Understanding the pattern of functional recovery after stroke

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Who is regaining dexterity and walking ability after stroke?

What are the biological regularities in the pattern of functional recovery after stroke and what is the evidence for our ability to modulate this pattern?

Who is regaining dexterity and walking ability after stroke?

Which mechanisms are responsible for the non-linear pattern of functional recovery after stroke?

What is changing when patients recover in terms of motor performance?

Recovery profiles of 10 random selected stroke patients with a first-ever MCA stroke
Individual curve fitting (N=89)

ANOVA (residuals)

Exponential model

Sigmoidal (floating) model

Linear model

ANOVA (p=0.002)

\[ F(t) = \frac{A_p}{1 + e^{-K(t - C)}} \]

\( t \) in weeks

\( F(t) \)

\( A_p \)

5 weeks

(Std: 6.8)

\( C \)

\( K \)

\( C \) versus \( A_p \): \( r_s = 0.69^{**}; p<0.001 \)

\( K \) versus \( A_p \): \( r_s = 0.47^{**}; p<0.001 \)

Coefficient of Scalability: 0.72 (week 26) < CS < 0.85 (week 3)
Logit item step difficulties (I) of the Rasch homogeneous 8-item Barthel scale (N=559).

Effects of intensive task-oriented upper and lower limb training (N=101)

Example of an immobilized patient in the control group
Are we able to modulate the pattern of functional recovery?

- Higher intensity of lower extremity rehabilitation improves lower limb motor function and gait-related activities in MCA stroke victims.
- Higher intensity of upper extremity rehabilitation results in improvements in motor function and dexterity of upper extremity.
- Both findings provide further evidence that exercise therapy primarily induces treatment effects in functions specifically trained for.
Task-oriented intensive treatment

Intensity vs. Task & (context) specificity

Which (exercise) interventions showed evidence?

Activity-level

Level A recommendations: STRONG EVIDENCE (n=67 RCTs)

- Intensity of training [20 RCTs; N=2686]
  - (functional) outcome: gait-related ADLs ↑

  Intervention: (by workstations) [14 RCTs; N=501]
  - Reaching while sitting [4 RCTs; N=108]
  - Standing up & sitting down [5 RCTs; N=156]
  - Functional-oriented fitness training
  - Early supported discharge [12 RCTs; n=1659]
  - Mobility services at home [8 RCTs; N=1143]
  - CIMT* [16 RCTs; N=569]

  * Some initial voluntary extension of the wrist and fingers is required

Level B recommendations: LIMITED EVIDENCE (n=46 RCTs)

- External auditory rhythms during gait [3 RCTs; N=80]
  - (functional) outcome: walking velocity ↑

- Cardio-respiratory fitness training
  - BATRAC [1 RCT; N=23]
  - Robot-assisted training of upper paretic limb [10 RCTs; N=218]
  - Mirror-therapy of the upper paretic limb* [2 RCTs; N=25]

  * Some initial voluntary extension of the wrist and fingers is required

- Functional NMS of upper* or lower paretic limb [24 RCTs; N=840]
  - (Functional) ADLs ↑

- Strategy training (dyspraxia) [4 RCTs; N=267]

  * Some initial voluntary extension of the wrist and fingers is required
**Which (exercise) interventions showed evidence?**

**Activity-level**

<table>
<thead>
<tr>
<th>Level A and B recommendations with NO or CONFLICTING evidence (n=86 RCTs):</th>
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</thead>
<tbody>
<tr>
<td>• Lower limb strengthening programs  (6 RCTs; N=213)</td>
</tr>
<tr>
<td>• Visual Feed Back Therapy while standing  (8 RCTs; N=214)</td>
</tr>
<tr>
<td>• Bio- and EMG-feedback training for upper or lower limb (13 RCTs, N=269)</td>
</tr>
<tr>
<td>• Treadmill training with and without body weight support for walking (15 RCTs, N=632)</td>
</tr>
<tr>
<td>• Limb loading/Garments for gait (1 RCT; N=24)</td>
</tr>
<tr>
<td>• Acupuncture post stroke (14 RCTs; N=1208)</td>
</tr>
<tr>
<td>• Amphetamines combined with exercise therapy (8 RCTs; N=243)</td>
</tr>
<tr>
<td>• Neurological approaches including Bobath therapy (21 RCTs; N=1033)</td>
</tr>
</tbody>
</table>

**Some methodological concerns:**

- Most studies show lack of treatment contrast
- Most studies are heavily underpowered due to low number of patients included
- Lower effect sizes are found in studies with high methodological quality
- A positive association is found between year of publication and methodological quality score

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*van Peppen et al, 2004: 18; 833-862*
Increasing intensity of task-oriented practice

Preventing patients to learn motor tasks

\[ \text{Effect} = \frac{\Delta \text{exp. group} - \Delta \text{control group}}{S \text{ pooled}} \]

Reducing heterogeneity by an appropriate selection of patients with potential for functional recovery

Understanding the pattern of functional recovery after stroke

- What are the biological regularities in the pattern of functional recovery after stroke and what is the evidence for our ability to modulate this pattern?
- Who is regaining dexterity and walking ability after stroke?

Mean recovery pattern of ARAT (N=102)

\[ P = \frac{1}{1 + \exp(-B_0 + B_1X_1 + B_2X_2 + B_nX_n))} \]

% of maximal score on ARAT

0 <= 10 ; 1 >= 10
### Probability of achieving dexterity (ARAT ≥ 10) after stroke:

<table>
<thead>
<tr>
<th>Week</th>
<th>Determinant (optimal cut-off)</th>
<th>FM-UE Probability (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- (MI-leg&lt;25)</td>
<td>0.14 (0.03-0.18)</td>
</tr>
<tr>
<td>Week 1</td>
<td>not included</td>
<td>0.74 (0.41-0.92)</td>
</tr>
<tr>
<td>Week 2</td>
<td>+ (FM-arm≥11)</td>
<td>0.90 (0.71-0.97)</td>
</tr>
<tr>
<td></td>
<td>+ (MI-leg≥25)</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>- (MI-leg&lt;25)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0.09 (0.03-0.18)</td>
</tr>
<tr>
<td>Week 3</td>
<td>+ (FM-arm≥13)</td>
<td>0.93 (0.74-0.96)</td>
</tr>
<tr>
<td></td>
<td>+ (MI-leg≥33)</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0.09 (0.03-0.20)</td>
</tr>
</tbody>
</table>

### Probability for achieving dexterity after MCA stroke (ARAT ≥ 10; N=102)

- (MI-leg<25) 0.14 (0.03-0.18)
- (MI-leg≥25) 0.51
- (MI-leg≥33) 0.37
Probability for achieving walking ability (FAC ≥ 4; N = 101)

Who is regaining dexterity and walking ability after stroke?

- Outcome of dexterity of the paretic limb is highly predictable within 1 month post stroke
- Recovery of independent gait is difficult to predict for those with a poor prognosis at onset
- Time seems to be an independent covariate that determines the accuracy of predicting functional outcome
Multilevel modeling of changes by random coefficient analysis:

\[ Y_{i,t-1} = \beta_0 + \beta_1(\text{progress of time})_t + \text{COVi} + \epsilon_t \]

- \( Y_{i,t-1} \): Change score for outcome \( Y \) for patient \( i \) from time \( t \) to \( t-1 \)
- \( \beta_0 \): Subject specific intercept
- \( \beta_1 \): Determinant 'progress of time' for patient \( i \) from time \( t \) to \( t-1 \)
- \( \text{COVi} \): Adjusted for clinical covariates (i.e., age, gender, type of stroke and type of intervention)
- \( \epsilon_t \): Random error

Impact of time on biweekly improvement of gait, dexterity and ADL (adjusted for age, gender, type of stroke and intervention):

<table>
<thead>
<tr>
<th>Progress of Time</th>
<th>( \Delta \text{FAC} ) (0-20)</th>
<th>( \Delta \text{ARAT} ) (0-57)</th>
<th>( \Delta \text{BI} ) (0-20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{week 0} \rightarrow 2 )</td>
<td>0.367** (0.088)</td>
<td>3.779** (0.747)</td>
<td>3.157** (0.265)</td>
</tr>
<tr>
<td>( \Delta \text{week 2} \rightarrow 4 )</td>
<td>0.432** (0.082)</td>
<td>3.180** (0.665)</td>
<td>2.027** (0.218)</td>
</tr>
<tr>
<td>( \Delta \text{week 4} \rightarrow 6 )</td>
<td>0.301** (0.083)</td>
<td>1.953** (0.607)</td>
<td>0.925** (0.219)</td>
</tr>
<tr>
<td>( \Delta \text{week 6} \rightarrow 8 )</td>
<td>0.079 (0.082)</td>
<td>1.648* (0.665)</td>
<td>0.893** (0.219)</td>
</tr>
<tr>
<td>( \Delta \text{week 8} \rightarrow 10 )</td>
<td>0.159 (0.084)</td>
<td>0.810 (0.677)</td>
<td>1.099** (0.219)</td>
</tr>
<tr>
<td>( \Delta \text{week 10} \rightarrow 12 )</td>
<td>0.111 (0.082)</td>
<td>0.435 (0.659)</td>
<td>0.235 (0.216)</td>
</tr>
<tr>
<td>( \Delta \text{week 12} \rightarrow 14 )</td>
<td>0.098 (0.082)</td>
<td>0.218 (0.658)</td>
<td>0.108 (0.215)</td>
</tr>
<tr>
<td>( \Delta \text{week 14} \rightarrow 16 )</td>
<td>0.121 (0.082)</td>
<td>0.139 (0.658)</td>
<td>0.066 (0.215)</td>
</tr>
</tbody>
</table>

Within first 4 months: ~8.1 units (~41%) ~11 units (~59%) ~11 units (~61%)

P-value based on -2Loglikelihood function with \( \chi^2 \)-distribution and 1 df

\( *p<0.01; **p<0.001 \)

Understanding the pattern of functional recovery after stroke:

- What are the biological regularities in the pattern of functional recovery after stroke and what is the evidence for our ability to modulate this pattern?
- Who is regaining dexterity and walking ability after stroke?
- Which mechanisms are responsible for the non-linear pattern of functional recovery after stroke?
I. Recovery of non-infarcted penumbral tissue

Marchal et al, Brain 1999;123:2387-2400

90% < 3 hours

Voxel-based O-PET of CBF ≈ 8.3 ml
Voxel-based O-PET of CRMO ≈ 0.87 ml

II. Reduction of temporary de-activated intact brain regions (elevation of diaschisis)

Seitz et al, Stroke 1999;30:1844-1850

Lesion-affected network (PC1)
Recovery-related network (PC3)
Spatial overlap of PC1 and PC3
Movement related network (PC8)

Functional improvement
III. Cortical reorganization due to tissue repair

Johansson, Stroke 2000; 31: 223-230

Unaffected hand


Functional improvement

A= Initial focusing

Feydy et al, Stroke. 2002;33:1610-1617

B= Progressive focusing


C= Persistent recruitment

0 10 20 30 40 50 60 70 80 90 100

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

weeks

fMRI changes

Functional recovery

?
IV. Behavioral compensation strategies

Hemispheric stroke in adult brain

- CST / M1 reversible or partly damaged
- Favorable prognosis for functional recovery
- Early widespread recruitment of functional related areas within affected hemisphere and non-affected hemisphere (e.g.: SMA, parietal cortex, cingulate cortex, basal ganglia and thalamus and cerebellum)
- Reduction in task-related recruitment in (sub)cortical activation focusing
- Persistent recruitment in task-related activation
- Predominantly negative associations between volume of recruited secondary motor areas in fMRI and functional recovery


Buurke et al, (submitted for publication)
Evidence for behavioral compensation strategies:

- Therapy-induced improvements in gait speed and walking ability occur without significant changes in EMG timing of the paretic leg while walking (Kautz et al., Neurorehabil & Neural Repair 2005;19:250-258)
- Improvement in control of standing balance occurs without significant changes in:
  a) EMG activation on the paretic side (Garland et al., Archives Phys Med Rehabil 2004; 84:1753-1758)
  b) weight bearing above the paretic leg (de Haart et al., Arch Phys Med Rehabil 2004; 85:886-895)
- Improvement of walking ability is weakly associated with observed changes in strength and synergism of the paretic leg (Kollen et al., Stroke 2005;36:2678-2685)
- Recovery of transport and hand orientation for grasping with the paretic upper limb strongly depends on adaptive trunk movements when distal deficits are present (Cirstea & Levin, Brain 2000;123:940-953)

What is changing when patients recover in terms of motor performance?

- Neural repair
- Behavioral compensation
- Skill acquisition

Diagram: Restitution + Substitution

Understanding the pattern of functional recovery after stroke: Key messages

- Neuro-rehabilitation is actually a special case of relearning to perform previously learned tasks in a different way by either using compensatory movement strategies or by adaptively recruiting alternative pathways.
- Rehabilitation is able to modulate the pattern of spontaneous recovery by intensive, task-specific training.
- Understanding the non-linear pattern of skills acquisition after stroke requires knowledge about the time-dependent nature of the mechanisms that reflect neural reorganization, recovery of body functions and use of behavioral compensation strategies.

What makes rehabilitation work?

- What exactly is learned during the acquisition of skills?
  - Restitution (repair)?
  - Substitution (compensation)?
- What is the best way to present therapeutic exercises to a patient?

Thank you for your attention!

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