FEDERATION OF THE EUROPEAN SOCIETIES OF NEUROPSYCHOLOGY

Brain Stimulation in Research and Practice

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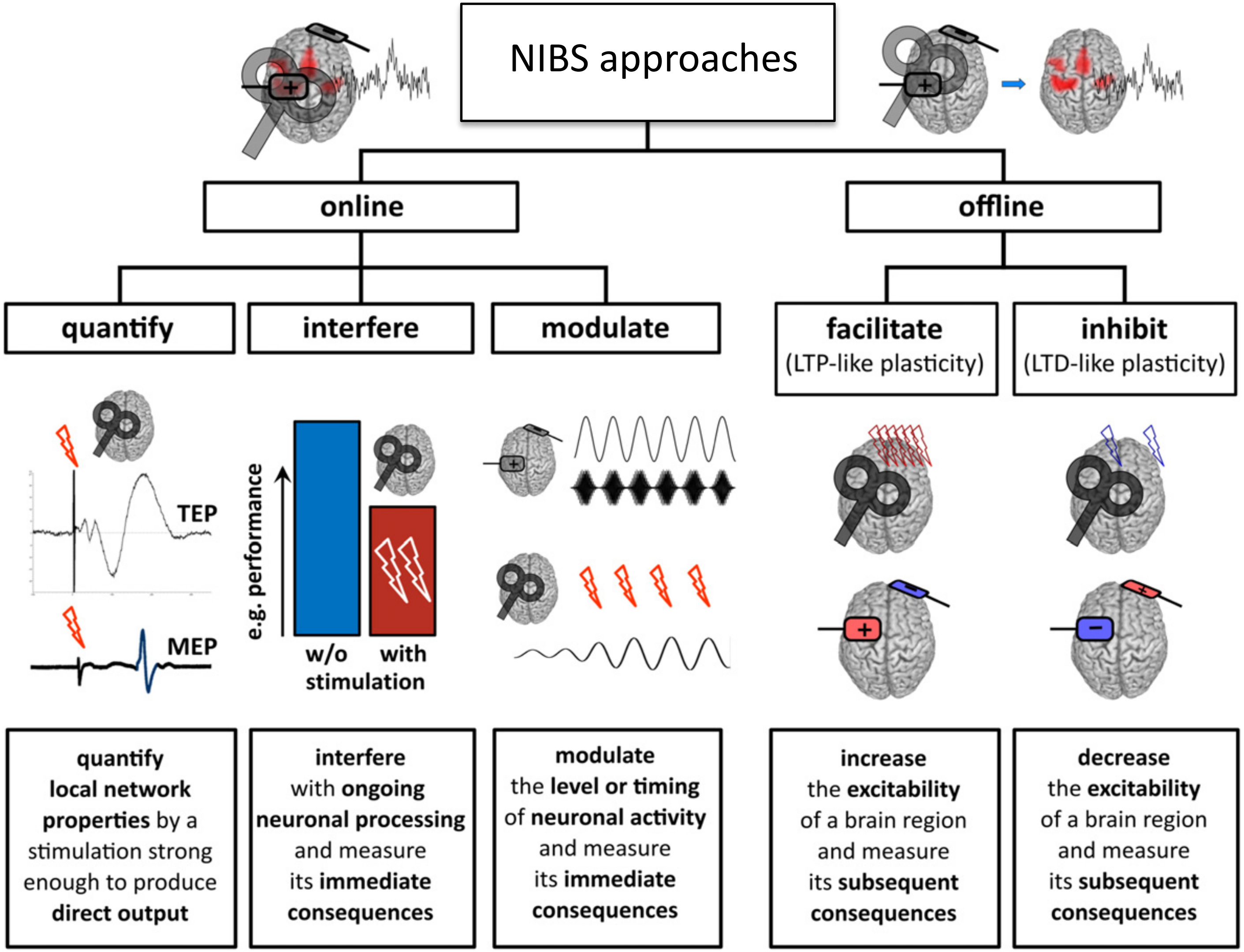
Lecture objectives

- Introduction to brain stimulation techniques
- Understand the basics of Non-invasive brain stimulation using TMS
- Understand advantages and disadvantages and potential uses of these techniques

NIBS offers a variety of approaches to study and modulate brain function

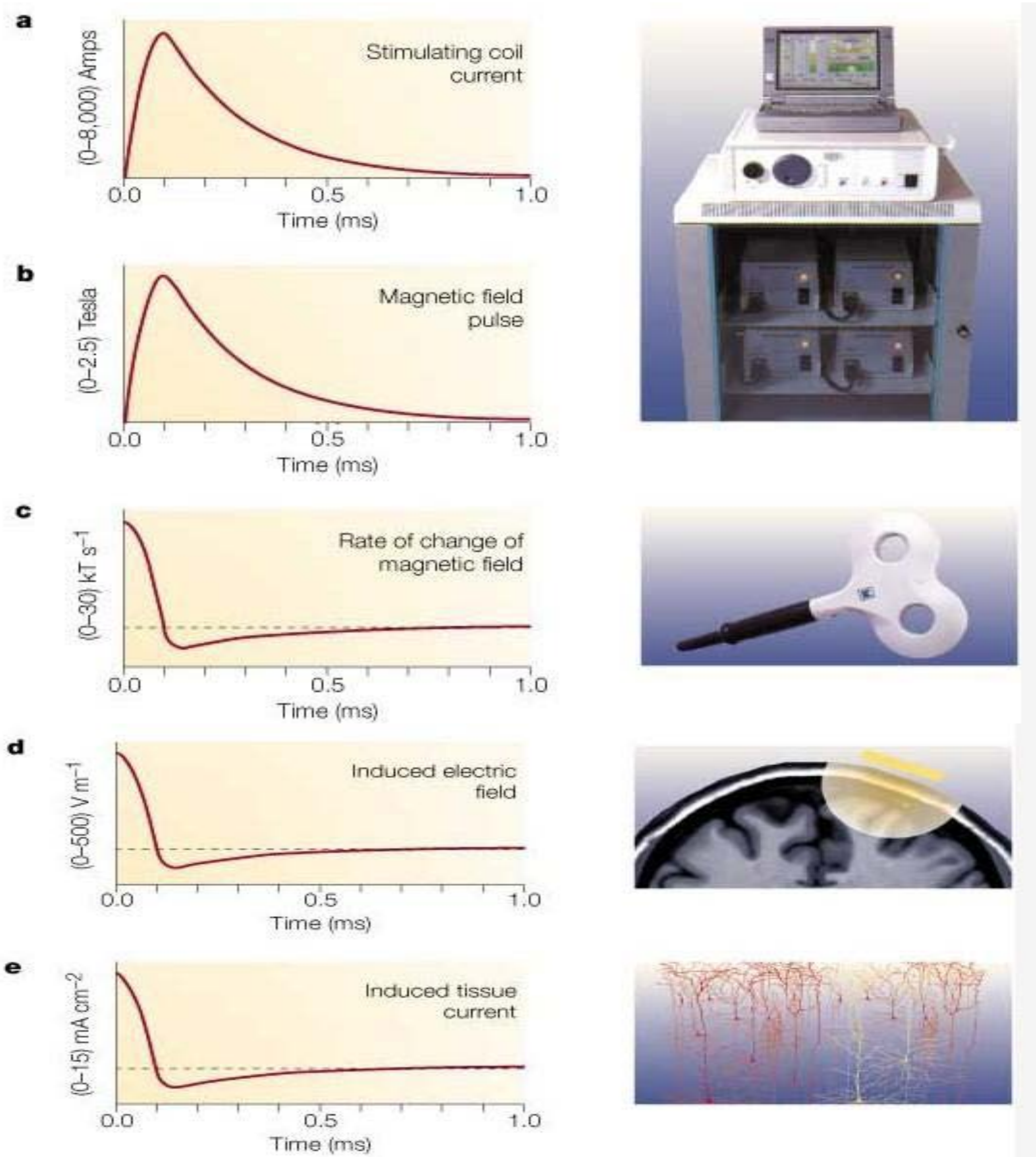


Bergmann et al., *NeuroImage*, 2016

TMS

- Relatively recent technique that induces current in the brain by using a magnetic field outside the skull

Mechanism of TMS action



Rapid-onset brief electrical current generated in the coil

Produces rapid-onset brief magnetic field pulse (up to 2 Tesla)

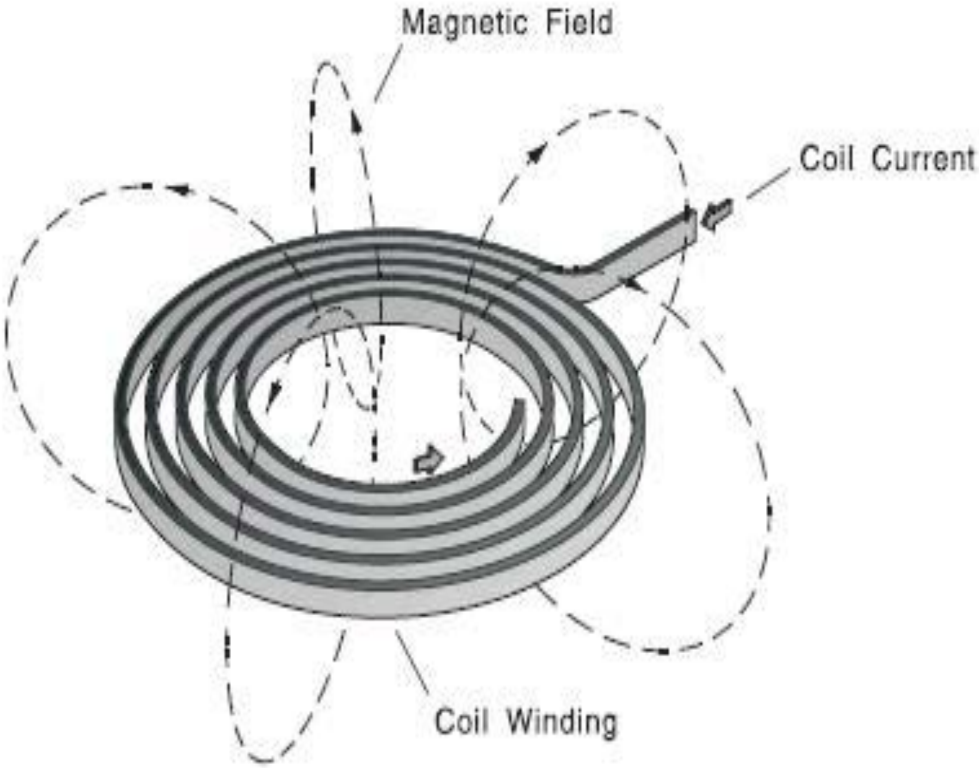
Induces rapid-onset brief electrical field

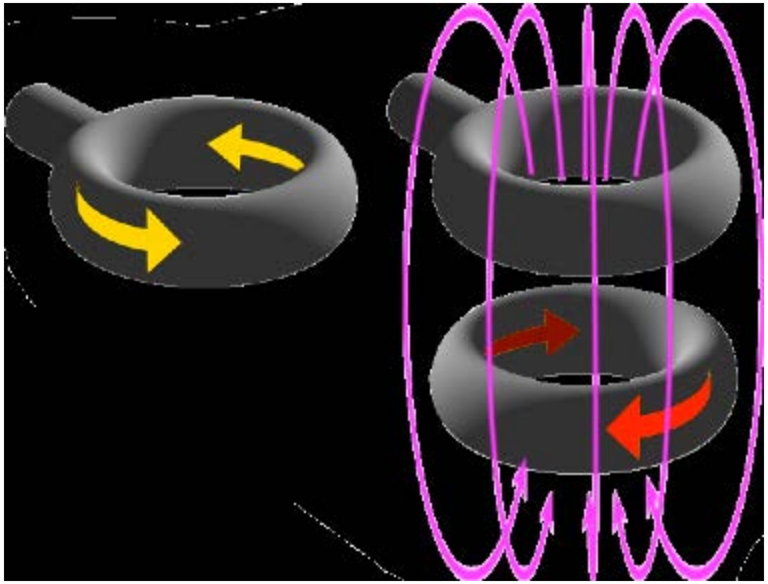
Induces rapid-onset brief electrical current in the brain (mostly cortex)

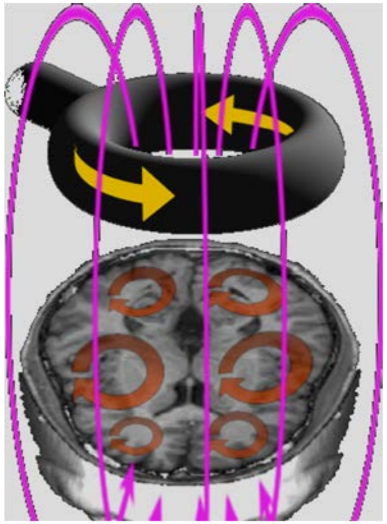
Which has an effect on some task

Walsh V & Cowey, 2000.

Electromagnetic induction

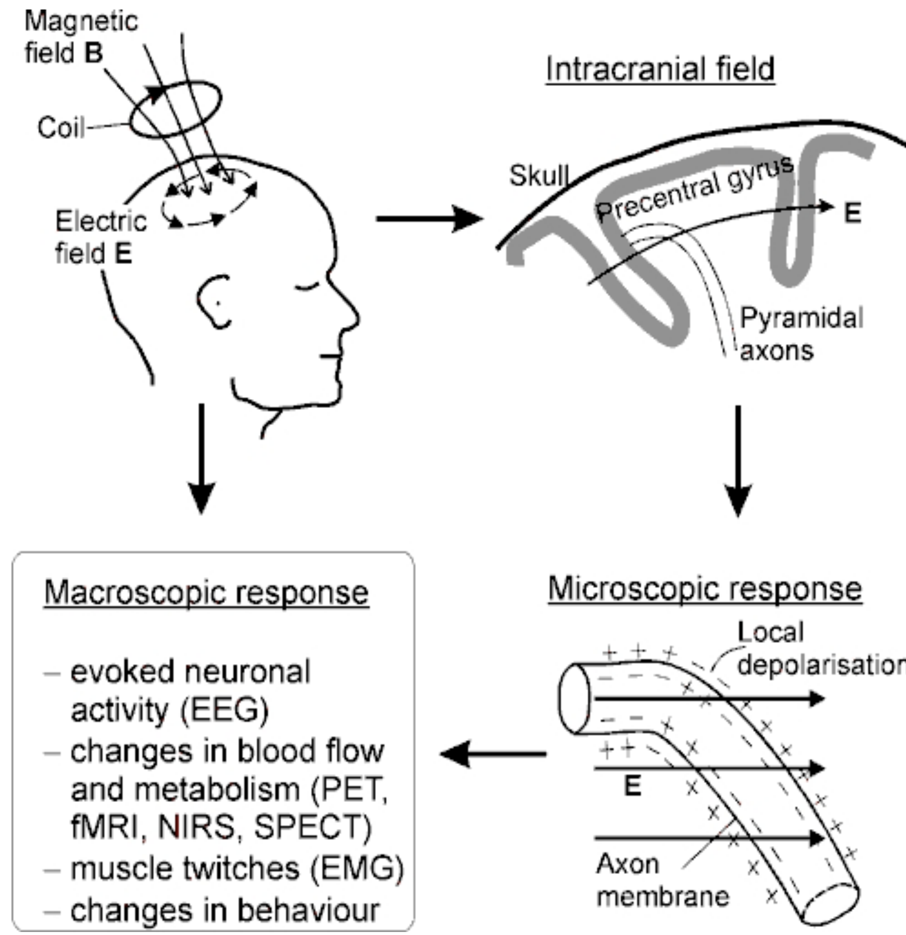






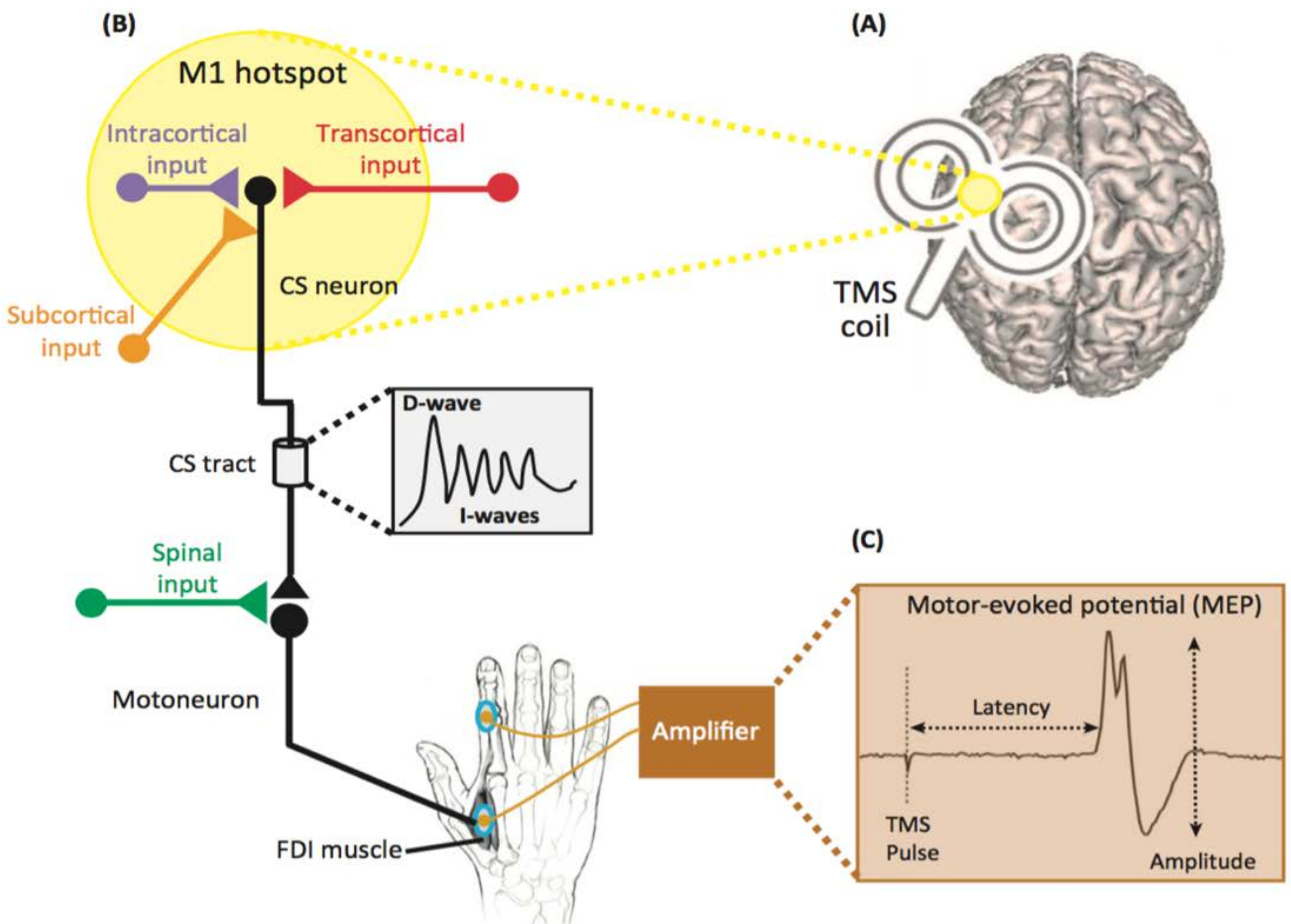
Basics of TMS

- Induces electric current in brain
- Non-invasive
- Painless
- Not deep stimulation
- Can be used repeatedly in humans

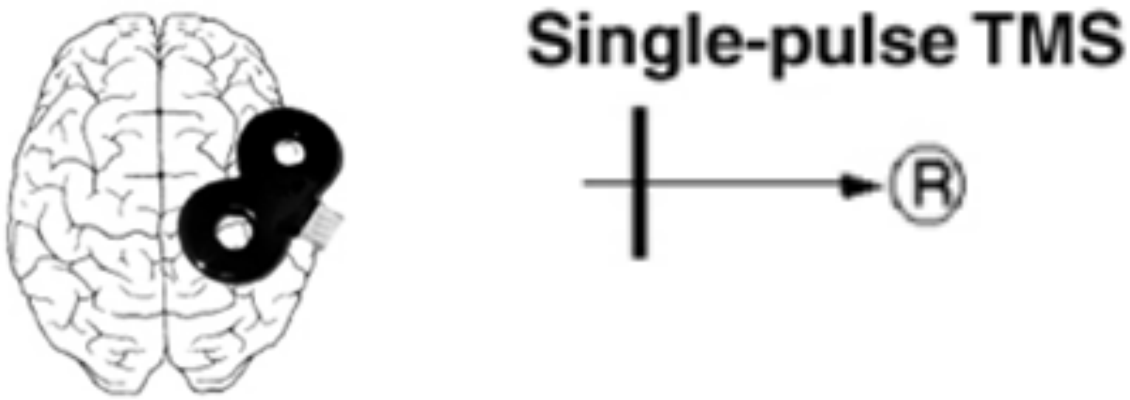


Using TMS to quantify brain function

Measuring motor evoked potential (MEP)



Types of TMS – Single TMS pulse



Single pulse TMS can be used to elicit motor-evoked potentials

A non-invasive method for assessing the integrity of the central motor pathway function and detecting abnormalities in corticospinal pathways in various diseases

Motor evoked potentials

TMS to motor cortex induces motor evoked potentials (MEP's) in muscle

MEPs are the most common measure of changes in cortical excitability

A variety of MEP parameters can be studied:

- Latency
- Amplitude
- Duration
- Area
- Silent period

Three basic physiological mechanisms may influence the size of the MEP:

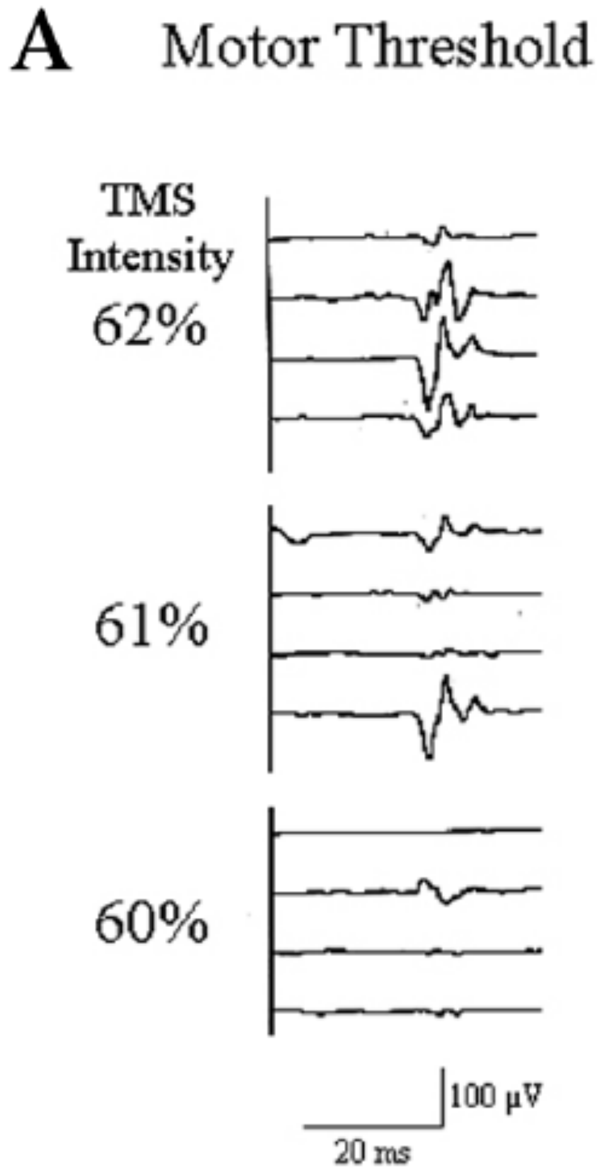
- The number of motor neurones recruited in the spinal cord
- The number of motor neurones discharging more than once to the stimulus
- The synchronisation of the TMS-induced motor neuron discharges

The Motor-evoked potential – Stimulation Intensity

The threshold of stimulation can be an indicator of abnormality in certain disorders

Threshold is defined as the power level at which a response can be detected in 50% of the trials

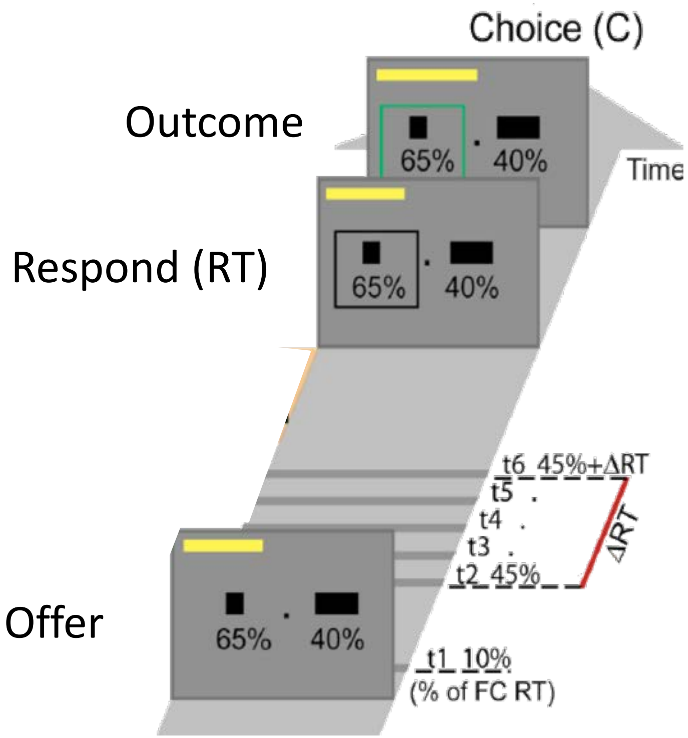
Thresholds can be measured at rest and when muscles are actively contracted

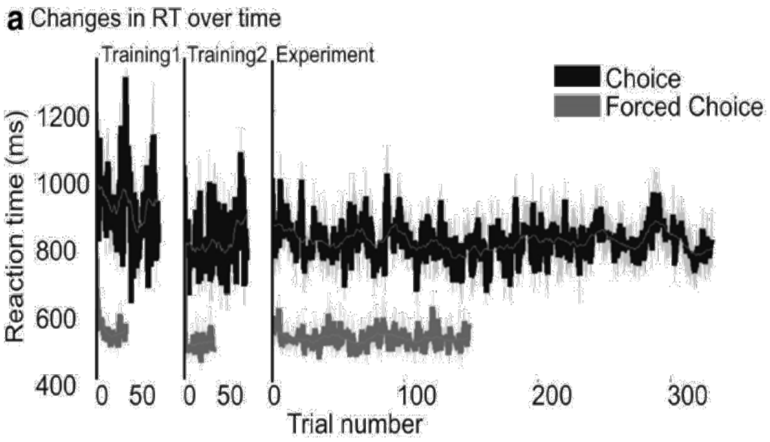


Pascual Leone et al., 1998

Using single pulse TMS to investigate changes in motor excitability during action selection

Single pulse TMS applied at different times during motor preparation period

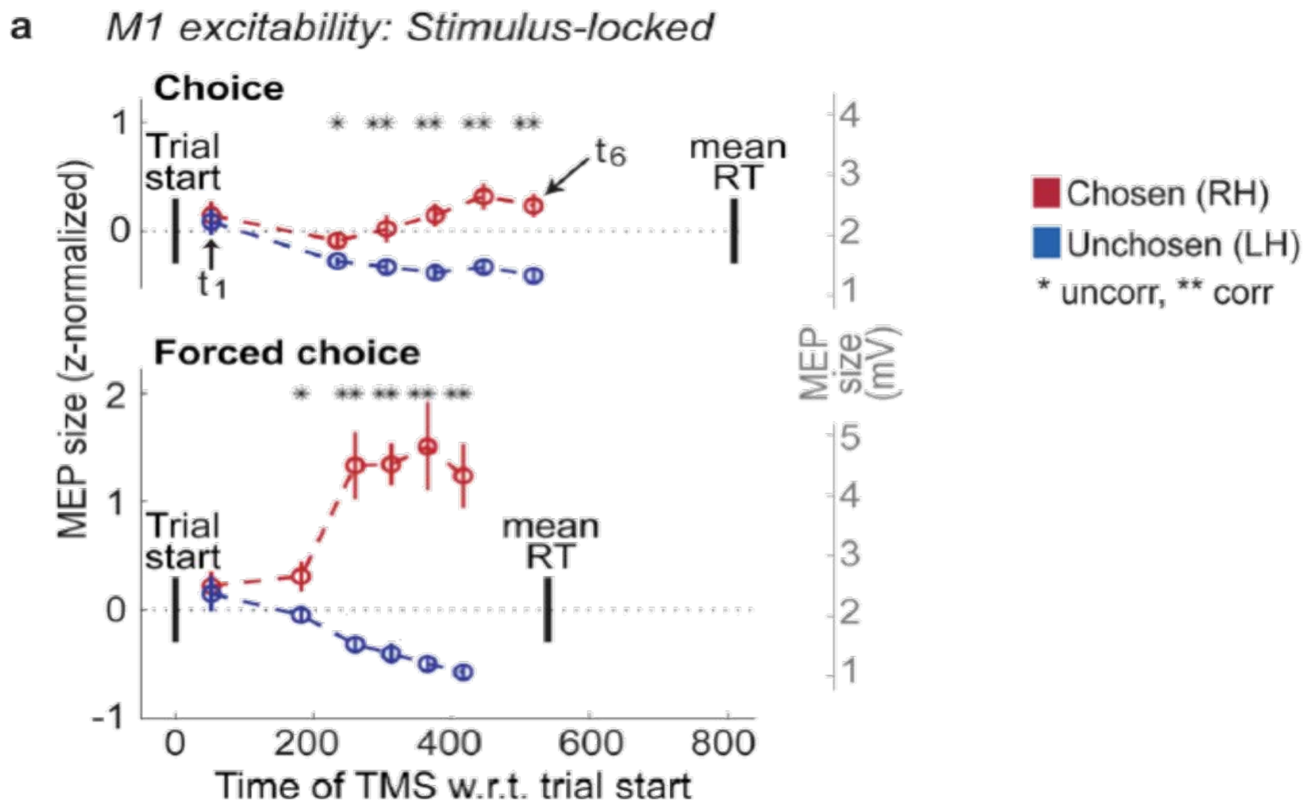




At level of M1/PMd, multiple options are initially specified in parallel but are then <u>gradually</u> eliminated through competitive process

Klein-Flugge & Bestmann, J Neurosci 2012

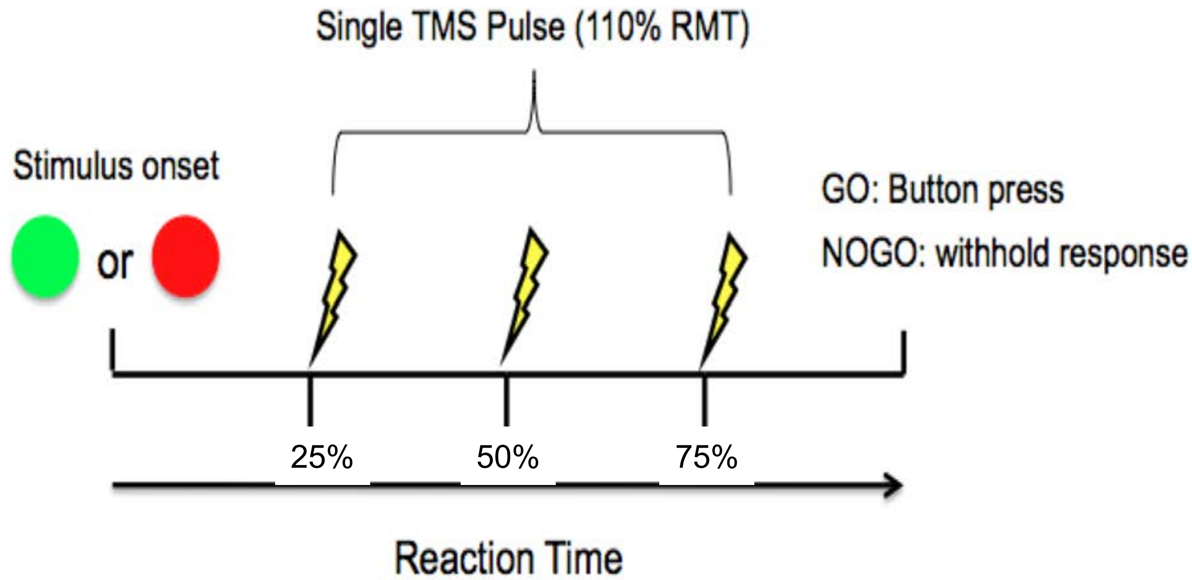
Gradual competition between action representations

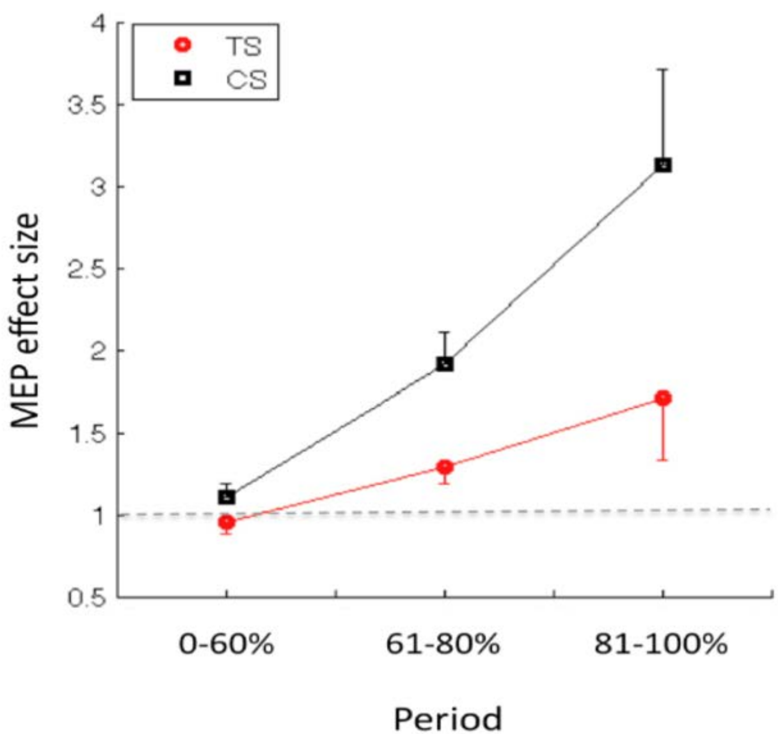


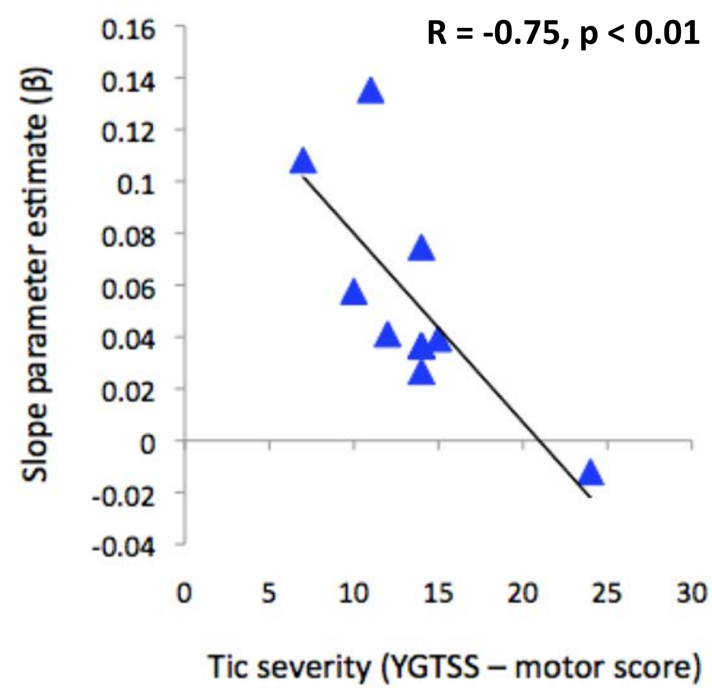
Excitability distinguishes between chosen vs. not-chosen actions early on (~200ms) in preparation/decision process

Klein-Flugge & Bestmann, J Neurosci 2012

Cortical excitability in M1 preceding volitional movements in Tourette syndrome



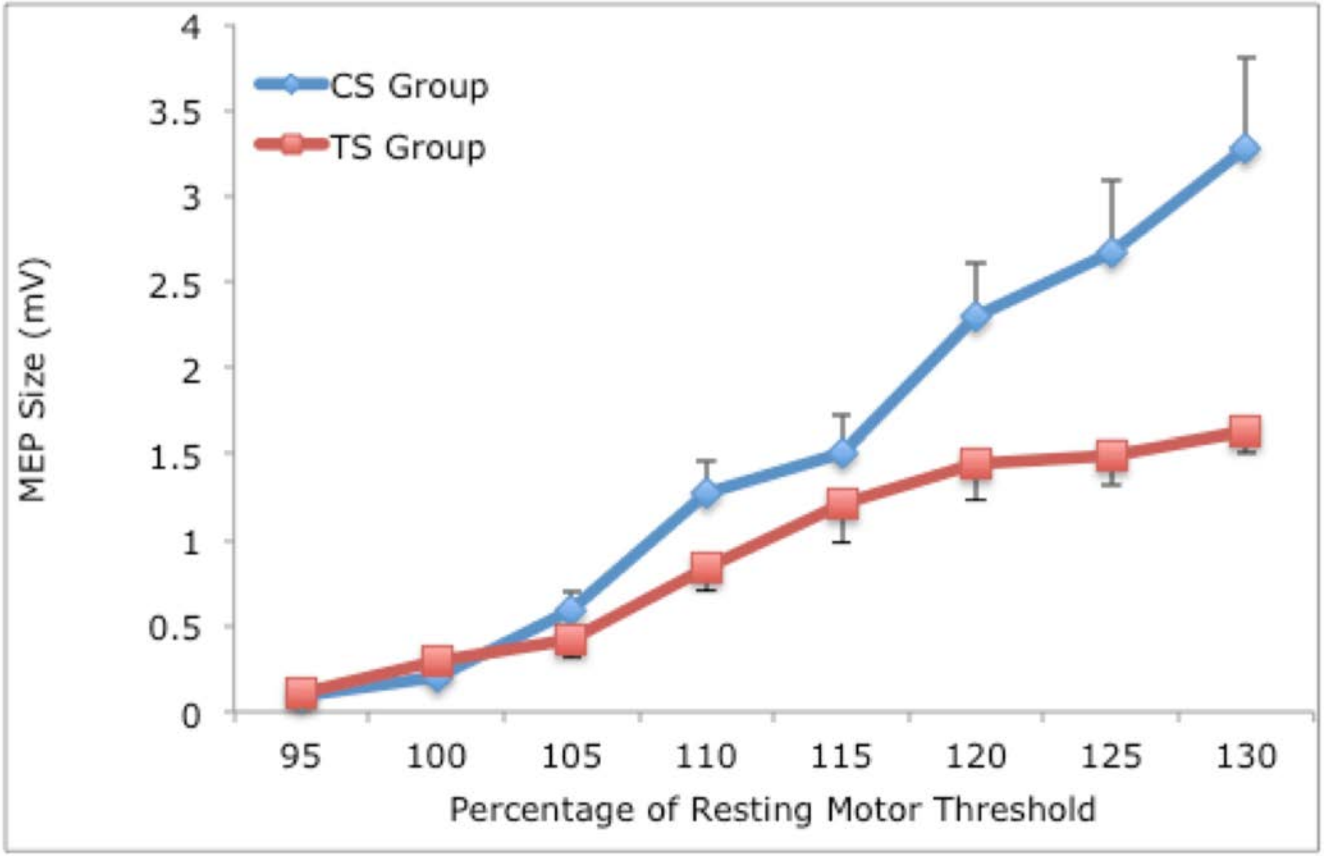




Draper et al., *J. Neuropsychology*, 2014

Differences in IO curves may signal important changes in cortical excitability

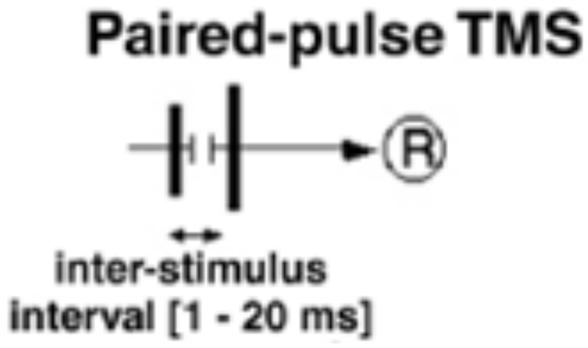
TMS recruitment curves for TS group and matched controls



Draper et al., *Current Biology*, 2014

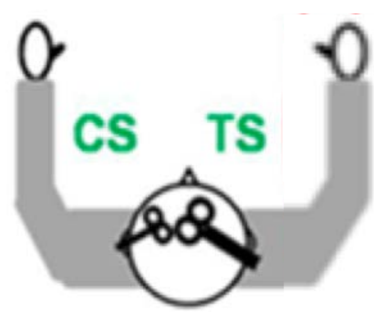
Types of TMS – Paired pulse techniques

Paired pulse TMS can be used to examine modulation of motor cortex excitability by local circuits or afferent input from other brain areas



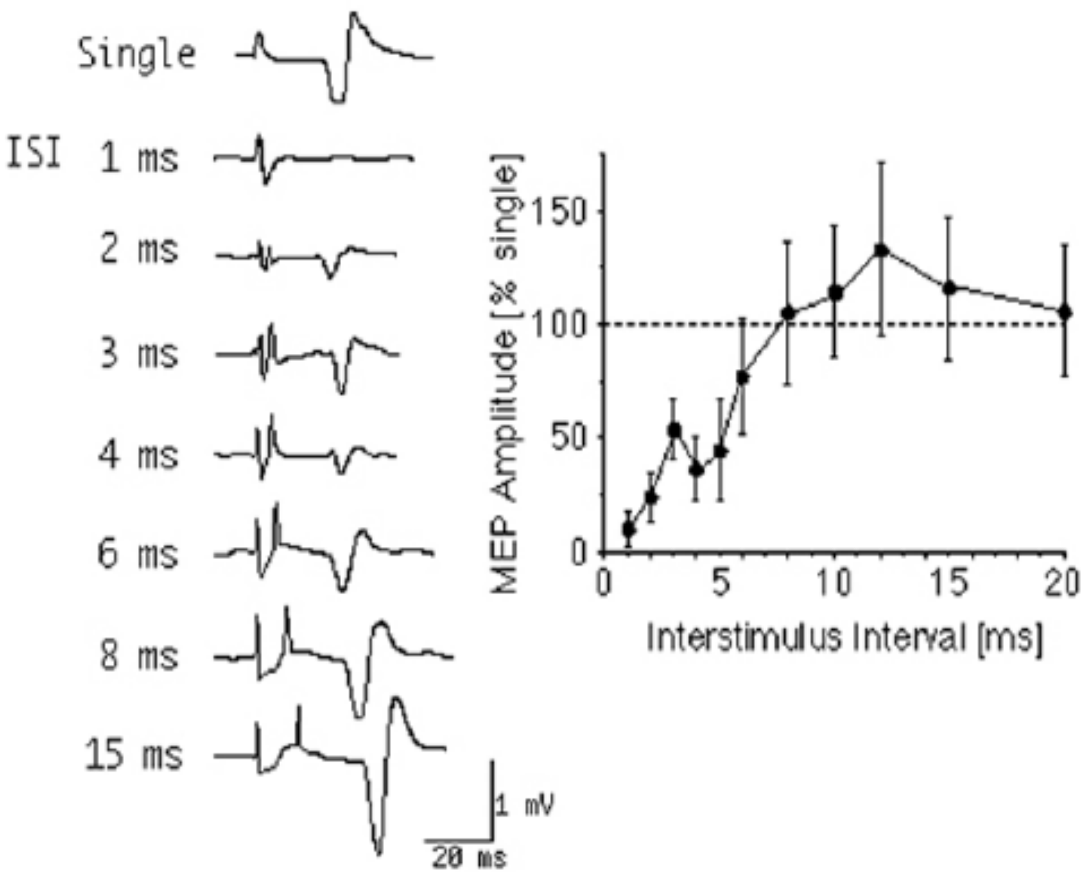
Dual (paired)-pulse TMS: stimulation with two distinct stimuli **<u>through the same coil</u>** at a range of different intervals. The intensities can be varied independently

Double TMS: stimulation **<u>with two separate stimulation coils</u>** applied to different cerebral loci; the timing and stimulus intensity are adjusted separately



The Motor-evoked potential – Paired pulse

Dual (paired)-pulse TMS

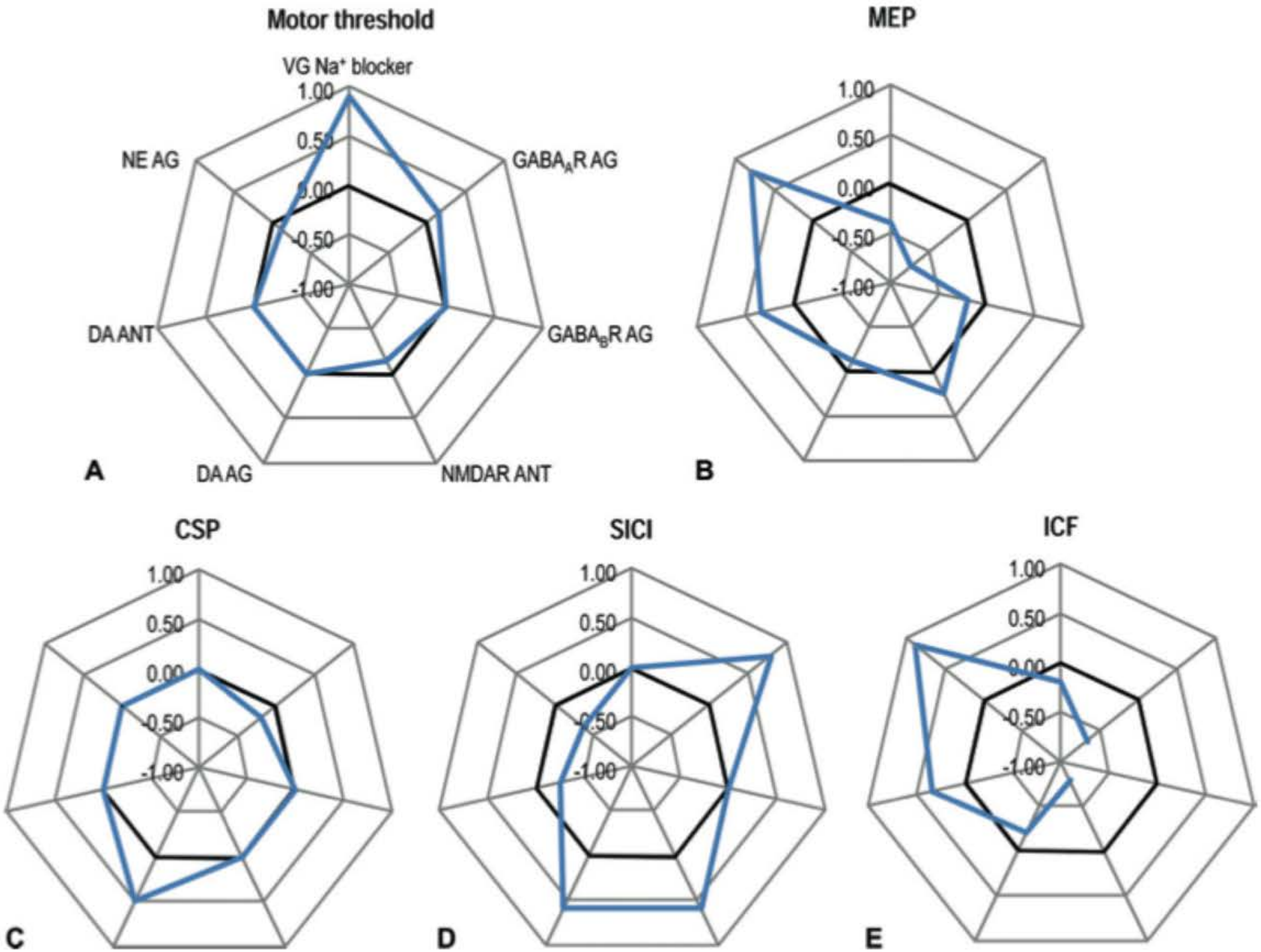


Short ISI's cause an inhibition of excitability - seen through a reduction in MEP amplitude

Long ISI's have an facilitatory effect - causing an increase in MEP amplitude

Pascual Leone et al., 1998

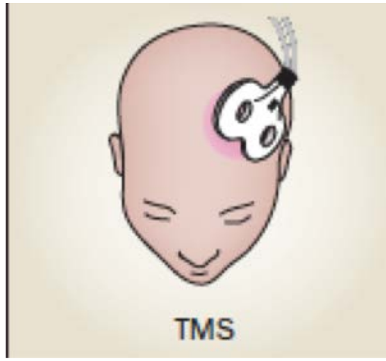
Drug effects on TMS measures

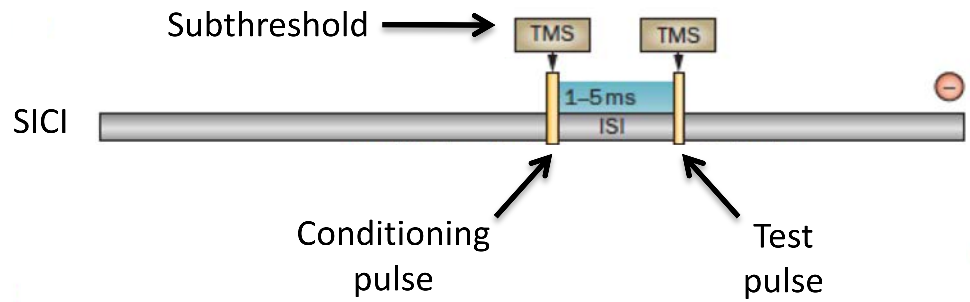


Ulf Zieman, 2013

Altered cortical GABA function in Tourette syndrome

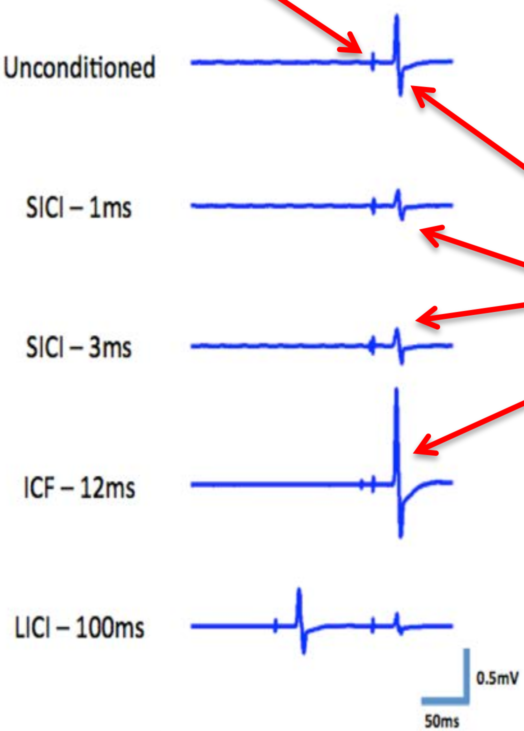
TMS studies using paired-pulse protocols indicate impaired $GABA_A$ dependent cortical inhibition.



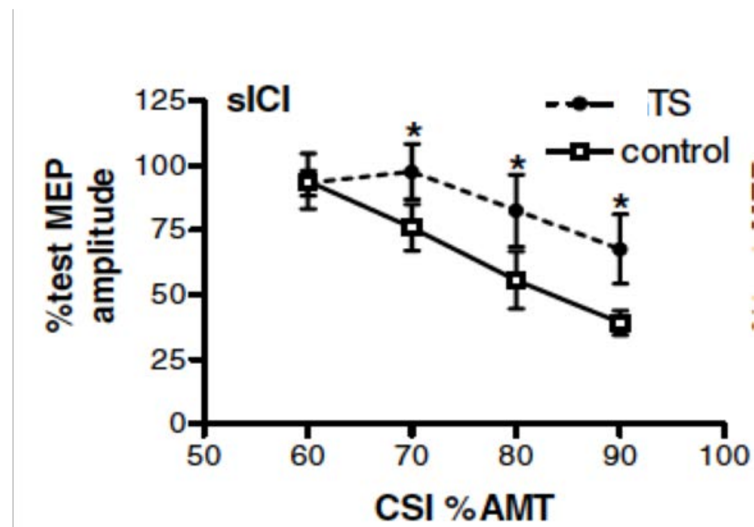


Adapted from Di Pino et al., *Nat. Rev. Neurol.*, 2014

TMS artefact



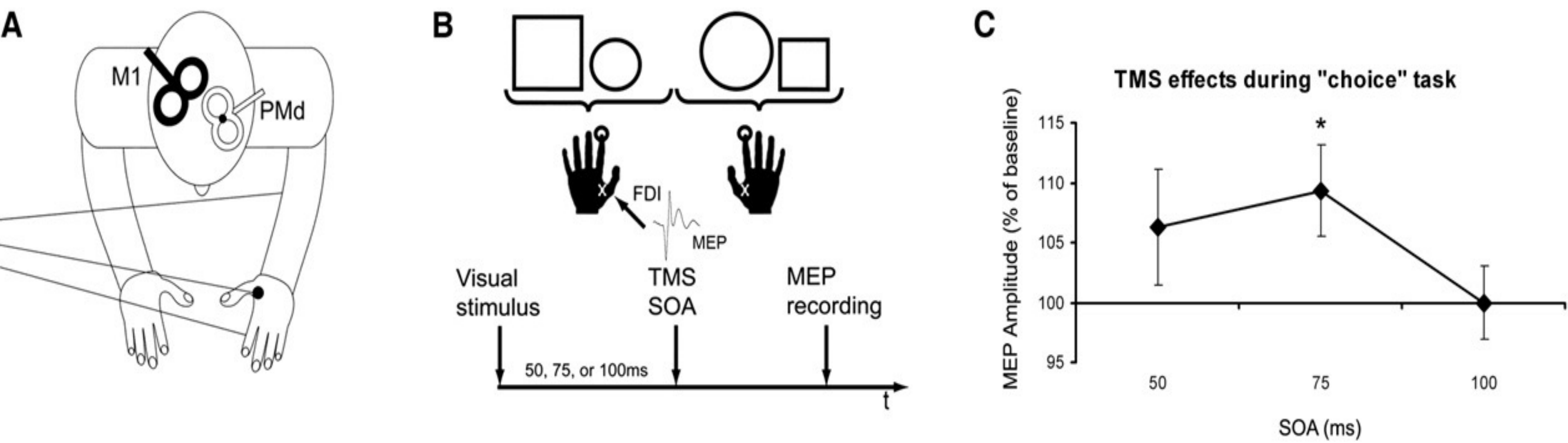
Test pulse MEP



Orth et al., *Brain*, 2005

Combining techniques: Investigating white matter pathways mediating functional connectivity

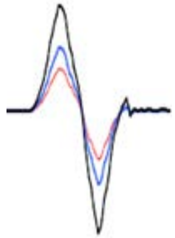
<u>Double coil TMS (Pmc – M1)</u>



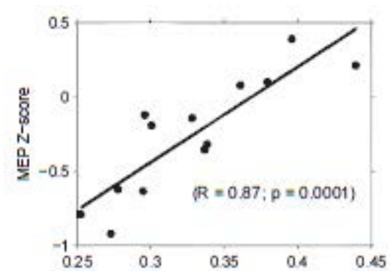
Boorman, O'Shea, Sebastian et al., *Current Biology*, 2007

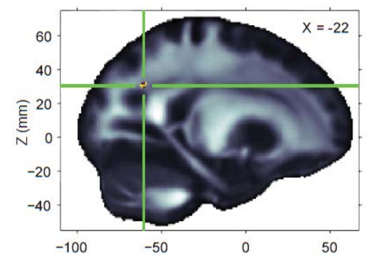
Combining techniques: Investigating white matter pathways mediating functional connectivity

Double coil TMS (Pmc – M1)

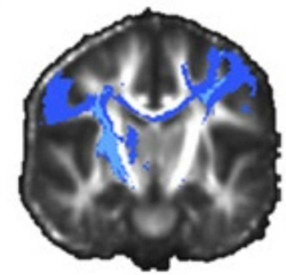


Functional connectivity measure



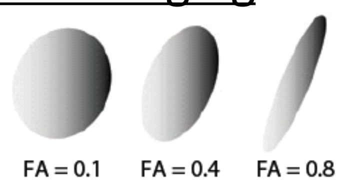


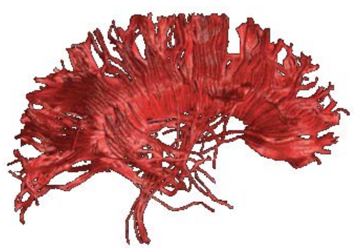
correlate



Fiber tracking from found clusters

Diffusion-weighted imaging



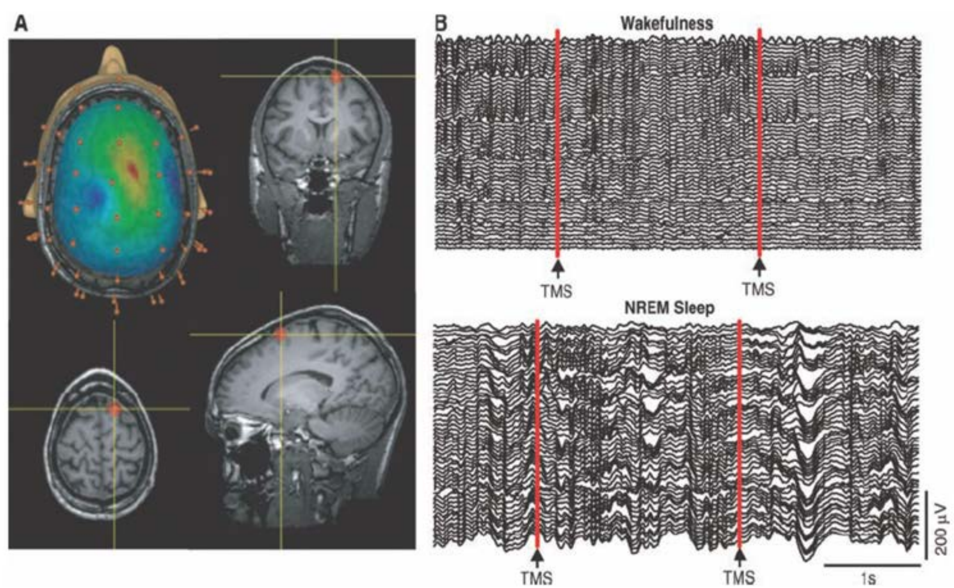


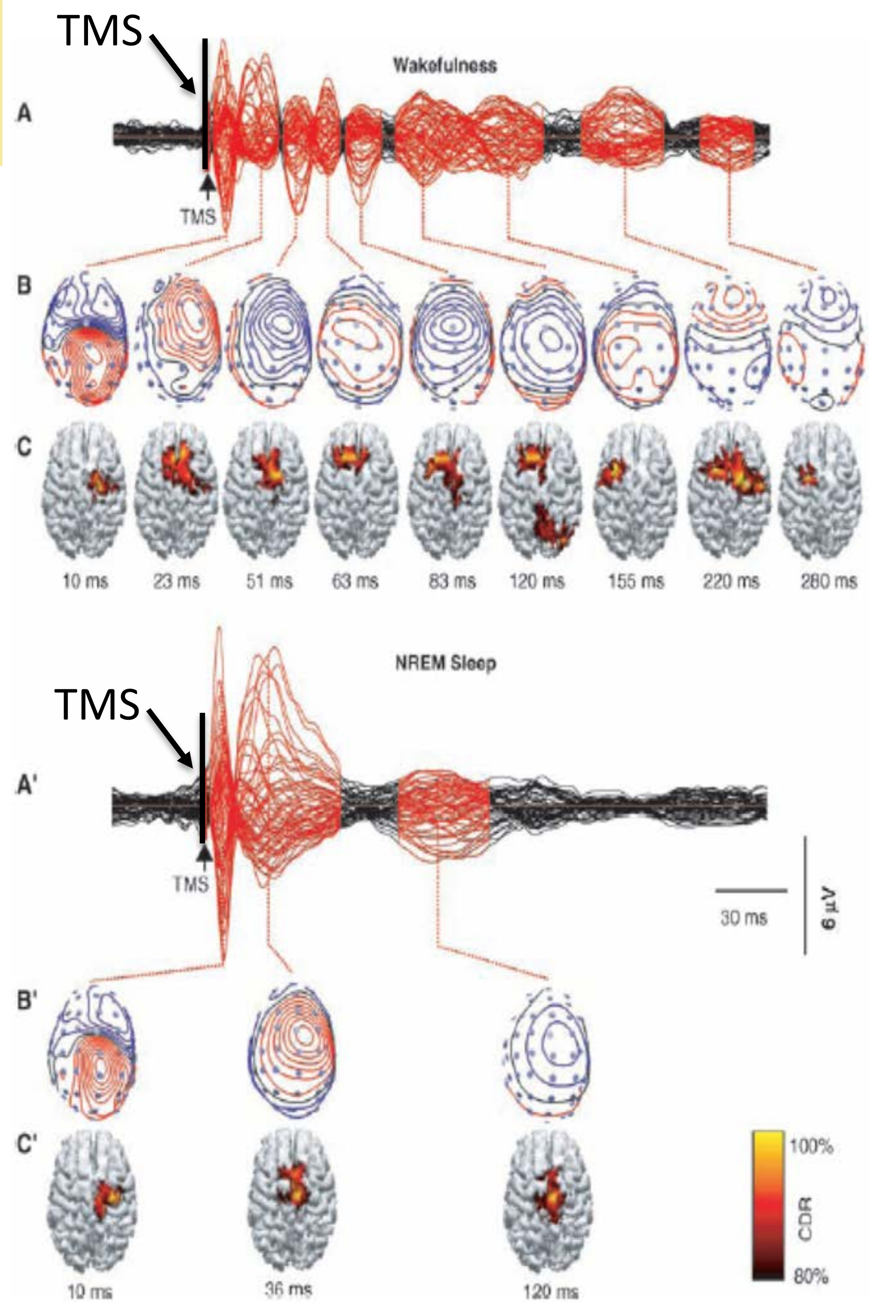
Structural connectivity measure

Boorman, O'Shea, Sebastian et al., *Current Biology*, 2007

Advantages of combining TMS and EEG recording.

- *Example application: altered brain connectivity during sleep*
- Single-pulse TMS applied to ***Premotor cortex***.
- TMS effects propagate to remote sites during wakefulness but ***NOT*** during NREM sleep

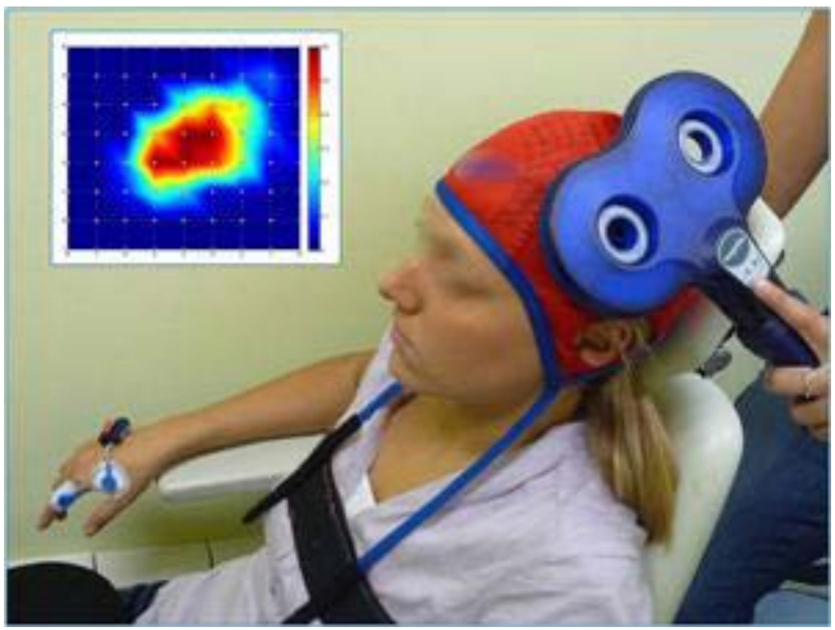


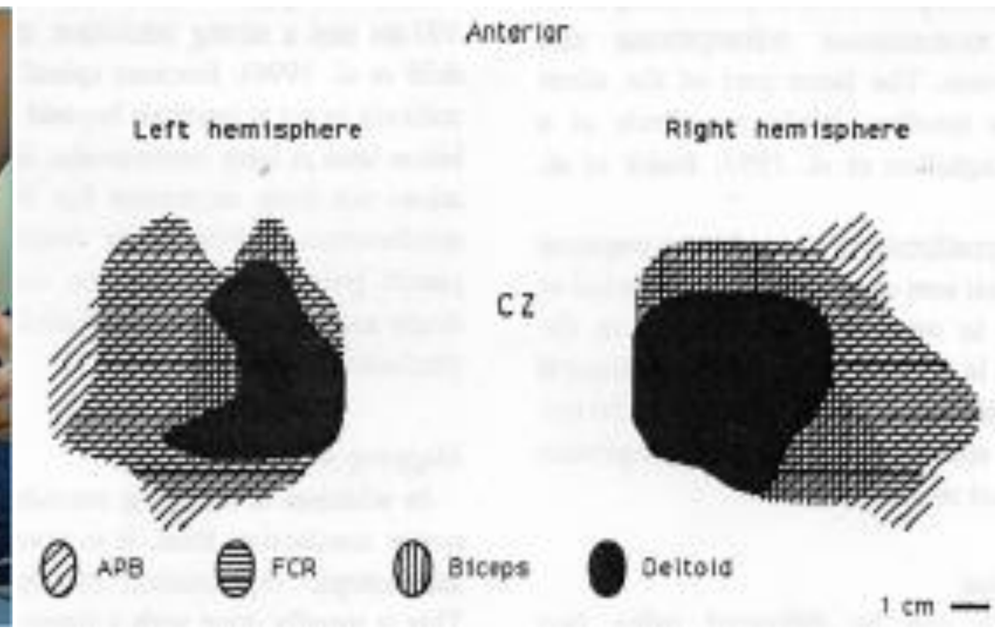


Massimini et al. ***Science***, 2005

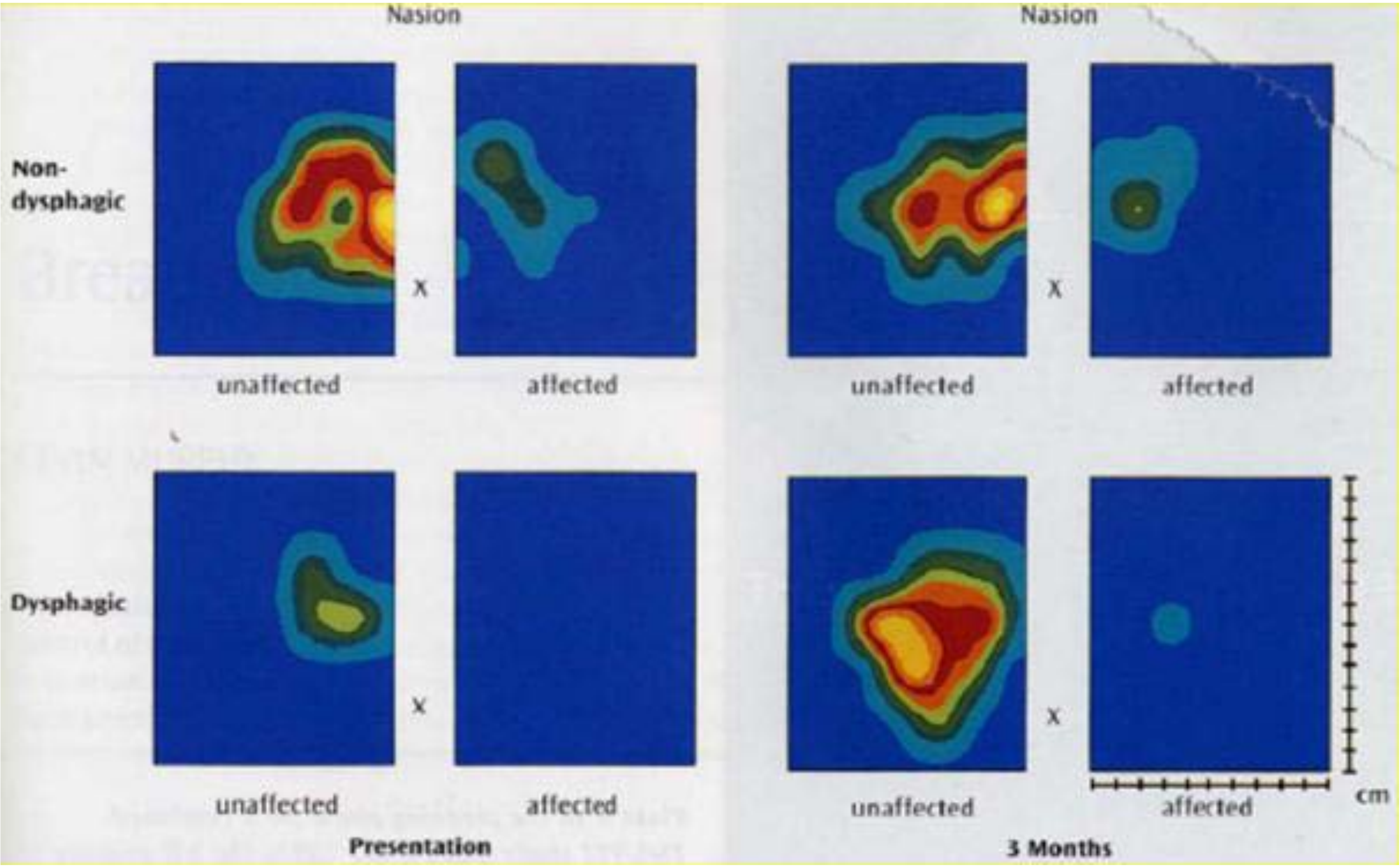
Cortical mapping

- TMS studies can address specifically the issue of cortical reorganization by mapping procedures





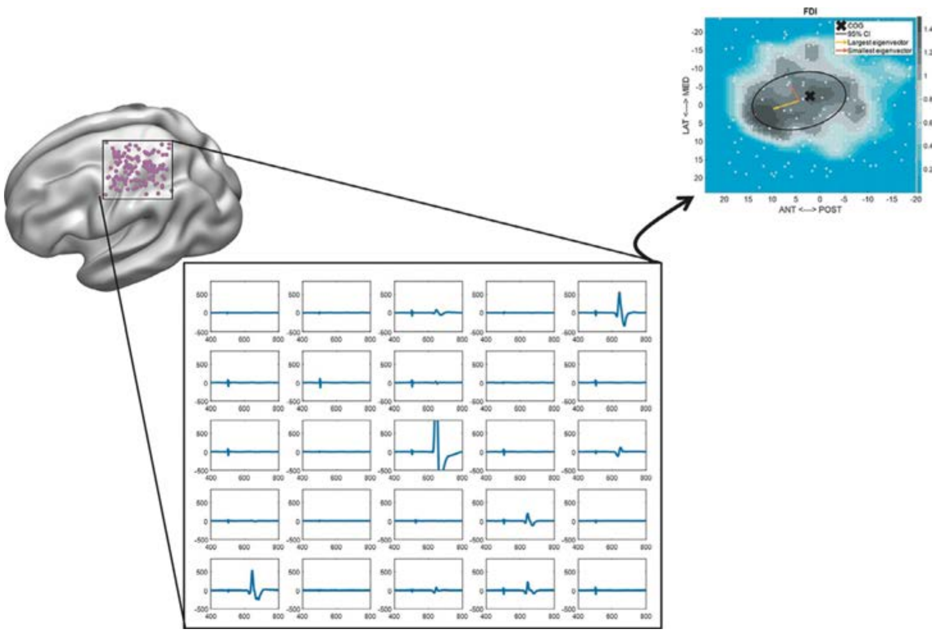
Cortical mapping – post stroke



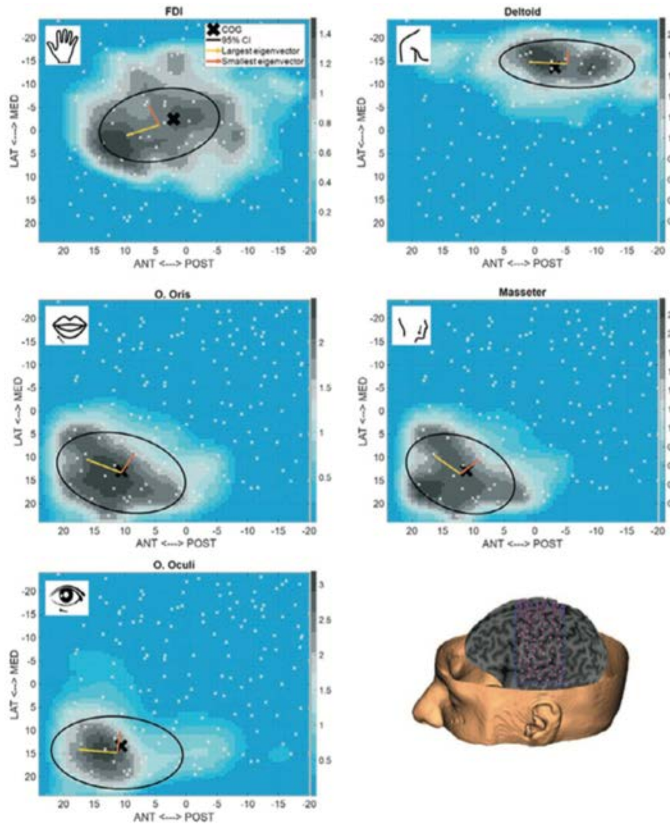
Hamdy et al 1996

Mapping muscle representations in motor cortex in Tourette syndrome using neuro-navigated TMS

A.



B.



Sigurdsson et al., *Cortex, 2020*

Using TMS to interfere with brain function; ‘virtual lesion’ approaches

Studying brain-behaviour relationships in humans

- Lesion Studies
  - Single or few case studies
  - Cognitive abilities may be globally impaired
  - Comparisons must be made to healthy controls
- Neuroimaging (Brain Mapping) Techniques
  - Non-invasive identification of brain injury correlated with a given behaviour
  - Association of brain activity with behaviour
  - Cannot demonstrate the necessity of a given region to a function
- Direct cortical Stimulation
  - Invasive
  - Time constraints limit the experimental paradigms
  - Retesting is not possible

Advantages of using TMS in the study of brain-behaviour relationships

- Study of normal subjects eliminates the potential confounds of additional brain lesions and pathological brain substrates
- Acute studies minimize the possibility of plastic reorganization of brain function
- Repeated studies in the same subject
- Study multiple subjects with the same experimental paradigm
- Study internal network interactions by targeting different brain structures during a single task and disrupting the same cortical regions during different related tasks

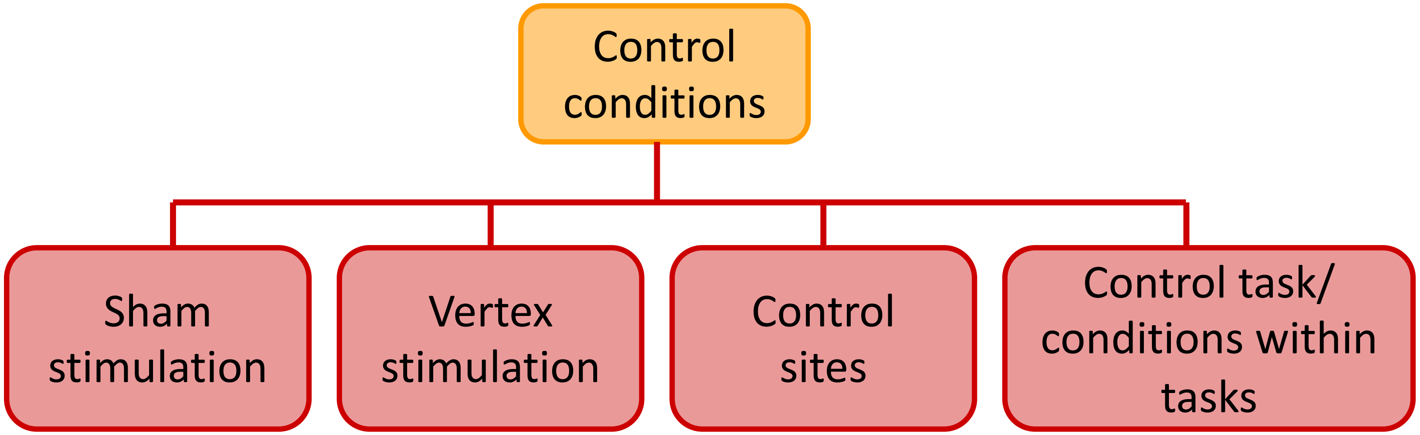
Important issues in TMS experimental design for behavioural studies

- Confounding effects
  - Loud “click” during each pulse (attention)
  - Tactile sensation at site of stimulation
  - Blink reflex and sometimes scalp twitching

>> Need to control for these reactions

Important issues in TMS experimental design for behavioural studies

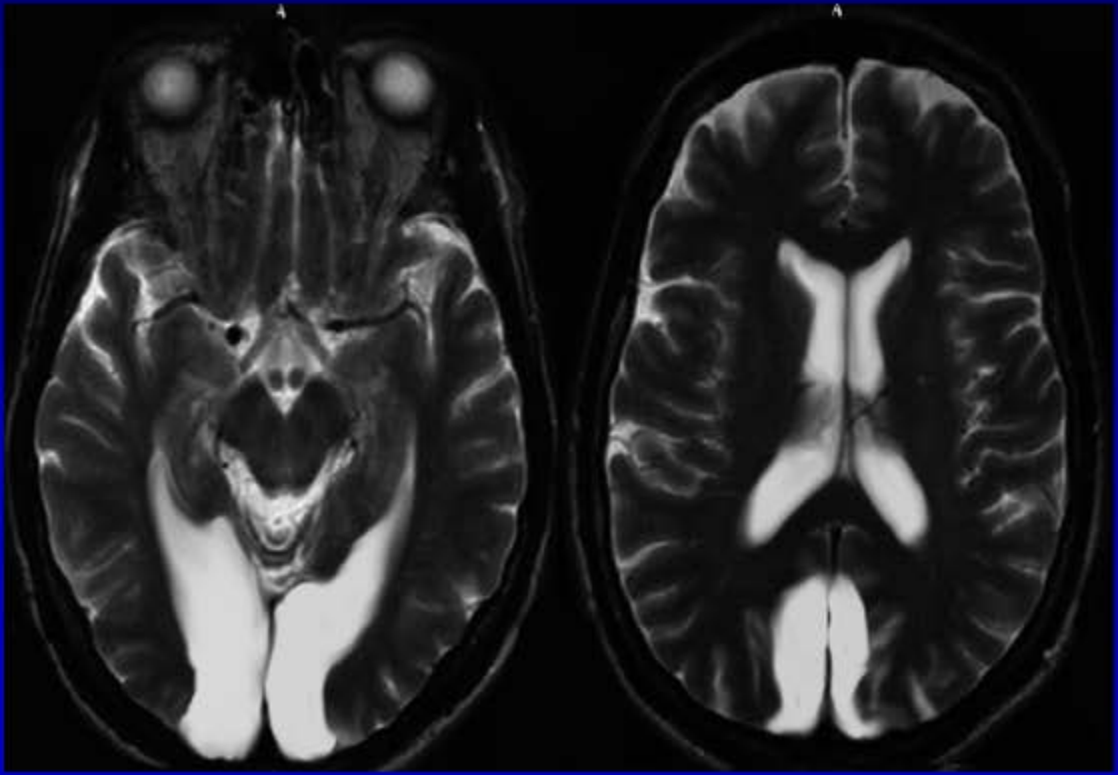
- Control conditions for TMS experiment
  - To ensure changes in performance be ascribed to TMS effects upon a specific brain area
  - Generally, need a combination of control conditions



An illustrative example

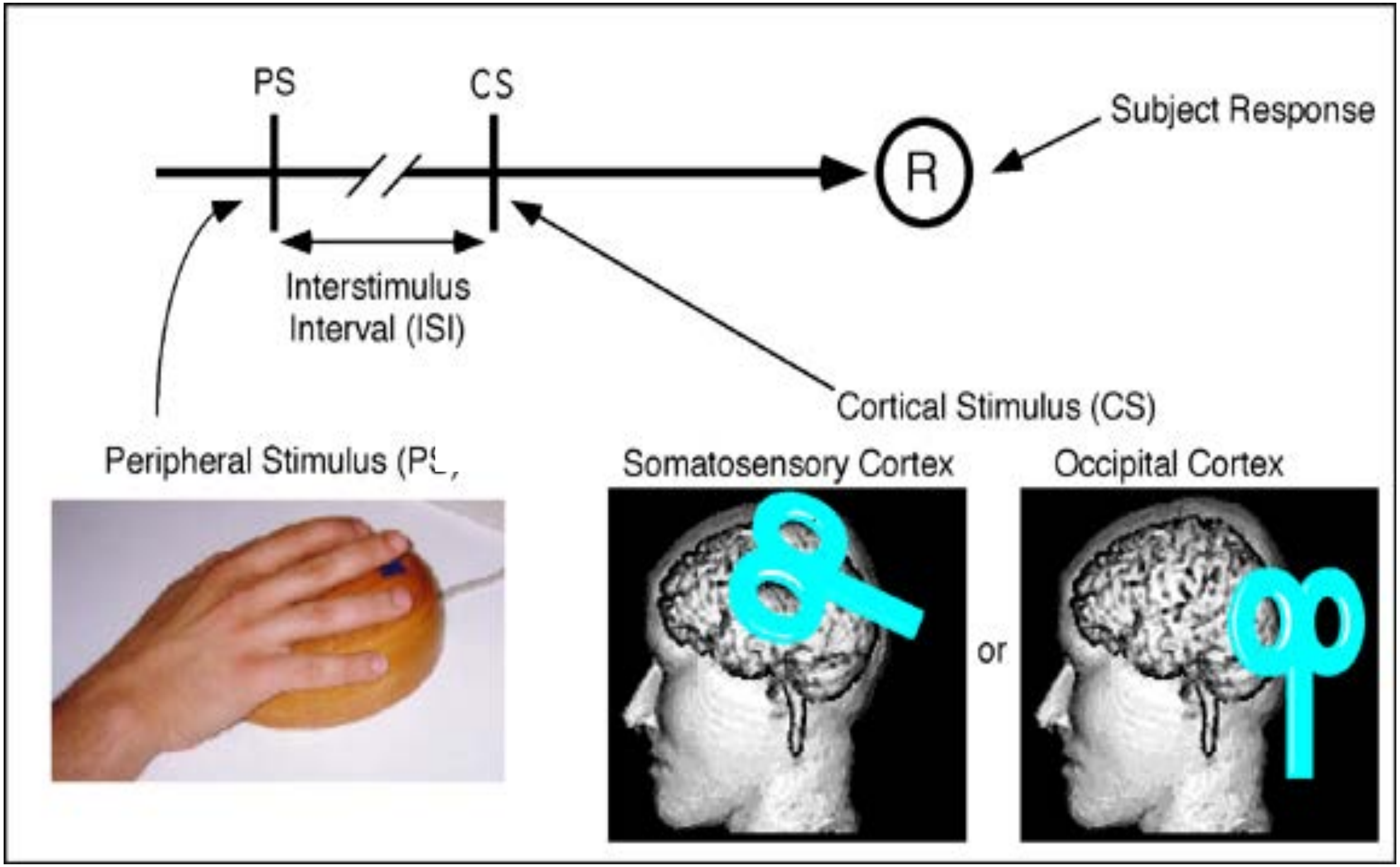
Braille Alexia

- 63 y/o woman
- Blind "since birth"
- Braille since age 7
- Braille 4-6 h/d
- Unable to read Braille after transient coma
- Normal neurological exam

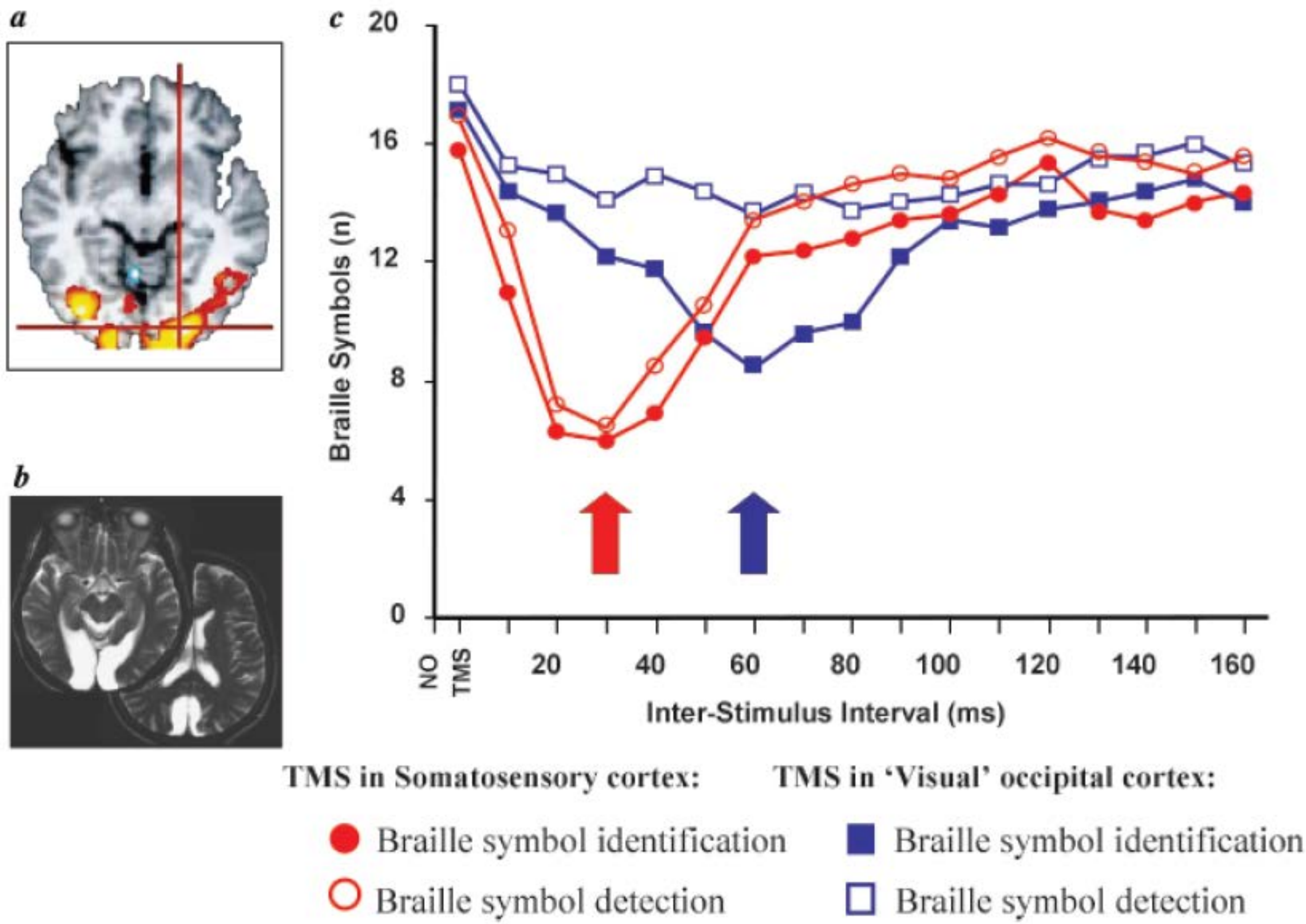


Hamilton et al. Neuroreport 2000

Role of "visual" cortex in tactile information processing in early blind subjects



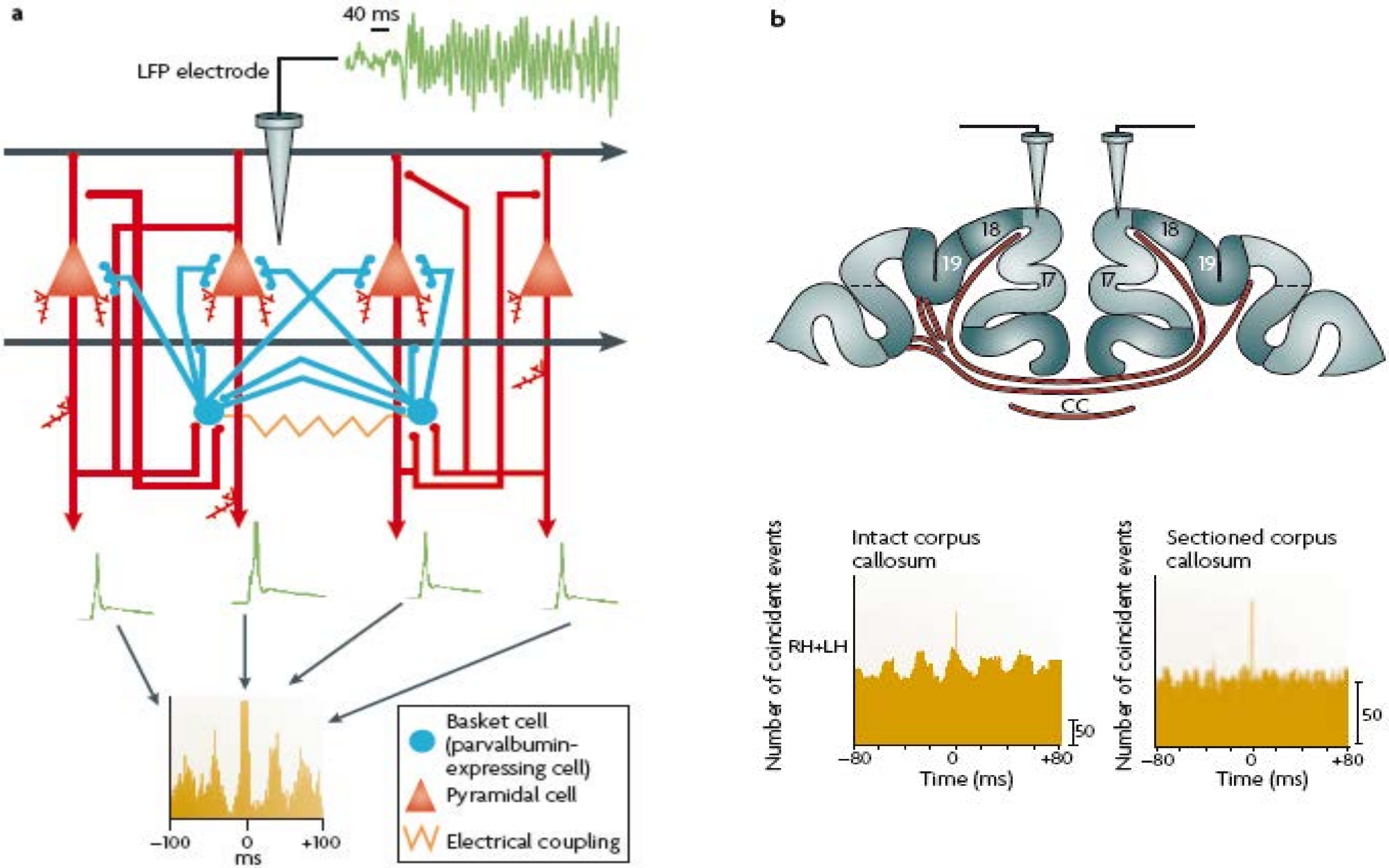
Hamilton et al. TICS, 2001



Hamilton et al. *TICS*, 2001

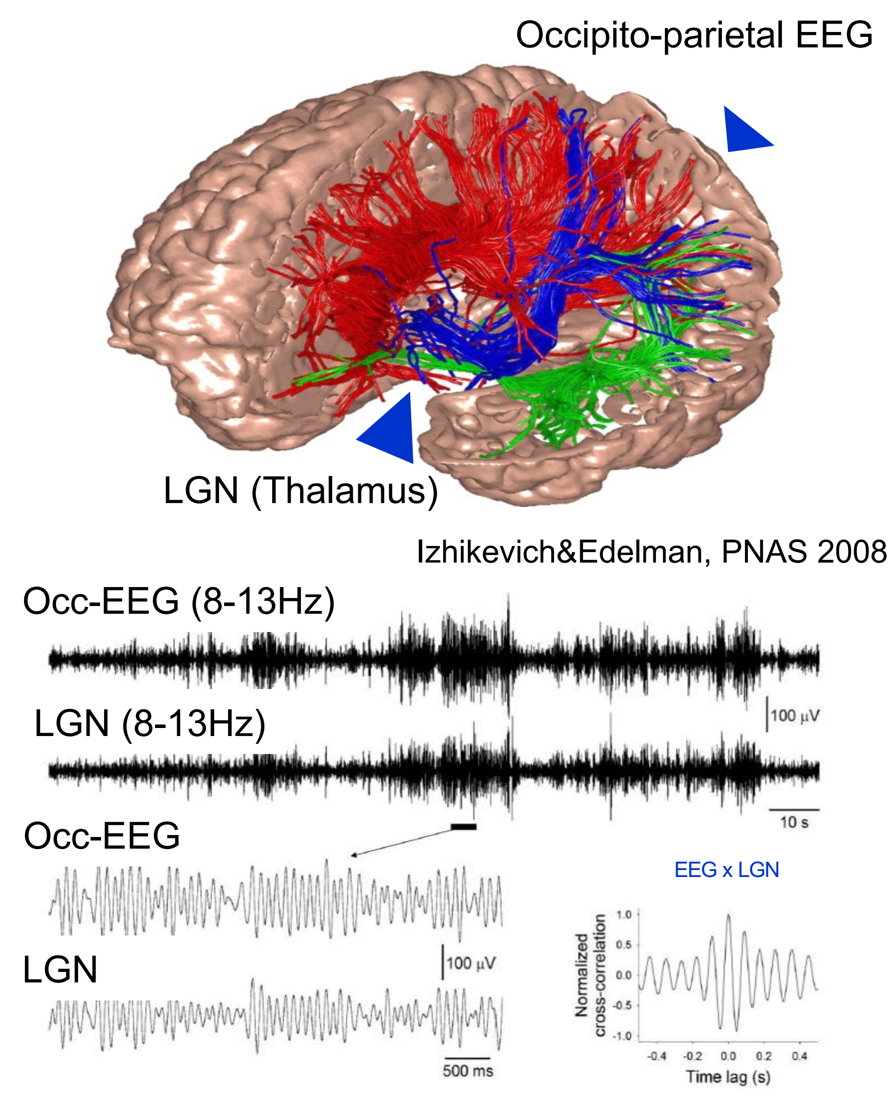
Using TMS to modulate with brain function

Neuronal oscillations, cortical excitability, balanced excitation and inhibition



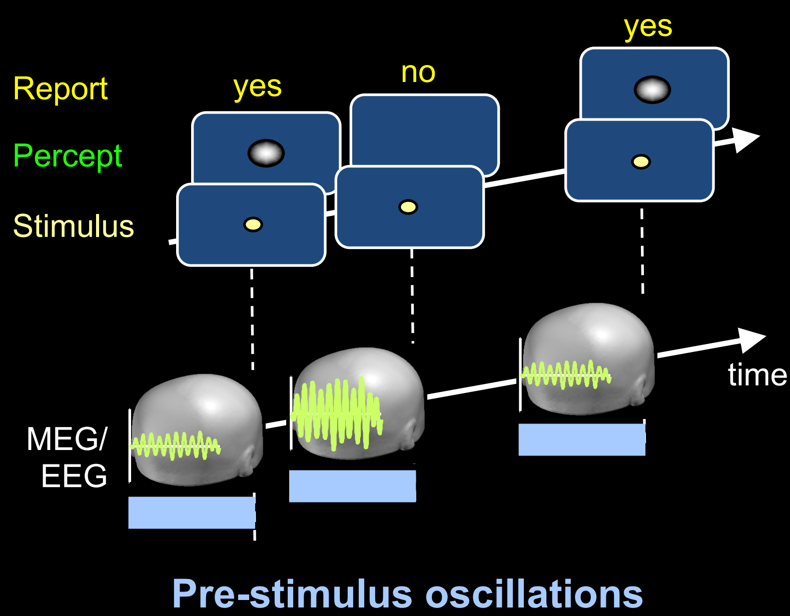
Uhlhaas & Singer (2010). *Nature Reviews Neuroscience*

Brain oscillations reflect synchronized firing of neural populations



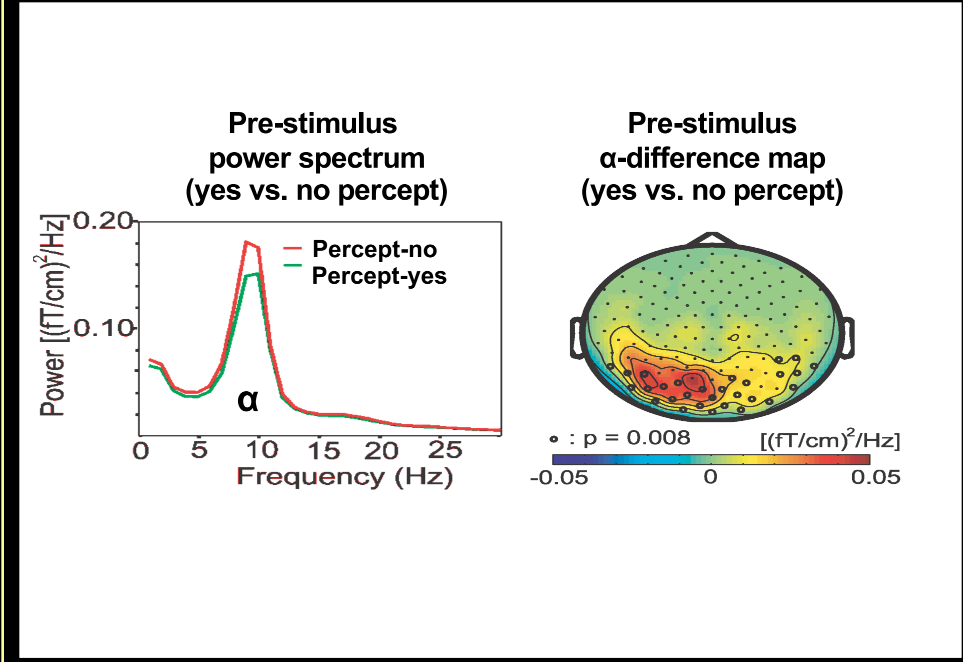
Alpha oscillations (8-13Hz) in LGN and over occipital areas are in synchrony (Crunelli et al., 2011)

Pre-stimulus cortical oscillations predicts perception



VanDijk et al. *J Neurosci*, 2008

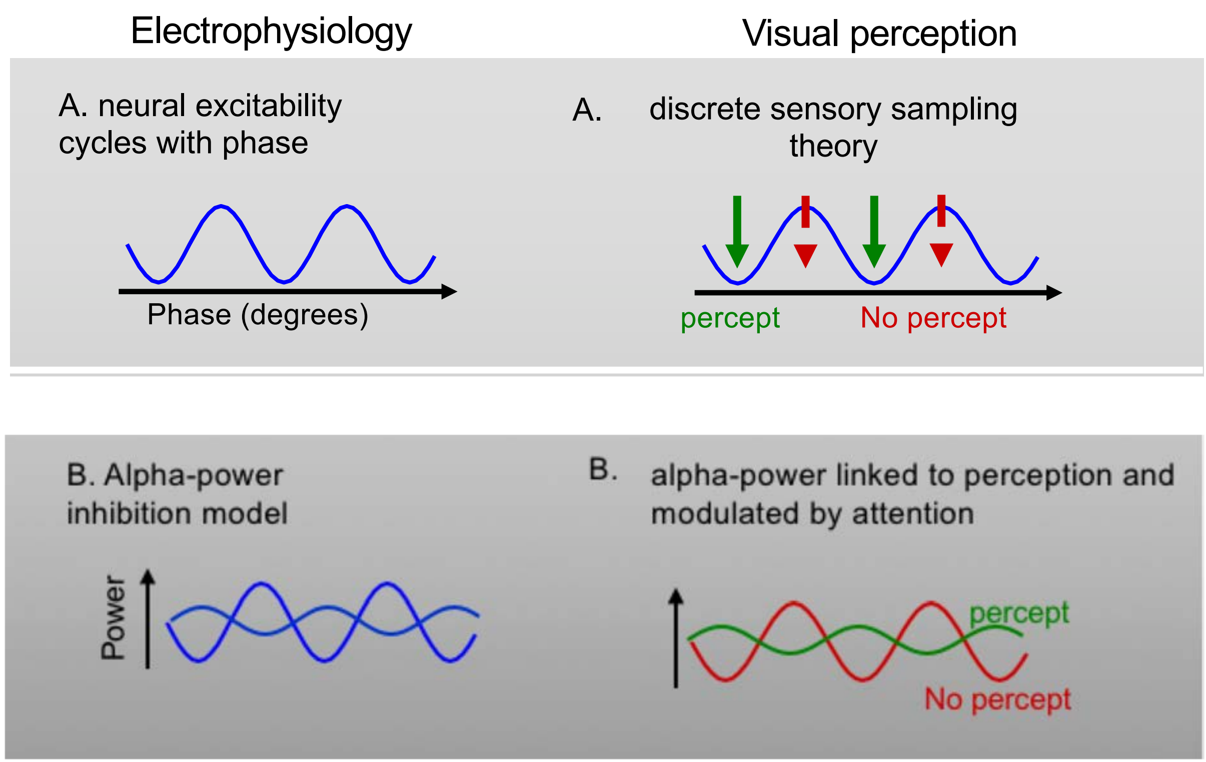
Pre-stimulus: -1000 to 0ms



Occipito-parietal oscillatory signatures in the alpha-band (8-14Hz) prior to a stimulus predicts the perceptual fate of the stimulus

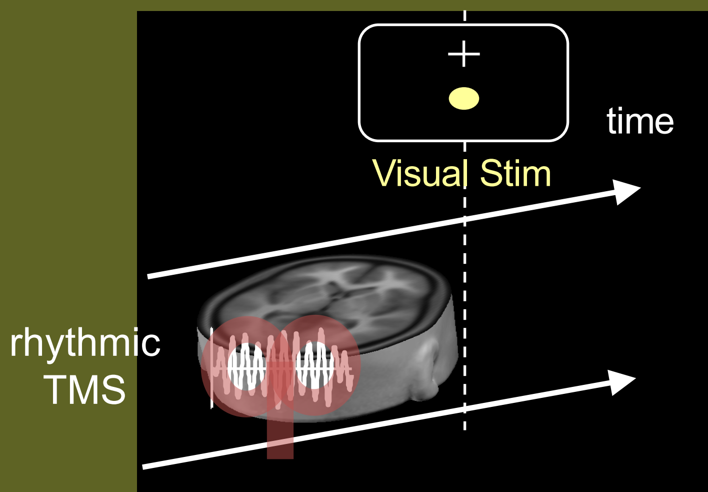
Behavioural performance is predicted by brain oscillations

Hypothesis: Visual perception is influenced by oscillatory power and phase



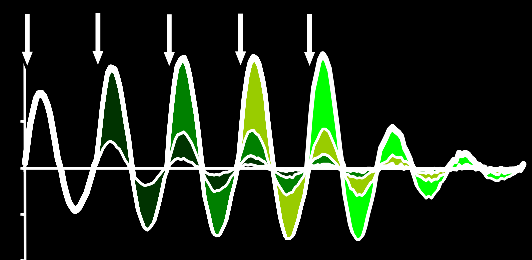
Can rhythmic TMS be used to entrain brain oscillations and alter behavior?

Rhythmic pre-stimulus TMS to entrain oscillations and bias perception



Hypothesis:
Entrainment conceivable!

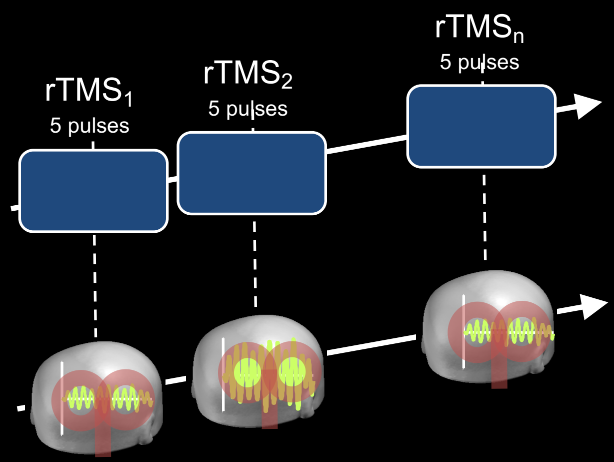
- **>1 TMS pulse that are in phase**



- **Synchronization of more and more neurons to the TMS train**

TMS-EEG

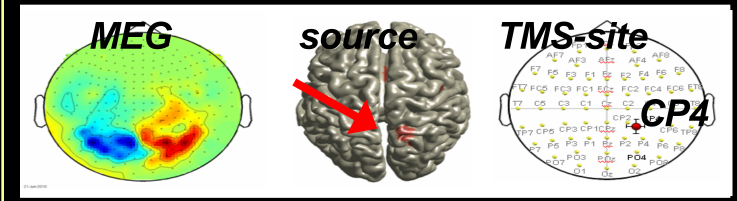
TMS-induced entrainment



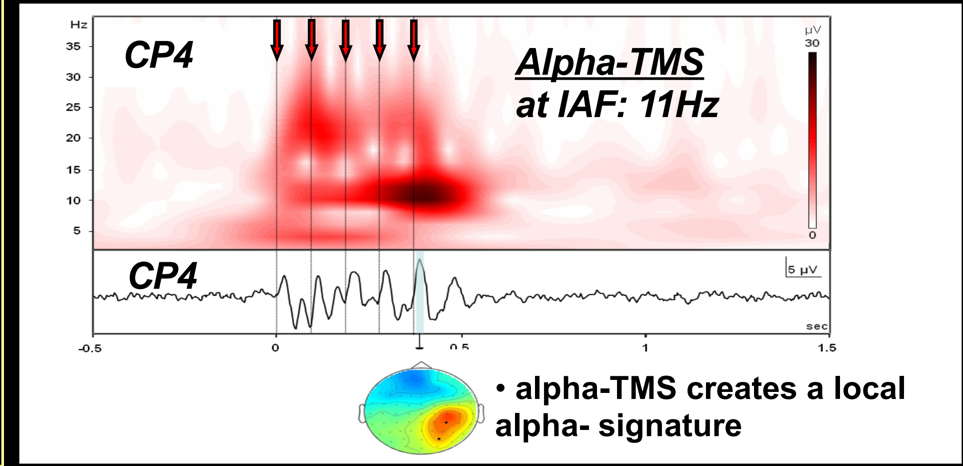
- short TMS bursts (n=5 pulses)
- TMS over right alpha generator
- TMS at individual alpha frequency
- several TMS controls
(including arhythmic TMS and sham TMS)

Pre-TMS MEG-session

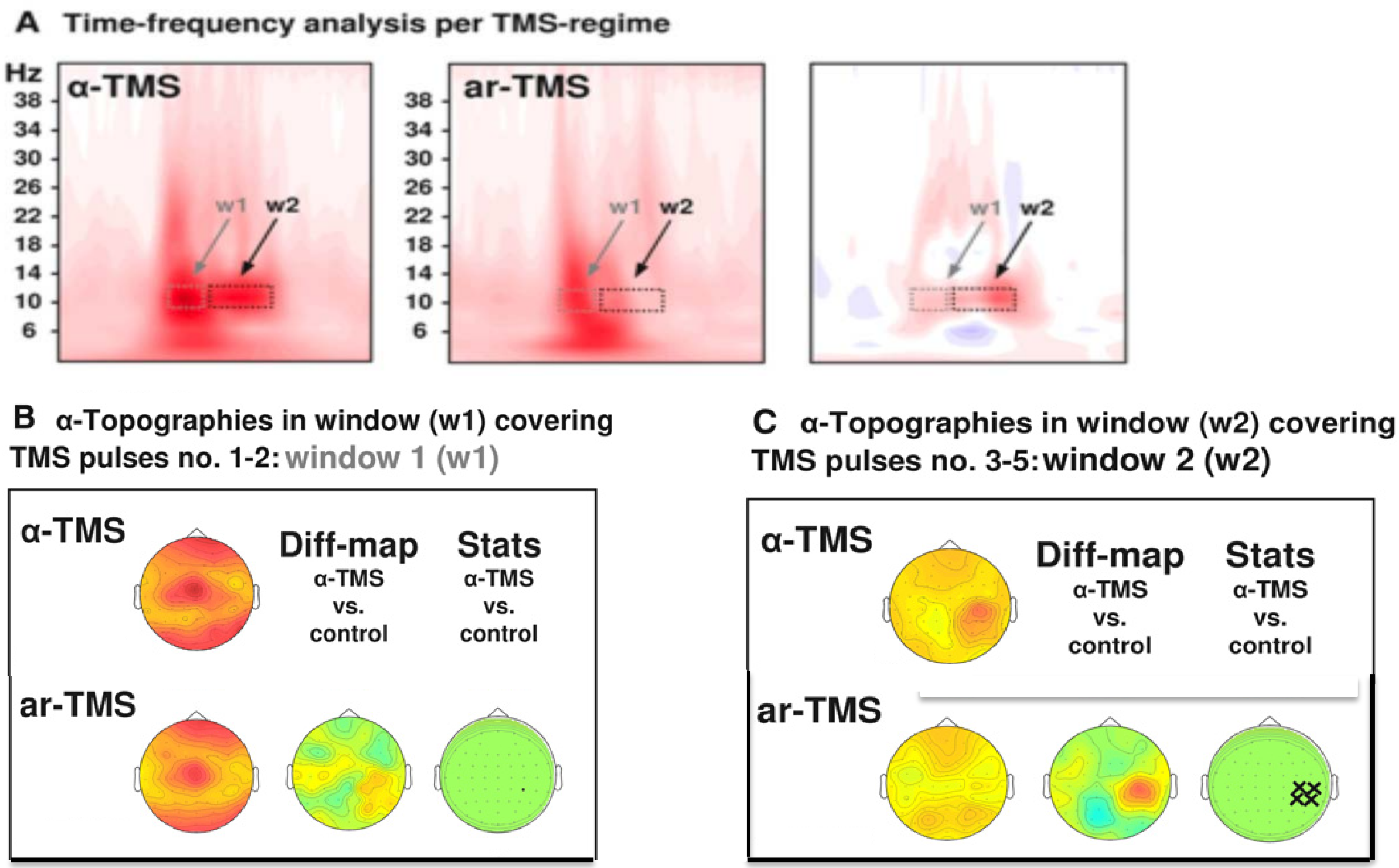
- Identification of individual alpha-generators (through spatial attention task)



TMS-EEG session

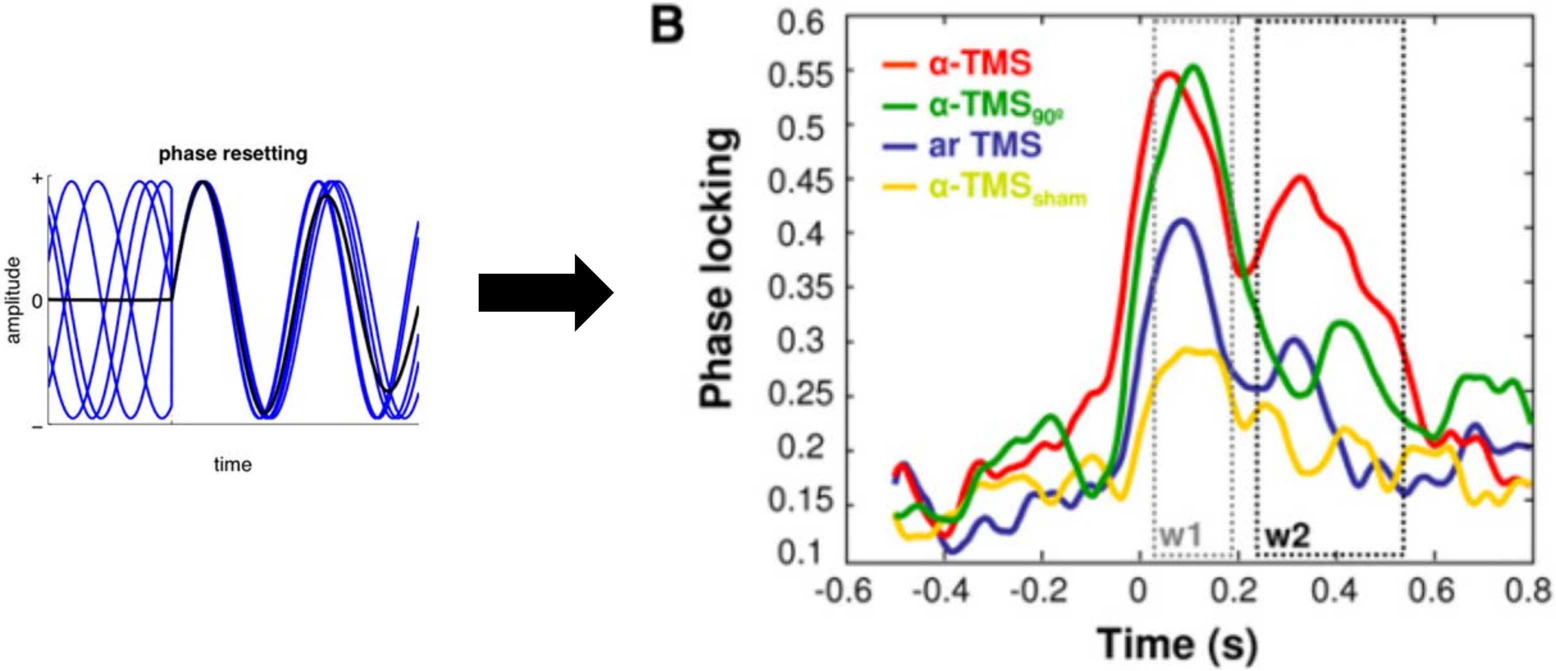


Thut et al. *Current Biology*, 2011



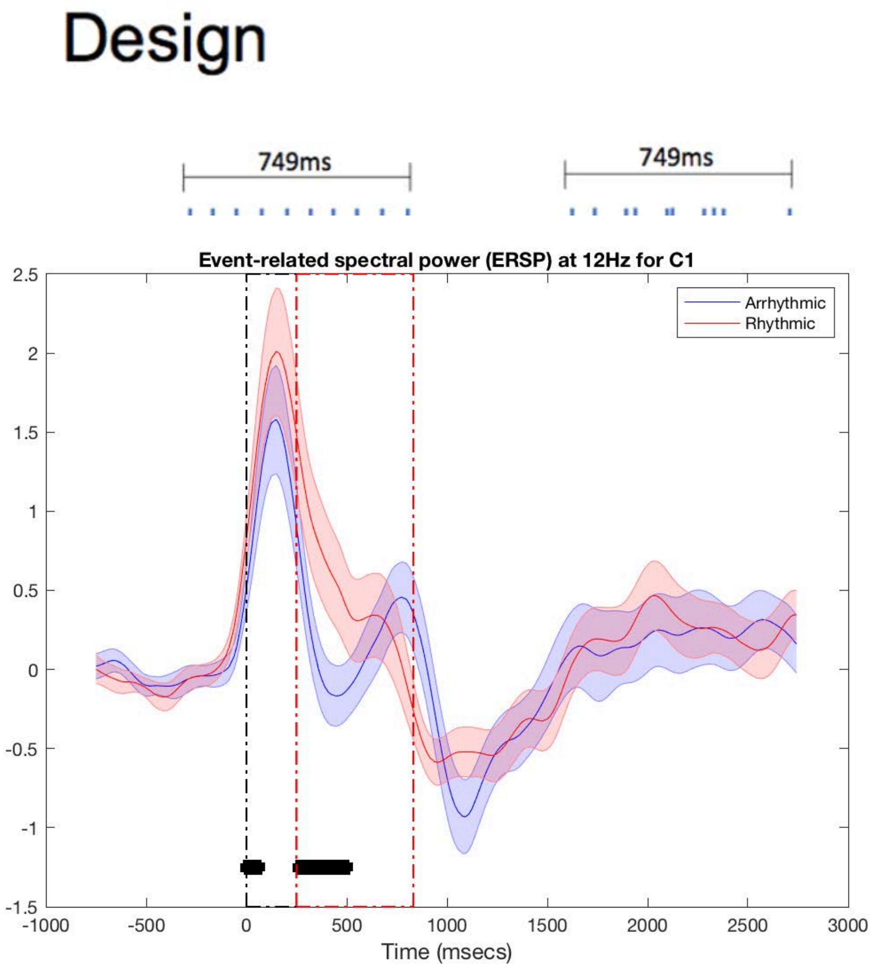
Thut et al. *Current Biology*, 2011

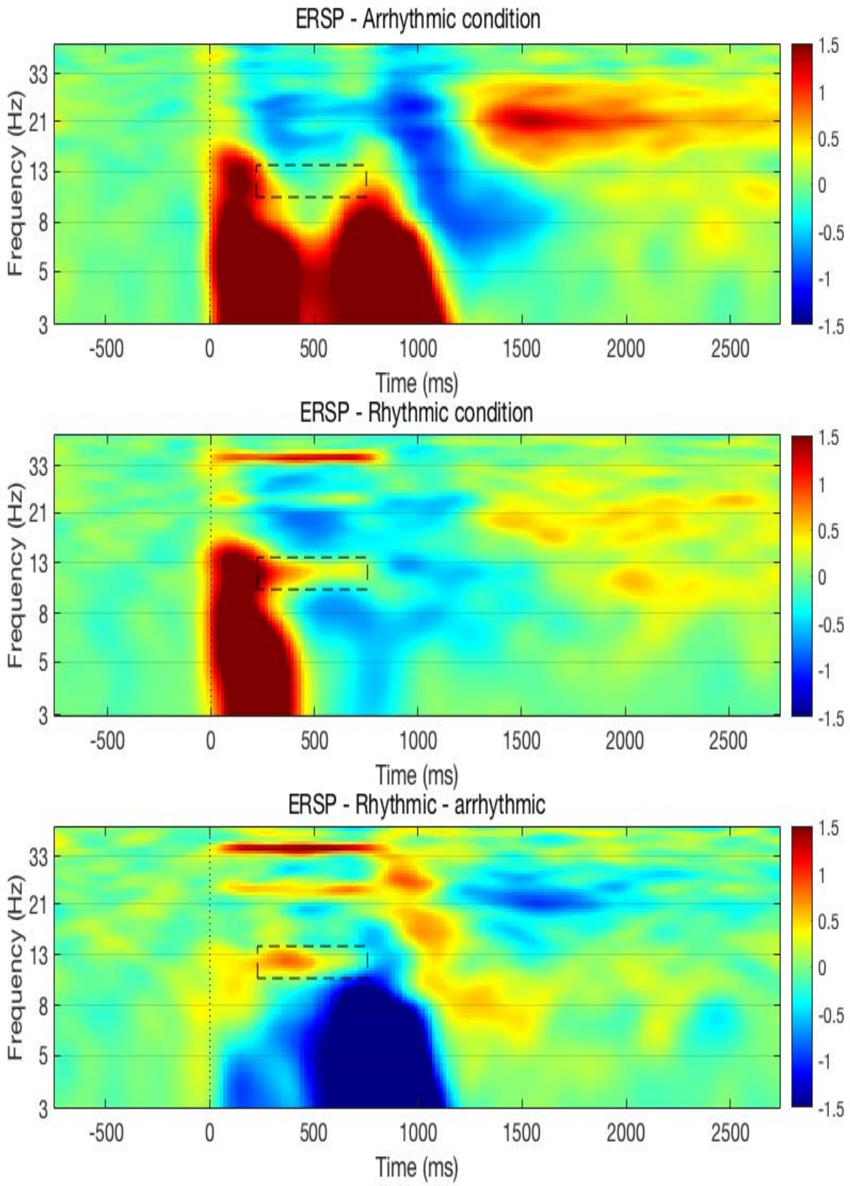
TMS induced phase-locking



<u>Thut et al. *Current Biology*, 2011</u>

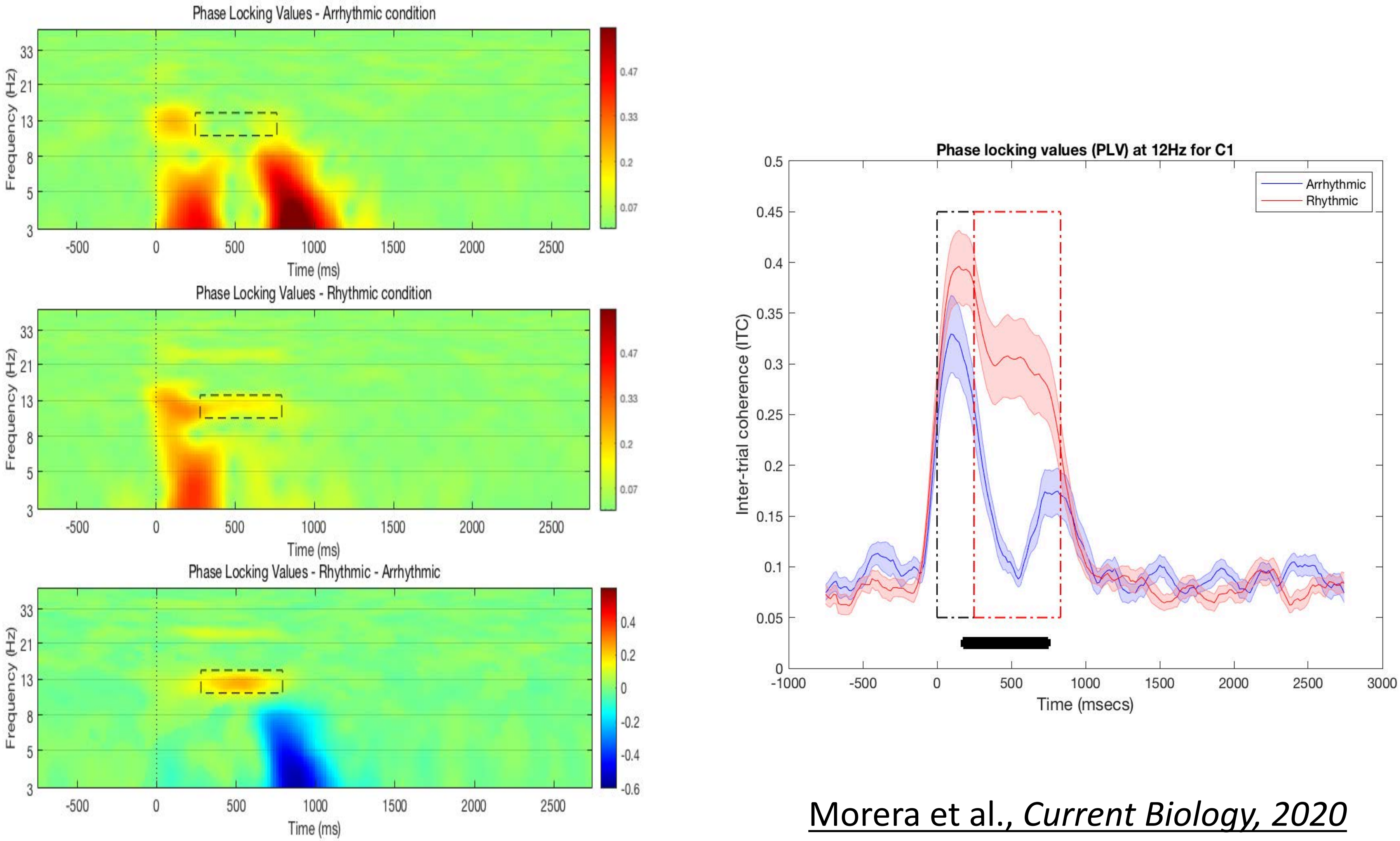
Motor cortical entrainment through median nerve stimulation





Morera et al., *Current Biology, 2020*

Motor cortical entrainment (inter-trial coherence)



Morera et al., *Current Biology, 2020*

Using TMS to induce ‘offline’ effects

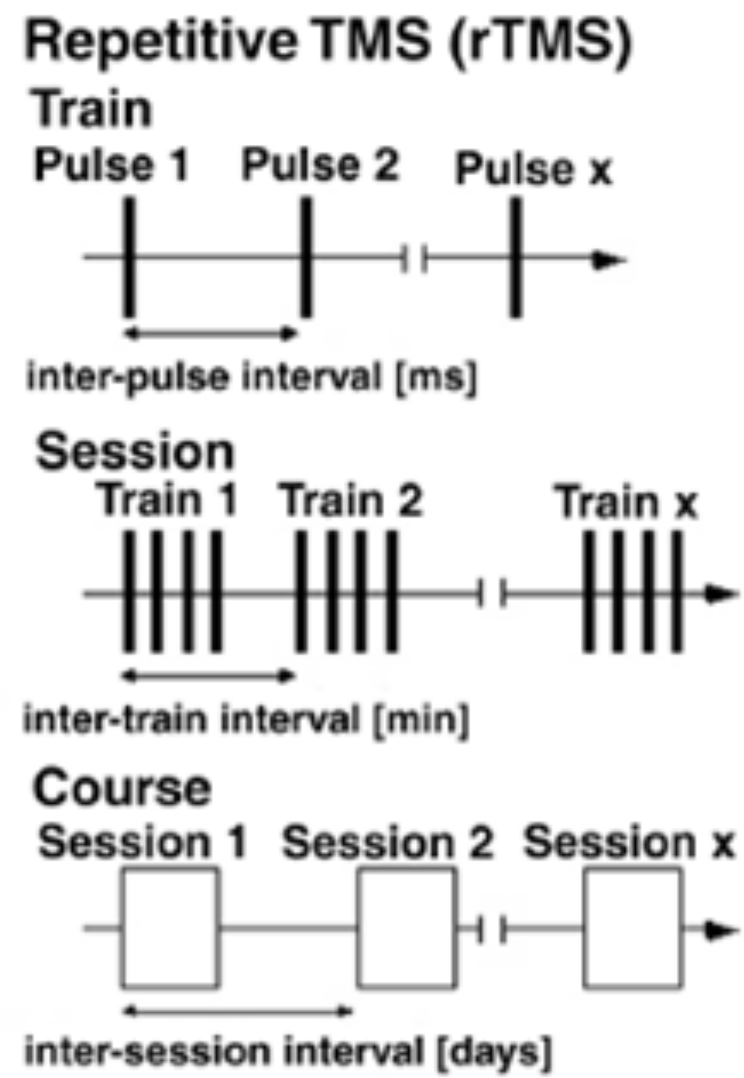
Types of TMS – Repetitive rTMS

Single pulse TMS shows surprisingly few effects on cognitive processes

Repetitive (r)TMS may induce effects that ***outlast*** the stimulation period

rTMS developed in part to probe higher order cortical function

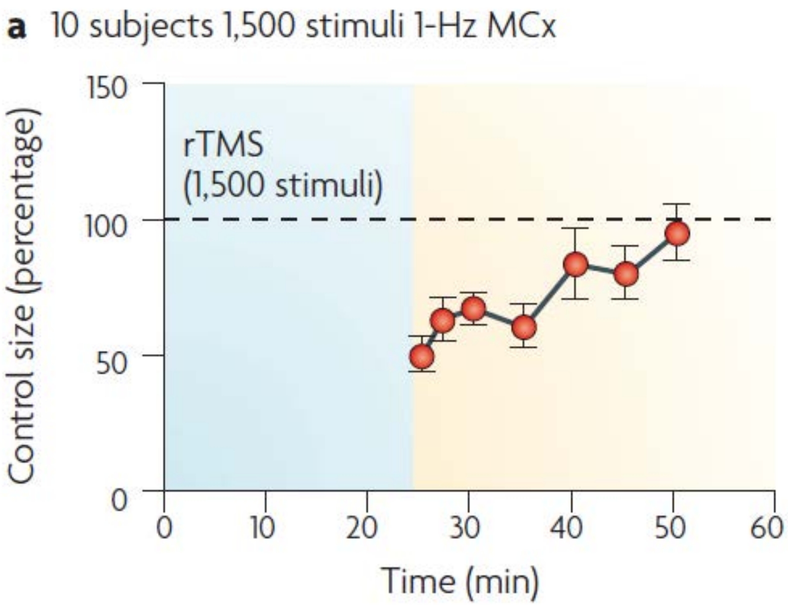
rTMS effects have been used as a tool to disrupt temporarily activity in local or remote cortical areas



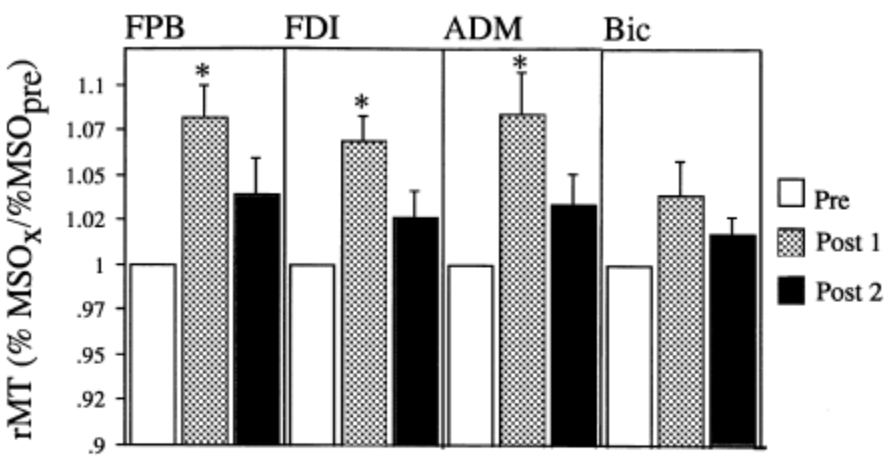
Effects on motor-evoked potentials – Low frequency rTMS

Low frequency (slow) TMS (<1Hz)

- Suppresses cortical excitability
- Raises motor threshold



Touge et al., 2001

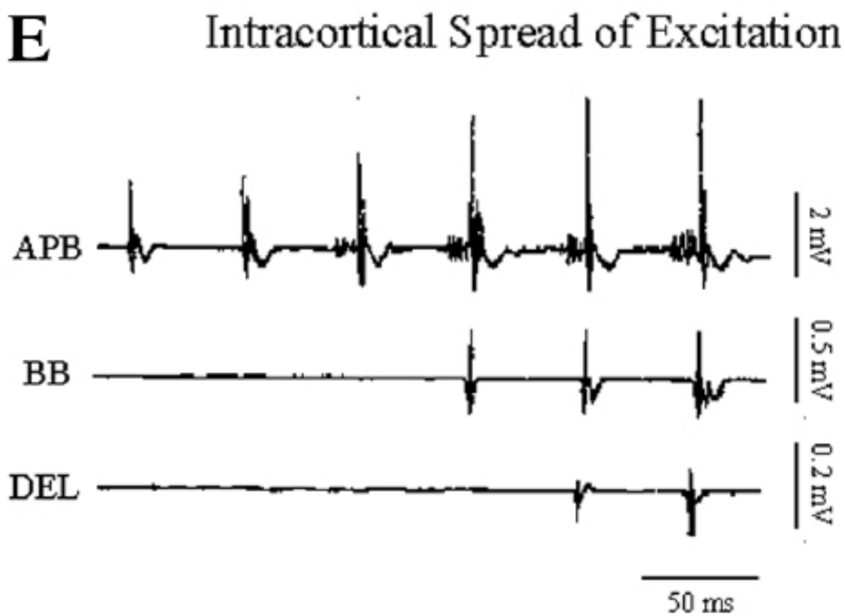


Muellbacher et al., 2000

The Motor-evoked potential – high frequency rTMS

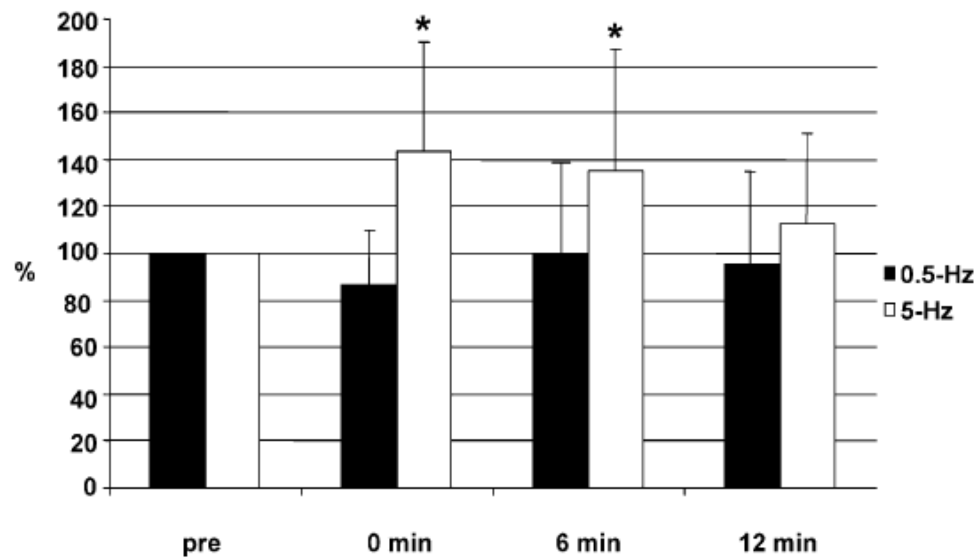
High frequency (rapid-rate) TMS (>1Hz)

- Enhances (facilitates) cortical excitability
- Lowers motor threshold



rTMS 20Hz, 120% RMT

Effects of 0.5Hz and 5Hz rTMS to M1 for FDI MEP amplitude

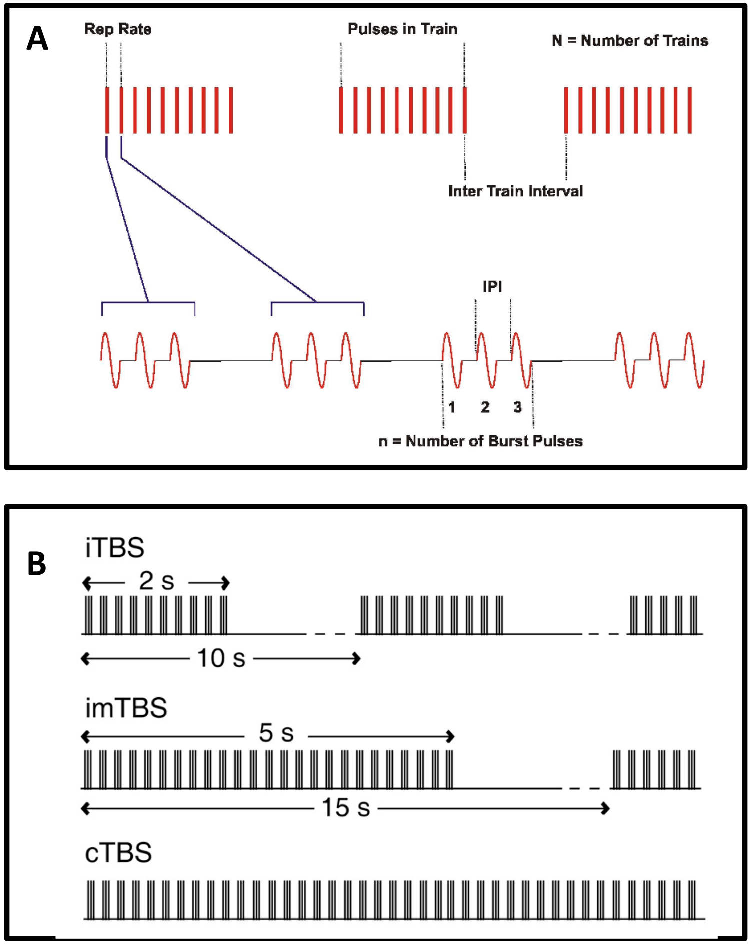


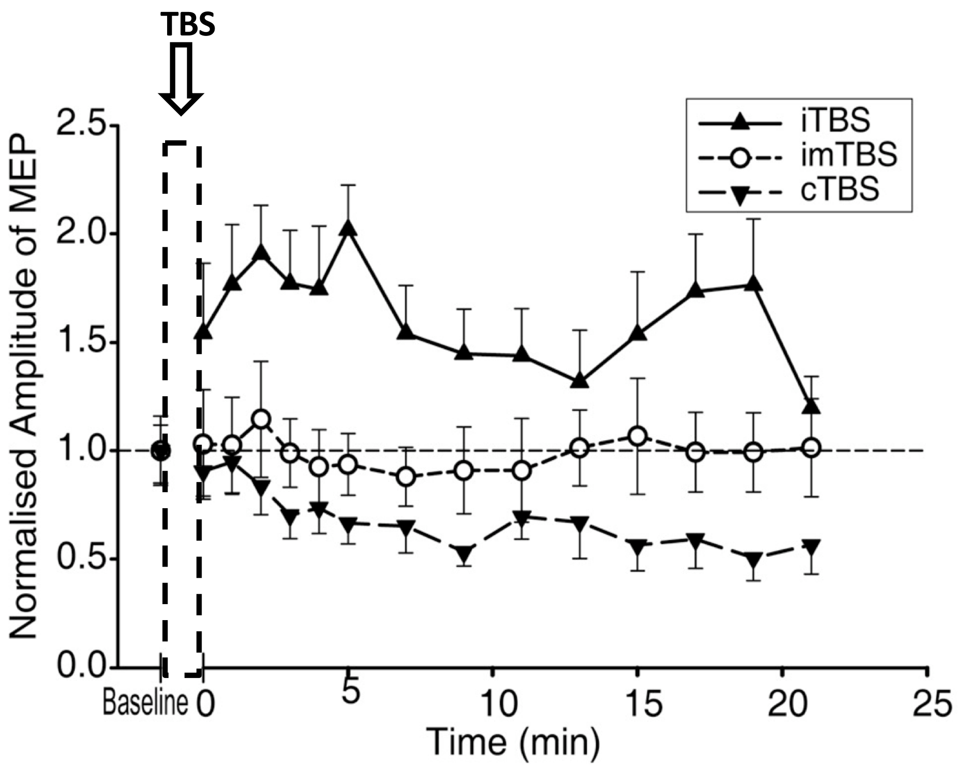
Pascual Leone et al., 1998

Gorsler et al., 2003

The Motor-evoked potential – Theta-burst

Repetitive TMS protocols may modulate cortical excitability

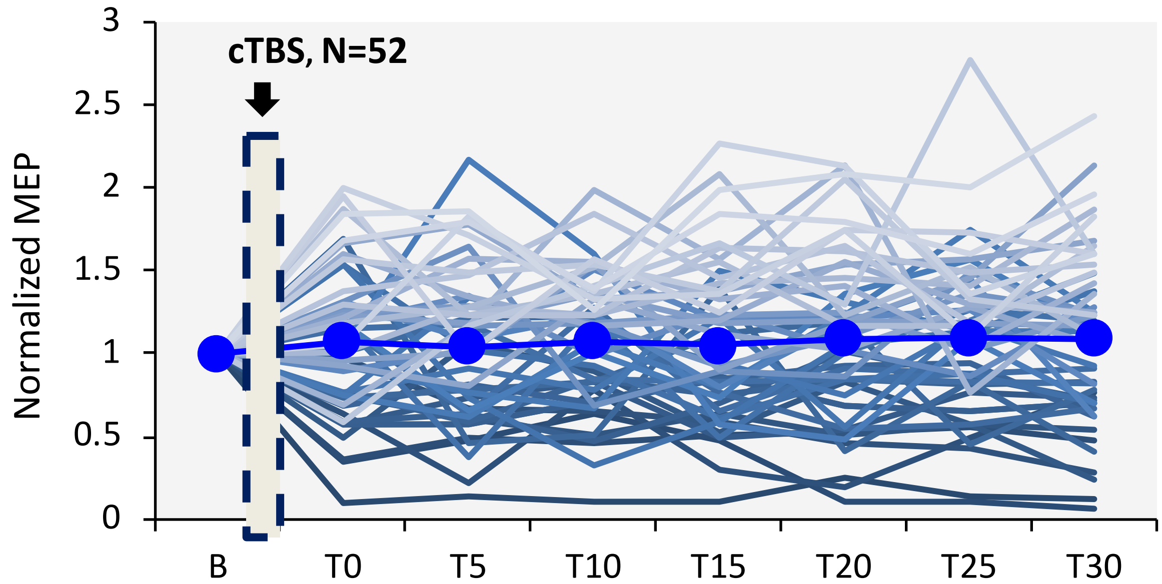




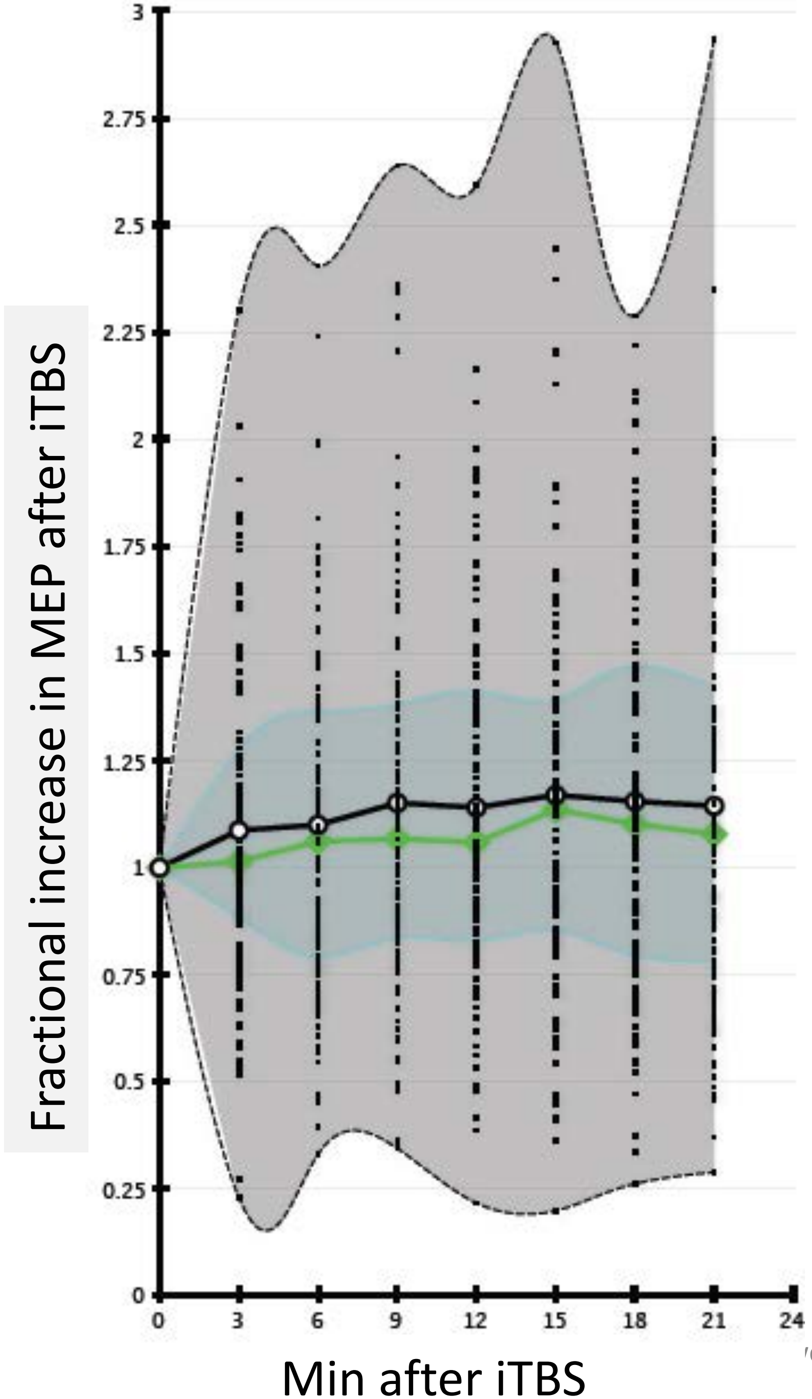
Huang et al., 2005

Variability of response to rTMS

Effects of rTMS on cortical excitability are highly variable across individuals



Hamada et al., 2012



Intermittent theta burst (iTBS) induced MEP plasticity is highly variable between subjects

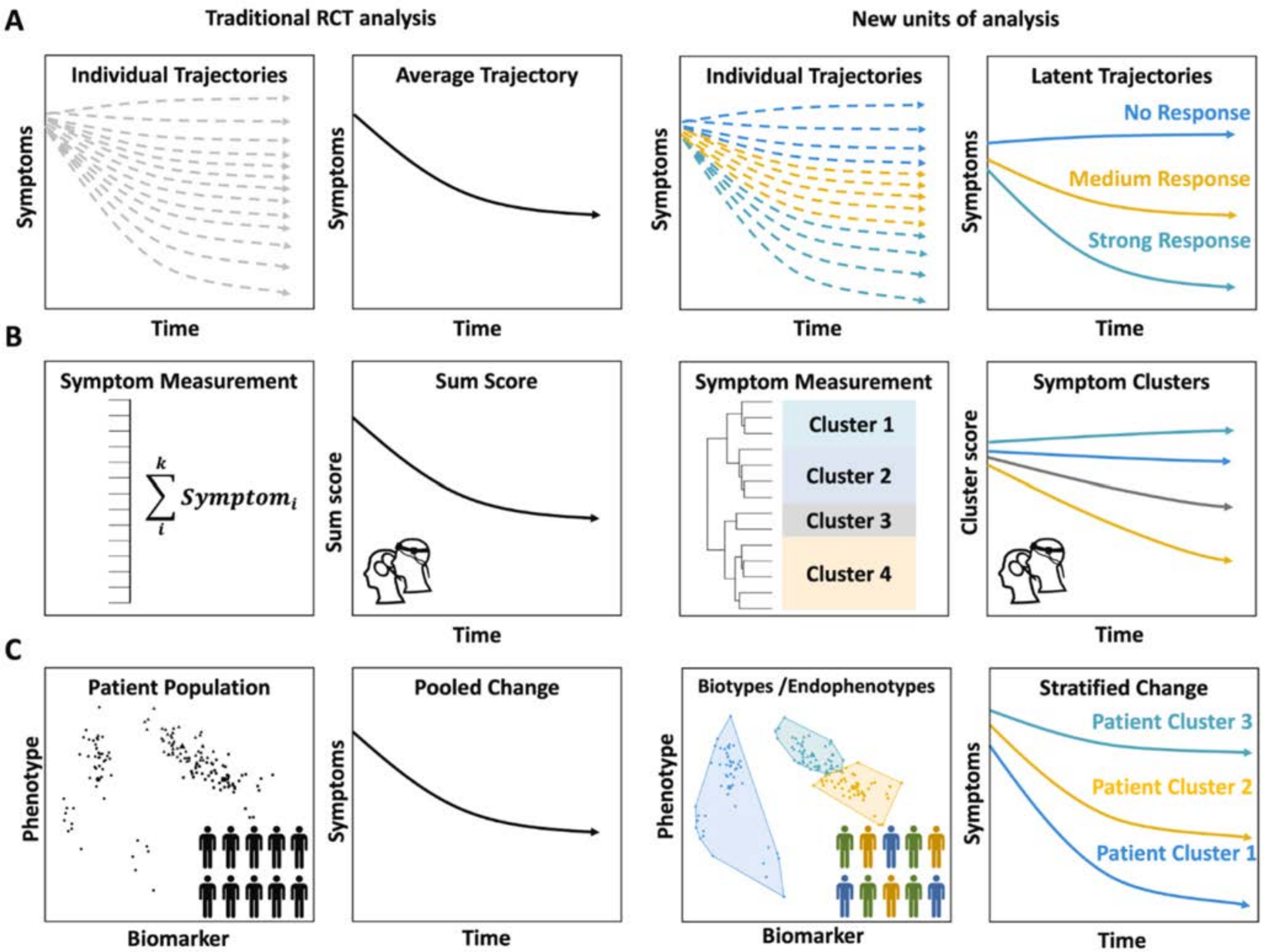
115 healthy volunteers aged mainly 18-22 years

Black: median
Green: mean

Rodil Midpoint Quality Analysis - Cheeran, Fernandez Del Olmo, Mir et al."

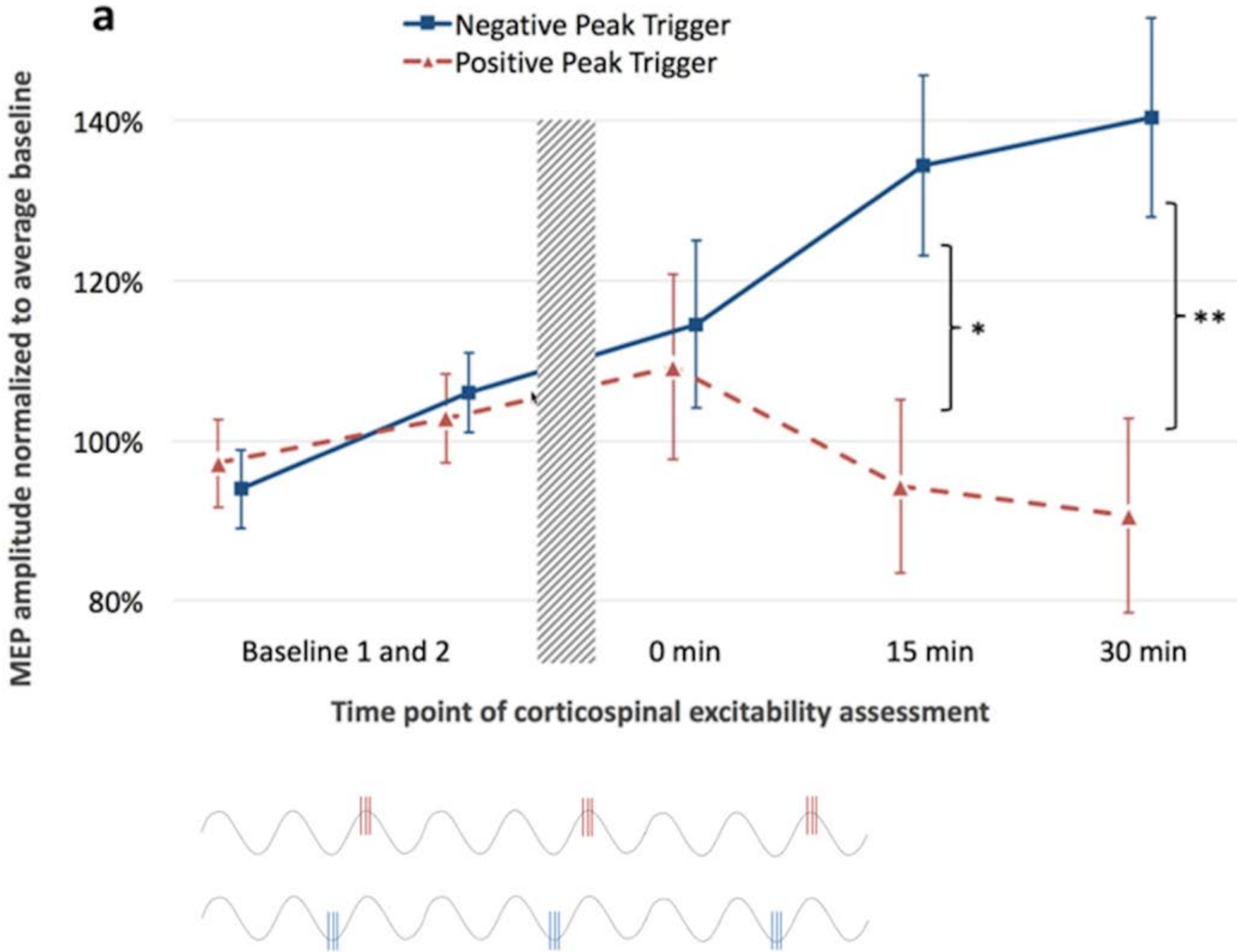
Personalising non-invasive brain stimulation in psychiatry

New units of analysis in the framework of precision psychiatry.



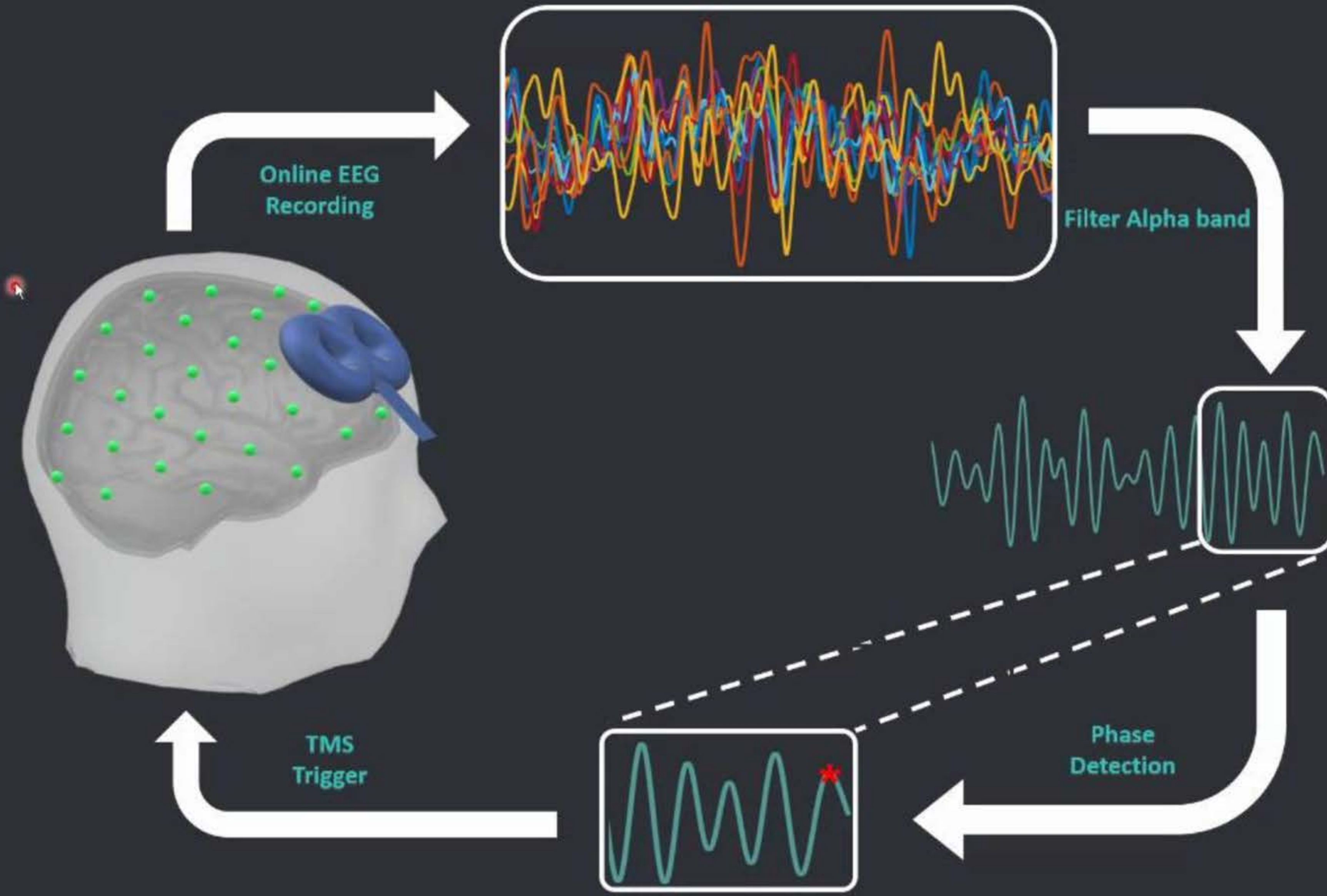
Padberg et al. *Experimental Neurology,* 2021

Does it matter when stimulation is delivered?



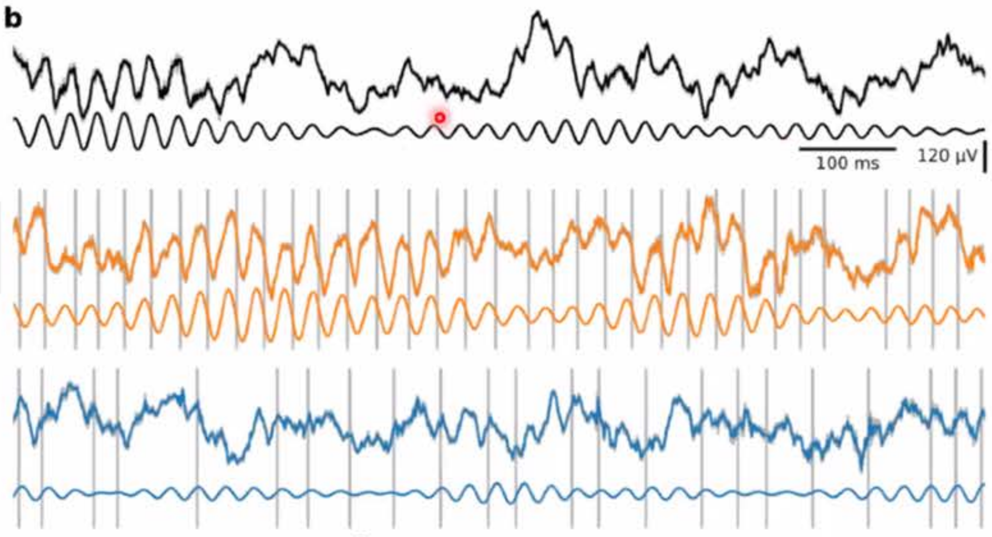
Zrenner et al., *Brain Stimulation*, 2018

Real-Time Closed-loop TMS-EEG



Rodent study of closed-loop phase-dependent stimulation

Closed-loop phase-dependent stimulation leads to sustained modulation of beta oscillations

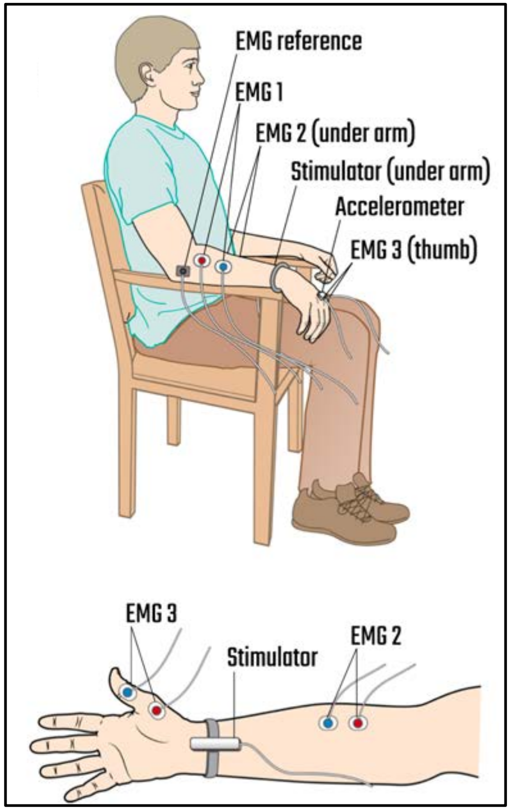


Open-field recordings

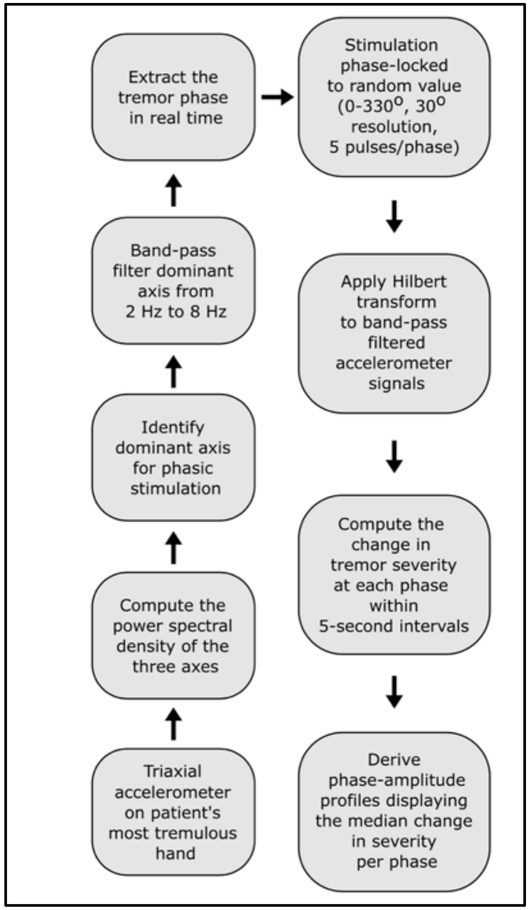
McNamara et al, Biorixv/In submission

Phase-dependent median nerve stimulation used to modulate tremor in Parkinson's disease

A.

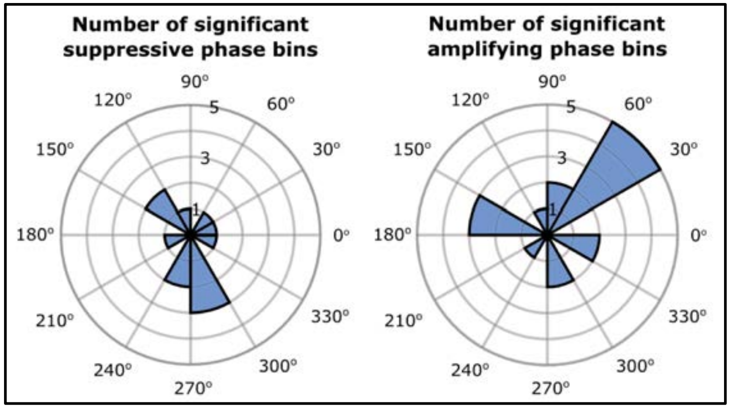


B.



C.

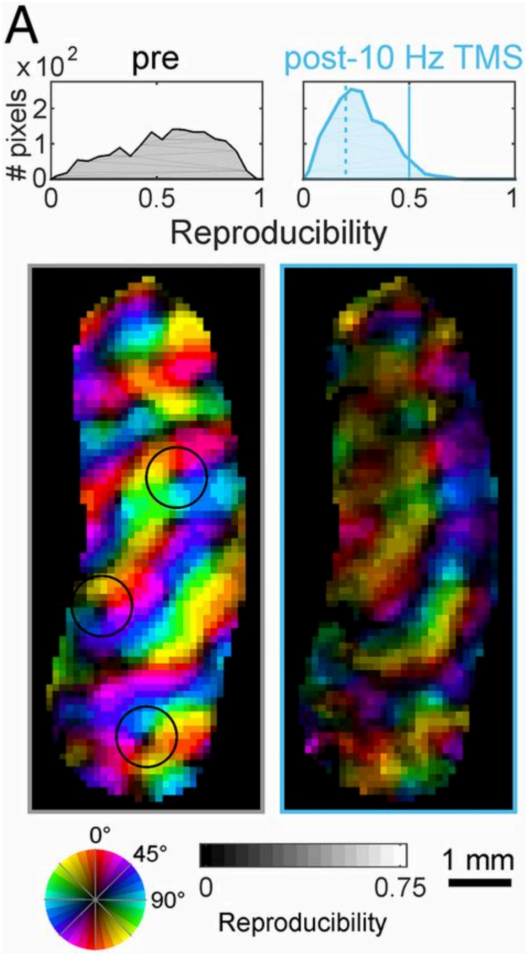
	Significant suppression	Significant amplification	Chance level
Bins	12/828	16/828	3.45/1656
Plots	12/69	12/69	3.45/138
Participants	5/10	6/10	1/20



Arruda et al., *J. NeuroEngineering and Rehab.*, 2021

Does rTMS enhance learning through inducing variability?

Inducing neural variability ('noise') using rTMS



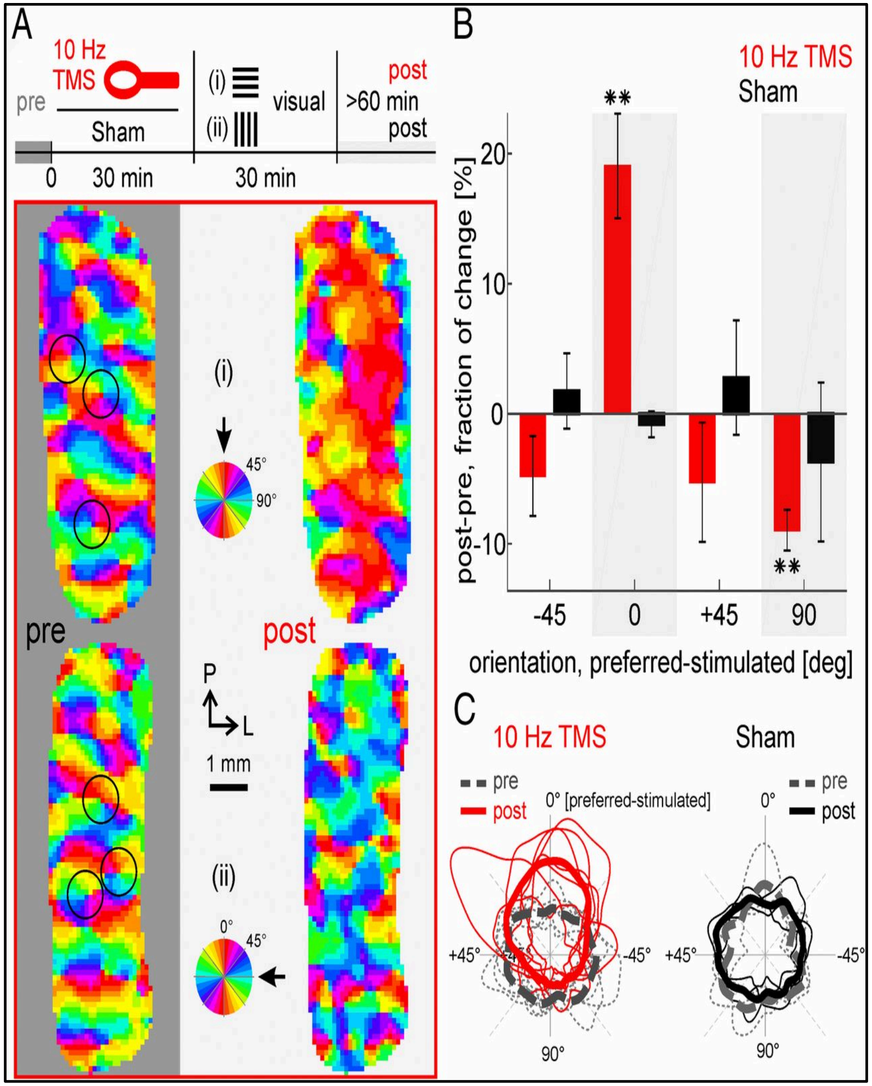
In a recent pre-clinical study 10HZ (excitatory) rTMS was applied to the visual cortex.

Surface map of V1: colours indicate the preference for lines of a particular orientation.

After rTMS the map has been altered. The orientation preferences are not as reproducible as prior to rTMS and are less specific to orientation (they are "noisier")

Kozyrev et al., *PNAS*, 2018

Does rTMS enhance learning through inducing variability?



Destablisation of visual maps makes the visual circuits more sensitive ('plastic') to new learning

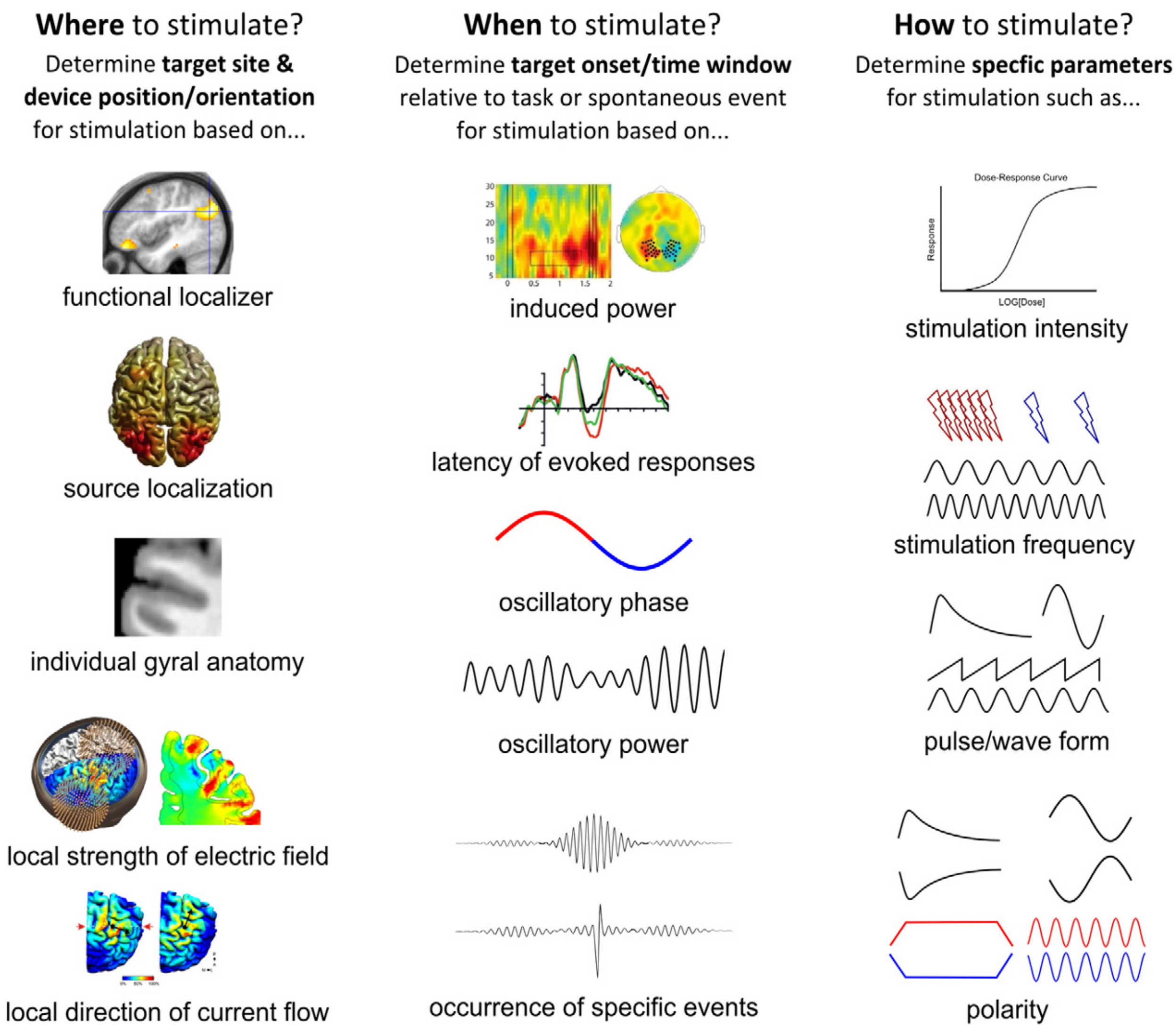
- 30 mins of 10Hz rTMS or sham rTMS delived
- 30 minutes presentation of stimuli at 0º (RED) or 90º (BLUE/GREEN) orientation
- After training orientation preference for -45º, 0º, 45º, 90º stimuli measured

Results

- rTMS significantly enhanced learning of ***trained*** orientations relative to sham-TMS
- No difference between rTMS and sham-TMS for non-trained orientations

Kozyrev et al., *PNAS*, 2018

Considerations for studies using NiBS



Bergmann et al., *NeuroImage*, 2016