Brain stimulation methods

Catriona Scrivener

MRC Cognition and Brain Sciences Unit

catriona.scrivener@mrc-cbu.cam.ac.uk

01/02/21

Overview

Why use brain stimulation?

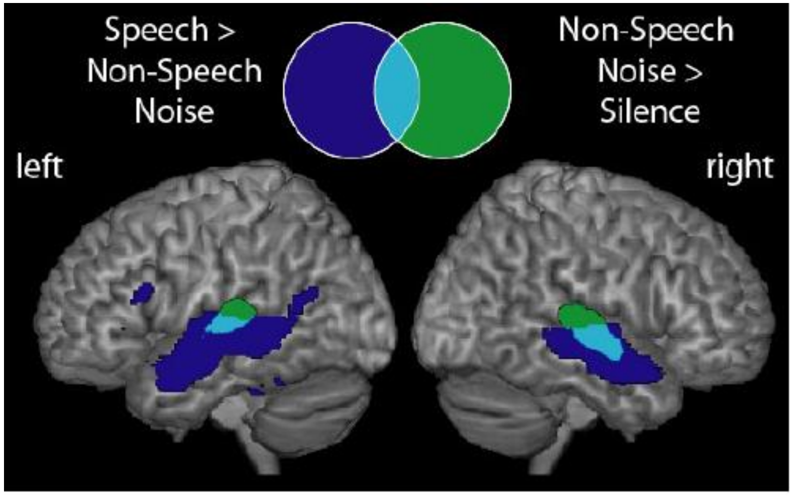
TMS and tES

- Mechanism
- Protocols
- Safety
- CBU equipment

Combined neuroimaging: TMS-fMRI

Motivation

Common experimental approach: manipulate presented stimuli as independent variable, measure neural activity

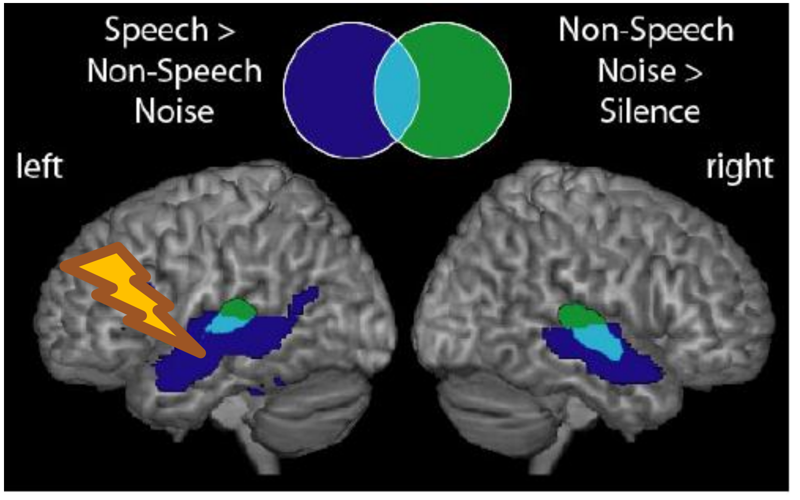


Activity in some areas is stronger for speech than noise, but are these areas necessary or causal?

Davis & Johnsrude, 2003

Motivation

TMS approach: selectively ‘disrupt activity’ in a region of interest, and compare changes in behaviour (and potentially neural activity) to a control region/session

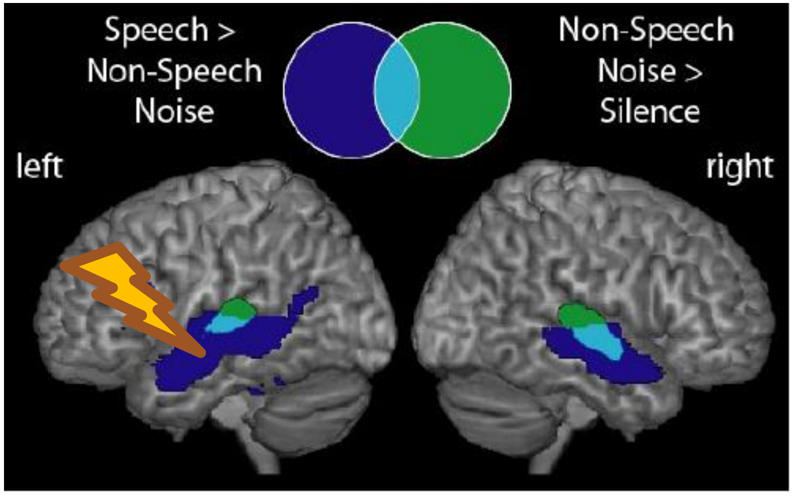


If TMS results in a relevant behaviour change, indicates that this region is important

Davis & Johnsrude, 2003

Motivation

TMS approach: selectively 'disrupt activity' in a region of interest, and compare changes in behaviour (and potentially neural activity) to a control region/session



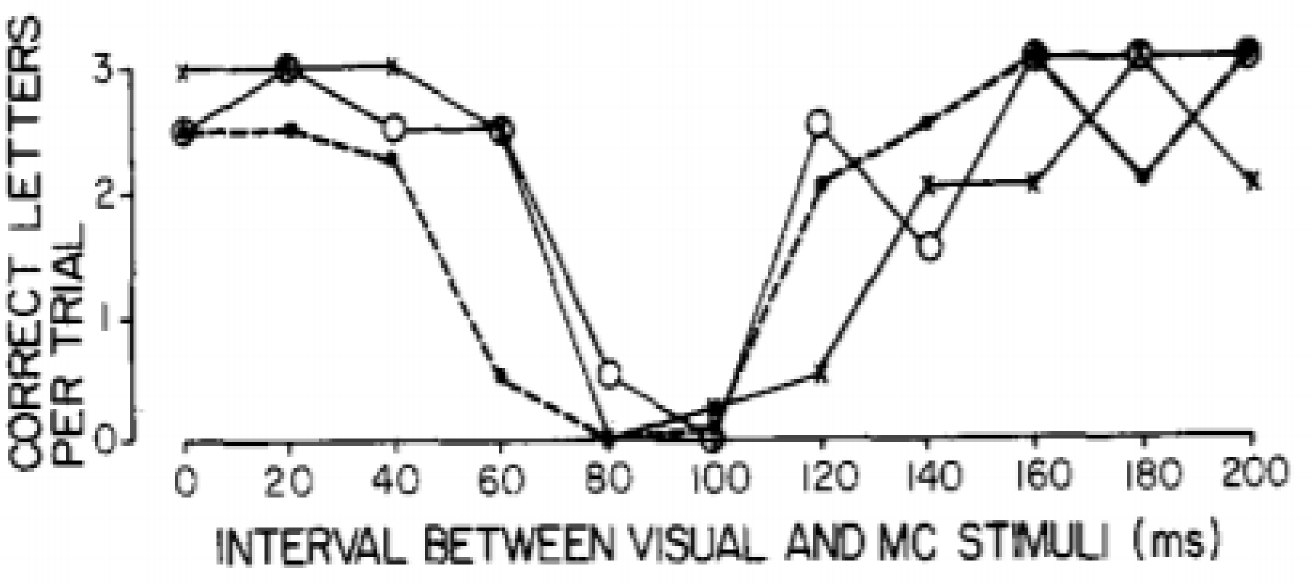
How can we established causation? (Bergmann & Hartwigsen, 2021)

Part 1

Transcranial magnetic stimulation (TMS)

What is TMS?

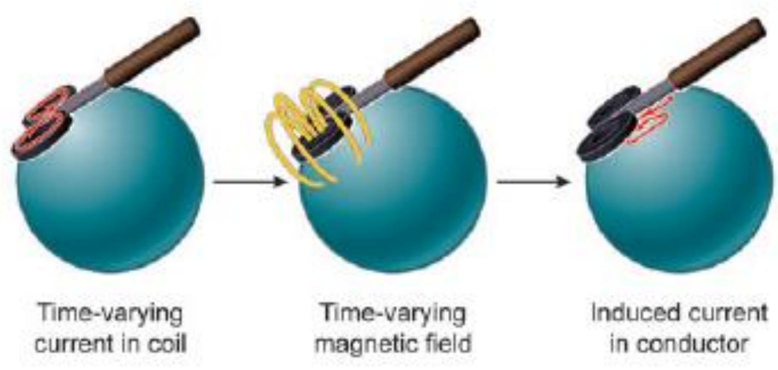
‘Classical dip’ – TMS to the visual cortex disrupts perception of visual stimuli when applied ~100ms after stimulus onset



Amassian et al. (1989)

What is TMS?

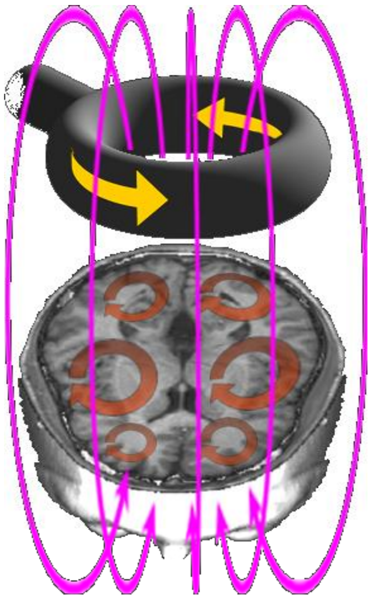
TMS relies on basic principles of electromagnetism (Faraday's law)

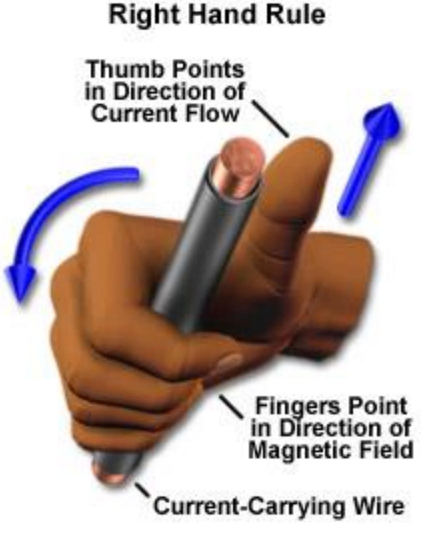


- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in a coil of wire.
- Electrical current momentarily generates a magnetic field.
- Magnetic field can reach up to about 2T and lasts approx. 100 µs
- Magnetic field penetrates scalp and skull - induces a current in the brain in a direction opposite to the original current in the coil.
- More accurately – "transcranial magnetically induced electrical stimulation"

What is TMS?

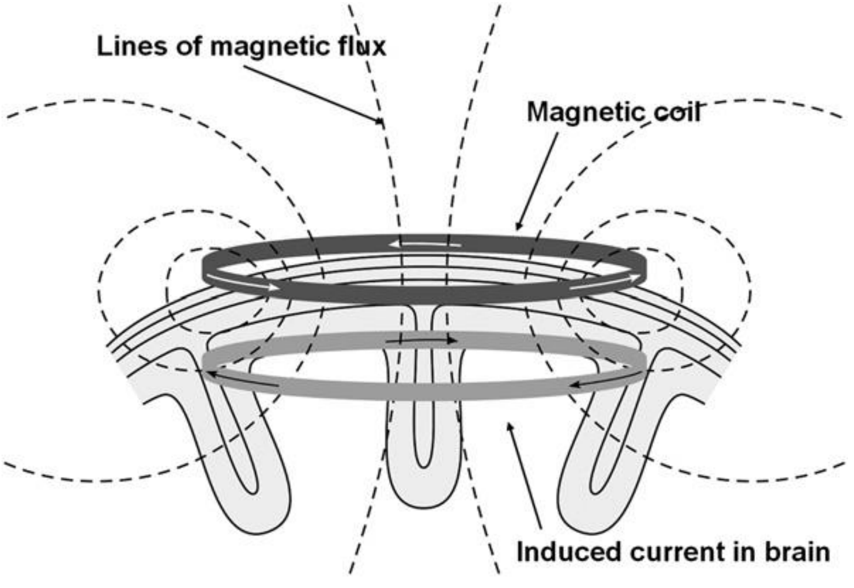
The electric field induced is perpendicular to the magnetic field

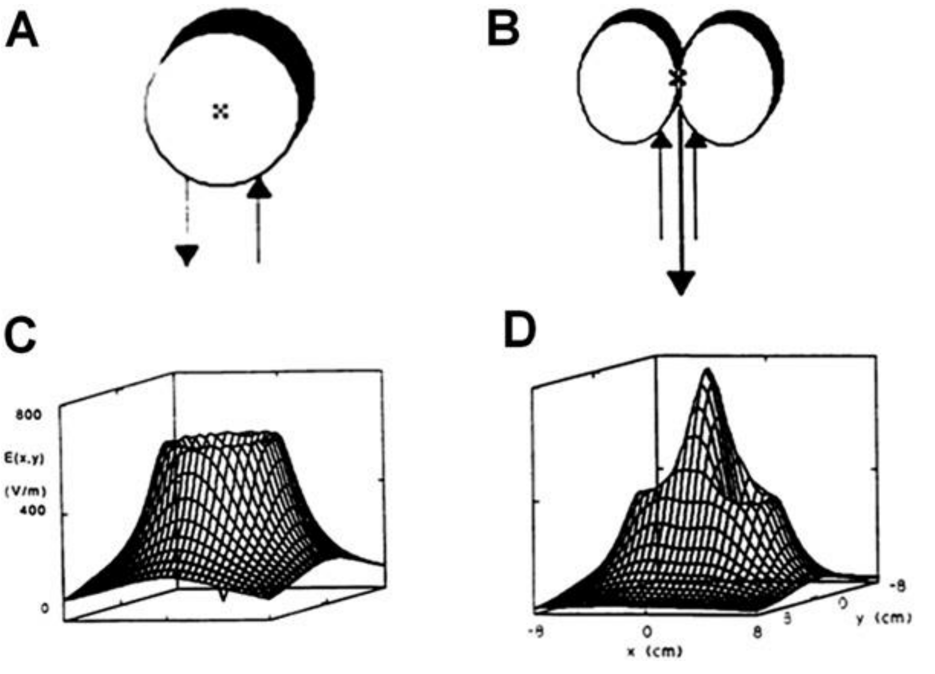




What is TMS?

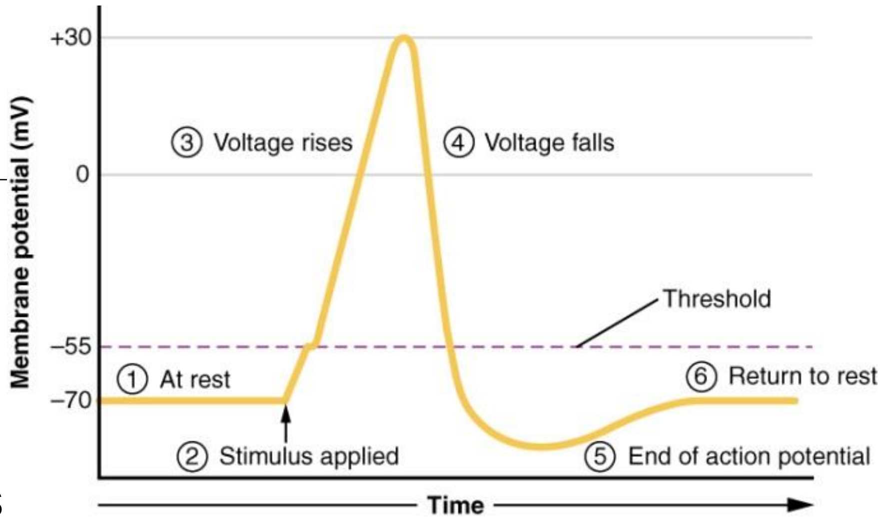
The shape and depth of the electric field is dependent on the coil type, with less focal fields penetrating deeper (Hallet, 2007; Deng, 2013)





NB: field strength can be less than half strength after only ~2 cm! (Barker, 1999)

What is TMS?



Mechanism of action:

- The flow of ions brought about by the induced electric field alters the electric charge stored on both sides of cell membranes.

- When the direction of the current is across the membrane, the induced current depolarizes cell membranes - eliciting action potentials.

- Currents induced by TMS will most likely stimulate nerve fibres that align tangential to the scalp.

- Stimulation occurs at a lower threshold where axons terminate, or bend sharply, in the relatively uniform electric field induced by TMS stimulation.

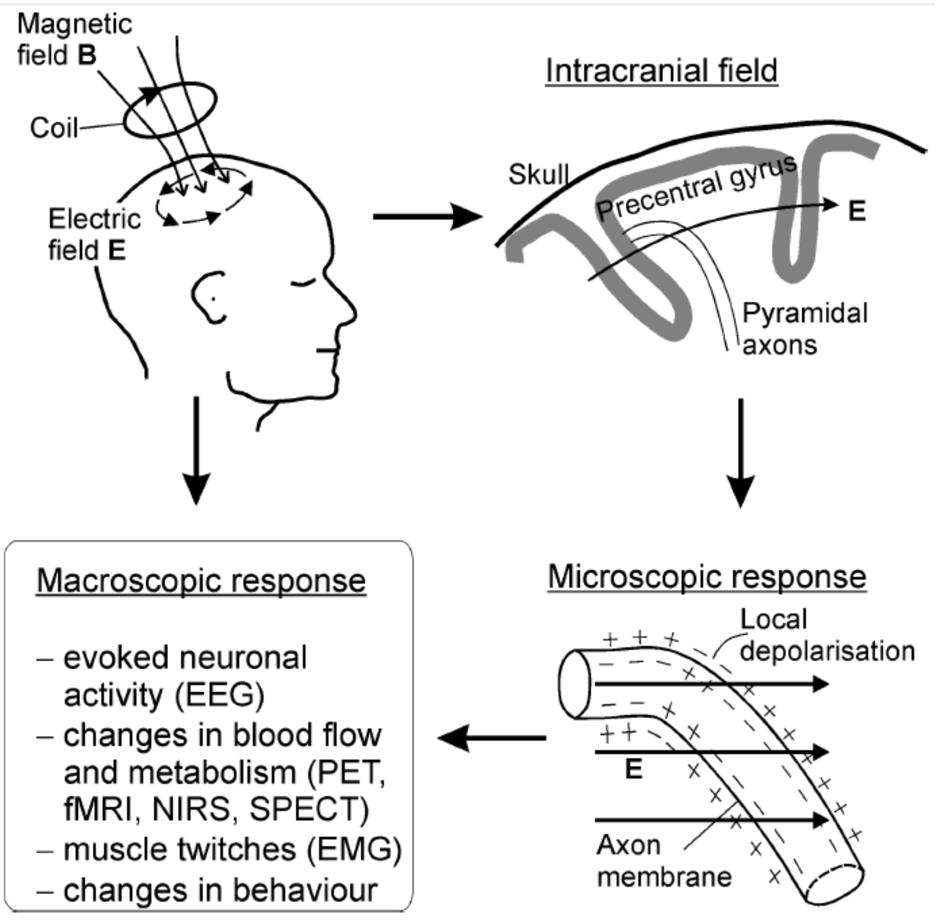
Ilmoniemi et al. (1999)

What is TMS?

Stimulation is dependent on the orientation of axons and dendrites with respect to the magnetic field

In the case of single pulse over M1:

- Cortical neurons at bends, terminals, and branches
- The axons of pyramidal cells projecting from the bank of the precentral gyrus to the spinal cord



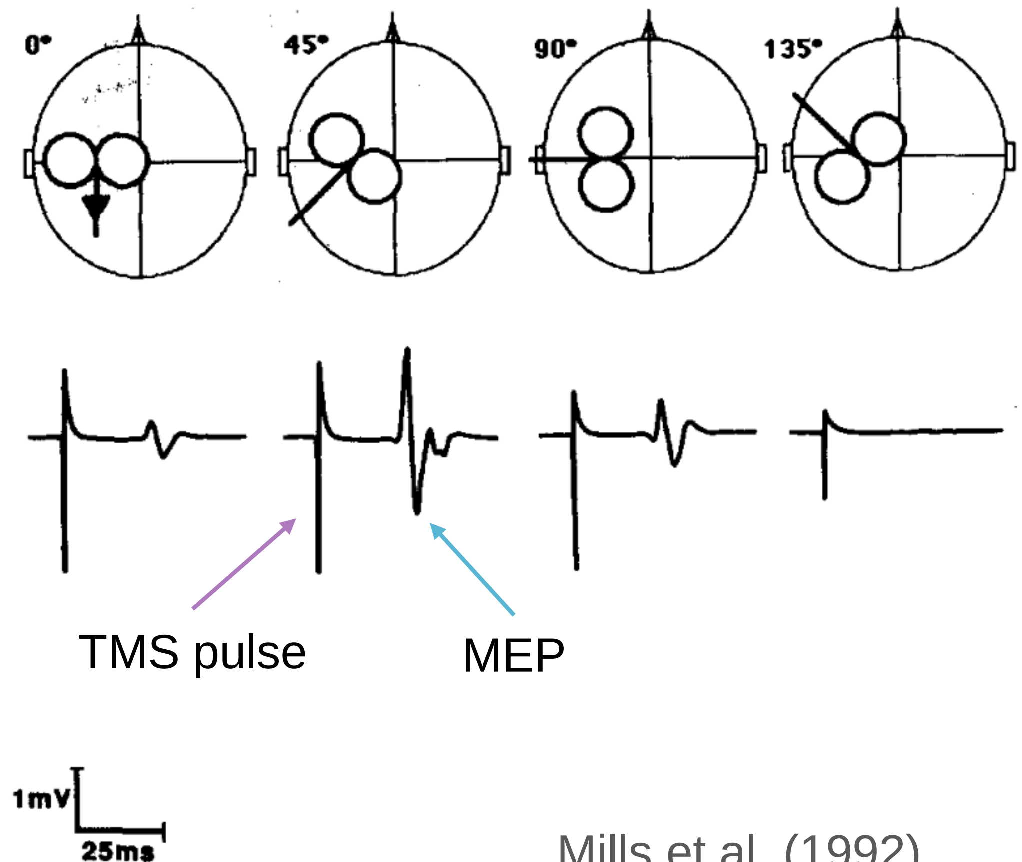
Ilmoniemi et al. (1999)

What is TMS?

Stimulation is dependent on the orientation of axons and dendrites with respect to the magnetic field

In the case of single pulse over M1:

- Because of the usual orientation of the motor cortex, a 45 degree angle is the most likely to produce an MEP
- However, there is some variation across subjects (Balslev, 2007)



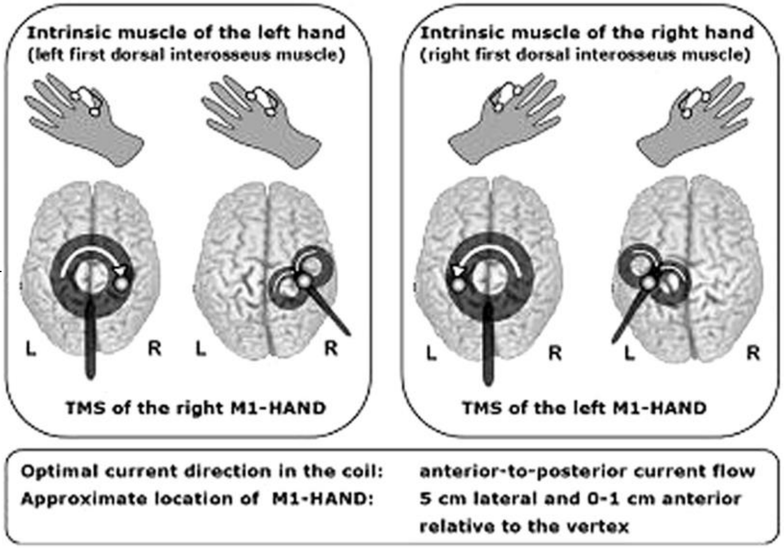
Mills et al. (1992)

Stimulation protocols

Characterised by five main factors:

- Intensity (%)
- Frequency (Hz)
- Duration (ms)
- Inter-train interval (ms)
- Online or offline

Intensity



Resting motor threshold

- Coil orientation must be 45°, coil handle posterior, coil surface orthogonal to skull
- Stimulate at a low level to show the participant what to expect

- Then, Rossini et al. (2015) method, participant hand relaxed
  - Start around 35% maximal stimulator output (MSO)
  - Increase by 5% until you consistently evoke MEPs with peak-to-peak amplitudes of >50 µV
  - Reduce by 1% until you no longer induce 10/20 >50 µV
  - This value plus 1 is the RMT

Groppa et al. (2012)

Stimulation protocols

Single pulse TMS

- Good temporal specificity
- Single pulse effects are not thought to last long beyond the time of stimulation (Pascual-Leone et al., 2002)
- Can for example be used for mapping of motor cortical outputs or studying motor conduction time

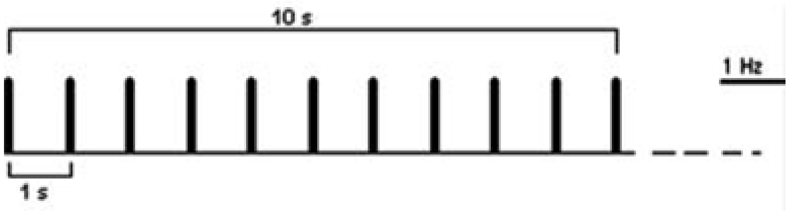
Paired pulse TMS (Inter pulse interval 1-100ms).

- Inter pulse interval 1-100 ms
- Delivered to a single target or two different brain regions using two different coils
- Timing can be varied to selectivity stimulate inhibitory or excitatory neurons (Fitzgerald et al., 2006)
    - Interval of 3 ms - excitatory
    - Interval of 1.5 ms - inhibitory
- Can for example be used to study cortico-cortical interactions

Stimulation protocols

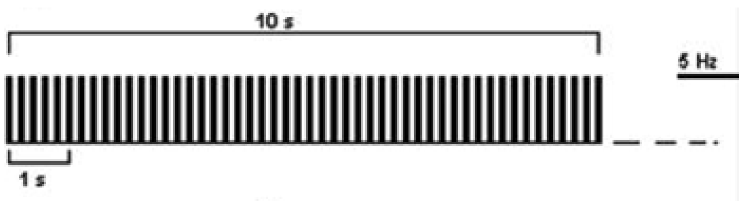
Repetitive TMS (rTMS)

Low frequency rTMS (<1Hz) reduces excitability



10 s of rTMS at 1 Hz

High frequency rTMS (>5Hz) increases excitability (Padberg et al., 2007)

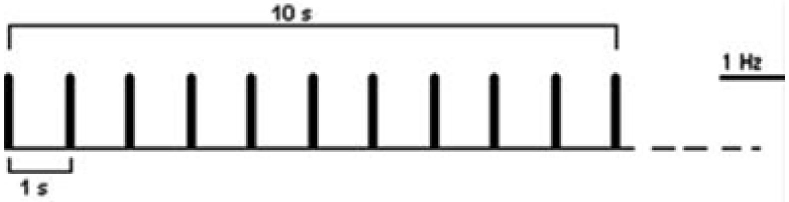


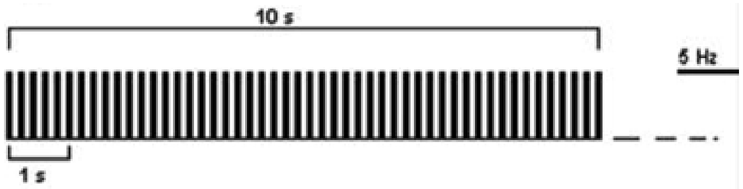
10 s of rTMS at 5Hz

Rossi et al. (2009)

Stimulation protocols

Repetitive TMS (rTMS)





However, in a recent meta analysis (Beynel et al., 2019)

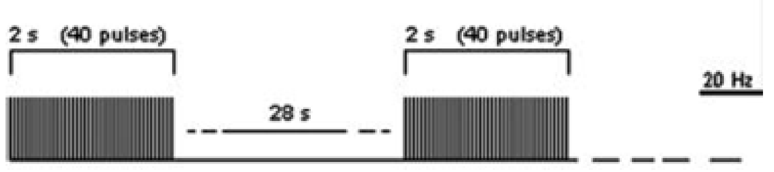
- 10 Hz and 20 Hz disrupted accuracy and slowed down reaction times
- No effects with 1 Hz or 5 Hz

Rossi et al. (2009)

Stimulation protocols

Patterned TMS (rTMS)

Repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation



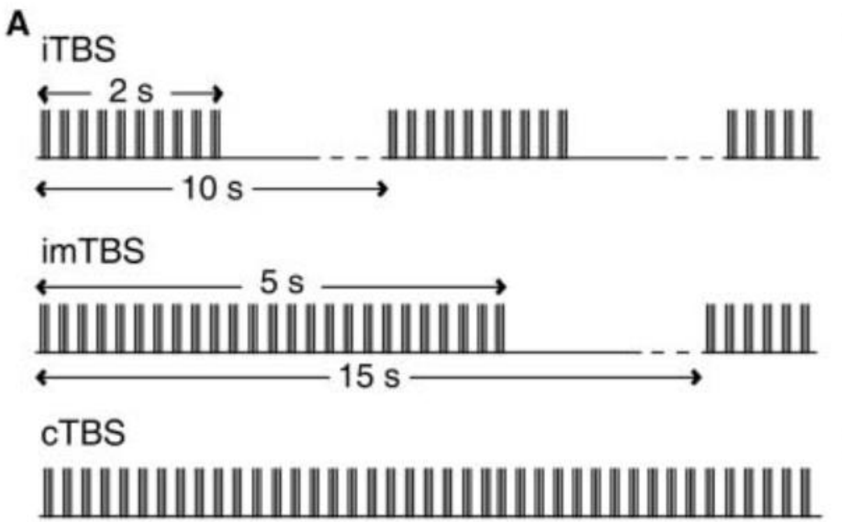
20 Hz application (trains of 2 s interleaved by a pause of 28 s)

Rossi et al. (2009)

Stimulation protocols

Theta burst stimulation (TBS): Based on natural firing pattern of pyramid cells in hippocampus (Kanel & Spencer, 1961) - theta-frequency pattern of neuronal firing

Three pulses of stimulation are given at 50 Hz, repeated every 200 ms (5 Hz)



iTBS: 2s train repeated every 10s for 190s (600 pulses)

imTBS: 5s train repeated every 15s for 110s

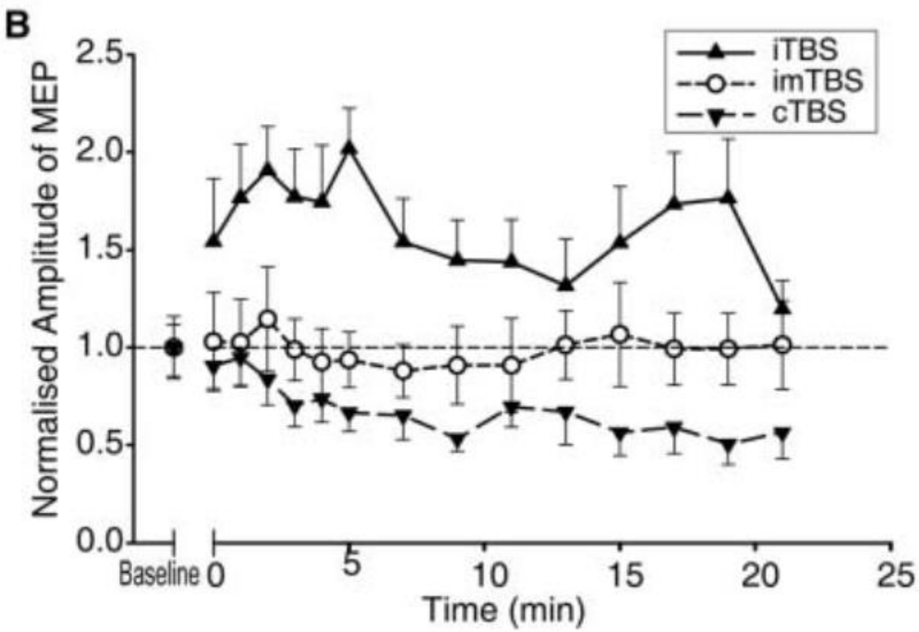
cTBS: 40s uninterrupted train

(Huang et al., 2005)

Stimulation protocols

Continuous theta burst (cTBS):
- Depression of cortical excitability
- Reduction in MEP amplitudes
- Impaired behaviour?

Intermittent theta burst (cTBS):
- Increase in cortical excitability
- Increase in MEP amplitudes
- Facilitated behaviour?

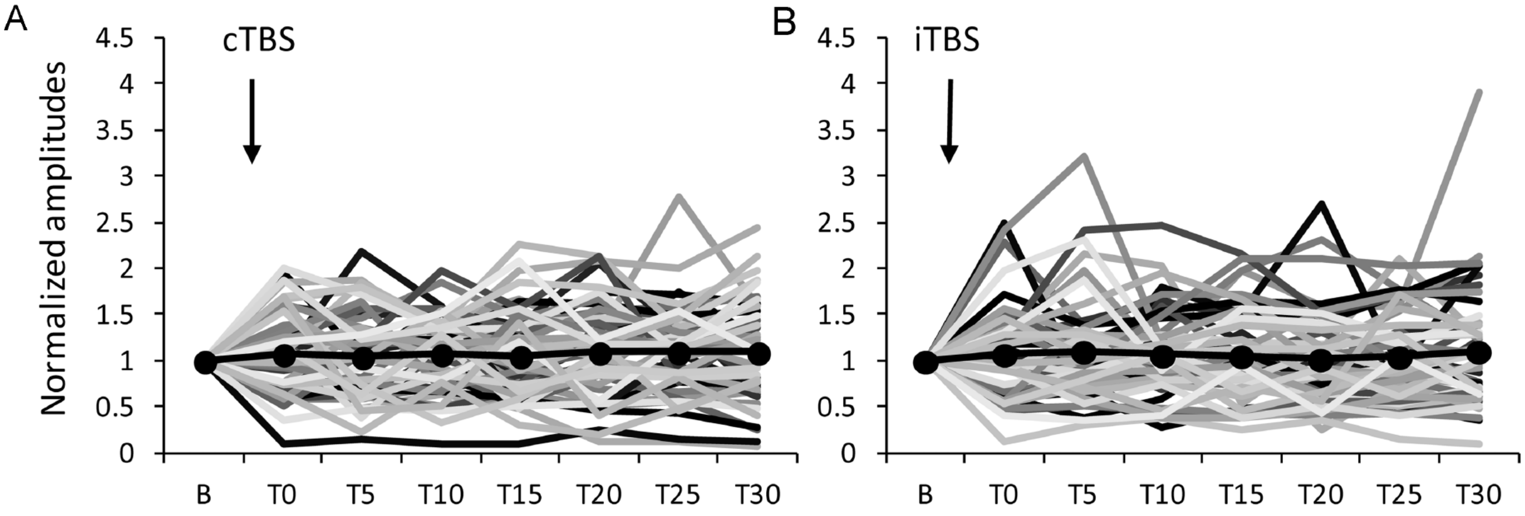


(Huang et al., 2005)

Stimulation protocols

However, cTBS vs. iTBS might not be as clear cut

- Hamada et al. (2013): large interindividual variability (in both directions)



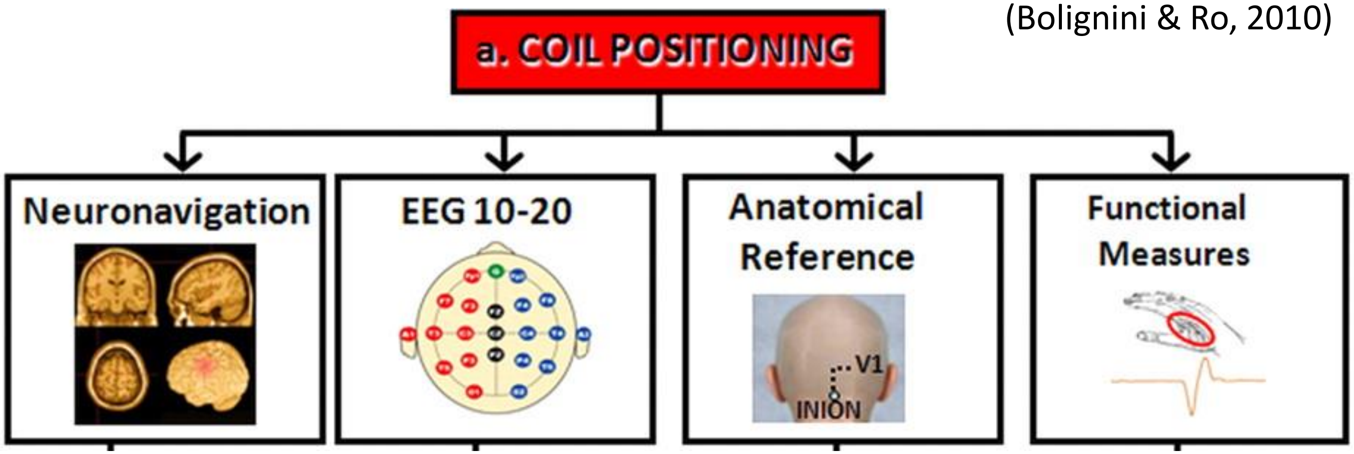
‘Virtual lesion’?

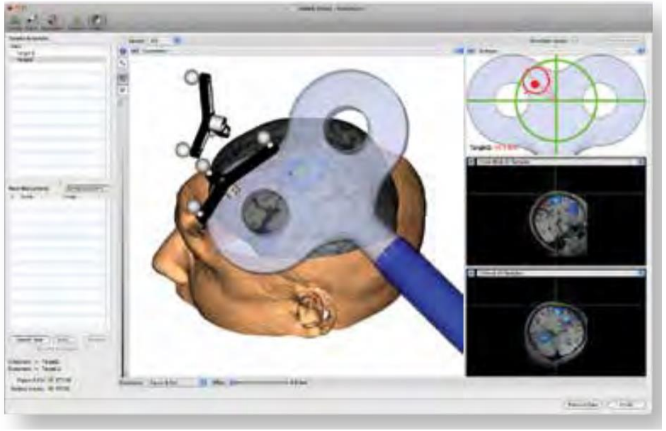
How useful is the term ‘virtual lesion’? (Miniussi et al., 2010)

- TMS often described as inducing a temporary reversible lesion in the stimulated area
- If this is correct, how can TMS sometimes lead to enhanced performance? (Harris et al., 2008b)
- Does TMS suppress neural signals, or does it add random neural noise in the stimulated area?
- Adding noise may enhance performance if the induced activity is synchronised with a weak underlying signal

Where to stimulate?

(Bolignini & Ro, 2010)

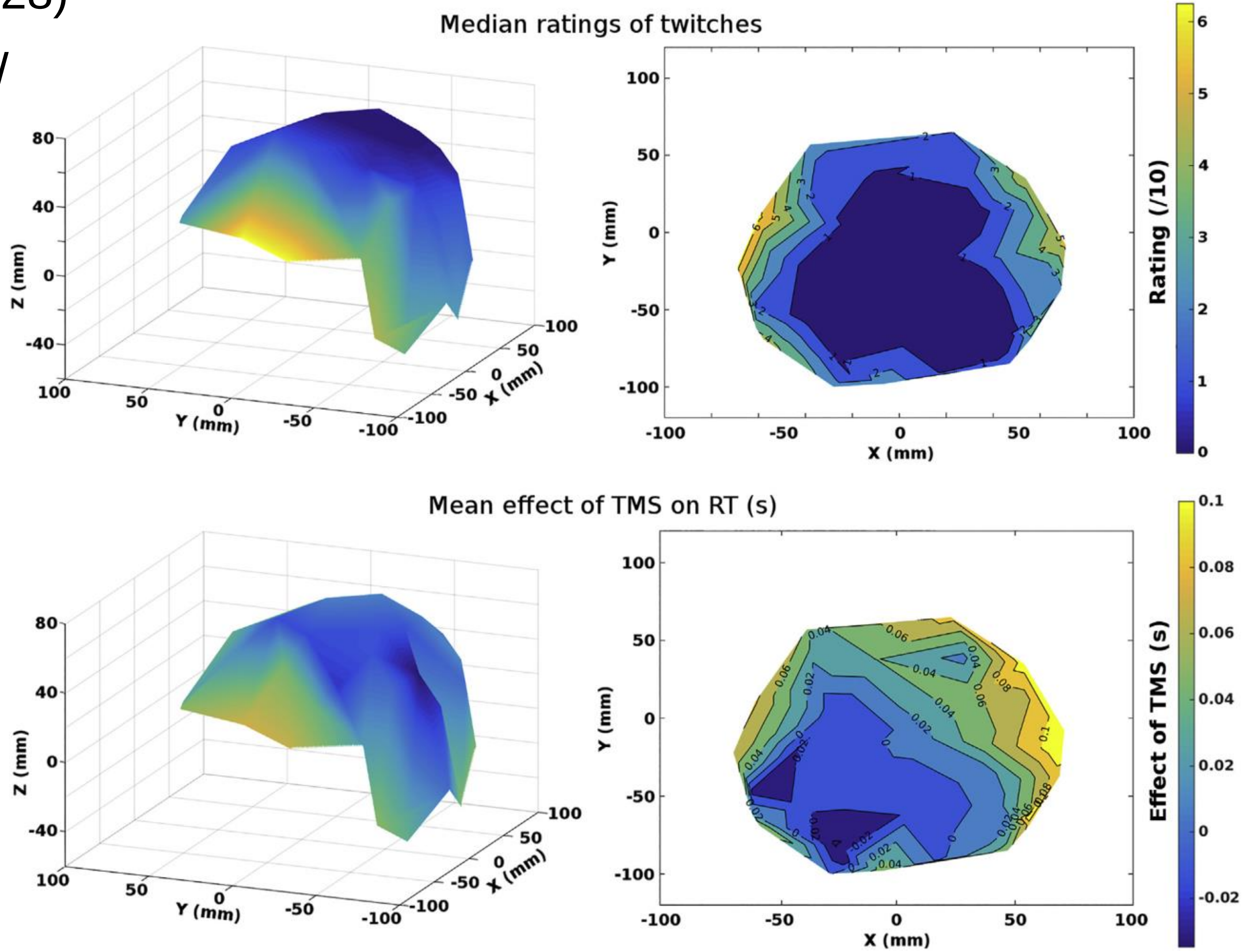




What is the best control?

Meteyard & Holmes (2028)

https://tms-smart.info/



Safety

Common side effects include

- Headache
- Pain or discomfort in neck
- Pain or discomfort in ears
- Temporary hearing loss or impairment
- Toothache
- Paraesthesia

Rare: syncope (fainting)

Very rare: seizure

- Safety guidelines: Rossi et al., (2020)

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 machines at HSB:

Magstim® Rapid2, 2002
Bistim System
Brainsight2 neuronavigation
EEG

Reading

- 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.

Questions?

Break

Part 2

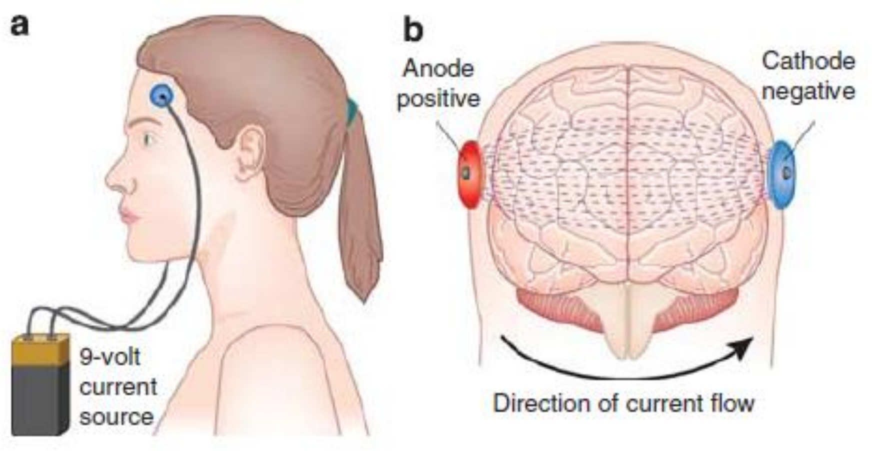
Transcranial electrical stimulation (tES)

tES

A small electrical current (0.5-2 mA) is passed between two electrodes places on the scalp

Stimulation is ~100x weaker than TMS, so does not directly cause action potentials

tES



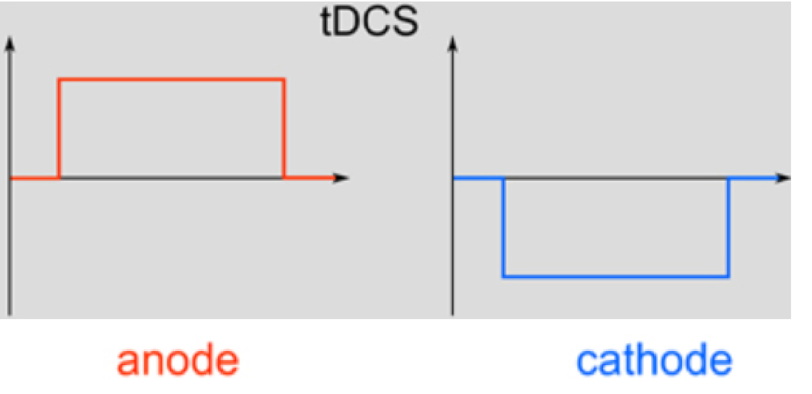
Current is delivered through the anode electrode, propagates through the head and is returned at the cathode

This modulates cortical excitability, with increased excitability at the anodal electrode, and decreased at the cathodal electrode

N.B. a large amount of the signal will take the path of least resistance along the scalp!

tES

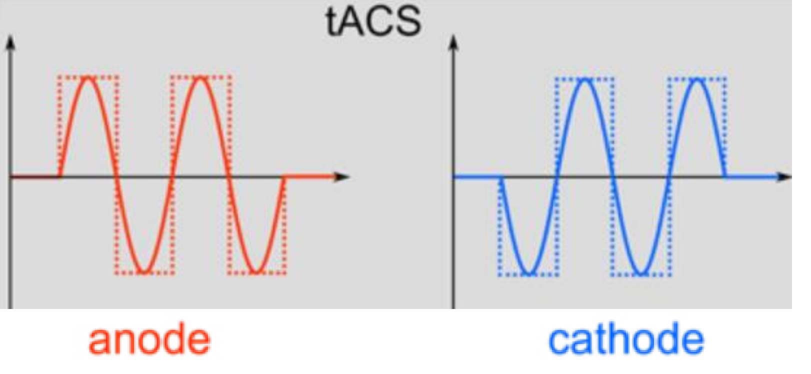
Direct current stimulation (tDCS) - Application of a constant current (Nitsche and Paulus,2000)



tES

Direct current stimulation (tDCS) - Application of a constant current (Nitsche and Paulus, 2000)

Alternating current stimulation (tACS) – Current is not constant (DC) but alternates between the anode and the cathode (switching polarity) with a sinusoidal waveform. Uses waveform at a specific frequency (e.g. 12Hz) (Antal et al.,2008). Alternating fields can increase or decrease power of oscillatory rhythms in the brain in a frequency-dependent manner - synchronizing or desynchronizing neuronal networks.



tES

Direct current stimulation (tDCS) - Application of a constant current (Nitsche and Paulus,2000)

Alternating current stimulation (tACS) – Current is not constant (DC) but alternates between the anode and the cathode (switching polarity) with a sinusoidal waveform. Uses waveform at a specific frequency (e.g. 12Hz) (Antaletal.,2008). Alternating fields can increase or decrease power of oscillatory rhythms in the brain in a frequency-dependent manner - synchronizing or desynchronizing neuronal networks.

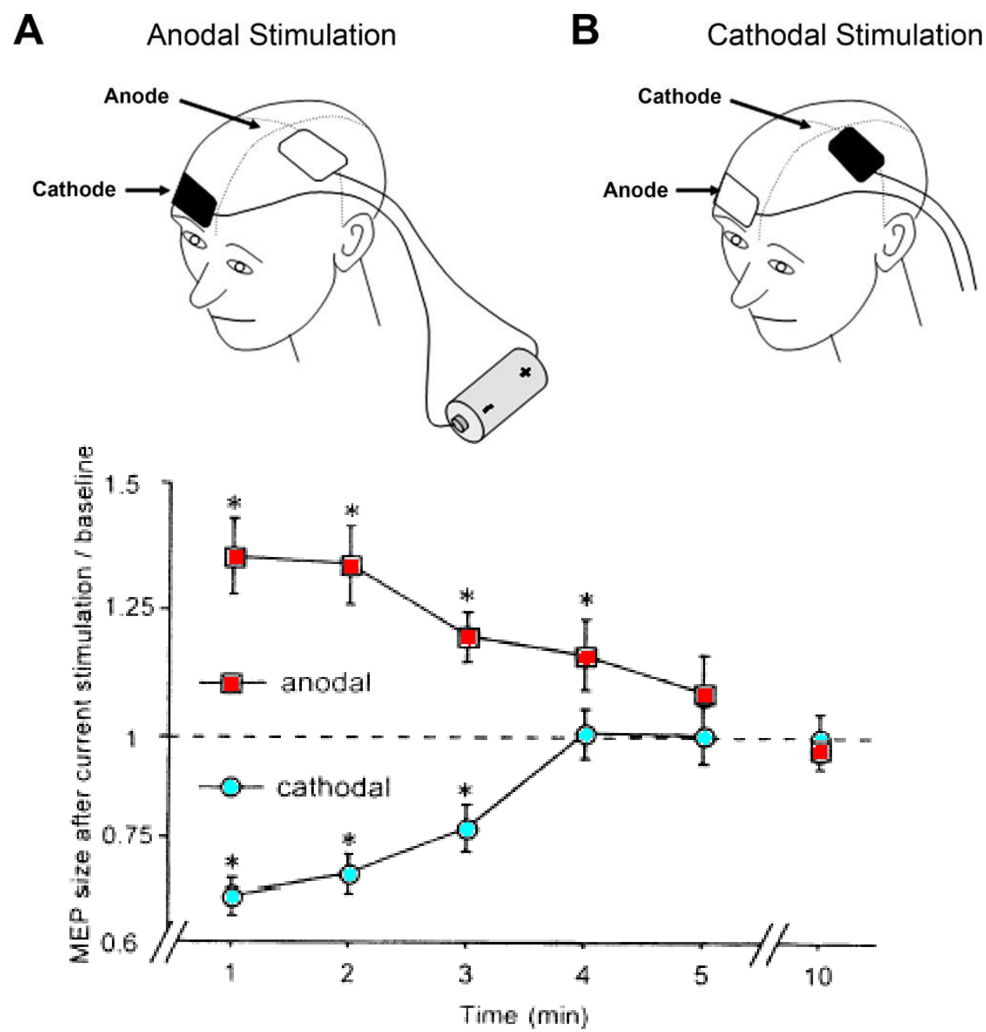
Random noise stimulation (tRNS) - Several frequencies applied within a normally distributed frequency spectrum (0.1 to 100Hz low-frequency; 101 to 640Hz high-frequency) (Terney et al.,2008).

tDCS

tDCS induces excitability changes in motor cortex (Nitsche & Paulus, 2000)

Scalp tDCS stimulation (for 5 min at 1 mA).

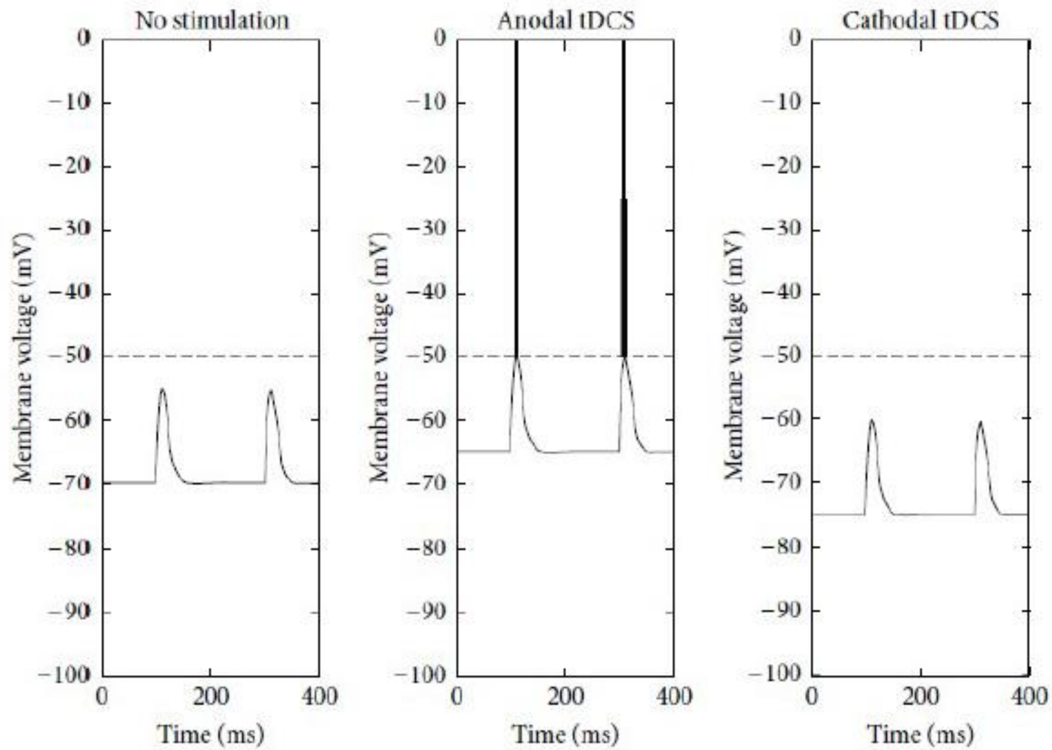
“After-effects" last up to 90 minutes after stimulation (depending on intensity and duration of stimulation)



tDCS

Current flow (inward) under anodal electrode induces a *lack* of positive ions (shifts membrane potential towards depolarization). **Increases excitability.**

Current flow (outward) under the cathodal electrode induces an *excess* of positive ions (shifts membrane potential towards hyperpolarization). **Decreases excitability.**



Antal and Herrmann, 2016

tDCS

For example, anodal tDCS to the right posterior parietal cortex increased performance on a visual working memory (change detection) task (Tseng et al., 2012)

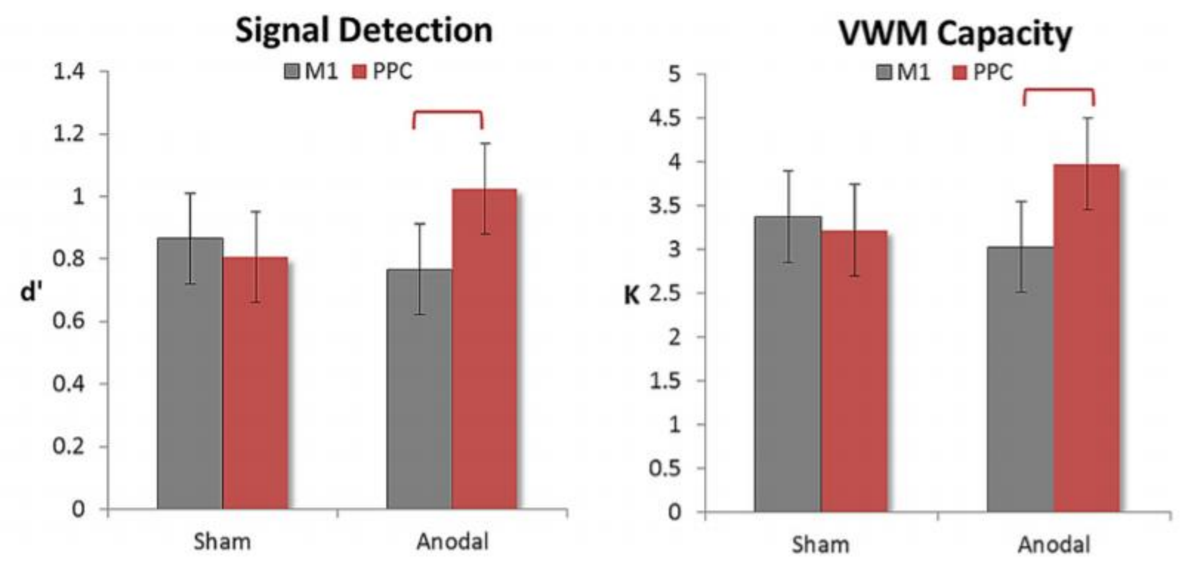
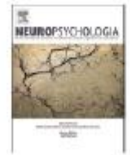


Figure 1. Top, Trial procedure. On half of the trials, one square would change color. Bottom, tDCS-induced improvements in signal detection (*d'*) and Cowan's *K* in Experiment 1. Change detection performance was evaluated with signal detection analysis and Cowan's *K*. Analyses showed significant increase in *d'* and *K* in the anodal rPPC tDCS condition. The same tDCS procedure was applied over M1 to rule out any nonspecific effects of tDCS. Error bars represent 95% confidence intervals.

Replicability?

Contents lists available at ScienceDirect
Neuropsychologia
journal homepage: www.elsevier.com/locate/neuropsychologia



Reviews and perspectives

Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review

Jared Cooney Horvath*, Jason D. Forte, Olivia Carter
University of Melbourne, School of Psychological Sciences, Melbourne, VIC, Australia

Contents lists available at ScienceDirect
Brain Stimulation
journal homepage: www.brainstimjrnl.com

Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS)

CrossMark

Jared Cooney Horvath*, Jason D. Forte, Olivia Carter
University of Melbourne, Melbourne School of Psychological Sciences, Redmond Barry Building, Melbourne, VIC 3010, Australia

NEUROSCIENCE

Cadaver study challenges brain stimulation methods

Unusual test of transcranial stimulation shows that little electrical current penetrates the skull

Underwood, Science 2016

Replicability?

ELSEVIER

Cortex

Volume 123, February 2020, Pages 141-151

Review

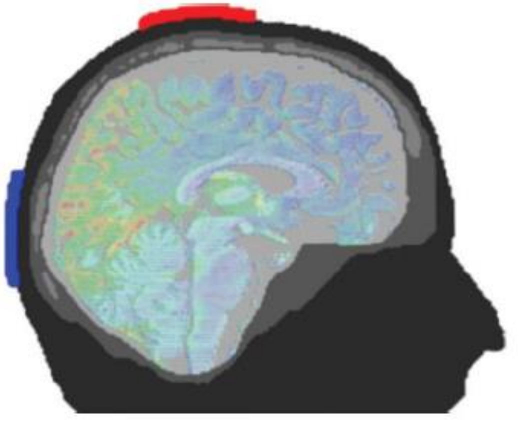
Modulating brain activity and behaviour with tDCS: Rumours of its death have been greatly exaggerated

Hannah L. Filmer [a], Jason B. Mattingley [a, b, c], Paul E. Dux [a]

Challenges

1. Effects are state-, amplitude- and duration-dependent
- "Anodal stimulation = excitatory" and "cathodal stimulation = inhibitory" too simplistic
- Only motor system well investigated

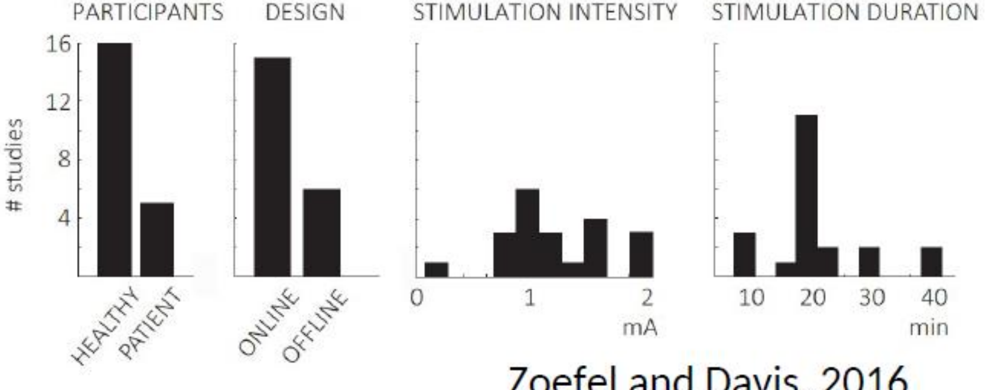
2. Current flow is more complicated than often assumed
- Effects of stimulation protocol, electrode position, electrode size, experimental task
- Position of "reference" electrode is critical
- Optimal stimulation parameters often unknown



Antal and Herrmann, 2016

3. Studies often not comparable
- Use of different stimulation protocols and/or tasks

4. Current flow relatively unspecific, stimulation of regions other than target cannot be excluded
- Ring electrodes offer improved focality



Zoefel and Davis, 2016

5. Effects are often small

Safety

Seizure induction

tDCS does not cause epileptic seizures or reduce seizure threshold in animals (Liebetanz et al., 2006). No reports of seizures using tES in humans.

Skin burning

Slight itching or heating under the electrode - (tRNS and tACS are less easily detectable). Follow recommended guidelines.

Other symptoms

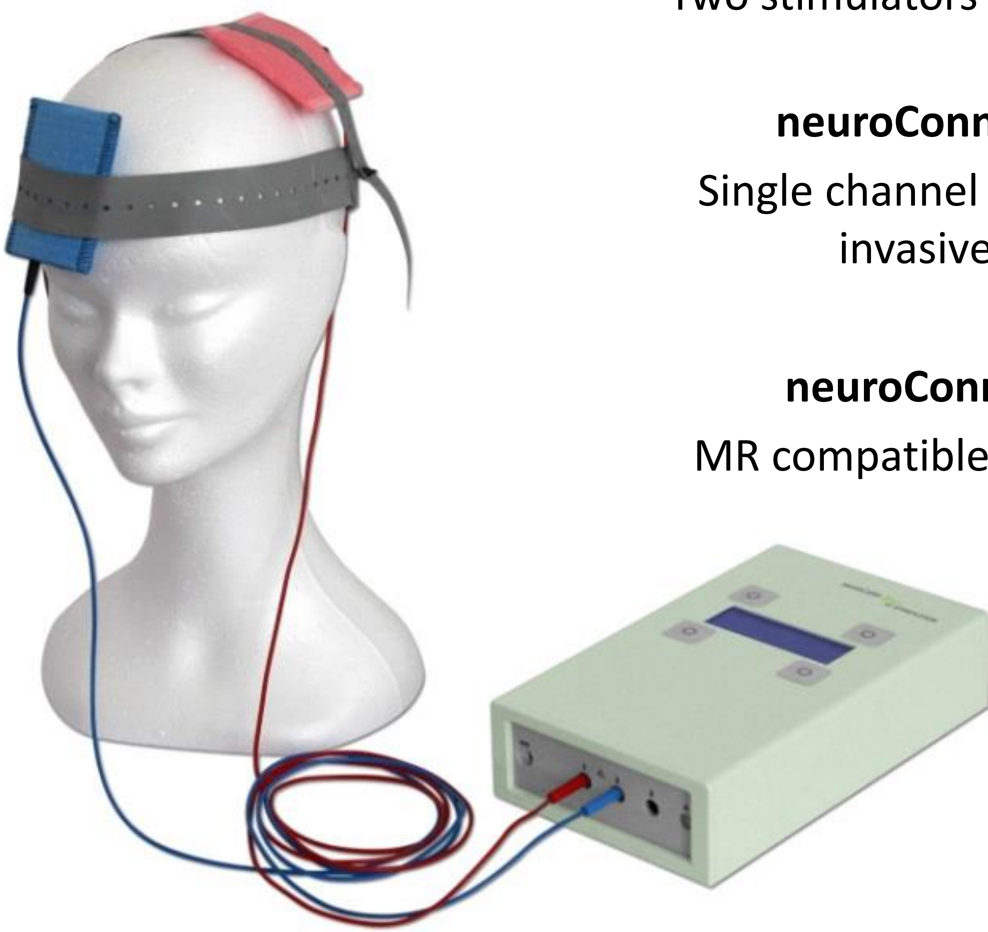
Headache, fatigue, and nausea only in very small minority of cases (Poreisz et al., 2007).

Cathodal or (reference electrode) can be placed on an extracephalic location (e.g. shoulder). Never place both electrodes on any other part of the body apart from the head - **currents passing across the heart can be dangerous!**

Sham stimulation

Not easily detectable, doubled-blinded.

CBU equiptment



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.

TMS vs. tES

- **tES** – less expensive, more portable, easier to design blind sham conditions, generally well tolerated

- **TMS** – greater effect on neural tissue, higher temporal and spatial resolution

Reading

- 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

Part 3

Combined TMS-fMRI

TMS-fMRI

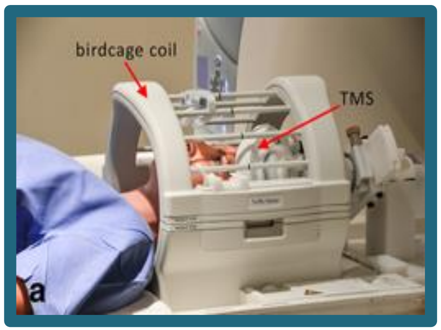
TMS	fMRI
Did stimulation affect interconnected networks?	Are activations necessary for specific functions?

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

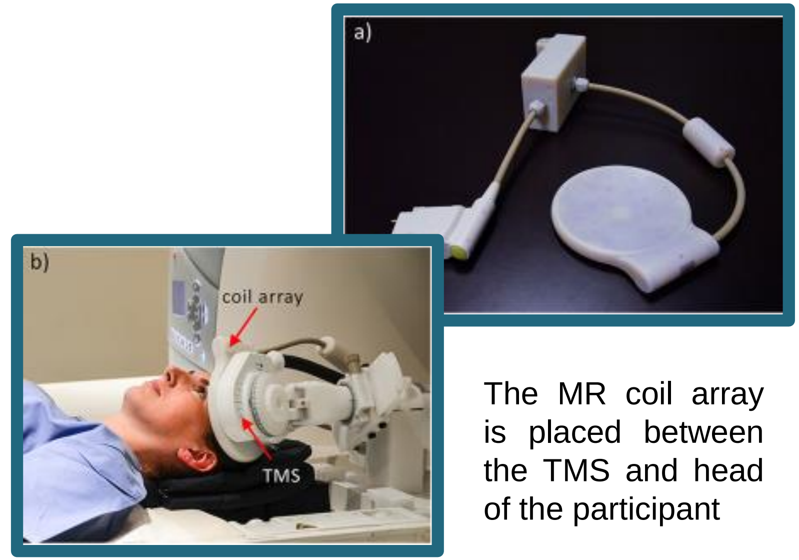
  - site of stimulation
  - entire brain

We can then relate these effects to participants behaviour

Surface coils



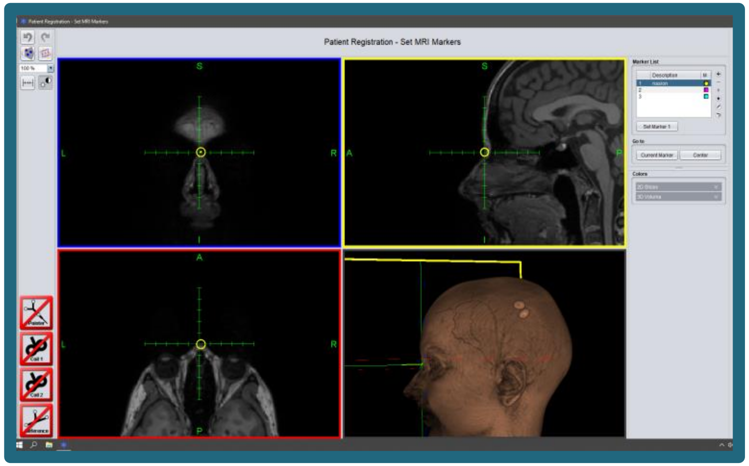
Restricted coil placement



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

- Avoids signal loss at site of stimulation
- Allows flexibility in coil placement
- Increases participant comfort

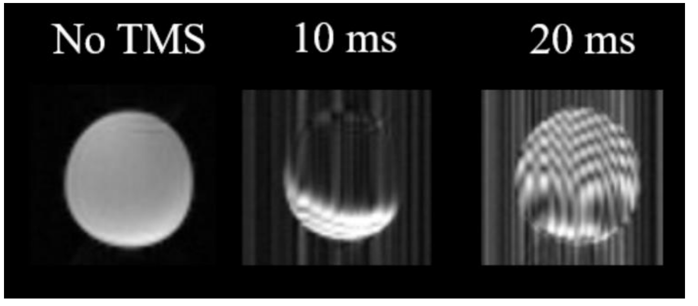
Neuronavigation



Neuronagivation

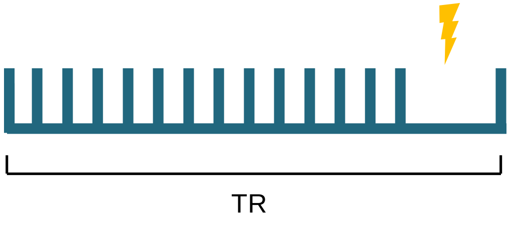
Protocol

- Remove the affected slices (interpolation)

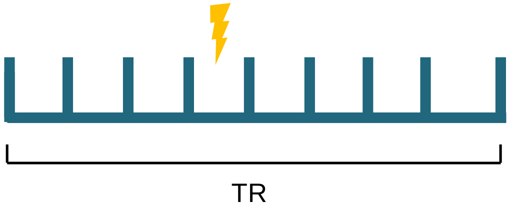


- Stimulate during gaps in acquisition

-Pulses delivered in delay at the end of TR

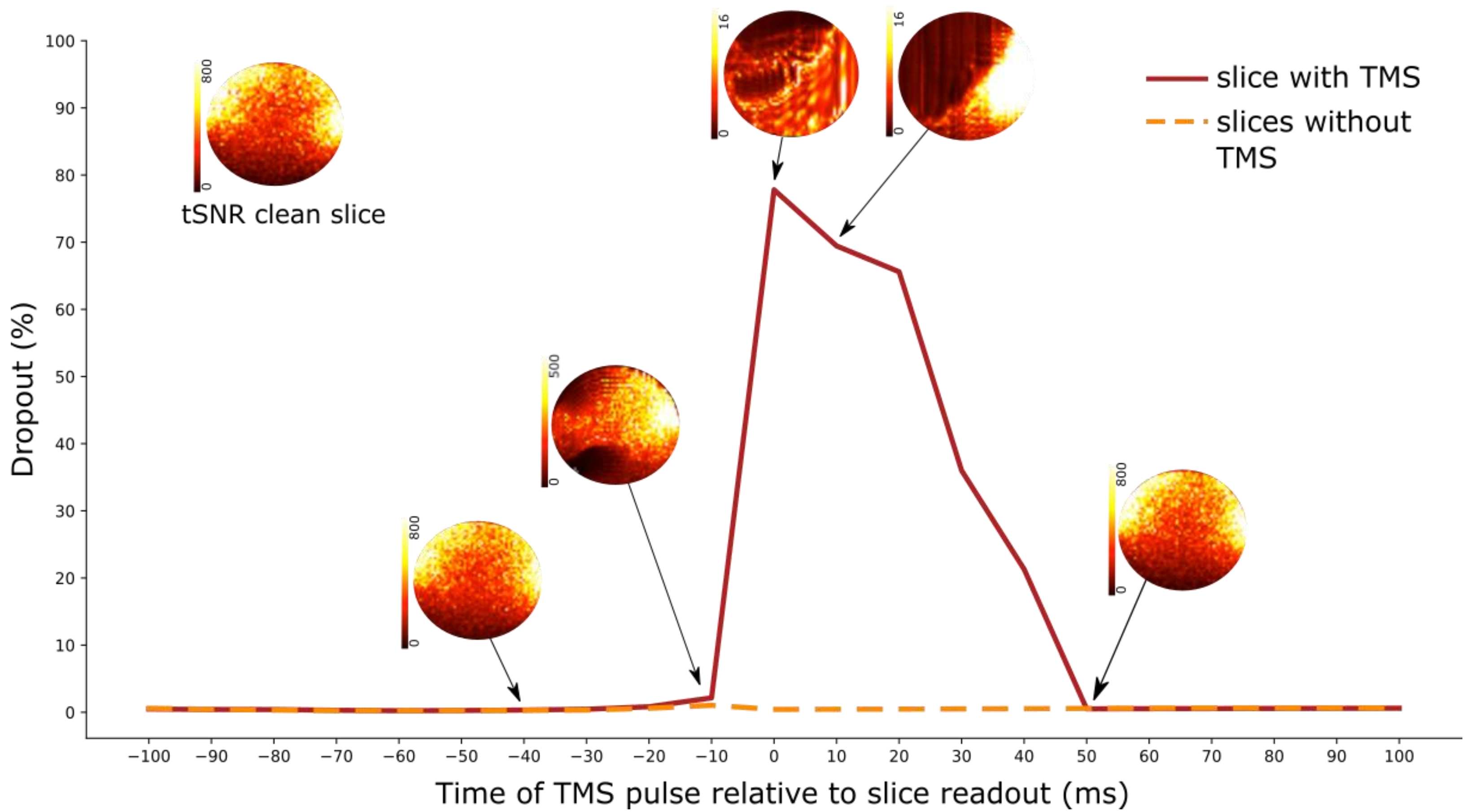


-Pulses delivered in silent gaps in between slices



Interslice TMS-fMRI

Scrivener, Jackson, Correia, Mada & Woolgar



The future of TMS?

- https://www.youtube.com/watch?v=qJ3OvleTV4I&ab_channel=BrainboxLtd

Questions?