Combining tCS and EEG

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axies that can be seen today make up just...
• Measuring tCS effects with EEG
  ➢ Measuring effects outside the motor cortex
  ➢ Measuring focality of tCS interventions

• Basics of EEG
  ➢ EEG signal: features and opportunities
  ➢ Analysis (ERP, Power, ...)
  ➢ Experimental example of EEG-tCS combination

• Beyond EEG
  ➢ TMS-EEG recording
Corticospinal excitability as an index of Brain excitability

Applied to tCS: limitation for online recording, only after effects
First evidence of tDCS after effect from Nitsche and Paulus, 2000

Changes in cortical excitability assessed using TMS-EMG
tDCS effect on corticospinal excitability: Online and Offline effects

Santarnecchi et al., 2014
tDCS Effects on the motor cortex: pre/during/post

Anodal and Cathodal tDCS modulate (increase/decrease excitability) right after the stimulation respect to Sham.

No significant effects During the stimulation.

Still limited to the motor cortex!
Are we stimulating the motor cortex?

Montage, Timing, Stimulation site, Duration, Intensity, etc. suggest a complex scenario underlying tCS effects

Kuo et al., 2013

TMS-EMG is not enough
Multifactorial model

**Brain state**
(electrophysiological recording - EEG)

**Individual trait**
(personality, cognitive profile)

**Genetics**
(e.g. BDNF)

**Neuroimaging ($$$)**

**Behavioural performance**

**Physiological measurements**
(EKG, EDR,..)
EEG/ERPs/???
fMRI?

**Behavioural scores**

**Electrophysiological responses**
EEG/ERPs/etc..

**Neuroimaging ($$$)**

BEFORE

DURING

AFTER
Targeting Optimization

**Where to stimulate?**
Determine **target site & device position/orientation** for stimulation based on...

- functional localizer
- source localization
- individual gyral anatomy
- local strength of electric field
- local direction of current flow

**When to stimulate?**
Determine **target onset/time window** relative to task or spontaneous event for stimulation based on...

- induced power
- latency of evoked responses
- oscillatory power
- occurrence of specific events

**How to stimulate?**
Determine **specific parameters** for stimulation such as...

- stimulation intensity
- stimulation frequency
- pulse/wave form
- polarity
Open questions..

- the effect of tCS on Non-Motor regions?

- distant effects and changes in the interplay between regions (connectivity) → *Network* effects?

- the Online effects of tCS on brain activity other than “excitability”?

Useful information to define tCS parameters and increase efficacy of interventions
1875: Richard Caton (1842-1926) measured currents in between the cortical surface and the skull, in dogs and monkeys.

1929: Hans Berger (1873-1941) first EEG in humans (his young son), description of alpha and beta waves.

Where does the signal come from?

• Signals stem from synchronous activity of large (~1000s) groups of neurons close to each other and exhibiting similar patterns of activity.

• Most of the signal generated by pyramidal neurons in the cortex (parallel to each other, oriented perpendicular to the surface).

• EEG measures synaptic currents, not action potentials (currents flow in opposite directions and cancel out!)
Primary intracellular currents give rise to volume currents and a magnetic field

Volume currents yield potential differences on the scalp that can be measured by EEG.
Pros and cons of EEG

Spatial resolution (log mm)
- Brain
- Lobe
- Map
- Column
- Layer
- Neuron

Temporal resolution (log sec)
- Millisecond
- Second
- Minute
EEG recording and analysis
EEG recording

- International 10-20 system
- Left side: odd numbers
- Right side: even numbers
- Numbers increase from the hemispheric line towards the edges. Letter indicates brain regions (lobes).

High-Density EEG (64-256 Channels)
• EEG records potential differences at the scalp using a set of active electrodes and a reference.
• The ground electrode is important to eliminate noise from the amplifier circuit.
• Potential differences are then amplified.

• The representation of the EEG channels is referred to as a montage:
  – **Unipolar/Referential** ⇒ potential difference between electrode and designated reference.
  – **Bipolar** ⇒ represents difference between adjacent electrodes (e.g. ECG, EOG).
1. SPONTANEOUS

- Meaningful data with ~5' of recording
- Eyes open/closed

2. EVOKED

Well known Evoked Response Potential (ERP) (P300, N100, ..)
From ERPs to Waveform

Time domain: 
-> when do things (amplitudes) happen?

Frequency domain (spectral): 
-> magnitudes and frequencies of waves- no time information.

Time-frequency (wavelet analysis): 
-> when do which frequencies occur?
EEG features

Amplitude (or Power)

\[ V(t) = \sum A_n \sin(2\pi f_n t - \phi_n) \]

Strength

(\( \mu V \) or \( \mu V^2 \))

Frequency

# of Cycles/Second

(\( Hz \))

10Hz

20Hz

Phase

(Radians)

fMRI
Event Related Potentials (ERPs)

Advantages: computationally simple

Example of auditory evoked potentials
How to disentangle oscillations
Jean Joseph Fourier (1768–1830):
“An arbitrary function, continuous or with discontinuities, defined in a finite interval by an arbitrarily capricious graph can always be expressed as a sum of sinusoids”.

Frequency Domain Analysis (EEG)
Time-Frequency Domain Analysis (EEG)
Connectivity Analysis (EEG)

Connectivity based on...

- Phase (e.g. phase-slope index)
- Power (e.g. coherence)
- Cross-frequency coupling
ambiguous audiovisual stimulus: two bars approached, briefly overlapped while a click sound was played, and moved apart from each other

Hipp et al., 2013
Connectivity Analysis (EEG)

Cohen et al., 2013
Advantages of tCS + EEG

- Understanding the role of brain oscillations in both **motor and non-motor regions**, in both the **healthy and pathological brain**

- **Measure both local and distant effects.**

- Guide tCS intervention on the basis of and online/offline monitoring of brain states.

How can tCS + EEG be implemented?
tCS + EEG approaches

**OFFLINE**
- Resting or Event related EEG
- tCS (no EEG recording)
- Resting or Event related EEG

**ONLINE**
- Resting or Event related EEG
- EEG recording during tCS
- Resting or Event related EEG

**EEG-Guided, closed-loop system**
- Resting or Event related EEG
- tCS guided by EEG recording
- Resting or Event related EEG
tCS and EEG: variables

**Choose Parameters**

<table>
<thead>
<tr>
<th>Input Location</th>
<th>scalp landmark</th>
<th>Brain atlas</th>
<th>MRI, DTI</th>
</tr>
</thead>
<tbody>
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**tES Input Parameters**

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Standard Guided</th>
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<td>Frequency</td>
<td>Standard EEG Guided</td>
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**Input Time**

Guided with respect to a brain state

**Closed Loop**

Feedback

**State Dependency**

State

**Controlled Brain State**

<table>
<thead>
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<th>Developmental state</th>
<th>Age</th>
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<td>Behavioral state</td>
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<td>Brain dynamics</td>
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<td>Disease duration, severity, etc</td>
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**Local/Network Effects**

**Output Location**

- Selected sensors or sources
- All sensors (topography)
- All sources (tomography)

**EEG Output Measures**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mechanisms</th>
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<tr>
<td>Amplitude e.g., ERP, GMFA</td>
<td>Local or global excitation/inhibition</td>
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<td>Power of each frequency e.g., ERS/ERD</td>
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<td>Intrinsic properties e.g., Resonant frequency</td>
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- Correlation
- Coherence
- Synchrony
- Phase-amplitude cross-frequency coupling

- Directed-transfer function
- Partial directed coherence

**Output Time**

- Relative to input time
- Relative to a brain state
EEG-Guided tCS: Location

Faria et al., 2012

EEG evaluation of a patient with Continuous spike-wave discharges during slow-wave sleep allowed identification of an epileptogenic focus.

Cathodal tDCS over the focus resulted in a significant decrease in interictal spikes.
EEG-Guided tCS: Stimulation Parameters (Frequency, phase, etc.)

Zahele et al., 2012

**Frequency**

*Individual Alpha frequency*

- **tACS** on the occipital cortex at individual alpha frequency

- **Resting EEG** → increase in alpha in parieto-central electrodes, no effects on surrounding frequencies
EEG-Guided tCS: Stimulation Parameters (Frequency, phase, etc.)

**Frequency**

*Individual Alpha frequency*

---

Vossen et al., 2015

![Graph showing aftereffect relative to Sham dB across different frequencies relative to IAF.](image)

**A** 70ms 100ms 130ms

**B** tACS < IAF 70ms 100ms 130ms

**C** tACS > IAF 70ms 100ms 130ms

*S1: postsynaptic  S2: presynaptic*
Phase

**Causal relationship between phase and perception**

**Neuling et al., 2012**: Used alpha-tDCS, the timing of the stimuli was arranged relative to the α-tDCS to present the stimuli in specific phase bins.

**Perception**: Detection thresholds were dependent on the phase of oscillation entrained by alpha tDCS.

**EEG rest**: Alpha power was enhanced after alpha tDCS.
State dependency: Eyes Open vs. Eyes Closed

Significant increase in alpha-power after individual-alpha frequency tACS when applied with Eyes open, but not with Eyes closed.

Neuling et al., 2013
Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation

Neurotransmitters balance  
Cortical “excitability”

Head-tissue morphology  
Fatigue, wakefulness, attention, habituation to stimuli ➔ can Flip the effect

age  
Circadian rhythm  
Hormonal levels

Silvanto et al., 2007
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Output Time

- Relative to input time
- Relative to a brain state
Closed-Loop Diagram

recording $\rightarrow$ analyze $\rightarrow$ computation $\rightarrow$ trigger/inform

measure

closed-loop brain state-dependent NTBS

brain state $\rightarrow$ modulate $\rightarrow$ stimulation
Closed-Loop Studies in Animal

Berenyi et al., 2012

- Rodent model of generalized epilepsy.
- Detection of interictal spikes triggers tCS at 1Hz

Aborts the spike-wave discharge burst
Closed-Loop Studies in human sleep

Clark et al., 2017
Closed-Loop Studies in human sleep

Enhancing slow waves improves memory
Closed-Loop Studies in human sleep

![Bar chart showing sleep quality comparison between Active and Sham treatments.](chart)

- Sleep quality (Karolinska Sleep Diary)
  - Active: Average 24.5, with a range of 24.2 to 24.8
  - Sham: Average 22.1, with a range of 21.9 to 22.3

The difference in sleep quality between the Active and Sham treatments is statistically significant with \( p < 0.05 \).
Choose Parameters

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EEG Output Measures

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Behavioral state
- anesthesia, sleep
- wakeful resting
- passive/active sensory processing
- motor movement
- cognitive performance

Brain dynamics
- current and history of dynamics
- a preceding stimulus

Disease state
- Disease duration, severity, etc
- Intervention strategies

Output Time
- Relative to input time
- Relative to a brain state
Output Measures: Power/Amplitude - Local effects

- Anodal tDCS on right Inferior Frontal Gyrus, Cathode on OFC
- Offline approach, tDCS + task, EEG before/after

Decrease in Theta power after tDCS
Output Measures: Power/Amplitude - Distant effect

- **Increased** Theta and Alpha power after Anodal tDCS
- **Decreased** Alpha power after Cathodal tDCS

Occipito-Parietal Electrodes...
Output: Connectivity

- 10' of **anodal** tDCS over M1
- **Cathode** on the contralateral Forehead
- 62 Channels **EEG recording Before & After, Resting & Task**
- **Output** → Connectivity metrics (Synchronization Likelihood) in directed and undirected graphs, for each frequency band.

**Polania et al., 2011**

**Task PRE – Task POST , High Gamma @ 60-90Hz**

**tDCS Increases** connectivity between motor, premotor and suppl. motor areas.
• tDCS **Increases** connectivity between left motor, premotor and suppl. motor areas.

• tDCS **Decreases** interhemispheric connectivity in High-Gamma during task.
Other multimodal approaches?

• tCS + TMS-EMG

• tCS + EEG (Resting – ERPs)

• tCS + fMRI

• tCS + NIRS

• ....tCS + TMS-EEG ?
TMS-EEG

TMS evoked potential (TEP)

Magnetic Field

Cortical Evoked Potentials

TMS Pulse

50 ms

5 ms

Motor Evoked Potentials

Peak-to-Peak Amplitude

Latency

20 ms

20 mV

Descending Volleys

I_1, I_4

0.2 mV

D
TMS-EEG

Cortical Evoked Potentials

N100

P30

Cortical Evoked Potentials

N100

P30

Cortical Evoked Potentials

N100

P30

Cortical Evoked Potentials

N100

P30
TMS-EEG to investigate local and distant tDCS effects

- 14 right-handed participants
- 0.75mA for 15’ (anodal tDCS) + Sham
- 60 Channels EEG
- Masking Noise for TMS click

Output: TMS-Evoked Potentials (TEP) as a cortical activity/reactivity measure

Global Excitability Index: Global Mean Field Power (GFMP)
Local Excitability Index: Local Mean Field Power (LMFP) over 6 different clusters of electrodes, left/right Frontal-Temporal-Parietal.

3 Time windows: 0-50ms, 50-100ms, 100-150ms
TMS-EEG to investigate local and distant tDCS effects

Global Mean Field Potential

Fig. 2 – Panel A (upper row) shows the Grand Average of GMFP computed by averaging the GMFPs calculated for each subject in the three experimental conditions (pre tDCS = blue trace ± SE; during tDCS = red trace ± SE; post tDCS = green trace ± SE). The lower row of Panel A represents the mean topographies computed in correspondence of the local maxima for each of the three time windows (0–50 msec = light gray, 50–100 msec = gray, 100–150 msec = dark gray) across the 14 study participants (see also Fig. 1). Panel B shows bar histograms representing the mean values ± SE of the integrated GMFP in the three time windows of interest (0–50 msec = light gray, 50–100 msec = ash, 100–150 msec = graphite) for each experimental condition.
TMS-EEG to investigate local and distant tDCS effects

Local Mean Field Potential as an index of distant effects

Effects are (i) mostly in the 0-50ms window, which is expression of inter-regional monosynaptic connections; (ii) exclusively in the POST tDCS

**ONLINE tDCS** → unclear
**OFFLINE tDCS** → more specific, network-based effects
Technical challenges

EEG-Guided, closed-loop system

Resting or Event related EEG

Stimulation Artifact during EEG recording

- tDCS
  - Relatively easier, Available tools (algorithm) to “clean” the data from Drifts

- tACS
  - Artifact is bigger and affects the EEG band of interest (!).
  - *Specific filtering* can be applied (reduces the available spectrum)
EEG during tDCS

SEP: somatosensory evoked potential

3rd order Butterworth filter (1-250Hz) to eliminate tDCS induced blurring of EEG response.

POSTPROCESSING
Moving Average + Principal Component Analysis to Capture and eliminate the artifact

Helfrich at al., 2014
Take home

- Understand Motor and non-Motor tCS effects
- Capture Distant effects other than cortical excitability (e.g. Power, Coherence, Connectivity)
- Guide tCS interventions (closed loop, etc.)
- Interact with complex dynamics (e.g. CFC, phase-related processing)

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Thank you for your attention

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