Utility of TMS (and other tools) in prediction of stroke outcome

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Prediction of stroke outcome

Overview

1. Stroke outcome – what do we want to know

2. Assessing corticospinal tract integrity to…..
   1. Correlate with impairment
   2. Predict motor outcomes
   3. Predict response to motor training

3. Assessing potential for plasticity enhancement
1. Stroke outcome – what do we want to know?

Recovery of arm function is unacceptably poor

- 60% of patients with non-functional arms 1 week post-stroke didn’t recover (Wade et al, 1983)
- 18 months post-stroke 55% of patients had limited or no dextrous function (Welmer et al, 2008)
- 4 years post-stroke only 50% had fair to good function (Broeks et al, 1999)
2. Prediction of stroke outcome

**Predicting upper limb function after stroke**

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Trials (participants)</th>
<th>Odds ratio (random) 95% CI</th>
<th>Odds ratio (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Demographics</td>
<td></td>
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<tr>
<td>Age (younger)</td>
<td>11(390)</td>
<td>1.54 [1.06, 2.24]</td>
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<tr>
<td>Sex (male)</td>
<td>11(424)</td>
<td>1.61 [1.11, 2.33]</td>
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<tr>
<td>Time since stroke (less time)</td>
<td>5(486)</td>
<td>1.13 [0.90, 1.42]</td>
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<tr>
<td>02 Severity of stroke - global</td>
<td></td>
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<tr>
<td>Global disability (less disability)</td>
<td>9(288)</td>
<td>3.64 [1.63, 8.13]</td>
<td></td>
</tr>
<tr>
<td>Type/Class of stroke (less severe)</td>
<td>2(256)</td>
<td>3.54 [0.46, 27.24]</td>
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<tr>
<td>Global impairment (less impairment)</td>
<td>2(209)</td>
<td>2.19 [0.35, 13.70]</td>
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<tr>
<td>Lesion size/volume (smaller)</td>
<td>3(65)</td>
<td>1.32 [0.74, 2.35]</td>
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<tr>
<td>Urinary incontinence (absent)</td>
<td>2(256)</td>
<td>4.12 [1.82, 9.33]</td>
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<tr>
<td>03 Severity of stroke - focal</td>
<td></td>
<td></td>
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<tr>
<td>UL impairment (less UL impairment)</td>
<td>20(1425)</td>
<td>14.84 [9.08, 24.25]</td>
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<tr>
<td>UL function (more UL function)</td>
<td>4(158)</td>
<td>36.62 [8.40, 177.55]</td>
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<tr>
<td>LL impairment (less LL impairment)</td>
<td>4(130)</td>
<td>11.83 [6.53, 21.43]</td>
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<tr>
<td>04 Co-factors</td>
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<tr>
<td>Side of stroke (left)</td>
<td>11(624)</td>
<td>1.47 [1.07, 2.02]</td>
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<tr>
<td>UL sensation (no deficit)</td>
<td>3(271)</td>
<td>1.92 [1.41, 2.61]</td>
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<tr>
<td>Cognition/Perception (no deficit)</td>
<td>4(462)</td>
<td>1.96 [0.91, 3.80]</td>
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<tr>
<td>Visual disorders (no deficit)</td>
<td>2(256)</td>
<td>5.22 [2.40, 11.35]</td>
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<tr>
<td>Sitting balance (no deficit)</td>
<td>2(256)</td>
<td>4.75 [0.28, 80.57]</td>
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<tr>
<td>Sensation (no deficit)</td>
<td>1(156)</td>
<td>9.15 [3.36, 24.91]</td>
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<tr>
<td>Comorbid conditions (less no.)</td>
<td>1(156)</td>
<td>1.96 [0.96, 4.00]</td>
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<tr>
<td>05 Neurophysiological factors</td>
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<tr>
<td>TMS variables; MEPs (present)</td>
<td>15(425)</td>
<td>11.76 [5.19, 26.64]</td>
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<tr>
<td>SSEPs (present)</td>
<td>2(97)</td>
<td>13.73 [2.73, 69.05]</td>
<td></td>
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<tr>
<td>DTT (preserved CST)</td>
<td>2(70)</td>
<td>35.46 [8.97, 140.18]</td>
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</tbody>
</table>
2. Prediction of stroke outcome

Assessing corticospinal damage after stroke
2. Prediction of stroke outcome

Natural history of corticospinal excitability after stroke

Motor thresholds elevated/
Recruitment curves flatter

Steeper RC, lower AMT & RMT =
less impairment in 1st month
2. Prediction of stroke outcome

_**Prognostic value of MEPs**_

The prognostic value of motor-evoked potentials in motor recovery and functional outcome after stroke – a systematic review of the literature

Bembenek et al, Funct Neurol 2012; 27(2):79-84

- Predictive value of MEPs within 14 days of stroke for UL outcome (1966-2012)
- 842 publications (Pubmed) → 15 met criteria
- 480 patients in total
  - Variable ++ MEP parameters (latency, amplitude, CMCT)
  - Variable ++ outcomes used
- 14/15 studies supported predictive value of early MEP parameters from AH
- NOT absolute – some patients with absent MEPs/high thresholds make substantial recovery
2. Prediction of stroke outcome

**Assessing corticospinal damage after stroke - dti**

Track from fMRI-defined hand areas in 4 different cortical motor areas

**Schulz et al., Stroke 2012; 43:2248-51**

Correlation with post-stroke hand grip strength
2. Prediction of stroke outcome

Automated assessment of corticospinal integrity after stroke

Can fully automated detection of corticospinal tract damage be used in stroke patients?

Nancy Kou, Chang-hyun Park, Mohamed L. Seghier, et al

*Neurology* 2013;80;2242-2245
2. Prediction of stroke outcome

**Predicting outcomes with early dti after stroke**

- Acute/Early DTI measures of CST correlate with later outcomes in unselected patients.
- Groisser et al looked at only mod-severe stroke patients on day 3-7.
- Early DTI (axial diffusivity) correlated well with motor scores at 6-7 months.
2. Prediction of stroke outcome

Predicting outcome with multimodal data

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
2. Prediction of stroke outcome

*Predicting treatment response with multimodal data*

- 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 symmetry predicted ΔFM ($r^2 = 0.38$)
- But better model by considering those with and without MEPs
- Time since stroke and baseline impairment improved model fit, but not predictive in isolation

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**Evaluation of functional potential to guide individualised upper limb rehabilitation**

- **YES** MEPs
  - FA < 0.25
    - Prime Ipsilesional M1
    - Augmented unilateral therapy
  - FA > 0.25
    - Prime Contralesional M1
    - Augmented bilateral therapy
  - Predict FM Score > 15
  - Predict ↑ response to rehabilitation with ↑ ipsilesional cortical activity
- **NO**
  - Intense unilateral therapy
  - Predict FM Score < 15
  - Predict ↓ response to rehabilitation and ↑ activity of contralesional cortex

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**Patient 2**

- Transcranial Magnetic Stimulation
- Motor Cortex Mapping
- Anatomical (T1 and T2 weighted) MRI
- Lesion Identification
- Functional MRI Experiment
- Affected hand opening and closing
  - Multiple Lateralisied Regions of interest
- Diffusion Tensor Imaging
  - Fractional Anisotropy - PLIC
  - Tractography of CST

**Patient 11**

2. Prediction of stroke outcome

*Predicting treatment response with dti*

Anatomy of Stroke Injury Predicts Gains From Therapy

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

*(Stroke, 2011;42:421-426.)*

Damage to M1 pathway limits response to robot assisted therapy
2. Prediction of stroke outcome

*Is corticospinal tract assessment enough?*

It’s not just the white matter pathways that are important.
2. Prediction of stroke outcome

*Multivariate pattern analysis for prediction after stroke*

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

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*Predicting language outcome and recovery after stroke: the PLORAS system*

Cathy J. Price, Mohamed L. Seghier and Alex R. Leff

2. Prediction of stroke outcome

**Summary I**

1. Assessment of CST can be performed with TMS and MRI
2. CST damage correlates with impairment in acute and chronic stage post-stroke
3. Acute/early CST damage correlates with later outcomes
4. Doesn’t take into account extent of cortical damage
5. Need to test value against other variables especially initial impairment
6. Would we expect early anatomy to predict outcome?
3. Prediction of response to treatment

*Enhancing Neuroplasticity – the key to recovery?*

**Biomarkers**
- TMS
- fMRI
- MR Spectroscopy
- M/EEG
- PET

**Plasticity enhancement**
- Drugs
- NIBS
- APBT

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*Enhancing post-stroke plasticity...*

Fluoxetine

TDCS

Excitation

Inhibition

Sources of variability?


...to maximise training effects
3. Prediction of response to treatment

*Post-stroke plasticity – what is the time course?*
3. Prediction of response to treatment

Longitudinal changes in inhibition/excitation

Less inhibition / more facilitation in all at 1 month and in those with more impairment at 3rd month
3. Prediction of response to treatment

**Longitudinal changes in inhibition/excitation**

- How is SICI modulated during movement preparation?
- How does this change after stroke?

Liuzzi et al., Neurology 201; 82:198-205

- Lower $\text{ICI}_{\text{mod}}$ in the acute phase = more recovery over 1 year
- Lower $\text{ICI}_{\text{mod}}$ driven by decrease in inhibition early in move preparation
- Resting SICI not associated with clinical change

Disinhibition of ipsilesional motor cortex may provide the ideal environment to support experience dependent plasticity
3. Prediction of response to treatment

Response of SICI to tDCS predicts training effect

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

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?

(Stroke. 2012;43:2185-2191.)
3. Prediction of response to treatment

*TBS effect is highly variable … but predictable*

- **cTBS** depresses *early I-waves* originating from monosynaptic excitatory connections to pyramidal cells.

- **iTBS** enhances *late I-waves* which are generated by more complex oligosynaptic circuits.

### Late I-waves

- AP >> LM latency = late I-waves

### Early I-waves

- AP = LM latency = early I-waves
3. Prediction of response to treatment

**TBS effect is highly variable but … predictable**

- **cTBS** depresses *early I-waves* originating from monosynaptic excitatory connections to pyramidal cells.
- **iTBS** enhances *late I-waves* which are generated by more complex oligosynaptic circuits.

- Those with bigger AP-LM difference (recruitment of later I-waves) had ‘expected response’.
- Those with smaller AP-LM difference (recruitment of earlier I-waves) had ‘opposite’ response.
Prediction of motor outcomes might be helped by assessment of CST

Information about cortical involvement also needed

Plasticity enhancement has variable inter-individual effects

Assessment of excitatory-inhibitory balance may help predict whether intervention enhances training in individuals

Neurophysiology and Neuroimaging should help in stratification

None used in clinical practice yet
Prediction of stroke outcome

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Penny Talelli

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