Transcranial Alternating Current Stimulation (tACS)

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Growing interest..

“tACS is a tool to modulate brain oscillations in a frequency specific manner”

• Oscillatory pattern and synchronicity in the brain
  ✓ tACS - Mechanism of action

• Examples of tACS Research
  ✓ Perception
  ✓ Cortical excitability
  ✓ Cognition
  ✓ Phase-Related activity
  ✓ State and Trait – dependency
  ✓ Therapeutic potential

• Future Directions
**Mechanism of action**

**DC Stimulation**
- Constant Fields
- Membrane Polarization
- Spike Rate Change

**AC Stimulation**
- Oscillating Fields
- Network Synchrony
- Spike Phase Change

**Synchrony Effect**

**Amplify Input**

**Direct Current**

**Alternating Current**
Sleep–wake cycles are evident even if external light conditions are held constant (grey shade). Intrinsic oscillators (circadian clocks) which cause periodicity in bodily function.

**What are oscillatory patterns and how they affect our behaviour?**

**Oscillatory pattern and periodicity in behaviour**

Sleep–wake cycles are evident even if external light conditions are held constant (grey shade).

**Intrinsic oscillators** (circadian clocks) which cause periodicity in bodily function.

**Frequency?**
Number of cycles x second
(1 cycle * second=1Hz)

**How do we measure rhythmicity?**

- Phase, angles, degrees.....
- Oscillators are in opposite phase (anti-phase)

**10Hz**

**2Hz**
Oscillatory pattern and periodicity in behaviour

- Are these oscillatory patterns immutable?

Oscillatory cycle establishes a recurrent temporal reference frame that allows for the coding of temporal relations between groups of neural elements.

This reference frame is not fixed but is subject to dynamic changes (phase resetting).

\[ \text{tACS induces entrainment of brain oscillations following the same principle (theta, alpha, beta, gamma, ..)} \]
Oscillatory pattern in the brain

• Why are oscillatory pattern so important?

1. Pulse processing

Rhythmic fluctuations in the local field potential (LFP), synchronous transmembrane currents in populations of neurons and thus represent cyclic changes in the excitability of local neuronal populations.

Ongoing oscillatory phase significantly modulates the probability of perceiving a near-threshold visual stimulus.

2. Hierarchical information processing

Multiplexing

• Various aspects of the stimulus are encoded in different oscillations simultaneously, but at different frequencies.
• Efficient coding scheme relying on the hierarchical organization of oscillations.
Oscillatory pattern in the brain

Storage of 7 ± 2 Short-Term Memories in Oscillatory Subcycles

John E. Lisman* and Marco A. P. Idiart

- **Theta (6Hz) = 6 cycles * second = 1 cycle → 0.16 seconds**
- **Gamma (40Hz) = 40 cycles * second = 1 cycle → 0.025 seconds**
- **Gamma cycles in each Theta cycle = 0.16/0.025 = 6.7 (~7).**
Why are oscillatory patterns so important?

3. “Communication-through-coherence Theory”

- Communication being facilitated when two oscillatory populations are aligned to their high excitability phases.

- Effective communication relies on spikes from the sending population reaching the receiving population at a phase of high excitability.

- Changes in synchronisation between distant brain areas (possibly reflecting communication) are systematically related to task performance.

\textit{tACS theoretically allows to modulate all these complex brain dynamics.}

\textit{Canolty et al., 2007}
Mechanism of action

neuronal oscillators

\[ f_i = \text{intrinsic frequency} \]

\[ \text{sum} \quad \text{mean vector} \]

\[ f_i \text{ amplitude} \]
tACS induce AC Fields in the Brain

- Effect of Stimulation Amplitude
  - Larger Amplitude
    - Homogenous Phase
    - More Neurons

Ozen et al., 2010

Rat (in-vivo)
**Endogenous Resonance Principle**

- tACS induced Oscillations
  - tACS ~1.5Hz
  - Phase-locked (25-50%)
  - No Phase-locked

- Synaptic mediated Oscillations
  - Exploring

**Mechanism of action**

S = sleep
R = rest
E = exploration

*Ozen et al., 2010*
tACS and Perception
What is frequency sensitivity of tACS evoked Visual Sensation?

### Rationale

Eye Open/Closed Alpha (Adrian, 1934)

### Design

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>Inion (+4cm) - Vertex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>0-40Hz, 0-1mA, 5s each</td>
</tr>
<tr>
<td>Subjects</td>
<td>8 Healthy</td>
</tr>
</tbody>
</table>
Results

- Occipital tACS can evoke phosphene perception
- Efficiency of stimulation is maximal at alpha band (dark) and beta band (light)

Kanai et al., 2008
**Question**

- Can tACS induce (cortically) tactile percept and if yes what is the frequency sensitivity?

**Design**

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>~C4 (TMS hot-spot) – P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>2-70Hz, 1.5mA, 5s each</td>
</tr>
<tr>
<td>Subjects</td>
<td>14 Healthy</td>
</tr>
</tbody>
</table>
Results

- Parietal tACS can induce cortically tactile sensation
- Efficiency of stimulation depends on frequency with peak at Alpha & high Gamma
tACS and Corticospinal Excitability
**Question**

Are beta oscillations in motor cortex functional or epiphenomenon?

- tACS over M1
- Amplitude of TMS induced MEP*

**Design**

- Electrodes: C4 (TMS hot-spot) + P4 (control) – Pz
- Current: 5, 10, 20, 40Hz, 0.5mA*, 90s
- Subjects: 15 Healthy

* Kept below phosphene or skin sensation threshold.

**Feurra et al., 2011b**

* MEP- Motor Evoked Potential, indicating the strength of the corticospinal response
Results

• Parietal tACS @ 20HZ specifically increases MEP amplitude

[Bar graph showing MEP Amplitude (µV) for different conditions]
tACS and Motor performance
**Question**

- Are beta oscillations in motor cortex functional or epiphenomenon?

**Design**

Visiomotor Task + 20Hz tACS/Sham → Reaction time + EEG-EMG

**Electrodes**
- C4 (TMS hot-spot) – P3

**Current**
- 20Hz, 0.6mA*, -2s to +8s

**Subjects**
- 14 Healthy

* Kept below phosphene or skin sensation threshold.
Results

- Parietal 20Hz tACS slowed (small effect) initial velocity.
- Parietal 20Hz tACS increased somatosensory-arm 20Hz coherence.
tACS and Cognition
**Rationale**

**Sleep Architecture**

- **Declarative memory**
  - Slow oscillation (neocortex)
  - Spindle (thalamus)
  - Sharp wave-ripple (hippocampus)

- **Non-Declarative memory**
  - PGO wave* (Pons-LGN)
  - Theta activity (hippocampus)

For further reading see Diekelmann, 2010

* PGO: ponto-geniculo-occipital
**Design**

**Paired Associated Learning Task**
- 46 word pairs

**Finger Sequence Tapping Task**
- 5-element sequences (e.g. 4-2-3-1-4) in 30s

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**Memory Consolidation**

- **Declerative memory**
  - 9p, 10:30p, 11p

- **Non-declarative memory**
  - 6:30a, 7a, 8:30a

**Electrodes**
- F3-Mastoid, F4-Mastoid (diam=1cm)

**Current**
- 0.75Hz, ~0.33A, 5min/1min ON/OFF

**Subjects**
- 13 Healthy
Results

Marshall et al., 2006

• Bilateral 0.75Hz frontal- tACS during early sleep selectively enhances hippocampus-dependent retention of declarative memory

**P < 0.01
• tACS entrained SWS and spindle power spectra in the prefrontal region

* Bands for slow oscillations (0.5–1 Hz); Bands for spindle oscillations (8-12 Hz)
Rationale

• Theta PFC Right > Left 

Risk Taking

(Gianotti, 2009)

• But... bilateral DLPFC tDCS (regardless of polarity) facilitate risk-adverse in Balloon Analog Risk Task (BART) (Fecteau, 2007)

PFC: prefrontal cortex
Does theta oscillation in PFC affect risky decision making?

**Question**

theta tACS PFC Left/Right/Sham pumps in Balloon Analog Risk Task

**Design**

Balloon Analog Risk Task (BART)

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>F3-CP5, F4-CP6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>6.5Hz, 0.5mA, -5min +10mins</td>
</tr>
<tr>
<td>Subjects</td>
<td>27 Healthy</td>
</tr>
</tbody>
</table>
Results

- Theta tACS over left and not right PFC increases risk taking behavior

Error bars indicate SEM. *p <0.05.
Fluid Intelligence

**Santarnecchi et al., Curr. Bio 2013**

**Question**

- Does tACS enhance Intelligence-related processing in a frequency and trial specific manner? Prefrontal gamma?

**Design**

- N=24; tACS 1.250mA

Logical and Relational Reasoning Stimuli

Stimulation sites
Results

• Decrease of Correct trials Response Time during gamma-tACS

• Selective effect for Logic trials.

• First evidence of a “causal” Role of gamma-oscillations in higher-order cognition.
tACS and Phase-locked activity
tACS and Phase Coupling: Working Memory

The Importance of Timing in Segregated Theta Phase-Coupling for Cognitive Performance

**Question**

- Can we modulate synchronization during working memory processing? Does it matter?

*Polania et al., Curr. Bio 2012*

**Sternberg Working memory task**

**Band-pass 6 +/- 1 Hz**
**Design and Results**

**A** 180° phase difference

**B** Sham

**C** 0° phase difference

**D** 6Hz tACS

**E** 35Hz tACS

*WM performance*

*Polania et al., Curr. Bio 2012*
Antiphase 40 Hz Oscillatory Current Stimulation Affects Bistable Motion Perception

Rationale and Design

A

Stroboscopic alternative motion (SAM)

Presented

Diagonally opposed pairs of LEDs

Perceived

Anti-phase Stimulation:
Experiment 1: 40 Hz tACS
Experiment 2: 4 Hz tACS

B

Unambiguous motion

In-phase Stimulation:
Experiment 3: 40 Hz tACS and 6 Hz tACS

Horizontal motion

Vertical motion

Horizontal motion

Vertical motion
**Results**

*Struber et al., 2013*

**Effect of tACS on motion dominance**

Changes in interhemispheric coherence after tACS + Task
State Dependency of tACS
State Dependency: Motor Imagery

State-Dependent Effects of Transcranial Oscillatory Currents on the Motor System: What You Think Matters

Feurra et al., JoN 2013

**Question**

- Does the effects of tACS depend on brain state?

N=18, tACS= 1mA (peak-to-peak).
Consistent increase of MEP size during MI versus the quiescence state, regardless of the type of tACS applied.

Dissociation between conditions of-tACS (5 Hz) and tACS (20 Hz), after removing the average facilitatory main effect of MI.
State Dependency

Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states

- Does the after-effects of tACS depend on the endogenous power of oscillations?

Exp. 1: 19 sbjs, 20' tACS at Individual Alpha frequency*, Eyes Open

Exp. 2: 29 sbjs 20’ tACS at Individual Alpha frequency*, Eyes Closed

*power peak in the alpha range (8–12Hz)
State Dependency

Results

Neuling et al., 2013

Experiment 1: Eyes Closed

Experiment 2: Eyes Open

tACS effect depend on brain states before the stimulation...
State Dependency

...tACS effect depend on the level of intrinsic organization of brain signal and their “pliability.”

![Diagram showing neuronal oscillators and tACS effect]
State Dependency

Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation

**Question**

- Phase-angle dependency of tACS effect?

**Design**

- Oddball task
- Stimuli presented at different phase-angles

*Helfrich et al., Curr. Bio. 2014*

14 sbjs, parieto-occipital tACS @ 10Hz
State Dependency

**Results**

*Helfrich et al., Curr. Bio. 2014*

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**Increase in alpha power after tACS**

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**Coherence and Target detection accuracy relative to the different phase angles**
Trait-dependency of tACS..?
Compared tACS and tRNS effect in both fluid intelligence and Working memory tasks.

\[ N=58 \]
\[ tACS=1.0 \text{ mA}, \]
\[ tRNS=1.0 \text{ mA} \]
Fluid Intelligence

- Effect of tACS reflect individual differences which are to be considered as a stable “Phenotype”

- Important for the ethical evaluation of cognitive enhancement intervention.

$tACS=1.0 \text{ mA}, \: tRNS=1.0 \text{ mA}$
Therapeutic Potential of tACS
Treating Optic Neuropathy?

**Visual Restitution Training (VRT)**

- Software designed for patients with visual field defects caused by optic nerve diseases and post-chiasmal brain lesions.

- Binocular visual stimulation within a **transition zone between the intact visual field area and the absolute field defect.**

*Kasten, 1998*
Question

• Can tACS restore lost vision in optic neuropathy?

Design

Sabel et al., 2011 (RCT)

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>Transobital (above-below eye)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>Individual alpha- flicker freq, phosphene threshold (&lt;1mA), 15min x 10 days</td>
</tr>
<tr>
<td>Subjects</td>
<td>24 patients with visual field loss caused by damage to the optic nerve</td>
</tr>
</tbody>
</table>
Treating Optic Neuropathy?

Results

HRP Visual Field

1. Intact 2. Relative defect 3. Absolute defect

Pre

Post

Restored pixels

Blue=increase, Red=decrease DA

Mean DA Change

1. Intact
2. Relative
3. Absolute

Sabel et al., 2011 (RCT)

Improved:
• temporal processing of visual stimuli
• detection performance in static perimetry
• visual acuity

2 month
tACs restored some lost vision in patients with optic neuropathy.

The effect was accompanied by an increase in occipital alpha spectrum.
Rationale

- Can tACS reduce tremor in PD patients?

Design

**Closed-loop** tACS – tremor phase (accelerometer) → Tremor amplitude (accelerometer)

Brittain et al., Curr. Bio 2013
Identification of the optimal Phase-Delay for tremor suppression

Phased-locked tACS reduced tremor by up to 50%
Rational

- Patients with tinnitus-related annoyance have lower alpha activity at the right PFC (Vanneste, 2010)

 Mean Alpha Spectrum

- tDCS (left temporal or bifrontal) reduce tinnitus intensity (e.g. Song 2012)

Red: high distress > low distress
Blue: high distress < low distress

Measured with EEG and Low Resolution Electromagnetic Tomography (LORETA)
Results

- left-right DLPFC tACS at alpha band was not effective as tDCS in reducing tinnitus intensity (and annoyance).

Vanneste et al., 2013 (RCT)
Principles of tACS

- Oscillations
- Endogenous Resonance

Summary

tACS probe oscillatory neural activities:

- Perception (vision, tactile)
- Cortical Excitability (somatomotor, vision)
- Cognition (intelligence, memory, risk-taking)

Potential therapeutic tool:

- Visual restoration, dystonia

Future Directions?
Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields

Ruffini et al. 2013
fMRI-based Multifocal tACS

Meta-analysis map of fMRI activation map during Executive functions tasks

Targets for Fronto-parietal desynchronization
Grazie dell’attenzione!

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