MRC | Cognition and Brain Sciences Unit

A stimulating lecture: Transcranial magnetic and electrical stimulation (TMS and tES)

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Introduction to NeuroImaging Methods 2nd April 2014

MRC Cognition and Brain Sciences Unit, Cambridge, UK.

Outline

- A brief history of brain stimulation

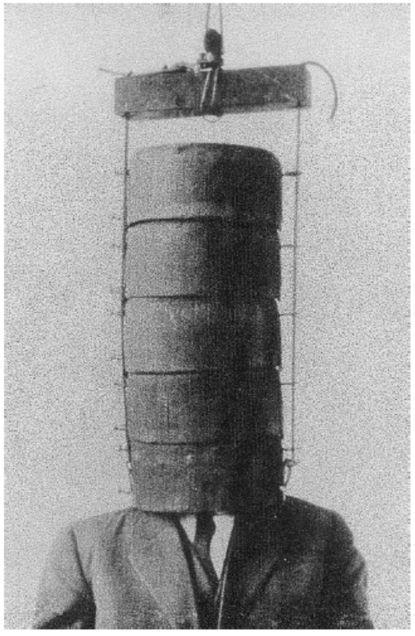
- Transcranial magnetic stimulation (TMS)
    - Principles of TMS - How does it work?
    - TMS protocols
    - Safety issues
    - Experimental work

- Transcranial electrical stimulation (tES)
    - Principles of tES - How does it work?
    - tES Protocols (tDCS, tACS, tRNS)
    - Use of tES as a scientific tool and therapy

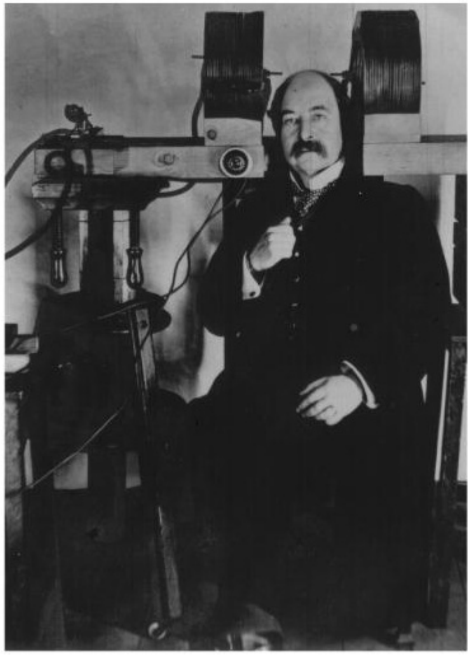
Part I: Transcranial Magnetic Stimulation (TMS)

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)

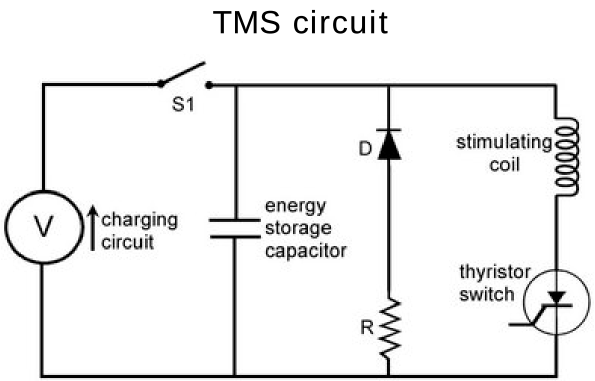


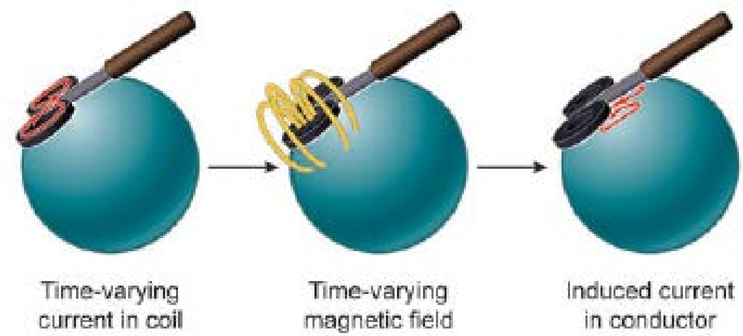
Thompson, 1910

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.

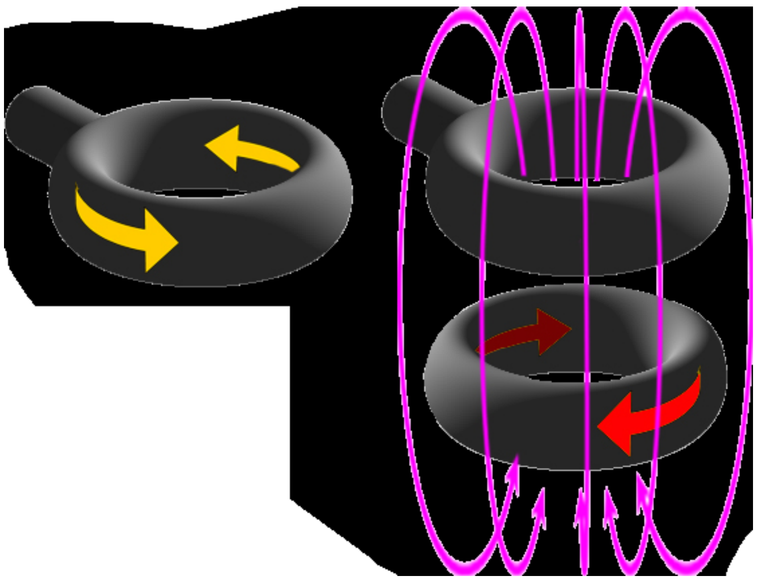
What is TMS?

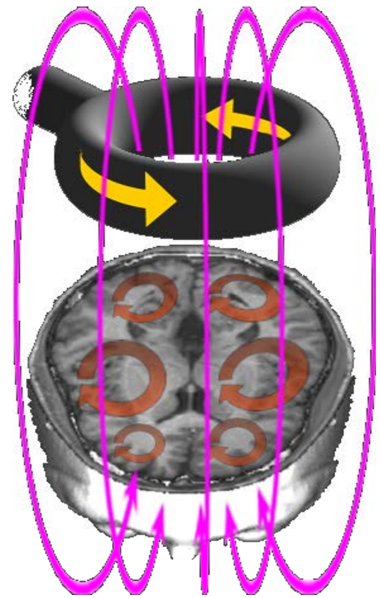


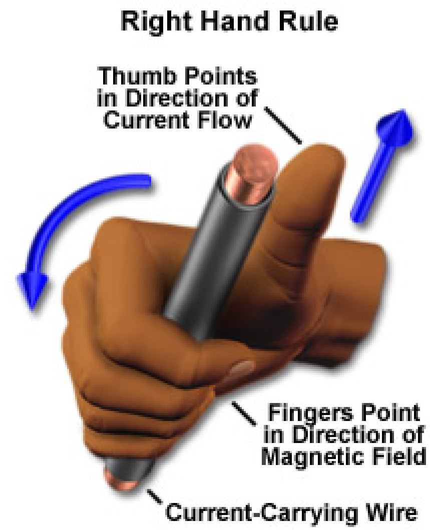


- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in a coil of wire.
- Electrical current momentarily generates a magnetic field.
- Magnetic field can reach up to about 2T and lasts approx. 100ms
- Magnetic field penetrates scalp and skull - induces a current 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?







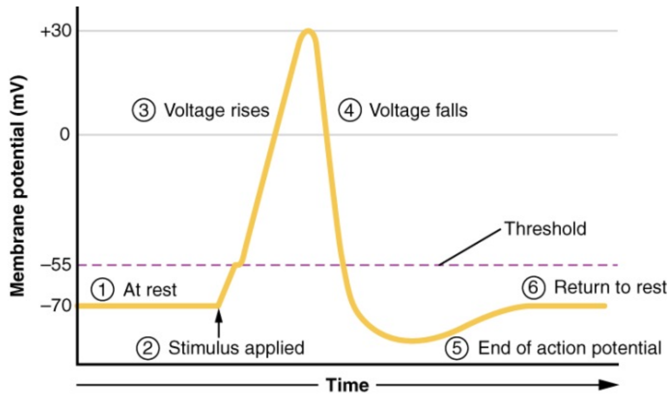
The electric field is induced perpendicularly to the magnetic field - causing ions to flow in the brain

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.

How does TMS work?

TMS produces a transient period of brain disruption - “virtual lesion”.

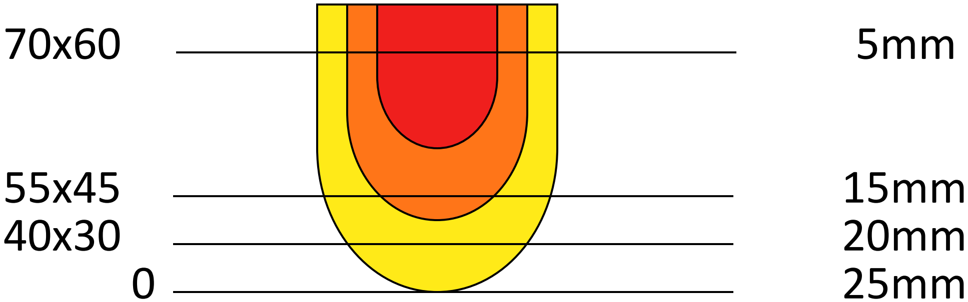
Induces disorder into an ordered system.

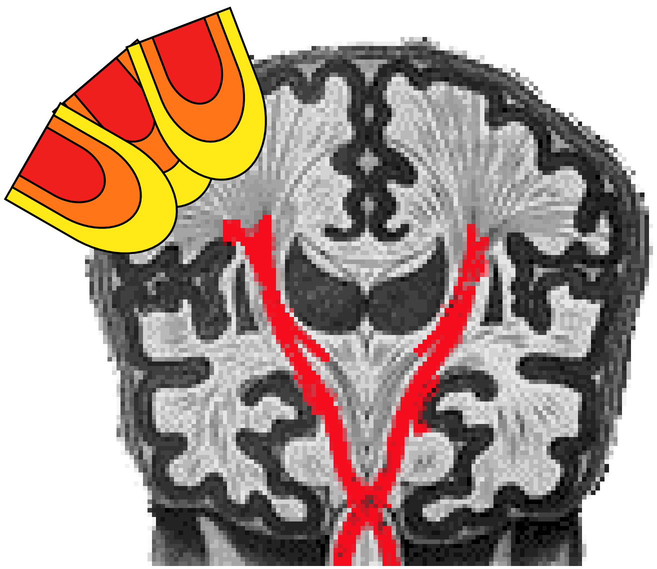
If a group of neurons are involved in a given task, introducing a TMS pulse is unlikely to selectively stimulate the same coordinated pattern of neural activity as performance of that task (Walsh & Cowey 2000).

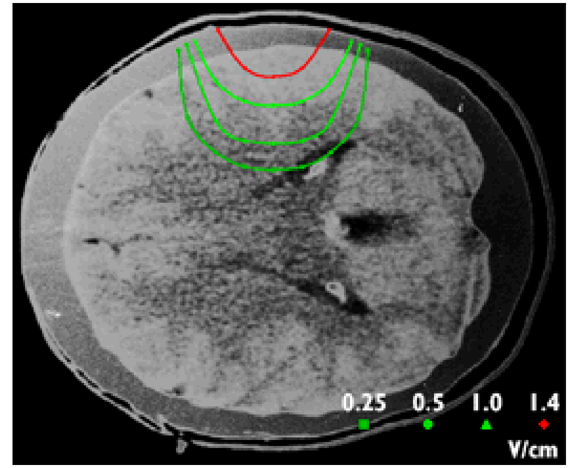
TMS induces activity that is random with respect to the goal-state of the area stimulated.

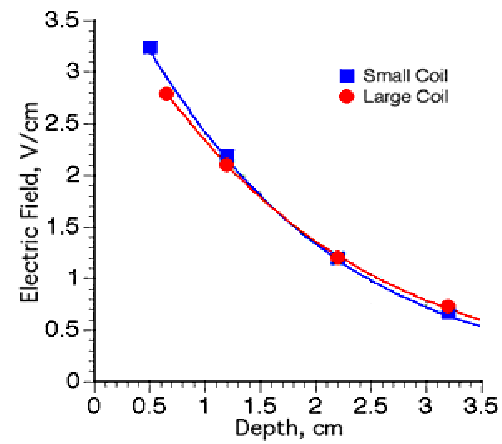
Disrupts task performance.

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

E.g. for mapping motor cortical outputs, studying motor conduction time – good temporal specificity - useful in targeting specific neural processes.

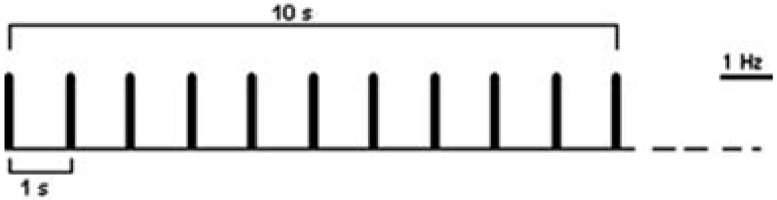
Paired pulse TMS (Inter pulse interval 1-100ms).

Delivered to a single target (or two different brain regions using two different coils). Cortico-cortical interactions. Timing can be varied to selectivity stimulate inhibitory or excitatory neurons.

TMS protocols

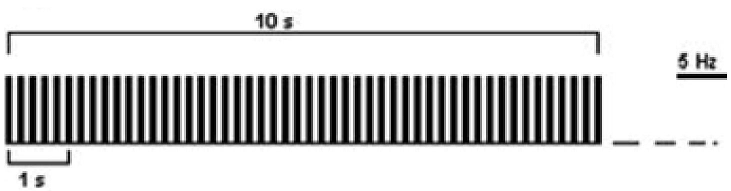
Repetitive TMS (rTMS)

Low frequency rTMS (<1Hz) reduces excitability



10 s of rTMS at 1 Hz

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

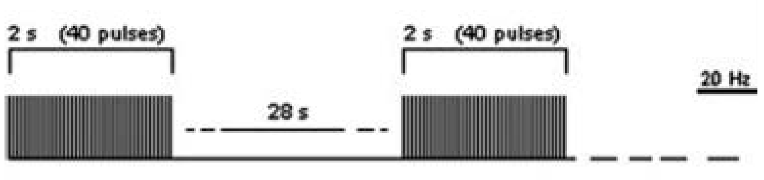


10 s of rTMS at 5Hz

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)

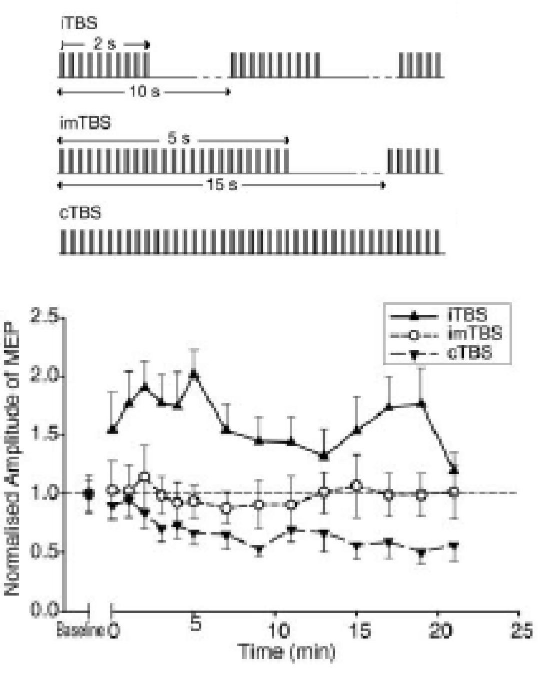
Continuous (cTBS)
Intermittent (iTBS)

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

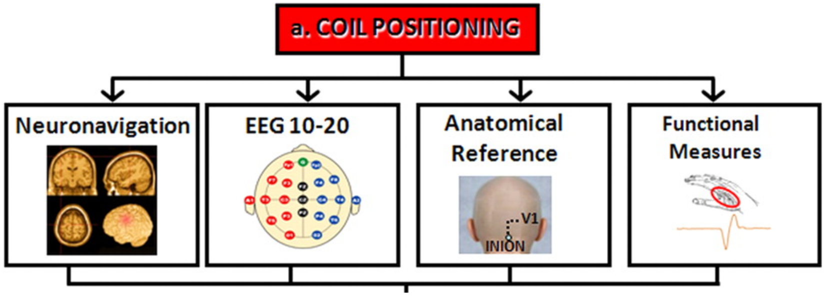
cTBS (over a period of 40s) leads to depression of cortical excitability

iTBS leads to increase in cortical excitability

Long lasting



How/where to stimulate?



(Bolignini & Ro, 2010)

Why use TMS?

- 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

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

Safety issues

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

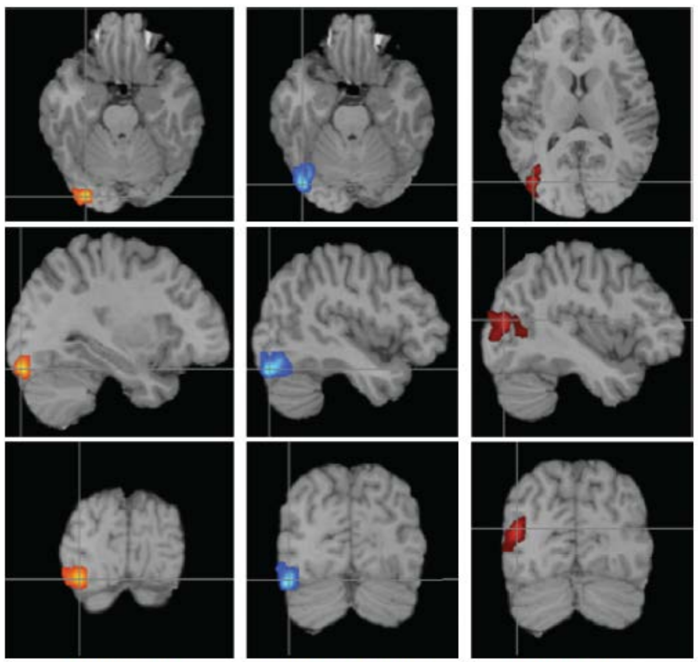
Three TMS machines at HSB:

Magstim® Rapid2
Magstim® 2002
Magstim® Bistim System

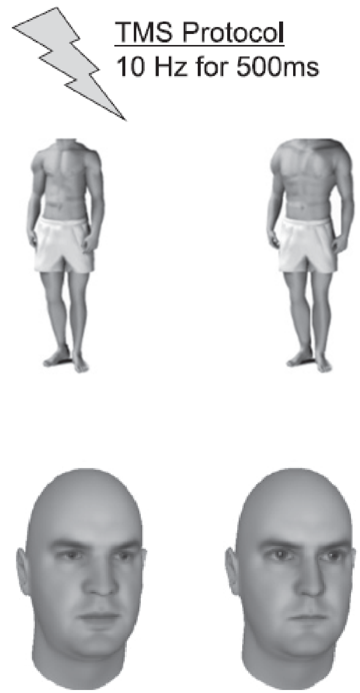
Neuronavigation software - Brainsight 2

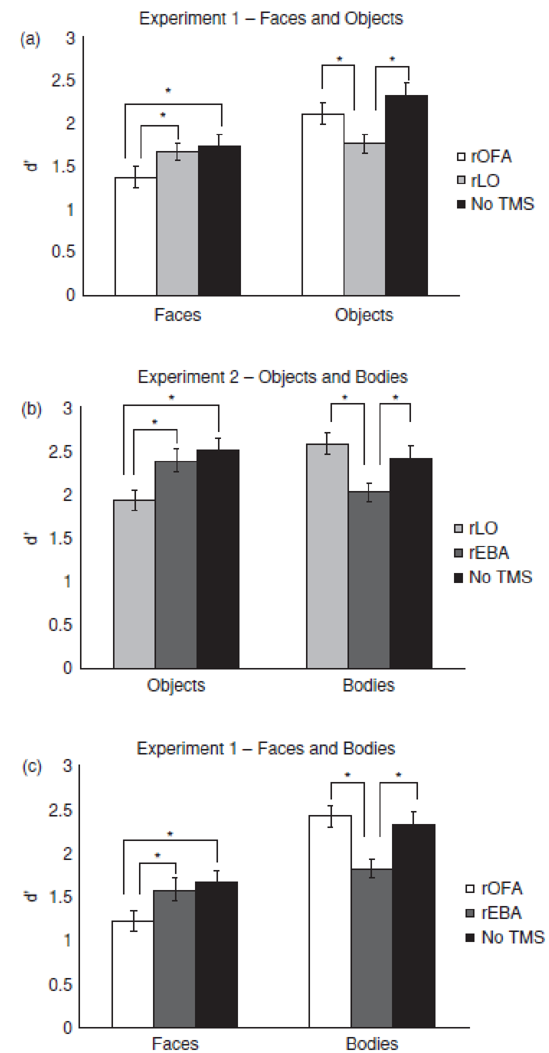
Examples of TMS studies

TMS and category specificity in visual cortex



Right occipital face area (rOFA) | Right lateral occipital area (rLO) | Right extrastriate body area (rEBA)





Face, object and body selective regions in occipitotemporal cortex.

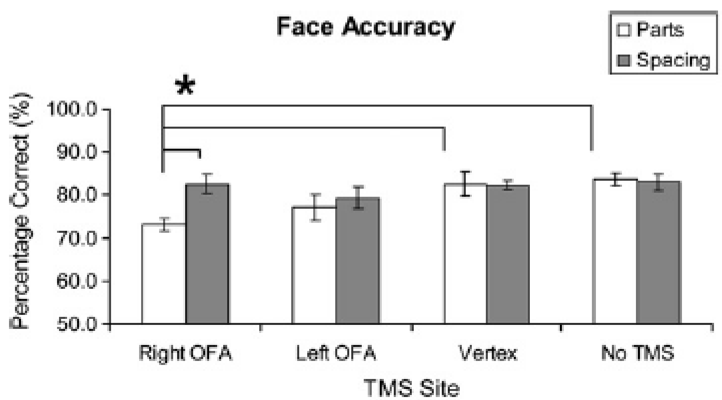
- rTMS onset concurrent with the onset of stimulus

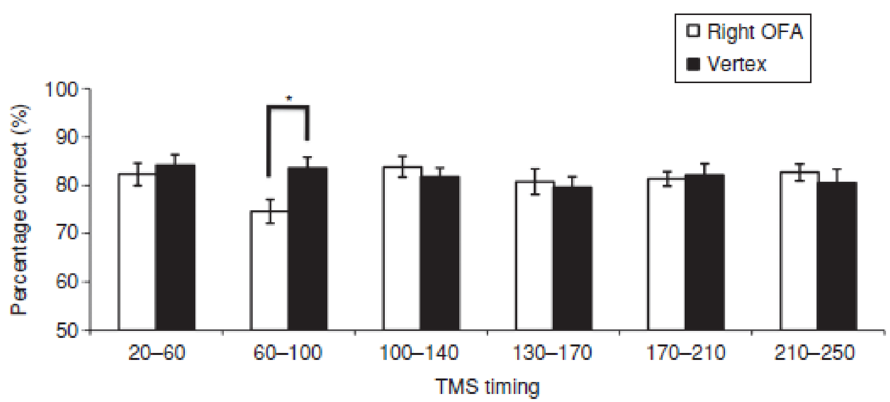
•TMS over rOFA impaired discrimination of faces but not objects or bodies
•TMS over rEBA impaired discrimination of bodies but not faces or objects
•TMS over rLO impaired discrimination of objects but not faces or bodies

Pitcher et al. (2009)

TMS and temporal aspects of face processing

Timing of face perception (Pitcher, 2007)





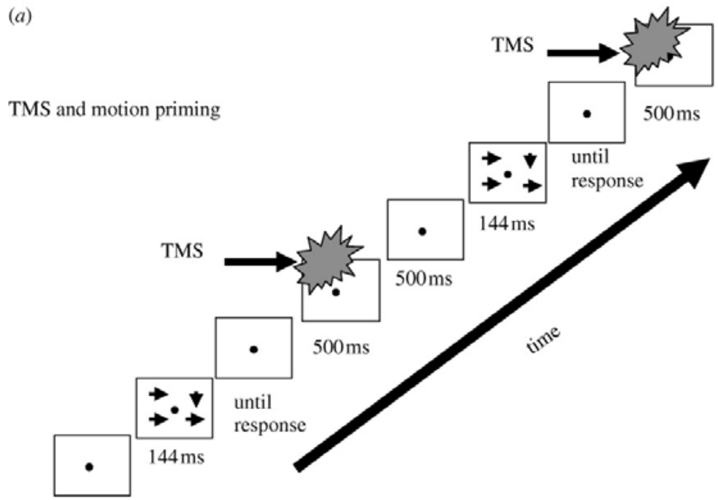
rTMS over OFA disrupted perception of face parts

Double pulse TMS separated by 40ms was delivered over the right OFA and vertex.

TMS to rOFA significantly affected discrimination only when delivered at 60 and 100 ms after stimulus presentation

Pulses coincided with the M100 (Liu et al., 2002).

TMS and motion priming



Four panels containing random dots moving in the same direction in three squares and a different direction in the fourth

rTMS applied over motion area V5/MT for 500 ms before trial

Motion priming effect is abolished by TMS delivered over V5/MT

No effect on colour priming

(Campana et al. (2002).

Therapeutic use of TMS

rTMS used for the clinical treatment of depression

Drug-resistant major depression - left prefrontal TMS superior over sham treatment.
- clinical benefits are marginal in the majority of reports (Loo & Mitchell, 2005).

Factors: younger age, lack of refractoriness to antidepressants, no psychotic features (Avery et al., 2008).

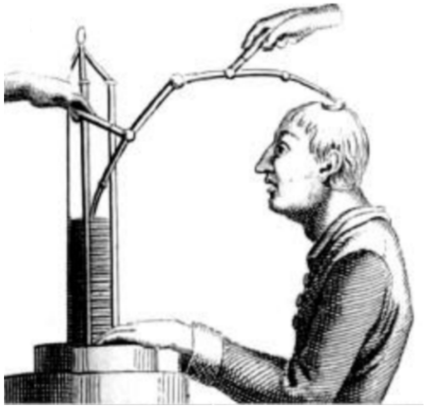
Optimal stimulation parameters?

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
  - Safety/tolerance issues
  - Not easily controlled sham

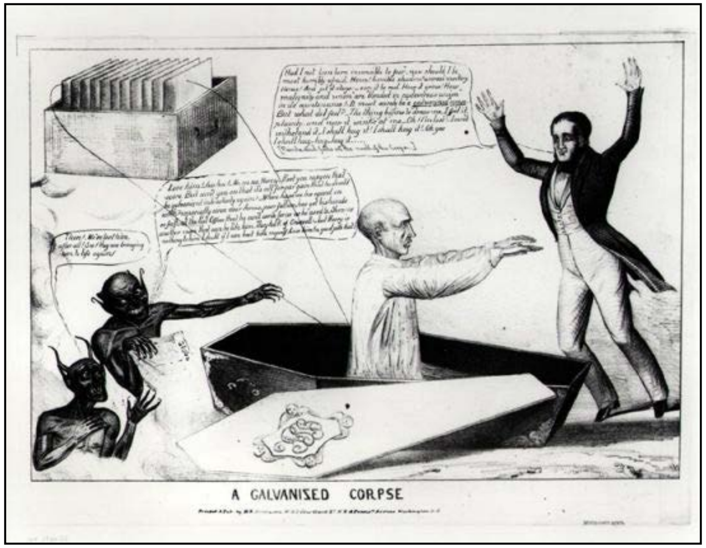
Part II: Transcranial electrical stimulation (tES)

History of electrical brain stimulation



Giovanni Aldini (1804)

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

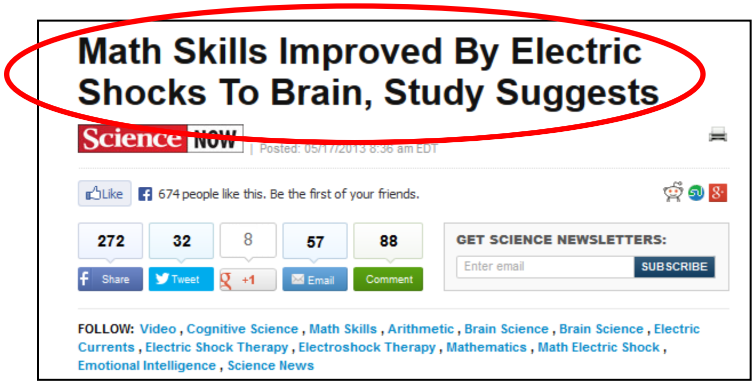


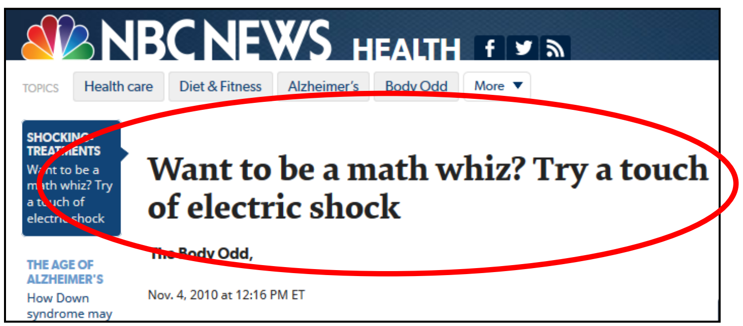
“Galvanism”

Electroconvulsive Therapy (1938-)

10,000 more power than tDCS

Transcranial electrical stimulation hysteria





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

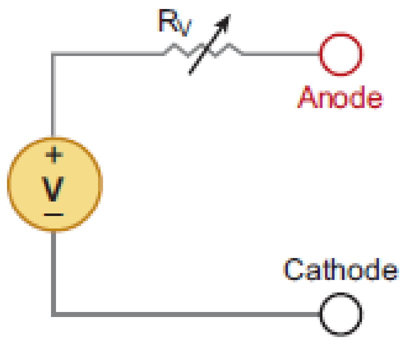
"Just a mild form of aversion therapy, which also never worked. What will these fools think of next? Unless you pass your exams you will be killed?" Torres, Fulham, United Kingdom

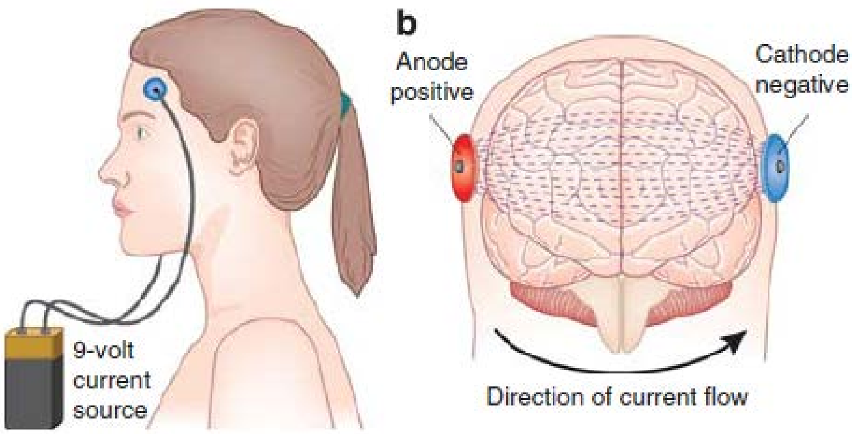
"Don't get me wrong, but since when was plugging ur head into the mains a "smart idea", Einstein didn't need to do it." Gowdy, Newcastle, United Kingdom

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

What is tDCS?

tDCS circuit





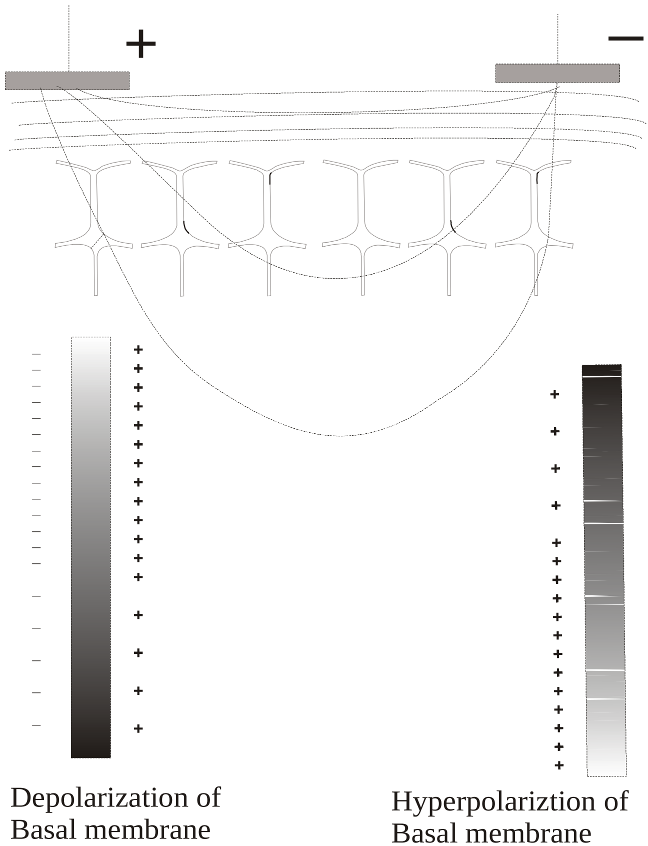
George & Aston-Jones (2010)

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

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?

tDCS electrical fields are far too weak to elicit action potentials:

2mA = ~0.3mv (15mv rest to AP threshold) – 100x weaker than TMS

- Increased spontaneous firing rate

Interacts with ongoing activity (Stagg & Nitsche, 2011).

- (Rate effects) - Increase in rate of action potential generation (Carandini and Ferster, 2000)
- (Timing effects) – Change in timing of action potential (Radman et al., 2007)
- Changes in synaptic efficacy (Hebbian reinforcement)

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 20 minutes.

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

tES - neurophysiology

Neurotransmitter changes:

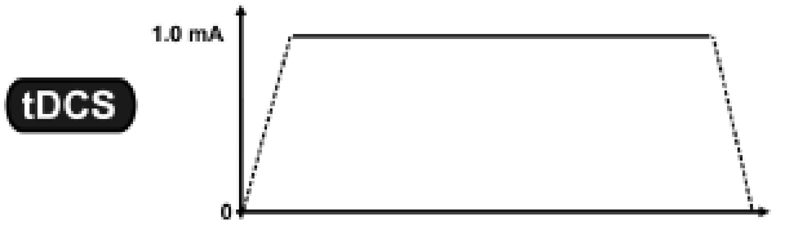
Anodal tDCS associated with reduction in GABA levels (Stagg et al., 2009).

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)

tES protocols

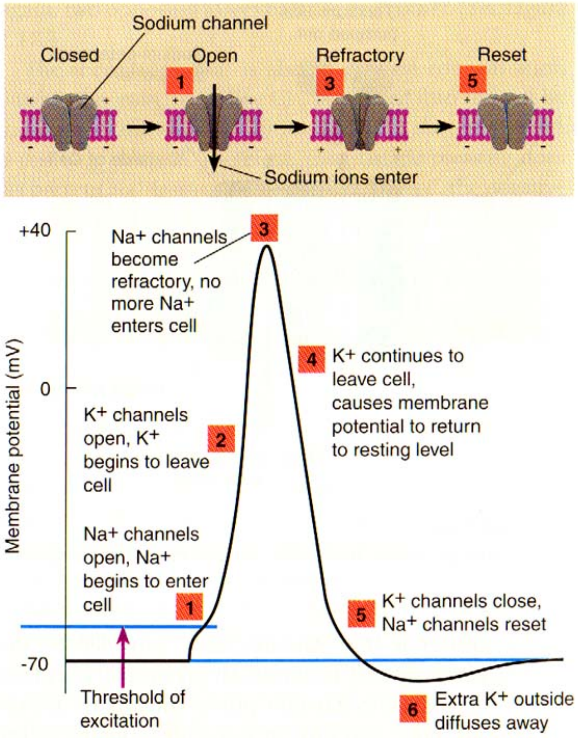
Alternating current stimulation (tACS) –

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

tES equipment

Equipment at CBU:

Two stimulators on site:

neuroConn DC-STIMULATOR PLUS

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

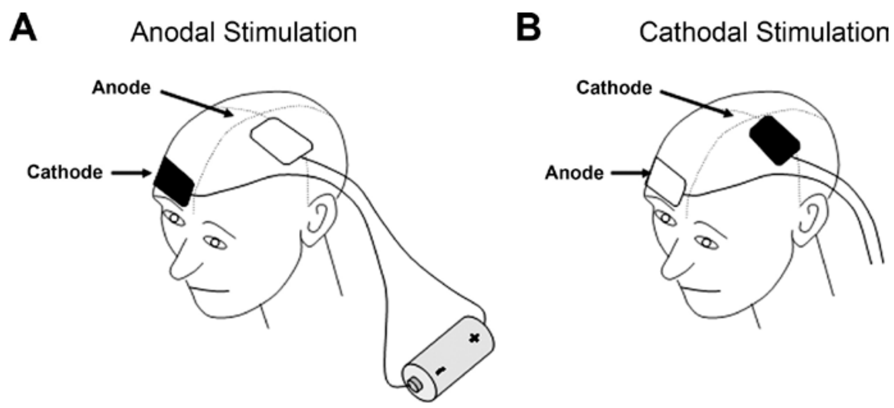
neuroConn DC- STIMULATOR MR

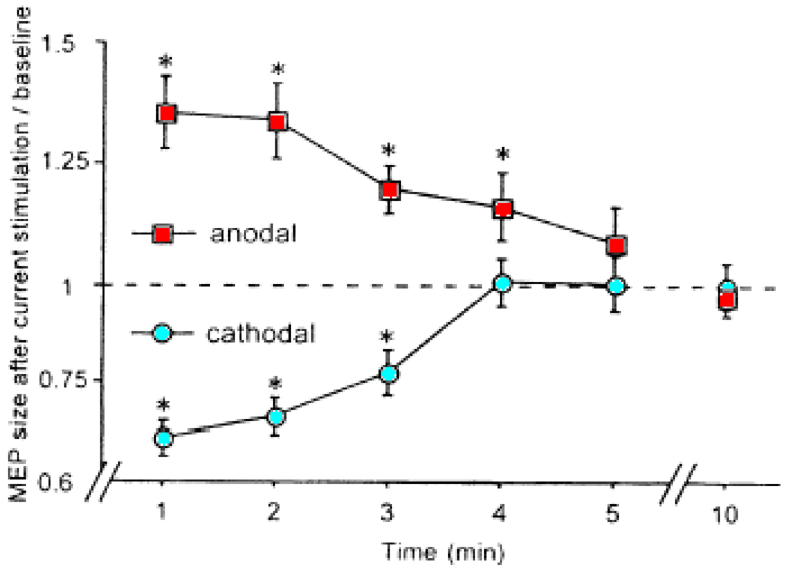
MR compatible version of DC-STIMULATOR PLUS.

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)

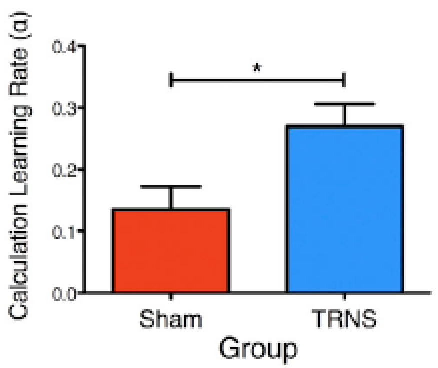
"After-effects" last up to 90 minutes after stimulation (depending on intensity and duration of stimulation)

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 ?

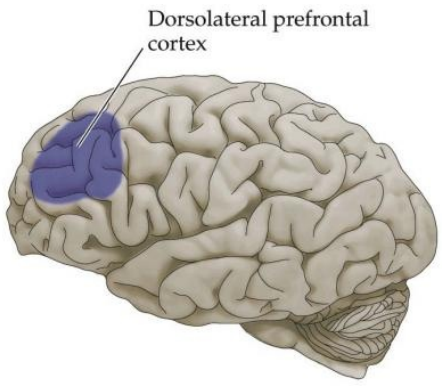
tRNS – Effects on arithemetic ability

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

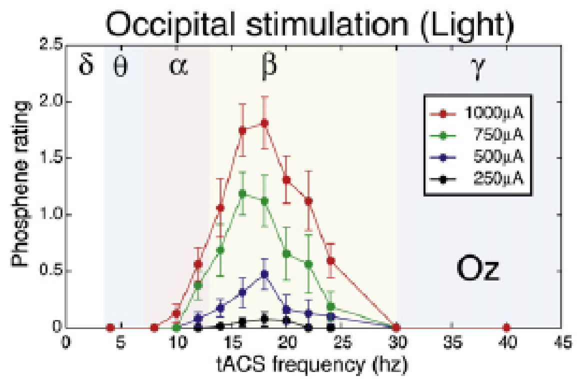
tACS – Effects on visual perception

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

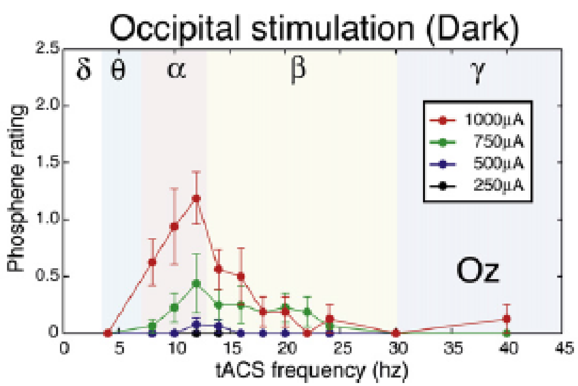
Distinct patterns of dominant frequency as a function of the presence or absence of visual input

- 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.



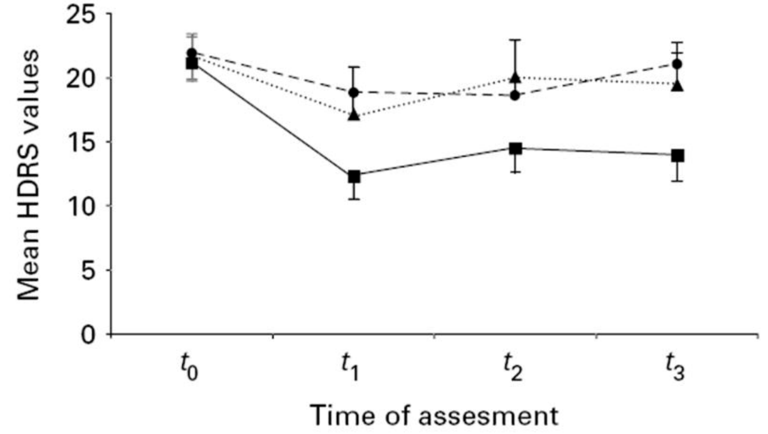
Stimulation at alpha range indices greater intensity phosphenes in dark conditions.

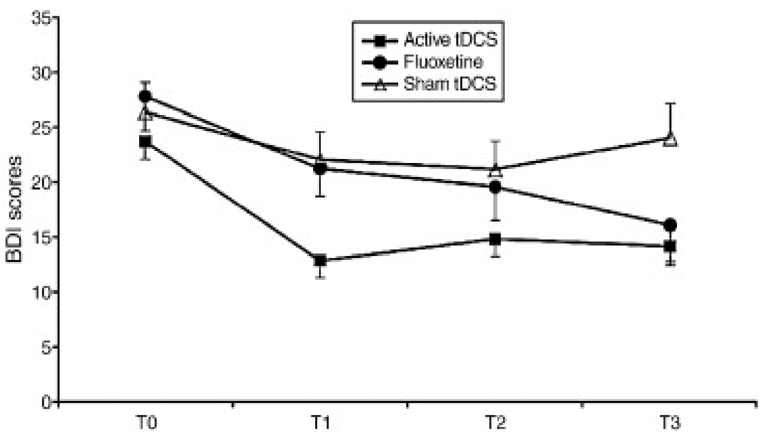
Therapeutic use of tES

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.

Reading

Useful papers

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

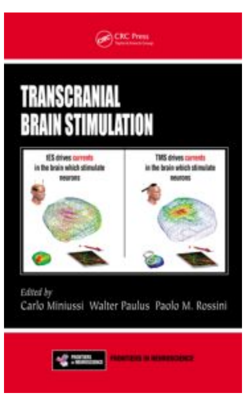
Wagner T, Valero-Cabre A, Pascual-Leone A. (2007) *Noninvasive human brain stimulation*. Annu Rev Biomed Eng 9:527–565.

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.

Books



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