Optimizing Stroke Recovery: Insights from Basic Science

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Overview

Learning Objectives:

1. An understanding of the biological recovery processes contributing to spontaneous and rehabilitation-induced post-stroke recovery

2. A better appreciation of how the timing and intensity of rehabilitation affect recovery

3. Some insights into why recovery plateaus after several months and what might be done to prevent this from occurring
Stroke is a Disease of Chronic Disability

- ~62,000 strokes per year in Canada
- At least 405K Canadians living with consequences of stroke\(^1\)
- Incidence of stroke expected to increase by 80% by 2038 (i.e. 650-725K)\(^1\)
- Nearly 50% have chronic disabilities at 6 mo\(^2\)
- Many patients after making initial functional gains show progressive decline over time

\(^1\) Krueger et al, Stroke, 2015
\(^2\) Teasell et al Exper Rev Neurother, 2014
Treating Upper Limb Dysfunction

Ploughman & Corbett, Arch Phys Med Rehabil, 2004
Is the Rat a Suitable Model for Studying Upper Limb Recovery?
Rat Model of Upper Limb Recovery
MCA = Middle Cerebral Artery

ET-1 Stroke Model
Staircase Reaching Test
Brain Plasticity Offers New Hope

• Historically thought that brain damage was irreversible, little hope for significant recovery

• This pessimistic view is changing due to discoveries in Neuroscience concerning neuroplasticity

• Neuroplasticity: Adaptive changes in response to injury and experience (e.g. sprouting of new connections, neurogenesis, angiogenesis)

• Harnessing neuroplasticity to dramatically improve stroke recovery is the new frontier in stroke research
Environmental Enrichment

Enrichment increases – Growth factors, dendritic growth, synaptogenesis, neurogenesis, angiogenesis & cortical thickness
Enriched Housing + Daily Reach Training = Enriched Rehab (ER)
Structural Remodeling of Layer V Motor Neurons

<table>
<thead>
<tr>
<th>Rehab Day</th>
<th>Trough Fill</th>
<th>Paw Availability</th>
<th>Trough Height</th>
<th>Trough Distance (away from wall)</th>
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<tbody>
<tr>
<td>1-3</td>
<td>Full</td>
<td>Both</td>
<td>4 cm</td>
<td>0 mm</td>
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<tr>
<td>4-5</td>
<td>Full</td>
<td>Both</td>
<td>4 cm</td>
<td>0 mm</td>
</tr>
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<td>Impaired Only</td>
<td>4 cm</td>
<td>0 mm</td>
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<td>Half</td>
<td>Impaired Only</td>
<td>13 cm</td>
<td>0 mm</td>
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<td>13-16</td>
<td>Half</td>
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<td>17-20</td>
<td>Half</td>
<td>Impaired Only</td>
<td>5 cm</td>
<td>6.4 mm</td>
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</tbody>
</table>
The Critical Period for Stroke Recovery

Murphy & Corbett, Nat Neurosci Rev, 2009
Inactive & Alone

In first few weeks after stroke people are alone ~60% of the time

- During waking hours they were inactive ~75% of the time (resting in bed or sitting)

  * Lack of stimulation, exercise & socialization is striking

Bernhardt et al., Stroke, 2004
Does Amount of Rehab Affect Recovery?

5 stroke groups given different amounts of post-stroke reaching practice

- Light STD  
  - n = 7

- Light ER  
  - n = 8

- Dark STD  
  - n = 7

- Dark ER Limited  
  - n = 8

- Dark ER Unlimited  
  - n = 9

STD = standard social housing

ER = Enriched rehab

Crystal MacLellan, PT, PhD
Enriched Rehabilitation

Rats housed in EE & have access to reach training apparatus 4 hr/day, 5 days per week
Cylinder Test  Montoya Staircase Test
Intensity of Rehabilitation Matters!

A

Reaching Success in Staircase Task

Contralateral Forelimb Reaching Success (% Baseline ± SEM)

- Dark STD
- Dark ER Lim
- Dark ER Unlim

Test Session (Post-MCAo)

6 Days 3 Weeks 5 Weeks 7 Weeks

B

Limb Use in Cylinder Task

Contralateral Forelimb Use (% ± SEM)

- Dark STD
- Dark ER Lim
- Dark ER Unlim

Test Session (Relative to MCAo)

Baseline 6 Days 3 Weeks 5 Weeks 7 Weeks

MacLellan et al. Neurorehab & Neural Repair, 2011
Increases in BDNF Levels Mirror Recovery

A

BDNF in the Contralateral Forelimb Motor Cortex

B

BDNF in the Contralateral Hippocampus
Reaching Dose Response

![Graph showing the relationship between number of reaching sessions and reaches per day. The x-axis represents the number of reaching sessions (1 to 4), and the y-axis represents reaches per day. Error bars indicate variability.]

![Graph showing the relationship between average reaches per day and average % pellets retrieved. The x-axis represents average reaches per day (0 to 500), and the y-axis represents average % pellets retrieved (0 to 120). Data points are plotted along a curve.]
Rethinking Recovery Plateaus

• Birkenmeier, 2010 (NNR) reported that the average number of upper limb repetitions per therapy session in human studies is ~ 32, in animal studies often > 300

• “Animal doses” of reach training can be delivered to stroke patients in 1 hour therapy sessions

• The use of much more intensive rehabilitation therapies for stroke patients is strongly supported.
Reaching Quality

A. Step 5

- Standard
- Rehabilitation

B. Joint Angle (degrees)

C. Reaching Direction

D. Images showing movement trajectories
Kinematics of Reaching
Does Rehab Matter?

• Failure to see improved outcomes in recent ICARE RCT increased dose rehab study (Winstein et al, JAMA 2016) where additional rehab on top of usual practice failed to improve outcome

• Krakauer, Byblow and Kwakkel argue that level of recovery is mainly determined by spontaneous biological processes within the first weeks after stroke irrespective of rehab

• Recovery patterns seem to follow a 70% “proportionality rule”
Proportional Recovery Model for the Upper Extremity

- “At 3 months, patients should get ~70% of their maximum potential recovery back”\(^4\)

\[ \Delta \text{FMA-UE}_{\text{pred}} = 0.7(66 - \text{FMA-UE}_{\text{initial}}) \]

- Holds true for all ages, both genders and in countries with different rehab services

- Fails in a subset of patients with severe hemiparesis (FM<20)

Krakauer and Marshall, 2015\(^4\)
• Does the human proportional recovery rule and its biomarkers also apply to animal models? (construct validity)

• Can these biomarkers be used to create a predictive model of post-stroke recovery and does rehabilitation modulate this model? (treatment efficacy)

• Can manipulation of recovery biomarkers influence recovery as predicted by the model? (model validity)

• Can we use biomarkers of recovery to accurately prescribe individualized intensities that will generate significant recovery of function? (personalized medicine)
Dataset Composition

Data for experiments within the Corbett lab that met the following criteria were collated into a single master dataset:

• Subjects – male, Sprague-Dawley rats, N=672
• Focal ischemia – unilateral intracerebral endothelin-1 (ET-1)
• Functional assessment – staircase or single-pellet
• Assessment timeline – minimum of 3 measurements: pre-stroke, within 1 week post-stroke & final assessment no earlier than 3 weeks post-stroke
• Impairment – post-stroke performance outside of the 95% confidence interval of pre-stroke performance (final N=593)
Evidence for a Cross Species Biological Stroke Recovery Process

[Graph showing data points for Non-Fitters and Fitters with a scatter plot and trend lines.]
Rehab Matters for Severe Impairment

A. No Rehab

B. Rehab

C. "Fitters" Only

D.
Can we use biomarkers of recovery to accurately prescribe individualized intensities that will generate significant recovery of function? (personalized medicine)

\[
\text{Desired recovery} + (0.606 \times \text{PR}_{\text{Initial}}) + (0.037 \times \text{Infarct volume}) - 5.124 = \frac{0.011}{\text{Number of repetitions in rehabilitation required per day}}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Formula</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>What percentage of rats that <strong>recover</strong> actually <strong>achieve</strong> their prescription?</td>
<td>[\frac{\text{True positive}}{\text{True positive} + \text{False negative}}]</td>
<td>81.43%</td>
</tr>
<tr>
<td>Specificity</td>
<td>What percentage of rats that <strong>do not recover</strong> also <strong>do not achieve</strong> their prescription?</td>
<td>[\frac{\text{True negative}}{\text{True negative} + \text{False positive}}]</td>
<td>75.47%</td>
</tr>
<tr>
<td>Positive Predictive Value (PPV)</td>
<td>How likely is a rat that <strong>achieves</strong> the prescription to actually <strong>recover</strong>?</td>
<td>[\frac{\text{True positive}}{\text{True positive} + \text{False positive}}]</td>
<td>81.43%</td>
</tr>
<tr>
<td>Negative Predictive Value (NPV)</td>
<td>How likely is a rat that <strong>does not achieve</strong> the prescription to also <strong>not recover</strong>?</td>
<td>[\frac{\text{True negative}}{\text{True negative} + \text{False negative}}]</td>
<td>75.47%</td>
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How does our rehabilitation prescription relate to the original classification of fitters, non-fitters and decliners?

- Animals originally predicted to fit the proportional recovery rule always recover
  - These subjects may recover even without rehabilitation

- Non-fitters had the potential to either recover if they met their prescription or not recover if they failed to achieve it
  - Intensive therapy is most critical for this group

- Decliners never met their rehabilitation prescription and also never recovered
• Does the human proportional recovery rule and its biomarkers also apply to animal models? (construct validity)
  • Yes, a subset of animals (30%) show a recovery pattern that is not statistically different from that seen in humans

• Can these biomarkers be used to create a predictive model of post-stroke recovery and does rehabilitation modulate this model? (treatment efficacy)
  • Yes, initial impairment, infarct volume and rehabilitation intensity can be used to predict recovery of any animal that receives rehabilitation
  • Manipulating these factors influences recovery in the direction predicted by the model

• Can we use biomarkers of recovery to accurately prescribe individualized intensities of rehabilitation that will generate significant recovery of function? (personalized medicine)
  • Yes, it is possible to individually prescribe rehabilitation based on desired level of recovery, initial impairment and infarct volume
  • This prescription is accurate in ~75-80% of subjects
Upper Limb Recovery Plateaus - Human vs Rat

Why Does Recovery Stall?

Stroke Injury & Gene Changes

BDNF, Gap-43 and c-Jun

CSPG’s and NOGO

Murphy & Corbett, Nat Rev Neurosci 2009
Critical Period Plasticity

Plasticity appears to be gated by networks of PV+ neurons

Perineuronal nets (PNNs) are condensed ECM structures associated with mature PV+ neurons

Hensch 2014. *Cell.*
Perineuronal Nets (PNNs)

Extracellular matrix structures

Wrap around the soma and proximal dendrites

Critical for synaptic stabilization

Limits plasticity and counteracts regeneration

Disruption of PNNs can reactivate plasticity

Image credit: Jessy Livingston-Thomas and Matthew Jeffers
PNNs and Stroke

Disruption of PNNs in the ischemic core, the peri-infarct region and in more distal areas following stroke\(^5,6\)

- **Peri-infarct area** = PNNs start to recover by \(\sim\)30 days
- **Areas remote from infarct core** = PNNs restored as early as 1 week post stroke\(^6\)

\(^5\) Carmichael et al., 2005, \(^6\) Karetko-Sysa et al., 2011
RESULTS

PNN density in the Perilesional Area

n= 3/group

Striatal + Cortical group
Fluoxetine for Stroke Recovery

- The FLAME trial suggests that FLX may promote motor recovery after stroke, independent of its antidepressant action.
- Fluoxetine (FLX) reopens critical periods in adult animals and reduces the expression of PV and PNNs.

Summary & Conclusions

• Rehabilitation should be stimulating, early (but not too early as in AVERT) and intensive but this is **NOT** enough...

• Combination therapies (e.g. enrichment, exercise, drugs, etc.) targeting *multiple* growth promoting mechanisms need to be used to create a “permissive”, regenerative state

• This may need to be combined with interventions to "switch off" inhibitory processes that act as "brakes" on the recovery process

• Recovery can be predicted based on knowledge of initial impairment, infarct volume and intensity of rehab

• More effective rehabilitation will only result from a better understanding of the biological processes of recovery
Trainees:
- Dr. Jessy Livingston-Thomas (post-doc)
- Dr. Matthew McDonald (post-doc)
- Clarissa Pedrini-Schuch (post-doc, Brazil)
- Mariana Gomez-Smith (PhD)
- Nicolay Hristozov (PhD)
- Gustavo Balbinot (PhD, joint program Brazil)
- Sabina Antonescu (MSc)
- Sudhir Karthikeyan (MSc)
- Gillian Lehay (BSc honours)
- Therese Gagnon (BSc honours)
- Sarah Gasinzigwa (BSc honours)

Staff:
- Matthew Jeffers (laboratory manager)
- Anthony Carter (research technician)
Recovery from stroke: Can we predict who will respond?

Lara Boyd, PT, PhD
Professor & Canada Research Chair
lara.boyd@ubc.ca
No Conflicts of Interest pertaining to the data in this presentation
The Problem: Stroke

Leading cause of adult, long-term disability in the world

Between 1998 and 2005 population-based quality of life showed a **clinically meaningful decline** among Canadians with stroke (related to decreased cognition and motor function)

(Edwards, Kohern, Levy & Boyd, 2010)
The Problem: Stroke

Variability in outcome AND in response to interventions make it hard to predict:

– Trajectories of recovery
– The best intervention for each individual

Goal: Develop biomarkers to predict response to treatment and potential for recovery
Neuroplasticity

All learning of new facts and skills as well as re-learning to support recovery from brain damage is represented neurologically by plasticity or structural change in the brain.

Brain plasticity supports all learning.

Neuroplasticity is activity dependent.

Brain plasticity after neurological insults contributes to recovery.

Specific interventions can facilitate positive plasticity throughout life.

What limits and what facilitates neuroplasticity?
Objectives:

I. Discuss potential for neuroplastic change after stroke.

II. Which interventions prime the brain for learning and facilitate recovery from stroke?

III. Which biomarkers may be used to indicate capacity for motor learning?
I. Discuss potential for neuroplastic change after stroke.
Neuroplastic change in humans is largely shown by changes in function activity in the cortical grey regions of the brain.
Change in Cortical Activity Supports Motor Learning

(Meehan & Boyd, 2011)
Unique Patterns of Brain Activity Support Motor Learning after Stroke

CPCA extracts functionally connected networks – here those associated with implicit motor sequence learning

(Wadden, Woodward & Boyd, 2015)
Each individual with stroke employed a relatively unique network to support motor learning.

Different networks noted despite a relatively homogenous group.

9 right-handed individuals with chronic, right sided lesions in the basal ganglia.

(Wadden, Woodward & Boyd, 2015)
Neuroplastic Change Associated with Motor Learning

Understanding of the impact of changes in white matter structures in the brain is rapidly evolving
White matter is disrupted by stroke, and associated with motor function and learning.

(Motor Learning)

Myelin Water Imaging is a validated marker of Myelin Content

(Laule et al., 2006, 2011)
Myelin is reduced after Stroke

(Borich, MacKay, Rauscher, Vavasour & Boyd, 2013)
Baseline MRI

Intervention
Dominant Limb VR Gameplay
10 sessions (2-3/week)
1000 movements/session
10,000 movements total

Follow-up MRI

MCRI Test – Retest ICC’s .96-.98

ROI ICC’s .83-.99

- Intraparietal Sulcus (IPS)
- Posterior Occiptital Sulcus (POS)
- Posterior Limb of Internal Capsule (PLIC)
Skilled Motor Practice Increases Myelin in the Healthy Human Brain

(Lakhani, Peters, Borich, Jackson, Vavasour, Rauscher, MacKay & Boyd, 2016)
Increased Myelin is associated with Motor Learning

Inverse relationship between LIPS MWF and rate of learning

Longer time to asymptote = more myelin change

(Lakhani, Peters, Borich, Jackson, Vavasour, Rauscher, MacKay & Boyd, 2016)
Myelin plasticity

(Fields 2015; Sampiao-Baptista 2013; Makenzie 2014)
Functional and structural change occur in parallel

Pre-post analysis of resting state fMRI reveals that a network including intraparietal sulcus activity and middle frontal gyrus

- **IPS**: Visual motor integration – there may be something special about L IPS
- **MFG**: Motor planning

(Lakhani, Villamayor, Rubino & Boyd, in preparation)
Despite these neuroplastic changes

Recovery from stroke is most often incomplete

• Severity of long-term motor impairments after stroke varies
  • Hard to predict outcome
  • Difficult to prescribe the most effective interventions for individual patients
  • Most trial outcomes are negative or inconclusive

• Factors that may contribute to variable outcomes include:
  • age at stroke onset, stroke severity, lesion size and location;
  • In combination these factors explain only 20% of the variance in functional recovery after stroke

(Mang et al., 2014)
One limit to recovery is underestimation of lesion load: covert lesions impact outcomes

(Auriat et al., in review)
One limit to recovery is underestimation of lesion load: covert lesions impact outcomes

(Auriat et al., in review)
What kind of practice changes the brain and promotes positive neuroplastic change?

9,600 retrievals over 4 weeks (Nudo et al., 1996)

10,000 repetitions of skilled movement (myelin; Borich, et al. 2013; Lakhani et al., 2014)

31,500 repetitions of a finger sequence over 35 days (Karni et al., 1995)
II. Which interventions prime the brain for learning and facilitate recovery from stroke?
Priming the Brain to Recover

Robotics, Almady et al, 2015

Exercise, Mang et al, 2016

Brain Stimulation, Meehan et al, 2012
Paired Associative Stimulation to Assess Long Term Potentiation-Like Synaptic Plasticity

Paired associative stimulation – 21 ms ISI
- Median nerve stimulation
- TMS at intensity that evokes 1 mV response
- 450 stimuli
- Pairing the two stimuli is thought to induce a form of spike dependent timing plasticity

Transcranial magnetic stimulation (TMS)
- Resting motor threshold (RMT) 5 out of 10 at 50 µV
- Recruitment curves – 90-150%RMT, 10% increments
Long-term potentiation-Like plasticity

PAS-21 following a period of rest and following high intensity exercise

Cerebellar Inhibition mapped with TMS

Mang et al, Neural Plasticity, 2014

Dashed line – M1 TMS
Solid Line – Cerebellar TMS + M1 (CBI)
A single bout of high intensity exercise facilitates cerebellar inhibition and enhances motor cortical excitability.
Can we exploit this knowledge to change behaviour and learning?
A single bout of exercise facilitates learning through motor memory consolidation.

Learning effects are only evident after a 24-hour delay.

Mang et al, MSSE, 2017
We are now considering if this approach to priming plasticity may be an effective tool to improve the effects of rehabilitation after stroke.

Mang et al. (2013) *Phys Ther:* 93 (12) 1707-16.
Boyd (PI) CIHR Project Grant 2016-2022
Boyd (PI) Donation 2015-2022
Using rTMS to stimulate motor learning after stroke
5 Hz rTMS over ipsilesional sensory cortex paired with practice facilitates motor learning.

(Brodie, Meehan, Borich, Cheung, & Boyd, 2014)
High degree of variability in response

(Brodie, Meehan, Borich, Cheung, & Boyd, 2014)
Is the effectiveness of 5Hz rTMS related to structural integrity?

Pre & Postcentral gyri to Cortex ratio

= (Segmented Gyral volume) / (Total cortical volume)

(Brodie, Borich & Boyd, 2014)
Sensory Cortex White Matter Volume is related to response to 5 Hz rTMS + practice

(A) Grey Matter

(B) White Matter

(Brodie, Borich & Boyd, 2014)
Objectives:

III. Which biomarkers may be used to indicate capacity for motor learning?
BIOMARKER

“Stroke recovery biomarkers are indicators of disease state that can be used clinically to reflect underlying molecular/cellular events and/or predict outcome associated with recovery from stroke. These may include markers of biology (blood, genetics), imaging (structural, functional, chemical), neurophysiology (patterns of brain excitability or electrical activity), or combinations of such.”

Lara Boyd, Chair
Nick Ward, Co-Chair

Integrity of the Corticospinal tract key for recovery

CST integrity can be mapped with MRI, TMS or clinical tests

PREP Algorithm

What is the impact of severity on these processes?

We know very little about (partial) recovery from severe stroke (UE FM <30)

(Hayward et al, 2016)
Different processes are at play after severe stroke

Severe Arm Impairment (n=15, chronic):
• Regression showed that after severe stroke age and ipsilesional transcallosal inhibition combined to explain 59% of variability in WMFT rate
• FA from prefrontal corpus callosum (region 1) alone explained 49% of variance

Mild-moderate arm impairment (n=14)
• No significant relationship with these variables

(Hayward et al, 2016, in review)
Different processes are at play after severe stroke (Hayward et al, 2016, in review)
Different processes are at play after severe stroke

Difference between partial recoverers and non-recoverers as identified by CARPSS algorithm is clinically meaningful for UE FM (6 point difference)

(Hayward et al, 2016, in review)
Importance of individuality in determining Responder status

If we consider group means ... “we might have an explanation for an ‘average’ subject, but it is an explanation that does not apply to any of the actual individuals making up the average.”

Averaging may preclude the discovery of important properties that help to explain why one individual responds and another does not.

(Brown and Heathcote, 2003; Wadden et al., 2016)
Crucial Question

Acute need to determine what characteristics define a responder to any given intervention

Need to move toward more personalized biomarker informed interventions

Other key considerations

– Genetics
– Neurophysiological profile (interhemispheric excitability profiles)
– Motivation
– Cognition
a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA