Transcranial Magnetic Stimulation in Neurorehabilitation

Giovanni Abbruzzese

Department of Neurosciences, Ophthalmology& Genetics

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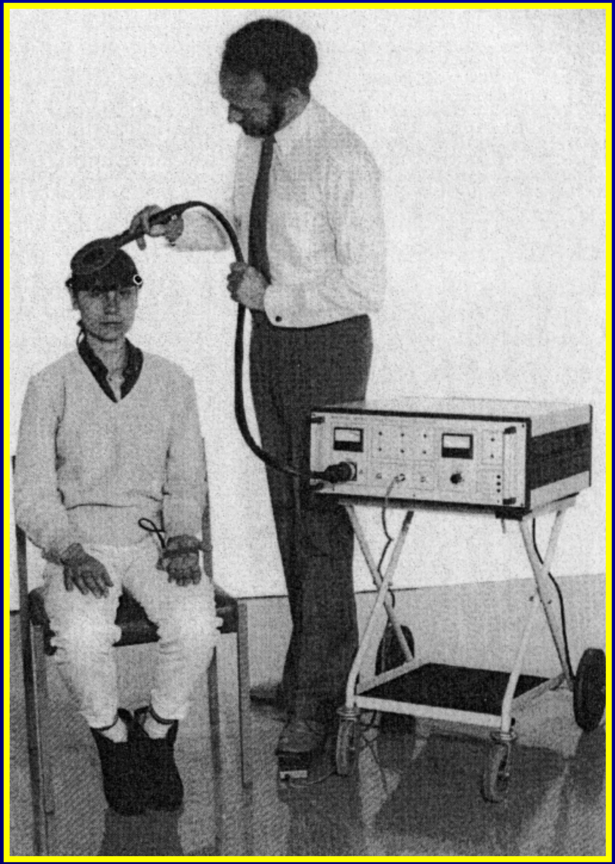
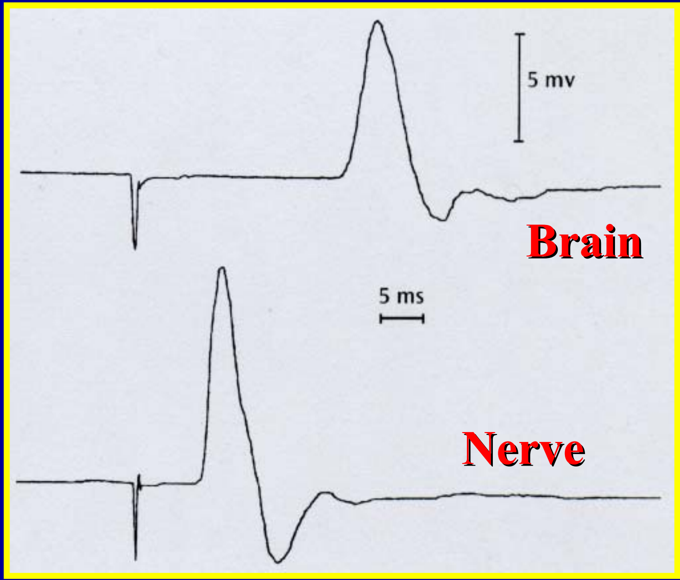
1. **Basic principles of TMS**

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

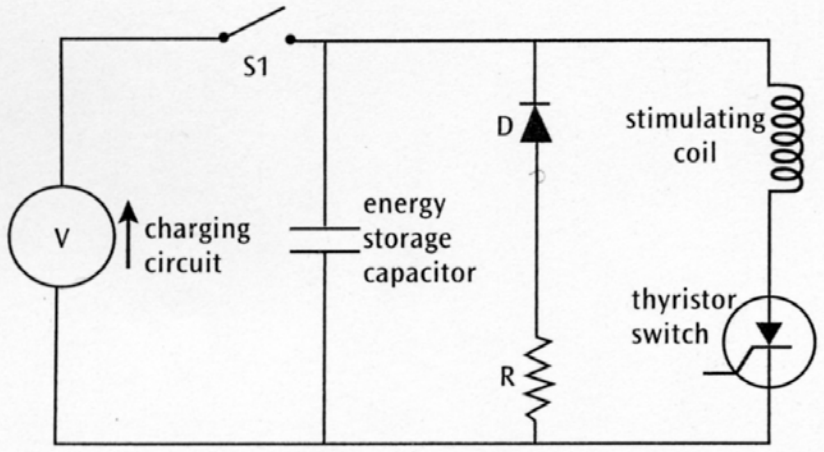
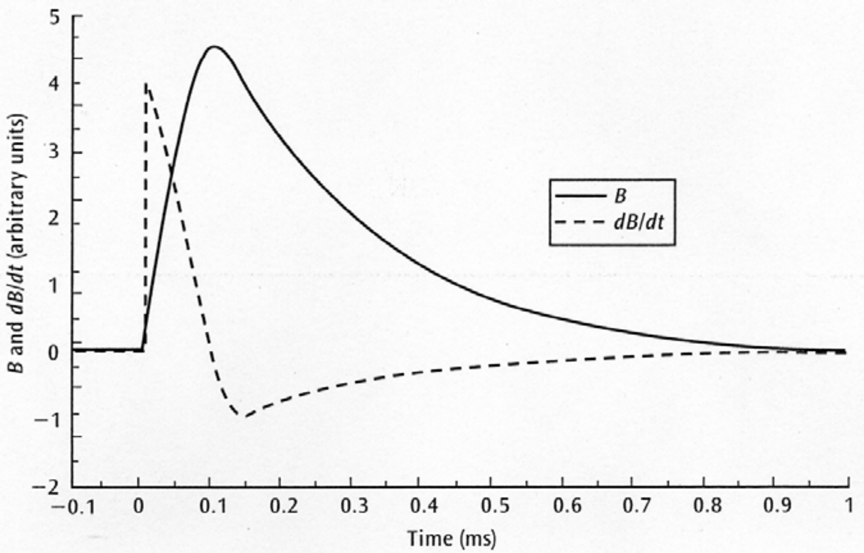


Figure 1.7 *Simplified schematic diagram of a standard rate magnetic nerve stimulator.*



Transcranial Magnetic Stimulation

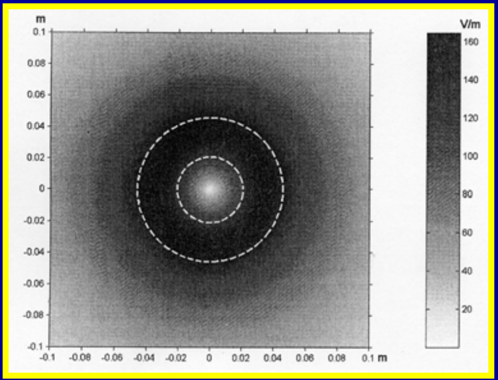
- Currents induced by rapidly transient magnetic fields with variable flow direction and intensity (1.5–2.5 Tesla)

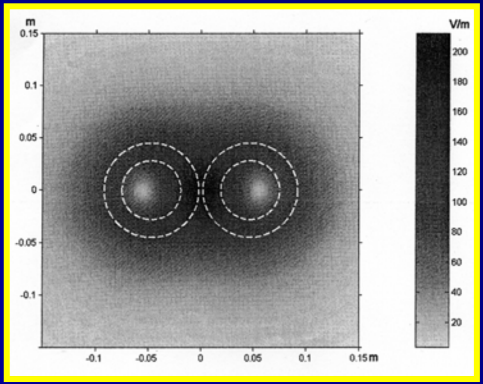
- The amount of stimulated brain tissue depends on:

  - the stimulus intensity

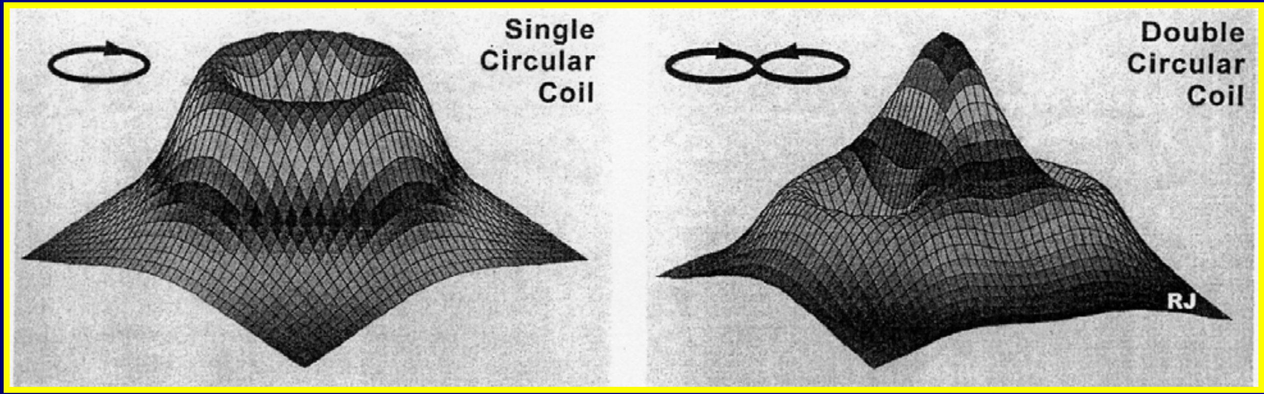
  - the coil shape

Magnetic fields with different shaped coils



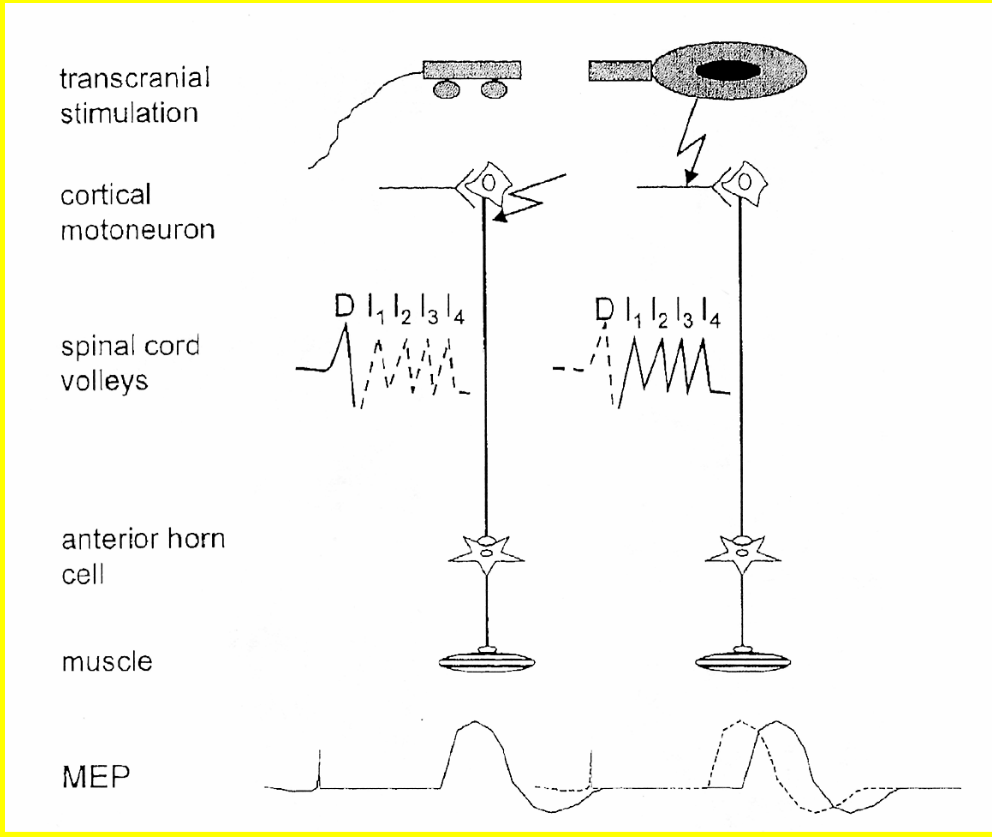


Stimulation is maximal, but not focal with a large circular coil, while a lower but more focal effect is obtained with a figure-of-eight coil.



Transcranial Magnetic Stimulation

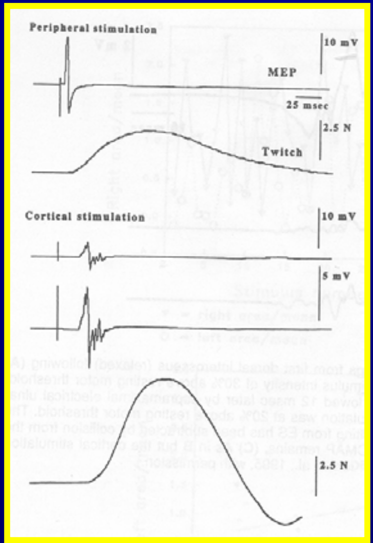
- **Magnetic stimulation (with a round coil parallel to the surface of the brain and threshold intensity) activates the pyramidal tract neurons <u>trans-synaptically</u> (to produce I-waves in the pyramidal tract), whereas electrical stimulation activates the axons <u>directly</u> to produce D-waves**

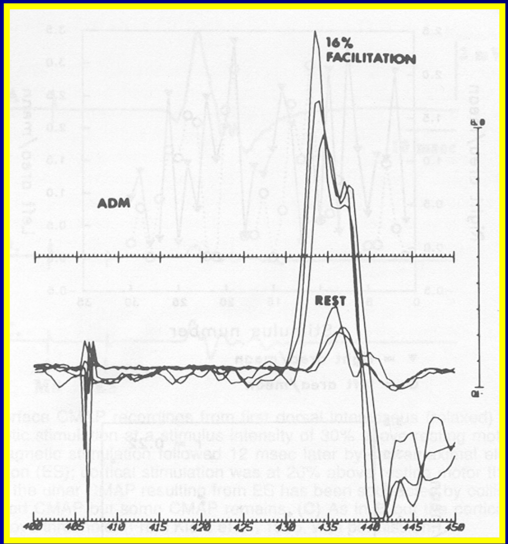


Transcranial Magnetic Stimulation

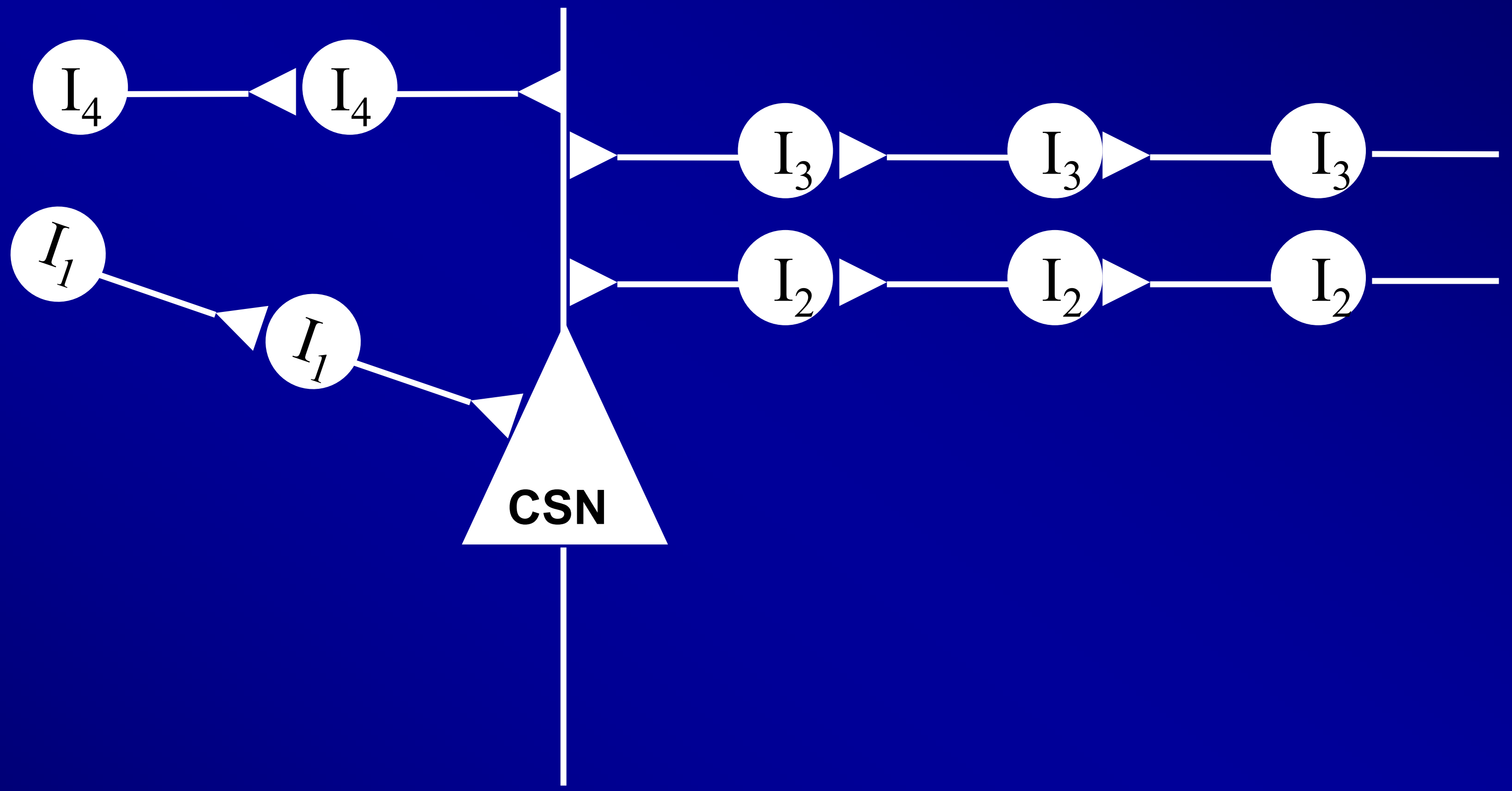
Motor evoked potentials (MEPs)

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





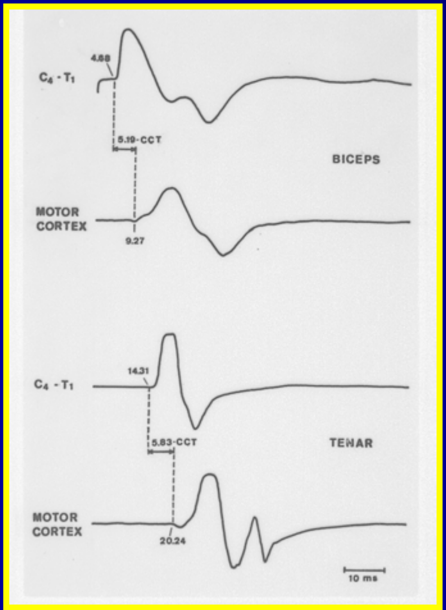
Coil orientation and activated neurons



All indirect I-waves depend on synaptic input to cortico-spinal neurons

Cortico-Motoneuronal 'conductivity'

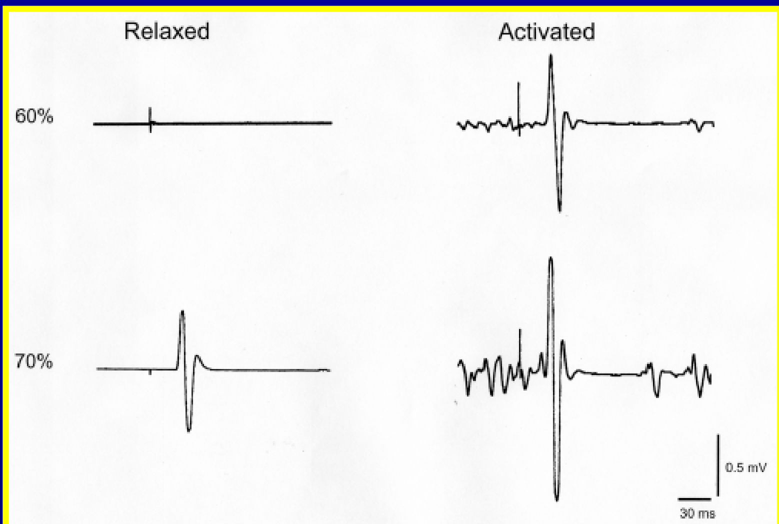
- Presence/Absence of MEPs
- MEP Latency (ms)
- Central Motor Conduction Time (ms)



- loss of axons
- slowing of conduction
- temporal dispersion of impulses

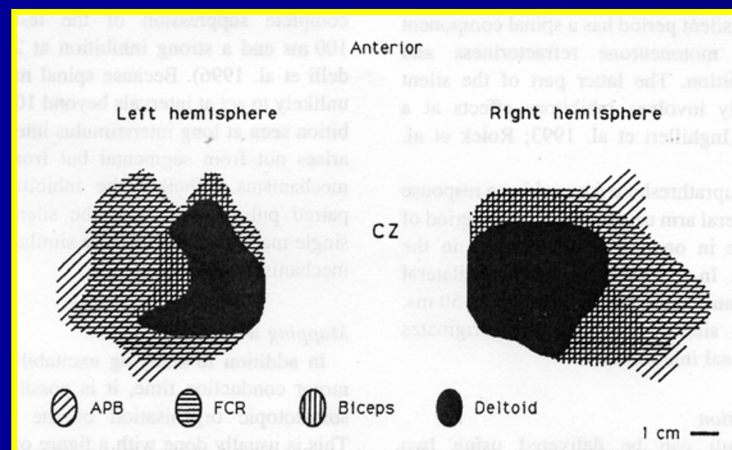
Cortico-Motoneuronal 'excitability'

MEP Threshold and Amplitude



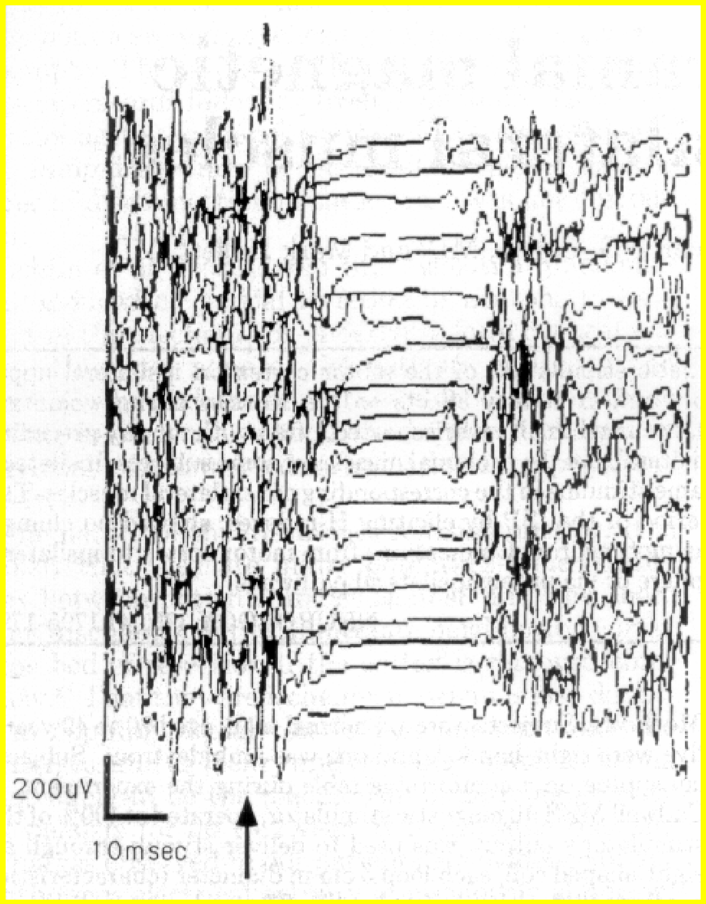
Measure of the portion of the spinal motoneurones discharged by TMS

Cortical Maps

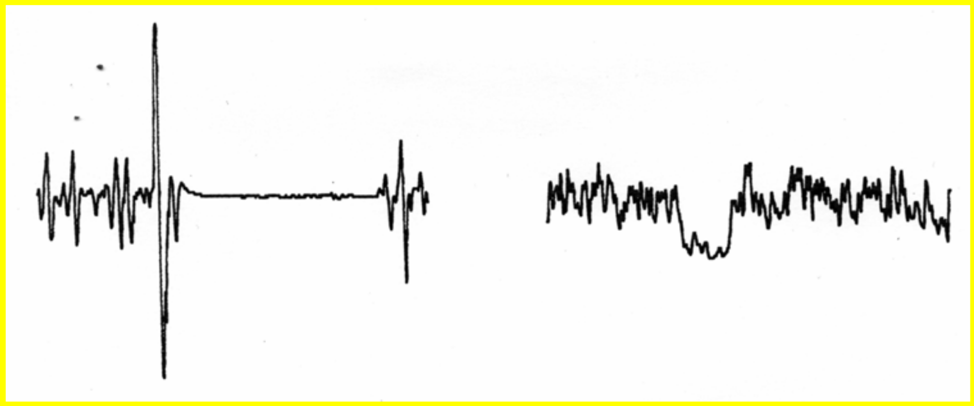


Measure of the number and topographical representation of excitable sites

Inhibitory effects of TMS

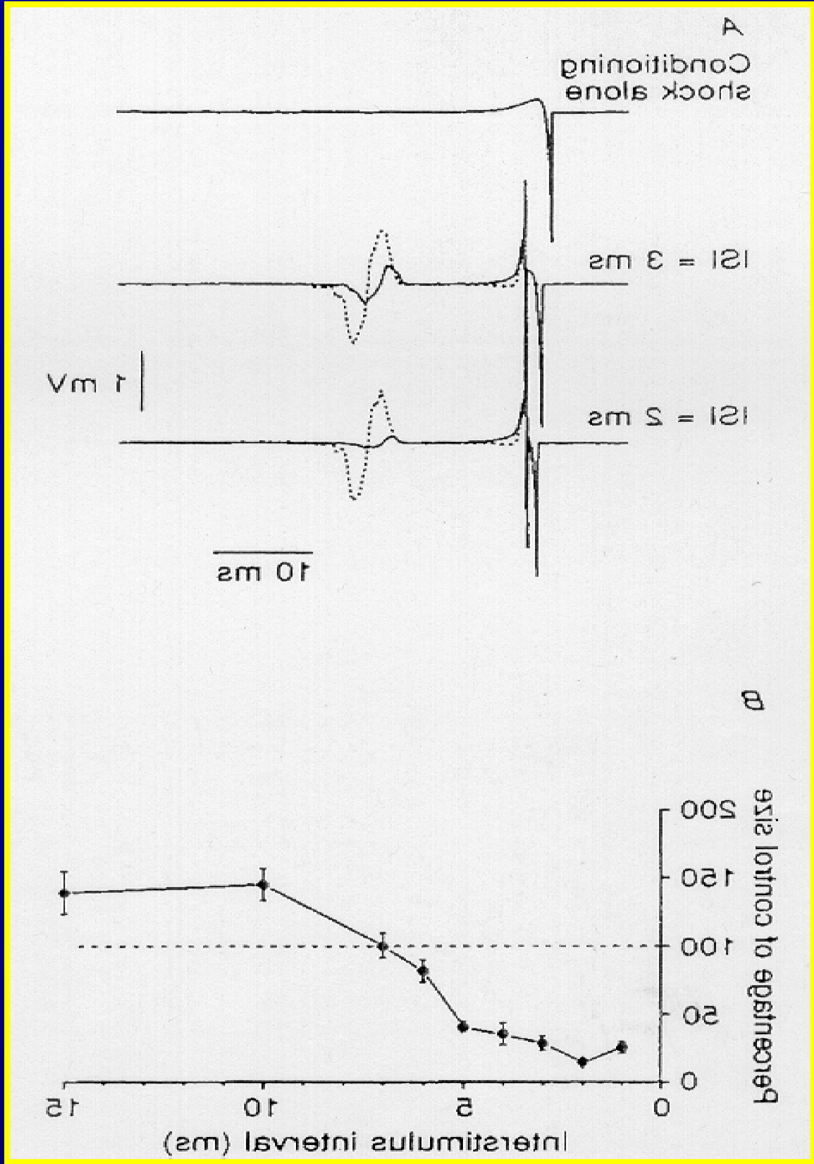


Silent Period



Contralateral **Ipsilateral**

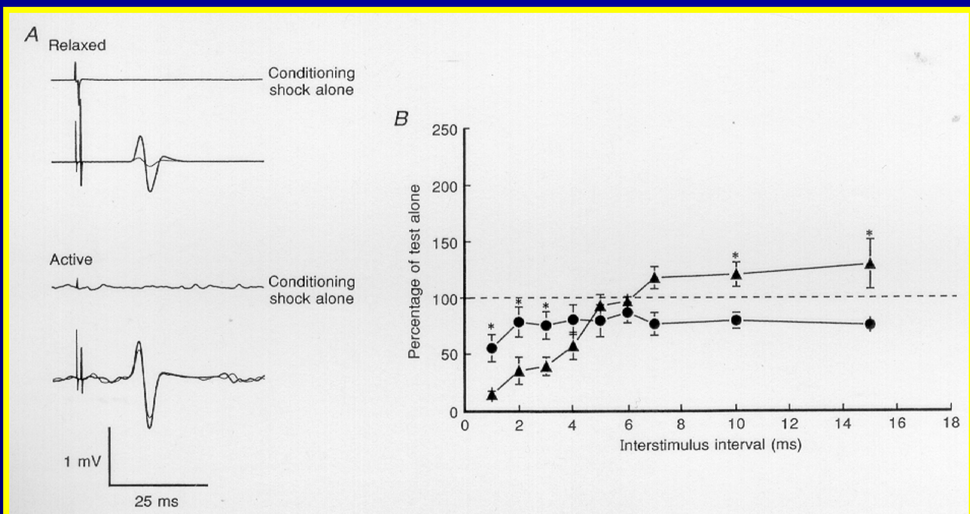
Paired-pulse TMS



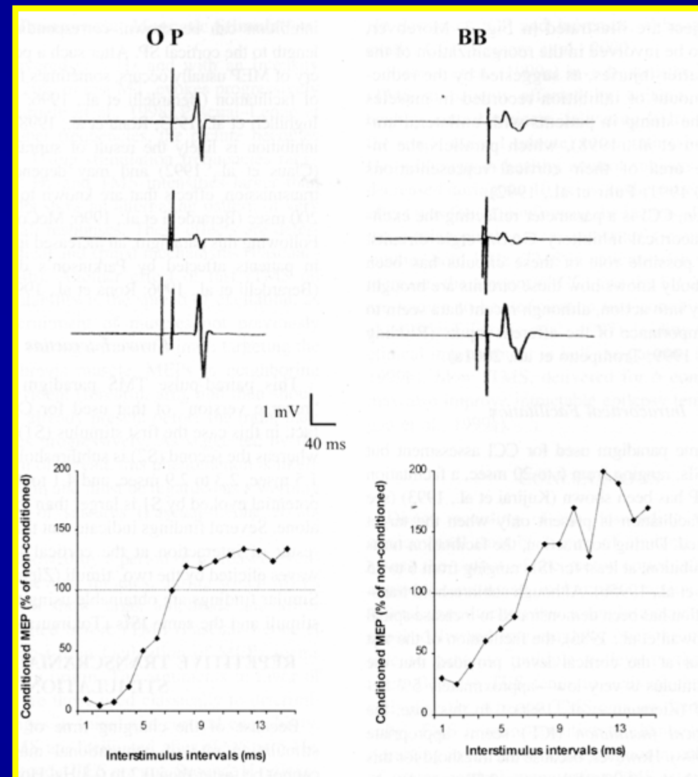
Kujirai et al. 1993

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	GABA-B
↓	↓
SICI	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

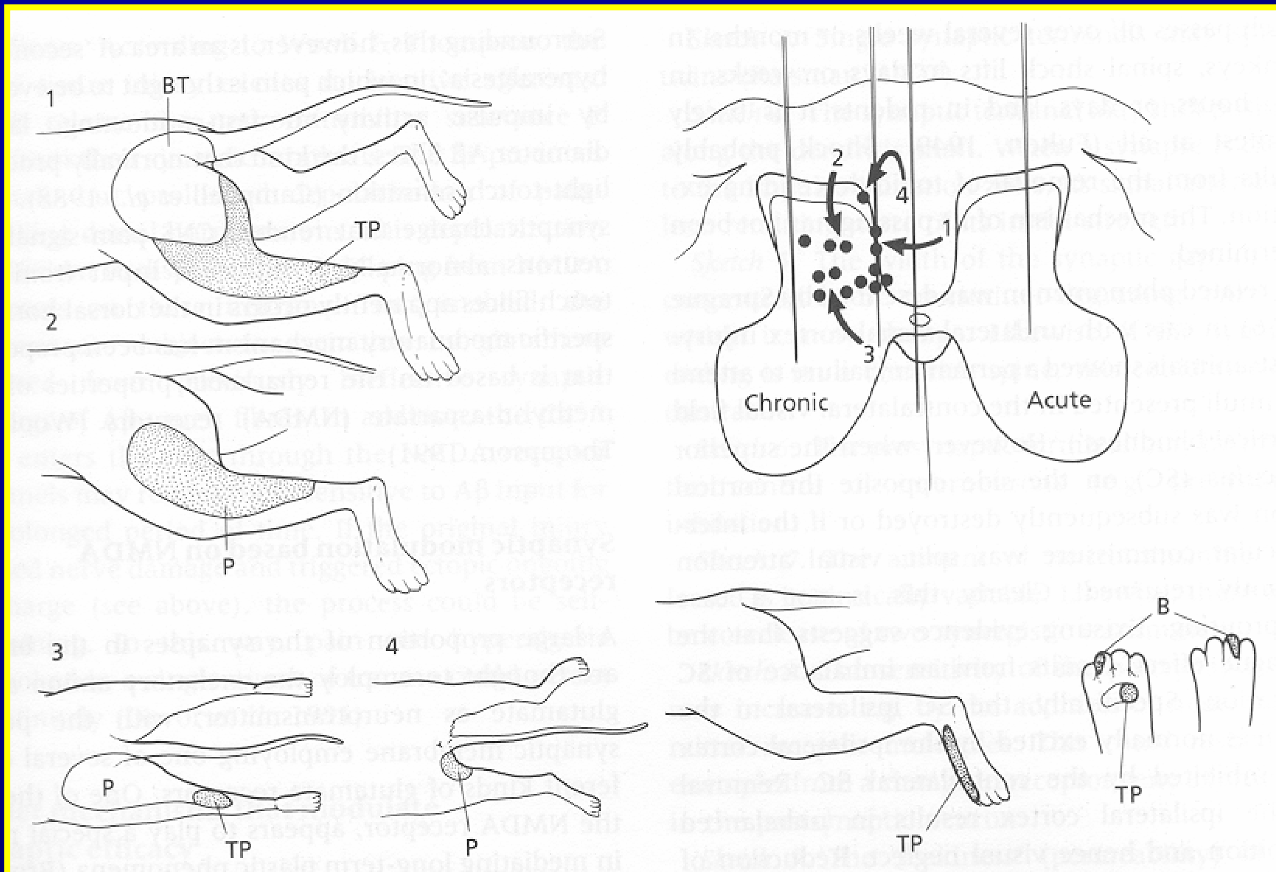
- **Cellular level**

  changes in single neurons responses

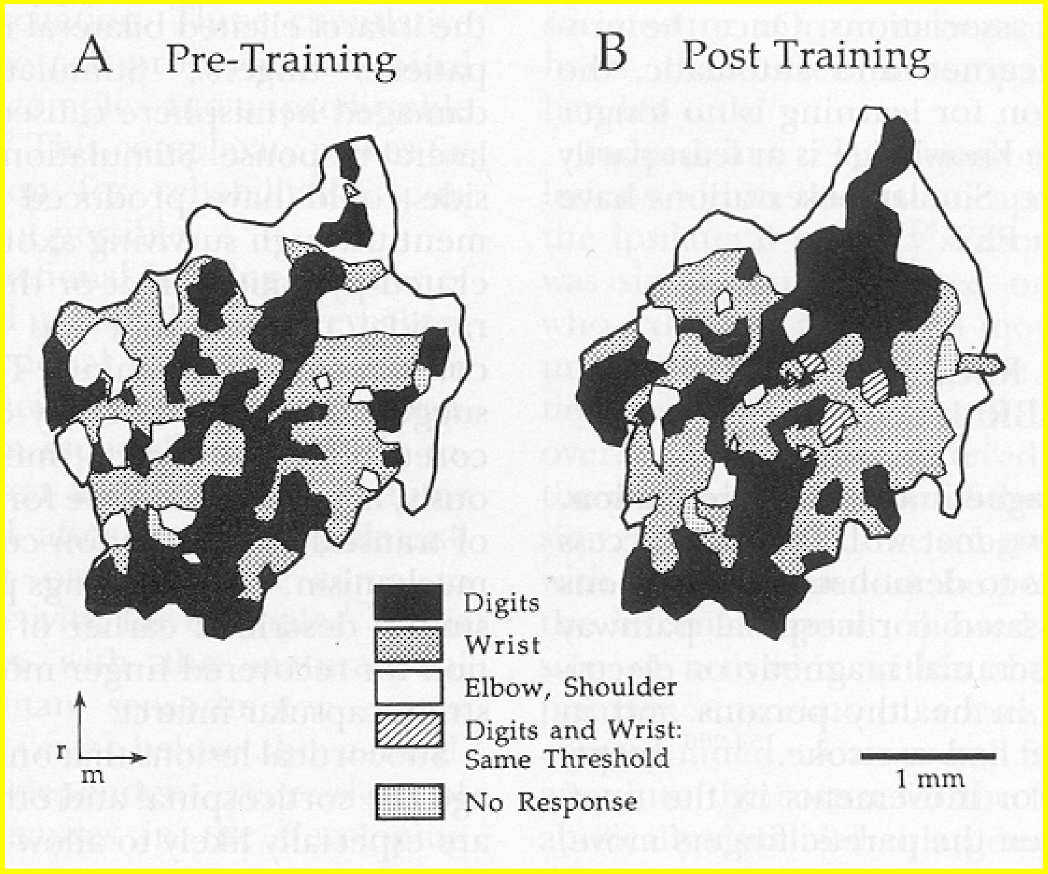
- **Regional level**

  changes in neuronal population responses

Remodeling of Neuronal Network

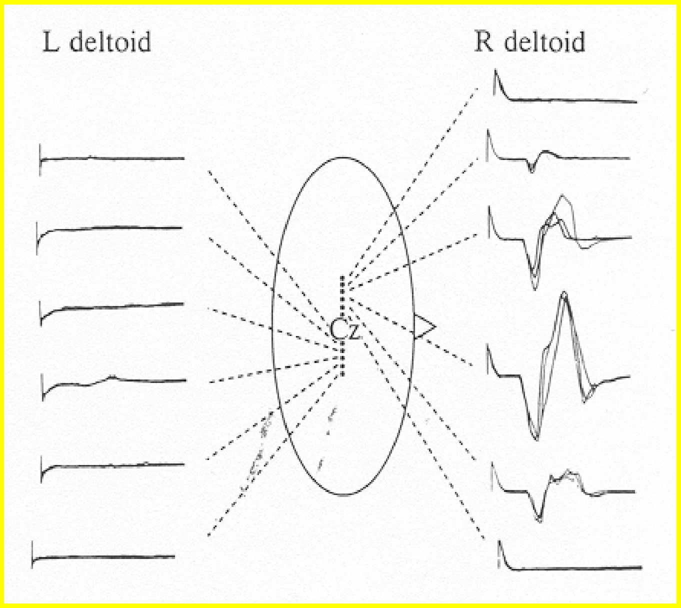


Plastic changes of cortical representation in monkeys

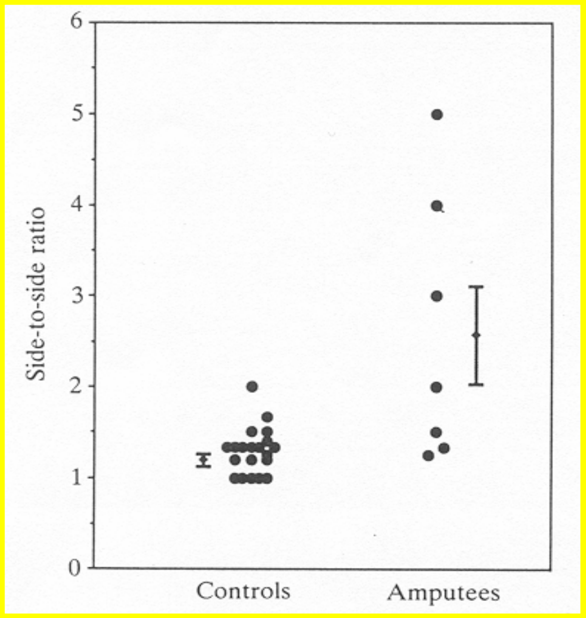


Merzenick et al. 1990

Peripheral Deafferentation



Cohen et al. 1991



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

- **Regional anaesthesia or ischaemic nerve block leads to an enlargement of MEPs proximal to the block**

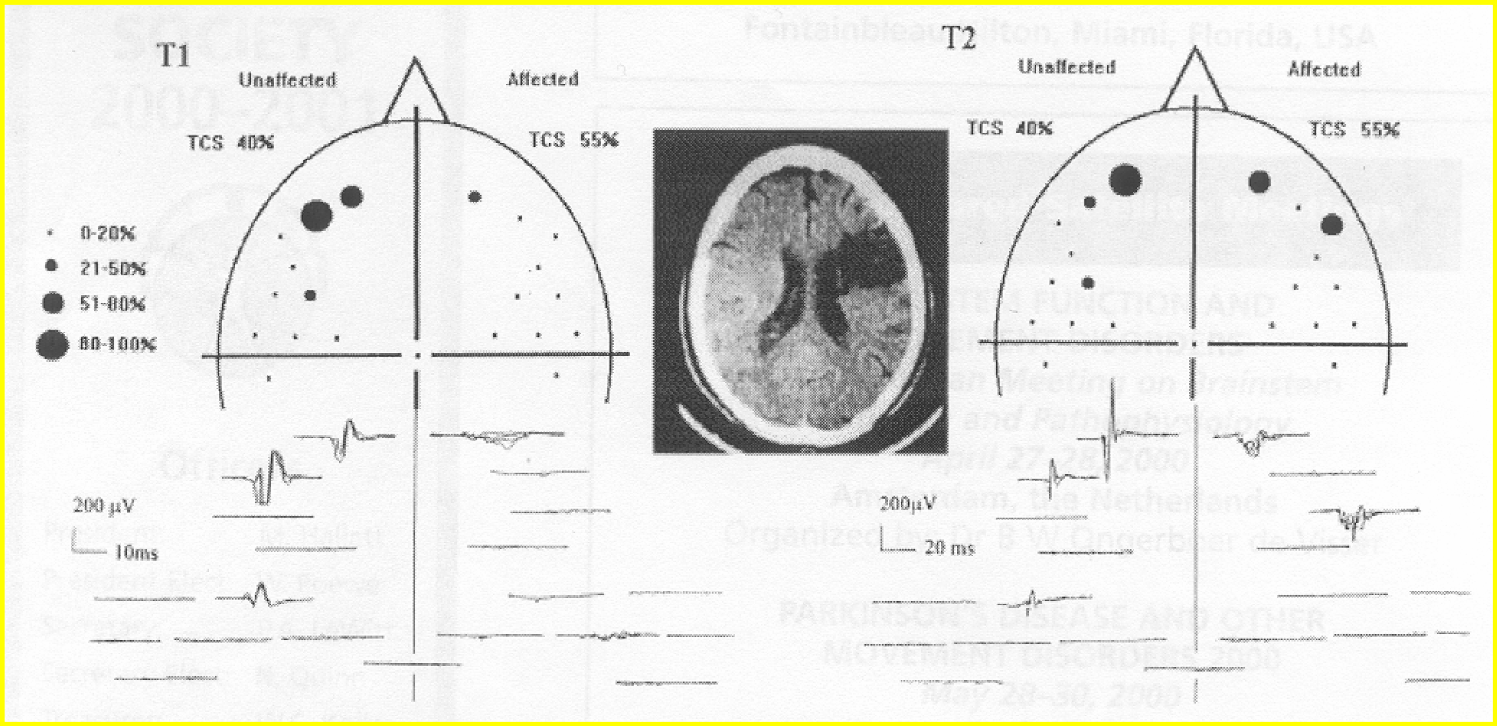
  (Brasil-Neto et al. 1992)

- **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

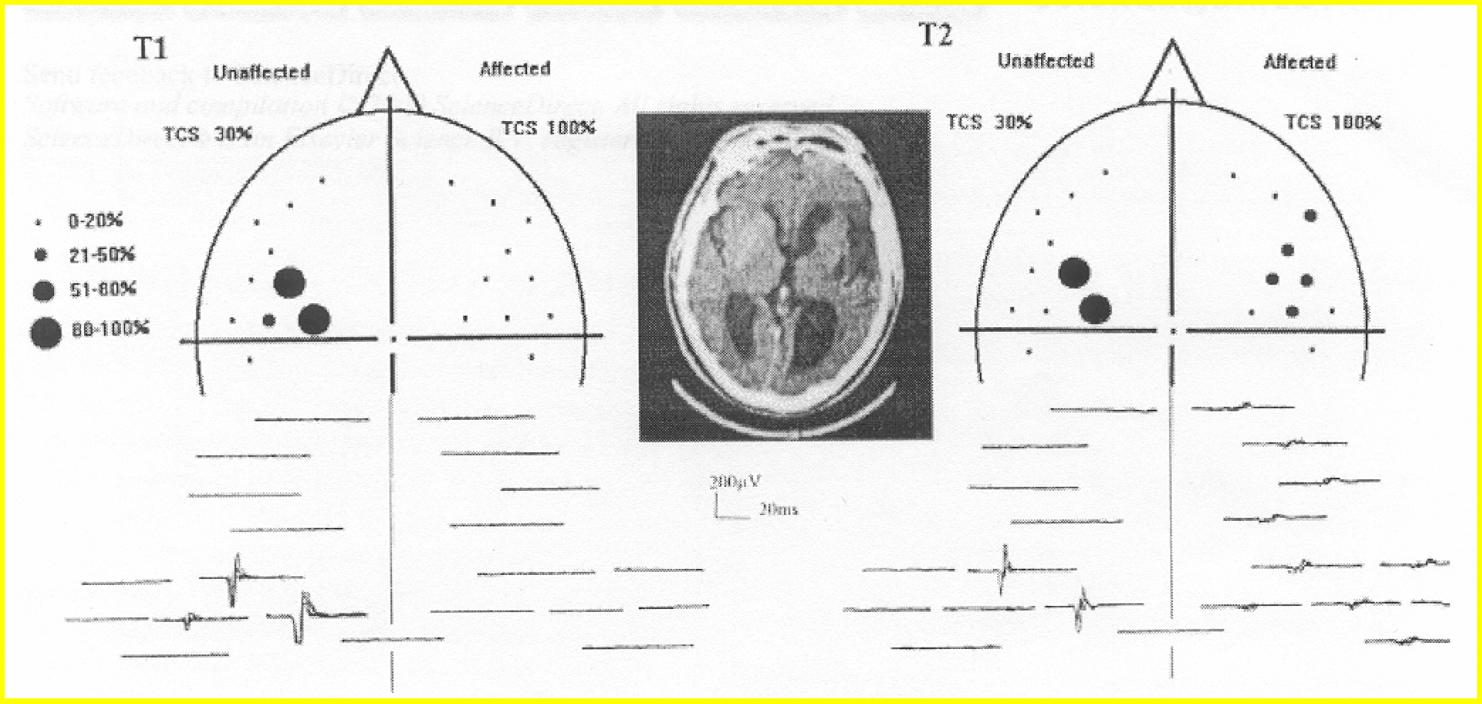


Traversa et. al. 1997

Plasticity and stroke

The cortical representation of paretic muscles is modified after stroke:

- ↓↑ size changes
- topographical shifts



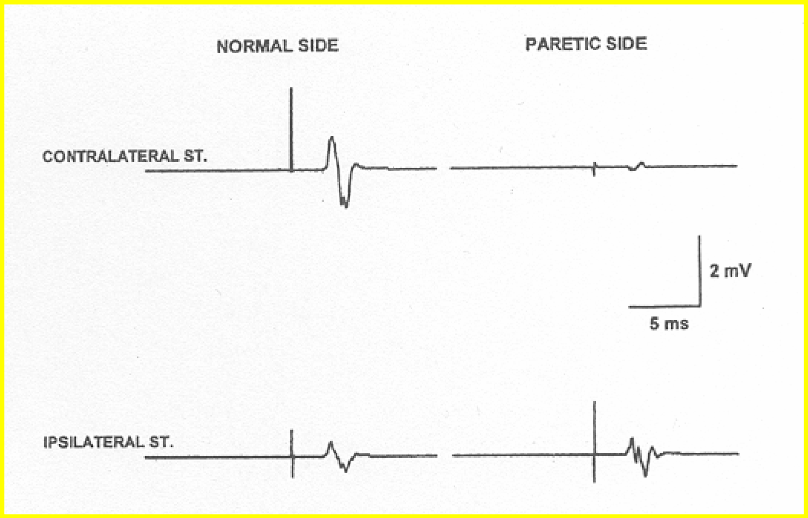
Traversa et. al. 1997

Plasticity and stroke

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

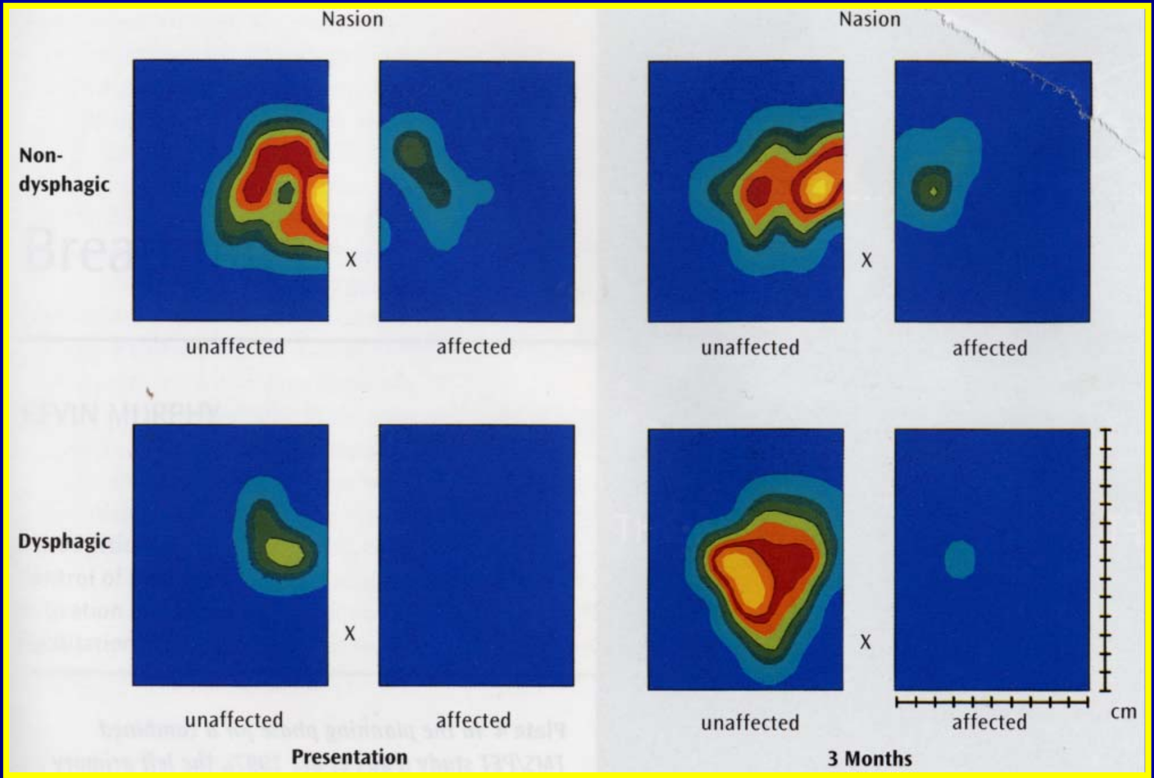
Caramia et al. 1996 – Turton et al. 1996

- **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



Hamdy et al. 1996

Decreased cortical representation of pharynx muscles in the affected hemisphere

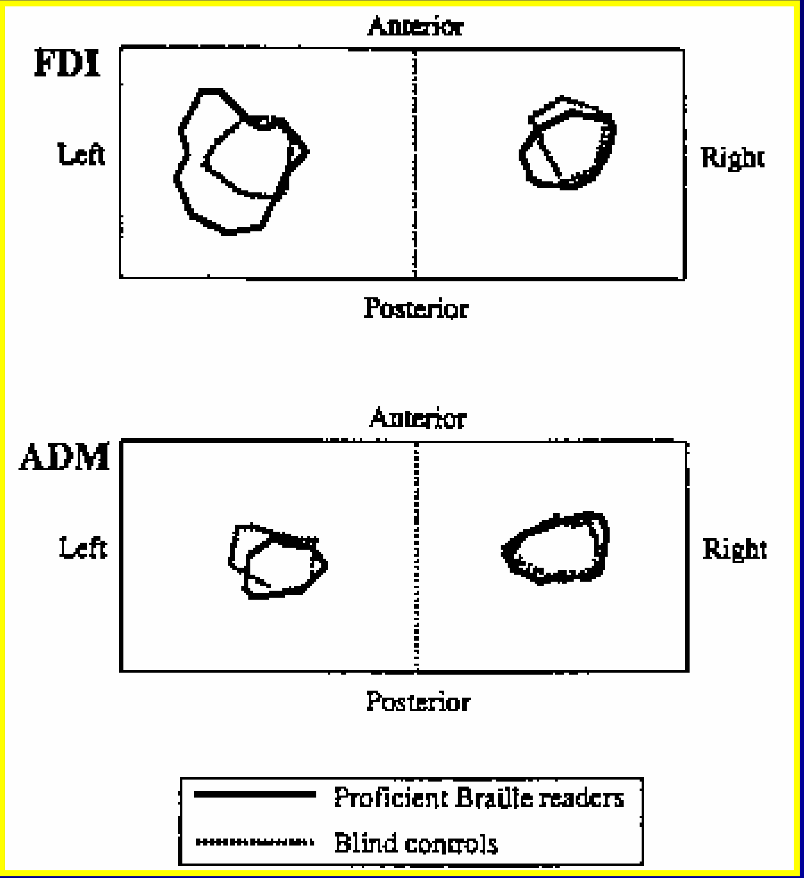
During recovery of swallowing, the cortical representation of pharynx muscles in the affected hemisphere remained small, whereas it increased in the unaffected hemisphere

TMS and Motor Learning

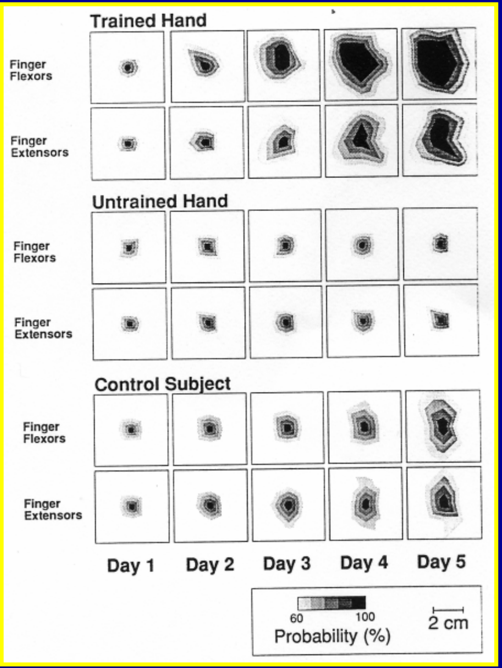
- In proficient Braille readers the representation of the FDI muscle of the reading hand was significantly larger than in the non-reading hand or in blind controls

Pascual-Leone et al. 1993

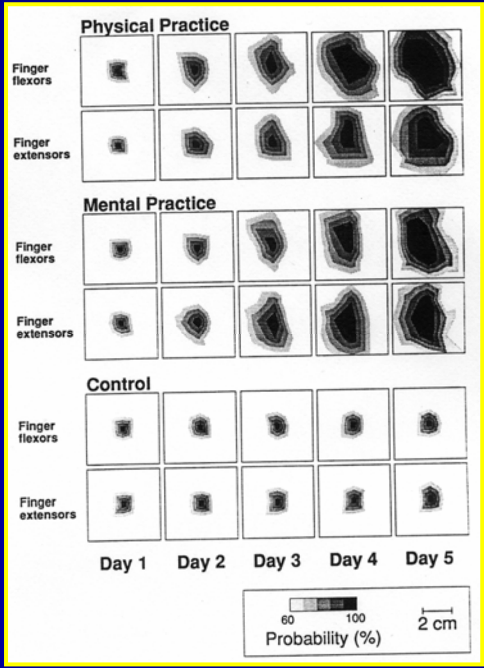
Plastic cortical changes may occur in relation to behavior



TMS and Motor Learning



Pascual-Leone et al. 1995



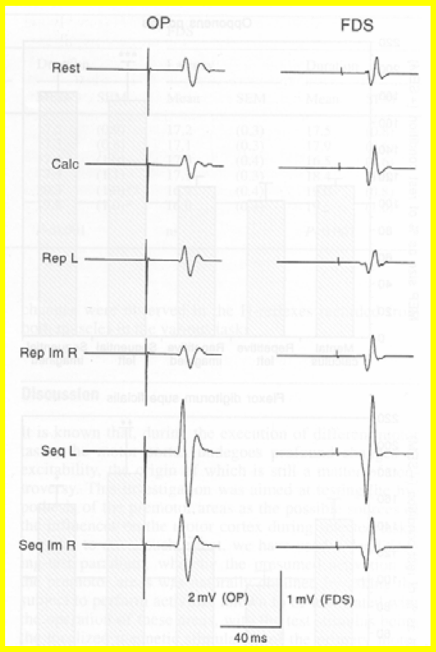
The size of cortical representation of hand muscles increased after 5-days learning period of a new skilled task (piano exercise)

‘Motor Imagery’

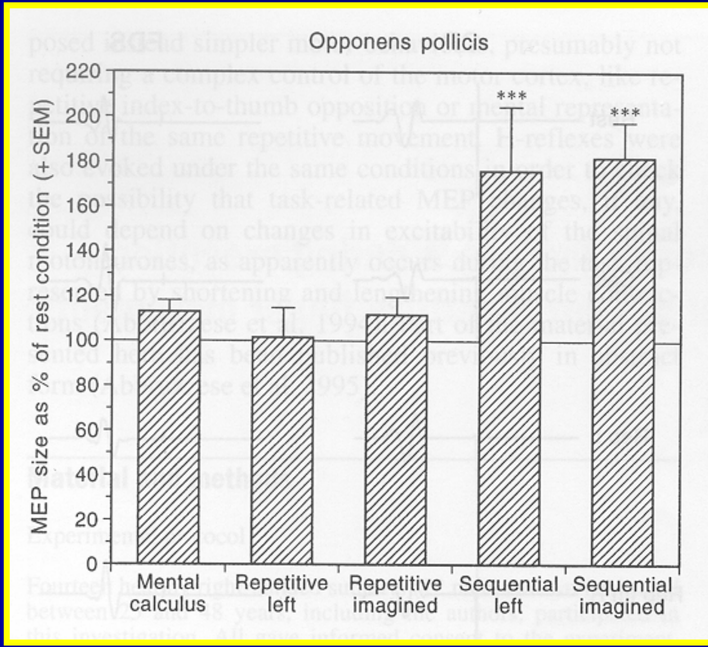
- ‘Motor Imagery’ is a cognitive state characterized by the ability of mentally simulate a motor activity without actually executing it.

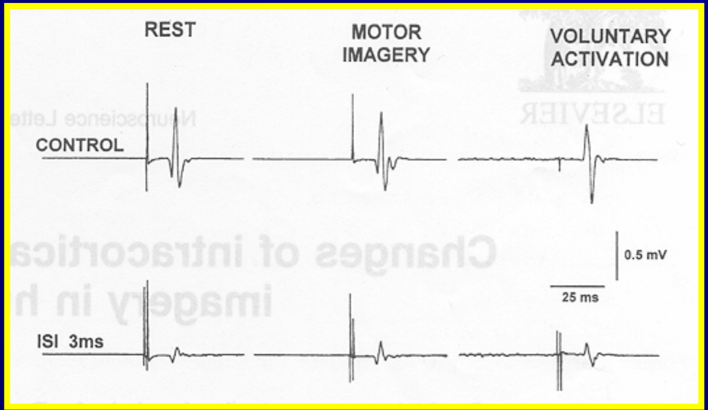
- During ‘motor imagery’ similar nervous mechanisms are operating as during actual execution, but the excitatory output is likely to be balanced by a parallel inhibitory output.

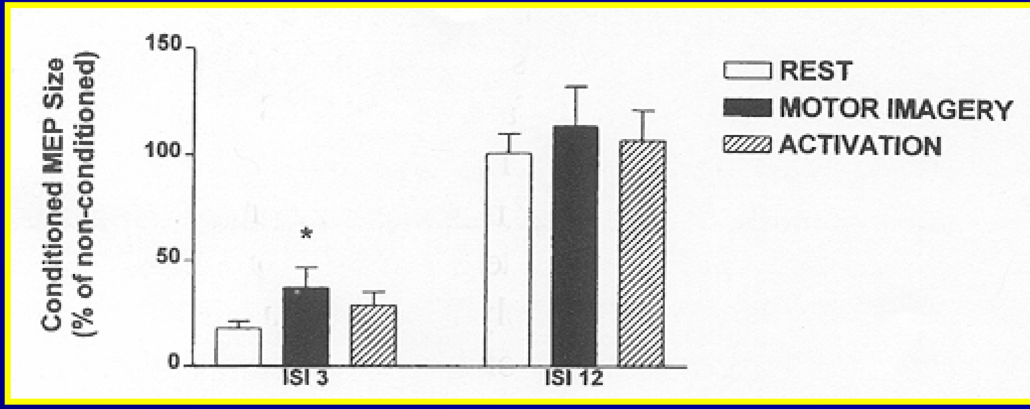
TMS and Motor Imagery



Abbruzzese et al.
1996 & 1999





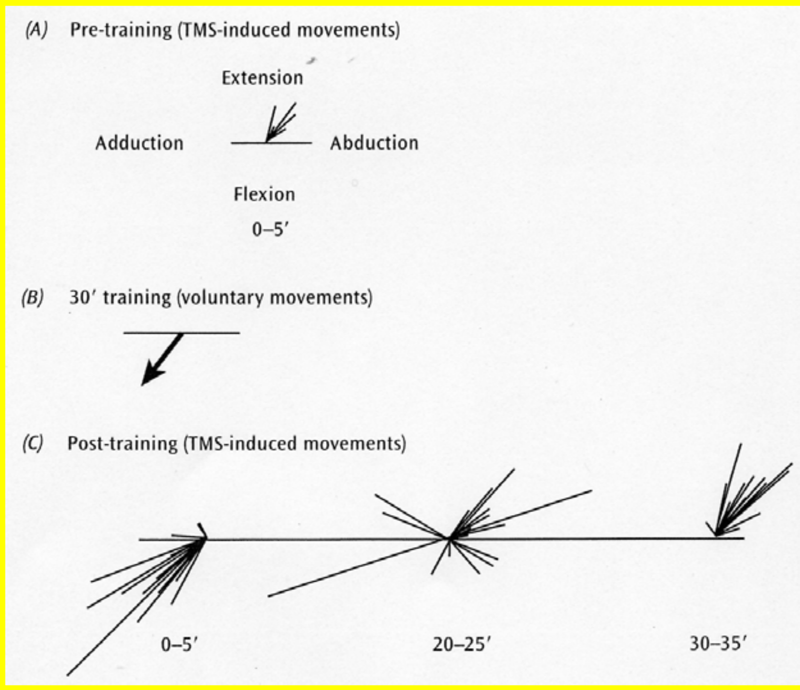


Use-dependent Plasticity

Before: TMS evoked an extension movement

Training: repetitive flexion movements

After: TMS evoked a flexion movement

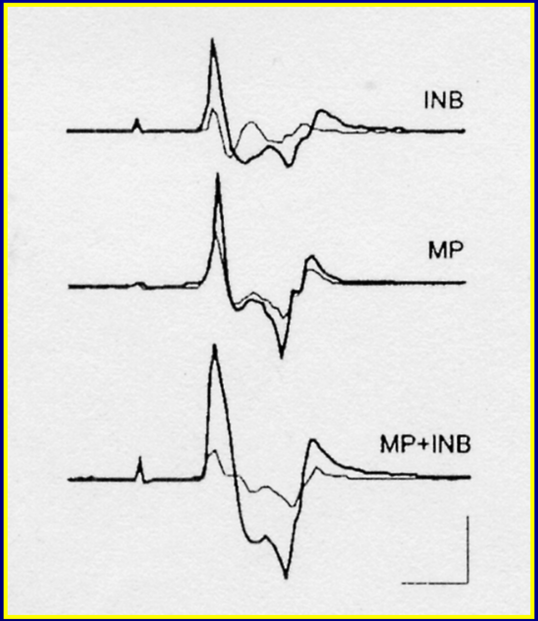


Classen et al. 1998

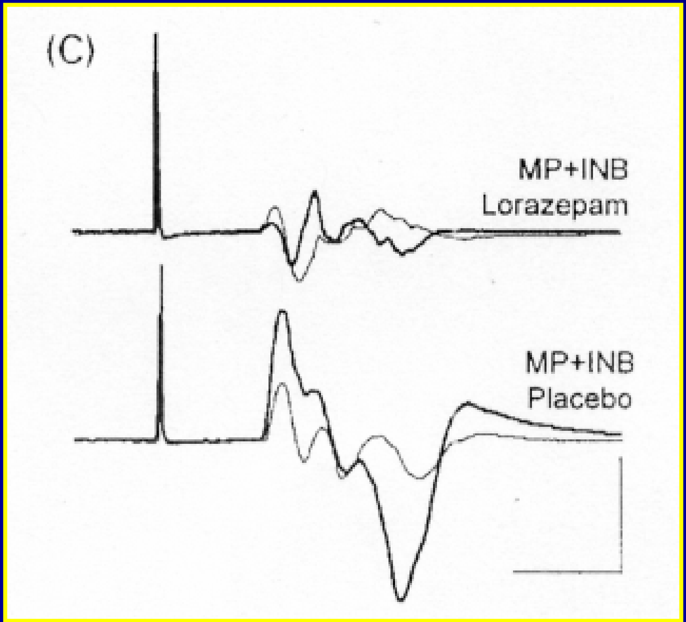
Demonstration of a shift in cortical excitability produced by natural inputs (repeated practice of an isolated thumb movement)

Modulation of practice-dependent plasticity

Ischaemic block: ⇒ < GABA$_A$



Lorazepam: ⇒ > 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**

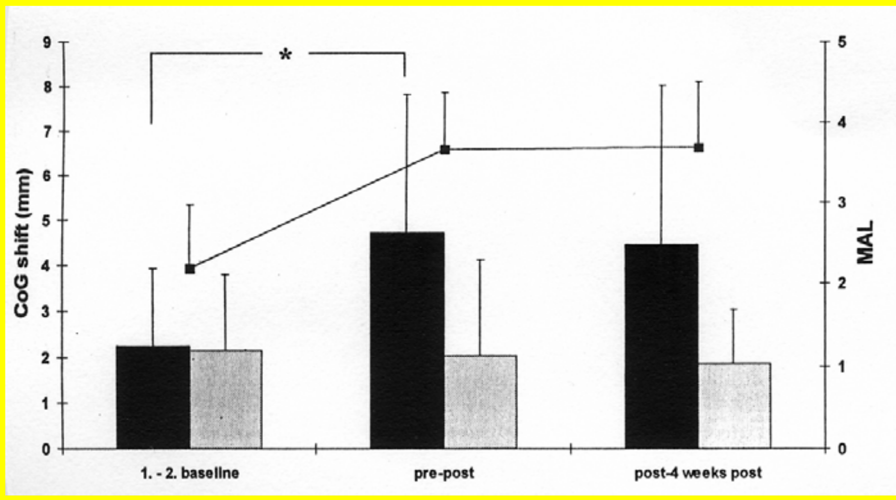
  Liepert et al. 1999

Rehabilitation in stroke patients

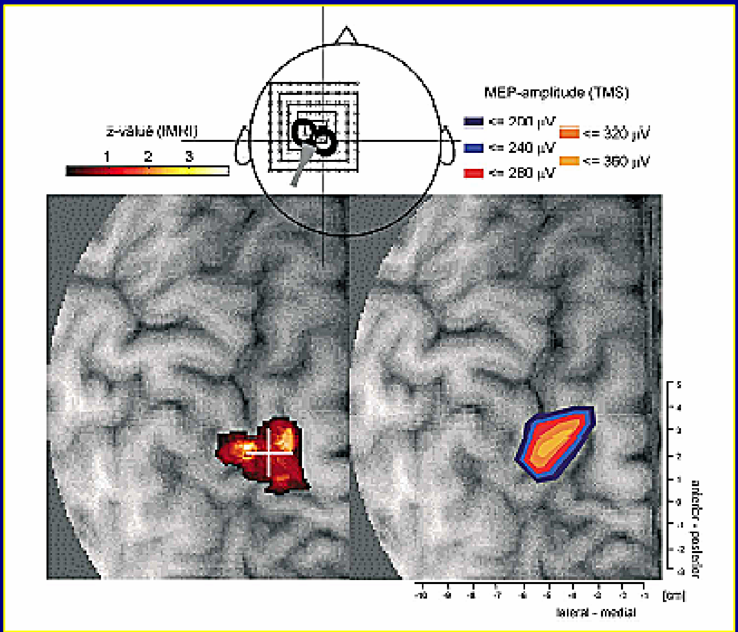
- 2-weeks 'constraint-induced therapy'
- 1-week conventional + 1-week forced-use 'therapy'

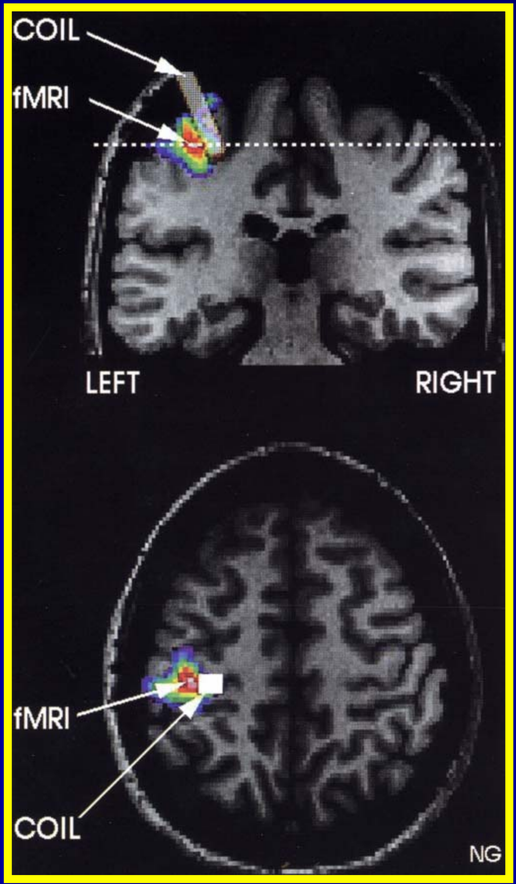
Increase of MEP size and shift of the output map center (recruitment of adjacent motor areas)

Liepert et al. 1998 & 2001



TMS and Imaging





Paus et al. 1997

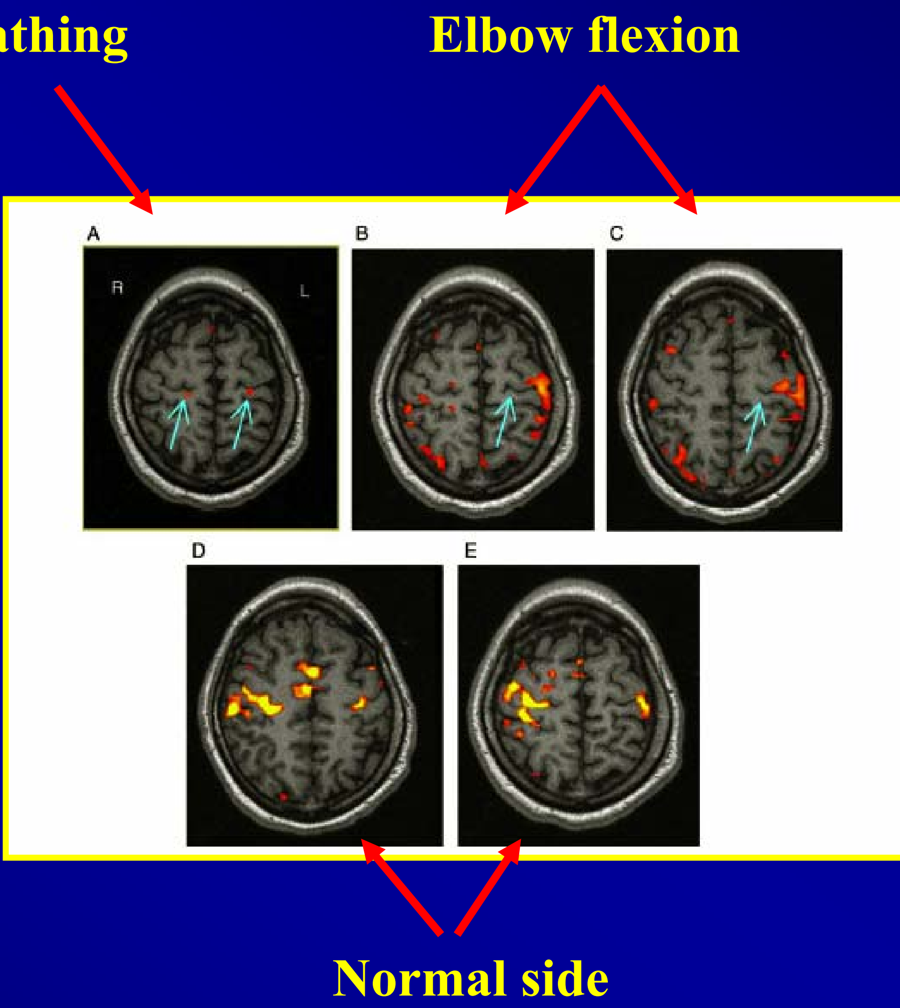
The combination of TMS with imaging techniques (PET, fMRI) can be used to investigate the functional connectivity between different cortical areas

Brain plasticity after muscle transfer

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**

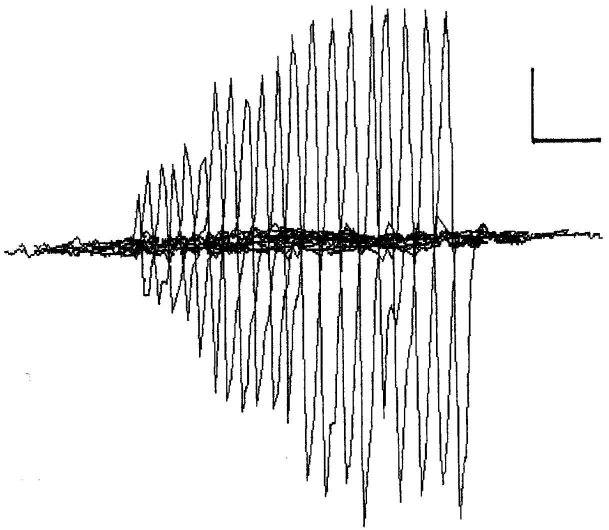


Fig. 1 Behavior of muscle-evoked potentials (MEPs) in ADM muscle during the conditioning train in a representative subject. Note the increase of MEP size during the train of stimuli. Horizontal calibration is 30 ms and vertical calibration is 0.5 mV

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)
  ↓ RT and MT - improved pegboard test
- Siebner et al. 1999 over M1 (subMTh at 5 Hz)
  After 20 min.: ↓ MT
- Siebner et al. 2000 over M1 (subMTh at 5 Hz)
  After 1 hr.: ↓ UPDRS - After 10 min.: ↑ SP duration
- Ikeguchi et al. 2003 over frontal c. (supraMTh at 0.2 Hz) 6 x 2 weeks
  ↓ rCBF - ↓ UPDRS and improved movements
- Siebner et al. 1999 over M1 (subMTh at 1 Hz) in WC
  Short-term: normalization SICI and ↑ SP duration
  Improved writing