Stroke recovery: From compensation to recovery

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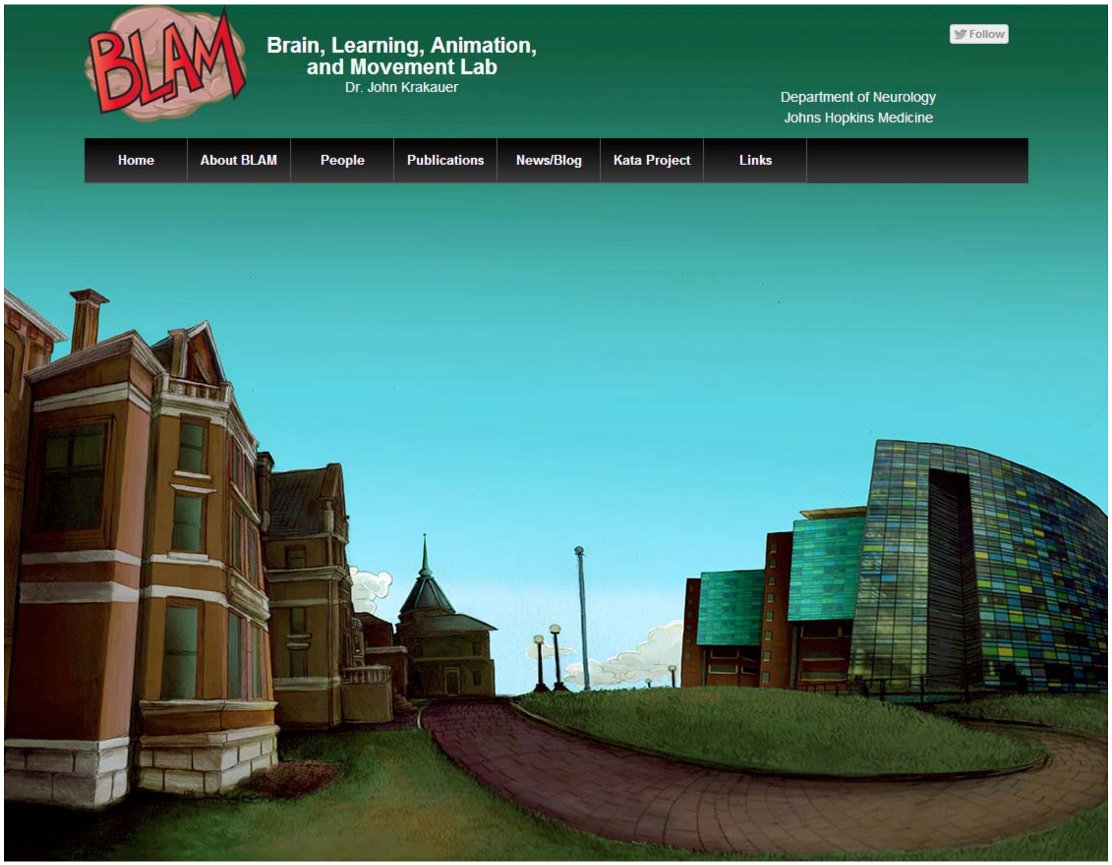
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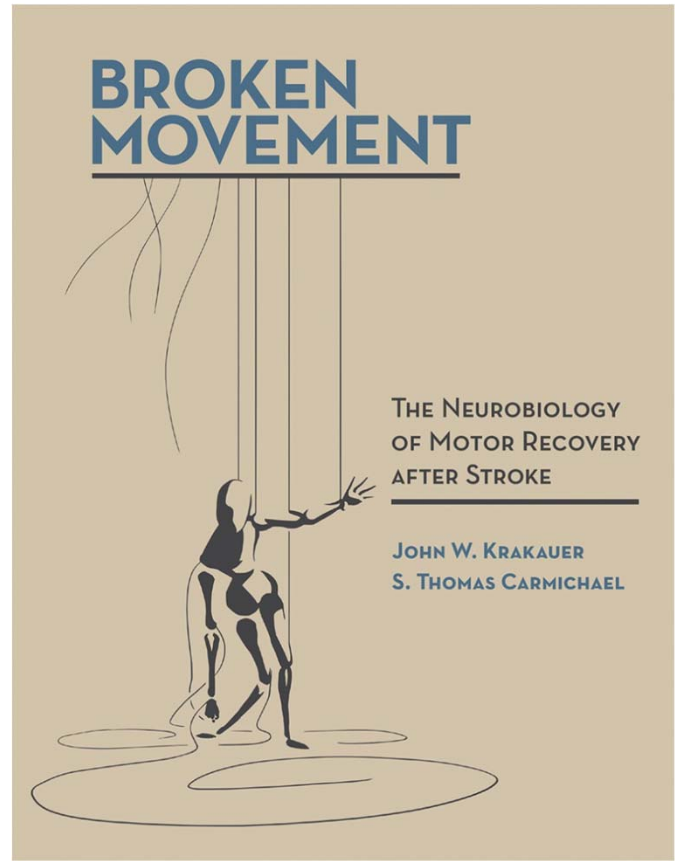
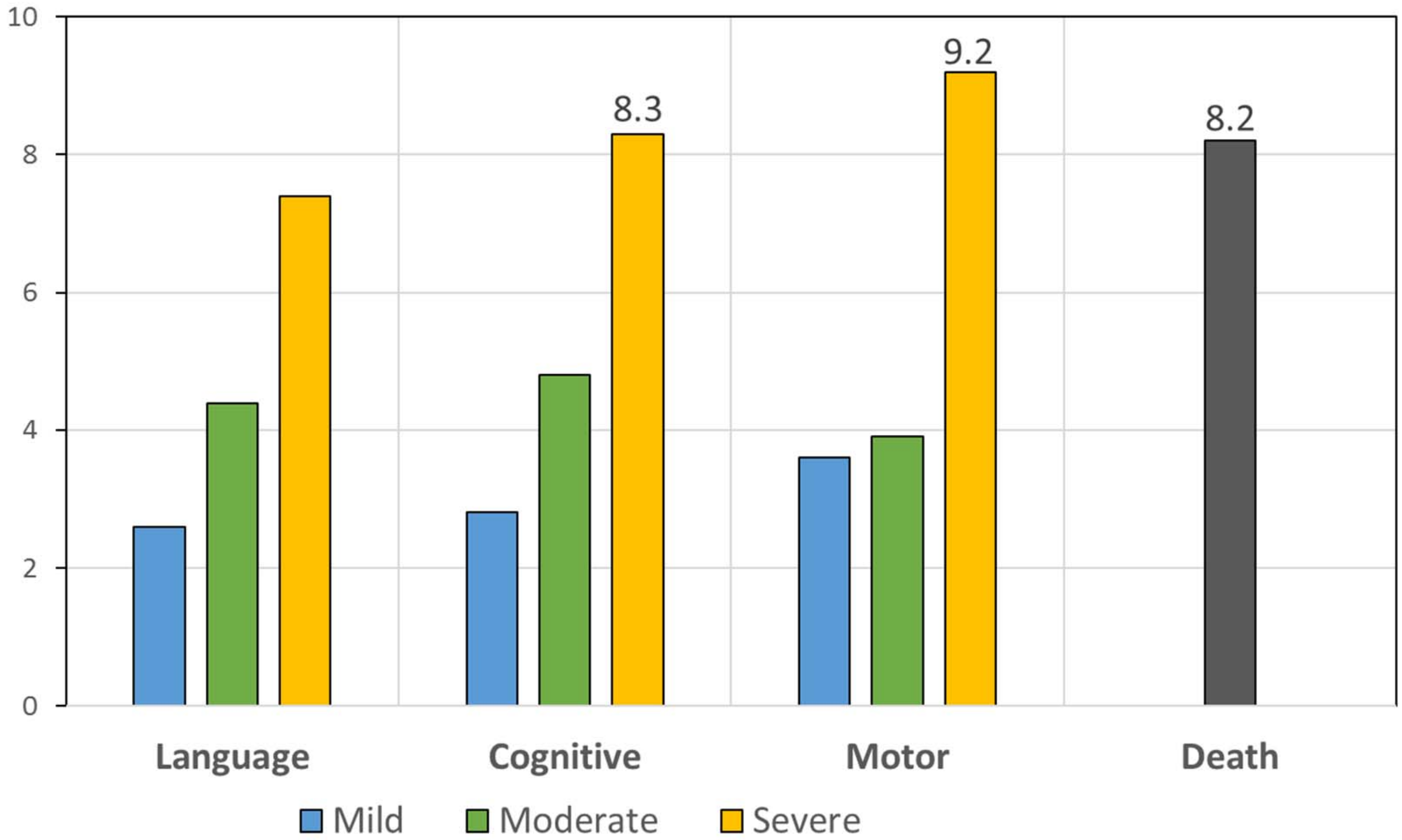
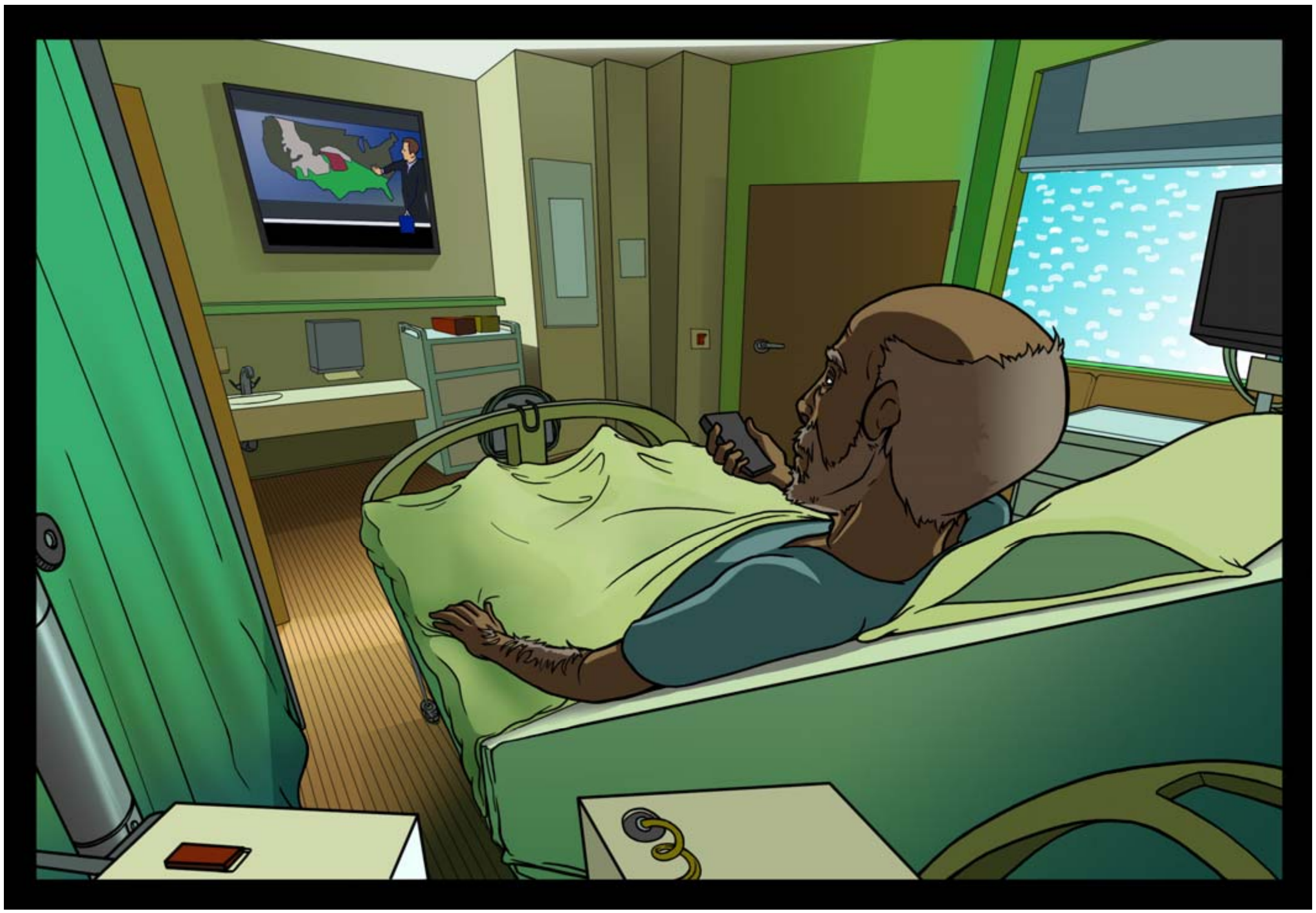

BROKEN MOVEMENT
THE NEUROBIOLOGY OF MOTOR RECOVERY AFTER STROKE
JOHN W. KRAKAUER
S. THOMAS CARMICHAEL

Aversion to Stroke Outcomes



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.

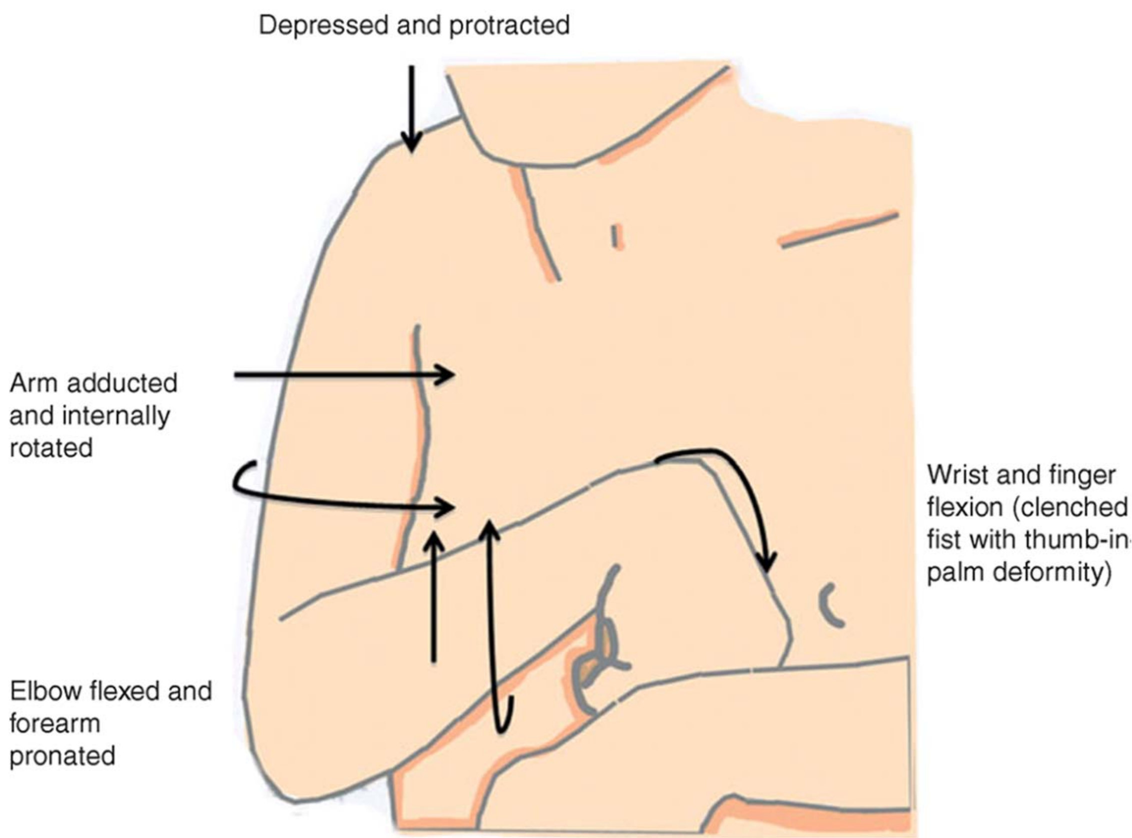
- Importance of careful analysis of behavior: kinematics.

- 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)

OXFORD
ACADEMIC

BRAIN
A JOURNAL OF NEUROLOGY

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

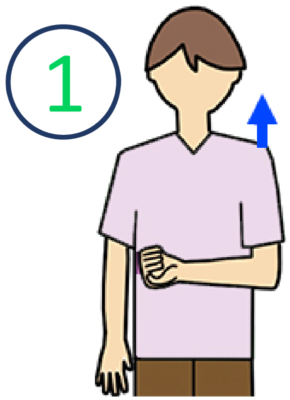
THE RESTORATION OF MOTOR FUNCTION FOLLOWING HEMIPLEGIA IN MAN

BY

THOMAS E. TWITCHELL[1]

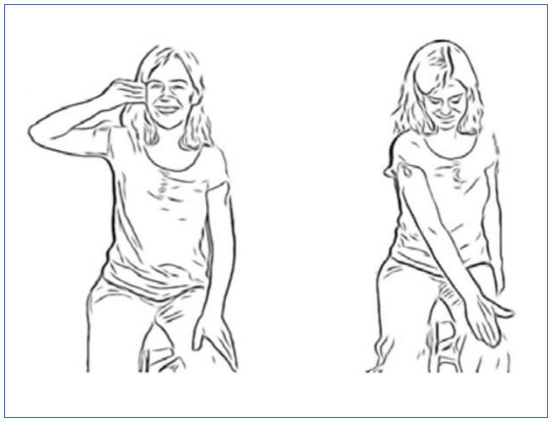
Brain, Volume 74, Issue 4, 1 December 1951, Pages 443–480

Twitchell recovery sequence



Shoulder flex

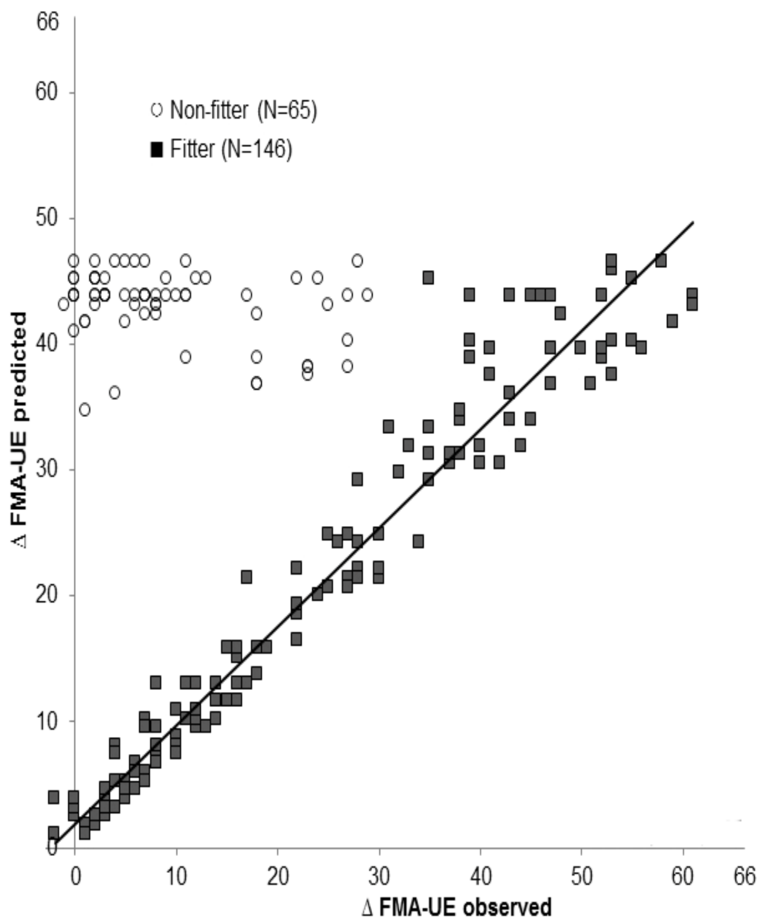
The Fugl-Meyer Scale for impairmemt



Arm: “within synergy”

Arm: “out of synergy”

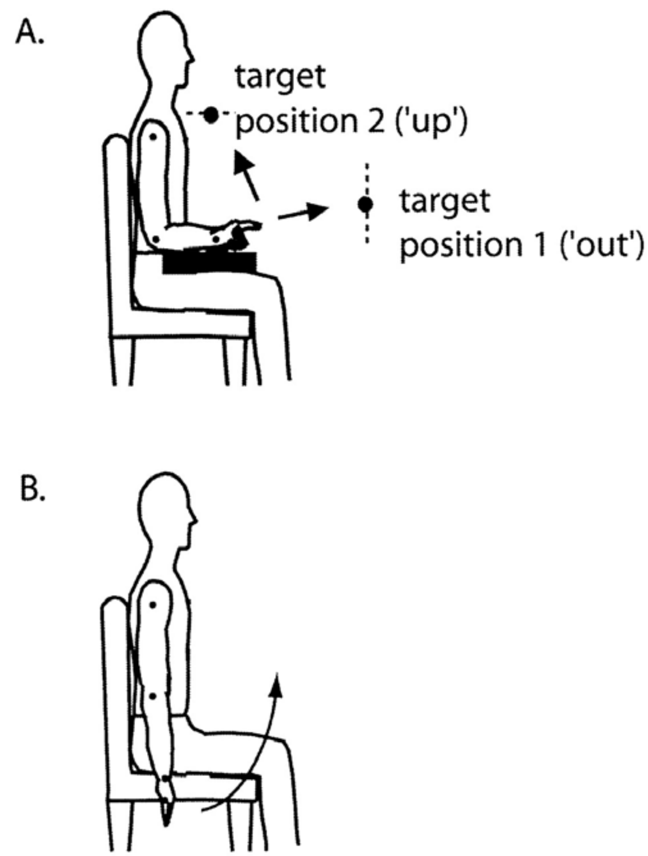
Proportional Recovery: a rule for spontaneous biological recovery, its existence implies no effect of current rehabilitation



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

Prahbakaran 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.

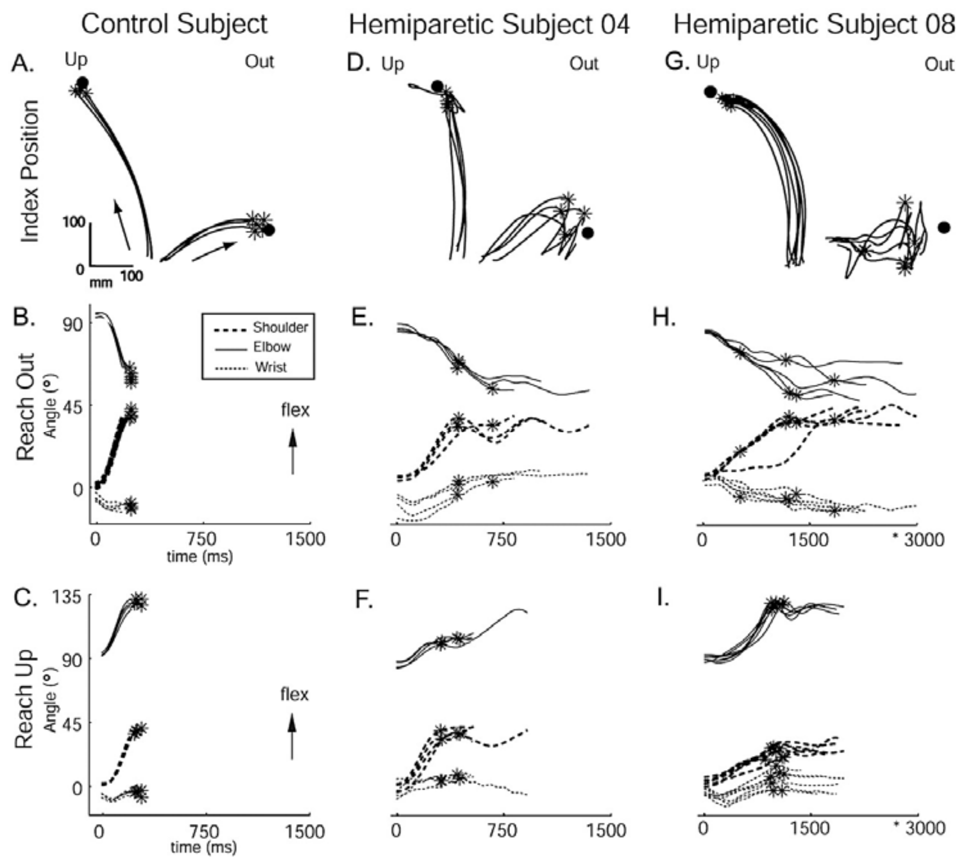


Zackowski K M et al. Brain 2004;127:1035-1046

The Guarantors of Brain 2003

BRAIN A JOURNAL OF NEUROLOGY

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').



Zackowski K M et al. Brain 2004;127:1035-1046

The Guarantors of Brain 2003

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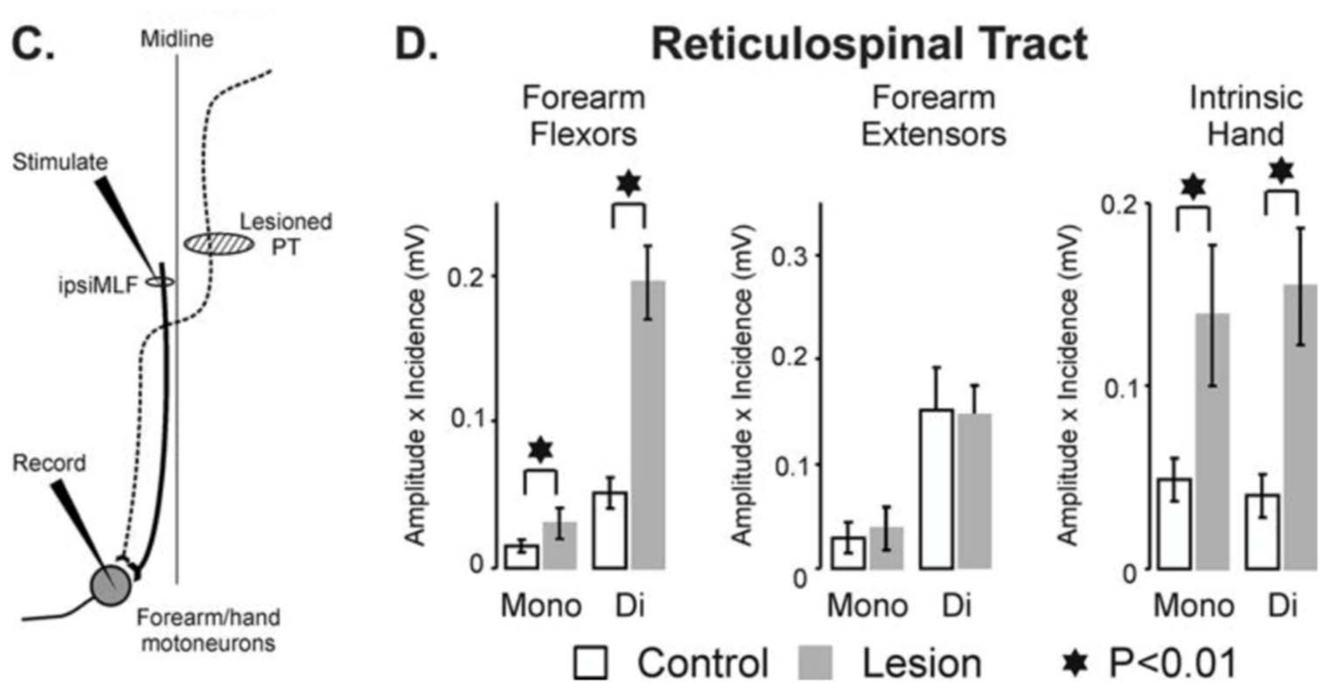
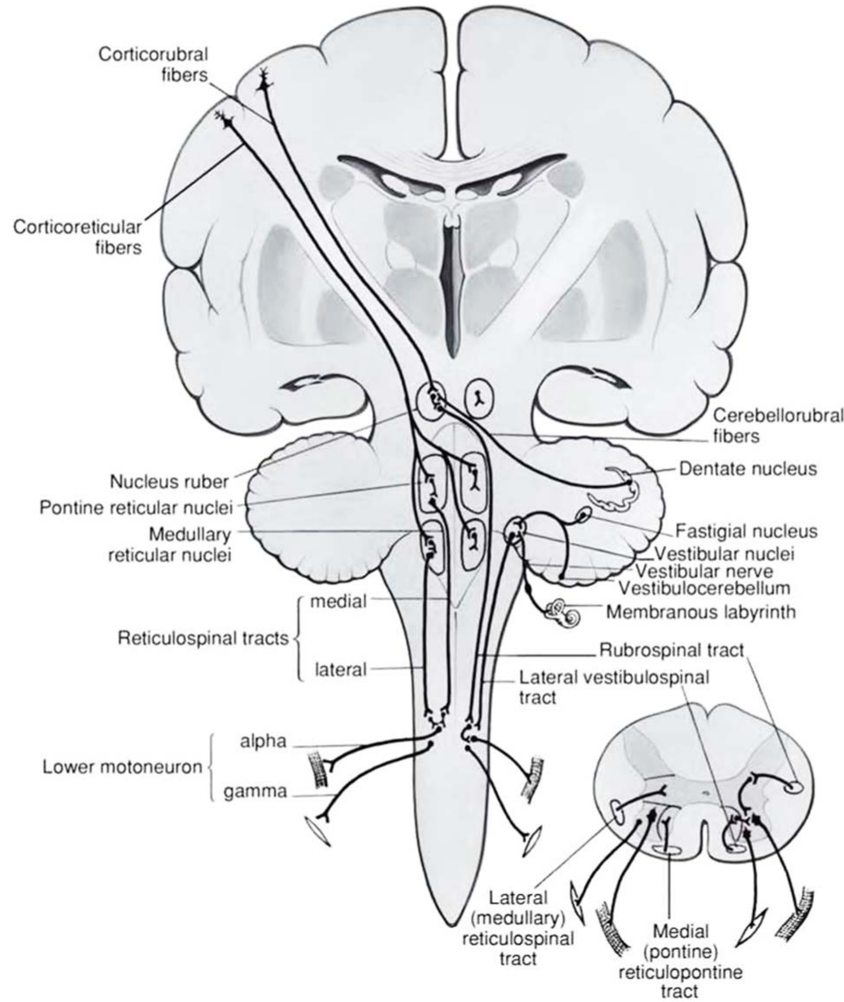
Where so synergies come from? Upregulation of the RST after lesion of the CST

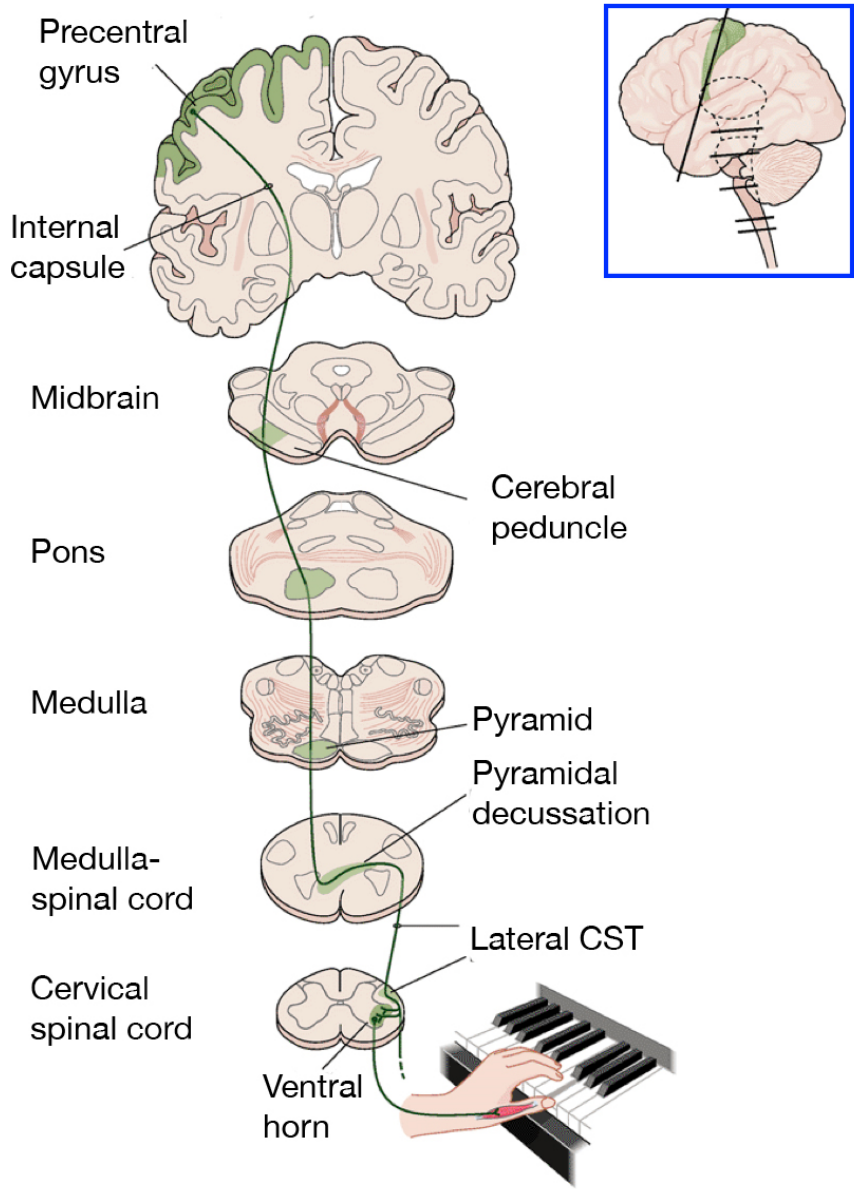


Zaaimi et al., *Brain* 2012

RST

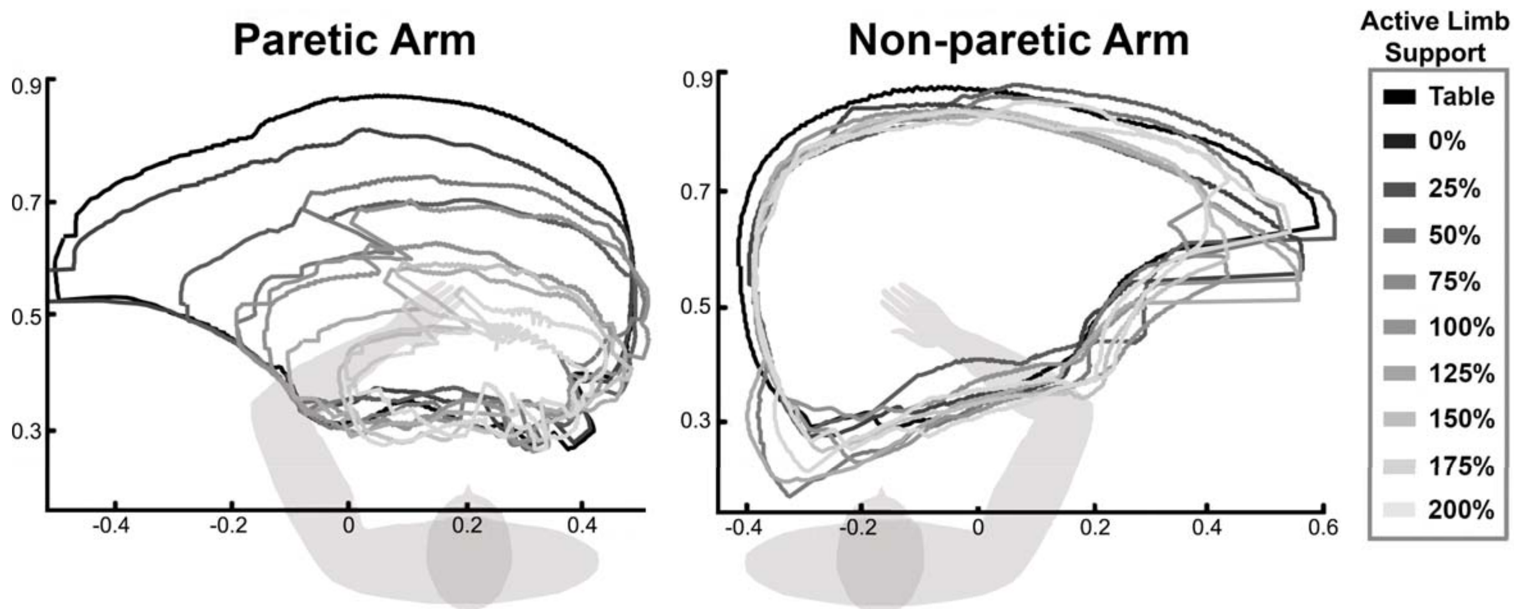

Corticorubral fibers
Corticoreticular fibers
Cerebellorubral fibers
Dentate nucleus
Nucleus ruber
Pontine reticular nuclei
Medullary reticular nuclei
Fastigial nucleus
Vestibular nuclei
Vestibular nerve
Vestibulocerebellum
Membranous labyrinth
Reticulospinal tracts
medial
lateral
Rubrospinal tract
Lateral vestibulospinal tract
Lower motoneuron
alpha
gamma
Lateral (medullary) reticulospinal tract
Medial (pontine) reticulopontine tract

Negative symptoms: The pyramidal tract and prehension



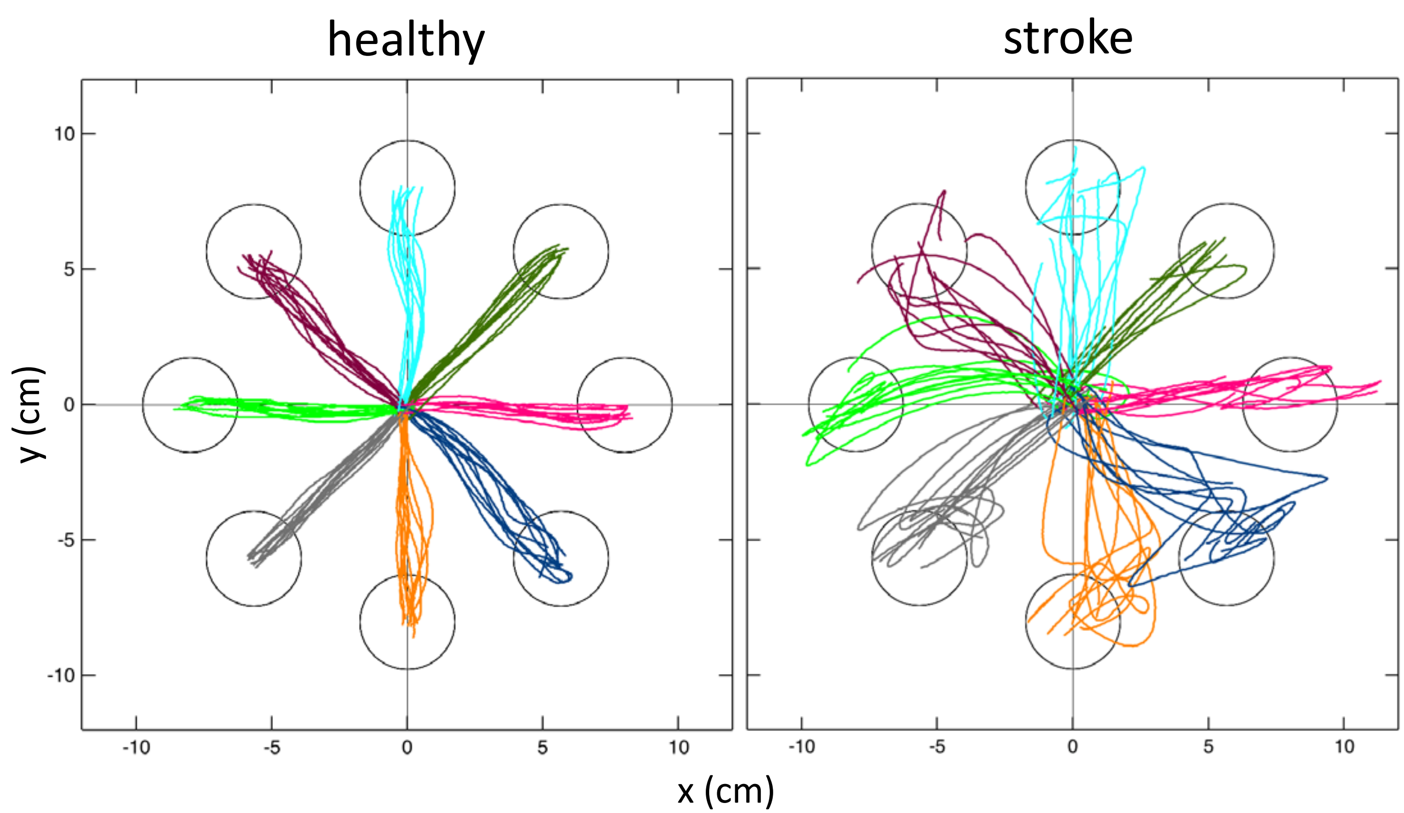
Precentral gyrus
Internal capsule
Midbrain
Cerebral peduncle
Pons
Medulla
Pyramid
Pyramidal decussation
Medulla-spinal cord
Lateral CST
Cervical spinal cord
Ventral horn

Supporting the weight of the arm reduces intrusion by flexor synergy due to ↑RST and allows expression of residual CST capacity



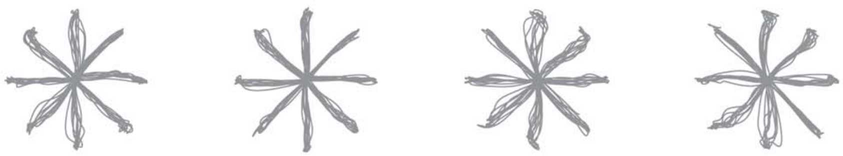
Courtesy of Jules Dewald

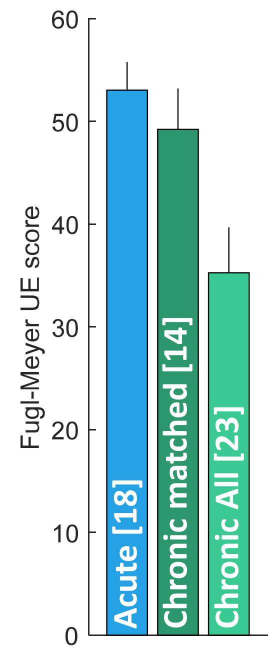
stroke disrupts arm trajectories



Uncoupling between synergies and motor control during recovery

Controls

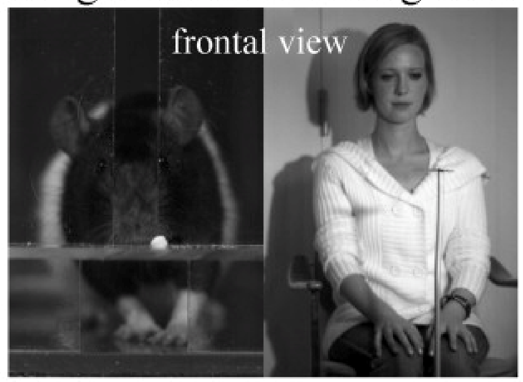




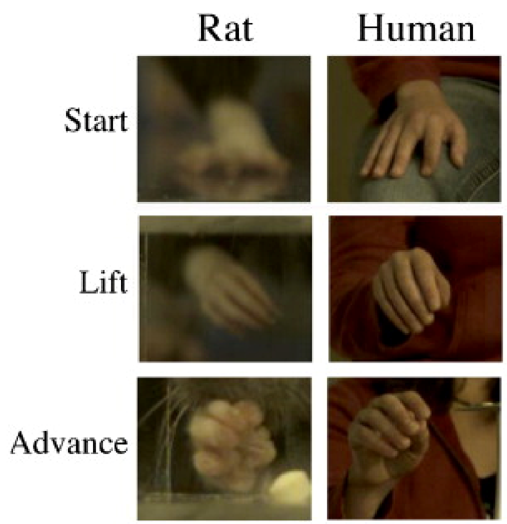
A critical window for post-stroke training

Steve Zeiler

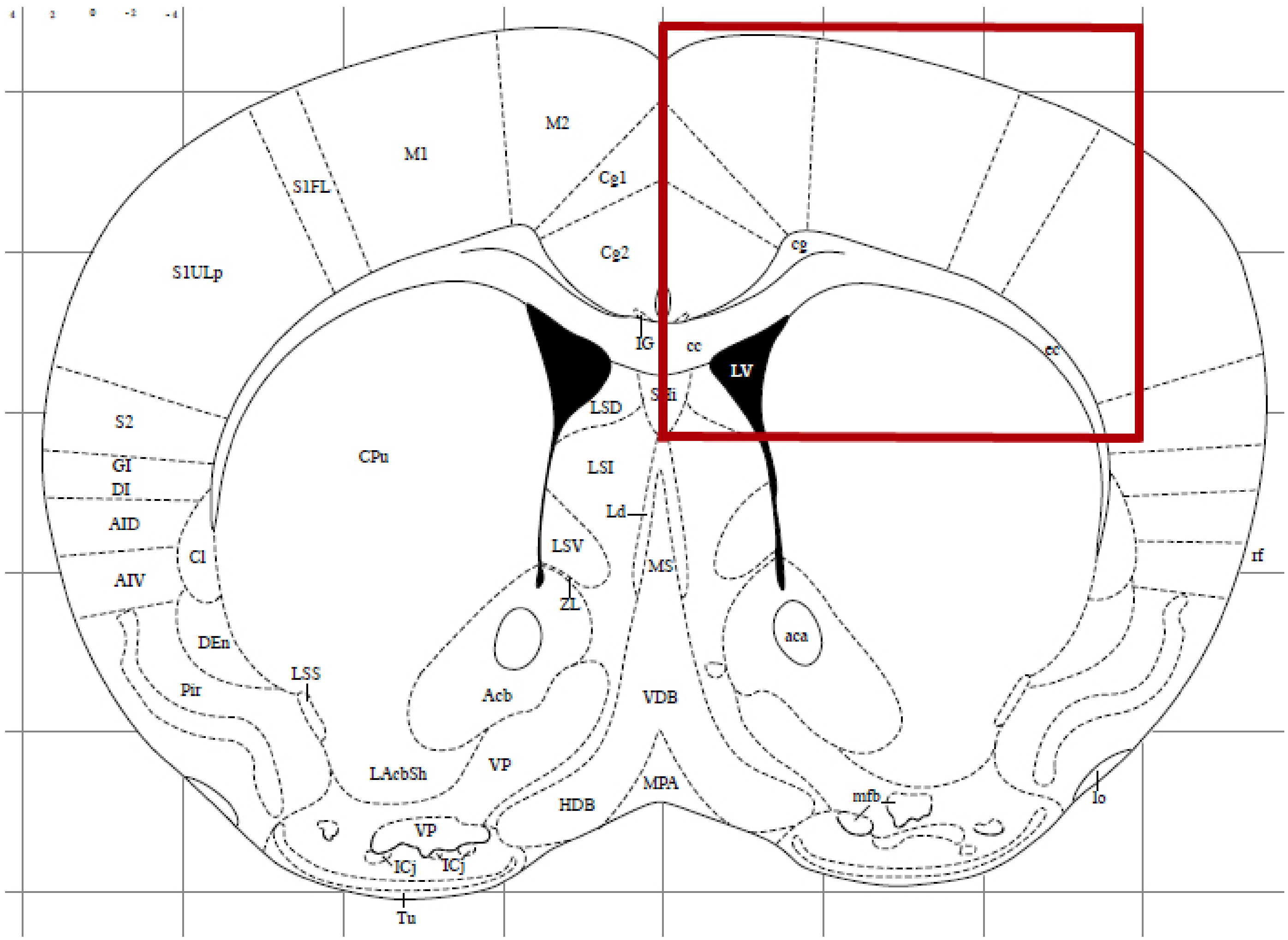
A Single Pellet Reaching Test

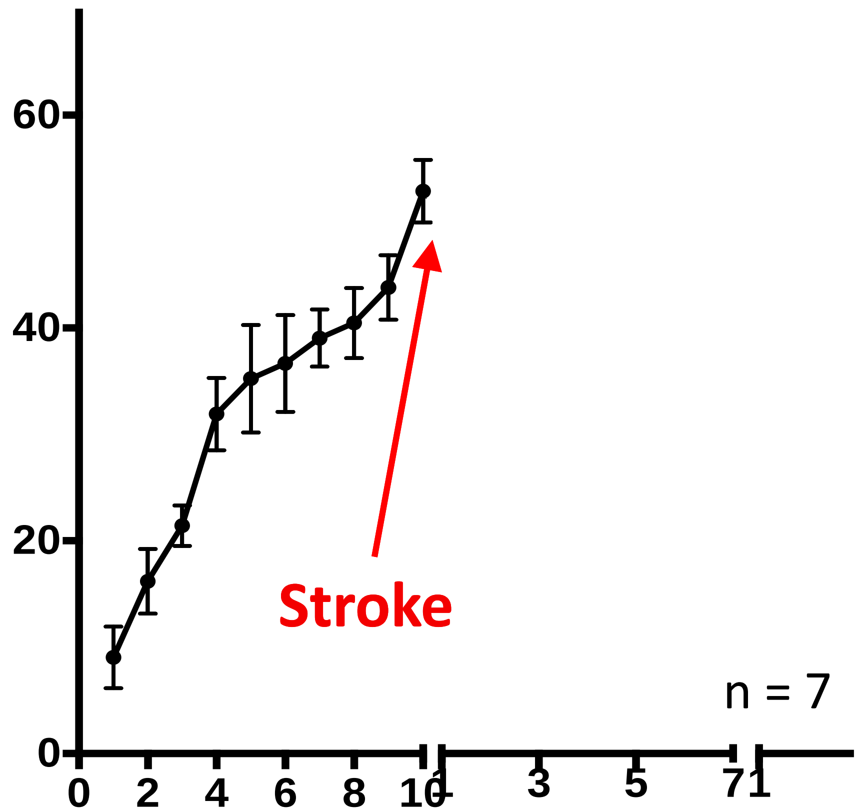


B Comparison of hand shaping movements



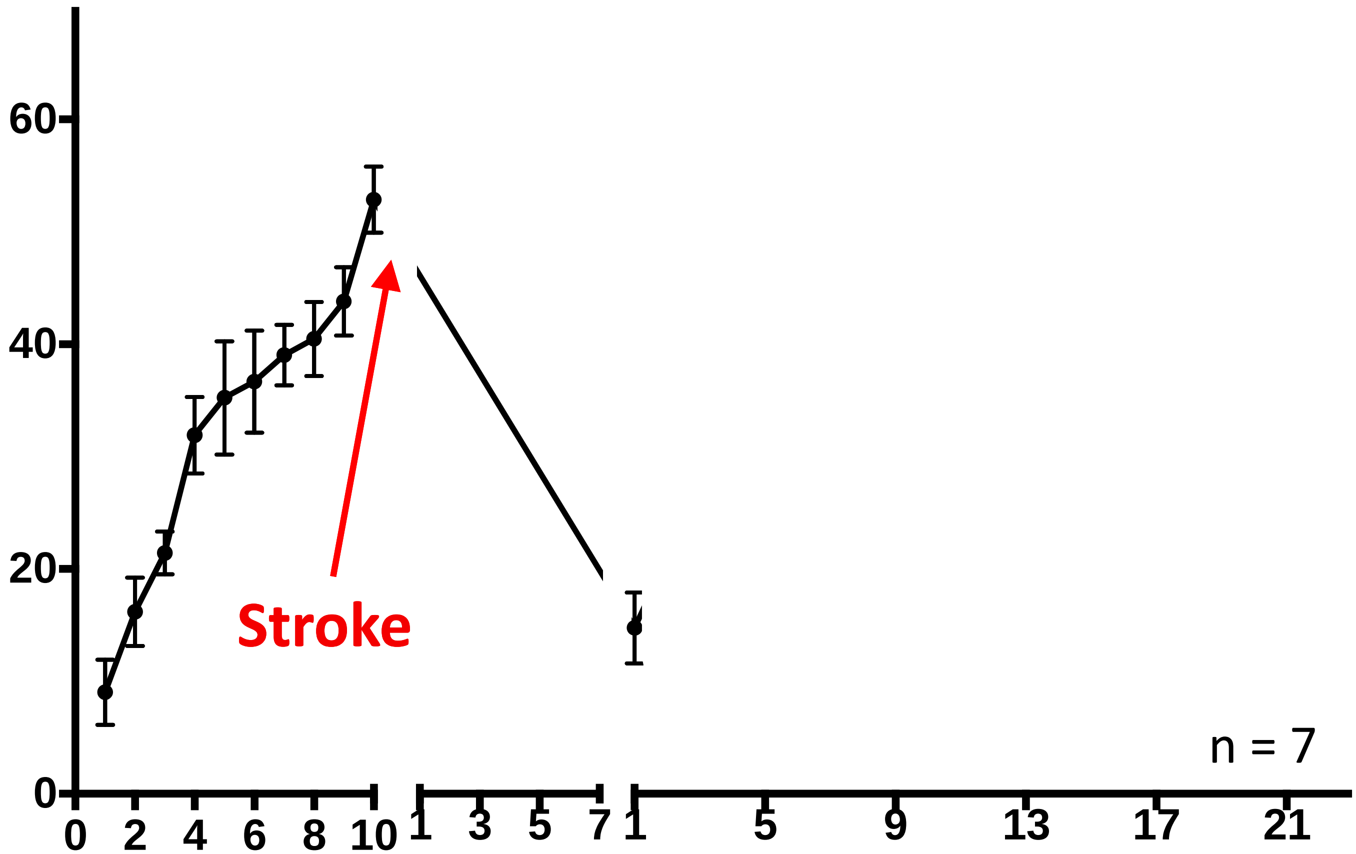
Mouse stroke



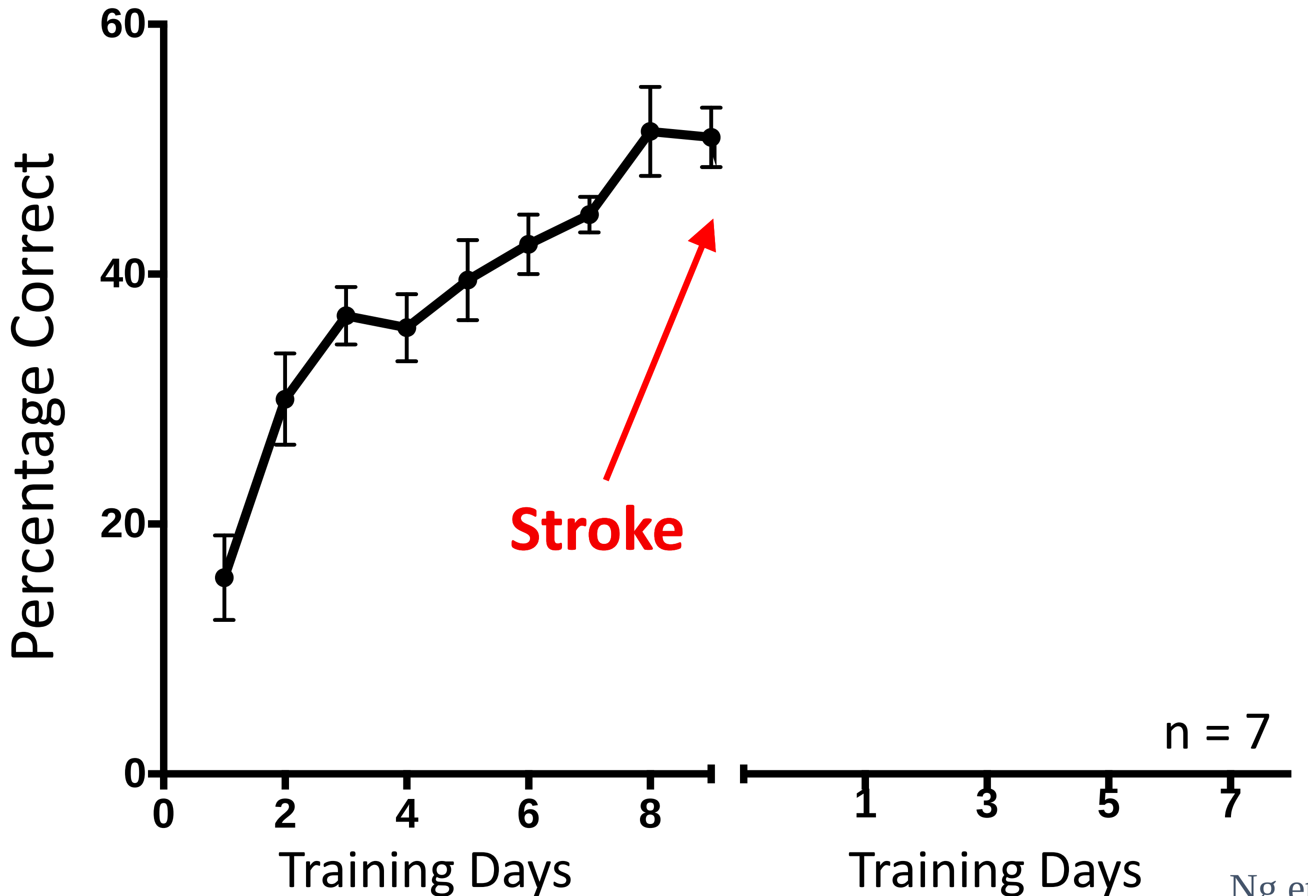


Ng et al (2015)

Delayed Retraining

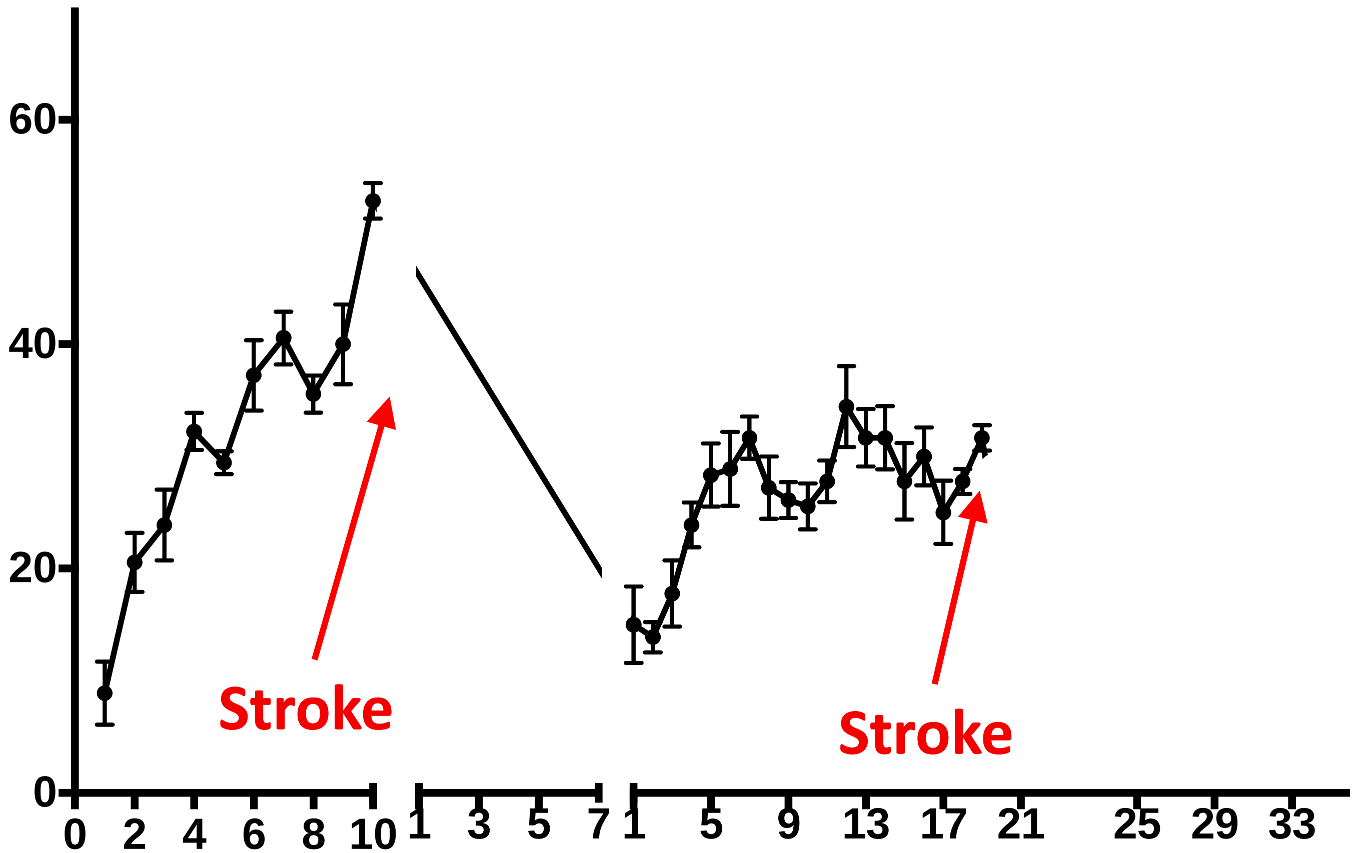


Early Retraining

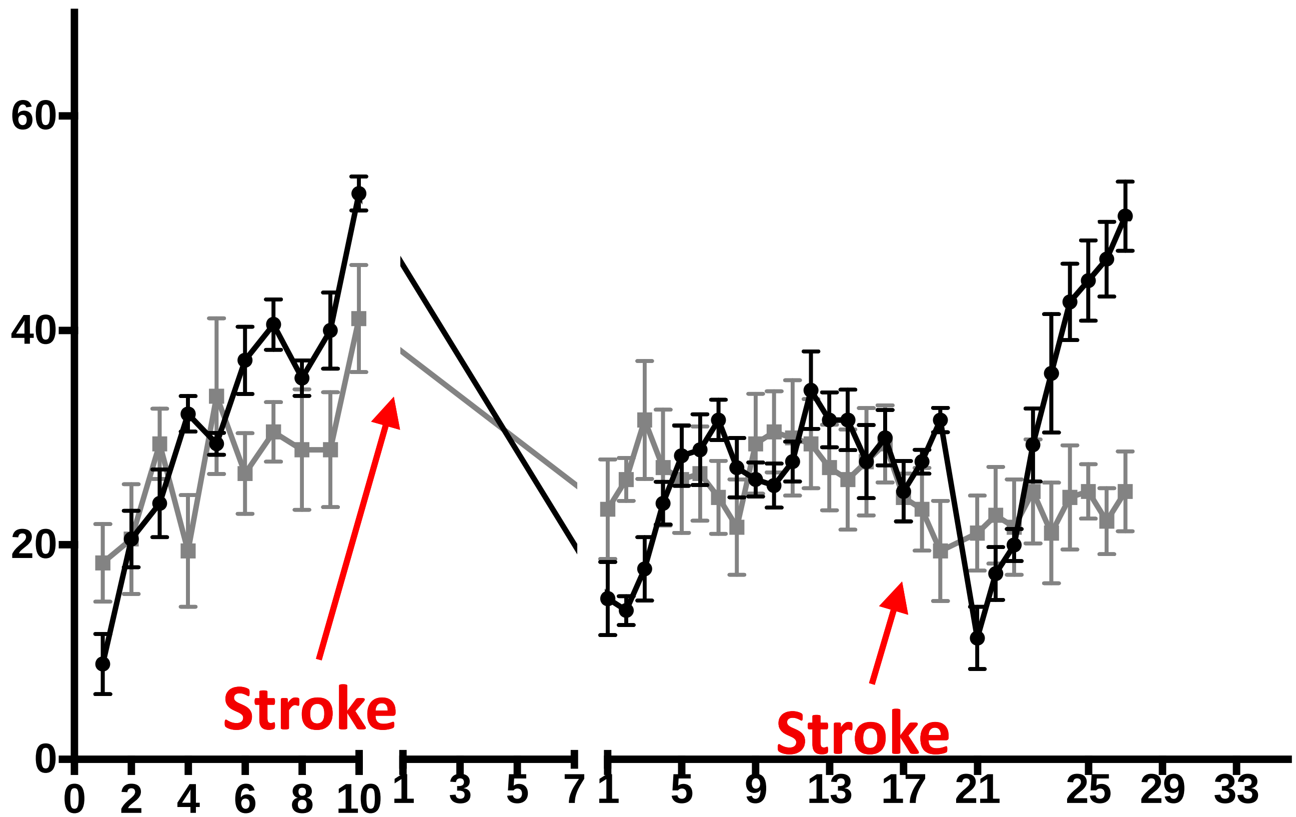


Ng et al (2015)

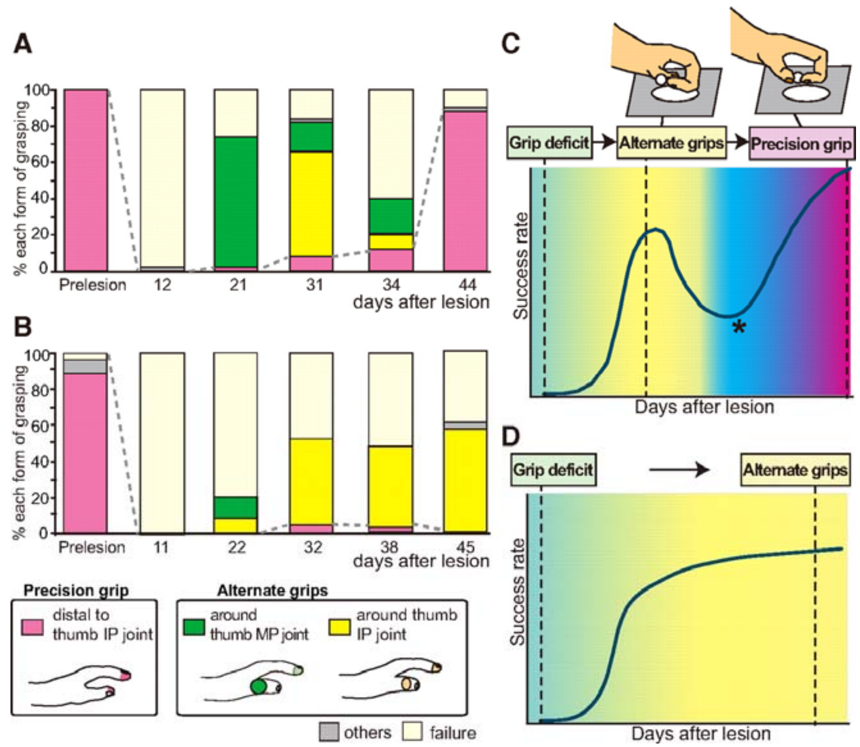
Sensitive period can be reset with a second stroke



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

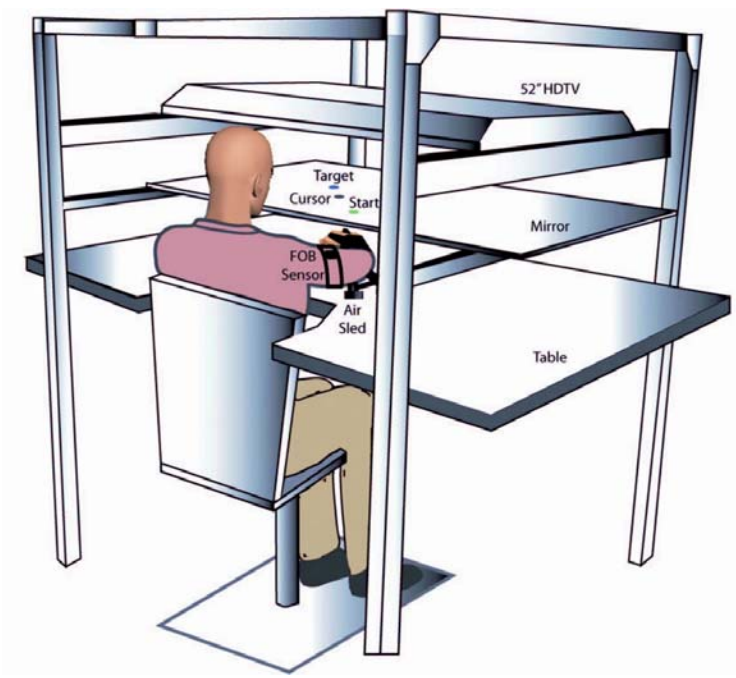
Funded by the JAMES S. MCDONNELL FOUNDATION

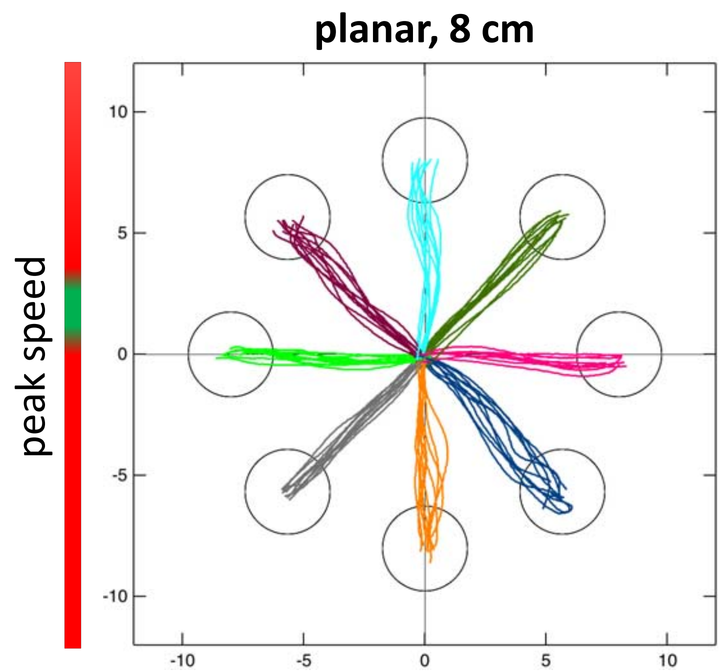
The arm after stroke

Juan Camilo Cortes

planar motor control task

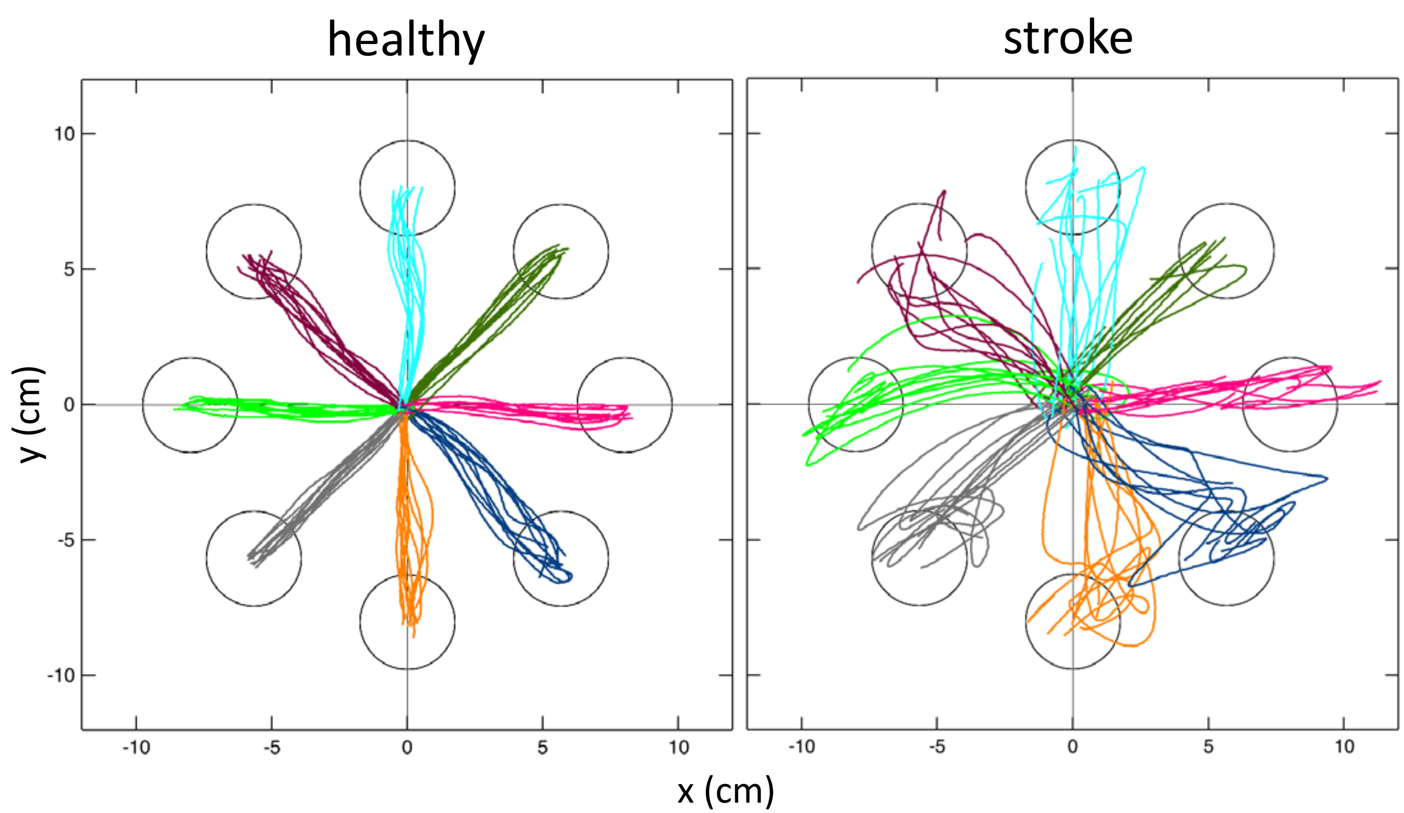
minimize compensation and antigravity effort



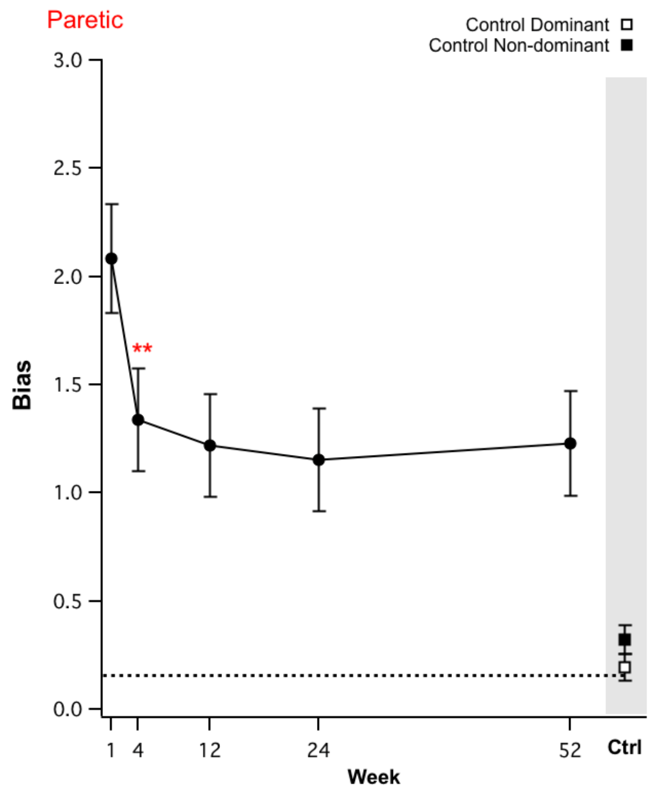


KineReach® figure adapted from Mani and Sainburg et al. *Brain* 2013

stroke disrupts arm trajectories



Spontaneous recovery of motor control of the arm is over in about a month



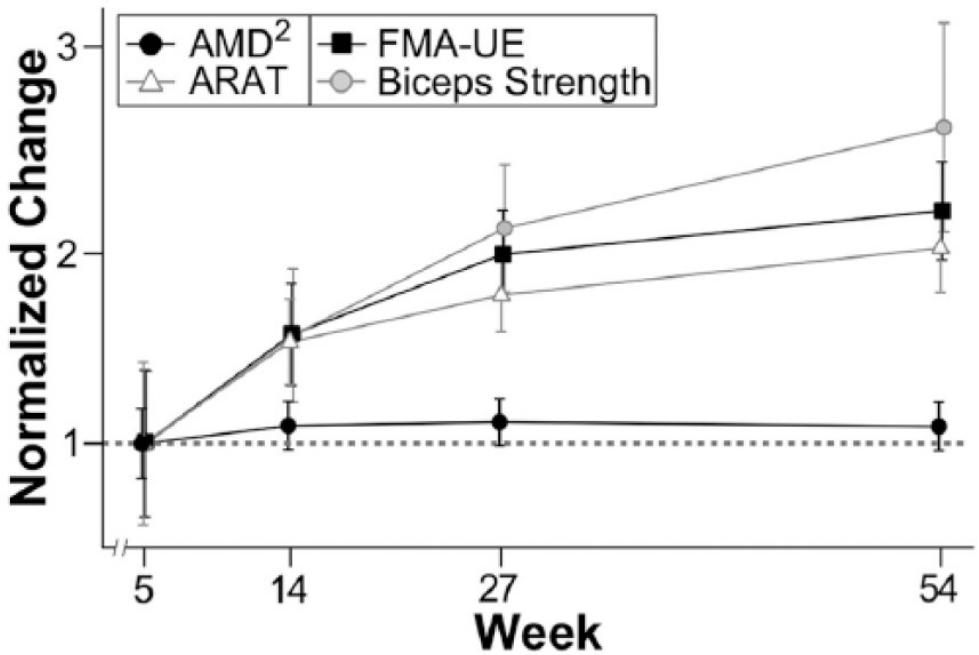


Figure 5. Normalized time course for all outcome variables: AMD2, Action Research Arm Test (ARAT), Fugl-Meyer Assessment of the upper extremity (FMA-UE), and biceps dynamometry (strength) *Z*-score. The dotted line indicates the normalized value of the recovery achieved between the first and the second 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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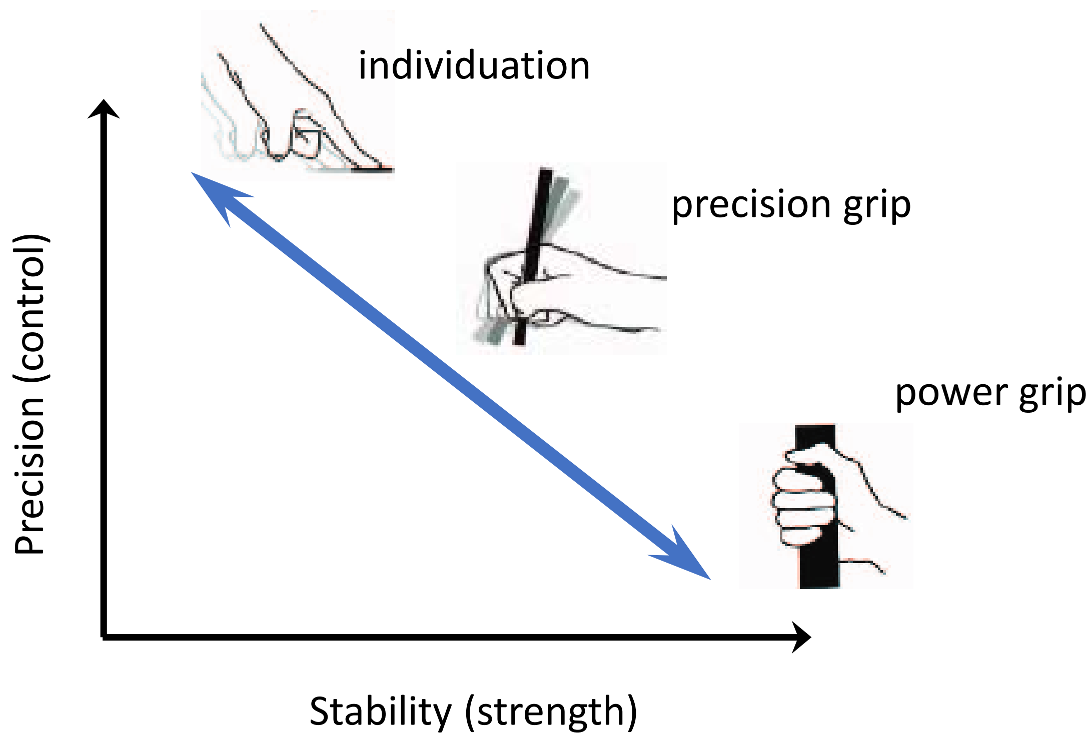
The hand after stroke

Jing Xu

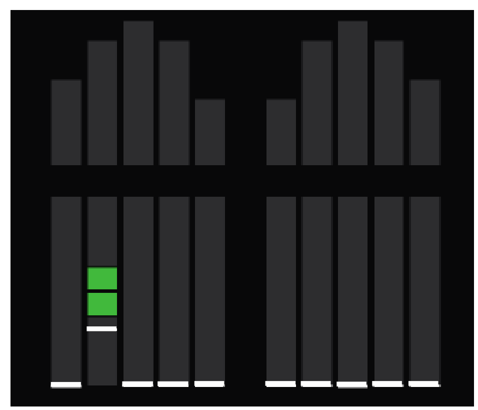
Taxonomy of hand movements



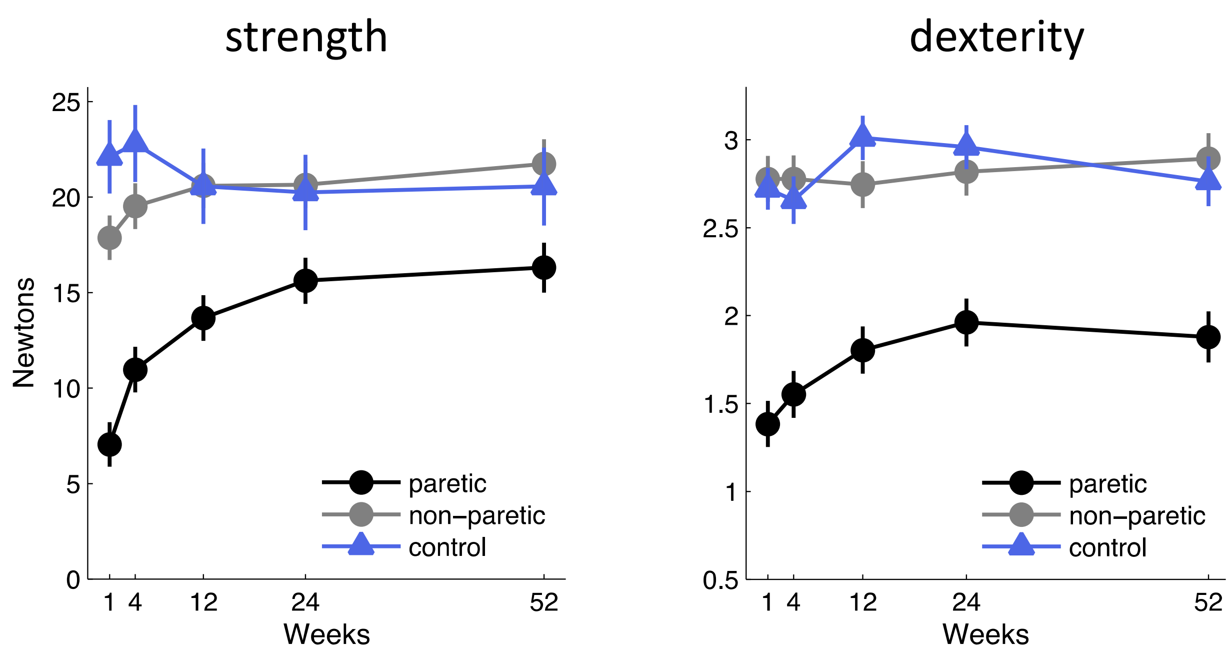
The individuation paradigm

Maximum Voluntary Contraction (MVC)

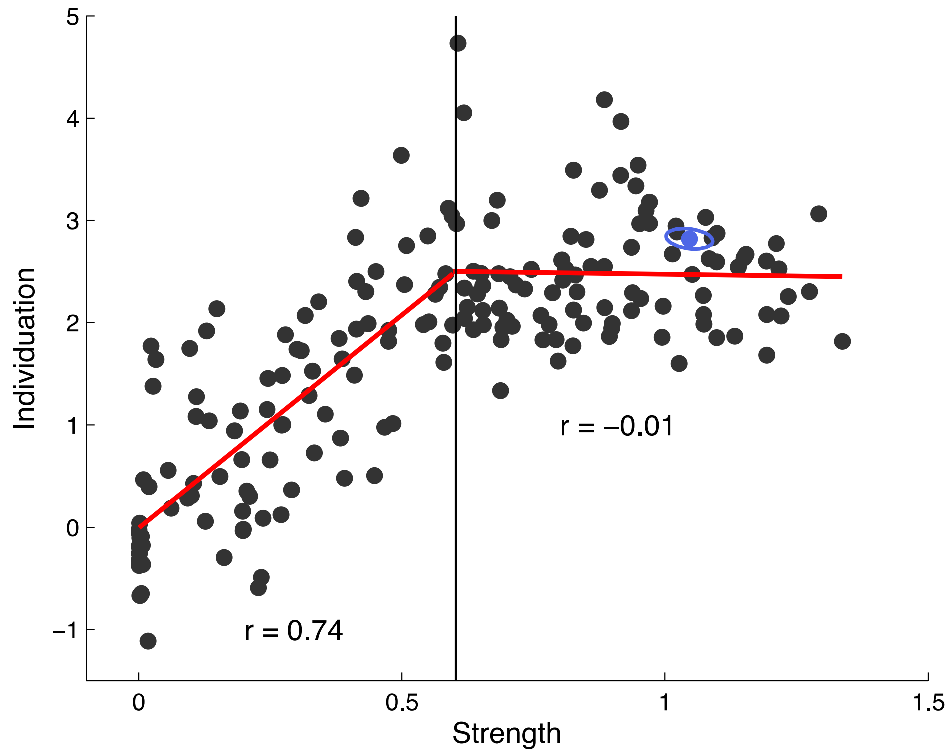
Individuation



Most recovery occurs in the first 3 months

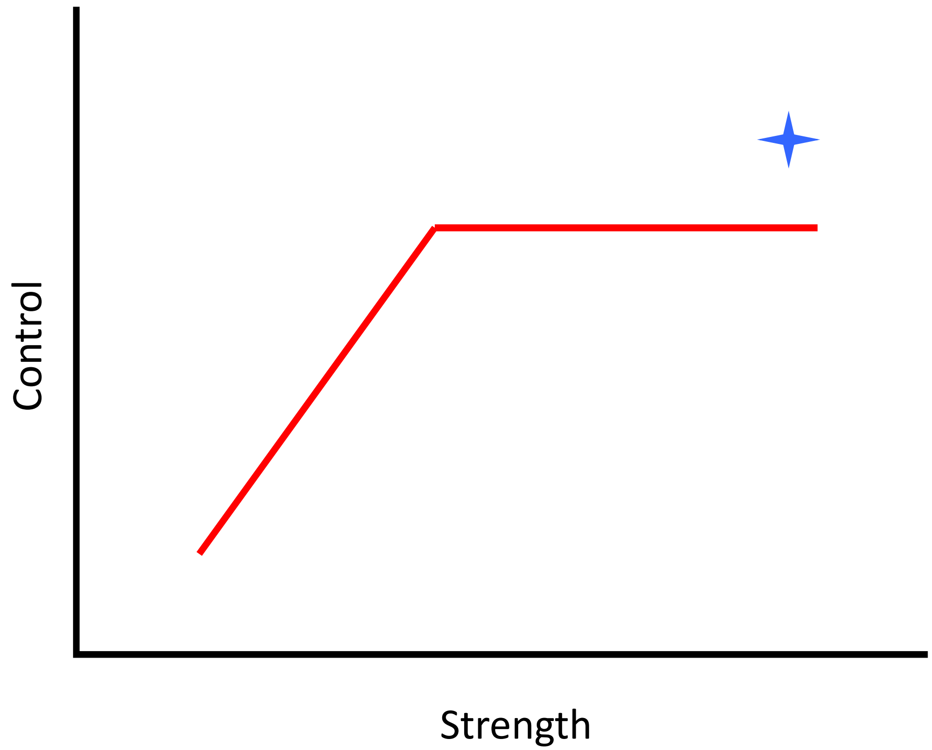


Patients N = 53
Controls N = 14

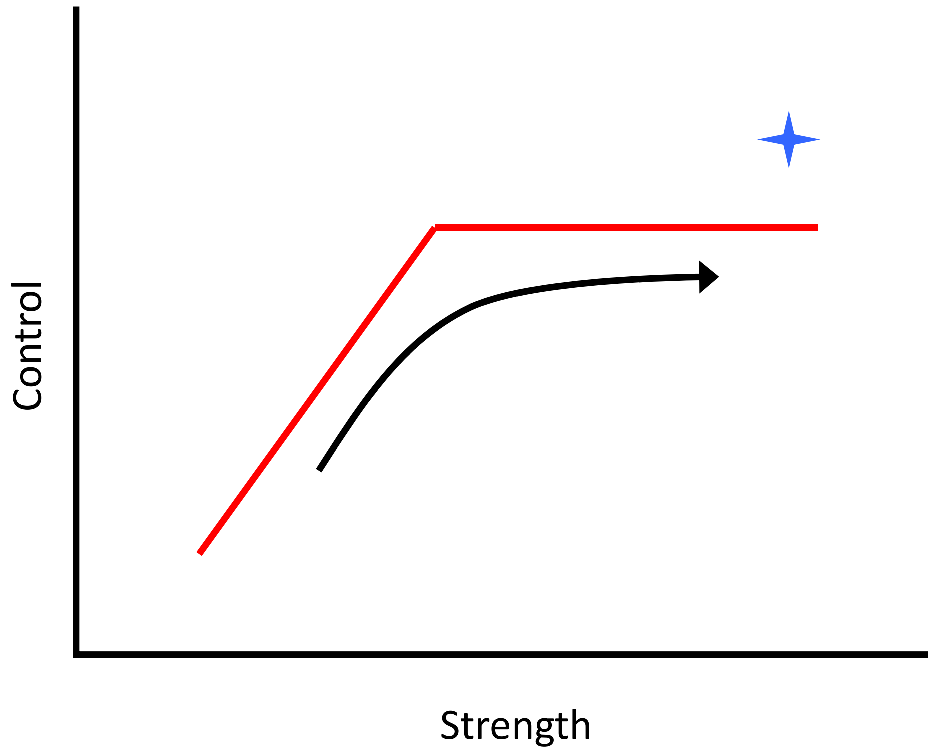


5
4
3
2
1
0
−1
Individuation
r = 0.74
r = −0.01
0
0.5
1
1.5
Strength

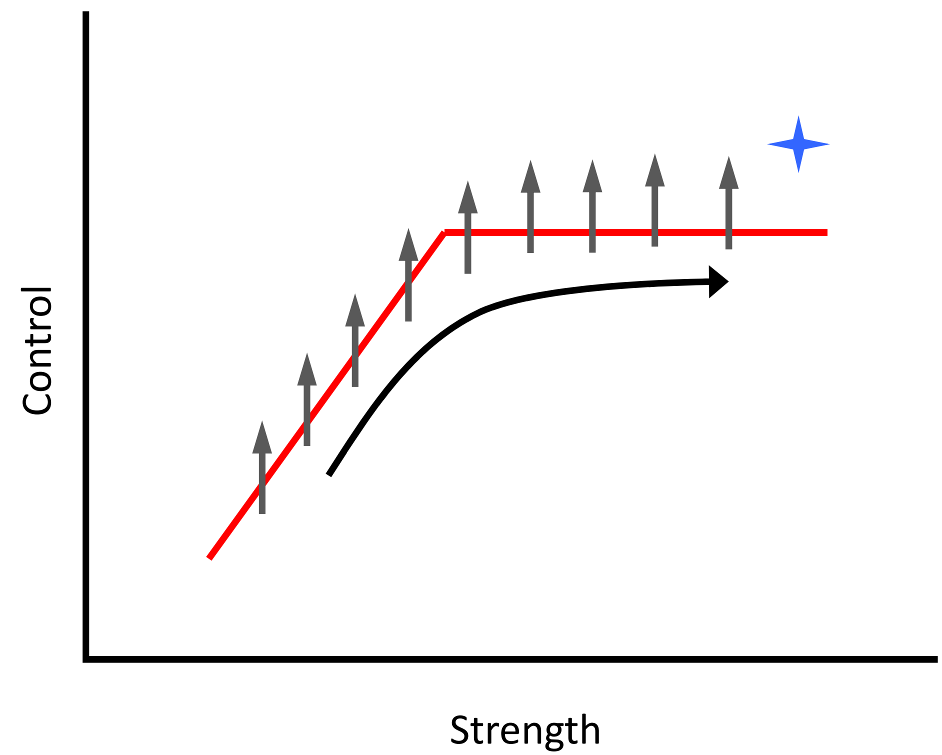
Time-invariant relationship between strength and control

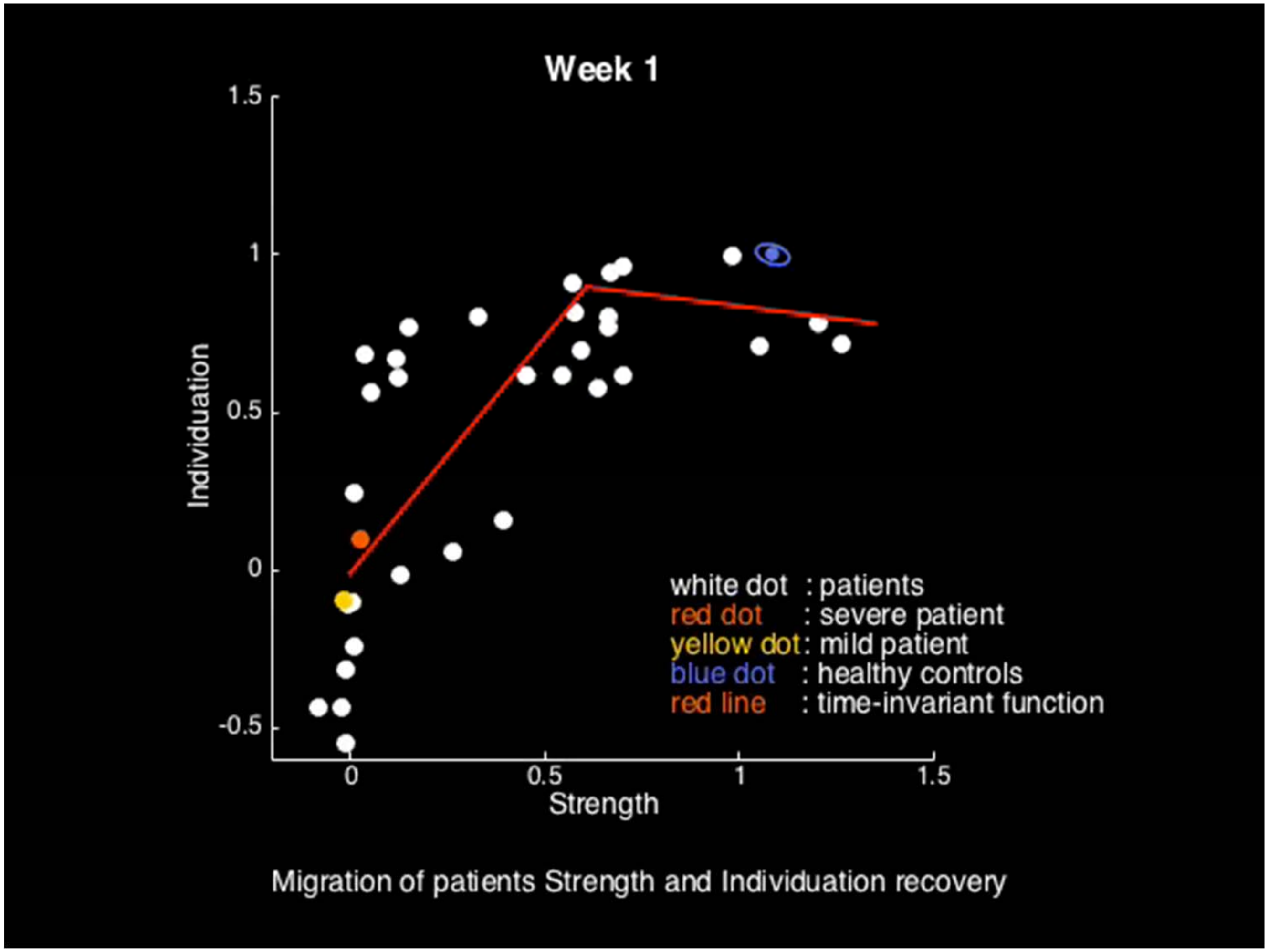


Main recovery traverses the time-invariant function

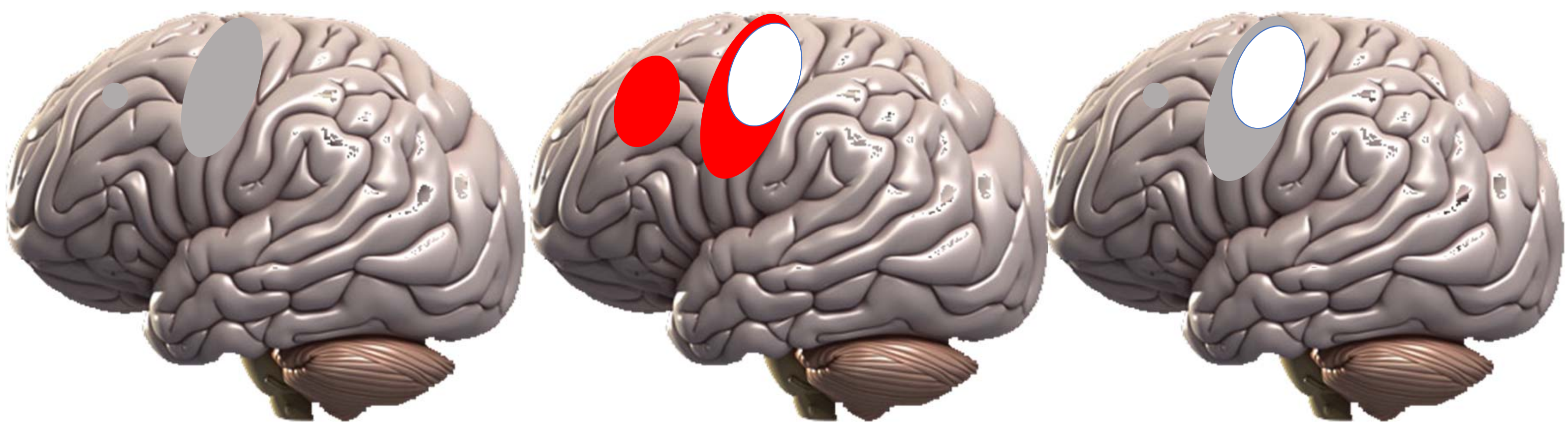


Two recovery systems for strength and control




Week 1
1.5
1
0.5
0
-0.5
Individuation
0
0.5
1
1.5
Strength
white dot : patients
red dot : severe patient
yellow dot: mild patient
blue dot : healthy controls
red line : time-invariant function
Migration of patients Strength and Individuation recovery

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)

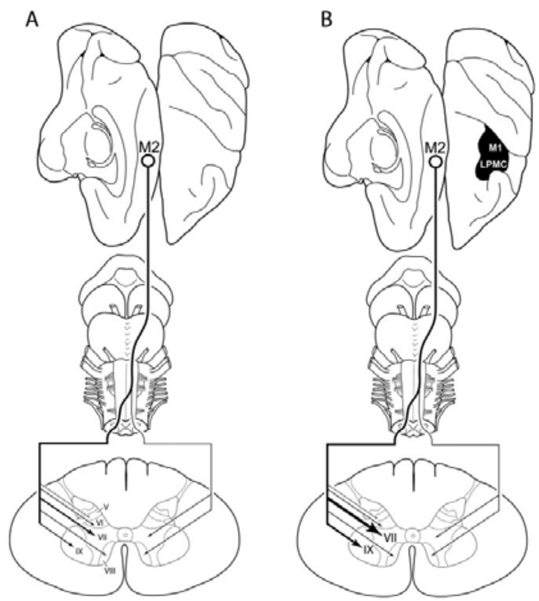
Changes in motor cortical excitability
Bestmann & Krakauer 2015; Stinear et al 2017

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)*

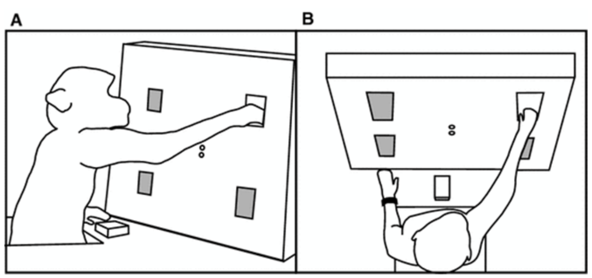
Hence: NIBS (TMS and tDCS) and Robotics also likely to have minimal therapeutic use

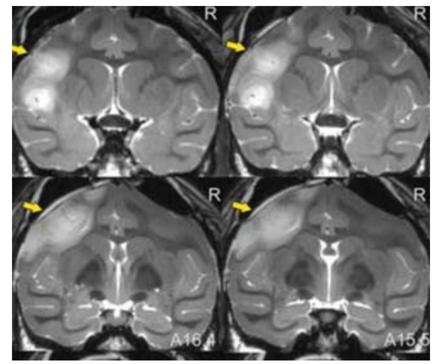
Cortico-subcortical changes a more plausible mechanism for recovery : selective long-term facilitation of the corticospinal projection from SMA following recovery from lateral motor cortex injury

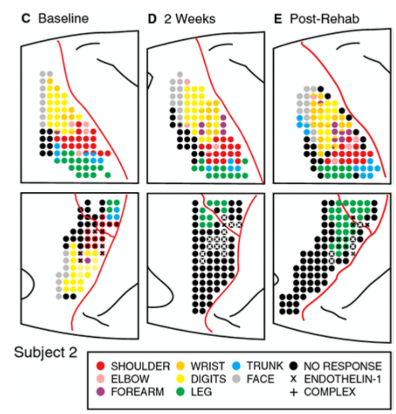


Journal of Comparative Neurology
Volume 518, Issue 5, pages 586-621, 16 SEP 2009 DOI: 10.1002/cne.22218
http://onlinelibrary.wiley.com/doi/10.1002/cne.22218/full#fig13

Another example of subcortical reorganization

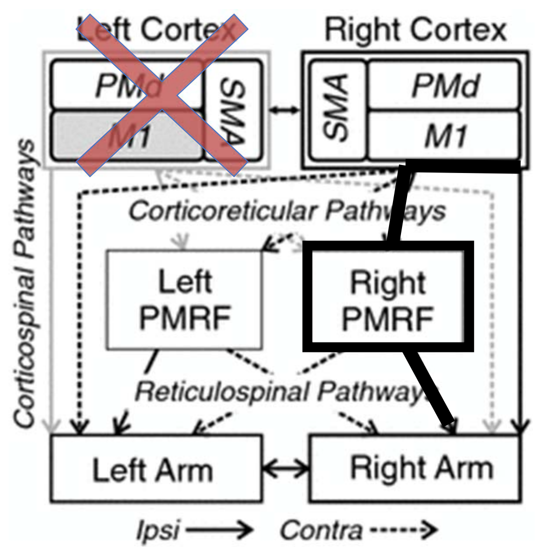






Herbert et al. 2015

Recovery via cortico-subcortical interactions



Herbert et al. 2015

A Model of Recovery

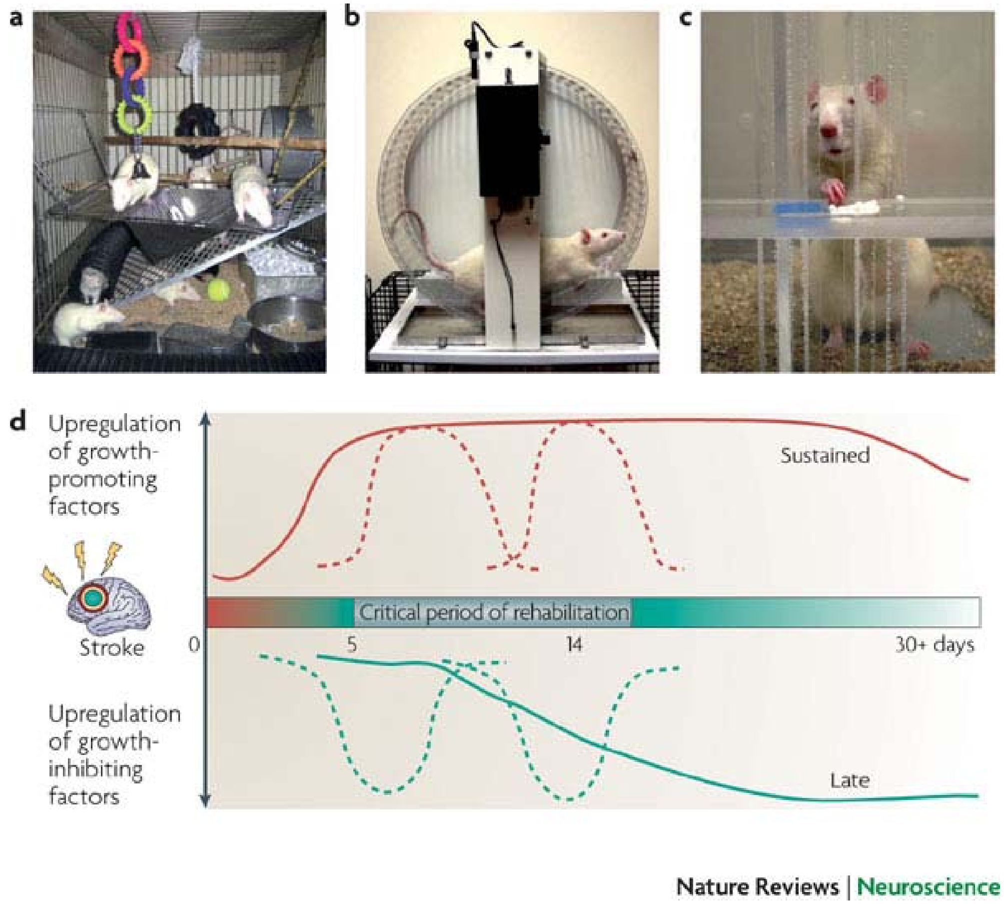
$$Restitution_{[magnitude]} = Behavior_{[dose]} \times Representation_{[residual\ amount]} \times Plasticity_{[level]}$$

Broken Movement: The neurobiology of motor recovery after stroke
Krakauer & Carmichael (MIT press, 2017)

Spontaneous biological recovery & responsivity to training: incomplete knowledge

	SBR	Increased Responsiveness to Training
Rodent	?	✓
Non-human Primate	✓	✓
Humans	✓	?

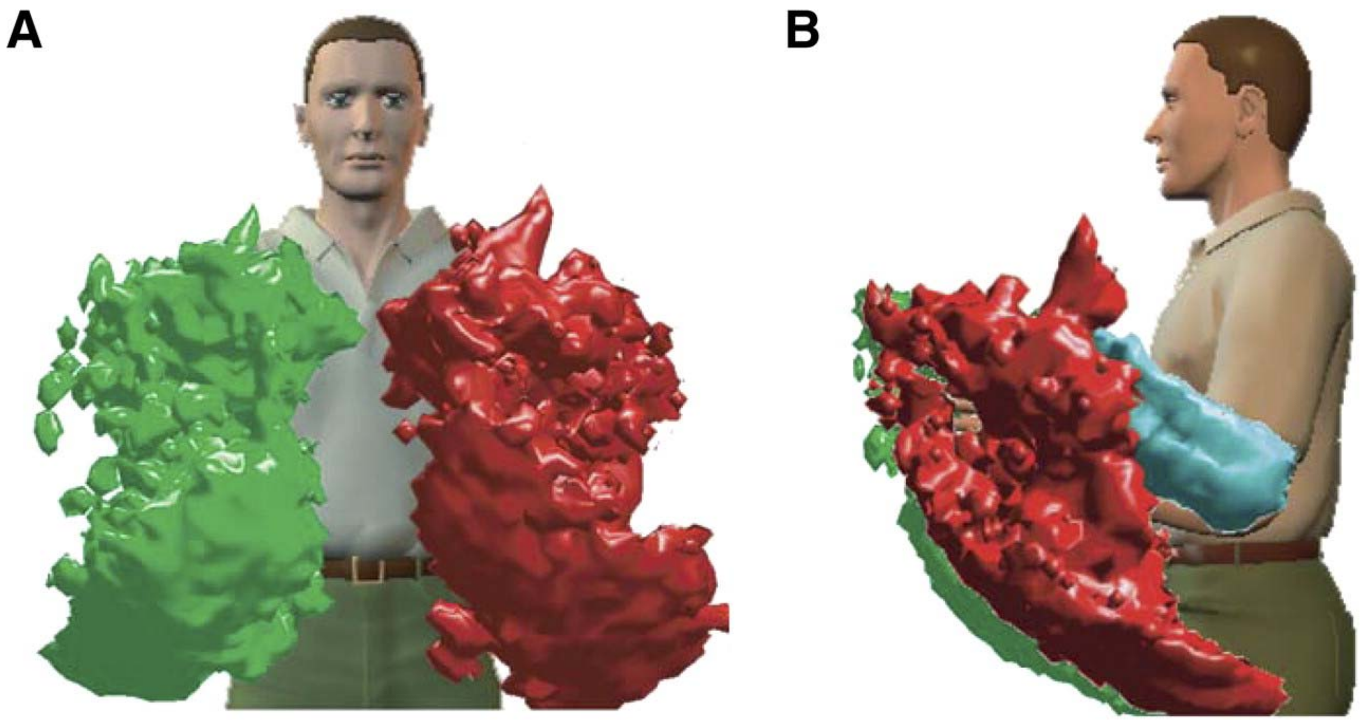
Enriched, playful environments promote general motor recovery



"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



Ian S. Howard et al. J Neurophysiol 2009;102:1902-1910

Journal of Neurophysiology

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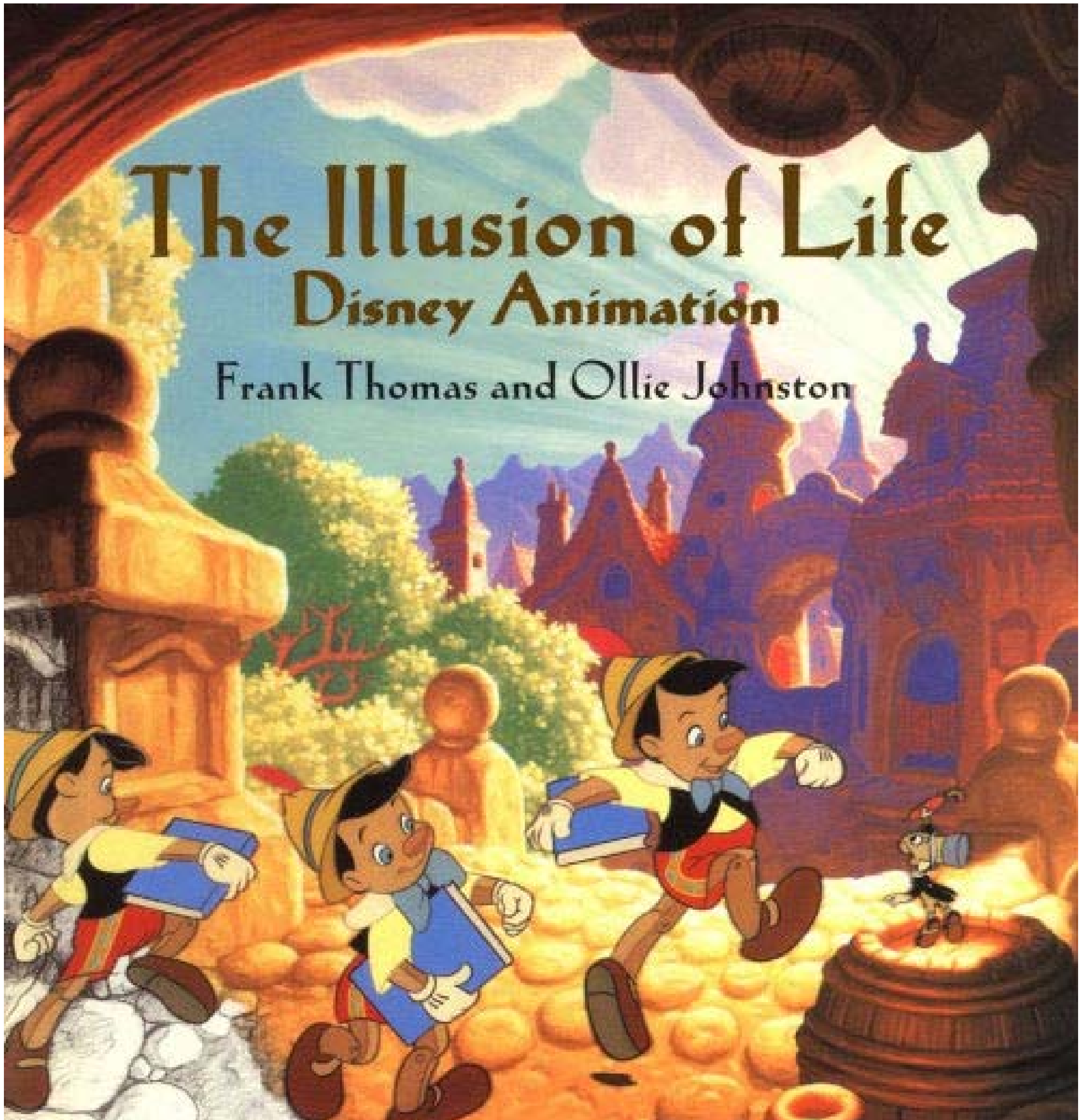
- What would an enriched environment for patients look like ?
- How should we promote playful non-task based exploratory behavior ?



The Illusion of Life
Disney Animation
Frank Thomas and Ollie Johnston

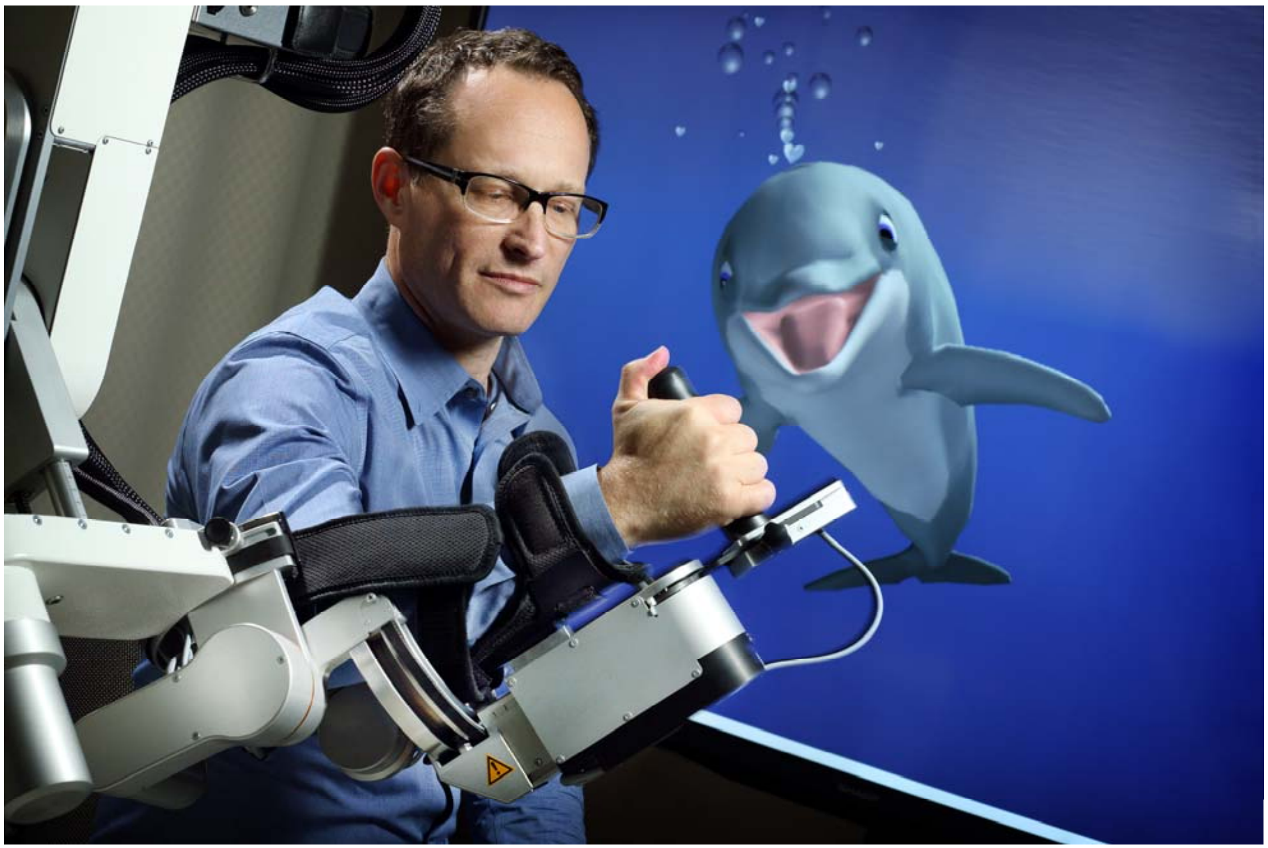
SMARTS II

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)

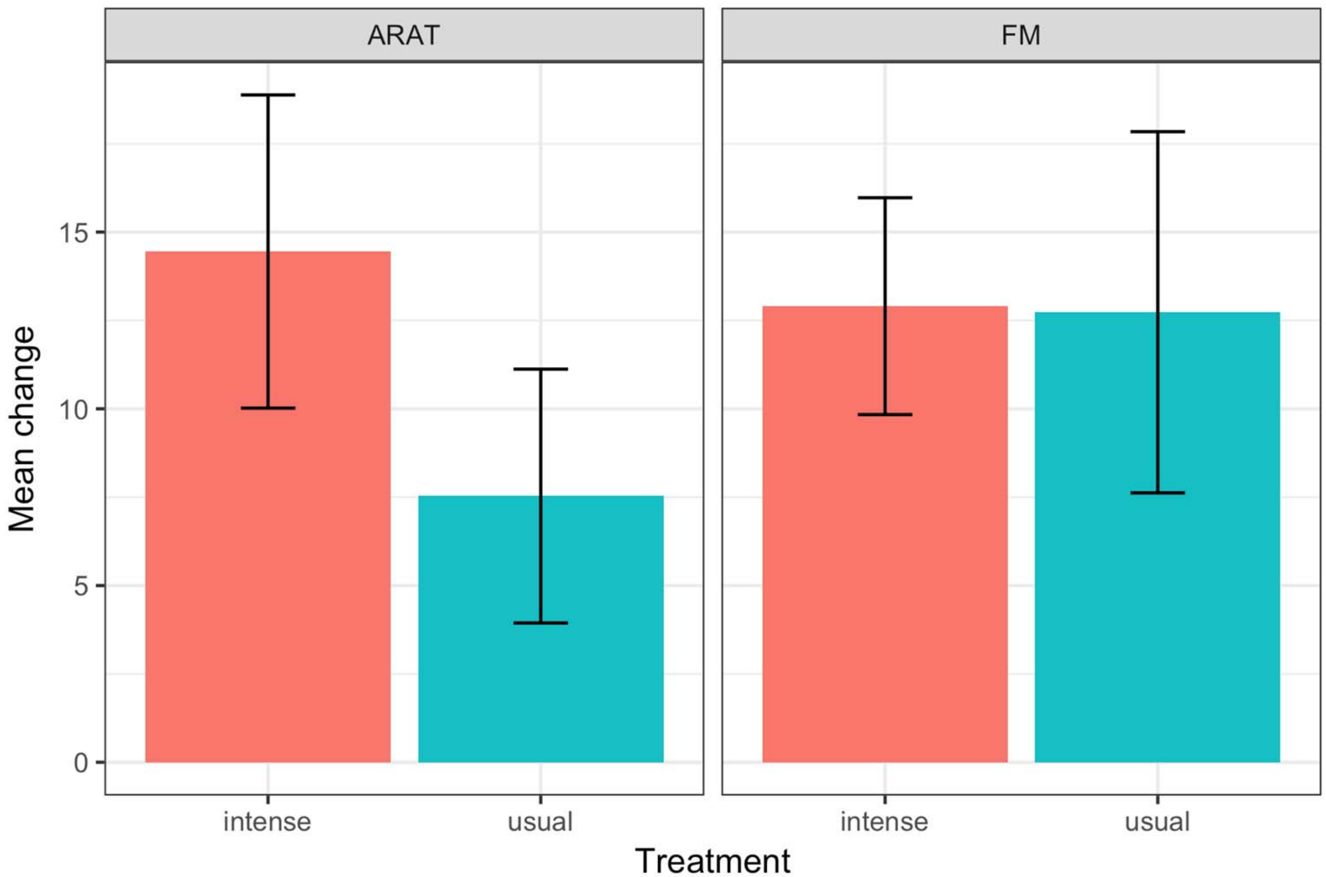
3-day Post-intervention Assessments

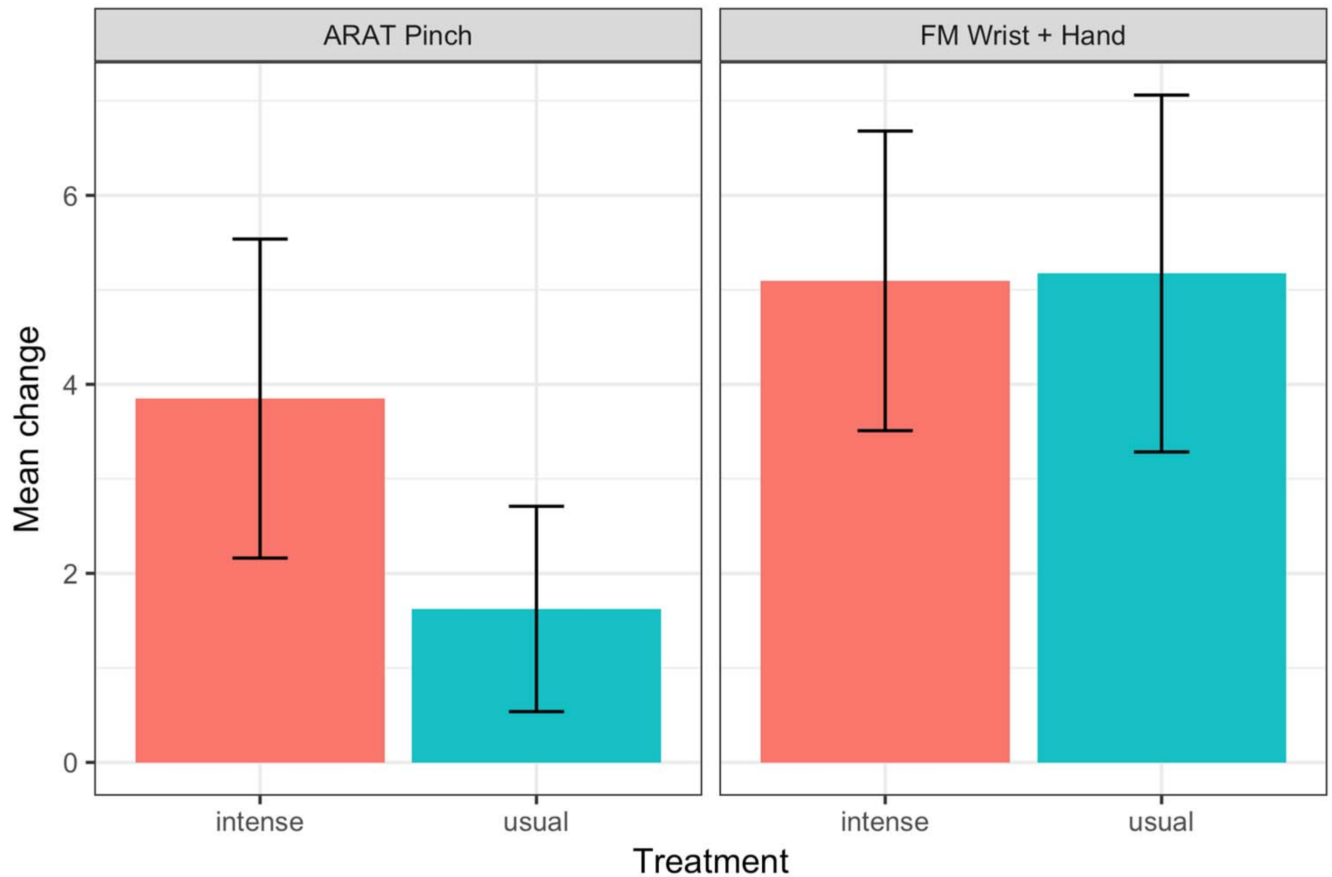
Day 30 Assessments

Day 60 Assessments

Day 90 Assessments

PRELIMINARY SMARTS 2 RESULTS




ARAT Pinch
FM Wrist + Hand
Mean change
0
2
4
6
intense
usual
intense
usual
Treatment

RESEARCH ARTICLE

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,[1,2,3] Michael J. Strube, PhD,[4]
Marghuretta D. Bland, PT, DPT, MSCI,[1,2,3] Kimberly J. Waddell, MSOT, OTR/L,[1]
Kendra M. Cherry-Allen, PT, DPT,[1] Randolph J. Nudo, PhD,[5]
Alexander W. Dromerick, MD,[6] and Rebecca L. Birkenmeier, OTD, OTR/L[1,2,3]

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.

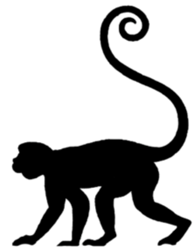
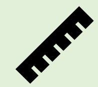
ANN NEUROL 2016;80:342–354

	Acute	Chronic
ARAT	↑	↑
FMA	–	↑

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 at 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)**

						
						
Motor Control	✓	✓	✓	✓	✓	?
Strength	✓	✓	✓	✓	✓	✓
Synergy	N/A		N/A		✓	?
Compensation	✓	✓	✓	✓	✓	✓

Andi Luft

Tomoko Kitago

Pablo Celnik

Joern Diedrichsen

Omar Ahmad
Amy Bastian
Meret Brandscheidt
Kelly Casey
Juan Camilo Cortes
Sandra Deluzio
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Jing Xu
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National Institute of Neurological Disorders and Stroke

James S. McDonnell Foundation

Orentreich Foundation for the Advancement of Science, Inc.

NSF

Johns Hopkins Malone Center for Engineering in Healthcare

BSi Brain Science Institute Johns Hopkins Medicine

Johns Hopkins Medicine School of Medicine

The Johns Hopkins University Science of Learning Institute