NIHR STROKE RESEARCH WORKSHOP, Cambridge, 11th September 2017

Stroke Recovery - What is the Future?

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Overview

1. Think carefully about delivering the right dose
2. Incorporate spontaneous biological recovery
3. Develop models to predict outcomes
Promoting Recovery After Stroke

*Stroke – post-stroke care*

People with stroke should accumulate **at least 45 minutes** of each appropriate therapy every day, at a frequency that enables them to meet their rehabilitation goals, and **for as long as they are willing and capable of participating** and showing measurable benefit from treatment.

Royal College of Physicians – National Clinical Guideline for Stroke

### SSNAP data

<table>
<thead>
<tr>
<th></th>
<th>Three monthly</th>
<th>Four monthly</th>
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</thead>
<tbody>
<tr>
<td><strong>6.1 Percentage of patients reported as requiring physiotherapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Oct-Dec 2015</td>
<td>85.6%</td>
<td>85.2%</td>
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<tr>
<td>Jan-Mar 2016</td>
<td></td>
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<td>Apr-Jul 2016</td>
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<tr>
<td>Aug-Nov 2016</td>
<td>85.2%</td>
<td></td>
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<tr>
<td><strong>6.2 Median number of minutes per day on which physiotherapy is received</strong></td>
<td>35.0</td>
<td>33.8</td>
</tr>
<tr>
<td><strong>6.3 Median % of days as an inpatient on which physiotherapy is received</strong></td>
<td>71.9%</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

- Average stay in ASU = **17 Days**
- **17 days*35 mins*74% = 7.3 hours** in total
- Only 10-25% of sessions ‘active’

- Reduce long-term dependency, admission to institutional care, length of admission (by 6 days)
- No clear differences in ADLs, subjective health status or mood
- No evidence that services without co-ordinated MDT input have any benefit (may cause harm)
1. How to turn non-recoverers into (proportional) recoverers?
2. How to improve on regaining 70% of what is lost?
Promoting Recovery After Stroke

*Upper limb treatment – early*

**Original Investigation**

Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke

The ICARE Randomized Clinical Trial

Carolee J. Weinstein, PhD; Steven L. Wolf, PhD; Alexander W. Dromerick, MD; Christianne J. Lane, PhD; Monica A. Nelsen, DPT; Rebecca Lewthwaite, PhD; Steven Yong Cen, PhD; Stanley P. Azen, PhD; for the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) Investigative Team

*JAMA. 2016;315*(6):571-581

Mean baseline FM-UL = 41 +/- 9

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30 hours over 10 weeks
Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial

Chao Han, Qiang Wang, Ping-ping Meng and Ming-zhu Qi

Table 2. Comparisons of outcomes of patients in three groups (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMA (UE)</td>
<td>6.70 ± 2.26</td>
<td>8.20 ± 3.43</td>
<td>6.50 ± 3.06</td>
<td>0.386</td>
</tr>
<tr>
<td>ARAT</td>
<td>0.80 ± 1.14</td>
<td>1.50 ± 1.58</td>
<td>1.10 ± 1.52</td>
<td>0.553</td>
</tr>
<tr>
<td>BI</td>
<td>51.50 ± 22.49</td>
<td>62.50 ± 20.98</td>
<td>50.50 ± 23.33</td>
<td>0.422</td>
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<tr>
<td><strong>6 weeks after treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMA (UE)</td>
<td>13.00 ± 6.38</td>
<td>19.70 ± 7.09</td>
<td>24.50 ± 7.96</td>
<td>0.005</td>
</tr>
<tr>
<td>ARAT</td>
<td>5.30 ± 3.40</td>
<td>8.70 ± 4.62</td>
<td>10.90 ± 3.60</td>
<td>0.008</td>
</tr>
<tr>
<td>BI</td>
<td>85.00 ± 11.79</td>
<td>88.00 ± 10.33</td>
<td>89.50 ± 6.85</td>
<td>0.590</td>
</tr>
</tbody>
</table>

FMA (UE), Fugl-Meyer Assessment (upper extremity); ARAT, Action Research Arm Test; BI, Barthel Index; Group A, Group B and Group C, each group received arm rehabilitation training for 1 hour, 2 hours and 3 hours a day respectively.

90 hours over 6 weeks

- Patients 40 (+/-20) days post-stroke
- Mean baseline FM 6-8
- Arm training 1, 2, 3 hrs/day, 5 days/wk, 6 wks
- Training depending on patient’s impairments
Promoting Recovery After Stroke

*Upper limb treatment – chronic*

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

**MIT-Manus**

36 hours over 12 weeks
127 patients (36 x 60 mins)
Mean baseline FM-UL = 17-20 +/- 10

robot vs matched = -0.1 on UL-FM*
robot vs usual = +2.17 on UL-FM*

**ARMin**

36 hours over 12 weeks

18 hours over 8 weeks
73 patients (24 x 45 mins)
Mean baseline FM-UL = 20 +/- 8

robot vs matched = +0.8 on UL-FM

**THE LANCET Neurology**

Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial

Lancet Neurol 2014; 13: 159–66
300 hours of UL therapy over 12 weeks = 8-11 points on UL-FM
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*Increasing the dose*

- Patricia Neal suffered a haemorrhagic stroke in 1965 aged 39
- “Surely one hour a day is not enough” Roald Dahl
- “......she pulled through with the assistance of Dahl, and a number of volunteers, who developed a gruelling style of therapy that fundamentally changed the way stroke patients were treated” Wikipedia
- “This method was viewed as cruel, and was at odds with standard rehabilitation techniques used at the time”
- She went back to acting in 1968 and received an Oscar nomination
- She received 1000’s of hours of ‘behavioural’ treatment

https://www.theguardian.com/books/2016/sep/12/roald-dahl-medical-pioneer-stroke-hydrocephalus-measles-vacci
Upper limb therapy - summary

• We don’t give enough to know what is possible through motor/behavioural training
• Dose response ‘emerging’ from clinical trials
• Need aspirational studies not pragmatic in rehab/restoration
• Research synthesis required “Can we stop doing what we know doesn’t work”
‘SPONTANEOUS BIOLOGICAL RECOVERY’

1. A window of opportunity after focal brain damage within which behavioural training will have a much greater impact than outside the window.

2. A rapid generalised improvement *in impairment* that is in contrast to modest gains made in the chronic phase.
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*Post-stroke plasticity – window of opportunity*

Efficacy of Rehabilitative Experience Declines with Time after Focal Ischemic Brain Injury

Jeff Biernaskie, Garry Cherenko, and Dale Corbett


Early retraining = improved recovery

increased the number of branches and complexity of layer V neurons
Promoting Recovery After Stroke

*Post-stroke plasticity – window of opportunity*
Promoting Recovery After Stroke

Response to injury – enhanced plasticity?

Wieloch & Nikolich, *Current Opinion in Neurobiology* 2006
Promoting Recovery After Stroke

Therapeutic opportunities to promote recovery

- Reducing GABAergic inhibition
- Increased BDNF expression

Fluoxetine

Targets α5 subunit of extrasynaptic GABA$_A$ receptor to reverse early (weeks) post-stroke tonic inhibition

Trials imminent in early human stroke

Clinical trials - FLAME / FOCUS

Other drugs?
rtMS/DCS?
Aerobic exercise?

Hypoexcitability

- GABA uptake
- Neuronal excitability
- Diminished recovery

Increased excitability

- AMPA receptor stimulation
- Neuronal excitability
- Enhanced LTP
- Axonal sprouting
- BDNF signaling
- Increased recovery

A biomarker is an indicator of disease state that is useful clinically as a substitute measure, reflecting underlying molecular/cellular events that are difficult to measure directly (in humans).

“...the spectral characteristics of M/EEG recordings provide a marker of cortical GABAergic activity”

Ward NS. *Brain* 2015;138:2811-3
Plasticity - summary

• Stroke induces critical period plasticity – we should seek evidence of this in humans to justify early intense therapy/training

• Window does not shut!

• Drugs available to manipulate plasticity in humans now!

• Need biomarkers to know who and when to treat
Promoting Recovery After Stroke

Stratification in clinical trials of recovery

Winters et al, Trials. 2016;17:468
Promoting Recovery After Stroke

Does recovery depend on CST?

Early Fiber Number Ratio Is a Surrogate of Corticospinal Tract Integrity and Predicts Motor Recovery After Stroke

Antoine Bigourdan, MD*; Fanny Munsch, PhD*; Pierrick Coupé, PhD; Charles R.G. Guttmann, MD; Sharmila Sagnier, MD; Pauline Renou, MD; Sabrina Debruxelles, MD; Mathilde Poli, MD; Vincent Dousset, MD, PhD; Igor Sibon, MD, PhD; Thomas Tourdias, MD, PhD

*Corresponding authors

Stroke. 2016;47:1053-1059

Subpopulation of severe patients (n=26)

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- iFnr<0.26 (n=11)
- iFnr>0.26 (n=15)
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*Does recovery depend on anatomy?*

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**Classification accuracy**

- **CST = 73%**
- **MOTOR = 87%**

Rondina J et al. JNNP 2017;88:737-743
Predicting language outcome and recovery after stroke: the PLORAS system

Cathy J. Price, Mohamed L. Seghier and Alex P. Leff  Nat Rev Neurol. 2010 Apr;6(4):202-10

Predicting language recovery - PLORAS

Hope et al., Neuroimage Clinical, 2013
Prediction & stratification - summary

• Best predictor of UL recovery is initial impairment

• Anatomical damage carries independently useful information – but not just CST

• Prediction will ultimately be useful information for patients, relatives, clinicians

• Stratifying patients in rehab trials based on expected outcomes should reduce size of samples required in RCTs or early recovery treatments
Promoting Recovery After Stroke

A mechanistic approach

**Prediction**
- New models to *predict* upper limb outcome
- brain structure?
- brain function?
- Poor recovery
- Good recovery

**Mechanism**
- Mechanistic understanding of early recovery *in humans*
- in vitro
- rodents
- mesoscopic
- macroscopic
- human

**Therapy**
- **Biomarkers** for identifying who and when to treat
- fluoxetine? (α5IA? hyperexcitability? hypoexcitability?)
- time post stroke
- cortic excitability
1. More is better. We don’t give enough physical or behavioural interventions to drive recovery.

2. Anatomy of damage in whole brain can help predict outcome and therefore stratification in restorative trials

3. There are clear lesion induced changes in structure that can support recovery – anti NoGo, inosine, GDF10, stem cells

4. Pushing inhibitory/excitatory balance away from inhibition opens door to structural plasticity

5. Need biomarkers of these processes in humans so we know what to target - drugs available now!

6. Too early for phase III trials - Understanding the mechanisms involved first (or at least in parallel) is crucial (fundors please note!)


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