EARLY PREDICTION OF THE UPPER PARETIC LIMB POST STROKE

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### Probability for return upper limb function post stroke (N=156)

**Action Research Arm Test (ARAT) score ≥ 10 points at 6 months**

<table>
<thead>
<tr>
<th>Action Research Arm Test (ARAT) score ≥ 10 points at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FINGER EXTENSION</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Model at day 2:</strong></td>
</tr>
<tr>
<td>FM-FE ≥1</td>
</tr>
<tr>
<td>FM-FE ≥1</td>
</tr>
<tr>
<td>FM-FE ≥1</td>
</tr>
</tbody>
</table>

34% full recovery  
(ARAT score = 57 points)

FM-FE: Fugl-Meyer Finger Extension  
MI-SA: Motricity Index Shoulder Abduction

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**Probability for return upper limb function post stroke (N=156)**

<table>
<thead>
<tr>
<th>Finger Extension</th>
<th>Shoulder Abduction</th>
<th>True Negatives N</th>
<th>False Negatives N</th>
<th>False Positives N</th>
<th>True Positives N</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model day 5</strong></td>
<td><em><em>P=1/(1+1</em>(EXP(-1.874+3.070</em>X1, +3.075*X2)))**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM-FE ≥1</td>
<td>MI-SA ≥9</td>
<td>+</td>
<td>+</td>
<td>38</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>FM-FE ≥1</td>
<td>MI-SA ≥9</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>104</td>
</tr>
<tr>
<td>FM-FE ≥1</td>
<td>MI-SA ≥9</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>104</td>
</tr>
</tbody>
</table>

Model day 9  
**P=1/(1+1*(EXP(-1.815+3.224*X1, +2.449*X2)))**

<table>
<thead>
<tr>
<th>Finger Extension</th>
<th>Shoulder Abduction</th>
<th>True Negatives N</th>
<th>False Negatives N</th>
<th>False Positives N</th>
<th>True Positives N</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model day 9</strong></td>
<td><em><em>P=1/(1+1</em>(EXP(-1.815+3.224</em>X1, +2.449*X2)))**</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FM-FE ≥1</td>
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<td>-</td>
<td>104</td>
</tr>
<tr>
<td>FM-FE ≥1</td>
<td>MI-SA ≥9</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>104</td>
</tr>
</tbody>
</table>

FM-FE: Fugl-Meyer Finger Extension  
MI-SA: Motricity Index Shoulder Abduction

Who shows upper limb recovery post stroke?

Probability (%)

PPV: 0.93 (95%CI: 0.88-0.96)

SAFE-algorithm
<72 hours (N=211)

NPV: 0.86 (95%CI: 0.77-0.93)

Moment of assessment post stroke (weeks)

Nijland et al, Stroke. 2010;41:745-50
Stinear et al, Lancet Neurol 2010; Dec;9(12):1228-32

Impact of time on improvement of outcome post stroke (N=101)

Kwakkel et al, Stroke. 2006 Sep;37(9):2348-53
Multilevel modeling of change scores by random coefficient analysis:

Change in $Y_{it\rightarrow t-1} = \beta_0i + \beta_1(\text{progress of time})_{it\rightarrow it-1} + \text{COV}_i + e_{it}$

$Y_{it}$: Change score for outcome Y for patient $i$ from time $t$ to $t-1$
$\beta_0i$: Subject specific intercept
$\beta_1$: Determinant ‘progress of time’ for patient $i$ from time $t$ to $t-1$
COV$_i$: Adjusted for clinical covariates (i.e., age, gender, type of stroke and type of intervention)
e$_{it}$: Random error

Kwakkel et al, Stroke. 2006 Sep;37(9):2348-53

Impact of time on biweekly improvement of motor function and dexterity (adjusted for age, gender, type of stroke and intervention) (N=102).

<table>
<thead>
<tr>
<th>impact of progress of time on outcome:</th>
<th>$\Delta$MI-Arm (0-100)</th>
<th>$\Delta$FM arm (0-66)</th>
<th>$\Delta$ARAT (0-57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• $\Delta$ week 0 → 2:</td>
<td>11.948** (1.178)</td>
<td>6.886** (0.710)</td>
<td>3.779** (0.747)</td>
</tr>
<tr>
<td>• $\Delta$ week 2 → 4:</td>
<td>7.042** (1.050)</td>
<td>3.844** (0.589)</td>
<td>3.180** (0.665)</td>
</tr>
<tr>
<td>• $\Delta$ week 4 → 6:</td>
<td>4.256** (1.064)</td>
<td>2.584** (0.597)</td>
<td>1.953** (0.670)</td>
</tr>
<tr>
<td>• $\Delta$ week 6 → 8:</td>
<td>2.921** (1.050)</td>
<td>1.548** (0.589)</td>
<td>1.648* (0.665)</td>
</tr>
<tr>
<td>• $\Delta$ week 8 → 10:</td>
<td>1.574 (1.088)</td>
<td>1.364* (0.601)</td>
<td>0.810 (0.677)</td>
</tr>
<tr>
<td>• $\Delta$ week 10 → 12:</td>
<td>0.168 (1.053)</td>
<td>0.793 (0.589)</td>
<td>0.435 (0.659)</td>
</tr>
<tr>
<td>• $\Delta$ week 12 → 14:</td>
<td>0.164 (1.050)</td>
<td>0.240 (0.587)</td>
<td>0.218 (0.658)</td>
</tr>
<tr>
<td>• $\Delta$ week 14 → 16:</td>
<td>0.800 (1.050)</td>
<td>0.502 (0.587)</td>
<td>0.139 (0.658)</td>
</tr>
</tbody>
</table>

Within first 4 months: ~26.2 units (~90%) | ~16.2 units (~91%) | ~11 units (~91%)

Kwakkel et al, Stroke 2006;37:2348-2353

*p<0.01; **p<0.001
What is the predictive validity of TMS-induced MEPs when compared to clinical SAFE model very early post stroke?

Kuijk AA et al, Neurorehabil Neural Repair. 2009 Jan;23(1):45-51
## Predictive validity of SAFE model compared to TMS-MEP measured at the end of the first week post stroke

<table>
<thead>
<tr>
<th>Clinical observation (N=159) (95%CI) at day 5</th>
<th>TMS ADM-MEP (N=35) (95%CI) at day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV : 0.93 (95%CI: 0.88 - 0.96)</td>
<td>1.00 (95%CI: 0.54 - 1.00)</td>
</tr>
<tr>
<td>NPV: 0.86 (95% CI: 0.77 - 0.93)</td>
<td>0.74 (95%CI: 0.59 - 0.90)</td>
</tr>
</tbody>
</table>

Kuijik AA et al, Neurorehab Neural Repair. 2009 Jan;23(1):45-51*

## Predictive validity of SAFE model and TMS-MEP for recovery of dexterity at 6 months using FMA ≥ 22 points as cut-off score (N=51)

<table>
<thead>
<tr>
<th>Clinical observation (95%CI) &lt; 48 hours</th>
<th>TMS ADM-MEP (95%CI) &lt; 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV : 0.95 (95%CI: 0.76–0.99)</td>
<td>0.85 (95%CI: 0.71 - 0.95)</td>
</tr>
<tr>
<td>NPV: 0.55 (95%CI: 0.44 – 0.58)</td>
<td>0.61 (95%CI: 0.44 - 0.72)</td>
</tr>
</tbody>
</table>

Hoonhorst (in preparation)*
Predictive validity of SAFE model and TMS-MEP for recovery of dexterity at 6 months using FMA ≥ 22 points as cut-off score (N=51).

Clinical observation (N=51) (95%CI) at 11 days
TMS ADM-MEP (N=51) (95%CI) at 11 days

PPV: 0.92 (95%CI: 0.78 - 0.99) 0.93 (95%CI: 0.81 - 0.99)
NPV: 0.67 (95%CI: 0.52 - 0.74) 0.76 (95%CI: 0.59 - 0.84)

Hoonhorst et al (in preparation)
SAFE: 0.880 (95%CI: 0.780 - 0.980)
SAFE + TMS-ADM: 0.905 (95%CI: 0.814 - 0.997)
TMS-ADM: 0.826 (95%CI: 0.695 - 0.958)

Z=2.06; p=0.039

Hoonhorst (submitted)

Wakana, S. et al. Radiology 2004;230:77-87
Should we stratify patients in stroke trials on the basis of initial clinical prognosis early post stroke-onset?

**SAFE-algorithm**

\textless 72 hours (N=211)

<table>
<thead>
<tr>
<th>Moment of assessment post stroke (weeks)</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;72h</td>
<td>100</td>
</tr>
<tr>
<td>5d</td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
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<tr>
<td>6</td>
<td>30</td>
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<tr>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

\textbf{PPV: 0.93} (95\%CI: 0.88-0.96)

\textbf{NPV: 0.86} (95\%CI: 0.77-0.93)

Nijland et al, Stroke. 2010;41:745-50
Stinear et al, Lancet Neurol 2010; Dec;9(12):1228-32

Prognosis for recovery of upper limb capacity

**SAFE model**

1,2

ARAT score \geq 10 points

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Full recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognosis</td>
<td>Partial recovery</td>
</tr>
</tbody>
</table>

| Stroke patients | Poor recovery |

Days post stroke

Winters et al. [in preparation]

Return of finger extension:
Prognosis for recovery of upper limb capacity (N=91)

N=91

Action Research Arm Test score (range: 0-57)

Time (weeks)

False negatives at 6 months: ARAT ≥ 10 points (N=42)
True negatives at 6 months: ARAT < 10 points (N=49)

Kaplan-Meyer curve for return of voluntary finger extension

False negatives at 6 months: ARAT ≥ 10 points (i.e.: N=42 of the 91)

Median time: 4 weeks (SE=0.54)
Upper percentile: 8 weeks (SE=0.70)
Prognosis for regaining upper limb capacity (N=91)

<table>
<thead>
<tr>
<th>LOWER LIMB MOTOR FUNCTION (MI)</th>
<th>VISUOSPATIAL NEGLECT (LCT)</th>
<th>SOMATOSENSORY DEFICIT (EmNSA)</th>
<th>Predicted probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>No</td>
<td>No</td>
<td>0.94</td>
</tr>
<tr>
<td>Poor</td>
<td>Yes</td>
<td>Yes</td>
<td>0.04</td>
</tr>
</tbody>
</table>

MI: Motricity Index leg, cutoff: 35 points;
LCT: Letter Cancellation Test, cutoff: asymmetry 2 points;
EmNSA: Erasmus MC modified Nottingham Sensory Assessment, cutoff 33 points.

Some facts ...

- Upper limb recovery is highly predictable.
- There is a critical time window in which some motor recovery should occur.
- There is a need for weekly screening of return of some voluntary finger extension within the first 12 weeks post stroke.
Prognostic algorithm for the upper paretic limb

Can the patient produce any voluntary muscle activity in the affected upper limb?

Not yet

Box 1
Compensatory Techniques

Return of shoulder abduction and elbow extension simultaneously?

Not yet

Box 2
• Hand Edema
• Cryotherapy
• Passive ROM
• Robotics
• Motor imagery
• Mirror Box
• Spasticity mgmt
  Shoulder (Box 9)

With the forearm prone on a table and the hand and fingers unsupported, can the patient initiate finger (and/or thumb) extension three times within a minute?

Not yet

Box 3
• Strengthen Shoulder and Elbow control by:
  Robotics
  -Trunk restraint
  -Motor imagery
  -Bilateral Arm Training
  -Video games
  -FES
  -Facilitate wrist/finger Extn. By Exercise, FES, mirror imagery,

Not yet

Box 4
• Task Specific
  • Mod-CIMT or signature CIMT
  • trunk restraint
  • mental practice
  • functional
  • strengthening
  • e.g. (GRASP)
  • Video Games
  • Virtual Reality

At 12 weeks Review goals and determine if a new approach is required

Wolf SL et al, Physiotherapy. 2015 Sep 26. pii: S0031-9406(15)03819-5. doi:

Stroke Rehab App.: http://www.viatherapy.org/

Wolf et al, J Physiotherapy 2015 Sep 26.)
Some facts ...

- Upper limb recovery is highly predictable.
- There is a critical time window in which some motor recovery should occur.
- There is a need for weekly screening of return of some voluntary finger extension within the first 12 weeks post stroke.
- Spontaneous neurological recovery is an important but still neglected feature of the clinical course of patients with stroke...

EPOS cohort study < 72 hours N=211

<table>
<thead>
<tr>
<th></th>
<th>Non-fitters: N=65</th>
<th>Fitters: N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta FMA_{\text{predicted}}$</td>
<td>44 points</td>
<td>18 points</td>
</tr>
<tr>
<td>$\Delta FMA_{\text{observed}}$</td>
<td>7 points</td>
<td>21 points</td>
</tr>
</tbody>
</table>

$\Delta FMA_{\text{observed}} = 0.78 \cdot (66 - FMA_{\text{initial}})$

Do all patients follow the same amount of spontaneous neurological recovery?

Proportional recovery rules following the FM-arm score (N=112; i.e., 896 measurements)

VFE onset (Favorable) N=56

Showing spontaneous recovery (i.e., Fitters) N=81

NO-VFE (Unfavorable) N=56

No spontaneous neurological recovery (i.e., Non-Fitters) N=31

~13 p. FM-arm

EPOS cohort study < 72 hours N=202

Non-fitters: N=27
ΔFMA-LE predicted = 21 points
ΔFMA-LE observed = 3 points

Fitters: N=175
ΔFMA-LE predicted = 8 points
ΔFMA-LE observed = 8 points
ΔFMA-LE observed ≈ 0.57 * (34 - FMA initial)

\[ Y = 0.84 \times + 2.50 \times FM\_leg; \quad R^2 \approx 77\% \]

Veerbeek et al., (in preparation)
Identification of fitters and non-fitters with respect to the ‘proportional recovery rule’ of the upper and lower paretic limb (expressed in %) in patients with a first-ever, ischemic lesion measured < 72 hours post stroke.

N=202
ARM & LEG

Veerbeek et al., (in preparation)

Letter cancellation task as a function of time post stroke (N=90)

Nijboer et al. Cortex 2013;49(8):2021-2027
Identification of fitters and non-fitters with respect to the ‘proportional recovery rule’ of motor recovery of the left upper paretic limb compared to those with visual inattention (expressed in %) measured in patients with a first-ever, ischemic right-hemispheric stroke lesion.
Evidence for a common underlying mechanism?

- Spontaneous motor recovery of the upper paretic limb is proportionally fixed in most patients with mild to moderate neurological deficits (~78%).

- Spontaneous recovery of visuo-spatial inattention (LCT) is proportionally fixed in most stroke patients with a right hemispheric lesion (~80%).

- Spontaneous recovery of speech (e.g. Western Aphasia Battery) is proportionally fixed in most aphasic stroke patients with a left hemispheric stroke lesion (~73%) (Lazar et al, 2010)

- There is strong evidence that the patients who are not following the expected amount of spontaneous recovery for one modality are also failing for other neurological modalities when affected in the same hemisphere.

Should we stratify randomized clinical trials into recovers and non-(spontaneous) recoveries early post stroke?

Evidence-based therapies?

Probability (%) to achieve ARAT ≥ 10 points 6 months post stroke (N=156)

SAFE-model
<72 hours

Favorable prognosis
Unfavorable prognosis

Nijland et al, Stroke. 2010;41:745-50
Stinear et al, Lancet Neurol 2010; Dec;9(12):1228-32
Interventions aimed to improve upper limb motor recovery after stroke

<table>
<thead>
<tr>
<th>Intervention or subcategory</th>
<th>Trials (number of participants)</th>
<th>SMD of outcome scale (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurophysiological approaches</td>
<td>76-86</td>
<td></td>
</tr>
<tr>
<td>Bilateral training&lt;sup&gt;9,30&lt;/sup&gt;</td>
<td>2 (111)</td>
<td></td>
</tr>
<tr>
<td>CMF&lt;sup&gt;26,52-53&lt;/sup&gt;</td>
<td>21 (546)</td>
<td></td>
</tr>
<tr>
<td>RMG biofeedback&lt;sup&gt;19,24&lt;/sup&gt;</td>
<td>4 (126)</td>
<td></td>
</tr>
<tr>
<td>Electrostimulation&lt;sup&gt;50,102&lt;/sup&gt;</td>
<td>13 (277)</td>
<td></td>
</tr>
<tr>
<td>High-intensity therapy&lt;sup&gt;74,227&lt;/sup&gt;</td>
<td>6 (521)</td>
<td></td>
</tr>
<tr>
<td>Mental practice&lt;sup&gt;37,374&lt;/sup&gt;</td>
<td>4 (73)</td>
<td></td>
</tr>
<tr>
<td>Repetitive task training&lt;sup&gt;25,31,34,109,42&lt;/sup&gt;</td>
<td>8 (414)</td>
<td></td>
</tr>
<tr>
<td>Robotics&lt;sup&gt;58,102&lt;/sup&gt;</td>
<td>10 (255)</td>
<td></td>
</tr>
<tr>
<td>Splinting or orthosis&lt;sup&gt;36,42&lt;/sup&gt;</td>
<td>4 (105)</td>
<td></td>
</tr>
<tr>
<td>Hand function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurophysiological approaches</td>
<td>24,75,37</td>
<td></td>
</tr>
<tr>
<td>Bilateral training&lt;sup&gt;29&lt;/sup&gt;</td>
<td>10 (264)</td>
<td></td>
</tr>
<tr>
<td>CMF&lt;sup&gt;15,35,58,84,86,94,61,69&lt;/sup&gt;</td>
<td>10 (264)</td>
<td></td>
</tr>
<tr>
<td>Electrostimulation&lt;sup&gt;56,151,154&lt;/sup&gt;</td>
<td>5 (73)</td>
<td></td>
</tr>
<tr>
<td>High-intensity therapy&lt;sup&gt;53,147&lt;/sup&gt;</td>
<td>4 (403)</td>
<td></td>
</tr>
<tr>
<td>Repetitive task training&lt;sup&gt;21,31,34,109,42&lt;/sup&gt;</td>
<td>5 (281)</td>
<td></td>
</tr>
<tr>
<td>Robotics&lt;sup&gt;51,102&lt;/sup&gt;</td>
<td>7 (159)</td>
<td></td>
</tr>
<tr>
<td>Splinting or orthosis&lt;sup&gt;36,142&lt;/sup&gt;</td>
<td>2 (43)</td>
<td></td>
</tr>
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</table>

Evidence for using forced-use paradigms (51 RCTs, N=1784)

- **Original CIMT (n=1)**
  - constraining non-paretic arm 90% of the waking hours;
  - task-oriented practice up to 6 hours a day;
  - behavioral strategies to improve compliance and transfer of practiced activities.
- **Modified versions of CIMT (n=44)**
- **Forced Use therapy (n=6)**

Langhorne et al, Lancet Neurol 2009

Subgroup analyses showed no interaction effects with timing, dose or type of (m)CIMT intervention post stroke.
Recruitment of 159 patients with a first-ever, ischemic stroke in one of the hemispheres leading to an upper limb motor impairment

The EXPLICIT-stroke trial (N=159)

- BMC Neurol. 2008 Dec 17;8:49.

De EXPLICIT-stroke trial (2008-2014)

www.explicit-stroke.nl
The EXPLICIT consortium, BMC Neurol. 2008 Dec 17;8:49.
Additional criteria for (prognostically) stratifying patients for the mCIMT or the EMG-NMS trial

The Explicit consortium, BMC Neurol. 2008 Dec 17;8:49.

The EXPLICIT design: Clinical outcomes

Primary outcome: Action Research Arm test (ARAT):
- 6 points difference favouring the mCIMT group.
- 10% more patients regaining some dexterity (ARAT ≥ 10) in the EMG-NMS group.

Secondary outcomes at level of body functions:
- Motricity Index of arm and leg (MI-arm, MI-leg)
- Fugl-Meyer motor score of the arm (FM-arm)
  - Erasmus modification of the Nottingham Sensory Assessment (EmNSA)
  - Letter Cancellation Task (LCT)
  - Hand oedema, Hemiplegic shoulder pain (HSP)

Secondary outcomes at level of activities:
- Wolf Motor Function Test (WMFT)
- Frenchay Arm Test (FAT), Nine-Hole-Peg test (NHPT)
- (Semi)structured participant interview of real arm use using the Motor Activity Log (MAL amount of use (AOU) and quality of use (QOU)),
- Stroke Impact Scale hand domain (SIS version 3.0)
- Nottingham Extended ADL (NEADL).
The EXPLICIT-stroke design

mCiMT or EMG-NMS (exp) versus usual therapy (cont)

- Clinimetrics
- Kinematics
- Haptic Robotics

Stroke onset

TMS, fMRI

TMS, fMRI

IMRI

0 1 2 3 4 5 8 12 26

Kappa=0.125, \( p = 0.112 \)

1272 (8 x 159) measurement sessions were intended to apply

Missing measurements:
- CIMT trial (N=58): 41/464 = 8.8%
- EMG-NMS trial (N=101): 63/808 = 7.8%

Kwakkel et al, Neurorehabilitation and Neural Repair 2016 (in press)
Effects of early mCIMT on ARAT

- Group\text{*}Time effect for first 5 weeks: $\beta = 1.757 (0.687)$; $p=0.011^*$
- Group\text{*}Time effect for first 8 weeks: $\beta = 1.312 (0.423)$; $p=0.002^*$
- Group\text{*}Time effect for first 12 weeks: $\beta = 0.615 (0.271)$; $p=0.023^*$
- Group\text{*}Time effect over 26 weeks: $\beta = 0.095 (0.110)$; $p=0.389$

Effects of early mCIMT on FM-arm

- Group\text{*}Time effect for first 5 weeks: $\beta = 0.396 (0.589)$; $p=0.501$
- Group\text{*}Time effect for first 8 weeks: $\beta = 0.203 (0.361)$; $p=0.574$
- Group\text{*}Time effect for first 12 weeks: $\beta = 0.005 (0.238)$; $p=0.984$
- Group\text{*}Time effect over 26 weeks: $\beta = -0.080 (0.089)$; $p=0.365$
Effects of early mCIMT on MI-arm

- Group*Time effect for first 5 weeks: $\beta = 0.832 (0.986); p=0.398$
- Group*Time effect for first 8 weeks: $\beta = 0.260 (0.567); p=0.647$
- Group*Time effect for first 12 weeks: $\beta = -0.036 (0.331); p=0.912$
- Group*Time effect over 26 weeks: $\beta = -0.011 (0.127); p=0.929$

Effects of early mCIMT on SIS hand function

- Group*Time effect for first 8 weeks: $\beta = 1.389 (0.669); p=0.038^*$
- Group*Time effect for first 12 weeks: $\beta = 0.357 (0.204); p=0.079$
- Group*Time effect over 26 weeks: $\beta = 0.044 (0.052); p=0.403$
Lessons of EXPLICIT program: *Understanding therapeutic-improvements*….

**Neural repair** + **Behavioral compensation**

- **Restitution (spontaneous)**
- **Substitution**

‘activities’


Can we influence return of finger extension by EMG-NMS and with that return of upper limb capacity? (N=101)

The EXPLICIT consortium: Neurorehabilitation and Neural Repair 2016 (in press)
GEE using a binomial distribution

• Group*Time effect for first 5 weeks: $\beta = -0.196 (0.169); \ p = 0.245$
• Group*Time effect for first 8 weeks: $\beta = -0.137 (0.074); \ p = 0.063$
• Group*Time effect for first 12 weeks: $\beta = -0.068 (0.042); \ p = 0.107$
• Group*Time effect over 26 weeks: $\beta = -0.019 (0.017); \ p = 0.255$

**EMG-NMS trial: return of voluntary finger extension**

**Time after stroke (weeks)**

<table>
<thead>
<tr>
<th>Number of patients with voluntary finger extension</th>
<th>USUAL CARE (N=51)</th>
<th>EMG-NMS (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 8 12 26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Task performance**

expression-dependent plasticity

*Learning-dependent*

Hebbian- and non-Hebbian learning processes

Hebbian- and non-Hebbian learning processes

Nerve growth factors (ie, BDNF, IGF-type I) and neurotransmitters

Experience-dependent plasticity

Reperfusion

Recovery of penumbral tissue

Angiogenesis

Alleviation of diachisis

**stroke**

- (bio)mecanical changes
- central ability to perceive and modulate
- substitution of function by compensation
- restitution of function by ‘true repair’
- (adaptive) motor control

**Non-learning dependent**

- Spontaneous neurobiological recovery
- cortical map plasticity (e.g., serial fMRI, TMS, PET)

**Learning-dependent**

- Reperfusion
- Recovery of penumbral tissue
- Angiogenesis
- Alleviation of diachisis

Buma et al, Rest Neurol Neuroscience 2013; 31(6):707-722
Thank you for your attention!

www.neurorehab.nl