Wetware Hacking or Artificial Means of Cognition Enhancement

The biophysical approaches

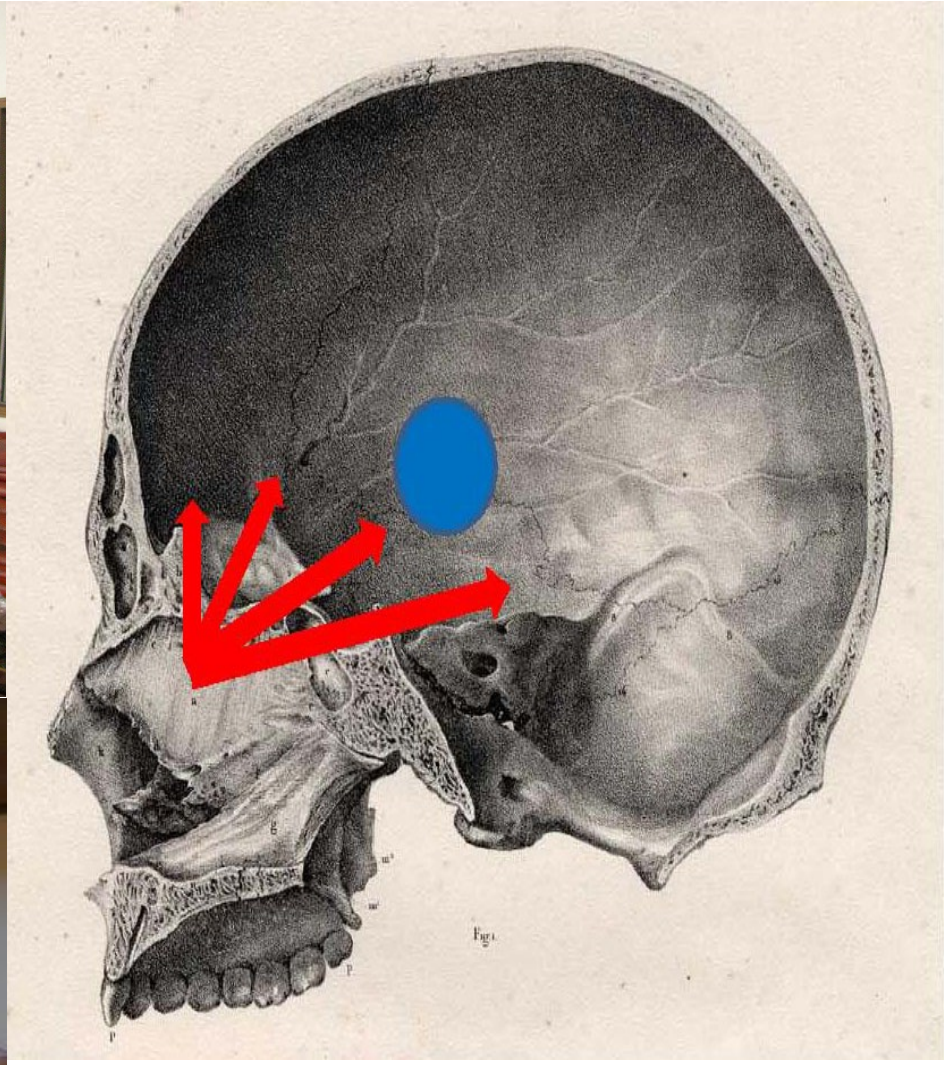
Potential non-invasive ways of biophysical influence upon human consciousness

- Acoustic, including infrasound, directed ultrasound (mechanoreception!), binaural rhythms
- Photoic (commonly used in EEG studies, «sound and light machines», near-IR laser or LED stimulation is the most promising)
- Transcranial Direct Current Stimulation (tDCS)
- Transcranial Pulsed Current Stimulation (tPCS)
- Transcranial Magnetic Stimulation (TMS)
- All of the above in different combinations
- In this talk I'll concentrate on tDCS/tPCS/TMS

Friggin lasers! ☺

- Stimulation with red or near-infrared light, either coherent (laser) or non-coherent (LED), wavelength window 600 to 1150 nm
- Laser light penetrates deeper, LED has a larger footprint
- Longer wavelength = deeper penetration, less power needed
- Pulsed light is reported to be more effective, in particular 10 Hz 50 % duty
- Both have the same action mechanism based on photosensitivity of cytochrome oxidase which increases mitochondrial metabolism
- Neuroprotection has been also reported
- Cortical oxygenation and blood flow to the affected areas are increased
- This distantly resembles both encephabol and vinpocetine, but with focal, targeted effect and ease of its regulation – could be a great auxiliary method to compliment other methods of cognition enhancement
- Can be administered intranasally where the bone is the thinnest
- Positive effects on memory, concentration, mood reported in both patients and healthy volunteers

Safe, relatively inexpensive devices!



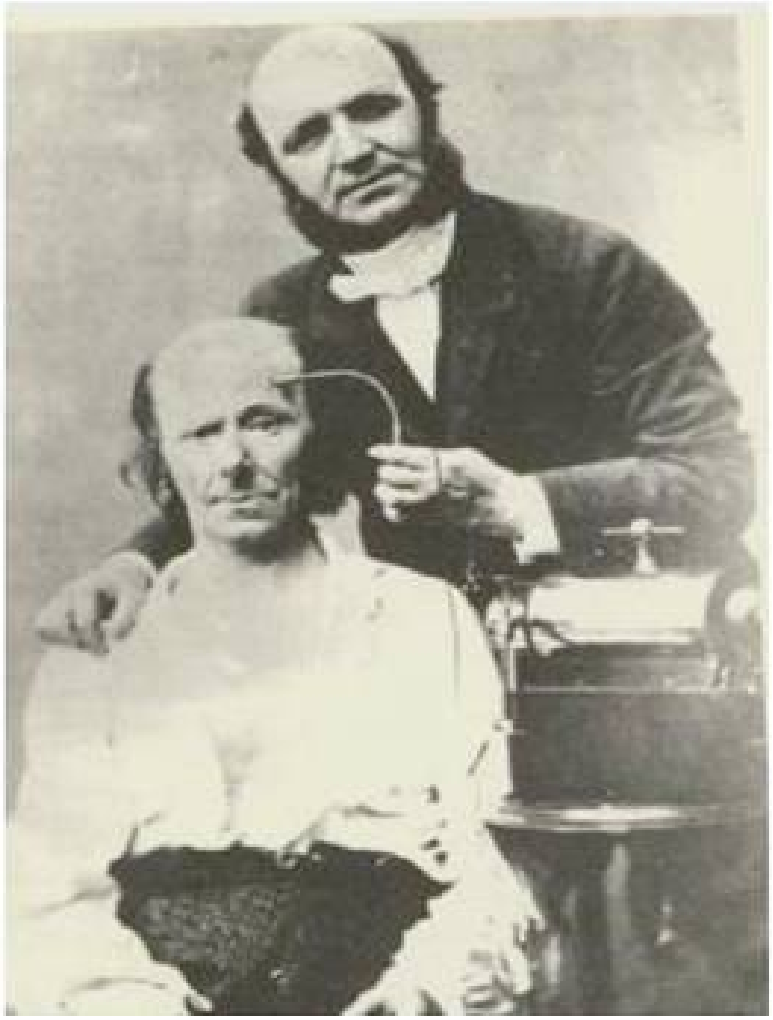
… and ultrasound

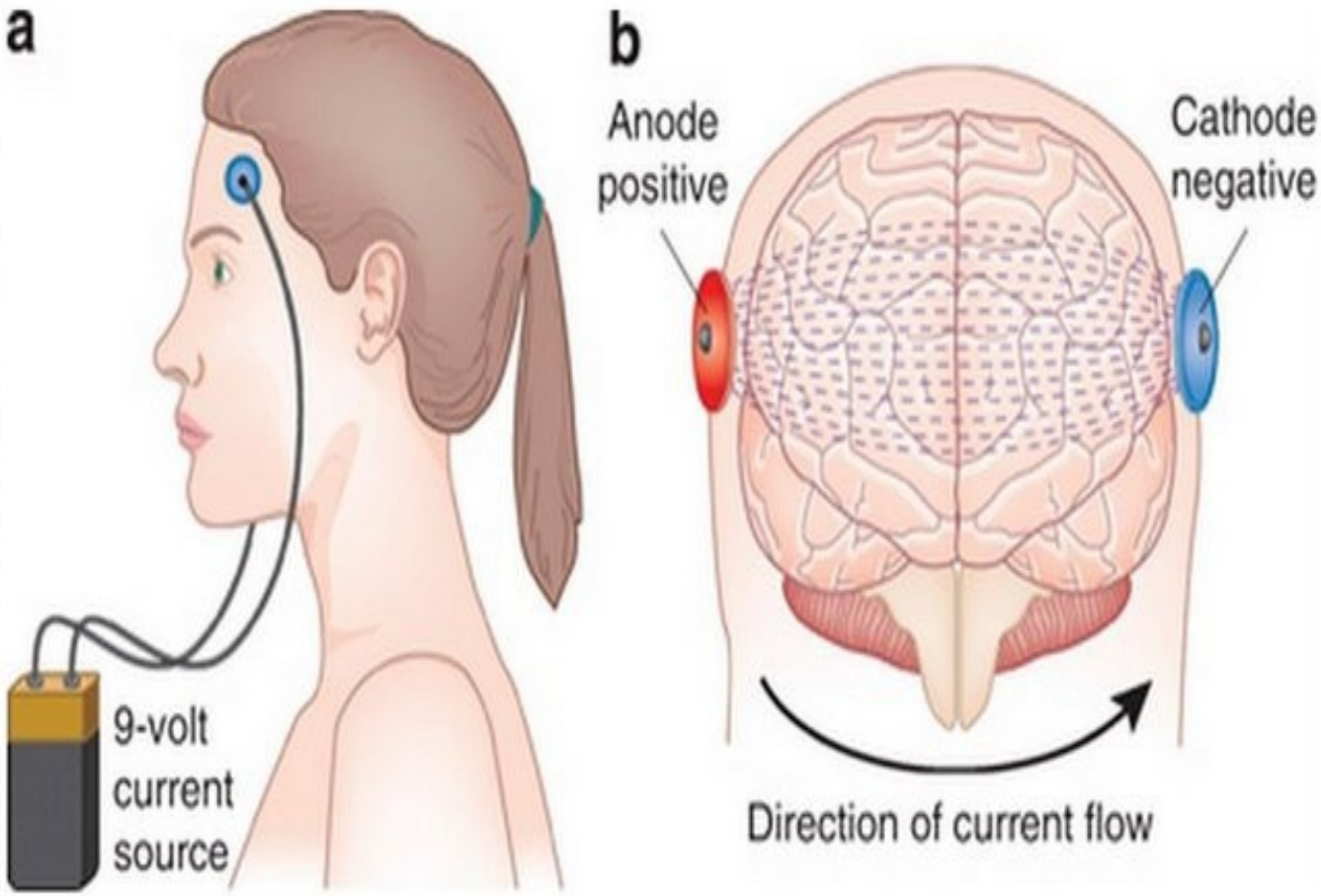
- Mechanical pulses in membranes produced
- Ion channels mechanosensitivity, NMDA receptor included
- Stimulation of neurotransmitter release (non-specific)
- Very low (<10 %) attenuation by the skull
- Gamma waves and fast ripples associated with memory triggered in vivo, BDNF expression increased
- Very high stimulation resolution down to 2 mm!
- Lower frequencies (e.g. 250 kHz as compared to 600 kHz) have larger stimulation success rate and require less power
- Tested in animals, little testing done in humans, any effects on cognition not reported yet, however mood improvement was recently reported

The basic framework to apply

- What can we manipulate? (input variables)
- What does it do? (action mechanisms)
- Can it improve cognition? (study reports)
- Subjecting the method to the nootropic action criteria used in the first part of the talk (verification and comparison)
- Decreasing potential side effects (good practice/safety rules for enthusiasts)

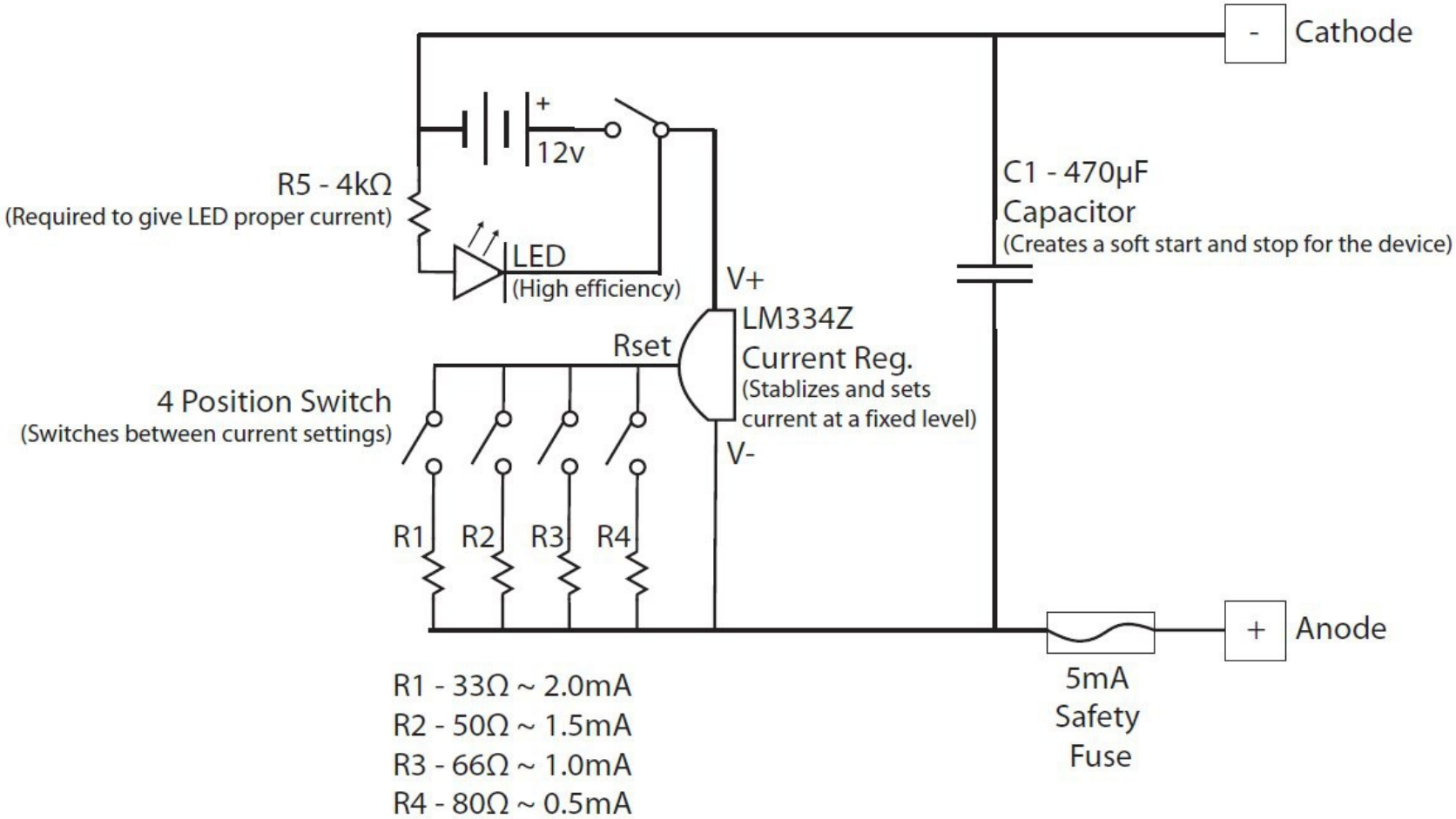
tDCS

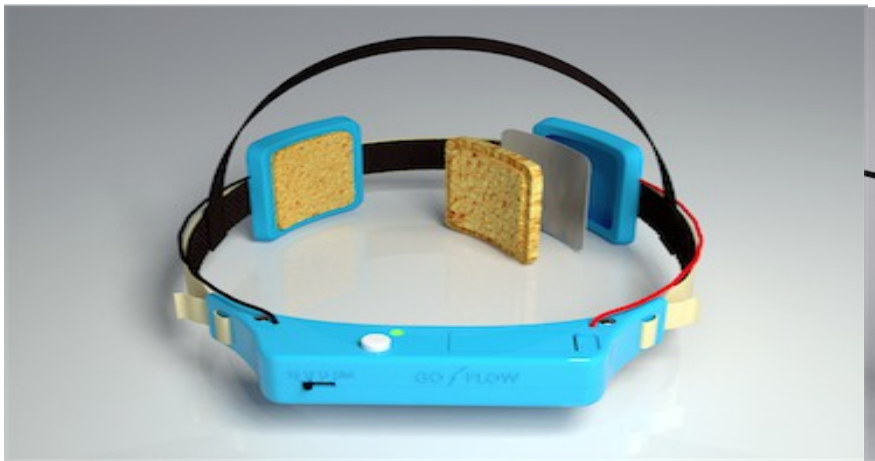


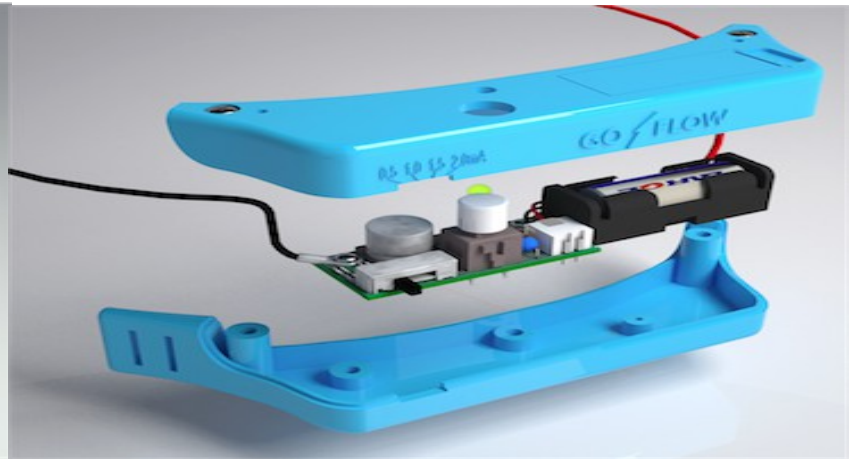


- They used to call it «galvanisation» (and still do in GVS — Galvanic Vestibular Stimulation)

From www.flowstateengaged.com

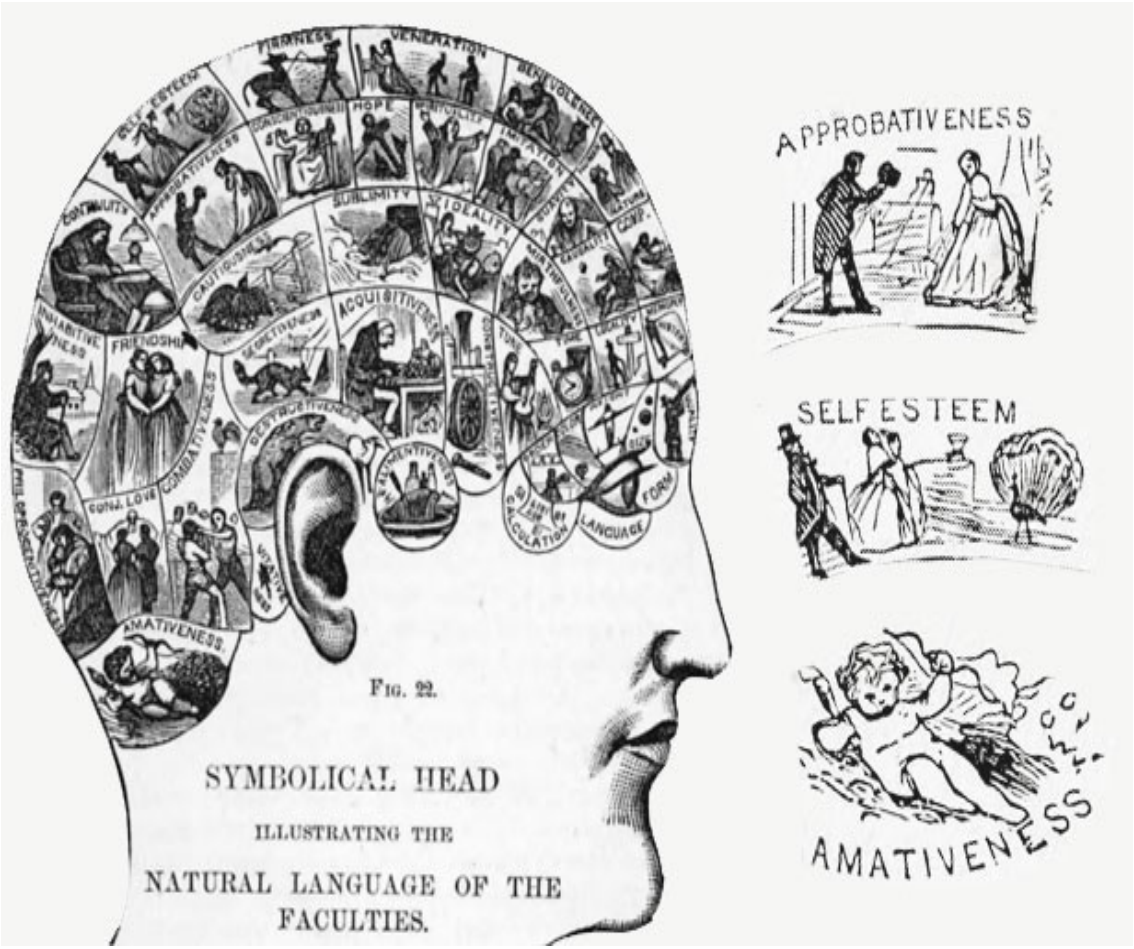






What can we manipulate?

- Current density (mA and electrodes size)
- Polarity («+» and «-»)
- Electrodes number and placement: you have to know brain areas and their function, an EEG cup can greatly assist in electrodes placement
- Duration of stimulation
- Ramping



What does it do?

- DC penetrates the skull and flows from **«+»** to **«-»**
- The current alters neuronal membranes potential
- ***However, it does not cause neurones to fire, it only affects their probability of firing***
- Current at anode shifts membrane potential towards depolarisation: neuronal excitability is increased
- Current at catode shifts membrane potential towards hyperpolarisation: neuronal excitability is decreased
- Neuronal excitability changes can go up to ~40 % of the norm and last minutes to hours after tDCS (at least ~9 min stimulation needed for long-lasting effects)
- The latter implies that LTP or LTD are involved
- The effect can spread to connected brain areas

Can it improve cognition?

- *In a nutshell, cognitive abilities related to the brain area under the anode (and probably other areas well-connected to it) are generally increased*
- There is an avalanche of publications showing such improvements in both healthy volunteers and patients (stroke recovery etc.), as well as rats
- The stimulation of frontal cortex seems to be of primary relevance to this talk, but not only
- The effects are long-lasting (e.g. detected in 6 months) and can be delayed, indicating that sprouting might be at work
- Neurones interconnectivity improvement was shown
- Working memory, motor learning, perception learning, verbal memory/grammar, maths skills, attention, insight, social skills...
- Interestingly, in a study on elderly tDCS was only effective in a group with a higher education level

Subjecting tDCS to the nootropic criteria proposed in the previous talk

- Are LTP/LTD involved? Yes, for long-lasting effects
- Are glutamate receptors involved? Long-lasting tDCS effects are blocked by NMDA antagonists. However, multiple transmitter systems will be affected in the area, its just that glutamate excitatory transmission in the brain is prevalent
- GABA reduced at both anode and cathode, glutamate at cathode only
- Is action neuromodulatory? Yes, natural neuronal activity is enhanced
- Is neuronal connectivity increased? Yes, including interhemispheric
- BDNF is involved. Sprouting was observed in cell culture tDCS studies – but *surprisingly towards the catode!* (McCaig)
- EEG effects: modulation of beta/gamma, theta/alpha (anodal) - *compare to nootropics!* - and delta/theta (cathodal) waves amplitude has been reported, increased connectivity in gamma range! ("binding factor"?)
- There is a single Russian publication (Lomarev, 2012) showing stimulation of inter/intrahemispheric connectivity or breaking pathological connections (in epilepsy)

Decreasing potential side effects

- What to do with the cathode? (*we do not really want a trade-off inhibition at the opposite brain side!*)
  - Place it on the neck or shoulder
  - Use an extracephalic reference electrode
  - Use a small anode (better focal targeting) and large cathode
  - ***Align the stimulation with the task performed!!!***
  - NB! do not forget that for a left-handed person you may have to use the opposite side of the head!
- Local unpleasant feelings like tingling and burning
  - Reduce the current
  - Never use rubber or metal electrodes
  - Ramp the current
- The neuronal sprouting issue still needs to be investigated, including in vivo

Cathodal stimulation use??

- Note the previous talk slide on using weak GABA agonists and the general approach of reducing noise rather than enhancing signal
- Cathodal stimulation looks perfect to be used for that (in the specific brain areas involved!)
- In Dockery at al study cathodal stimulation enhanced planning ability when applied at early learning/acquisition stage minimizing the learning curve!
- Anodal stimulation improved performance when the task is already learned, so a more complex stimulation protocol that reflects learning phases (and tasks!) can be developed!
- Einstallung (set) effect: can we counter it?
- Allan Snyder: left cathodal + right anodal anterior temporal lobes increases insight-requiring task solving 3 times!
- **“Lateral thinking” can be artificially enhanced!**

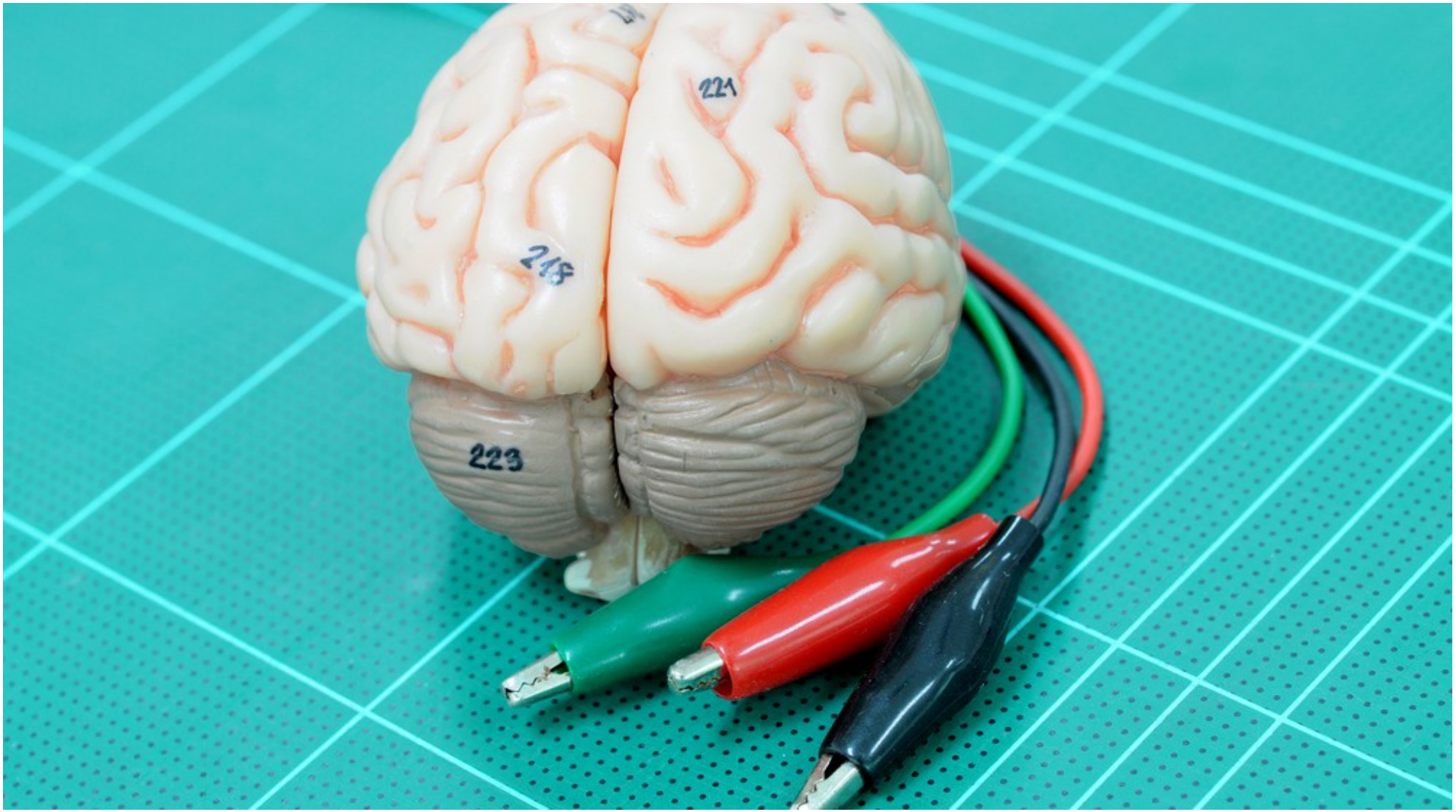
What about trade-offs?

- Developing one ability can naturally come at the cost of another
- Dominant excitation in one area of the brain can provide inhibitory input to another connected area
- In tDCS there is always a cathode (“return electrode”) somewhere ☺
- Luculano & Kadosh: a trade-off between a new numerical notation learning (posterior parietal cortex stimulation) and automaticity of the already learned numerical skill (dorsolateral prefrontal cortex stimulation) reported
- Could there be similar costs in other cases, even with an exocephalic cathode, and especially in relation to hemispheric symmetry?
- However, these costs can be technically bypassed, and even more -become foundational for more complex stimulation protocols design
- Or, can they be acceptable as a matter of personal choice/lifestyle?

Phenomena to consider

- Anodal tDCS applied before the learning task can actually have an opposite effect (a use case for the cathodal tDCS of the same area switched to anodal later to reinforce learning?)
- Anodal tDCS applied for too long can also have an inverse effect, and intervals in tDCS application are important; such stimulation and interval times could be learning task and learning phase - specific
- Repetitive tDCS effects do build up – same as with ampakines!
- Anodal tDCS is more effective at higher task load (like the ampakines!)
- tDCS preconditioning can abolish cognitive enhancement by rTMS
- Watch out for tDCS interaction with psychoactive drugs!
  - D-Cycloserine (a potential nootropic!) largely enhances anodal stimulation while having no effect on cathodal inhibition – a potential for combined use demonstrated!
  - Nicotine patch can block tDCS effects!
  - Na and Ca channel blockers abolish anodal stimulation effects
  - L-DOPA can convert anodal stimulation into inhibition!
  - Citalopram (an SSRI) can convert cathodal inhibition into stimulation and prolong it!

tACS, tPCS



What can we manipulate?

- Amplitude (Voltage)
- Frequency
- Duty
- Wave shape/function (typically a byphasic square wave is employed but could be quite complex)
- Wave modulation (FM, AM etc.)
- Sweeping (frequency, amplitude)
- Pulses and bursts
- Ramping
- Combination of AC and DC stimulation can be used
- Duration of stimulation
- Electrodes size, number and placement (less critical than in tDCS)

But any decent function/signal generator will really do the job...

What does it do?

- Electrosleep was the first tPCS treatment in therapeutic use
- LIDA machine, «electrohypnotist» (note that capacitor plates can be used instead of head electrodes)
- The current is diffused across the scalp and about 40 % of it gets into the brain (from temporal placement limbic diffusion predominates)
- Unlike tDCS, tPCS/tACS can cause neurones to fire, if the depolarising threshold is reached
- Below the threshold AC will cause cycles of depolarisation / hyperpolarisation (e.g. -40mV ↔ -80mV) → producing noise!
- It will entrain different oscillators or resonators in the brain, including the brain waves, but not only!
- It can affect a specific neurotransmitter system (e.g. Limoge or Lebedev current and endorfines release)
- Action on peripheral (cranial, vagal) nerves can be important (GVS!)
- As compared with tDSC, tPCS/tACS action appears as more «pharmacological», with tDSC targeting specific brain areas and tPCS/tACS — specific frequency/amplitude/phase ranges

Can it improve cognition?

- Typical current medical use of tPCS/tACS include treating anxiety, depression, insomnia, chronic pain
- It can induce both LTP and LTD providing the stimulation is sufficiently prolonged/repetitive
- Memory is affected by sleep (primarily Phase 4, delta waves) and there were reports that electrosleep improves memory more than normal sleep
- There are physiologically justified correlations between some forms of memory and brain waves (in partucular gamma and theta activity)
- So, if we entrain the “right” brainwave(s) we will cause memory improvement, not? If only it was that simple...

A few words on brainwave entrainment (phase locking) approach

- The so-called «entrainment movement» started in 60-es and peaked in 70-es, but then lost popularity as it did not meet the (overblown) expectations. But why did it happen?
- Correlation is not causation (see pirates vs global warming!)
- Many links between «brainwave X» and «state of consciousness Y» turned out to be rather dubious
- Brainwave bands usually correspond to rather general, non-specific consciousness changes (e.g. arousal, relaxation)
- Where in the band spectrum would you stimulate/entrain?
- Spatial distribution of waves in the brain is important, and tPCS/tACS is not the method of choice to entrain them focally
- The brainwave bands are (non-linearly) interconnected
- When trying to entrain a specific brainwave you can hit other oscillators/resonators at lower levels of brain organisation, producing unpredictable or even adverse effects!

Type	Frequency (Hz)	Brain Location	Cognitive Description
Delta	up to 4	•Frontal (adults) •Posterior (children)	•Occurs in sleeping adults and is frequent in babies •Indicative of a continuous attention task (Kirmizi-Alsan et al. 2006)
Theta	4 to < 8	•Various locations	•Common frequency found in young children •Indicative of drowsiness or arousal in older children and adults •Idling •Has been found to spike when person is actively attempting to repress an action or response
Alpha	8 to 13	•Posterior regions of head, both sides •Higher in amplitude on dominant side •Central sites at rest	•Indicative of a relaxed/reflecting state •Closing of eyes
Beta	>13 to 30	•Occurs on both left and right sides of brain •Has a symmetrical distribution of activity •Most evident frontally	•Indicative of an alert or focused working state, active, busy or anxious thinking or active concentration
Gamma	30 to 100+	•Somatosensory cortex (both left and right sides of brain, midline to front and back)	•Indicative of sensory processing (hence association with somatosensory cortex) •Also shown during short term memory activities.

Some relevant study reports

- **Dementia:** word recall, face recognition and motivation boosts by tACS have been reported
- **Healthy volunteers:**
  - Entraining fast hippocampal ripple oscillations (100 to 250 Hz) associated with memory encoding
    - 10 min tACS with 1mA 140 and 250 Hz improved motor learning
  - 60 Hz tACS applied over visual cortex enhanced contrast perception
  - Motor learning improvement over M1 — 10Hz, 400 microA – alpha wave entrainment could be a noise reduction measure and note that with age alpha activity goes down, so promoting it can counter aging effects!
  - Significant improvement of attention — 15 kHz (why such a high frequency was selected?)

tSOS = tDCS + tPCS

- tSOS (anodal slow oscillation stimulation) studies
- tSOS = tDSC + 0.75Hz 260 microA sine wave pulsed current
- Studies during sleep period 4 (delta, non-REM):
  - tSOS improves declarative memory consolidation
  - Enhancement of 0.5-1Hz delta power, but also increase in counts and power of slow sleep spindles (8-12Hz)
  - Sleep stage 4 (delta) composes only 5–15 percent of total sleep time and may be completely missing after 40 years of age – but can we trigger it with tSOS hence alleviating aging effects?
- Studies during wakefulness (same protocol):
  - No effect on consolidation of memory, however memory encoding is facilitated if tSOS applied during learning
  - Most interestingly, apart from enhancing slow wave oscillations strong increase in global Theta (and in a state of quiet wakefulness — Beta) activity occured

Subjecting CES to the nootropic criteria proposed in this talk

- Are LTP/LTD involved? They can even be triggered! And long-lasting effects of tACS/tPCS are evident. A common view of "high frequency stimulation -> LTP, low frequency stimulation -> LTD" has been recently challenged
- Are glutamate receptors involved? At least in in vitro studies in hippocampal slices it seems to be the case
- Generally, you can entrain any brain wave band with AC, and both glutamate (e.g. in Theta) and GABA (e.g. in Gamma) waves generation/manipulation are involved
- Is the action neuromodulatory? Yes, if it is below the depolarisation threshold
- Is neuronal connectivity increased? In terms of sprouting we do not know, but neuronal synchrony via entrained oscillations surely is! *Can we really "entrain the binding factor"?*
- Note that stress-protecting, adaptogenic, anti-anxiety effects of tPCS/tACS are known, and many nootropes have such effects

Decreasing Potential Side Effects

- Phosphenes: are they really that annoying, after all?
  - Do not place electodes above/close to the eyes
  - Do not place electrodes on occipital area unless required
  - Reduce the current
- Vestibular side effects such as dizziness at 0.5Hz
  - Use earlobe electrodes, reduce the current
- Local unpleasant feelings like tingling and burning
  - Reduce the current
  - Never use rubber or metal electrodes
  - Use earlobes electrodes
- Tolerance build-up/adaptation
  - Modify stimulation parameters of consequent sessions
- Hitting a wrong frequency at wrong amplitude
  - A published example: 5Hz theta-range tSOS during slow sleep decreased memory consolidation
  - Been there, did that, suffered the consequences, ouch!

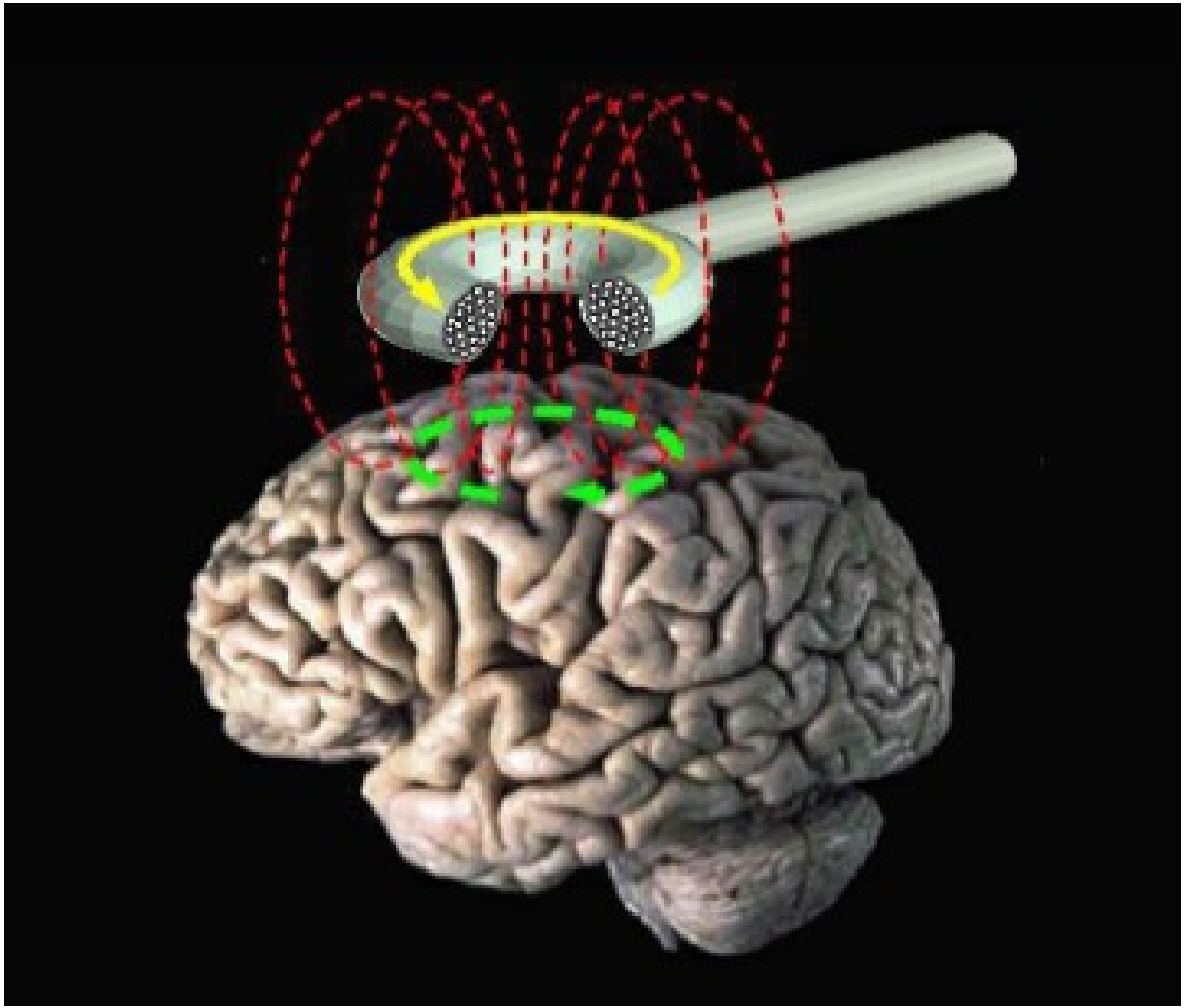
tRNS!

- Transcranial Random Noise Stimulation (tRNS) is the most recent approach in the field
- 0.1-100Hz, 101-640Hz, 0.1-640Hz bands were used, higher frequencies surprisingly appear to be more effective
- What good can ever come from bombarding your neurones with random noise?!!!
- However, tRNS improved motor and visual perception learning
- Enter stochastic resonance, where the optimal level of input noise amplifies output signal, mind the coherence resonance too
- We have already encountered it when discussing tACS below the depolarisation threshold
- tRNS is neuromodulatory ("tDCS for the whole brain" effect?)
- Adaptation to tRNS is impossible, since its random
- There is no polarity effects as in tDCS
- tRNS can increase amplitude of a dominant brain wave (such as ampakines do!)
- tRNS produces minimum local sensations (~3x A more than tDCS)

Noise applications to consider

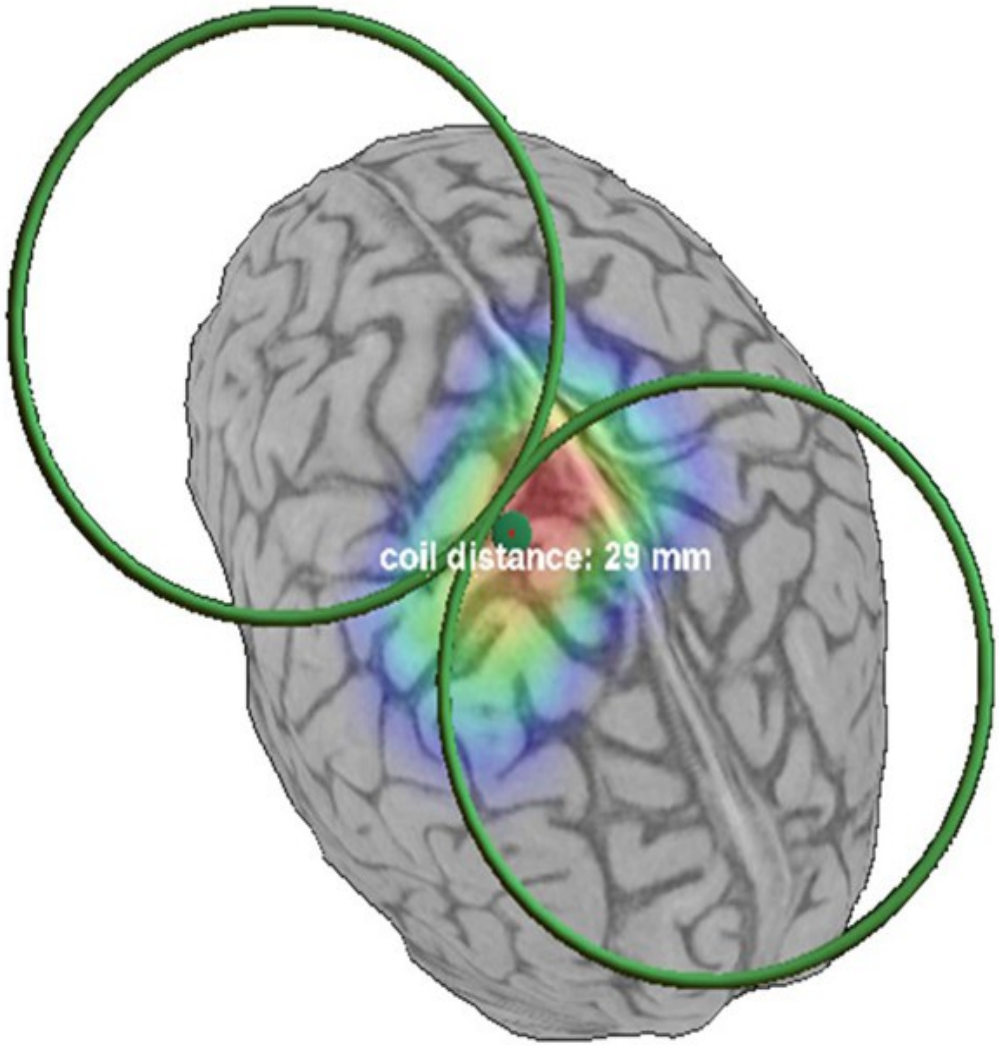
- Can tRNS really break thinking “anti-patterns” or reduce Einstellung effect?
- At which level noise injection becomes adverse?
- Can we combine tRNS with other stimulation methods (“hiding patterns in noise”)?
- What about magnetic rather than electric application of noise?
- Does it have to be random? What will be the effects of pseudorandomness introduced?
- Using colours of the noise, especially pink (1/f)!

High Power TMS

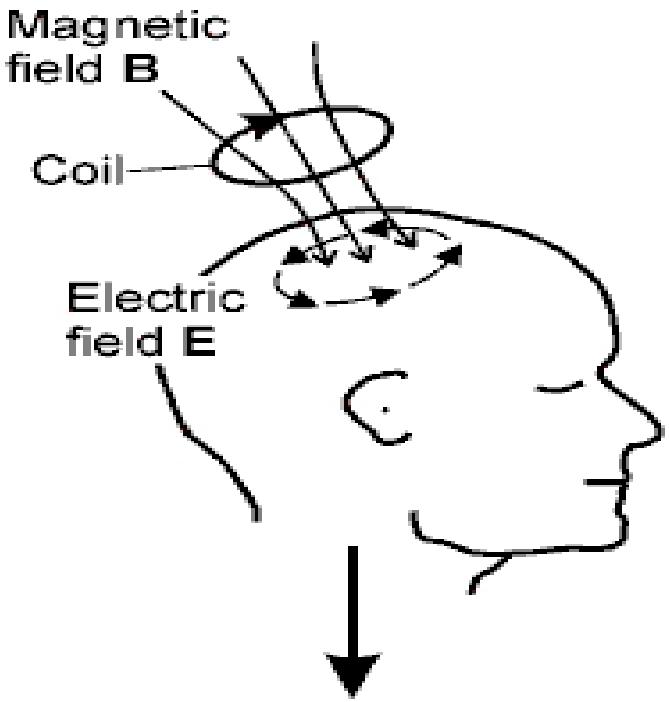


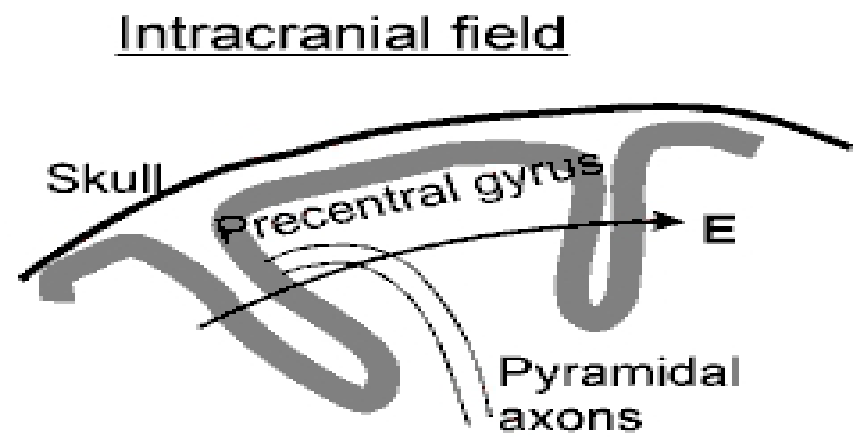
What can we manipulate?

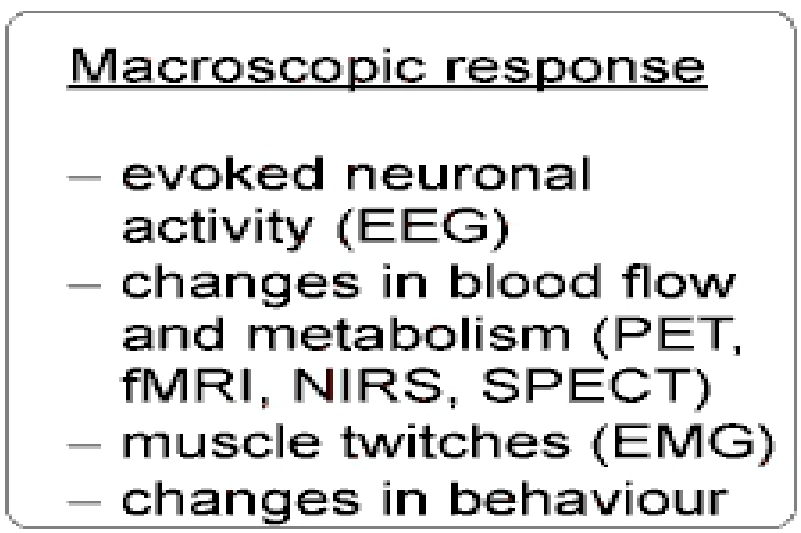
- Amplitude (inductivity) around 1 Tesla
- Frequency of stimulation
- Waveform and phase
- Pulses, bursts, sweeps
- Coil clockwise or anti-clockwise current
- Continuous or interrupted
- Ramping
- Polarity (North or South)
- Number of coils
- Orientation, position, shape of the coil(s)
- Duration of stimulation

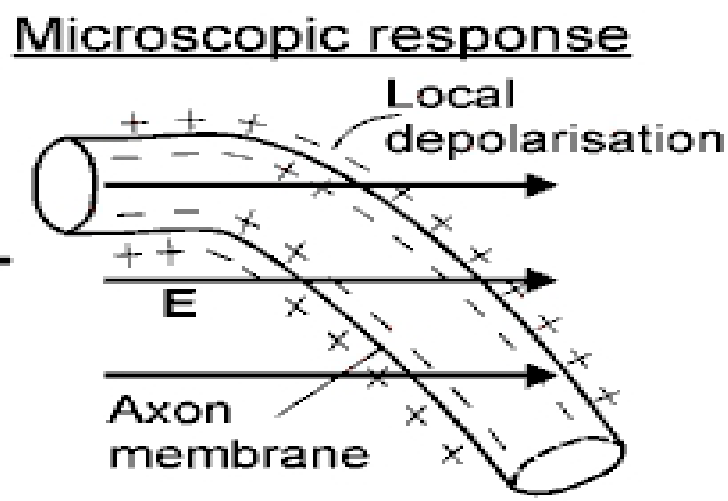


What does it do?







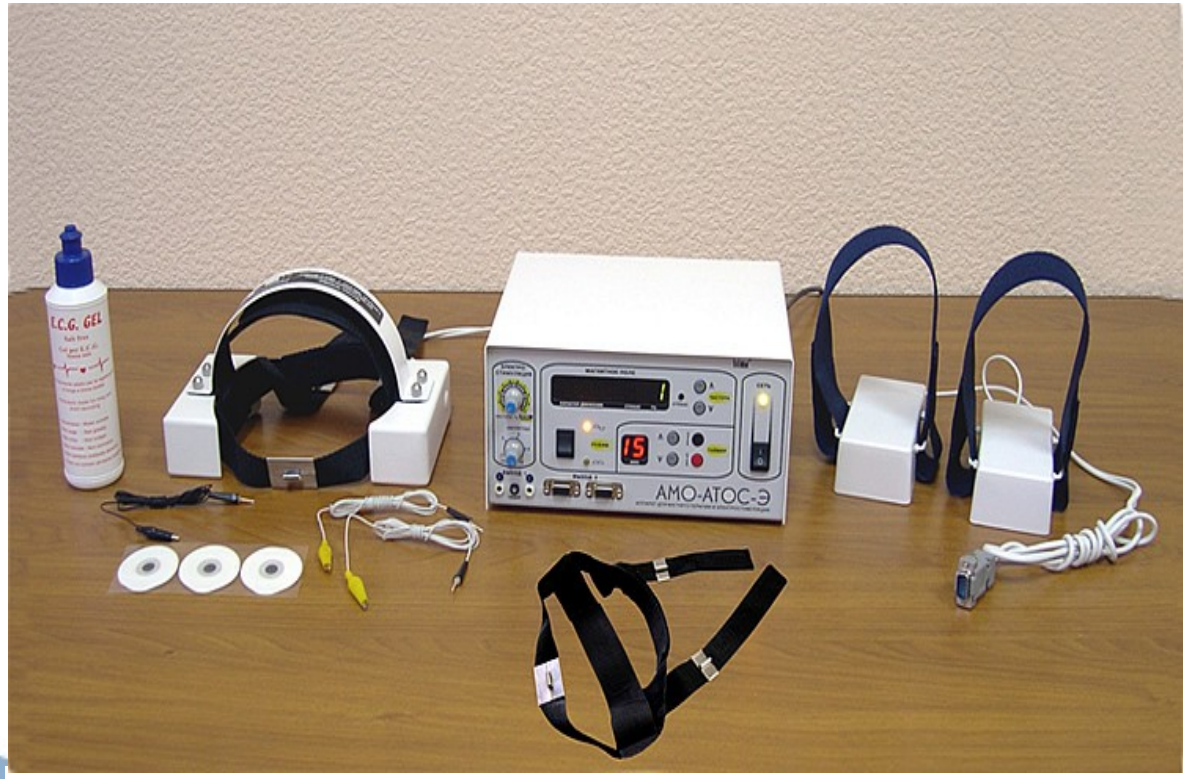


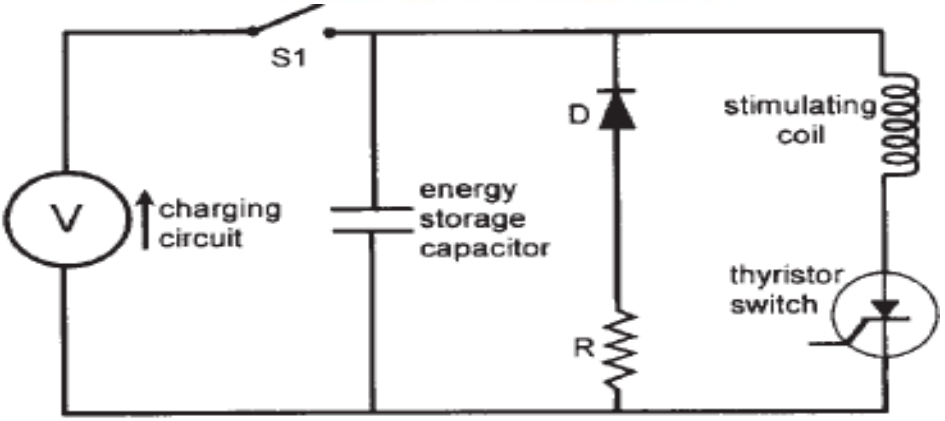
At such power levels (kilovolts fed into the coil) the actual acting agent is the induced electrical current, not the magnetic field itself

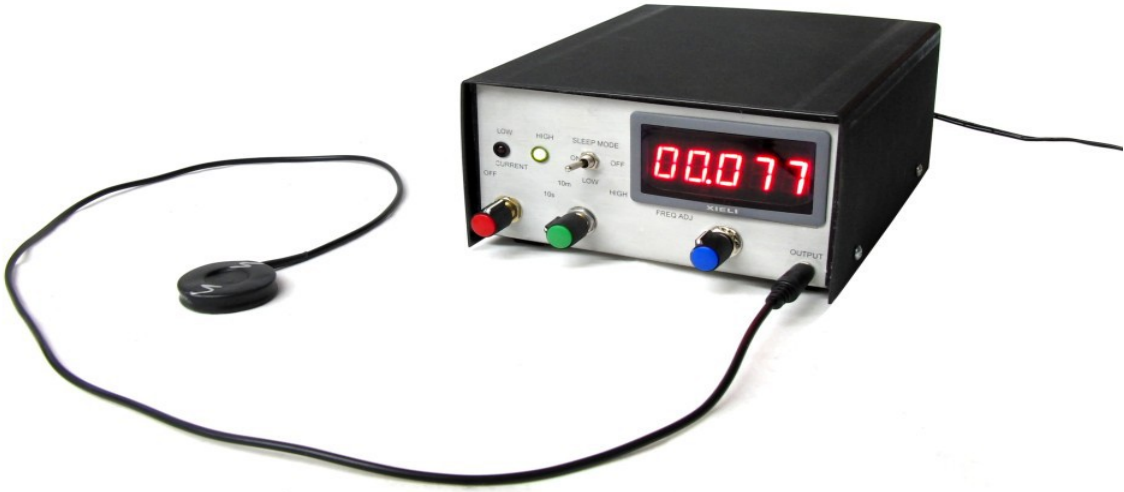
What is so special about TMS?

- In essense, it allows to combine targeting specific brain areas as in tDCS (but with a better resolution) with frequency-dependent effects as with tACS/tPCS
- So,both the location and a specific mechanism at it can be targeted (though the former is hard in rats)
- Typically, low frequency TMS (~1Hz) causes inhibitory effects, while higher frequency TMS (5-20Hz usually used) is excitatory
- Which means TMS can induce either LTP or LTD — in the specific brain area of interest! (resolution down to 1-2 cm?)
- Inhibitory TMS can induce the so-called «virtual lesion» - switch off the targeted brain area for a brief period of time to help studying its function

Still accessible for enthusiasts...







Can it improve cognition?

- Numerous rat and human studies indicate it can
- Higher frequencies can cause improvement, lower — suppression of different types of learning and memory
- Theta-burst stimulation (TBS) protocol: three pulses at 50 Hz, repeated five times per second
- Continuous (cTBS) → LTD, intermittent (iTBS)→ LTP
- iTBS prior to learning enchances it in rats
- TBS enhances not only theta, but also gamma waves (!)
- Both theta and gamma tie together hippocampus and neocortex, as well as different areas of hippocampus (CA3 and CA1) providing «dialogue» between them
- «drugs that increase theta and gamma power should improve encoding of memories» (Buzsaki)
- And so does the TBS (also see the effects of piracetam on theta in hippocampus on the previous talk slide)

What about inhibitory TMS?

- Allan Snyder and Co: savant skills are dormant in us and can be awakened with inhibitory TMS
- Savants are more «literal», «savant genius» works its way from tiny details up to the whole "Sherlock Holmes-style"
- Top-down inhibition, conceptual, abstract thinking, concentration on the whole blocks our access to «raw», «low level» data
- Left frontotemporal lobe seem to orchestrate this top-down inhibition and cases of injuries to it awakened savant skills are known
- By inducing a «virtual lesion» to this area with 0.5 —1 Hz TMS the «left brain top-down inhibition» can be temporarily removed
- … potentially leading to appearance of artistic, numeric, and other savant skills, and reduction of false memories

Subjecting TMS to the nootropic criteria proposed in this talk

- Are LTP/LTD involved? Sure.
- Is the effect long-lasting? Yes
- Are glutamate receptors involved? NMDA for sure, other – probably yes, including the metabotropic receptors
- Are GABA receptors involved? Yes. Generally, neurotransmitters release by TMS protocols described is not very selective
- Is the action neuromodulatory? *Not at the magnetic field induction strength used in such studies*
- Is neuronal connectivity increased? In terms of sprouting we do not know: pulsed magnetic fields were reported to increase / regulate neuronal growth in vitro, but at much lower field strengths. However, BDNF gene polymorphism does affect TMS
- Theta Burst Stimulation affects brain wave bands likely to be involved in memory encoding etc.
- Inter and intra-hemispheric connectivity increase as a result of TMS has been reported (compare with ampakines)

Decreasing Potential Side Effects

- Can induce seizures or muscle twitching
- Fainting (rarely)
- Mild headache due to scalp and neck muscles activation (easily removed by ibuprofen etc.)
- Phosphenes (oh, gosh!)
- Loud clicking noise from coils
- Interference with any electronic implants
- Strong current induced in metal objects

- Reduce the power (where we will eventually arrive to weak field TMS working through very different mechanisms)
- Increase the interval between pulse trains
- No piercings and electronic implants!
- High power TMS simulators are high voltage devices, so take the usual precautions when operating them. Also, the coils may overheat.

Neurostimulation for fun and profit?!

- Enhancing visual, audio and even gustatory, olfactory and tactile perception experience could have (harmless?) recreational uses
- Amphetamine enhances anodal tDCS effects, the opposite can also be true – a potential for both addiction treatment and abuse (a criminal-produced "ampbox"?)! More studies into interactions between physical neurostimulation and drugs of abuse are clearly needed!
- Enhancing training in some sports – no doping control possible! Fairness!?
- Gaming industry, online gaming for cash, even gambling (e.g. poker)!
- "Moral manipulation" is possible! And brings in hard ethical/legal issues…
- Reduction of both false memories and ability to lie can be achieved – very handy for law enforcement / intelligence agencies but is, essentially, a non-intrusive interrogation method (legal/rights issues abound!)
- Alterations of self-esteem, self-deception, deceptive, risk assessment and risk taking behaviours, perception of fairness, and even suppression of "magical thinking" (apophenia) were reported with tDCS and TMS
- Could be both useful and abusive, strong and sound regulations based upon solid research and not prejudice are required!