Motor recovery after stroke

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UCL Institute of Neurology MSc Lectures, Queen Square, March 2014
Recovery After Stroke: Neurorehabilitation

I. The problem – framework for approaches to upper limb treatment after stroke

II. Neuroplasticity as the key to recovery?

III. Enhancing neuroplasticity to promote recovery

IV. Barriers to translation

slides at www.ucl.ac.uk/ion/departments/sobell/Research/NWard
Motor recovery after stroke

I. How do we treat people after stroke?

1. Preservation of tissue
2. Avoid complications
3. Enhancement of plasticity
4. Task specific training
5. Compensation

Rehabilitation → Recovery
Motor recovery after stroke

I. How do we treat people after stroke?

Upper limb recovery after stroke is unacceptably poor

• 60% of patients with non-functional arms 1 week post-stroke didn’t recover (Wade et al, 1983)

• At 18 months post-stroke, 55% of patients had limited or no dextrous function (Welmer et al, 2008)

• 4 years post-stroke only 50% had fair to good function (Broeks et al, 1999)
Rehabilitation is a process of active change by which a person who has become disabled acquires the knowledge and skills needed for optimum physical, psychological and social function.

Treatments aimed at reducing impairments

Task-specific training

- cortical stimulation
- other
- drugs
Motor recovery after stroke

I. How do we treat people after stroke?

Task-specific training is better than general exercise

Works better in patients with reasonable residual motor control

Optimal dose is important but not clear

Augmented training
Constraint induced therapy
Robotic assisted devices
Virtual environments
Motor recovery after stroke

I. How do we treat people after stroke?

Performance improvement proportional to amount of practice

1. Distributed practice - frequent and longer rest periods
2. Variable practice - varying parameters of task
3. Contextual interference - random ordering of related tasks

Better retention and generalisation of learning to new tasks

Motor recovery after stroke

1. How do we treat people after stroke?

A Self-Administered Graded Repetitive Arm Supplementary Program (GRASP) Improves Arm Function During Inpatient Stroke Rehabilitation
A Multi-Site Randomized Controlled Trial

Jocelyn E. Harris, MSc; Janice J. Eng, PhD; William C. Miller, PhD; Andrew S. Dawson, MD

(Stroke. 2009;40:2123-2128.)

- multi-site single blind randomized controlled trial
- 4-week self-administered graded repetitive upper limb program in 103 stroke patients approx 3 weeks post stroke
- 3 grades (mild, moderate, severe)
- Provided with exercise book with instructions
- Repetitions, inexpensive equipment
- strength, range of motion, gross and fine motor skills
- GRASP group showed greater improvement in upper limb function
- GRASP group maintained this significant gain at 5 months post-stroke
Motor recovery after stroke

1. How do we treat people after stroke?

Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke
The EXCITE Randomized Clinical Trial

Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N ENGL J MED 362:19 NEJM.ORG MAY 13, 2010
1. How do we treat people after stroke?
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Barthel</th>
<th>ARAT</th>
<th>GRIP</th>
<th>NHPT</th>
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<tr>
<td>Patient A</td>
<td>20/20</td>
<td>57/57</td>
<td>98.7%</td>
<td>78.9%</td>
</tr>
<tr>
<td>Patient B</td>
<td>20/20</td>
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<td>64.2%</td>
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</table>
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Recovery recapitulates ontogeny

Steven C. Cramer and Michael Chopp

Several studies support the hypothesis that after stroke, specific features of brain function revert to those seen at an early stage of development, with the subsequent process of recovery recapitulating ontogeny in many ways. Many clinical characteristics of stroke recovery resemble normal development, particularly in the motor system. Consistent with this, brain-mapping studies after an ischemic insult suggest re-emergence of childhood organizational patterns: recovery being associated with a return to adult patterns. Experimental animal studies demonstrate increased levels of developmental proteins, particularly in the area surrounding an infarct, suggesting an active process of reconditioning in response to cerebral ischemia. Understanding the pattern between normal development and stroke recovery might be of value in its treatment.

Wieloch & Nikolich, CoNb 2006

![Diagram showing various aspects of neuroplasticity and therapies related to motor recovery after stroke.](image-url)
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Activity takes advantage of plastic changes, but also enhances them.

These are therefore therapeutic targets for the promotion of recovery after stroke.
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Brain plasticity! Hold on ….. the cortex is not capable of plasticity but is hardwired and immutable. Once damage occurs, cortical neurons either die or at best do not change their projection patterns….."
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Dendritic growth *in vivo*

Axon arborisation *in vivo*

Niell et al., Nat Neurosci 2004; 7:254-260

Hua et al., Nature 2005; 434:1022-1026
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II. Neuroplasticity - the key to recovery?

- In general - reduced activity at GABAergic interneurons allows plasticity e.g. reopening critical period in adults

- In general - enhanced glutamatergic signalling leads to LTP of connections

- In general - altering the balance of inhibition/excitation away from inhibition is important in allowing new periods of plasticity in adult cortex
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II. Neuroplasticity - the key to recovery?

Brain Excitability in Stroke
The Yin and Yang of Stroke Progression
S. Thomas Carmichael, MD, PhD
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Motor thresholds elevated

Less inhibition / more facilitation
Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Steeper RC, lower AMT & RMT = less impairment in 1st month

Less inhibition/ more facilitation
In all at 1 month and in those with more impairment at 3rd month
II. Neuroplasticity - the key to recovery?

Motor recovery after stroke

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Motor recovery after stroke

II. Neuroplasticity - the key to recovery?

Functional Recovery After Ischemic Stroke Is Associated With Reduced GABAergic Inhibition in the Cerebral Cortex: A GABA PET Study

Yu Kyeong Kim, MD, PhD¹, Eun Joo Yang, MD, PhD², Kyehee Cho, MD², Jong Youb Lim, MD², and Nam-Jong Paik, MD, PhD²

Neurorehab Neural Repair 2014 Jan (Epub ahead of print)

- 10 stroke patients studied at 1 month and 3 months using $[^{18}\text{F}]$FMZ PET.
- Decrease in GABA$_A$ receptor availability throughout the cerebral cortex and cerebellum, especially the contralateral hemisphere.
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II. Neuroplasticity - the key to recovery?

“...the spectral characteristics of MEG recordings provide a marker of cortical GABAergic activity”

BASELINE BETA-BAND POWER
- Increased by diazepam (GABA_A effect?)
- Increased by cTBS (decreases excitability)
- Increased with ageing

POST-MOVEMENT REBOUND
- Increased by tiagabine, but not diazepam (GABA_B effect?)

MOVEMENT RELATED BETA-DECREASE
- Increased further by diazepam and tiagabine (GABA_A effect?)
- in patients with more impairment - less in contralateral M1, more in ipsilateral M1 (shift of normal mechanisms to iM1?)
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II. Neuroplasticity - the key to recovery?

Q1. Time course ....? 

- intensive training here?
- enhance potential for plasticity here?

motor function

‘plasticity’

time post stroke
Rehabilitation is a process of active change by which a person who has become disabled acquires the knowledge and skills needed for optimum physical, psychological and social function.

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III. Enhancing neuroplasticity to promote recovery

Treatments aimed at reducing impairments

Task-specific training

- cortical stimulation
- other
- drugs
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III. Enhancing neuroplasticity to promote recovery

Enhancing post-stroke plasticity....

Drugs

NIBS

BAT

... to maximise training effects
Motor recovery after stroke

III. Pharmacotherapy after stroke

Restoration of Function After Brain Injury

By

A. R. LURIA

Translated from the Russian by

Translation edited by
O.L. ZANGWILL
Professor of Experimental Psychology
at the University of Cambridge

To Lord Brain
with kindest regards

A. R. Luria

Nov. 22, 1965
Motor recovery after stroke

III. Pharmacotherapy after stroke

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex
José Fernando Maya Vetencourt,1* Alessandro Sale,1 Alessandro Viegi,1 Laura Baroncelli,1 Roberto De Pasquale,1 Olivia F. O’Leary,3 Eero Castrén,3 Lamberto Maffei1,2

We investigated whether fluoxetine, a widely prescribed medication for treatment of depression, restores neuronal plasticity in the adult visual system of the rat. We found that chronic administration of fluoxetine reinstates ocular dominance plasticity in adulthood and promotes the recovery of visual functions in adult amblyopic animals, as tested electrophysiologically and behaviorally. These effects were accompanied by reduced intracortical inhibition and increased expression of brain-derived neurotrophic factor in the visual cortex. Cortical administration of diazepam prevented the effects induced by fluoxetine, indicating that the reduction of intracortical inhibition promotes visual cortical plasticity in the adult. Our results suggest a potential clinical application for fluoxetine in amblyopia as well as new mechanisms for the therapeutic effects of antidepressants and for the pathophysiology of mood disorders.

www.sciencemag.org SCIENCE VOL 320 18 APRIL 2008

- chronic administration of SSRI fluoxetine reinstates ocular dominance plasticity in adulthood i.e. reopens critical period for plasticity
- ...reverses amblyopia
- ...reduces intracortical inhibition
- ...blocked by diazepam (GABA_A agonist)
- ...increases expression of BDNF

In humans (healthy and stroke), a single dose
- increases simple motor performance
- increases motor cortex activity (fMRI)
- increases motor cortex excitability (TMS)
Motor recovery after stroke

III. Pharmacotherapy after stroke

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoît Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Lancet Neurol 2011;10:123-30

- 118 patients with ischemic stroke and hemiparesis (Fugl-Meyer scores ≤55)
- fluoxetine (n=59; 20 mg once per day, orally) or placebo (n=59)
- 3 months starting 5 to 10 days after the onset of stroke
- All patients had physiotherapy as delivered in local unit
- The primary outcome measure was change in the FM score between day 0 and 90
Motor recovery after stroke

III. Pharmacotherapy after stroke

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Lancet Neurol 2011;10:123-30

Improved FM score at 90 days
Improved mRS score at 90 days
Several agents considered:

- Acetylcholinesterase inhibitors
- Amphetamine
- DA agonists (e.g. DARS in UK)

Reduced GABAergic inhibition?
Increased glutamatergic/BDNF mediated LTP?
Enhanced plasticity
Enhancing *ipsilesional* excitability or decreasing *contralesional* excitability of motor cortex might enhance motor learning by altering balance of excitation/inhibition.
III. Non-invasive brain stimulation after stroke

Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations

Archy O. de Berker¹ *, Marom Bikson² and Sven Bestmann¹

¹ Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, University College London, London, UK
² Neural Engineering Laboratory, Department of Biomedical Engineering, The City College of New York of City University of New York, New York, NY, USA

FIGURE 1 | Examining current distributions in the cortex. (A) The classic montage used by Hitzchoe and Paulus (2000) to modulate MEP size. (B) Finite element modeling of current distribution with the classic montage illustrates the broad swathes of cortex affected. (C) Voltage drops across membranes considered as resistors explain the mixture of hyperpolarization and depolarization seen in. (D) Superficially depolarizing currents produce hyperpolarization in dendrites and depolarization in the cell soma. (E) The direction of current flow varies considerably within the stimulated area. All figures bar (C) reprinted with permission from Rahman et al. (2010).
Motor recovery after stroke

III. Non-invasive brain stimulation after stroke

Effects of Repetitive Transcranial Magnetic Stimulation on Motor Functions in Patients With Stroke
A Meta-Analysis

Wan-Yu Hsu, MSc; Chia-Hsiung Cheng, MSc; Kwong-Kum Liao, MD; I-Hui Lee, MD, PhD; Yung-Yang Lin, MD, PhD

<table>
<thead>
<tr>
<th>Study name</th>
<th>Effect size</th>
<th>Statistics for each study</th>
<th>Mean effect size and 95% CI</th>
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<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
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<tr>
<td>Mansur et al, 2005</td>
<td>0.75</td>
<td>-0.53</td>
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<td>1.00</td>
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<td>0.70</td>
<td>-0.12</td>
<td>1.63</td>
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<td>Khadr et al, 2009 (3 Hz)</td>
<td>0.68</td>
<td>-0.15</td>
<td>1.50</td>
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<td>Amei et al, 2006 (cortical)</td>
<td>-0.16</td>
<td>-0.62</td>
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<td>0.05</td>
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<td>0.04</td>
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</table>

Figure 1. Forest plot of the mean effect sizes for motor outcome measures. Six articles contributed >1 study condition. 

(Stroke, 2012;43:1849-1857.)
Motor recovery after stroke

III. Non-invasive brain stimulation after stroke


TABLE 2. Fixed-effects Meta-analysis of Eight Studies that Examined the Pre–Post Effects of Anodal tDCS on Motor Function in Stroke Survivors

<table>
<thead>
<tr>
<th>Included Studies</th>
<th>Outcome Measure</th>
<th>Baseline Measure</th>
<th>Post-measure</th>
<th>Standard Mean Difference</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total (n)</td>
<td>Mean</td>
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<tr>
<td>Boggio et al.9</td>
<td>JTT</td>
<td>54</td>
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<td>Fregni et al.10</td>
<td>JTT</td>
<td>63.8</td>
<td>18.22</td>
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<tr>
<td>Hummel, 2005</td>
<td>JTT</td>
<td>43.57</td>
<td>23.6</td>
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<tr>
<td>Hummel et al.13</td>
<td>RT</td>
<td>273.5</td>
<td>15.4</td>
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<td>PS</td>
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<td>11</td>
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<tr>
<td>Kim et al.14</td>
<td>BBT</td>
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<td>18.59</td>
<td>10</td>
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<td>Kim et al.14</td>
<td>FM Test</td>
<td>31</td>
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<td>CS</td>
<td>1.59</td>
<td>1.55</td>
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Butler AJ et al, J Hand Ther 2013;26(2):162-70
Motor recovery after stroke

III. Other approaches to prime motor cortex

Active-Passive Bilateral Training

APBT
- Reduces ipsilesional motor cortex (GABAergic) inhibition (Stinear et al, Brain 2008)

APBT prior to motor training
- Increases effect of training in chronic patients (Stinear et al, Brain 2008)
- Speeds up recovery in early stroke patients (Stinear et al, Stroke 2014)

Action Observation

AO + PT
- increased magnitude of motor memory formation
- Had more marked effect on corticomotor excitability of the muscles involved in trained/observed movements (Celnik et al Stroke, 2008)
Motor recovery after stroke

IV. Barriers to translation

None have entered into routine clinical practice – why?

Point of View: Directions for Research

The Future of Restorative Neurosciences in Stroke: Driving the Translational Research Pipeline From Basic Science to Rehabilitation of People After Stroke

Cumberland Consensus Working Group: Binith Cheeran, Leonardo Cohen, PhD, Bruce Dobkin, MD, Gary Ford, Richard Greenwood, MD, David Howard, PhD, Masud Husain, MD, Malcolm Macleod, PhD, Randolph Nudo, PhD, John Rothwell, PhD, Anthony Rudd, James Teo, Nicholas Ward, MD, Steven Wolf, PhD
Motor recovery after stroke

IV. Barriers to translation

Ward and Cohen, Arch Neurol 2004
Motor recovery after stroke

IV. Barriers to translation

Will the same treatment strategy work in these patients?
Motor recovery after stroke

IV. Barriers to translation

Q1. Time course ....?  
- Intensive training here?
- Enhance potential for plasticity here?

Q2. Effect of intervention ....?  
- Fluoxetine
- TDCS
- ... or...
- Early?
- Late?

Q3. Impact on training....?
- Training wrist control - tracking targets
Recovery after stroke: Neurorehabilitation

Summary

• Advances in neurorehabilitation are coming about through advances in neuroscience

• The dose of treatment is critical - more is generally better

• Enhancement of plasticity is possible

• Neuroimaging should help in stratification

• Understanding the mechanisms of recovery and treatment might allow targeted or individualised therapy after stroke in future
Recovery after stroke: Neurorehabilitation

Additional References


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Holly Rossiter
Marie-Helen Boudrias
Karine Gazarian
Ella Clark
Stephanie Bowen
Sven Bestmann
John Rothwell
Penny Talelli

Some more slides at www.ucl.ac.uk/ion/departments/sobell/Research/NWard

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