Stroke recovery: From compensation to recovery

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Aversion to Stroke Outcomes

![Bar chart showing aversion to different stroke outcomes.](chart.png)

- **Language**: Mild (2), Moderate (4), Severe (8.3)
- **Cognitive**: Mild (3), Moderate (8.3), Severe (9.2)
- **Motor**: Mild (2), Moderate (4), Severe (9.2)
- **Death**: Mild (0), Moderate (0), Severe (8.2)

Solomon et al. 1994
INACTIVE AND ALONE
Motor recovery after stroke

- Vexed issue of non-human animal models versus human studies.

- In the early 20th century, neurology and systems neuroscience tracked each other for the study of hemiparesis. This physiological emphasis has waned and we need it back.

- Importance of careful analysis of behavior: kinematics.

- Need for behavioral interventions to be primary and drugs/brain stimulation secondary.
- “cortical disease led to two sets of symptoms, ‘negative’ from loss of the controlling cortex and ‘positive’ from the emergence of the lower center”
  HUGHLINGS JACKSON

- The “dual nature of hemiplegia” – the combination of loss of voluntary movement and the intrusion of positive phenomena: spasticity and synergies
  F.M.R. WALSHE
Positive symptoms: synergies
Depressed and protracted

Arm adducted and internally rotated

Elbow flexed and forearm pronated

Wrist and finger flexion (clenched fist with thumb-in-palm deformity)
THE RESTORATION OF MOTOR FUNCTION FOLLOWING HEMIPLEGIA IN MAN

BY

THOMAS E. TWITCHELL¹

Brain, Volume 74, Issue 4, 1 December 1951, Pages 443–480

Thomas Evans Twitchell
M.D.
(1923-2017)
Twitchell recovery sequence

Shoulder flex +

Elbow flex +

Wrist & fingers flex

Shoulder & elbow ext + flex out of synergy

Finger individuation
The Fugl-Meyer Scale for impairment

Arm: “within synergy”

Arm: “out of synergy”
Proportional Recovery: a rule for spontaneous biological recovery, its existence implies no effect of current rehabilitation

\[ \Delta FM = \beta FM_{ii} \quad (\beta = 0.7) \]

Prahbakan et 2008 NNR;
(Figure adapted from Winters et al. 2015)
Fig. 1 Schematic of (A) reaching condition, target position 1 for reach ‘out’ and target position 2 for reach ‘up’; and (B) shoulder individuation task.

Fig. 2 Overlaid single trials for index finger paths, and associated excursions of the shoulder, elbow, and wrist joints from both reaching conditions ('up' and 'out').

Where so synergies come from? Upregulation of the RST after lesion of the CST

Zaaimi et al., Brain 2012
Negative symptoms: The pyramidal tract and prehension
Supporting the weight of the arm reduces intrusion by flexor synergy due to $\uparrow$RST and allows expression of residual CST capacity.
stroke disrupts arm trajectories

healthy

stroke
Uncoupling between synergies and motor control during recovery
A critical window for post-stroke training

Steve Zeiler
A  Single Pellet Reaching Test

B  Comparison of hand shaping movements

<table>
<thead>
<tr>
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<th>Rat</th>
<th>Human</th>
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<tbody>
<tr>
<td>Start</td>
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Mouse stroke
Training Days vs. Percentage Correct

- Stroke

$n = 7$

Ng et al (2015)
Delayed Retraining

![Graph showing delayed retraining with a stroke label at the 10-day mark.](graph.png)
Early Retraining

Percentage Correct

Training Days

n = 7

Ng et al (2015)
Sensitive period can be reset with a second stroke.
Sensitive period can be reset with a second stroke.
Training vs. Spontaneous Biological Recovery in non-human primate

Murata et al. 2008
Humans: acute stroke
Study of Motor Learning and Acute Recovery
Time-course after Stroke

SMARTS

John Krakauer, Andreas Luft, Pablo Celnik, Tomoko Kitago, Joel Stein
Columbia University, Johns Hopkins University and University of Zurich
Funded by the JAMES S. MCDONNELL FOUNDATION
The arm after stroke

Juan Camilo Cortes
planar motor control task

minimize compensation and antigravity effort

KineReach® figure adapted from Mani and Sainburg et al. Brain 2013
stroke disrupts arm trajectories
Spontaneous recovery of motor control of the arm is over in about a month.
Figure 5. Normalized time course for all outcome variables: AMD2, Action Research Arm Test (ARAT), Fugl-Meyer Assessment of the upper extremity (FMA-UE), and biceps dynamometry (strength) Z-score. The dotted line indicates the normalized value of the recovery achieved between the first and the second visit for each measure, which is 1. AMD2 plateaued at week 5, while all clinical measures continued to improve through the first year after stroke.

Published in: Juan C. Cortes; Jeff Goldsmith; Michelle D. Harran; Jing Xu; Nathan Kim; Heidi M. Schambra; Andreas R. Luft; Pablo Celnik; John W. Krakauer; Tomoko Kitago; Neurorehabilitation and Neural Repair 31, 552-560.
DOI: 10.1177/1545968317697034
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The hand after stroke

Jing Xu
Taxonomy of hand movements

- **Stability (strength)**
  - Power grip

- **Precision (control)**
  - Individuation
  - Precision grip

The diagram illustrates the trade-off between stability and precision in hand movements, with power grip being more stable but less precise, and individuation being more precise but less stable.
The individuation paradigm

Maximum Voluntary Contraction (MVC)  Individuation
Most recovery occurs in the first 3 months

![Graph showing strength and dexterity over weeks for patients and controls.]
Time-invariant relationship between strength and control
Main recovery traverses the time-invariant function
Two recovery systems for strength and control
Normal Acute Post-Stroke Chronic Post-Stroke

Brain = normal  Brain = damage  Brain = damaged
Plasticity = normal  Plasticity = hyper  Plasticity = normal

Zeiler and Krakauer, 2013
Likely irrelevant to motor recovery after stroke

**Use-dependent plasticity**
*Broken Movement – Krakauer & Carmichael 2017 (MIT press)*

**Motor learning**
*Broken Movement – Krakauer & Carmichael 2017 (MIT press)*

**Changes in inter-hemispheric imbalance**
*Broken Movement – Krakauer & Carmichael 2017 (MIT press); Stinear et al 2017; Xu et al 2018 (under revision)*

**Changes in motor cortical excitability**
*Bestmann & Krakauer 2015; Stinear et al 2017*

**Changes in cortical maps**
*Broken Movement – Krakauer & Carmichael 2017 (MIT press)*
Makin, Diedrichsen, & Krakauer (in press)

**Changes in cortical functional connectivity**
*Nijboer et al 2017; Brandscheidt et al (in prep)*

Hence: NIBS (TMS and tDCS) and Robotics also likely to have minimal therapeutic use
Cortico-subcortical changes a more plausible mechanism for recovery: selective long-term facilitation of the corticospinal projection from SMA following recovery from lateral motor cortex injury.
Another example of subcortical reorganization

Herbert et al. 2015
Recovery via cortico-subcortical interactions

Herbert et al. 2015
A Model of Recovery

\[ Restitution_{\text{magnitude}} = \text{Behavior}_{\text{dose}} \times \text{Representation}_{\text{residual amount}} \times \text{Plasticity}_{\text{level}} \]

*Broken Movement: The neurobiology of motor recovery after stroke*

Spontaneous biological recovery & responsivity to training: incomplete knowledge

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<tr>
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Enriched, playful environments promote general motor recovery

“Getting Neurorehabilitation right: What can we learn from animal models? ” Krakauer et al. NNR (2012);
“The interaction between training and plasticity in the post-stroke brain” Zeiler & Krakauer COiN (2013)
Way Forward
THE STATISTICS OF ARM MOVEMENTS IN EVERYDAY LIFE

A

B


©2009 by American Physiological Society
• What would an enriched environment for patients look like?
• How should we promote playful non-task based exploratory behavior?
The Illusion of Life
Disney Animation
Frank Thomas and Ollie Johnston
SMARTS II

Columbia University, Johns Hopkins University and University of Zurich

Funded by the JAMES S. MCDONNELL FOUNDATION
TRACKING AND ALTERING THE TIME COURSE OF
SPONTANEOUS BIOLOGICAL RECOVERY AFTER STROKE (SMARTS II)

(JOHN KRAKAUER PI)
PABLO CELNIK (Johns Hopkins), ANDREAS LUFT (Zurich, Cereneo), JOEL STEIN, TOMOKO KITAGO (Columbia)
(Funding: McDonnell Foundation)
Study to enhance Motor Acute Recovery with intensive Training after Stroke (SMARTS2)

Study Type: Randomized Clinical Trial
Enrollment: 21 participants
Intervention Model: Parallel Assignment
Blinding: Single (Outcomes Assessor)
Study Start Date: May 2015
Completion Date: December 2017

Sponsor:
Johns Hopkins University

Collaborators:
Columbia University
University of Zurich

ClinicalTrials.gov identifier:
NCT02292251
James S. McDonnell Foundation:
JSMF220020220
Study to enhance Motor Acute Recovery with intensive Training after Stroke (SMARTS2)

Inclusion Criteria:
✓ Ischemic stroke confirmed by imaging within the previous 6 weeks
✓ No history of prior stroke with associated motor deficits
✓ Residual unilateral arm weakness with FMA 6-40
✓ Ability to give informed consent and understand the tasks involved

Exclusion Criteria:
X Space-occupying hemorrhagic transformation or associated ICH
X Cognitive impairment, with score on MoCA ≤ 20.
X Inability to sit in a chair for one hour at a time
X Terminal illness
Study to enhance **Motor Acute Recovery with intensive Training after Stroke** (SMARTS2)

- Baseline Assessments (FMA, ARAT, Kinematics)
  - 3 weeks Time-matched COT (n=11)
  - 3 weeks Immersive Robotic Arm Therapy (n=10)

- 3-day Post-intervention Assessments
  - Day 30 Assessments
  - Day 60 Assessments
  - Day 90 Assessments
PRELIMINARY SMARTS 2 RESULTS

![Graph showing mean change in ARAT and FM for intense and usual treatments.](image)
Dose Response of Task-Specific Upper Limb Training in People at Least 6 Months Poststroke: A Phase II, Single-Blind, Randomized, Controlled Trial

Catherine E. Lang, PT, PhD,\textsuperscript{1,2,3} Michael J. Strube, PhD,\textsuperscript{4} Margheurettta D. Bland, PT, DPT, MSCI,\textsuperscript{1,2,3} Kimberly J. Waddell, MSOT, OTR/L,\textsuperscript{1} Kendra M. Cherry-Allen, PT, DPT,\textsuperscript{1} Randolph J. Nudo, PhD,\textsuperscript{5} Alexander W. Dromerick, MD,\textsuperscript{6} and Rebecca L. Birkenmeier, OTD, OTR/L\textsuperscript{1,2,3}

\textbf{Interpretation:} Overall, treatment effects were small. There was no evidence of a dose-response effect of task-specific training on functional capacity in people with long-standing upper-limb paresis poststroke.

\textit{ANN NEUROL 2016;80:342–354}
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<thead>
<tr>
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<td>↑</td>
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<tr>
<td>FMA</td>
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**Goldstein et al.** *JAMA* 2018  
**RATULS** – Turner et al. 2018  
**EXPLICIT** - Kwakkel et al *NNR*  
**SMARTS 2** Krakauer et al  
**Ward** et al  
**NICHE** trial – Harvey et al. *STROKE* 2018  
**McCabe** et al *APMR* 2015  
**Allman C** et al *Sci Transl Med.* 2016
• Thus far early intervention seems to have an effect on prehension (negative symptoms).
• May need a physiological approach to the movement disorder (positive symptoms)
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