Brain Repair After Stroke

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Disclosures
Dr. Cramer serves as a consultant for MicroTransponder, Dart Neuroscience, Neurolutions, Regenera, Abbvie, SanBio, and TRCare.

Main points
- Spontaneous recovery after stroke
- Therapies to improve recovery--brain repair
- Variability in response to restorative stroke therapies
Main points

- Spontaneous recovery after stroke
- Therapies to improve recovery—brain repair
- Variability in response to restorative stroke therapies

Molecular and cellular events underlying stroke recovery

<table>
<thead>
<tr>
<th>Individual changes</th>
<th>Contralateral changes</th>
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<tbody>
<tr>
<td>Inflammatory markers</td>
<td>Anti-inflammatory markers</td>
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<tr>
<td>Growth-associated proteins</td>
<td>Growth-associated proteins</td>
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<td>Cell cycle proteins</td>
<td>Cell cycle proteins</td>
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<tr>
<td>GABA receptor downregulation</td>
<td>NMDA receptor binding</td>
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<tr>
<td>Neuronal hyperexcitability</td>
<td>Hyperexcitability</td>
</tr>
<tr>
<td>Dendrite branching/spine density</td>
<td>Increased synaptogenesis</td>
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<tr>
<td>Neuronal sprouting</td>
<td>Cortical thickness</td>
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<tr>
<td>Extracellular matrix remodelling</td>
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</table>
Slide 7
Molecular/cellular changes: temporal course

Slide 8
Molecular/cellular changes: temporal window

Slide 9
Main points
• Spontaneous recovery after stroke
• Therapies to improve recovery—brain repair
• Variability in response to restorative stroke therapies
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, IDCS, IACS, 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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**Slide 13**

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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**Slide 14**

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**Slide 15**

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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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. 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.

**Slide 17**

Issues with quantity of rehab therapy after stroke

During inpatient or outpatient stroke rehabilitation, the mean # functional UE repetitions per session was 32.

**Slide 18**

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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5) Environmentally and ecologically relevant

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, MEd
Jutta Heckhausen, PhD
Vu Le, MS
Jill See, MPT
Robert Zhou
Steve Cramer, MD

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 of 1 hour that was required and structured, plus 1 optional hour of free play. Plus 3 videoconferences per week.

Dodakian et al, Neurorehab Neural Repair. 2012;29(1):17
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 of 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)

Average of 24,607 arm repetitions over 28 days
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 Telehabilitation
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

FDA: non-significant risk device study

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

clinicaltrials.gov NCT02360488
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

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Main points

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Slide 31

**Stroke**

Origin:
1250–1300; Middle English strok, strak (noun), probably continuing Old English strāc

www.dictionary.com

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Slide 32

- Study power
- Sample size
- Study duration
- Number of sites

Cramer SC. Stroke. 2010

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Slide 33

**Many factors can affect the outcome after stroke**

<table>
<thead>
<tr>
<th>pre-stroke disability</th>
<th>brain function</th>
</tr>
</thead>
<tbody>
<tr>
<td>genetics</td>
<td>acute stroke interventions</td>
</tr>
<tr>
<td>age</td>
<td>time post-stroke</td>
</tr>
<tr>
<td>handedness</td>
<td>post-stroke depression</td>
</tr>
<tr>
<td>medical co-morbidities</td>
<td>medications (+ and -)</td>
</tr>
<tr>
<td>initial and final deficits</td>
<td>caregiver, social factors</td>
</tr>
<tr>
<td>Injury: location, side, mechanism, volume</td>
<td>quantity, quality, and timing of post-stroke therapy</td>
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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

Brain injury predicts gains in a clinical trial:

Measuring extent of corticospinal tract injury to stratify patients (May et al., Stroke 2011)

Extent of injury to this key wire bundle predicted treatment gains (better than global injury, baseline behavior, demographics, etc.) (May et al., Stroke 2011)
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

Pattern of δ coherence predicts motor gains over subsequent 4 wks

Wu et al. Brain 2015; 1D8:1299-3299
Slide 40

Brain function predicts gains from 4 wks telerehabilitation

PLS model predicting UE-FM score change

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

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

\[ r^2 = 0.61 \]

\[ p = 0.0099 \]

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

PLS model predicting UE-FM score change

Brain function predicts gains from 4 wks telerehabilitation

Coherence (20–30 Hz) with L M1 predicts motor learning: 

\[ A-B \] after target-directed training in HC

\[ C-D \] after visuomotor training in HC

\[ E \] after chronic stroke (r\(^2\) = 0.37, M\(_1\)-PAR)

\[ J \text{ Neurophysiol.} \ 2018;119:490-498 \]

\[ \text{Neuroimage.} \ 2014;91:84-90 \]

\[ \text{Front Neurol.} \ 2018 \text{ Jul 24;9:597} \]

Slide 41

Brain function predicts gains from training

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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.

\[ A \text{ et al, JAMA 2009; Zheng et al, NEJM, 2008} \]
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.

Thus interest in combining effect of many genes in polygenic models that assign points for the presence of risk alleles and calculates an overall risk of disease

Example: in a study of 5 SNPs associated with prostate cancer.

<table>
<thead>
<tr>
<th>Risk Alleles</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>1 SNP</td>
<td>1.6</td>
</tr>
<tr>
<td>4 SNPs</td>
<td>4.5</td>
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The many proteins of the dopamine system
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滑 46

Dopamine gene score

滑 47

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

滑 48
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Constructed a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine.

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Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

Lower dopamine gene scores, i.e. lower dopamine neurotransmission, associated with greater depression scores.

Pearson-Fuhrhop et Dunn et al PLOS-ONE 2014

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