Transcranial Magnetic Stimulation in Neurorehabilitation

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1. Basic principles of TMS

2. TMS studies on mechanisms of ‘plasticity’

3. Future therapeutic perspectives of TMS in neurorehabilitation
Stimulating the Brain!!

TMS

Barker et al., 1985
Principles of TMS

Figure 1.7 Simplified schematic diagram of a standard rate magnetic nerve stimulator.
Transcranial Magnetic Stimulation

- Currents induced by rapidly transient magnetic fields with variable flow direction and intensity (1.5–2.5 Tesla)

- The amount of stimulated brain tissue depends on:
  - the stimulus intensity
  - the coil shape
Magnetic fields with different shaped coils

Stimulation is maximal, but not focal with a large circular coil, while a lower but more focal effect is obtained with a figure-of-eight coil.
Transcranial Magnetic Stimulation

- Magnetic stimulation (with a round coil parallel to the surface of the brain and threshold intensity) activates the pyramidal tract neurons trans-synaptically (to produce I-waves in the pyramidal tract), whereas electrical stimulation activates the axons directly to produce D-waves.
Transcranial Magnetic Stimulation

Motor evoked potentials (MEPs)

- contralateral distribution
- short latency with proximo-distal progression
- variable amplitude
  (larger in distal muscles)
- sensitivity to voluntary contraction
Coil orientation and activated neurons

All indirect I-waves depend on synaptic input to cortico-spinal neurons
Cortico-Motoneuronal 'conductivity'

- Presence/Absence of MEPs
- MEP Latency (ms)
- Central Motor Conduction Time (ms)
  - loss of axons
  - slowing of conduction
  - temporal dispersion of impulses
Cortico-Motoneuronal 'excitability'

**MEP Threshold and Amplitude**

Measure of the portion of the spinal motoneurones discharged by TMS

**Cortical Maps**

Measure of the number and topographical representation of excitable sites
Inhibitory effects of TMS

Silent Period

Contralateral

Ipsilateral
Paired-pulse TMS

Kujirai et al. 1993
The physiological role of SICI
Focusing motor cortical excitation onto the pertinent groups of neurons

Ridding et al. 1995

Abbruzzese et al. 1999
GABA-A

SICI

GABA-B

SP

Hanajima et al. 1998

Werhahn et al. 1999
TMS Applications

TMS can be used to:

- Test or measure **conduction** of descending motor impulses
- Map **functional corticomotor representations** in the brain
- Assess **excitability** of brain regions
- Induce a brief **functional deactivation** of brain regions
- Improve transiently a distinct brain function
Plasticity

• **Synapse level**
  changes of EPSP amplitudes

• **Cellular level**
  changes in single neurons responses

• **Regional level**
  changes in neuronal population responses
Remodeling of Neuronal Network
Plastic changes of cortical representation in monkeys

Merzenick et al. 1990
Peripheral Deafferentation

In patients with amputation of the arm (at the elbow level) motor representation of muscles proximal to the stump were larger.

**CHANGE IN EXCITABILITY OR MOTOR REPRESENTATION**

*Cohen et al. 1991*
• Regional anaesthesia or ischaemic nerve block leads to an enlargement of MEPs proximal to the block
  
  *(Brasil-Neto et al. 1992)*

• Sensory deprivation *(Rossini et al. 1996)* or limb immobilization *(Liepert et al. 1997)* can reduce the motor maps of specific muscles

  Motor cortex is capable of fast modulating the outputs to specific muscle groups
Plasticity and stroke

MEPs may be absent in acute stroke and reappear during motor recovery

Traversa et al. 1997
Plasticity and stroke

The cortical representation of paretic muscles is modified after stroke:
- ↓↑ size changes
- topographical shifts

Traversa et. al. 1997
Plasticity and stroke

Ipsilateral pathway may assist recovery in stroke patients, although ipsilateral MEPs have been documented usually in patients with poor motor recovery

*Caramia et al. 1996 – Turton et al. 1996*

- Some patients with a good motor recovery show in the paretic muscles larger MEPs upon stimulation of the ipsilateral hemisphere

*Trompetto et al. 2000*
Plasticity and recovery of bilaterally organized functions

Decreased cortical representation of pharynx muscles in the affected hemisphere

During recovery of swallowing, the cortical representation of pharynx muscles in the affected hemisphere remained small, whereas it increased in the unaffected hemisphere.
TMS and Motor Learning

- In proficient Braille readers the representation of the FDI muscle of the reading hand was significantly larger than in the non-reading hand or in blind controls

*Pascual-Leone et al. 1993*

**Plastic cortical changes may occur in relation to behavior**
The size of cortical representation of hand muscles increased after 5-days learning period of a new skilled task (piano exercise)

Pascual-Leone et al. 1995
‘Motor Imagery’

• ‘Motor Imagery’ is a cognitive state characterized by the ability of mentally simulate a motor activity without actually executing it.

• During ‘motor imagery’ similar nervous mechanisms are operating as during actual execution, but the excitatory output is likely to be balanced by a parallel inhibitory output.
TMS and Motor Imagery

Abbruzzese et al. 1996 & 1999
Use-dependent Plasticity

Before: TMS evoked an extension movement

Training: repetitive flexion movements

After: TMS evoked a flexion movement

Demonstration of a shift in cortical excitability produced by natural inputs (repeated practice of an isolated thumb movement)

Classen et al. 1998
Modulation of practice-dependent plasticity

Ischaemic block: $\Rightarrow < \text{GABA}_A$

Lorazepam: $\Rightarrow > \text{GABA}_A$

Ziemann et al. 2001
Rehabilitation in stroke patients

- Single session of physiotherapy induces an increase of MEP representation, paralleling the dexterity improvement and lasting 24 hrs.  
  
  *Liepert et al. 2000*

- Synchronous movements of hand and foot induce a short-lasting modulation of motor output  
  
  *Liepert et al. 1999*
Rehabilitation in stroke patients

- 2-weeks ‘constraint-induced therapy’
- 1-week conventional + 1-week forced-use ‘therapy’

Increase of MEP size and shift of the output map center (recruitment of adjacent motor areas)

Liepert et al. 1998 & 2001
The combination of TMS with imaging techniques (PET, fMRI) can be used to investigate the functional connectivity between different cortical areas.

*Paus et al. 1997*
Patient with reconstructed biceps m. innervated by the intercostal nerves.

TMS mapping and fMRI show that the upper limb area rather than the trunk area of the motor cortex controlled the reconstructed muscle.

*Chen et al. 2003*
Repetitive TMS

- Rapid rate stimulators capable of producing tens of pulses per second in bursts lasting up to 1 minute

- rTMS can transiently change the functional state of the brain

Fig. 1 Behavior of muscle-evoked potentials (MEPs) in ADM muscle during the conditioning train in a representative subject. Note the increase of MEP size during the train of stimuli. Horizontal calibration is 30 ms and vertical calibration is 0.5 mV
Repetitive TMS

rTMS stimuli can be delivered at various frequencies (0.1 – 50 Hz) producing different changes of cortical excitability

- **High frequency (> 1-5 Hz)**
  increases cortical excitability ⇒ **FACILITATION**
  *Pascual Leone et al. 1994 - Berardelli et al. 1998*

- **Low frequency (< 1 Hz)**
  decreases cortical excitability ⇒ **INHIBITION**
  *Chen et al. 1997*
Manipulating cortical excitability
Associative long-term potentiation

- Stimulation of peripheral sensory afferents for several minutes can lead to long-lasting (1-2 hr) MEP changes
  
  *Ridding et al. 2000 – Charlton et al. 2003*

- Paired stimulation (rTMS 0.1 Hz + suprathreshold MN shock) increases cortical excitability for 30 min.
  
  *This effect depends on LTP and is blocked by NMDA-antagonists*
  
  *Stefan et al. 2000*
rTMS in Movement Disorders

- Pascual-Leone et al. 1994 over M1 (subMTh at 5 Hz)
  \(\downarrow\) RT and MT - improved pegboard test

- Siebner et al. 1999 over M1 (subMTh at 5 Hz)
  After 20 min.: \(\downarrow\) MT

- Siebner et al. 2000 over M1 (subMTh at 5 Hz)
  After 1 hr.: \(\downarrow\) UPDRS - After 10 min.: \(\uparrow\) SP duration

- Ikeguchi et al. 2003 over frontal c. (supraMTh at 0.2 Hz)
  6 x 2 weeks
  \(\downarrow\) rCBF - \(\downarrow\) UPDRS and improved movements

- Siebner et al. 1999 over M1 (subMTh at 1 Hz) in WC
  Short-term: normalization SICI and \(\uparrow\) SP duration
  Improved writing