Current Issues in Cognitive Neuroscience III: Translational Research

Recovery of upper limb motor recovery after stroke

How could we do better?

NICK WARD, UCL INSTITUTE OF NEUROLOGY, QUEEN SQUARE
Motor recovery after stroke

Upper limb recovery after stroke – doing better

I. Approaches to promoting UL recovery after stroke

II. Differences in residual structural & functional architecture

III. Neuroplasticity – the key to stroke recovery?
Motor recovery after stroke

1. How do we treat people after stroke?
Motor recovery after stroke

1. 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)

- 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)
Motor recovery after stroke

I. How do we treat people after stroke?

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

Rehabilitation → Recovery
Motor recovery after stroke

1. How do we treat people after 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.

Treatments aimed at reducing impairments

Task-specific training

cortical stimulation

other

drugs
Motor recovery after stroke

1. 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

I. How do we treat people after stroke?

Intensity of Aphasia Therapy, Impact on Recovery

Sanjit K. Bhogal, BA (Hon); Robert Teasell, MD; Mark Speechley, PhD

Background—It has been speculated that the conflicting results demonstrated across poststroke aphasia therapy studies might be related to differences in intensity of therapy provided across studies. The aim of this study is to investigate the relationship between intensity of aphasia therapy and aphasia recovery.

Methods—A MEDLINE literature search was conducted to retrieve clinical trials investigating aphasia therapy after stroke. Changes in mean scores from each study were recorded. Intensity of therapy was recorded in terms of length of therapy, hours of therapy provided per week, and total hours of therapy provided. Pearson correlation was used to assess the relationship between changes in mean scores of outcome measures and intensity of therapy.

Results—Studies that demonstrated a significant treatment effect provided 8.8 hours of therapy per week for 11.2 weeks versus the negative studies that only provided ~2 hours per week for 22.9 weeks. On average, positive studies provided a total of 98.4 hours of therapy, whereas negative studies provided 43.6 hours of therapy. Total length of therapy time was found to be inversely correlated with hours of therapy provided per week ($P=0.003$) and total hours of therapy provided ($P=0.001$). Total length of therapy was significantly inversely correlated with mean change in Porch Index of Communicative Abilities (PICA) scores ($P=0.0001$). The number of hours of therapy provided in a week was significantly correlated to greater improvement on the PICA ($P=0.001$) and the Token Test ($P=0.027$). Total number of hours of therapy was significantly correlated with greater improvement on the PICA ($P<0.001$) and the Token Test ($P<0.001$).

Conclusions—Intense therapy over a short amount of time can improve outcomes of speech and language therapy for stroke patients with aphasia. *(Stroke. 2003;34:987-993.)*

Problem: average amount of out-patient speech therapy $\sim 12$ hours
Motor recovery after stroke

I. 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

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; Junier J. Eng, PhD; William C. Miller, PhD; Andrew S. Dawson, MD

Background and Purpose—More than 70% of individuals who have a stroke experience upper limb deficits that impact daily activities. Increased amount of upper limb therapy has positive effects; however, practical and inexpensive methods of therapy are needed to deliver this increase in therapy.

Methods—This was a multi-site single blind randomized controlled trial to determine the effectiveness of a 4-week self-administered graded repetitive upper limb supplementary program (GRASP) on arm recovery in stroke. 103 participants with stroke were randomized to the experimental group (GRASP group, n=53) or the control group (education protocol, n=50). The primary outcome measure was the Chedoke Arm and Hand Activity Inventory (CAHA), a measure of upper limb function in activities of daily living. Secondary measures were used to evaluate grip strength and practice upper limb use outside of therapy time. Intention-to-treat analysis was performed. Group differences were tested using analysis of covariance.

Results—At the end of the 4-week intervention (approximately 7 weeks poststroke), the GRASP group showed greater improvement in upper limb function (CAHA) compared to the control group (mean difference 6.6, 95% CI 1.3 to 11.9; P=0.001). The GRASP group maintained this significant gain at 6 months poststroke. Significant differences were also found in favor of the GRASP protocol for grip strength and practice upper limb use. No serious adverse effects were experienced.

Conclusion—A self-administered homework exercise program provides a core, time-, and treatment-effective delivery model for improving upper limb recovery in subacute stroke. (Stroke, 2009;40:3123-3128.)

Key Words: stroke • rehabilitation • upper limb

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

Dose is important

Motor – 1000’s of repetitions
Language – 100 hours
Motor recovery after stroke

I. 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

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(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

I. How do we treat people after stroke?

- Robotic treadmill training
- Robotic arm training
- Home video arm/hand training
Motor recovery after stroke

1. How do we treat people after stroke?

https://www.eyesearch.ucl.ac.uk/

http://www.readright.ucl.ac.uk/index.php
Motor recovery after stroke

I. How do we treat people after stroke?

Upper Limb Rehabilitation Clinic

Do you still have difficulty using your arm after a stroke?

If you or a relative have suffered a stroke and still have problems using your arm, then you might be interested in this NHS service at The National Hospital for Neurology and Neurosurgery (NHN), Queen Square.

The multidisciplinary service is run by Dr Nick Ward (Consultant Neurologist), Peer Bander (Physiotherapist), and Kate Fally (Occupational Therapist) with expertise in assessing and treating upper limb problems.

In the clinic, we offer advice on the management of patients with neurological upper limb deficits secondary to central nervous system disease. We are particularly interested in those stroke survivors who might benefit from more intensive treatment of upper limb deficits, especially early after stroke.

The service offers the following:

- A detailed upper limb functional assessment and report.
- A thorough discussion of goals and prognosis.
- Advice on symptom management.
- When appropriate, we will suggest further intensive in-patient treatment (stretching at least 4 hours therapy per day, as part of a 3 or 4 week programme at Queen Square).
- Alternatively, referral to outpatient physio- and occupational therapy for further specific treatment based on our detailed assessment will be made.
- Where required, we will make referrals to other NHNN services (e.g. spasticity assessment clinic, upper limb Functional Electrical Stimulation Clinic, specialist occupational rehabilitation clinic, etc).

We will liaise closely with local outpatient and community services when appropriate.

Patients will have access to ongoing clinical trials of upper limb treatment where appropriate.

Referrals

The service is available to all patients over 16 years of age with a confirmed stroke or other central nervous system diagnosis. Referrals are accepted from (i) GPs, (ii) NHNN staff and (iii) other stroke units, (iv) other neurologists, and (v) Community Rehabilitation Teams.

If you or your relative has suffered a stroke and would like to be referred, please ask your GP to send a brief clinical summary and reason for the referral.

Referrals should be sent to:

Dr Nick Ward
Reader in Clinical Neurology & Honorary Consultant Neurologist
The National Hospital for Neurology and Neurosurgery (Box 146)
Queen Square, WC1N 3BG

www.camden.nhs.uk/gps/upper-limb-rehabilitation-clinic

www.ucl.ac.uk/ion/departments/sobell/Research/NWard/patientsprofile/infoforpatients/upperlimbclinic
Motor recovery after stroke

1. How do we treat people after stroke?
Motor recovery after stroke

II. Residual structural and functional architecture

- Infarct Size
- Infarct Location
- Pre-stroke medical co-morbidities
- Pre-stroke experience, education, age
- Severity of initial stroke deficits
  - Breadth of stroke deficits
  - Acute stroke interventions
  - Medications during stroke recovery period
  - Amount of post stroke therapy
  - Types of post stroke therapy
  - Medical complications after stroke
  - Socioeconomic status
  - Depression
  - Caregiver status
  - Genotype

30-50% of variance in outcomes
Motor recovery after stroke

II. Residual structural and functional architecture

Predictors of upper limb recovery after stroke: a systematic review and meta-analysis

Fiona Coupar¹, Alex Pollock², Phil Rowe³, Christopher Weir⁴ and Peter Langhorne⁵

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Trials (participants)</th>
<th>Odds ratio (random) 95% CI</th>
<th>Odds ratio (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (younger)</td>
<td>11(590)</td>
<td>1.54 [1.06, 2.24]</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>11(424)</td>
<td>1.61 [1.11, 2.33]</td>
<td></td>
</tr>
<tr>
<td>Time since stroke (less time)</td>
<td>5(486)</td>
<td>1.13 [1.00, 1.27]</td>
<td></td>
</tr>
<tr>
<td>Severity of stroke - global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global disability (less disability)</td>
<td>9(238)</td>
<td>3.64 [1.63, 8.13]</td>
<td></td>
</tr>
<tr>
<td>Type/Class of stroke (less severe)</td>
<td>2(256)</td>
<td>3.54 [1.62, 7.72]</td>
<td></td>
</tr>
<tr>
<td>Global impairment (less impairment)</td>
<td>2(209)</td>
<td>2.18 [1.35, 3.43]</td>
<td></td>
</tr>
<tr>
<td>Lesion size/volume (smaller)</td>
<td>3(65)</td>
<td>1.32 [0.74, 2.35]</td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence (absent)</td>
<td>2(256)</td>
<td>4.12 [1.82, 9.33]</td>
<td></td>
</tr>
<tr>
<td>Severity of stroke - focal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL impairment (less UL impairment)</td>
<td>20(1425)</td>
<td>14.04 [9.06, 24.25]</td>
<td></td>
</tr>
<tr>
<td>UL function (more UL function)</td>
<td>4(158)</td>
<td>38.62 [8.40, 177.55]</td>
<td></td>
</tr>
<tr>
<td>LL impairment (less LL impairment)</td>
<td>4(130)</td>
<td>11.83 [6.53, 21.43]</td>
<td></td>
</tr>
<tr>
<td>Co-factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of stroke (left)</td>
<td>11(624)</td>
<td>1.47 [1.07, 2.02]</td>
<td></td>
</tr>
<tr>
<td>UL sensation (no deficit)</td>
<td>3(771)</td>
<td>1.92 [1.41, 2.61]</td>
<td></td>
</tr>
<tr>
<td>Cognition/Perception (no deficit)</td>
<td>4(462)</td>
<td>1.88 [1.01, 3.18]</td>
<td></td>
</tr>
<tr>
<td>Visual disorders (no deficit)</td>
<td>2(256)</td>
<td>5.22 [2.40, 11.35]</td>
<td></td>
</tr>
<tr>
<td>Sitting balance (no deficit)</td>
<td>2(256)</td>
<td>4.75 [0.28, 80.57]</td>
<td></td>
</tr>
<tr>
<td>Sensation (no deficit)</td>
<td>1(156)</td>
<td>9.15 [3.36, 24.91]</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions (less no.)</td>
<td>1(156)</td>
<td>1.96 [0.96, 4.00]</td>
<td></td>
</tr>
<tr>
<td>Neurophysiological factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMS variables; MEPs (present)</td>
<td>15(425)</td>
<td>11.76 [5.19, 26.64]</td>
<td></td>
</tr>
<tr>
<td>SSEPs (present)</td>
<td>2(97)</td>
<td>13.73 [2.73, 69.05]</td>
<td></td>
</tr>
<tr>
<td>DTT (preserved CST)</td>
<td>2(70)</td>
<td>35.46 [8.97, 140.18]</td>
<td></td>
</tr>
</tbody>
</table>
Motor recovery after stroke

II. Residual structural and functional architecture

1. SAFE = shoulder abduction + finger extension (MRC scale) 72 h after stroke (range 0–10)
2. TMS at 2 weeks
3. MRI/DTI at 2 weeks

The PREP algorithm predicts potential for upper limb recovery after stroke

Cathy M. Stinear,1,2 P. Alan Barber,1,2,3 Matthew Petoe,1,2 Samir Anwar4,5 and Winston D. Byblow2,5

Motor recovery after stroke

II. Residual structural and functional architecture

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<tr>
<th>Recovery</th>
<th>Definition</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>The patient has the potential to return to normal or near-normal hand and arm function within 12 weeks.</td>
<td>Rehabilitation could focus on task-specific therapy in order to facilitate a return to full or near-full use of the hand and arm in activities of daily living.</td>
</tr>
<tr>
<td>Notable</td>
<td>The patient has the potential to be using their affected hand and arm in most activities of daily living within 12 weeks, though normal function is unlikely.</td>
<td>Rehabilitation could focus on strength, coordination and fine motor control, in order to maximize recovery of function and minimize compensation with the other hand.</td>
</tr>
<tr>
<td>Limited</td>
<td>The patient has the potential to have some movement in their affected hand and arm within 12 weeks, but it is unlikely to be used functionally for activities of daily living.</td>
<td>Rehabilitation could focus on reducing impairment by strengthening the paretic upper limb and improving active range of motion, in order to promote adaptation and incorporation of the affected upper limb in daily activities wherever possible.</td>
</tr>
<tr>
<td>None</td>
<td>The patient can expect to have minimal movement in their affected hand and arm, with little improvement at 12 weeks.</td>
<td>Rehabilitation could focus on prevention of secondary complications, such as spasticity and shoulder instability, and reducing disability by learning to complete activities of daily living with the unaffected hand and arm.</td>
</tr>
</tbody>
</table>
II. Residual structural and functional architecture
Track from fMRI-defined hand areas in 4 different cortical motor motor areas

Correlation with post-stroke hand grip strength

Shultz et al, Stroke 2012

Motor recovery after stroke

II. Residual structural and functional architecture
Motor recovery after stroke

II. Residual structural and functional architecture

Can treatment response be predicted from CST damage?

Damage to M1 pathway limits response to robot assisted therapy

Riley et al., Stroke 2011; 42: 421-6
II. Residual structural and functional architecture

Can fully automated detection of corticospinal tract damage be used in stroke patients?

Nancy Kou, Chang-hyun Park, Mohamed L. Seghier, et al.
Neurology 2013;80;2242-2245
Motor recovery after stroke

II. Residual structural and functional architecture

It’s not just the white matter pathways that are important

Park et al., in preparation
Motor recovery after stroke

II. Residual structural and functional architecture

left hemisphere for predicting and accounting for limb dynamics
right hemisphere for stabilizing limb position through impedance control mechanisms

left hemisphere damage - greater errors in movement direction
right hemisphere damage - greater errors in movement extent
Motor recovery after stroke

II. Residual structural and functional architecture

Predicting language outcome and recovery after stroke: the PLORAS system
Cathy J. Price, Mohamed L. Seghier and Alex P. Leff

1. Database of (i) hi-res structural MRI, (ii) language scores and (iii) time since stroke

2. MRI converted to 3D image with index of degree of damage at each $2\text{mm}^3$ voxel

3. This lesion image compared to others in database and similar patients identified

4. Different ‘recovery’ curves can then be estimated for different behavioural measures
Motor recovery after stroke

II. Residual structural and functional architecture
Motor recovery after stroke

II. Residual structural and functional architecture

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Barthel</th>
<th>ARAT</th>
<th>GRIP</th>
<th>NHPT</th>
</tr>
</thead>
<tbody>
<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>
<td>57/57</td>
<td>64.2%</td>
<td>14.9%</td>
</tr>
</tbody>
</table>
Motor recovery after stroke

II. Residual structural and functional architecture

Increasing ‘main effect’ of left hand grip

affected hemisphere

more CS damage

less CS damage

Ward et al., Brain 2006
Motor recovery after stroke

II. Residual structural and functional architecture

Increasing ‘main effect’ of left hand grip

affected hemisphere

more CS damage

less CS damage
Motor recovery after stroke

II. Residual structural and functional architecture

TMS to premotor cortex after stroke

more effect in good recoverers

affected hemisphere

more effect in poor recoverers

unaffected hemisphere

Fridman et al, 2004

Johansen-Berg et al, 2002
Motor recovery after stroke

II. Residual structural and functional architecture
Motor recovery after stroke

II. Residual structural and functional architecture

Robot-based hand motor therapy after stroke

Craig D. Takahashi, Lucy Der-Yeghiaian, Vu Le, Rehan R. Motiwala and Steven C. Cramer

Less activity in M1 limits response to robot assisted therapy
Motor recovery after stroke

II. Residual structural and functional architecture

Power and Coherence are measures of changes in MEG data at particular frequencies...

- **Power** is an increase or decrease in synchrony of the underlying neuronal population = 1 source
- **Coherence** represents the amplitude and phase correlation between two sources = 2 sources
Motor recovery after stroke

II. Residual structural and functional architecture

Time-frequency Spectrograms - Control
CM1

IM1

Time-frequency Spectrograms – Patient CB
CM1

IM1
Motor recovery after stroke

II. Residual structural and functional architecture

Beta coherence

Gamma coherence

Rossiter et al 2012
Motor recovery after stroke

II. Residual structural and functional architecture

21 patients with at least moderate language impairment post stroke
fMRI at 12 days post stroke
Clinical scores at 12 days and 6 months (‘good’ and ‘bad’ outcome groups defined)
Support Vector Machine calculates the characteristics of each scan that classifies it as being from patient with ‘good or ‘bad’ outcome

Accuracy always better with age and initial impairment added to fMRI
From 76 to 86% using ‘mask’ data for outcome
From 75 to 86% using R Frontal data for improvement
Motor recovery after stroke

II. Residual structural and functional architecture

**Co-factors**

- Side of stroke
- Sensory loss
- Cognitive dysfunction
- Visual disorders
- Fatigue
- Spasticity / loss of ROM
- Genotype
Motor recovery after stroke

II. Residual structural and functional architecture

Ward and Cohen, Arch Neurol 2004
Motor recovery after stroke

II. Residual structural and functional architecture

Differential Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation Over Ipsilesional Primary Motor Cortex in Cortical and Subcortical Middle Cerebral Artery Stroke

Mitra Ameli, MD,1 Christian Goetzes, MD,1,2 Friederike Kemper, MD,1 Florian P. Rieger, MS,1 Anne K. Rohner, MS,1 Hans Karche, MD, PhD,3 Gesina R. Fink, MD, PhD,1,4 and Dennis A. Nowak, MD, PhD1,4,5


A index finger tapping

A rTMS responders

B rTMS non-responders
Motor recovery after stroke

II. Residual structural and functional architecture

Will the same treatment strategy work in these patients?
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

III. Neuroplasticity - the key to recovery?
III. Neuroplasticity - the key to recovery?

Motor recovery after stroke

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
Motor recovery after stroke

III. 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
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

Similarities with the developing brain

1. Molecular events associated with cerebral infarction
   - Re-emergence of proteins normally only increased during times of development e.g. nestin, MAP-2, GAP43, synaptophysin, BDNF
   - These proteins associated with neuronal growth, apoptosis, angiogenesis, cellular differentiation in the developing brain

2. Cellular events associated with cerebral infarction
   - after unilateral cortical lesion, increases in dendritic branches and synapse formation in both hemispheres
   - overshoot followed by pruning, as seen in development

3. Other changes
   - Perilesional and distant hyperexcitability of cortical neurons enhancement of LTP.
   - LTP is activity dependant
Motor recovery after stroke

III. 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

III. Neuroplasticity - the key to recovery?

Q1. Time course ....? 

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

motor function

'plasticity'

time post stroke
Motor recovery after stroke

III. 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
III. 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

III. Neuroplasticity - the key to recovery?

Motor thresholds elevated

Less inhibition / more facilitation
Motor recovery after stroke

III. 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
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?
10 stroke patients studied at 1 month and 3 months using $[^{18}\text{F}]$FMZ PET.

- decrease in $\text{GABA}_A$ receptor availability throughout the cerebral cortex and cerebellum, especially the contralateral hemisphere.
Motor recovery after stroke

III. 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?)
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

III. Neuroplasticity - the key to recovery?
III. Neuroplasticity - the key to recovery?

Motor recovery after stroke

Enhancing post-stroke plasticity....

Drugs

NIBS

BAT

... to maximise training effects

Motor recovery after stroke

III. Neuroplasticity - the key to recovery?
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex

José Fernando Maya Vetencourt,² Alessandro Sale,¹ Alessandro Viegi,¹ Laura Baroncelli,³ 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.

In humans (healthy and stroke), a single dose

• 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 (GABAₐ 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. Neuroplasticity - the key to recovery?

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. Neuroplasticity - the key to recovery?

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

Improved FM score at 90 days

Improved mRS score at 90 days
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

Several agents considered:
- Acetylcholinesterase inhibitors
- Amphetamine
- DA agonists (e.g. DARS in UK)

To Lord Brain

With kinder regards

A. R. Luria

Nov. 22, 1965

Enhanced plasticity

Reduced GABAergic inhibition?
Increased glutamatergic/BDNF mediated LTP?
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

Enhancing *ipsilesional* excitability or decreasing *contralesional* excitability of motor cortex might enhance motor learning by altering balance of excitation/inhibition
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

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

![Image](https://example.com/image.png)
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

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>Mean effect size and 95% CI</th>
<th>Statistics for each study</th>
<th>Effect size</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Relative weight</th>
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<tr>
<td>Mansur et al, 2005</td>
<td>-0.53 - 2.03</td>
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<td>Malcom et al, 2007</td>
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<td>1.63</td>
<td>0.02</td>
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<td>Dafotakis et al, 2008</td>
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<td>Takeuchi et al, 2008</td>
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<td>Khadir et al, 2006 (1 Hz)</td>
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<td>Amei et al, 2006 (cortical)</td>
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<td>Amei et al, 2006 (subcortical)</td>
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<td>Khadir et al, 2010 (10 Hz)</td>
<td>0.67 - 1.46</td>
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<td>Emara et al, 2010 (1Hz)</td>
<td>0.69 - 1.33</td>
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<td>Emara et al, 2010 (5 Hz)</td>
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<td>0.68</td>
<td>0.31</td>
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<td>Chang et al, 2010</td>
<td>0.28 - 0.50</td>
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<td>Ackerley et al, 2010 (TBS)</td>
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<td>Thelij et al, 2011</td>
<td>0.04 - 0.76</td>
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<td>0.92</td>
<td>4.83</td>
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</tbody>
</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. Neuroplasticity - the key to recovery?


http://dx.doi.org/10.1016/j.jht.2012.07.002

<table>
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<tr>
<th>Included Studies</th>
<th>Outcome Measure</th>
<th>Baseline Measure Mean</th>
<th>SD</th>
<th>Total (n)</th>
<th>Post-measure Mean</th>
<th>SD</th>
<th>Total (n)</th>
<th>Weight (%)</th>
<th>IV, Fixed (95% CI)</th>
<th>Standard Mean Difference</th>
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<tbody>
<tr>
<td>Boggio et al.⁹</td>
<td>JTT</td>
<td>54</td>
<td>16.2</td>
<td>4</td>
<td>49.4</td>
<td>12.4</td>
<td>4</td>
<td>4.6</td>
<td>0.28 (−1.12, 1.68)</td>
<td>−0.4 (−0.72, 0.55)</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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<td>59.33</td>
<td>16.54</td>
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<td>7</td>
<td>0.24 (−0.90, 1.37)</td>
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<td>Hummel, 2005</td>
<td>JTT</td>
<td>43.57</td>
<td>2.36</td>
<td>6</td>
<td>39.72</td>
<td>2.15</td>
<td>6</td>
<td>4.9</td>
<td>1.57 (0.21, 2.94)</td>
<td>0.16 (−0.60, 0.94)</td>
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<td>Hummel et al.¹¹</td>
<td>KT</td>
<td>273.5</td>
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<td>11</td>
<td>256.6</td>
<td>13.9</td>
<td>11</td>
<td>12.9</td>
<td>1.11 (0.20, 2.02)</td>
<td>−0.08 (−0.85, 0.70)</td>
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<td>Hummel et al.¹¹</td>
<td>PS</td>
<td>318.8</td>
<td>23</td>
<td>11</td>
<td>214.8</td>
<td>24</td>
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<td>10.9</td>
<td>0.25 (−0.59, 1.09)</td>
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<tr>
<td>Kim et al.¹²</td>
<td>BBT</td>
<td>35.8</td>
<td>18.59</td>
<td>10</td>
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<td>20.19</td>
<td>10</td>
<td>11.6</td>
<td>0.37 (−0.52, 1.26)</td>
<td>−0.08 (−0.85, 0.70)</td>
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<tr>
<td>Kim et al.¹²</td>
<td>FM Test</td>
<td>31</td>
<td>11.17</td>
<td>6</td>
<td>45.5</td>
<td>12.25</td>
<td>6</td>
<td>5.7</td>
<td>1.14 (−0.12, 2.40)</td>
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<tr>
<td>Mahmoudi et al.²¹</td>
<td>JTT</td>
<td>10.6</td>
<td>7.43</td>
<td>10</td>
<td>9.46</td>
<td>6.52</td>
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<td>11.8</td>
<td>0.16 (−0.72, 1.03)</td>
<td>−0.08 (−0.85, 0.70)</td>
</tr>
<tr>
<td>Stagg et al.¹⁴</td>
<td>KT</td>
<td>593</td>
<td>259.22</td>
<td>13</td>
<td>551.89</td>
<td>215.73</td>
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<td>15.3</td>
<td>0.17 (−0.60, 0.94)</td>
<td>−0.08 (−0.85, 0.70)</td>
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<tr>
<td>Stagg et al.¹⁴</td>
<td>CS</td>
<td>1.59</td>
<td>1.55</td>
<td>13</td>
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<td>15.3</td>
<td>0.40 (0.10, 0.70)</td>
<td>−0.08 (−0.85, 0.70)</td>
</tr>
</tbody>
</table>

Butler AJ et al, J Hand Ther 2013;26(2):162-70
III. Neuroplasticity - the key to recovery?

Enhancing plasticity in the motor cortex

Modulation of GABAergic and glutamatergic synapses
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

Active-Passive Bilateral Arm 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)
III. Neuroplasticity - the key to recovery?

Getting plasticity enhancement into clinical practice

Q1. Time course ....?  
- Intensive training here? 
- Enhance potential for plasticity here? 
- Motor function 
- Plasticity 
- Time post stroke

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

Q3. Impact on training....?  
- Training wrist control - tracking targets
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?
Motor recovery after stroke

III. Neuroplasticity - the key to recovery?

None have entered into routine clinical practice – why?

---

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

Summary

- We are not that good at predicting – would this help?
- Understanding residual brain structures might help
  - Predict outcome
  - Predict response to treatment
- A number of factors might contribute to poor outcome
- Increasing the dose would undoubtedly help
- Is capacity for motor learning preserved after stroke?
Motor recovery after stroke

Additional References


Predicting UL recovery after stroke

Acknowledgements

FIL:
Richard Frackowiak
Rosalyn Moran
Karl Friston
Will Penny
Jennie Newton
Peter Aston
Eric Featherstone

ABIU/NRU:
Fran Brander
Kate Kelly
Diane Playford
Alan Thompson
All QS nurses, physios, OTs, SLTs

SOBELL DEPARTMENT:
Marie-Helen Boudrias
Holly Rossiter
Chang-hyun Park
Karine Gazarian
Ella Clark
John Rothwell
Penny Talelli

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

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FUNDING:
Wellcome Trust
MRC Medical Research Council
Brain Research Trust
European Research Consortium
Plasticise
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