

Neurorehabilitation Pilot Studies Suggest Efficacy RCT's Often Reveal Little

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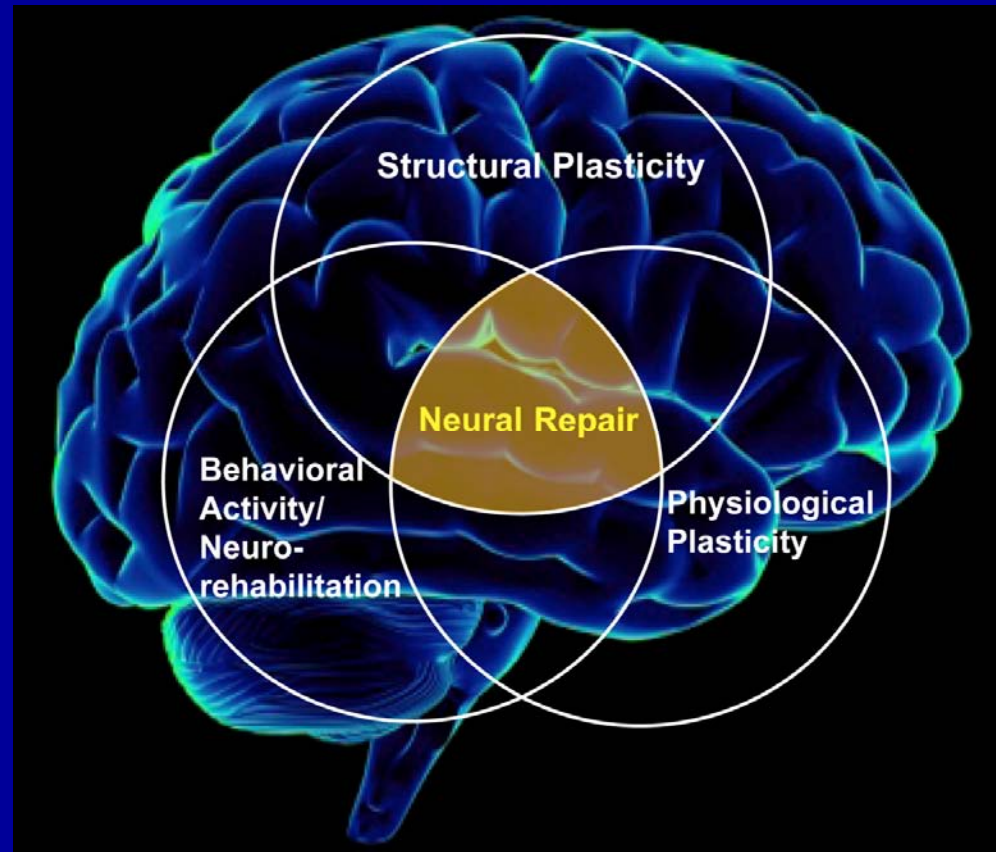
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Motor and cognitive gains in neurological diseases



Training and repair remold mechanisms of development and memory/learning = neuroplasticity

Key Translational Problems for Robotics (or any new intervention)

- What is the conceptual basis for the device/new strategy?
- What is the subgroup of level of impairment/disability most likely to benefit? Compared to what? Are more strategies needed for mild-moderately impaired subjects, or for highly impaired ones?
- How will the device be used to augment real-world functional gains? What is the interaction between the new training strategy and tasks that patients want to perform better?
- How will clinically meaningful gains be assessed? “Others used certain lab-based tools, so I will too.”
- Should/can we monitor the type, quantity, and quality of practice in the community during trials and for daily care?
- Should/can we measure key outcomes that reflect performance in the community, rather than rely on laboratory-based tests?

BWSTT evolved slowly over 20 years: The Cure: Progressive staging of pilot studies

Stage 1, consideration-of-concept: a small convenience sample (N=8-12) to examine the conceptual basis and strategy for the experimental intervention.

Stage 2, development-of-concept: optimize components of the intervention, settle on blinded outcome measures, phase-in period for chronic impairments to test baseline stability, examine dose-response effects.

Stage 3, demonstration-of-concept: test at least 15 participants randomized to experimental and active arms with blinded outcomes. A third arm could receive a larger dose or combinational intervention. Publish a well-designed study even no efficacy found, to counterweight confirmation bias in positive small trials. Reproduce positive outcomes based on the optimal training procedures and dose.

Stage 4, proof-of-concept MRCT: go forward if based on an effect size that requires no more than 50-75 subjects in each arm.

High Intensity: Locomotor Training Program that includes Body-weight supported treadmill training



Step training affording sensory experience and practice of walking with manual trainers using BWS and treadmill



Translation of skills acquired on the treadmill to overground & community

BWSTT MRCTs in SCI and Stroke in nonambulators at onset

SCILT – TM with OG vs OG training 30 min/day for 36 inpt/outpt sessions.

- No differences (90% indep walkers). (Dobkin, Neurology, 06)

GISACI – BWSTT (20min) + need-based PT (40min) vs PT (60min).

- 4 wks post-stroke; inpt rehabilitation; 20 sessions in 4 wks.
- End tx: speed = .6-.7m/s; at 6 mo = .7-.8. No differences.
(Franceschini, Stroke, 09)

MOBILISE – BWSTT (30min) vs) OG (30min) starting 4 wks after stroke.

- Treated until walking 15m without aids or discharged.
- BWS achieved goal 1-2 wks sooner, no diff at f/u. (Ada, Stroke, 10)

LEAPS – Home-based exercise vs walking on TM and OG.

- Stratified for initial walking speed & timing (2 vs 6 mo after stroke).
- Inherent passive control for 6- vs 2-mo TM groups.
- Cardiovascular fitness test and training at different HRs.
(Duncan, BMC Neurology, 2007)

INTERNATIONAL
STROKE INPATIENT REHABILITATION
REINFORCEMENT OF WALKING SPEED TRIAL
(SIRROWS MRCT with blinded outcomes)

18 sites randomized 178 patients.
Compared a single daily report about walking speed
during a 10-m walk to no feedback about speed.

Dobkin et al. *Neurorehabil Neural Repair*, 2010

SIRROWS Baseline Summary

	DRS	NRS	P-value
#	88	91	.91
Age	63 (12)	65 (12)	.85
Stroke onset to entry (days)	27 (78)	30 (53)	.78
Initial walking speed (m/s)	0.45 (.37)	0.46 (.34)	.98
NIHSS	6.4 (3.5)	6.6 (3.1)	.74
FAC \geq 4	4.9%	4.8%	1
mRS \geq 2	99%	97%	.62

Results of SIRROWS

	DRS	NRS	p-value
Walking speed (m/s)	0.91 (.57)	0.72 (.44)	.01
LOS in rehab (days)	42.8	40.4	0.62
Walking distance (m)	132 (75)	112 (61)	0.09
FAC \geq 4	36%	24%	0.12

A little feedback about performance may go a long way

FES: 30 years and still going

Mobilization aide for gait or use of UE.
Training aide to augment gains.
Reduce shoulder sublux, not pain.

Introduces the potential for exoskeletal devices.

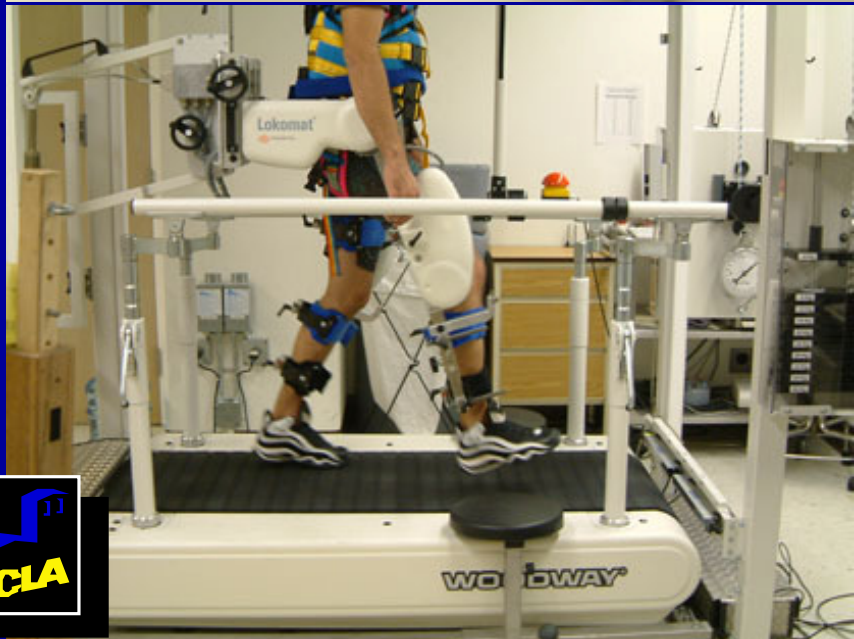
Electromechanical Man



Assist training

Exoskeletal
support

Strategies for Lokomat-Assisted Step Training





MIT-Manus

Next generation and others

Upper Extremity Trials

CIMT: 10 years to EXCITE and still going.... But have target and comparison groups or outcome measures evolved?

Everest Trial: Dural electrode stimulation over the M1 hand area no better than intensive practice alone. Target group?

Imagery, VR, mirror therapy: fMRI is not an outcome measure.

Transcranial Magnetic Stimulation: Excitation to increase skills learning may augment practice in mild-moderate hand paresis.

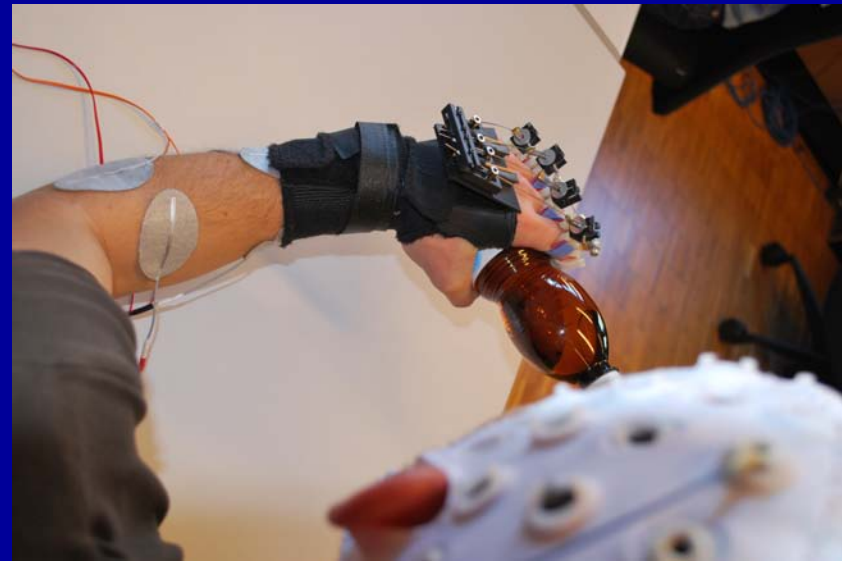
Peripheral Nerve Stimulation and combos: For whom and what functional movement?

BCI - Orthotic - FES (shared controls)



Users train to address a task at cognitive level and all low level details are handled automatically

Intelligent robotics



Pharmacological Interventions (where's the beef?)

Ropinirole RCT with adequate trial size:
UE training plus dopamine receptor agonist
did not augment UE gains (Cramer, Dobkin; Stroke, 2010).

Amphets, citicholine, piracetam, amantadine/dopa,
methylphenidate, modafinal, BDNF, NGF Outcomes?

Conceptual basis: What are the characteristics of a
cognitive/learning-cascade drug that can augment training?

Major problem for neurological disease drug trial designs and the FDA approval process: measuring a clinically important change that reaches statistical significance for real-world outcomes.

Monitoring skills practice, exercise, & activity in the home and community during interventions or in daily care.

Outcome measures with interval scales are needed, rather than ordinal scales and questionnaires about physical functioning (QOL), to quantify the *type, intensity, and quality* of motor activities.

Personal Activity Monitors (PAMs)



Triaxial accelerometer with USB download and recharging

Ankle PAM



SIRRACT (daughter of SIRROWS)

Feedback about gait speed 3x/week during inpt stroke rehab

VS

Feedback about speed, distance, steps, repetitions of exercise, time of exercise at same frequency

All wear PAMs all day.

Outcomes: speed & amount of exercise; dose-response with continuous outcomes for behaviors; transfer to home walking.

Some of the issues to discuss during this conference

- The conceptual basis for the device/new strategy is not sound.
- What is the subgroup of impairment/disability level that is most likely to benefit? Compared to what - best conventional strategies? We may not need more strategies for mild-moderately impaired subjects - aim for highly impaired ones.
- Define and test the interaction between the new training strategy and performance of tasks that patients want to perform.
- Assess clinically meaningful gains. Should we dump the F-M, walk speed, timed lab tasks, activity-related QOL?
- We must monitor the type, quantity, and quality of practice at home during trials and daily care and provide feedback.
- We can measure key outcomes based on performance in the community, rather than rely on ecologically unsound tests.



Westwood, the UCLA medical campus