MRC Cognition and Brain Sciences Unit

UNIVERSITY OF CAMBRIDGE

Introduction to neurostimulation methods

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Overview

Part 1: TMS

- Why use TMS?
- What is TMS?
- TMS coils
- E-fields
- Motor threshold
- Parameters and protocols
- Determining stimulation site
- Neuronavigation
- Controls
- Safety
- Chain of causation

Part 2: TES

- What is TES?
- Why use TES?
- tDCS
- tACS
- Reliability of TES
- Safety aspects
- CBU equipment

Part 3: Combining TMS with fMRI

- Offline vs online
- Why use TMS-fMRI?
- MR-dedicated coils
- Setup in the scanner
- Artifacts caused by pulses
- Variability
- Future directions
- TMS at the CBU

Transcranial magnetic stimulation (TMS)

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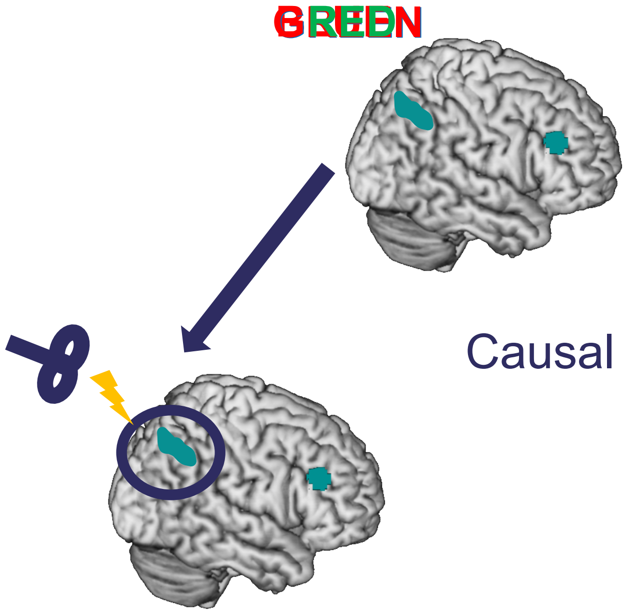
Why use TMS?

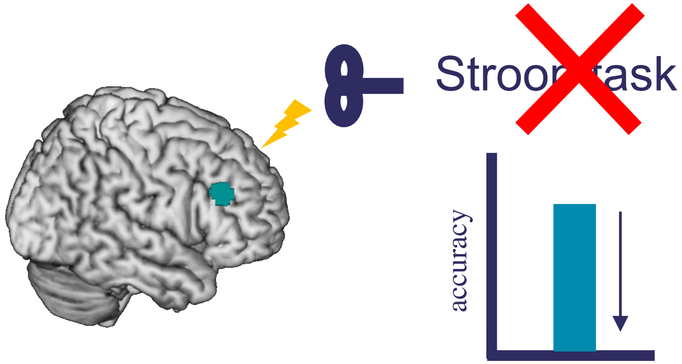
fMRI

Stroop task



Causal involvement?

TMS



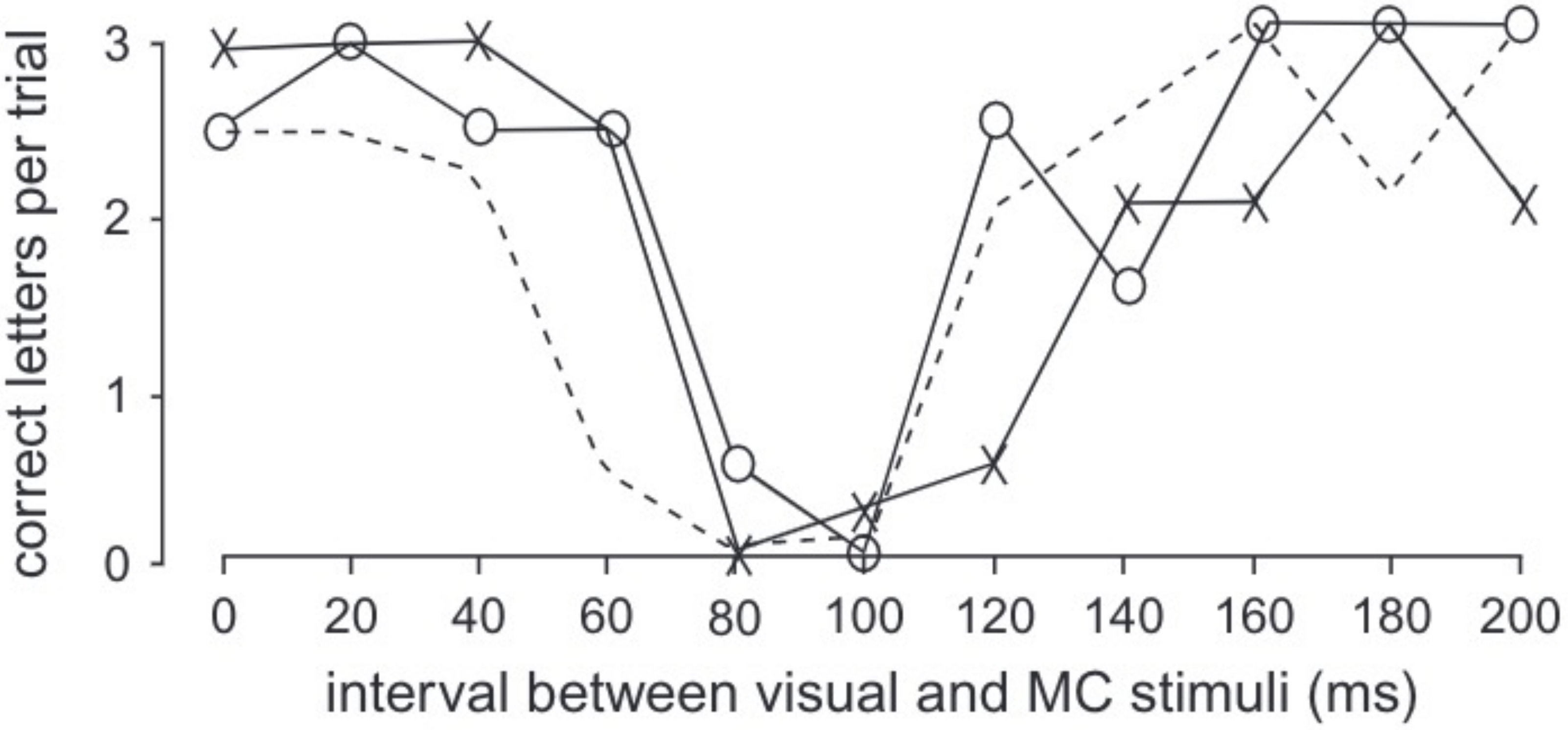
Why use TMS?

- Establish causal relations between brain sites and their associated networks and specific cognitive processes and behaviours
- Examine spatial / temporal causal relations of brain regions' contributions to specific behaviours
- In combination with imaging look at interactions between brain regions at rest or during their engagement in a task
- Used in treatment protocols e.g. **pharmacotherapy-nonresponsive major depressive disorder[1,2,3], obsessive-compulsive disorder[4]**, **smoking cessation[5]**, and **migraine[6]**

[1]Blumberger et al. *The Lancet.* 2018; [2]George et al. *Archives General Psychiatry.* 2010; [3]O'Reardon et al. *Biological Psychiatry.* 2007; [4]Carmi et al. *Brain Stimulation.* 2018; [5]Zangen et al. *World Psychiatry.* 2021; [6]Lipton et al. *Lancet Neurology.* 2010

Virtual lesions

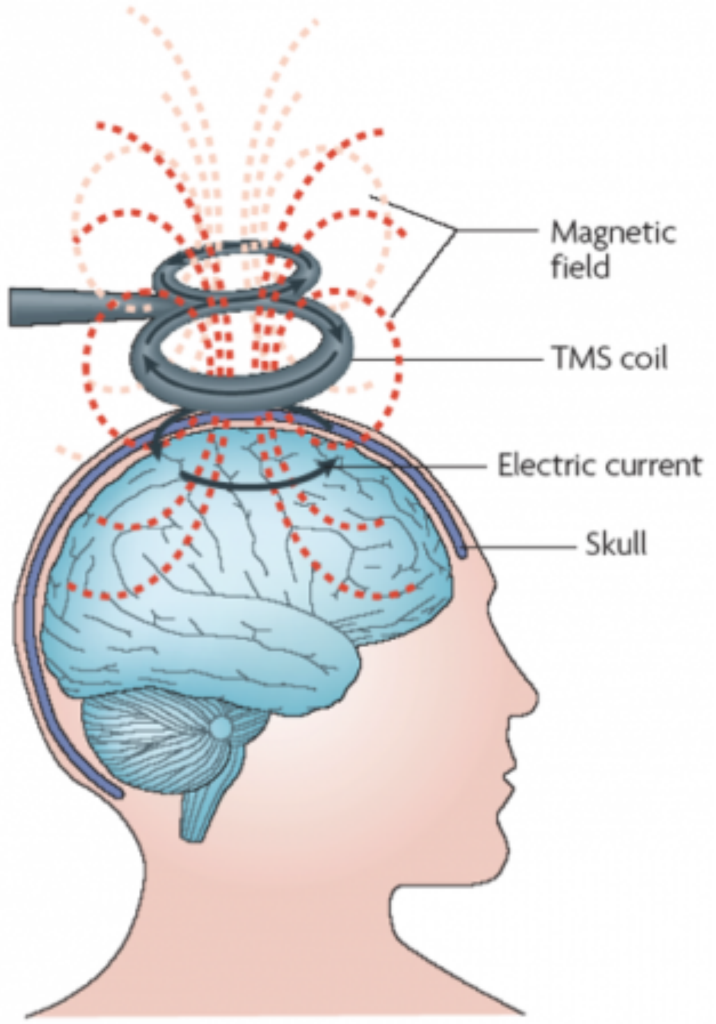
Starting point for the concept of virtual lesions induced by TMS



Amassian et al. *Journal of Clinical Neurophysiology.* 1989

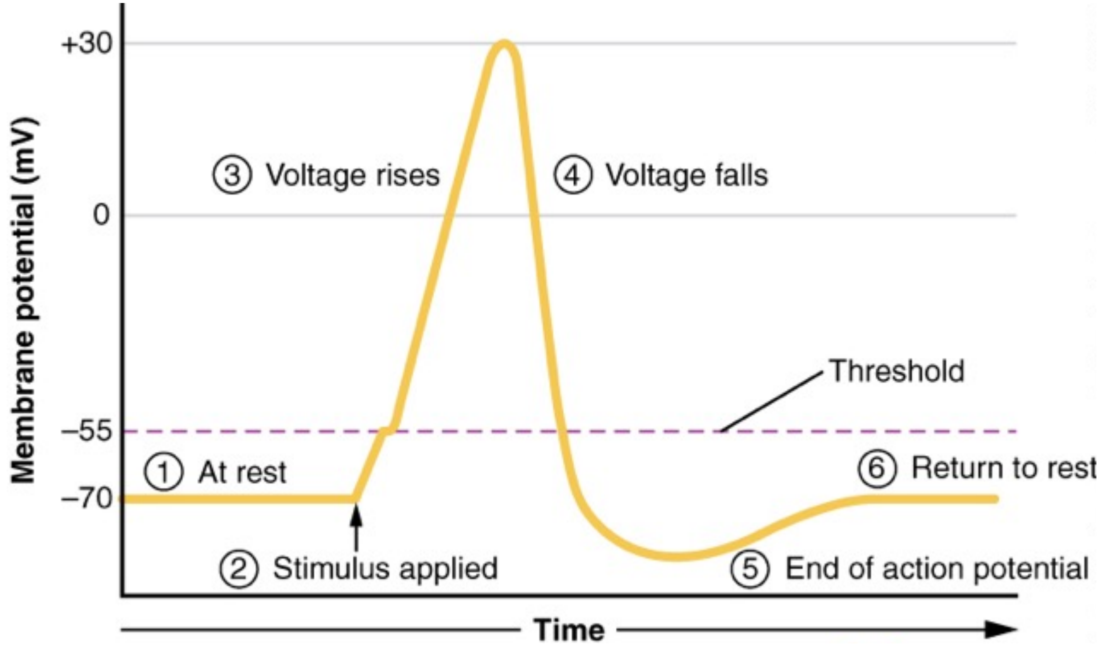
What is TMS?

- Brain stimulation based on magnetic induction principles discovered by Faraday
- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in coil of wire inside a protected case
- Current generates powerful magnetic field (up to 2T) capable of inducing electric current in excitable tissues
- Magnetic field penetrates scalp and skull - induces a current in brain in direction opposite to original current in the coil



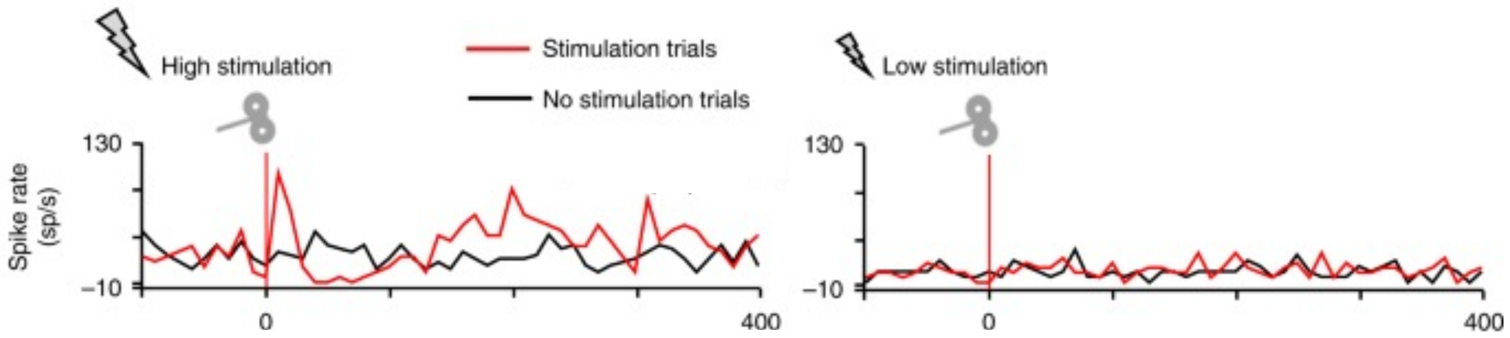
Mechanism of action

- Flow of ions brought about by induced electric field alters electric charge stored on both sides of cell membranes
- When direction of current across membrane, induced current depolarises cell membranes, eliciting action potentials
- Action potentials transsynaptically affect connected neurons -> excitatory and inhibitory postsynaptic potentials
- Net effect is complex



Mechanism of action

- Excites random neural elements
- Results in subsequent suppression of neural activity
- Highly synchronized activity in target ROI based on excitation-inhibition pattern
- Key parameters not assessed (stimulation intensities, frequencies, and train durations)



Romero et al. *Nature Communications.* 2019

Impact on cognitive function

- Excitation leads to neuronal noise in stimulated circuits which may impair or delay task-relevant neuronal computations.

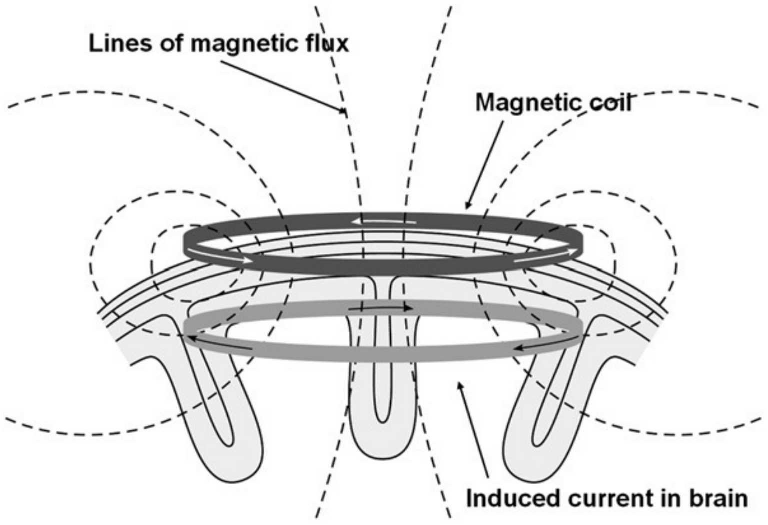
- Inhibition phase further interrupts and delays processing or cause signal loss

- Excitation-inhibition phase lowers number of possible activity patterns in network and reduces information representation capacity of synchronised network

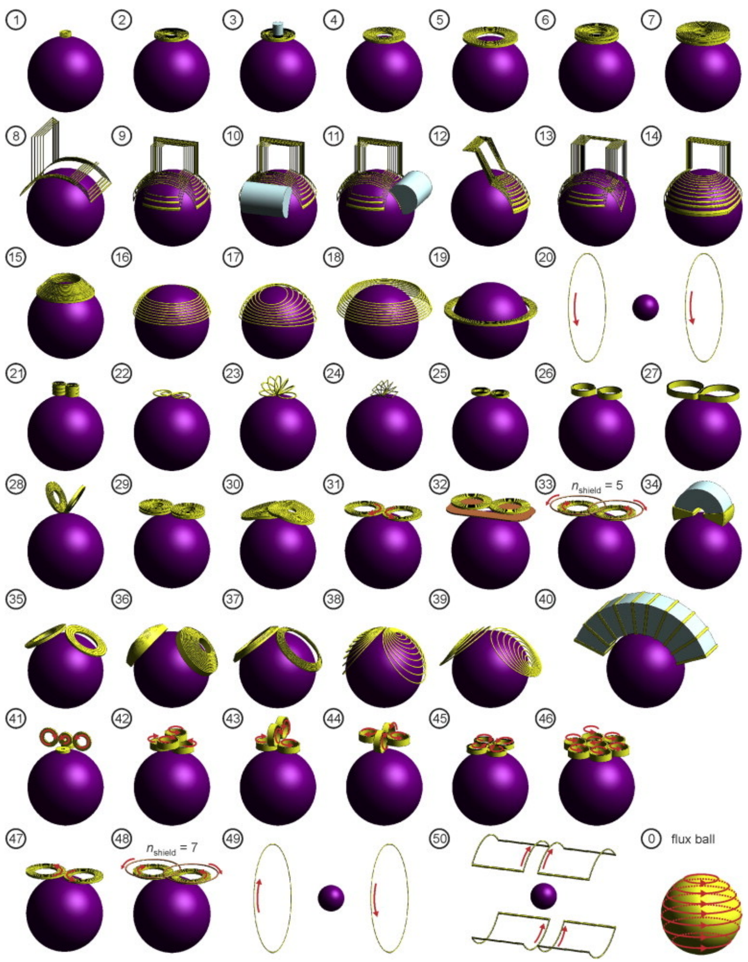
- Effect can vary across participants, exact protocol, etc

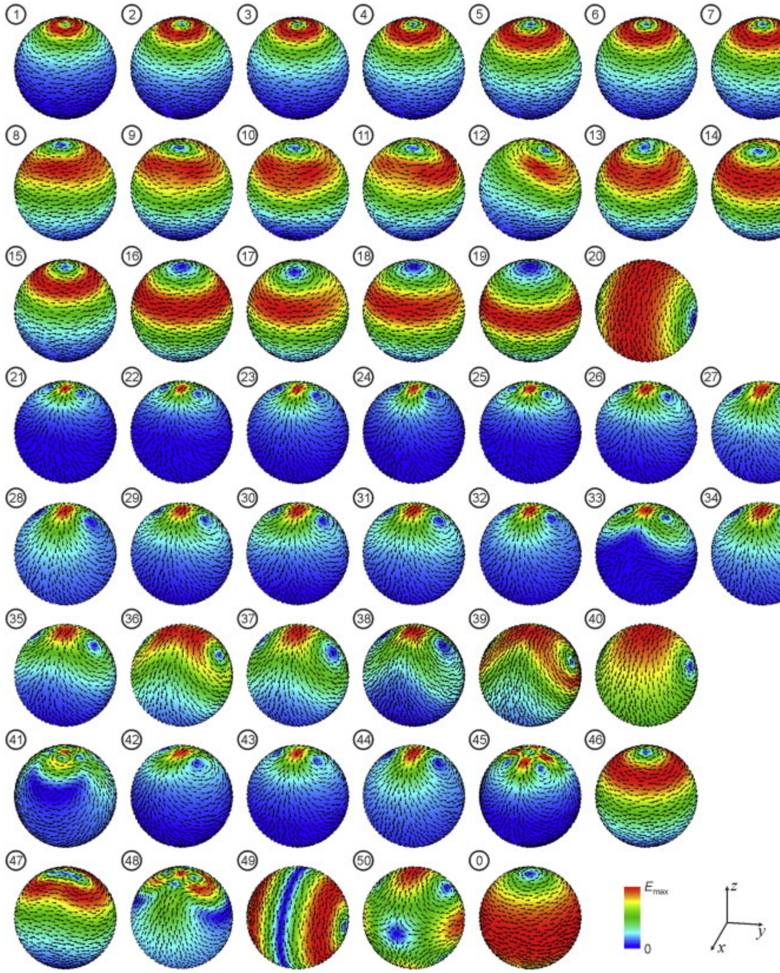
TMS coils

- Two electric field spatial features of particular interest are depth of penetration and focality
- Coil designs have often been developed with the objective of improving one or both characteristics
- Standard figure-8 combination -> relatively focal electric field
- Field strength can be less than half strength after only 2 cm



TMS coils

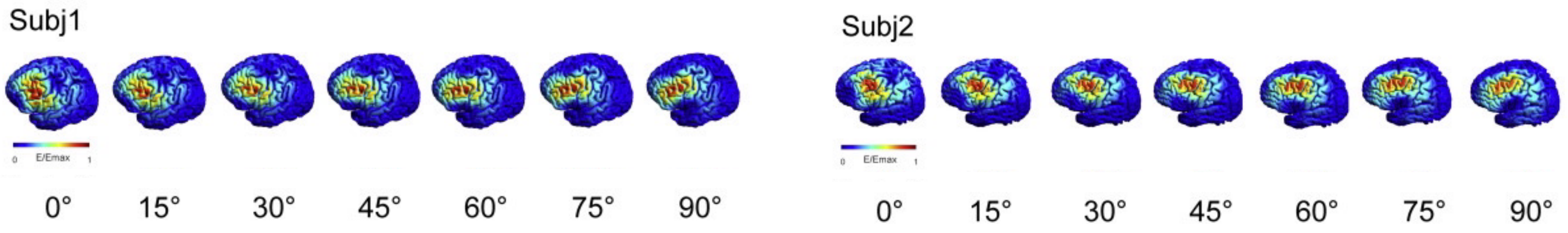




Deng et al. *Brain Stimulation.* 2013

E-field in target region

- Induced E-field in brain decays exponentially with distance from the TMS coil
- Distribution depends on anatomical distribution of brain tissues with different conductivities (grey matter, white matter, corticospinal fluid) and individual gyrification of underlying cortex
- Simulations show that location of maximum E-field varies across brain regions/individuals and not simply located directly under coil
- To establish effective stimulation intensity is achieved at target coordinate, individualised E-field modelling is advised



Opitz et al. *Brain Stimulation.* 2016

Finding the motor threshold (MT)

Overview

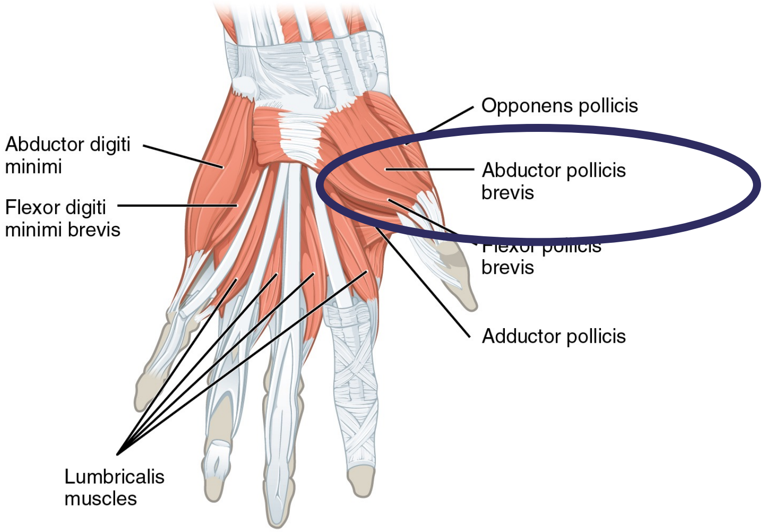
- MT considered an indicator of cortical excitability and often used to define intensity parameters for assessing other cortical circuitry

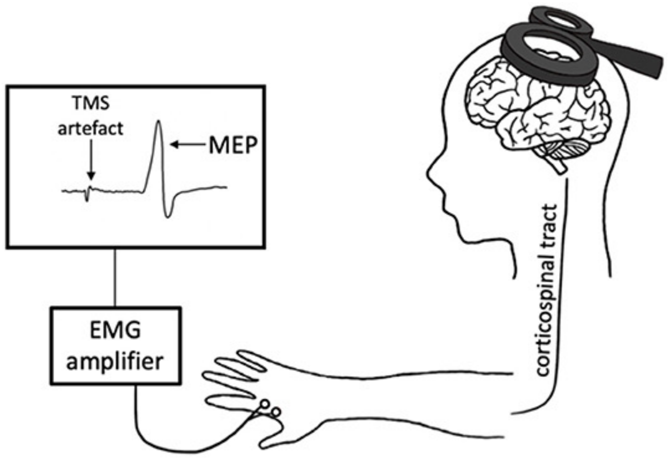
- Efficient determination of MT is important to reduce number of TMS pulses delivered to individuals

Methods

- Visible twitch/MEPs

- Active/resting motor threshold

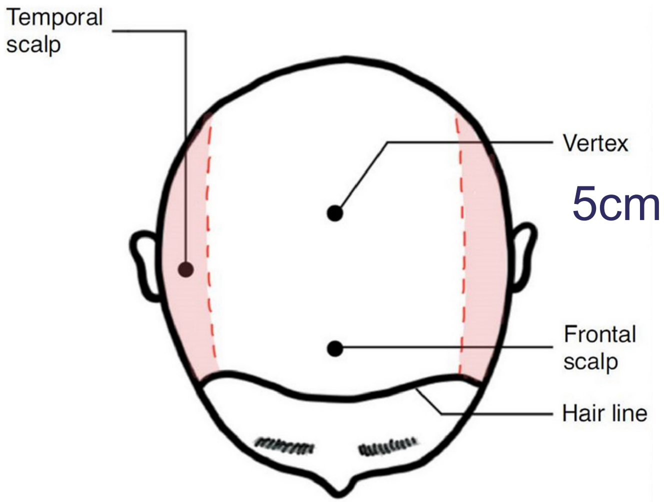




Finding the motor threshold (MT)

Steps

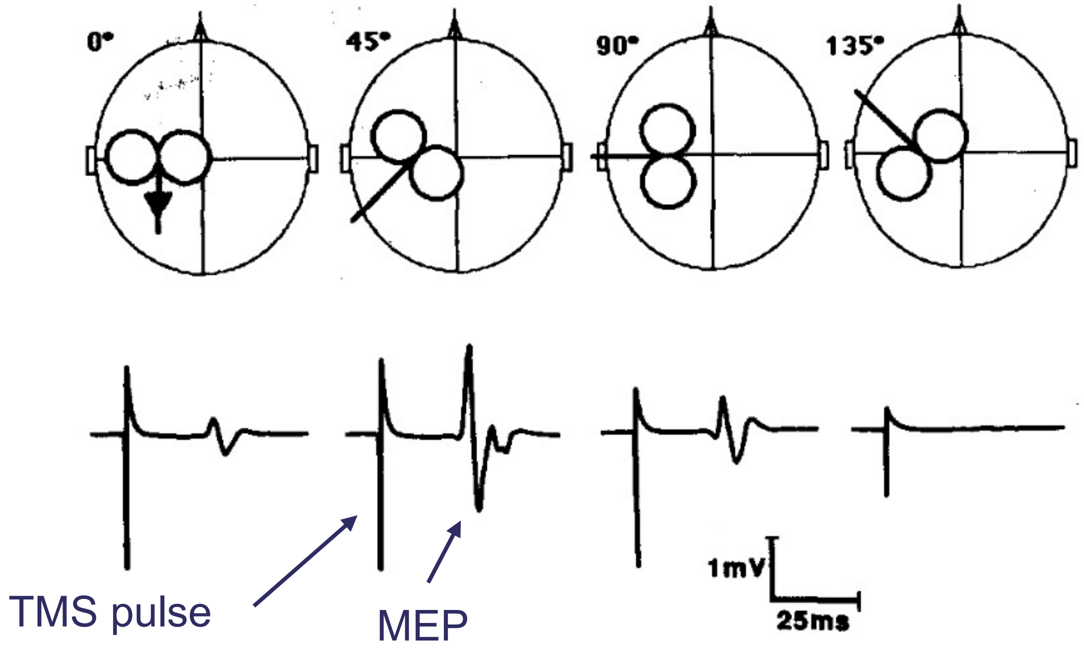
- Set up participant (e.g. safety – screening, ear plugs, explain TMS protocol)
- Stimulate at low level to show participants what to expect
- Find the “hot spot”
- Find MT (adjust intensity of stimulation)



5cm lateral from vertex

Finding the motor threshold (MT)

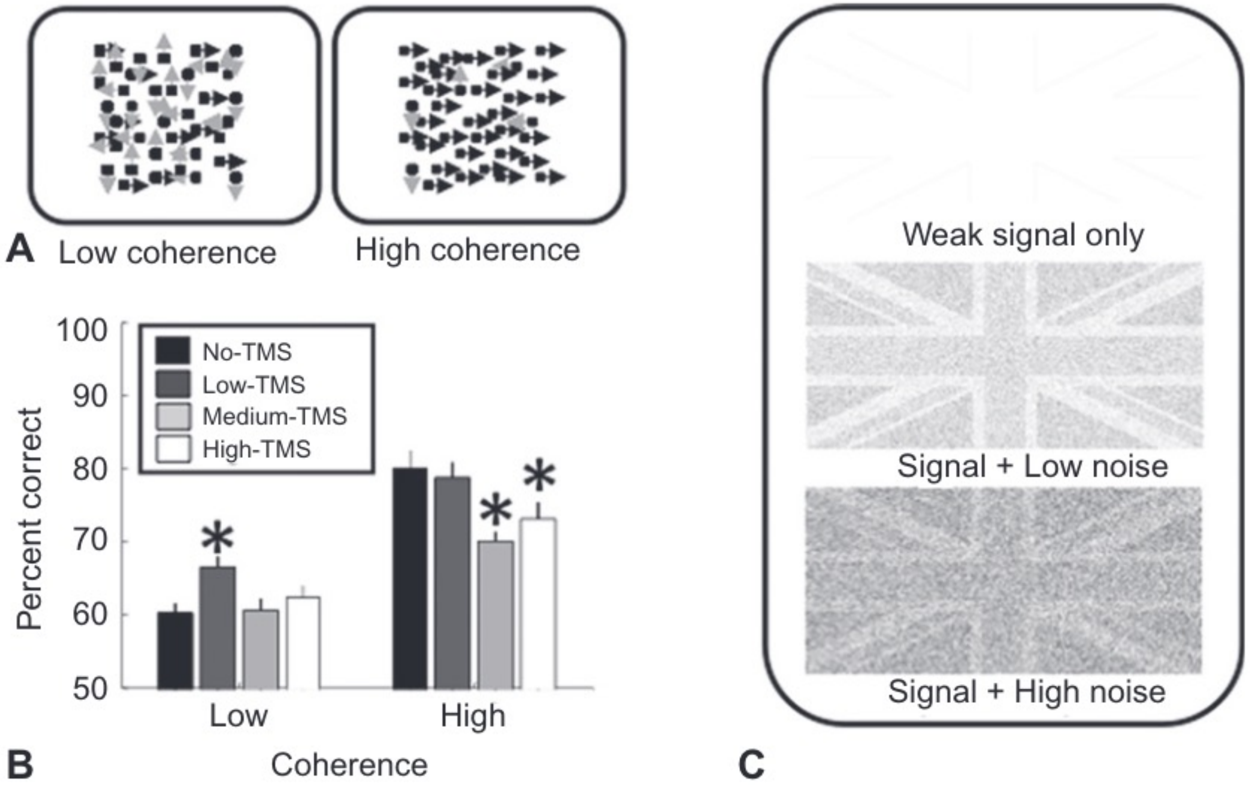
- Stimulation dependent on orientation of axons and dendrites with respect to the magnetic field
- Due to usual orientation of motor cortex, a 45° angle is most likely to produce a MEP
- Important note: Variation across participants!



Mills et al. *Electroencephalography and clinical neurophysiology.* 1992

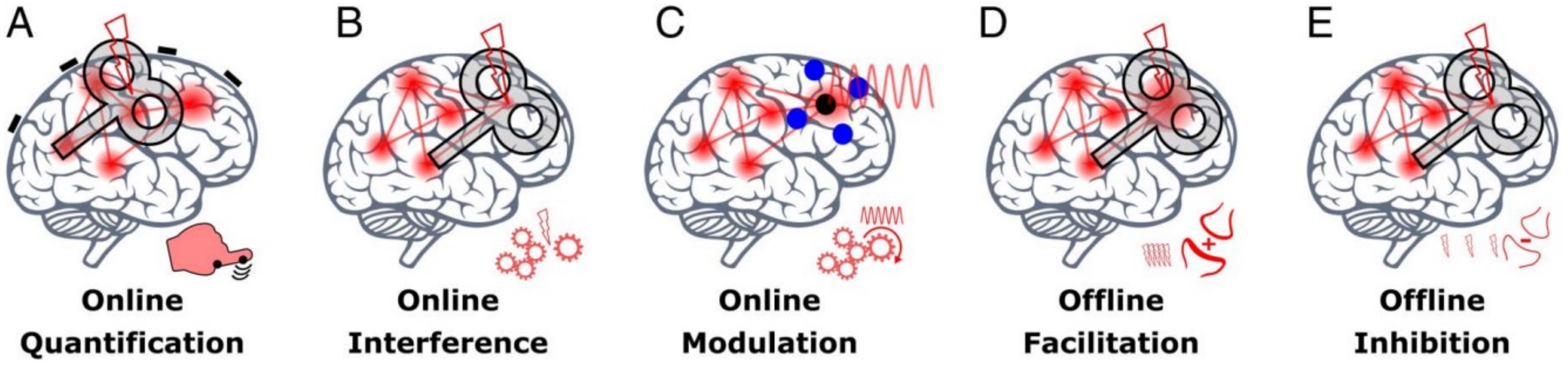
Intensity of stimulation

- In general high intensity used for effective TMS (motor threshold or above)
- Low intensity (below motor threshold) used as control or for facilitation
- Stochastic resonance – optimal amount of noise pushes signal pixels above threshold



Schwarzkopf et al. *Journal of Neuroscience*. 2011

Stimulation protocols



Online

A) motor evoked potentials / phosphene reports
B) interfere with ongoing task-related / spontaneous neuronal activity
C) moderate modulation of level or timing

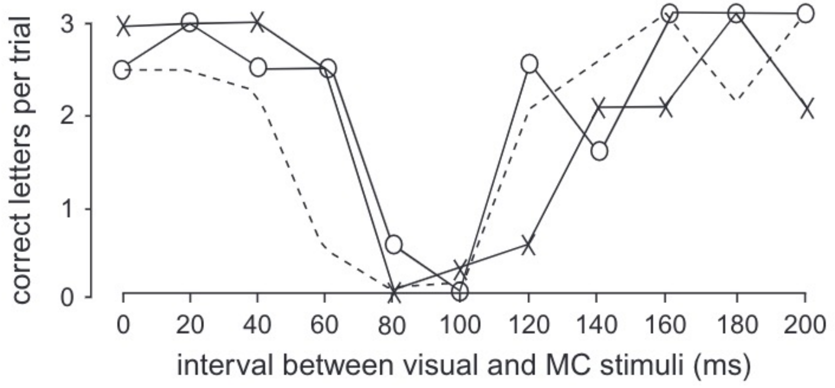
Offline

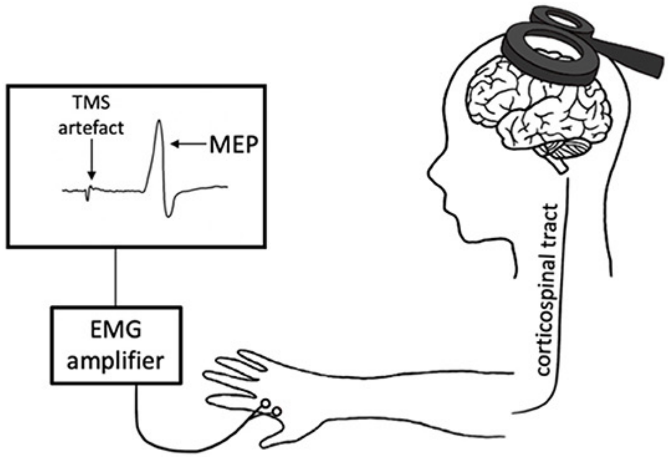
D) facilitate neuronal excitability for extended periods (LTP)
E) inhibit for extended periods (LTD)

Stimulation protocols

Single pulse TMS

- Good temporal specificity
- Single pulse effects are not thought to last long beyond the time of stimulation
- Can for example be used for mapping of motor cortical outputs

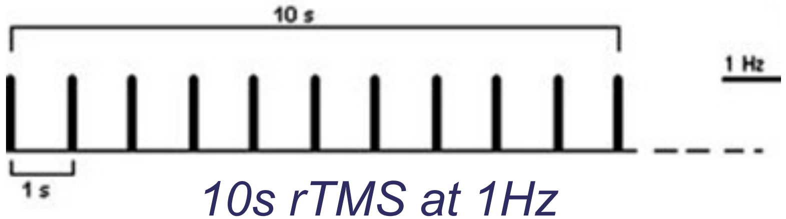




Stimulation protocols

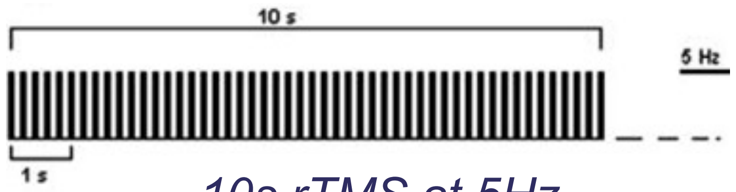
Repetitive TMS (rTMS)

- Low frequency rTMS (<1Hz) reduces excitability



10s rTMS at 1Hz

- High frequency rTMS (>5Hz) increases excitability



10s rTMS at 5Hz

- Higher frequencies of rTMS at 10 Hz and 20 Hz shown to disrupt accuracy for attention, executive, language, memory, motor, and perception domains

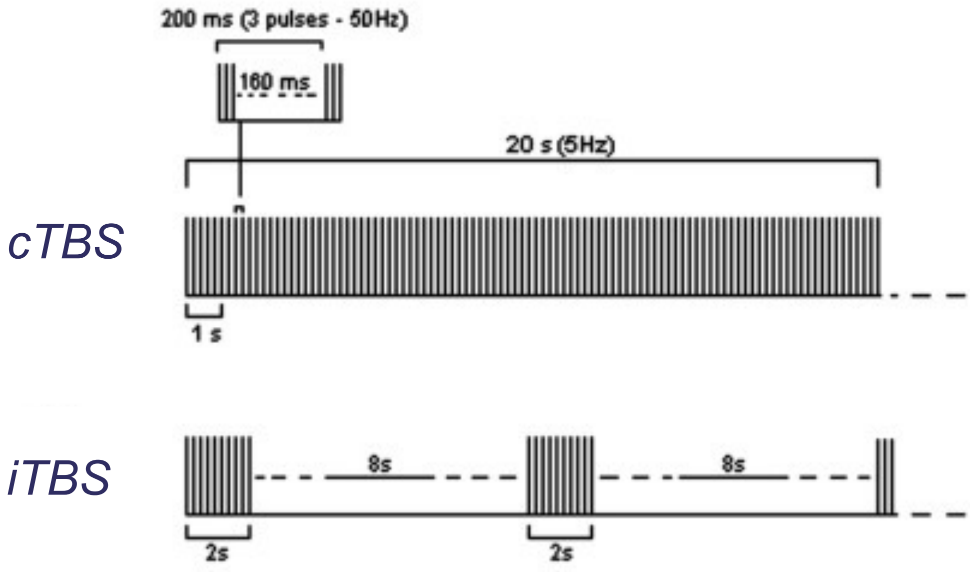
- No effects were found with 1 Hz or 5 Hz

Rossi et al. *Clinical Neurophysiology.* 2009; Beynel et al. *Neuroscience & BioBehav Reviews.* 2019

Stimulation protocols

Patterned rTMS

- Repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation
- Most used is theta burst stimulation (TBS) based on brain's natural theta rhythm in hippocampus
- Direction of after-effects depends on whether bursts are delivered continuously or intermittently



Rossi et al. *Clinical Neurophysiology.* 2009

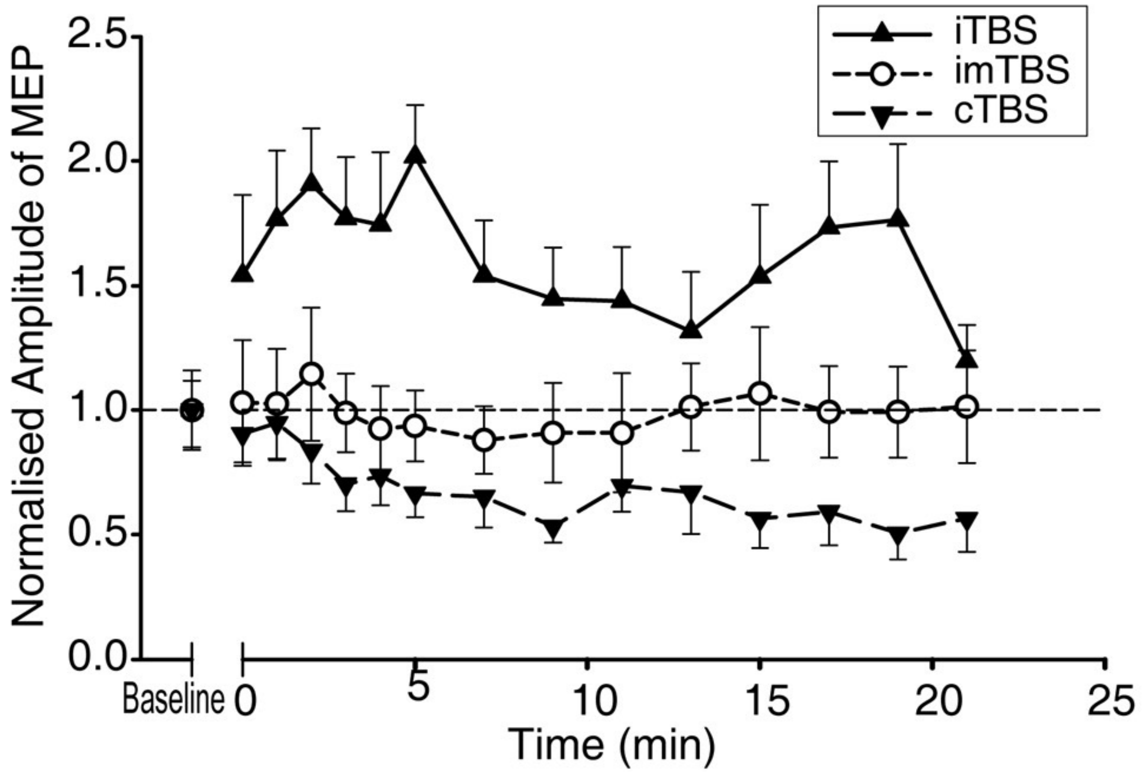
Stimulation protocols

Intermittent theta burst (iTBS)

- Increase in cortical excitability
- Increase in MEP amplitudes
- Facilitated behaviour?

Continuous theta burst (cTBS)

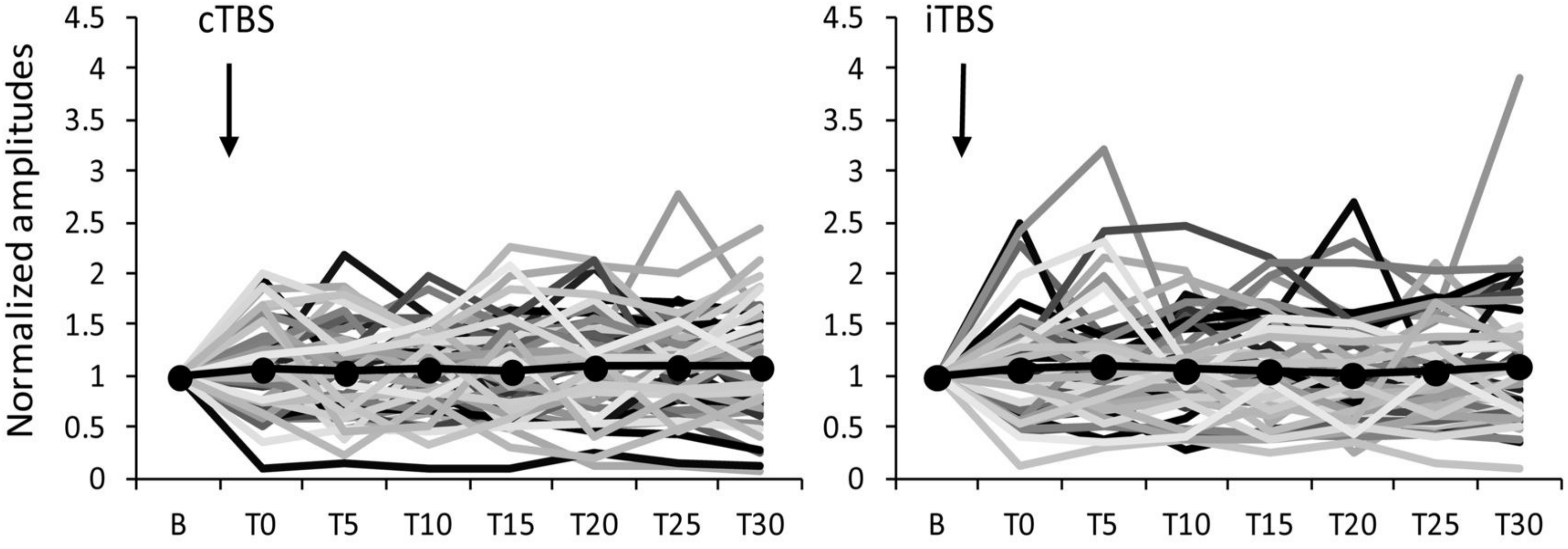
- Depression of cortical excitability
- Reduction in MEP amplitudes
- Impaired behaviour?



Huang et al. *Neuron.* 2005

Stimulation protocols

- Note large variability between individuals with cTBS and iTBS



Hamada et al. *Cerebral Cortex.* 2012

Stimulation protocols

Individual variability

- ‘**Big TMS Data Collaboration**’ where individual participant TMS data shared across studies to increase sample size and statistical power. Here 22 studies.
- Moderate levels of within participant reliability for TBS protocols
- Large variability of between participant responses to TBS
- Baseline MEP amplitude, target muscle, age, and time of day significantly predicted response to TBS

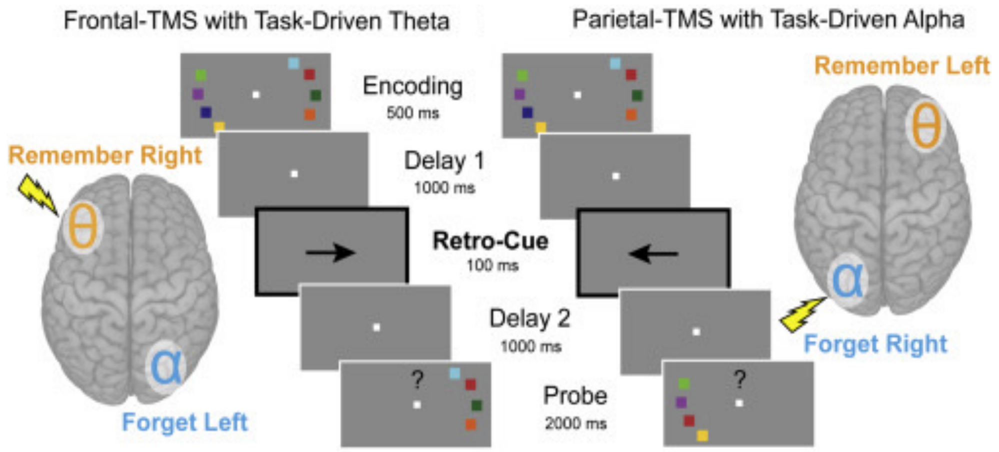
Corp et al. *Brain stimulation.* 2020

Stimulation protocols

Entraining neuronal activity

- Rhythmic TMS at a certain frequency is used to entrain neuronal activity with the aim to synchronise and enhance endogenous brain oscillations

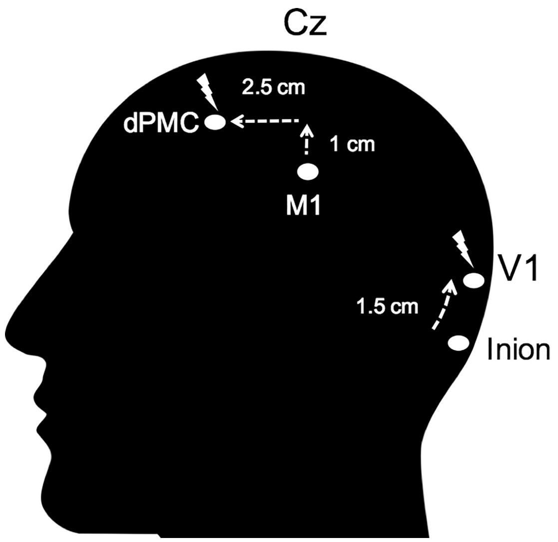
- Suprathreshold TMS may directly evoke waves of synchronised excitation and inhibition, potentially phase-resetting existing oscillatory activity



Riddle et al. *Current Biology.* 2020

Determining stimulation site

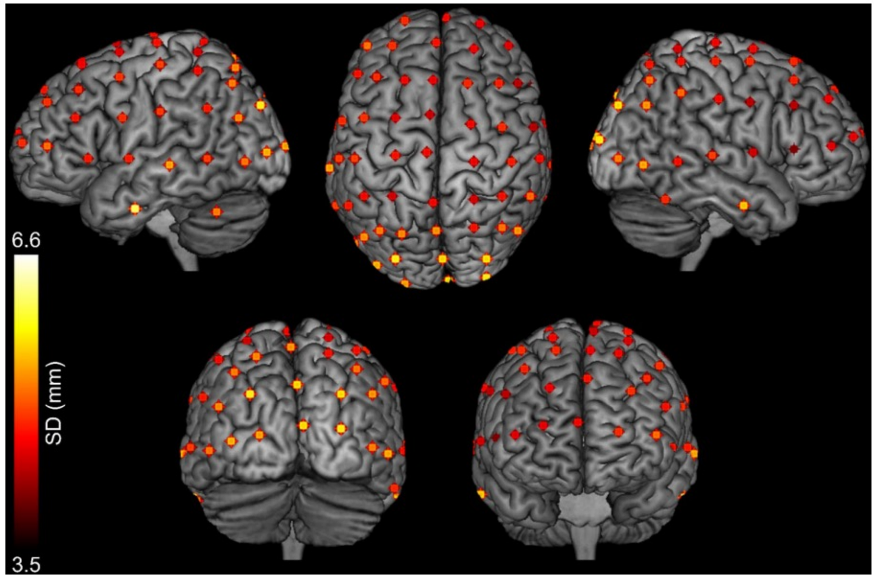
- Different approaches for defining target site
- Anatomical references (e.g. inion)
- Functional measures (e.g. phosphenes)



Lega et al. *PLoS One.* 2016

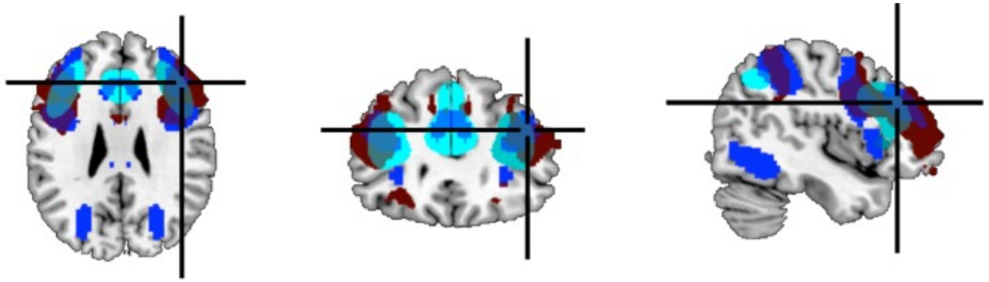
Determining stimulation site

- EEG electrode position-guided TMS



- MRI-guided stimulation (structural/functional)

Selection of TMS target: ***Cross-referenced to activation/connectivity maps***



MD definition from Fedorenko, Duncan et al. 2013
Frontoparietal network from Cole et al. 2013
MD definition from Duncan and Owen 2000

Scrivener & Reader. *Brain & Behaviour.* 2022; Jackson et al. *Communications Biology*. 2021

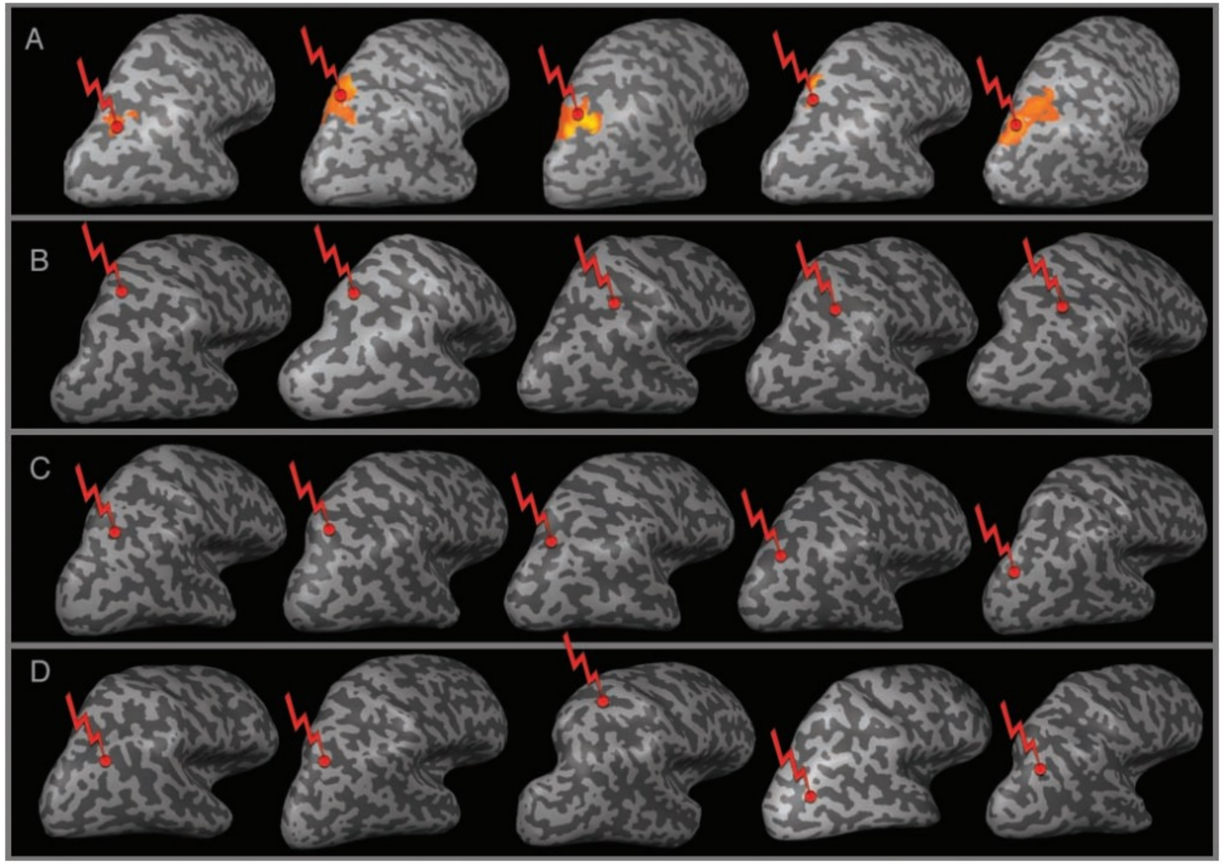
Determining stimulation site

5 participants sufficient

9 participants sufficient

13 participants sufficient

47 participants sufficient



fMRI-guided neuronavigation

MRI-guided neuronavigation

Talairach coordinates

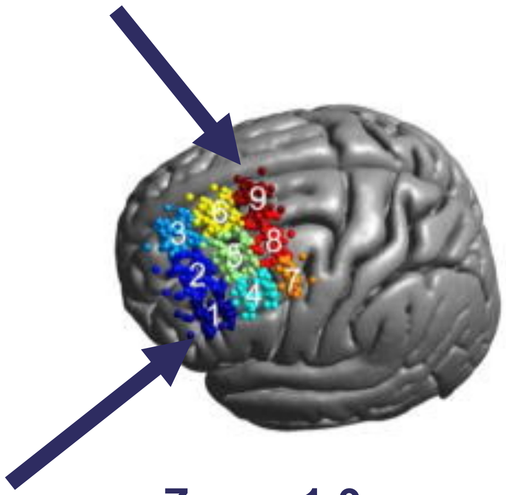
10–20 EEG system

Sack et al. *JoCN*. 2009

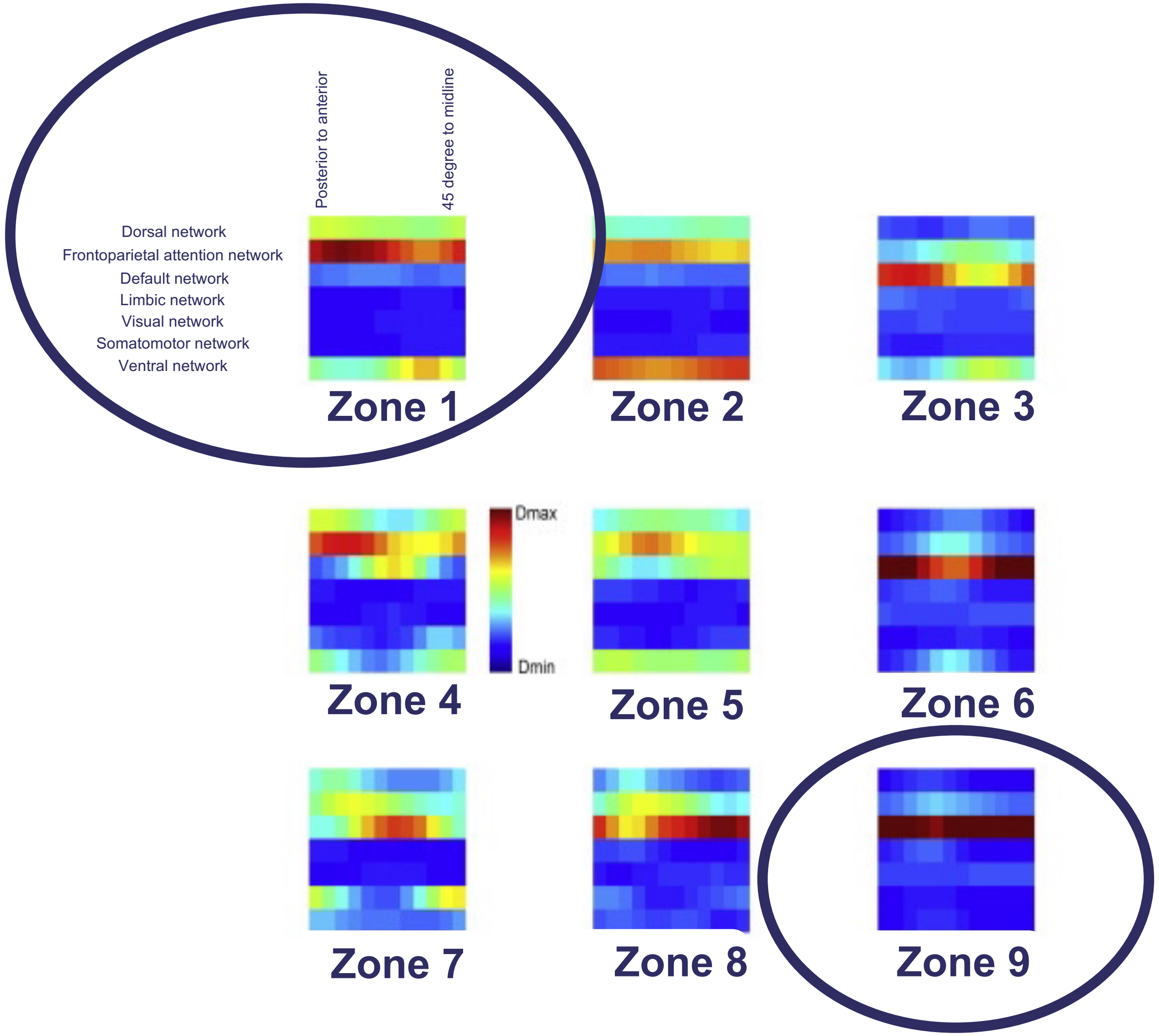
Neuronavigation

- Increases accuracy of coil placement
- Shortest path with the smallest angle to reach a given cortical target
- Real time render and track online visualisation of position of TMS coil on 3D reconstruction of each participant head

Location/orientation dependent networks



Zones 1-9



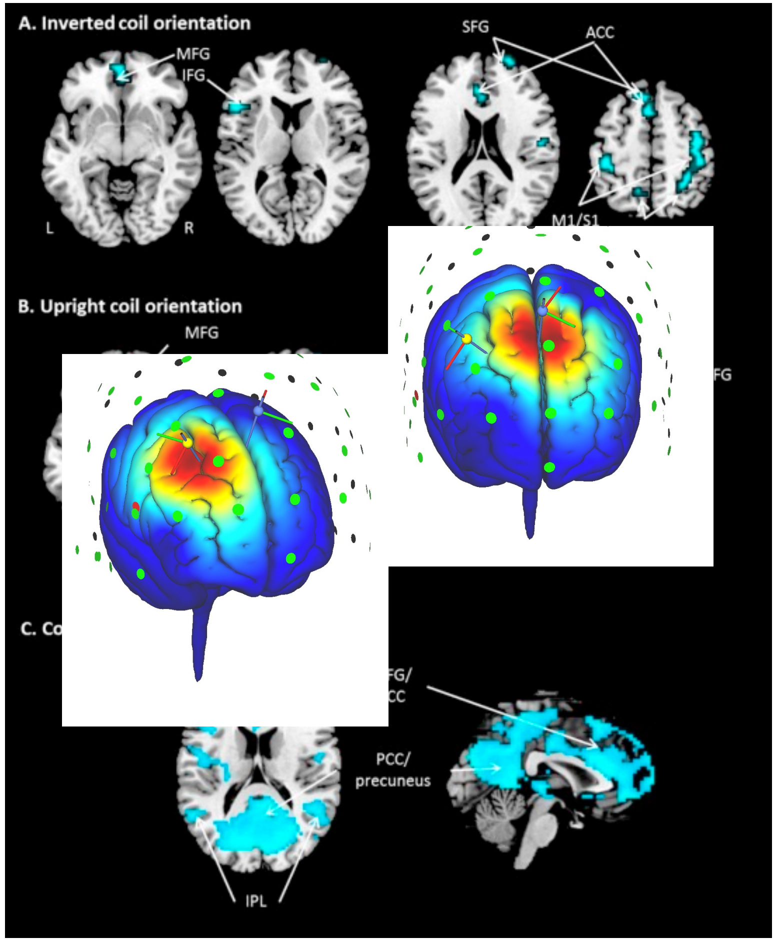
Opitz et al. *Brain Stimulation.* 2016

Control conditions

- Stimulation-free condition
- Sham TMS
- Control via ineffective stimulation protocols
- Control tasks (task specificity)
- Control regions (anatomical specificity)
- Control time points (temporal specificity)
- Control frequencies (frequency specificity)

Control region

- Difficult to define
- Vertex often used as control site (relies on assumption that vertex stimulation does nothing)
- Ideally use a control region not involved in your task
- Compare target with control site by e-field modelling



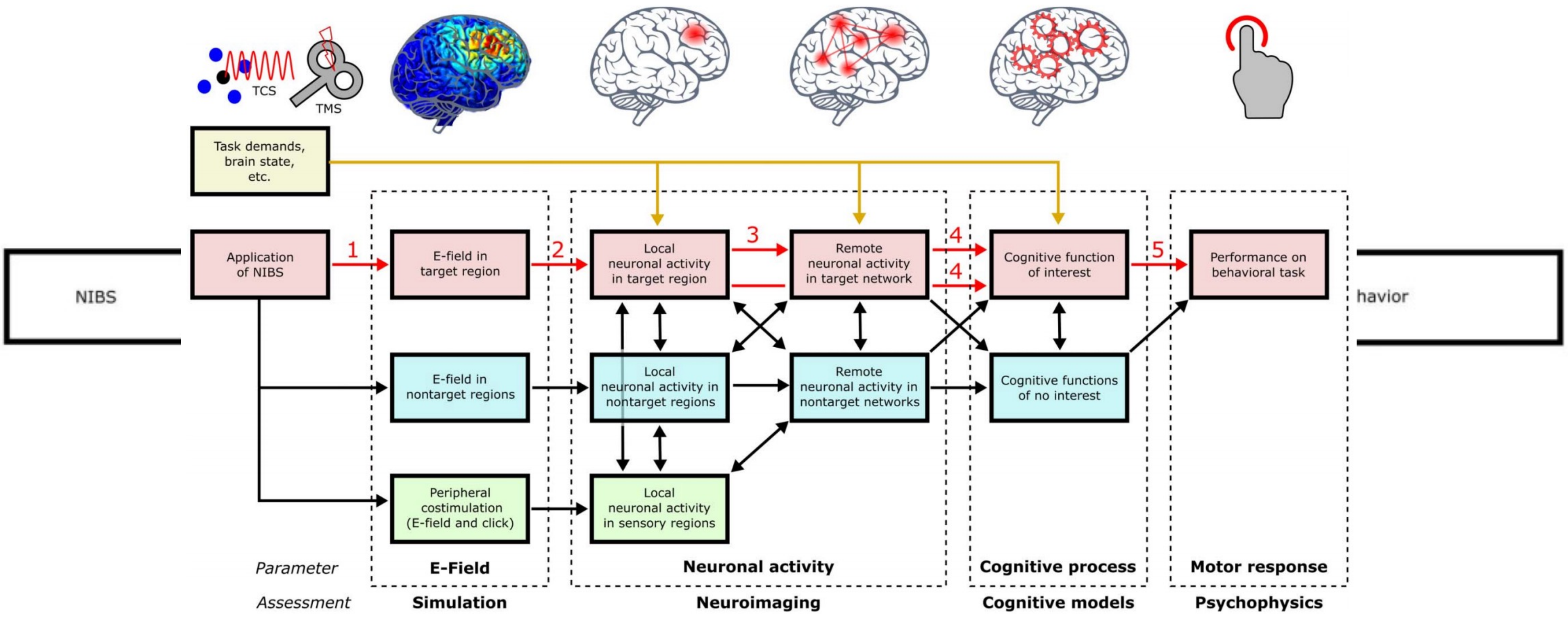
Jung et al. *Brain Stimulation*. 2016

Safety considerations

- Common side effects: local pain (headache, neck, toothache)
- Serious side effects: Hearing loss/impairment, syncope, seizure
- Intake of or withdrawal from certain active drugs lowers seizure threshold
- Screening questionnaire necessary
- Follow all safety guidelines (CBU guidelines on intranet)
- Potential risk of long-term adverse event for TMS operators due to daily close exposure

Rossi et al. *Clinical Neurophysiology.* 2021

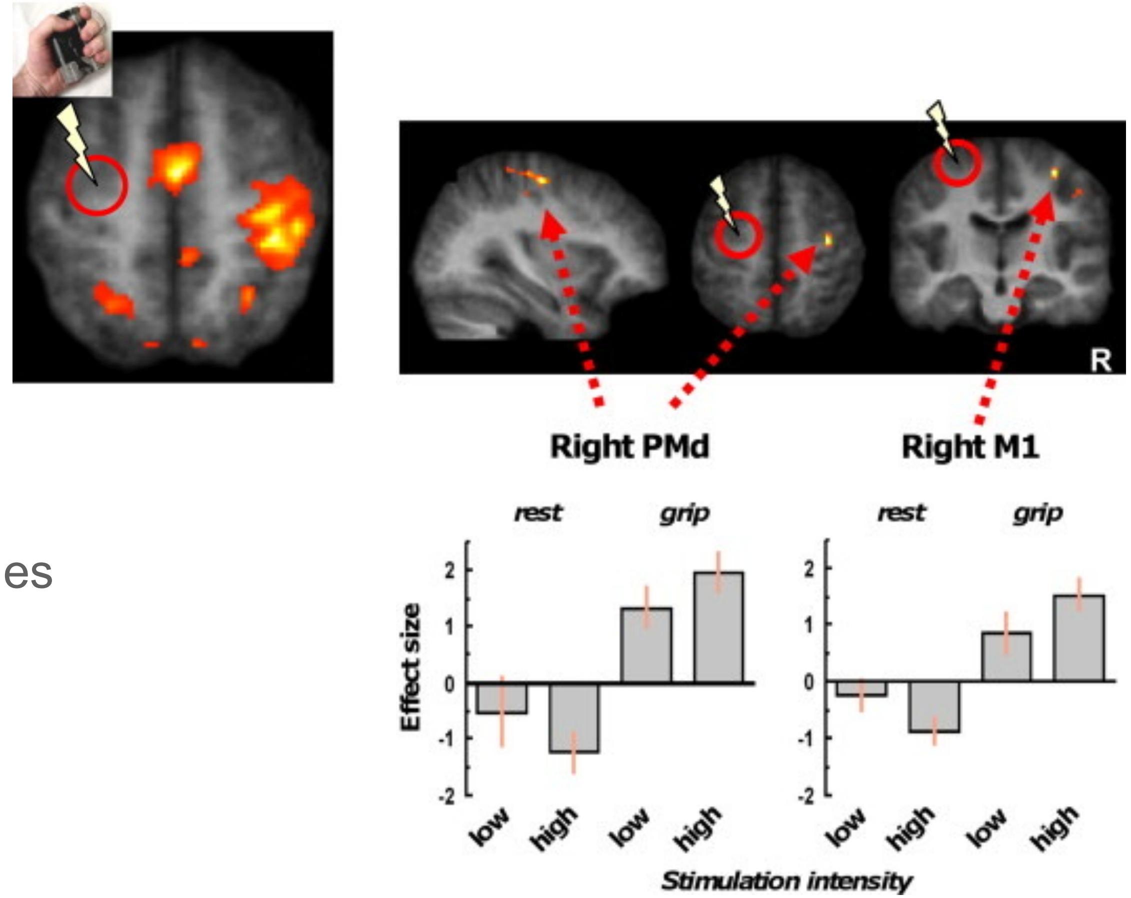
Chain of causation



Bergmann et al. *JoCN*. 2021

Example factors influencing chain of causation

- Costimulation of nontarget regions
- Participants' beliefs/expectations
- Task demands/learning effects/cognitive abilities
- Current brain state



Bestmann et al. *Cerebral Cortex*. 2008

Future directions

Spatial parameters

- Coil geometry/stimulation target/targeting strategy/stimulation intensity

Temporal parameters

- Pulse train frequency, number of pulses, inter-trial interval, timing of pulses relative cognitive processes

Large parameter space and huge variation between studies

- Systematic evaluation of how stimulation parameters impact TMS effects on human behaviour

Reading

- Bergmann, T. O., & Hartwigsen, G. (2021). Inferring causality from noninvasive brain stimulation in cognitive neuroscience. *Journal of cognitive neuroscience*, *33*(2), 195-225

- Pitcher, D., Parkin, B., & Walsh, V. (2021). Transcranial Magnetic Stimulation and the understanding of behavior. *Annual Review of Psychology*, *72*

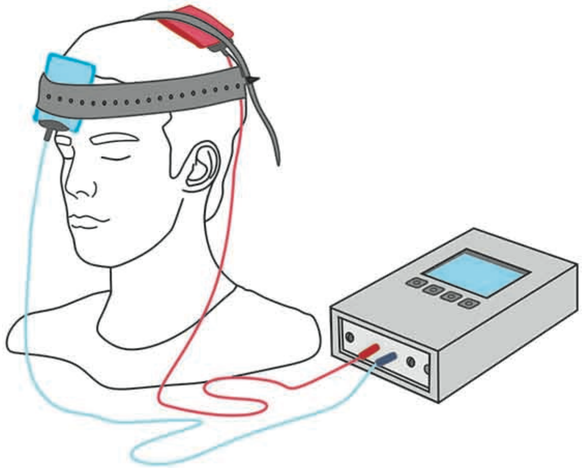
- Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., ... & Hallett, M. (2020). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

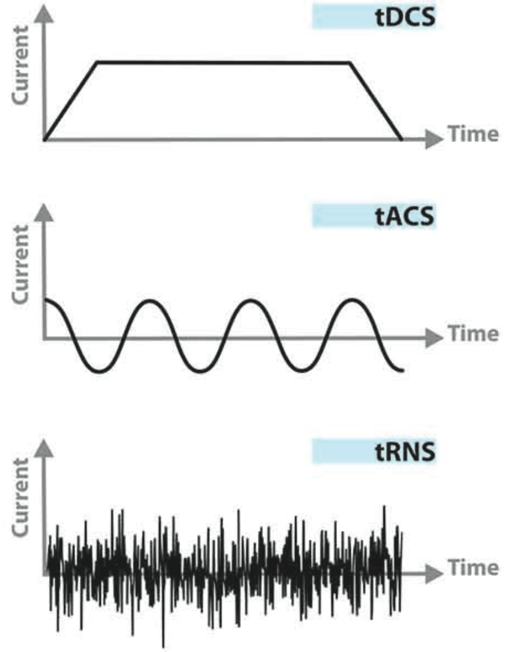
- Valero-Cabré, A., Amengual, J. L., Stengel, C., Pascual-Leone, A., & Coubard, O. A. (2017). Transcranial magnetic stimulation in basic and clinical neuroscience: a comprehensive review of fundamental principles and novel insights. *Neuroscience & Biobehavioral Reviews*, *83*, 381-404

Transcranial electrical stimulation (tES)

What is tES?

- Class of brain stimulation techniques comprising direct current (DC), alternating current (AC), and random noise (RN)
- Small electrical current (0.5-2 mA) applied to scalp via two or more electrodes. A portion of the current penetrates scalp and is conducted through brain, altering neuronal excitability
- Applied currents constant over time (transcranial direct current stimulation (tDCS)), or alternate at certain frequency (transcranial alternating current stimulation (tACS))

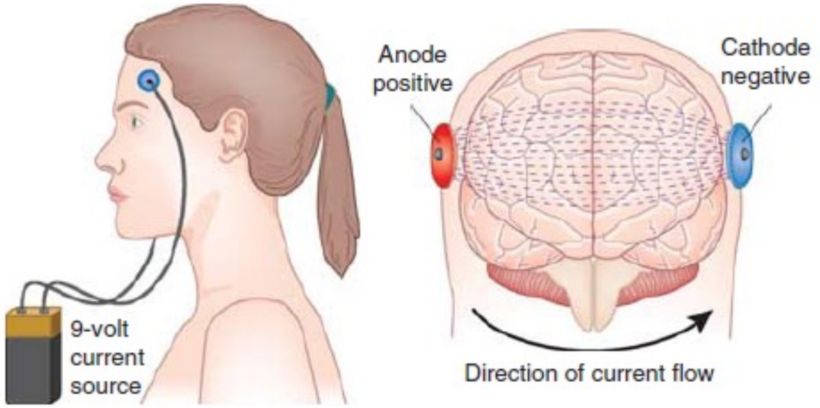




Hermann et al. *Front Hum Neurosci*. 2013

What is tES?

- Stimulation is ~100x weaker than TMS, so does not directly cause action potentials
- Generally current is delivered through the anode electrode, propagated through the head and returned at cathode
- This modulates cortical excitability, with increased excitability at the anodal electrode, and decreased at the cathodal electrode

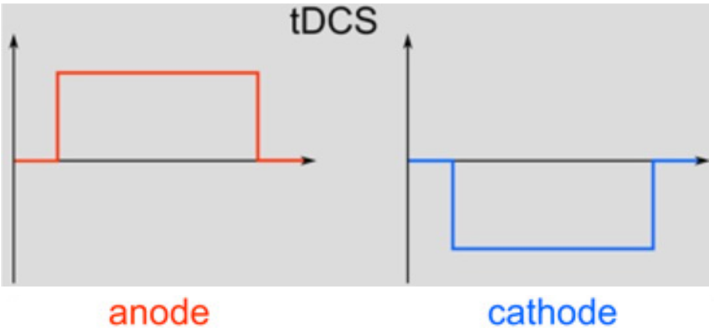


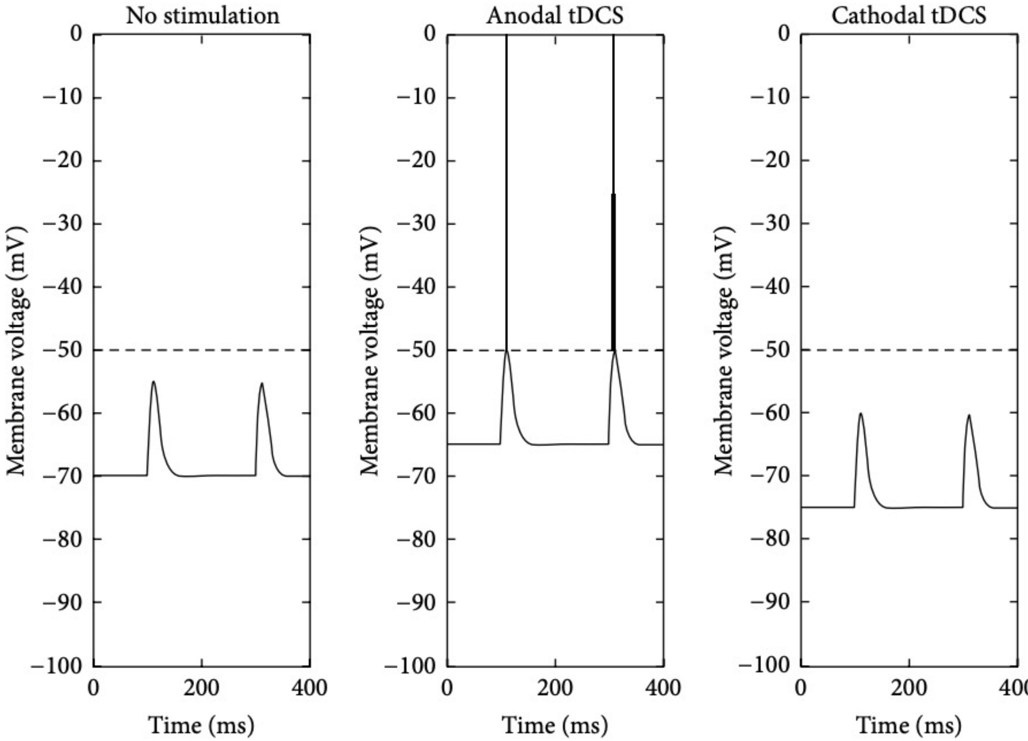
Why use tES?

- Spatial/temporal resolution and neural effect of TMS is superior but tES tools more cost-effective and easier to operate
- tES is also more portable, easier to design blind sham conditions and well-tolerated by participants
- Absent of any serious adverse effects

Direct current stimulation (tDCS)

- Application of a constant current
- tDCS changes threshold for discharge of stimulated neurons changing likelihood of their discharge
- "After-effects" last up to 90mins after stimulation (depending on intensity/duration of stimulation)





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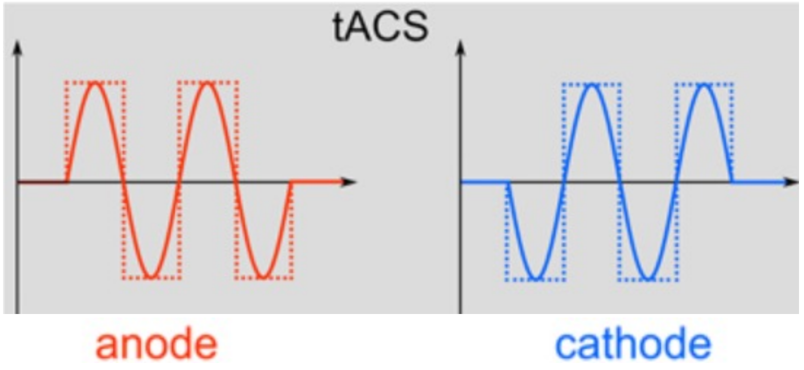
Hermann et al. *Neural Plasticity*. 2016

Alternating current stimulation (tACS)

- Current is not constant but alternates between anode and cathode (switching polarity) with a sinusoidal waveform
- With **tDCS** the two electrodes are referred to as anode and cathode because of the current crossing into the body being positive and negative, respectively
- In one half cycle of tACS oscillation, one electrode serves as anode, other cathode, and current strength will increase and decrease following a half sine wave. In other half cycle, pattern reverses and former anode considered cathode and vice versa
- tACS not intended to excite/inhibit cortical activity but to influence brain oscillations



Reliability

- Systematic review pooled 30 neurophysiological outcome measures (e.g. ERPs, MT, etc) and tDCS was found to have a reliable effect on only one: MEP amplitude

- Second review pooled cognitive outcome measures (executive function, language, memory, and miscellaneous) explored by at least two different research groups utilising healthy adults, same stimulation-to-task relationship, same active electrode location, and comparing to a sham condition

- tDCS not found to generate a significant effect on any outcome measure. Therefore, a single-session of tDCS does not seem to have reliable effect on cognitive tasks in healthy populations

Horvath et al. *Neuropsychologia*. 2015; Horvath et al. *Brain Stimulation.* 2015

Reliability

Criticisms of tDCS

Suggested solutions	Insufficient current induced	Unknown mechanisms	Variable effects	Poor experimental design	Failures to replicate	Overselling of findings
Sufficient control conditions			✓	✓	✓	
Sufficient power/ sample size			✓	✓	✓	
Use sensitive performance measures			✓	✓	✓	
Assessing/utilising individual differences		✓	✓			
Use animal models for low-level mechanisms	✓	✓				
Combining tDCS with neuroimaging	✓	✓				
Improve/validate models of current flow	✓	✓				
Encourage replications					✓	
Registered reports		✓		✓	✓	✓
Educate public in scientific practice						✓
Discourage overselling						✓

Filmer et al. *Cortex*. 2020

Safety

- Conventional tDCS protocols has not produced any reports of a serious adverse effect over 33,200 sessions and 1000 subjects with repeated sessions
- No reports of seizures using tES in humans
- Slight itching, heating, burning sensation under the electrode, contact dermatitis
- Headache, fatigue, and nausea only in very small minority of cases
- Never place both electrodes on any other part of the body apart from the head - currents passing across the heart can be dangerous

Poreisz et al. *Brain Research Bulletin*. 2007; Bikson et al. *Brain Stimulation,* 2016; Maksumoto et al. *Clinical Neurophysiology Practice,* 2017

CBU equipment

Two stimulators on site

- **neuroConn DC-STIMULATOR PLUS**

Single channel stimulator suitable for non-invasive tDCS, tACS or tRNS

- **neuroConn DC- STIMULATOR MR**

MR compatible version of DC-STIMULATOR PLUS

Readings

- Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in human neuroscience*, *7*, 279
- Reed, T., & Kadosh, R. C. (2018). Transcranial electrical stimulation (tES) mechanisms and its effects on cortical excitability and connectivity. *Journal of inherited metabolic disease*, *41*(6), 1123-1130
- Westwood, S. J. (2020, February 12). Investigating cognitive and therapeutic effects of transcranial electric stimulation (TES): a short guide for reproducible and transparent research. https://doi.org/10.31234/osf.io/8qms2

Combining TMS with fMRI

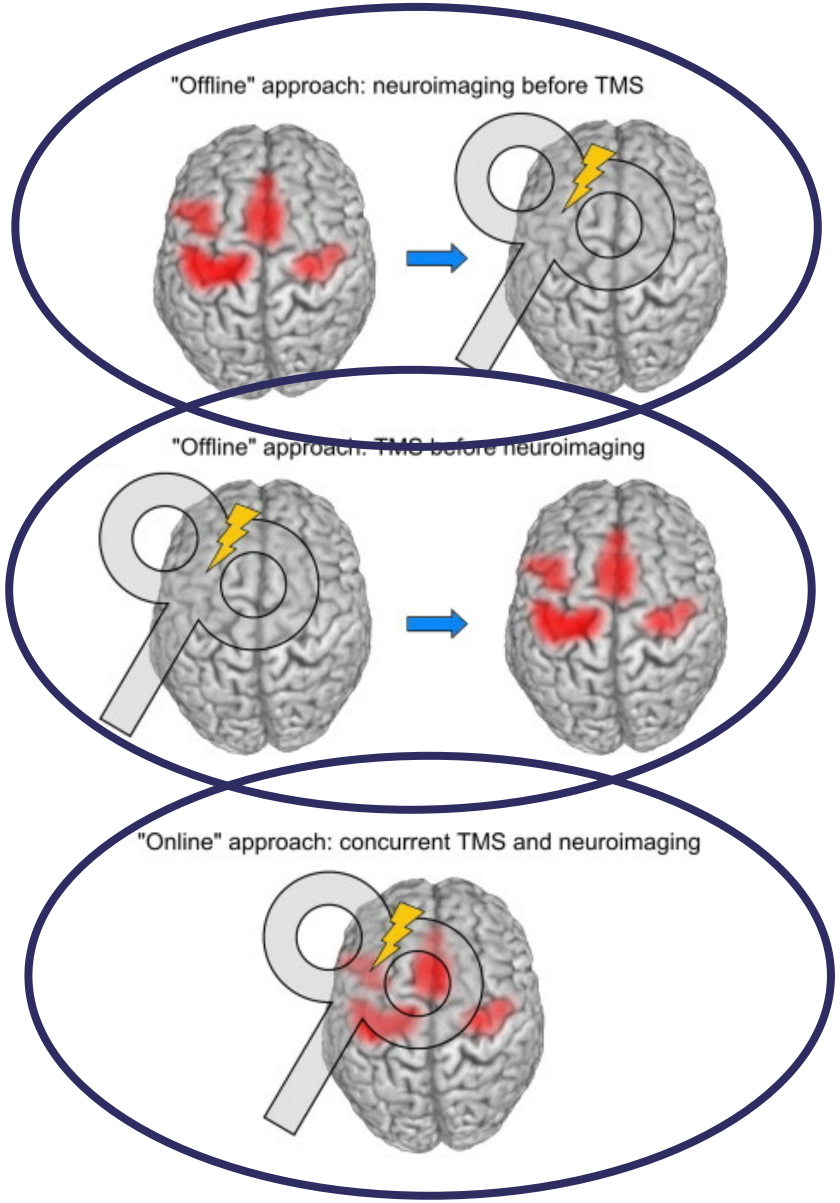
Offline vs online

- TMS may be applied “offline” before/after neuroimaging

- This approach is technically easier to establish as TMS and neuroimaging are separated in time (and space)

- TMS can be applied outside MRI suite when conducting an offline TMS-fMRI study

- No specific methodologic precautions are necessary when offline TMS is combined with any available neuroimaging techniques



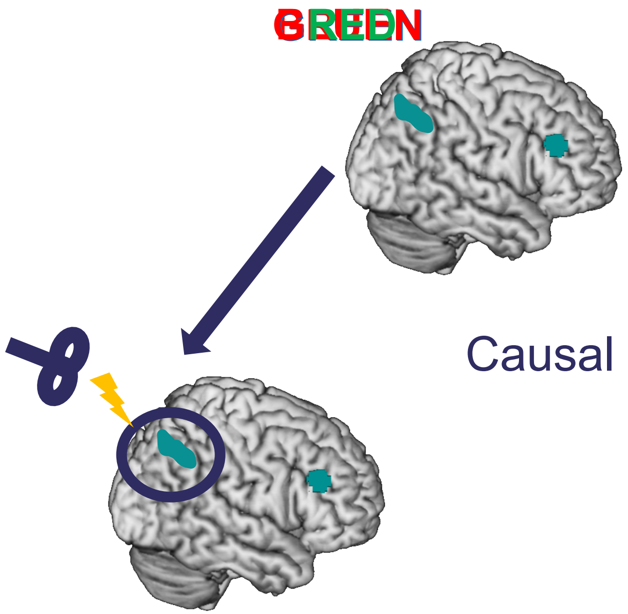
Siebner et al. *Brain Stimulation*. 2009

Why use TMS-fMRI?

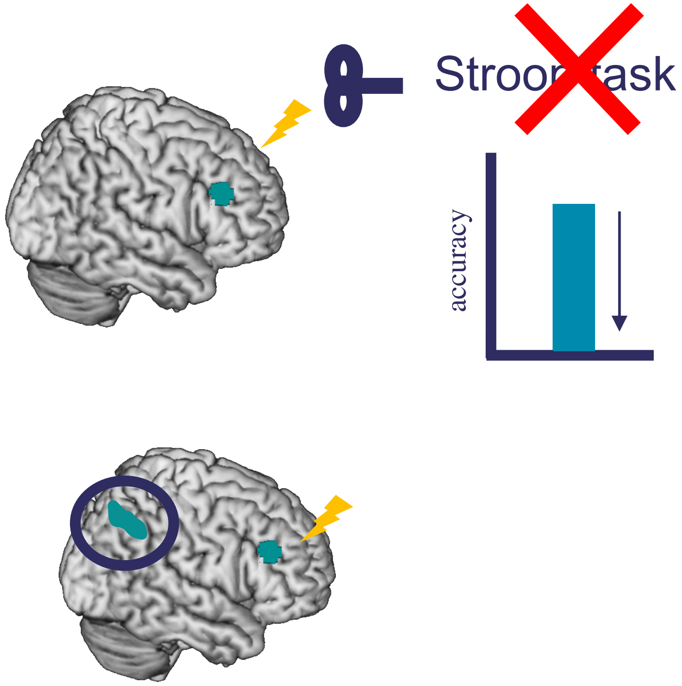
fMRI
Causal involvement?

TMS
Impact on interconnected networks?

Stroop task

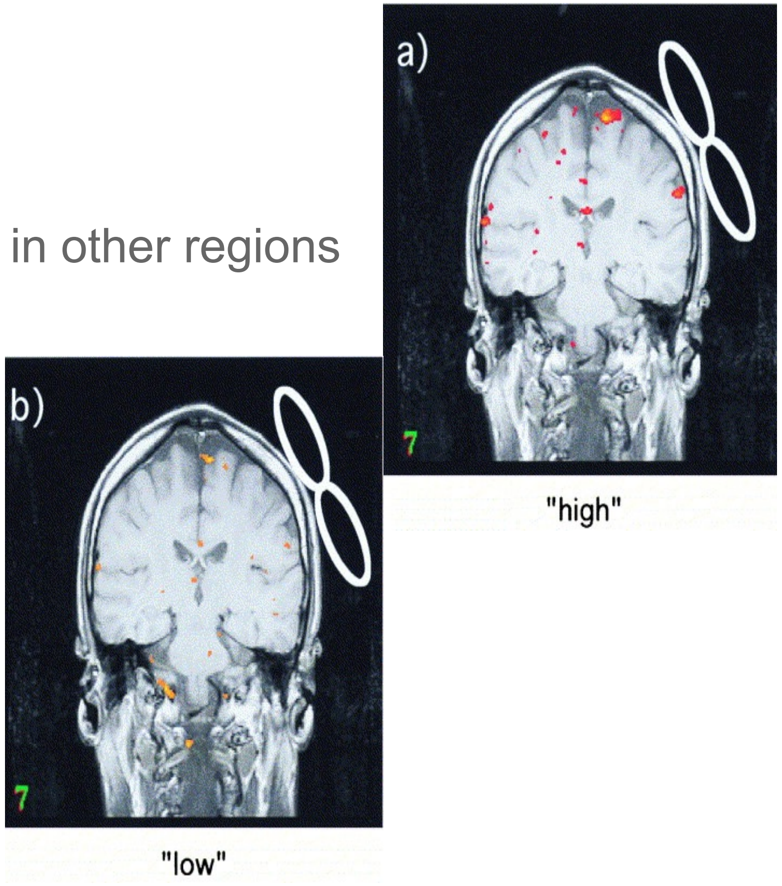


Causal involvement?



Why use TMS-fMRI?

- TMS can evoke activity in areas remote from the stimulation site
- Dose-dependent; higher intensities evoke larger activity changes in other regions
- Remote effects can be facilitatory/inhibitory
- Hidden in behavioural studies



Bohning et al. *Biological Psychiatry,* 1999

Why use TMS-fMRI?

- **TMS-fMRI** allows us to stimulate one part of the brain and measure changes in activity at:

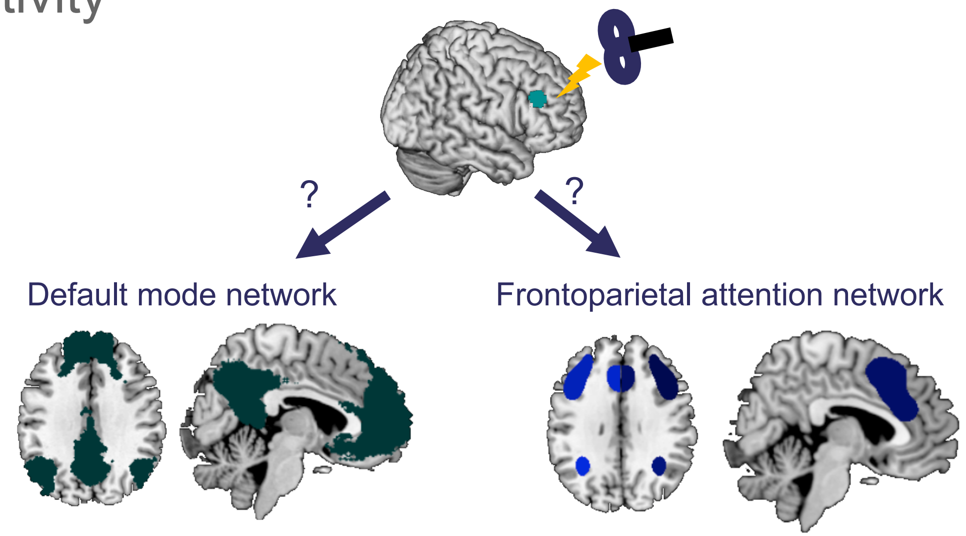
  - site of stimulation
  - entire brain

- Understanding of TMS effects on neural activity

- Effective connectivity

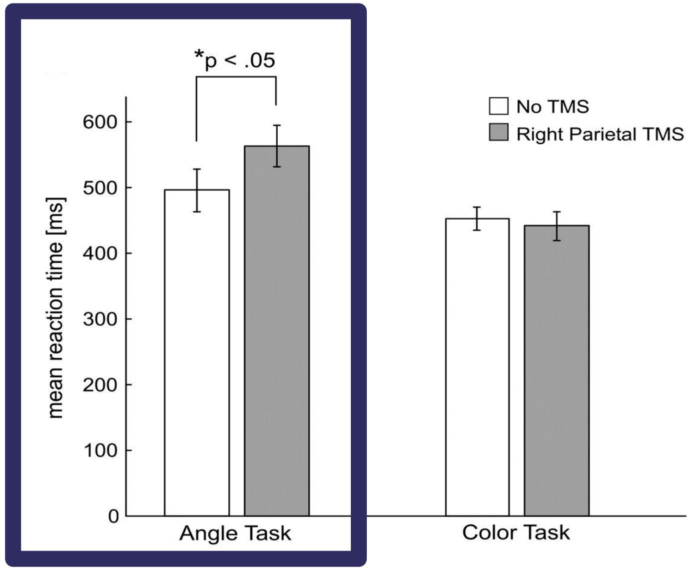
- Individualised intervention

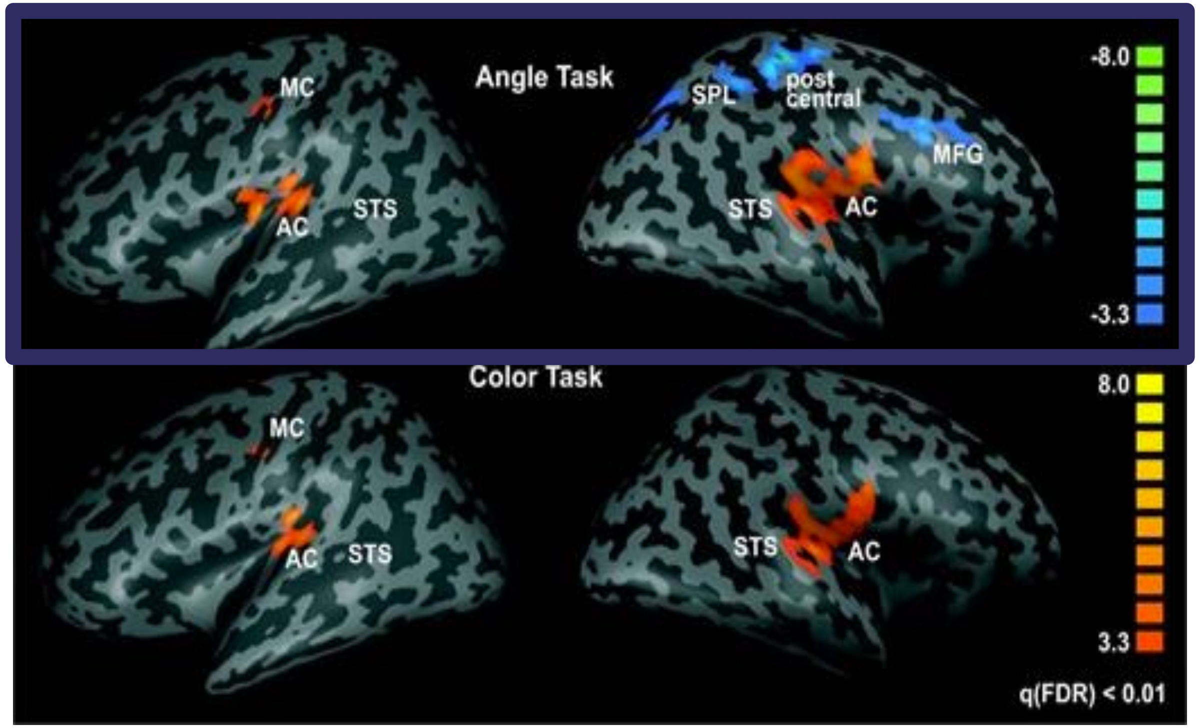
- Mechanisms of neurostimulation



Why use TMS-fMRI?

- Neural basis for cognitive function
- Relate neural effects to behaviour





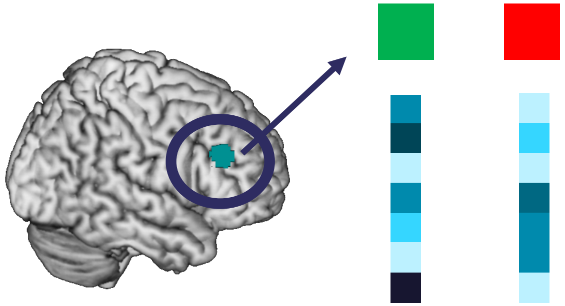
Sack et al. *Cerebral Cortex,* 2007

Why use TMS-fMRI?

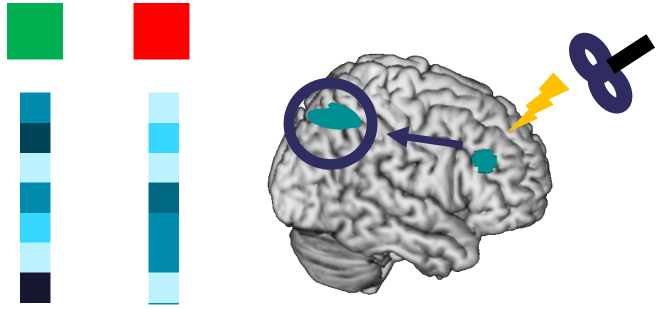
MVPA

Stroop task

Stimuli: RED BLUE



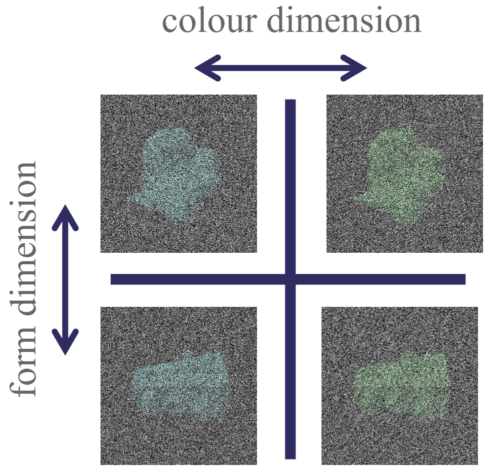
TMS-MVPA

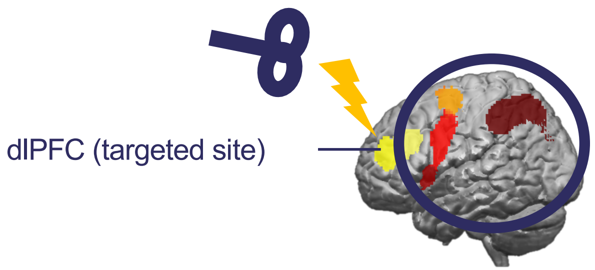


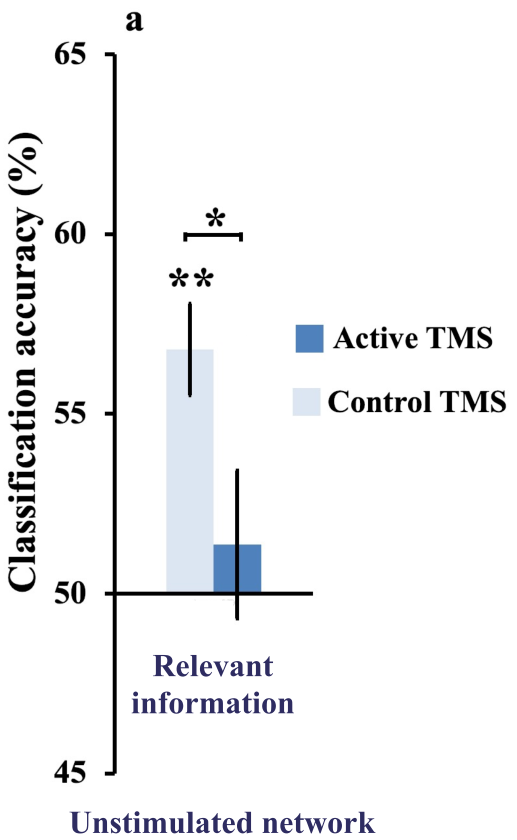
- Test causal influences on information representation across the brain
- Draw links between stimulation, information coding and behaviour

Why use TMS-fMRI?

- Mechanistic insight

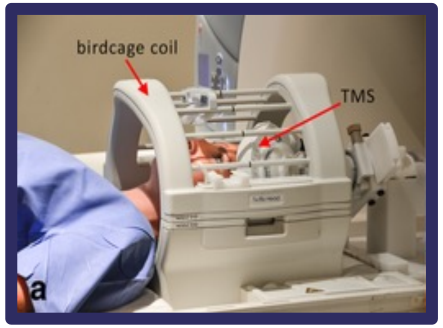






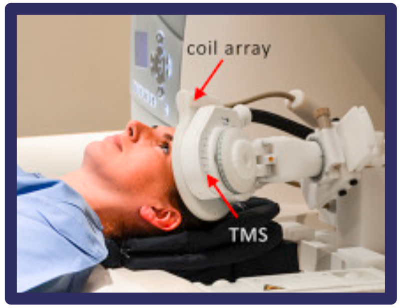
Jackson et al. *Communications Biology*, 2021

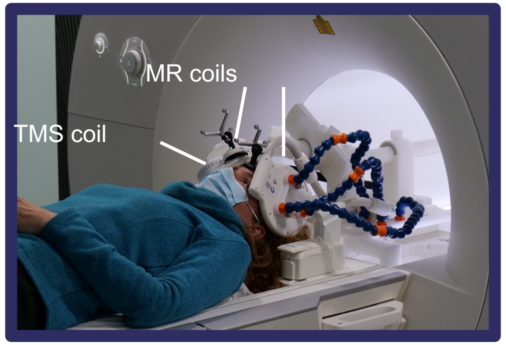
MR-dedicated RF coils



Restricted coil placement

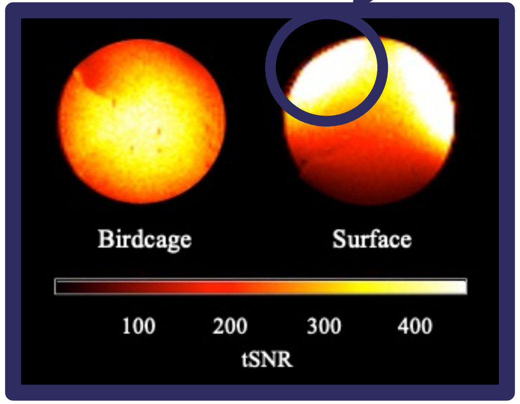
MR coil array is placed between the TMS and head of the participant





Supplementary MR coil

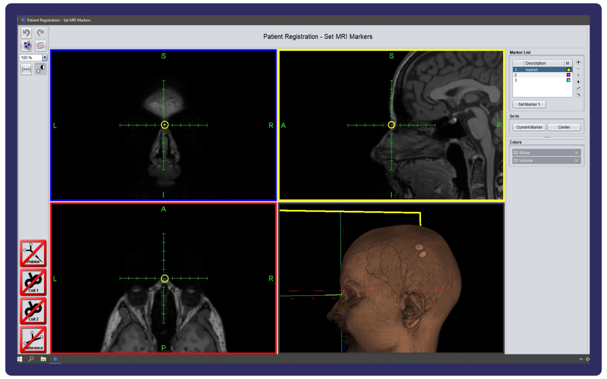
area under TMS coil



- Avoids signal loss at site of stimulation
- Allows flexibility in coil placement
- Check targeted region

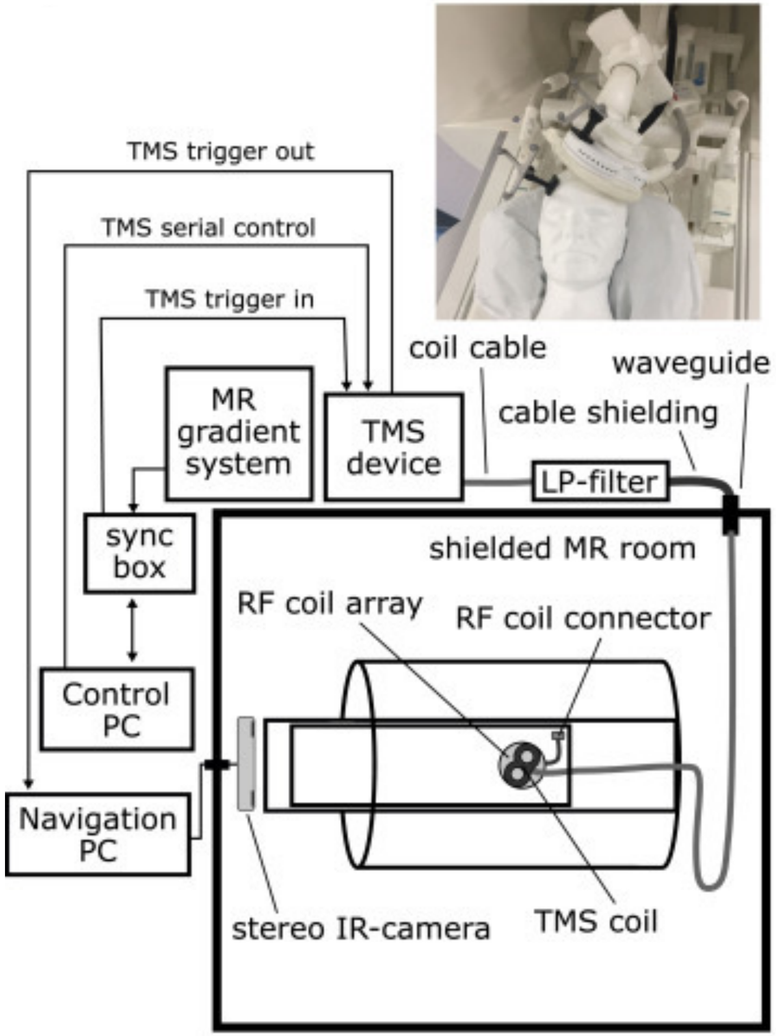
Navarro de Lara et al. *Magnetic Resonance in Medicine,* 2017

MR neuronavigation



Setup in the scanner

- MR-compatible TMS coils must not contain ferromagnetic material and must resist mechanical load resulting from interaction of static magnetic field (B_0) of MR and dynamic magnetic field of TMS pulse
- Stimulator itself placed outside MR room or within a dedicated shielded metal cabinet
- TMS coil must be connected via a waveguide and an additional low-pass filter to remove external high-frequency noise
- Required extra-long power cable and low-pass filter result in power loss and reduce stimulation by ~15 %



Bergmann et al. *NeuroImage*, 2021

Setup in the scanner

- Setup very time-consuming

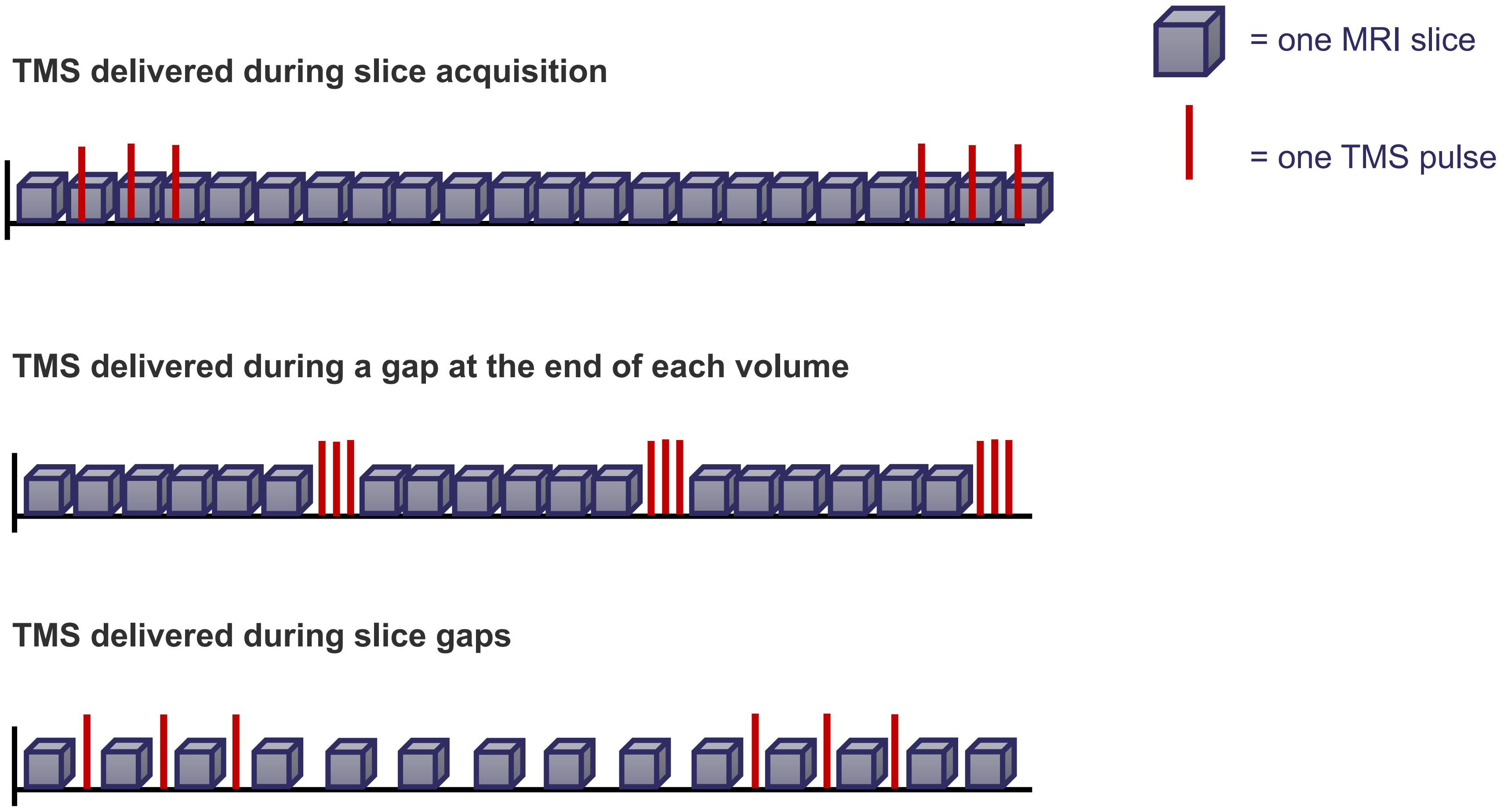
- Need to get TMS coil in the correct position and maintain this exact position throughout the entire recording

- Stabilisation achieved with MR-compatible coil holders BUT need extra stabilisation for newer RF coils
  - adhesive tape, Velcro straps, sandbags and vacuum packs used to secure coil to subject's head

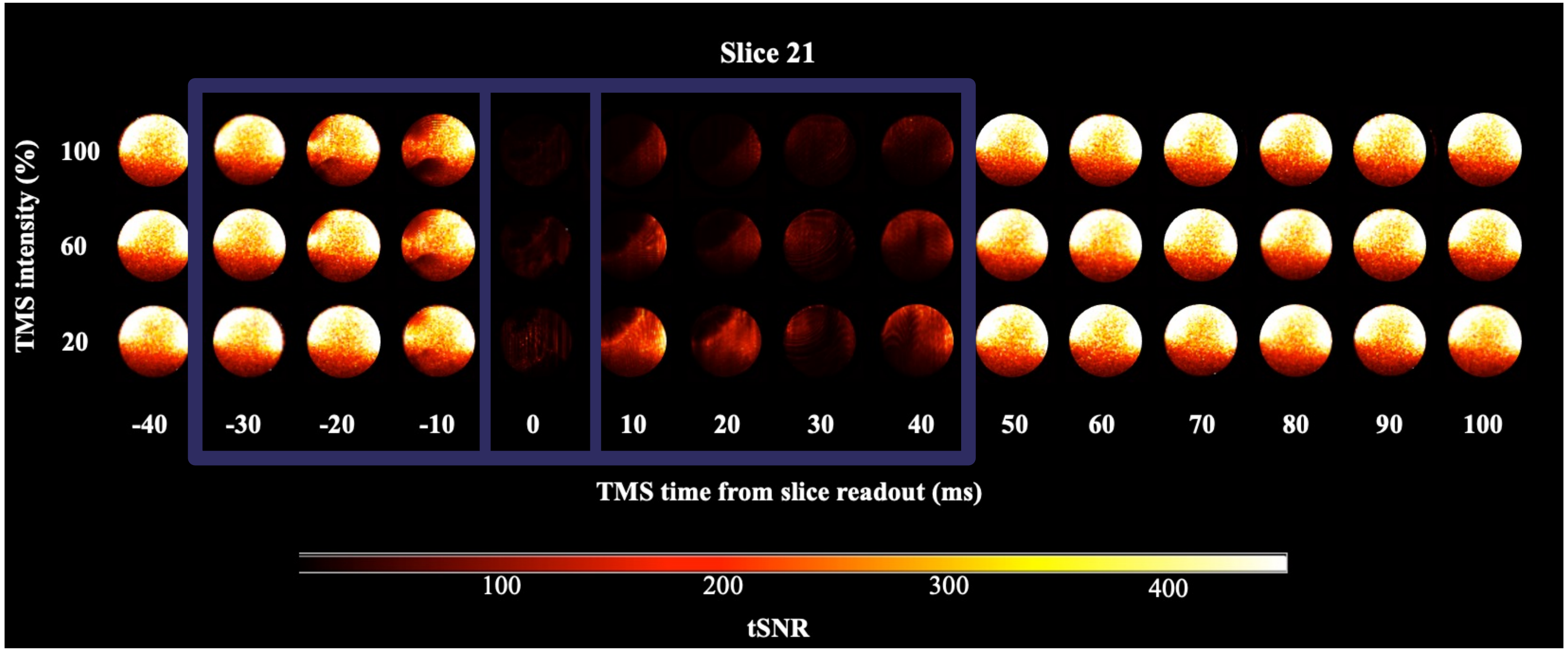
- Head motion results from: constant pressure of the TMS coil, strong coil vibration during pulse delivery, induced muscle twitches, a startle response

- Online neuronavigation can monitor the coil position continuously throughout acquisition

Artifacts caused by TMS pulse



Artifacts caused by TMS pulse

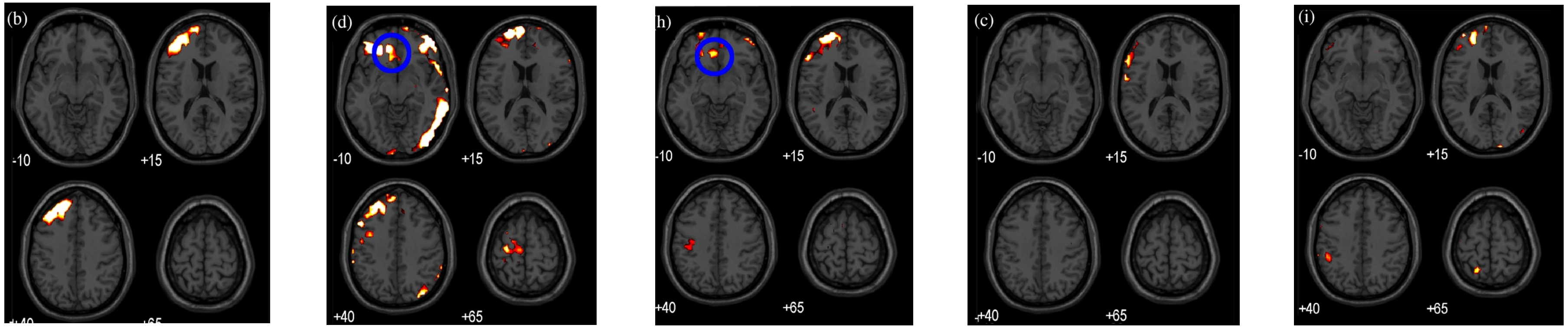


- Circular phantom with TMS-dedicated MR surface coils
- TR 1.85, MB factor 2, 40ms gap in between slices

Scrivener*, Jackson* et al. *BioRxiv,* 2021

Variability

- If TMS coil placement is well-controlled and head movement is limited, TMS-induced brain activity can still be variable between participants



- Stimulation of the same region can result in different propagation patterns of TMS-evoked activity

Vink et al. *Human Brain Mapping,* 2018

TMS-fMRI summary

Great potential for

- Understanding mechanisms of TMS
- Connectivity, neural basis for cognition and relating neural responses to behaviour
- Is information we read out meaningful?

Future directions

- New sequences/protocols to avoid artifacts
- Available coil holders good for birdcage coil but not for RF coils mounted to TMS coil. A large percentage of time is spent on practical hassles of precise coil positioning
- Providing real-time feedback of deviations from the target coil position, may allow the subject to self-correct their head-position accordingly
- Remote robotic positioning of the TMS-coil in the MR scanner

Readings

- Bergmann, T. O., Varatheeswaran, R., Hanlon, C. A., Madsen, K. H., Thielscher, A., & Siebner, H. R. (2021). Concurrent TMS-fMRI for causal network perturbation and proof of target engagement. *NeuroImage*, *237*, 118093.

- Bestmann, S., & Feredoes, E. (2013). Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Annals of the New York Academy of Sciences*, *1296*(1), 11-30.

- Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., ... & Rossini, P. M. (2009). Consensus paper: combining transcranial stimulation with neuroimaging. *Brain stimulation*, *2*(2), 58-80.

TMS at the CBU

CBU stand-alone TMS

DuoMag XT-100
Frequencies up to 100Hz
Biphasic pulses
Minimum inter-train interval of 10ms
Brainsight2 neuronavigation

CBU MRI-TMS

MagPro XP
Frequencies up to 250Hz
Biphasic pulses
Minimum inter-train interval of 10ms
Localite neuronavigation

TMS-EEG???

Questions