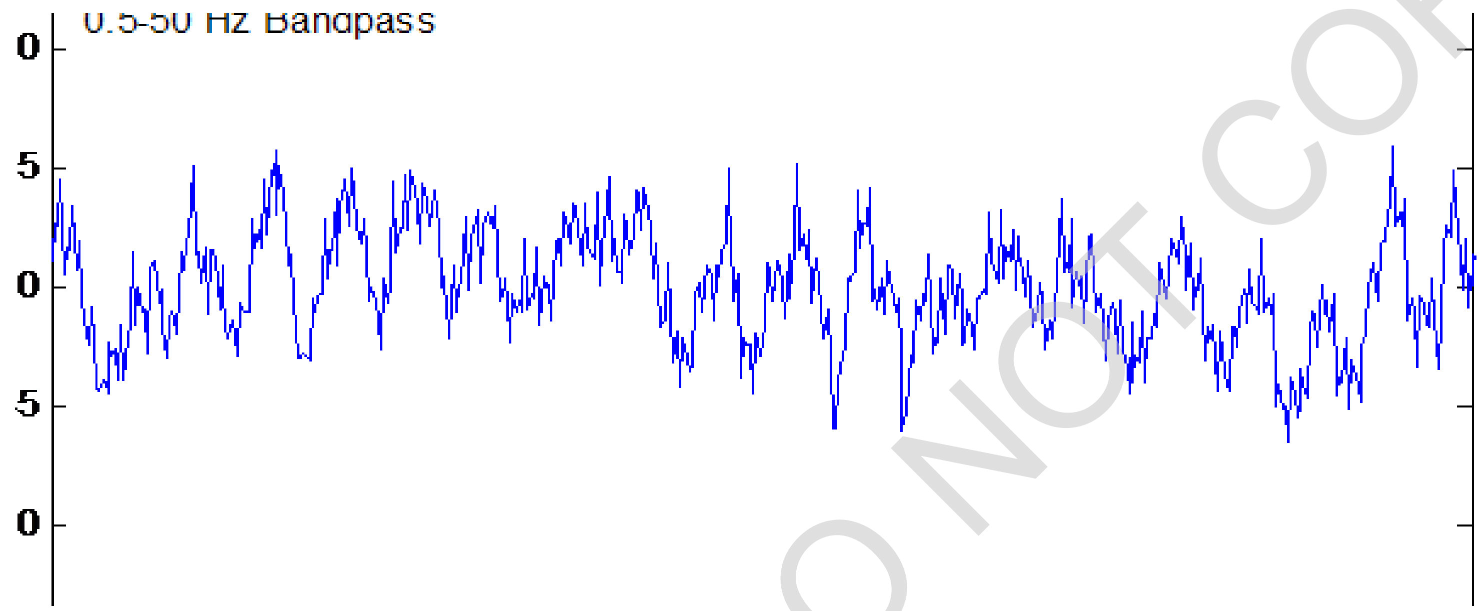
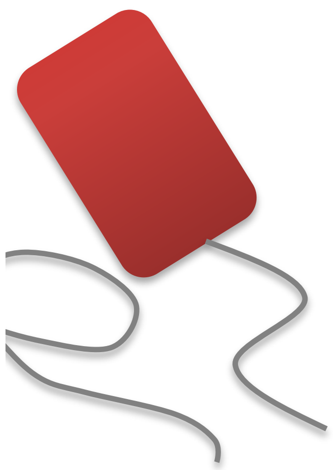
Combining tCS and EEG





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Boston, 23rd June 2019

Berenson-Allen Center For Noninvasive Brain Stimulation

VE RI TAS HARVARD

axies that can be seen today make up ju

NASA

Observable Universe

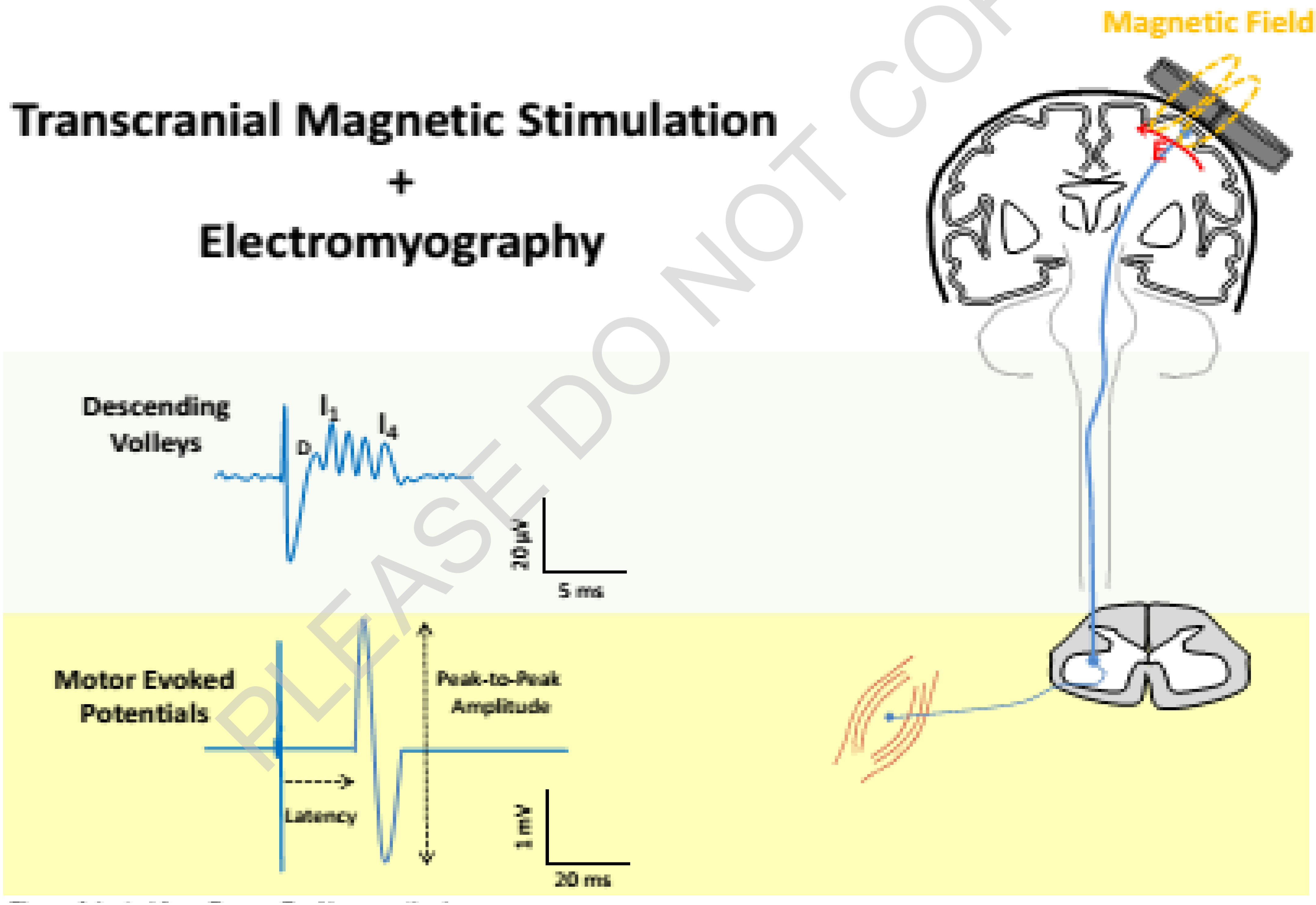
Observable Universe Planet Earth

Outline

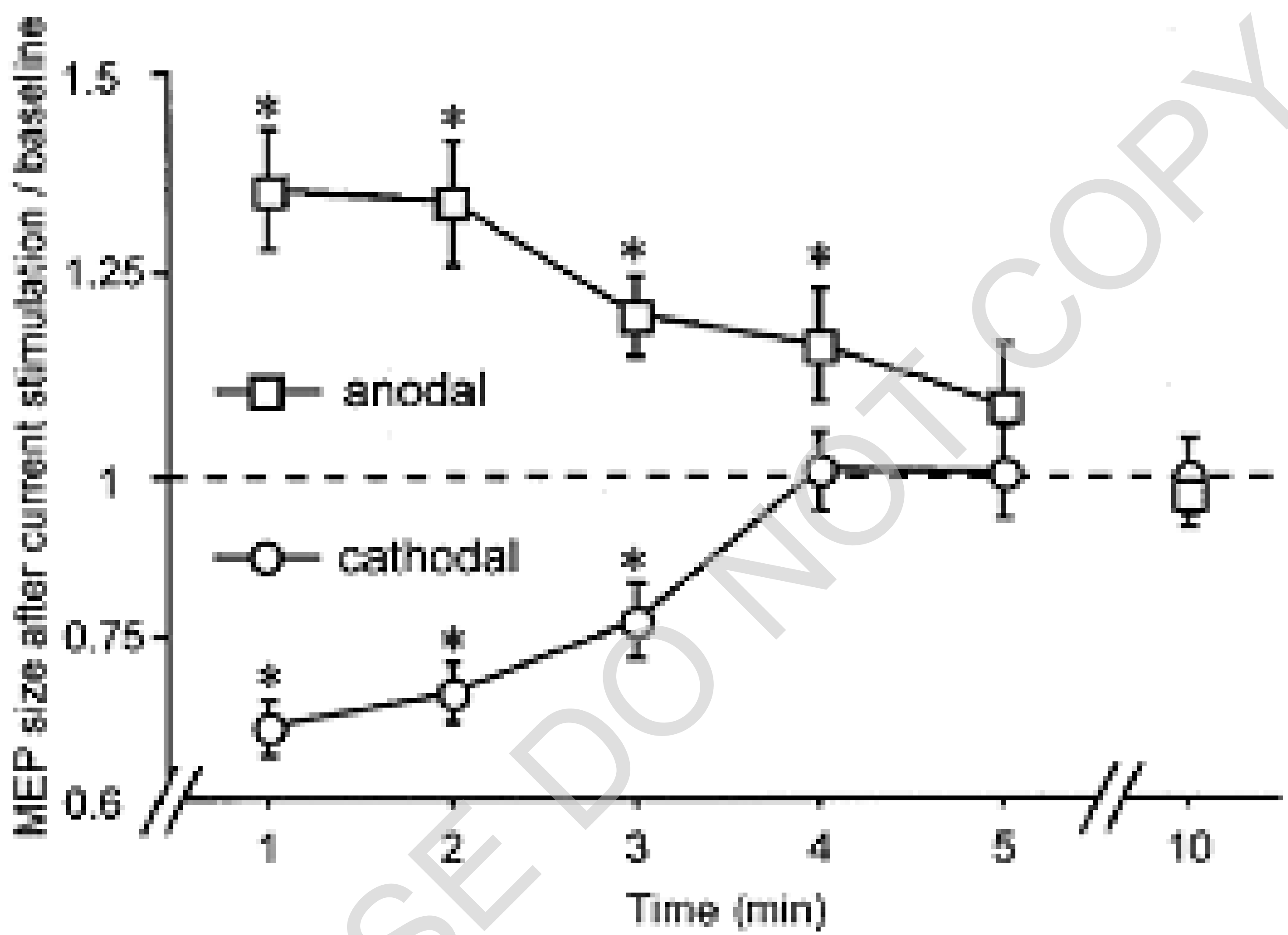
- **Measuring tCS effects with EEG**
  - ➢ Measuring effects outside the motor cortex
  - ➢ Measuring focality of tCS interventions
- **Basics of EEG**
  - ➢ EEG signal: features and opportunities
  - ➢ Analysis (ERP,Power, ...)
  - ➢ Experimental example of EEG-tCS combination
- **Beyond EEG**
  - ➢ TMS-EEG recording

Corticospinal excitability as an index of Brain excitability

Applied to tCS: limitation for online recording, only after effects



Measuring tCS effects without EEG

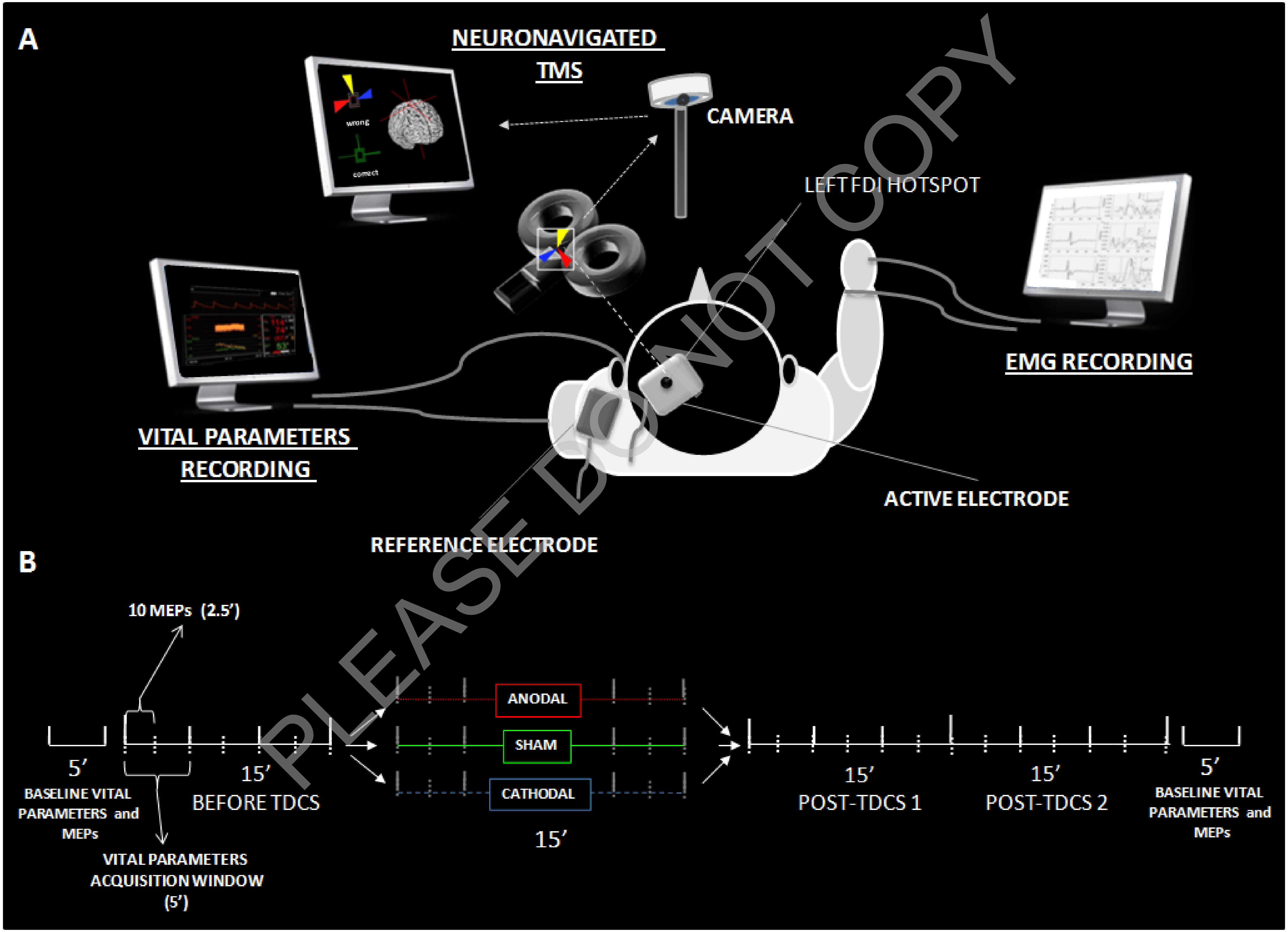


First evidence of tDCS after effect from **Nitsche and Paulus, 2000**

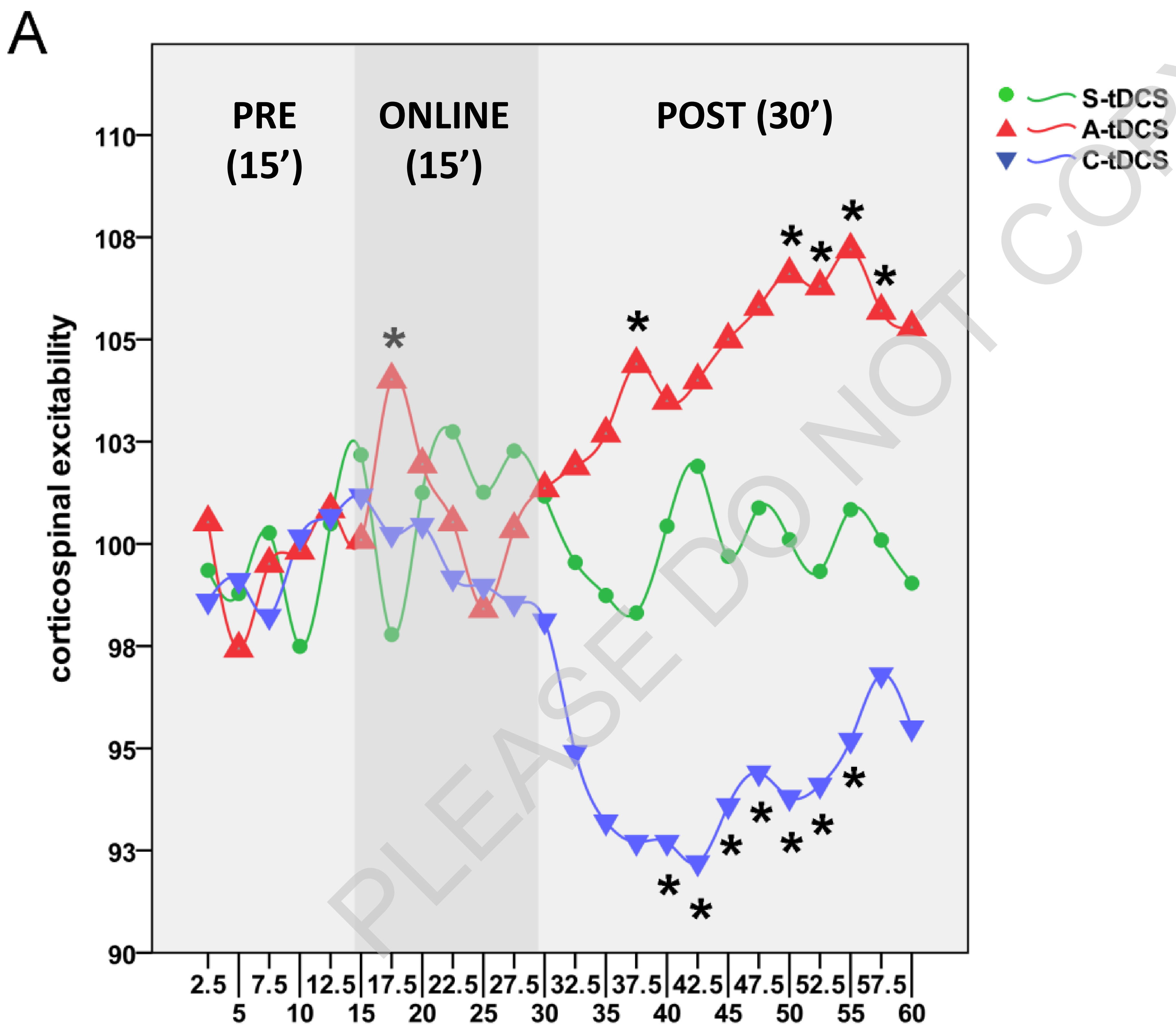
Changes in cortical excitability assessed using TMS-EMG

tDCS effect on corticospinal excitability:Online and Offline effects

Santarnecchi et al., 2014



tDCS Effects on the motor cortex: pre/during/post



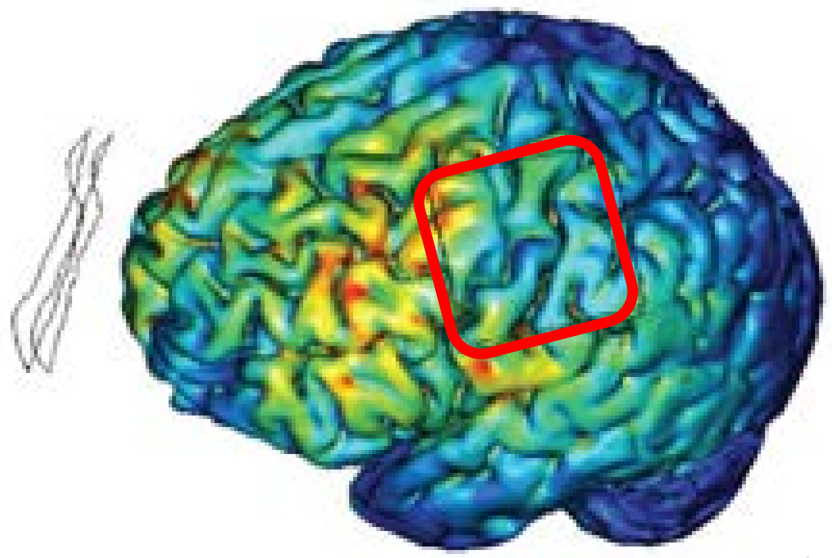
Anodal and Cathodal tDCS modulate (increase/decrease excitability) right after the stimulation respect to Sham.

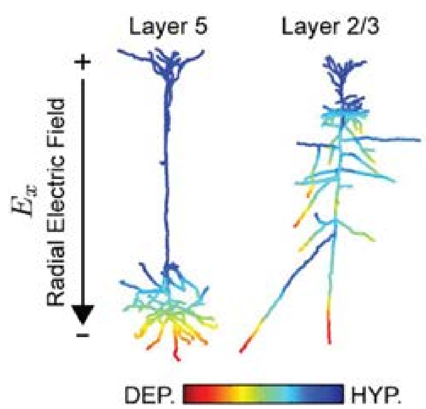
No significant effects During the stimulation.

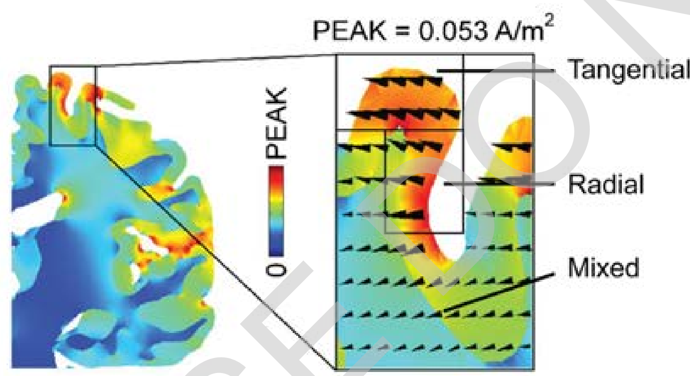
Still limited to the motor cortex!

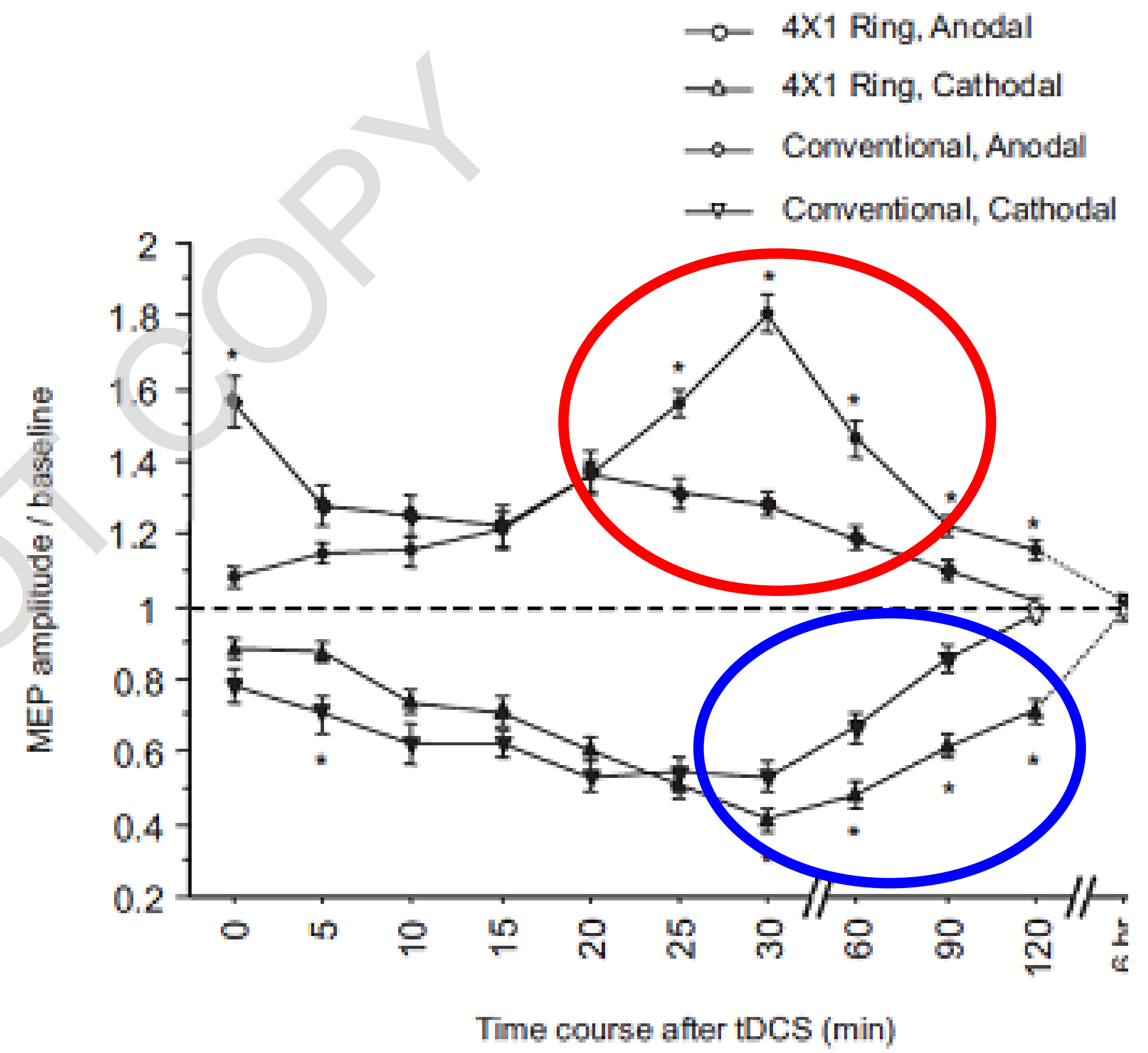
Are we stimulating the motor cortex?

Kuo et al., 2013

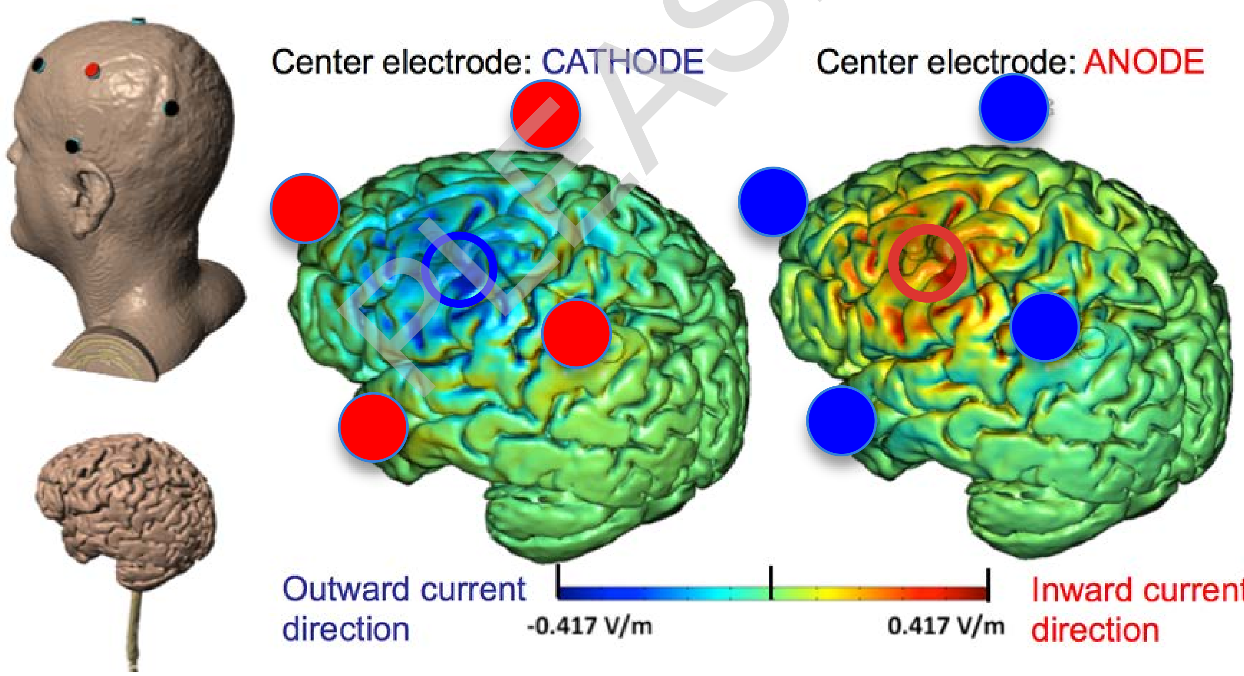








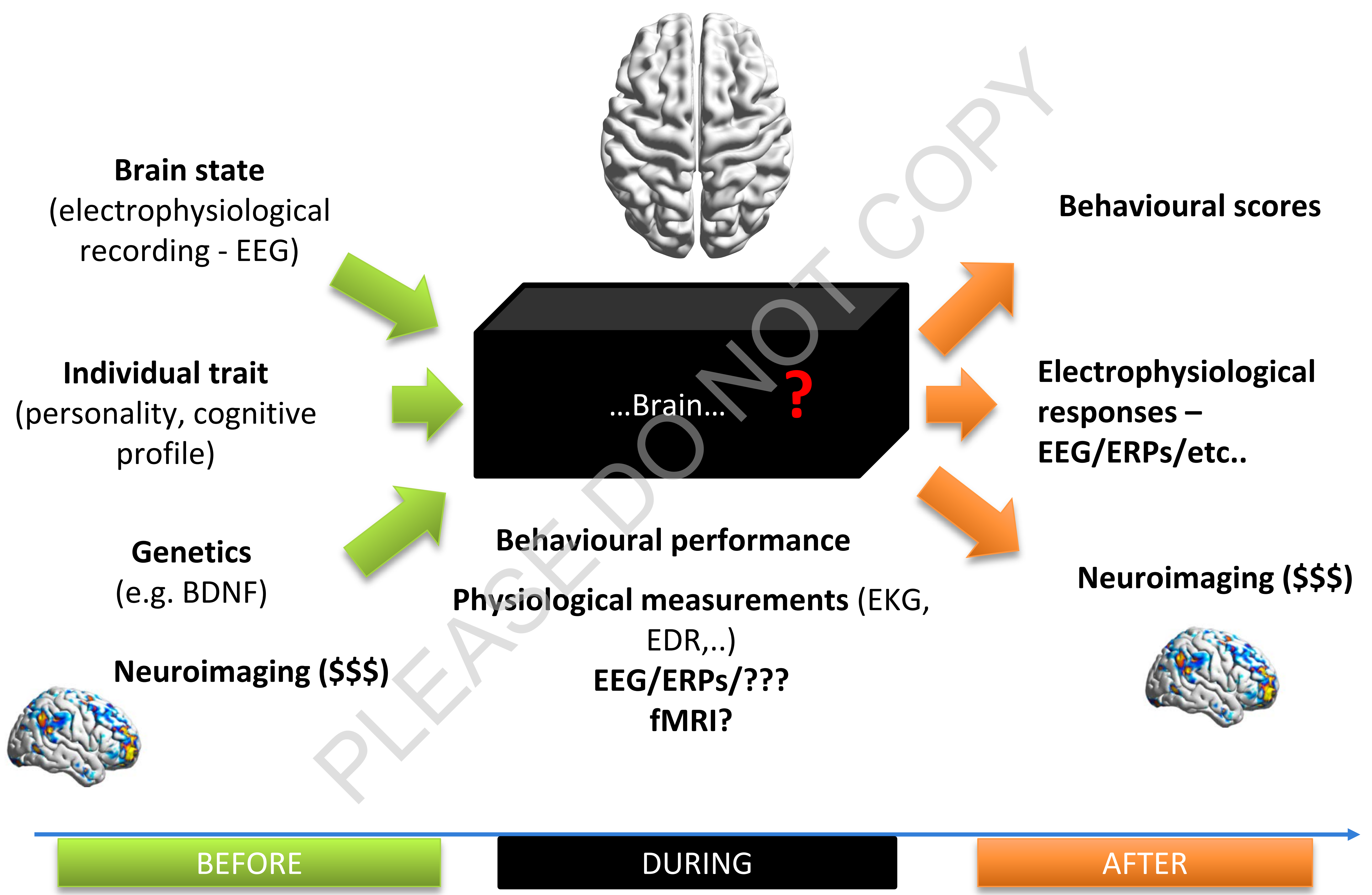
HD-tDCS



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

TMS-EMG is not enough

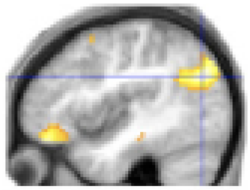
Multifactorial model



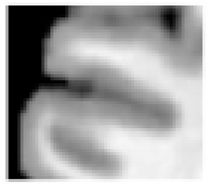
Targeting Optimization

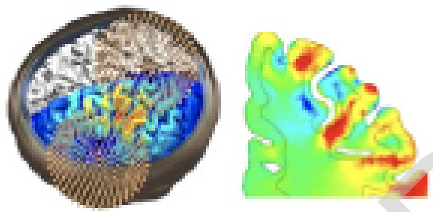
Where to stimulate?

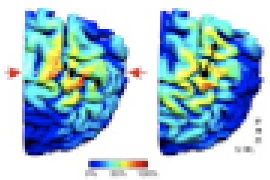
Determine **target site & device position/orientation** for stimulation based on...


functional localizer


source localization

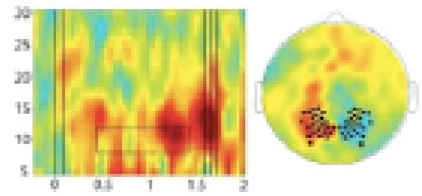

individual gyral anatomy

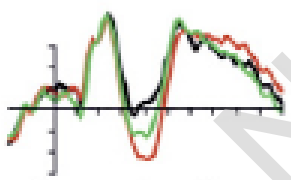

local strength of electric field

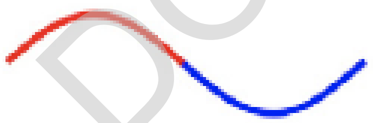

local direction of current flow

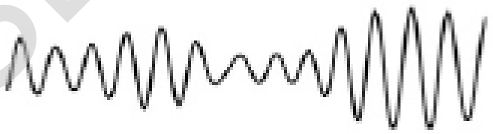
When to stimulate?

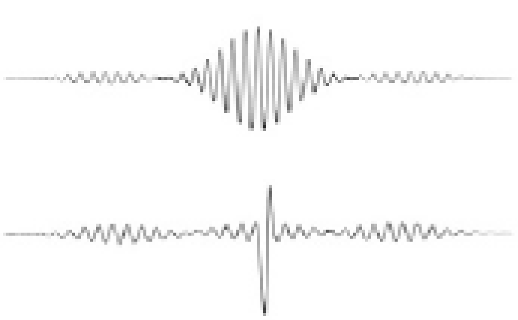
Determine **target onset/time window** relative to task or spontaneous event for stimulation based on...


induced power


latency of evoked responses

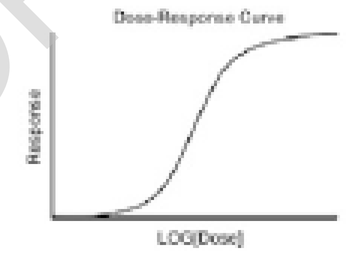

oscillatory phase


oscillatory power

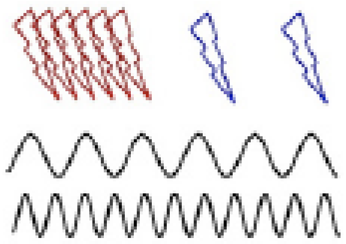

occurrence of specific events

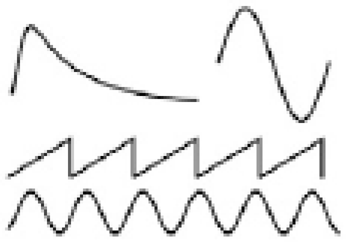
How to stimulate?

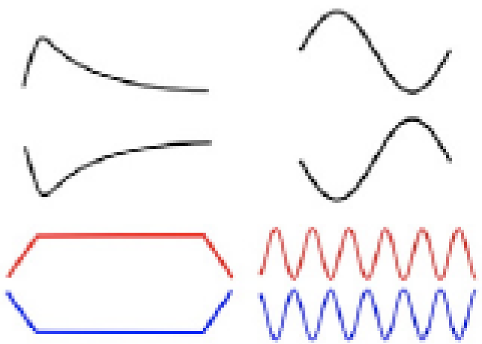
Determine **specfic parameters** for stimulation such as...



stimulation intensity


stimulation frequency

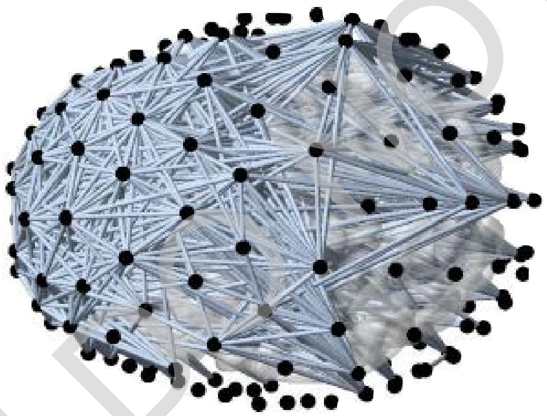

pulse/wave form


polarity

Open questions..

• the effect of tCS on Non-Motor regions?

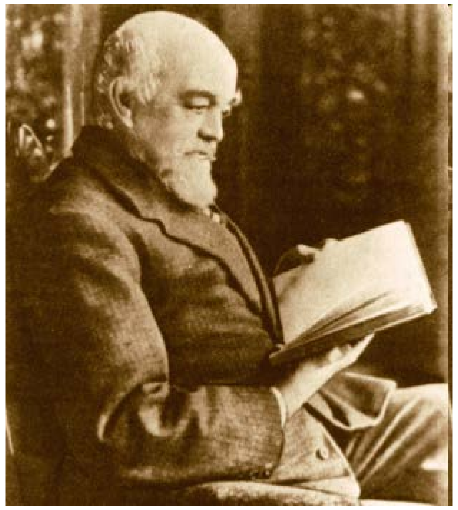
• distant effects and changes in the interplay between regions (connectivity) → ***Network*** effects?



• the Online effects of tCS on brain activity other than "excitability"?

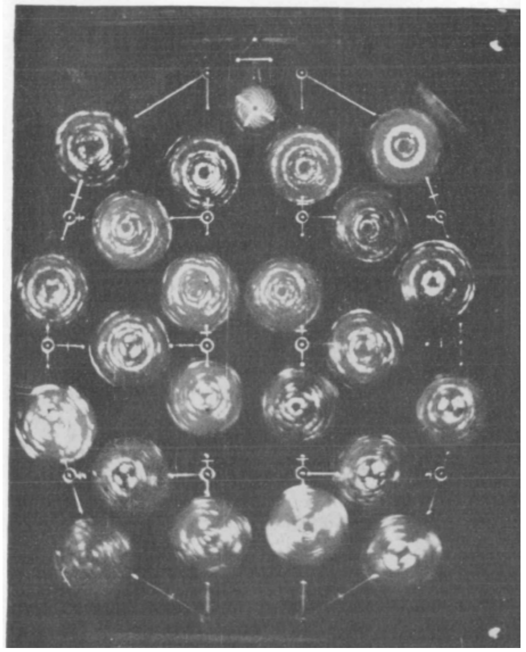
Useful information to define tCS parameters and increase efficacy of interventions

Electroencephalography



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



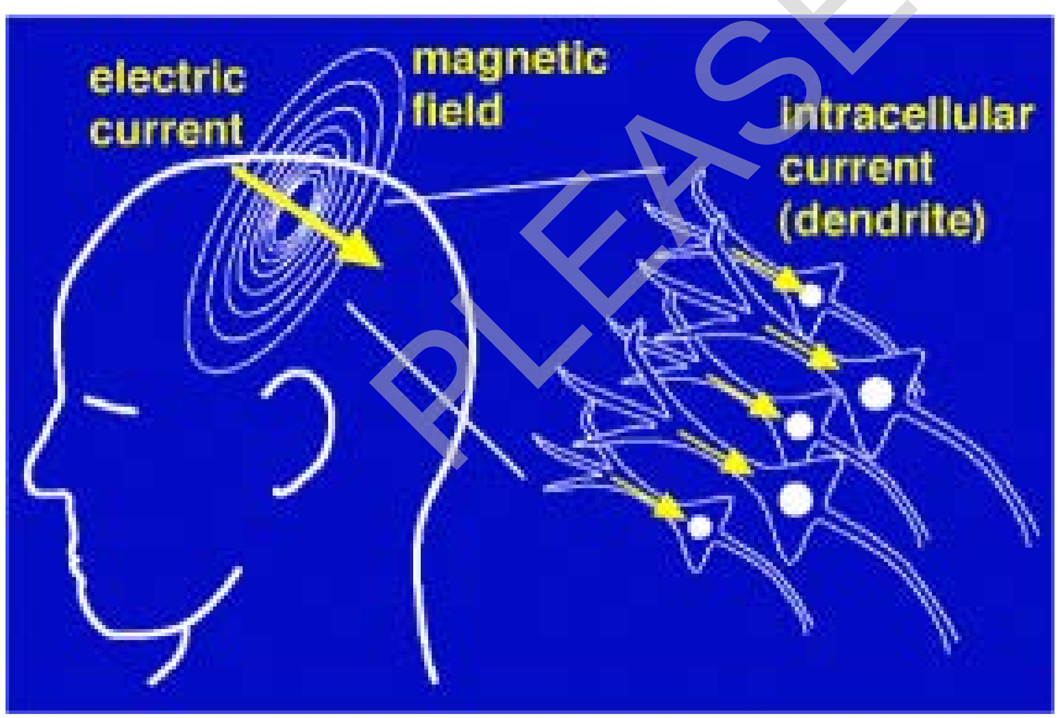
1950s. Grey Walter (1910 – 1977). Invention of topographic EEG maps.

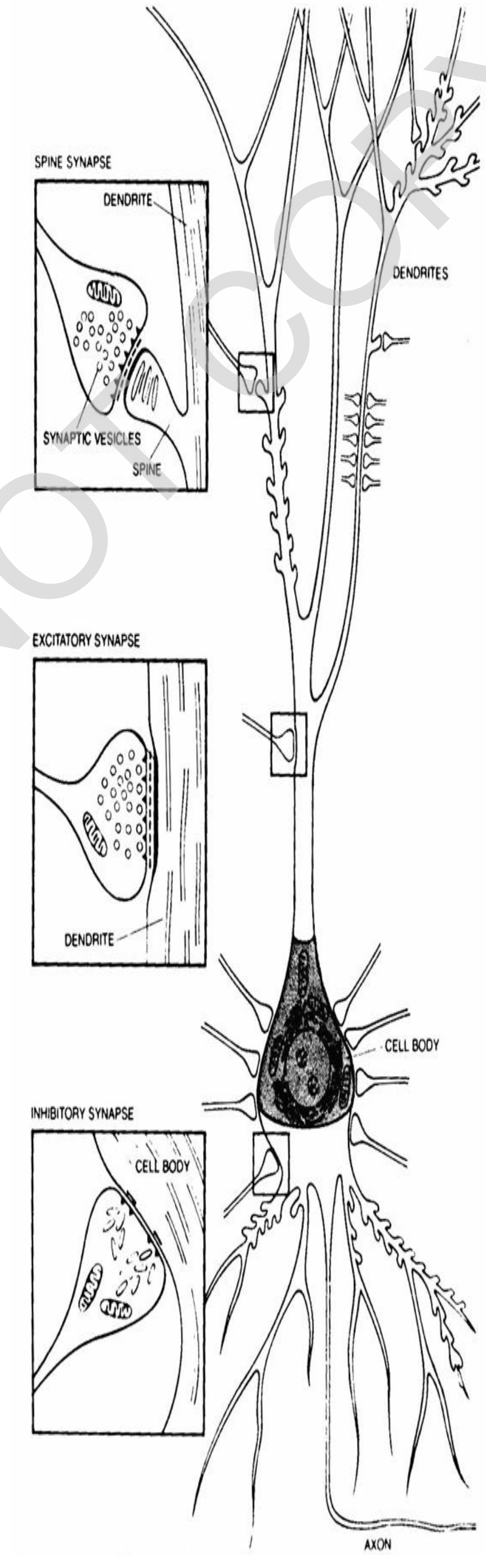
Where does the signal come from?

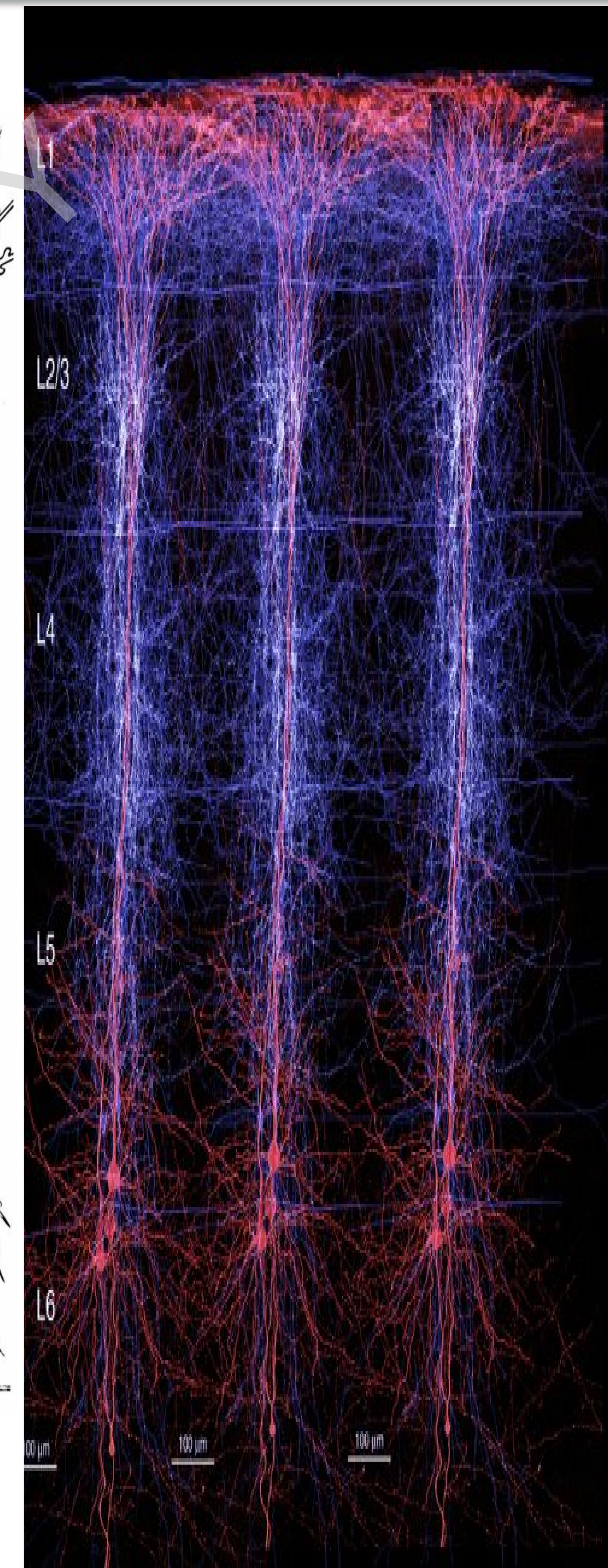
- Signals stem from ***synchronous activity of large (~1000s) groups of neurons*** close to each other and exhibiting similar patterns of activity

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

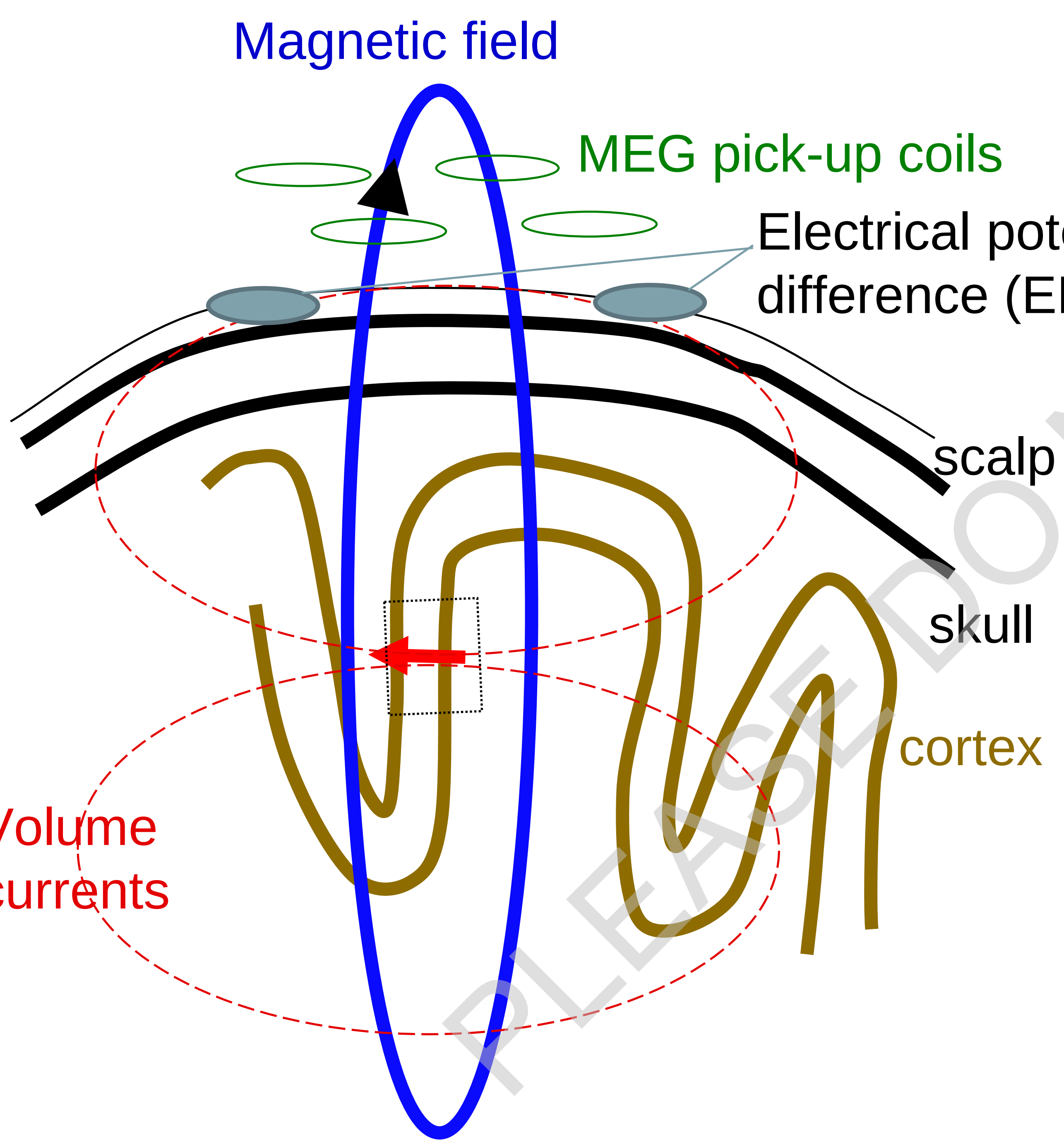
- EEG measures ***synaptic currents***, not action potentials (currents flow in opposite directions and cancel out!)

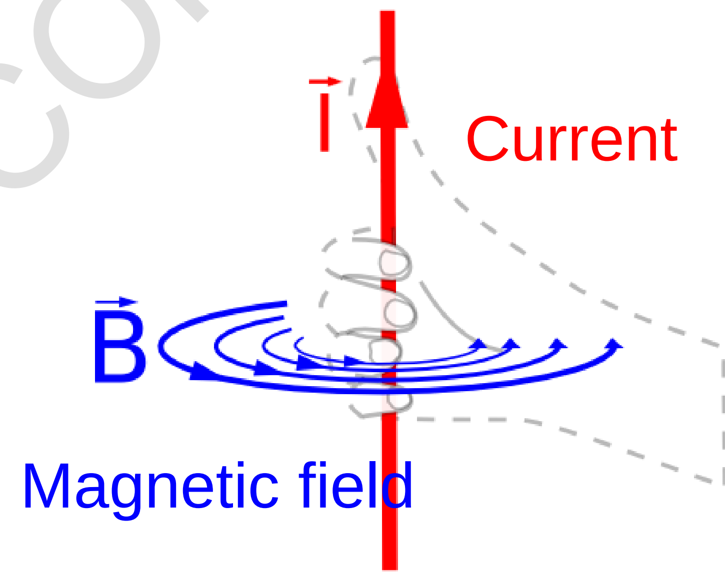


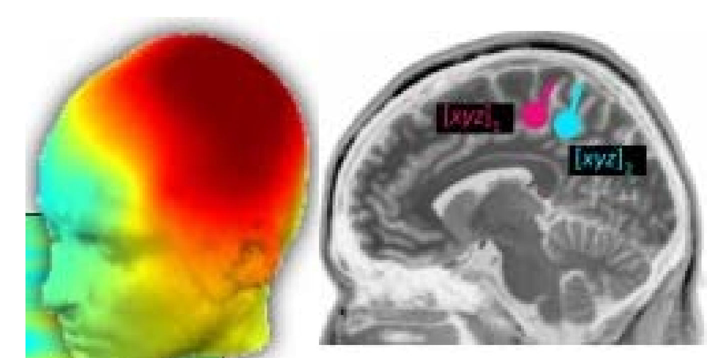


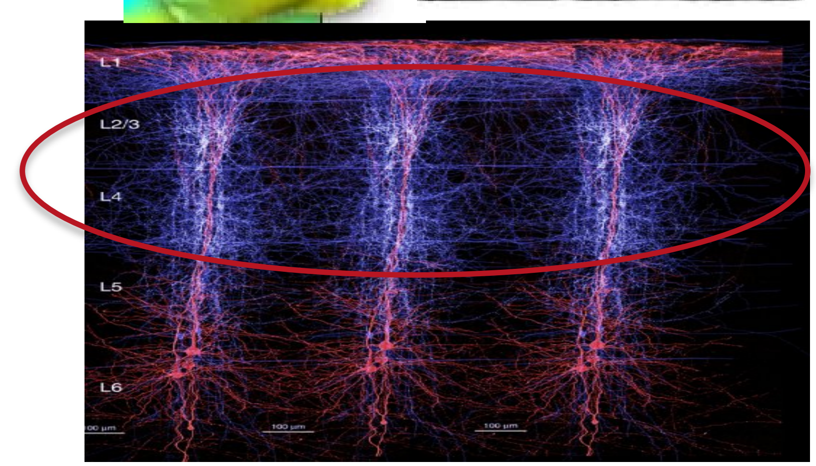


Primary intracellular currents give rise to volume currents and a magnetic field



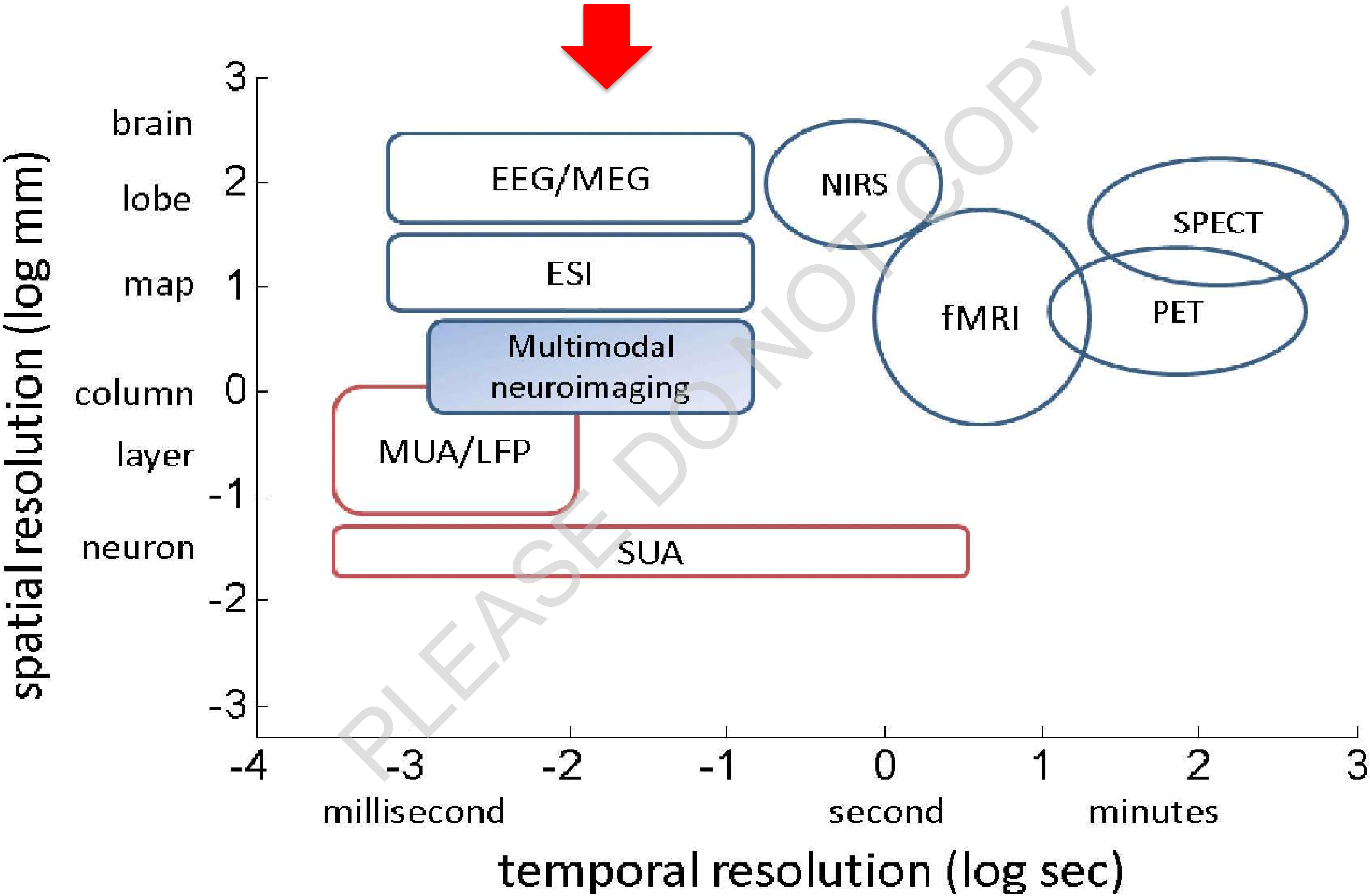






Volume currents yield potential differences on the scalp that can be measured by EEG

Pros and cons of EEG

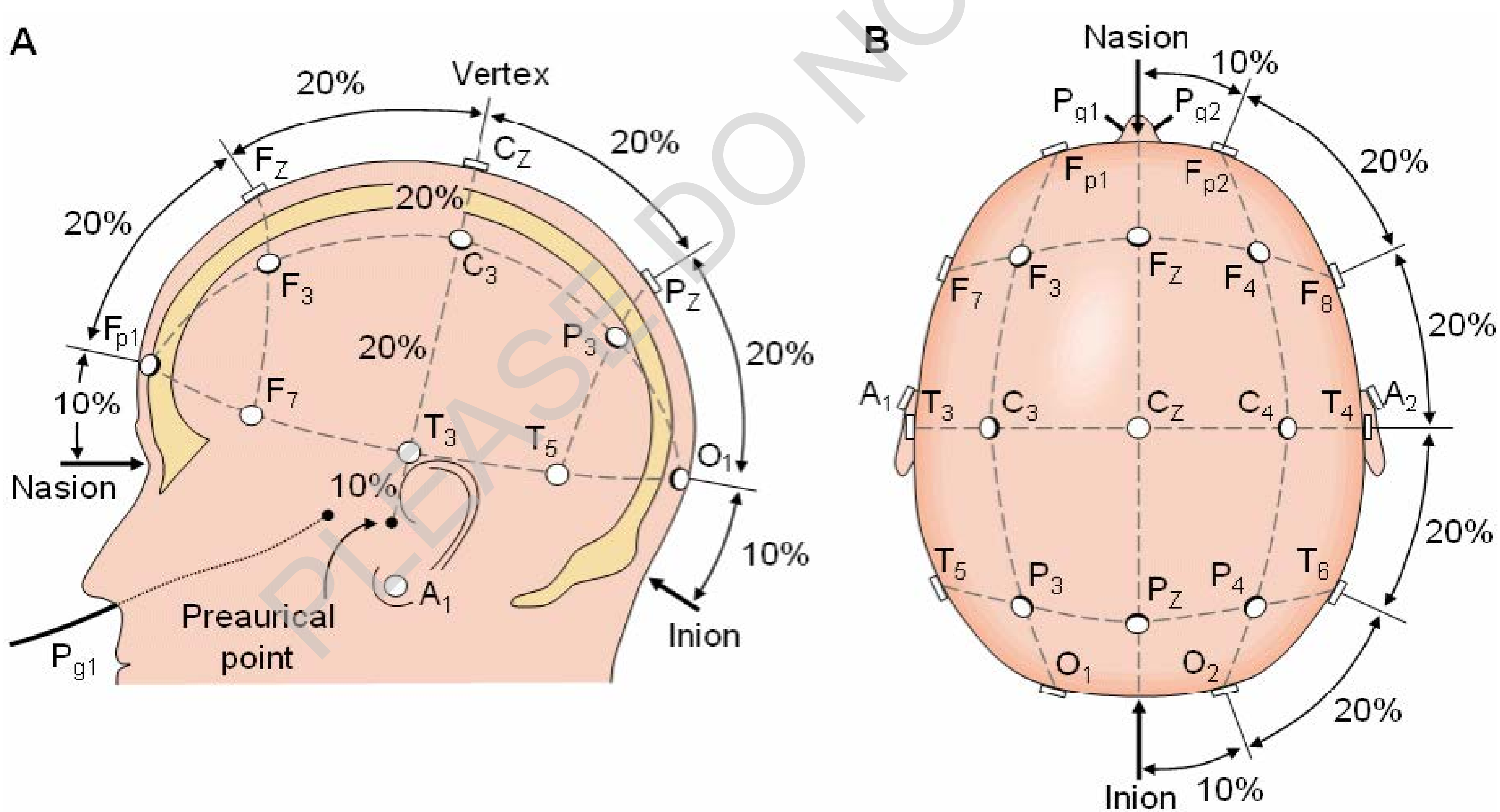


EEG recording and analysis

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).

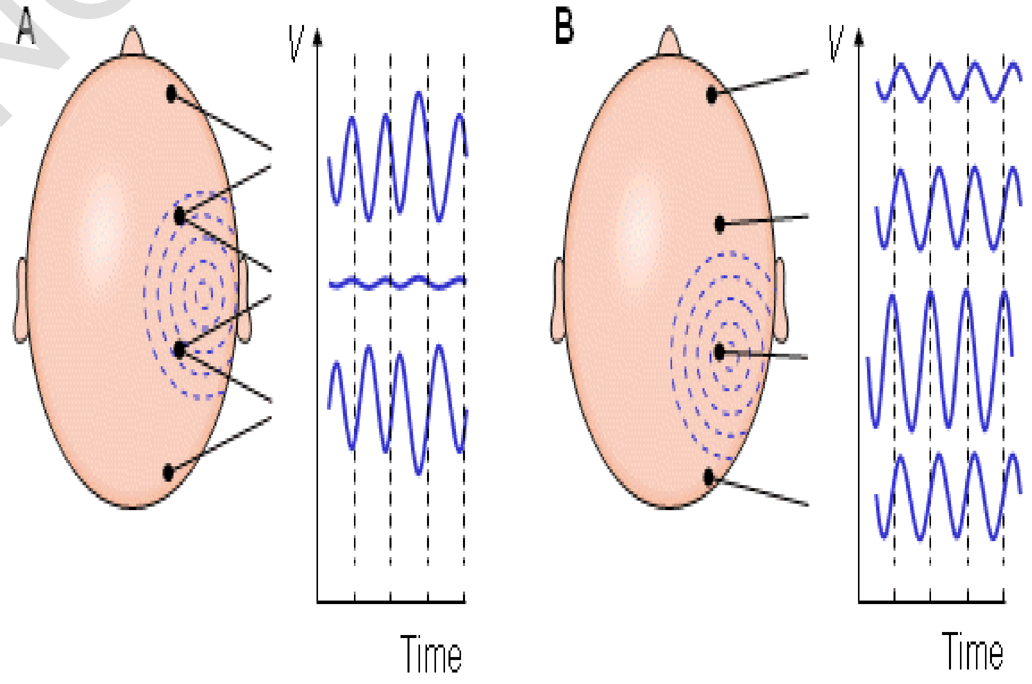
High-Density EEG (64-256 Channels)



EEG recording

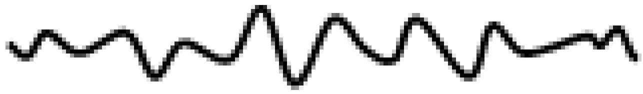
- EEG records potential differences at the scalp using a set of active electrodes and a reference
- The ground electrode is important to eliminate noise from the amplifier circuit
- Potential differences are then amplified

- 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)



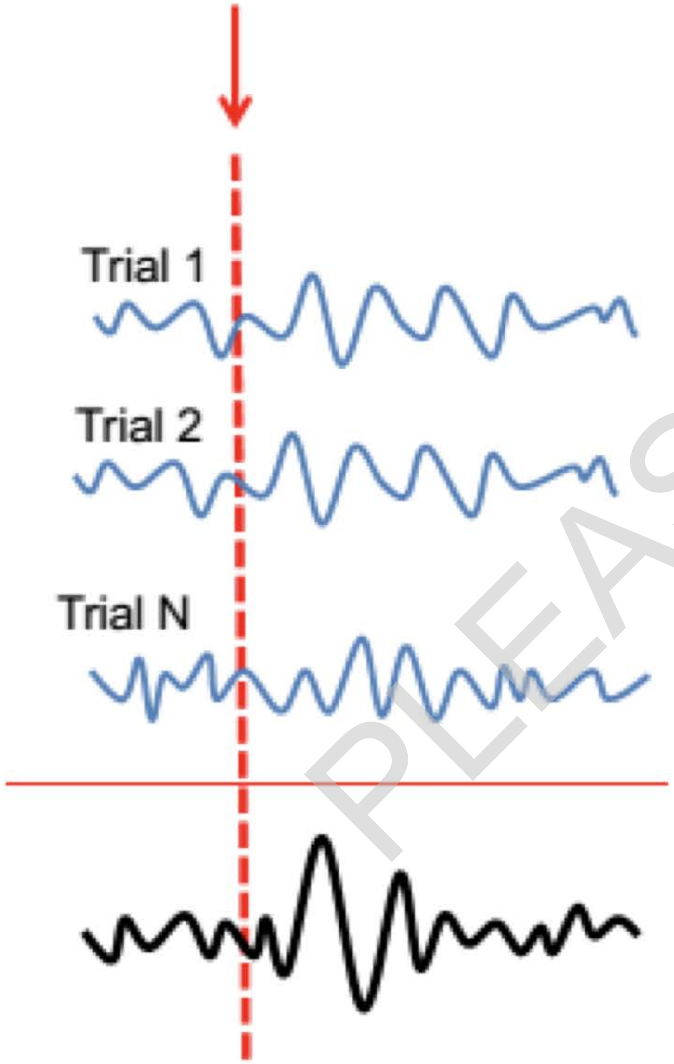
EEG recording

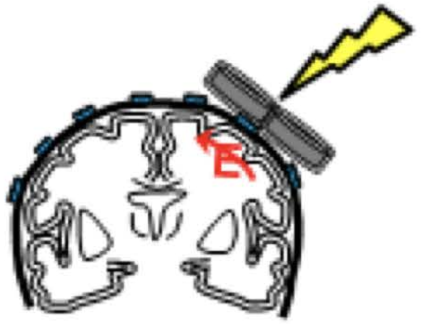
1. SPONTANEOUS



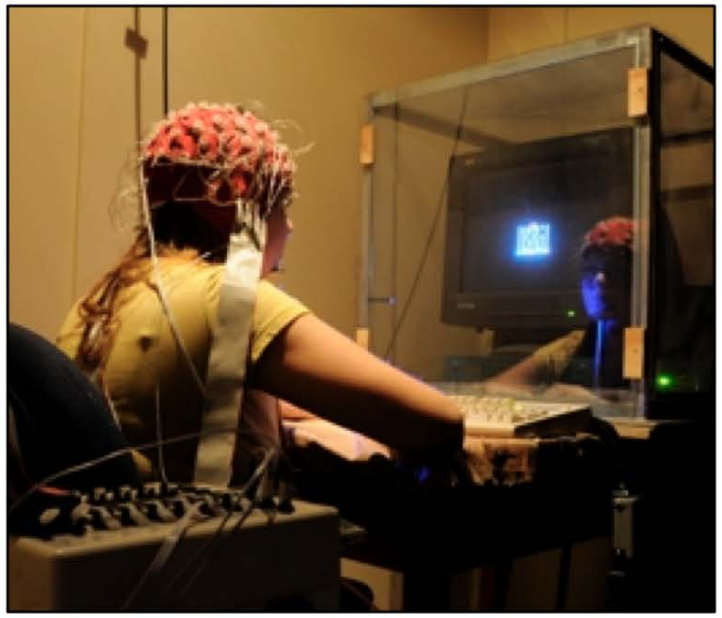
- Meaningful data with ~5’ of recording
- Eyes open/closed

2. EVOKED





TMS-EEG



Well known Evoked Response Potential (ERP)(P300, N100, ..)

From ERPs to Waveform

Time domain:

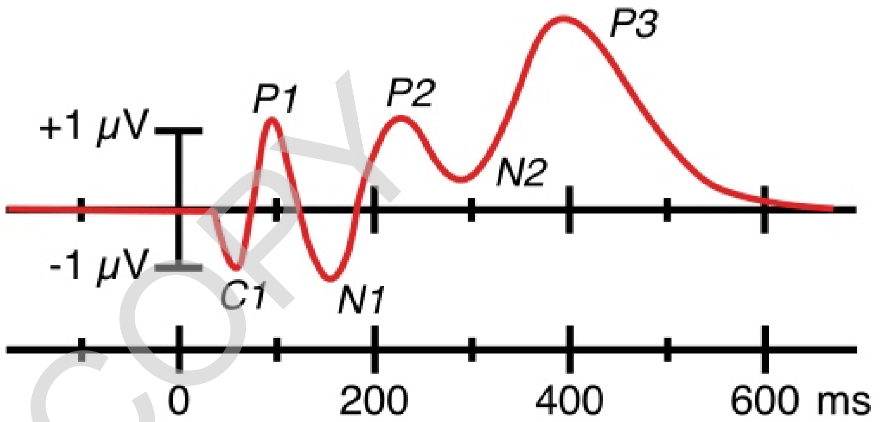
-> when do things (amplitudes) happen?

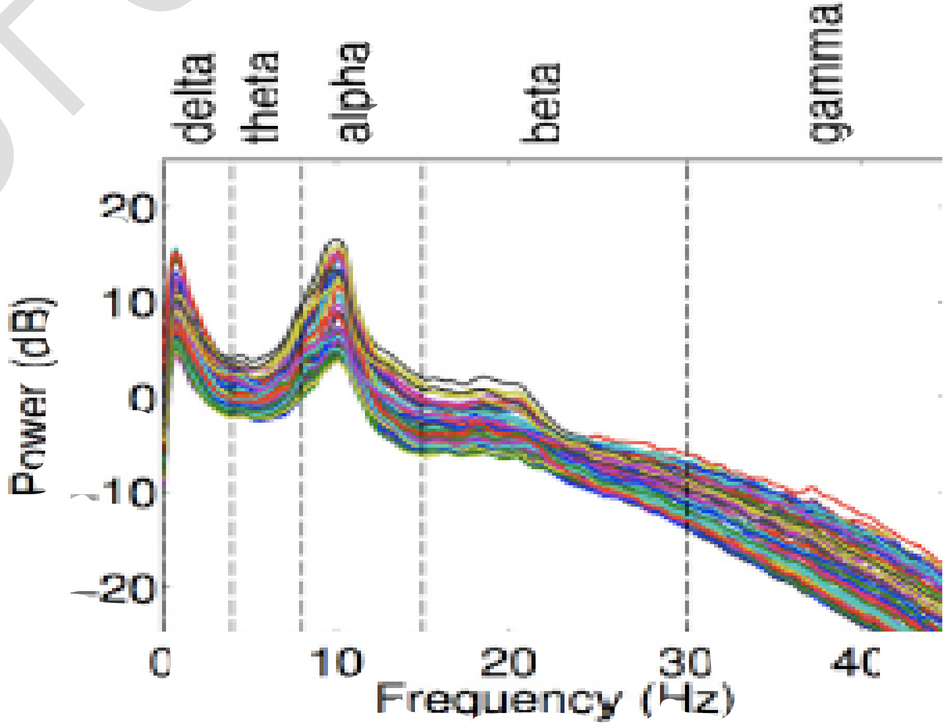
Frequency domain (spectral):

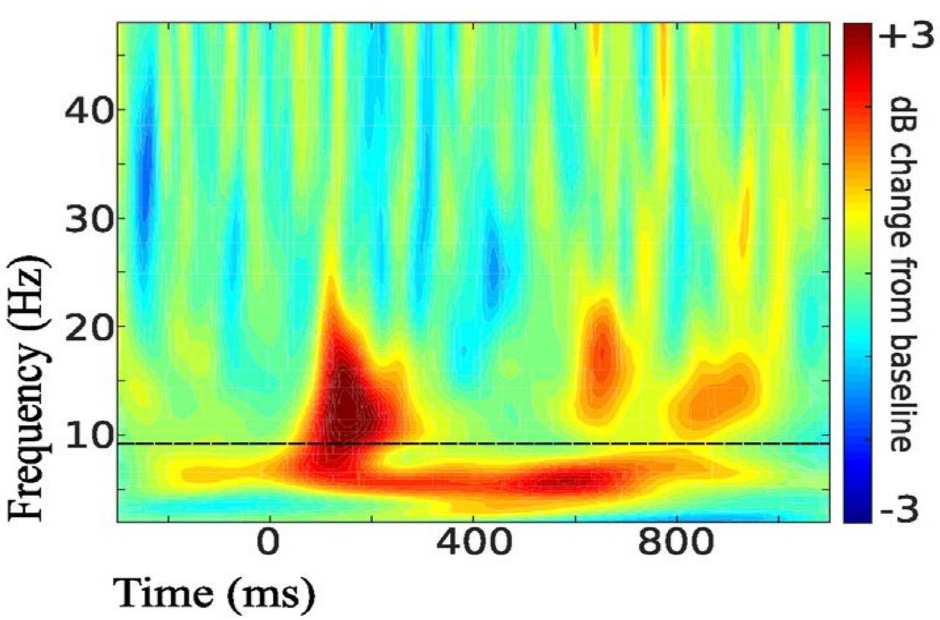
-> magnitudes and frequencies of waves- no time information.

Time-frequency (wavelet analysis):

-> when do which frequencies occur?







EEG features

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

Amplitude (or Power)

Strength

(μV or μV^2)

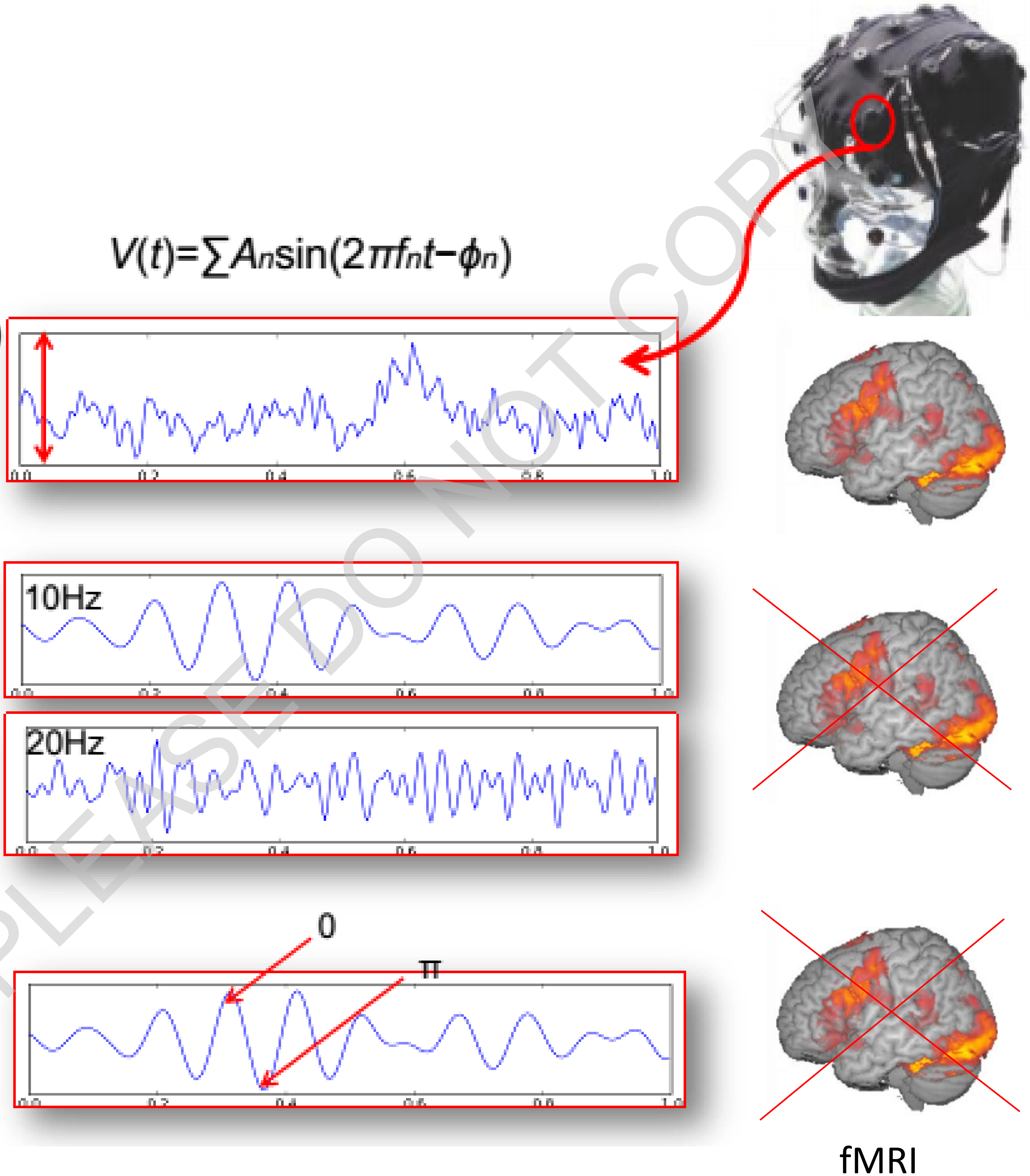
Frequency

# of Cycles/Second

(Hz)

Phase

(Radians)

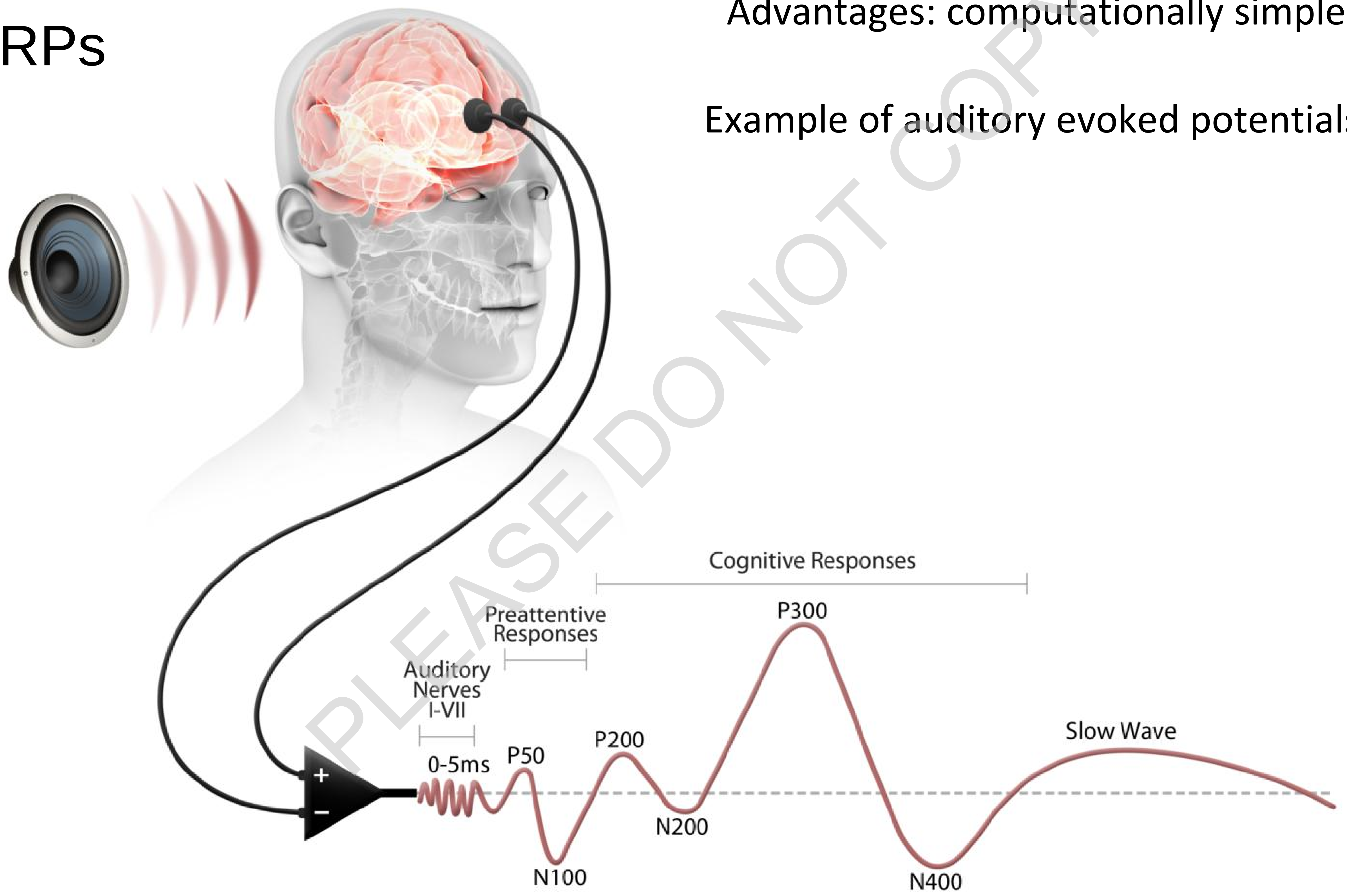


Time domain Analysis

Event Relate Potentials
ERPs

Advantages: computationally simple

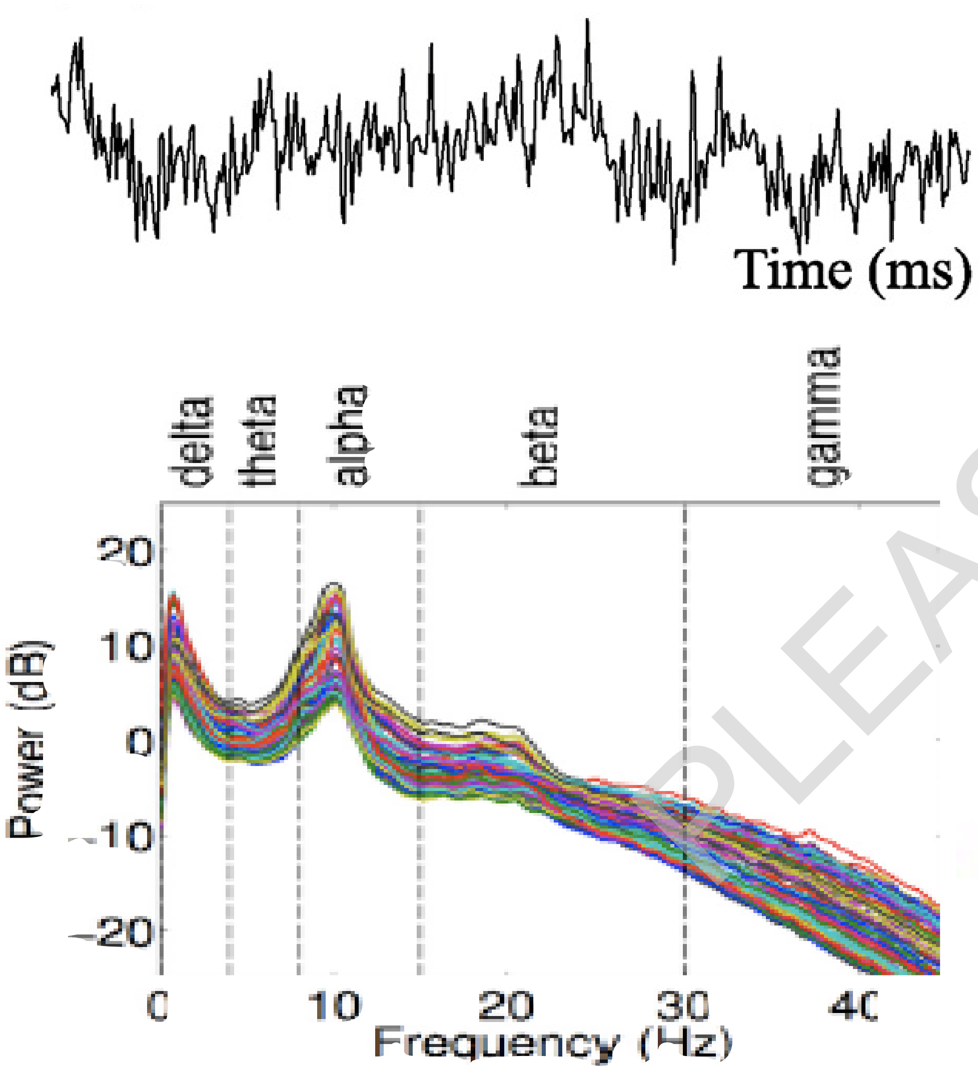
Example of auditory evoked potentials

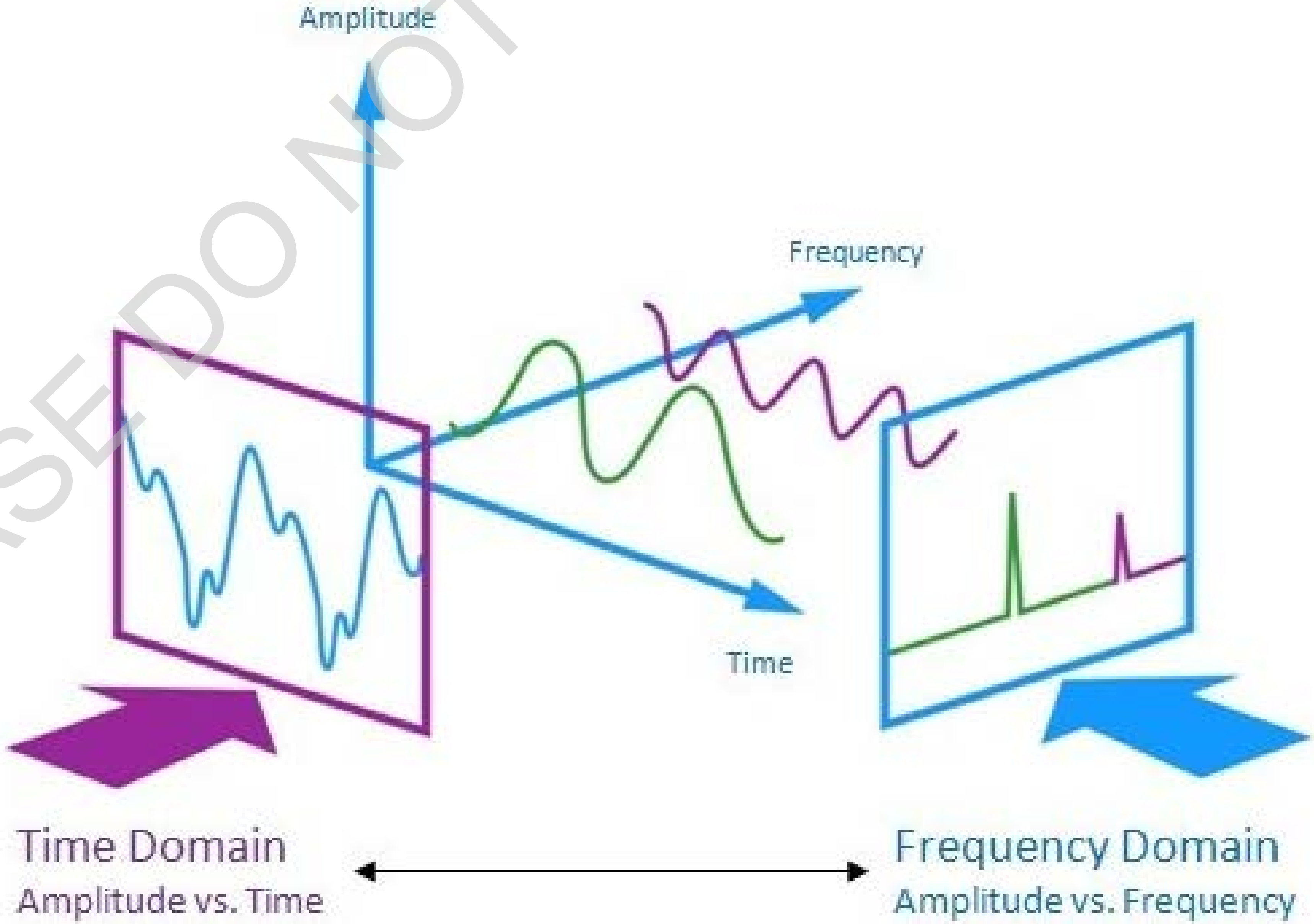


How to disentangle oscillations

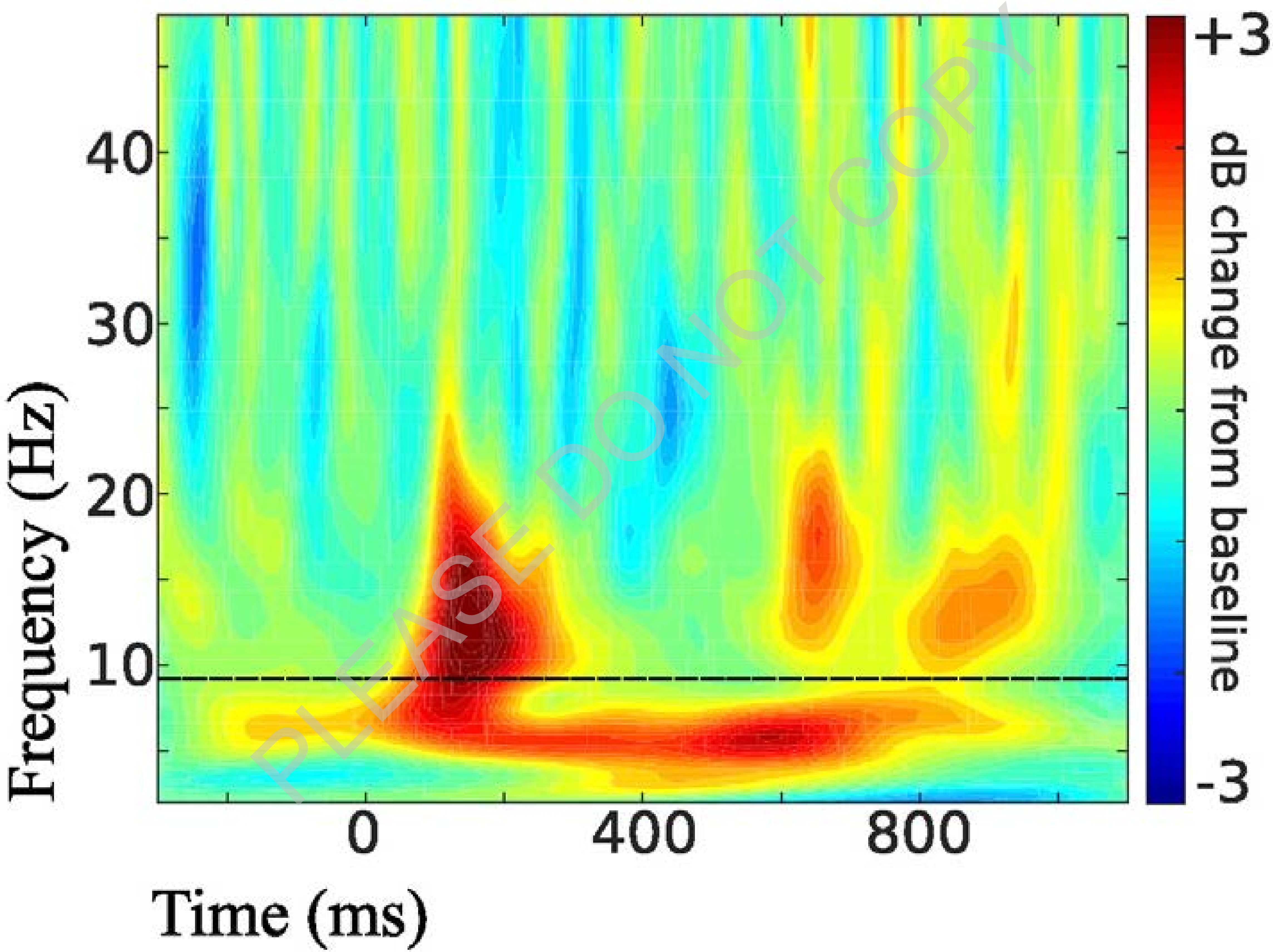
Jean Joseph Fourier (1768–1830):

“An arbitrary function, continuous or with discontinuities, de ned in a finite interval by an arbitrarily capricious graph can always be expressed as a sum of sinusoids”.



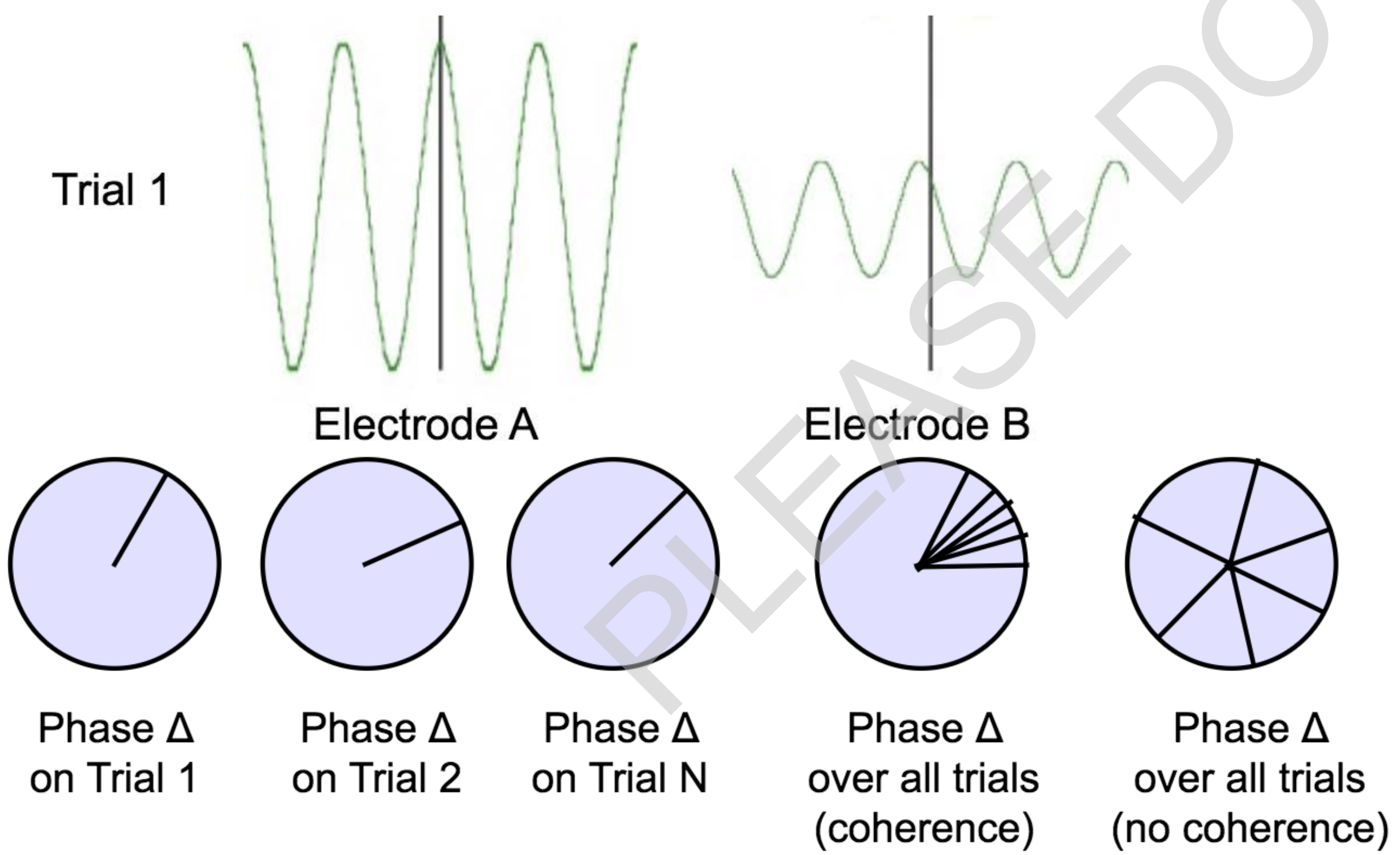


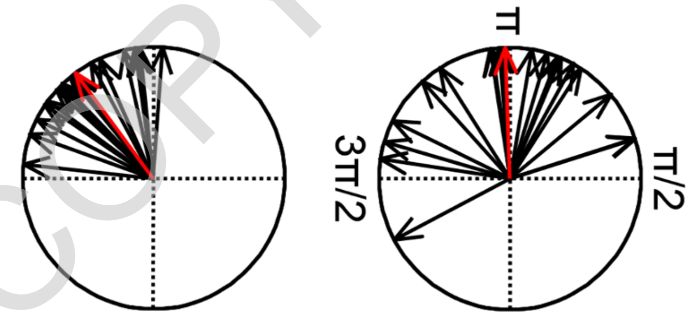
Time- Frequency Domain Analysis (EEG)

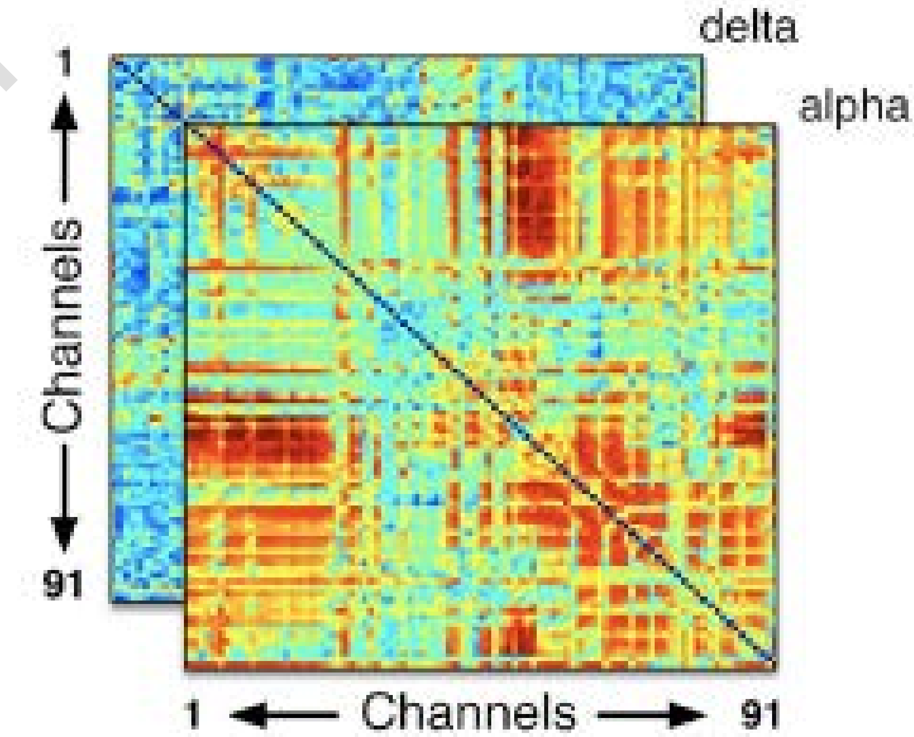


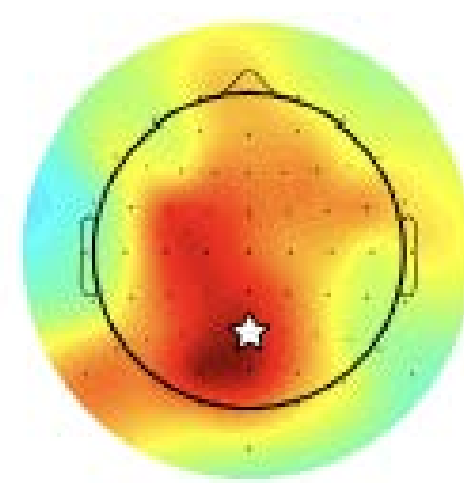
Connectivity based on…

- .Phase (eg. phase-slope index)
- .Power (eg. coherence)
- .Cross-frequency coupling







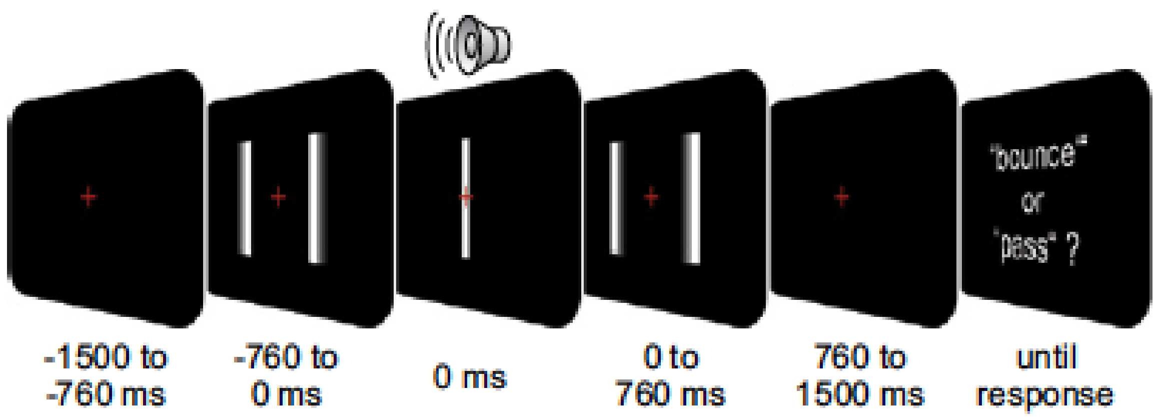


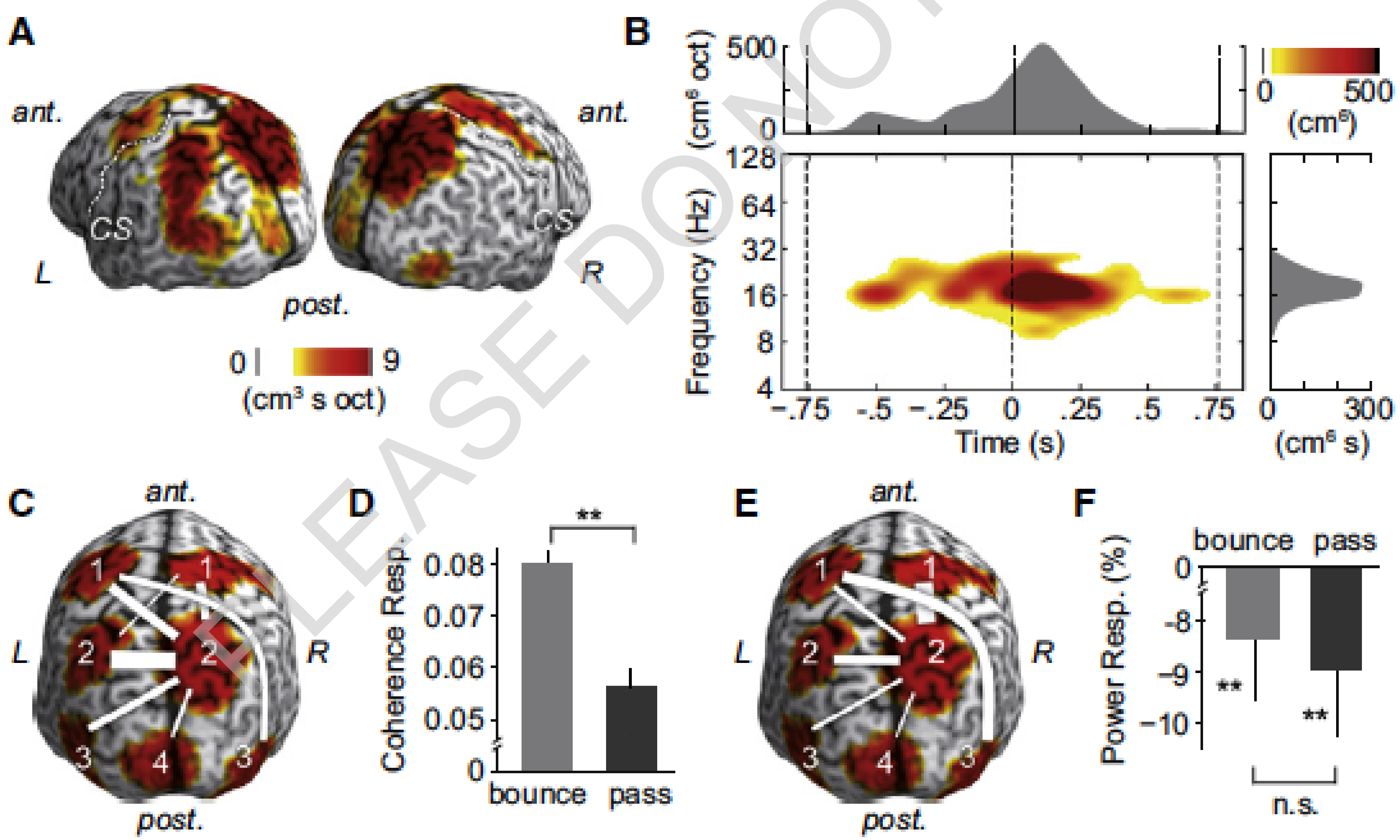
Topoplot:
100-300 ms
10-15 Hz

Connectivity Analysis (EEG)

ambiguous audiovisual stimulus: two bars approached, briefly overlapped while a click sound was played, and moved apart from each other

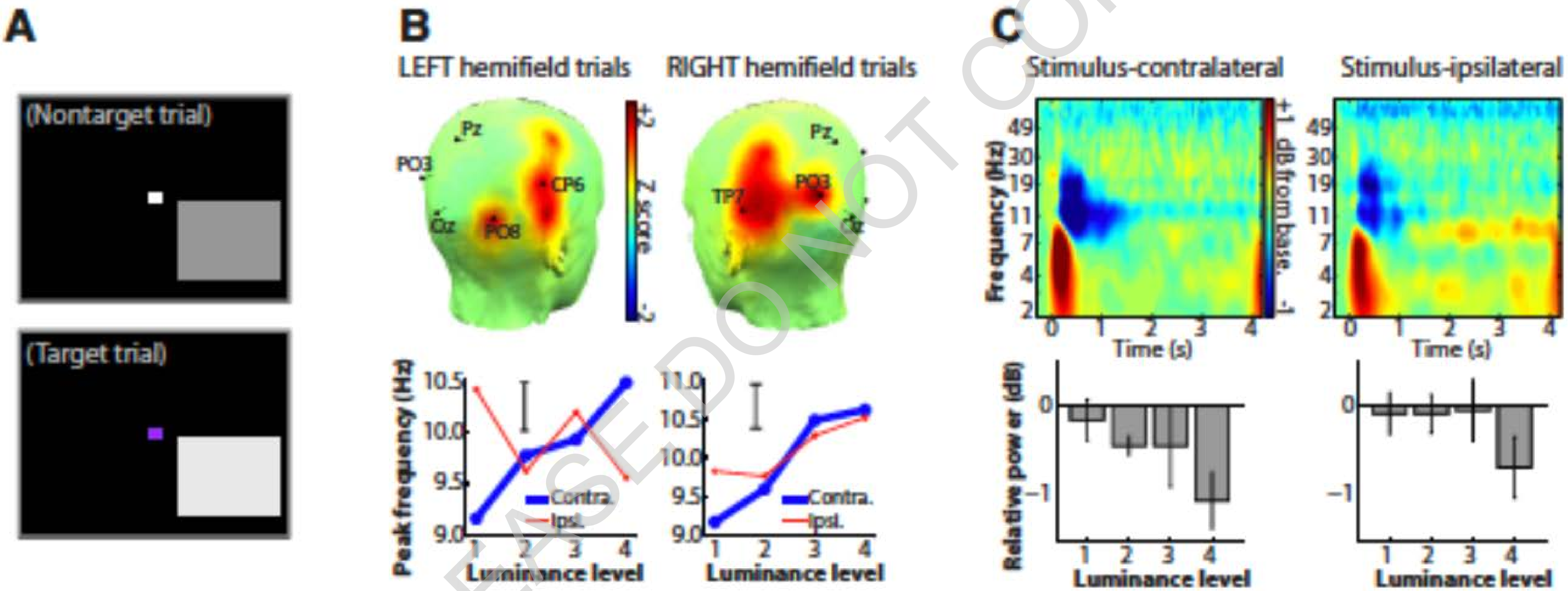
Hipp et al., 2013





Connectivity Analysis (EEG)

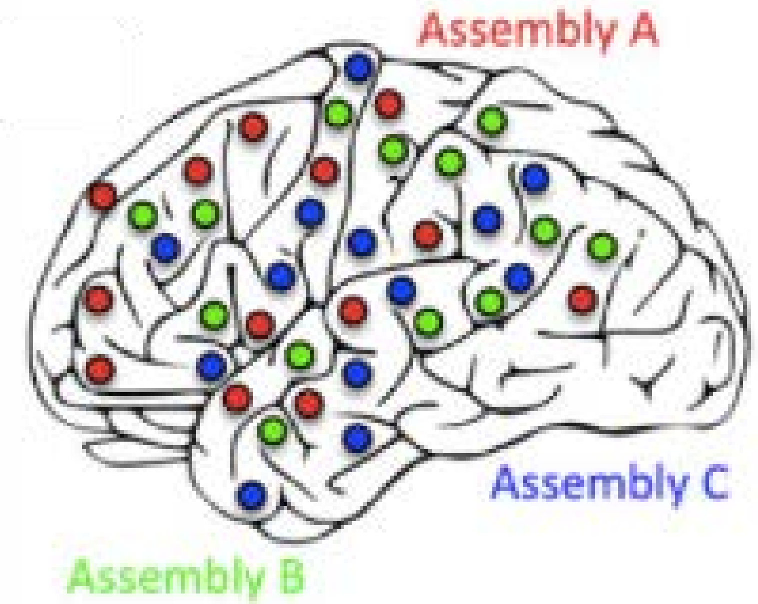
Cohen et al., 2013



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

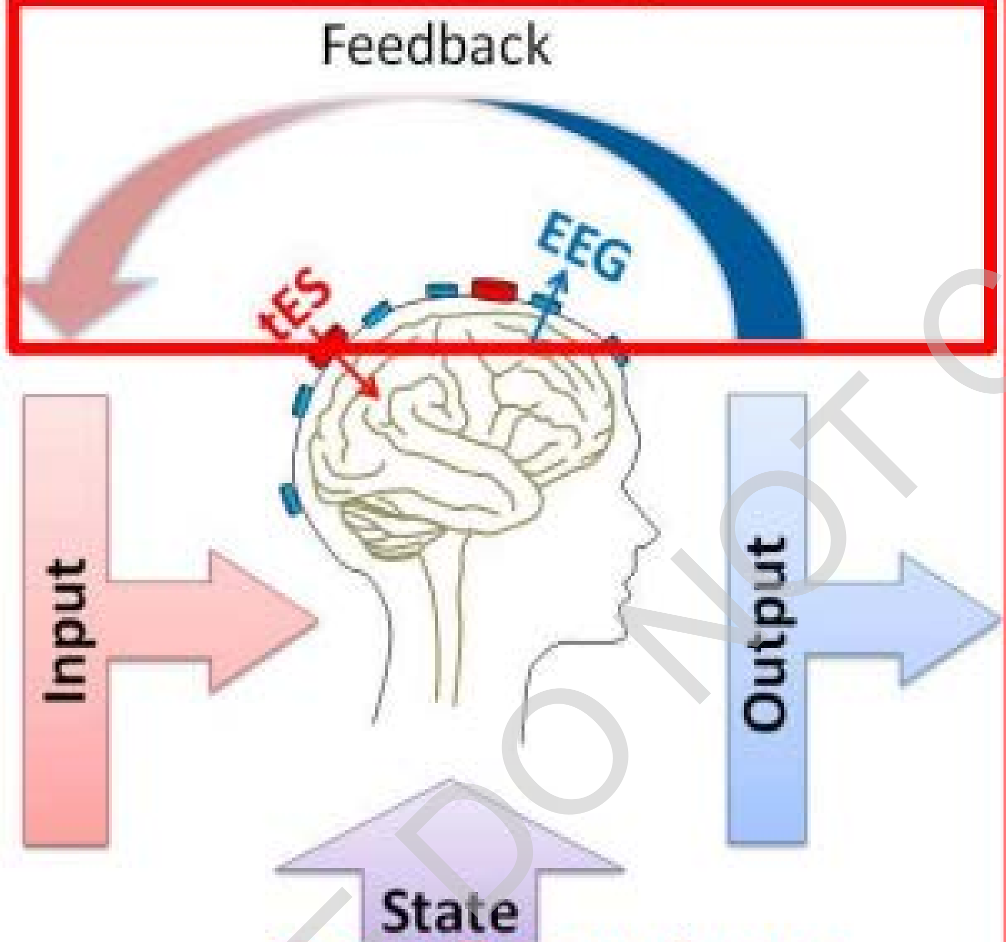
Choose Parameters

Input Location	
Anatomically guided	Scalp landmark Brain atlas MRI, DTI
Functionally guided	fMRI TMS EEG

tES Input Parameters	
Intensity	Standard Guided
Frequency	Standard EEG Guided

Input Time
Guided with respect to a brain state

Closed Loop



State Dependency

Controlled Brain State	
Developmental state	• Age
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

Local/Network Effects

Output Location
• Selected sensors or sources • All sensors (topography) • All sources (tomography)

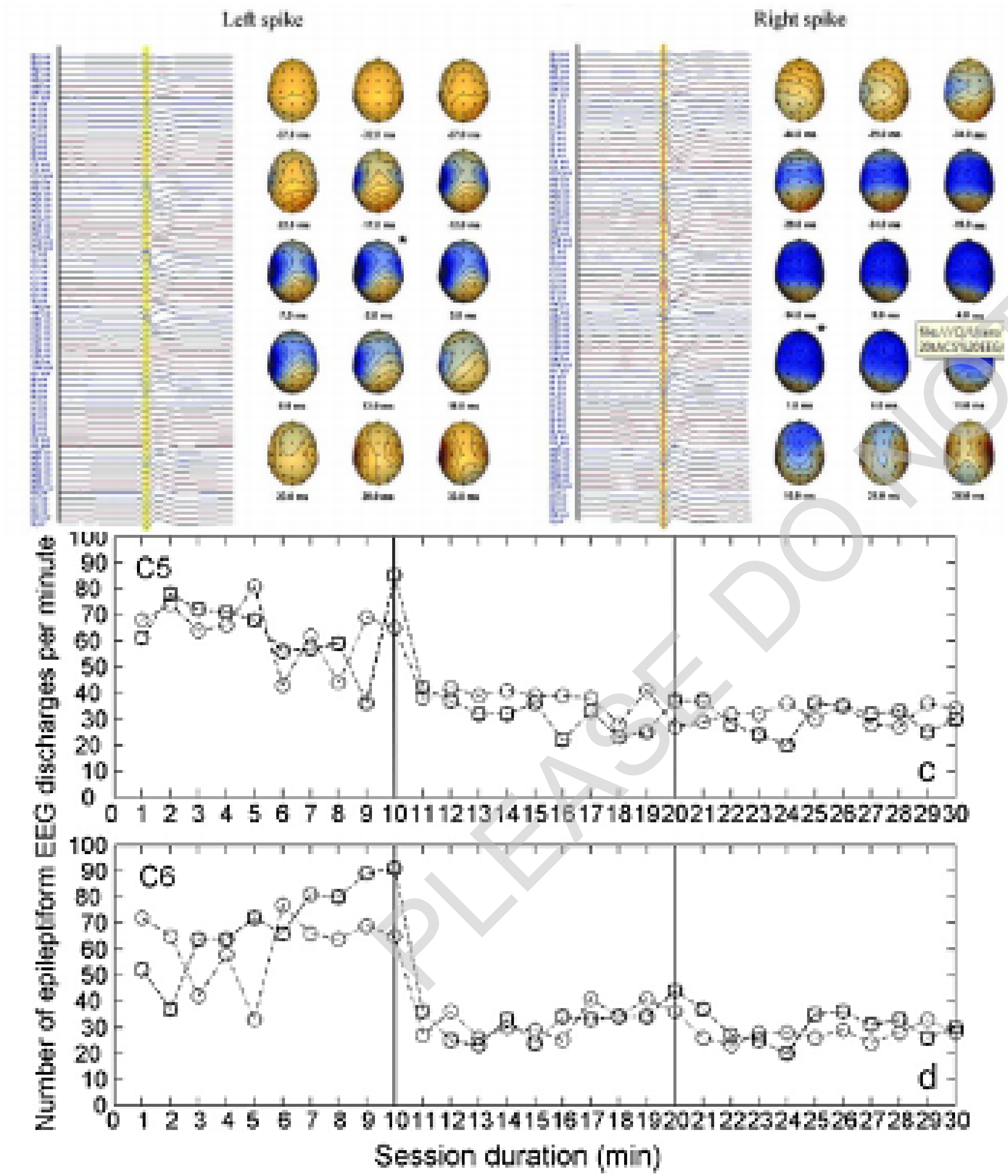
EEG Output Measures

Analysis	Mechanisms
Amplitude e.g., ERP, GMFA	Local or global excitation/inhibition
Power of each frequency e.g., ERS/ERD	Local or global synchronization
Power as a function of time & frequency e.g., ERSP	Intrinsic properties e.g., Resonant frequency
• Correlation • Coherence • Synchrony • Phase-amplitude cross-frequency coupling	Functional connectivity e.g., Amplitude, frequency and phase coupling between two or more signals
• Directed-transfer function • Partial directed coherence	Directed functional connectivity e.g., Information flow

Output Time
• Relative to input time • Relative to a brain state

EEG-Guided tCS: Location

Faria et al., 2012



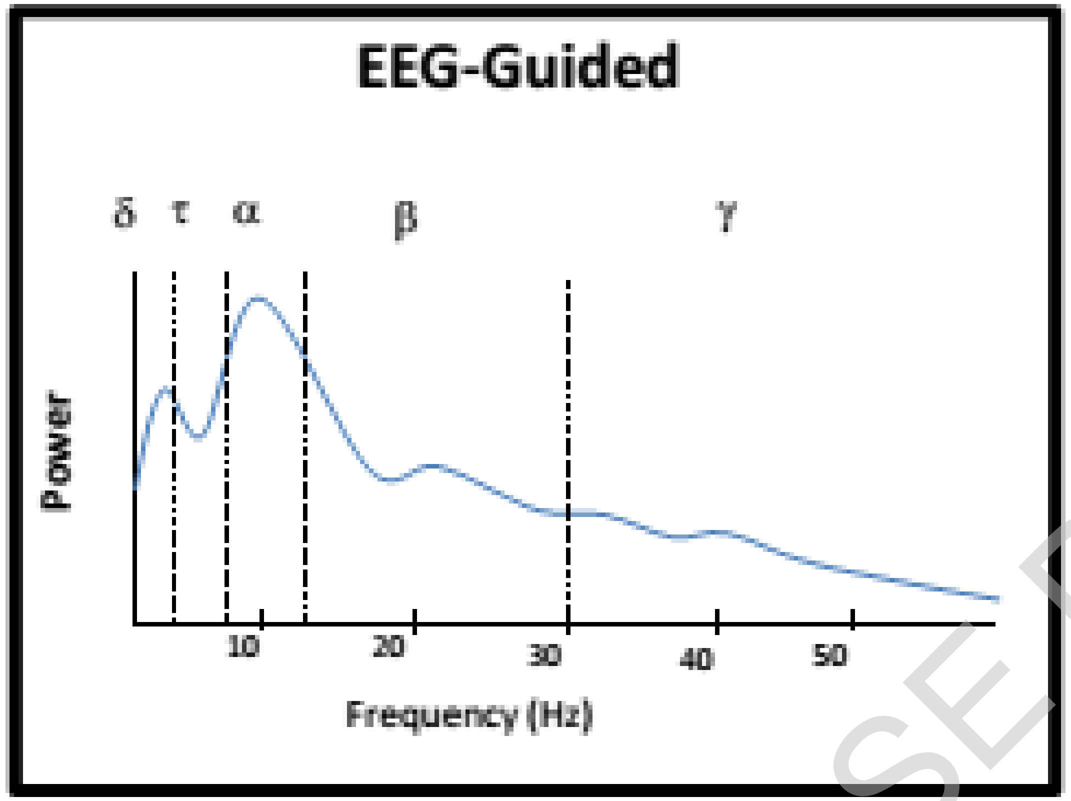
EEG evaluation of **a patient with Continuous spike-wave discharges** during slow-wave sleep allowed identification of an **epileptogenic focus.**

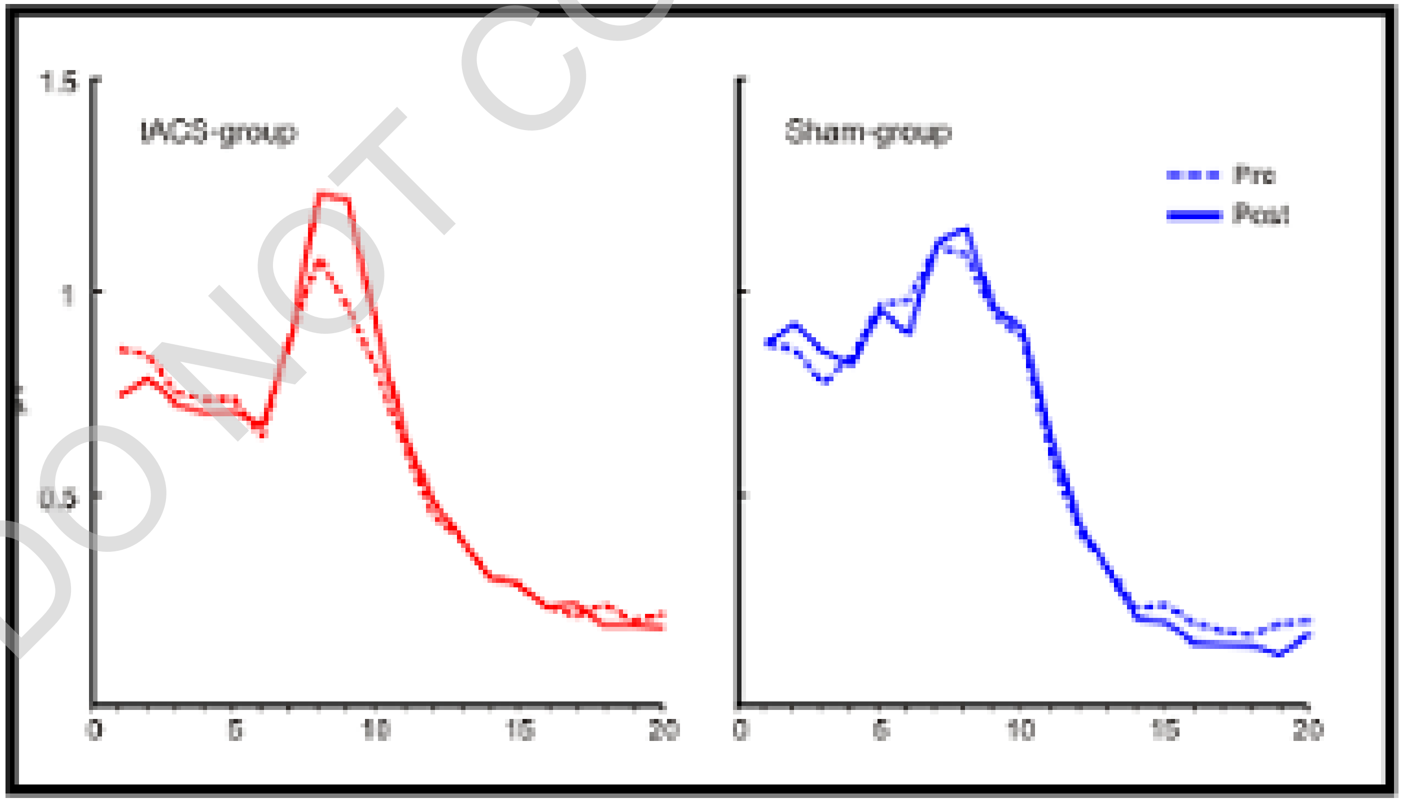
Cathodal **tDCS** over the focus resulted in a significant decrease in interictal spikes.

Zahele et al., 2012

Frequency

Individual Alpha frequency





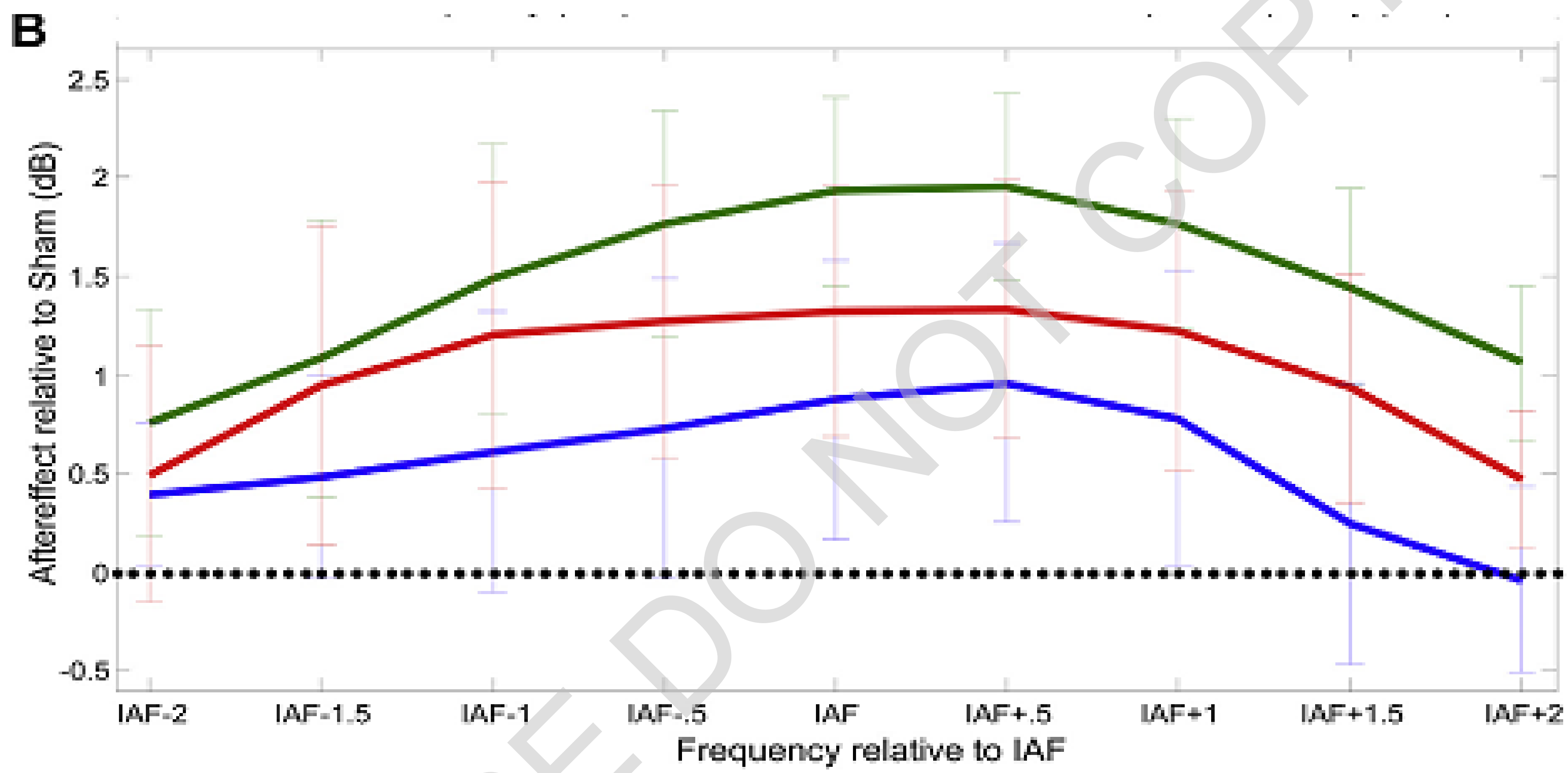
- **tACS** on the occipital cortex at individual alpha frequency

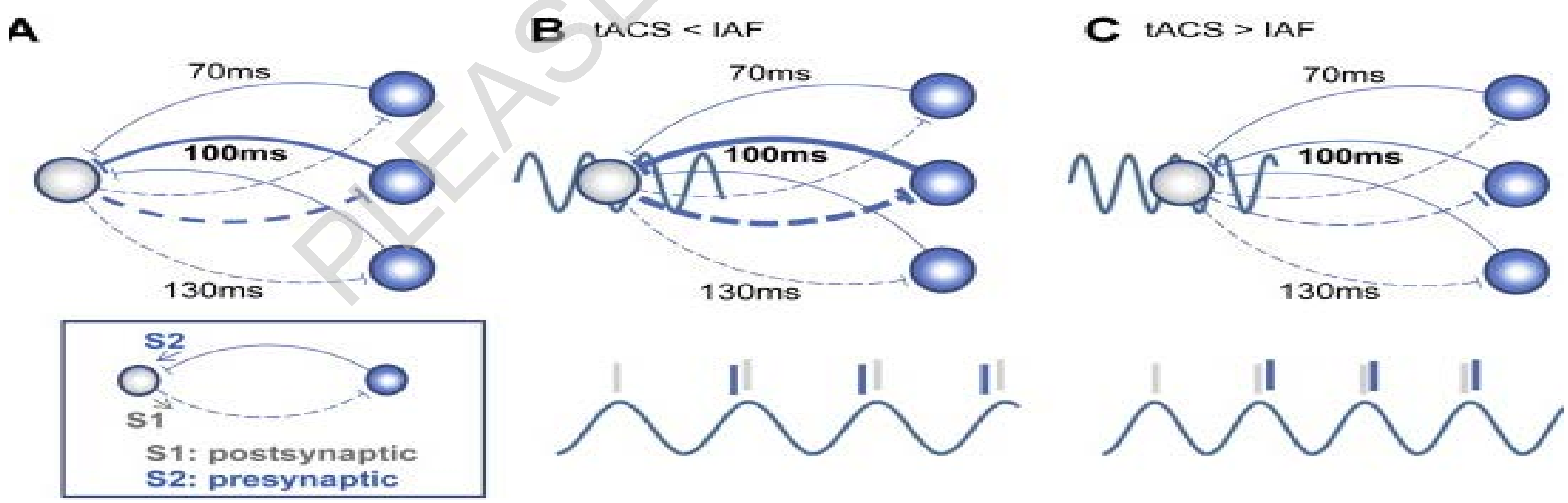
- **Resting EEG →** increase in alpha in parieto-central electrodes, no effects on surrounding frequencies

Vossen et al., 2015

Frequency

Individual Alpha frequency





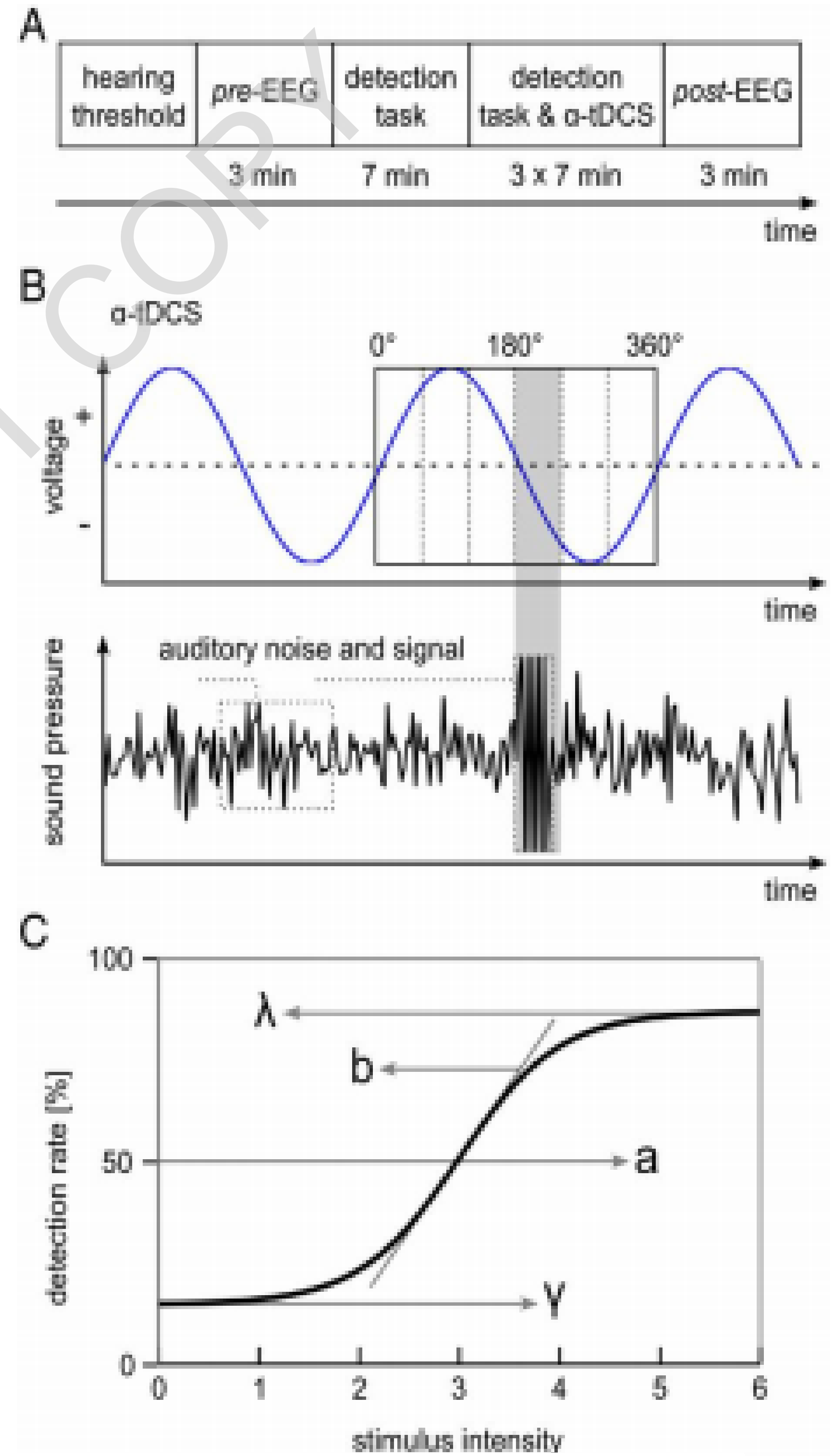
EEG-Guided tCS: Stimulation Parameters (Frequency, phase,etc.)

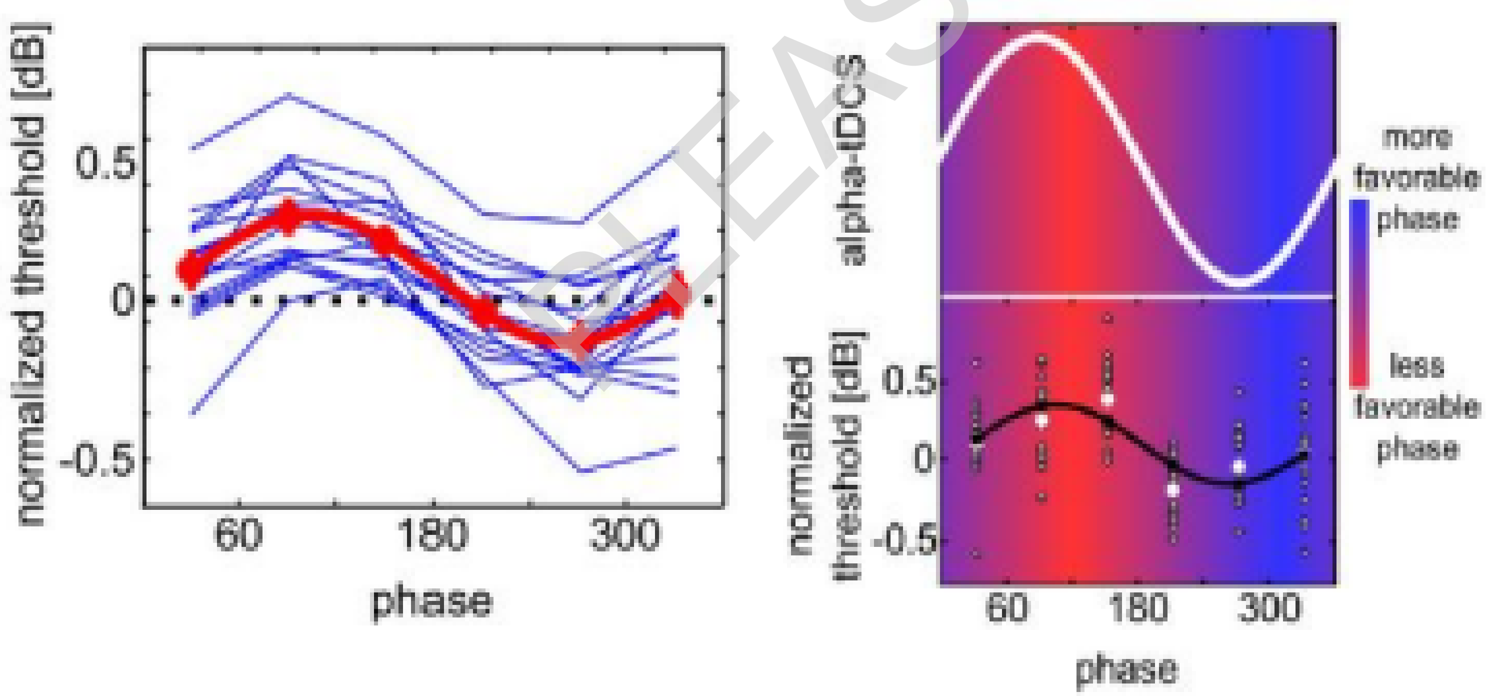
***Neuling* et al., 2012**

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





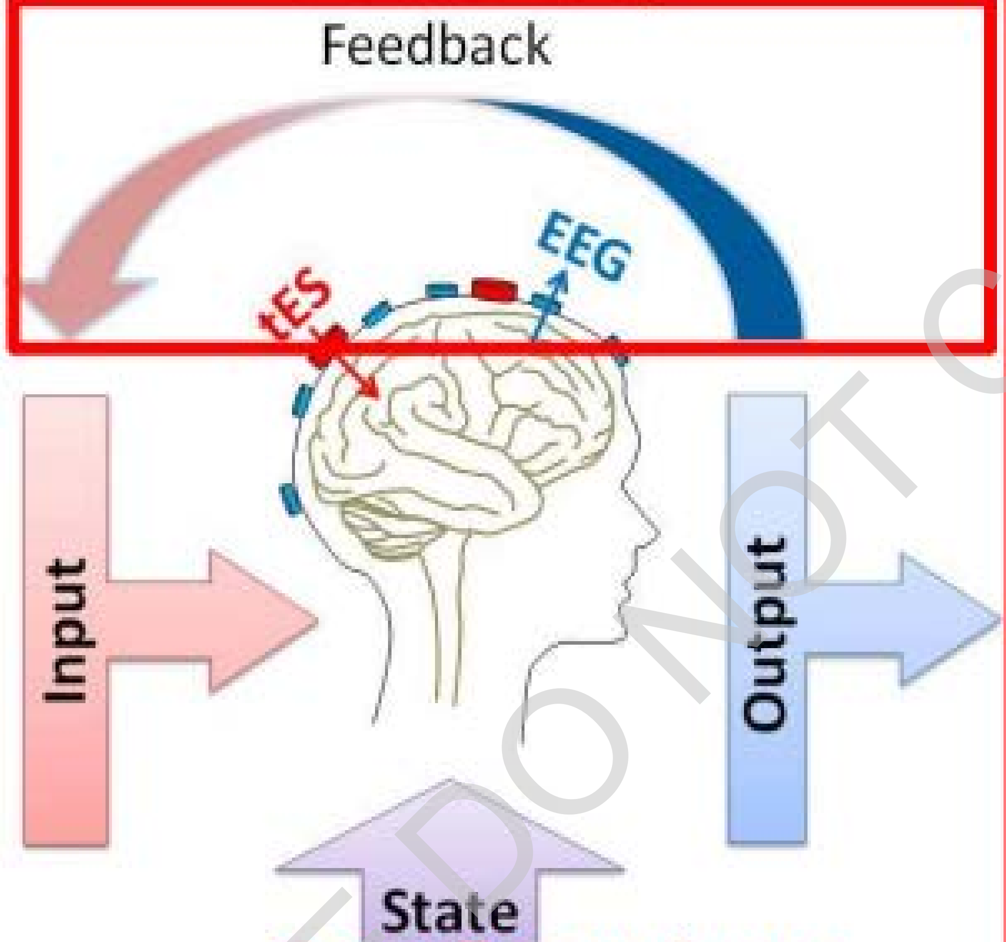
Choose Parameters

Input Location	
Anatomically guided	Scalp landmark Brain atlas MRI, DTI
Functionally guided	fMRI TMS EEG

tES Input Parameters	
Intensity	Standard Guided
Frequency	Standard EEG Guided

Input Time
Guided with respect to a brain state

Closed Loop



State Dependency

Controlled Brain State	
Developmental state	• Age
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

Local/Network Effects

Output Location

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

EEG Output Measures

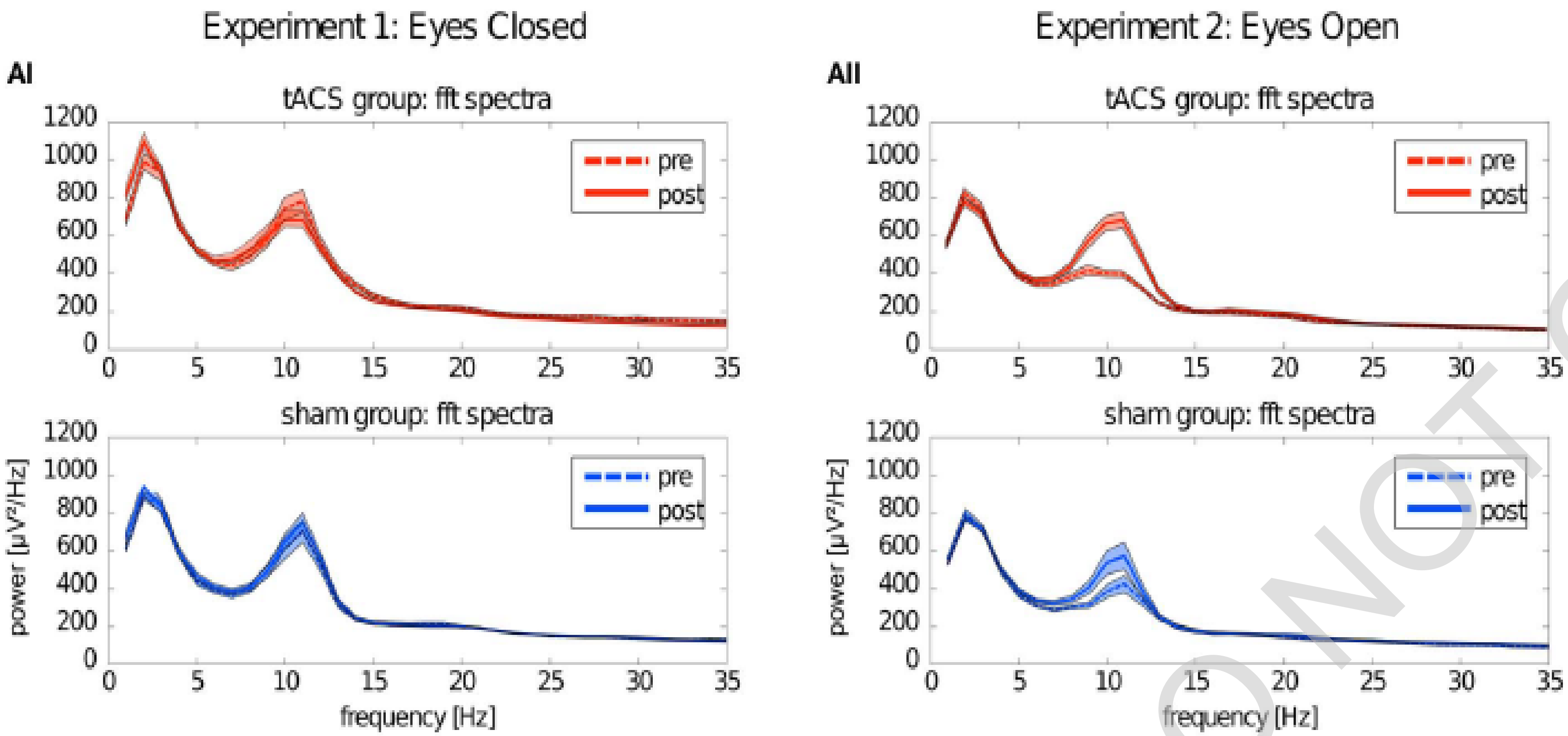
Analysis	Mechanisms
Amplitude e.g., ERP, GMFA	Local or global excitation/inhibition
Power of each frequency e.g., ERS/ERD	Local or global synchronization
Power as a function of time & frequency e.g., ERSP	Intrinsic properties e.g., Resonant frequency
• Correlation • Coherence • Synchrony • Phase-amplitude cross-frequency coupling	Functional connectivity e.g., Amplitude, frequency and phase coupling between two or more signals
• Directed-transfer function • Partial directed coherence	Directed functional connectivity e.g., Information flow

Output Time

- Relative to input time
- Relative to a brain state

State dependency: Eyes Open vs. Eyes Closed

***Neuling* et al., 2013**

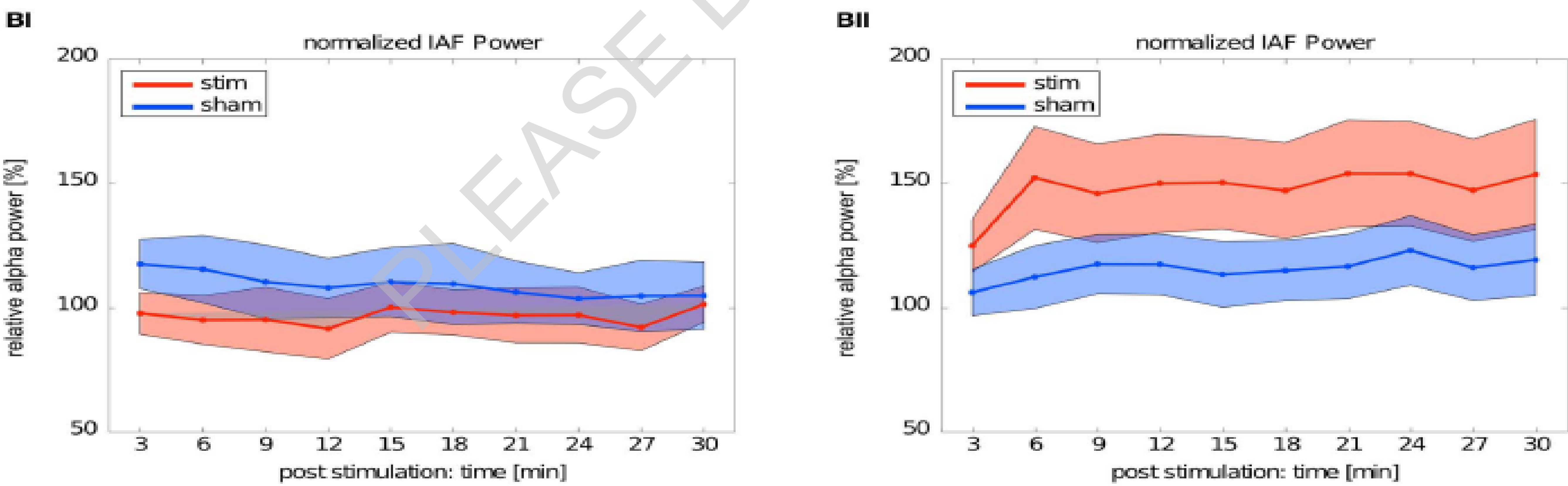


Significant increase in alpha-power

after individual-alpha frequency tAC

when applied with **Eyes open**, but no

with **Eyes closed**.



State-Trait dependency

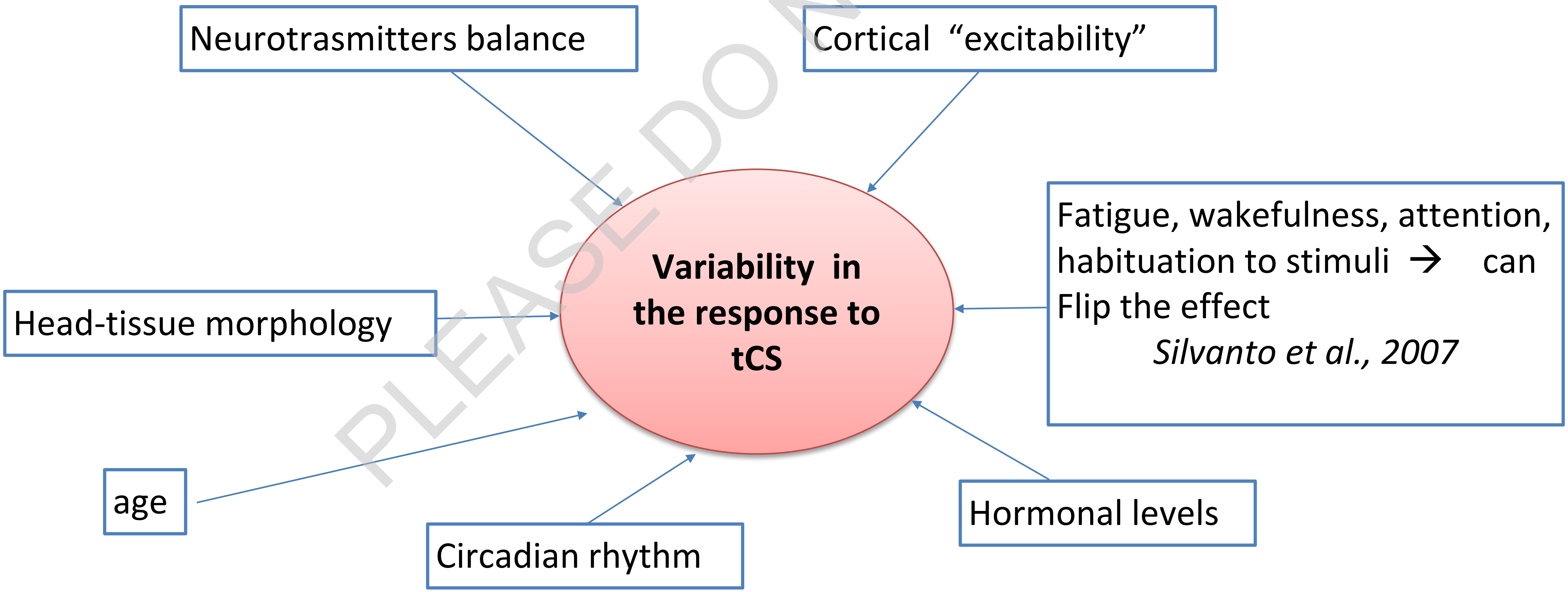
frontiers in
SYSTEMS NEUROSCIENCE

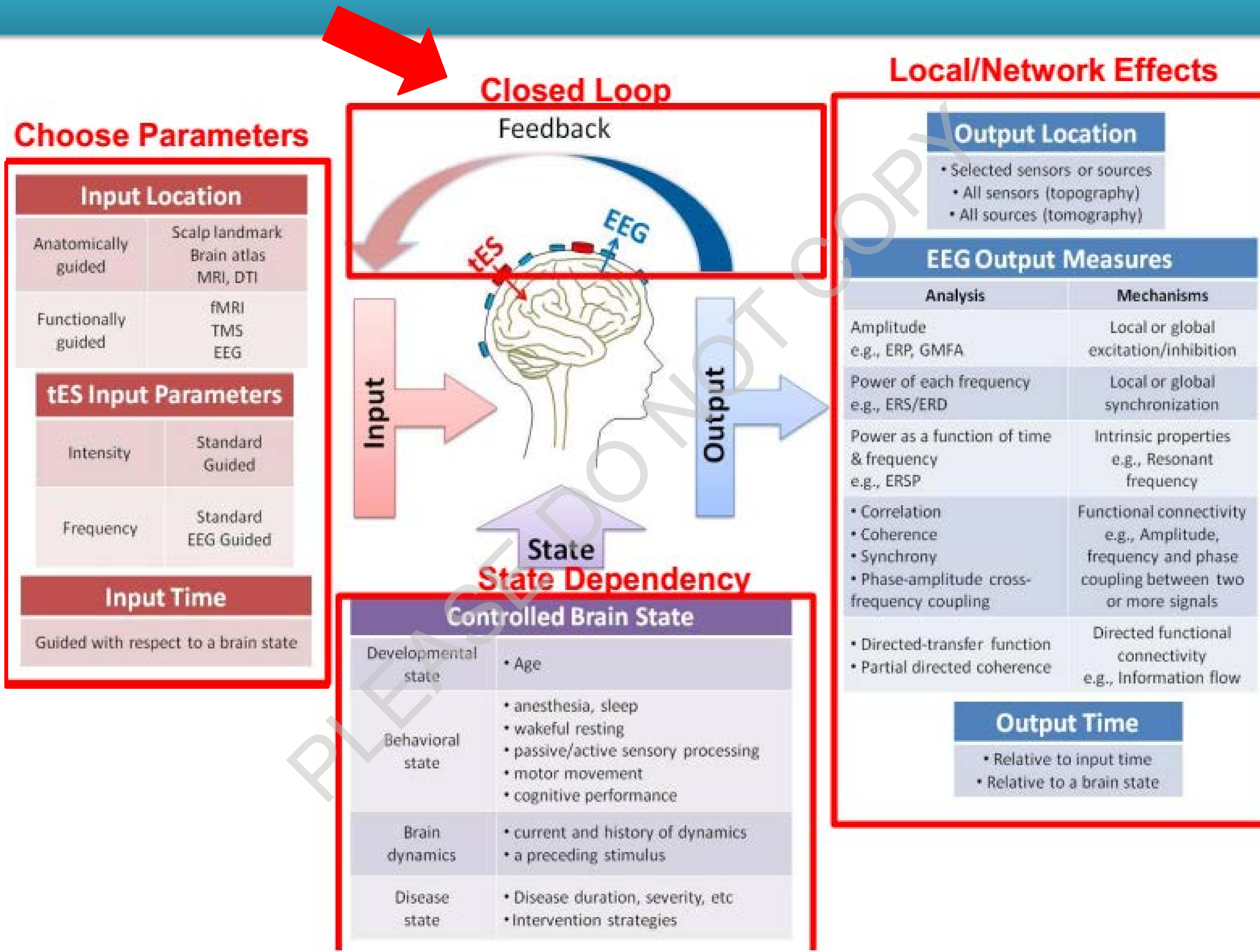
REVIEW ARTICLE
published: 24 February 2014
doi: 10.3389/fnsys.2014.00025

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




Choose Parameters
Input Location
Anatomically guided
Scalp landmark
Brain atlas
MRI, DTI
Functionally guided
fMRI
TMS
EEG
tES Input Parameters
Intensity
Standard
Guided
Frequency
Standard
EEG Guided
Input Time
Guided with respect to a brain state
Closed Loop
Feedback
tES
EEG
Input
Output
State
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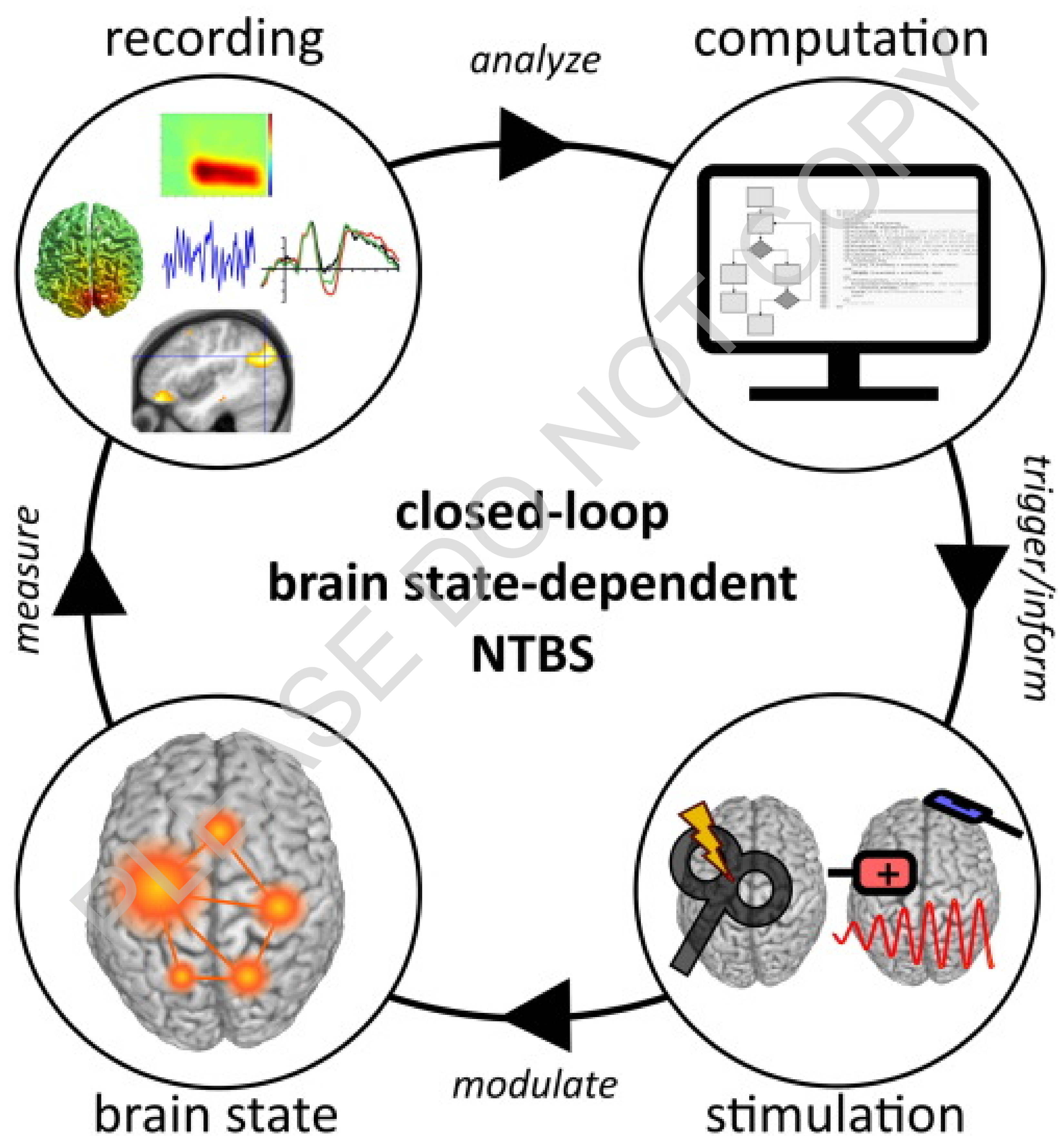
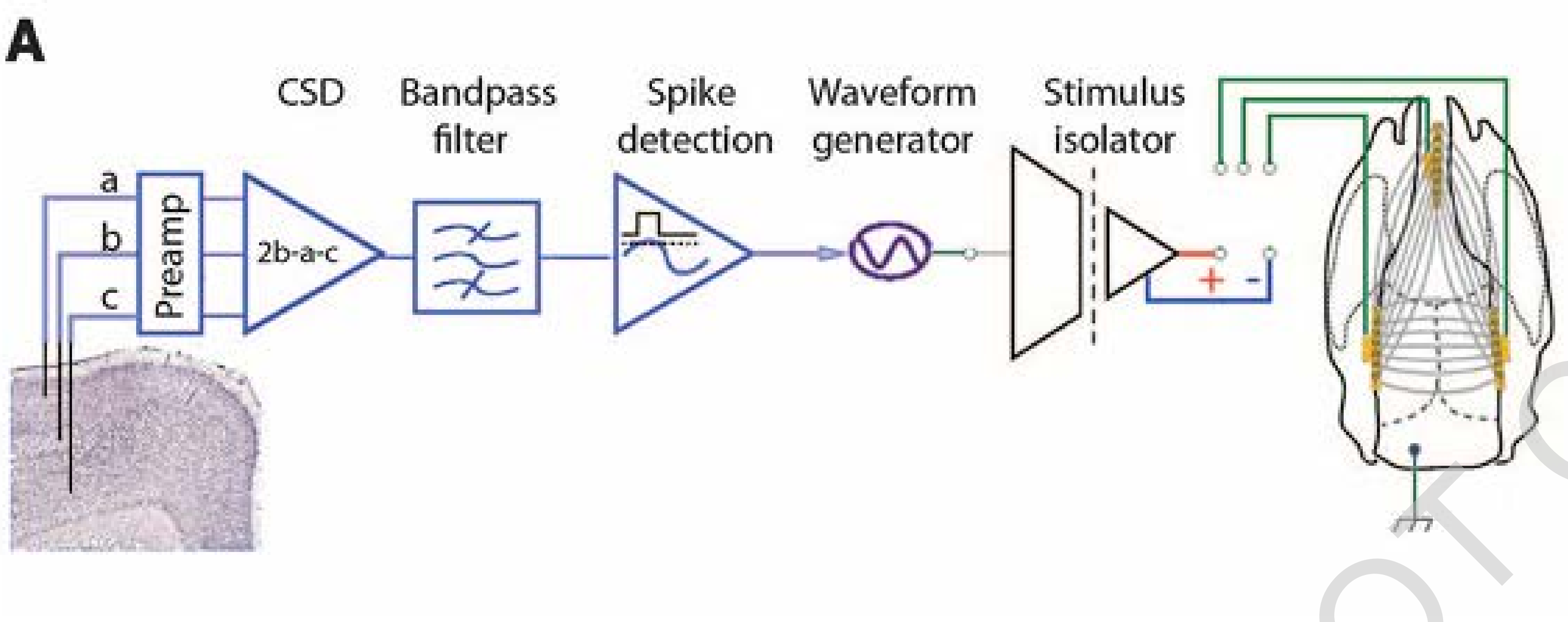
• Directed-transfer function
• Partial directed coherence
Directed functional connectivity
e.g., Information flow
Output Time
• Relative to input time
• Relative to a brain state

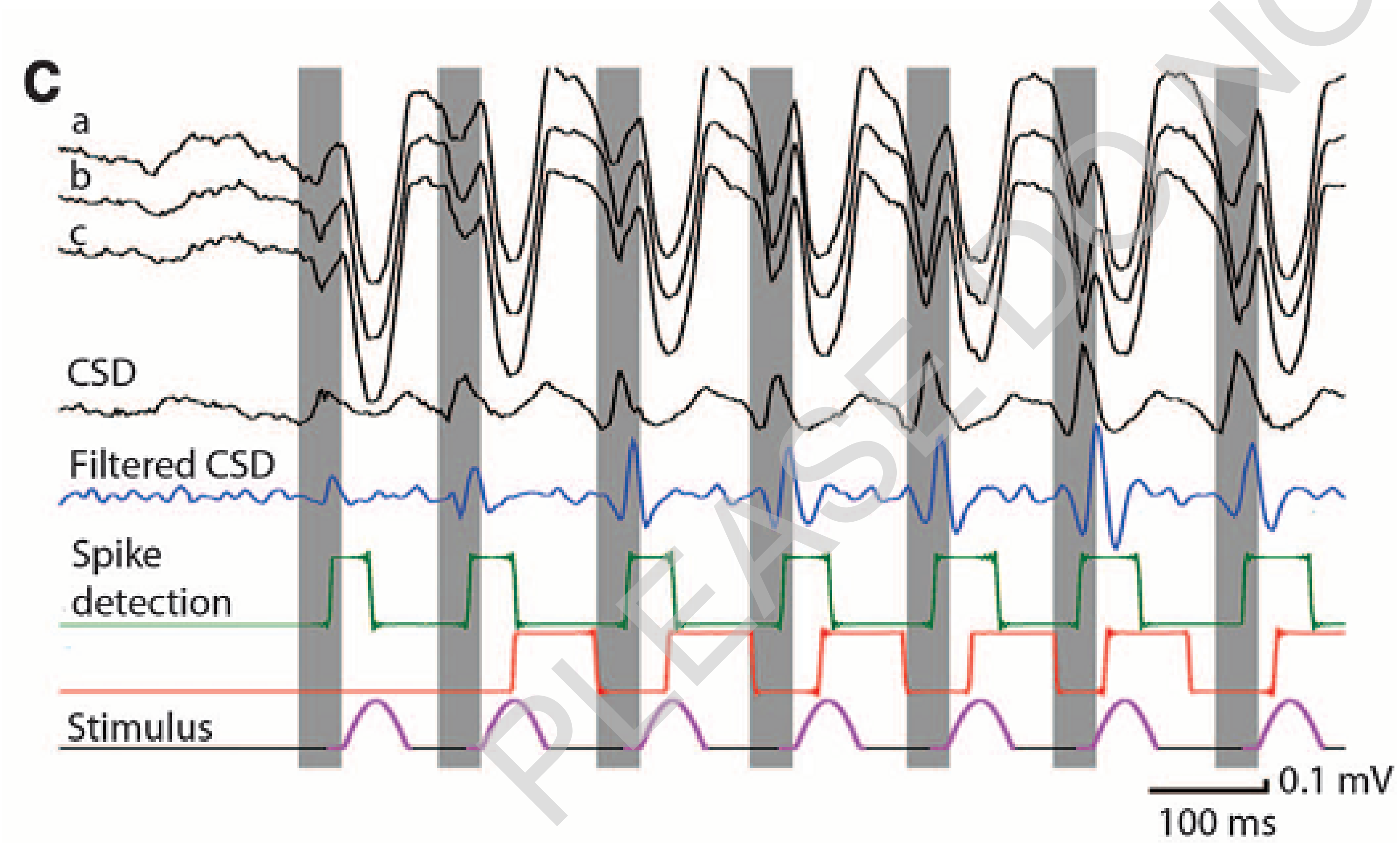
Closed-Loop Diagram



Closed-Loop Studies in Animal

Berenyi et al., 2012



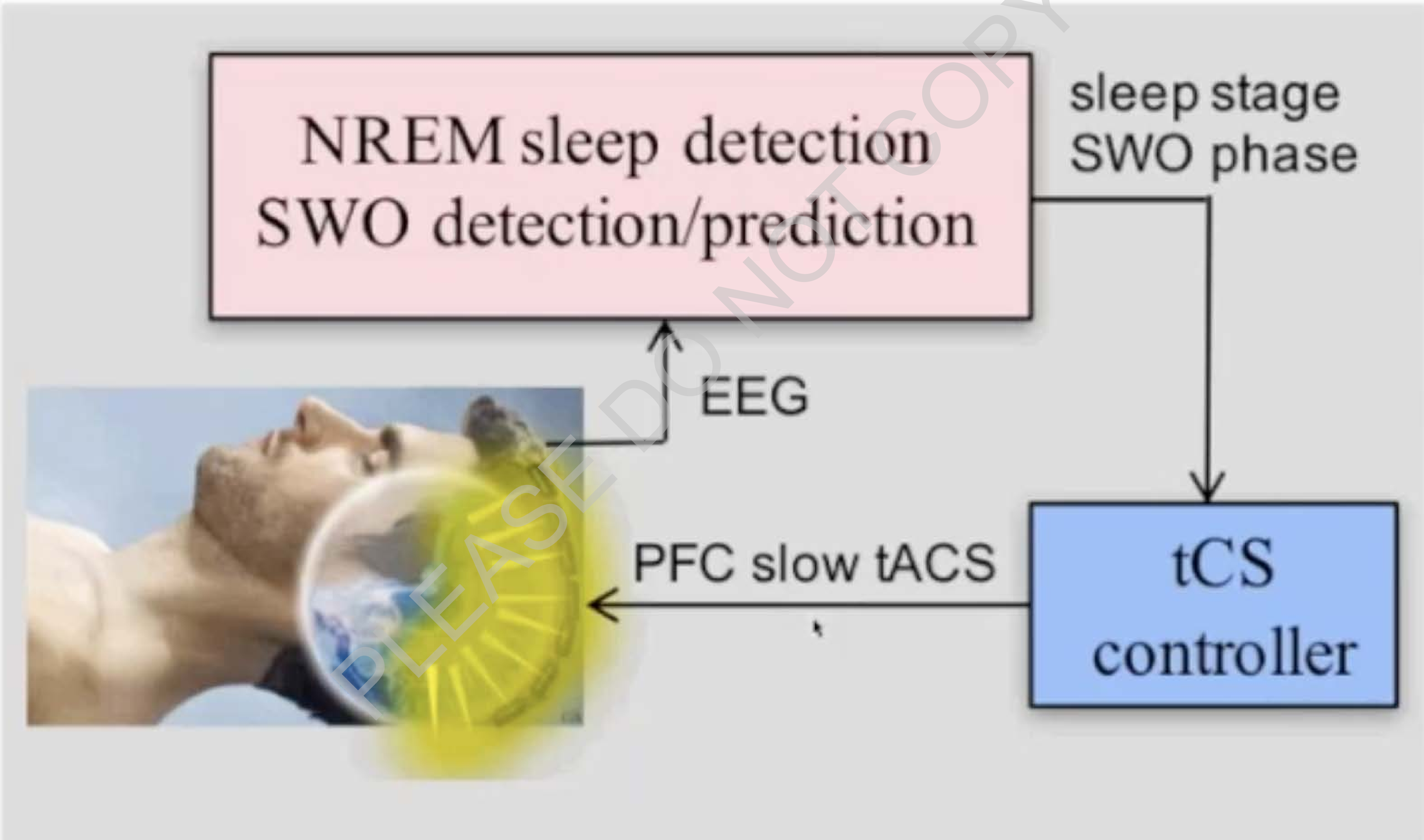


- Rodent model of generalized epilepsy.
- Detection of interictal spikes triggers tCS at 1Hz

<u>Aborts the spike-wave discharge burst</u>

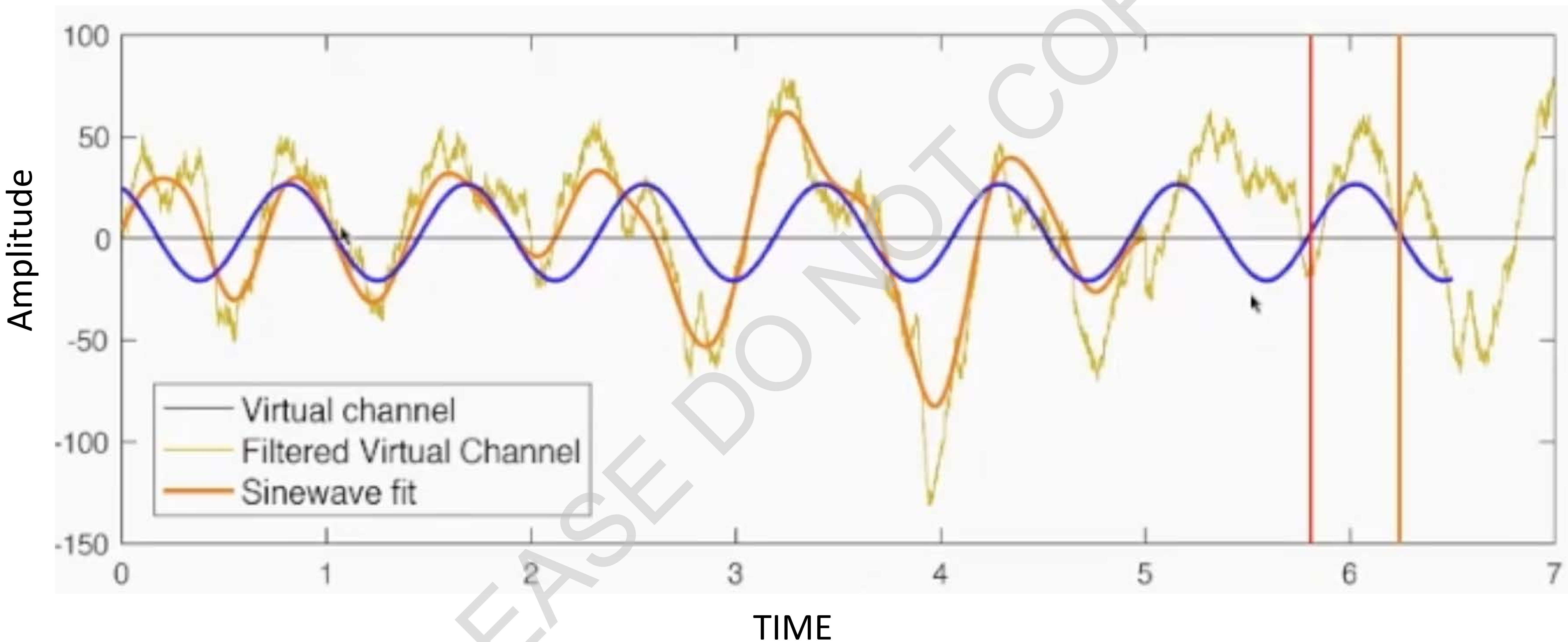
Closed-Loop Studies in human sleep

Clark et al., 2017

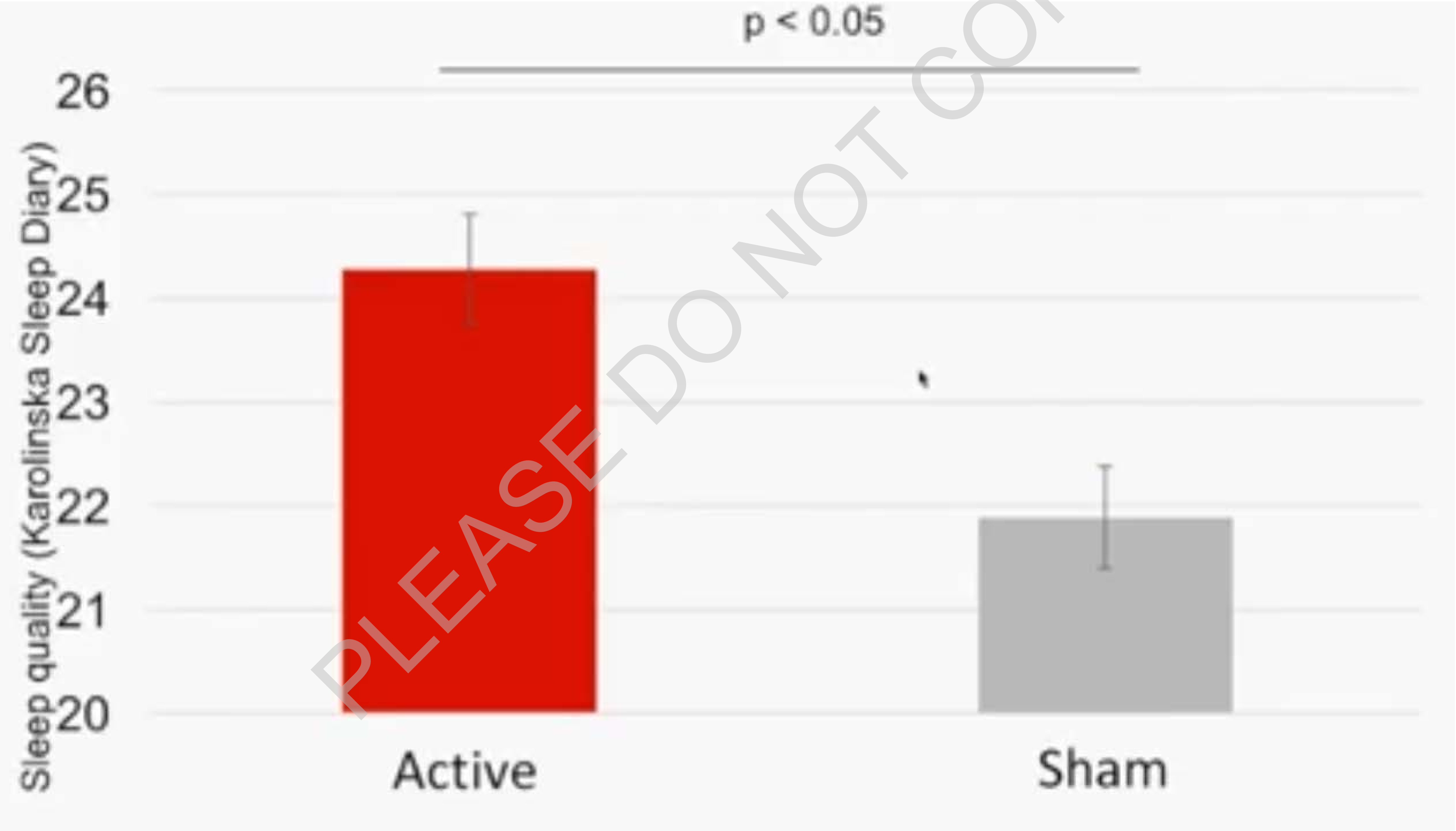


Closed-Loop Studies in human sleep

Enhancing slow waves improves memory



Closed-Loop Studies in human sleep



Choose Parameters

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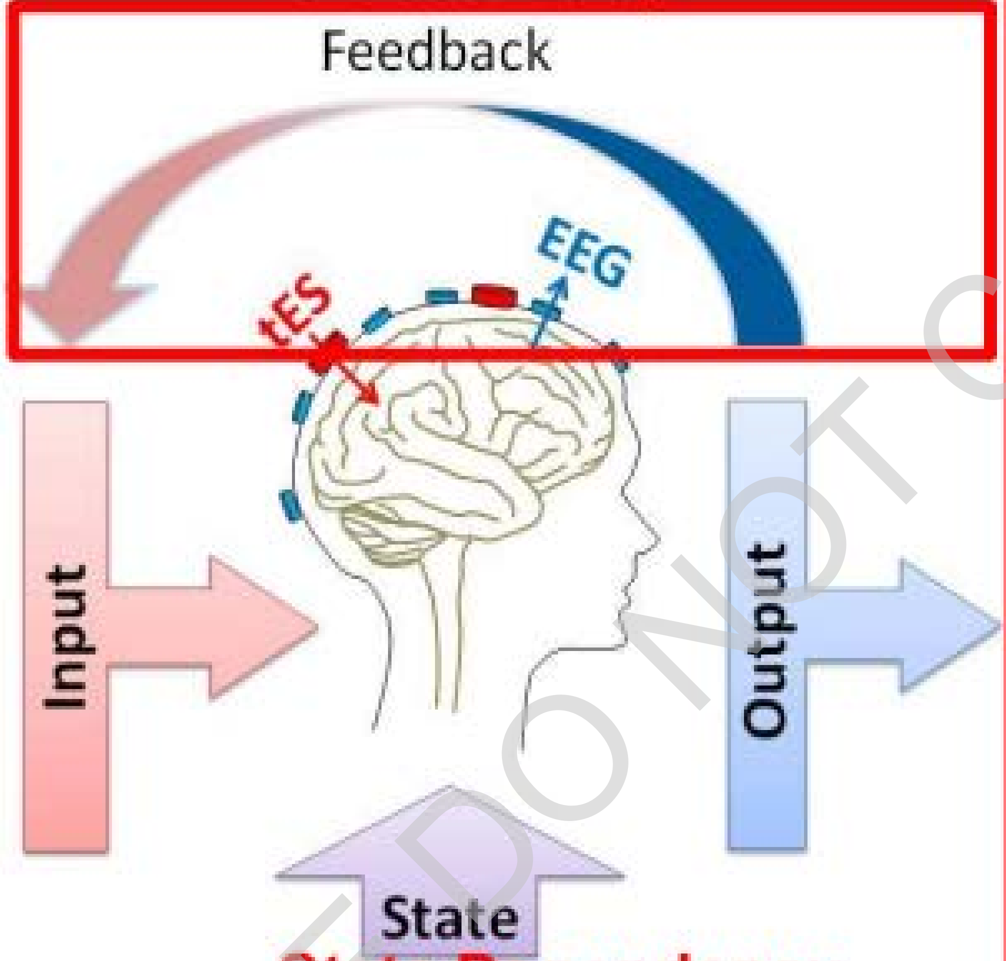
Input Time
Guided with respect to a brain state

Closed Loop



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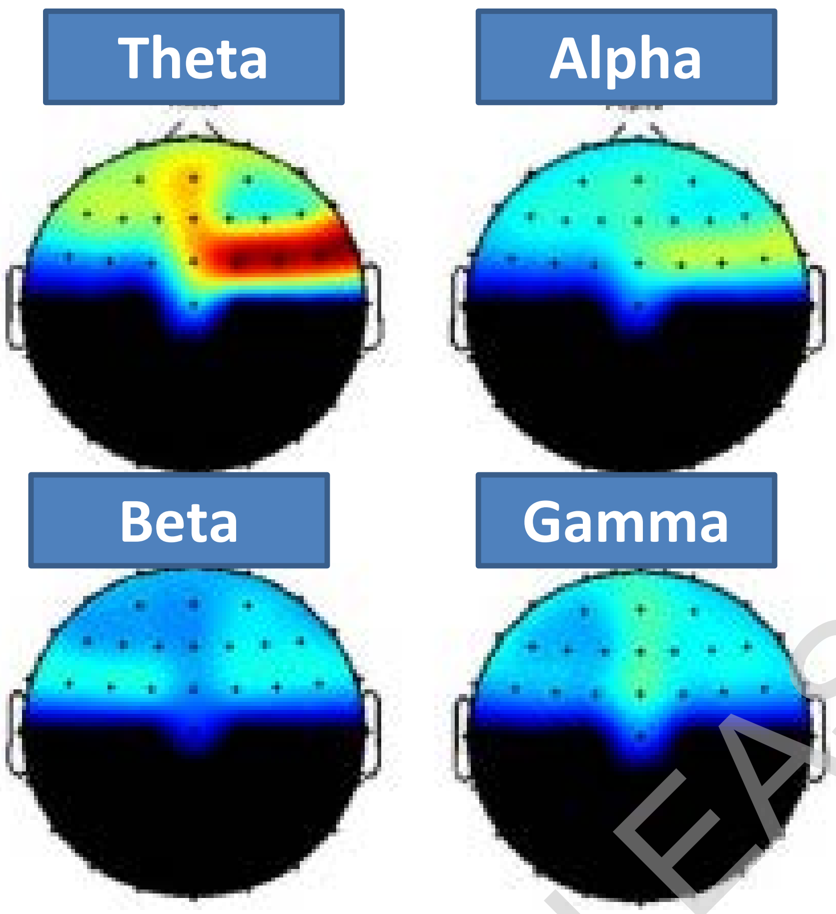
• Directed-transfer function • Partial directed coherence	Directed functional connectivity e.g., Information flow

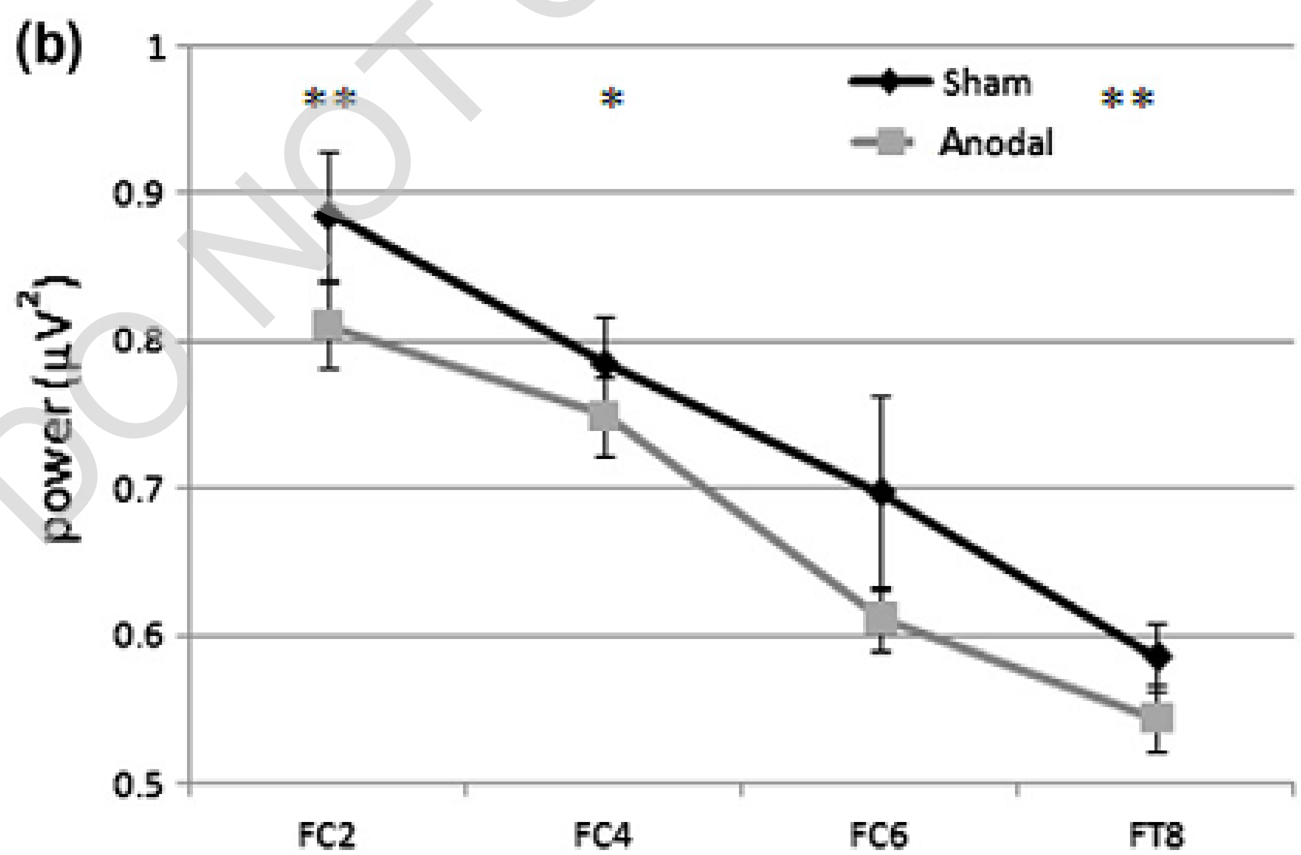
Output Time
• Relative to input time • Relative to a brain state

Output Measures: Power/Amplitude - Local effects

Jacobson et al., 2012

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

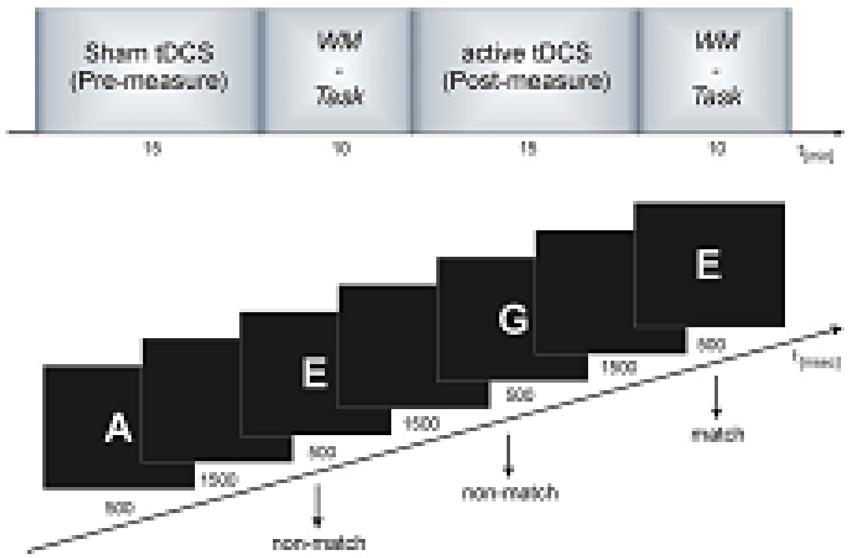


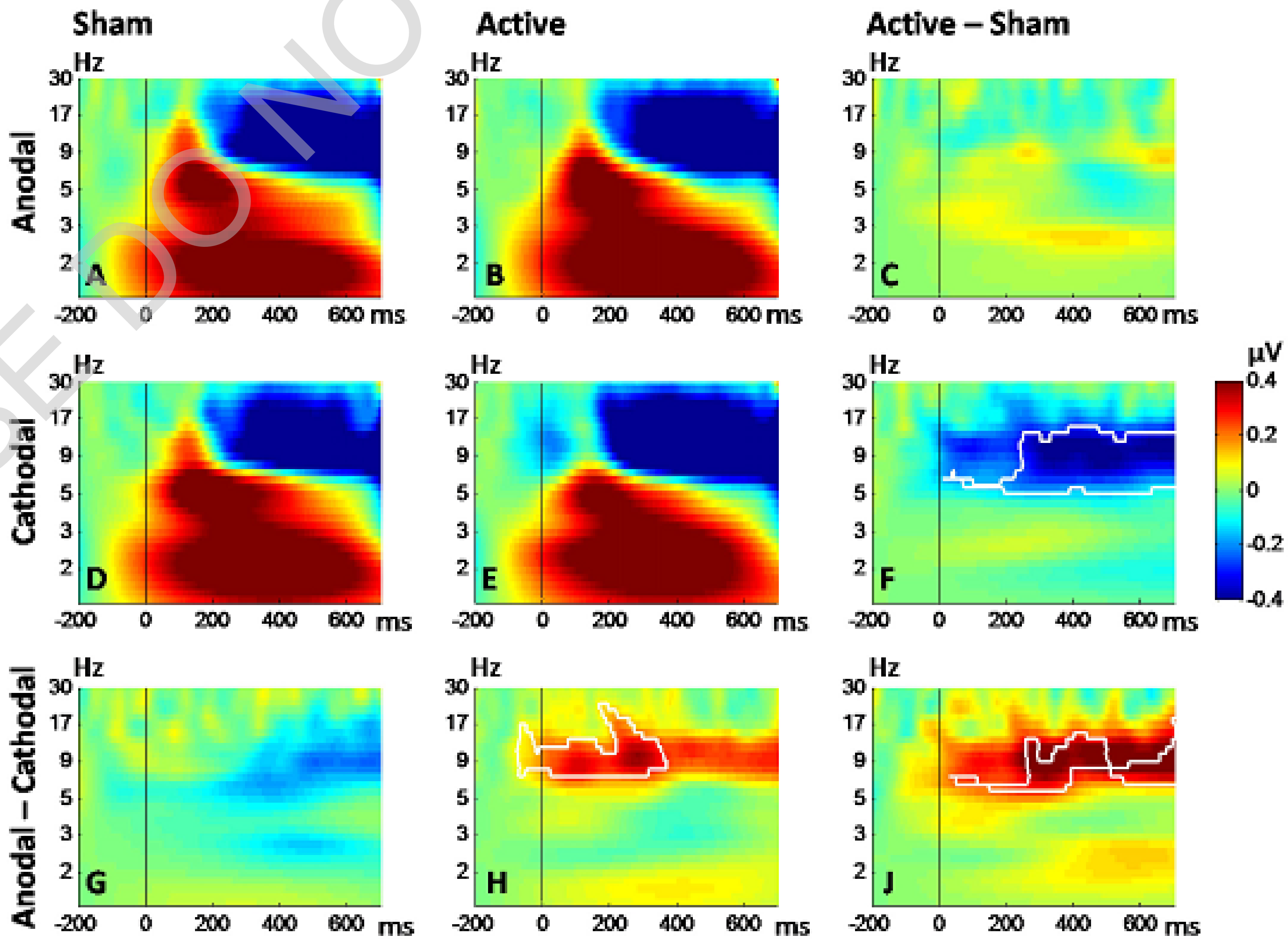


Decrease in Theta power after tDCS

Output Measures: Power/Amplitude - Distant effect

Occipito-Parietal Electrodes…





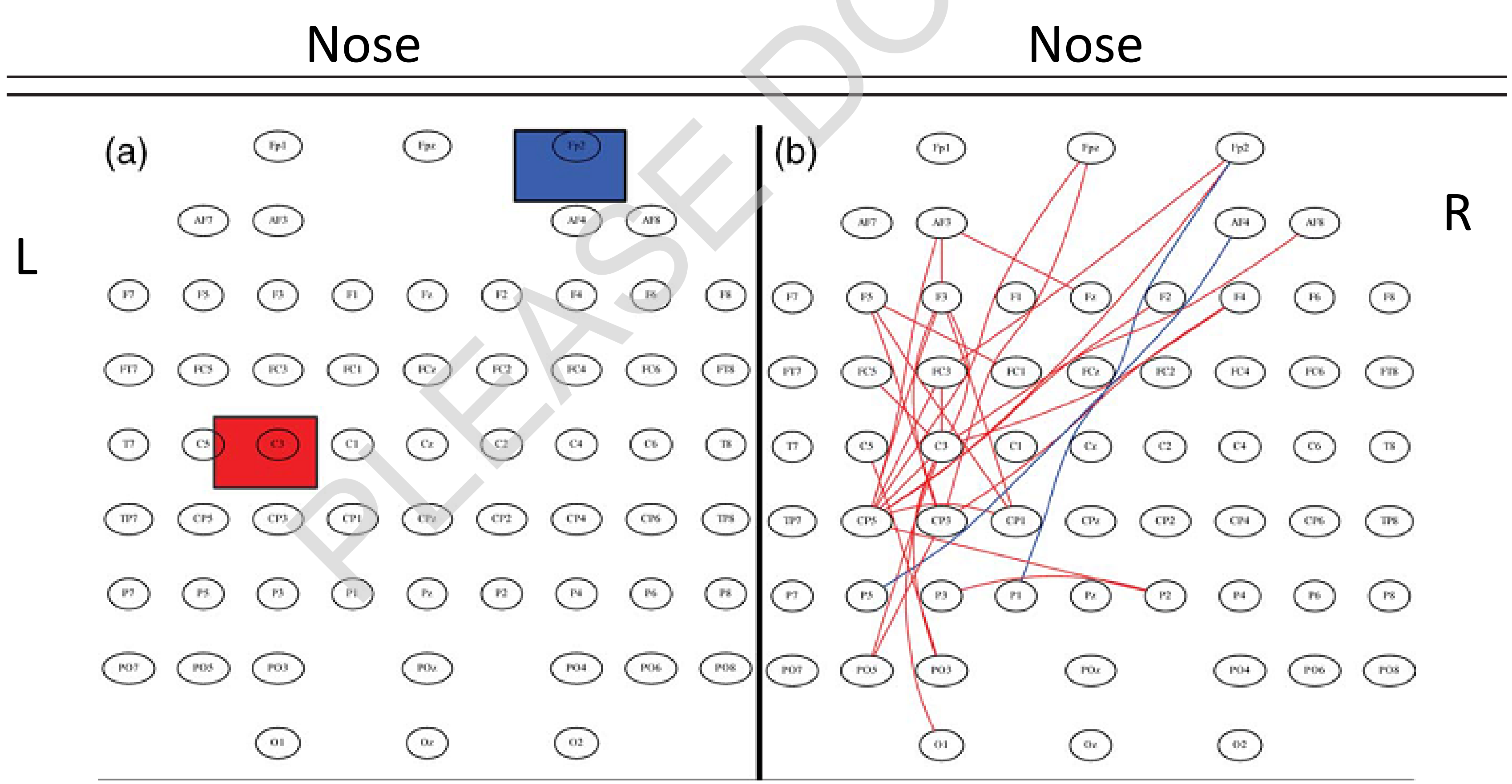
- **Increased** Theta and Alpha power after Anodal tDCS
- **Decreased** Alpha power after Cathodal tDCS

Output: Connectivity

Polania et al., 2011

- 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.

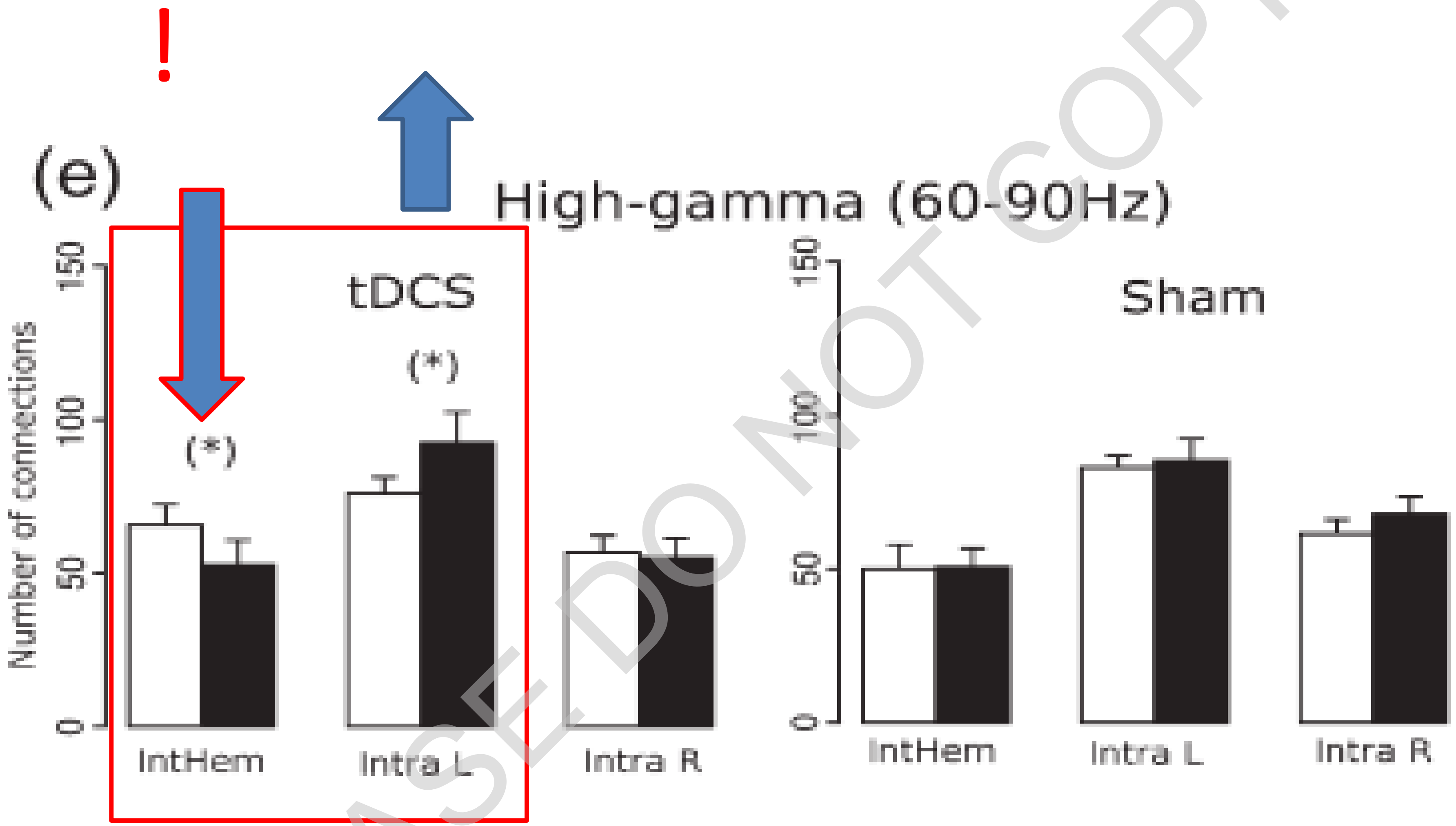
Task PRE – Task POST , High Gamma @ 60-90Hz
tDCS **Increases** connectivity between motor, premotor and suppl. motor areas.



Output: Connectivity

Polania et al., 2011

ACTIVITY DURING MOTOR TASK



- tDCS **Increases** connectivity between left motor, premotor and suppl. motor areas.
- tDCS **Decreases** interhemispheric connectivity in High-Gamma during task.

Other multimodal approaches?

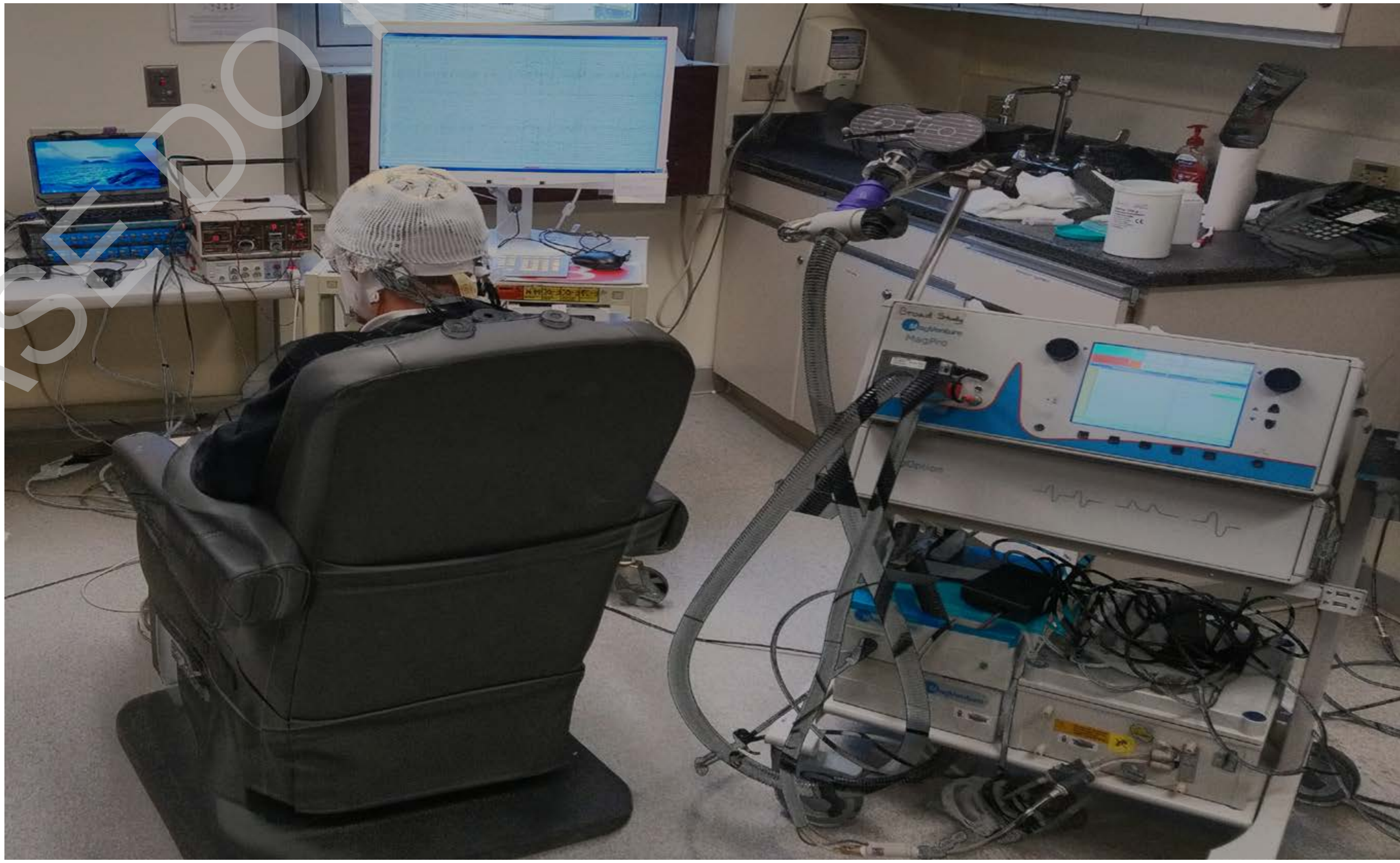
- **tCS + TMS-EMG**

- **tCS + EEG (Resting – ERPs)**

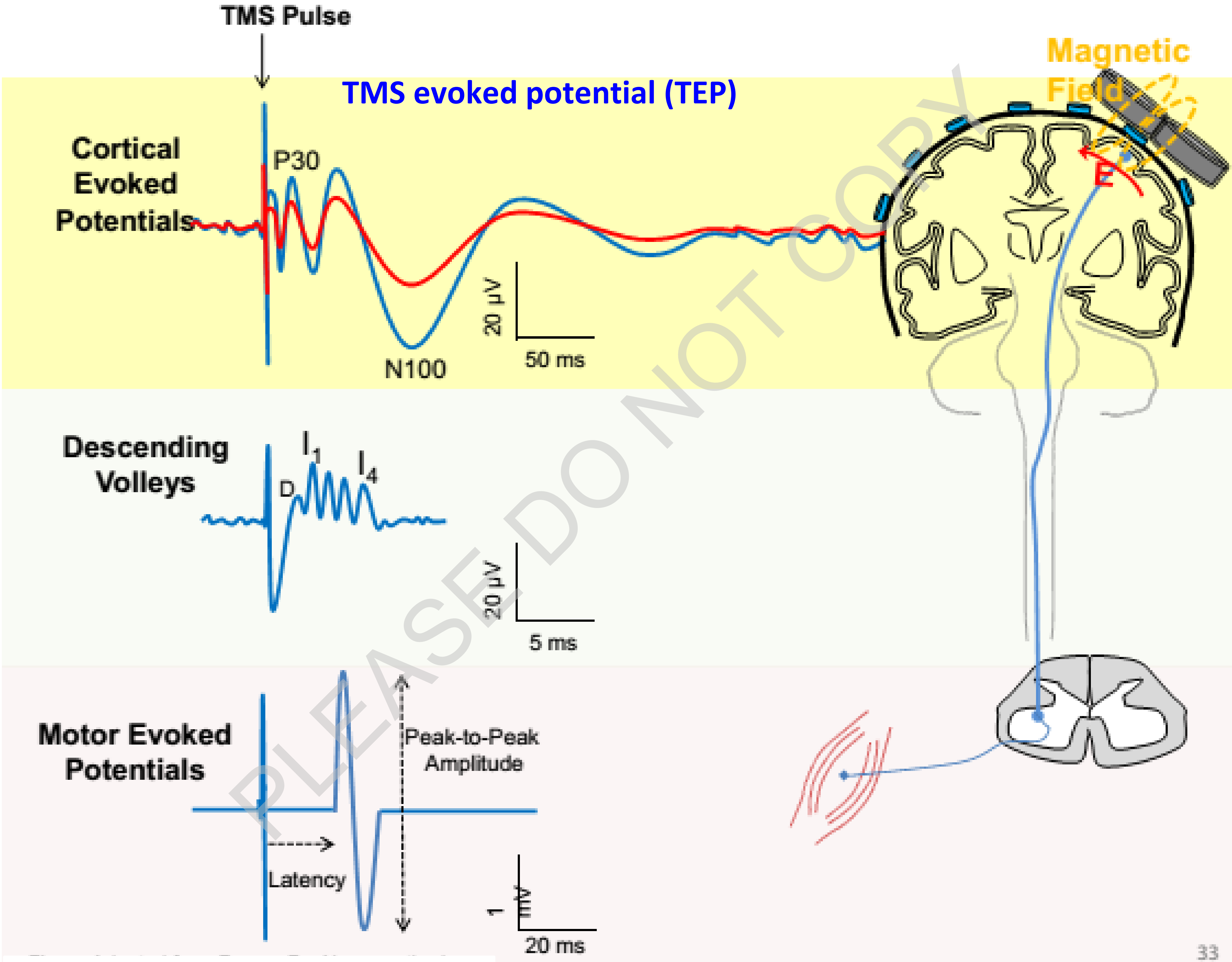
- ***tCS + fMRI***

- ***tCS + NIRS***

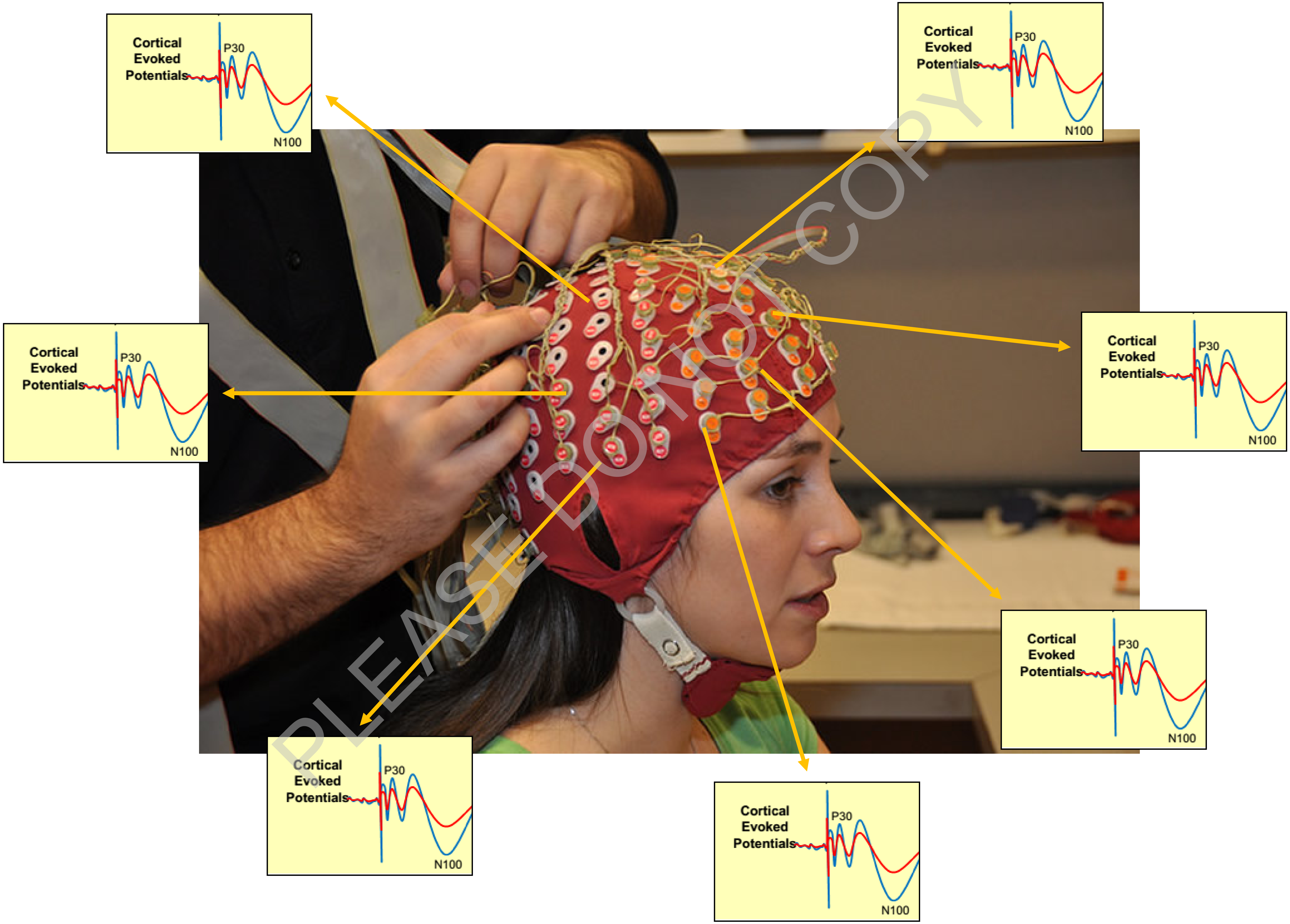
- ***….tCS + TMS-EEG ?***



TMS-EEG

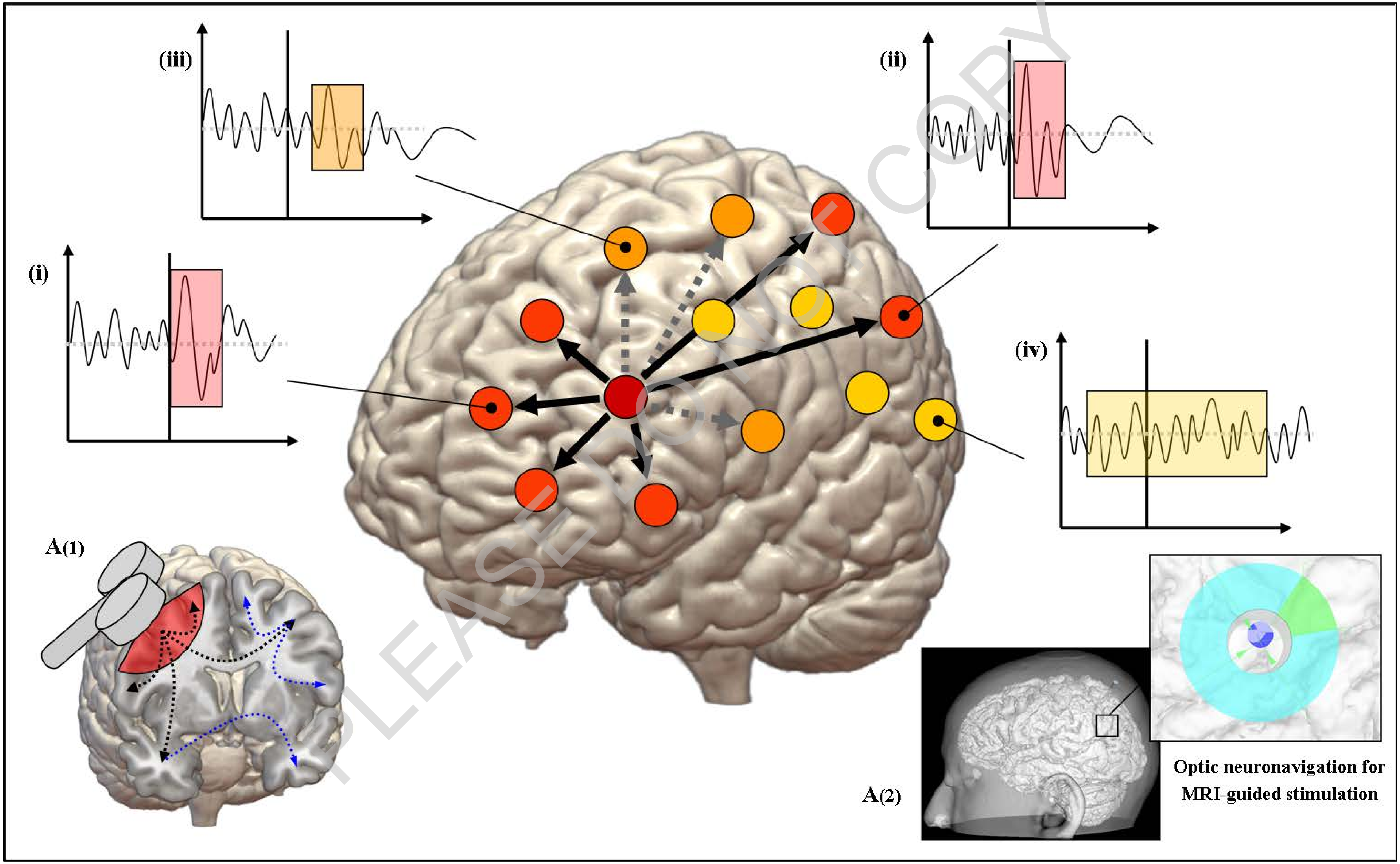

TMS Pulse
TMS evoked potential (TEP)
Magnetic Field
E
Cortical Evoked Potentials
P30
N100
20 µV
50 ms
Descending Volleys
D
I1
I4
20 µV
5 ms
Motor Evoked Potentials
Peak-to-Peak Amplitude
Latency
1 mV
20 ms

TMS-EEG


Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100
Cortical Evoked Potentials
P30
N100

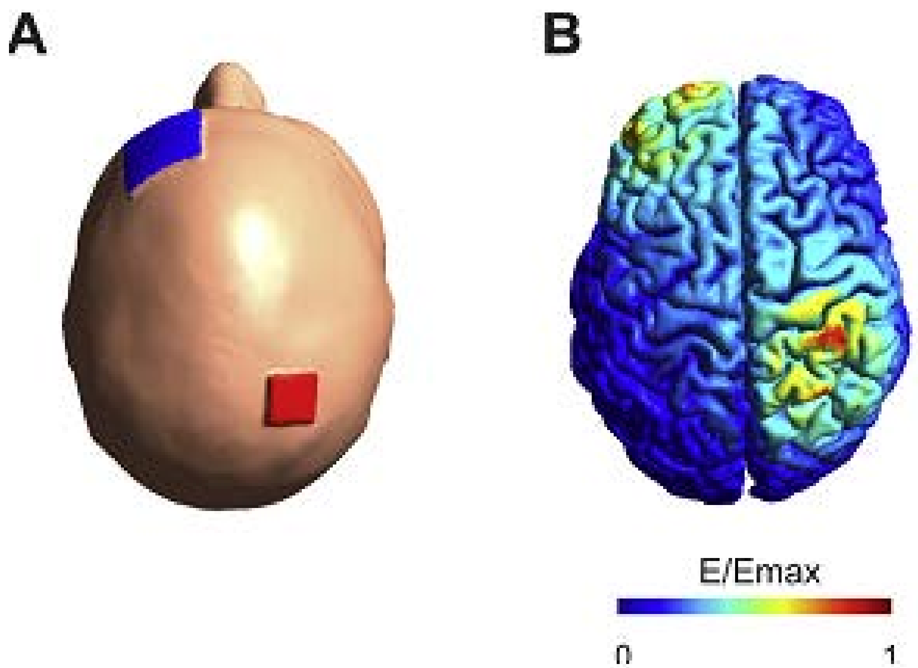
TMS-EEG

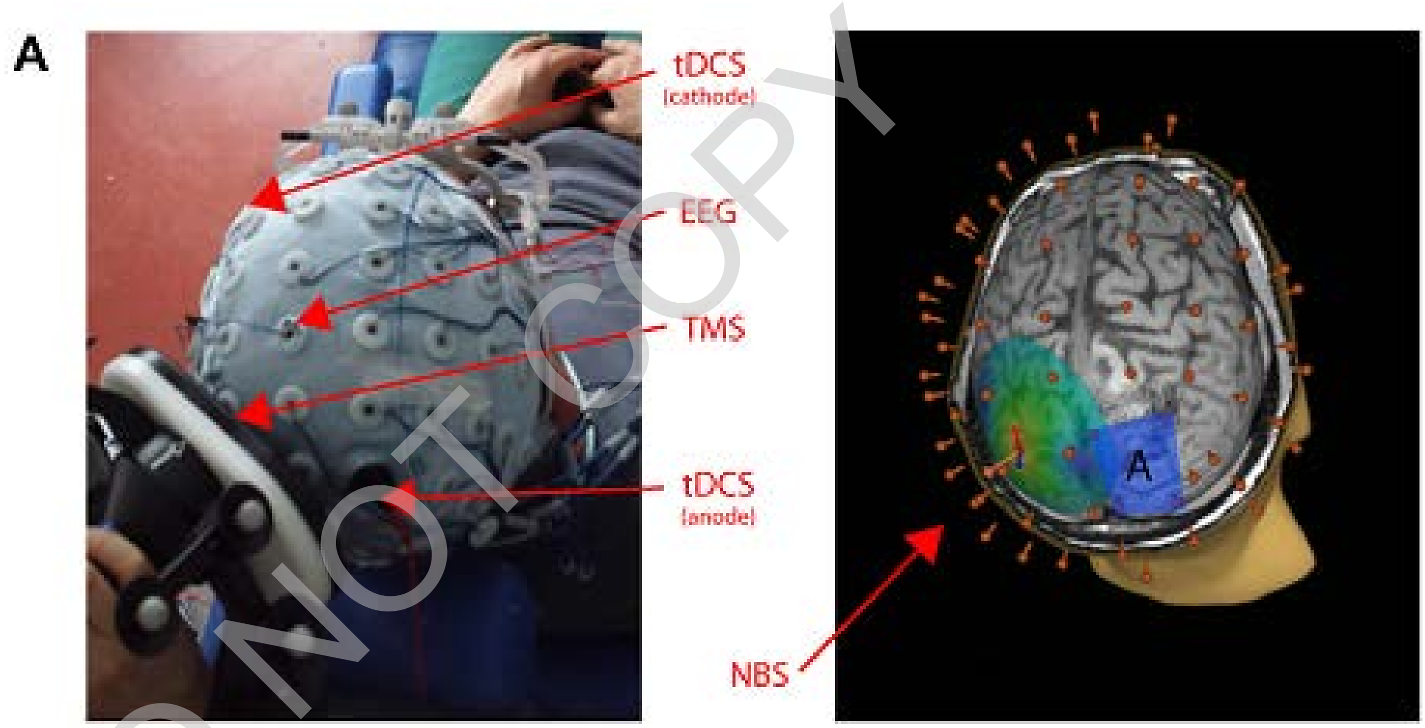
Santarnecchi et al. 2016, SPJ



TMS-EEG to investigate local and distant tDCS effects

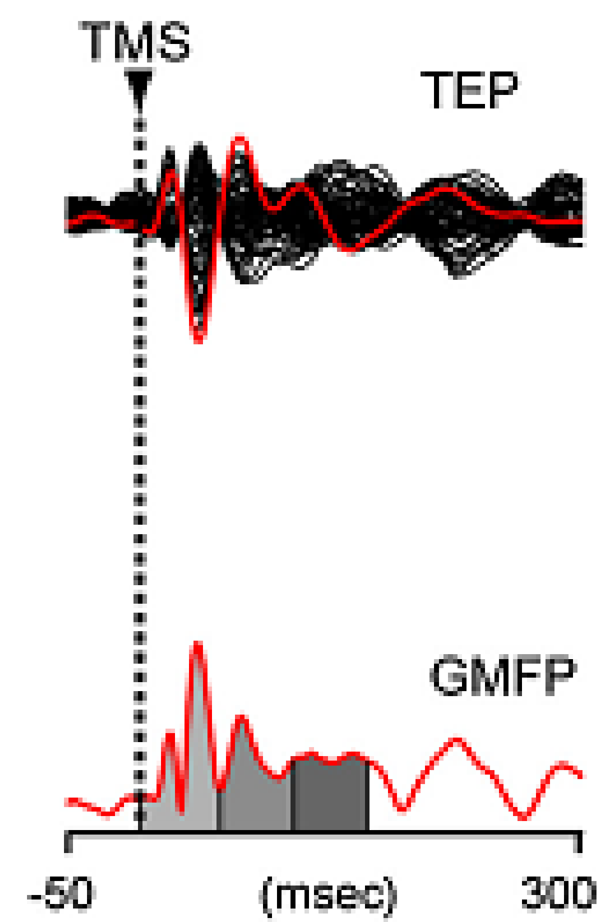
Romero Lauro et al., 2014





- 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

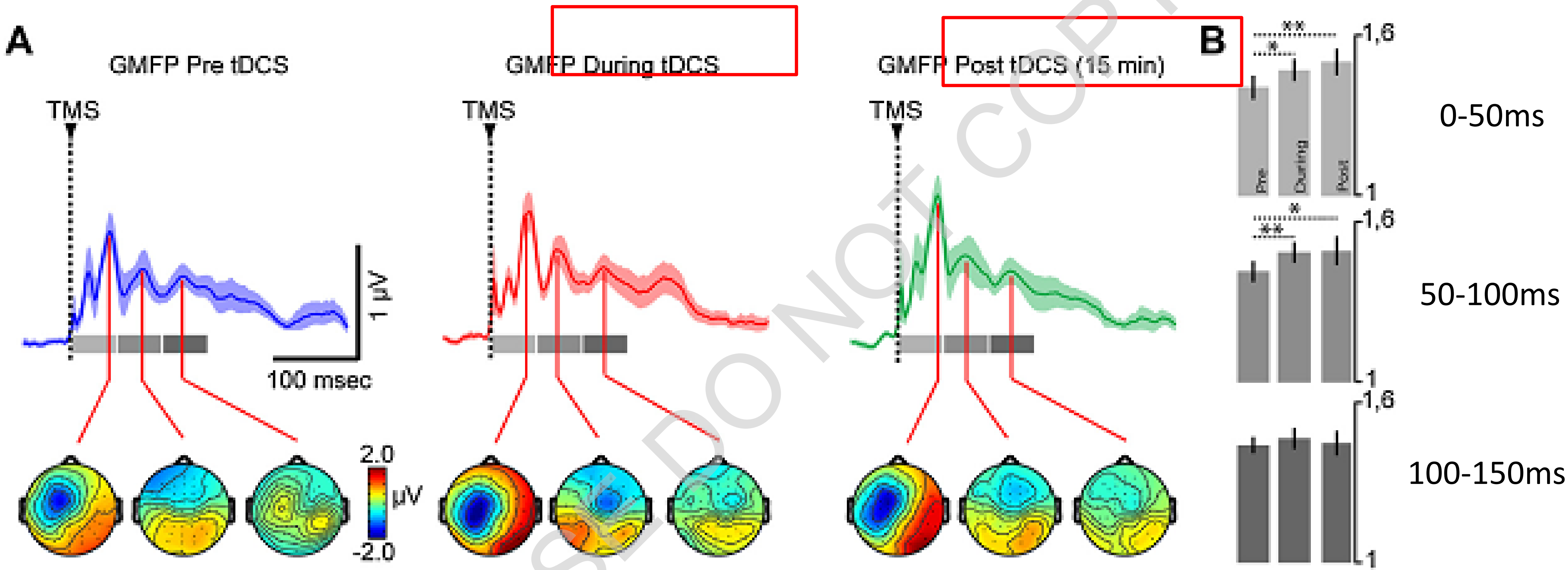
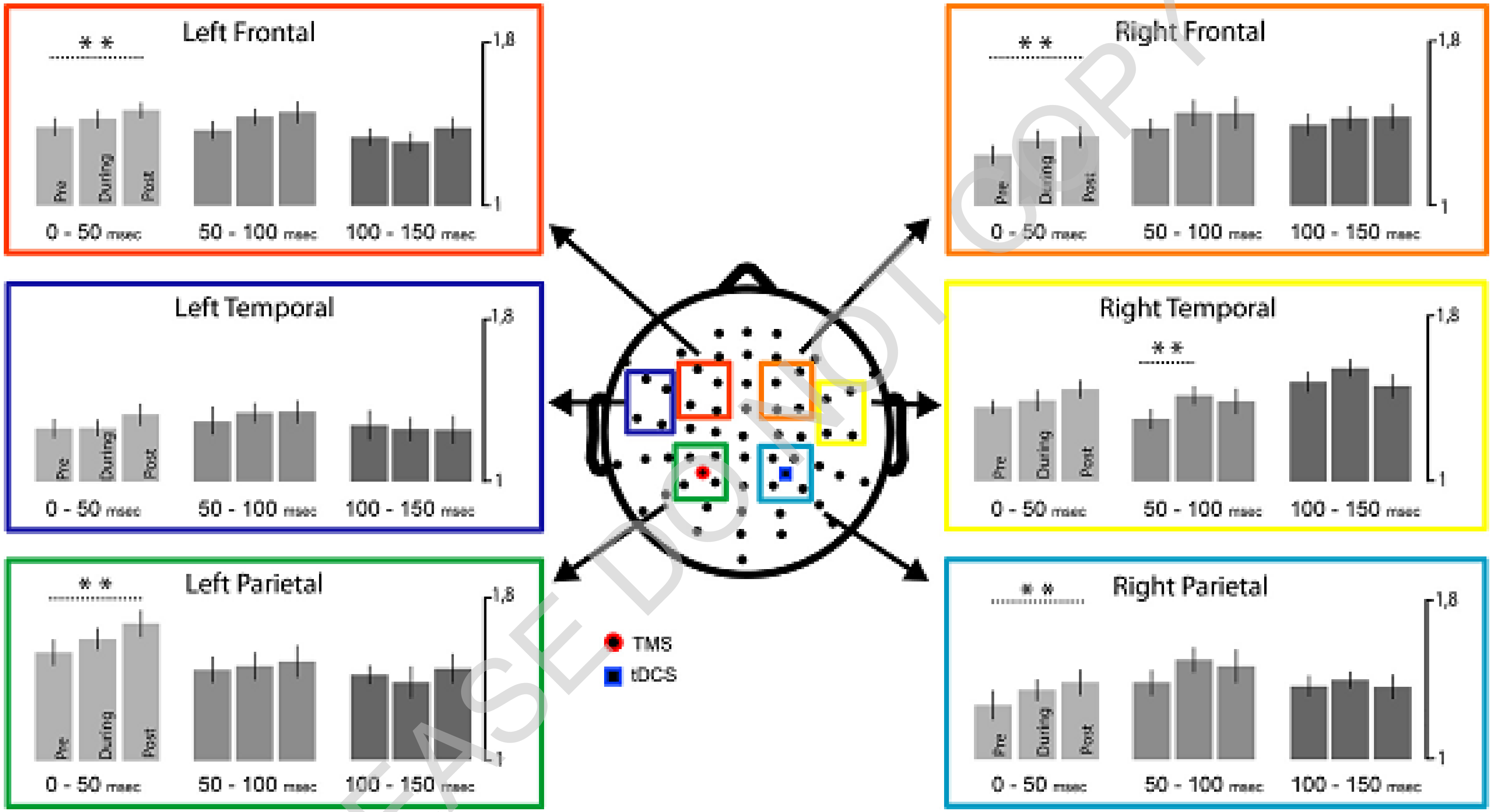


Fig. 2 – Panel A (upper row) shows the Grand Average of GMFP computed by averaging the GMFPs calculated for each subject in the three experimental conditions (pre tDCS = blue trace ± SE; during tDCS = red trace ± SE; post tDCS = green trace ± SE). The lower row of Panel A represents the mean topographies 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 → **tCS guided by EEG recording** → **Resting or Event related EEG**

Stimulation Artifact during EEG recording

tDCS

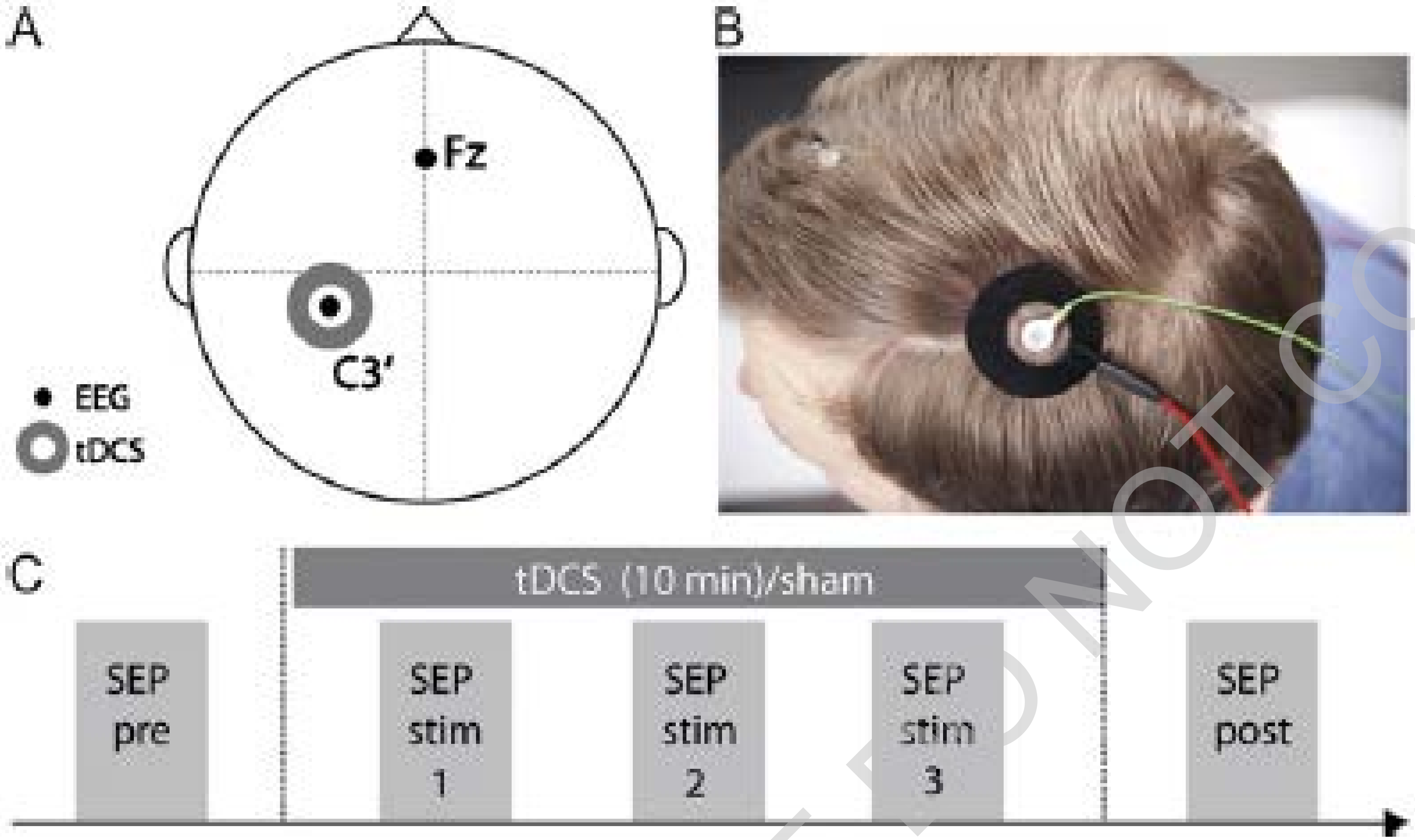
- Relatively easier, Available tools (algorithm) to “clean” the data from Drifts

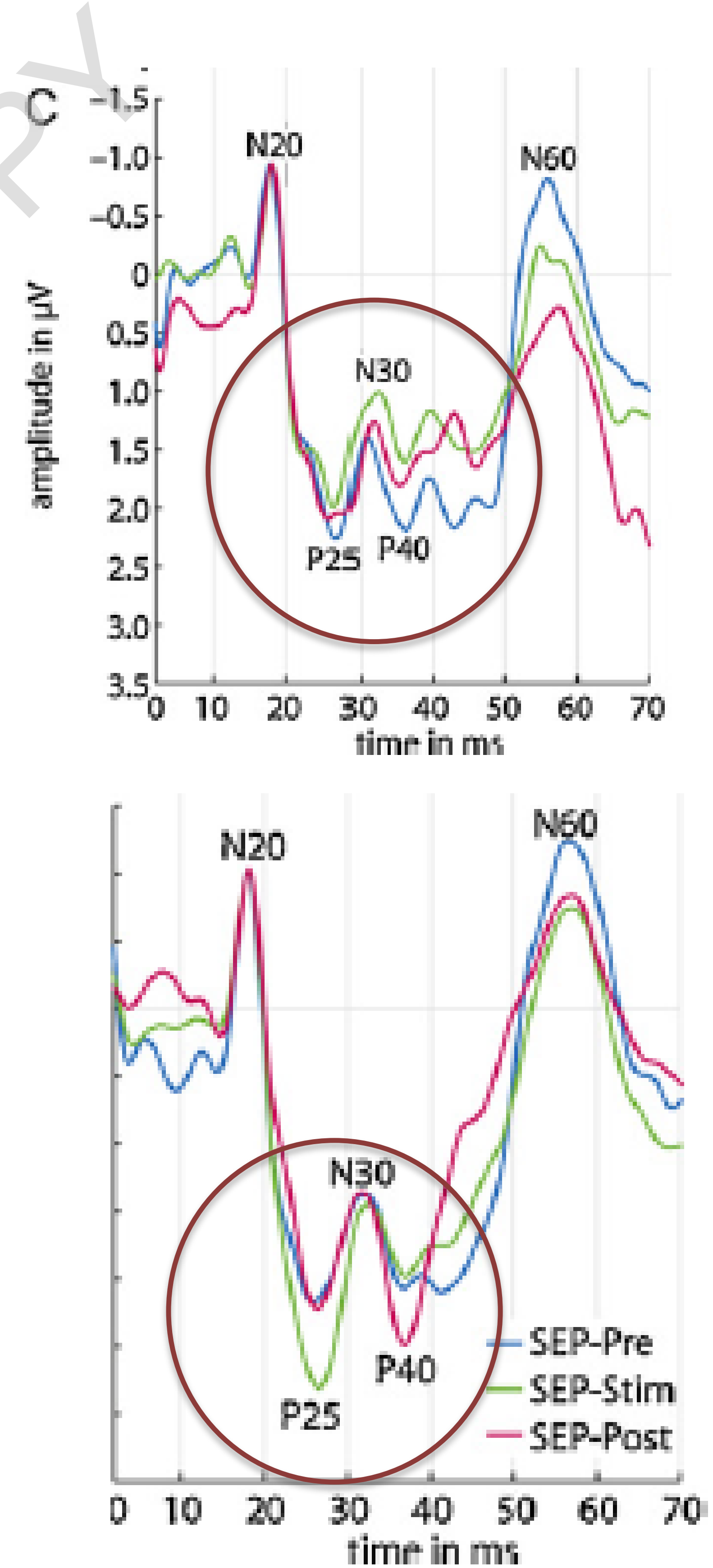
tACS

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

EEG during tDCS

Sehm et al., 2013





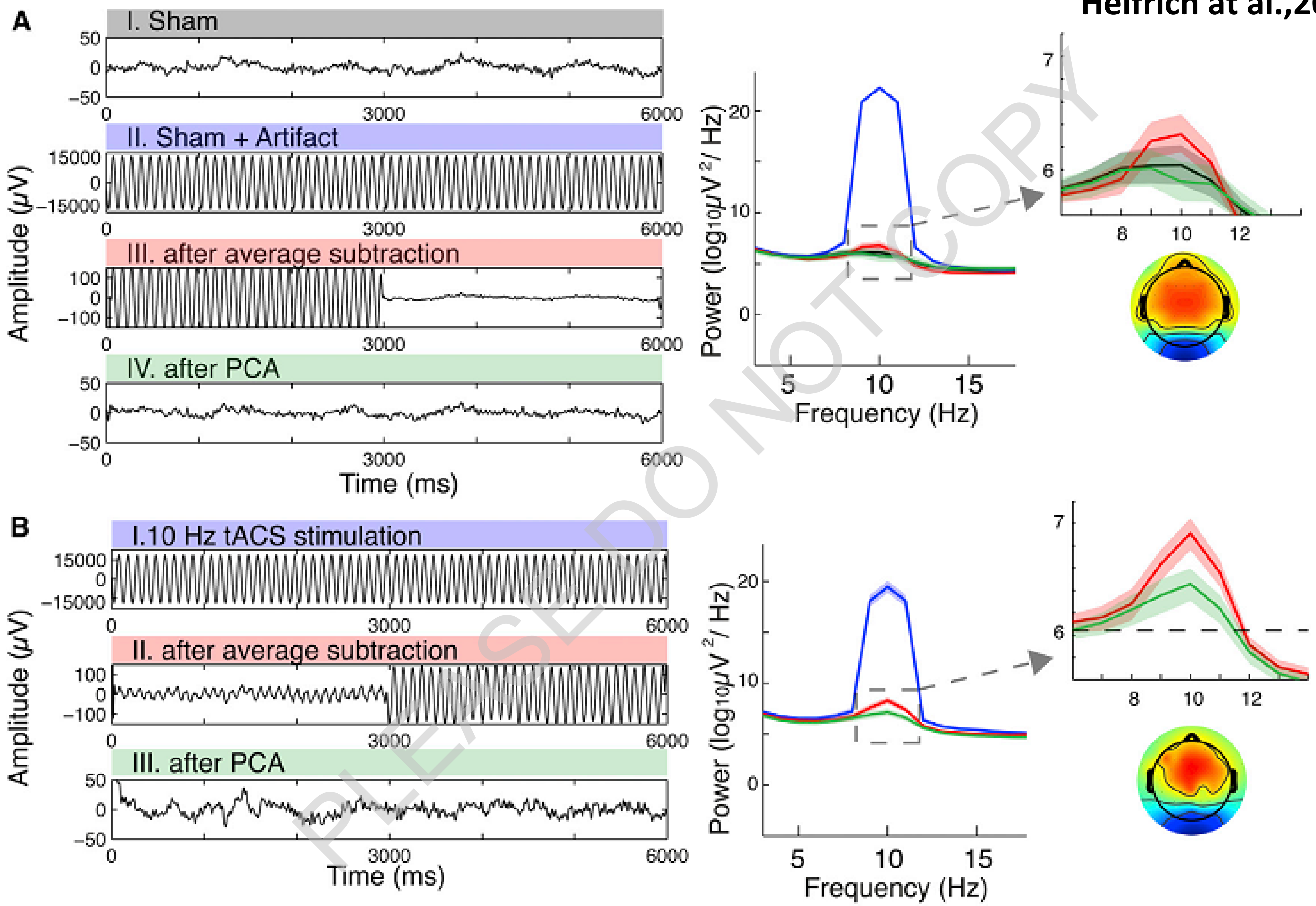
SEP: somatosensory evoked potential

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

POSTPROCESSING

EEG during tACS

Helfrich at al.,2014



Moving Average + Principal Component Analysis to Capture and eliminate the artifact (?)

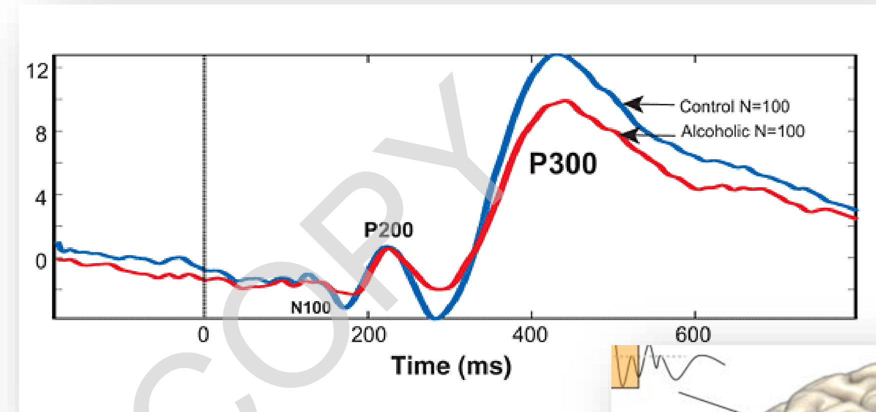
Take home

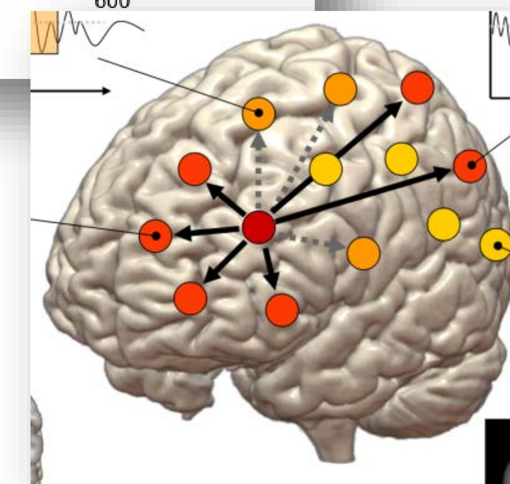
- Understand of Motor **<u>and non-Motor</u>** tCS effects

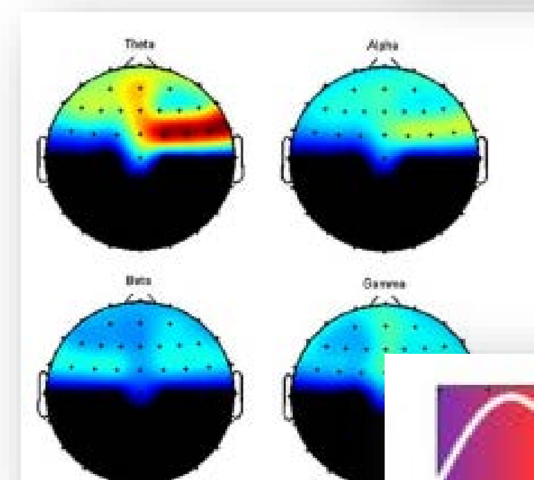
- Capture **Distant effects** other than cortical excitability (e.g. Power, Coherence, Connectivity)

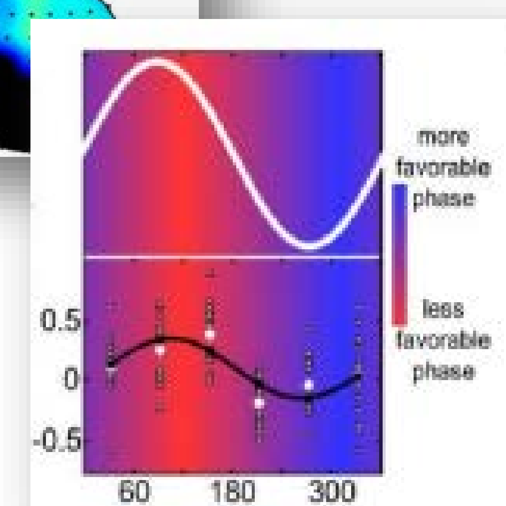
- Guide tCS interventions (***closed loop***, etc.)

- Interact with complex dynamics (e.g. CFC, phase-related processing)









Questions? Comments? Ideas? Feedback?

- dcappon@bidmc.harvard.edu

- davide.balos.cappon@gmail.com

Thank you for your attention

dcappon@bidmc.harvard.edu