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

Santaronechi et al. 2015 Curr Opin Behav Sci
• 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: Transcranial Stimulation Techniques

<table>
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<tr>
<th>Technique</th>
<th>Current</th>
<th>Stimulation Parameters</th>
<th>Mechanism</th>
<th>Effect on</th>
<th>Neuronal effect</th>
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<tr>
<td>Direct Current Stimulation (tDCS)</td>
<td>Constant/Direct</td>
<td>Anode: excitatory, Cathode: inhibitory</td>
<td>Membrane polarization</td>
<td>Cortical excitability</td>
<td>During and After</td>
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<tr>
<td>Random Noise Stimulation (tRNS)</td>
<td>Oscillatory/Alternating</td>
<td>1-640 Hz (random), 100-640 Hz: excitatory</td>
<td>Stochastic resonance</td>
<td>Cortical excitability</td>
<td>During and after</td>
</tr>
<tr>
<td>Alternating Current Stimulation (tACS)</td>
<td>Oscillatory/Alternating</td>
<td>Frequency (Hz), Phase (Degrees)</td>
<td>Entrainment</td>
<td>- Brain oscillations (power, phase), - Cortical excitability (&gt;100Hz)</td>
<td>During and After</td>
</tr>
</tbody>
</table>
Mechanism of action

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

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tACS effect

Pre stimulation spectral power and average phase

B(t)

Santarnecchi and Rossi (2017)
Why tACS?
Brain Oscillatory Activity

Hans Berger (1921)

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**Delta**: Frequency ~ 10 Hz, Instantaneous Phase ~ -\( \pi/2 \), Instantaneous Amplitude ~ 24 \( \mu V \)

**Theta**: Frequency ~ 20 Hz, Instantaneous Phase ~ +\( \pi/2 \), Instantaneous Amplitude ~ 5 \( \mu V \)

**Alpha**: Frequency ~ 10 Hz, Instantaneous Phase ~ -\( \pi/2 \), Instantaneous Amplitude ~ 24 \( \mu V \)

**Beta**: Frequency ~ 20 Hz, Instantaneous Phase ~ +\( \pi/2 \), Instantaneous Amplitude ~ 5 \( \mu V \)

**Gamma**: Frequency ~ 10 Hz, Instantaneous Phase ~ -\( \pi/2 \), Instantaneous Amplitude ~ 24 \( \mu V \)
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

**Alpha**: visual perception

**Theta**: spatial orienting

"Natural Frequencies"
EEG Oscillations and PATHOLOGY

• Reduced synchrony in Schizophrenia
• Reduced amplitude in Alzheimer
• Increased Amplitude in Bipolar dis.

• Reduced synchrony in Schizophrenia
• Reduced synchrony in Alzheimer

• Reduced coherence in Alzheimer
• Increased phase-locking at Frontal and Central electrodes in Schizophrenia

• Reduced Coherence in Alzheimer and Schizophrenia
• Increased amplitude in Parkinson
• Increased Coherence in Bipolar dis.

• Decreased/increased amplitude in Schizophrenia (?)
• Increased Phase-locked response in ADHD
Inducing “Entrainment”

- Are these oscillatory patterns immutable?

**Entrainment** of endogenous oscillatory pattern → Changes in behaviour

- 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.

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

*Tuth* et al. 2012, Current Biology
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)

Phase?
Phase, angles, degrees.....

Oscillators are in opposite phase (anti-phase)

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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>
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 → Homogenous Phase
  - More Neurons

*Ozen et al., 2010*
Endogenous Resonance Principle

**tACS induced Oscillations** ↔ **Synaptic mediated Oscillations**

Coherent

Incoherent

Sleep

Exploring

tACS ~ 1.5Hz

Phase-locked (25-50%)

S = sleep

R = rest

E = exploration

Ozen et al., 2010

Push & pull

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tACS in humans: effects on cortico-spinal Excitability
**Question**

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

**Design**

- **tACS over M1**
- Amplitude of TMS induced MEP*

**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

Peak-to-Peak Amplitude

Latency

Magnetic Field
tDCS effects on the motor cortex

Santarnecchi et al., 2014
tDCS effects on the motor cortex

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

- 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..

High spatial and temporal resolution analyses.
tACS and Motor performance - III

- 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.

*PLEASE DO NOT COPY*
tACS and Cognition
Sleep Architecture

Rationale

Declarative memory

Non-Declarative memory

Memory Consolidation

for further reading see Diekelmann, 2010

* PGO: ponto-geniculooccipital

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Paired Associated Learning Task

Finger Sequence Tapping Task

**Design**

- **Declarative memory**
  - 46 word pairs
  - 5-element sequences (e.g. 4-2-3-1-4) in 30s

- **Non-declarative memory**
  - 0.75Hz, ~0.33A, 5min/1min ON/OFF

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

**Current**
- 13 Healthy

**Subjects**
• 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)

**Fluid Intelligence – Abstract Reasoning**

*Santarnechi et al., Curr. Biology 2013*

**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
**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.

*Santarnecchi et al., Curr. Biology 2013*
**Design and Results**

- Torrance Test of Creative Thinking (TTCT)
- In-phase tACS over the prefrontal lobes
- Sham, 10Hz and 40Hz tACS

*Lustenberger et al., Cortex 2015*
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?
tACS and Phase Coupling: Working Memory

**Design and Results**

Polania et al., Curr. Bio 2012

**Online tACS protocol**

**180° phase difference**

**Sham**

**0° phase difference**

**6Hz tACS**

**35Hz tACS**

**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?

Feurra et al., 2013,
Journal of Neuroscience

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

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

- 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.
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
Trait-dependency of tACS?
Individual differences in response to tACS?

Santarnecchi 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

tACS=1.0 mA, tRNS=1.0 mA
State-Trait dependency

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

Variability in the response to tCS

- Neurotransmitters balance
- Cortical “excitability”
- Head-tissue morphology
- Fatigue, wakefulness, attention, habituation to stimuli ➔ can Flip the effect
- Silvanto et al., 2007
- Hormonal levels
- Circadian rhythm
- age
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 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

- 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).
Future tACS Clinical Applications

Gamma frequency entrainment attenuates amyloid load and modifies microglia

Iaccarino et al. 2016 (Nature)

High-frequency visual stimulation in the gamma band in rats

Decrease in hippocampal amyloid-β after 40Hz stimulation visible at Immunohistochemistry
Ongoing studies (DARPA; BIDMC)

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)

T0 T1 T2 T3

Daily gamma-tACS intervention in Alzheimer Disease patients
fMRI-based Multifocal tACS

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

Ruffini et al. 2013

fMRI activation map

tCS solution with 2 electrodes

Multifocal tCS solution with 8 electrodes
fMRI-EEG based Multifocal tACS

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

Targets for Fronto-parietal desynchronization
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

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

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

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

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