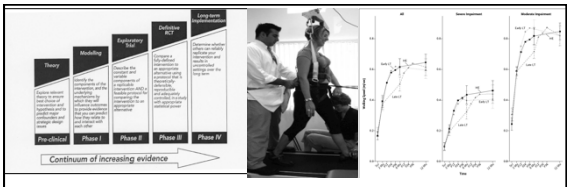
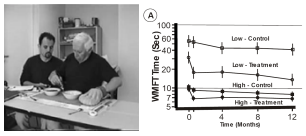


Translating the Science into Neurorehabilitation Practice: Challenges and Opportunities

Carolee J. Winstein, PhD, PT, FAPTA

Director, Motor Behavior and Neurorehabilitation Laboratory



The Kenneth Viste, Jr. MD Lecture, ASNR Annual Meeting, Washington, DC, Nov 13th , 2014

Ken Viste

1941-2005

Historical Context

War, Politics, And Philanthropy

The History of Rehabilitation Medicine

Richard Verville

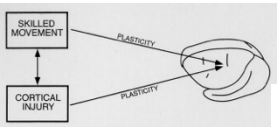
University Press 2009

Paradigm Shift - Plasticity in Neuroscience

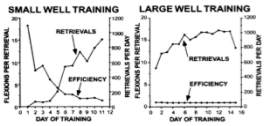
Science. 1996 Jun 21;272(5269):1791-4.

Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct

Randolph J. Nudo,* Birute M. Wise, Frank SiFuentes, Garrett W. Millikent



Nudo, Barbay, & Kleim, 2000



Plautz et al., 2000

HEMIPLEGIA—FRANZ, SCHEETZ AND WILSON

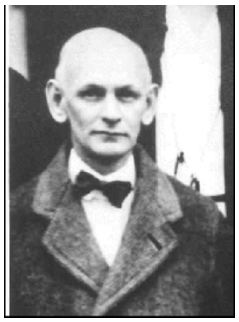
THE POSSIBILITY OF RECOVERY OF MOTOR FUNCTION IN LONG-STANDING HEMIPLEGIA

A PRELIMINARY REPORT

SHEPHERD IVORY FRANZ, Ph.D., Hon. M.D., LL.D.
Scientific Director, Government Hospital for the Insane
MILDRED E. SCHEETZ, M.S., M.D.
Assistant Physician
AND
ANITA A. WILSON, A.B., M.D.
Assistant Physician
WASHINGTON, D. C.

It is well known that in the hemiplegias due to cerebral lesions, there are usually early recoveries of function for different segments when the other acute symptoms of hemorrhage, or embolism, or trauma, subside. The trunk muscles are affected the least in a hemiplegia, and there may be a complete return of voluntary control of them shortly after the cerebral accident. The legs also frequently recover to a great extent, and although in many cases the distal segments may show evident signs of functional impairment, the larger muscles for the thigh and knee movements may be used with a surprising degree of ease and force. Voluntary control of the arm movements is less likely to return; but if there is a return it is, as with the leg, better for the proximal than for the distal elements. These recoveries ensue within a few weeks or months and are

JAMA, Dec 18, 1915



Shepherd Ivory Franz (1874-1933)

"Neurorehabilitation at a crossroads"

Development of a mature clinical-behavioral science grounded in the principles of psychology and neuroscience

Continuing the status quo, which in the current environment of strong economic pressure, might lead to marginalization of the field—social impact especially for those of modest economic means

Corbetta & Fitzpatrick, *NNR*, 2011

What is necessary to ensure the development of a mature clinical-behavioral science grounded in the principles of psychology and neuroscience?

- 7 -

Clinical Trials in Neurorehabilitation

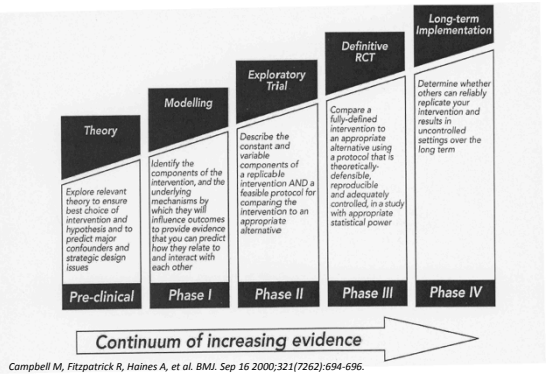
- Phase III RCTs in Neurorehabilitation are a relatively new clinical research endeavor (EXCITE published in 2006)
- We are '*approaching the end of the beginning*'. (Michael Weinrich)
- What have we learned? What is the future?

- 8 -

Evidence—Practice Gap

- Current clinical practice is behind the state of knowledge/ evidence in neurorehabilitation
  - 2013 First Commissioned Practice Guidelines for Stroke Rehabilitation from AHA/ASA
  - First Phase III RCT was funded in 1999 (EXCITE)
  - Only 5 Phase III RCTs in the area of Stroke Rehabilitation and one in the area of SCI.
    - SCILT (Dobkin, Neurology, 2006), EXCITE (Wolf, JAMA 2006), VA-Robot (Lo, NEJM 2010), LEAPS (Duncan, NEJM 2011), Everest (Harvey & Winstein, NNR, 2009; in review), ICARE (embargoed, to be released in 2015)

- 9 -



Campbell M, Fitzpatrick R, Haines A, et al. BMJ. Sep 16 2000;321(7262):694-696.

- 10 -

NEUROLOGY

Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI

B. Dobkin, D. Apple, H. Barbeau, M. Basso, A. Behrman, D. Deforge, J. Ditunno, G. Dudley, R. Elashoff, L. Fugate, S. Harkema, M. Saulino, M. Scott and the Spinal Cord Injury Locomotor Trial (SCILT) Group

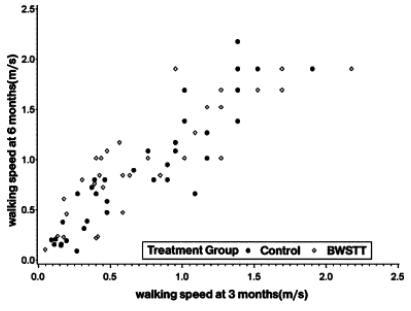
Neurology 2006;66;484-493

DOI: 10.1212/01.wnl.0000202600.72018.39

[redacted]

- 11 -

SCILT Dobkin et al. *Neurology*. 2006,**66**:484-93.



- 12 -

EDITORIALS

JAMA, *2006;**296** (17):2095-2104*

Stroke Recovery—Moving in an EXCITE-ing Direction

Andreas R. Luft, MD
Daniel F. Hanley, MD

ORIGINAL CONTRIBUTION

Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke

The EXCITE Randomized Clinical Trial

Steven L. Wolf, PhD, PT
Carolee J. Winstein, PhD, PT
J. Philip Miller, AB
Edward Taub, PhD
Glenadoo Uswatte, PhD
David Morris, PhD, PT
Carol Giuliani, PhD, PT
Kathey E. Light, PhD, PT
Deborah Nichols-Larsen, PhD, PT
for the EXCITE Investigators

Context Single-site studies suggest that a 2-week program of constraint-induced movement therapy (CIMT) for patients more than 1 year after stroke who maintain some hand and wrist movement can improve upper extremity function that persists for at least 1 year.

Objective To compare the effects of a 2-week multisite program of CIMT vs usual and customary care on improvement in upper extremity function among patients who had a first stroke within 3 to 9 months.

Design, Setting, and Patients The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial, a prospective, single-blind, randomized, multisite clinical trial conducted at 7 US academic institutions between January 2001 and January 2003.

Participants Two hundred twenty-two individuals with predominantly ischemic stroke.

Interventions Participants were assigned to receive either CIMT (n=106), wearing

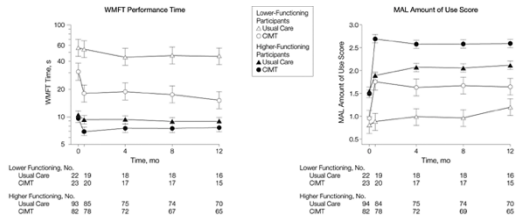
'The EXCITE trial is the first multisite randomized study to demonstrate the efficacy of a rehabilitative intervention. It therefore moves neurorehabilitative care into the area of evidence-based medicine'.

'As the first large controlled trial in neurorehabilitation, the study …..leaves important questions for future trials'*. [Luft & Hanley, p 2141]*

13

Excite: Constraint Therapy

Wolf, S. L. et al. JAMA 2006;296:2095-2104



Large Multi-site Robot-Assisted Therapy Trial

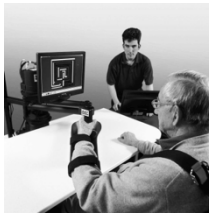
This article (10.1056/NEJMoa0911341) was published on April 16, 2010, at NEJM.org.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

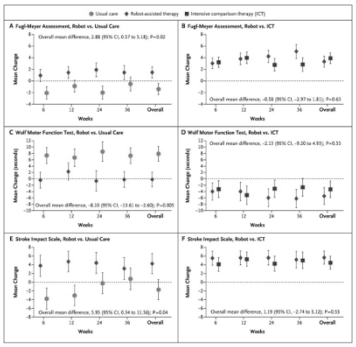
Albert C. Lo, M.D., Ph.D., Peter D. Guarino, M.P.H., Ph.D., Lorie G. Richards, Ph.D., Jodie K. Haselkorn, M.D., M.P.H., George F. Wittenberg, M.D., Ph.D., Daniel G. Federman, M.D., Robert J. Ringer, Pharm.D., Todd H. Wagner, Ph.D., Hermano I. Krebs, Ph.D., Bruce T. Volpe, M.D., Christopher T. Bever, Jr., M.D., M.B.A., Dawn M. Bravata, M.D., Pamela W. Duncan, Ph.D., Barbara H. Corn, Ph.D., Alysia D. Maffucci, J.D., Stephen E. Nadeau, M.D., Susan S. Conroy, D.Sc., P.T., Janet M. Powell, Ph.D., Grant D. Huang, Ph.D., and Peter Peduzzi, Ph.D.



ABSTRACT

In patients with long-term upper-limb deficits after stroke, robot-assisted therapy did not significantly improve motor function at 12 weeks, as compared with usual care or intensive therapy. In secondary analyses, robot-assisted therapy improved outcomes over 36 weeks as compared with usual care but not with intensive therapy. (ClinicalTrials.gov number, NCT00372411.)

Robot Assisted Therapy Lo, et al. NEJM 2010;362(19):1772-83



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Body-Weight–Supported Treadmill Rehabilitation after Stroke

Pamela W. Duncan, P.T., Ph.D., Katherine J. Sullivan, P.T., Ph.D., Andrea L. Behrman, P.T., Ph.D., Stanley P. Azen, Ph.D., Samuel S. Wu, Ph.D., Stephen E. Nadeau, M.D., Bruce H. Dobkin, M.D., Dorian K. Rose, P.T., Ph.D., Julie K. Tilson, D.P.T., Steven Cen, Ph.D., and Sarah K. Hayden, B.S. for the LEAPS Investigative Team

N Engl J Med 2011; 364:2026-2036 | May 26, 2011

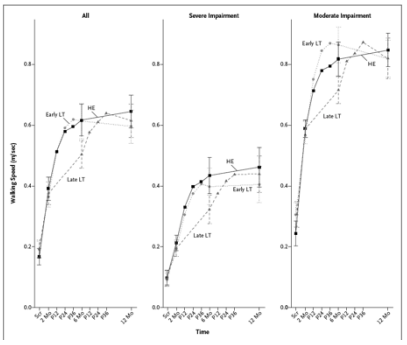
Abstract

Locomotor training, including the use of body-weight support in treadmill stepping, is a physical therapy intervention used to improve recovery of the ability to walk after stroke. The effectiveness and appropriate timing of this intervention have not been established.

CONCLUSIONS

Locomotor training, including the use of body-weight support in stepping on a treadmill, was not shown to be superior to progressive exercise at home managed by a physical therapist. (Funded by the National Institute of Neurological Disorders and Stroke and the National Center for Medical Rehabilitation Research; LEAPS ClinicalTrials.gov number, NCT00243919.)

LEAPS Trial Outcomes: LT and HE were equivalent



Duncan et al., NEJM, 2011

The EVEREST Trial: what went wrong?

Cortical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded EVEREST Trial (in review)

Concept: Cortical Stimulation for Stroke Recovery

- Cerebral cortex has the ability to reorganize synaptic connectivity in response to injury – *neuroplasticity*
- When combined with rehabilitation, cortical stimulation may facilitate neuroplasticity and improve function

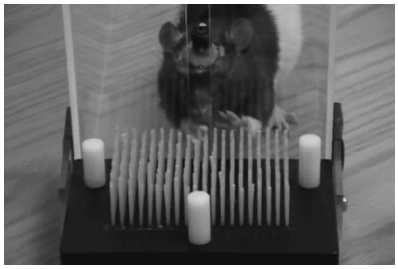
- 19 -

Pre-Clinical Studies of Cortical Stimulation for Stroke Recovery

Institution	Investigator	Model
University of Texas, Austin	T. Jones, PhD	Rodent
University of Calgary	G. Campbell Teskey, PhD	Rodent
University of Lethbridge	Jeff Kleim, PhD	Rodent
University of Kansas	Randy Nudo, PhD	Primate

- 20 -

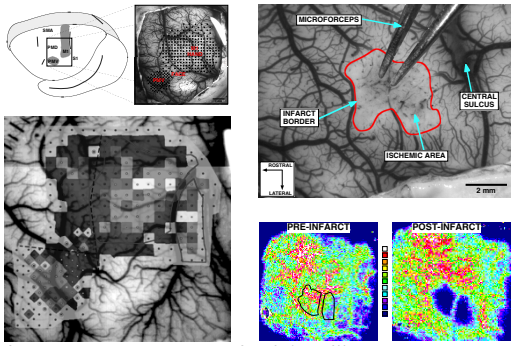
Pre-Clinical Studies in Rats:
Pasta Matrix Test Apparatus



Source: G.C. Teskey (U of Calgary)

- 21 -

Neurophysiological Mapping Techniques (ICMS)

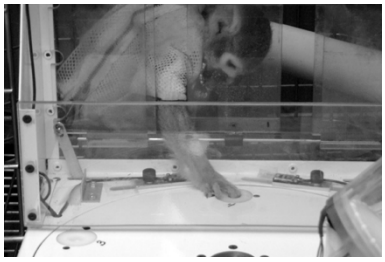


Source: Plautz et al, Presented at the International Stroke Conference, 2005

- 22 -

Primate Studies

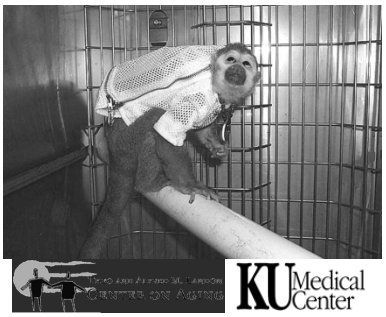
- Food retrieval task
- Tests average time to retrieve pellets from series of wells



Source: R. Nudo (KUMC)

- 23 -

Pre-Clinical Studies in Primates



Source: R. Nudo (KUMC)

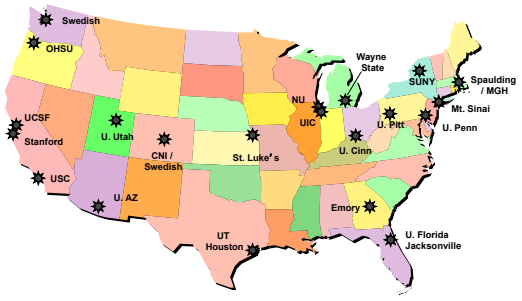
- 24 -

Cortical Stimulation for Stroke Recovery Clinical Trials

ADAMS (2003) Phase I	BAKER (2004) Phase II	EVEREST (2008) Pivotal
Safety	Safety & Efficacy	Safety & Efficacy
N = 8	N = 24	N = 151
3 US sites	9 US sites	21 US sites

- 25 -

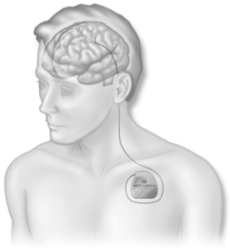
EVEREST Clinical Sites (21 sites)



- 26 -

Cortical Stimulation System

- fMRI used to identify activation site for hand
- Epidural electrode placed over cortical target indicated by fMRI
- Implantable pulse generator
- Overnight hospital stay
- Subthreshold stimulation delivered only during rehabilitation
- Patient does not feel stimulation

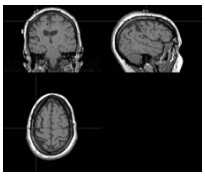


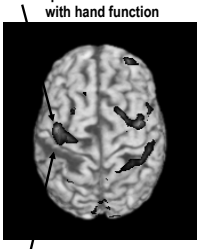
Caution: Investigational device. Limited by federal (or US) law to investigational use.

- 27 -

Stimulation site identification coupled with behavior

- Locate site of cortical activation associated with hand function
- Neuronavigation based on fMRI data used to identify stimulation site

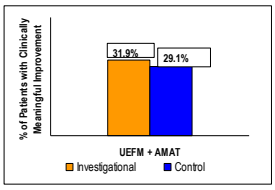




- 28 -

EVEREST Composite Primary Efficacy Endpoint

Composite Primary Efficacy Endpoint Outcome: The percentage of investigational patients that achieved a clinically meaningful result in both the UEFM and AMAT at the 4-week endpoint was not different.

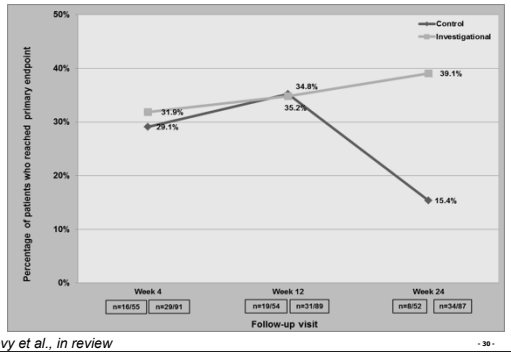


UEFM ≥4.5 & AMAT ≥0.21

	N Success	N Total	%
Investigational	29	91	31.9%
Control	16	55	29.1%

- 29 -

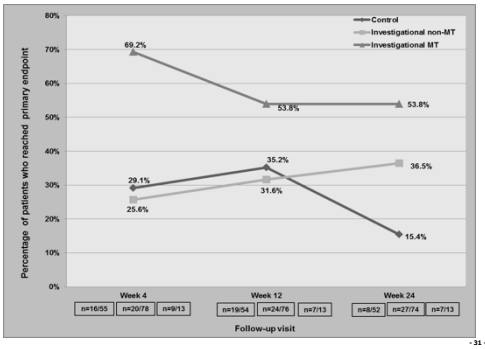
Re-analysis beyond the primary efficacy endpoint



Levy et al., in review

- 30 -

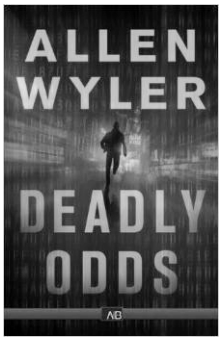
Sub-group analysis including investigational MT group



Allen Wyler, neurosurgeon and fiction writer retired as the Director of Northstar Neuroscience, Inc. in 2008

Northstar Neuroscience Shuts Down, Ending Experimental Depression Trial (Jan 9, 2009)

"Northstar Neuroscience is toast. The Seattle-based medical device company, which failed to develop an electrical stimulation machine that would enable stroke patients to regain arm movement, said today its board has decided to shut down the company and liquidate its assets".



What have we learned? Very little…

- ❑ Usual and Customary ≠ Optimal
- ❑ Earlier rehab not necessarily better than later
- ❑ Therapist supervised = Home based
- ❑ Different methods ~ Equivalent effects
- ❑ Intensity/Dose appear to matter*
- ❑ Mechanism of action???

*Intensity may be a proxy for something else like engagement or meaningfulness

Considerations for Moving Forward

- Reconsider primary efficacy endpoints (e.g. constructs they capture)
  - Animal vs human studies (e.g. neuroplasticity vs behavior)
  - Participation and QOL, behavior change, self-management
- Time course for the hypothesized mechanism
  - learning, adaptation, behavior change
- Secondary outcomes may be critical for advancing science and understanding mechanism
  - Secondary analysis (e.g., mediation modeling, Mulroy et al., *PTJ*, 2011)
- Clinical trial design to understand mechanism
  - NIMH initiative-Trial proposals will need to identify a target or mediator (Thomas Insel, 2014)

Mechanism of action

- Some of our efficacy endpoints do not tell us much about how the behavior was improved or what constitutes a meaningful change in function.
  - WMFT time score (e.g. 39 s vs 2 s)
  - FM score (e.g., 4.5 point change)
- Rarely do we gather information directly from the participant about what changed, worthwhileness of participation or what impact the intervention had on participation and QOL (e.g., autonomy, social-relatedness, competence)

We have only scratched the surface

- What is the mechanism for faster movement? (i.e., EXCITE results)?
  - Restitution-substitution continuum of recovery
- For non-superiority trials, were there responders and non-responders? If yes, what characteristics distinguished them?
- What is the mechanism for the delayed resistance to decay/decline in the sub-threshold direct CS group? (i.e., EVEREST results)

Before 2-week intensive practice

2.5 yrs post L hemisphere CVA

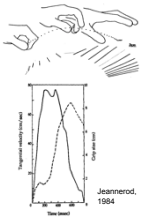
(pilot subject)

Item on Wolf Motor Function Test

39 s for task completion

- 37 -

After 2-week intensive arm focused practice



Jeannerod, 1984

Item on the Wolf Motor Function Test

2 s for task completion

- 38 -

Re-thinking Clinical Trial Design in Rehabilitation (after NIMH)

- "…a positive result will require not only that an intervention ameliorated a symptom, *but that it had a demonstrable effect on a target*, such as neural pathway implicated in the disorder or a key cognitive operation".
- "In the current climate, with funding tight and clinical needs urgent, we will be shifting to trials that focus on targets as a way of defining the next generation of treatments. The goal is better outcomes, measured as improved real-world functioning as well as reduced symptoms. ***We believe that better outcomes will require a deeper understanding of the disorders.*** These new clinical trials are designed to provide that".

The National Institute of Mental Health: http://www.nimh.nih.gov/about/director/2014/a-new-approach-to-clinical-trials.shtml

- 39 -

Theory-Driven Rehabilitation Treatment Taxonomy

ACRM Archives of Physical Medicine and Rehabilitation

ORIGINAL ARTICLE

Development of a Theory-Driven Rehabilitation Treatment Taxonomy: Conceptual Issues

John Whyte, MD, PhD,[a] Marcel P. Dijkers, PhD, FACRM,[b] Tessa Hart, PhD,[a] Jeanne M. Zanca, PhD, MPT,[b] Andrew Packel, MSPT,[a] Mary Ferraro, PhD, OTR/L,[a] Theodore Tsaousides, PhD[b]

Abstract

- 40 -

Whyte et al., *APMR*, 2014

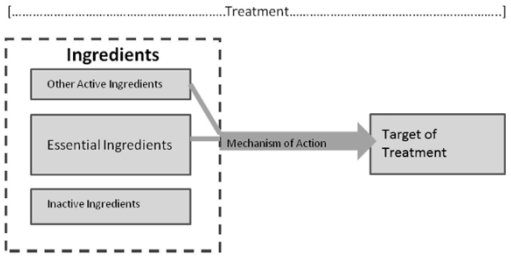


Fig 1 Illustration of the basic structure of all treatment theories. Ingredients (on the left) exert forces of change on a treatment target (on the right) through a known or hypothesized mechanism of action. A treatment must contain the defining essential ingredients pertinent to the specific treatment theory and may also contain other active ingredients, each of which contributes to the effects on the treatment target through the specific mechanisms of action. The inactive ingredients, although delivered with the treatment, exert no effects on the treatment target.

- 41 -

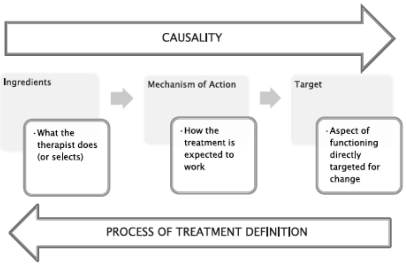


Fig 1 Casual and temporal aspects of the tripartite structure of treatment theory.

Hart et al., *APMR*, 2014

- 42 -

What is necessary to ensure the development of a mature clinical-behavioral science of rehabilitation?

Motor Behavior and Neurorehabilitation Laboratory

Envisioning the Future of Neurorehabilitation

To advance clinical practice in neurorehabilitation. Our research must be:

1) theoretically inspired
2) hypothesis-driven
3) grounded in psychological and neuroscience
4) use mixed methods (i.e., quantitative and qualitative measures)
5) be patient-centered

Summary/Conclusions

- Deeper understanding of the disorder (problem)
- Require intervention trials to not only impact function, but to have a demonstrable effect on the target of treatment.
- Consider the tripartite structure of treatment theory (ingredients, mechanism of action, target)

Acknowledgements/Collaborators

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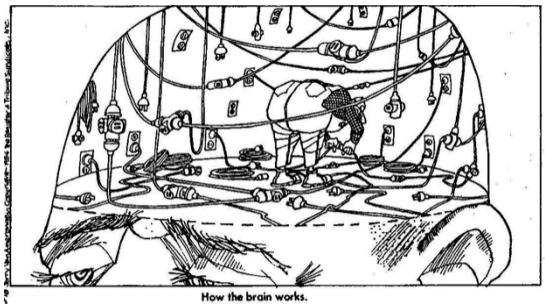
NIH/NICHD R01 HD065438 Optimizing the Dose (Schweighofer/Winstein, Multiple PI)
American Heart Association Mirror Neuron (Aziz-Zadeh; Winstein, Co-I)
NIH/NINDS/NICHD U01 NS056256 ICARE (Winstein; Wolf; Dromerick; Multiple PI)
NIDRR H133E080024 OPTT-RERC (Winstein/PD/PI; Requejo Co-PI)
SC CTSI-Point-of-Care Mobility Monitoring system (Blanco, Winstein, Pis)



How the brain works.