offer cost-effective alternatives to current practice