MRC Cognition and Brain Sciences Unit
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An introduction to transcranial brain stimulation (TMS and tES)

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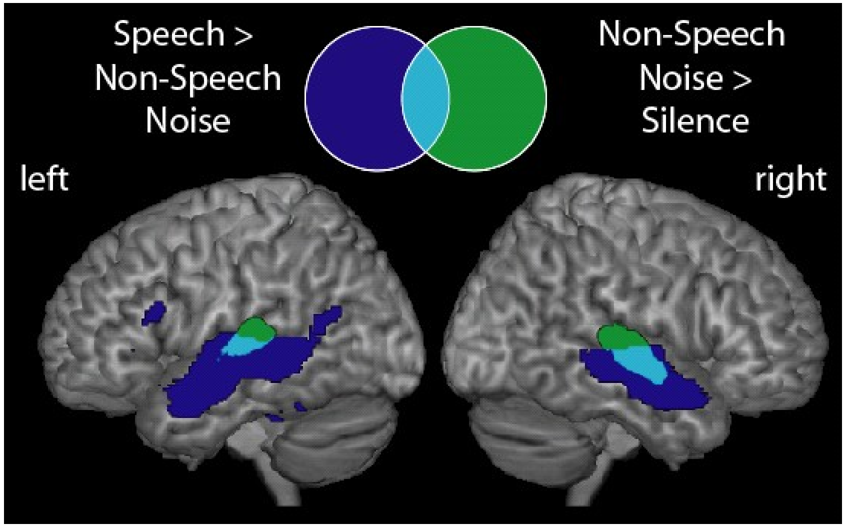
Introduction to NeuroImaging Methods, 4th April 2019.

MRC Cognition and Brain Sciences Unit, Cambridge, UK.

* Thanks to Michael Ewbank

Introduction

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

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
- Given brain plasticity, connections might be modified following lesions

USING BRAIN STIMULATION, WE CAN TEMPORARILY ENHANCE OR DISRUPT NEURAL ACTIVITY

"When the electrode was applied to the speech cortex, it did not cause a man to speak.
It seemed at first to have no effect.
But if the patient tried to speak while the electrode was in place, he discovered to his astonishment (and to ours at first) that he could not find his words."

Penfield (1965)

Deep brain stimulation

https://www.youtube.com/watch?v=uBh2LxTW0s0

RECENT TECHNIQUES ENABLE SELECTIVE MANIPULATION OF NEURAL ACTIVITY WITHOUT SURGERY

Outline

- **Transcranial magnetic stimulation (TMS)**
  - Principles of electromagnetic stimulation
  - Physiological effects of TMS
  - TMS protocols (Single pulse, rTMS, Theta burst)
  - Examples of experimental work

- **Transcranial electrical stimulation (tES)**
  - How does tES work?
  - Physiological effects of electrical stimulation
  - tES Protocols (tDCS, tACS, tRNS)
  - Example of tES as a scientific and therapeutic tool
  - How effective is tES?

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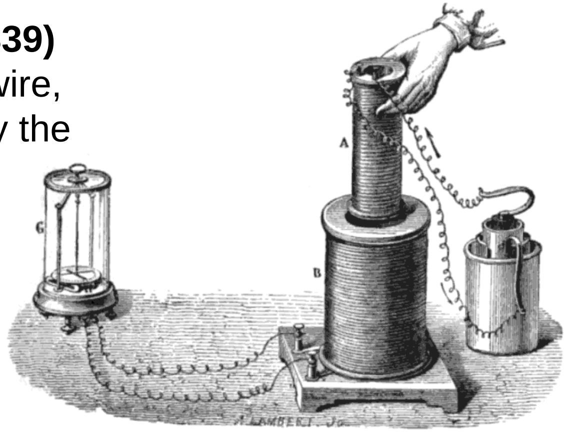
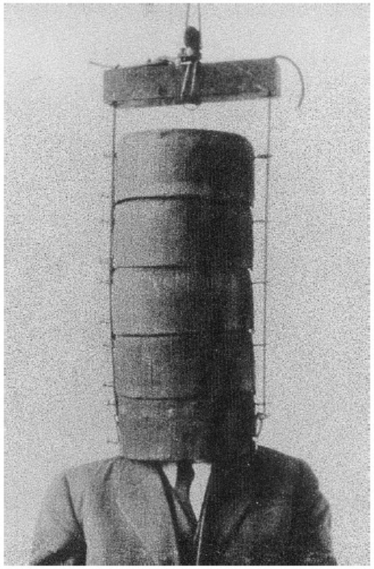
Part I: Transcranial Magnetic Stimulation (TMS)

History of TMS

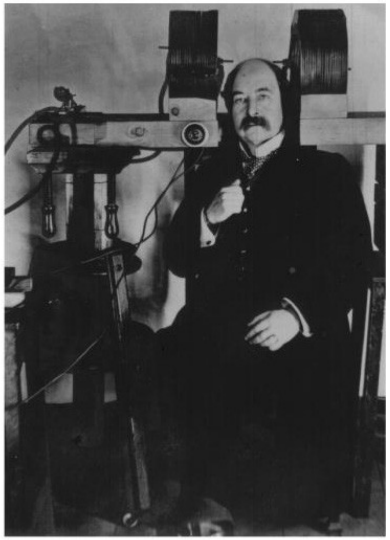
Electromagnetic Induction - Faradays experiments (1831, 1839)
When an electric current is turned on or off in a (primary) coil of wire, another electric current is induced in a nearby (secondary) coil by the fluctuating magnetic field around the primary coil



The current in the TMS coil produces a magnetic field which, if changed rapidly enough, will induce an electric field sufficient to stimulate neurons.



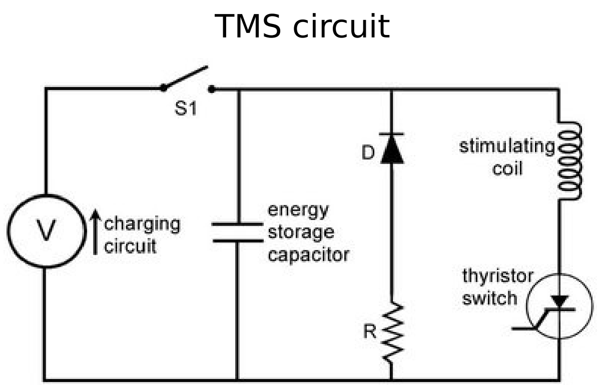
Magnusun & Stevens (1911; 1914)

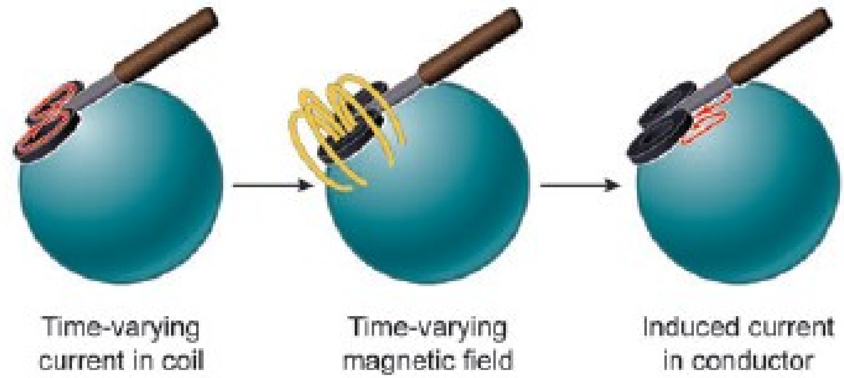


Thompson, 1910

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

What is TMS?

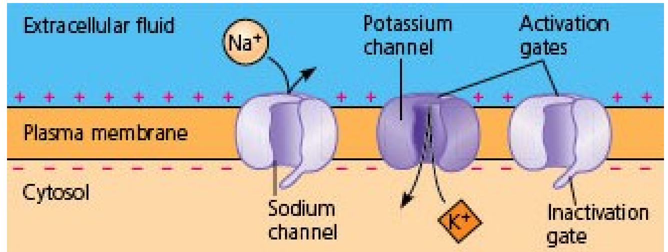




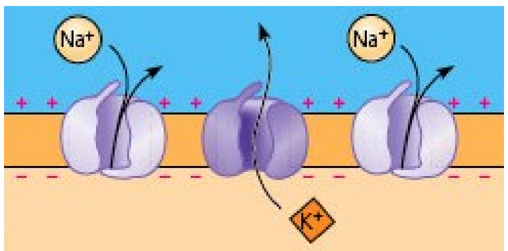
- Electric charge stored in a capacitor is discharged producing a brief, high-current pulse in a coil of wire.
- Electrical current momentarily generates a magnetic field.
- Magnetic field between 1.5T - 3T and lasts approx. 100ms
- Magnetic field penetrates scalp and skull - induces a current in the brain in a direction opposite to the original current in the coil.
- More accurately – “transcranial magnetically induced electrical stimulation”

How does stimulation work? – Action potentials

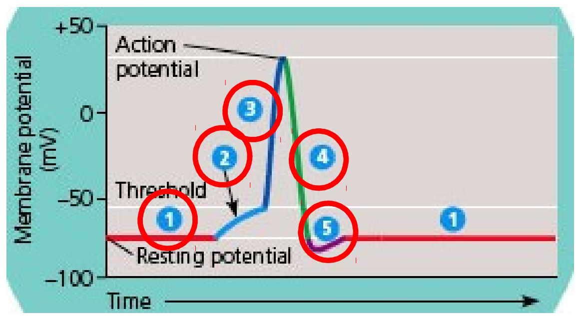
Transmission of a signal within a neuron is carried out by the opening and closing of voltage-gated ion channels.

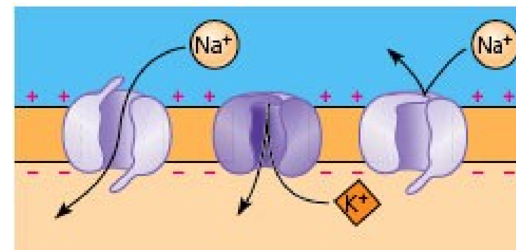


1. Resting state – membrane resting potential of -70 to -80mV

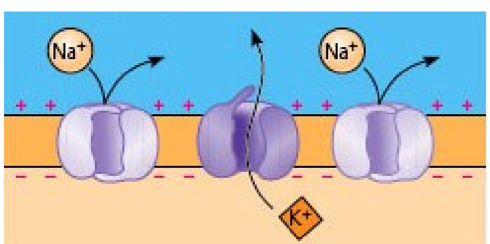


5. Undershoot - Potassium channels still open causing light undershoot. Sodium channels return cell to resting potential.

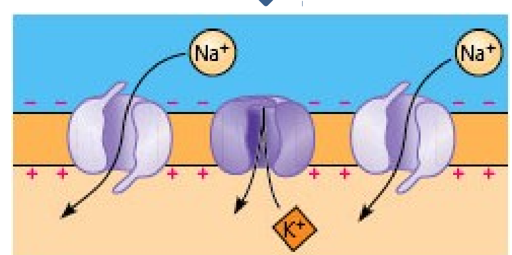




2. Depolarization – Stimulus opens sodium channels. Influx depolarizes membrane (Threshold between -55 and -50mV)

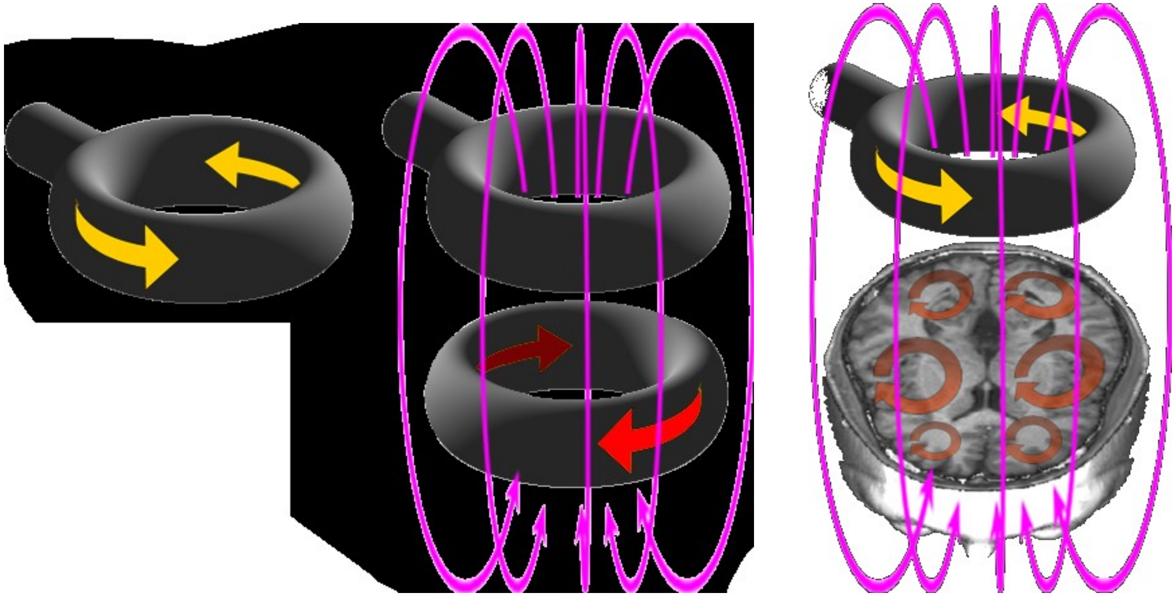


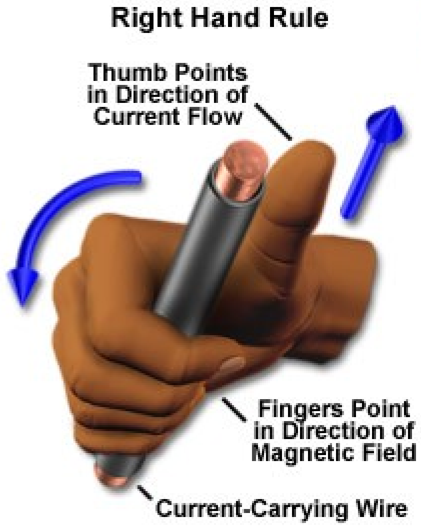
4. Falling phase - Sodium channels close. Potassium channels open. Potassium efflux makes inside of cell negative.



3. Rising phase – Opening of sodium channels makes inside of membrane positive with respect to outside (Potential shifts to +30 to +50mV).

How does TMS work?



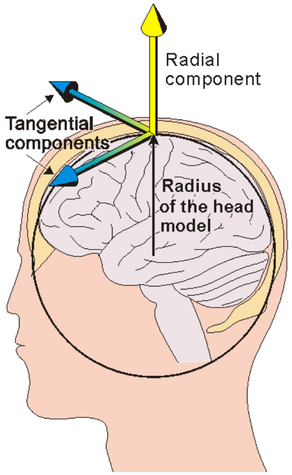


The electric field is induced perpendicularly to the magnetic field - causing ions to flow in the brain

The flow of ions alters the electric charge stored on both sides of cell membranes.

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

Electrical field is tangential to the scalp. TMS will most likely stimulate nerve fibers that align tangential to the scalp.

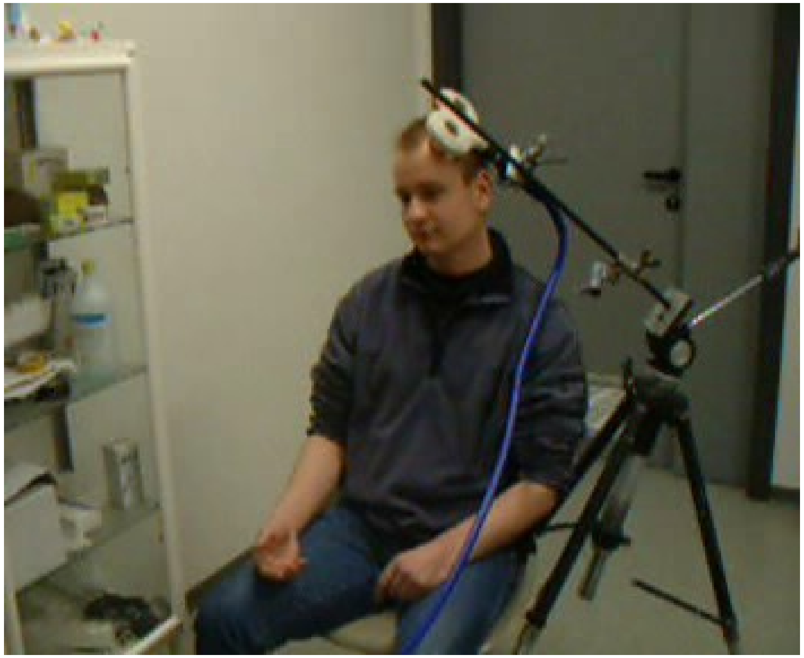


Depth-focality trade off - the ability to directly stimulate deeper brain structures comes at the expense of wider electrical field spread (Deng et al., 2013).

Coils with larger half-value depth cannot be as focal as more superficial coils.

Effects of TMS

TMS effects depend on the brain region being stimulated and protocol used.



When applied over motor cortex, electrical impulses are sent to the peripheral nerves causing muscle twitches. Muscle contraction can be measured as a ‘motor evoked potential’ (MEP).

TMS protocols

Single pulse TMS

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

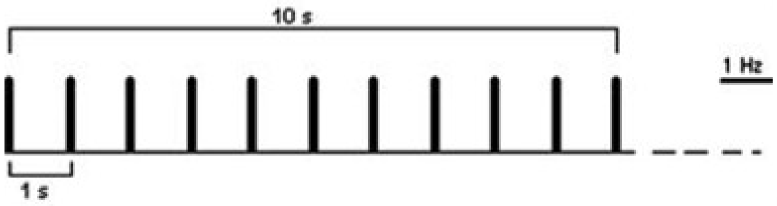
Paired pulse TMS

- Inter pulse interval 1-100 ms
- Delivered to a single target or two different brain regions using two different coils
- Can be used to study cortico-cortical interactions
- 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

TMS protocols

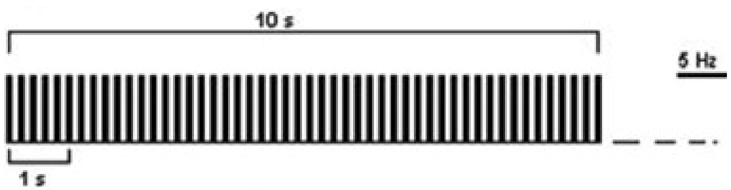
Repetitive TMS (rTMS) – rTMS generates longer-lasting changes in cortical excitability beyond the period of stimulation (hours to days but strongly dependent on protocol).

Low frequency rTMS (<1Hz) reduces excitability:



10 s of rTMS at 1 Hz

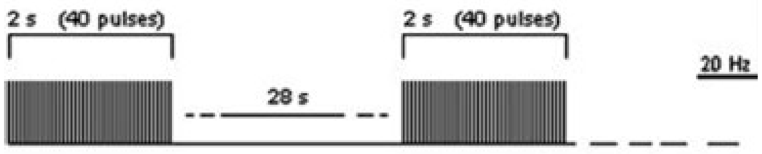
High frequency rTMS (>5Hz) increases excitability (Padberg et al., 2007):



10 s of rTMS at 5Hz

TMS protocols

Patterned rTMS
Repetitive application of short rTMS bursts interleaved by short pauses of no stimulation



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

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

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 (up to 60mins).
    - iTBS leads to increase in cortical excitability.

Sham stimulation

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

Safety issues

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

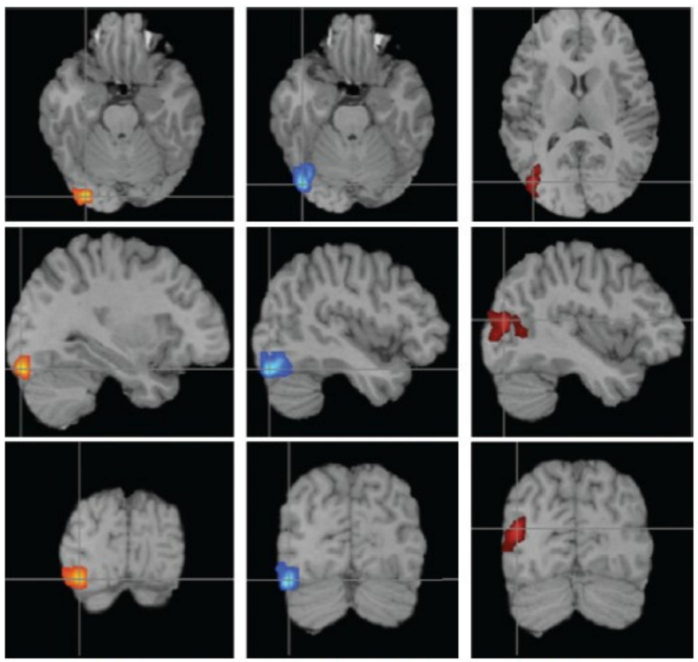
TMS produces loud click (90-130 dB) in the most sensitive frequency range (2–7 kHz). rTMS = more sustained noise. Reduced considerably with earplugs.

Local pain, headache, discomfort - More common with rTMS
depends on location of the coil

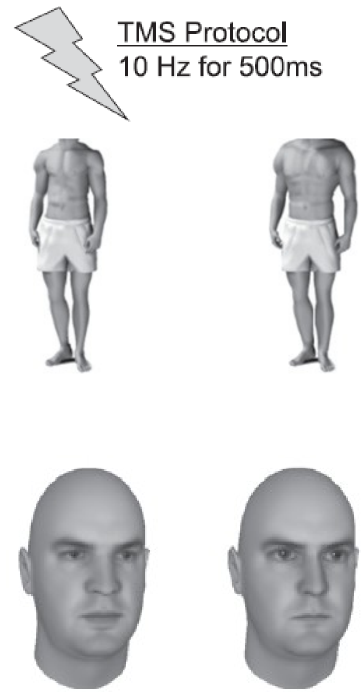
Examples of TMS studies

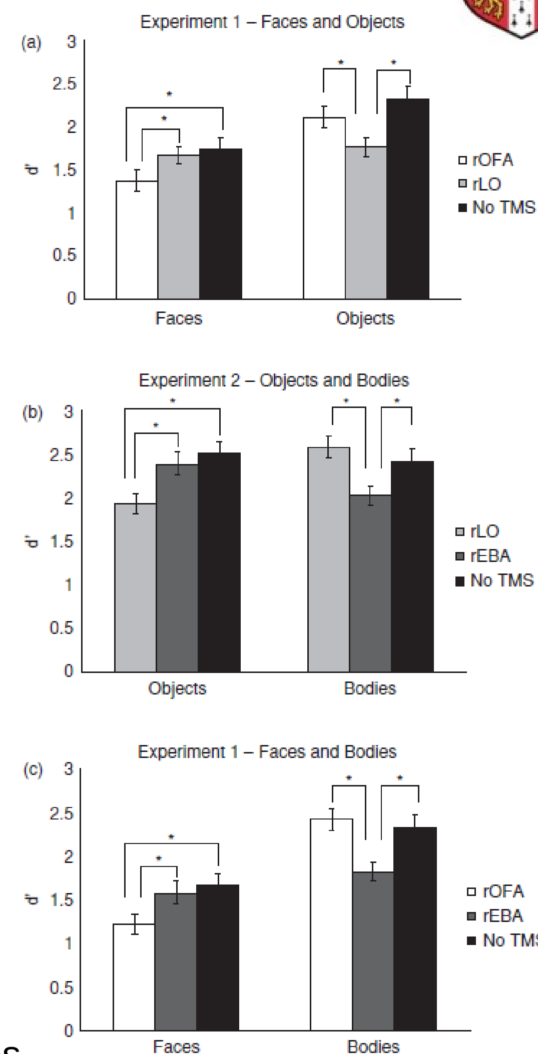
TMS and category specificity in visual cortex

Alpha rhythm, assumed to have an inhibitory role in the brain



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





Regions of occipitotemporal cortex appear to be selective for faces, bodies and objects.

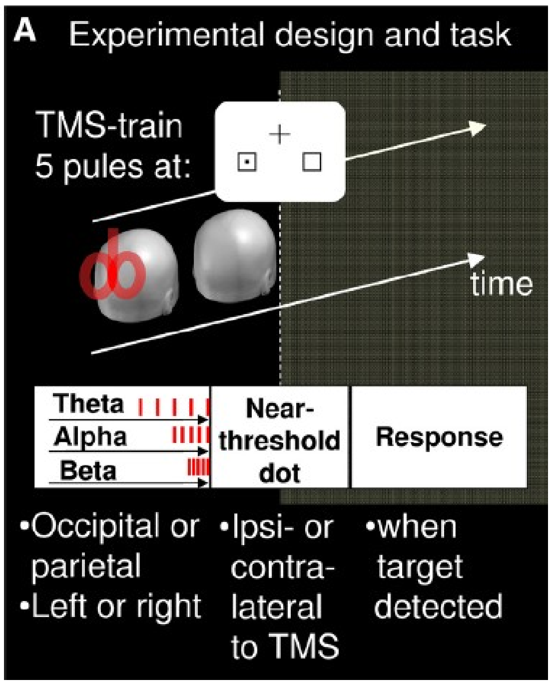
- rTMS onset concurrent with the onset of stimulus

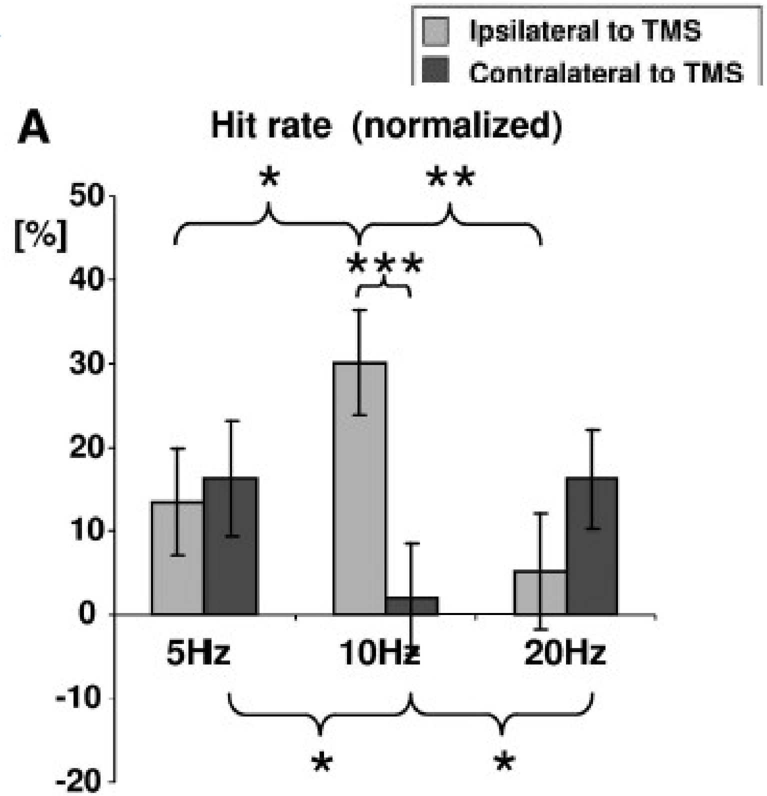
- TMS over rOFA impaired discrimination of **faces** but not objects or bodies
- TMS over rEBA impaired discrimination of **bodies** but not faces or objects
- TMS over rLO impaired discrimination of **objects** but not faces or bodies

Pitcher et al. (2009)

On the Role of Prestimulus Alpha Rhythms over Occipito-Parietal Areas in Visual Input Regulation: Correlation or Causation?

Vincenzo Romei,[1,2,3] Joachim Gross,[1] and Gregor Thut[1]





TMS affects visual detection in a frequency- and spatially specific manner

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

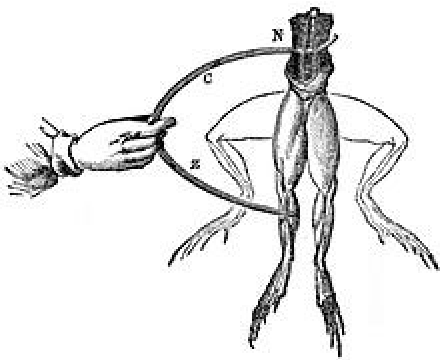
- Superiority of rTMS over a sham control, though the degree of clinical improvement is not large.
- Greater efficacy with longer treatment courses.
- Large variation in approaches (stimulation site, stimulus parameters etc) (Loo & Mitchell, 2005*).*

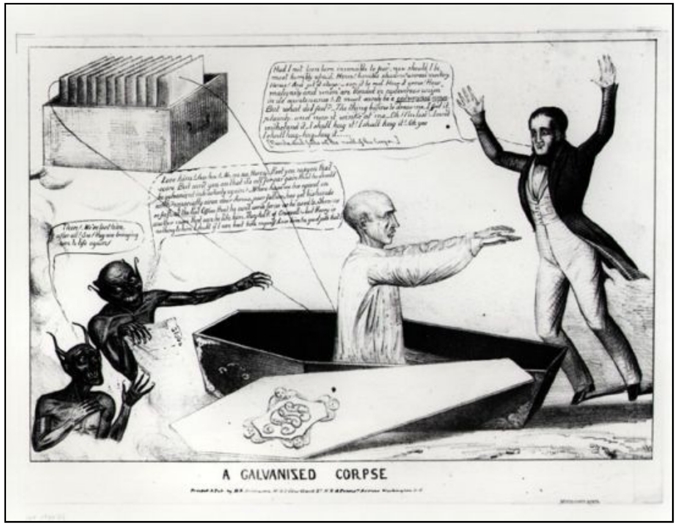
TMS Summary

- **Transcranial magnetic stimulation (TMS)**
  - Works via electromagnetic induction
  - Evokes action potentials in the brain
  - rTMS can increase or decrease neuronal excitability
  - Excellent temporal resolution/ good spatial resolution
  - Safety/tolerance issues
  - Not easily controlled sham

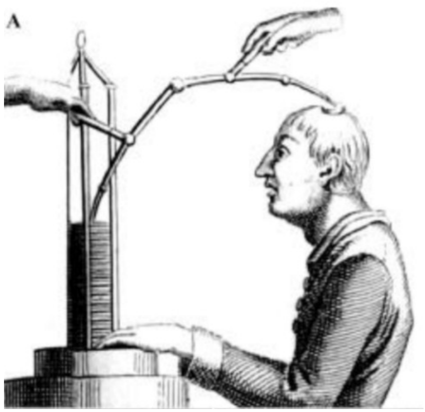
Part II: Transcranial electrical stimulation (tES)

History of electrical brain stimulation





"Galvanism" - Luigi Galvani (1737-1798)



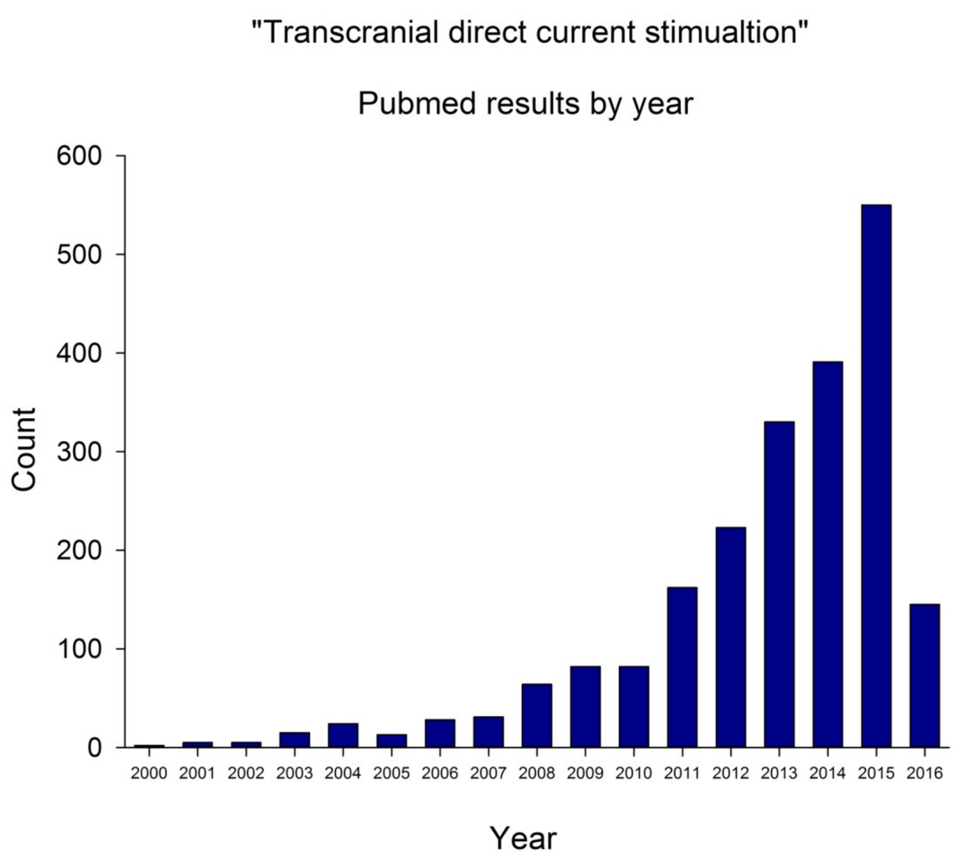
"Complete rehabilitation" of depression/psychosis following transcranial administration of electric current.

Giovanni Aldini (1804)

Electroconvulsive Therapy (ECT) (1938-)

10,000 x more power than tES

Transcranial electrical stimulation ‘hysteria’



Math Skills Improved By Electric Shocks To Brain, Study Suggests

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

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

THE AGE OF ALZHEIMER'S How Down syndrome may

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

The Body Odd,

Nov. 4, 2010 at 12:16 PM ET

The Telegraph

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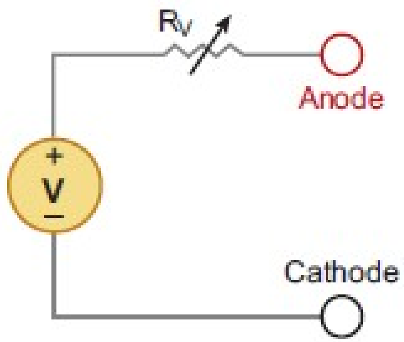
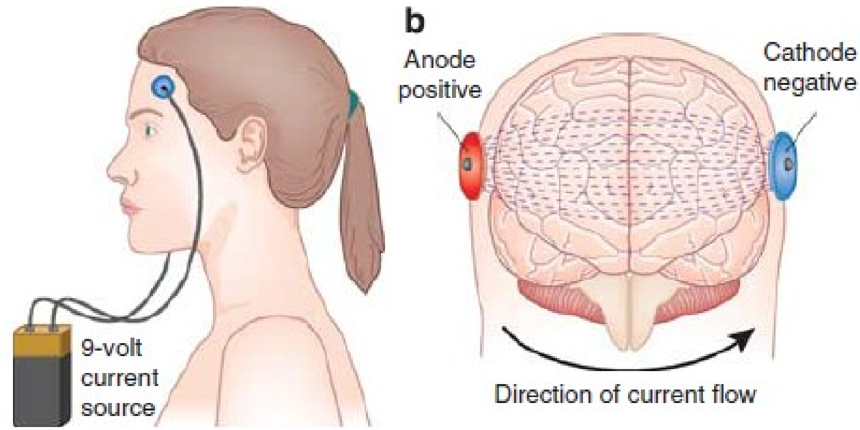
Electric shock treatment 'improves academic performance'

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

What is tES?

Simplest tES setup





George & Aston-Jones (2010)

Transcranial direct current stimulation (tDCS):

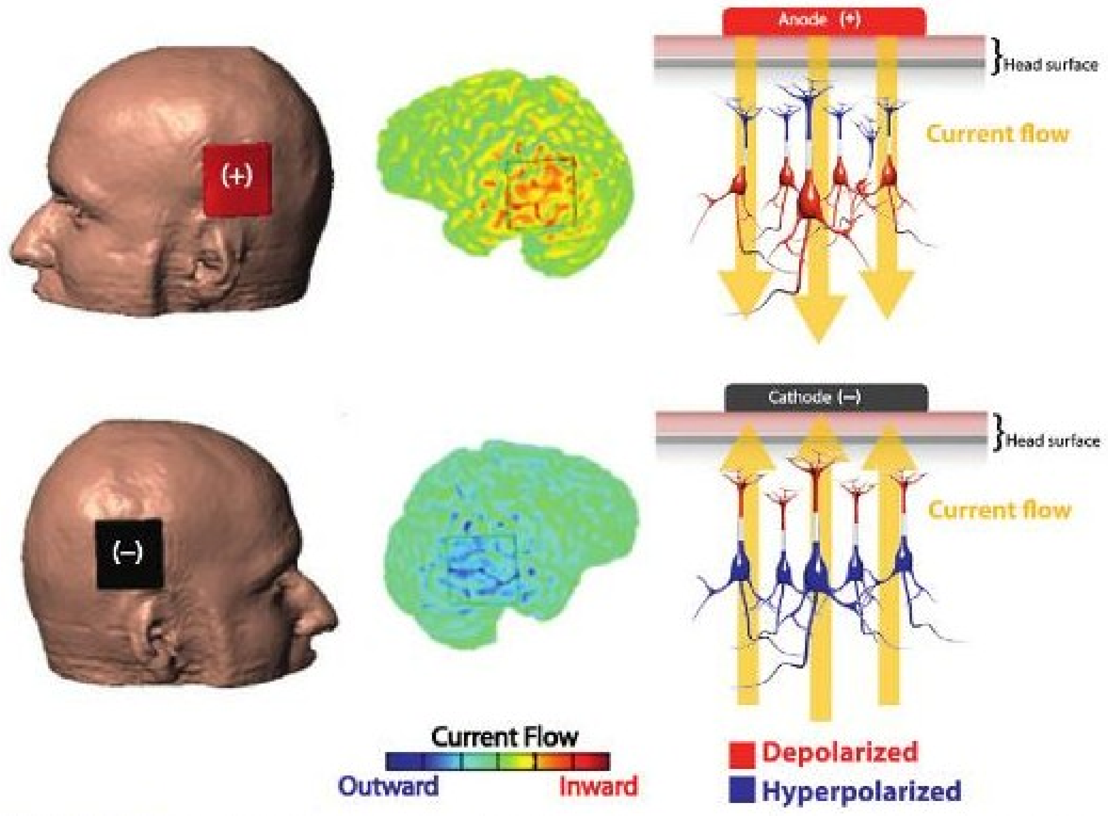
A constant direct current (DC) is applied (*i.e. a flow of electric charge that does not change direction*).

“Anodal” (“cathodal”) stimulation refers to anode (cathode) placed above or close to target of stimulation. Other electrode (often called “reference” or “return” electrode) rather arbitrarily placed above brain or body region not directly involved in task

Transcranial alternating current stimulation (tACS):

Alternating current (AC) is applied (*i.e. flow of electric charge changes direction at certain frequency*).

How does tES work? Theoretical perspective



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

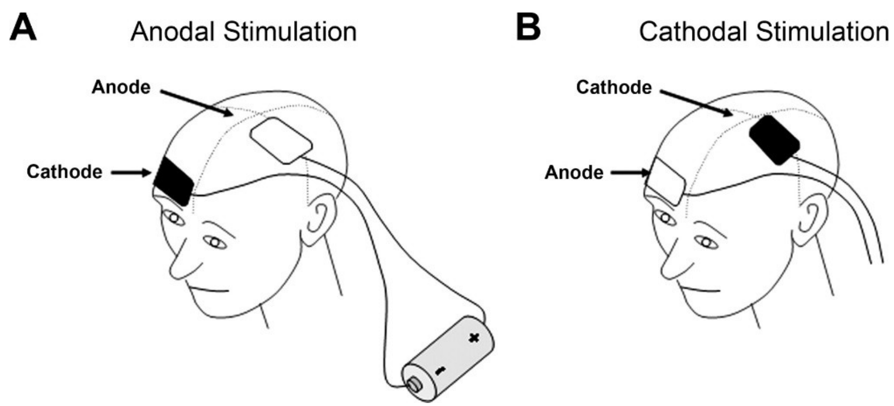
Part of the electric current reaches the cortex.

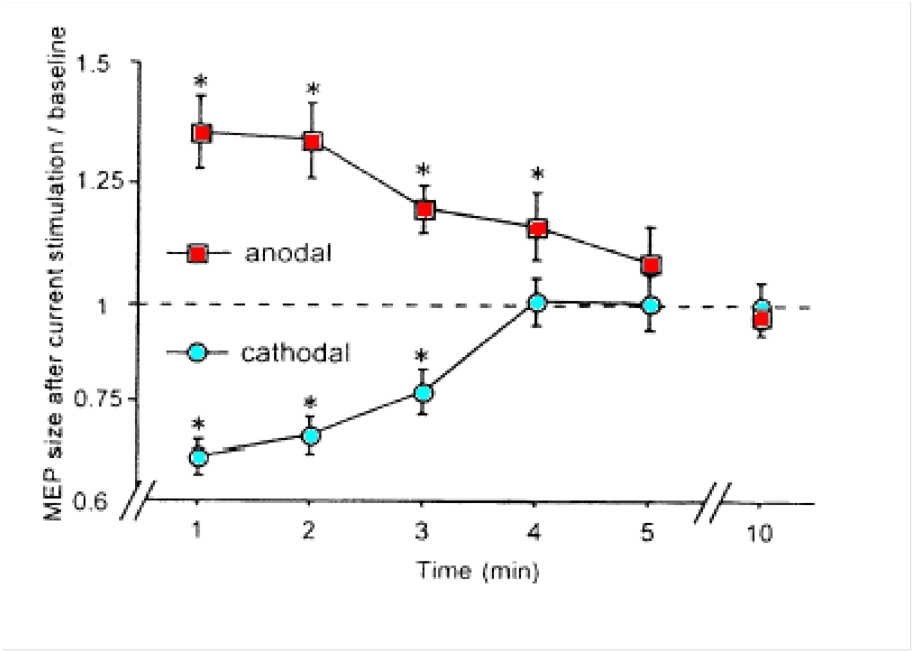
Current flow (inward) under anodal electrode shifts membrane potential towards depolarization: **Increases excitability.**

Current flow (outward) under cathodal electrode shifts membrane potential towards hyperpolarization: **Decreases excitability**.

tES with TMS

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





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

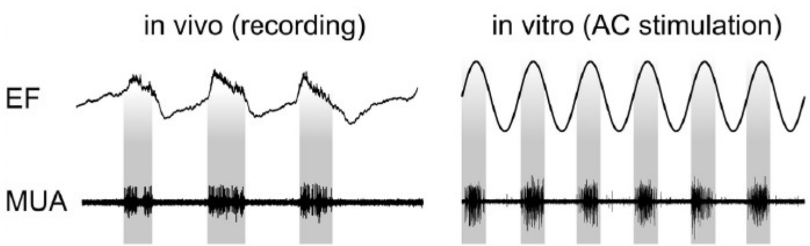
Nitsche & Paulus (2000)

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

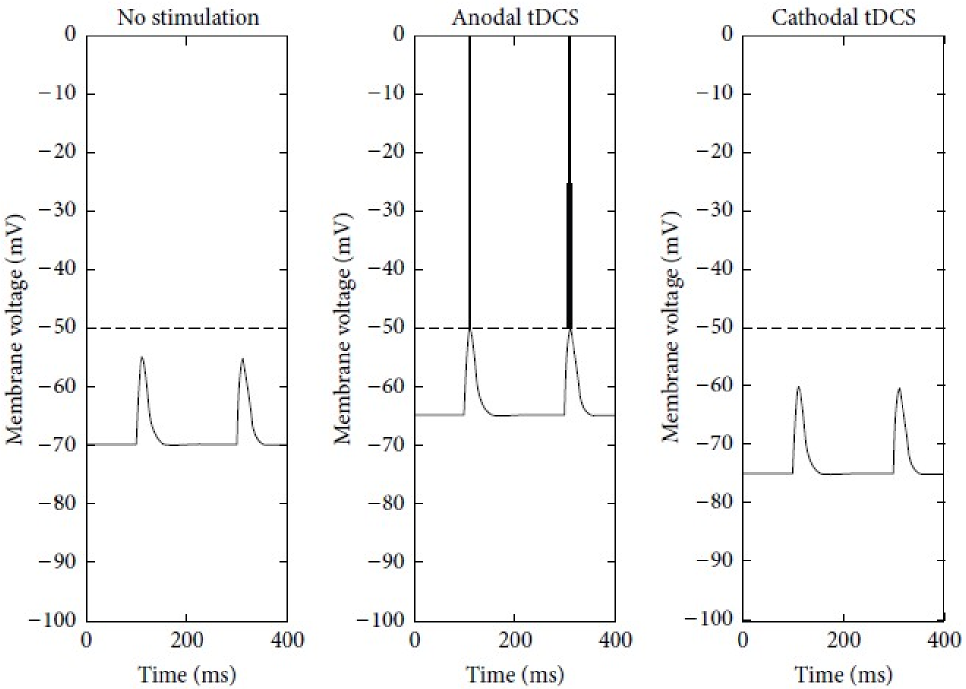
How does tES work?

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 tES applied?

Rubber electrodes in saline soaked sponge pads or using sticky paste, placed on the scalp.

Electrode size from ~9 – 35 cm2

Stimulation sites usually based on EEG electrode placement locations

currents of 1 – 2 mA

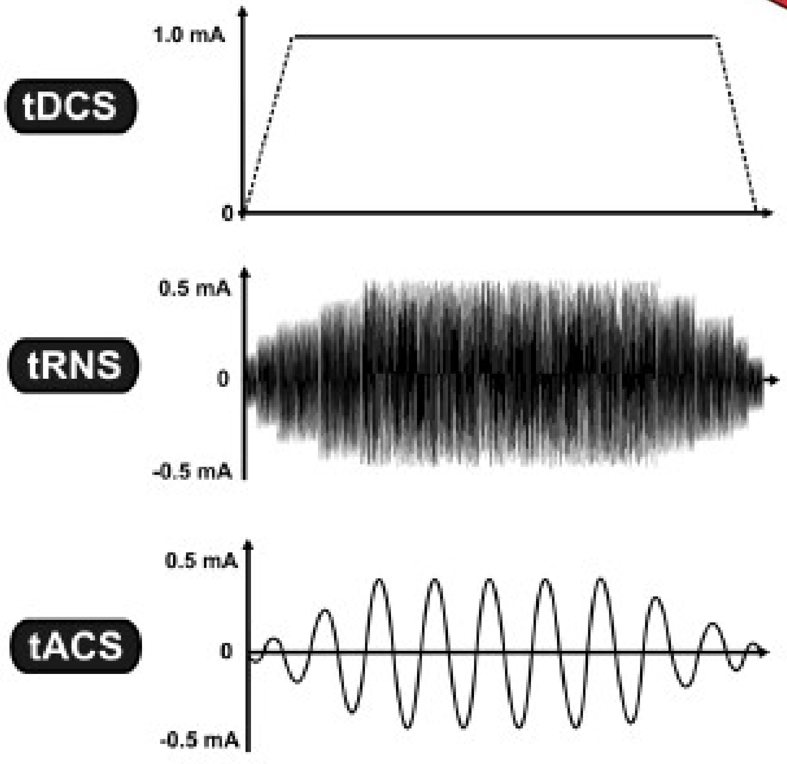
Applied for durations of up to 30 minutes.

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 but alternates between the anode and the cathode (switching polarity) with a sinusoidal waveform. Uses waveform at a specific frequency (Herrmann et al., 2013).



Saiote 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, sodium channels enter an inactivated state (refractory period), but repeated stimulation may allow Na channels to 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).

Stochastic resonance –

A signal that is too weak to be detected can be boosted by adding white noise to the signal –

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

tES – state, duration and amplitude dependent effects

State dependent effects of tDCS

- Anodal stimulation increases excitability of motor cortex during passive condition.
- When performing a motor exercise, excitability was lower after both anodal and cathodal stimulation (Antal et al., 2007).

Non-linear stimulation intensity-dependent effects

- 1 mA cathodal tDCS decreases motor cortex excitability.
- At 2 mA, both anodal and cathodal tDCS resulted in an increase of excitability (Batsikadze et al., 2013).

Duration of stimulation

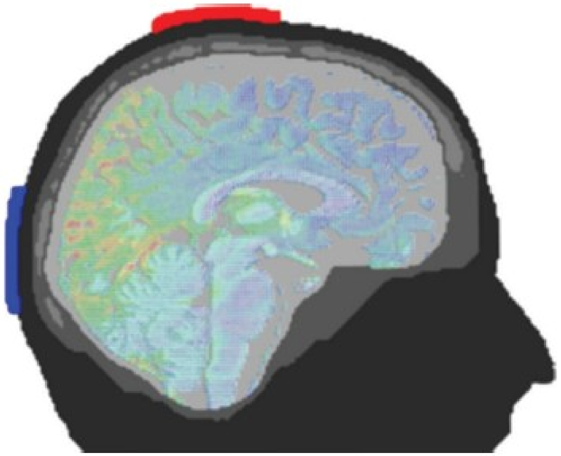
- 13 min anodal tDCS enhances excitability for up to 60 min.
- Prolonging stimulation duration for 26 min converts the after-effects into inhibition (Monte-Silva et al., 2013).

Unclear whether similar effects exist for other (sensory) systems

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

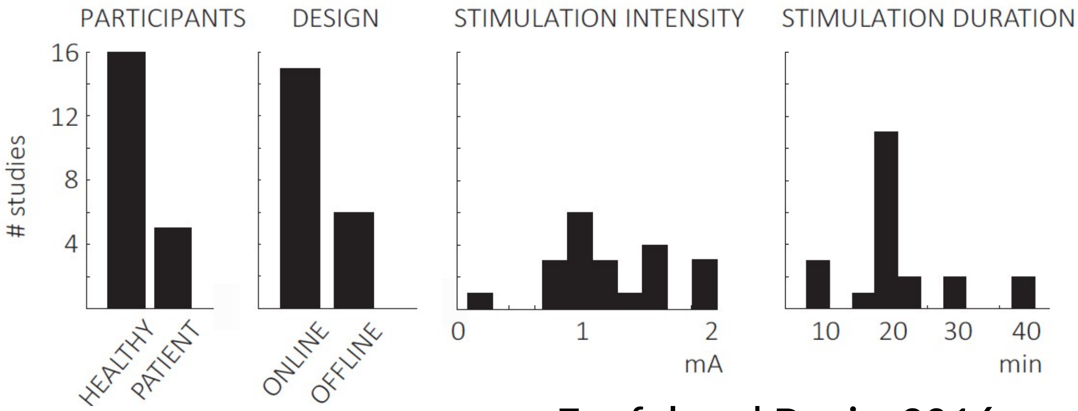


Antal and Herrmann, 2016

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

tES – Safety issues

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

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

Sham stimulation
Current flow is ramped up and down (e.g., for 15 seconds).
Not easily detectable

Safety: Cathodal 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!**

tES vs. TMS

Pros – tES easily tolerated, silent, sham hard to distinguish, low cost, portable

Cons – Lower spatial resolution; underlying mechanisms less understood

Examples of tES studies

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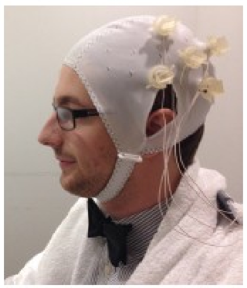
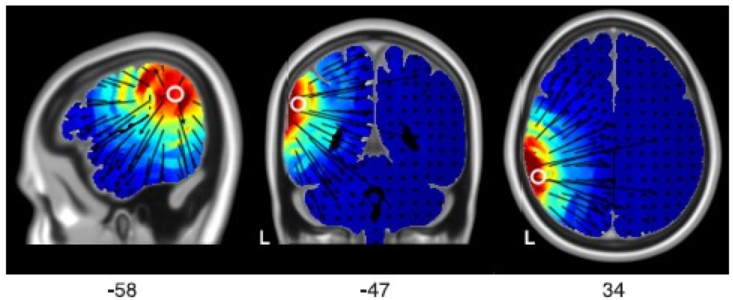
Causal Evidence for a Mechanism of Semantic Integration in the Angular Gyrus as Revealed by High-Definition Transcranial Direct Current Stimulation

Amy Rose Price,[1,2] Jonathan E. Peelle,[3] Michael F. Bonner,[1] Murray Grossman,[1,2] and Roy H. Hamilton[1,2]

Electrode placement



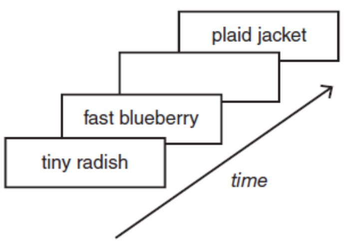
Left angular gyrus electrode montage



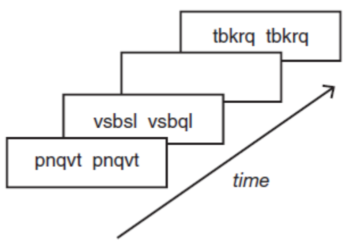
A Word-pair results

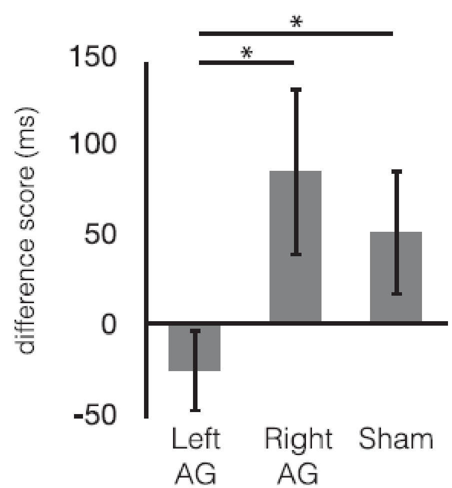
B Letter-string results

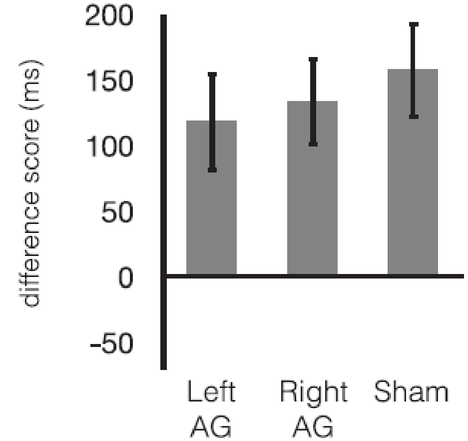
A Word-pair task



B Letter-string task

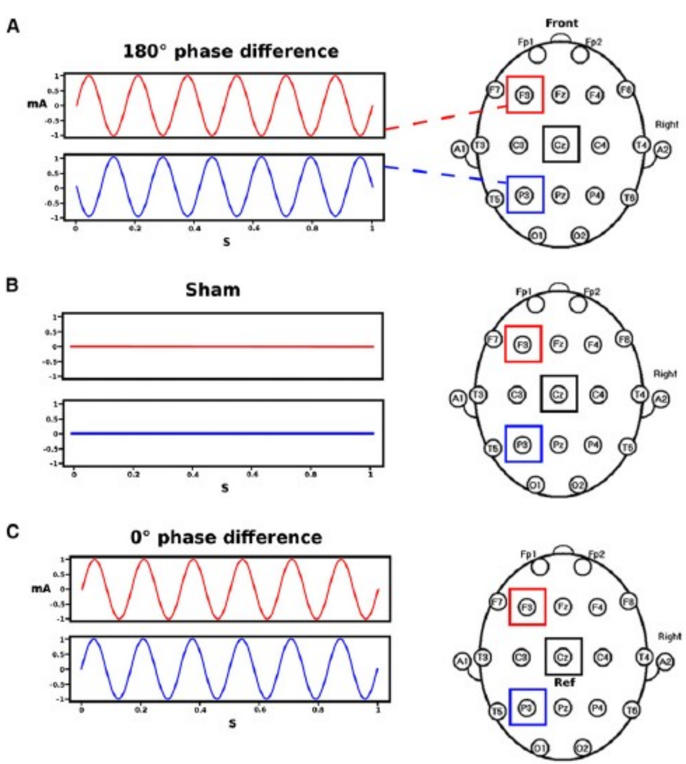


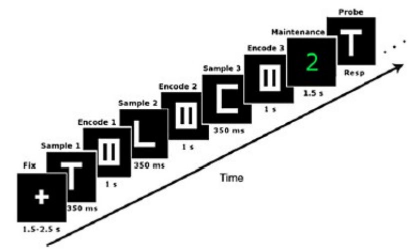




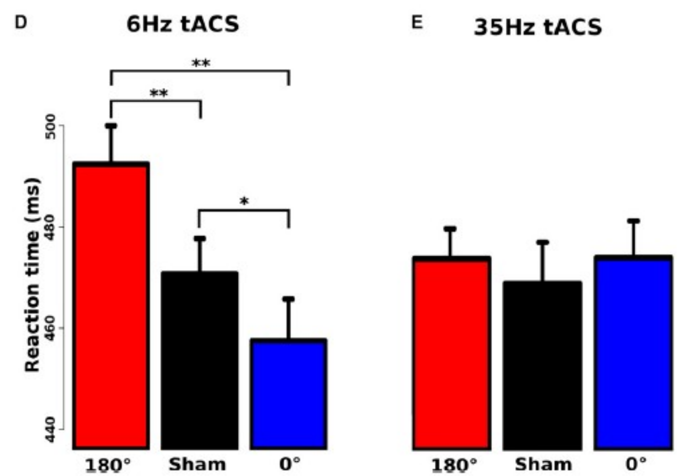
tACS – Effects of phase coupling on cognitive performance

Cortical circuits for central executive functions have been shown to emerge by theta (~6 Hz) phase coupling of cortical areas.





Subjects performed a delayed letter discrimination task.



tACS simultaneously applied at 6 Hz over left prefrontal and parietal cortex with

- Relative 0° (“synchronized” condition) phase
- 180° (“desynchronized” condition) phase
- Sham condition.

Frontoparietal theta synchronization improves visual memory-matching. Desynchronization deteriorates performance.

Evidence of causality of theta phase-coupling of distant cortical areas for cognitive performance.

Polonia et al., (2012)

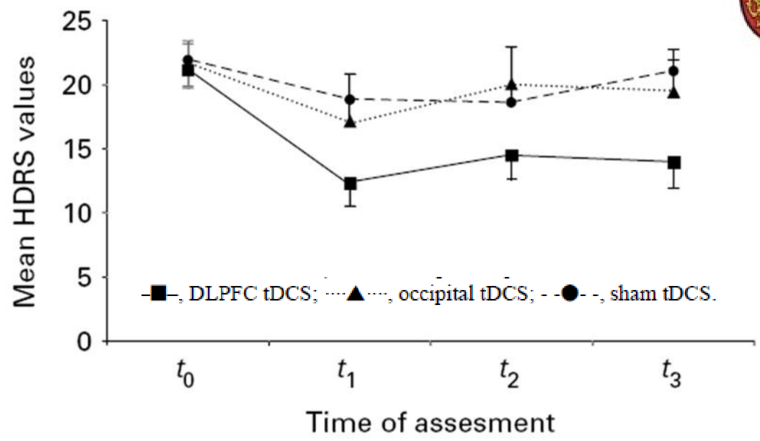
Therapeutic use of tES

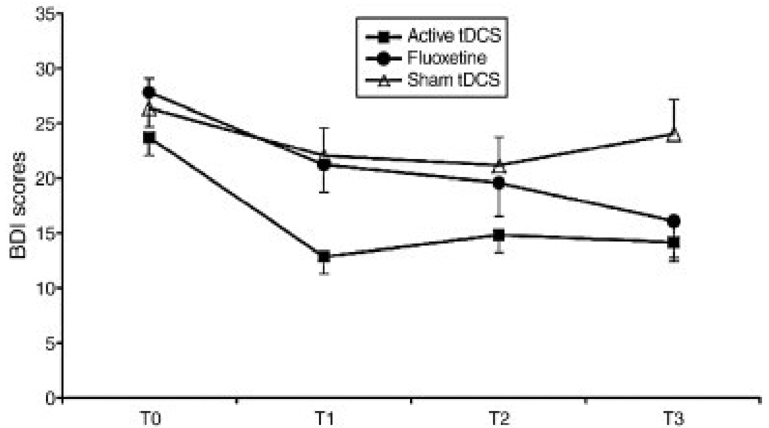
Treatment of depression

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

- 10 sessions tDCS - 2mA

Only prefrontal tDCS reduced depressive ratings
- 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).

How effective is tES? On the one hand…

MRC
Cognition and Brain Sciences Unit

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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

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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

New interventions that promise cognitive enhancement (such as brain stimulation) are typically marked by high levels of early positive results that are typically not sustained over longer periods - probably due to publication bias (Dwan, Gamble, Williamson & Kirkham, 2013; Scherer & Langenberg, 2007).

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

- **Transcranial electrical stimulation (tES)**
  - 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.

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.*

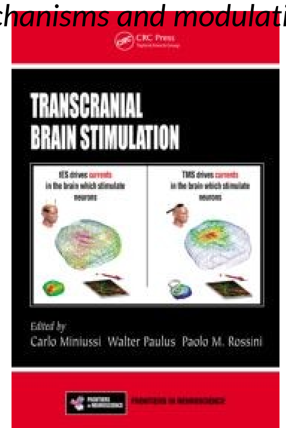
J Neuroscience, 30(29): 9647-50

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).