2nd Queen Square Upper Limb Neurorehabilitation Course

Managing the upper-limb after stroke

NICK WARD, UCL INSTITUTE OF NEUROLOGY, QUEEN SQUARE

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Upper limb recovery after stroke

Overview

1. How do we treat (upper limb dysfunction) after stroke?
2. How do we increase the dose?
3. Neuroimaging in neurorehabilitation – what is it for?
4. Enhancing plasticity in neurorehabilitation
Upper limb recovery after stroke

1. How do we treat people after stroke?
Upper limb 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
Upper limb recovery after stroke is *unacceptably poor*....

- ¾ of stroke survivors will have upper limb symptoms after acute stroke (Lawrence et al, 2001)
- **Initial severity** is most significant predictor of long term outcome (Coupar et al, 2013), but also anatomical damage
- 60% of patients with non-functional arms 1 week post-stroke didn’t recover function at 6 months (Wade et al, 1983)
- Those showing some synergistic movement in UL within 4 weeks after stroke have 90% chance of improving (Kwakkel et al, 2003)

I. How do we treat people after stroke?
Upper limb recovery after stroke

I. How do we treat people after stroke?

The dose of UL treatment after stroke is *unacceptably low*...

- Patients engaged in ‘activity’ for *only 13%* of the day (Bernhardt et al, 2004)

- Patients were *alone* for *over 60%* of the day (Bernhardt et al, 2004)

- Practice of task-specific, functional UL movements in *only 51%* of ‘UL sessions’ (Lang et al, 2009)
Is there evidence to support ‘increased dose’ - time on task?

• 2-3 hours of arm training a day for 6 weeks improved both FM and ARAT when started 1-2 months after stroke (Han et al, 2013)

• Other studies equivocal but high variability in design
  – *extra* = 2 hrs/week to 3 hrs/day
  – some initiated early, some late
Is there evidence to support ‘increased dose’ – repetitions?

- In animals, changes in primary motor cortex synaptic density occur after 400 (but not 60) reaches (Remple et al, 2001)
- Most rodent studies involve hundreds of repetitions in a training session
- In human stroke patients, typical number of repetitions in a session is 30 (Lang et al, 2009)
- Ability to perform repetitions related to function – might be a ‘threshold’ above which UL use improves and below which it decreases (Schweighofer et al, 2009)
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1. How do we treat people after stroke?

Is there evidence to support task-specific training?

- Is task-specific training enough?
- Cochrane review ‘says no’
- To be useful, task-specific training must be both retained and generalizable (Krakauer, 2006)
- Apply ‘principles of motor learning’
  1. Distributed practice - frequent and longer rest periods
  2. Variable practice - varying parameters of task
  3. Contextual interference - random ordering of related tasks
Upper limb recovery after stroke

II. Increasing the dose of what?

Motor learning principles for neurorehabilitation

TOMOKO KITAGO* AND JOHN W. KRAKAUER
Motor Performance Laboratory, Department of Neurology, The Neurological Institute,
Columbia University College of Physicians and Surgeons, New York, NY, USA


ADAPTATION

• Motor system responds to altered environment in order to regain former levels of performance
• Driven by prediction error
• Can occur in single session
• Short lived after effect

SKILL LEARNING

• Acquiring new patterns of muscle activation to achieve higher levels of performance
• Not just faster or more accurate – both
• Driven by reward and reinforcement
• Occurs within session and with extended practice
• Number of repetitions determines acquisition
• Other factors promote retention and generalisability
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II. How do we increase dose?

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

Dose is important
Motor – 1000’s of repetitions
Language – 100 hours
Upper limb recovery after stroke

II. How do we increase dose?

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
Upper limb recovery after stroke

II. How do we increase dose?

Saebo ReJoyce

Biometrics

Robotic arm training

ImAble
Upper limb recovery after stroke

II. How do we increase dose?
Upper limb recovery after stroke

II. How do we increase dose?

- Detailed upper limb assessment and report
- A thorough discussion of goals and prognosis
- Advice on symptom management
- When appropriate we will suggest further intensive in-patient treatment (involving at least 4 hours therapy per day) as part of a 3 week programme at Queen Square
- Where required, we will make referrals to other NHNN services (e.g. spasticity assessment clinic, upper limb Functional Electrical Stimulation clinic, specialist vocational rehabilitation clinic, orthotics clinic)
- We will liaise closely with local outpatient and community services where appropriate
- In all cases we will advise on how to achieve long term self-management where able

www.ucl.ac.uk/cnr/clinical/QS/nswmd

Referrals to:
Dr Nick Ward
n.ward@ucl.ac.uk
1. Predicting long term outcome
   - e.g. EXPLICIT, PREP, PLORAS

2. Predicting response to treatment
   - behavioural training
   - plasticity enhancement
Predictors of upper limb recovery after stroke: a systematic review and meta-analysis

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

Abstract
Objective: To systematically review and summarize the current available literature on prognostic variables relating to upper limb recovery following stroke. To identify which, if any variables predict upper limb recovery following stroke.

Data sources: We completed searches in MEDLINE, EMBASE, AMED, CINAHL and Cochrane CENTRAL databases. Searches were completed in November 2010.

Review methods: Studies were included if predictor variables were measured at baseline and linked to an outcome of upper limb recovery at a future time point. Exclusion criteria included predictor variables relating to response to treatment and outcome measurements of very specific upper limb impairments such as spasticity or pain. Two independent reviewers completed data extraction and assessed study quality.

Results: Fifty-eight studies met the inclusion criteria. Predictor variables which have been considered within these studies include; age, sex, lesion site, initial motor impairment, motor-evoked potentials and somatosensory-evoked potentials. Initial measures of upper limb impairment and function were found to be the most significant predictors of upper limb recovery; odds ratio 1.84 (95% confidence intervals (CI) 1.08–2.42) and 38.62 (95% CI 8.40–177.53), respectively.

Conclusions: Interpretation of these results is complicated by methodological factors including variations in study populations, upper limb motor outcome scales, timing of baseline and outcome assessments and predictors selected. The most important predictive factors for upper limb recovery following stroke appears to the initial severity of motor impairment or function.
Upper limb recovery after stroke

**III. Predicting outcome after stroke**

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**
Upper limb recovery after stroke

III. Predicting outcome after stroke

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
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 2mm³ voxel

3. A machine learning approach is used to compare lesion images to others in database and similar patients identified

4. Different ‘recovery’ curves can then be estimated for different behavioural measures
Damage to M1 pathway limits response to robot assisted therapy
Upper limb recovery after stroke

III. Predicting treatment effect after stroke

Robot-based hand motor therapy after stroke

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

Less activity in M1 limits response to robot assisted therapy

Cramer et al., Stroke 2007; 38: 2108-14
Upper limb recovery after stroke

III. Predicting treatment effect after stroke

- 17 chronic stroke patients (FM 4-25) 30 days of UL training – 30 mins +/- APBT
- Change in FM relatively small 0 – 6 points
- Overall FA (DTI) symmetry predicted ΔFM ($r^2 = 0.38$)
- But better model by considering those with and without MEPs
Upper limb recovery after stroke

III. Predicting treatment effect after stroke

Needs to inform......

‘what kind of treatment?’ not ‘who should we treat?’
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**IV. Experience dependent plasticity after stroke**

Plasticity takes place in the cortex

- changing strength of existing connections
- new connections
- getting rid of unused connections
Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

Dendrite

Axon

dendrites

axon
Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Barthel</th>
<th>ARAT</th>
<th>GRIP</th>
<th>NHPT</th>
</tr>
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<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>
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</tbody>
</table>
Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

Enhancing post-stroke plasticity....

Drugs

NIBS

BAT

... to maximise training effects
Several agents considered:

- Acetylcholinesterase inhibitors
- Amphetamine
- SSRIs (e.g. FLAME, FOCUS in UK)
- DA agonists (e.g. DARS in UK)

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

IV. Experience dependent plasticity 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></td>
<td>Mean</td>
<td>SD</td>
<td>Total (n)</td>
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<tr>
<td>Boggio et al. 3</td>
<td>JTT</td>
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<td>16.2</td>
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<tr>
<td>Fugl-Meyer et al. 4</td>
<td>JTT</td>
<td>63.8</td>
<td>18.22</td>
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<tr>
<td>Hummel, 2005</td>
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<td>43.37</td>
<td>2.36</td>
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<tr>
<td>Hummel et al. 13</td>
<td>RT</td>
<td>273.5</td>
<td>15.4</td>
<td>11</td>
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<tr>
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<td>PS</td>
<td>118.8</td>
<td>23</td>
<td>11</td>
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<tr>
<td>Kim et al. 12</td>
<td>BRT</td>
<td>35.8</td>
<td>18.59</td>
<td>10</td>
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<tr>
<td>Kim et al. 12</td>
<td>FM Test</td>
<td>31</td>
<td>11.17</td>
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<tr>
<td>Mahmoudi et al. 22</td>
<td>JTT</td>
<td>10.6</td>
<td>7.43</td>
<td>10</td>
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<tr>
<td>Stagg et al. 14</td>
<td>RT</td>
<td>560</td>
<td>259.22</td>
<td>13</td>
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<tr>
<td>Stagg et al. 14</td>
<td>GS</td>
<td>1.59</td>
<td>1.55</td>
<td>13</td>
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<tr>
<td>Total</td>
<td></td>
<td>90</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>
Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

Why not perform large RCTs?

Inhibitory TBS?  Excitatory TBS?

TBS (and TDCS) is very variable!

Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

Getting plasticity enhancement into clinical practice

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

Q2. Effect of intervention ....?  
- Fluoxetine  
- ... OR...  
- TDCS  

Early?  
Late?

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

IV. Experience dependent plasticity after stroke

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;43:2185-2191.)

ctDCS to contralesional M1 reduced
SICI (less inhibition) in ipsilesional M1

tDCS-induced enhancement of skill acquisition

Reduced intracortical inhibition re-opens periods of plasticity in chronic stroke?
Upper limb recovery after stroke

IV. Experience dependent plasticity after stroke

Intracortical networks

Task related networks

Large scale networks

MESOSCOPIC

MACROSCOPIC
Upper limb recovery after stroke

Summary

• Upper limb recovery after stroke is *unacceptably poor*....
• The dose of UL treatment after stroke is *unacceptably low*...
• We need to increase the dose of therapy
• Technology and new clinical services can help achieve this
• Neuroscience will help to understand the mechanisms of recovery allowing us to target appropriate interventions to appropriate patients
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Some more slides at www.ucl.ac.uk/ion/departments/sobell/Research/NWard

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References