Transcranial Alternating Current Stimulation - tACS

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A rapidly growing field

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

**TMS**: Transcranial Magnetic Stimulation

**tDCS**: transcranial Direct Current Stimulation

**tACS**: transcranial Alternate Current Stimulation

**tRNS**: transcranial Random Noise Stimulation
• Oscillatory pattern and synchronicity in the brain
  ✓ tACS - Mechanism of action

• tACS evidence
  ✓ Perception (Hands-On session tomorrow)
  ✓ *Cortico-spinal excitability and effects on the motor system*
  ✓ Cognition
  ✓ Phase-Related activity
  ✓ *State and Trait – dependency*
  ✓ Therapeutic potential

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Emiliano Santarnecchi serves as consultant for EBNeuro, a joint stock company developing biomedical devices for neurostimulation, neuromodulation and electroencephalography.

He has no actual or potential conflict of interest in relation to this presentation, none of the tools presented in the following slides are property of EBNeuro.
• Experience with EEG/Brain Oscillations?

• Experience with tACS?
### tCS techniques

#### A

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<td>Membrane polarization</td>
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<td>Oscillatory/Alternating</td>
<td>Frequency (Hz), Phase (Degrees), Entrainment, Brain oscillations (power, phase), Cortical excitability (&gt;100Hz)</td>
<td>Entrainment</td>
<td>During and After</td>
<td></td>
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</table>

**Santarnecchi et al. 2015 Curr Opin Behav Sci**
**DC Stimulation**

- Constant Fields
  - Membrane Polarization
  - Spike Rate Change

**Synchrony Effect**

- Synchronize the Input
- Amplify the Output

**AC Stimulation**

- Oscillating Fields
  - Network Synchrony
  - Spike Phase Change

**Mechanism of action**

- Amplify the Output
Pre stimulation spectral power and average phase

B(t)
Why tACS?
EEG Oscillations and Behavioural Correlates

- Delta (1 – 4 Hz): Sleep, learning, motivational processing
- Theta (4 – 8 Hz): Memory, emotional regulation, creativity
- Alpha (8 – 13 Hz): Active inhibition of task-irrelevant areas
- Beta (13 – 30 Hz): Mainly Motor activity
- Gamma (30 – 80 Hz): Abstract mental activity, cognitive control, perceptual binding
**Alpha**: automatic movements

**Beta**: movement

**Gamma**: selective attention

**Theta**: working/long-term memory

**Theta**: spatial orienting

**Alpha**: visual perception
**EEG Oscillations and PATHOLOGY**

- **Delta (1 – 4 Hz)**
  - Reduced synchrony in Schizophrenia
  - Reduced amplitude in Alzheimer
  - Increased Amplitude in Bipolar dis.

- **Theta (4 – 8 Hz)**
  - Reduced synchrony in Schizophrenia
  - Reduced synchrony in Alzheimer

- **Alpha (8 – 13 Hz)**
  - Reduced coherence in Alzheimer
  - Increased phase-locking at Frontal and Central electrodes in Schizophrenia

- **Beta (13 – 30 Hz)**
  - Reduced Coherence in Alzheimer and Schizophrenia
  - Increased amplitude in Parkinson
  - Increased Coherence in Bipolar dis.

- **Gamma (30 – 80 Hz)**
  - Decreased/increased amplitude in Schizophrenia (?)
  - Increased Phase-locked response in ADHD
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), especially in pathological states.

**Entrainment** of endogenous oscillatory pattern $\rightarrow$ Changes in behaviour

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

**tACS induces entrainment of brain oscillations following the same principle** (theta, alpha, beta, gamma, ..)

*Tuth et al. 2012, Current Biology*
Cyclic patterns 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.

Phase?

Oscillators are in opposite phase (anti-phase).

Phase, angles, degrees.....

Frequency?

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

10Hz

2Hz
tACS: experimental evidence
Rationale

Early evidence: tACS and Phosphenes..

What is frequency sensitivity of tACS-evoked Visual Sensation?

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>
tACS and Phosphene: frequency specific effects

**Results**

- Occipital tACS can evoke phosphene perception (*via the retina*...probably)
- Greater stimulation at alpha band (dark) and beta band (light)
tACS might shift intrinsic dominant oscillations and “tune the system”

Higher stimulation frequency
First animal evidence

- tACS at 1.5Hz (delta) induce AC Fields in the Brain

- Effect of Stimulation Amplitude

Larger Amplitude \rightarrow Homogenous Phase

More Neurons

Rat (in-vivo)

Ozen et al., 2010
tACS induced Oscillations

Synaptic mediated Oscillations

Coherent

Incoherent

Push & pull

Coherent

Incoherent

tACS ~1.5Hz

Sleep

Exploring

Endogenous Resonance Principle

Ozen et al., 2010

S=sleep
R=rest
E=exploration

Phase-locked (25-50%)

No Phase-locked
tACS in humans: effects on cortico-spinal Excitability
**Question**

- Are beta (20Hz) oscillations in motor cortex functional or epiphenomenon?

**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.

* MEP- Motor Evoked Potential, indicating the strength of the corticospinal response.
tDCS effects on the motor cortex

Transcranial Magnetic Stimulation + Electromyography

Descending Volleys

Motor Evoked Potentials

Latency

Peak-to-Peak Amplitude

Magnetic Field
tDCS effects on the motor cortex

Santarnecchi et al., 2014


Diagram B: 10 MEPs (2.5'), 5' Before TDCS, 15' Post-TDCS 1, 15' Post-TDCS 2, 5' Baseline Vital Parameters and MEPs.
tDCS effects on the motor cortex

Santarnechi et al., 2014

Anodal and Cathodal tDCS modulate (increase/decrease excitability) right after the stimulation respect to Sham.
Parietal tACS @ 20HZ specifically increases MEP amplitude
tACS and Motor Performance
Question

• Are Gamma oscillations in motor cortex functional or epiphenomenon?

Muthukumaraswamy 2010

• Tracking task using MEG
• Observed an Increase in Gamma activity (~90HZ) in the motor cortex during movement.

• What does Gamma oscillations in the motor cortex represent..?
Question

- Are Gamma oscillations in motor cortex functional or epiphenomenon?

**Visuomotor task + 10, 20, 60, 80Hz and Sham tACS** on the motor cortex.

Effects on several components of the motor program: Acceleration, Pursuit, Loops, Turns, etc.

(o)

High spatial and temporal resolution analyses.
- Significant enhancement of performance during TURNS during Gamma tACS (80Hz), with a trending result for 60Hz tACS.

- Effect is present in a specific time window (200-700ms after each TURN), coherently with MEG studies showing increase in EEG power at 90HZ during a similar task.

- No effects during Loop, Acceleration, Pursuit
tACS and Cognition
Sleep Architecture

Rationale

Memory Consolidation

Declarative memory

Non-Declarative memory

for further reading see Diekelmann, 2010

* PGO: ponto-geniculooccipital
Memory Consolidation

**Design**

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

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

**Declarative memory**

**Non-declarative memory**

Learning:
- 9p
- 10:30p
- 11p

Recall:
- 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**

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

**P < 0.01**
Results

- 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)


Memory Consolidation
Fluid Intelligence – Abstract Reasoning

Question

• Does tACS enhance Intelligence-related processing in a frequency and trial specific manner? Is prefrontal gamma an epiphenomenon?

Design

N=24; tACS 1.250mA

Logical and Relational Reasoning Stimuli
• 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.

Santarnecchi et al., Curr. Biology 2013

Fluid Intelligence

Results
Creativity

Design and Results

Lustenberger et al., Cortex 2015

• Torrance Test of Creative Thinking (TTCT)
• In-phase tACS over the prefrontal lobes
• Sham, 10Hz and 40Hz tACS
Phase-Related Modulation by tACS
"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 synchronization between distant brain areas (possibly reflecting communication) are systematically related to task performance.
**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**

**Fronto-parietal Phase-lag**

**Band-pass 6 +/- 1 Hz**
tACS and Phase Coupling: Working Memory

Polania et al., Curr. Bio 2012

Design and Results

A. 180° phase difference

B. Sham

C. 0° phase difference

D. 6Hz tACS

E. 35Hz tACS

Online tACS protocol

WM performance
State Dependency of tACS
State Dependency: Motor Imagery

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

**Question**

- Does the effects of tACS depend on brain state?

N=18, tACS= 1mA (peak-to-peak).

Feurra et al., 2013, *Journal of Neuroscience*
State Dependency

Results

Consistent increase of MEP size during Motor Imagery versus the quiescence state, regardless of the type of tACS applied.

Dissociation between tACS (5 Hz) and tACS (20 Hz), after removing the average facilitatory main effect of motor imagery.

Feurra et al., 2013, Journal of Neuroscience
State Dependency

Neuling et al., 2013

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)
tACS effect depend on brain states During the stimulation...

- Alpha reaches a plateau during Eyes Closed condition?
Cyclic Excitability Changes

Rhythmic fluctuations in the local field potential (LFP), synchronous trans-membrane 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.
tACS and Phase-related activity

State-dependency

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.

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![Graphical representation of the study's findings](image-url)
Trait-dependency of tACS?
Individual differences in response to tACS?

Santarnechchi et al., 2016

Compared tACS and tRNS effect in both fluid intelligence and Working memory tasks.

N=58
tACS=1.0 mA,
tRNS=1.0 mA

Replicated previous finding
Individual differences in response to tACS?

- Effect of tACS reflect individual differences, which can be considered a stable “Phenotype”

- Relevant for the ethical evaluation of cognitive enhancement intervention

\[ tAC斯 = 1.0 \text{ mA}, \ tRNS = 1.0 \text{ mA} \]
State-Trait dependency

Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation

Beatrix Krause* and Roi Cohen Kadosh
Department of Experimental Psychology, University of Oxford, Oxford, UK

Variability in the response to tCS

- Neurotransmitters balance
- Cortical “excitability”
- Head-tissue morphology
- Age
- Circadian rhythm
- Fatigue, wakefulness, attention, habituation to stimuli \( \rightarrow \) can Flip the effect
  - Silvanto et al., 2007
- Hormonal levels
Trait dependency

Perturbation-based Physiologic Biomarkers by means of Non-Invasive Brain Stimulation and EEG

- tACS @ multiple frequency bands (theta, alpha, beta, gamma) & TMS-EEG
- over multiple different locations
- EEG recording Before, During and After stimulation

Look for region-specific responses, also depending on frequency of stimulation
Therapeutic Potential of tACS
Ninety-eight patients that had suffered ischemic stroke 21.4 months earlier were randomly assigned to either:

1) **group D** (n = 30) receiving conventional drug therapy
2) **group ACS** (n = 32) treated for 12 days with tACS (~20Hz, 30’)
3) **group D/ACS** (n = 36) receiving combined drug therapy/tACS.

*Stroke severity level (SSL)* was assessed by the NIH-NINDS stroke scale **before** and **after treatment** and at a **1-month follow-up** to evaluate motor impairments (weakness, ataxia), sensory loss, visual field defects, and cortical deficits (aphasia, neglect).

At each time point standard **EEG recordings** (10–20 system) were conducted.
### Table 3

Results of SSL assessment (NIH-NINDS stroke scale) for ischemic post-stroke patients before, after 12 days and 1 month follow-up

<table>
<thead>
<tr>
<th>NIH-NINDS scale</th>
<th>Group D, n = 30</th>
<th>Group ACS, n = 32</th>
<th>Group D/ACS, n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>1.56</td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td>Motor arm right</td>
<td>0.75</td>
<td>0.70</td>
<td>1.17</td>
</tr>
<tr>
<td>Motor arm left</td>
<td>0.44</td>
<td>0.44</td>
<td>0.17</td>
</tr>
<tr>
<td>Motor leg right</td>
<td>0.63</td>
<td>0.57</td>
<td>1.25</td>
</tr>
<tr>
<td>Motor leg left</td>
<td>0.50</td>
<td>0.50</td>
<td>0.17</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>1.38</td>
<td>1.38</td>
<td>1.50</td>
</tr>
<tr>
<td>Sensory</td>
<td>1.13</td>
<td>1.13</td>
<td>1.08</td>
</tr>
<tr>
<td>Formerly neglect</td>
<td>1.13</td>
<td>1.13</td>
<td>1.08</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>0.50</td>
<td>0.45</td>
<td>0.58</td>
</tr>
<tr>
<td>Aphasia</td>
<td>0.25</td>
<td>0.20</td>
<td>0.42</td>
</tr>
<tr>
<td>SSL</td>
<td>8.27</td>
<td>8.0</td>
<td>8.92</td>
</tr>
</tbody>
</table>

SSL: Stroke severity level. Significant differences between post minus pre or follow-up minus pre measurements are marked with * ($p < 0.05$).
Rationale

• Can tACS reduce tremor in PD patients?

Design

Closed-loop tACS - tremor phase (accelerometer)  
Tremor suppression?

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

- **tDCS** (left temporal or bifrontal) reduces tinnitus intensity (e.g. Song 2012)
- Patients with tinnitus have lower alpha activity at the right Prefrontal Cortex

Mean Alpha Spectrum

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

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

Vanneste et al., 2013 (RCT)

**Tinnitus Intensity Rating**

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

![Graph showing tACS and tDCS results](image-url)
Gamma frequency entrainment attenuates amyloid load and modifies microglia

Decrease in hippocampal amyloid-β after 40Hz stimulation visible at Immunohistochemistry

High-frequency visual stimulation in the gamma band in rats
Ongoing studies (DARPA; BI DMC)

Santarnecchi et al. 2013, 2015, 2016, 2017

Enhanced executive functioning during 40Hz tACS stimulation

**Initial Evaluation:**
1 Visit Outpatient
- Consent
- Screening

**Pre-Intervention Evaluation:**
3 days, 2 night
Inpatient in the Clinical Research Center
- Medical exam
- Clinical evaluation
- Neurological exam
- Neuropsychological exam
- Blood tests
- MRI:
  - resting-state fMRI
  - perfusion MRI (ASL)
  - DTI
  - anatomical
- EEG
- TMS-EEG
- TMS-Plasticity
- tACS-EEG
- Genetics (saliva sample)
- PET – Aβ/TAU/Microglia
- Lumbar Puncture (optional)

**Intervention:**
4 weeks, Mon.-Fri.
Daily 2-hr visits
Outpatient in the Berenson-Allen Center
- EEG before, during, after intervention
- Safety evaluation after each session

**Post-Intervention Evaluation:**
3 days, 2 night
Inpatient in the Clinical Research Center
- Medical exam
- Clinical evaluation
- Neurological exam
- Neuropsychological exam
- Blood tests
- MRI:
  - resting-state fMRI
  - perfusion MRI (ASL)
  - DTI
  - anatomical
- EEG
- TMS-EEG
- TMS-Plasticity
- tACS-EEG
- PET – Aβ/TAU/Microglia
- Lumbar Puncture (optional)

Daily gamma-tACS intervention in Alzheimer Disease patients
Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields

Ruffini et al. 2013
fMRI-EEG based Multifocal tACS

Targets for Fronto-parietal desynchronization

Meta-analysis map of fMRI activation map during Executive functions tasks
MRI-perfusion based Multifocal tCS in Brain Tumors

Santarnecchi et al. (in preparation)
Principles of tACS

- Oscillations
- Endogenous Resonance

**tACS probe oscillatory neural activities**

- Perception (vision, tactile)
- Cortico-Spinal Excitability
- Cognition (Intelligence, memory, risk-taking,...)

Potential therapeutic tool

- Tremor, stroke, Alzheimer...

Future Directions?
### tDCS & tACS

#### Transcranial Direct Current Stimulation (tDCS)
- **Current:** Constant/Direct
- **Stimulation parameters:** Anode: excitatory
  Cathode: inhibitory
- **Mechanism:** Membrane polarization
- **Effect on:** Cortical excitability
- **Neuronal effect:** During and After

#### Transcranial Random Noise Stimulation (tRNS)
- **Current:** Oscillatory/Alternating
- **Stimulation parameters:** 1-640 Hz (random)
  100-640 Hz: excitatory
- **Mechanism:** Stochastic resonance
- **Effect on:** Cortical excitability
- **Neuronal effect:** During and after

#### Transcranial Alternating Current Stimulation (tACS)
- **Current:** Oscillatory/Alternating
- **Stimulation parameters:** Frequency (Hz)
  Phase (Degrees)
- **Mechanism:** Entrainment
  - Brain oscillations (power, phase)
  - Cortical excitability (>100Hz)
- **Effect on:** Cortical excitability
- **Neuronal effect:** During and After
Thank you for your attention

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