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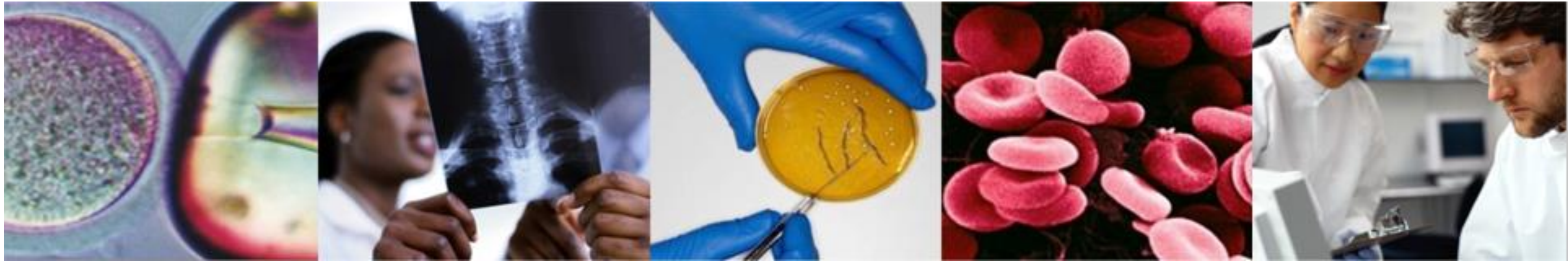

Brain Stimulation

Olaf Hauk

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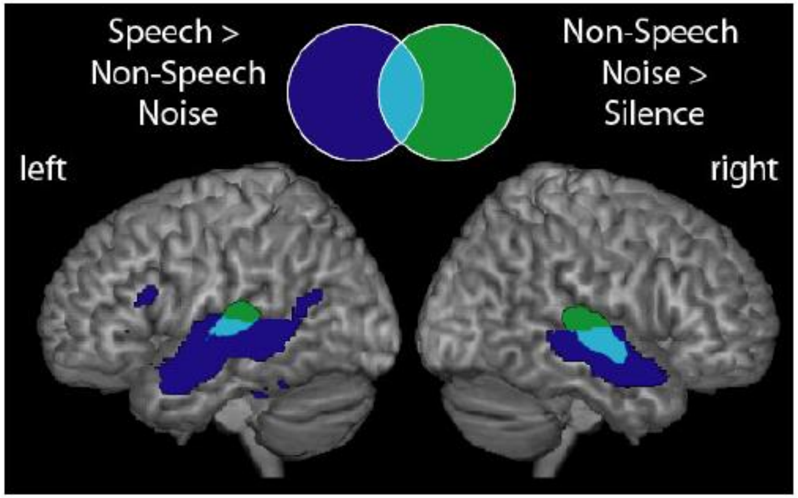
With big thanks to Benedikt Zoefel, Jade Jackson and Michael Ewbank!

Introduction to Neuroimaging Methods, 7.2.2020

Motivation

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



Davis and Johnsrude, 2003

Neural activity in certain brain regions is stronger for speech than for noise

Cannot provide evidence that neural activity is necessary or causal

WE NEED TO MANIPULATE NEURAL ACTIVITY AS AN INDEPENDENT VARIABLE

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Why use brain stimulation?

- fMRI
  - Correlational

- Lesion Studies
  - Single or few case studies
  - Might be more than a single lesion – extend beyond area under study
  - The damaged region cannot be reinstated to obtain control measures
  - Comparisons must be made to healthy controls; no internal double dissociations
  - Given brain plasticity, connections might be modified following lesions

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Reading

Useful papers

Walsh V, Cowey A. (2000) *Transcranial magnetic stimulation and cognitive neuroscience*. Nature Reviews Neuroscience 1 (1): 73-80.

Wagner T, Valero-Cabre A, Pascual-Leone A. (2007) *Noninvasive human brain stimulation*. Annu Rev Biomed Eng 9:527–565.

Bolignini N, Ro, T. (2011) *Transcranial magnetic stimulation: disrupting neural activity to alter and assess brain function.*

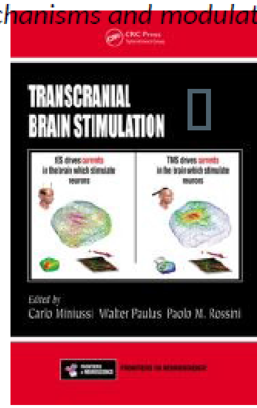
J Neuroscience, 30(29): 9647-50

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N et al. (2008) *Transcranial direct current stimulation: State of the art 2008*. Brain Stimul 1: 206-223

Stagg CJ, Nitsche MA. (2011) *Physiological basis of transcranial direct current stimulation*. Neuroscientist 17, (1): 37–53.

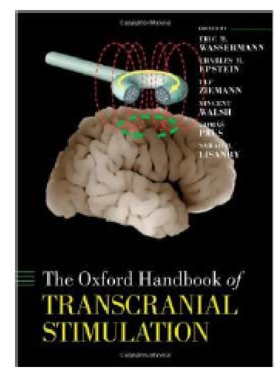
Herrmann CS, Rach S, Neuling T, Struber D (2013) *Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes*. Front Hum Neurosci 7: 279.

Books



Transcranial Brain Stimulation
(Edited by Miniussi, Paulus, Rossini).

Oxford Handbook of Transcranial Stimulation
(Edited by Wassermann, Epstein, Ziemann, Walsh & Lisanby).



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Part I: Transcranial Magnetic Stimulation (TMS)

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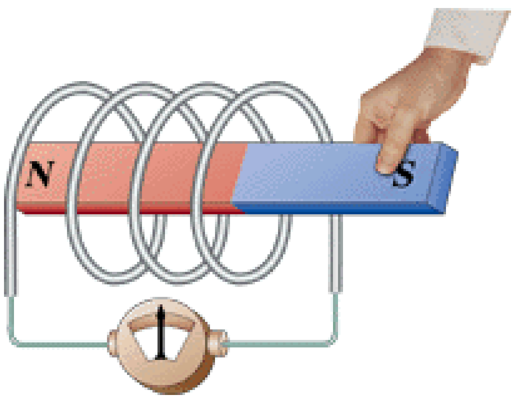
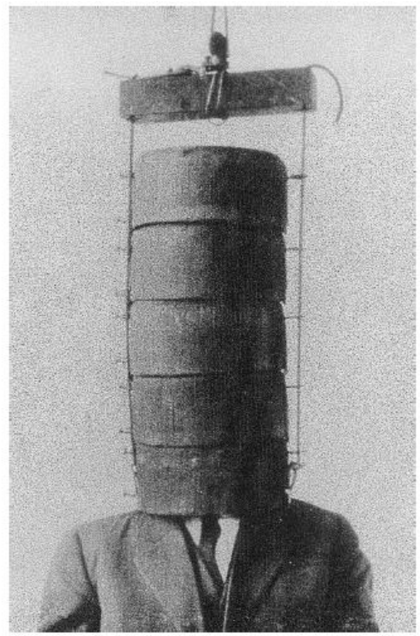
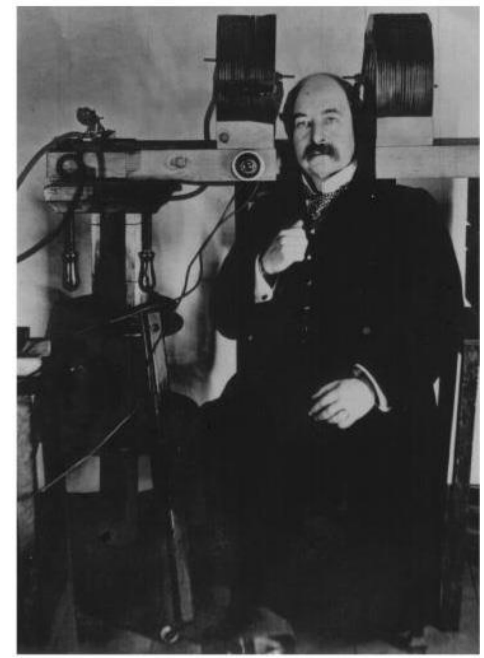
History of TMS

Electromagnetic Induction
When an electric current is turned on or off in a (primary) coil of wire, another electric current is induced in a nearby (secondary) coil by the fluctuating magnetic field around the primary coil (Faraday, 1831, 1839).





Magnusun & Stevens (1911; 1914)



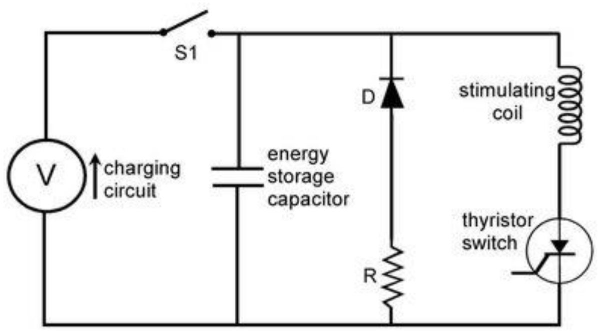
Thompson, 1910

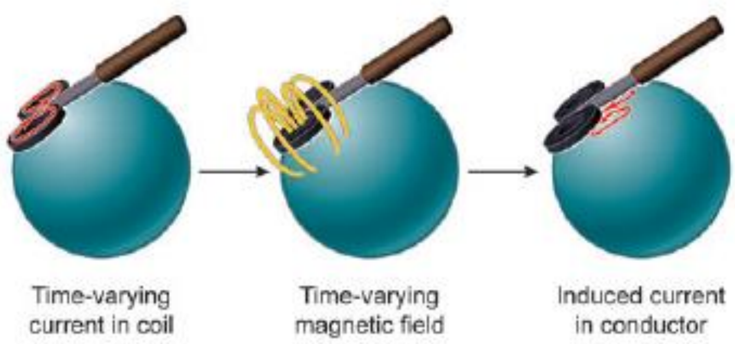
Stimulation with magnetic fields induces phosphenes (Thompson, 1910).

TMS of motor cortex. Barker AT, Jalinous R & Freeston I. 1985. *Non-invasive magnetic stimulation of the human motor cortex*. Lancet 1:1106-1107.

What is TMS?

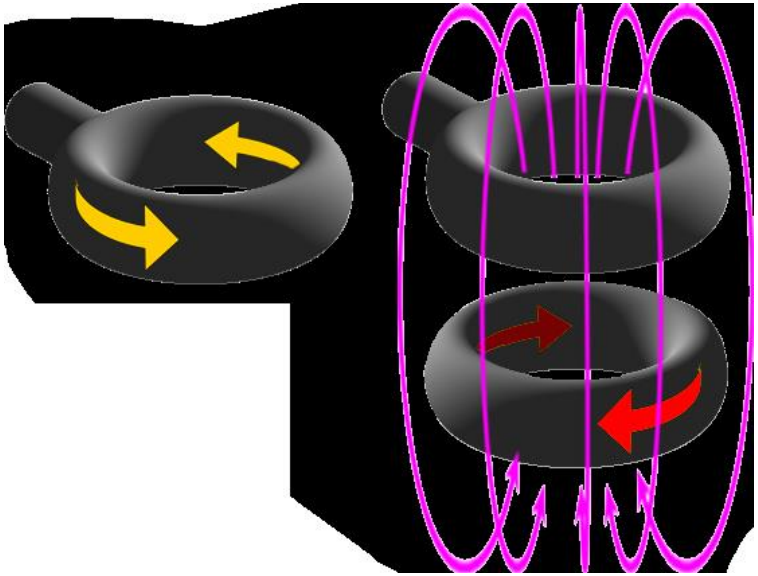
TMS circuit

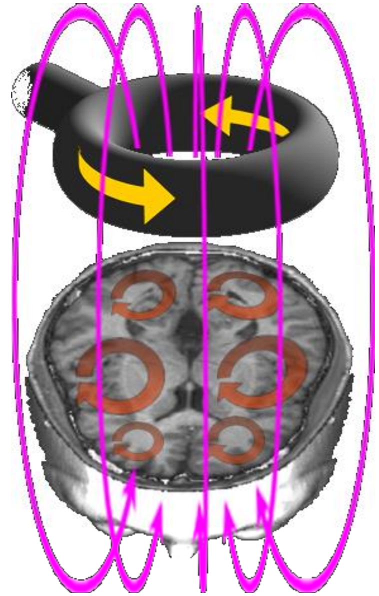




- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in a coil of wire.
- Electrical current momentarily generates a magnetic field.
- Magnetic field can reach up to about 2T and lasts approx. 100ms
- Magnetic field penetrates scalp and skull - induces a current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

How does TMS work?





The electric field is induced perpendicularly to the magnetic field - causing ions to flow in the brain

Coil Types

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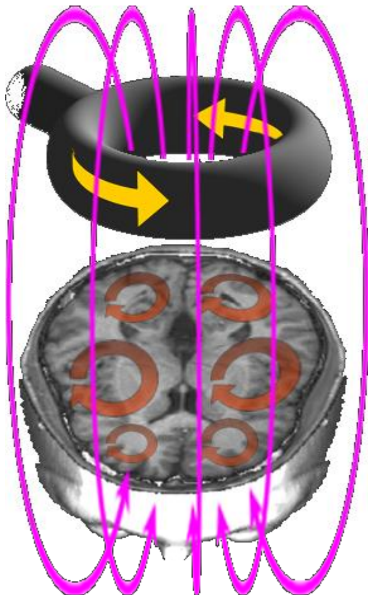


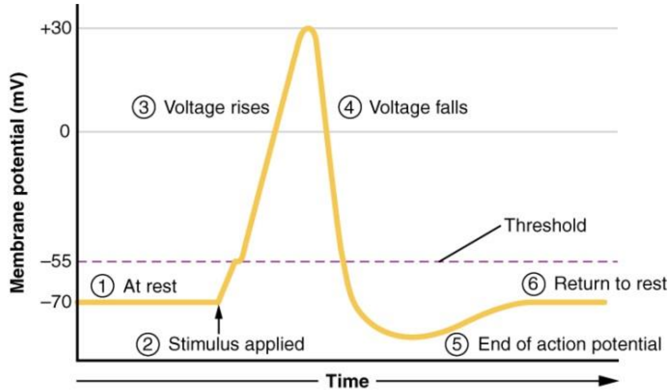
“Figure-of-eight” coils produce a more focal magnetic field due to superposition of fields from two coils

How does TMS work?

Membrane potential - difference between the electrical charge on the interior and exterior of a biological cell.

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.

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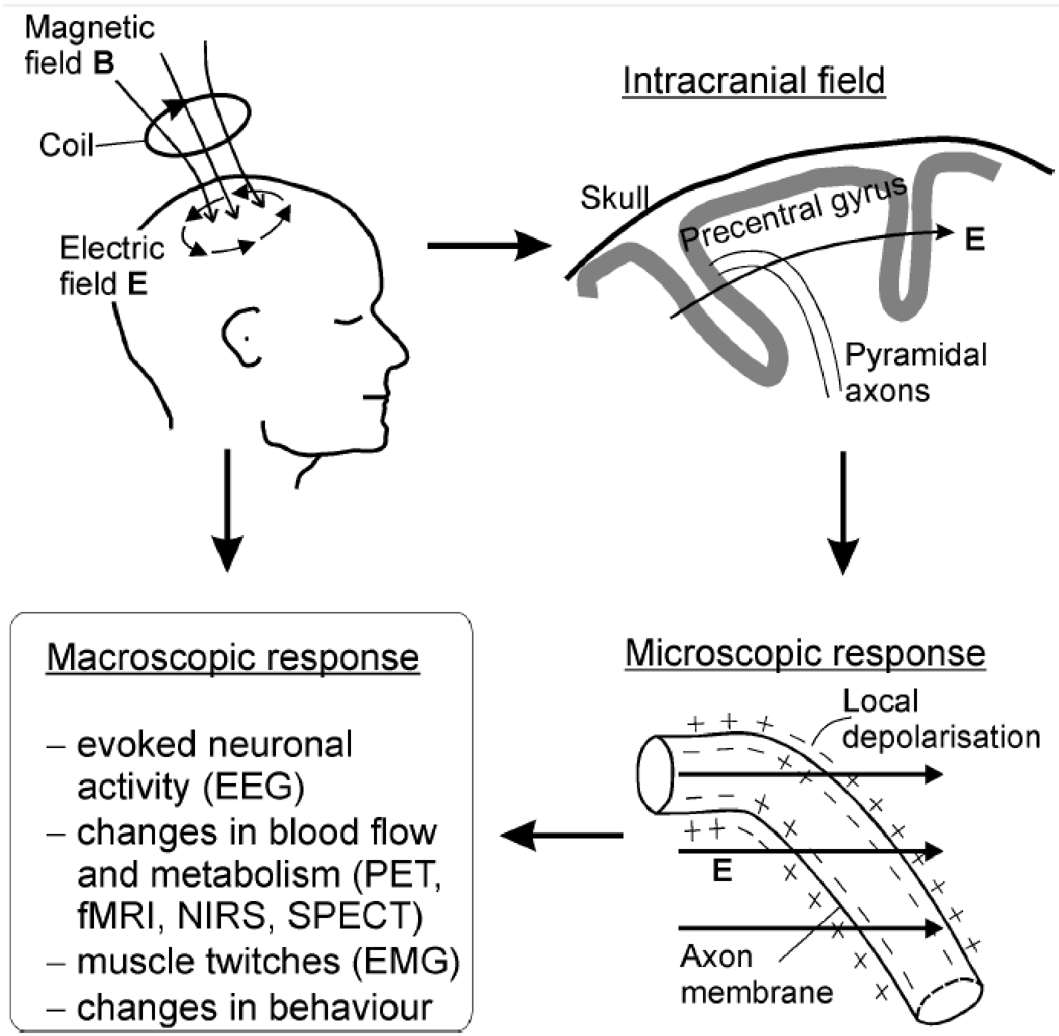
How does TMS work?



Ruohonen, Dissertation, Espoo 1998

How does TMS work?

TMS produces a transient period of brain disruption (“virtual lesion”), but can also facilitate processing in a brain area.

Induces disorder into an ordered system (or the other way round)?

If a group of neurons are involved in a given task, introducing a TMS pulse is unlikely to selectively stimulate the same coordinated pattern of neural activity as performance of that task (Walsh & Cowey 2000).

TMS induces activity that is random with respect to the goal-state of the area stimulated.

Disrupts task performance.

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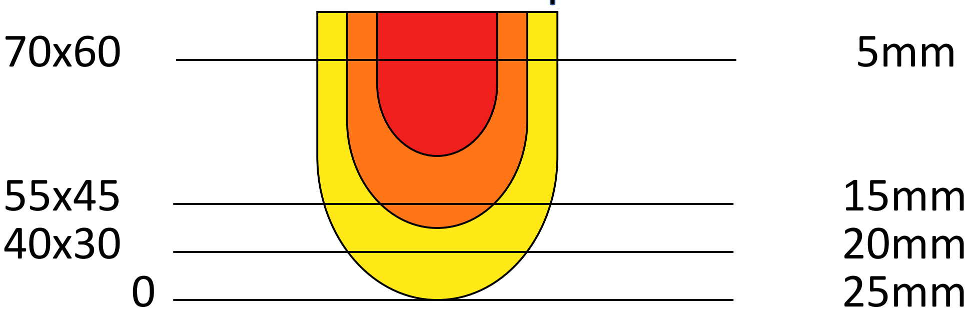
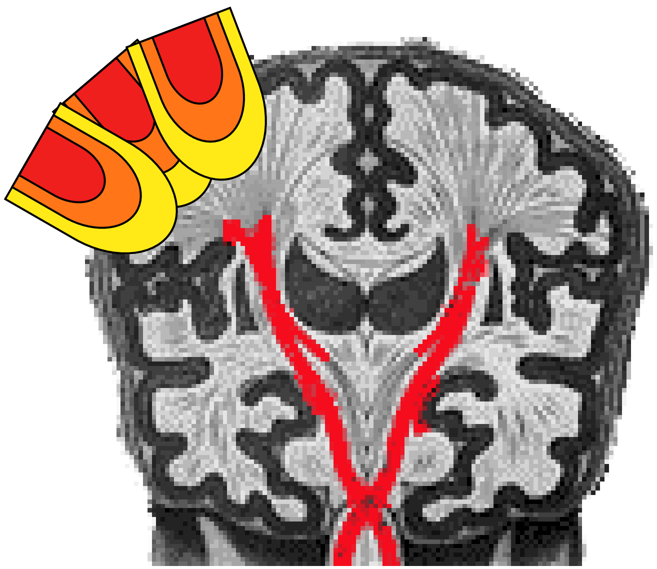
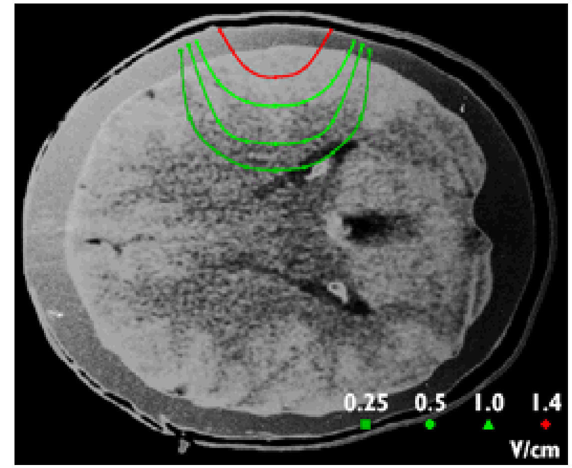
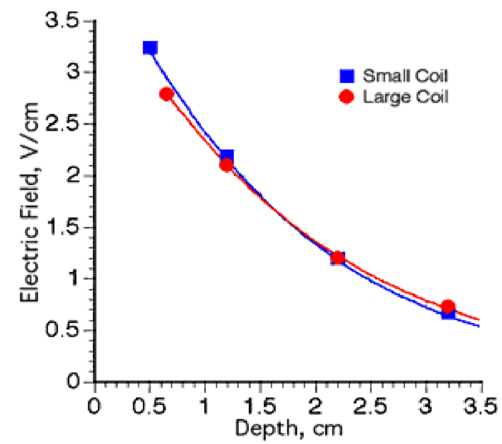
Stimulation depth









(Barker, 1999)

A depth-focality trade off - the ability to directly stimulate deeper brain structures comes at the expense of wider electrical field spread (Deng et al., 2013).

The locus of activation in the brain is approximately where the induced electrical field is maximal.

No greater than 2.5cm from the surface of the skull (Barker, 1999) . 50 TMS configurations - Ranging between 1.0–3.5 cm and 0.9–3.4 cm (Deng et al., 2013).

TMS 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

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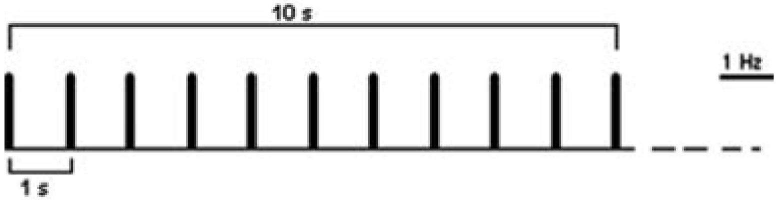
TMS protocols

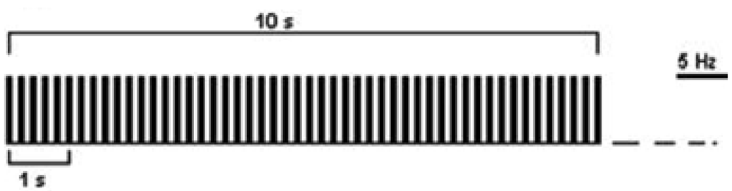
Repetitive TMS (rTMS)

Low frequency rTMS (<1Hz) reduces excitability



10 s of rTMS at 1 Hz

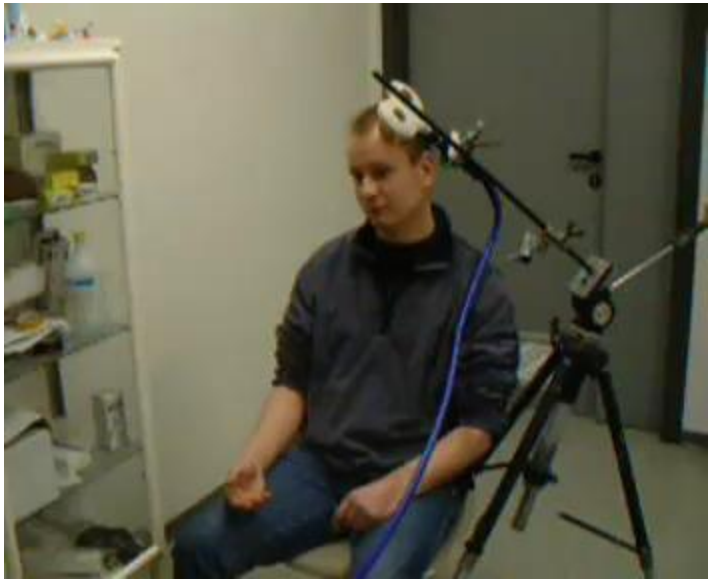
High frequency rTMS (>5Hz) increases excitability (Padberg et al., 2007)



10 s of rTMS at 5Hz

TMS for temporary excitation and inhibition

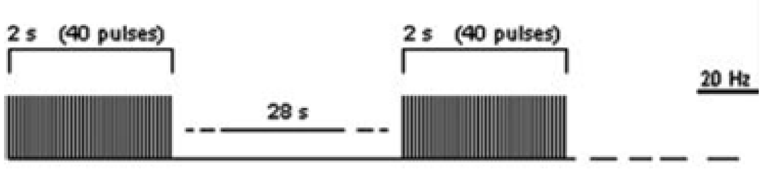
Guess what happens next…



rTMS protocols

Patterned 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)

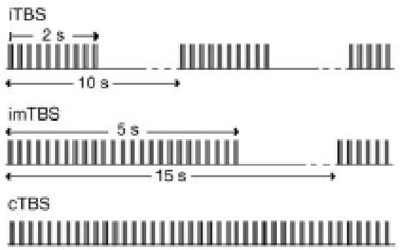
Patterned rTMS protocols

Theta burst stimulation (TBS) (5Hz). Based on natural firing pattern of pyramid cells in hippocampus (Kanel & Spencer, 1961) - theta-frequency pattern of neuronal firing (theta rhythm).

TBS uses three pulses of 50-Hz repeated at intervals of 200ms (5Hz)

Continuous (cTBS)
Intermittent (iTBS)

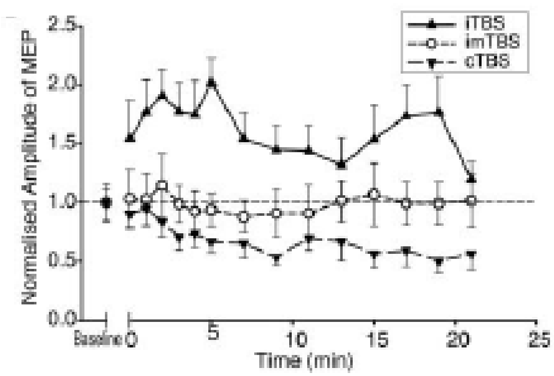
Continuous and intermittent patterns of delivery have opposite effects on synaptic efficiency (Huang et al., 2005)



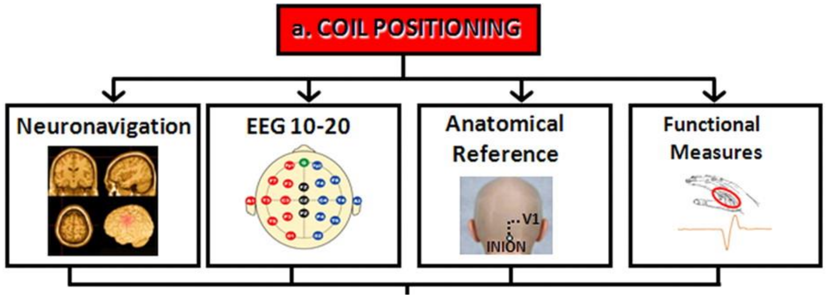
cTBS (over a period of 40s) leads to depression of cortical excitability

iTBS leads to increase in cortical excitability

Long lasting



How/where to stimulate?



(Bolignini & Ro, 2010)

Why use TMS?

- Provides information about the causal role of a brain region ("virtual lesion technique")
- Can be used repeatedly in same subjects (internal double dissociations)
- High spatial and temporal resolution
- Restricted to brain regions close to the skull

Sham stimulation

- Use a control region
- Tilting coil 45° – maintains acoustic artefact and contact sensation – but still substantial stimulation (Lisamby et al., 2000)
- Sham coil – with acoustic artefact
- Experimenter is not blinded to procedure

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Therapeutic Use of TMS

Approved for use in treating migraine and treatment-resistant depression.

Typical use of rTMS (or theta burst) for treatment of depression – 20-40min, 5 days a week, 4-6 weeks.

Clinical benefits are marginal in the majority of reports

- Superiority of rTMS over a sham control, though the degree of clinical improvement is not large.
- Greater efficacy with longer treatment courses.
- Large variation in approaches (stimulation site, stimulus parameters etc) (Loo & Mitchell, 2005*)*.

What can we do with TMS-fMRI?

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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

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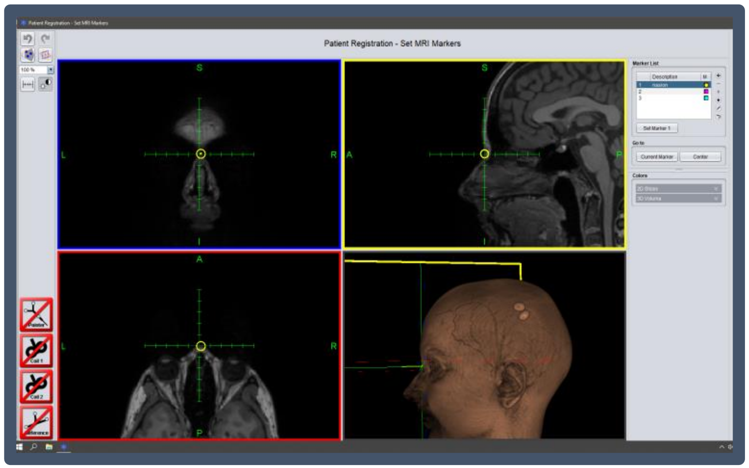
MRI compatible TMS/neuronavigation system

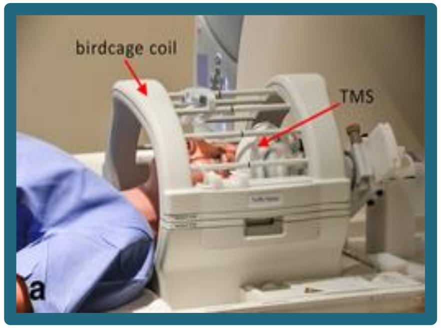
Registration



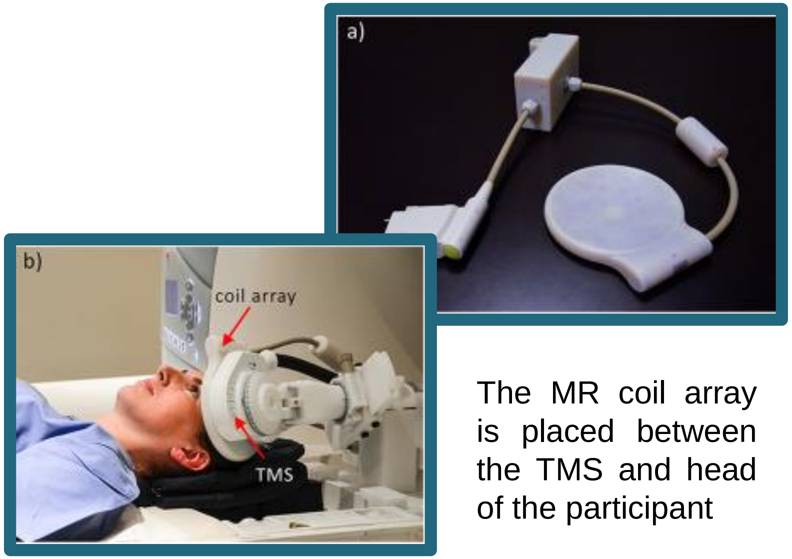
MRI compatible TMS/neuronavigation system

TMS coil navigation

TMS-fMRI dedicated MR RF coils



Restricted coil placement



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

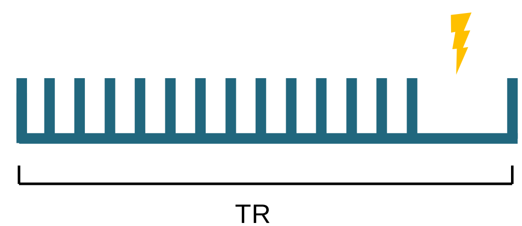
- Avoids signal loss at site of stimulation
- Allows flexibility in coil placement
- Increases participant comfort

Navarro de Lara et al. 2015

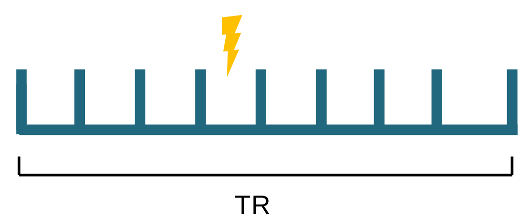
Artefact removal

- 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

Safety issues of TMS

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Seizure induction
Single-pulse TMS has only produced seizures in patients. rTMS has caused seizures in patients (approx 1.4%) and neurotypical volunteers (<1%). Only one case with TBS.

Hearing loss
TMS produces loud click (90-130 dB) in the most sensitive frequency range (2–7 kHz) every time a pulse is delivered. rTMS = more sustained noise. Reduced considerably with earplugs.

Local pain, headache, discomfort
More common with rTMS

TMS equipment at and around 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

TMS Summary

- **Transcranial magnetic stimulation (TMS)**
  - Works via electromagnetic induction
  - Evokes action potentials in the brain
  - Create “virtual lesions”
  - rTMS can increase or decrease neuronal excitability
  - Allows inferences about causal role of regions
  - Excellent temporal/ good spatial resolution
  - TMS can be combined with EEG and fMRI
  - Safety/tolerance issues
  - Not easily controlled sham

Part II: Transcranial electrical stimulation (tES)

History of electrical brain stimulation

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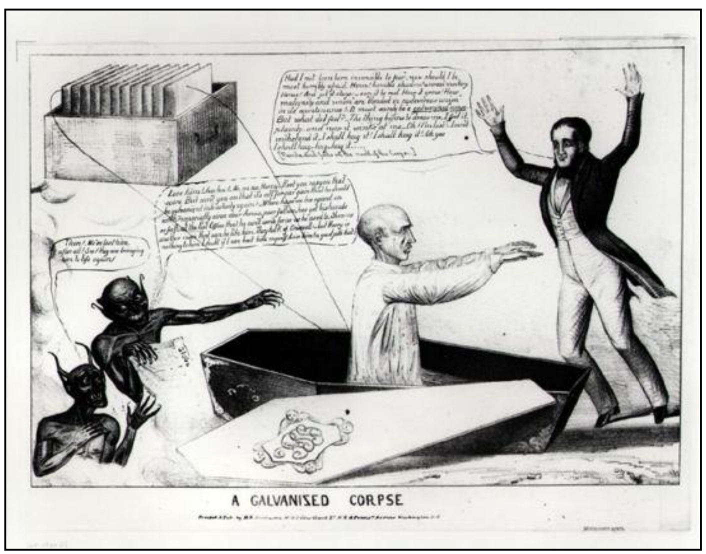
Ancient Egypt, 2750 BC: Electric Fish ("Thunderer of the Nile")
Some Roman writers mention electric shocks as an ailment for headaches (~ 0 AC).

Giovanni Aldini (1804)

"Complete rehabilitation" of depression/psychosis following transcranial administration of electric current.



"Galvanism"

Electroconvulsive Therapy (1938-)

10,000 more power than tDCS

Transcranial electrical stimulation hysteria

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Math Skills Improved By Electric Shocks To Brain, Study Suggests

Science NOW | Posted: 05/17/2013 8:36 am EDT

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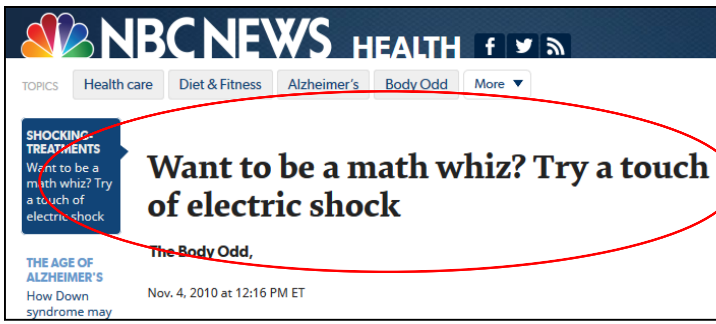

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SHOCKING TREATMENTS Want to be a math whiz? Try a touch of electric shock

Want to be a math whiz? Try a touch of electric shock

The Body Odd,

Nov. 4, 2010 at 12:16 PM ET

THE AGE OF ALZHEIMER'S How Down syndrome may

The Telegraph

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Electric shock treatment 'improves academic performance'

Stimulating the brain with tiny electric shocks can boost people's learning and memory ability, research has found.

Readers comments….

"I think this idea originally came from a guy by the name of Milgram. Worth reading his work." aduckers, skelmersdale, United Kingdom.

"This used to be called ECT (Electro Convulsive Therapy) After a course or two you would be cured or they would give you another one :)" Puddleduck, This side of the pond

"Just a mild form of aversion therapy, which also never worked. What will these fools think of next? Unless you pass your exams you will be killed?" Torres, Fulham, United Kingdom

"Don't get me wrong, but since when was plugging ur head into the mains a "smart idea", Einstein didn't need to do it." Gowdy, Newcastle, United Kingdom

http://www.dailymail.co.uk/sciencetech/article-2589829/Now-THATS-thinking-cap-Electric-hat-zaps-brain-make-smarter.html#ixzz2xXfsmMtT

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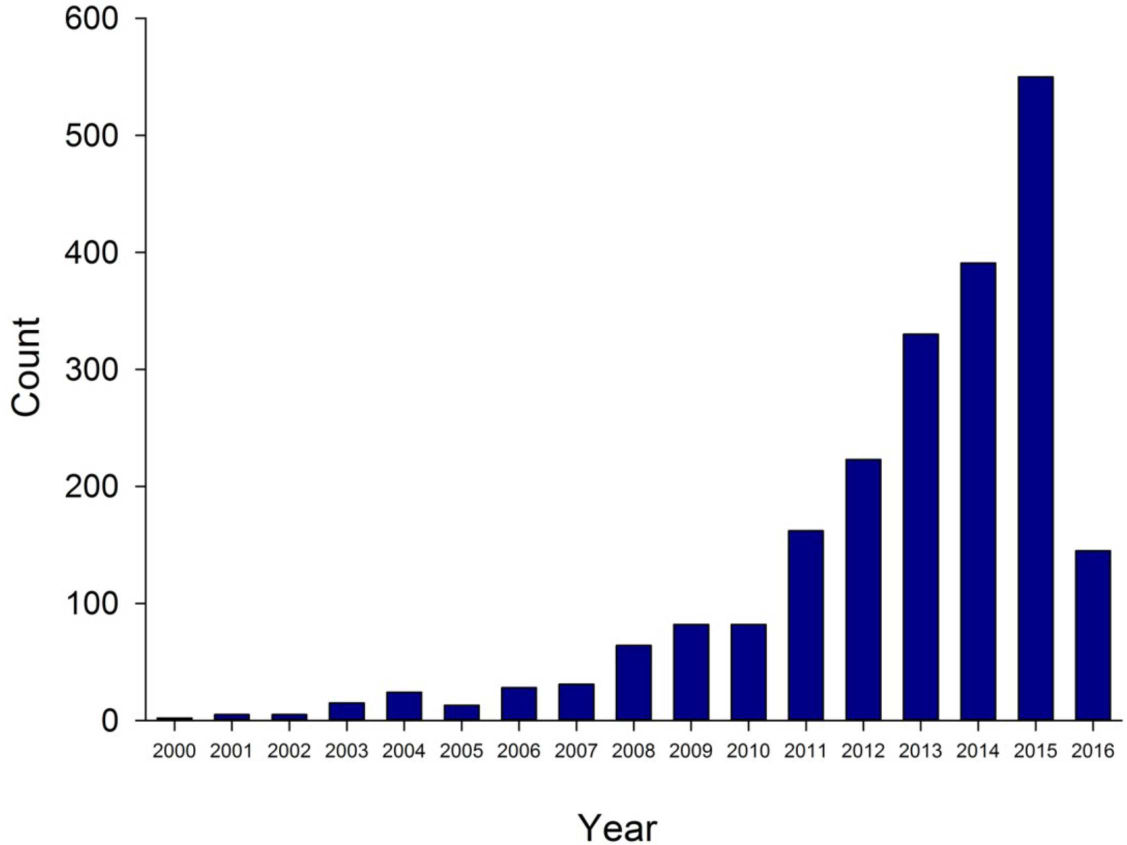
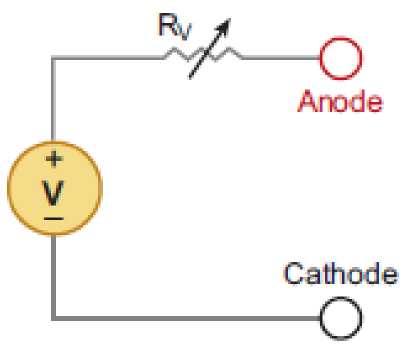
"Transcranial direct current stimualtion"

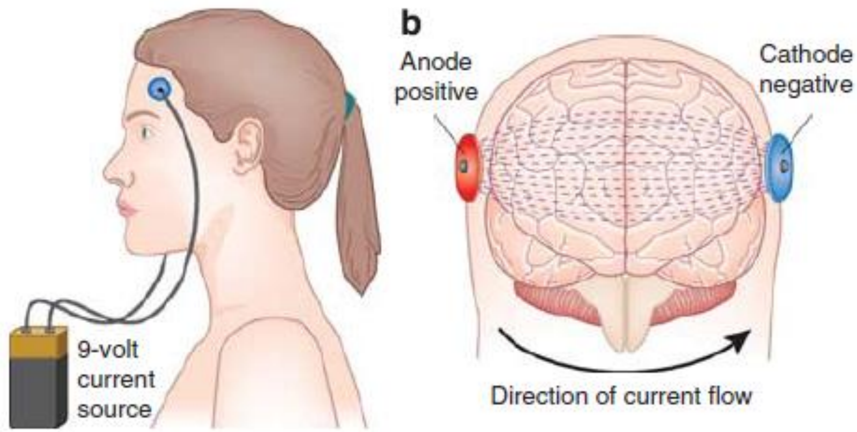
Pubmed results by year



What is tDCS?

tDCS circuit





George & Aston-Jones (2010)

A constant direct current (DC) (*i.e. a flow of electric charge that does not change direction*).

Transcranial direct current stimulation (tDCS) can induce excitation or inhibition depending on direction of current:

Anodal stimulation – excitatory; Cathodal stimulation – inhibitory.

Note: Current will take the way of least resistance, i.e. most of it will flow through the scalp (the figure at top right is not correct).

Conductivities of tissues

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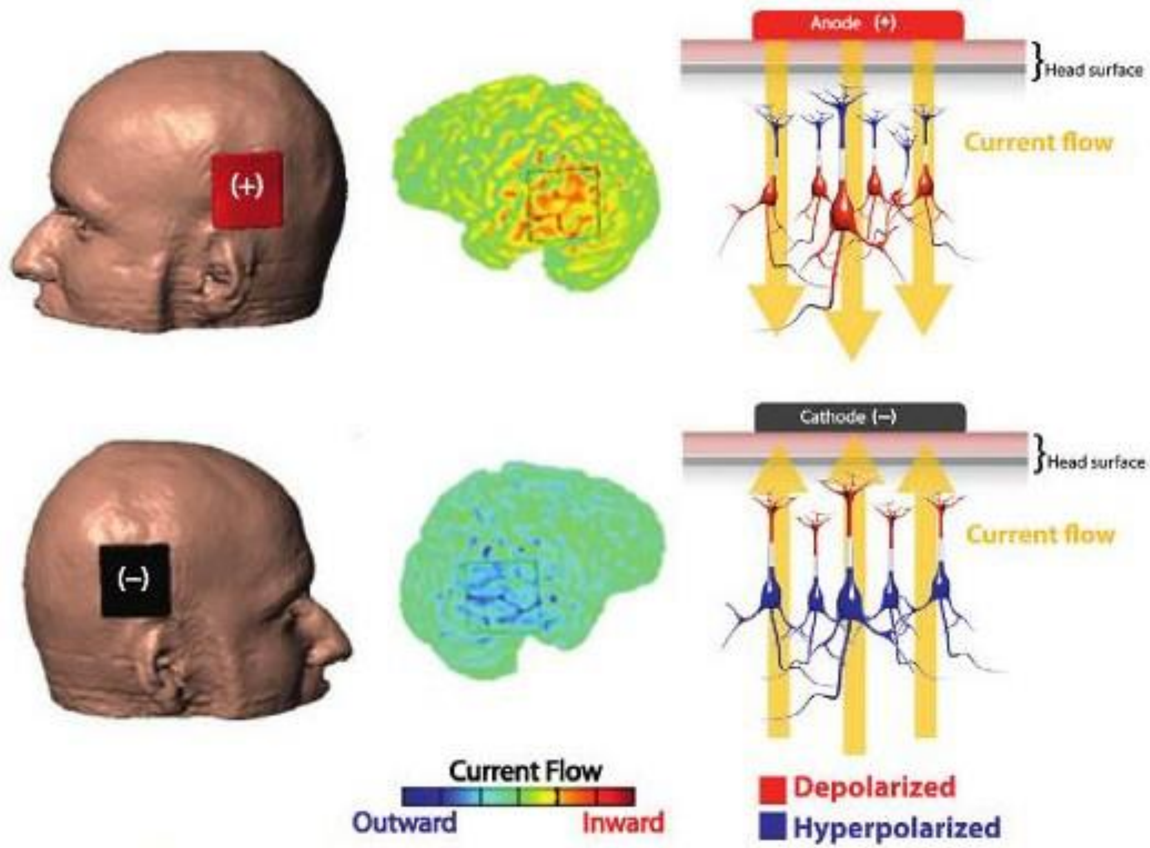
Table 2 Isotropic conductivity values of single tissue types used in human head volume conductor modeling

Tissue	Conductivity in S/m	Reference
Brain gray matter	0.45	Logothetis et al. 2007
Brain white matter	0.1	Akhtari et al. 2010
Spinal cord and cerebellum	0.16	Haueisen et al. 1995
Cerebrospinal fluid	1.79	Baumann et al. 1997
Hard bone (compact bone)	0.004	Tang et al. 2008
Soft bone (spongiform bone)	0.02	Akhtari et al. 2002
Blood	0.6	Gabriel et al. 2009
Muscle	0.1	Gabriel et al. 1996, 2009
Fat	0.08	Gabriel et al. 2009
Eye	1.6	Pauly and Schwan 1964; Lindenblatt and Silny 2001
Scalp	0.43	Geddes and Baker 1967
Soft tissue	0.17	Haueisen et al. 1995
Internal air	0.0001	Haueisen et al. 1995

Haueisen & Knösche, Chapter of “Magnetoencephalography” by Supek & Aine (edts.)

How does tDCS work?



An electric current flows between two electrodes (anodal and cathodal) on the scalp.

Part of the electric current passes through the cortex (~50%).

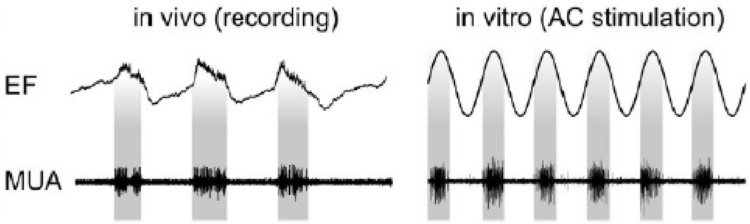
Current flow (inward) under anodal electrode induces a *lack* of positive ions (shifts membrane potential towards depolarization). **Increases excitability.**

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

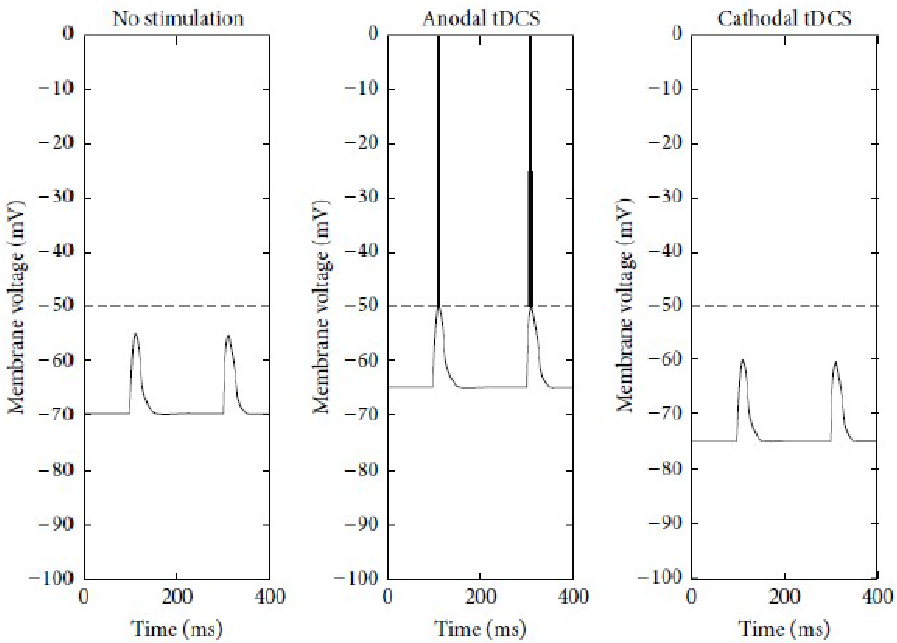
How does tDCS work?

tES electrical fields are far too weak to elicit action potentials:
- 2mA = ~0.3mv (15mv rest to AP threshold) – 100x weaker than TMS

Interacts with ongoing activity (Stagg & Nitsche, 2011), i.e. with **active** regions.



Frohlich and McCormick, 2010



Antal and Herrmann, 2016

How is tDCS applied?

Saline soaked sponge pads placed on the scalp.

tES studies generally use relatively-large wet sponges - sizes ranging from $3cm^2$ to $10cm^2$.

Stimulation sites usually based on EEG electrode placement locations.

Currents of 1 – 2 mA.

Applied for durations of up to 30 minutes.

Cathodal electrode often termed “reference electrode” – use larger size electrodes.

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tES - neurophysiology

Neurotransmitter changes:

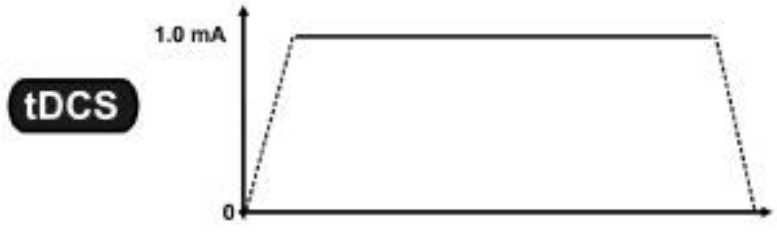
Anodal tDCS associated with reduction in GABA levels (Stagg et al., 2009).

May increase glutamatergic plasticity (Ziemann et al., 1998).

Direct current stimulation induces long-lasting synaptic potentiation - NMDA-receptor dependent (Fritsch et al., 2010; Monte Silva et al., 2012).

tES protocols

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



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).

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).

Saitoe et al., (2013)

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tES protocols

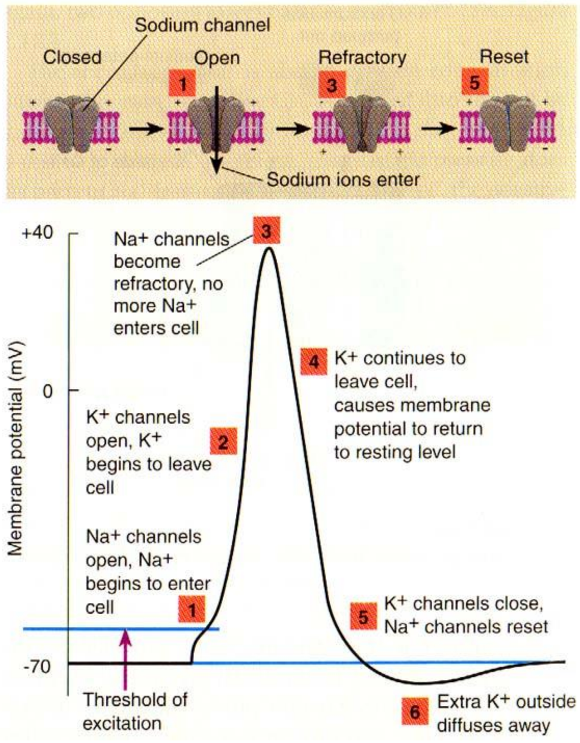
Alternating current stimulation (tACS) –

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) –

After a depolarization, repolarization of sodium channels generally takes some time, but if a repeated stimulation is applied Na channels can be reopened in a shorter time (Schoen and Fromherz, 2008).

A DC stimulus can open Na channels just once, whereas repeated pulses (tRNS) can induce multiple ionic influxes (Terney et al., 2008).



http://www.mediahex.com/Action_Potential

Stochastic resonance - Amplification of subthreshold oscillatory activity - might increase neural firing synchronization within stimulated regions.

tES – Safety issues

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.

Current flow is ramped up and down for a period of 10 seconds.

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.

tES vs. TMS

Pros – tES easily tolerated, sham hard to distinguish, enables blinded testing, low cost, portable

Cons – Lower temporal and spatial resolution

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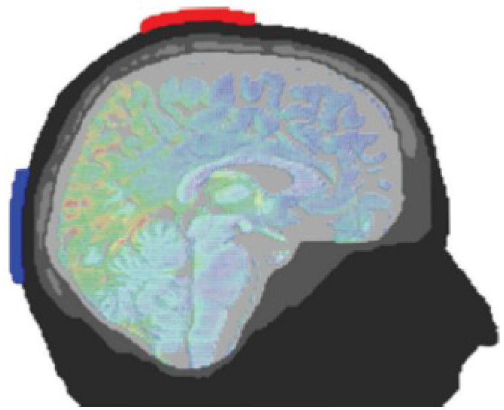
tES – current challenges

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

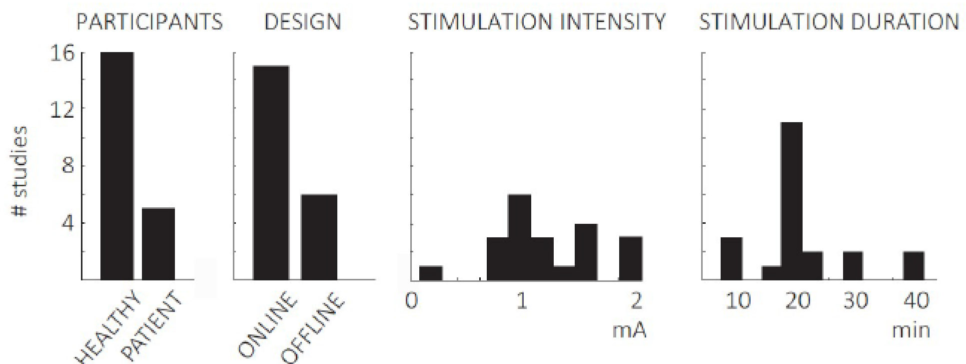


Antal and Herrmann, 2016

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

5. Effects are often small



Zoefel and Davis, 2016

How effective is tES – on the one hand…

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Direct effects of transcranial electric stimulation on brain circuits in rats and humans

Mihály Vöröslakos, Yuichi Takeuchi, Kitti Brinyiczki, Tamás Zombori, Azahara Oliva, Antonio Fernández-Ruiz, Gábor Kozák, Zsigmond Tamás Kincses, Béla Iványi, György Buzsáki & Antal Berényi

Nature Communications **9**, Article number: 483 (2018) | Cite this article

"Our combined results establish that neuronal circuits are instantaneously affected by intensity currents that are higher than those used in conventional protocols."

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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

NEUROSCIENCE

Cadaver study challenges brain stimulation methods

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

Underwood, Science 2016

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

How effective is tES? On the other hand…

Conceptual and Procedural Shortcomings of the Systematic Review "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" by Horvath and Co-workers

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Combining studies with a large variability in experimental factors to a meta-analysis might not been useful

Animal studies have demonstrated consequences of tES in electrophysiological recordings

"Fishing" for tES effects might not be the right approach – systematic tests based on clear hypotheses are needed

Summary - tES

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- Electric current flows into brain
- tDCS shifts neuronal membranes towards (or away from) depolarization
- Direct or alternating current or more “complicated” protocols
- Interacts with active brain regions – “neuromodulation”
- Easily tolerated
- Well controlled sham
- Relatively poor spatial resolution
- Efficacy still unclear and several challenges to overcome

TMS and tES are promising tools to investigate the causal role of neural activity for stimulus processing. Standardized protocols have yet to be found for tES.

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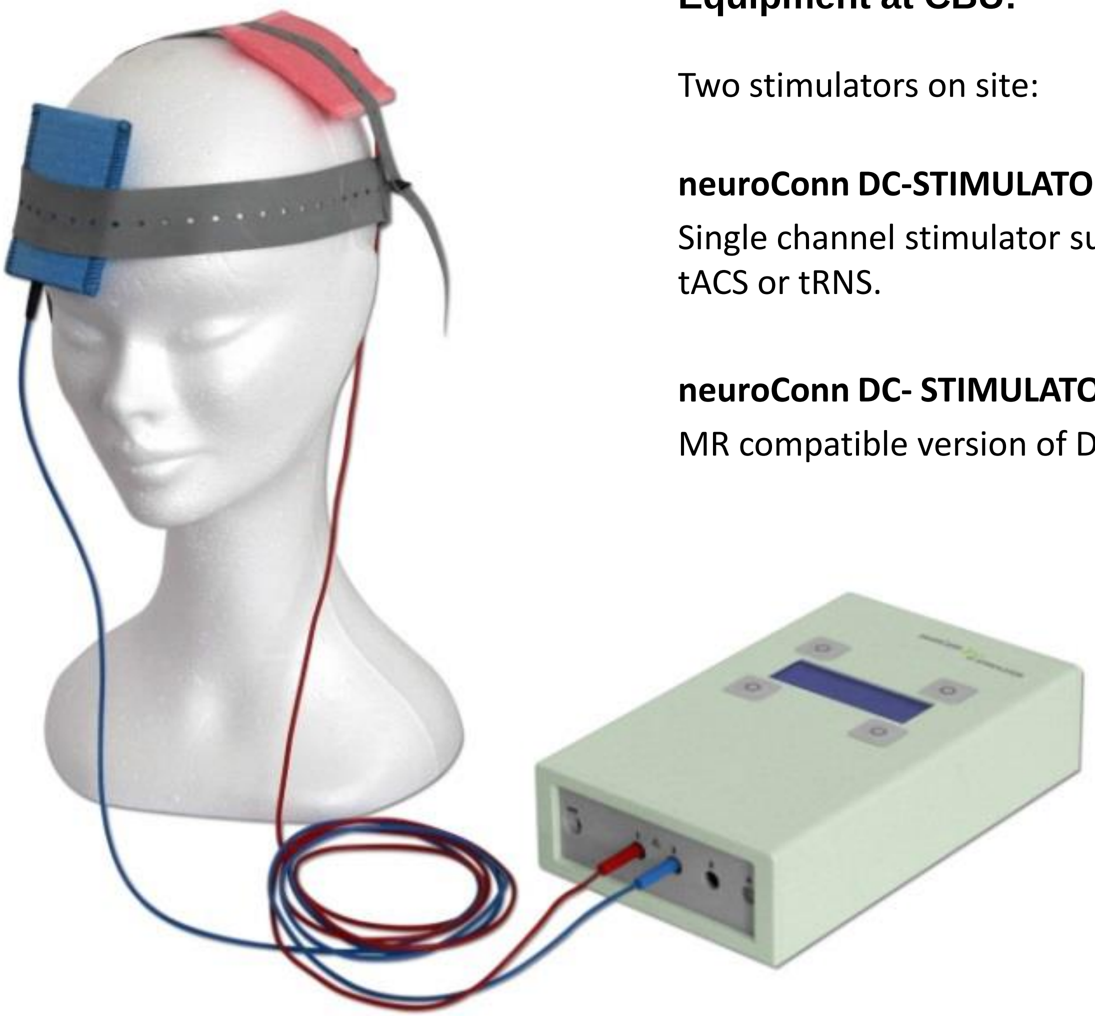
tES equipment



Equipment at CBU:

Two stimulators on site:

neuroConn DC-STIMULATOR PLUS

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

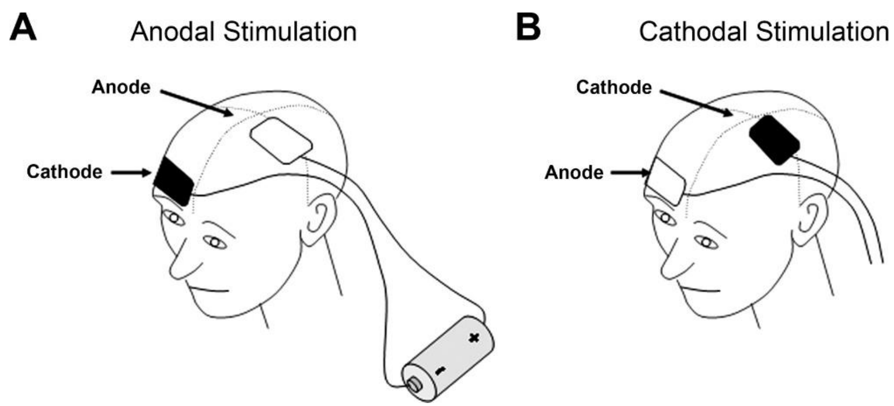
neuroConn DC- STIMULATOR MR

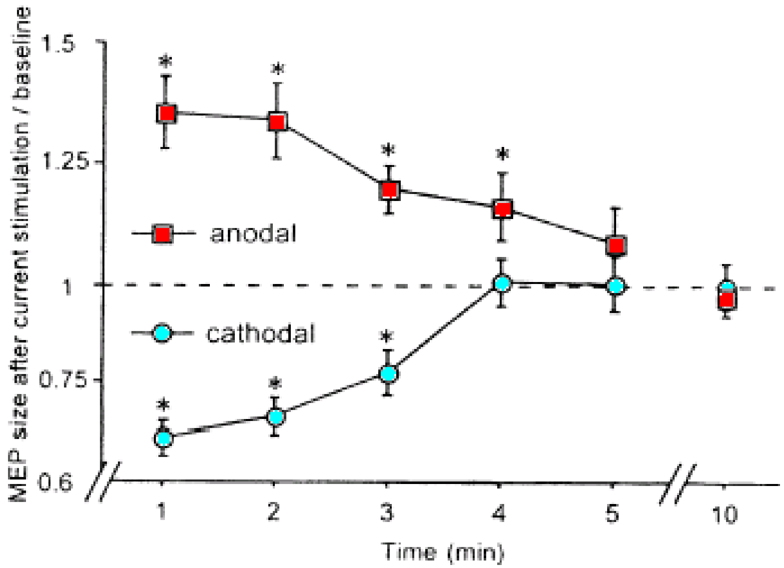
MR compatible version of DC-STIMULATOR PLUS.

Examples of tES studies

tES with TMS

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





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

Nitsche & Paulus (2000)

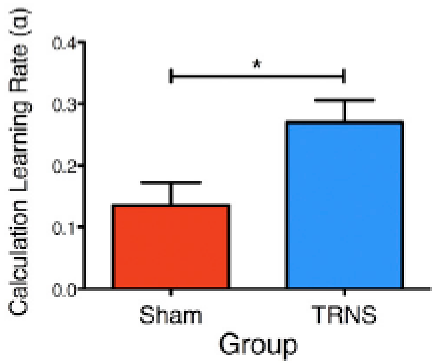
“After-effects" last up to 90 minutes after stimulation (depending on intensity and duration of stimulation)

tES studies

- Working memory tasks (e.g. Ohn et al., 2008; Zaehle et al., 2011)
- Language tasks (Holland et al., 2011)
- Mental arithmetic (Cohen Kadosh et al., 2010; Snowball et al., 2013)
- Adults with depression (Oliveira et al., 2013; Wolkenstein & Plewnia, 2013)
- Patients following stroke (Jo et al., 2009)
- Patients with Parkinson's disease (Boggio et al., 2006)
- Chronic pain conditions (Fregni, et al., 2006)
- Traumatic spinal cord injury (Fregni, et al., 2006)
- Face perception ?

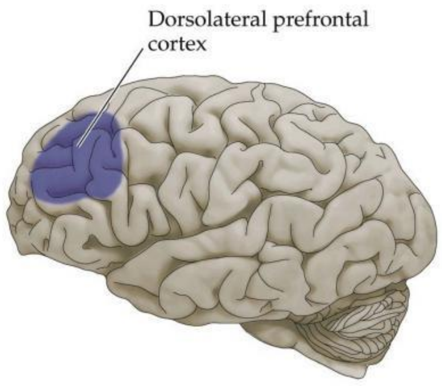
tRNS – Effects on arithemetic ability

The effect of tRNS on arithmetic performance (Snowball et al., 2013)



(Snowball et al., 2013)

Five consecutive days of tRNS-accompanied cognitive training (algorithmic manipulation)



Arithmetic performance improved following tRNS to bilateral dorsolateral prefrontal cortex.

Faster learning rate in subjects receiving tRNS.

Shorter RTs for old and new (unlearned) material.

Effects persist after 6 months period

tACS – Effects on visual perception

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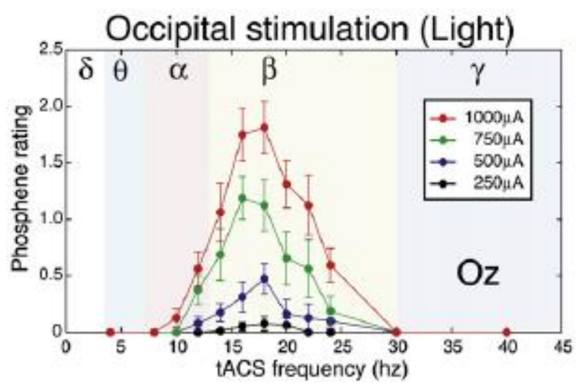
Frequency dependent modulation of primary visual cortex (Kanai et al., 2008).

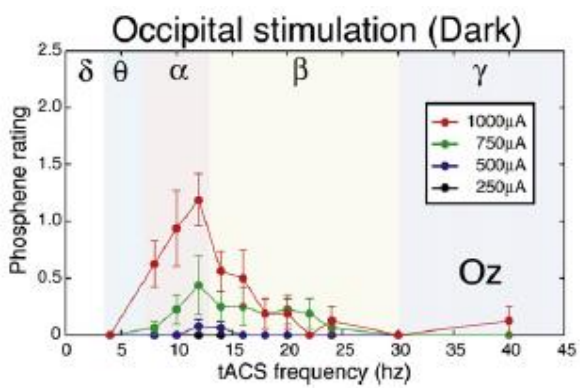
Distinct patterns of dominant frequency as a function of the presence or absence of visual input

- Alpha activity dominant during eyes-closed or in-the-dark resting conditions
- Brain activity at higher frequencies (beta range) when eyes-open, in the light.

tACS over Oz at theta (4–8 Hz), alpha (8–14 Hz), beta (14–22 Hz), and gamma (> 30 Hz)



Stimulation at beta range indices greater intensity phosphenes in light conditions.



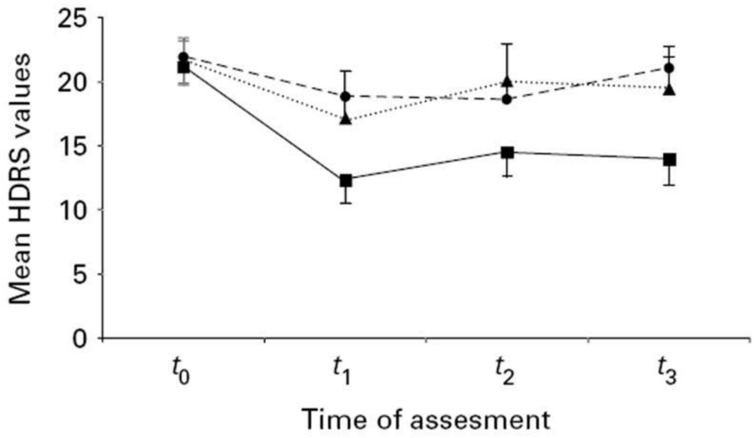
Stimulation at alpha range indices greater intensity phosphenes in dark conditions.

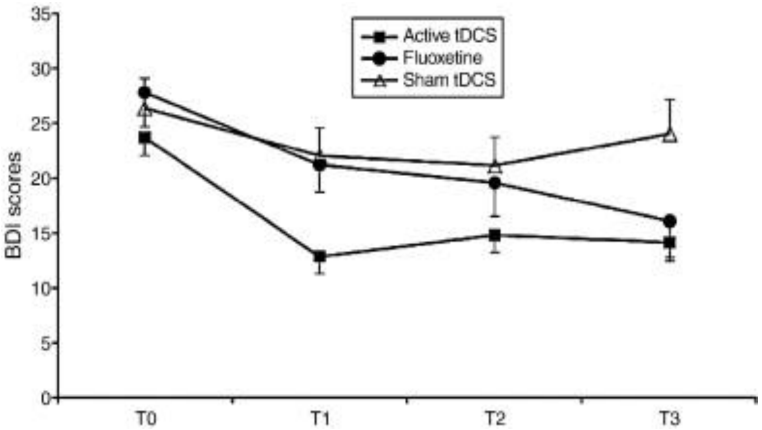
Therapeutic use of tES

Treatment of depression

40 patients with moderate to severe major depression
- Left DLPFC (21 patients),
- occipital (9 patients)
- sham stimulation (10 patients).

Only prefrontal tDCS reduced depressive symptoms
- effects were stable 30 days later (Boggio et al.,2008).





(i) Size of clinical improvement delivered by tDCS to DLPFC similar to effects of antidepressant medication

(ii) Effects of tDCS faster than those of pharmacological treatment

(Rigonatti et al., 2008).

Summary

Transcranial electrical stimulation (tES).

- Electric current flows into brain
- Shifts neuronal membranes towards (or away from) depolarization
- Interacts with task – “neuromodulation”
- Easily tolerated
- Well controlled sham (double blind procedure)
- Moderate spatial resolution/ poor temporal resolution
- Long term changes in learning and rehabilitation.