
Neurorehabilitation and Brain Plasticity

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Slides at www.ucl.ac.uk/ion/departments/sobell/Research/NWard or look on twitter @WardLab
Overview

1. What is neuroplasticity?
2. Enhancing potential for neuroplasticity in stroke
3. RCTs? - Barriers to translation
4. Imaging the potential for neuroplasticity in humans
1. When is neuroplasticity relevant in neurorehabilitation?

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
Neuroplasticity After Stroke

1. What is plasticity?

Changes in strength of a synaptic connection (or at a systems level, network connection) in response to either an environmental stimulus or increase in synaptic activity.
Neuroplasticity After Stroke

1. What is plasticity?

Plasticity takes place in the cortex

- changing strength of existing connections
- new connections
- getting rid of unused connections
Neuroplasticity After Stroke

1. What is plasticity?

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

dendrites

axon
Neuroplasticity After Stroke

1. Changes in residual functional architecture
Neuroplasticity After Stroke

2. Enhancing potential for neuroplasticity

Enriched Environments

Drugs

NIBS

... to maximise training effects
Neuroplasticity After Stroke

2. Spontaneous Biological Recovery?

Neuroplasticity After Stroke

2. Enriched environments for neuroplasticity

- **a.** Standard cage
- **b.** Enriched cage
- **c.** Appearance of nerve cells, mouse cerebrum
- **d.** Appearance of nerve cells, mouse cerebrum
Neuroplasticity After Stroke

2. Enriched environments for neuroplasticity

- Enriched environments plus training leads to significant improvements in skilled reaching
- Running exercise immediately before reaching practice increases efficacy of training
- If training started after day 30 it is largely ineffective (day 90 in humans?)

Neuroplasticity After Stroke

2. Enriched environments for neuroplasticity

Neuroplasticity After Stroke

2. Enriched environments for neuroplasticity

- Robotic treadmill training
- Home video arm/hand training
- Robotic arm training
In the cortex **GABA** is inhibitory, glutamate is excitatory.

Reduced activity at **GABAergic** interneurons allows plasticity in adults.

Enhanced **glutamatergic** signalling leads to LTP.

So …altering the **balance of inhibition/excitation** is important in reopening new periods of plasticity in adult cortex.

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**Neuroplasticity After Stroke**

2. **Inhibition-Excitation – a therapeutic target?**
Neuroplasticity After Stroke

2. Inhibition-Excitation – a therapeutic target?

Enhancing post-stroke plasticity...

Drugs

NIBS

... to maximise training effects
Neuroplasticity After Stroke

2. Enhancing potential for neuroplasticity - pharmacological

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

SSRIs (e.g. FLAME, FOCUS in UK)

Acetylcholinesterase inhibitors

amphetamine
chronic administration of fluoxetine (in rats) reopens critical period of plasticity in adulthood

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex
José Fernando Maya Vetencourt,1,4 Alessandro Sale,1 Alessandro Viegi,1 Laura Baroncelli,1 Roberto De Pasquale,1 Olivia F. O’Leary,3 Eero Castrén,3 Lamberto Maffei1,2

These effects were accompanied by reduced intracortical inhibition and increased expression of brain-derived neurotrophic factor

In humans (healthy and stroke), a single dose
- increases simple motor performance
- increases motor cortex activity (fMRI)
- increases motor cortex excitability (TMS)
After effects of tDCS

- Increase in NMDA-dependent intracortical facilitation
- Reduces GABA-ergic intracortical inhibition
- Reduces intracortical GABA (MR Spectroscopy)

2. Enhancing potential neuroplasticity potential – NIBS?

**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>
</tr>
</thead>
<tbody>
<tr>
<td>Boggio et al.1</td>
<td>JTT</td>
<td>54 ± 16.2</td>
<td>49.4 ± 12.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Fregni et al.10</td>
<td>JTT</td>
<td>63.8 ± 18.22</td>
<td>59.33 ± 16.54</td>
<td>6</td>
</tr>
<tr>
<td>Hummel, 2005</td>
<td>JTT</td>
<td>43.37 ± 2.36</td>
<td>39.72 ± 2.15</td>
<td>6</td>
</tr>
<tr>
<td>Hummel et al.13</td>
<td>RT</td>
<td>273.5 ± 15.4</td>
<td>256.6 ± 13.9</td>
<td>11</td>
</tr>
<tr>
<td>Hummel et al.13</td>
<td>PS</td>
<td>118.8 ± 23</td>
<td>124.8 ± 24</td>
<td>11</td>
</tr>
<tr>
<td>Kim et al.12</td>
<td>BBT</td>
<td>35.8 ± 18.59</td>
<td>43.3 ± 20.19</td>
<td>10</td>
</tr>
<tr>
<td>Kim et al.12</td>
<td>FM Test</td>
<td>31 ± 11.17</td>
<td>45.5 ± 12.25</td>
<td>6</td>
</tr>
<tr>
<td>Mahmoudi et al.22</td>
<td>JTT</td>
<td>10.6 ± 7.43</td>
<td>9.46 ± 6.52</td>
<td>10</td>
</tr>
<tr>
<td>Stagg et al.14</td>
<td>RT</td>
<td>590 ± 259.22</td>
<td>551.89 ± 215.73</td>
<td>13</td>
</tr>
<tr>
<td>Stagg et al.14</td>
<td>GS</td>
<td>1.59 ± 1.55</td>
<td>1.47 ± 1.4</td>
<td>13</td>
</tr>
</tbody>
</table>

Total | 90 | 90 | 100 | 0.40 (0.10, 0.70) |
Neuroplasticity After Stroke

3. Barriers to translation ... sources of variability

Why not perform large RCTs?

Enhancing post-stroke plasticity....

... to maximise training effects

Neuroplasticity After Stroke

3. Barriers to translation …sources of variability

Why not perform large RCTs?

Enhancing post-stroke plasticity...

fluoxetine

TDCS

inhibition

excitation

infarct

10 days post stroke

17 days post stroke

24 days post stroke

31 days post stroke

3 months post stroke

... to maximise training effects

Neuroplasticity After Stroke

3. Barriers to translation …sources of variability

Why not perform large RCTs?

Enhancing post-stroke plasticity....

excitation

inhibition

sources of variability?

fluoxetine

TDCS

weak arm

(CF3)


... to maximise training effects

Time course ....?
Neuroplasticity After Stroke

3. Barriers to translation …sources of variability

Why not perform large RCTs?

Inhibitory TBS?  Excitatory TBS?

TBS (and TDCS) is very variable!


Enhancing post-stroke plasticity....

... to maximise training effects
Neuroplasticity After Stroke

3. Biomarkers of potential for plasticity?

Getting plasticity enhancement into clinical practice in stroke

**Effect of intervention ....?**

- fluoxetine
- TDCS

... or ...

**Impact on training....?**

Training wrist control - tracking targets

Early?

Late?

Biomarker

Behaviour
Neuroplasticity After Stroke

3. Biomarkers of potential for plasticity?

**Modulation of Training by Single-Session Transcranial Direct Current Stimulation to the Intact Motor Cortex Enhances Motor Skill Acquisition of the Paretic Hand**

Máximo Zimerman, MD; Kirstin F. Heise, MSc; Julia Hoppe, MD; Leonardo G. Cohen, MD; Christian Gerloff, MD; Friedhelm C. Hummel, MD

*(Stroke. 2012;43(2):185-2191.)*

- ctDCS to contralesional M1 reduced SICI (less inhibition) in ipsilesional M1
- tDCS-induced enhancement of skill acquisition

**Relationship between the effects of tDCS on training and on SICI**

Reduced intracortical inhibition re-opens periods of plasticity in chronic stroke?
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4. Biomarkers at a range of scales of brain architecture

A mechanistic approach to studying recovery requires an appropriate level of description.
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4. Enhancing Neuroplasticity – mesoscopic scale?

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

**BASELINE BETA-BAND POWER**
- Greater baseline beta-power = more GABA inhibition?
- Increased by diazepam (GABA<sub>A</sub> effect?)
- Increased with ageing

**MOVEMENT RELATED BETA-DECREASE**
- Greater decrease in beta-power with grip = more GABA inhibition?
- Increased by diazepam and tiagabine (GABA<sub>A</sub> effect?)
- Less MRBD in chronic stroke patients (particularly those with more impairment)
Neuroplasticity After Stroke

4. Enhancing Neuroplasticity – macroscopic scale?

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Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans

Anne K. Rehme¹ and Christian Grefkes¹,²

¹Neurorehabilitation, Max Planck Institute for Neurological Research, Cologne, Germany
²Department of Neurology, University of Cologne, Cologne, Germany

Network connectivity with DCM for fMRI
Neuroplasticity After Stroke

4. Enhancing Neuroplasticity – macroscopic scale?

Network connectivity with Graph Theory for fMRI/MEG

graph metrics - efficiency
Neuroplasticity After Stroke

4. Putting it all together

Bridge the gap ...

Mechanistic framework ...

Platform for stratification ...

- Bridge the gap ...
  - mesoscopic
  - macroscopic
  - behaviour

- Mechanistic framework ...
  - Predictions
  - motor
  - language
  - cognitive

- Platform for stratification ...
  - patients
  - biomarkers
  - interventions

b biomarkers
stratification
Neuroplasticity After Stroke

Summary

- Neuroscience can help advances in neurorehabilitation
- The dose of treatment is critical - more is generally better
- Increasing the potential for experience dependent plasticity appears possible
- Neuroimaging should help in stratification
- Understanding the mechanisms of recovery and treatment might allow targeted or individualised therapy in future
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