Pharmacologic & Non-Pharmacologic Adjuncts for Stroke Recovery

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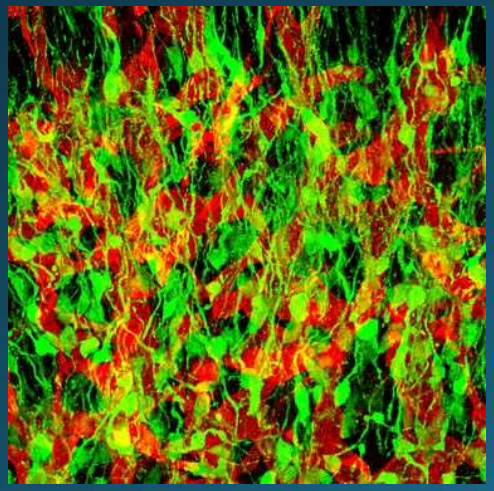
Overview - Pharmacologic Adjuncts

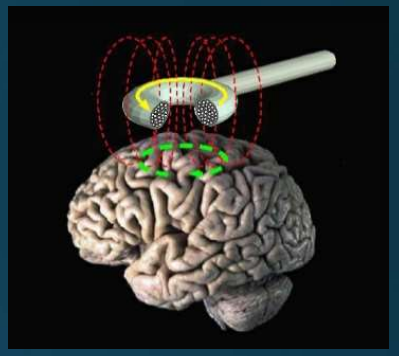
- SSRIs
- Antioxidants / Free Radical Scavengers
- Excitotoxic / Ion Channel Blockade
- Anti Inflammatory
- Anti DM
- Anti Microbial
- Other

Overview – Non Pharmacologic Adjuncts

- Biologicals
  - Stem Cells
  - Monoclonal Antibodies
  - Growth Factors



- Brain Stimulation
  - Non Invasive
    - tMS
    - tCDS
  - Invasive
    - SPGS
    - VNS
    - Epidural Cortical Stimulation

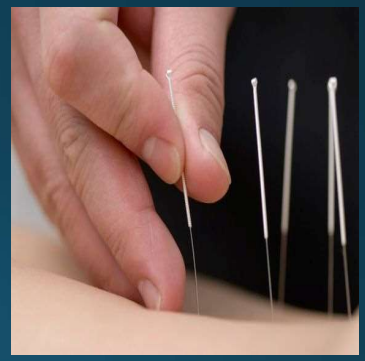


- Lesion Bypass
  - Brain Computer Interface
  - Neuroprosthetics

Overview – Non Pharmacologic Adjuncts (3)

- Activity Based Therapy
  - Conventional Rehabilitation (PT/OT/ST)
  - Robotics Assisted Therapy
  - Telerehabilitation
  - Virtual Reality

- Complementary & Alternative
  - Acupuncture
  - Herbal Medications / Supplements



- Other
  - Hypothermia
  - Hyperbaric Oxygen
  - Remote Ischemic Preconditioning

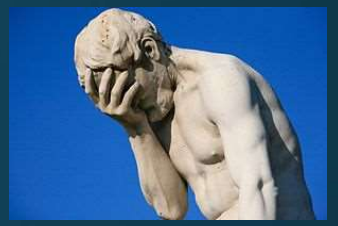
TL;DR

- Many agents have been identified in preclinical studies
- However, translation to human subjects has not yielded any agents with clinical benefit
- Future studies based on consensus standards should help address prior study design critiques

Adjuncts to Recovery

- Neuro-protection
  - Prevent secondary injury from ischemia and reperfusion
  - Hyperacute phase
  - Preserve ischemic penumbra
  - Extend time windows for interventions
  - Usually via reduced inflammation, excitotoxicity, apoptosis or via increased free radical scavenging
- Neuro-recovery
  - Promote recovery / plasticity
  - Subacute phase
  - Neurotrophicity, neuroplasticity, neurogenesis

SSRIs



	Population	Intervention	1' Outcome Measure	Results
FLAME (2011)	118 patients, median NIHSS = 13, ischemic stroke only	Fluoxetine 20mg vs placebo within 5-10d x90d	Fugl Meyer Motor Score @ 90d	Significant change in FMMS, more patients in mRS 0-2 @90d
FOCUS (2019)	3127 patients, median NIHSS = 6, included ICH, UK only	Fluoxetine 20mg vs placebo 2-15d x6mon	mRS @ 6mon	No difference in 1' outcome, ↓ depression, ↑ fractures, trend for more seizures, falls
AFFINITY (2020)	1280 patients, median NIHSS = 6, included ICH, Australia, NZ, Vietnam	Fluoxetine 20mg vs placebo 2-15d x6mon	mRS @ 6mon	No difference in 1' outcome, ↑ fractures, fall with injury, seizures
EFFECTS (2020)	1500 patients, median NIHSS =3, included ICH, Sweden only	Fluoxetine 20mg vs placebo 2-15d x6mon	mRS @ 6mon	No difference in 1' outcome, ↓ depression, ↑ fractures, hypoNa
Notes: FOCUS, AFFINITY, EFFECTS did not standardize the rehab provided Mostly mild strokes in study population				

Anti Oxidants

- ↑ free radicals during acute ischemia → cerebral edema

Trial	Intervention	Mechanism	Notes
SAINT (2008)	NXY-059	Free radical scavenger	
URICO – ICTUS (2014)	Uric acid	Anti oxidant	
Clark et al. (2001)	Citicholine	Free radical scavenger	
Van der Loo et al. (2020)	Deferoxamine	Iron chelator	
Enomoto et al. (2019)	Edavarone	Free radical scavenger	Approved in Japan
RHAPSODY (2019)	3k3A APC	Anticoagulant / cytoprotective	

Reducing Excitotoxicity

- ↑ glutamate stimulates NMDAr → triggers cell death via PTEN, cdk5, DAPK1, and other downstream pathways, etc

Trial	Intervention	Mechanism	Notes
FAST MAG (2015)	Magnesium	Vasodilatory, neural / glial protection	1700 pts, hyper acute intervention
Ladurner et al. (2005) CARS (2016)	Cerebrolysin	Purified pig brain protein with neurotrophic / protective properties	Widely used in Europe, Russia, Asia; may help with cognition?
VENUS (2001)	Nimodipine	Ca channel blockade	
ESCAPE-NA1 (2020)	Nerinetide	Inhibitor of postsynaptic density protein-95	
Albers et al. (2001)	Aptiganel HCl	Selective ligand for NMDAr	
Davis et al. (2000)	Selfotel	NMDAr antagonist	Stopped early due to potential harm

Nerinitide

- ESCAPE-NA1 (2020)
  - 1105 pts, double blinded RCT, 48 sites, 8 countries
  - IV tPA in most patients (~60%)
  - Thrombectomy attempted in all patients
  - Primary outcome = mRS @ 90d
  - No significant difference in mRS, mortality
  - 40% of group who did not receive tPA but received nerinitide had functional improvement and mortality benefit

	Adjusted outcomes (prespecified primary analysis)		Unadjusted effect size		
	No alteplase (n=446), RR (95% CI)	Alteplase (n=659), RR (95% CI)	No alteplase (n=446)		
			Placebo (n=227)	Nerinetide (n=219)	RR (95% CI)
Primary outcome					
mRS 0–2	1·18 (1·01 to 1·38)	0·97 (0·87 to 1·08)	113 (49·8%)	130 (59·3%)	1·19 (1·01 to 1·41)
Secondary outcomes					
NIHSS 0–2	1·14 (0·97 to 1·34)	0·92 (0·82 to 1·04)	113 (49·8%)	129 (58·9%)	1·18 (1·00 to 1·40)
mBI 95–100	1·14 (0·97 to 1·34)	0·97 (0·88 to 1·08)	114 (50·2%)	128 (58·4%)	1·16 (0·98 to 1·38)
Mortality*	0·66 (0·44 to 0·99)	1·08 (0·70 to 1·66)	46 (20·3%)	28 (12·8%)	0·63 (0·41 to 0·97)

Immunomodulators

- Complicated immune response after stroke → ↑ microglia activation, ↑ macrophages, lymphocytes, dendritic cells

Trial	Intervention	Mechanism	Notes
Zhu et al. (2015)	Fingolimod	S1P Receptor modulator	Small study suggests ↑ outcomes
ACTION2 (2016)	Natalizumab	mAb against CAMα4 integrin	Stopped due to lack of efficacy
AXIS A (2010)	Filgrastim	GCS factor	
Emsley et al. (2005)	IL-1r antagonist	IL-1 blocks cells death	Phase 2, 34 patients, showed safety and relevant biological activity but too small to determined clinical benefit

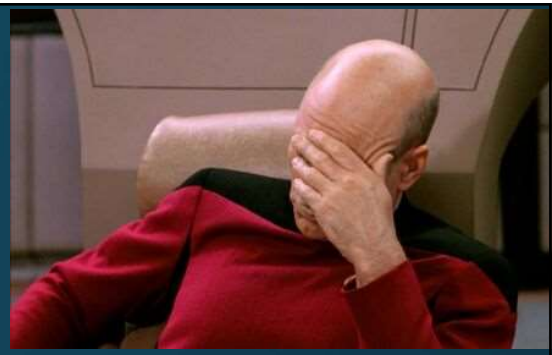
Anti Diabetes

- Sodium Glucose-linked cotransporter 2 (SGLT2) inhibitors
  - May have a role in cerebral edema
  - Suppression of SGLT2 may reduced hyperglycemia → reduce infarct size
  - Neuroprotective effects, anti oxidant / anti inflammatory
  - Approved agents: empaglifozin, dapaglifozin, canaglifozin
- Glucagon-like Peptide 1 (GLP-1) receptor agonists
  - Neuroprotective effects: enhances neurogenesis, promotes synaptic function, reduced apoptosis, antioxidant effects, increased CBF
  - Approved agents: exenatide, lixisenatide, semaglutide, dulaglutide, liraglutide
- Sulfonylurea receptor inhibitor
  - Reduces cerebral edema
  - Approved agent: glyburide, glipizide, glimepiride
- Trials are ongoing

Antimicrobials

- Minocycline
  - Tetracycline → ↓ microglial activation, T cell migration, MMP, also is a free radical scavenger
  - Studied in TBI, ischemic / hemorrhagic stroke, SAH but only in small studies
- Maraviroc
  - CCR5 is upregulated in neurons post stroke
  - Inhibition of CCR5 signaling → enhanced learning, memory, plasticity in hippocampal and cortical circuits
  - Maraviroc = anti retroviral that is also CCR5 antagonist
    - Works in mice
  - Human carriers of CCR5delta32 mutation have better outcomes post stroke

Others



- Chlorpromazine / promethazine → CNS depression, may enhance effects of hypothermia
  - Zhu et al (2019) → 64 patients, safe but no effect
- L – dopa → modulates striatal function and potentially motor learning
  - DARS (2019) → 593 patients, 1° outcome = ability to walk ind, no benefit
- S44819 ($GABA_A$ α5 antagonist) → inhibits peri lesion inhibition
  - RESTORE BRAIN (2020) → 585 patients, 1° outcome = mRS@90d, no benefit
- D – amphetamine
  - Goldstein et al. (2018) → pilot study 32 patients, 1° outcome = Fugl Meyer, no benefit
- Modafinil / Amantadine
  - Leclerc et al. (2020) → 205 ICU patients, 1° outcome = improved wakefulness with amantadine or both but not modafinil only
- Rapamycin, Caffeine, ethanol, etc…

More…

- Estrogen / progesterone
- micro RNAs – regulate mRNA translation
- Small peptides
- Growth factors

Caveats

- Pay attention to:
  - Sample (usually heterogenous)
  - Severity of stroke (often low)
  - Primary outcome measures (impairment vs disability score)
  - How / when is the intervention delivered?

- Why is nothing working?
  - Mice ≠ humans → imperfect model
    - does not account for comorbidities, age
    - Heterogeneity of stroke patients
    - Improvements in animal studies are usually shown on impairment tests
    - Variability in therapy provided (dosing, intensity)

Non-Pharmacologic Interventions

Stem Cells

- No standard protocols
- Differences in type of stem cell used, sources, delivery, dose, and timing

- RECOVER – Stroke
  - 100 patients, 60 intervention, Intracarotid infusion of ALD-401 stem cells
  - Safe but ineffective – no change in mRS@90d, Barthel Index, QoL @1yr
- PISCES II
  - Intracerebral implantation of neuronal progenitor stem cells ipsilateral to infarct
  - 23 patients, 15 patients showed improved on at least 1 scale
  - PISCES III – on hold
- Mesenchymal stem cells
  - Intravenous infusion of mesenchymal stem cells (phase 1 /2)
  - Improvement in Barthel

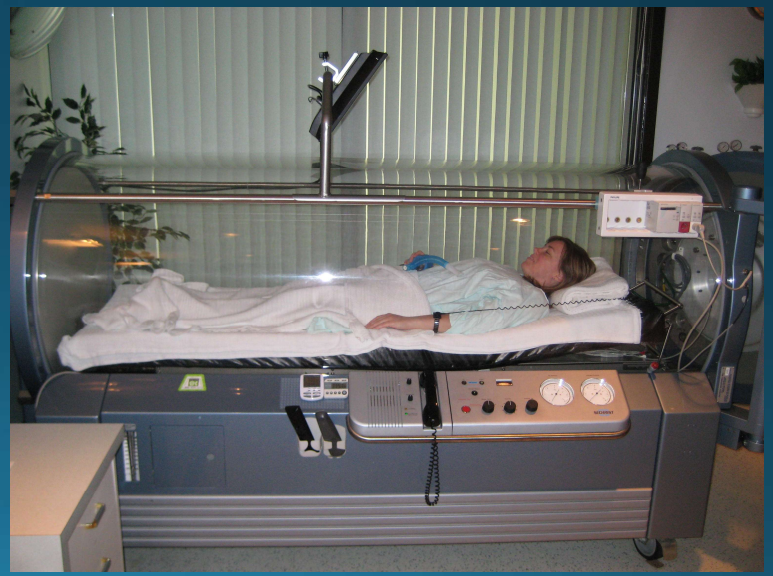
Hypothermia

- Prevents secondary injury via ? reducing oxygen consumption / metabolic demand, membrane stabilization, acidosis
- Shown to benefit post cardiac arrest

- ICTuS 2 (2016) → stopped due to increased mortality

Hyperbaric Oxygen

- ? ↑ Brain oxygen
- Bennett et al. (2011) meta analysis of 11 RCTs → no benefit
  - May be useful for strokes related to air embolism
  - Possible harm



Remote Ischemic conditioning

- Induce transient ischemia at remote site
  - Inflate cuff around arm or leg
  - Preconditioning, preconditioning, postconditioning depending on timing of intervention
- Effective in reducing stroke volume in animal studies
- Mechanism unknown – activates salvage kinases and prevents opening of mitochondrial transition pores?
- Cheap, simple, no side effects
- RESCUE BRAIN (Pico et al, 2020) – 188 patients, RIC within 6 hrs of stroke: no effect of infarct volume, mRS, mortality
  - May be more effective if given pre hospitalization? (Ongoing – RESIST and REMOTE CAT)
  - No consistent protocols

Non Invasive Brain Stimulation

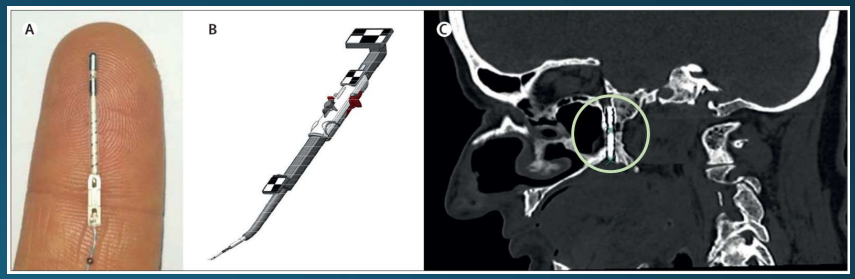
- Transcranial Magnetic Stimulation (tMS)
- Transcanial Direct Current Stimulation (tDCS)

- Can facilitate or inhibit cortical excitability depending on parameters
  - Facilitate neuronal activity ipsilateral to lesion or inhibit contralateral to lesion
  - May facilitate long term potentiation / depression

- Optimal parameters have not been defined

Invasive Brain Stimulation

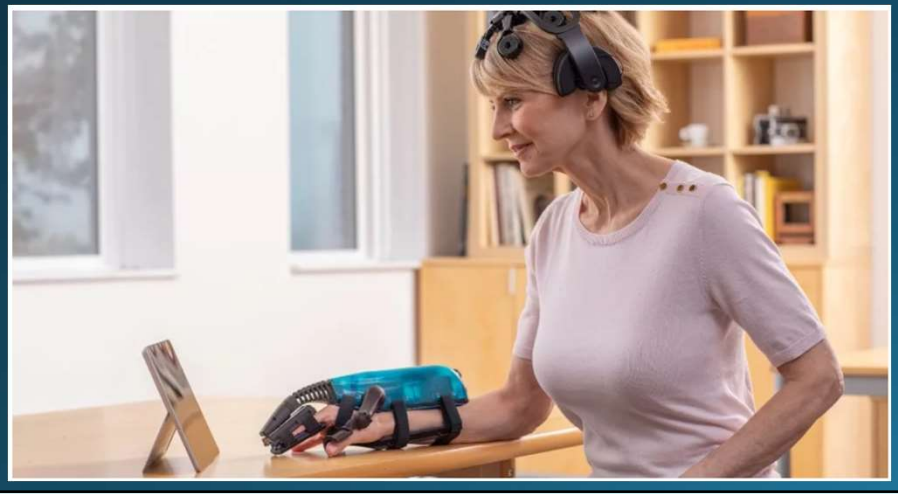
- Vagal Nerve Stimulation (VNS)
  - VNS-REHAB (2021) showed improvement in FMA UE
  - Cholinergic modulation of motor cortex neurons
- Sphenopalatine Ganglion Stimulation (SPGS)
  - ImpACT-24B (2019) → neutral results
  - Stimulation → increased arterial dilation and increased cerebral blood flow → enhance collateral circulation and reduce infarct size



- Epidural Cortical Stimulation
  - Everest (2016) – epidural stimulator implanted at ipsilesional motor cortex
  - No difference at 4 weeks in FMA UE

Lesion Bypass

- Brain Computer Interface
  - Invasive – implanted electrodes
  - Non invasive – EEG, MEG
- Neuroprosthetics
  - IpsiHand



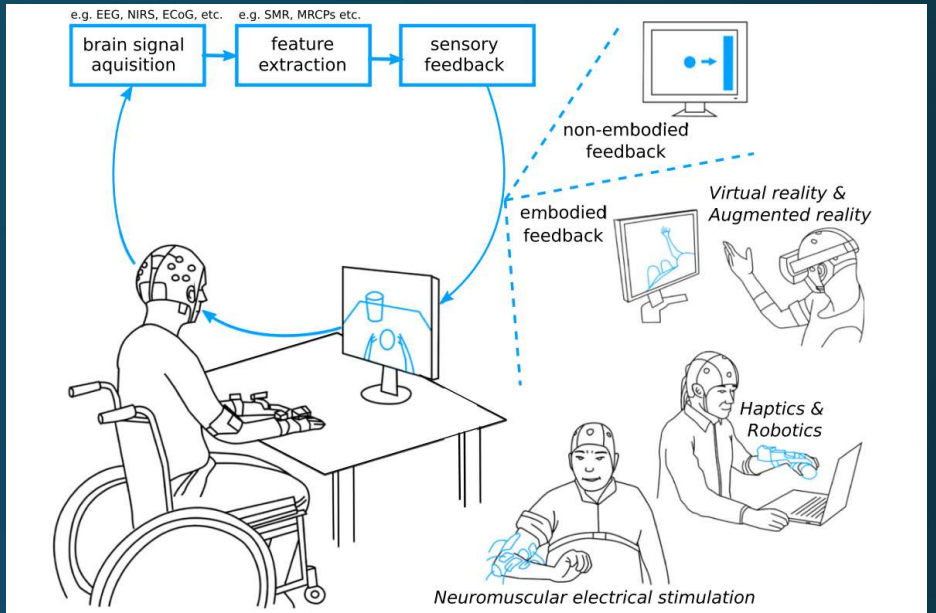
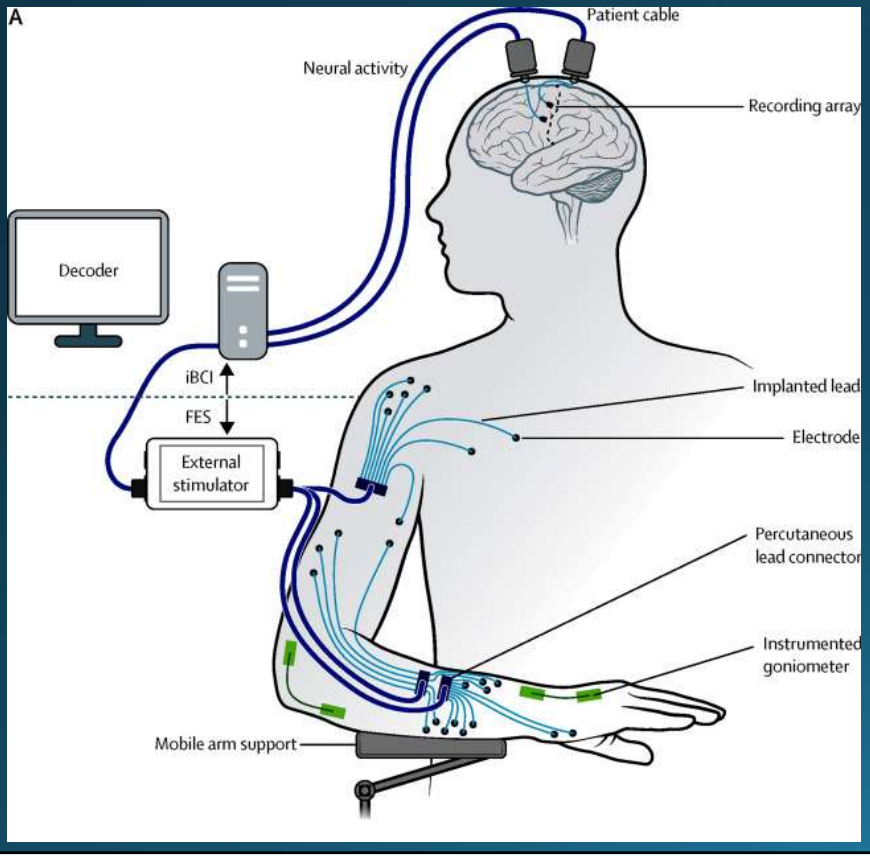
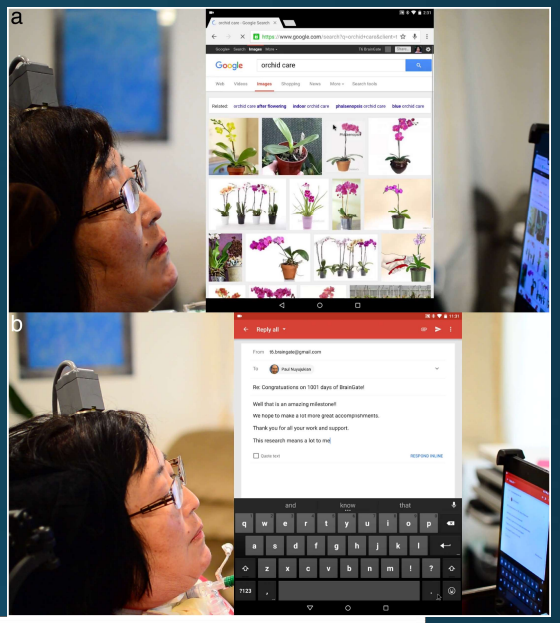
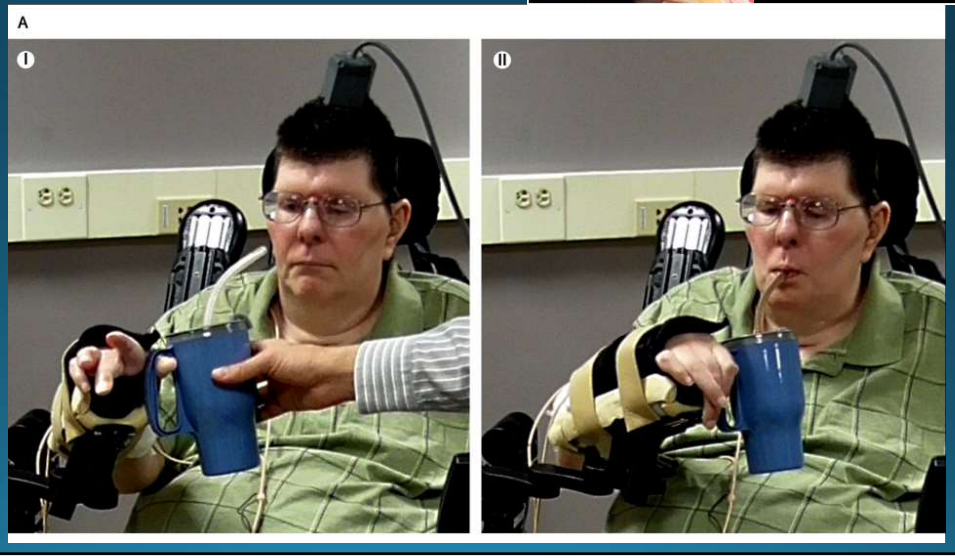


Figure 1. Illustration of typical brain-computer interface (BCI) systems used in post-stroke motor rehabilitation highlighting sensory feedback modalities. EEG = electroencephalography, NIRS = near-infrared spectroscopy, ECoG = electrocorticography, SMR = sensorimotor rhythm, MRCP = motor-related cortical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

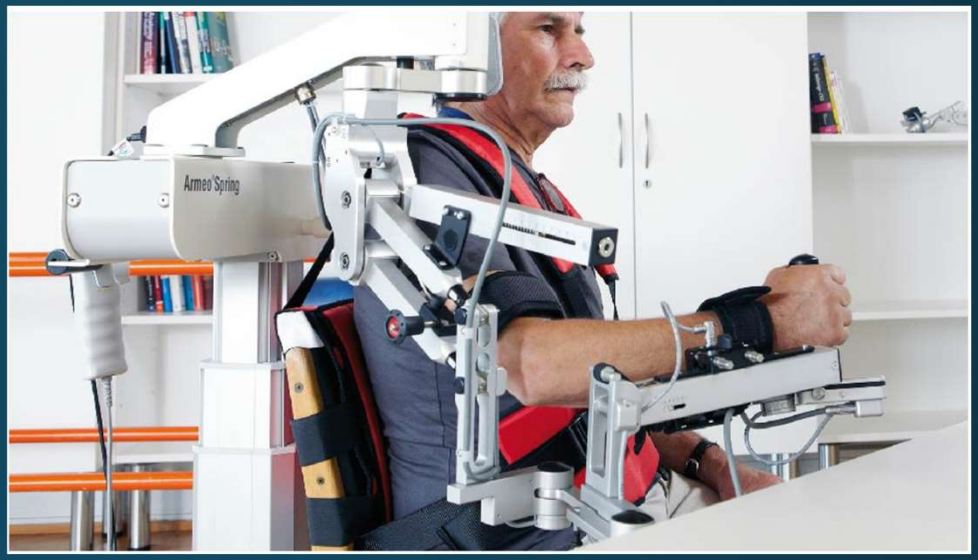
Lesion Bypass







Robotics



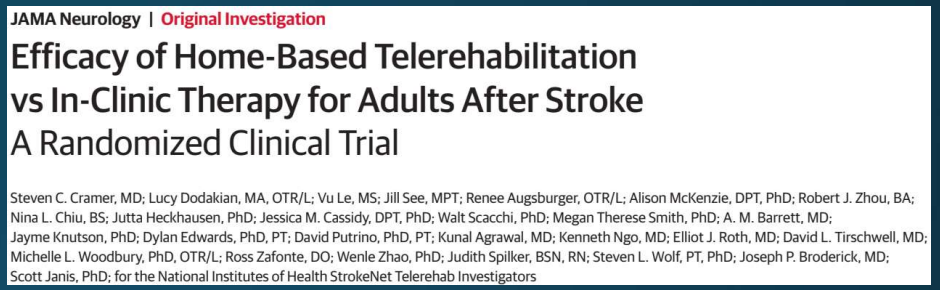
- High intensity, reproducible
- No standardized protocols (duration, frequency, amount, device)

- Lo et al 2010 – 127 patients, >6+ months post stroke: robot assisted vs intensive vs usual care. No significant difference, robot > usual but similar to intensive. Small gains on Fugl Meyer (~2 points)
  - 1000+ reps / session
- RATULS - Rodgers et al 2019 – 770 patients, 1 week – 5 years post stroke: robot assisted vs intensive vs usual care. No difference in ARAT

Robotics

Telerehabilitation

- 6 week course of intensive home based telerehab for arm movements vs dose matched in clinic therapy
  - → Non inferior for improving FMA UE and for improving stroke knowledge

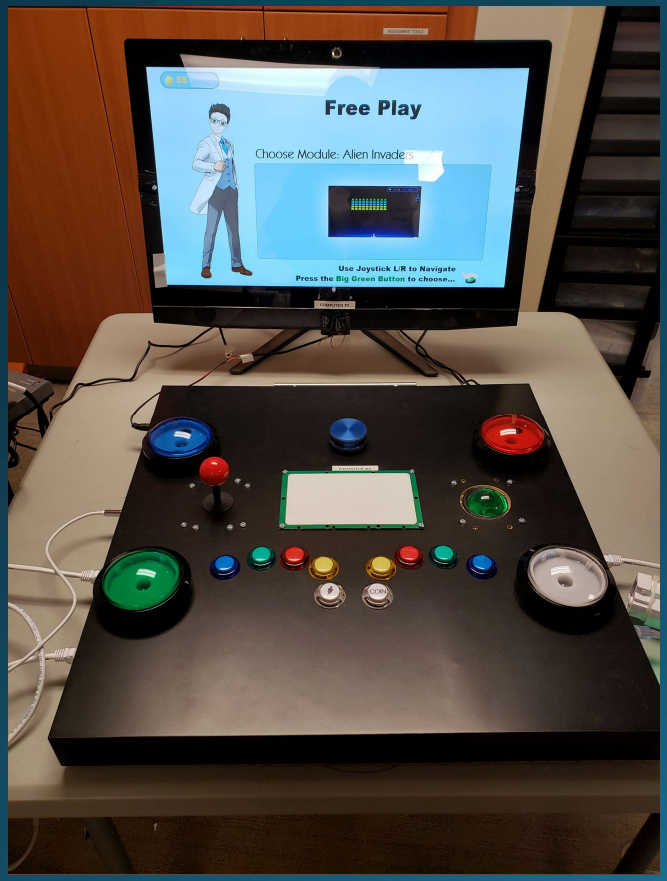


JAMA Neurology | Original Investigation

Efficacy of Home-Based Telerehabilitation vs In-Clinic Therapy for Adults After Stroke
A Randomized Clinical Trial

Steven C. Cramer, MD; Lucy Dodakian, MA, OTR/L; Vu Le, MS; Jill See, MPT; Renee Augsburger, OTR/L; Alison McKenzie, DPT, PhD; Robert J. Zhou, BA; Nina L. Chiu, BS; Jutta Heckhausen, PhD; Jessica M. Cassidy, DPT, PhD; Walt Scacchi, PhD; Megan Therese Smith, PhD; A. M. Barrett, MD; Jayme Knutson, PhD; Dylan Edwards, PhD, PT; David Putrino, PhD, PT; Kunal Agrawal, MD; Kenneth Ngo, MD; Elliot J. Roth, MD; David L. Tirschwell, MD; Michelle L. Woodbury, PhD, OTR/L; Ross Zafonte, DO; Wenle Zhao, PhD; Judith Spilker, BSN, RN; Steven L. Wolf, PT, PhD; Joseph P. Broderick, MD; Scott Janis, PhD; for the National Institutes of Health StrokeNet Telerehab Investigators

Telerehabilitation

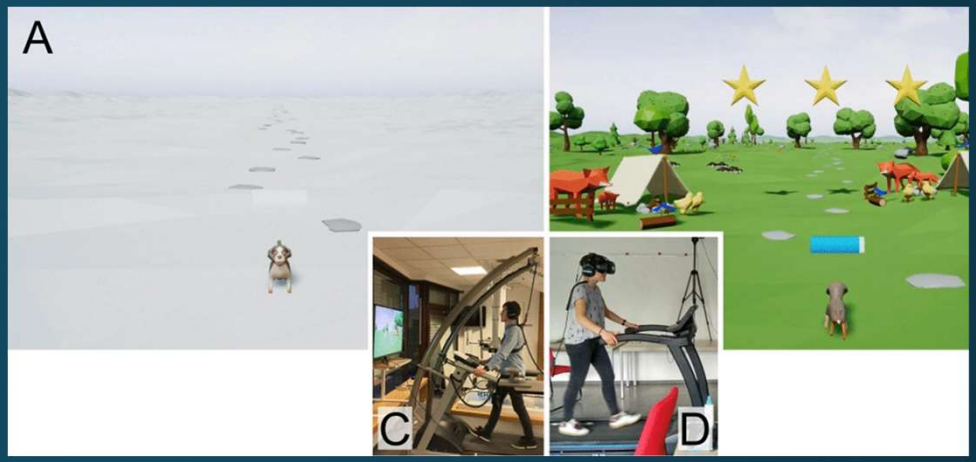


Virtual Reality

- "Gamification" of rehabilitation
  - Goal oriented, high rep, provided feedback (inherently rewarding), able to adjust difficulty, novel (may ↑ engagement, motivation, enjoyment)
  - May be difficult to apply in less tech savvy patients

- Has not been demonstrated to be superior to conventional therapy but in some cases, is non inferior and may be a useful adjunct

Virtual Reality

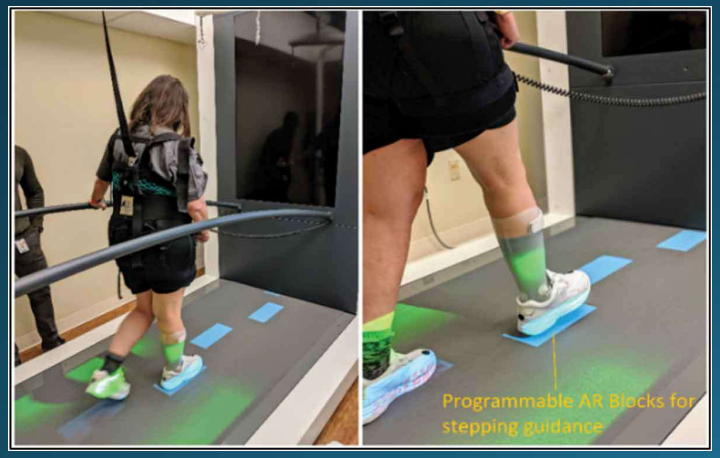


- Immersive
  - Oculus Rift, HTC Vive

- Non Immersive
  - Commercial products: Nintendo Wii (EVREST, 2016), Microsoft Kinect, PlayStation EyeToy, Move
  - Therapy specific
    - Ex: SaeboVR

Augmented Reality

- Microsoft HoloLens
- Other proprietary hardware



Complementary and Alternative Medicine

- Acupuncture
  - 2018 Cochrane Review- no benefit, many studies are at high risk of bias
  - 6.2% adverse events (pain, dizziness, syncope) → 1.2% discontinuation

- Eastern Traditional Medicines
  - Wu et al 2007
  - Poor quality studies due to risk of bias, poor methodology
  - Insufficient evidence to recommend but due to potential benefit and low risk of adverse events, may be worth further investigation

Thanks!