Neuroplasticity & Stroke Recovery

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Mission of the Canadian Partnership for Stroke Recovery:

We restore quality of life to people affected by stroke by harnessing the collective expertise of leading national and international stroke recovery researchers to create, share and apply new knowledge.
Some Facts About Stroke

A clinically-evident stroke occurs every 10 minutes in Canada.

Stroke is the leading cause of adult neurological disability, the second leading cause of dementia and the third leading cause of death.

There is an urgent need to focus on stroke recovery and rehabilitation since it offers the most hope for stroke survivors.
Stroke Recovery: Research, Knowledge Translation & Advocacy

- **Baycrest**
  - Designing cognitive therapies for stroke recovery, stroke recovery databases

- **Memorial University**
  - Exercise, rehabilitation, and cellular & molecular basis of stroke recovery

- **uOttawa/Ottawa Hospital Research Institute**
  - Molecular & cellular mechanisms of brain repair

- **Sunnybrook Health Sciences & Toronto Rehab**
  - Imaging, rehabilitation, exercise & other interventions to optimize stroke recovery

- > 125 scientists
- 20 projects in 3 areas of focus
- International peer review
Strategic Research Areas

• Focus 1: Exercise, stroke recovery & brain health

• Focus 2: Small Vessel Disease, Cognitive Function, Covert Stroke & Alzheimer’s Disease

• Focus 3: Regenerative Approaches to Stroke Recovery & Brain Health

• Knowledge Translation
How Big a Problem is Stroke?

- **Overt Strokes**: 50,000 /year
- **Covert Strokes**: 250,000-400,000 /year

Problem solving, planning, strategy formation
Combating Stroke

• Prevention
  – Reduce risk factors

• Minimizing the Insult
  – Recognize warning signs
  – Clot busting drugs

• Neuroprotection
  – Drugs, hypothermia

• Promoting Recovery
  – Rehabilitation, exercise, drugs,
  – Growth factors, electrical stimulation
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
“Stroke” results in a decreased cortical representation of the hand. However, post-stroke training (i.e., rehabilitation) increased cortical representation of the hand. Surviving cortical regions previously occupied by the hand were taken over by shoulder and elbow. Regions previously occupied by the digits took over control of the elbow and shoulder.
Beginnings

Dr. Richard Jonas, Cardiac Surgeon, Children’s Hospital, Harvard University, Boston, MA 1985
Therapeutic Hypothermia
Translation of Basic Research

'Actually felt good when I woke up. I wasn’t cold or anything,' says Berkley Hutton, here with his wife Cathy. He was treated last month with therapeutic hypothermia.

Chilling helped heart patient survive

Globe and Mail, March 28, 2006
Foothills Hospital Calgary
Treating Upper Limb Dysfunction

Ploughman & Corbett, Arch Phys Med Rehabil, 2004
Rat Model of Upper Limb Recovery
MCA = Middle Cerebral Artery

ET-1 Stroke Model developed by Victoria Windle, PT, PhD
Staircase Reaching Test
Enriched Rehabilitation

Rats housed in EE & have access to reach training apparatus 4 hr/day, 5 days per week.
Research Questions

- Do stimulating or enriched environments combined with task specific reach training improve recovery of upper limb deficits?
- How does enriched-rehabilitation change the post-stroke brain?
- Is there an optimal time window following stroke when the brain is most sensitive to rehabilitation?
- Is the amount or intensity of rehabilitation important for recovery?
Enriched Housing

Daily Reach Training

Stroke

Start Rehabilitation

14d

Behavioural Assessment

Post 1
4 weeks

Post 2
9 weeks
Staircase Reaching Task

Biernaskie and Corbett J. Neurosci., 2001
Enrichment + Reach Training

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)

Contrasts with enriched environment are striking: lack of stimulation, exercise & socialization

Bernhardt et al., Stroke, 2004
Further studies showed that there is a “critical” or “sensitive” period following stroke when interventions are most effective.

Enrichment + Rehab was an effective therapy when initiated early (5-14 days) after stroke, but had limited benefit when started later (30 days).

Biernaskie et al (2004), J Neurosci, 1245-54
The Critical Period for Stroke Recovery

Murphy & Corbett, Nat Neurosci Rev, 2009

D

Upregulation of growth promoting factors

Stroke

Upregulation of growth inhibiting factors

Critical Period

0 5 14 30 + days

sustained

late

Murphy & Corbett, Nat Neurosci Rev, 2009
Does BDNF Play A Critical Role in Stroke Recovery?

BDNF promotes neuronal survival, sprouting of new connections, increases dendritic spine formation.

Implicated in learning and memory in animals and humans.

Michelle Ploughman, PT, PhD
Recovery of Skilled Reaching is Prevented by Blocking BDNF

Ploughman et al., Stroke, 2009
Recovery Plateaus?

• Stroke patients typically reach a plateau of motor recovery ~ 6-10 weeks after injury

• How much of this “apparent” plateau is due to a limit on the brain’s plasticity versus limitations of current rehabilitation practice?

• Could the amount or intensity of rehabilitation determine the level of recovery?
Experimental Design

5 groups all with Stroke

- Light STD  
  n = 7

- Light ER
  n = 8

- Dark STD
  n = 7

- Dark ER Limited
  n = 8

- Dark ER Unlimited
  n = 9

Crystal MacLellan, PT, PhD
Intensity of Rehabilitation Matters!

(A) Reaching Success in Staircase Task

(B) Limb Use in Cylinder Task

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

A

BDNF in the Contralateral Forelimb Motor Cortex

B

BDNF in the Contralateral Hippocampus

Group

Light STD  Light ER  Dark STD  Dark ER Lim  Dark ER Unlim

BDNF (μg/mL ± SEM)

0  10  20  30  40  50  60

Group

Light STD  Light ER  Dark STD  Dark ER Lim  Dark ER Unlim

BDNF (μg/mL ± SEM)
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.
Where are the Seeds of Recovery Sown?

Neurological Deficit Score (NDS)

Ischemia

Histology

ST = Standard Housing
EE = Enriched Environment
RT = Daily Reach Training
ER = Enriched Rehab

Infarct Volume

*FosB/ΔFosB a marker of use-dependent neuronal activity
While all groups showed similar recovery, there is a trend suggests that treatments groups (EE, RT, ER) were showing signs of enhanced recovery after only a few days compared to ST animals.
Peri-infarct Increases in Neuronal Activity

ER increases FosB expression in cortical regions layer II/III

EE or RT alone does not show this pattern of increased activity
Pharmacological Enhancement of Recovery

- Intensive rehabilitation enhances recovery in animal models and some stroke patients.
- Many patients unable to tolerate such intensive therapy due to depression, fatigue, or frustration and recovery often incomplete.
- Other interventions are needed, one possibility is to facilitate recovery by drugs that foster neuroplasticity.
Altered Brain Excitability in Peri-Infarct Cortex After Stroke

• Following stroke there is loss of function in surviving peri-infarct cortex
• Over time new maps are formed or new representations are created
• Peri-infarct cortex thought to be critical for stroke recovery
• Changes in excitability in this region may provide clues for drug therapy to enhance recovery
Reversing GABA Inhibition in Peri-Infarct Cortex Improves Recovery

• Tonic inhibition is mediated by GABA$_A$ receptors
• Carmichael & colleagues used a selective inverse agonist (L655,708) to block GABA mediated inhibition
• Improves motor recovery when given 3 days after photothrombotic stroke in mice but earlier administration worsens outcome
Mobilization of Endogenous Stem & NPCs With EGF/EPO Accelerates Recovery

(Left) Rehab + EGF/EPO animals recovered significantly more than non-rehab conditions after 2 weeks of rehabilitation. (Right) This effect was also apparent at 6 weeks. Additionally, the Rehab + aCSF group recovered significantly more than animals in the No Rehab + EGF/EPO group.

* = p < 0.05

Jeffers & Corbett, Stroke, submitted
Should we be Optimistic Given Past Failure in Stroke?

• Neural restoration interventions are given at a delay when patients are in hospital or clinic

• Treatments are given after all cell death has ceased and the patient is medically stable

• Tremendous progress in identifying diverse ways to enhance plasticity (rehab, exercise, electrical stimulation, drug therapy)
How The Brain Protects Itself

Iadecola & Anrather, Nat Neurosci, 2011
Take Home Messages

• Therapeutic interventions should augment a central “recovery program” similar to how hypothermia enhances the brain’s “protection program”

• Stimulating environments & exercise are examples of interventions that “prime” the brain to make it more receptive to task specific therapy

• BDNF plays a key role in stroke recovery (Ploughman et al., 2009; Clarkson et al., 2011)

• Timing, repetition & intensity matter - there is a critical threshold of rehabilitation needed for stroke recovery

• Combination/cocktail therapies (e.g. enriched rehabilitation, exercise, hypothermia) are superior to monotherapies