The Future of Stroke Rehabilitation

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Disclosures

- Research support
  - Nexstim
  - Realiteer
- Consultation
  - Rex Bionics
  - Tyromotion

Prior Recipients of the C. Miller Fisher Award

- 2016 Jonathan Rosand, MD
- 2015 Robert G. Holloway, Jr, MD
- 2014 Mitchell S. V. Elkind, MD
- 2013 Steven R. Levine, MD
- 2012 J.P. Mohr, MS, MD
- 2011 Steven M. Greenberg, MD, PhD
- 2010 Michael P. Alexander, MD
- 2009 Lee H. Schwamm, MD,
- 2008 Daniel E. Singer, MD
- 2007 Christopher S. Ogilvy, MD
- 2006 Walter Koroshetz, MD
- 2005 Michael Moskowitz, MD
- 2004 Robert H. Ackerman, MD
- 2003 Marc Fisher, MD
- 2002 J. Philip Kistler, MD
- 2001 Carlos Kase, MD
- 2000 Philip A. Wolf, MD
- 1999 Robert G. Ojemann, MD
- 1998 Louis R. Caplan, MD
- 1997 Nicholas T. Zervas, MD

C. Miller Fisher

- Born in Canada in 1913, and lived to age 98, active professionally almost to the very end of his life.
- Served in the Canadian Navy in WWII, and spent 3.5 years in a German prison camp during the war after his ship was sunk
- Spent most of his career at the MGH where he was a founder of the stroke service
- Essentially founded the field of vascular neurology, describing TIA's, how atrial fibrillation causes stroke, the relationship between carotid stenosis and stroke, and characterizing lacunar stroke syndromes.
- His name is attached to a variant of Guillain-Barre syndrome which he described

Stroke Rehabilitation: Where are we now?

- Describing natural history of recovery
- Improving prediction tools for outcomes
- Developing empiric evidence base for rehab therapies
- Developing new technologies
- Working to understand dosing and timing

Neurological Recovery

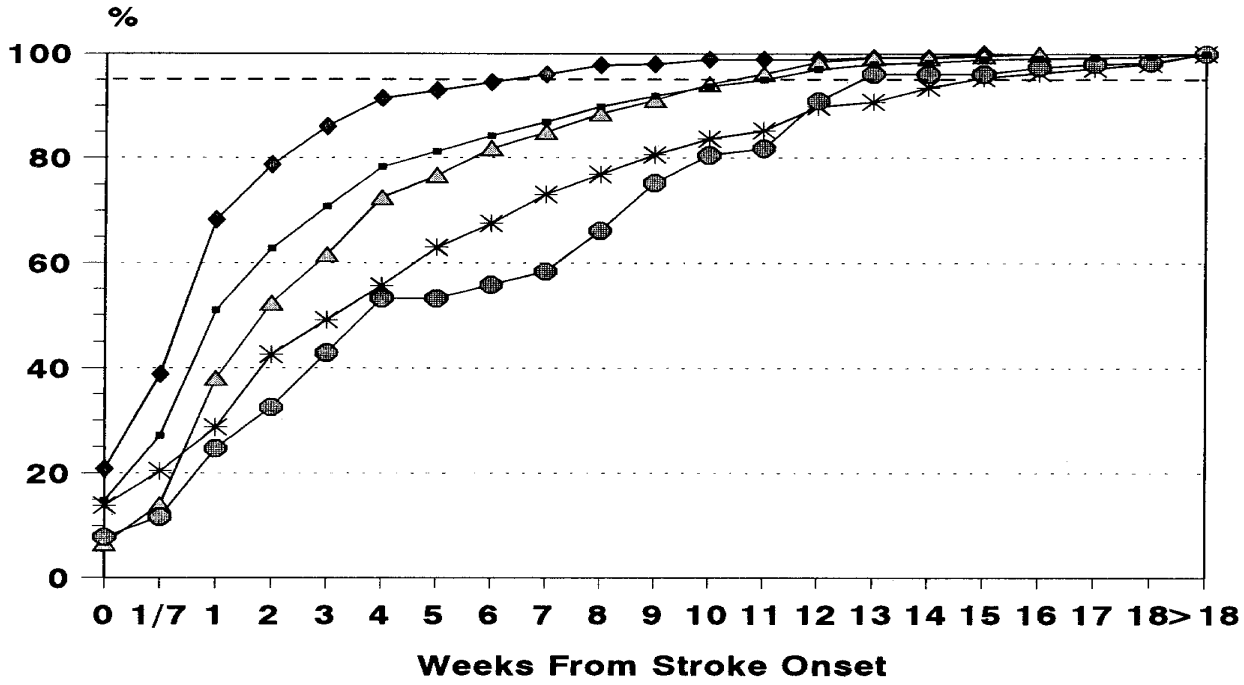
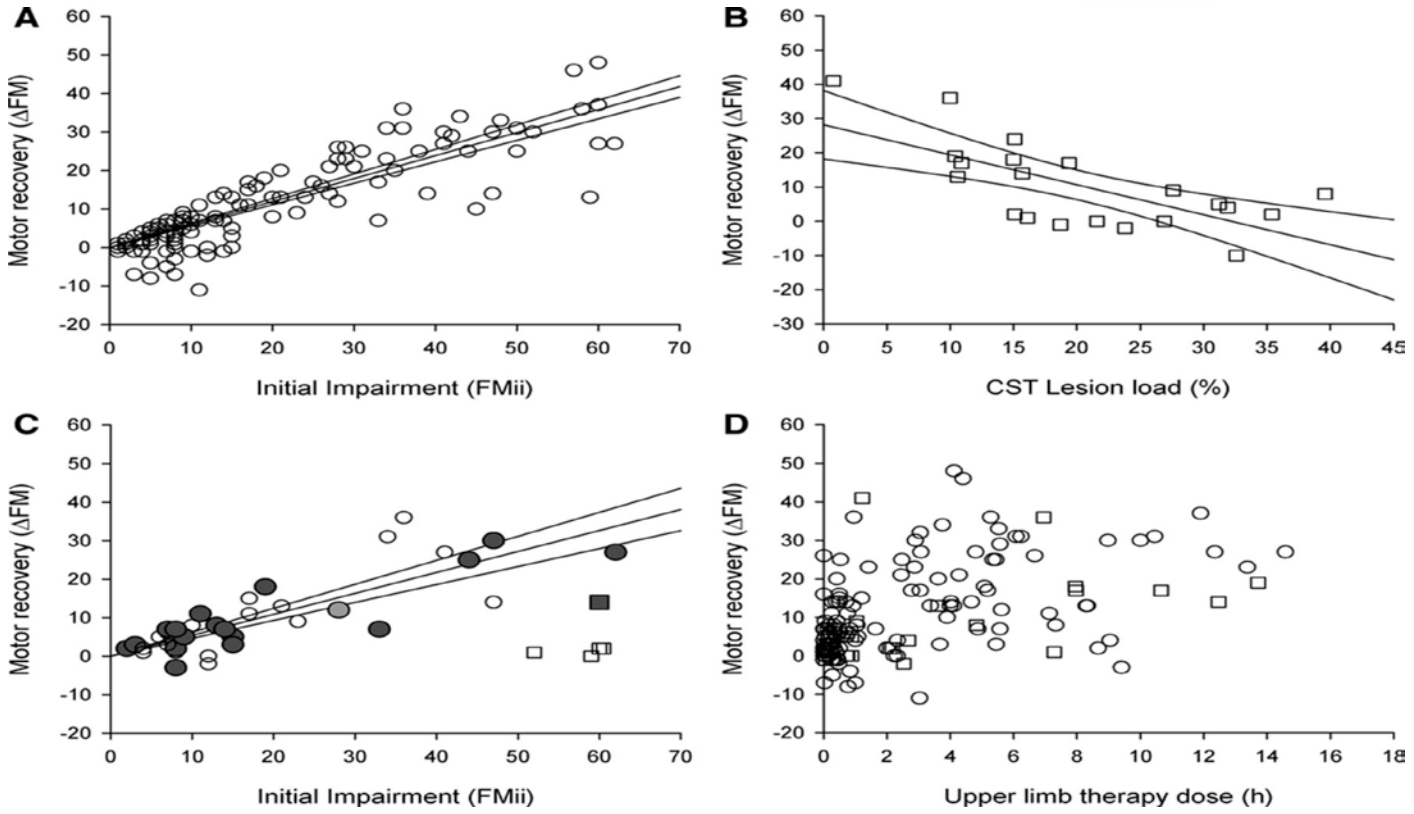


Fig 1—The time course of recovery in survivors shown as the cumulated rate of patients having reached their best neurological outcome. Rates are given for all patients, ■; for patients with initial mild stroke severity, ◆; for patients with initial moderate stroke severity, ▲; for patients with initial severe stroke severity, *; for patients with initial very severe stroke severity, ●. The ANOVA test showed an overall difference in the time course of recovery between the groups, $p < 0.0001$. Further analyses showed that the time course of recovery differed significantly between patients with initially mild strokes versus moderate strokes, $p < 0.0001$, and between patients with moderate strokes versus severe strokes, $p < 0.03$. No difference was found between patients with severe versus very severe strokes, $p = 0.19$.

Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: The copenhagen stroke study. Arch Phys Med Rehabil 76: 27-32, 1995

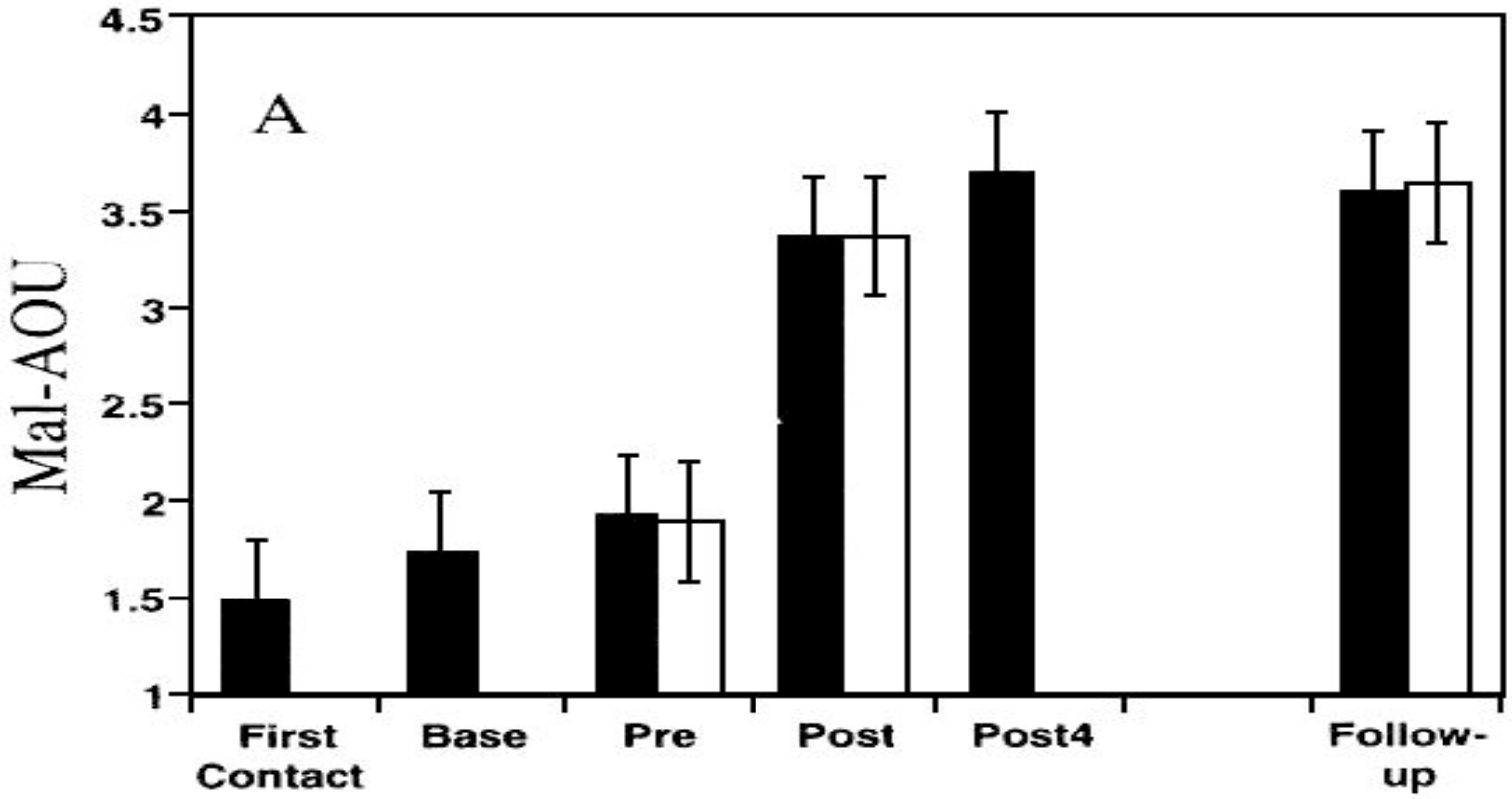
Proportional Recovery

- For patients with an intact Corticospinal tract, most patients make a proportional recovery of about 63% (95% CI 55%-70%)
- Model unreliable in patients without functional CST (Motor evoked potential negative)



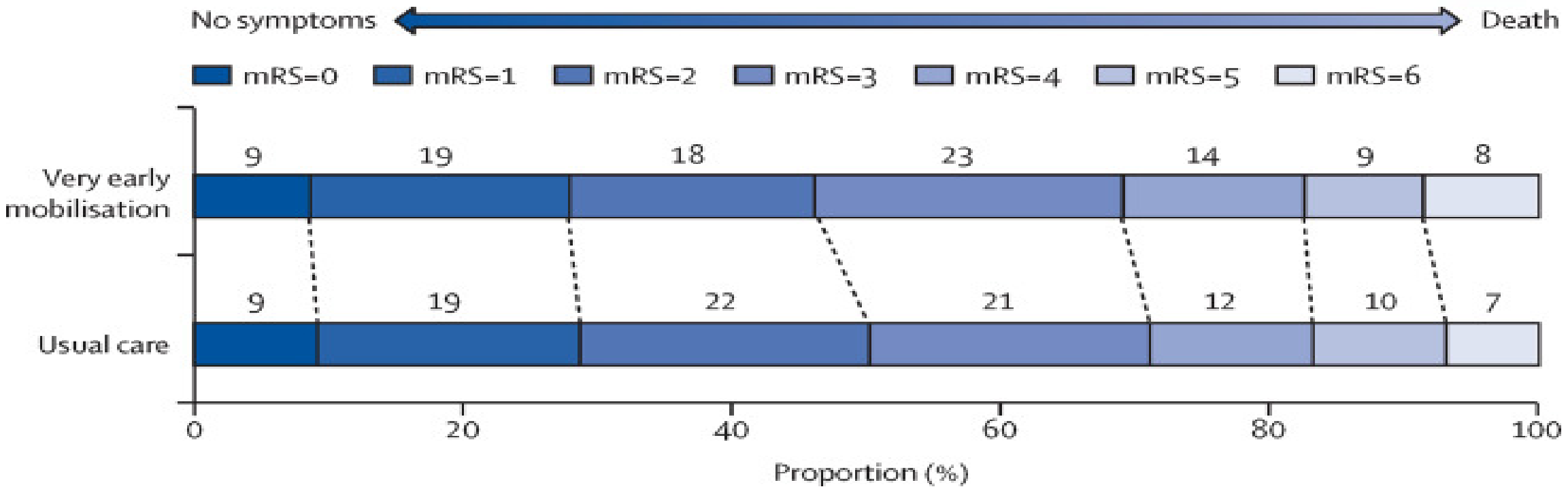
Stinear, Cathy M., et al. "Proportional Motor Recovery After Stroke." Stroke 48.3 (2017): 795-798.

But…we can still change: CIMT 5 years post-stroke



Miltner WH; Bauder H; Sommer M; Dettmers C; Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. Stroke. 30(3):586-92, 1999

AVERT – Early Mobilization: Too much, too soon



n = 2104

Berhardt J, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. The Lancet 386(9988): 46-55, 2015.

Does more therapy improve outcomes?

- ICARE: Task-Oriented Practice
- RCT with 361 subacute stroke patients (14 to 106 days) randomized to 3 groups:
  - Usual Care (mean of 11.2 hours of OT)
  - Task-oriented upper limb training (30 hours over 10 weeks)
  - Dose-matched conventional OT
- No differences in motor outcomes

Winstein, Carolee J., et al. "Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial." JAMA 315.6 (2016): 571-581.

New Technologies: Robot-aided rehabilitation

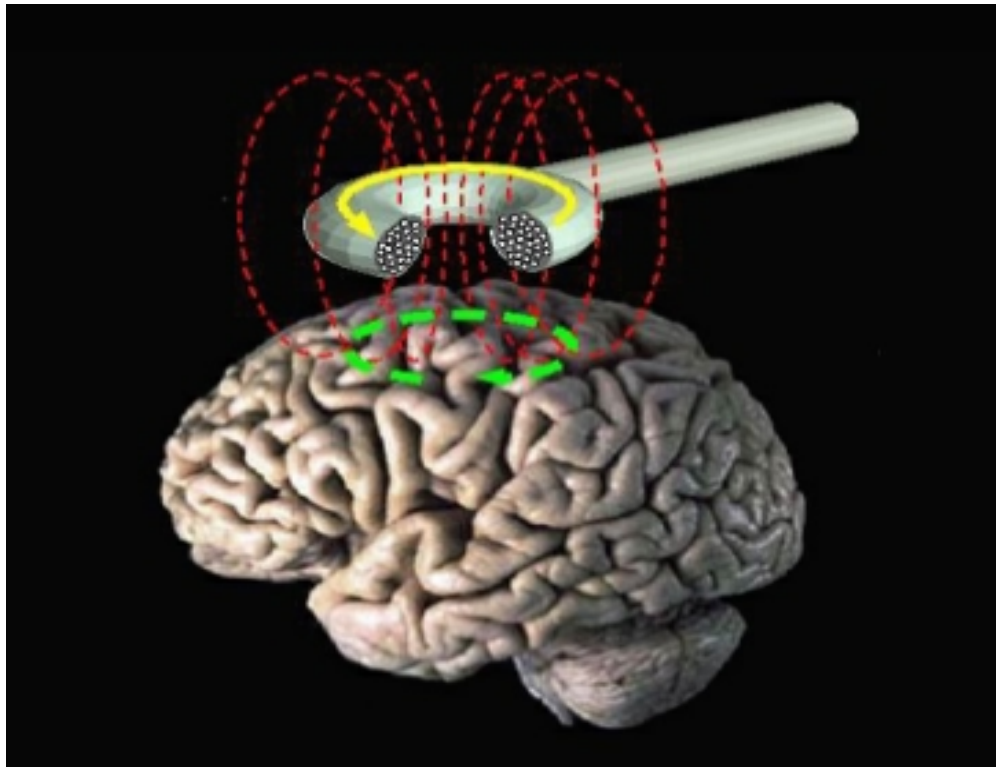
Photo courtesy of Hocoma

"Hey, we have one of those. You hang your laundry on it."

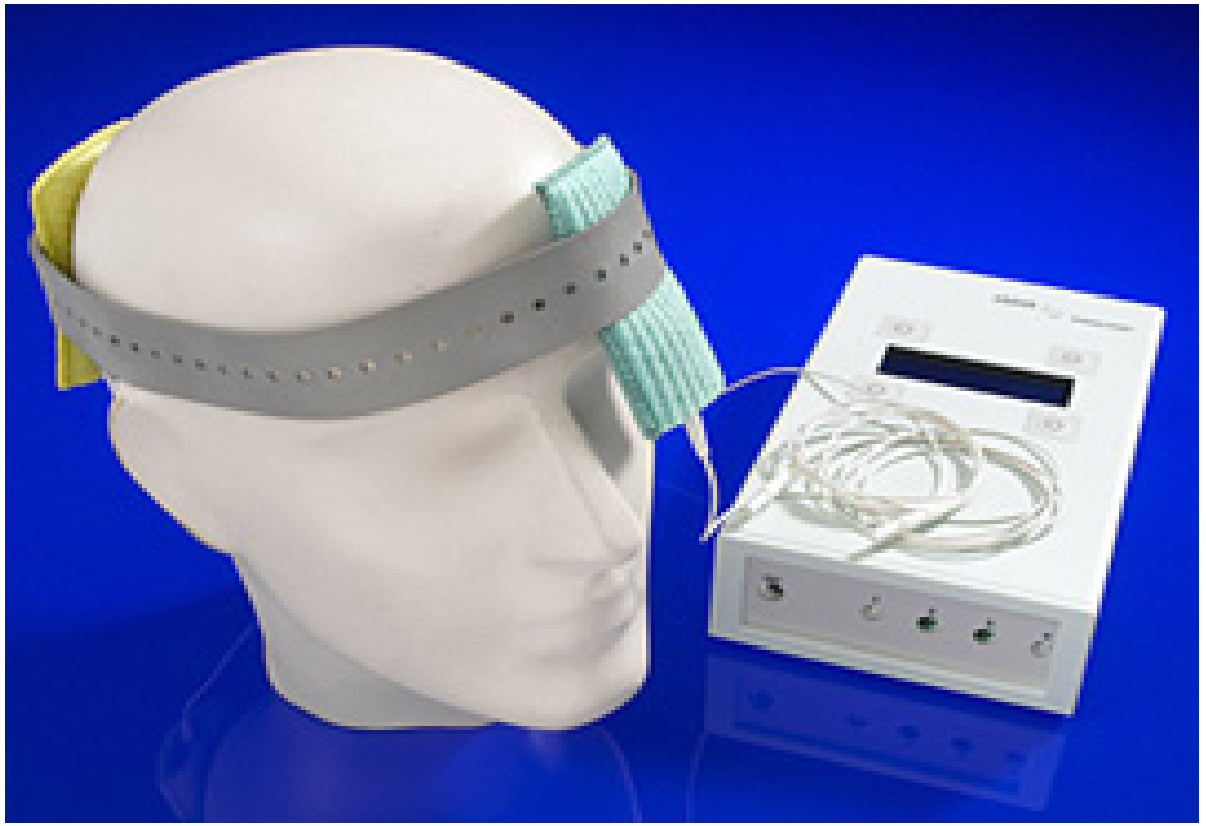
Consumer Market Virtual Reality/Gaming Devices

Xbox Kinect

Transcranial Magnetic Stimulation (TMS)



Transcranial Direct Current Stimulation (TDCS)



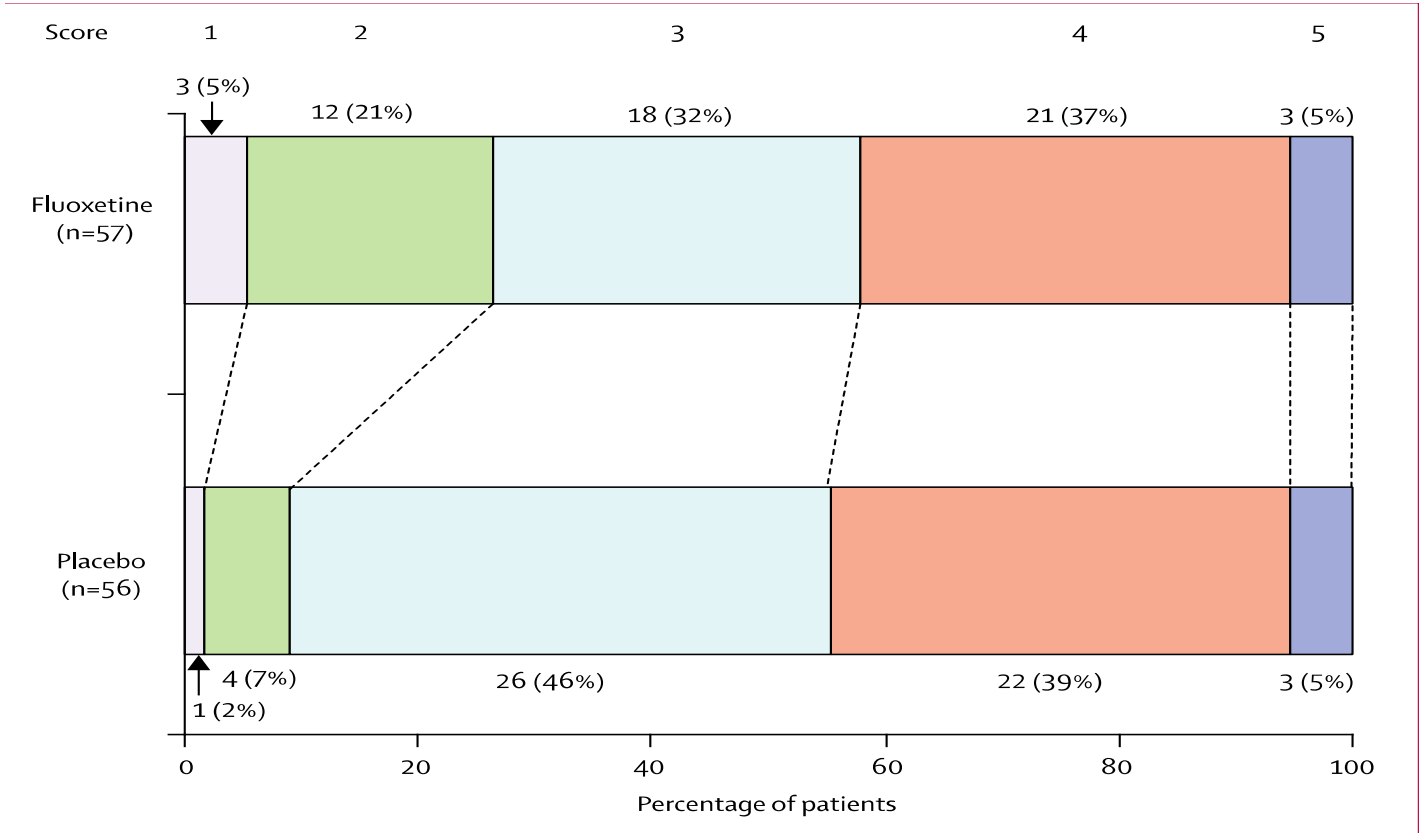
Therapeutic Electrical Stimulation

Neuromove – EMG triggered Therapeutic Electrical Stimulation

Bioness Therapeutic Electrical Stimulation System

Medications: The FLAME Study

Modified Rankin Score at 90 Days (%)



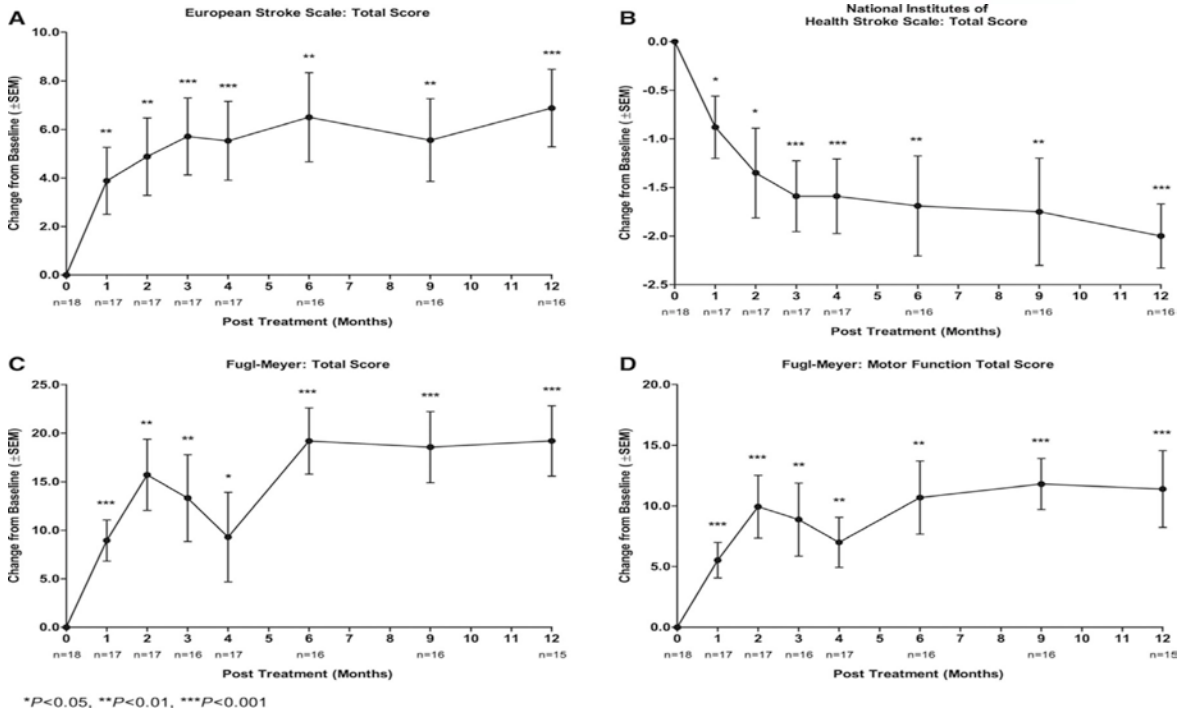
Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurology. 10(2):123-30, 2011

Combination Therapy

- Combining two or more treatments concurrently or consecutively to maximize recovery
- Types of treatments
  - Therapeutic Exercise/Task Practice
  - Limb stimulation (electrical, acupuncture)
  - Brain stimulation
  - Medications
  - Growth Factors
  - Stem Cells
  - Others?

Phase 1/2a study of Modified Mesenchymal Stem Cells

- SB623 Cells (SanBio), autologous marrow-derived cells with transient transfection with a plasmid containing human *Notch-1* intracellular domain.
- Pre-clinical studies with reduction in peri-infarct cell loss, promotion of neuronal stem cell migration and differentiation and production of extracellular matrix factors that provide trophic support for damaged cells.
- In rodent models, the SB623 cells only survive 1 month post implantation.
- Open-label study, stereotactically implanted as single dose in 18 chronic stroke survivors
- Complications included a Subdural fluid collection and seizure attributed to the surgical procedure.



Steinberg, Gary K., et al. "Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study." *Stroke* (2016): 47: 1817-1824

Stroke Rehabilitation: The future

- Clarifying the mechanisms of recovery
  - Animals given a second stroke may have improvement in deficits from a prior stroke (Zeiler, et al)
  - Understanding recovery better will allow us to facilitate it better

Zeiler SR, Hubbard R, Gibson EM, Zheng T, Ng K, O'Brien R, Krakauer JW. Paradoxical motor recovery from a first stroke after induction of a second stroke: reopening a postischemic sensitive period. Neurorehabilitation and neural repair. 2016 Sep;30(8):794-800.

Stroke Rehabilitation: The future

- Clarifying the optimal dose, of exercise therapies
  - Amount – How many hours?
  - Intensity – How “hard” should the exercises be?
  - Timing – When should they start?
  - Type of exercise therapy
  - Duration – When should exercises end?

Stroke Rehabilitation: The future

- Advancing the evidence base for rehabilitation interventions
  - Only a handful of major clinical trials in stroke rehabilitation completed
  - Many have been essentially negative (LEAPS, Icare, AVERT), or show marginal benefits (VA Robotics)
  - Strokenet is a powerful tool to develop and complete clinical trials

Stroke Rehabilitation: The future

- Personalizing therapy
  - Why do we expect the rehabilitation for a large MCA stroke to be similar to a pontine lacunar infarct?
  - What are the genetic factors that influence recovery?

Stroke Rehabilitation: The future

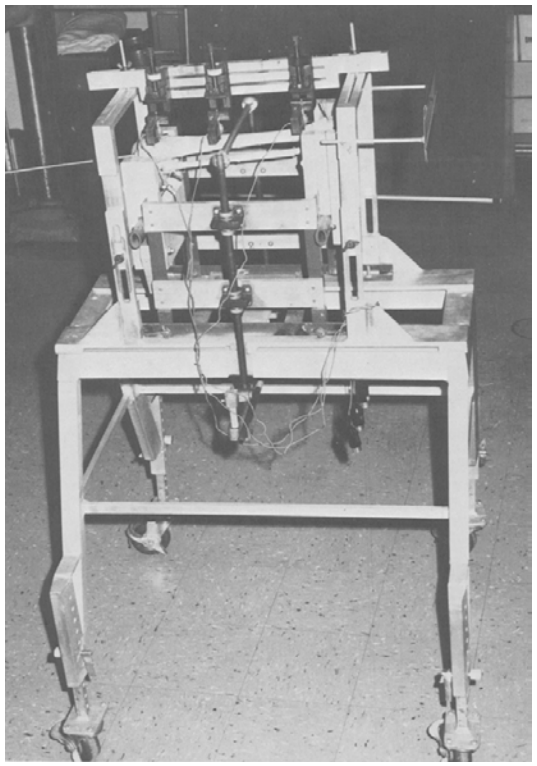
- Achieving greater efficiency
  - Can robots help achieve the optimal doses of exercise?
  - Can we lower costs?
  - Can we return patients home sooner?
  - Are we at risk for degrading care through cost-savings efforts (e.g. Site-neutral payments for post-acute care)?

Stroke Rehabilitation: The future

- Bending the recovery curve
  - Remains largely aspirational at this time – the benefits of existing therapies are modest
  - Do we need biological therapies to truly bend the curve?
  - Are cell replacement therapies achievable? What sort of rehabilitation would these require?


The Future
NEXT EXIT

Special Thanks…



In Vivo Testing of the Tibia 283

FIGURE 1. The tibiometer. The entire device is shown, with a demonstration tibiofibular set in testing position. The recording device is the modified console of the instron TM-L static tester, not shown.

Stein, Ira D., and Gerald Granik. "The human tibia: Static testing in bending by an in vivo method." Annals of biomedical engineering 10.6 (1982): 281-294.