Brain plasticity post stroke

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BASP: Advanced Stroke Medicine, 24th March 2012
after thrombolysis ........
Brain Plasticity & Stroke
Stroke – what’s the problem?

stroke damage
Brain Plasticity & Stroke

Stroke – what’s the problem?

stroke damage  damaged pathways  damaged cortex
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.

1. Assessment
2. Goal setting
3. Intervention
   i. treatments, which affect the process of change
   ii. support, which maintains the patient's quality of life and his or her safety
4. Evaluation to check on the effects of any intervention

How is that long term improvement taking place?

Should we challenge the idea of the recovery plateau?
Brain Plasticity & Stroke
Rehabilitation

.....assuming that we can avoid the complications of stroke
PLASTICITY is

- the formation of new functional connections between nerve cells
- the withdrawal of inappropriate connections
- the modulation of strength between the cell-cell connections called synapses

changes that occur in the organization of the brain as a result of experience (and that improve function)
Brain Plasticity & Stroke

What is brain plasticity?

Rapid presynaptic firing produces strong activation of the AMPA receptor hence strong postsynaptic depolarisation. This removes the voltage-dependent Mg$^{2+}$ block of the NMDA receptor enabling a postsynaptic influx of calcium.

**Lesion induced changes:**

**Activity**

**Inactivity**

**Cortical plasticity**

**LTP induction**

experience

brain injury

functional outcome

structural plasticity

behavior

secondary degeneration
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What is brain plasticity?

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…..”
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Can we see it?

Dendritic growth *in vivo*

Axon arborisation *in vivo*

What do we mean by reorganisation?

dendrites

axon
Brain Plasticity & Stroke
Can we see it?

Brain Plasticity & Stroke
What is brain plasticity?

“... the cortex is not capable of plasticity but is hardwired and immutable. Once damage occurred, cortical neurons either died or at best did not change their projection patterns.....”

The structure of the brain is constantly changing – this is the basis of learning both in health and disease.

However, it requires ‘activity’ to take advantage of these processes and create new connections and networks.
Motor learning: its relevance to stroke recovery and neurorehabilitation
John W. Krakauer

Purpose of review
Much of neurorehabilitation rests on the assumption that patients can improve with practice. This review will focus on six movements and address the following questions: (i) What is motor learning? (ii) Do patients with hemiparesis have a learning deficit? (iii) How does recovery after injury occur? (iv) Are approaches based on motor learning principles useful for rehabilitation? (v) Recent findings
Motor learning can be broken into kinematic and dynamic components. Studies in healthy subjects suggest that retention of motor learning is best accomplished with variable training schedules. Animal models and functional imaging in humans show that the mature brain can undergo plastic changes during both learning and recovery. Quantitative motor control approaches allow differentiation between compensation and true recovery, although both improve with practice. Several promising new rehabilitation approaches are based on theories of motor learning. These include: (i) Impaired-oriented training (IOT), constraint-induced movement therapy (CIMT), electromyogram (EMG)-triggered neurostimulation, robotic interactive therapy and virtual reality (VR).

Summary
Motor learning mechanisms are operative during spontaneous stroke recovery and interact with rehabilitative training. For optimal results, rehabilitation techniques should be geared towards patients’ specific motor deficits and possibly combined, for example, CIMT with VR. Two critical questions that should always be asked of a rehabilitation technique are whether gains persist for a significant period after training and whether they generalize to untrained tasks.

Key words
hemiparesis, motor control, motor learning, reaching, rehabilitation, stroke recovery.

Curt Opp Opinnen: 1984-90 © 2005 Lippincott Williams & Wilkins.
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Introduction
‘Rehabilitation, for patients, is fundamentally a process of relearning how to move to carry out their needs successfully’ [1]. This statement succinctly points out the fact that rehabilitation is predicated on the assumption that practice or training leads to improvement of skills after hemiparesis. Despite this underlying assumption, evidence in motor control and motor learning has only recently been brought to bear on the practice of rehabilitation. Instead, stroke rehabilitation has focused either on passive facilitation of isolated movements or teaching patients to function independently using movements alternative to the ones they used before their stroke. In addition, inordinate emphasis has been placed on therapy for spasticity despite substantial evidence indicating that it does not make a significant contribution to movement dysfunction [2].

Motor control and motor learning in healthy subjects
Motor learning does not need to be rigidly defined in order to be effectively studied. Instead it is better thought of as a fuzzy category [3]** that includes skill acquisition, motor adaptation, such as prism adaptation, and decision making, that is, the ability to select the correct movement in the proper context. A motor skill is the ability to plan and execute a movement goal. The computational steps required to go from goal to action for reaching movements have been extensively studied over the last 20 years (see the monograph by Shadmehr and Wise [4])** but the knowledge of motor control gained has only recently begun to be applied to the characterization and treatment of the motor deficit after hemiparesis.

Motor control sciences make an important distinction between the geometry and speed of a movement (kinesiology) and the forces needed to generate the movement (dynamics). This distinction can be better

Task specific training ..... 1. is better than general exercise
2. works better in patients with reasonable residual motor control
3. optimal dose is important but not clear
4. Better retention and generalisation can be achieved by:
   a) Distributed practice - frequent and longer rest periods
   b) Variable practice - varying parameters of task
   c) Contextual interference - random ordering of related tasks
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How to enhance plastic change?

Enhancing Plasticity

• Cortical stimulation with task oriented training e.g. rTMS or TDCS
• Motor imagery, action observation
• Pharmacotherapy e.g. amphetamine, DA agonists (DARS), Fluoxetine (FLAME)

Enhancing Wiring

Review

Promoting axonal rewiring to improve outcome after stroke

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Brain Plasticity & Stroke
Barriers to translation?

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

Background. Major advances during the past 50 years highlight the immense potential for restoration of function after neural injury, even in the damaged adult human brain. Yet, the translation of these advances into clinically useful treatments is painstakingly slow. Objective. Here, we consider why the traditional model of a "translational research pipeline" that transforms basic science into novel clinical practice has failed to improve rehabilitation practice for people after stroke. Methods. We find that (1) most treatments tested in vitro and in animal models have not yet resulted in obviously useful functional gains in patients; (2) most clinical trials of restorative treatments after stroke have been limited to small-scale studies; (3) patient recruitment for larger clinical trials is difficult; (4) the determinants of patient outcomes and what patients want remain complex and ill-defined, so that basic scientists have no clear view of the clinical importance of the problems that they are addressing; (5) research in academic neuroscience centers is poorly integrated with practice in front-line hospitals and the community, where the majority of patients are treated; and (6) partnership with both industry stakeholders and patient pressure groups is poorly developed, at least in the United Kingdom where research in the translational restorative neurosciences in stroke depends on public sector research funds and private charities. Conclusions. We argue that interaction between patients, front-line clinicians, and clinical and basic scientists is essential so that they can explore their different priorities, skills, and concerns. These interactions can be facilitated by funding research consortia that include basic and clinical scientists, clinicians and patient/carer representatives with funds targeted at those impairments that are major determinants of patient and carer outcomes. Consortia would be instrumental in developing a lexicon of common methods, standardized outcome measures, data sharing and long-term goals. Interactions of this sort would create a research-friendly, rather than only target-led, culture in front-line stroke rehabilitation services.

........ assuming that all patients have similar likelihood of response [Ward, CoN 2008]
Brain Plasticity & Stroke
Driving plastic change

Ward and Cohen, Arch Neurol 2004
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Lesion induced brain reorganisation

Affected hand

Unaffected hand
Brain Plasticity & Stroke
Variability in lesion induced brain reorganisation - fMRI

Ward et al., Brain 2006

Increasing ‘main effect’ of left hand grip

affected hemisphere

more CS damage

less CS damage
Brain Plasticity & Stroke

Variability in lesion induced brain reorganisation - fMRI

Increasing ‘main effect’ of left hand grip

affected hemisphere

more CS damage

less CS damage

Ward et al., Brain 2006
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Is this reorganisation doing something useful?

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
Disruption to CST leads to a shift of activity away from primary to secondary motor areas.

Ipsilateral and secondary motor areas may be using non-monosynaptic pathways.

These areas often associated with motor synergies e.g. flexor synergy.

Can this be functionally useful?


Brain Plasticity & Stroke
Variability in lesion induced brain reorganisation
Brain Plasticity & Stroke
Variability in lesion induced brain reorganisation

<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>
Before and after treatment fMRI studies – what do they tell us?

### Table 1: Studies Using fMRI to Study Effects of Restorative Poststroke Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Mean Age (yr)</th>
<th>Handedness (RI)</th>
<th>Side of Lesion (RI)</th>
<th>Control Group</th>
<th>Hours Feltab Therapy</th>
<th>Time From Stroke Onset</th>
<th>Location</th>
<th>Primary Clinical Outcome Measure</th>
<th>Primary fMRI Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindberg et al.</td>
<td>10 (8/2)</td>
<td>58.4</td>
<td>2/0</td>
<td>2/0</td>
<td>None</td>
<td>10-13</td>
<td>25.3</td>
<td>2 cortical</td>
<td>MCP joint extension, UE MAS</td>
<td>Voxel count, visual intensity</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>16 (11/5)</td>
<td>60.1±14.5</td>
<td>14/2</td>
<td>8/8</td>
<td>Sham-treated stroke patients</td>
<td>60</td>
<td>35.5</td>
<td>3 cortical, 10 subcortical, 1 cortical &amp; subcortical, 2 brainstem</td>
<td>Box and block, MAL, JMT</td>
<td>Voxel count, visual intensity, Intensity Index</td>
</tr>
<tr>
<td>Luft et al.</td>
<td>21 (12/9)</td>
<td>BATRAC, 63.3±16.3 DMTE, 50.6±10.5</td>
<td>NR</td>
<td>14/7</td>
<td>CMTE-treated stroke patients</td>
<td>6</td>
<td>60.3</td>
<td>12 cortical, 6 subcortical, 3 brainstem</td>
<td>UE FMA, WMFT</td>
<td>Voxel count</td>
</tr>
<tr>
<td>Paioni et al.</td>
<td>8 (5/3)</td>
<td>61.7</td>
<td>NR</td>
<td>3/5</td>
<td>Placebo-treated stroke patients</td>
<td>Single session</td>
<td>0.5</td>
<td>7 subcortical, 1 brainstem</td>
<td>Finger tapping</td>
<td>Voxel intensity</td>
</tr>
<tr>
<td>Schmahotter et al.</td>
<td>4 (3/1)</td>
<td>57±17</td>
<td>44</td>
<td>1/3</td>
<td>Healthy subjects</td>
<td>40</td>
<td>12.5</td>
<td>2 cortical, 1 subcortical, 1 brainstem</td>
<td>MAL, UE FMA, WMFT</td>
<td>Voxel intensity, Laterality Index</td>
</tr>
<tr>
<td>Casey et al.</td>
<td>10 (6/4)</td>
<td>60.7±13.3</td>
<td>8/1</td>
<td>4/6</td>
<td>Healthy controls and stroke patients</td>
<td>13±20</td>
<td>66.4</td>
<td>1 cortical, 6 subcortical, 2 cortical &amp; subcortical, 1 brainstem</td>
<td>Box and block, finger tracking</td>
<td>Voxel count, Laterality Index</td>
</tr>
<tr>
<td>Johansson-Berg et al.</td>
<td>7 (6/2)</td>
<td>55.6</td>
<td>6/1</td>
<td>3/4</td>
<td>None</td>
<td>14</td>
<td>27.6</td>
<td>6 cortical, 1 subcortical</td>
<td>Grip strength, UE Motility Index, JTHT</td>
<td>Laterality Index, voxel count, z score, recovery weighted activation</td>
</tr>
<tr>
<td>You et al.</td>
<td>10 (7/3)</td>
<td>54</td>
<td>NR</td>
<td>7/3</td>
<td>Stroke patients</td>
<td>20</td>
<td>19.3</td>
<td>10 subcortical</td>
<td>FAC, mMAS</td>
<td>Voxel count, Laterality Index</td>
</tr>
<tr>
<td>Levy et al.</td>
<td>2 (1/1)</td>
<td>48.6</td>
<td>1/1</td>
<td>1/1</td>
<td>None</td>
<td>30</td>
<td>6.8</td>
<td>2 cortical</td>
<td>WMFT, MAL</td>
<td>Voxel count, Laterality Index</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>6 (5/0)</td>
<td>64.8</td>
<td>6/0</td>
<td>2/3</td>
<td>None</td>
<td>98</td>
<td>21.4</td>
<td>4 cortical</td>
<td>FMA, 9-hole peg test, JTHT</td>
<td>Voxel count</td>
</tr>
<tr>
<td>Lempert et al.</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>None</td>
<td>60</td>
<td>23</td>
<td>2 cortical, 6 subcortical, 3 cortical &amp; subcortical, 1 brainstem</td>
<td>MAL, UE FMA</td>
<td>Activation volume, Location voxel of maximum activation</td>
</tr>
<tr>
<td>Crainz et al.</td>
<td>12 (6/6)</td>
<td>61</td>
<td>5/6</td>
<td>6/6</td>
<td>Ambidextrous</td>
<td>45</td>
<td>23</td>
<td>2 cortical, 6 subcortical, 3 cortical &amp; subcortical, 1 brainstem</td>
<td>OT + epidural stimulation</td>
<td>Voxel count, visual intensity, Intensity Index</td>
</tr>
<tr>
<td>Casey et al.</td>
<td>11 (8/0)</td>
<td>50</td>
<td>1/0</td>
<td>6/1</td>
<td>None</td>
<td>12</td>
<td>20</td>
<td>1 brainstem</td>
<td>Ankle movement measures</td>
<td>Voxel count, visual intensity, Intensity Index</td>
</tr>
</tbody>
</table>

**Table Notes:**
- **BATRAC:** bilateral arm training with auditory cuing.
- **DMTE:** dose-matched therapeutic exercise.
- **RI:** right hand.
- **UE:** upper extremity.
- **MAL:** Motor Activity Log.
- **mMAS:** modified Motor Assessment Scale.
- **CMTE:** cholesterol-modified training exercise.
- **OT:** occupational therapy.
- **JTHT:** Jodell-Taylor Hand Test.
- **mA:** motor activity.
- **MAS:** Modified Ashworth Scale.
- **JTHT:** Jodell-Taylor Hand Test.
- **MAL:** Motor Activity Log.
- **MCP:** metacarpophalangeal.
- **UE:** upper extremity.
- **Voxel:** volume of interest.

**Abbreviations:**
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- MCP: metacarpophalangeal.
- UE: upper extremity.
- Voxel: volume of interest.

**Footnotes:**
1. Total treatment group, in months; mean values except median for Luft et al.
2. Total treatment group, crossed over to treatment.
3. Five treatment, four controls.
4. Includes 1 trauma patient.
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Treatment induced changes in brain reorganisation

- Variability amongst trial designs, although all post vs pre design
- The majority of studies were performed on well-recovered patients
- Treatment associated increase in activation in ipsilesional M1, PMd, SMA

- However, in patients with more severe baseline deficits,
  - post treatment increases in the contralesional motor regions, and
  - shifts in laterality towards the uninjured hemisphere have been found (Schaechter et al, 2002, Luft et al., 2004)
Will the same treatment strategy work in these patients?
Brain Plasticity & Stroke
Assessment of structural damage

Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke

**ABSTRACT**

Objectives: Motor impairment after stroke has been related to infarct size, infarct location, and integrity of motor tracts. To determine the value of diffusion tensor imaging (DTI) as a predictor of motor outcome and its role as a structural surrogate marker of impairment in chronic stroke, we tested correlations between motor impairment and DTI-derived measures of motor tract integrity.

Methods: Thirty-five chronic stroke patients with varying degrees of recovery underwent DTI and motor impairment assessments. Fibers originating from the precentral gyrus were traced and segmented into pyramidal tract (PT) and alternating motor fibers (AMF). Asymmetry indices of fiber number and regional fractional anisotropy (FA) values were calculated for each patient and compared to an age-matched control group.

Results: Fiber number and regional FA value asymmetry significantly differed between the groups with lower values in the patients' affected hemispheres. Both measures significantly predicted motor impairment with stronger predictions when both motor tracts were combined as compared to predictions using only the PT. The patterns of motor tract damage (PT only vs PT and AMF) led to a classification of mild, moderate, or severe impairment with significant between-group differences in motor impairment scores.

Conclusions: Diffusion tensor imaging-derived measures are valid structural markers of motor impairment. The integrity of all descending motor tracts, not merely the pyramidal tract, appears to account for stroke recovery. A 3-tier, hierarchical classification of impairment categories based on the pattern of motor tract damage is proposed that might be helpful in predicting recovery potential. *Neurology* 2013;74:260–267

Non-invasive mapping of corticofugal fibres from multiple motor areas—relevance to stroke recovery

Jennifer M. Newton,1 Nick S. Ward,1,2 Geoffrey J. M. Parker,4 Ralf Deichmann,1 Daniel C. Alexander,3 Karl J. Friston1 and Richard S. J. Frackowiak1,3,5,6

doi:10.1093/brain/awl106

Brain (2006), 129, 1844–1858

[Image showing brain scans and diagrams]
Anatomy of Stroke Injury Predicts Gains From Therapy

Jeff D. Riley, MD; Vu Le, MS; Lucy Der-Yeghiazian, MA, OTR/L; Jill Sea, MPT; Jennifer M. Newton, PhD; Nick S. Ward, MD, FRCP; Steven C. Cramer, MD

Background and Purpose—Many therapies are emerging that aim to improve motor function in people with stroke. Identifying key biological substrates needed for treatment gains would help to predict treatment effects and to maximize treatment impact. The current study addressed the hypothesis that behavioral gains from therapy targeting distal upper extremity are predicted by the structural integrity of key motor system white matter tracts.

Methods—Twenty-three subjects with chronic left-sided stroke underwent robotic therapy targeting the distal right upper extremity. MRI was obtained at baseline and used to outline the infarct. For each subject, the degree to which stroke injured each of 4 descending white matter tracts (from the primary motor cortex, supplementary motor area, dorsal premotor cortex, and ventral premotor cortex, respectively) was determined. Correlations between tract-specific injury and behavioral gains from therapy were then examined.

Results—Numerous examples were found whereby tract-specific injury predicted treatment gains. The strongest correlations pertained to stroke injury to tracts descending from the primary motor cortex and dorsal premotor cortex. Infarct volume and baseline behavior were weak predictors of treatment gains.

Conclusions—Extent of injury to specific motor tracts predicts behavioral gains from treatment in subjects with chronic stroke. This supports a role for these tracts in mediating treatment effects and reinforces the importance of lesion location in stroke. Tract-specific injury was stronger than infarct volume or baseline clinical status at predicting gains, identifies subjects with sufficient biological substrate to improve from therapy, and so might be useful as an entry criterion in repair-based trials. (Stroke. 2011;42:2142-2146.)
Brain Plasticity & Stroke

What is brain plasticity?

The brain is ‘plastic’ even months and years after stroke.

Some rehabilitation treatments take advantage of plasticity (as long as you avoid the complications of stroke).

Brain imaging might help us to understand who will benefit from which type of treatment.
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