Brain Repair After Stroke

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Main points

• Spontaneous recovery after stroke
• Therapies to improve recovery--brain repair
• Variability in response to restorative stroke therapies
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• Variability in response to restorative stroke therapies
Molecular and cellular events underlying stroke recovery

**Ipsilesional changes**
- inflammatory markers
- growth-associated proteins
- cell cycle proteins
- growth factors
- GABA receptor downregulation
- NMDA receptor binding
- angiogenesis
- hyperexcitability & facilitation of LTP
- synaptogenesis
- dendrite branching/spine density
- neuronal sprouting
- extracellular matrix remodelling
- cortical thickness

**Contralesional changes**
- inflammatory markers
- growth-associated proteins
- GABA receptor downregulation
- NMDA receptor binding
- neuronal hyperexcitability
- dendrite branching/spine density
- synaptogenesis
- cortical thickness

Molecular/cellular changes: temporal course

Growth-promoting genes
*Li & Carmichael, Neurobiol Dis; 23:362*

Increased synaptogenesis
*Stroemer et al, Stroke; 29:2381*

Increased dendrite branches
*Jones & Schallert, Brain Res 581:156*
Molecular/cellular changes: temporal course
Molecular/cellular changes: temporal window

Reperfusion, neuroprotection
Endogenous repair mechanisms at peak
Brain is galvanized for recovery

Neural repair remains accessible, but with dampened magnitude
Main points

• Spontaneous recovery after stroke

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Brain repair: a definition

Brain repair: restoring brain structure or function after injury
Potential human restorative therapies

- **Small molecules** eg, SSRIs, amphetamine, levodopa, niacin, memantine, etc
- **Growth factors** eg, EPO, hCG, G-CSF, b-FGF, OP-1, etc
- **Monoclonal Ab** , other large molecules eg, anti-MAG Ab
- **Stem cells**
- **Brain stimulation** eg, TMS, tDCS, tACS, epidural stim, deep brain stim; vagal nerve stim
- **Telemedicine**
- **Intensive physiotherapy, robotics, other training**
- **Lesion bypass** eg, BCI, nerve transfer
- **Motor imagery, observation, environmental enrichment, other cognitive Rx**
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Double-blind, placebo-controlled trial of 118 patients enrolled 5–10 after stroke to 20 mg fluoxetine or placebo QD x 3 mo

Baseline NIHSS = 13, but severe weakness

Primary endpoint outcome: Larger Fugl-Meyer score change with fluoxetine (34 vs. 24 points, p=0.003)

Also: significant effect for mRS (% ≤ 2) but not NIHSS (% ≤ 5)
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Motor deficits are a major contributor to post-stroke disability.

Animal studies with favorable plasticity use high rehab doses.  
(600 repetitions of pellet retrieval/day, Nudo 1996)

In humans, higher rehab therapy doses may improve outcomes.
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In humans, higher rehab therapy doses may improve outcomes.

**Quantity** of rehab therapy often low in humans, however:
(1) financial constraints
(2) patient can’t travel to a rehab therapy provider
(3) shortage of rehabilitation care in some regions
(4) poor patient compliance with assignments
(5) limited dose during stroke rehabilitation
(mean of 32 arm repetitions/session, Lang 2009)

Unmet need: delivery of large doses of rehab therapy
During inpatient or outpatient stroke rehabilitation, the mean # functional UE repetitions per session was 32.
Quality of rehab also important; greater plasticity when a task is
(1) challenging and varied
(2) accompanied by appropriate feedback
(3) motivating and goal-oriented
(4) interesting
(5) environmentally and ecologically relevant
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We reasoned that telerehabilitation is ideally suited to efficiently provide a large dose of useful rehab therapy after stroke.
The team includes

Lucy Dodakian, MA, OTR/L
Alison McKenzie, PT, DPT, PhD
Walt Scacchi, PhD
Erin Burke
Renee Augsberger, OTR/L, MHA, C/NDT
Jutta Heckhausen, PhD
Vu Le, MS
Jill See, MPT
Robert Zhou
Steve Cramer, MD

Pilot Study Of Home-Based Telerehabilitation After Stroke
Eligibility

Patients had to be 3-6 months post-stroke; could have mild, moderate, or severe arm weakness (FM score 22-55)

Treatment

We delivered and assembled our system to their home.

Each subject received 28 days of telerehabilitation.

Each day consisted 1 hour that was required and structured, plus 1 optional hour of free play.

Plus 3 videoconferences per week
Today's Itinerary

☐ 1. Play the "Piano" game.
☐ 2. Play the "Drum" game.
☐ 3. Play the "Targetting" game.
☐ 4. Play the "Space Invaders" game.
☐ 5. Play the "Driving" game.
☐ 6. Play the "Plinko" game.
☐ 7. Play the "Blackjack" game.
☐ 8. Play the "Slots" game.
☐ 9. Play the "Poker" game.
☐ 10. Play the "Carnival Shooting" game.
☐ 11. Play the "Duck Hunt" game.
☐ 12. Play the "Simon" game.
☐ 13. Play the "Mimic" game.
☐ 14. Play the "Put It There" game.
☐ 15. Play the "Memory" game.
Compliance was excellent
Subjects engaged in therapy 329 of 336 (97.9%) assigned days.

Improved arm movement
FM score started at 39 ± 12 (range 23-55), increased by 4.8 ± 3.8 points (p=0.0015); met clinically important difference in 6 of 12.

Findings not dependent on computer skills
Computer literacy scores declined with age (r = -0.92, p<0.0001), but were not related to arm motor gains or to home compliance.

Holistic care in parallel
--Daily education increased stroke knowledge by 39% (p=0.001)
--Videoconference screen detected depression in 3/12 patients
--Home BP measurement validated (r = 0.99; p<0.0001)

Dodakian et al, Neurorehab Neural Repair. 2017; 31:923-933
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Average of 24,607 arm repetitions over 28 days

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

124 subjects with stroke 4-36 weeks prior and arm motor deficits

Randomized at 11 US sites to intensive arm motor therapy
(a) traditional In-Clinic, versus
(b) in-home Telerehabilitation

Treatment
36 sessions (18 superv’d, 18 unsuperv’d), 70 min, over 6-8 wk
Intensity, duration, and frequency of therapy matched

Assessor-blind, randomized, non-inferiority design

clinicaltrials.gov NCT02360488
FDA: non-significant risk device study
Telerehabilitation

Transfer Object

Grasp and hold object with one hand. Transfer object to other hand. Reverse. Use objects of different shapes, sizes and weight.

In the past week of arm-related therapy you have been doing as part of this research study, how satisfied are you with the therapy?

I find the tasks/games:

Very understandable: 1 2 3 4 5 6

Very understandable.

Score: 5

Time: 125

Score: 0

Time: 127

Score: 8

Time: 21

Score: 0

Time: 106
Results
Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

University of California, Irvine
Kessler Institute for Rehabilitation
Case Western Reserve University
Burke Medical Research Institute
University of California, San Diego
Brooks Rehabilitation
Northwestern University
University of Washington
Medical University of South Carolina
Harvard University
Emory University

clinicaltrials.gov NCT02360488
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Stroke

*Origin:*
1250–1300; Middle English *strok, strak* (noun), probably continuing Old English *strāc*
Stratifying Patients With Stroke in Trials That Target Brain Repair

Steven C. Cramer, MD

Abstract—A number of therapies are emerging that have the potential to reduce poststroke disability by promoting repair. Careful evaluation of patients with stroke might help distinguish those who are most likely to respond to a restorative therapy from those who lack biological substrate needed to achieve gains. Potential approaches to such stratification are considered, including measures of brain injury or of poststroke brain function. (Stroke. 2010;41[suppl 1]:S114-S116.)
Many factors can affect the outcome after stroke

- pre-stroke disability
- genetics
- age
- handedness
- medical co-morbidities
- initial and final deficits
- injury: location, side, mechanism, volume
- brain function
- acute stroke interventions
- time post-stroke
- post-stroke depression
- medications (+ and -)
- caregiver, social factors
- quantity, quality, and timing of post-stroke therapy
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Brain injury predicts gains in a clinical trial

Measuring extent of corticospinal tract injury to stratify patients

Riley et al, Stroke; 2011
Brain injury predicts gains in a clinical trial

Extent of injury to this key wire bundle predicted treatment gains
(better than global injury, baseline behavior, demographics, etc)

Riley et al, Stroke; 2011

$r = -0.65$
$p < 0.005$
Dense array EEG

256 leads
Data collection feasible in ER, ICU, rehab unit, etc
From “hello” to start data collection in 5 minutes
Current methods require only 3 minutes of data collection
Brain function predicts gains from 4 wks telerehabilitation

PLS model predicting UE-FM score change

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Pattern of \( \beta \) coherence predicts motor gains over subsequent 4 wks

\[ r^2 = 0.61 \]
\[ p = 0.0099 \]

Brain function predicts gains from 4 wks telerehabilitation

3 minutes of resting dense array EEG:
a rapid, inexpensive, easy, bedside, safe test of brain function

PLS model predicting UE-FM score change

Pattern of $\beta$ coherence predicts motor gains over subsequent 4 wks

$r^2=0.61$
$p=0.0099$
Polygene score

Most genetic effects have RR in range of 1.1-1.4; effect of any single gene is generally small--ApoE is a major exception.
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Example: in a study of 5 SNPs associated with prostate cancer, risk of disease associated with increasing # risk alleles:
OR = 1.6 with risk allele at 1 SNP, OR = 4.5 with 4 risk alleles

The many proteins of the dopamine system
The many proteins of the dopamine system

rs4680
rs28363170
rs4532
rs1800497
rs6280

Nemoda et al. Neurosci Biobehav Rev 35:1665–1686; 2011
Dopamine gene score

Construct a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine.
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Hypothesized subjects with lower dopamine neurotransmission would have:
- less learning
- greater boost in learning with L-Dopa
- more depression
- poorer impulse control, greater improvement with Ropinirole.
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Genetic Variation in the Human Brain Dopamine System Influences Motor Learning and Its Modulation by L-Dopa

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Day 1 2 3 4 5 6 7 8 9 10

2 week washout

Legend
- TMS
- Baseline assessments
- Pill intake
- Skilled task practice

Pearson-Fuhrhop et al PLOS-ONE 2013
Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

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a Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
b Department of Women’s and Children’s Health, Karolinska Institutet, Astrid Lindgren Children’s Hospital, Stockholm, Sweden
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Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

Kristin M. Pearson-Fuhrhop¹, Erin C. Dunn²,³,⁴,⁹, Sarah Mortero¹, William J. Devan², Guido J. Falcone², Phil Lee²,³,⁴, Avram J. Holmes³,⁵, Marisa O. Hollinshead⁶, Joshua L. Roffman³, Jordan W. Smoller²,³,⁴, Jonathan Rosand²,⁷,⁸, Steven C. Cramer¹,⁹,*
Lower dopamine gene scores, i.e. lower dopamine neurotransmission, associated with greater depression scores.

Pearson-Fuhrhop et Dunn et al PLOS-ONE 2014
Main points

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