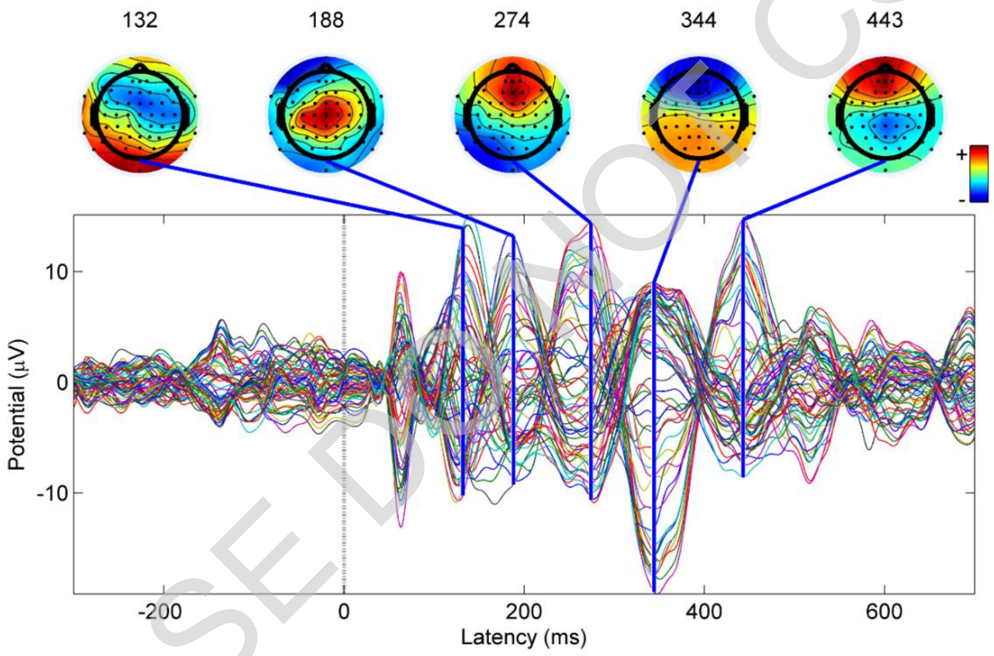
Combining TMS and EEG



Mouhsin Shafi, MD/PhD

Recep Ozdemir, PhD

Harvard Medical School

mshafi@bidmc.harvard.edu

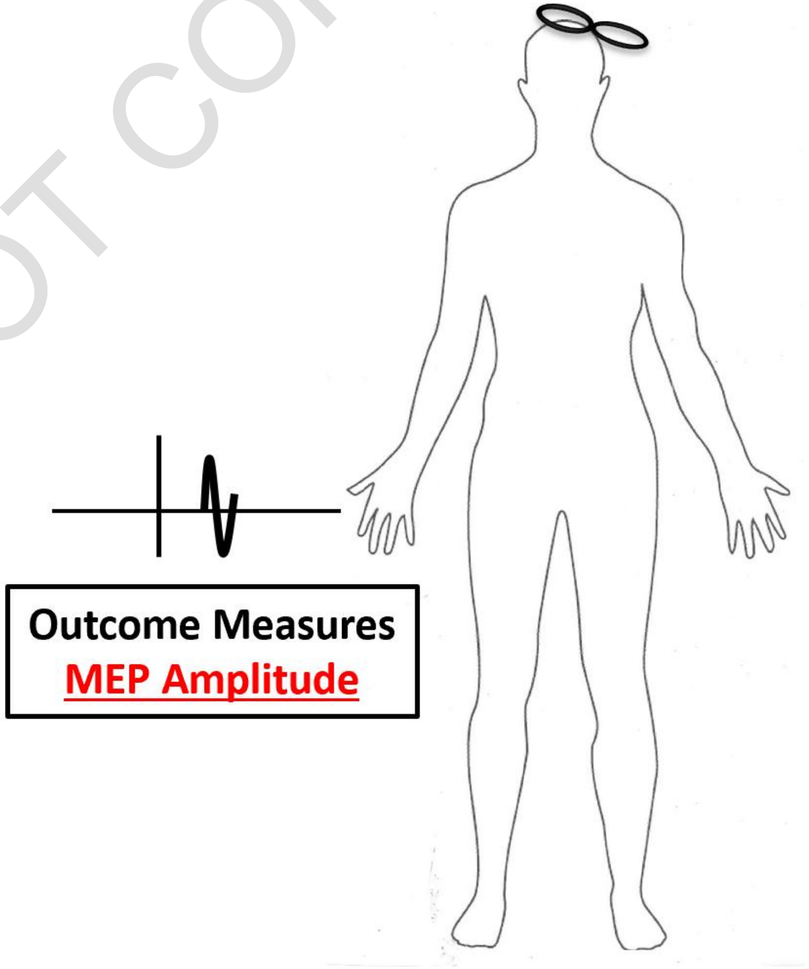
Talk Overview

- Intro to TMS and EEG
- Technical issues and challenges
- Neuroscience Applications of TMS-EEG
  - Understanding mechanisms and effects of TMS
  - Neurobiology and Cognitive Neuroscience
- Clinical Applications of TMS-EEG
  - Diagnosis
  - Monitoring
  - Targeting

TMS: What do we know?

TMS Protocols

- Single Pulse TMS
  - Cortical Mapping
  - Motor Threshold
  - Central Conduction Time
- Paired Pulse TMS
  - One Region
  - Two Regions
- Repetitive TMS
- CLINICAL APPLICATIONS
  - Across a wide spectrum of neurologic and psychiatric diseases



This is FINE, But ...

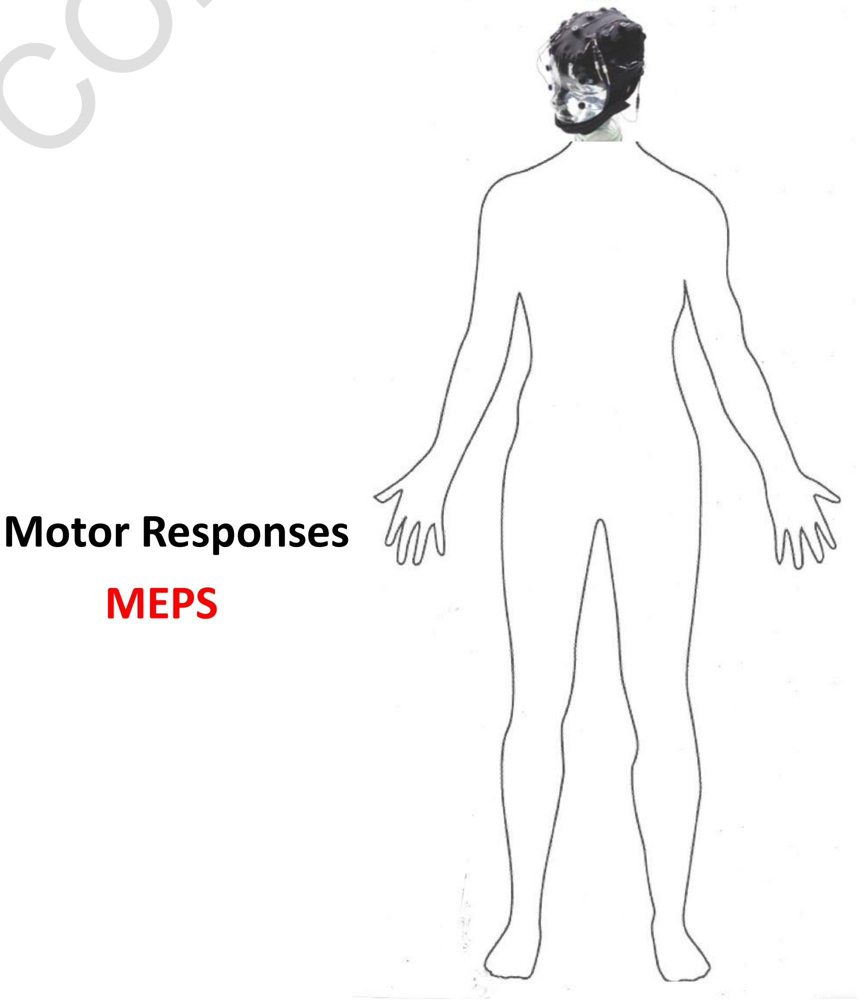
What Is Missing?

Cortical origin?

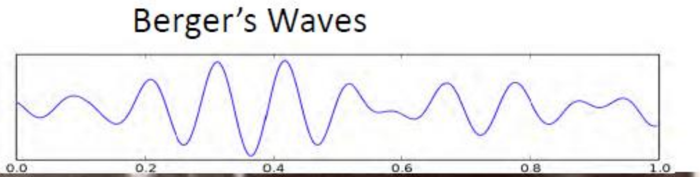
Non-motor regions?

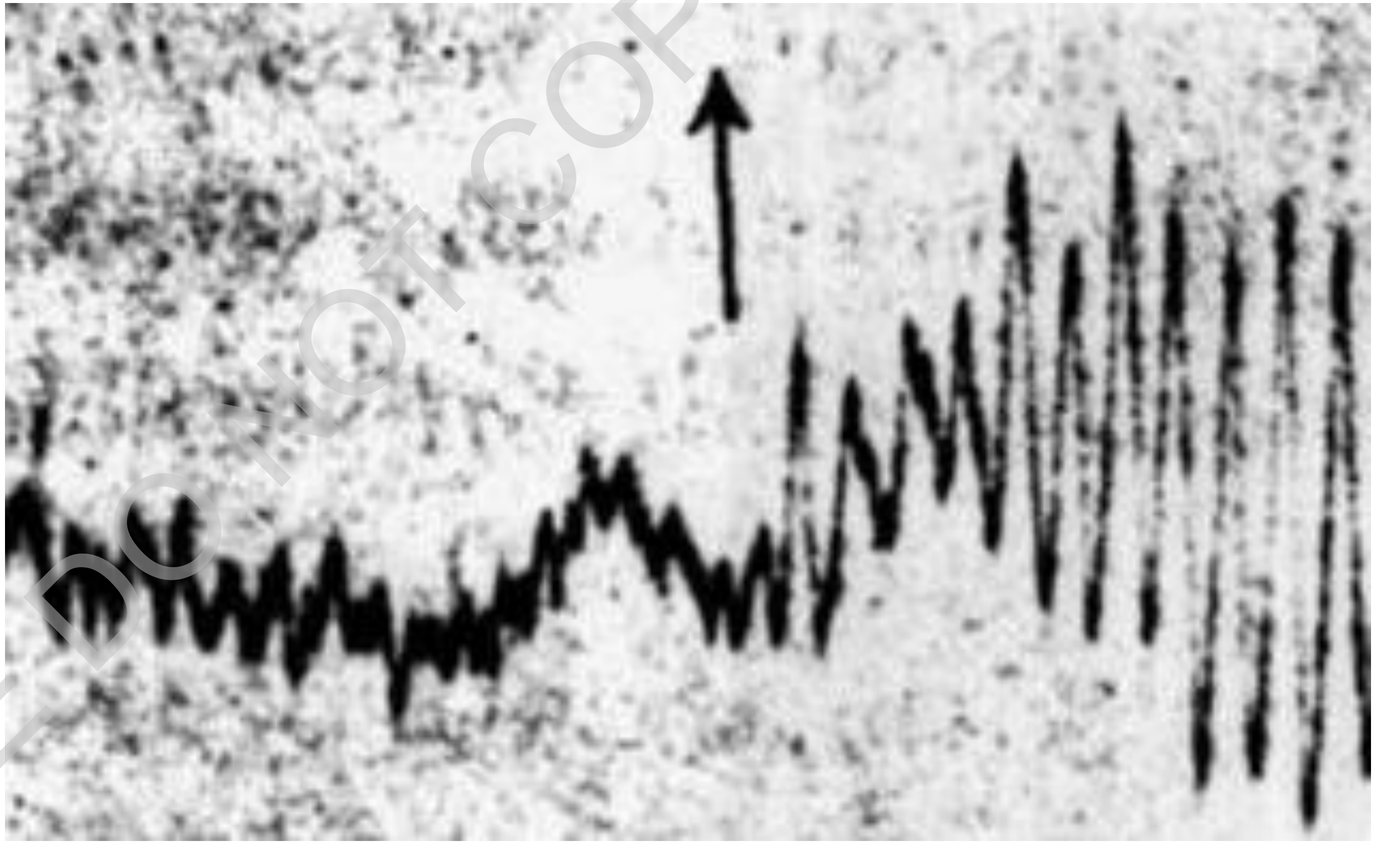
State-Dependency?

Changing brain activity states in disease conditions?



EEG to the rescue?





German psychiatrist. First EEG recorded in 1924 and reported in 1929.

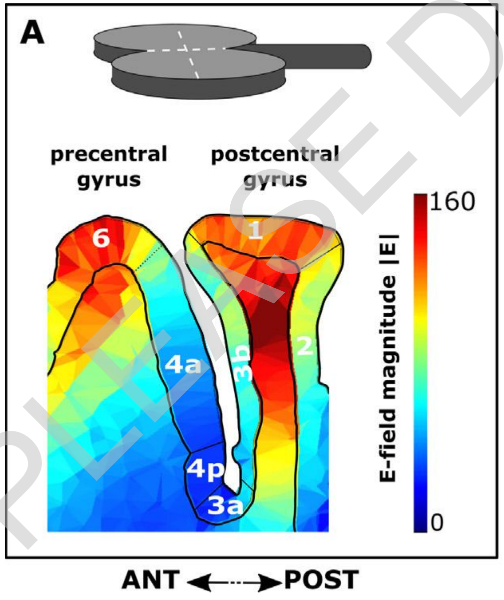
An early EEG recording performed by Hans Berger. Prior to the arrow the subject is performing a mental arithmetic task. After the task stops, alpha returns.
(Jensen, Spaak, Zumer 2014)

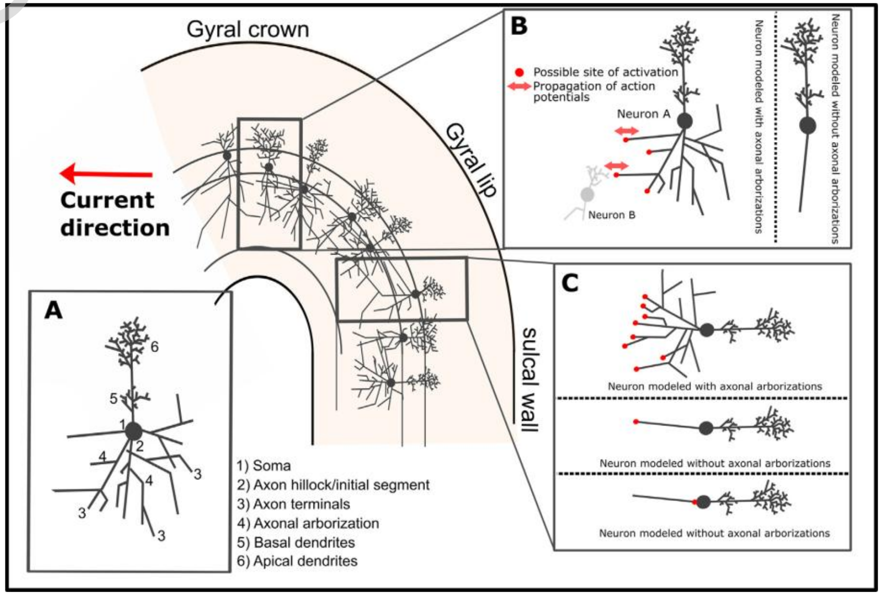
EEG: What are we recording?

- Mostly captures the synaptic activity at the surface of the cortex.
- EPSP + IPSP generated by synchronous activity of thousands of neurons oriented in parallel to each other.
- Interplay between excitatory pyramidal neurons and inhibitory interneurons

What is stimulated by TMS?

Thousands of pyramidal cells, interneurons and axons with maximum efficiency at the surface of the cortex.

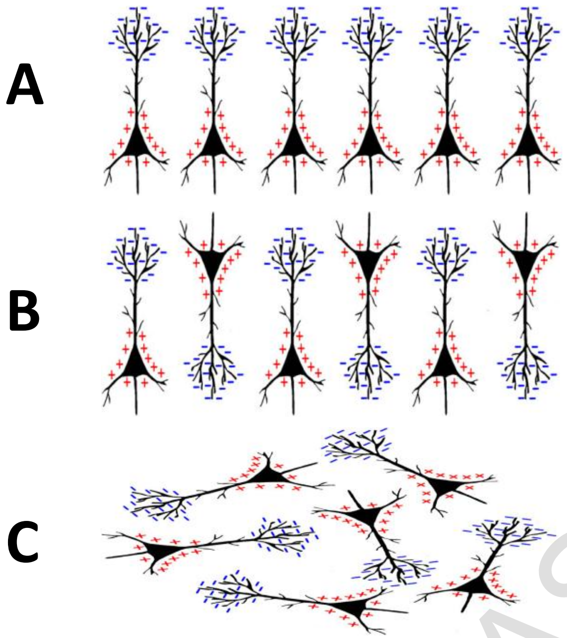




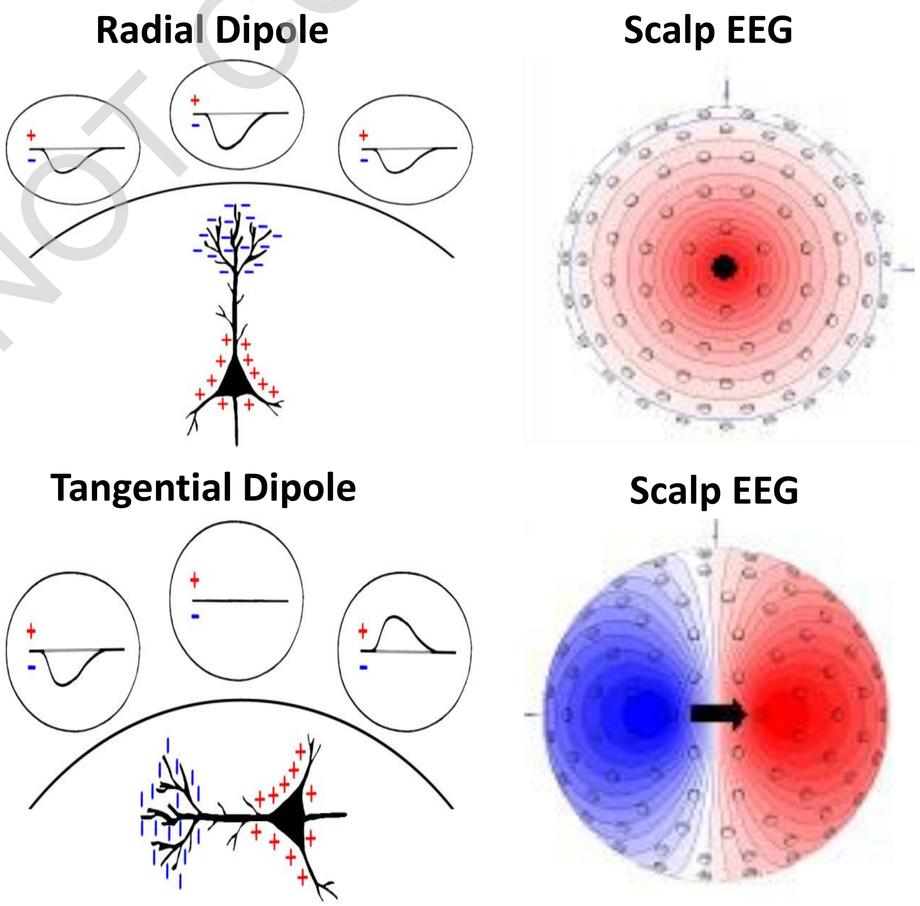
Siebner et al., 2022

EEG: What are we recording?

- Orientation is critical and dictates what we can see at the scalp



EEG detects only A



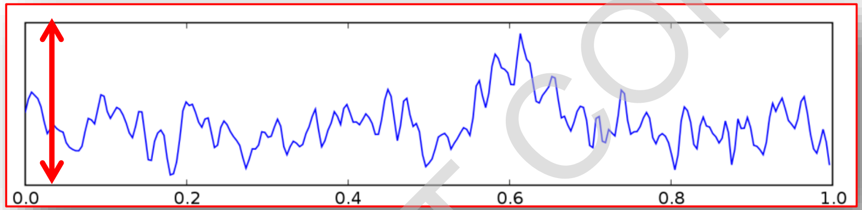
Jackson and Bolger, 2014, *Pyschophysiology*.

EEG language?

Amplitude (or Power)

Strength

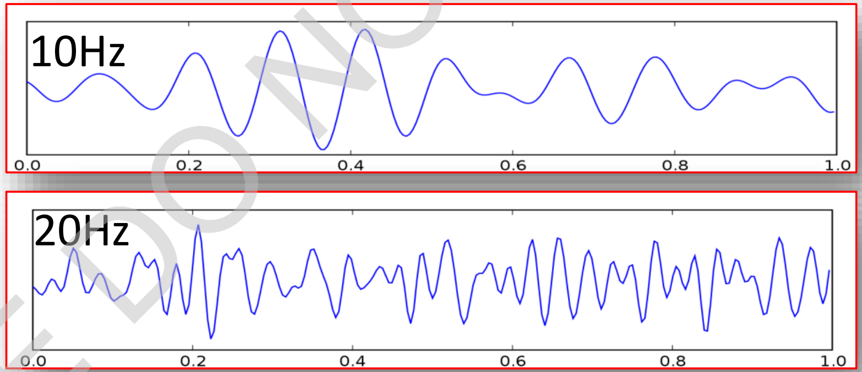
(μV or μV^2)



Frequency

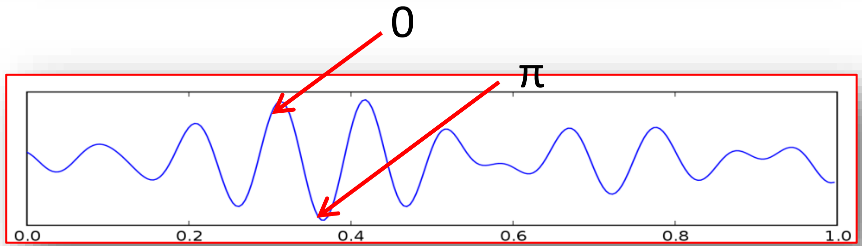
# of Cycles/Second

(Hz)



Phase

(Radians)



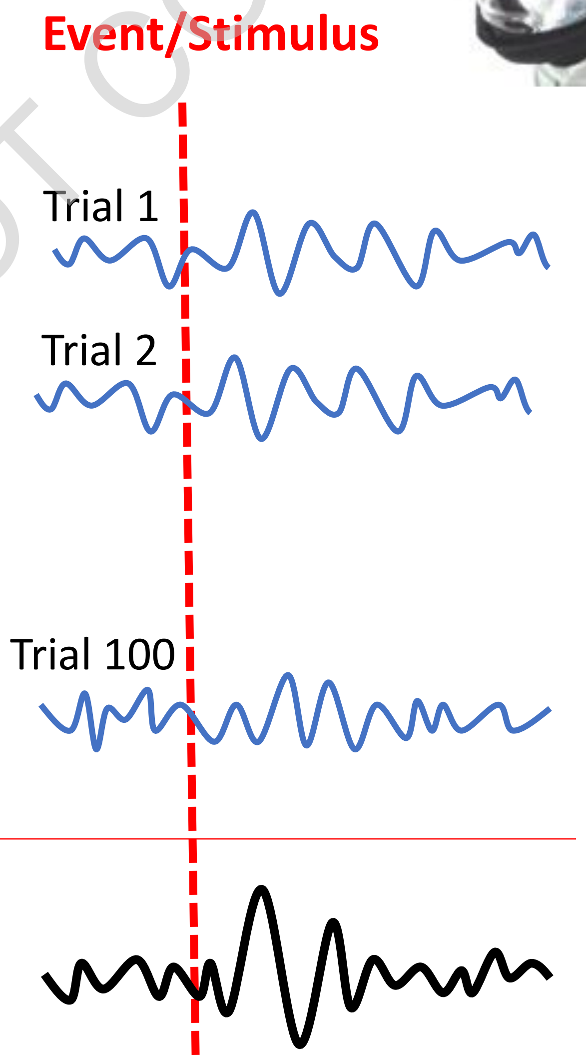
When/How to Record EEG?

Continuous Recording (No Event)

- Anesthesia,
- Sleep
- Resting (eyes open/closed)

Relative to An Event/Stimulation

- Sensory, motor, cognitive processing
- Electrical stimulation

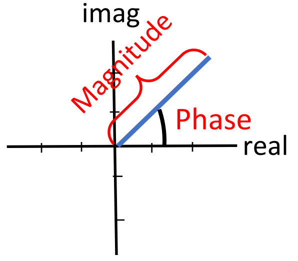


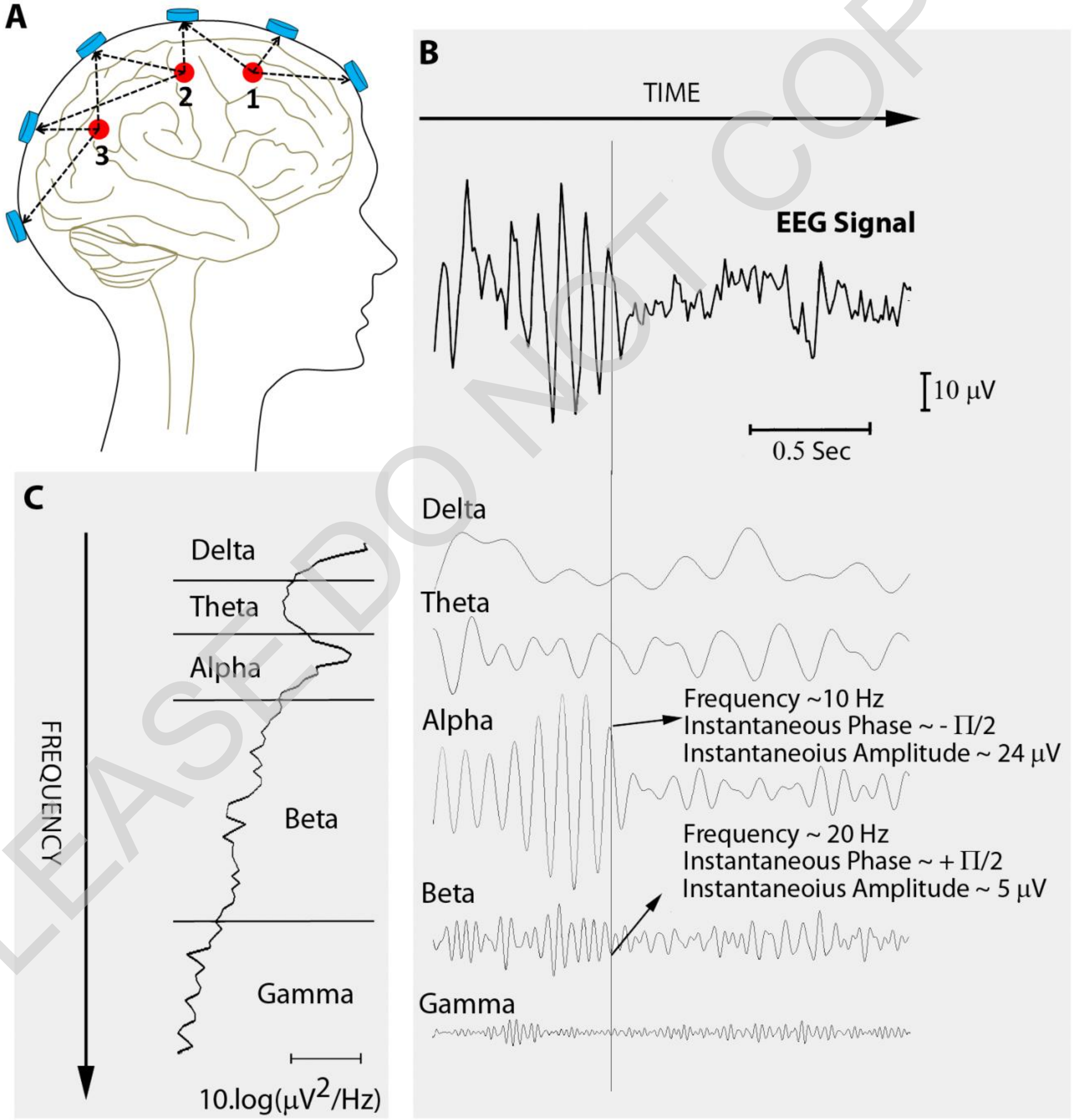
Time: Event Related Potential or Evoked potentials
Frequency: Event Related Spectral Perturbation
Phase

How to Analyze EEG?

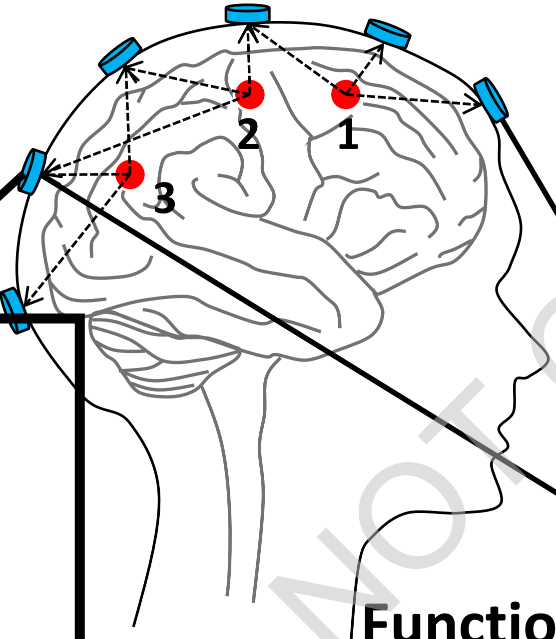
Time vs. Frequency Domain

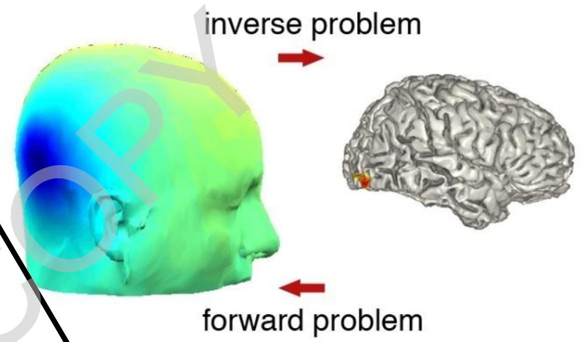
Frequency Domain $X_i\,(f)$



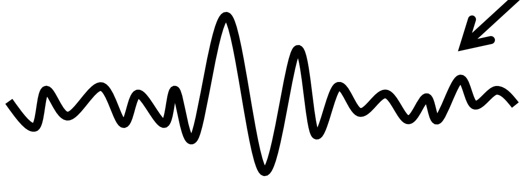


How to Analyze EEG?





Local Response



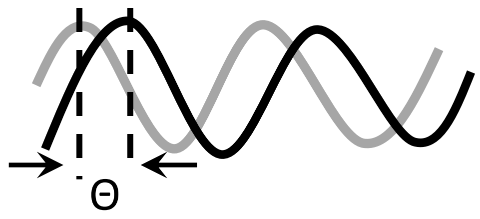
- Amplitude/Power
- Frequency
- Phase

Spontaneous EEG:
Spectral Power

EEG + Event:
Event-Related Potentials (**ERP or EP**)
Event-Related Spectral Perturbation (**ERSP**)
Event-Related Synchronization (**ERS**)
Event-Related Desyncronization (**ERD**)

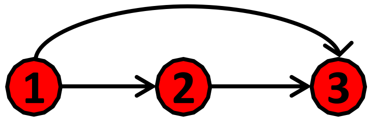
Functional Connectivity

Correlation (time)
Coherence (frequency)
Synchrony (phase-locking)



Cross-Frequency Phase-Amplitude Coupling

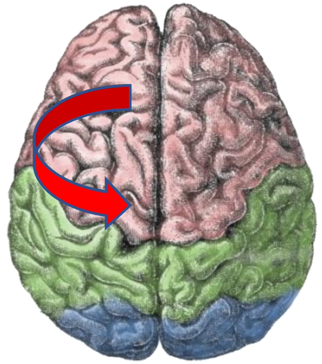
Direction of Information Flow
Directed Transfer Function
Directed Partial Coherence



In summary what can EEG tell us?

Excitability of cortical tissue, and the balance of excitation and inhibition

Brain state and the integrity of different networks



Dynamics of interactions within and between different brain regions

Talk Overview

- Intro to TMS and EEG
- Technical issues and challenges
- Neuroscience Applications of TMS-EEG
  - Understanding mechanisms and effects of TMS
  - Neurobiology and Cognitive Neuroscience
- Clinical Applications of TMS-EEG
  - Diagnosis
  - Monitoring
  - Targeting

Marrying TMS with EEG … the problems …

- Very brief (5min) Summary here.
- More detailed illustrations and explanations during TMS-EEG hands on session.

Initial Problems?

EEG Amplifiers Saturated!

Ives et al., 2006, Clinical Neurophysiology

TMS pulse generated too high a voltage (> 50mV) for most amplifiers to handle. Amplifiers were saturated or even damaged!

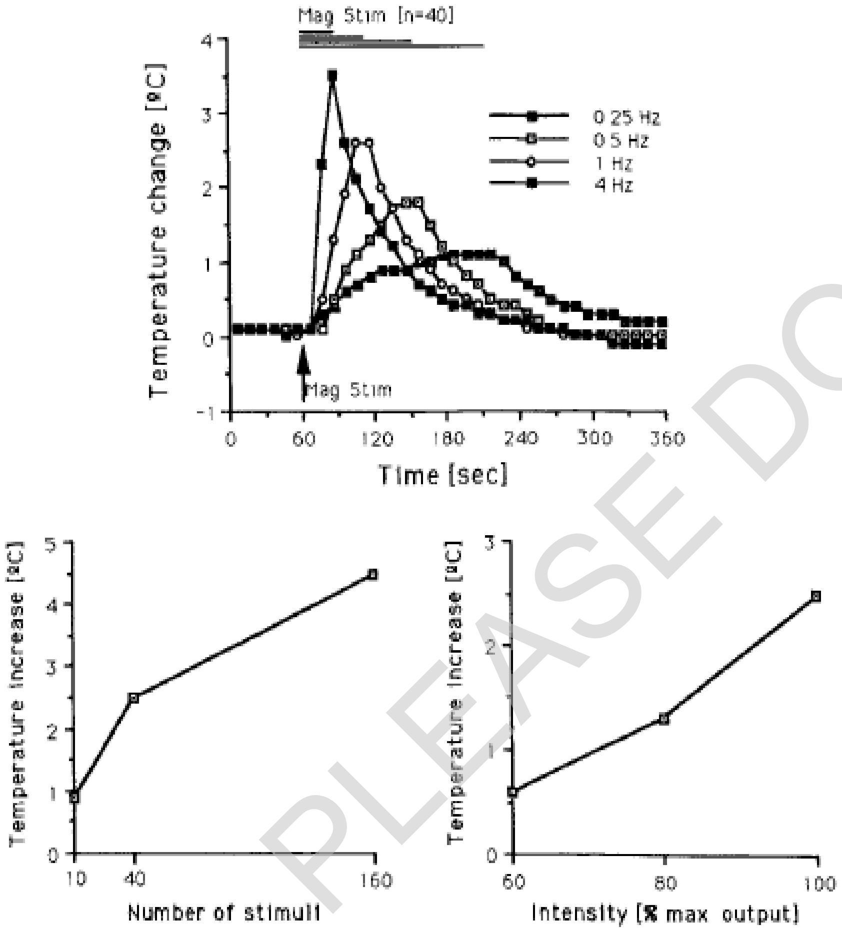
Problem 1: EEG Amplifier Saturation

Some Solutions

- **De-coupling:** TMS pulse is short (.2 to .6ms), so block the amplifier and reduce the gain for -50µs to 2.5 ms relative to TMS pulse.
  Virtanen et al., Med Biol Eng Comput, 1999; **Nexstim (Helsinki, Finland)**
- **Increased Sensitivity & Operational Range:** Adjust the sensitivity (100 nV/bit) and operational range of EEG amplifiers so that amplifiers would not saturate by large TMS voltage **BrainProducts (Munich, Germany)**
- **DC-Coupling/High Sampling Rate:** A combination of DC-coupling, fast 24-bit analog digital converter (ADC) resolution (i.e., 24 nV/bit) compared to older 16-bit ADC resolution that was limited to 6.1 mV/bit, and high sampling rate (20 kHz)=> capture the full shape of artifact and prevent amplifier clipping. **NeuroScan (Compumedics)**
- **Limited Slew Rate**: Limiting the slew rate (the rate of change of voltage) to avoid amplifier saturation; Artifact removed by finding the difference between two conditions. **Thut et al., 2003; Ives et al., 2006;**

References: Vaniero et al, 2009; Ilmoniemi et al, 2010

TMS Heated Up Electrodes!



Skin temperature changes during magnetic stimulation.

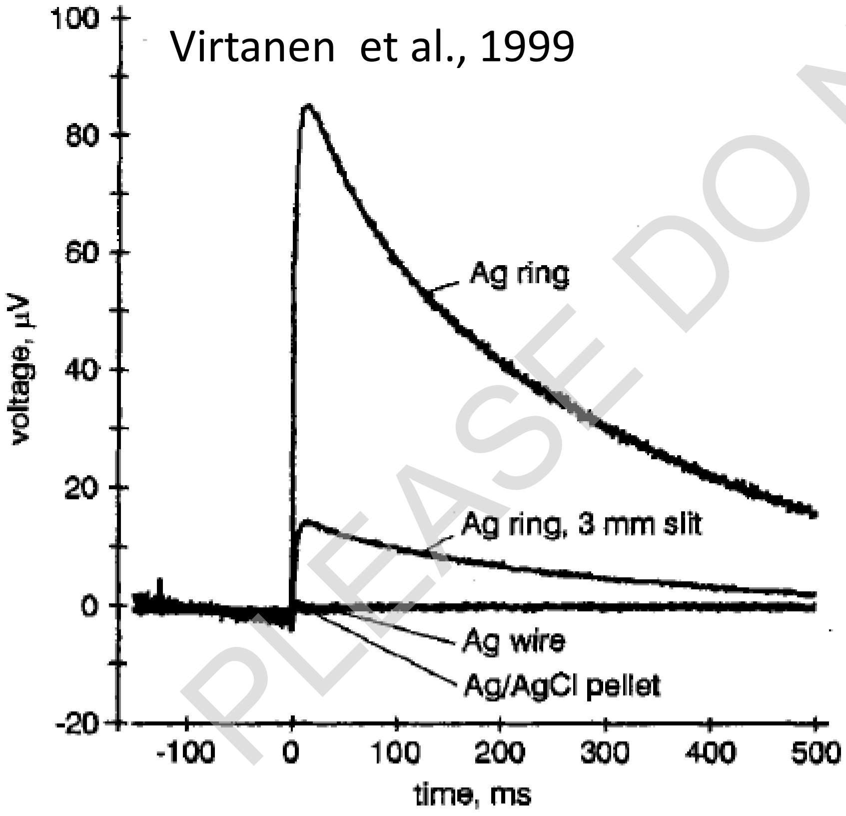
One of the subjects had a burn on the skin, to test whether this had anything to do with rTMS, they placed electrodes on their arm and stimulated the electrode with different number of stimuli, different intensity and different duration of stimulation.

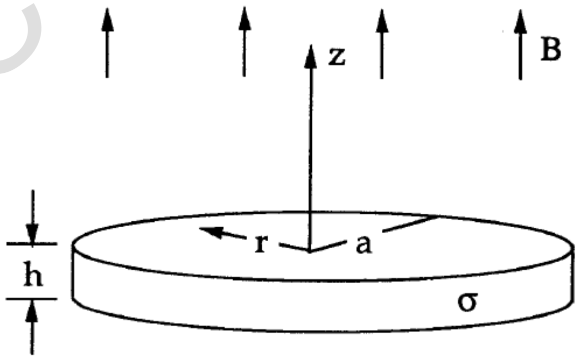
Reference: Pascual-Leone et al., 1990, Lancet

Problem 2: Electrode Heating

Some Solutions

Small Ag/AgCl Pellet Electrodes





Temp ~ r^2
Temp ~ B^2
Temp ~ metal electrical conductivity (σ)

There were all kinds of other issues too …

- We learned that TMS induces a secondary current (eddy current) in near by conductors. Well… EEG electrodes are conductors!

High frequency noise in the electrode under the coil

- Movement of electrodes by TMS coil, muscle movement or electromagnetic force.

Slow frequency movement & motion artifact in EEG recording

- Capacitor recharge also induced artifact in the EEG.

Smaller amplitude TMS artifact sometime after TMS pulse

References: Vaniero 2009; Ilmoniemi 2010;

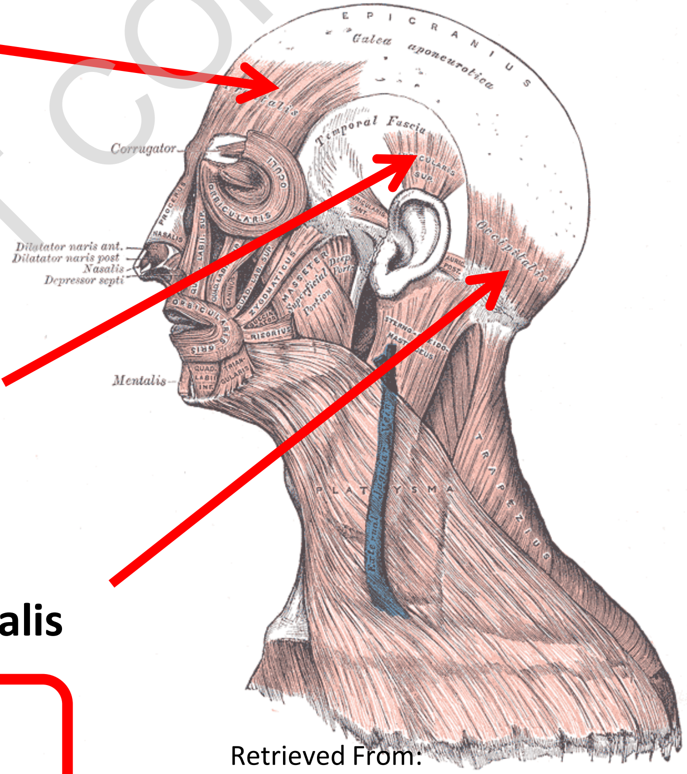
And some remain problematic…

TMS may cause motor responses in scalp muscles

Frontalis

Temporalis

Occipitalis



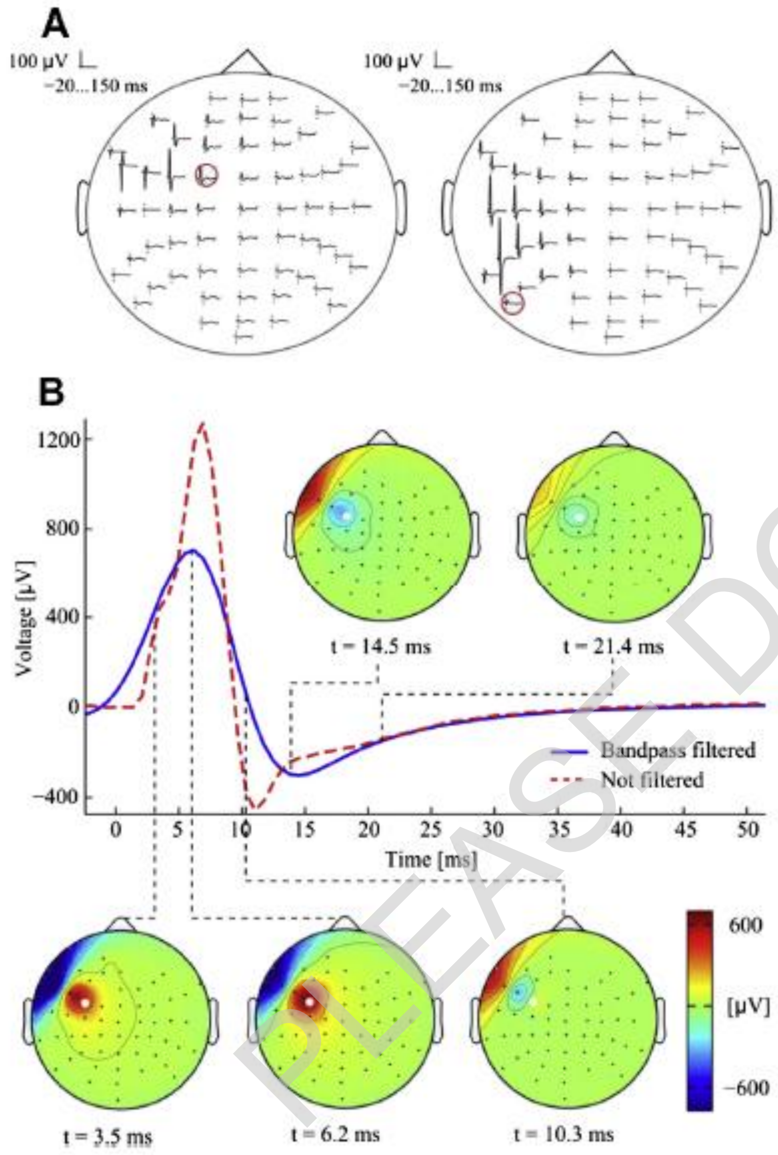
Retrieved From: http://education.yahoo.com/reference/gray/illustrations/figure?id=378

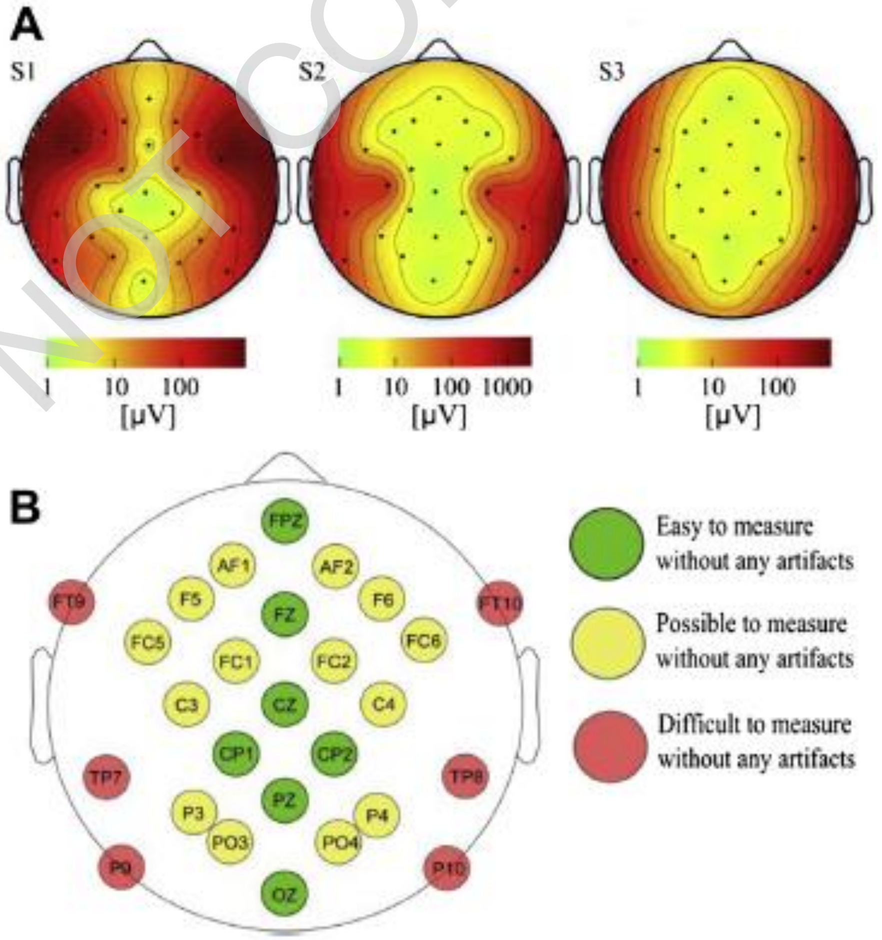
Some Solutions

Changing the coil angle to stimulate muscles less

EMG artifact removal after recording
Independent Component Analysis

Site of stimulation is critical

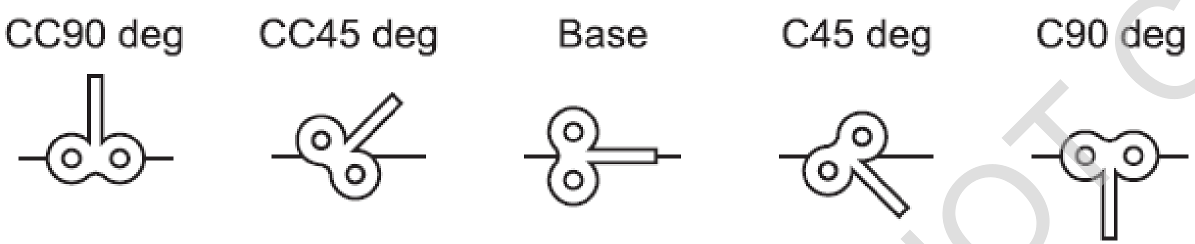


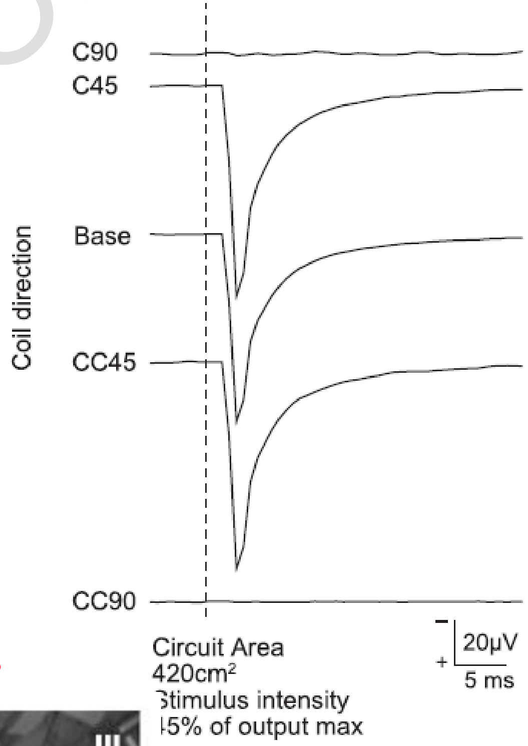


Mutanen 2012

Minimizing recorded artifact online

Coil Orientation with Respect to the Electrode Wires

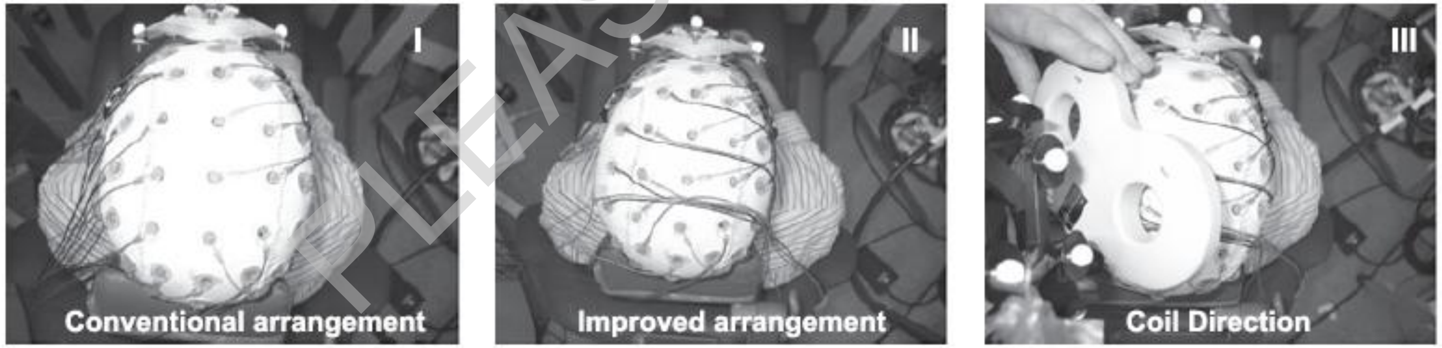




- Large positive depression after the stimulus onset for Base, C45, and CC45 directions,

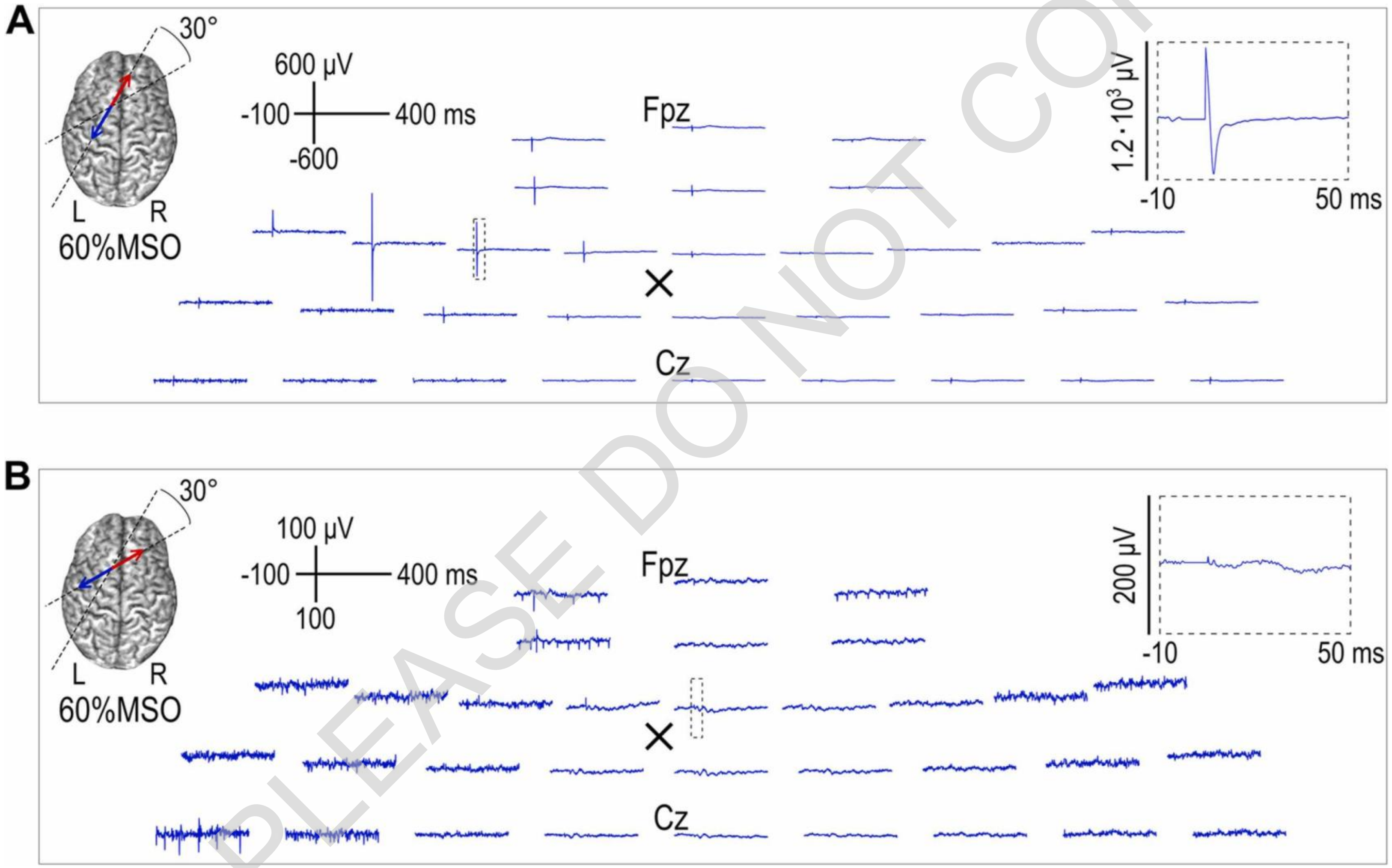
- Residual artifacts were negligible at both 90 positions

Solution: Rearrange the lead wires relative to the coil orientation.



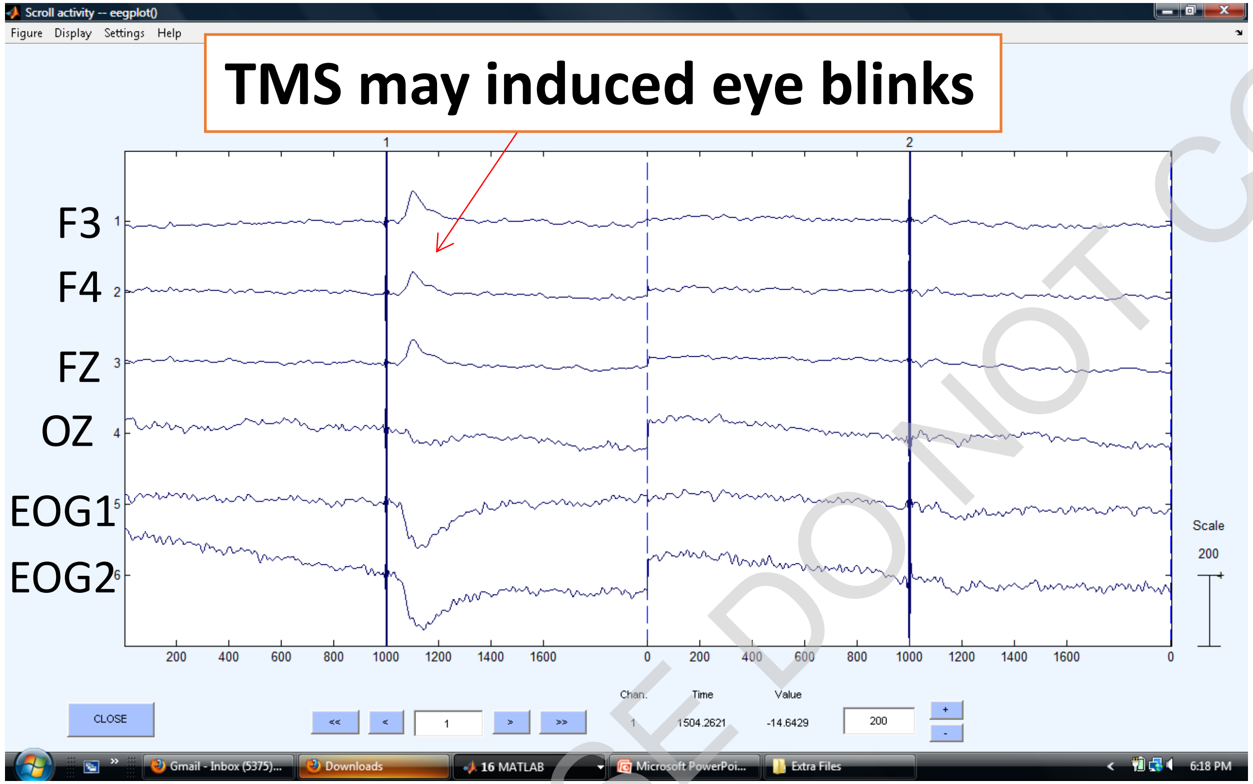
Results from: H. Sekiguchi et al., Clinical Neurophysiology

Potential solution: Real-time visualization of TEPs



Casarotto 2022 Brain Stim

Other difficulties



Some Solutions

EOG Calibration Trial

Delete Contaminated Trials

Independent Component Analysis (ICA)

Minimizing recorded artifact Offline

Deleting, Ignoring, or ‘Zero-Padding’

Remove by setting the artifact to zero

References: Esser 2006; Van Der Werf and Paus 2006; Huber 2008; Farzan 2010;

Temporal Subtraction Method

Create a temporal template of TMS artifact and subtract it; Example: TMS only condition; TMS+Task Condition, then subtract TMS Only from TMS+Task

References: Thut et al. 2003; 2005.

Removing Artifact and Interpolate

Interpolation: Cut the artifact and connect the prestimulus data point to artifact free post stimulus

Refereces: Kahkonen et al. 2001; Fuggetta et al. 2005; Reichenbach et al. 2011.

PCA and ICA

Parse out EEG recording into independent (ICA) or principle (PCA) components and remove the component that are due to noise;

References: Litvak et al. 2007; Korhonen 2011 Hamidi 2010; Maki & Ilmoniemi 2011; Hernandez-Pavon 2012; Braack 2013, Rogasch 2014

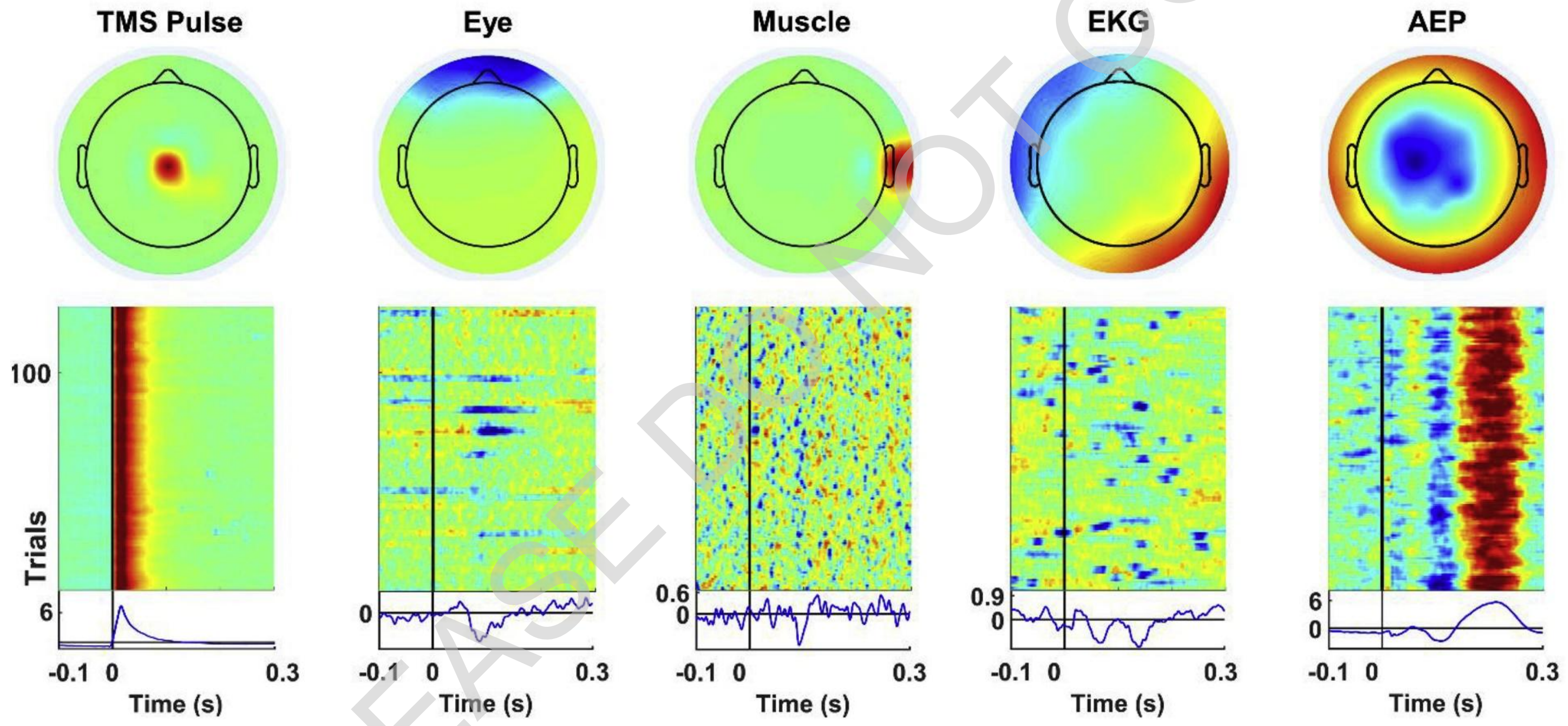
Filtering

Non-linear Kalman filter to account for TMS induced artifact

References: Morbidi et al., 2007

M/F

ICA can remove artifactual components



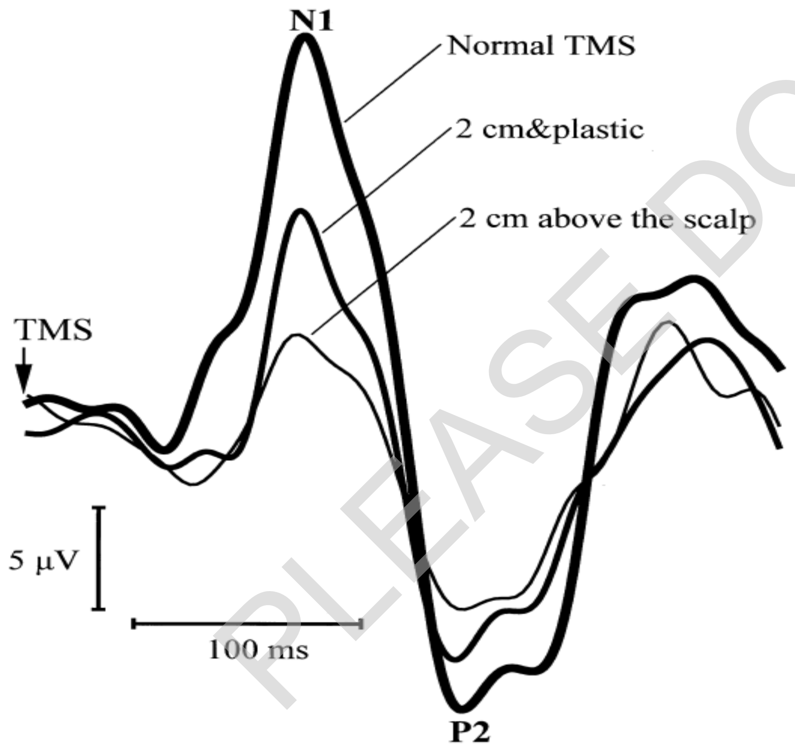
Ozdemir et al, Brain Stim 2021

TMS Sound

TMS click is loud!
~ 100 dB 5 cm of the coil

TMS induces auditory evoked potentials

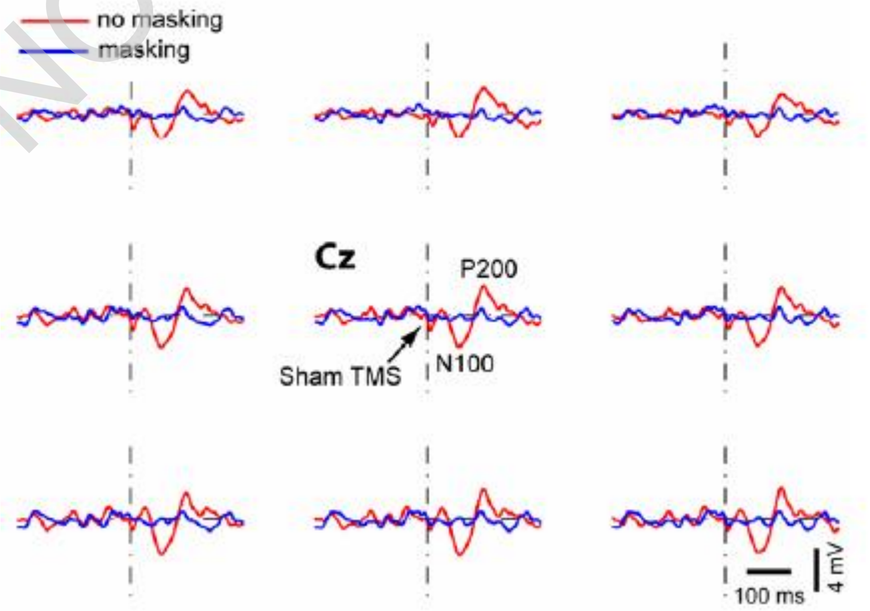
Air & Bone Conducted



Nikouline 1999

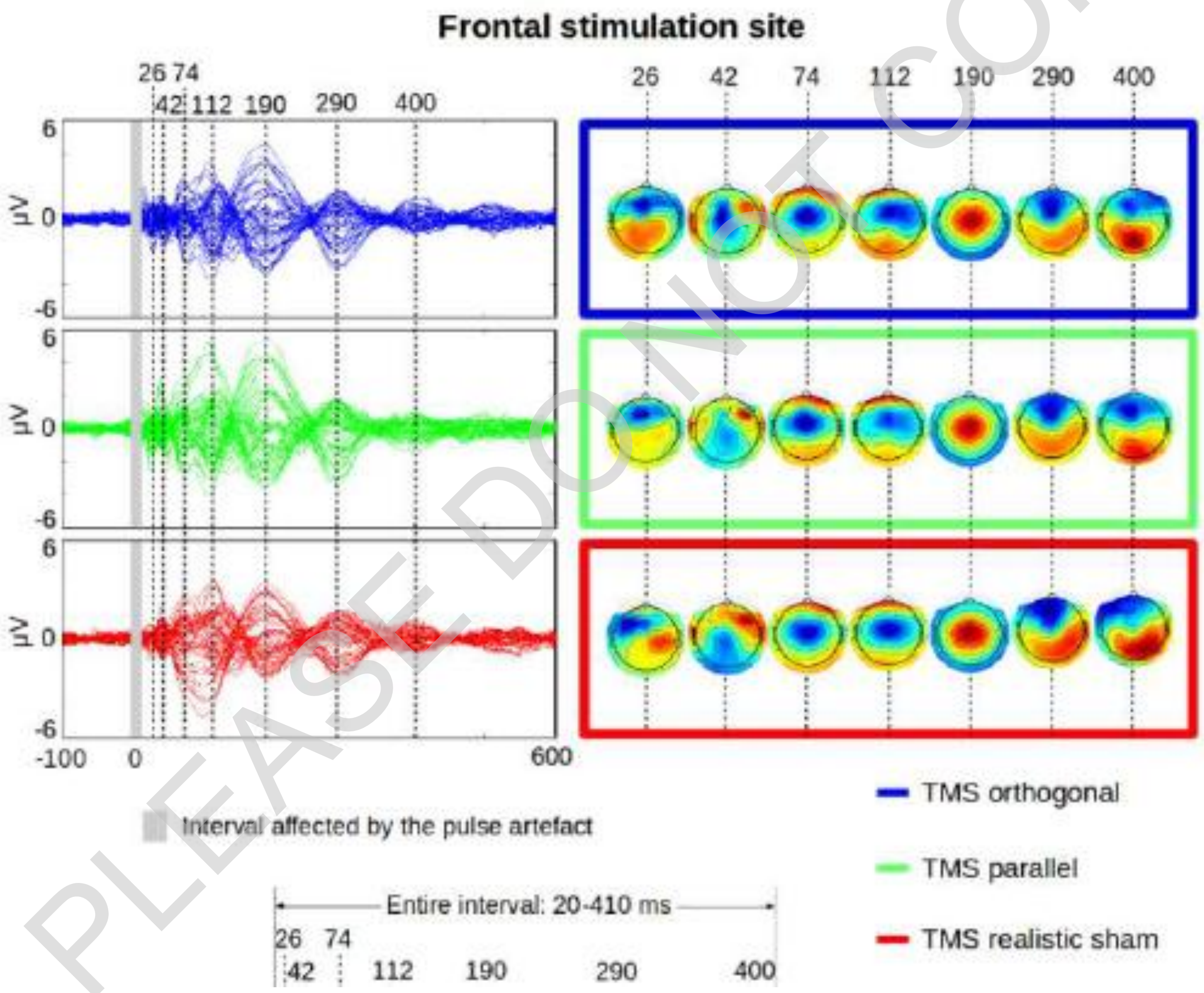
Some Solutions

Auditory masking with a frequency matched to the spectrum of the TMS click



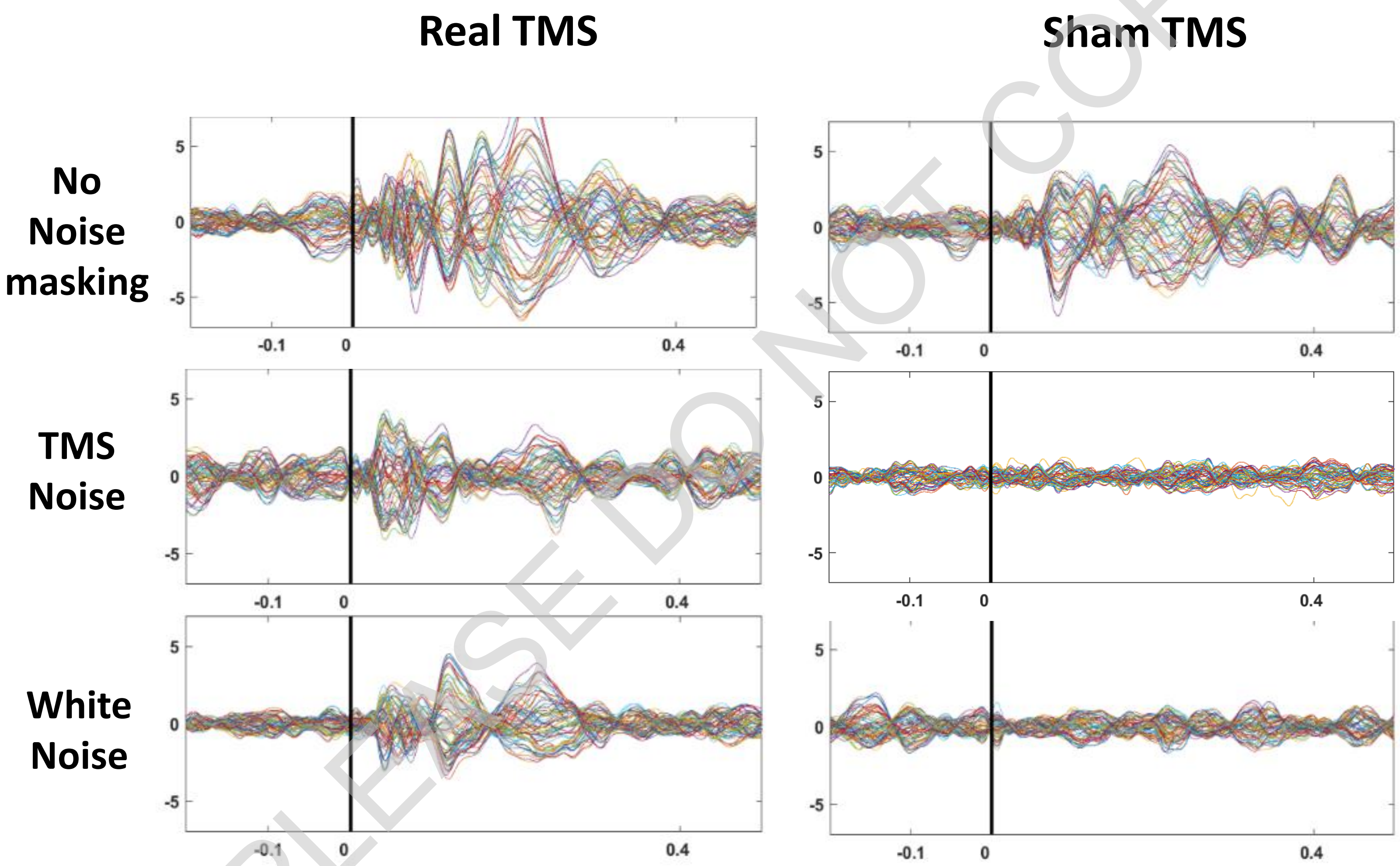
Massimini 2005

TMS sound: Auditory Evoked Potentials (AEPs)



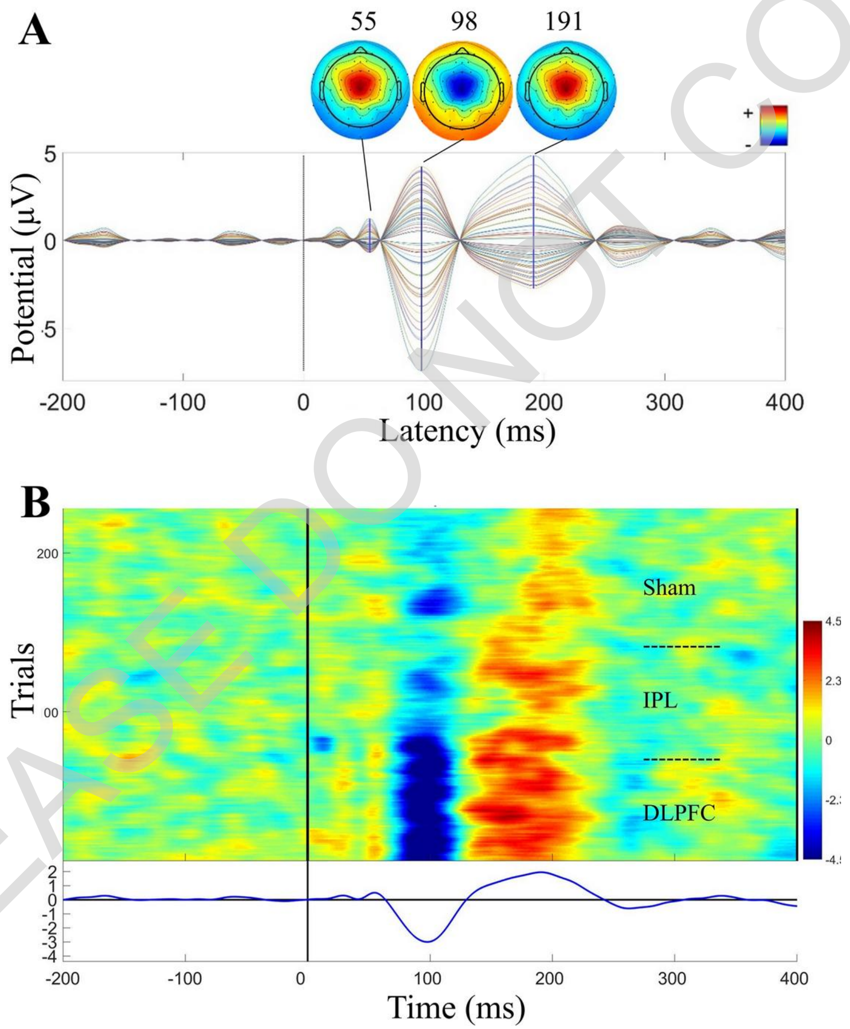
Conde 2019 Neuroimage

Auditory Noise for AEP removal



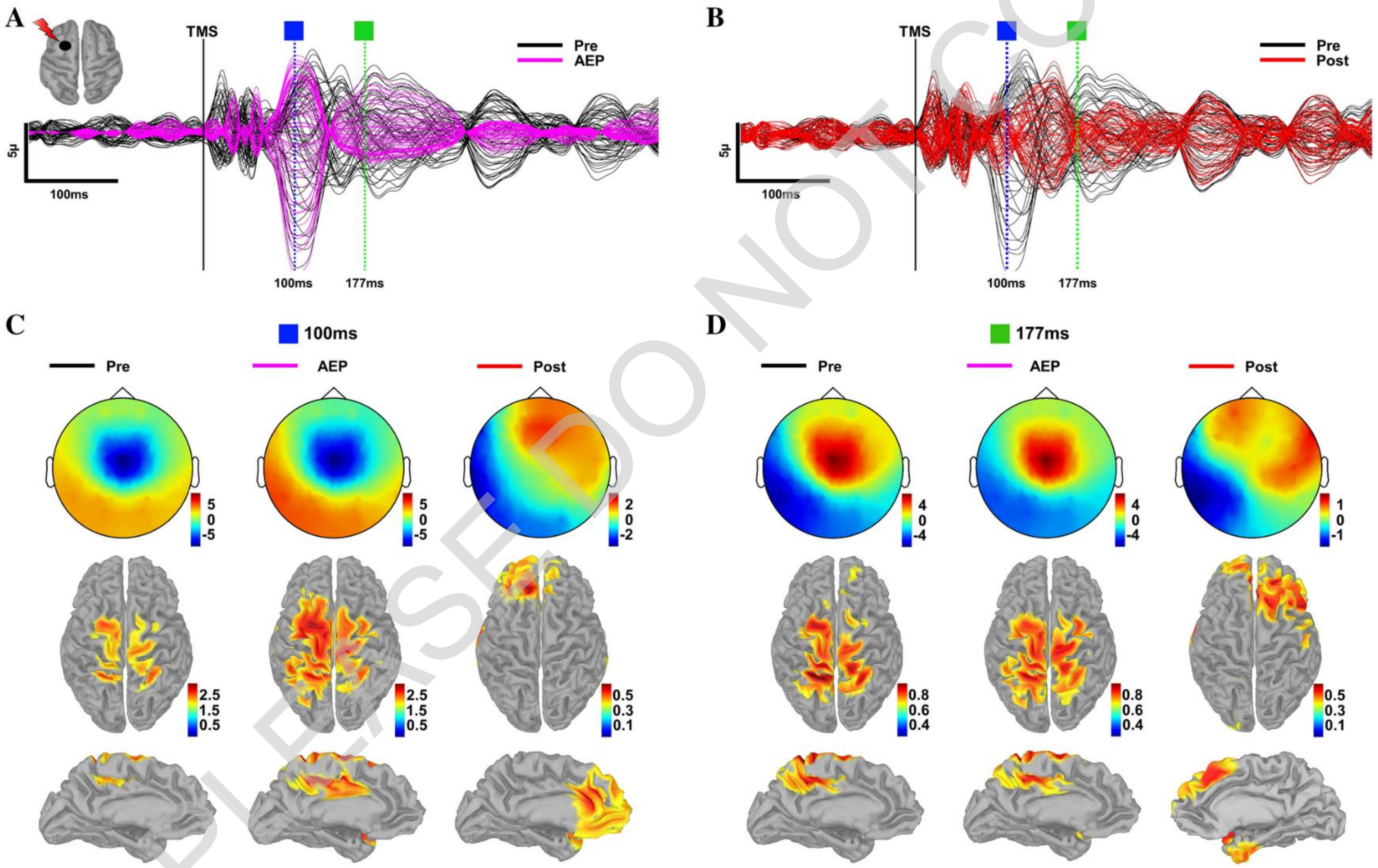
In house data

Sham informed ICA for AEP removal



Ross et al, Scientific Reps, 2022

Sham informed ICA for AEP removal



Ross et al, Scientific Reps, 2022

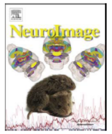
TMS-EEG preprocessing Tools

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

ELSEVIER



Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software

Nigel C. Rogasch[a,*], Caley Sullivan[b], Richard H. Thomson[b], Nathan S. Rose[c], Neil W. Bailey[b], Paul B. Fitzgerald[b], Faranak Farzan[d], Julio C. Hernandez-Pavon[e]

[a] Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Australia
[b] Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University, Australia
[c] Department of Psychology, University of Notre Dame, USA
[d] Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto, Canada
[e] Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, Espoo, Finland

frontiers in Neural Circuits

METHODS
published: 07 October 2016
doi: 10.3389/fncir.2016.00078

TMSEEG: A MATLAB-Based Graphical User Interface for Processing Electrophysiological Signals during Transcranial Magnetic Stimulation

Sravya Atluri[1,2†], Matthew Frehlich[1,3†], Ye Mei[1], Luis Garcia Dominguez[1], Nigel C. Rogasch[4], Willy Wong[2,3], Zafiris J. Daskalakis[1,5] and Faranak Farzan[1,5]*

HUMAN BRAIN MAPPING

Received: 14 February 2017 | Revised: 29 October 2017 | Accepted: 14 December 2017

DOI: 10.1002/hbm.23938

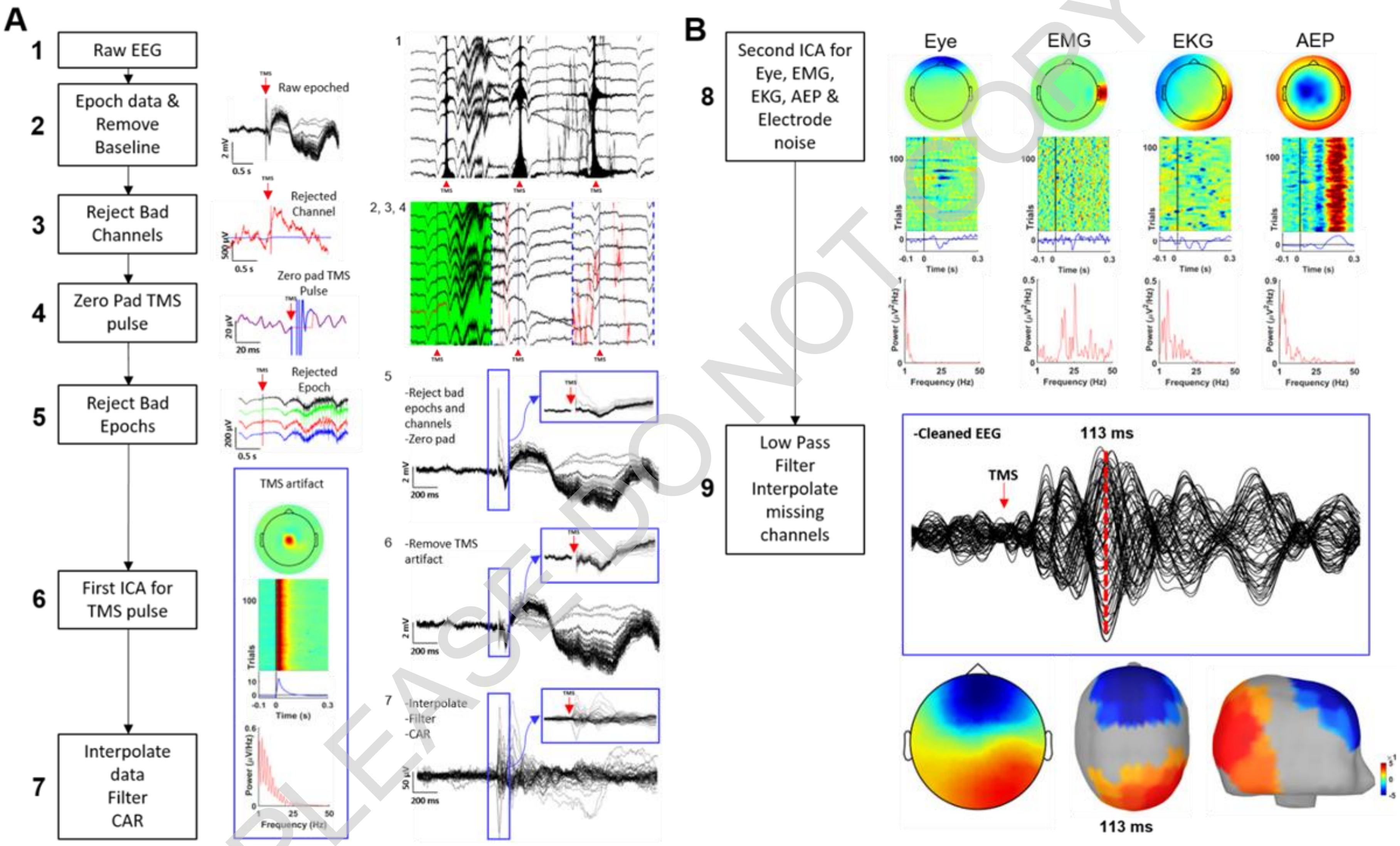
RESEARCH ARTICLE

WILEY

ARTIST: A fully automated artifact rejection algorithm for single-pulse TMS-EEG data

Wei Wu[1,2,3,4] | Corey J. Keller[1,2,3] | Nigel C. Rogasch[5] | Parker Longwell[1,2,3] | Emmanuel Shpigel[1,2,3] | Camarin E. Rolle[1,2,3] | Amit Etkin[1,2,3]

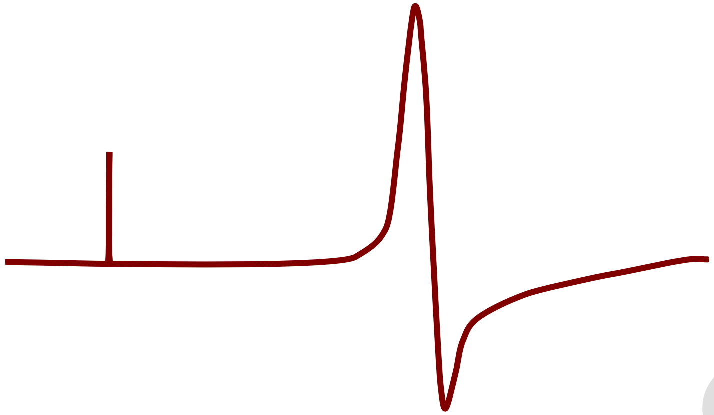
Our Pipeline



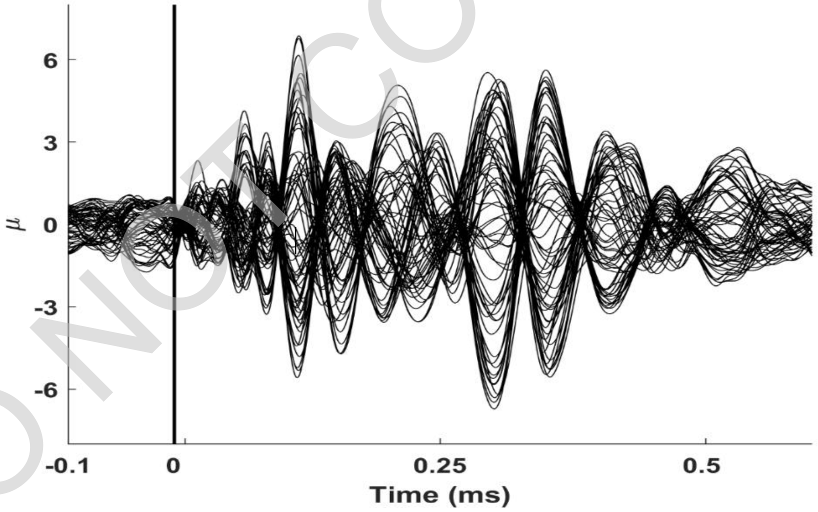
Ozdemir et al, PNAS, 2020

Is it worth the trouble?

MEPs



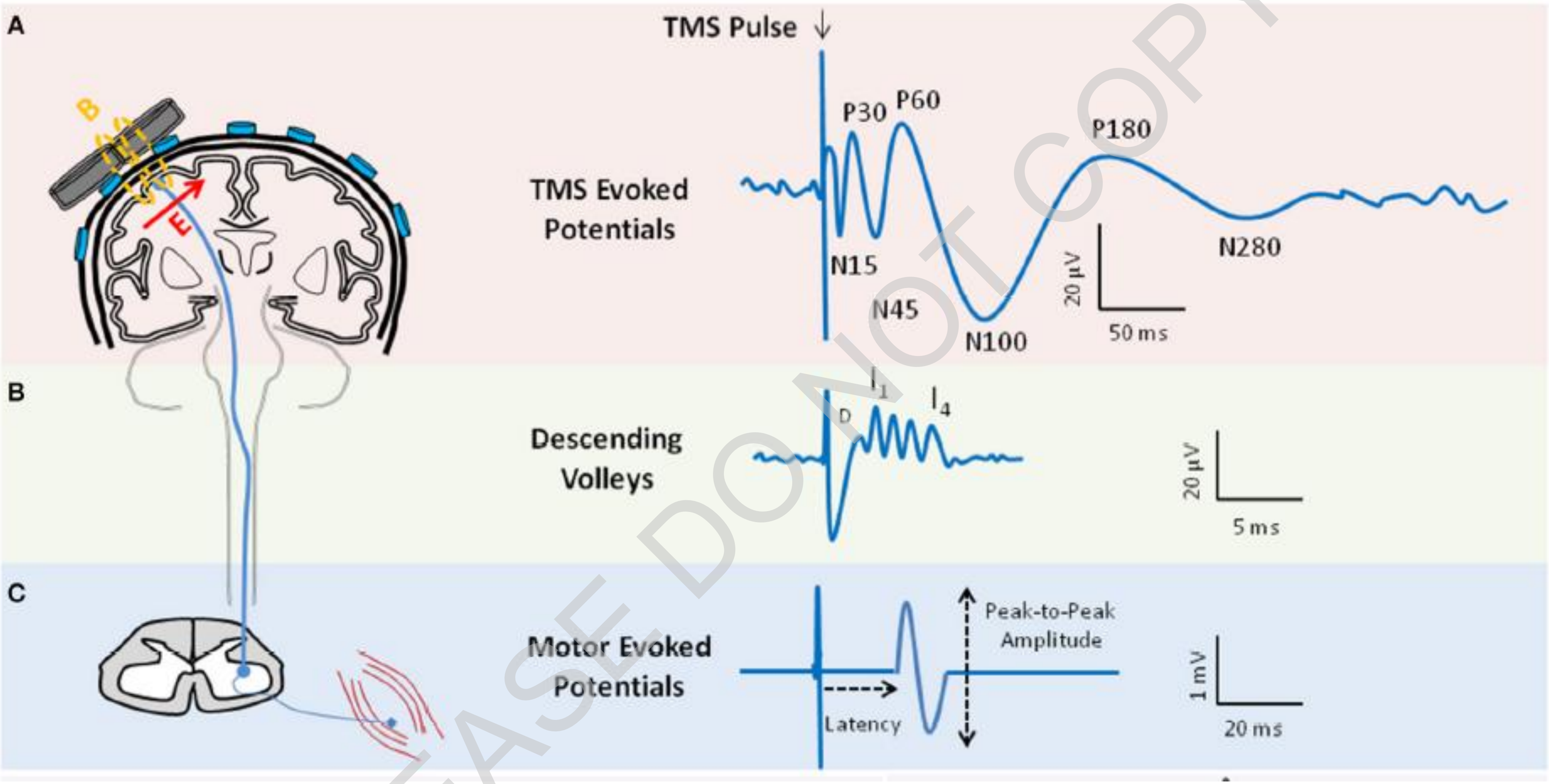
TEPs



- Rich temporal and spatial and oscillatory information.

- *But it comes with a price!!!*
    - *More time, expense, and technical expertise.*

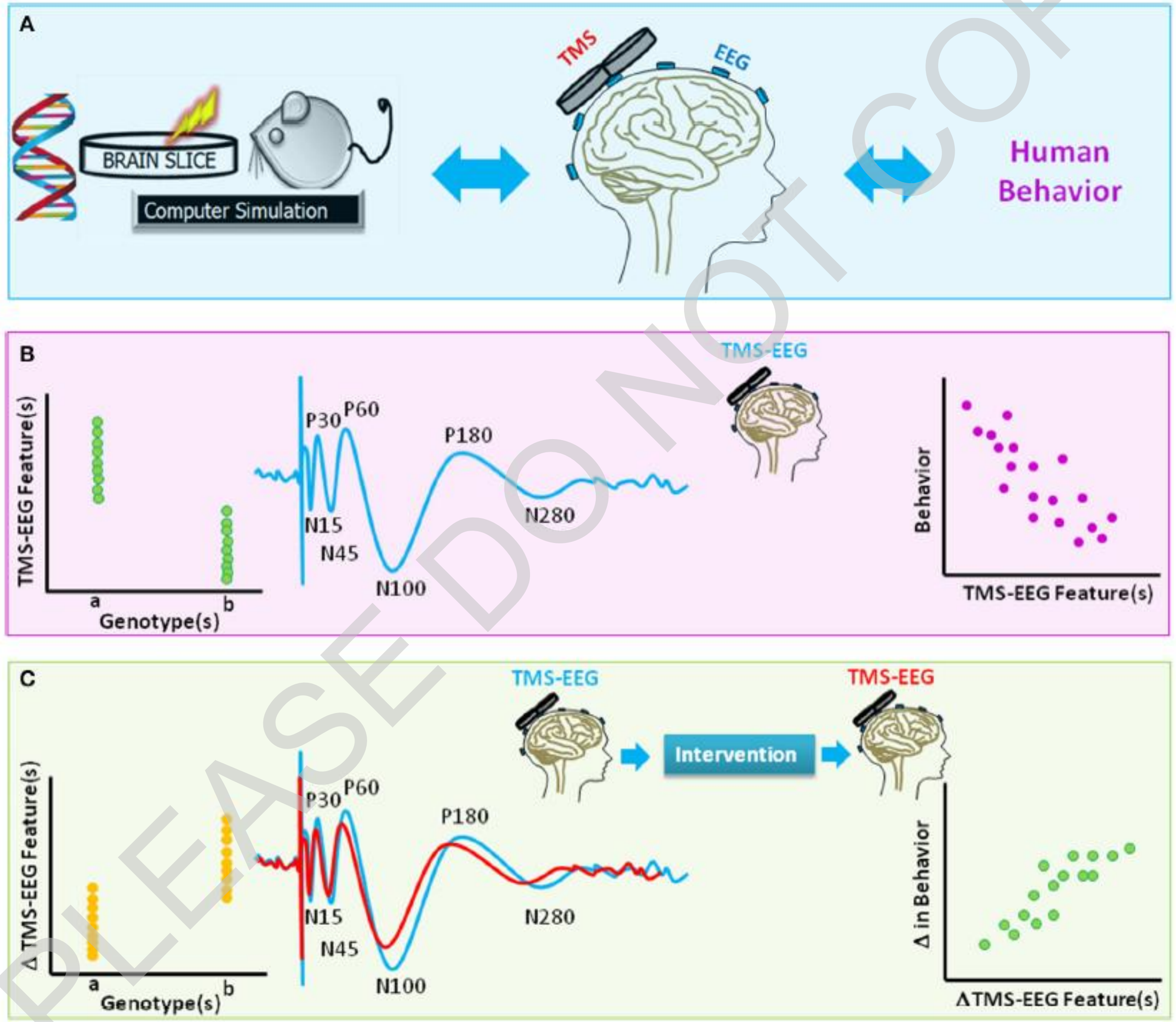
What is the added value?



Examine the TMS effect more directly & understand brain physiology *in vivo*

Farzan 2016 Frontiers Neural Circuits

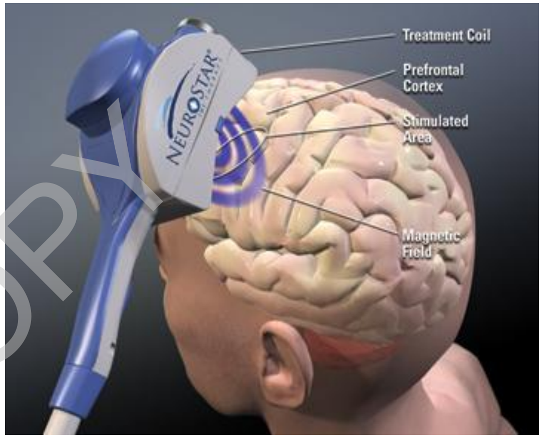
And understand relationship between brain and behavior



Farzan 2016 Frontiers Neural Circuits

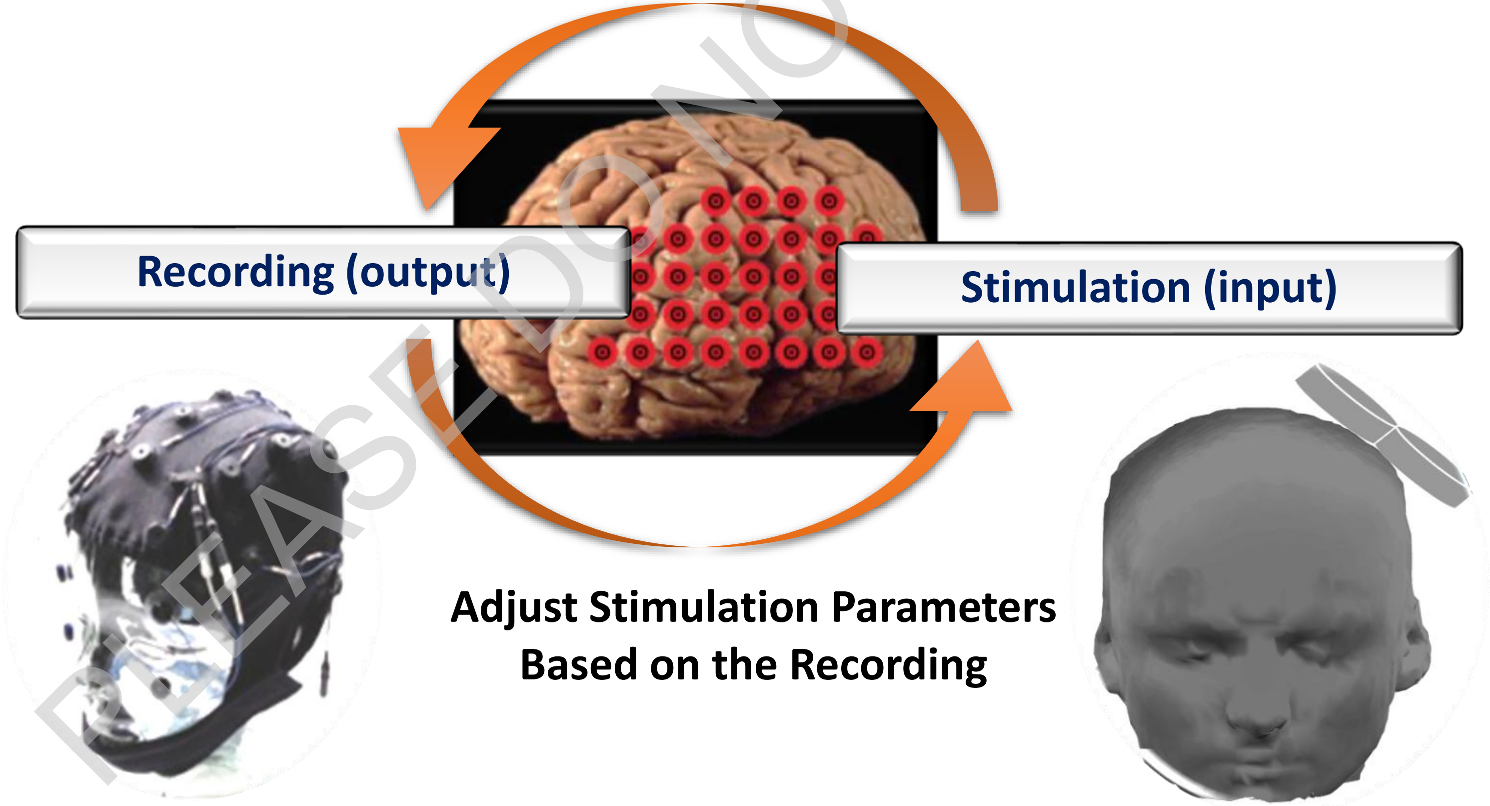
And …

EEG-gated TMS!



Manual Adjustment

Concurrently Stimulate & Record



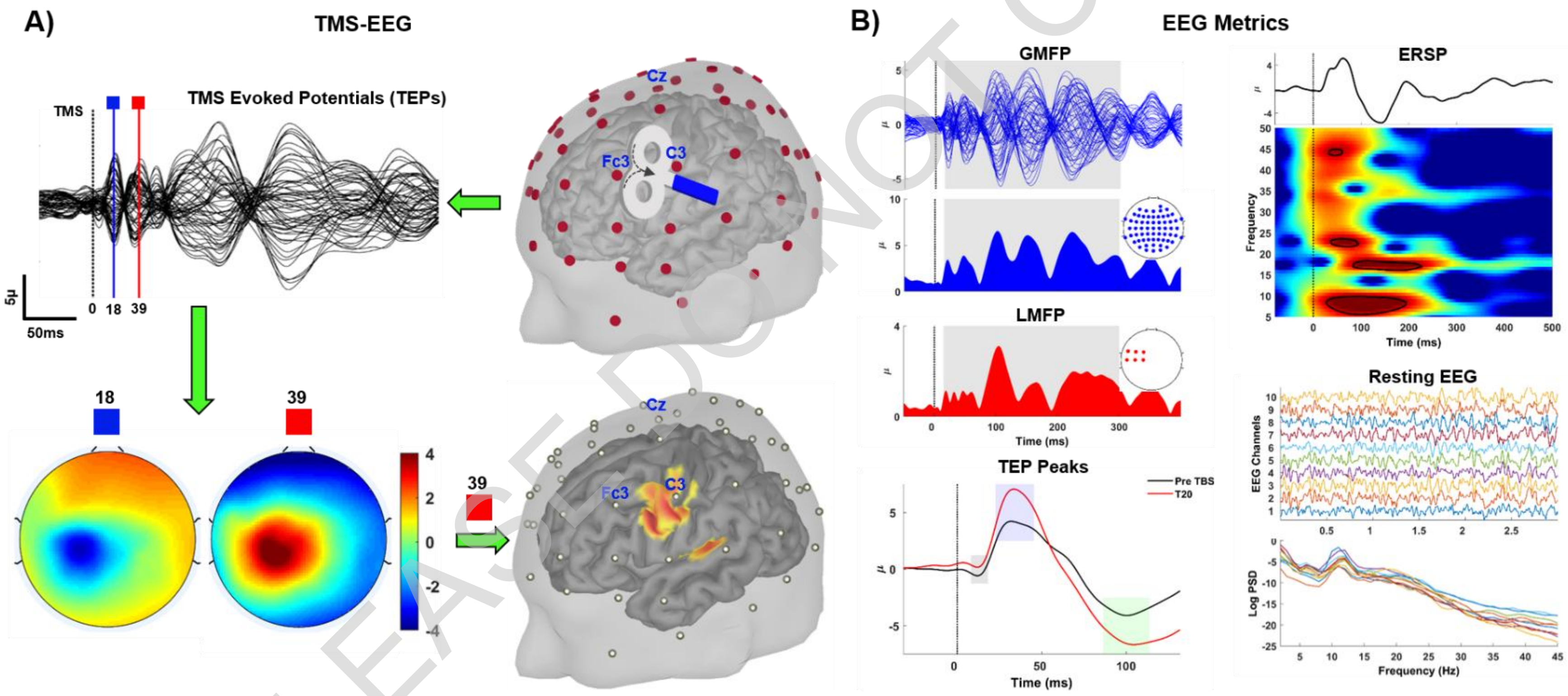
Adjust Stimulation Parameters Based on the Recording

Talk Overview

- Intro to TMS and EEG
  - What does EEG measure and TMS generate/activate in the brain!!!
- Technical issues and challenges
  - EEG compatibility
  - Artifacts, artifacts and artifacts!!!
- Neuroscience Applications of TMS-EEG
- Clinical Applications of TMS-EEG
  - Diagnosis
  - Monitoring
  - Targeting

Single Pulse TMS-EEG

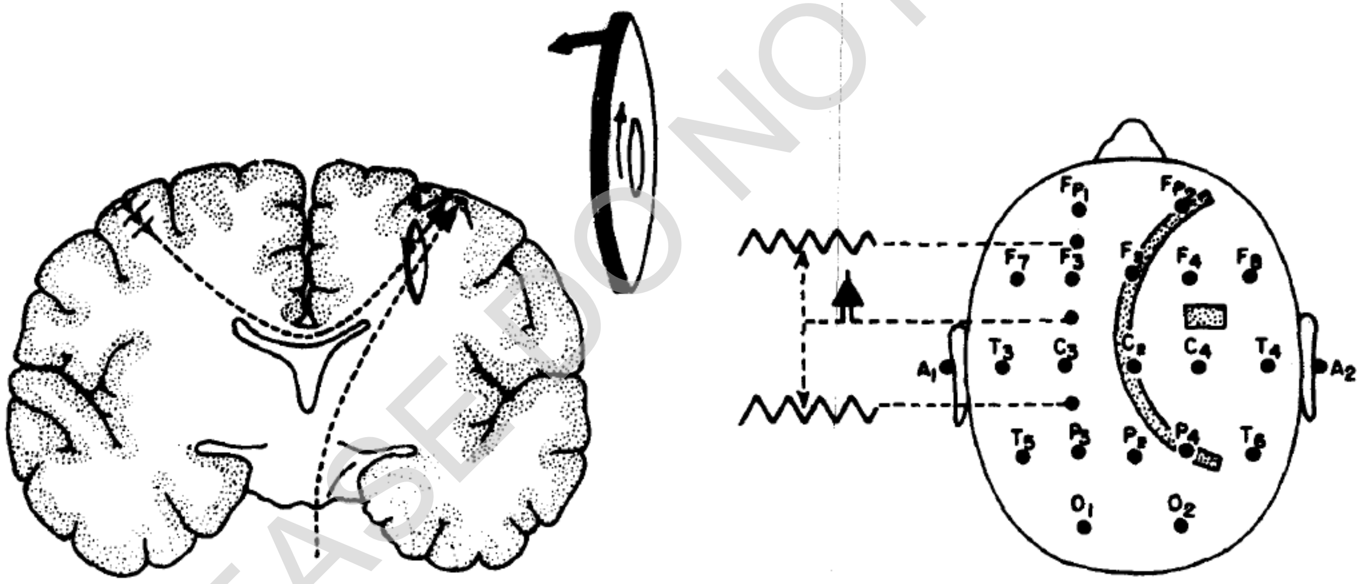
- TMS evoked EEG potentials (TEPs)



Transcallosal Transfer Time in Motor Cortex

Giving Credit to the First Published TMS-EEG Attempt

In **1989**, Cracco et al., examined transcallosal responses by applying TMS to one side and recording EEG from the other side (8.8–12.2 msec)



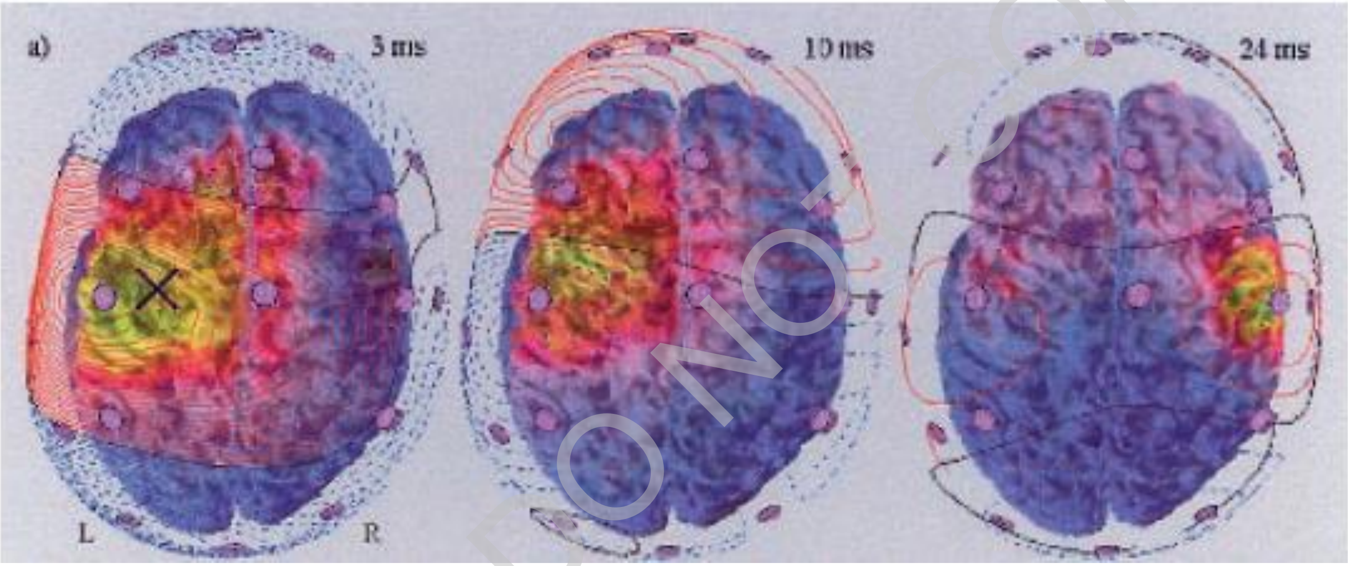
Artifact reduced by adjusting the arrangement between the coil and the electrode and placing a steel strip ground electrode in between the coil and the recording electrodes

Before Fancy Amplifiers!! Cracco et al., 1989, Electroencephalogr Clin Neurophysiol

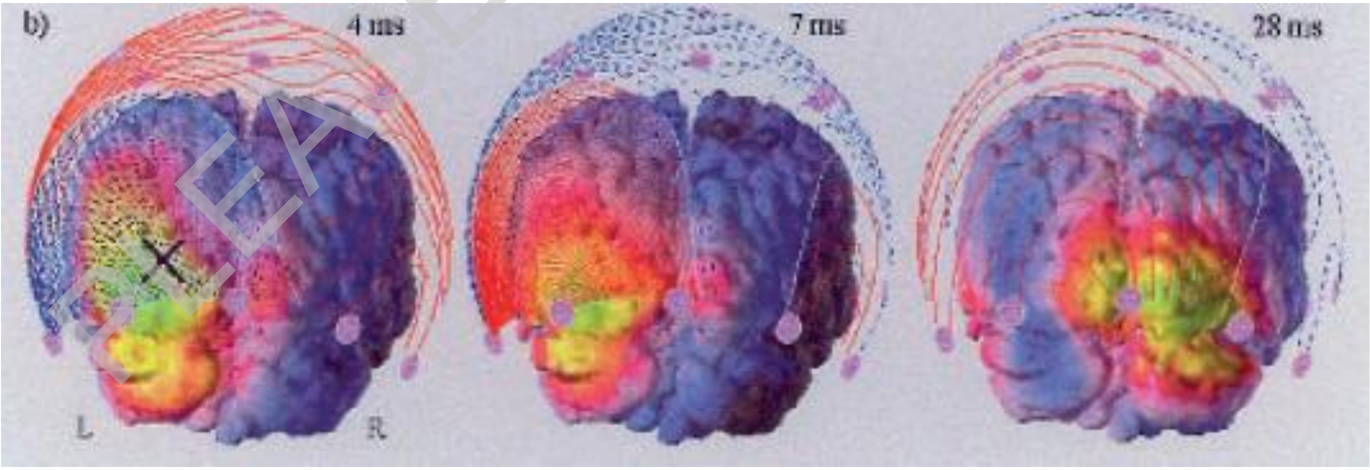
Temporal Evolution of early TEPs

Ilmomiemi et al., Neuroreport 1997

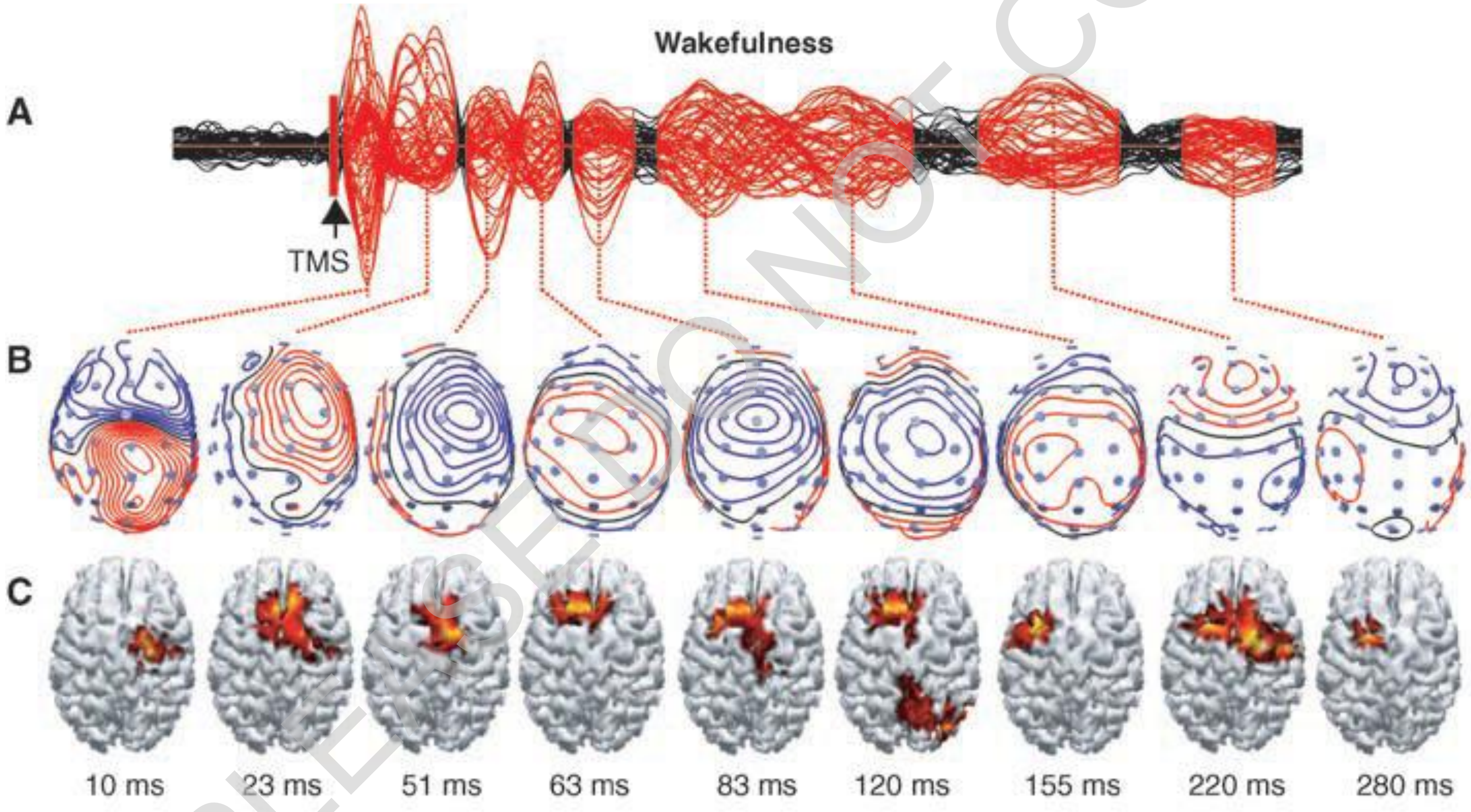
Motor Cortex



Visual Cortex

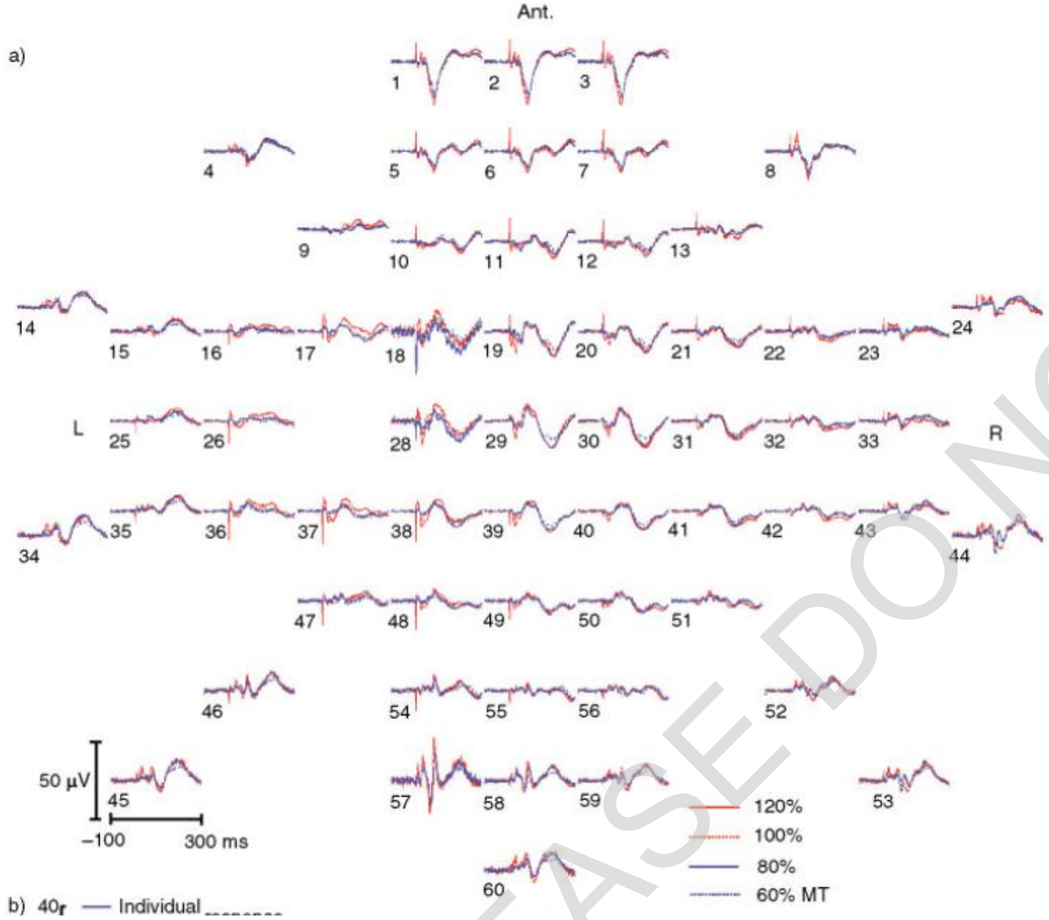


Temporal Evolution of early and late TEPs

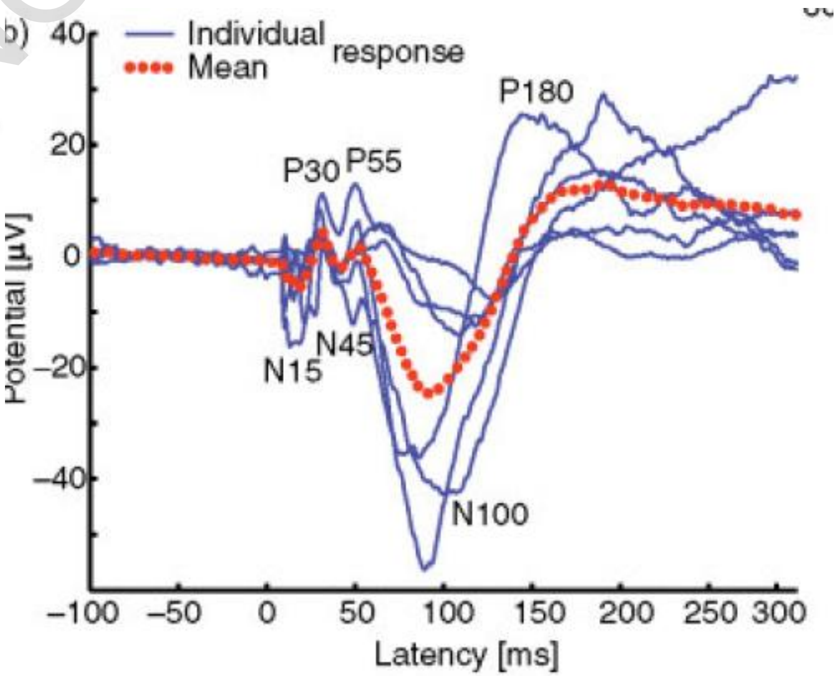


Massimini 2005

TMS Induces Several EEG Peaks, But….



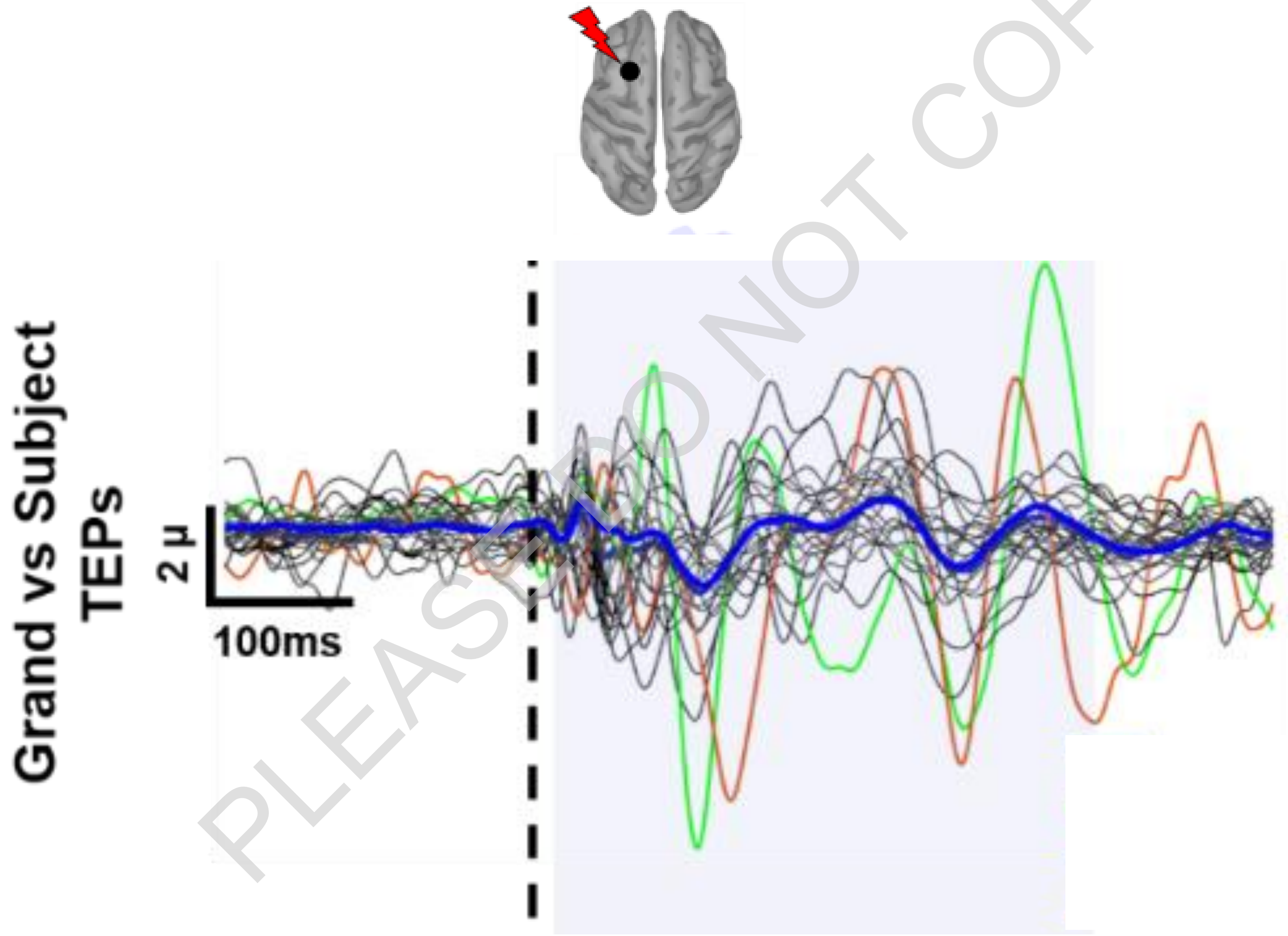
N15–P30; N45; P55; N100; P180



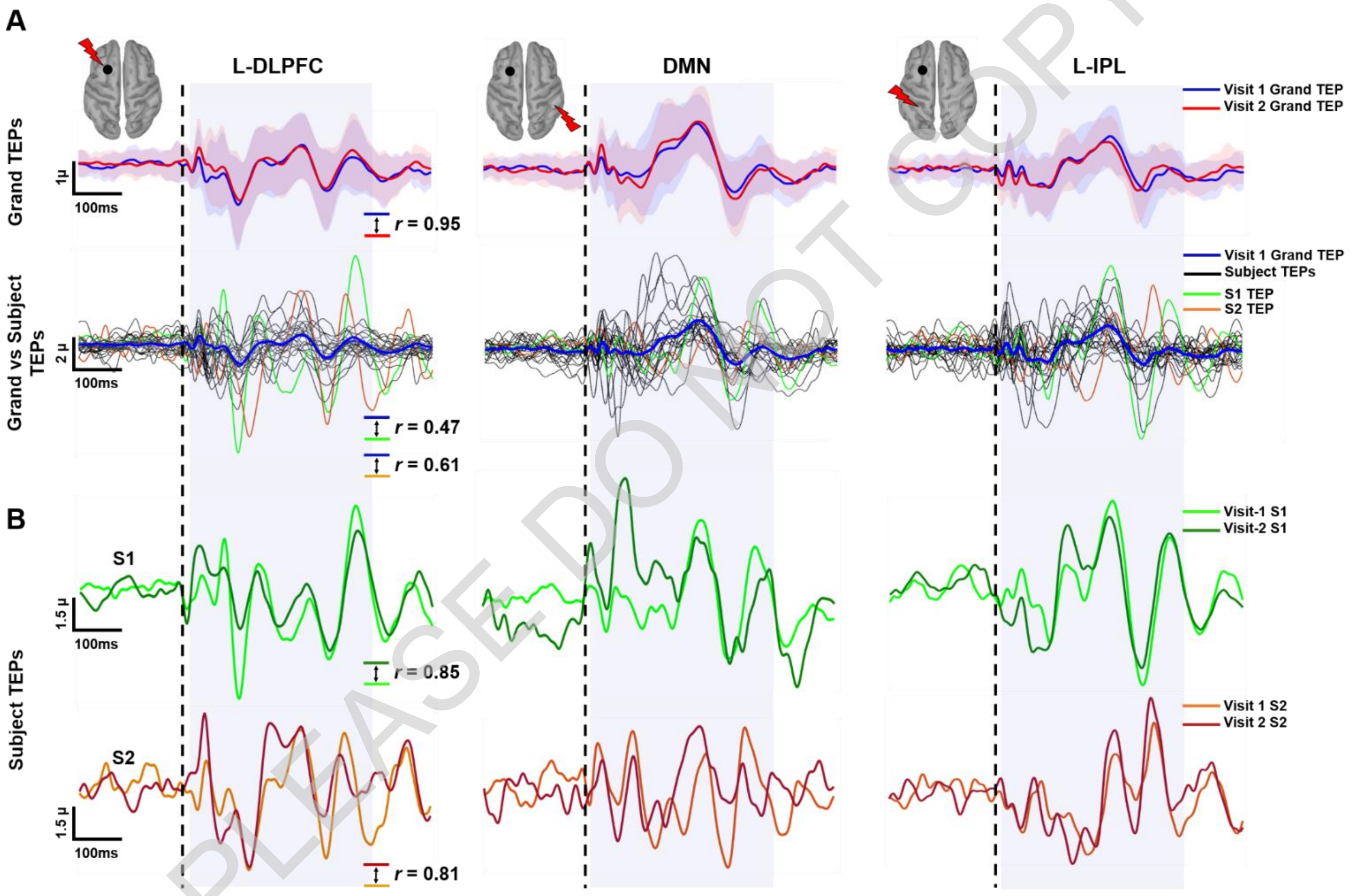
Komssi, Human Brain Mapping, 2004

Other Earlier or Later References: Paus 2001; Komssi, 2002; Ferreri 2010;

- **Be careful with TEP peaks outside the Motor cortex !!!**



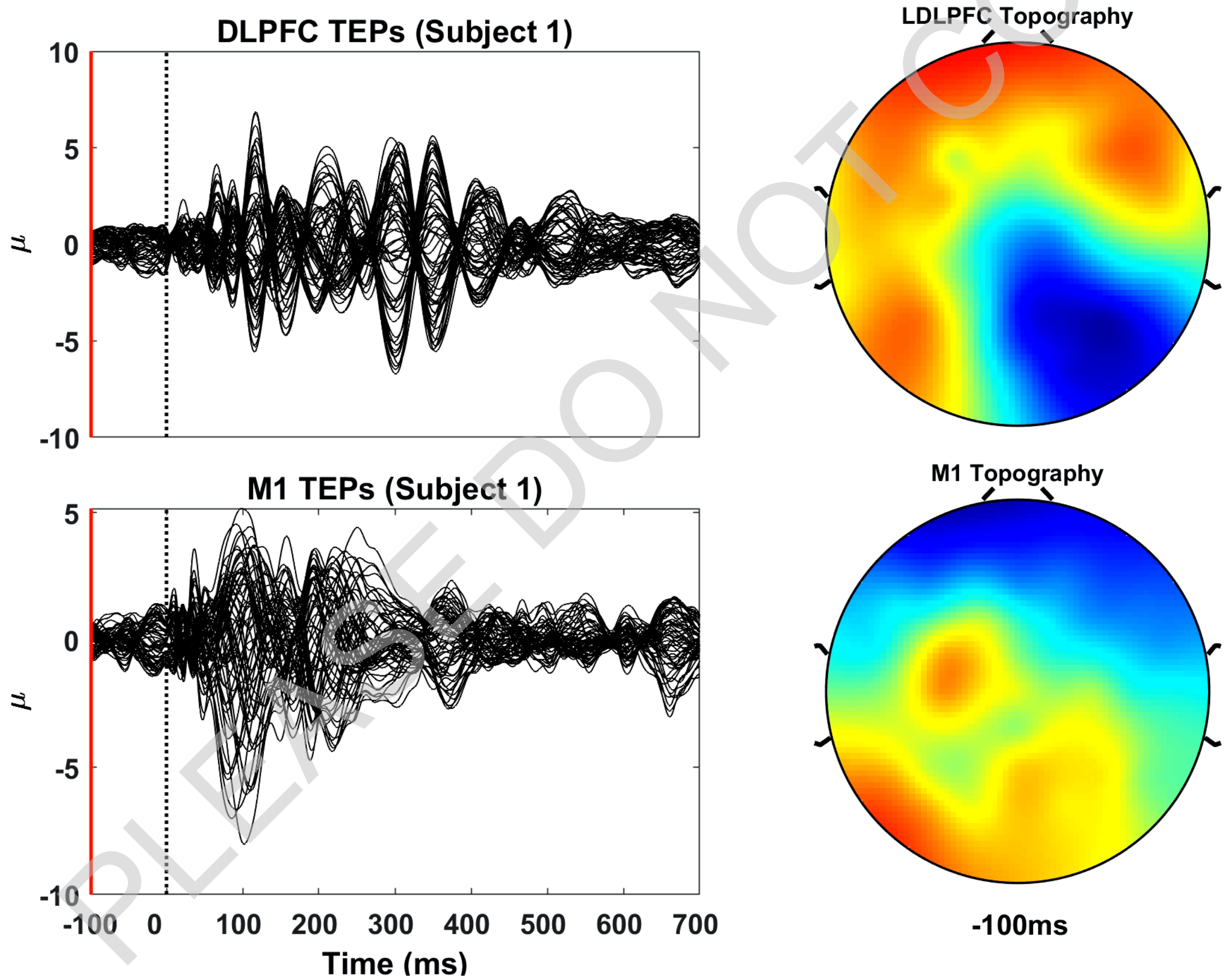
- **Characteristics of TEPs outside the Motor cortex !!!**



Ozdemir 2021 Brain Stimulation

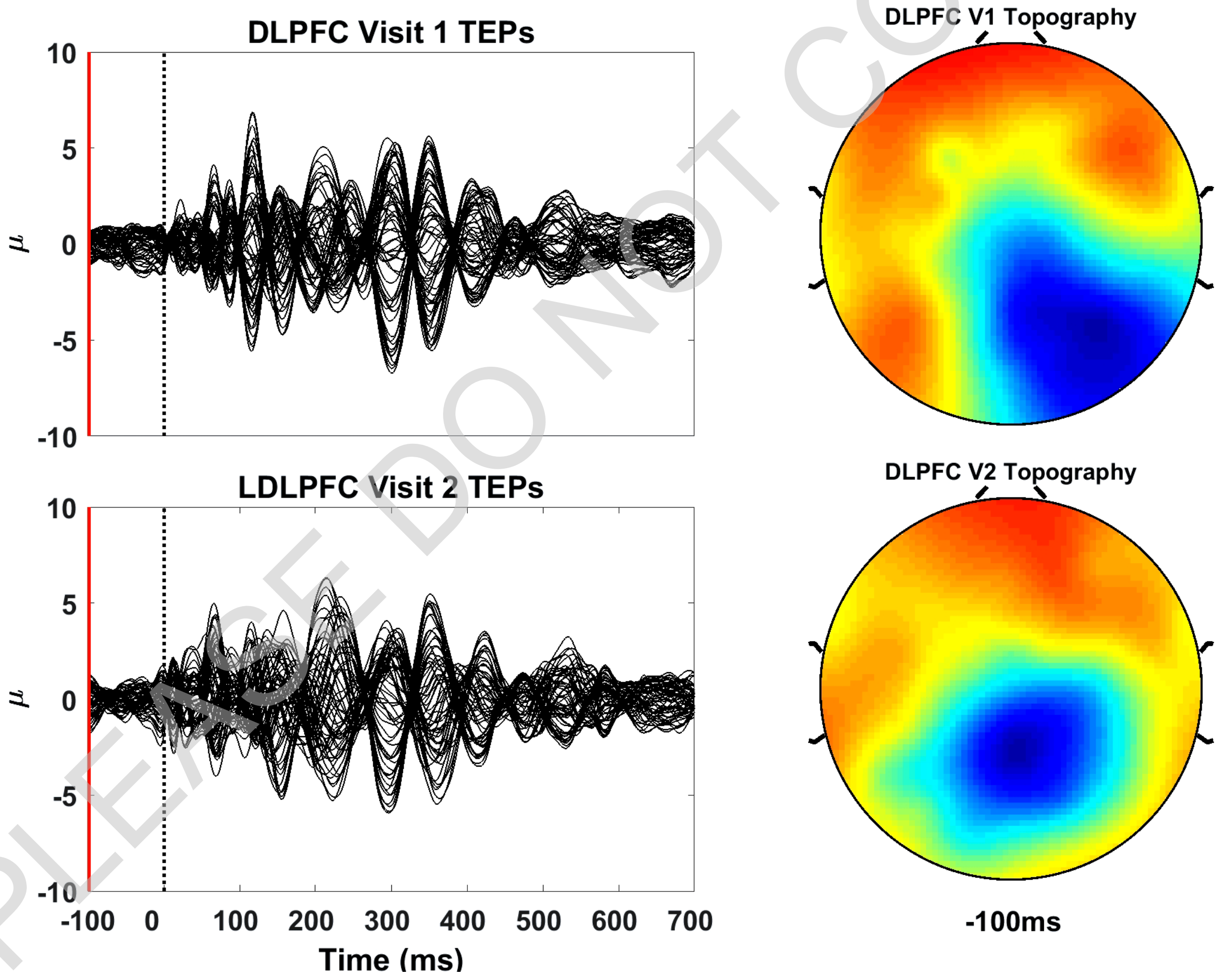
Site Specificity of TEPs

- TEPs are Specific to stimulation site

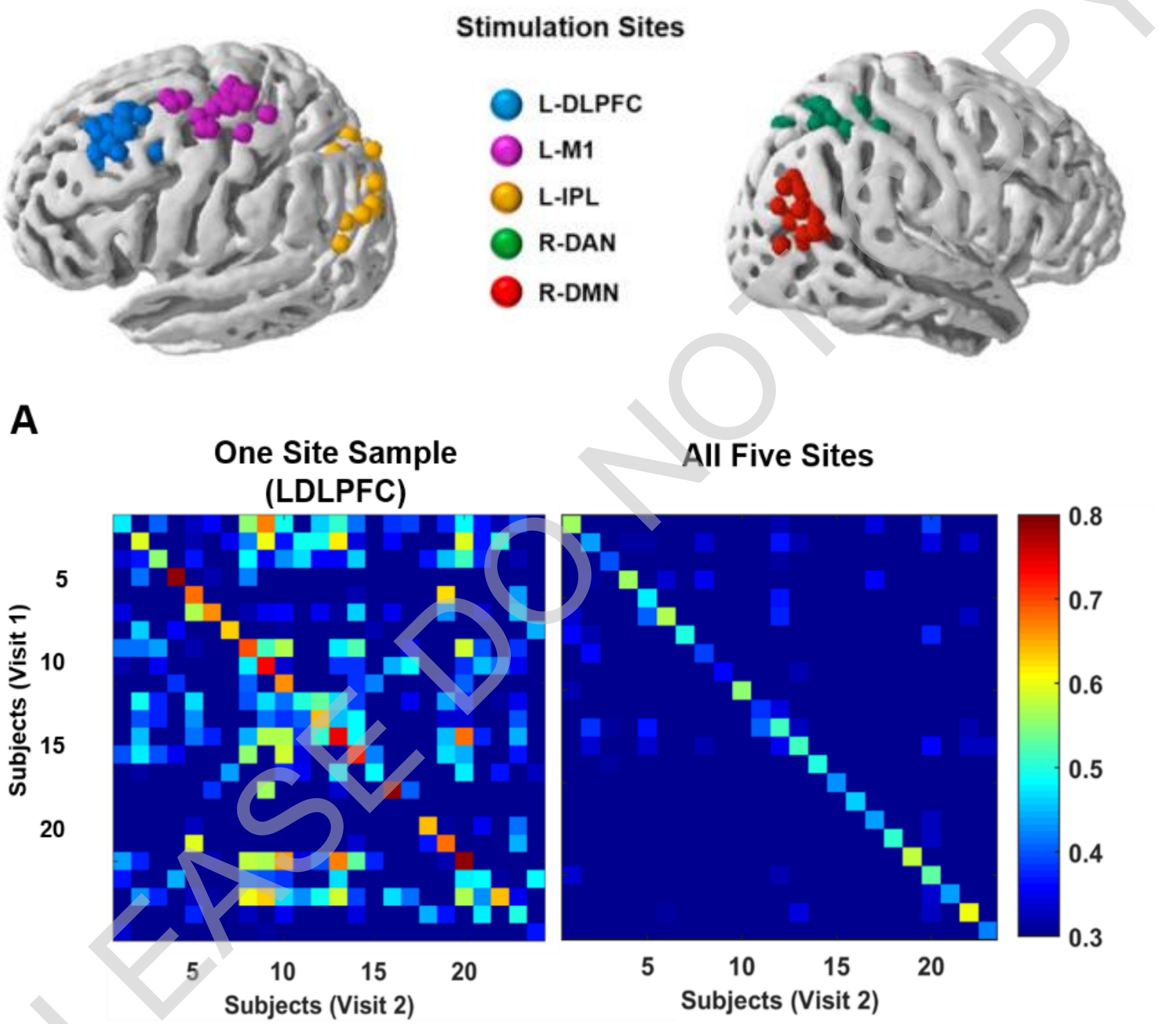


Individual Consistency

- TEPs are Reproducible within the Individual!

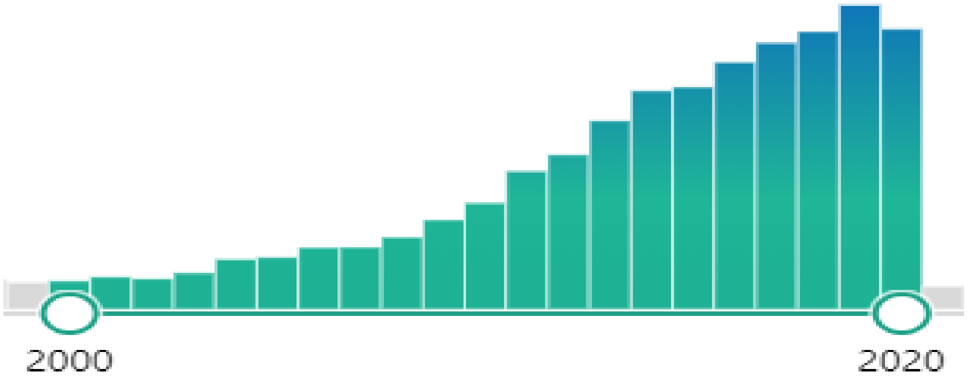


Brain Fingerprinting

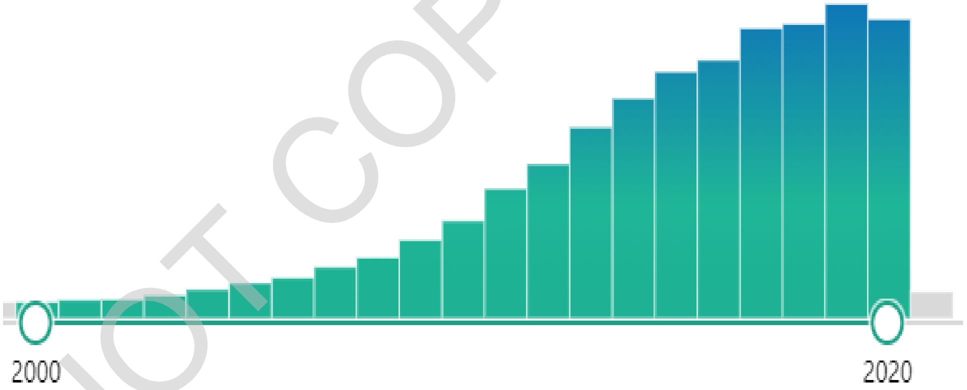


Ozdemir et al, 2021 Brain Stimulation

Brain connectivity analysis is exploding



M/EEG

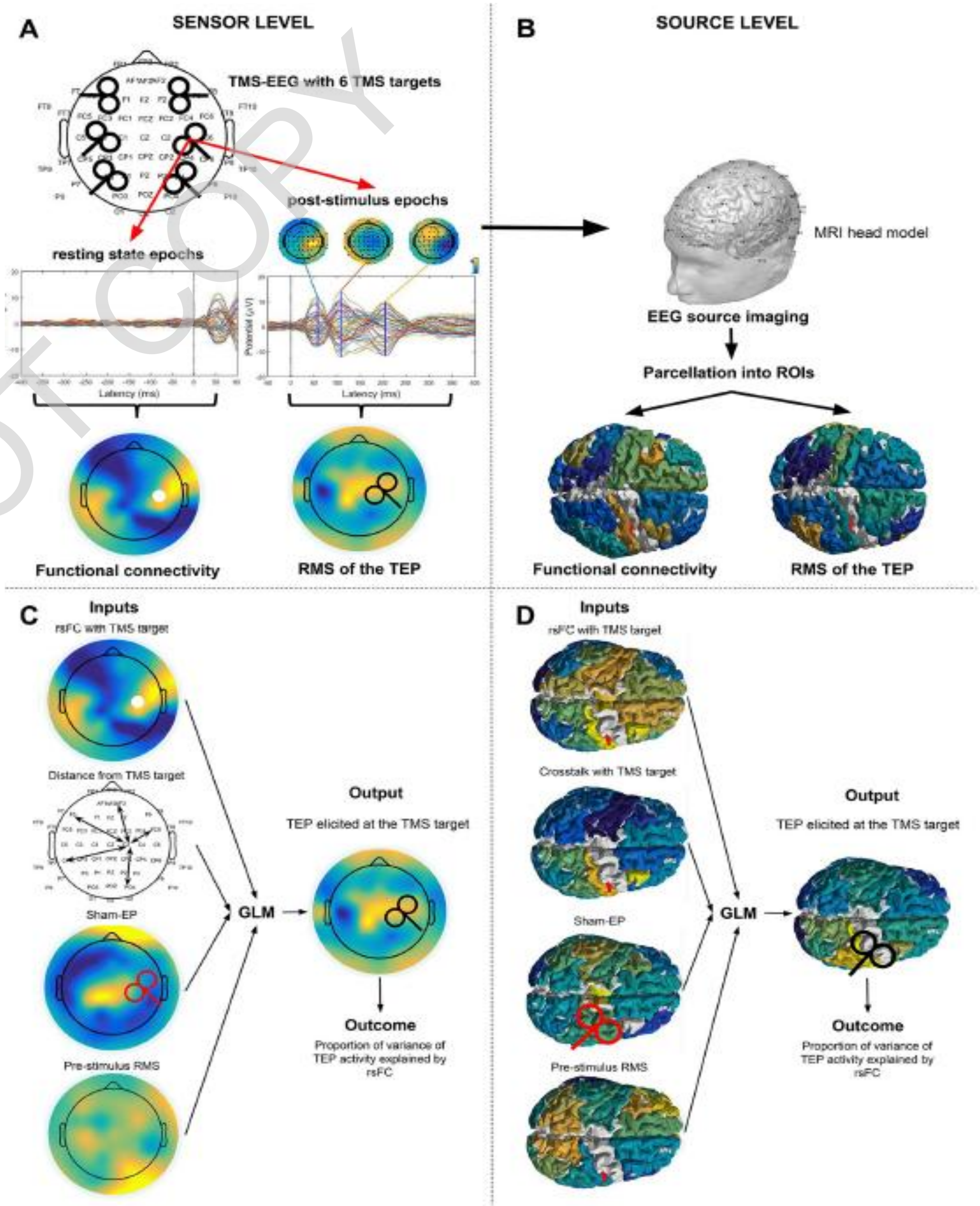


fMRI

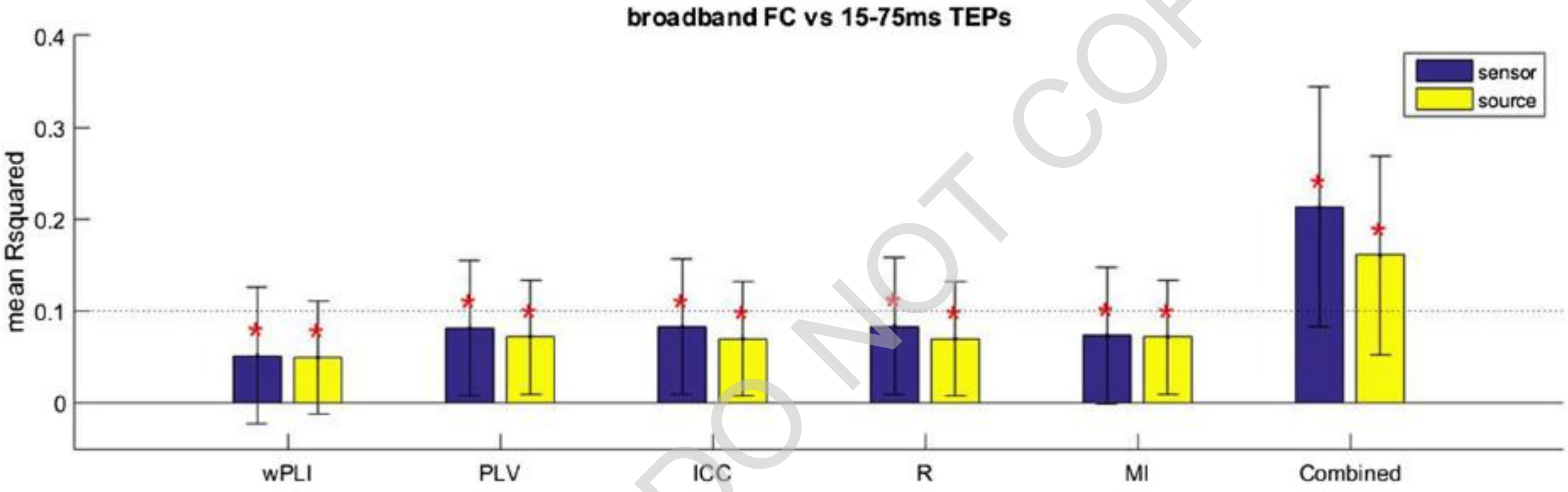
- Analysis of the human connectome has become a core goal of Neuroscience
  - NIH Human Connectome Project 2009 Blueprint Grand Challenge
  - 7332 EEG/MEG “connectivity” papers from 2000-2020
  - 27090 fMRI “connectivity papers”
  - A large number of these studies focus on “resting-state” “functional” connectivity
- Unanswered question: Do functional connectivity measures actually capture causal brain interactions? We can evaluate CAUSAL brain interactions with TMS and EEG

TMS-EEG to assess EEG connectivity?

- Vink 2020 *Brain Topography*: Assessed whether resting-state EEG functional connectivity predicted propagation of the TMS-evoked EEG potential

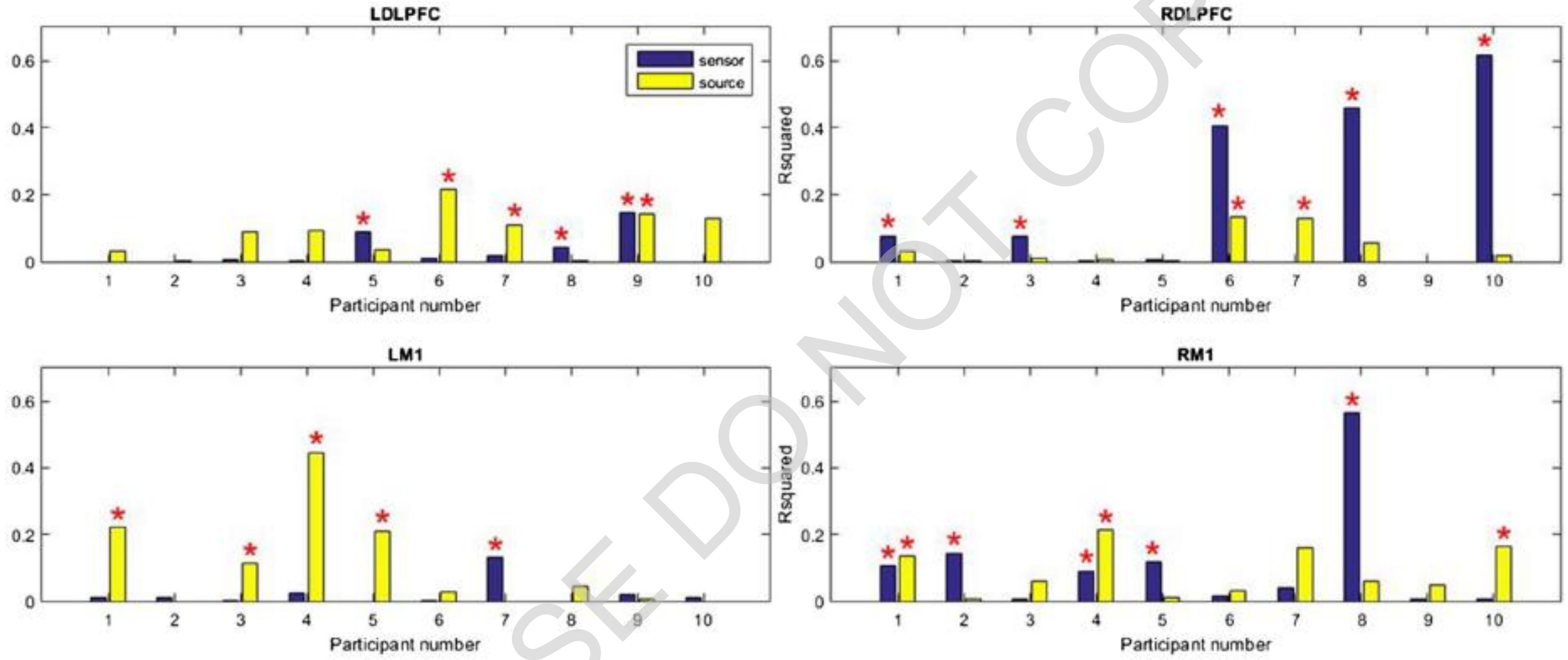


Does EEG connectivity predict propagation?



- All functional connectivity measures were only weak predictors of propagation of the TMS-EEG potential
  - True in both sensor and source space
  - Combination of information from multiple connectivity measures improved the predictive power of the model

Marked variability across subjects & sites

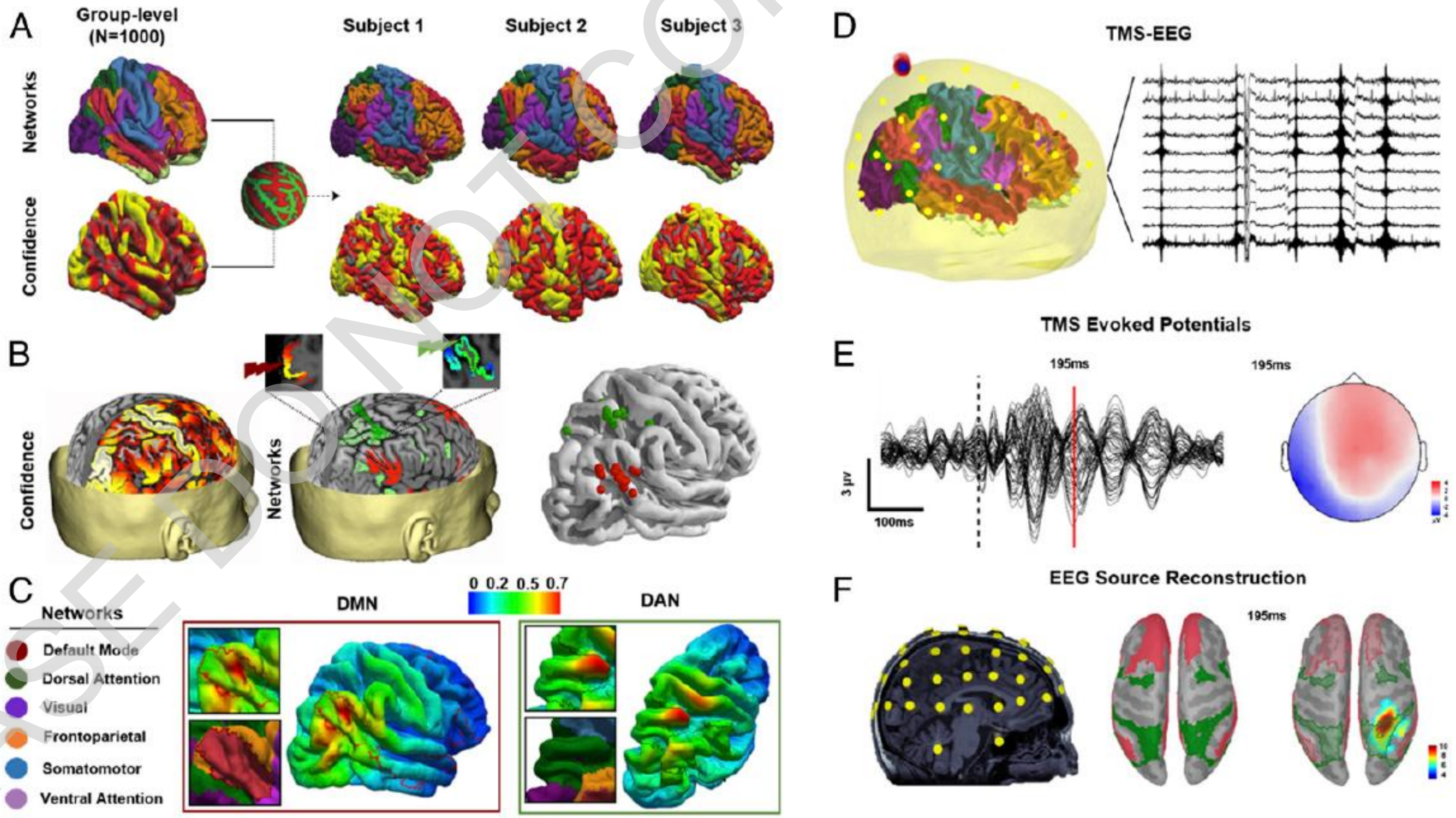


- Key takeaway: EEG connectivity is not a reliable predictor of propagation of evoked activity

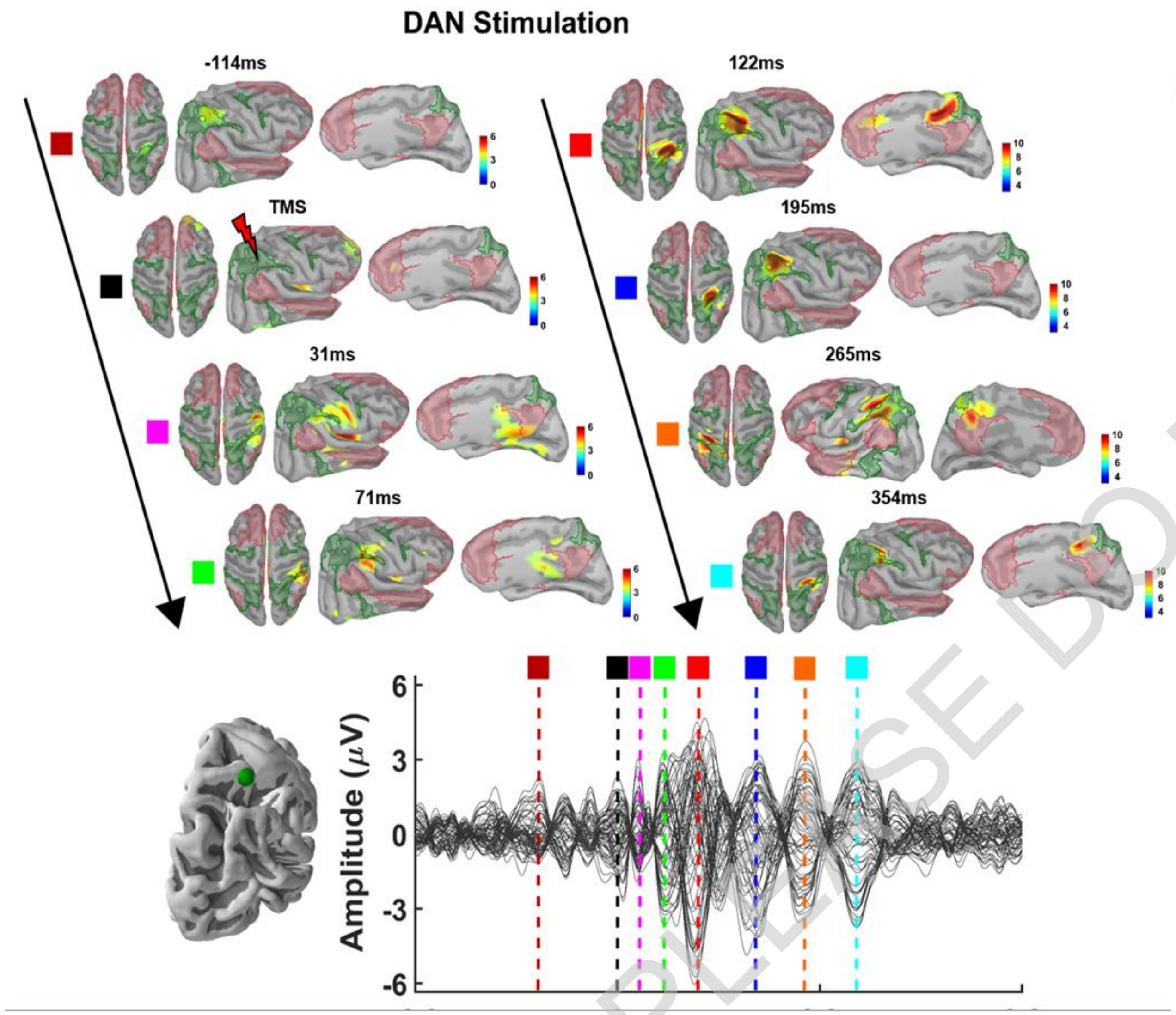
Vink 2020

What about resting-state fMRI connectivity?

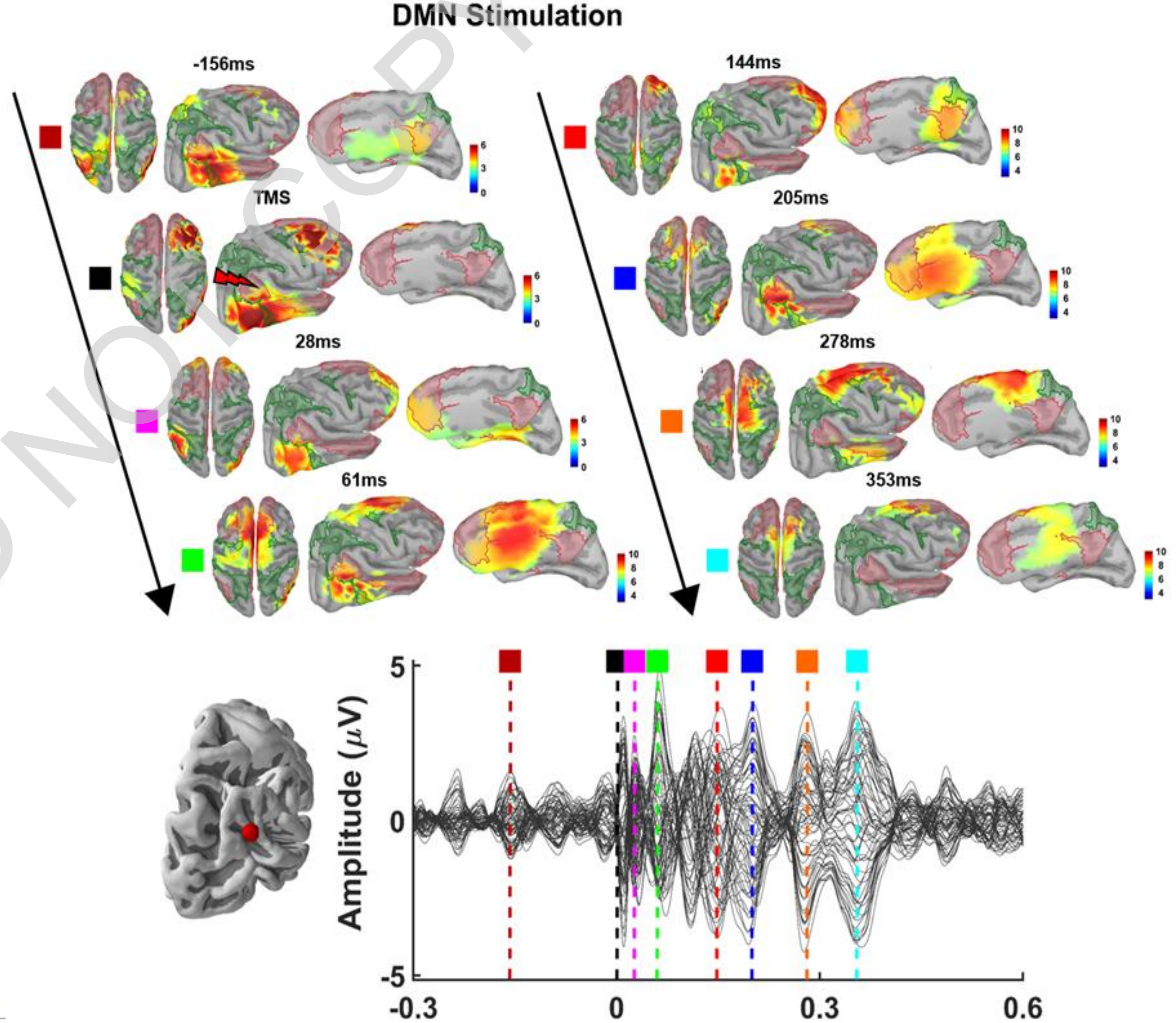
- Ozdemir 2020 *PNAS*: Assessed whether TMS to individually defined nodes of the default-mode network versus dorsal attention network produced network-specific brain dynamics
- Networks and targets identified based on group-level connectivity



Network Stimulation and Evoked Activity

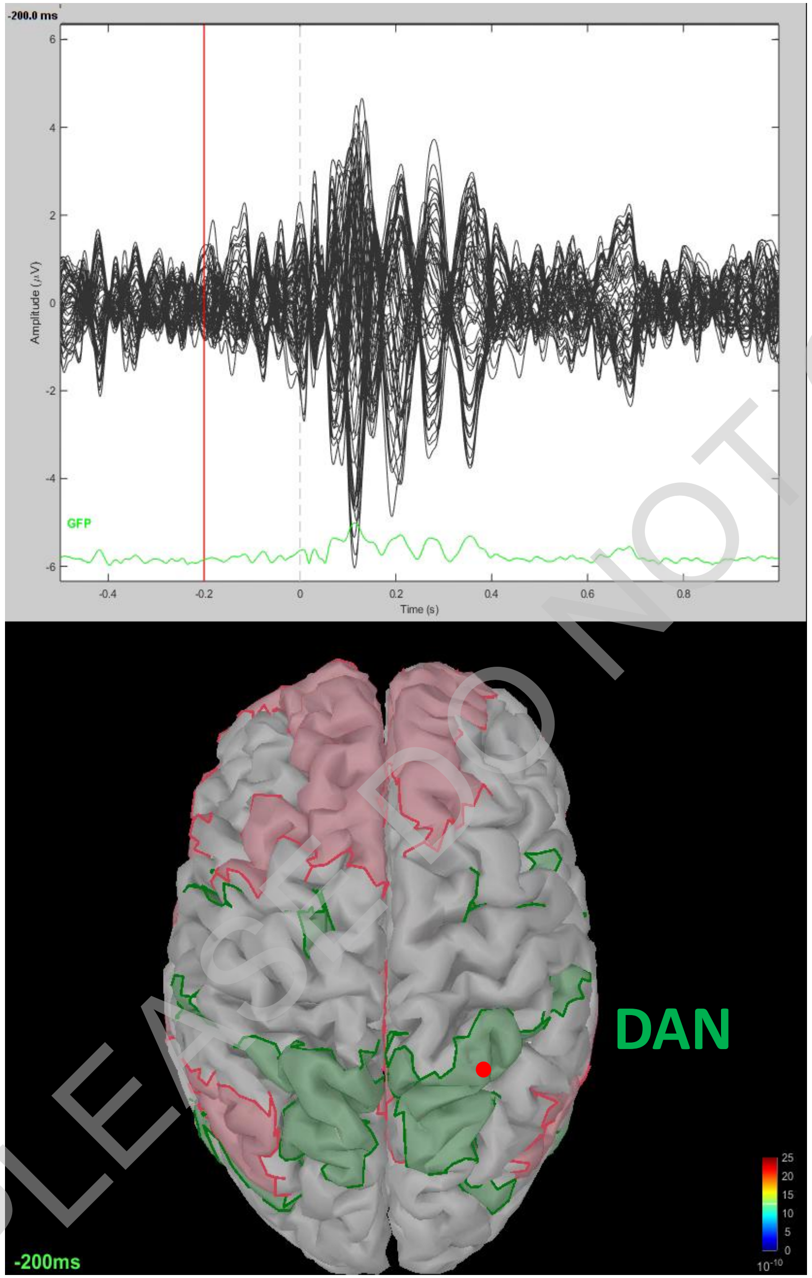


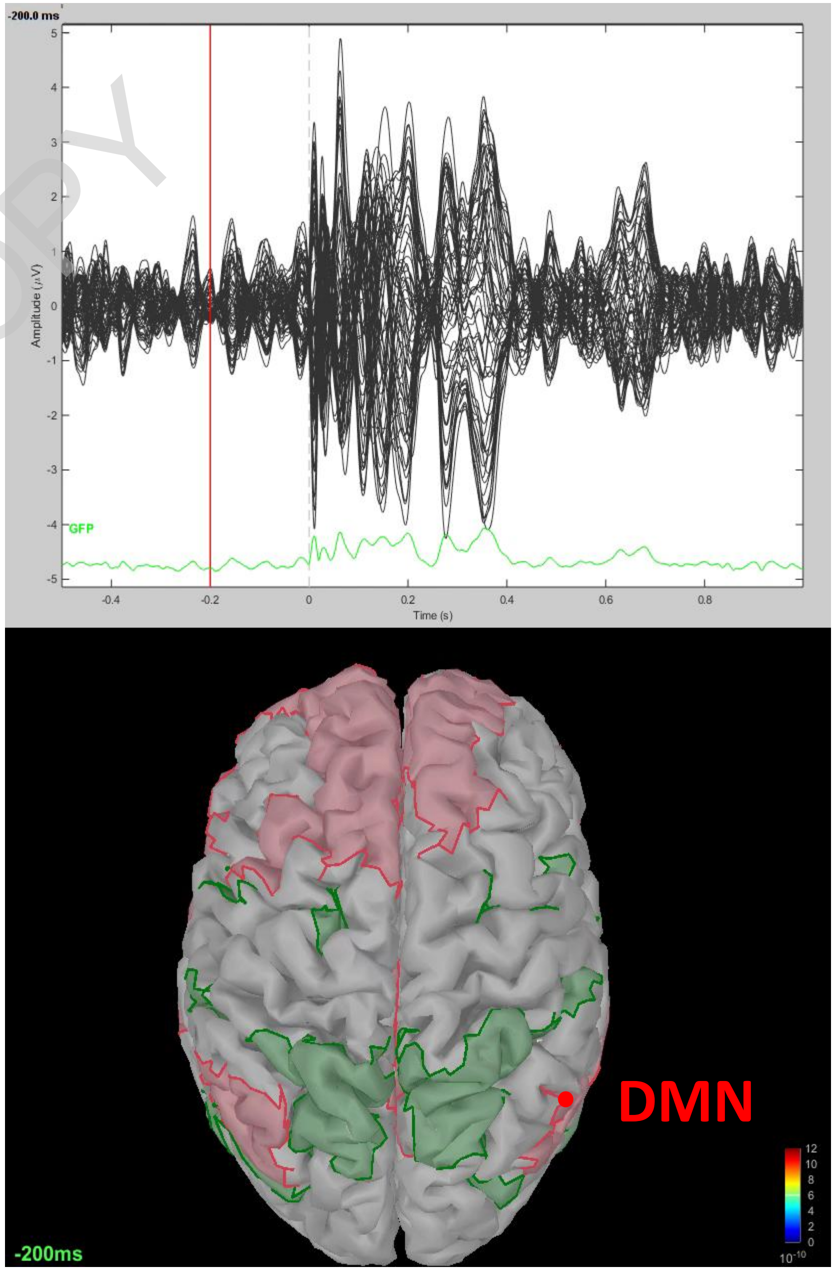
Ozdemir 2020 *PNAS*



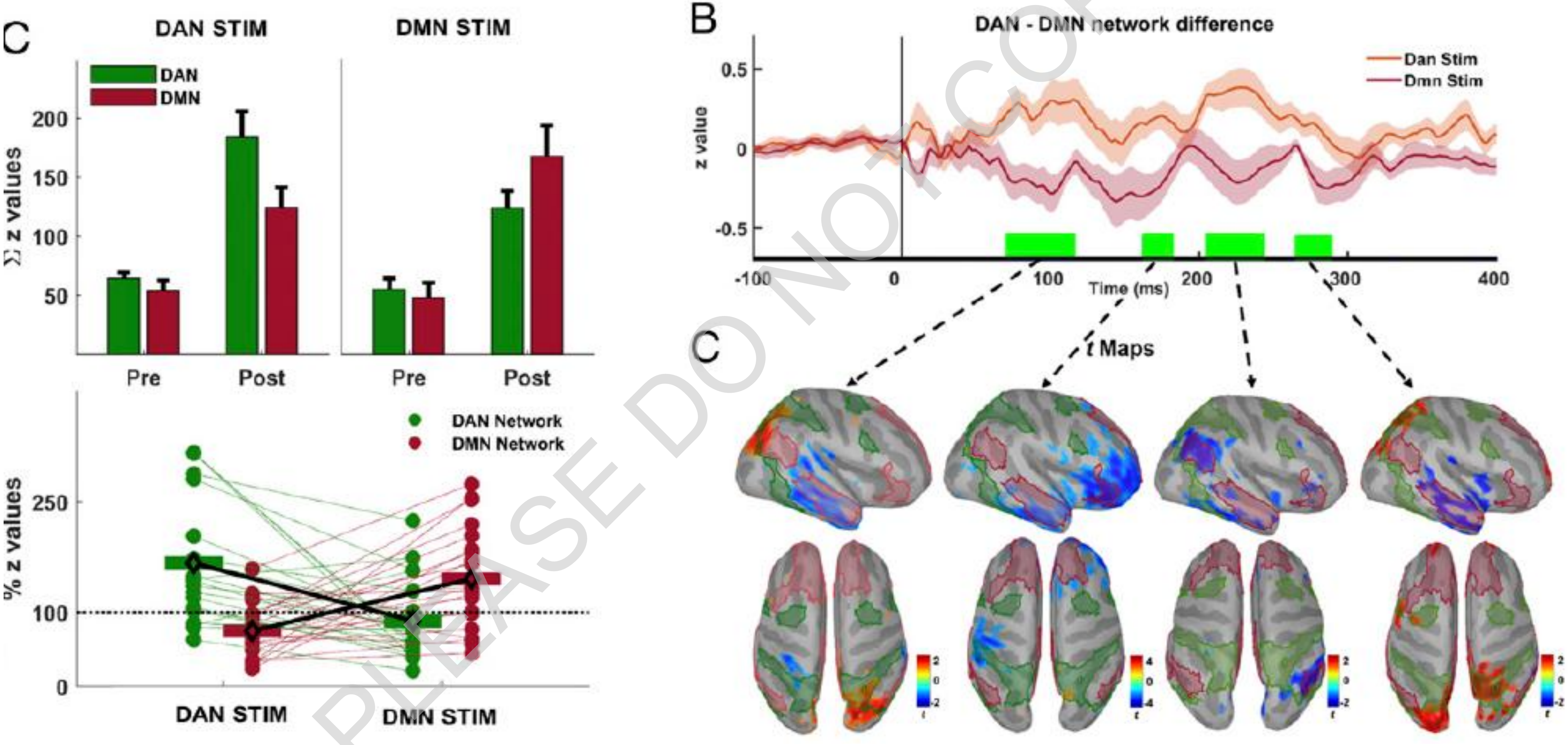
Ozdemir 2020 *PNAS*

Network Evoked Activity





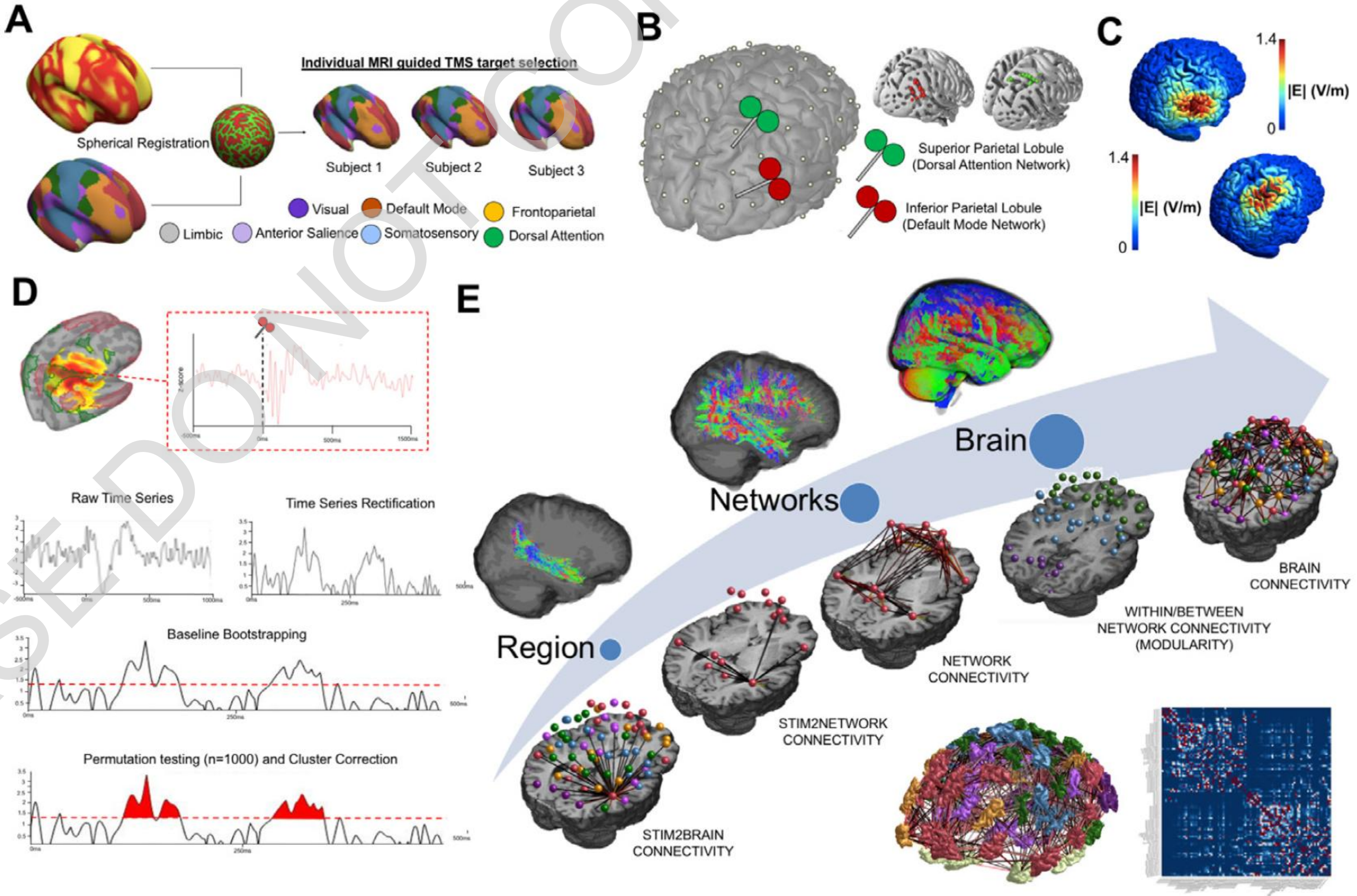
Network-specific activations



Ozdemir 2020

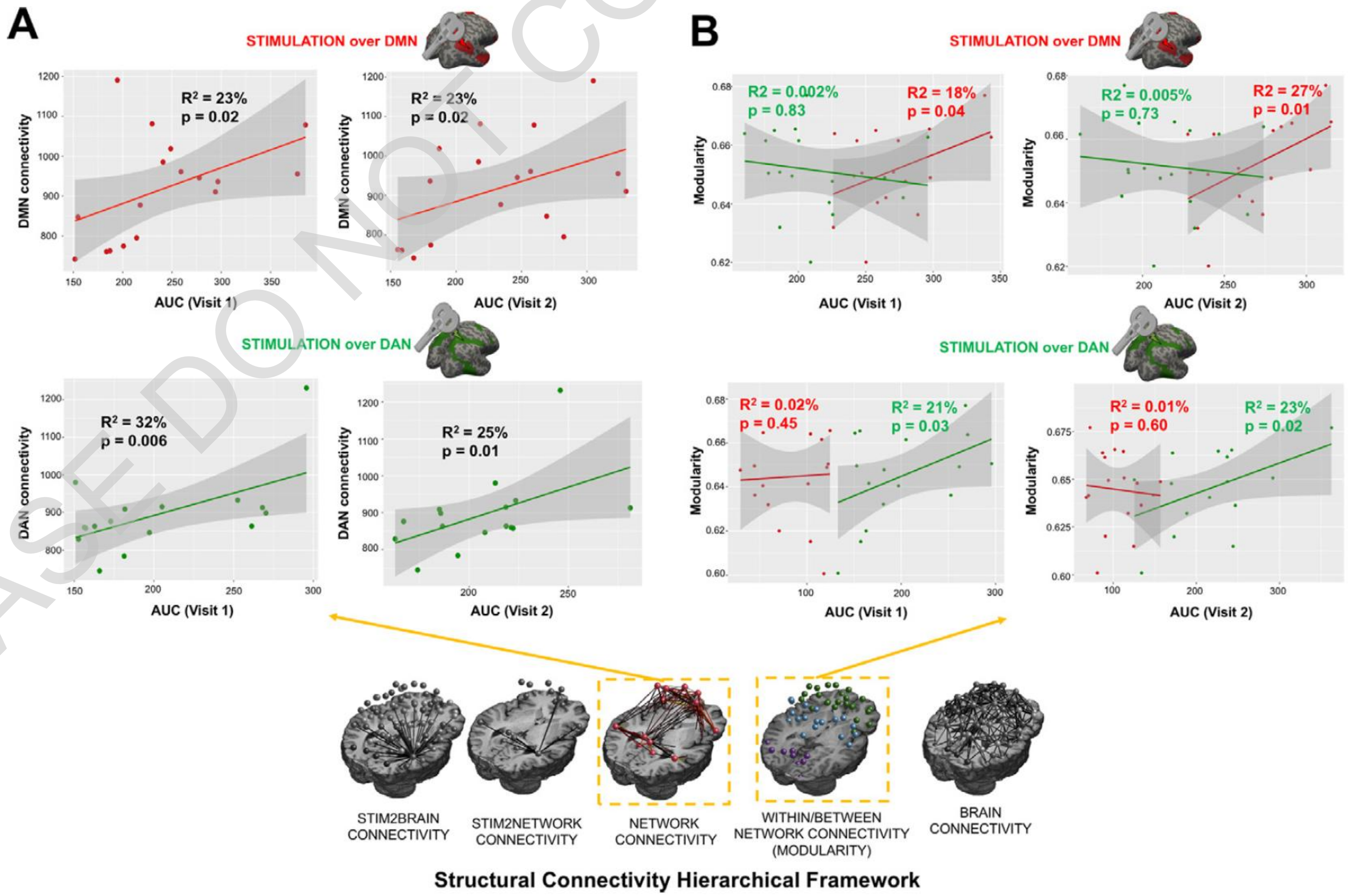
What about structural connectivity?

- Momi 2021 *NeuroImage*
  - Evaluated whether and how DTI connectivity predicts TMS-evoked EEG activity
  - Evaluated whether regional, network-level or whole brain connectivity better predicted TEPs



Evoked activity correlated with network connectivity and modularity

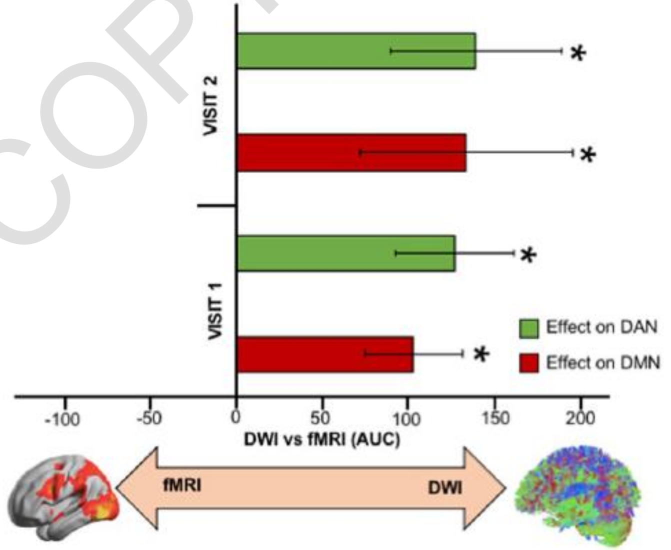
- Magnitude of evoked activity correlated with the total connectivity within the stimulated network, and with the modularity of the stimulated network, but NOT connectivity of the stimulated region or whole brain connectivity

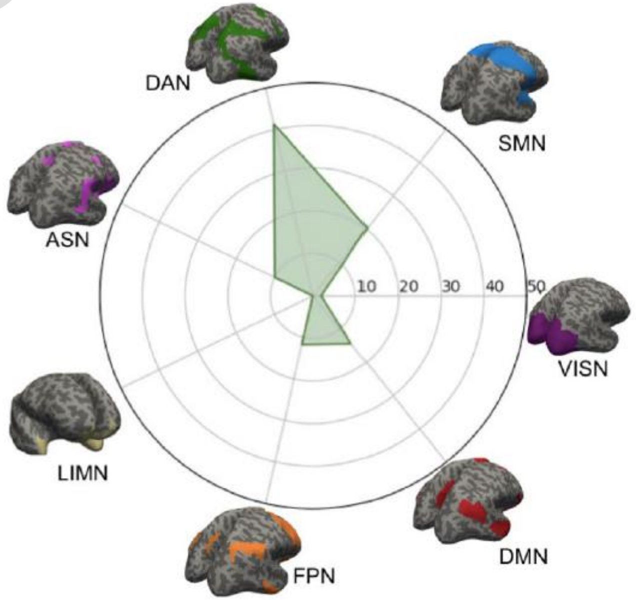


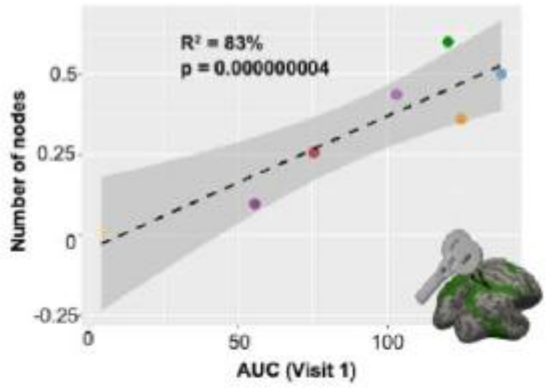
Momi 2021

Structural connectivity more predictive than functional connectivity

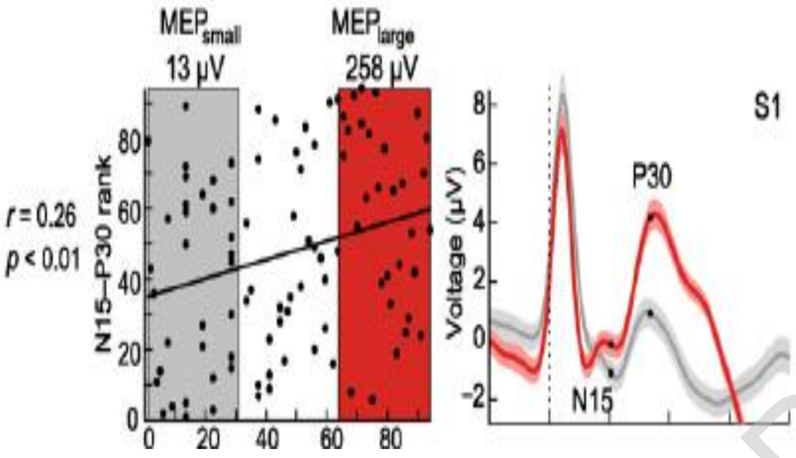
- Momi 2021 *Scientific Reports*: Assessed whether TMS-evoked EEG activity is better predicted by MRI structural connectivity (DTI) or resting-state functional connectivity (rs-fcMRI)
- Top: propagation of TMS-evoked activity is better predicted by structural rather than functional connectivity
- Bottom: The structural connectivity to different networks predicts the TMS-evoked activity within each network





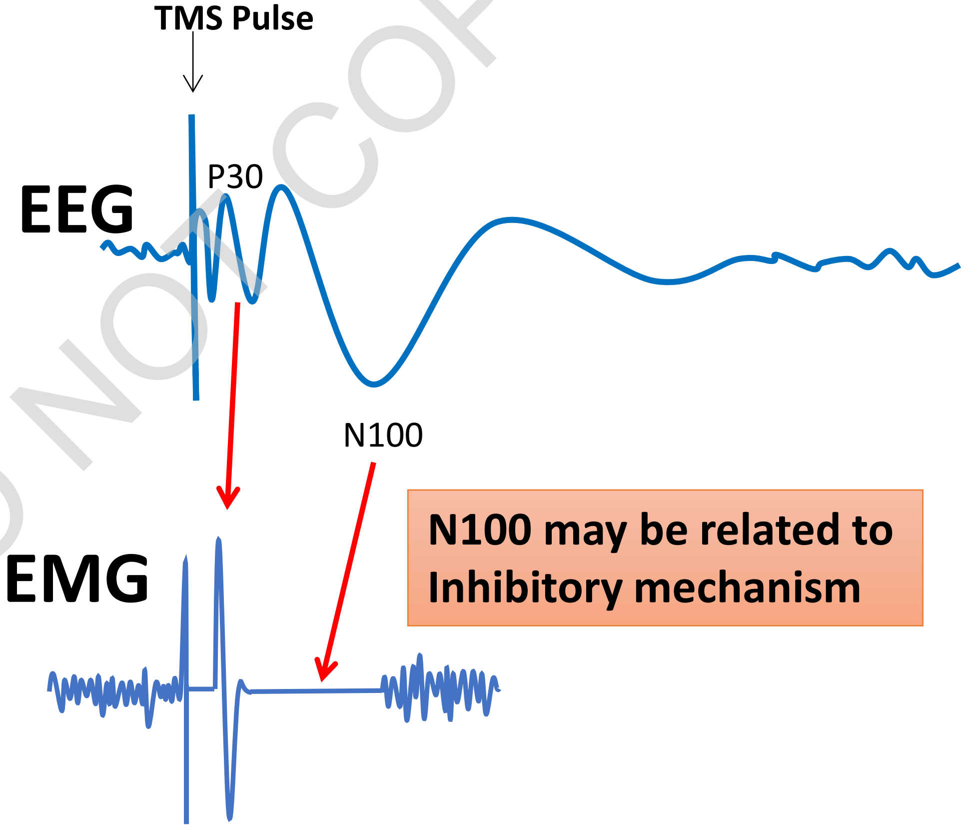


TEPs and MEPs



The N15-P30 correlated with the amplitude of MEP

Maki & Ilmoniemi 2010

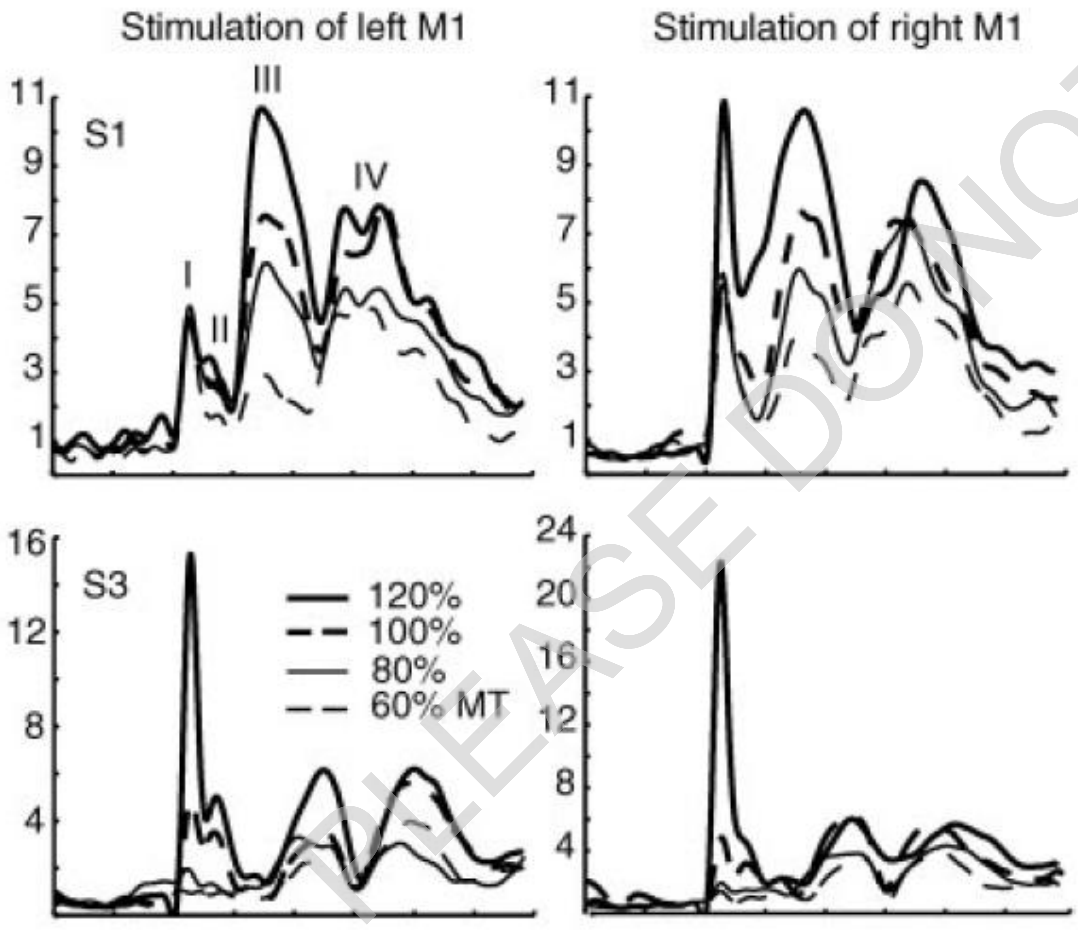


N100 may be related to Inhibitory mechanism

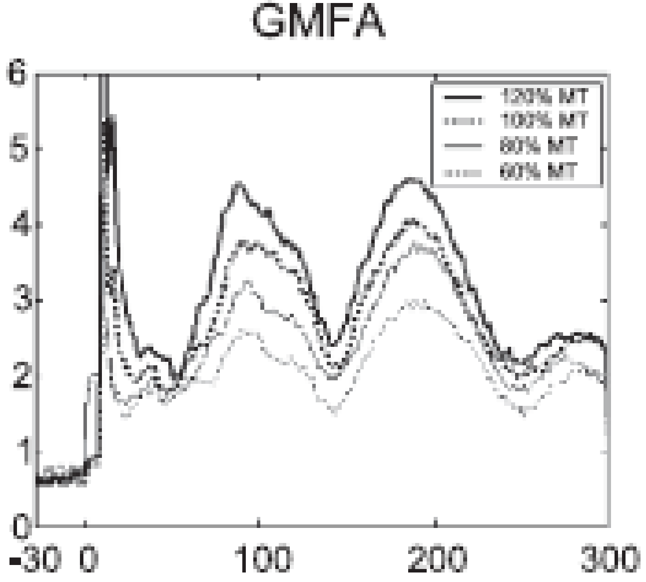
Bender et al., 2005; Bonato et al., 2006
Farzan et al., 2013

TMS generates TEPs even below motor threshold!

60% motor threshold was enough to evoke a cortical response!



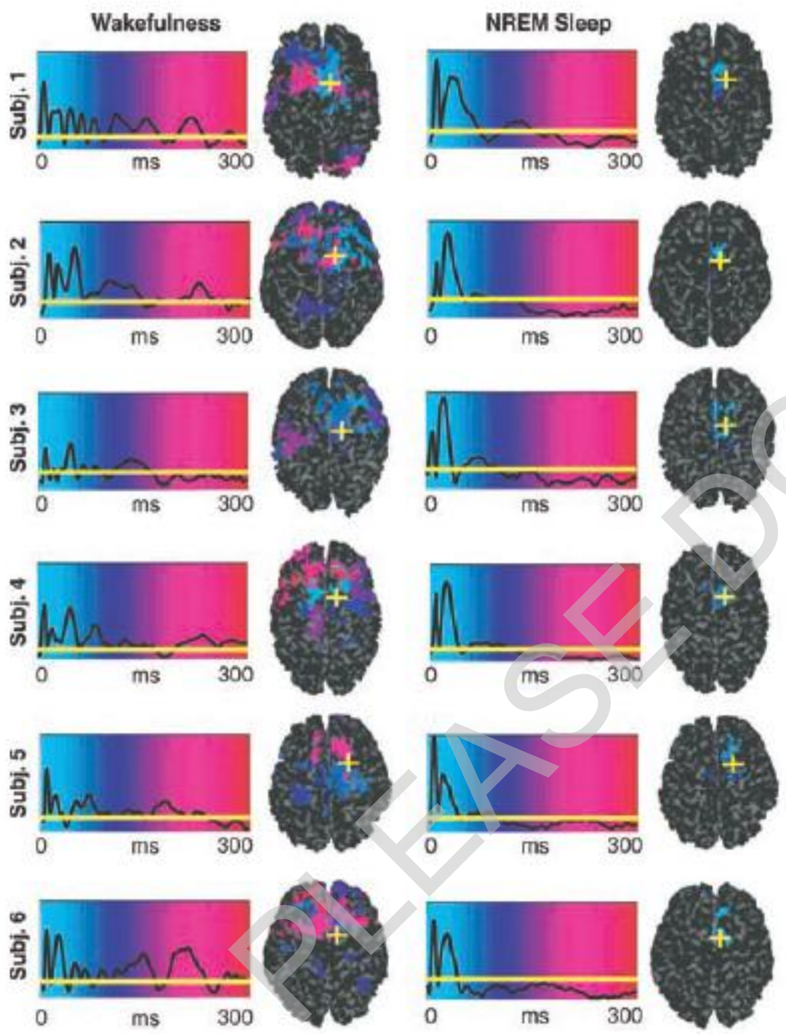
Komissi et al, Human Brain Mapping, 2004



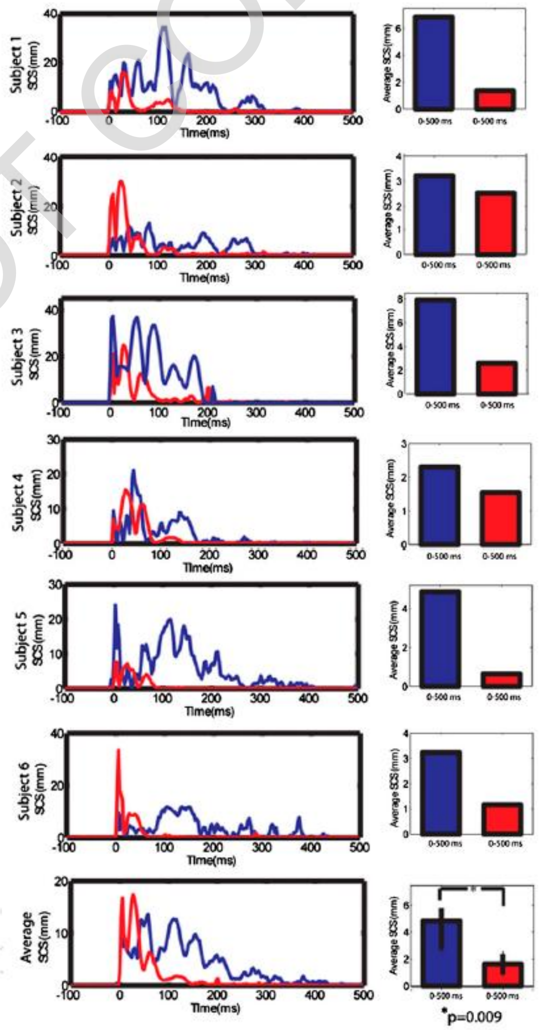
Kahkonen 2005

Complexity of TEPs at Different Brain States

Breakdown of effective connectivity during sleep and with anesthesia



Massimini 2005

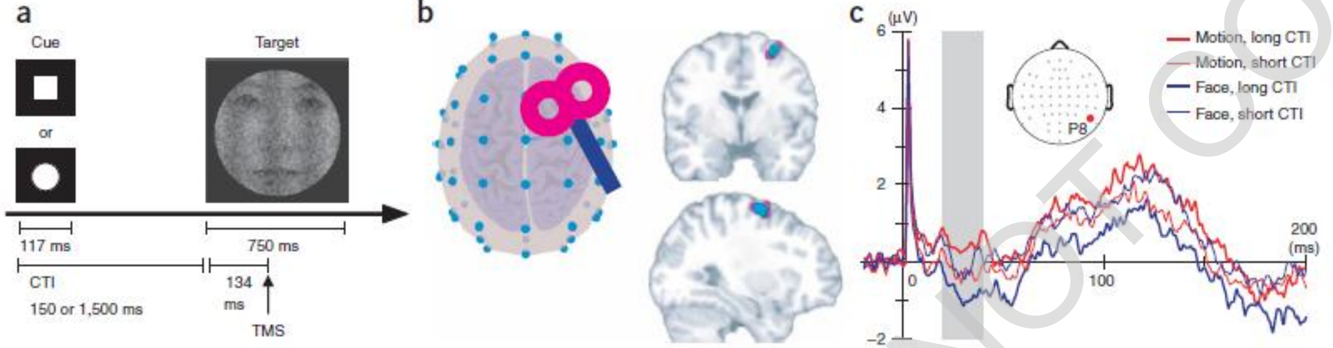


Ferrarelli 2010

M/F

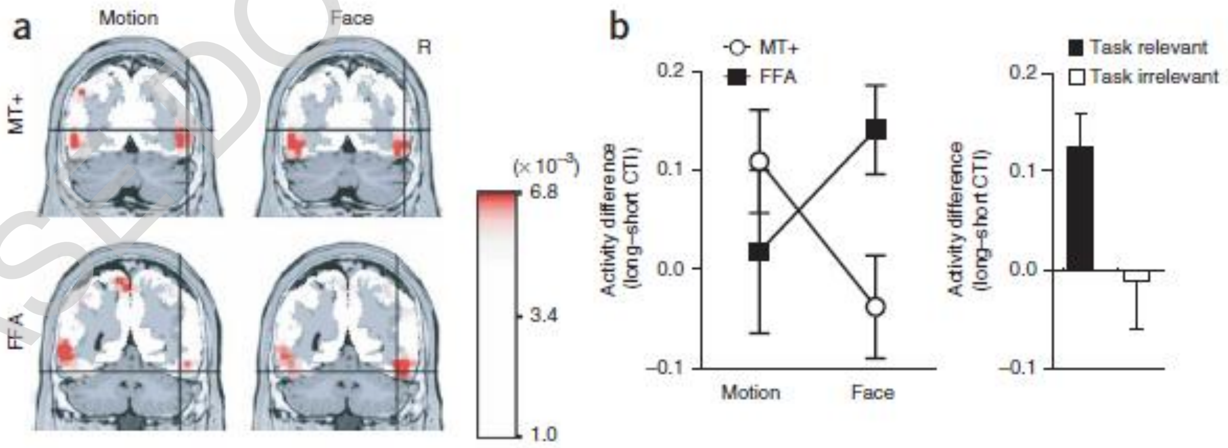
Examining Causality in brain-behavior relationships using TEPs (Cognitive Brain States)

Signal transmission from PFC during visual attention task

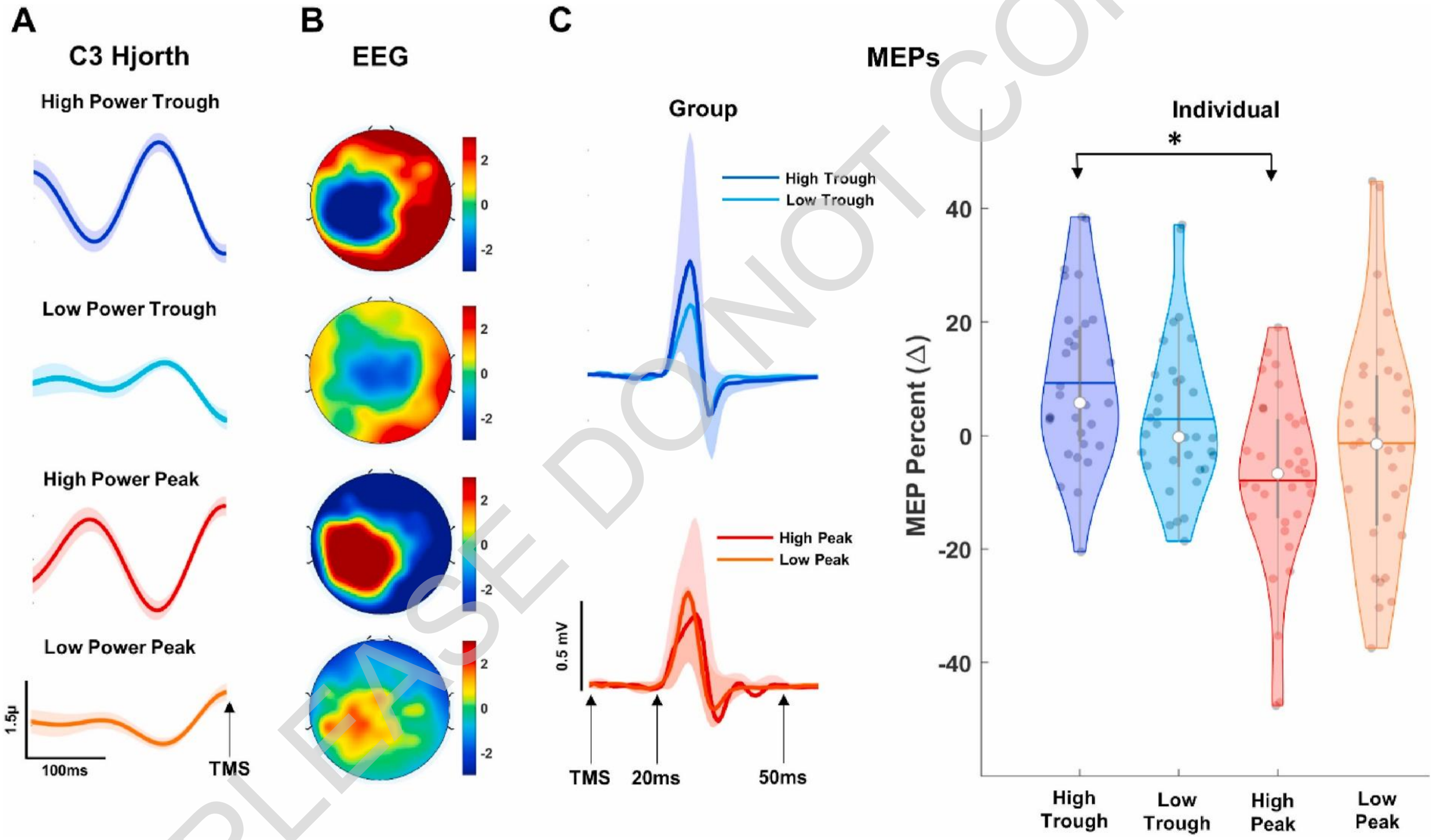


Morishima 2009 Nature Neuroscience: TMS applied to FEF during performance of a visual discrimination task for motion direction or visual gender.

The study found that the transmission of neural impulses from the prefrontal cortex is task-specific. **M**/F



Instantaneous Brain State and MEPs



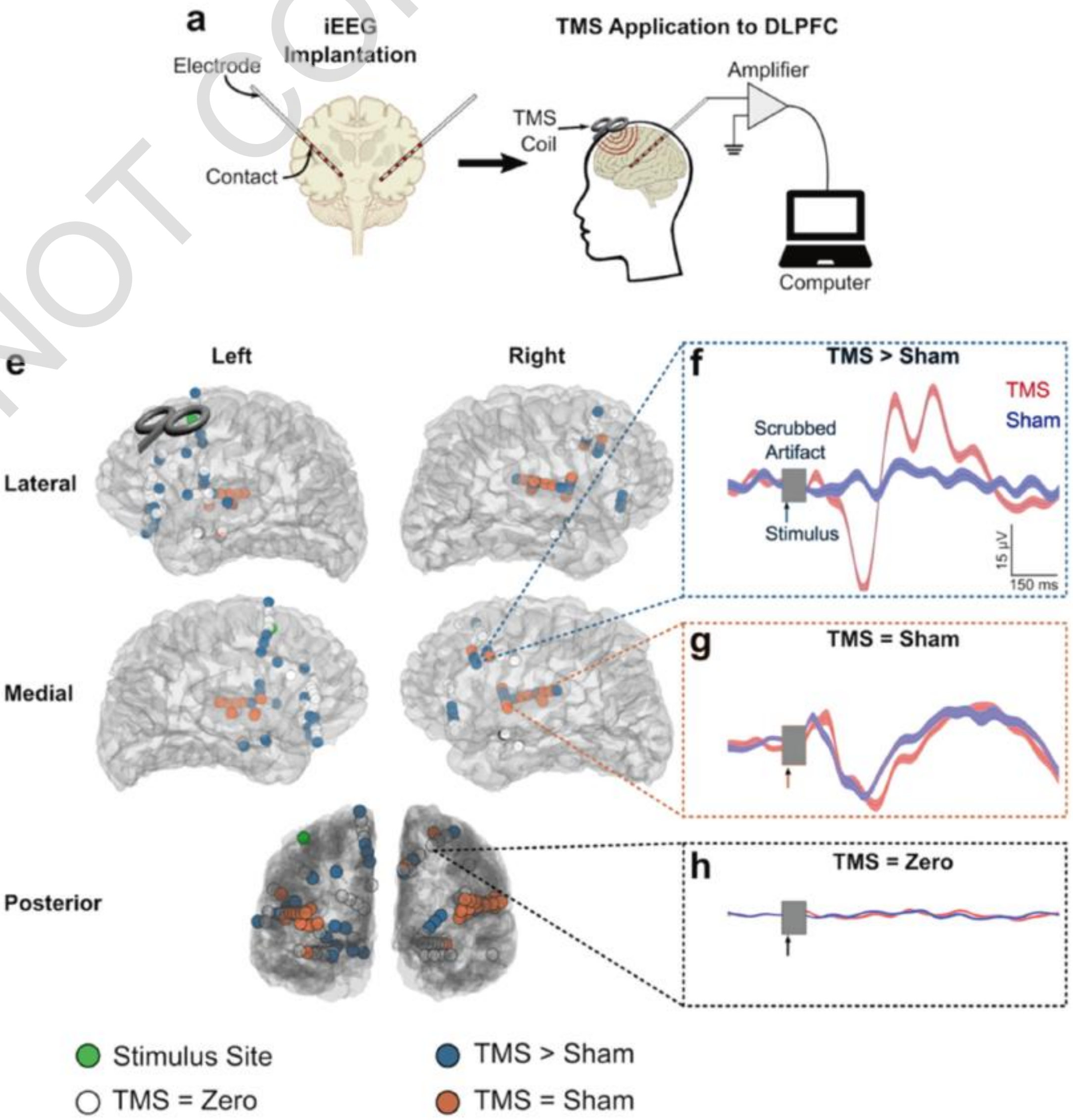
Ozdemir 2022 *Neuroimage: Reports*

TMS with intracranial EEG

- Patients with medically refractory epilepsy sometimes undergo intracranial EEG recordings with implanted electrodes
- Work led by Aaron Boes at U-Iowa (a former CNBS alum) showed that TMS in patients with implanted intracranial electrodes is safe and feasible
- Permits “ground truth” assessment of human physiology at rest, during tasks, and in response to TMS

Effects of transcranial magnetic stimulation on the human brain recorded with intracranial electrocorticography

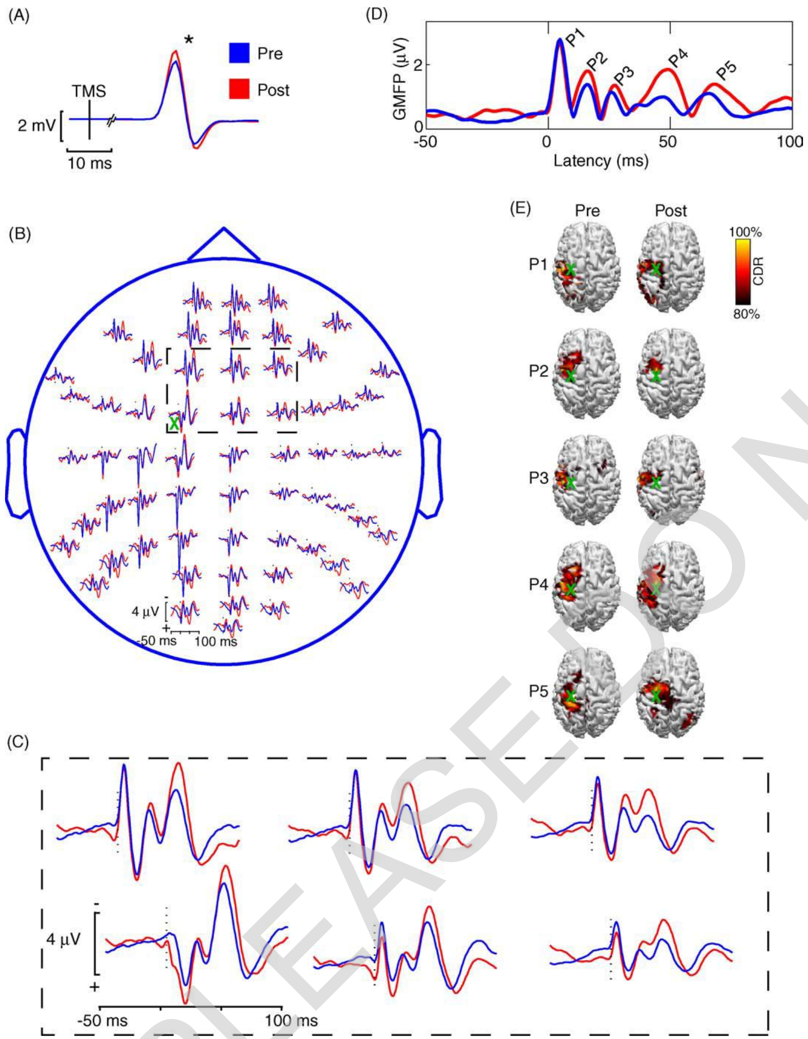
Jeffrey B. Wang[1,2,11], Umair Hassan[2,3,4,11], Joel E. Bruss[5,6], Hiroyuki Oya[7], Brandt D. Uitermarkt[6], Nicholas T. Trapp[8,9], Phillip E. Gander[7,10], Matthew A. Howard III[7], Corey J. Keller[2,3,4,12] and Aaron D. Boes[5,6,8,9,12]✉

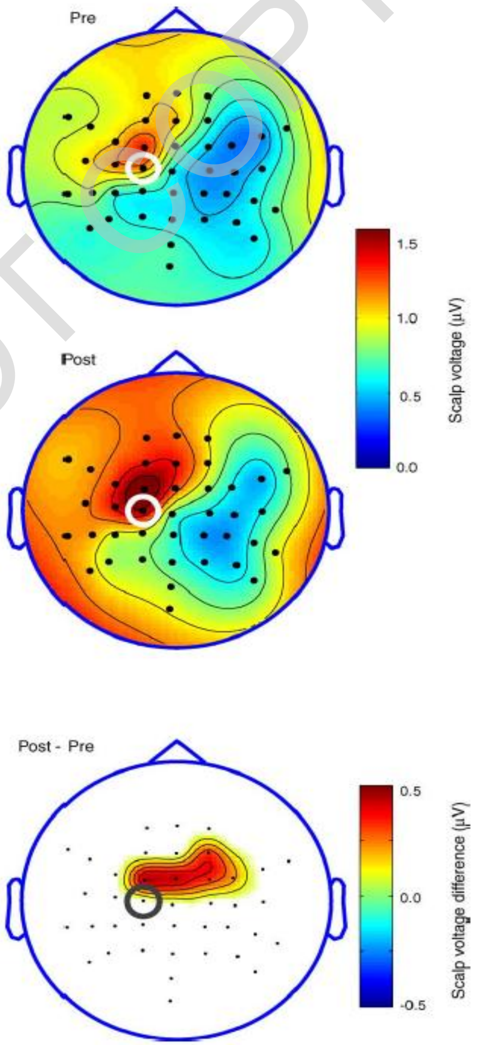


Wang 2024 *Molecular Psychiatry*

Repetitive TMS

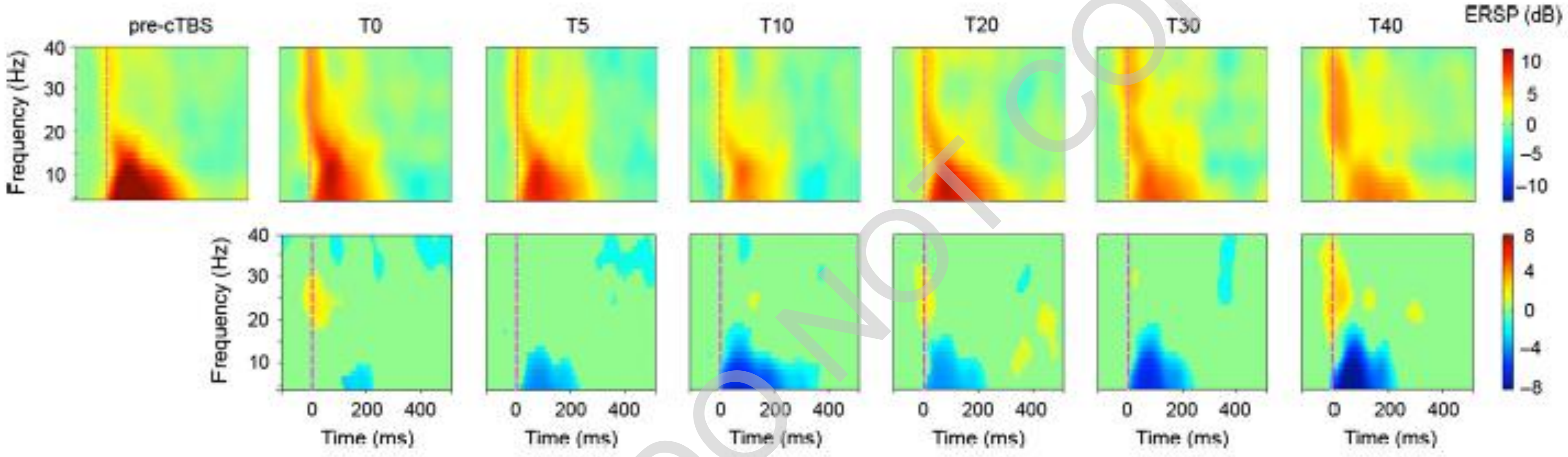
LTP-like Plasticity with rTMS



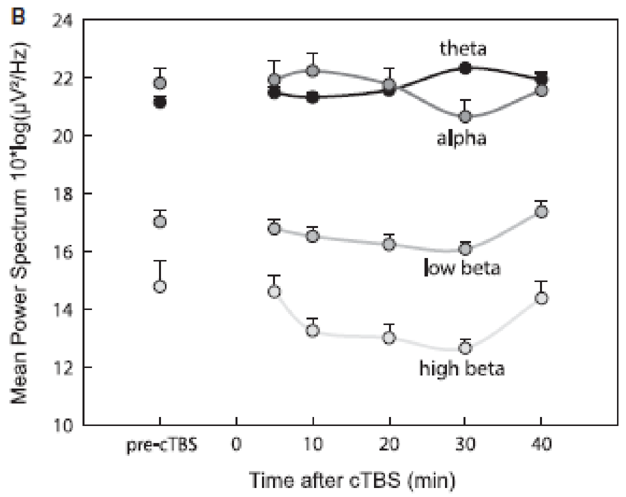


Esser 2006: Following, 5 Hz rTMS to motor cortex, a potentiation of the EEG potentials between 15 and 55ms

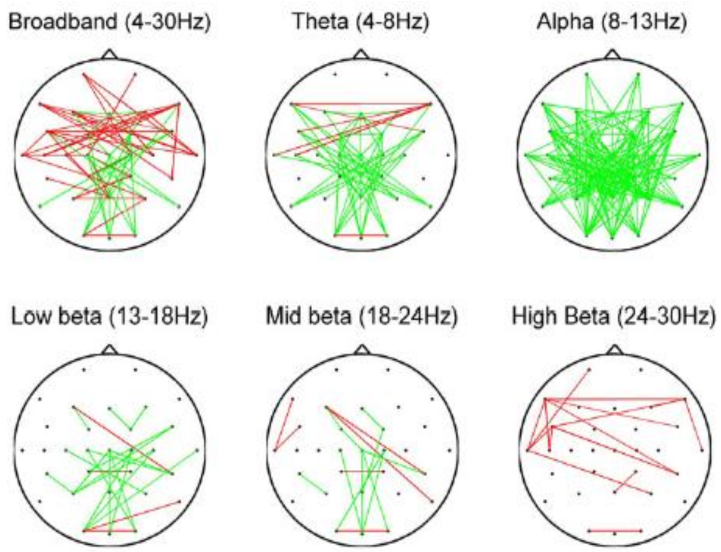
TMS-evoked oscillations

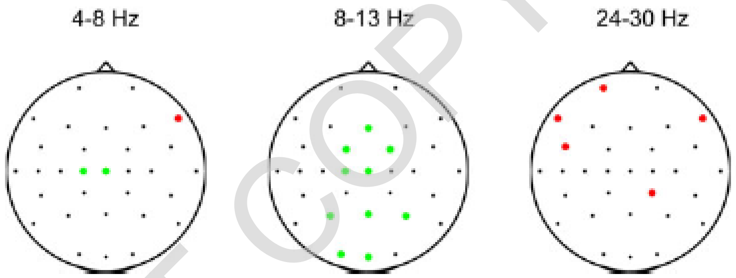


Vernet 2012: TMS-evoked theta and alpha oscillations significantly decreased after cTBS, while TMS-evoked beta activity increased. Significant decrease in resting-state beta power after cTBS

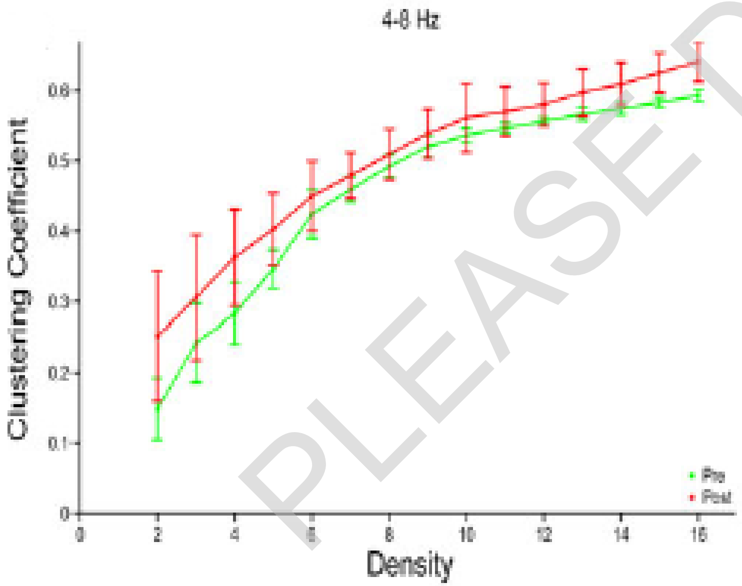


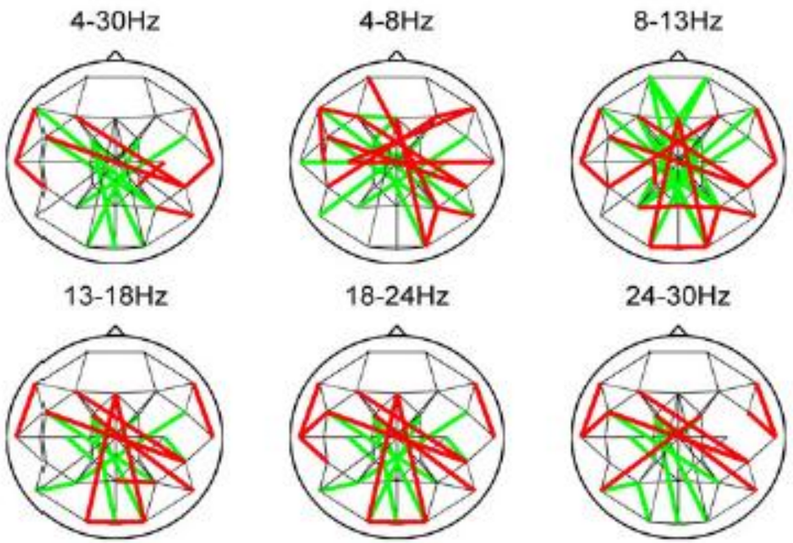
And network connectivity



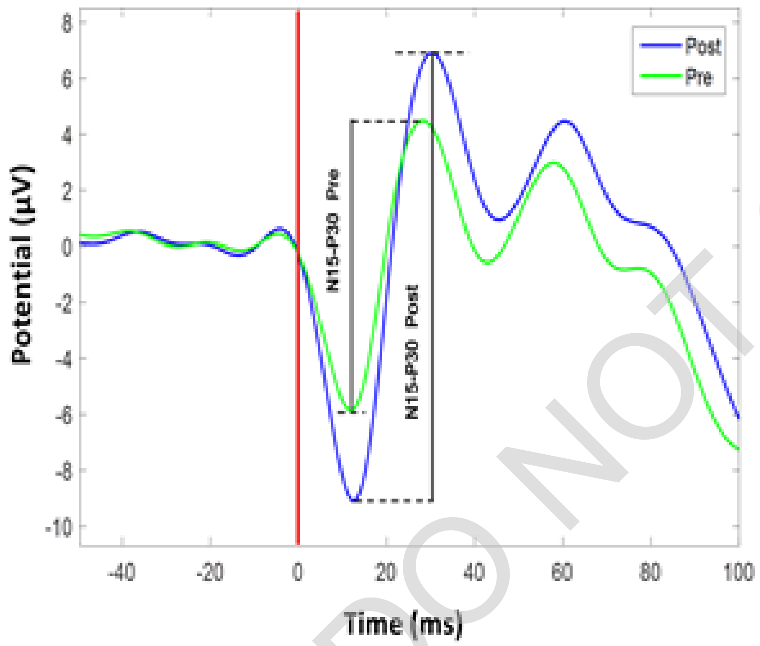


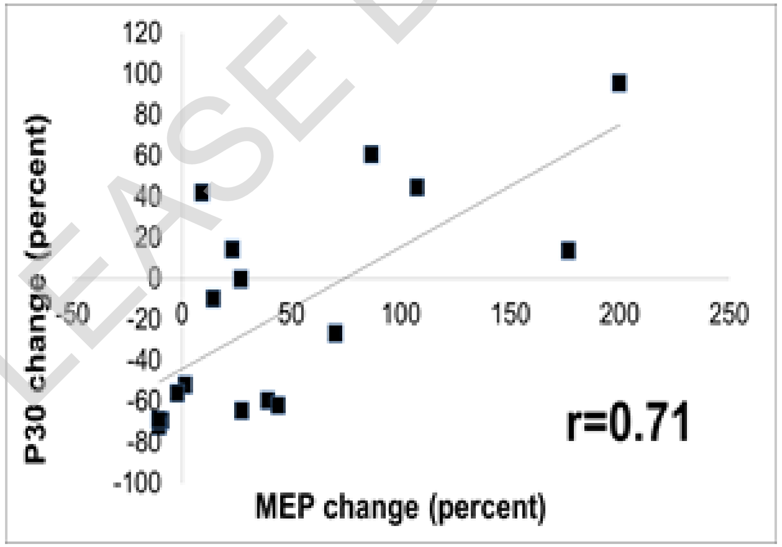
Shafi 2014: cTBS produced distributed frequency-specific changes in network connectivity, resulting in shifts in network topology and graph-theoretic metrics with implications for brain information processing





TMS-EEG effects correlate with MEP effects





Gedankian 2017

HOWEVER !!!

Assessing the rTMS cortical excitability hypothesis

Table 2
Review of the effects of high frequency rTMS on motor cortical excitability

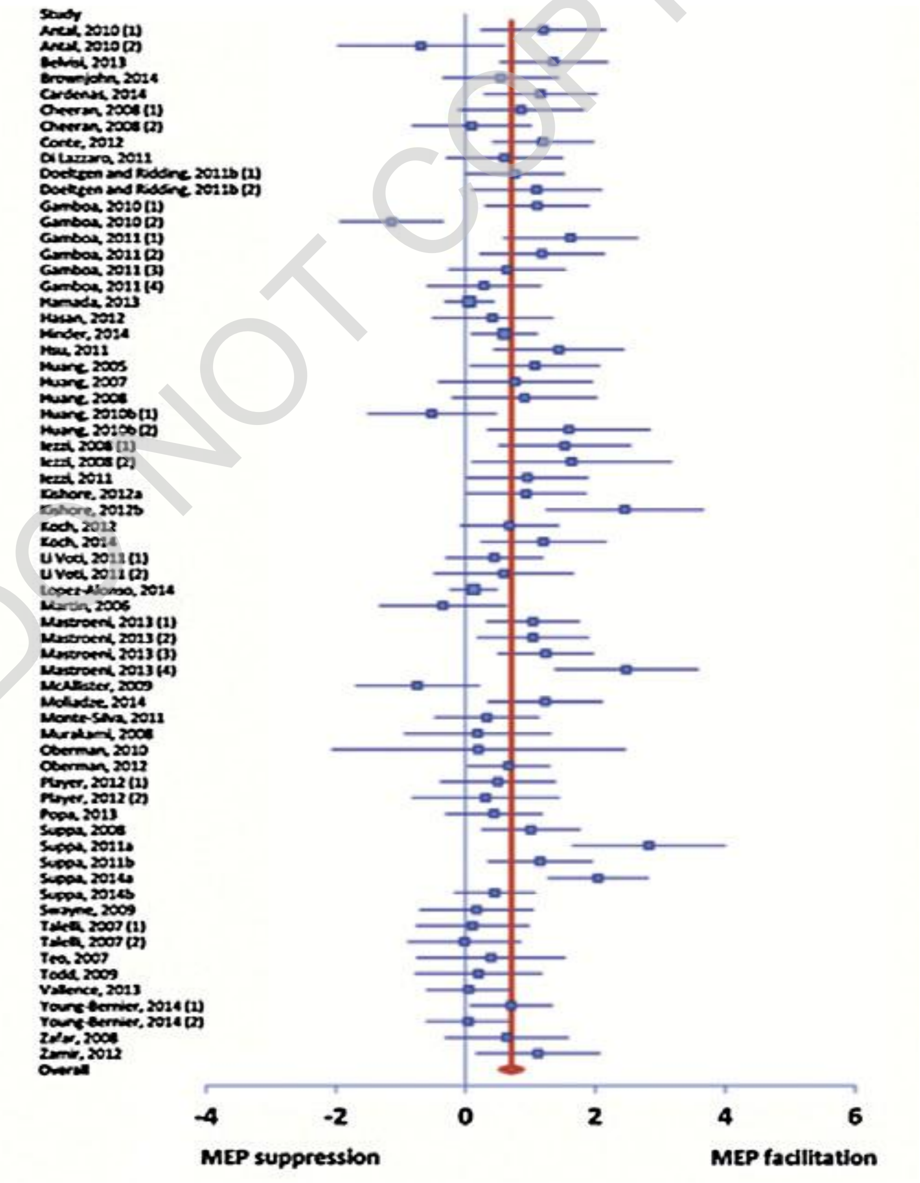
Study (*n*)	rTMS intensity	Frequency (Hz)	No. of rTMS pulses	Time points of measurement	Finding
Ipsilateral cortical excitability					
(Jennum et al., 1995) (13)	120% RMT	2, 3, 5, 10, 20	9	Within train	↑ MEP amplitude only at 2,3 Hz; variation throughout
(Jahanshahi et al., 1997) (6)	105–110% AMT	20	400	Within train	↑ MEP amplitude in 2 subjects
(Berardelli et al., 1999) (8)	110, 120% RMT	3, 5	11, 20	Within train	No change in active MEP amplitude
(Romeo et al., 2000) (8)	90%, 100%, 110%, 140% RMT	2, 3, 5, 10, 15	10 and/or 20	Within train	No change in active MEP amplitude
(Lorenzano et al., 2002) (27)	120% RMT	5, 10, 20	80	Within train	↑ MEP amplitude within train at all frequencies
(Inghilleri et al., 2006) (20)	120% RMT	5	100	Within train	↑ MEP amplitude
(Inghilleri et al., 2004) (16)	120% RMT	5	80	Within train	↑ MEP amplitude
(Quartarone et al., 2005a,b) (10)	90% RMT, 90% AMT	5	1500	Within train and post train	No change in MEP amplitude at 90% AMT; ↑ MEP amplitude post train at 90% RMT
(Berardelli et al., 1998) (13)	120% RMT	5	100	Within train and immediately post train (900 ms)	↑ MEP amplitude within train and lasting 600-900 ms post train
(Fierro et al., 2001) (8)	100%, 115%, 130% RMT	7	50	Within train	No change in active MEP amplitude
(Wassermann et al., 1996) (4)	100% RMT	20	400	Post Train	No change in MEP size
(Daskalakis et al., 2006) (12)	90% RMT	10, 20	900	Post train	No change in RMT, MEP amplitude
(Wu et al., 2000) (8)	120% RMT	5	30	Post train	No change in MEP amplitude
		15			↑ MEP amplitude for 30 sec
(Di Lazzaro et al., 2002) (10)	100% AMT	5	50	Post train	No change in MEP amplitude
(Lang et al., 2004) (10)	100% AMT	5	100	Post train	No change in MEP amplitude
(Pascual-Leone et al., 1994) (14)	150% RMT	3	20	Post train	↑ MEP amplitude
	150% RMT	5			↑ MEP amplitude
	110% RMT	10, 20			↑ MEP amplitude
	150% RMT	10, 20			↑↓ MEP amplitude
(Modugno et al., 2001) (11)	100% RMT	5	4–20	Post train	↓ MEP amplitude
	130% RMT	10, 20			↑ MEP amplitude with 5 Hz at higher frequency and intensity
	150% RMT				
(Siebner et al., 2000) (10)	90% RMT	5	2250	Post train	No change in MT
(Peinemann et al., 2004) (8)	90% RMT	5	150	Post train	No change
			1800		↑ MEP amplitude lasting 30 min
(Maeda et al., 2000b) (36)	90% RMT	10	240	Post train and 1 day post train	No change
		20	240		↑ MEP amplitude (modulatory effect greater on Day 2)
(Maeda et al., 2000a) (36)	90% RMT	10	240, 1600	Post train	10 Hz: ↑ % change in MEP area with 1600 pulses but not 240 pulses
Contralateral cortical excitability					
(Gorsler et al., 2003) (13)	95% RMT	5	1800	Post train	Left motor cortex investigated; ↑ MEP amplitude lasting 6 min

P.B. Fitzgerald et al. / Clinical Neurophysiology 117 (2006) 2584–2596

Last systematic review was in 2006!!!

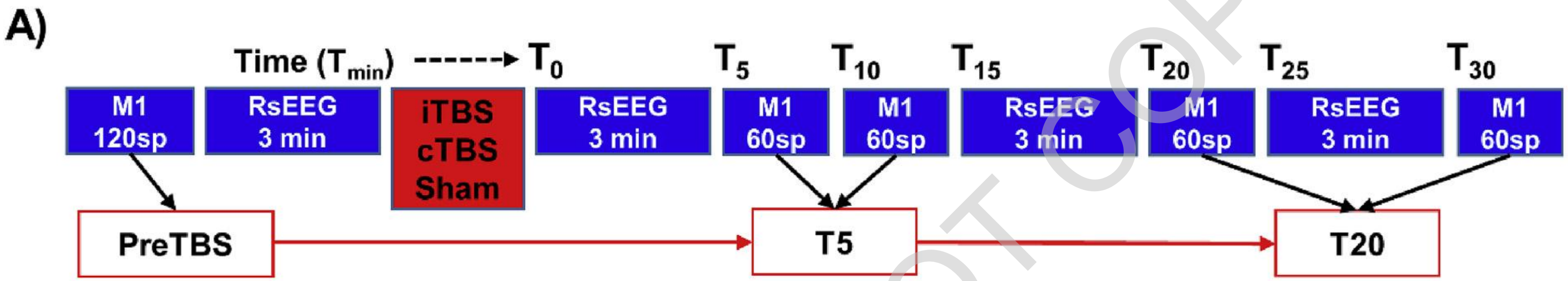
What about iTBS?

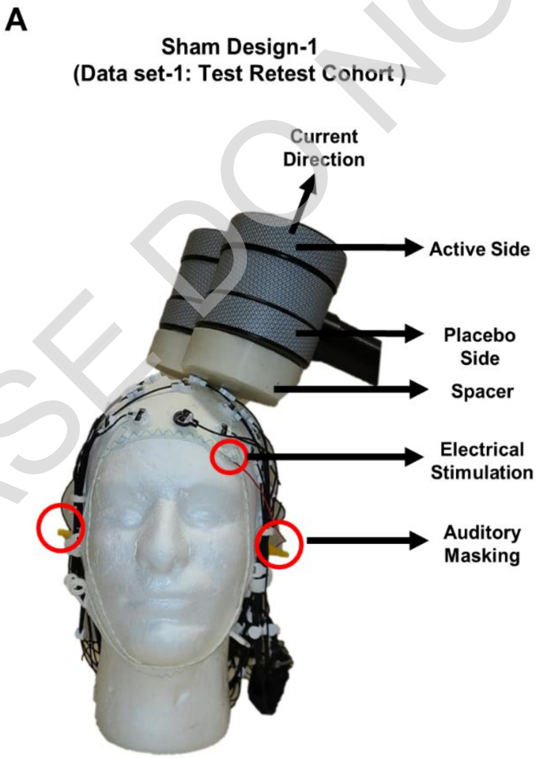
Out of 87 studies only 3 employed Sham



Chung et al., 2016

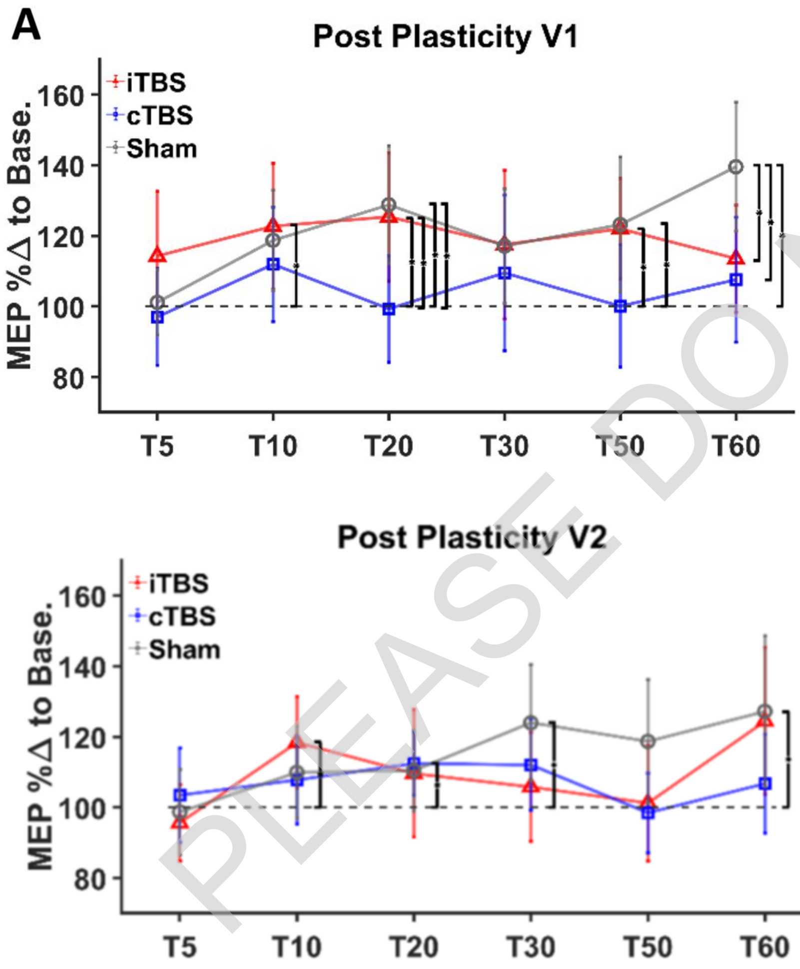
Testing the cortical excitability hypothesis of rTMS effects with sham controls and repeat tests

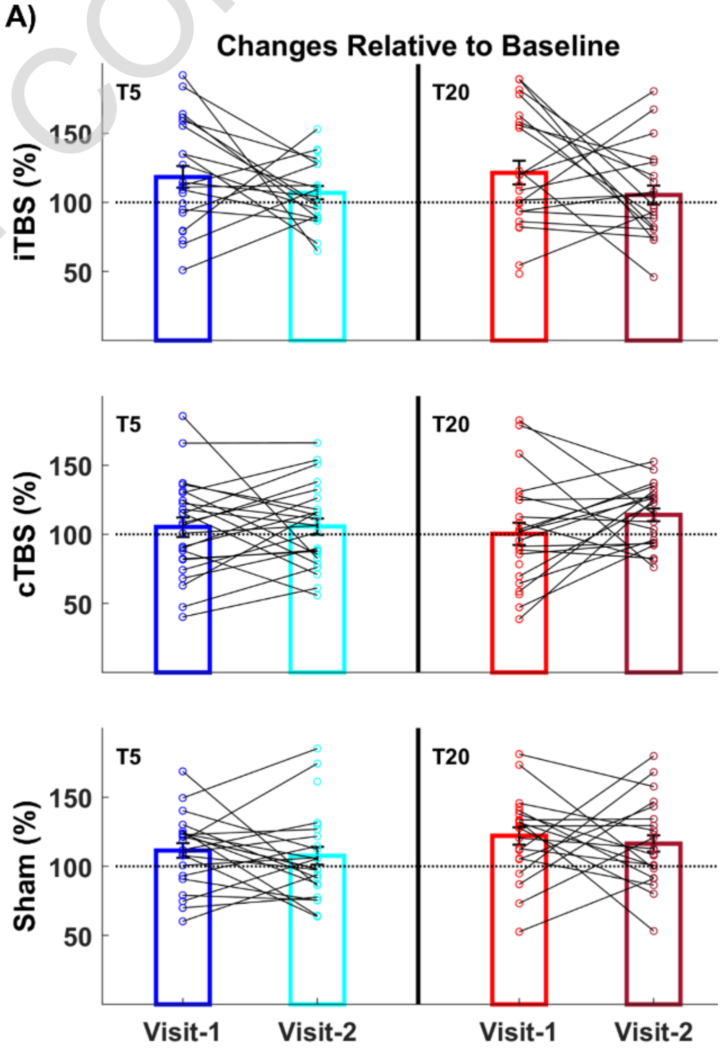




Testing the cortical excitability hypothesis of rTMS effects with sham controls and repeat tests

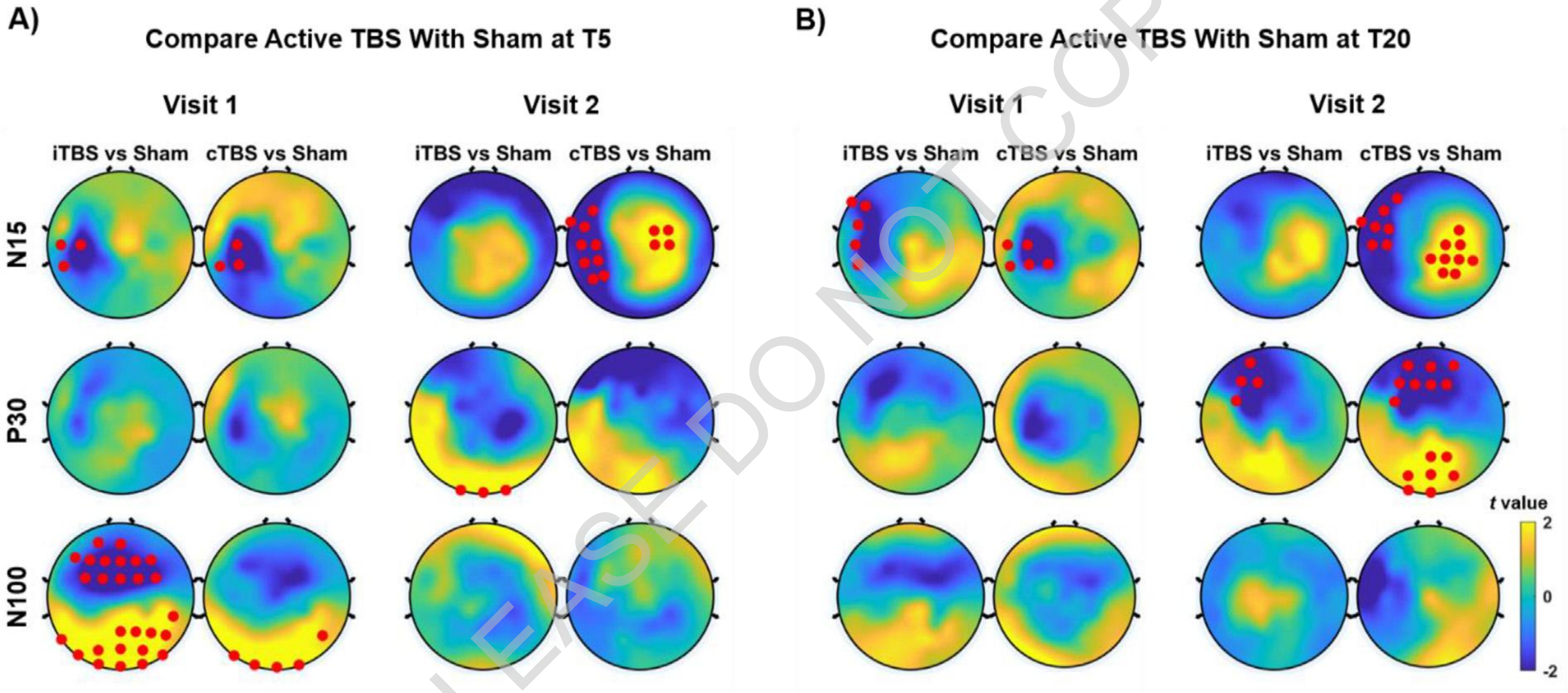
Theta-burst effects on MEPs are not different from sham at most time points at the group level





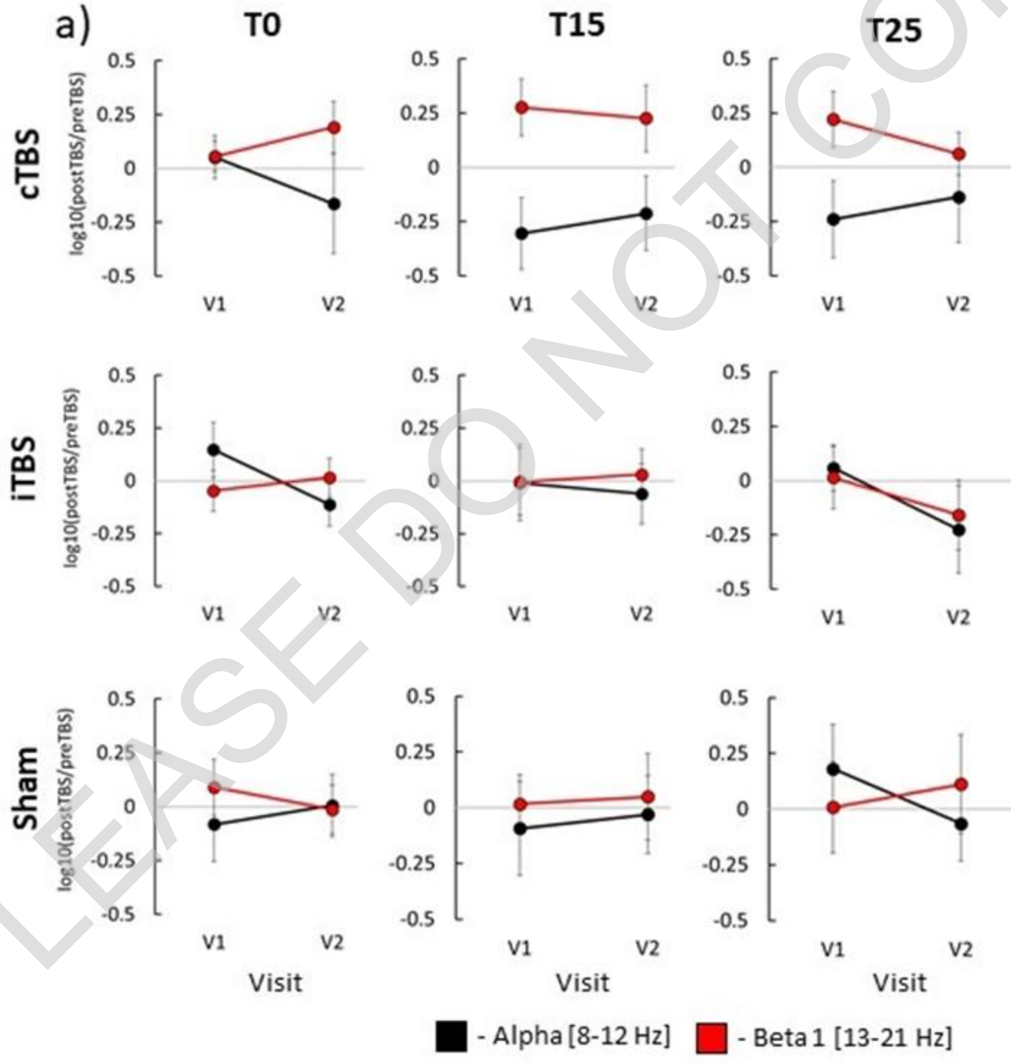
Boucher 2021 *Scientific Reports*

Theta-burst effects on TEPs are not reproducible



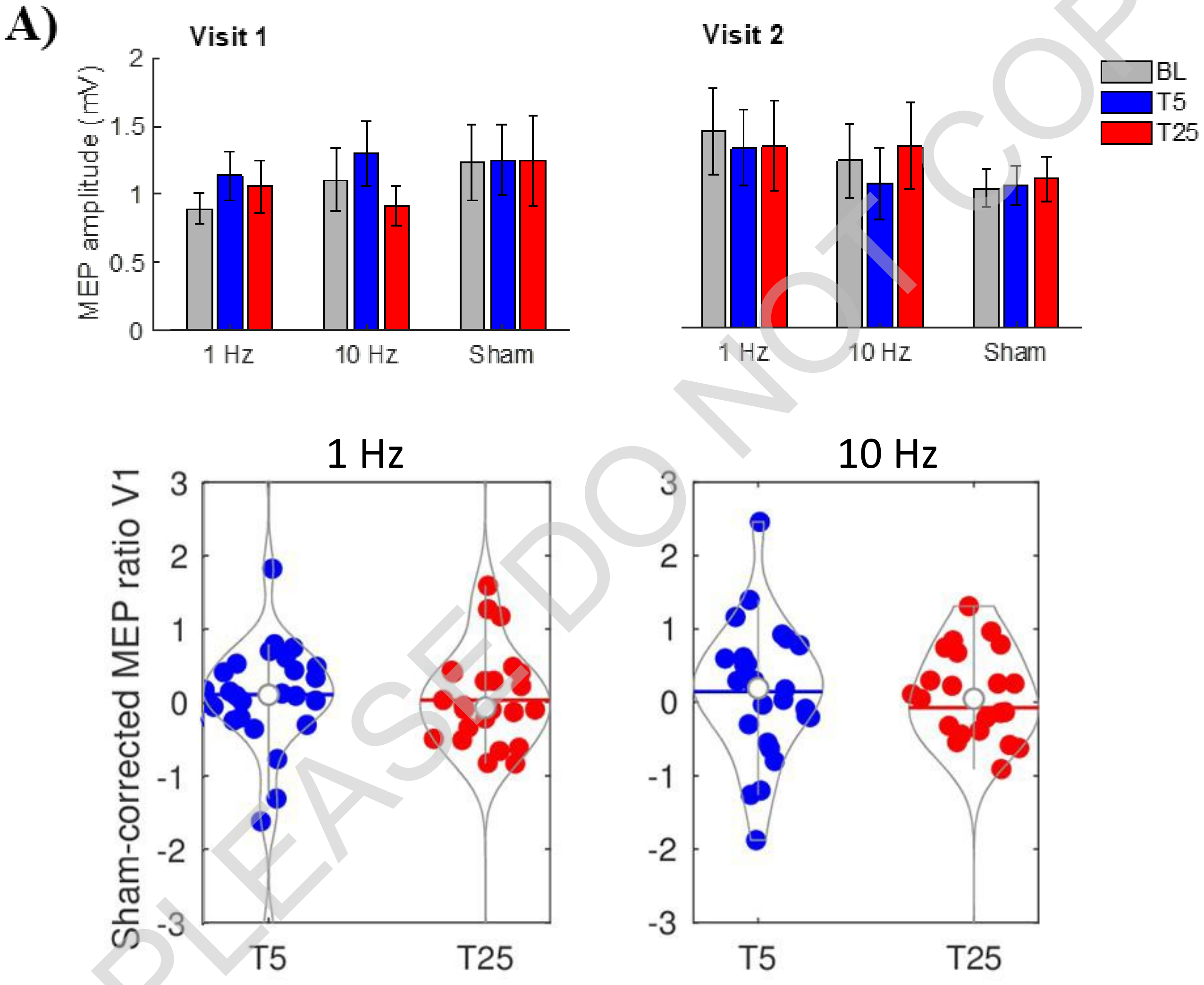
Ozdemir et al., 2021 Brain Stimulation

How about rsEEG oscillations



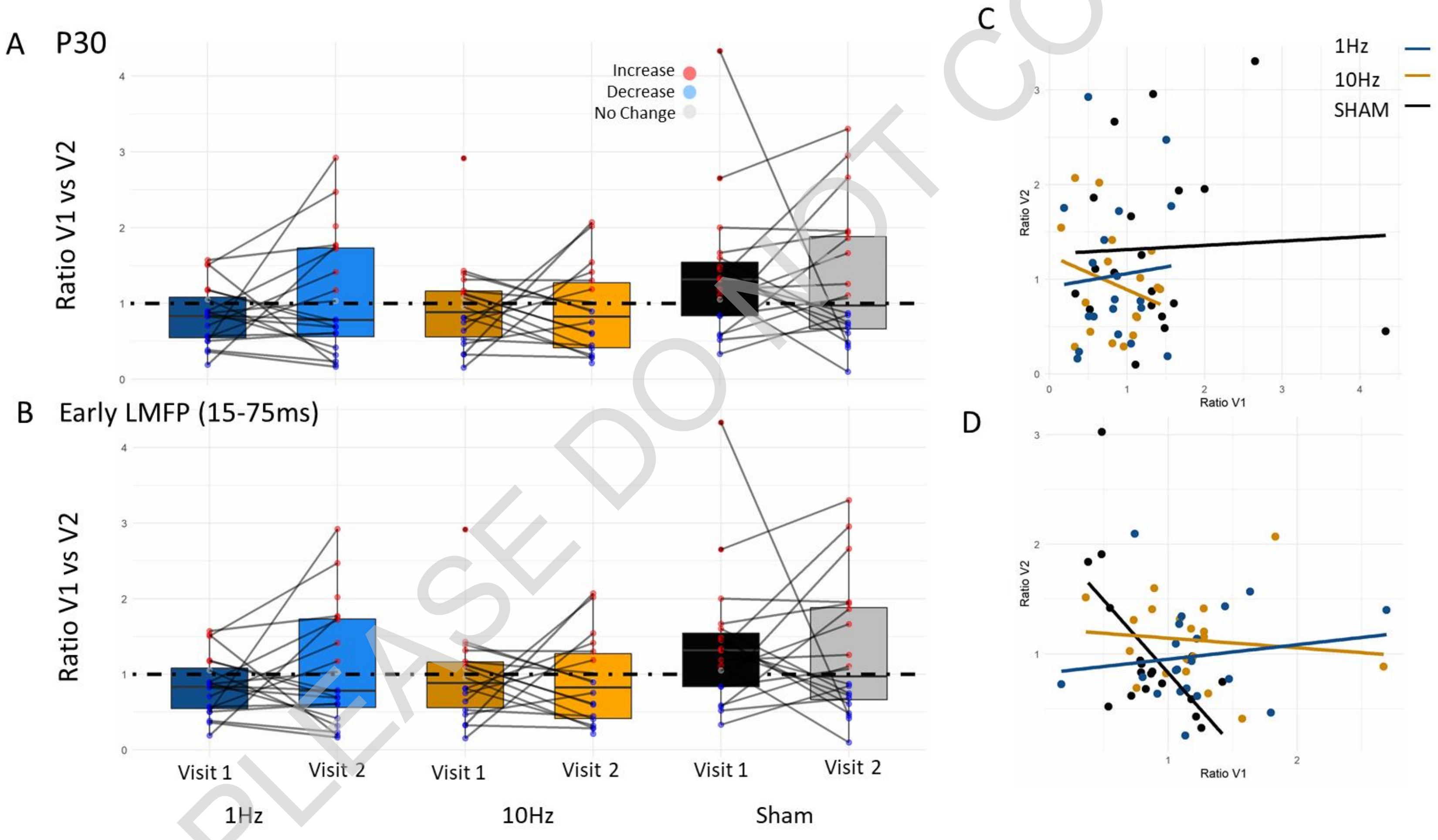
Rodionov et al., 2023 *Scientific Reports*

What about conventional rTMS? 1 Hz or 10 Hz effects on MEPs were not different than Sham



Magnuson et al., 2023

1 Hz or 10 Hz did not change TEPs compared Sham



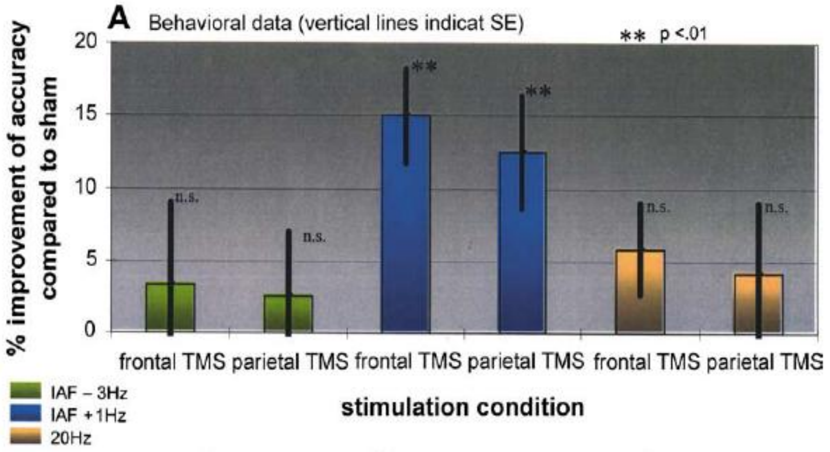
Passera et al., submitted

Take Home Message for Cortical Excitability and rTMS effects

- Sham controls and repeat tests are critical for validation
- Cortical Excitability Mechanism assumptions may not be true (Alternative mechanisms)
- Single session rTMS is not effective.

EEG-Guided TMS

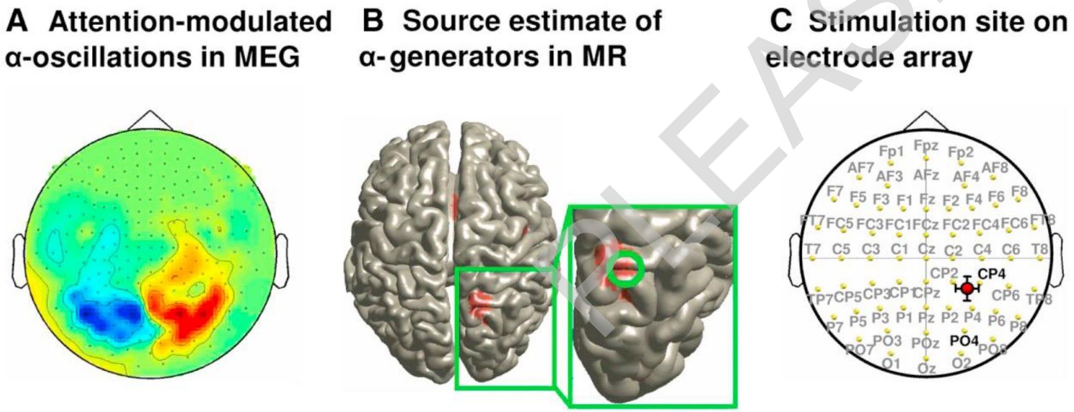
Use EEG and rTMS to Induce Natural Brain Oscillations Observed During Cognitive Tasks



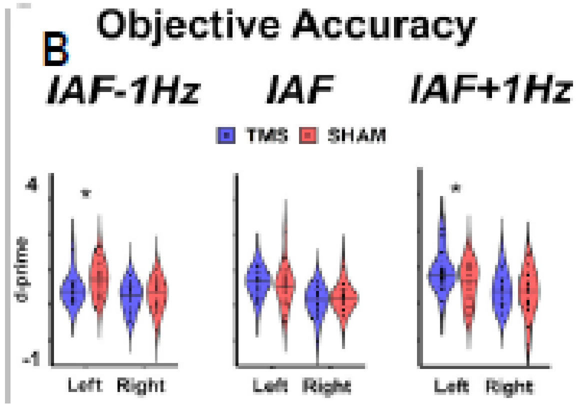
Klimesch 2003: Showed that rTMS at individual alpha frequency to frontal and parietal sites led to significant improvement in mental rotation. Same effect was not present at other frequencies

See also: Sauseng 2009, Romei 2010

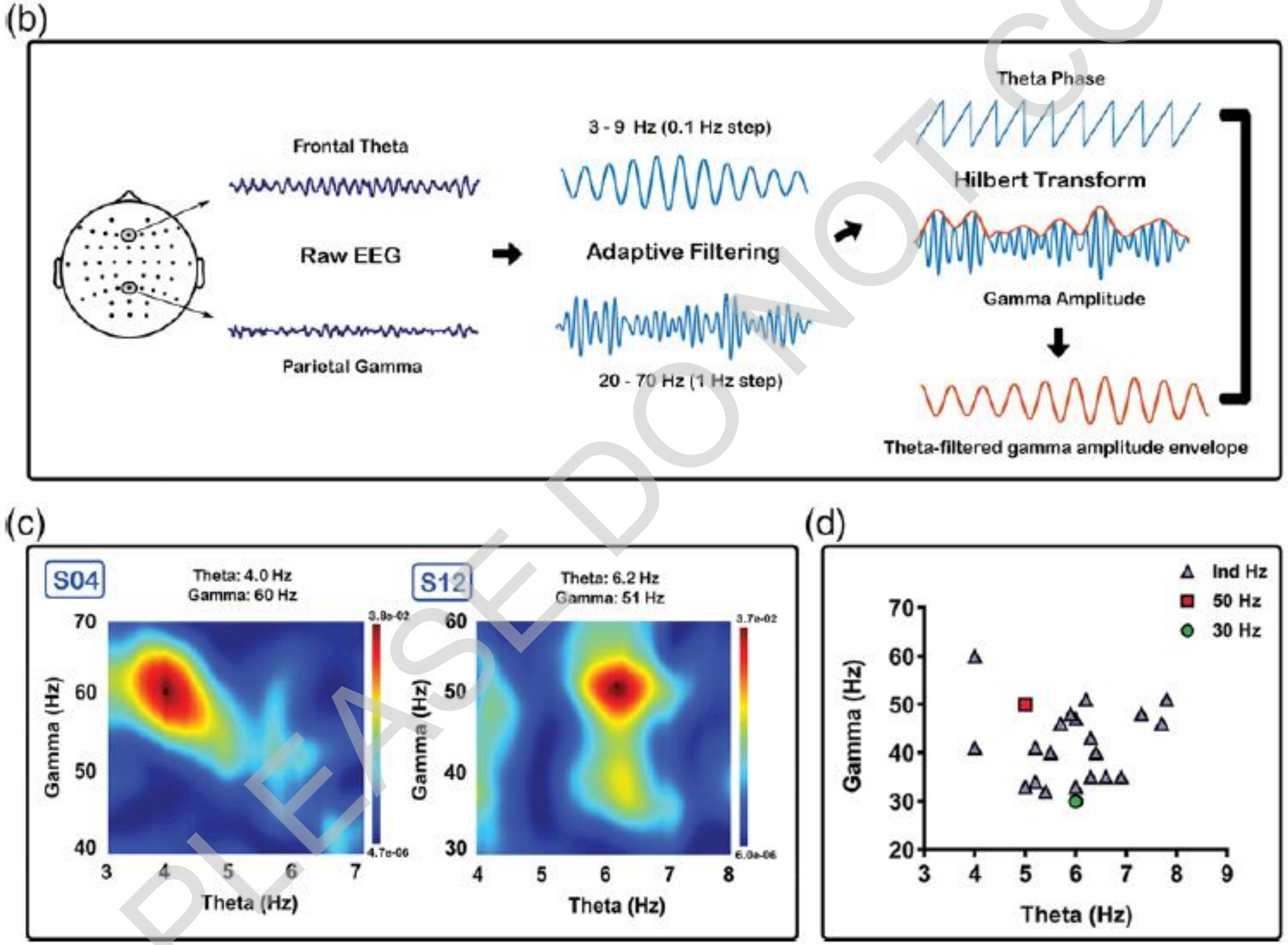
Thut 2011: Showed that alpha-TMS targeted to the source of EEG alpha activity can upregulate the targeted alpha-oscillations in the attention network. **Thut 2022**: Showed stimulation at IAF +1 Hz improves task performance



M/F

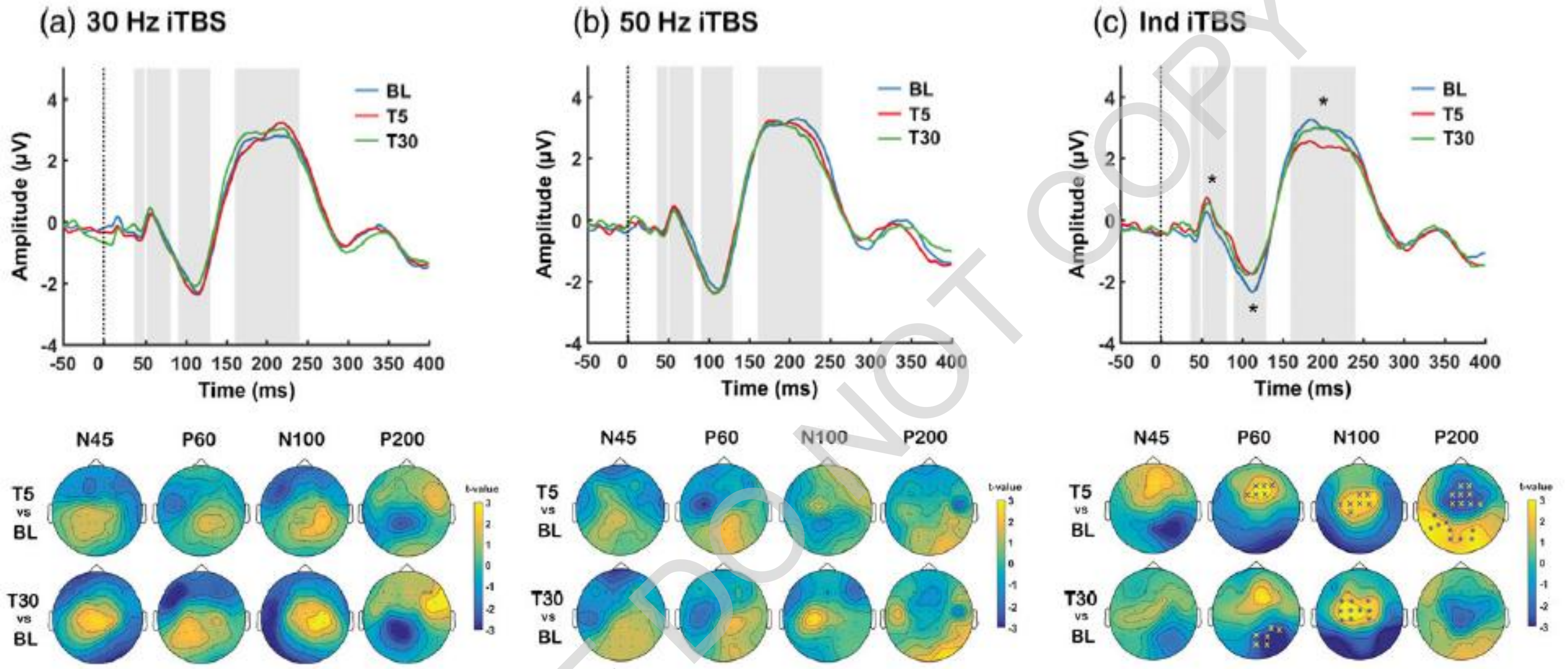


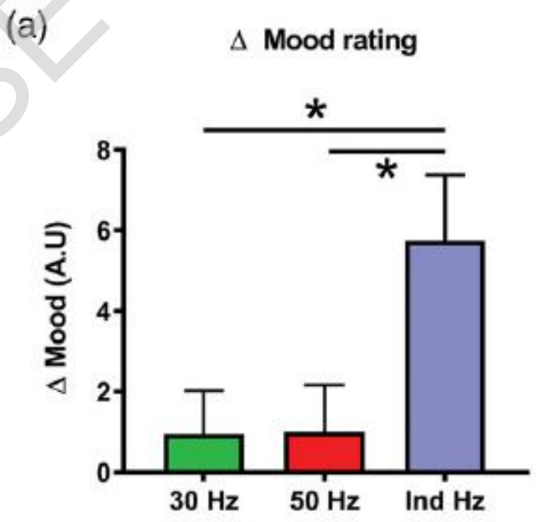
Theta burst using individual theta-gamma coupling



Chung 2018 *Human Brain Mapping*

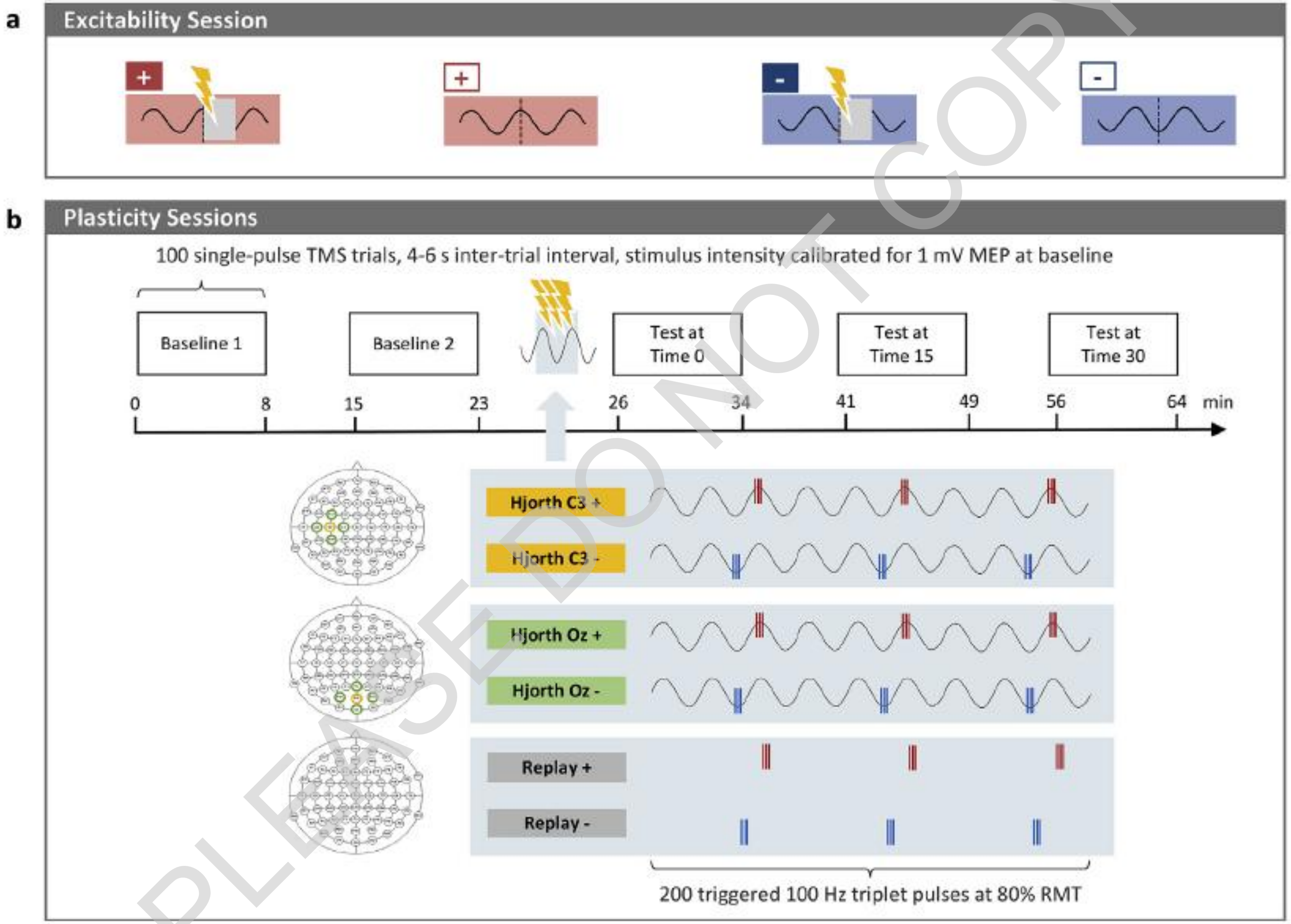
Effects of individualized iTBS?





Chung 2018 Human Br Map

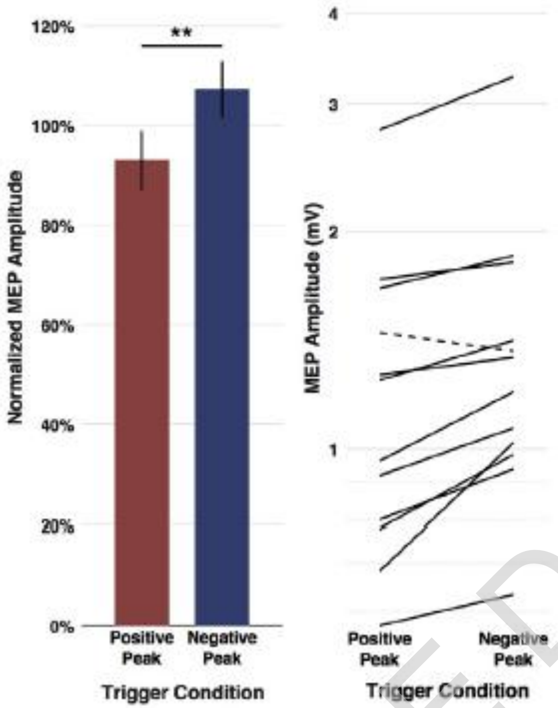
EEG-gated TMS – effect of ongoing rhythms

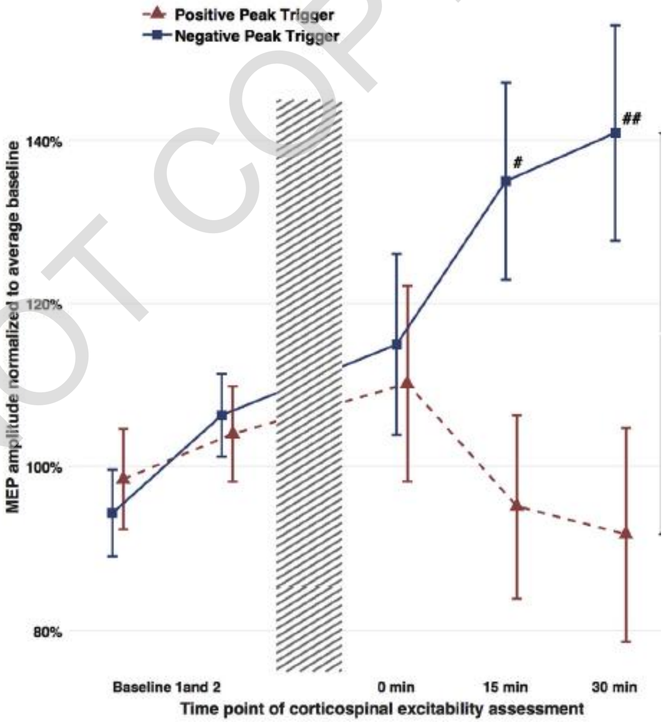


EEG-gated TMS administration

Zrenner 2018 Brain Stimulation

EEG-Gated TMS – brain state effects





- Administering single pulses of TMS at the negative peak of the ongoing Mu rhythm resulted in a larger evoked MEP
- Plasticity protocol: 200 triple pulses (3 pulses at 100 Hz) and 80% RMT administered at peak vs trough of Mu rhythm. Significant increase in cortical excitability with trough stimulation only

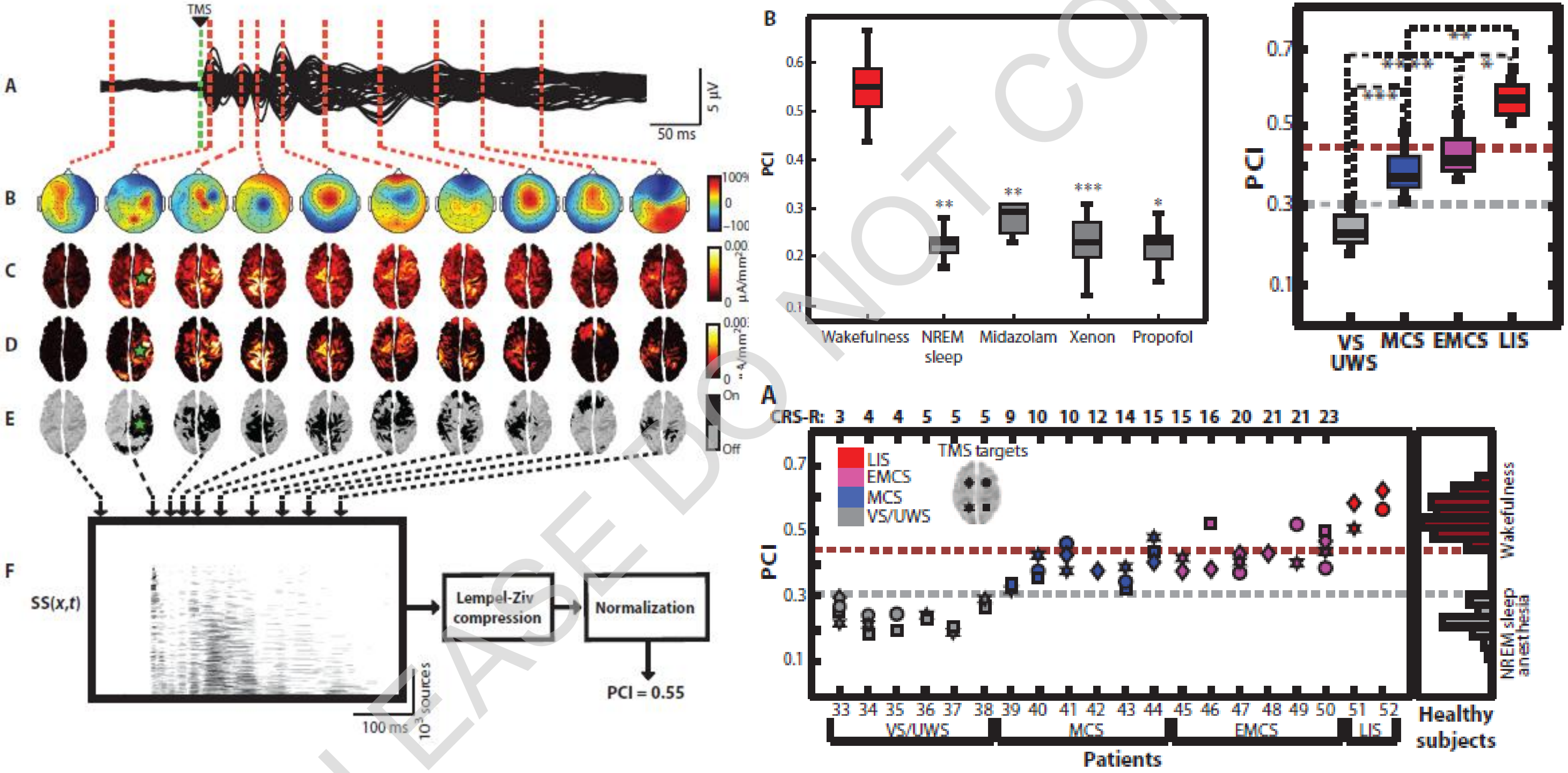
Zrenner 2018

Talk Overview

- Intro to TMS and EEG
  - What does EEG measure and TMS generate/activate in the brain!!!
- Technical issues and challenges
  - EEG compatibility
  - Artifacts, artifacts and artifacts!!!
- Neuroscience Applications of TMS-EEG
- Clinical Applications of TMS-EEG

Diagnosis of Persistent Vegetative vs Minimally Conscious State

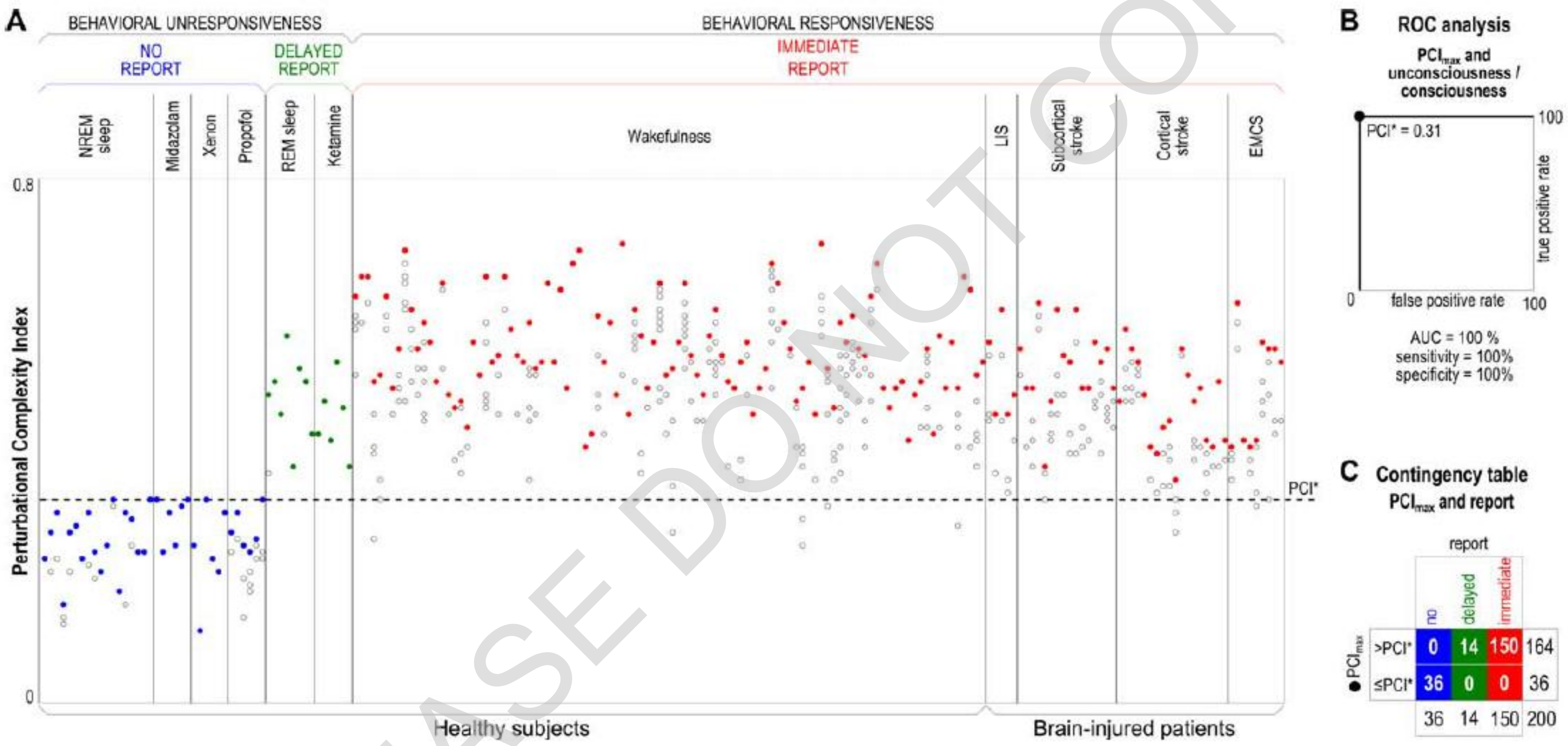
Casali 2013



Decreased complexity of evoked response in subjects with loss of consciousness due to any etiology, and in patients with vegetative versus minimally conscious versus locked-in states

M/F

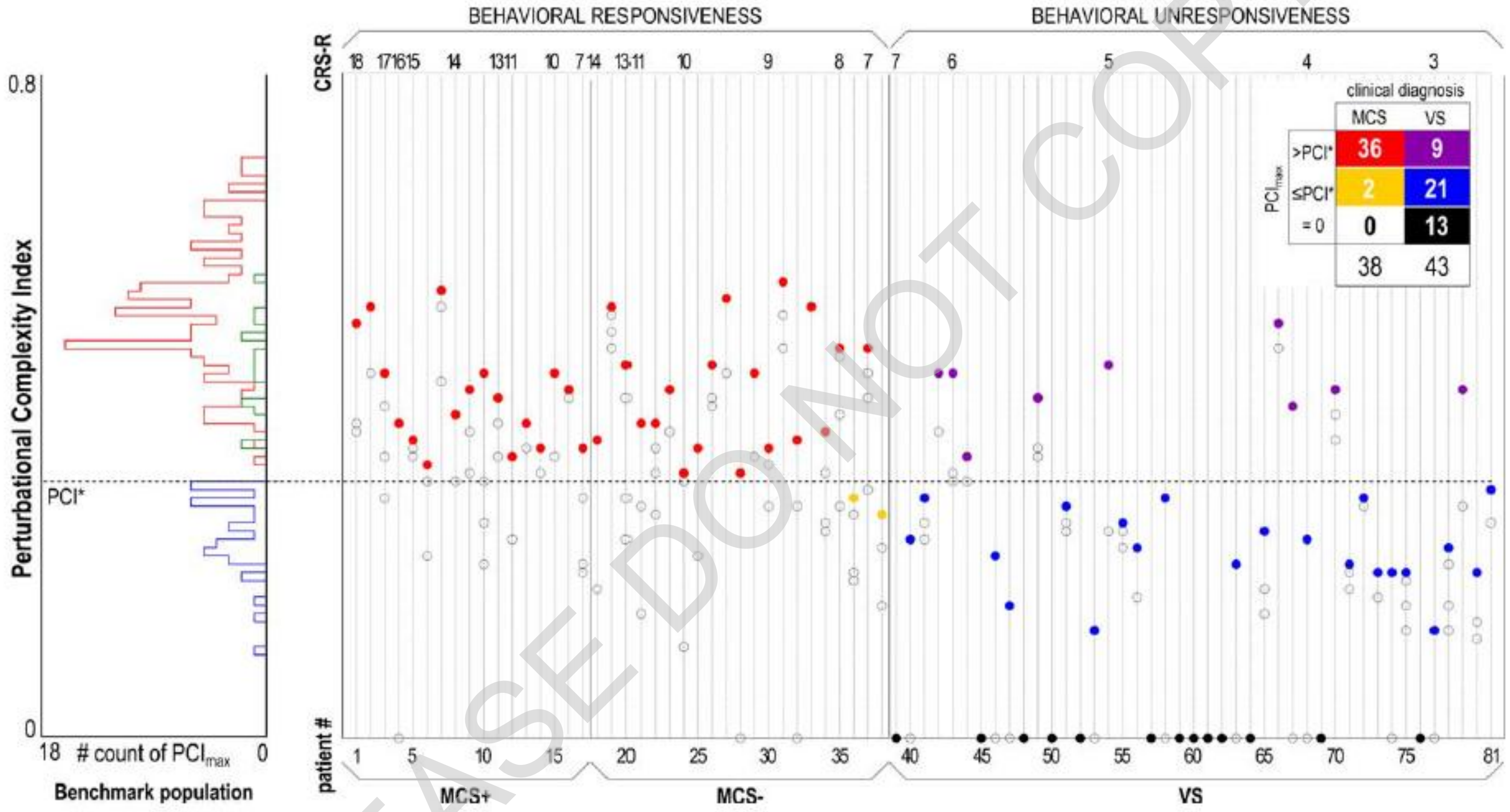
Then assessed across large population



Identified a threshold PCI of 0.31 that differentiated between conscious and unconscious individuals

Casarotto 2016 *Ann Neurol*

And applied to a large new population

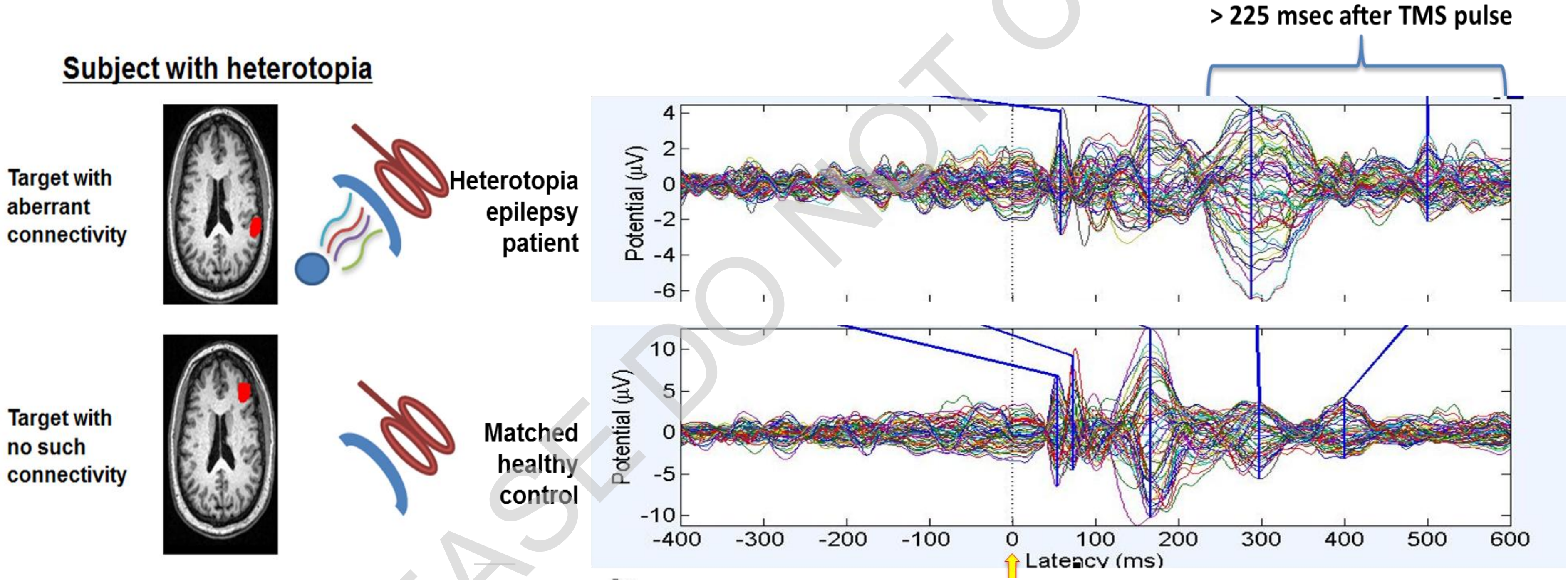


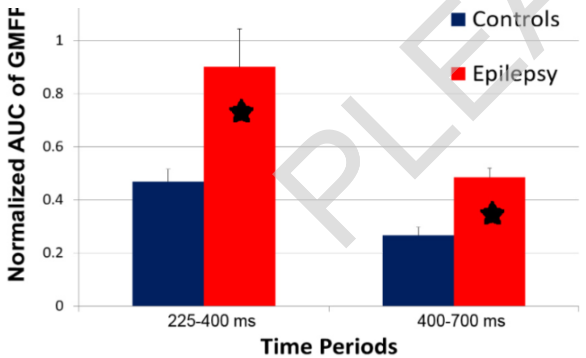
- Max PCI threshold correctly identified 36/38 minimally conscious patients
- Vegetative patients divided into 3 categories: 13 with no obtainable complex response, 21 with subthreshold PCI, and 9 with suprathreshold PCI
- 6 months after testing, 6/9 suprathreshold PCI VS patients became MCS, versus only 5/21 subthreshold and 0/13 absent PCI

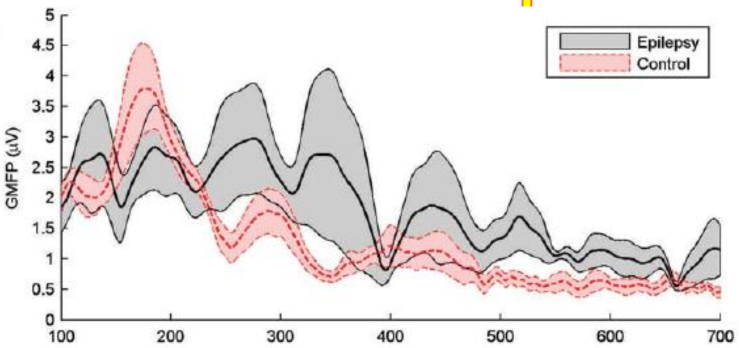
Casarotto 2016 *Ann Neurol*

Increased TEPs in epilepsy

Increase in delayed evoked activity in patients with active epilepsy as compared to controls. Abnormal delayed activity is more prominent in regions with functional connectivity to regions of abnormal cortical development



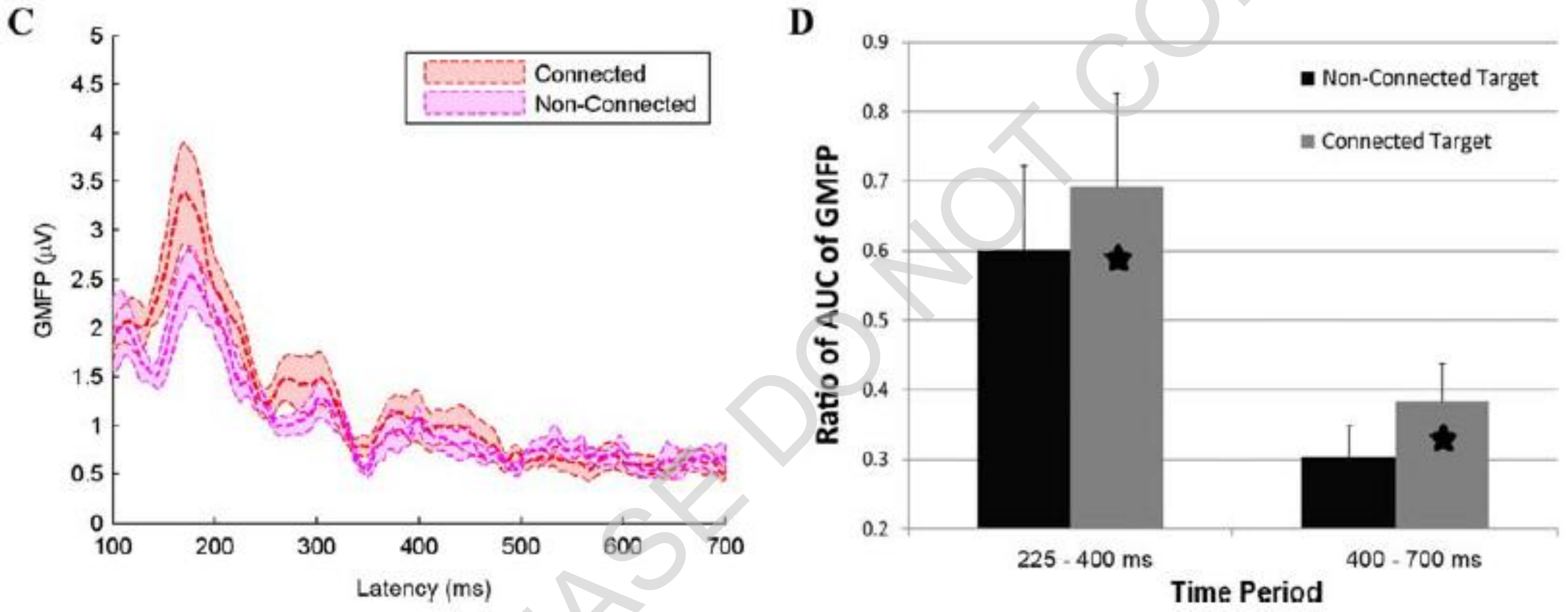




Event-related potential tracings associated with TMS stimulation

Shafi, 2015 *Ann Neurol*

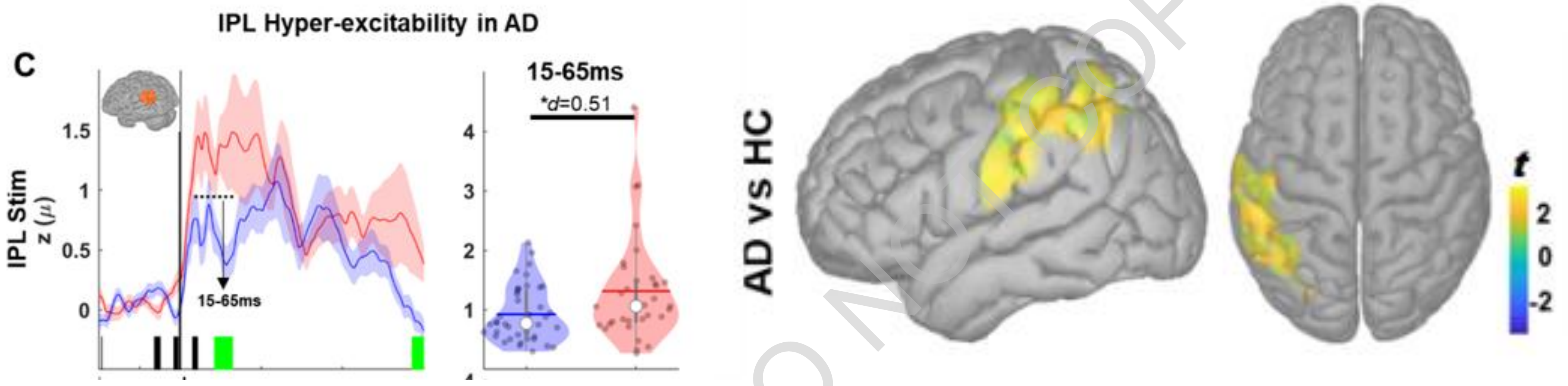
Site-specificity of abnormal evoked activity



- Significantly greater delayed activity with stimulation of site functionally connected to heterotopic nodules

Shafi 2015 *Ann Neurology*

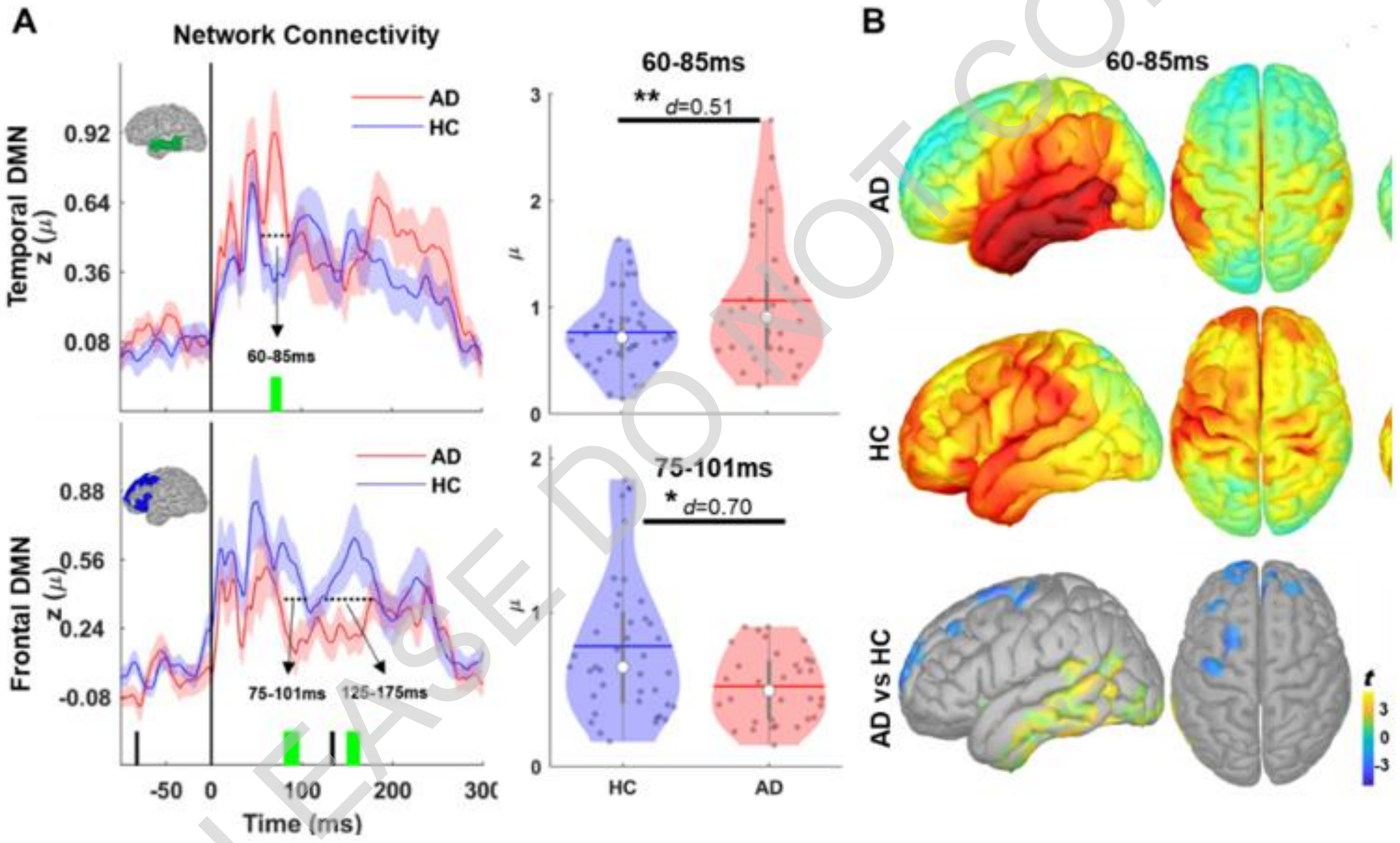
Cortical physiology abnormalities in AD



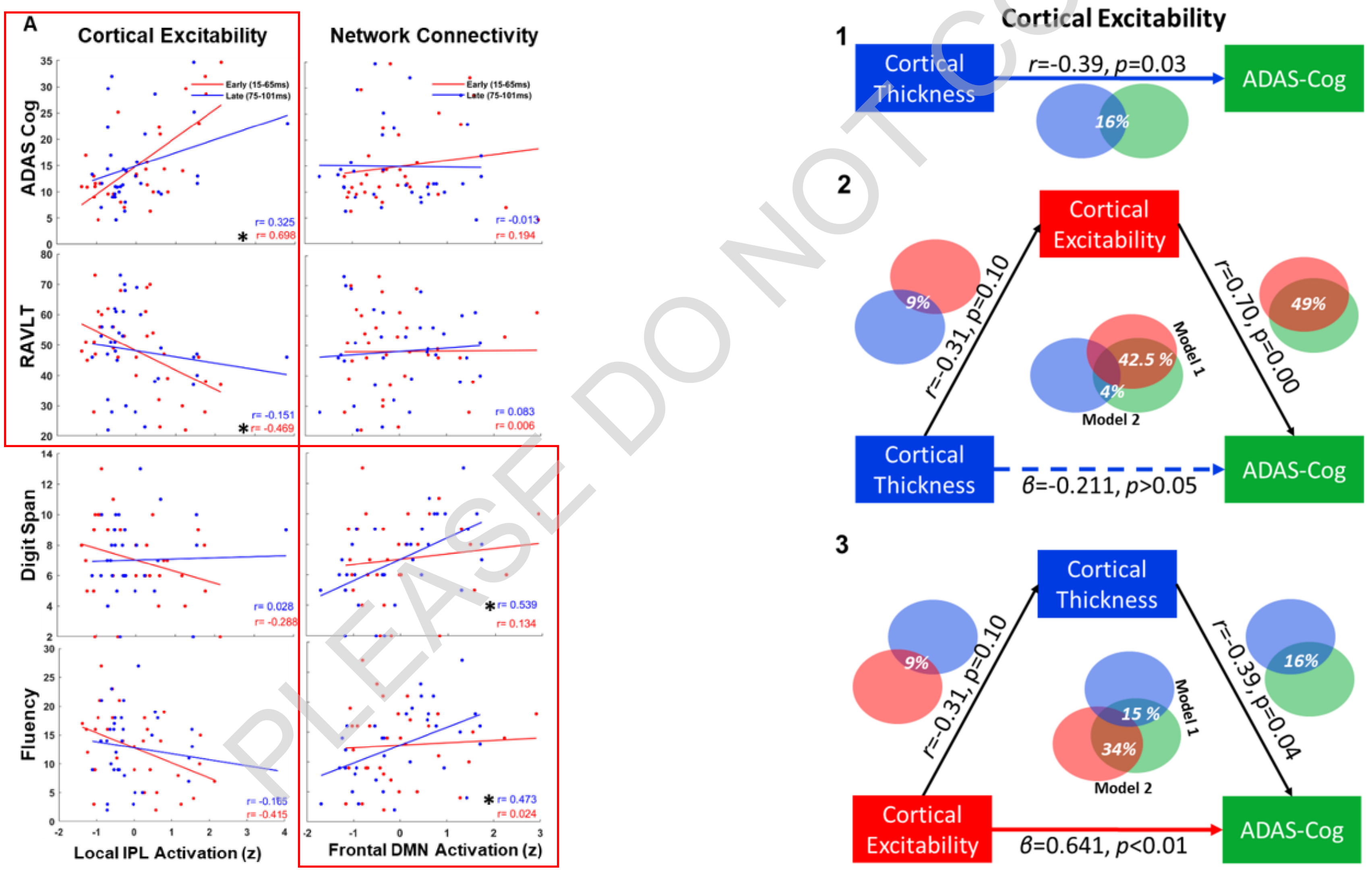
- Animal models and imaging studies suggest that there is hyperexcitability within the Default-Mode Network in early AD that contributes to cognitive symptoms and disease progression
- Here, TMS-EEG is used to demonstrate local hyperexcitability with stimulation of the inferior parietal node of the DMN in humans with AD

Ozdemir 2025, *Scientific Advances*

Temporal hyper- but frontal hypo-connectivity



Highly correlated with cognition and mediates effects of structural atrophy



What is the Added Value of TMS+EEG

Advanced Technology

Monitor cortical activation with **high temporal resolution**

A more **direct** measure of TMS effect

EEG guided TMS

Neuroscience

Examine physiology of motor AND non-motor regions at various mental states of sleep, rest, cognitive processing

- Local excitation, inhibition & plasticity
- Functional (causal!!!) connectivity between regions
- Investigate the mechanisms and effects of rTMS
- Disrupt behavior to examine causality

Clinical Application

Diagnosis and prognosis

Biomarkers to track response to therapy

Safety monitoring during rTMS (e.g., in epilepsy)

Learn more!

TMS combined with EEG: Recommendations and open issues for data collection and analysis

Julio C. Hernandez-Pavon[a, b, c, 1, *], Domenica Veniero[d, 1, **], Til Ole Bergmann[e, f], Paolo Belardinelli[g, h], Marta Bortoletto[i], Silvia Casarotto[j, k], Elias P. Casula[l], Faranak Farzan[m], Matteo Fecchio[n], Petro Julkunen[o, af], Elisa Kallioniemi[p], Pantelis Lioumis[q, r], Johanna Metsomaa[q, r], Carlo Miniussi[g], Tuomas P. Mutanen[q, r], Lorenzo Rocchi[s, t], Nigel C. Rogasch[u, v, w], Mouhsin M. Shafi[x], Hartwig R. Siebner[y, z, aa], Gregor Thut[ab], Christoph Zrenner[h, ac, ad, ae], Ulf Ziemann[h, ad], Risto J. Ilmoniemi[q, r]

Review

Clinical utility and prospective of TMS–EEG: Updated review from an international expert group☆

Ulf Ziemann[a,b,*], Yang Bai[c,d], Fiona M. Baumer[e,f], Mikkel M. Beck[g], Paolo Belardinelli[b,h], Daniele Belvisi[i,j], Stephan Bender[k], Til Ole Bergmann[l,m], Marta Bortoletto[n], Silvia Casarotto[o,p], Elias Casula[q,r], Arthur R. Chaves[s,t], Daniel Ciampi de Andrade[u], Antonella Conte[i,j], Zafiris J. Daskalakis[v], Faranak Farzan[w,x,y], Fabio Ferrarelli[z], Paul B. Fitzgerald[aa,ab], Pedro C. Gordon[a,b], Christian Grefkes[ac], Sylvain Harquel[ad], Julio C. Hernandez-Pavon[ae], Aron T. Hill[af], Kate E. Hoy[ag], Friedhelm C. Hummel[ah,ai,aj], Petro Julkunen[ak,al], Elisa Kallioniemi[am], Corey J. Keller[f,an,ao], Vasilios K. Kimiskidis[ap], Melissa Kirkovski[af], Giacomo Koch[aq,ar], Giorgio Leodori[i,j], Pantelis Lioumis[as,at], Sara Määttä[au,av], Inbal Maidan[aw,ax,ay], Marcello Massimini[o,p], Annerose Mengel[a,b], Johanna Metsomaa[as], Carlo Miniussi[h], Tuomas P. Mutanen[as], Yoshihiro Noda[az,ba,bb], Recep A. Ozdemir[bc,bd], Estelle Raffin[ad], Lorenzo Rocchi[be], Nigel C. Rogasch[bf,bg,bh], Mario Rosanova[o], Emiliano Santarnecchi[bc,bi], Simone Sarasso[o], Siobhan M. Schabrun[bj,bk], Mouhsin M. Shafi[bc,bd], Hartwig R. Siebner[g,bl,bm], Else A. Tolner[bn,bo], Leo Tomasevic[g,bp,bq], Sara Tremblay[s,br,bs,bt,bu], Caroline Tscherpel[ac], Domenica Veniero[bv], Viviana Versace[bw], Daphne Voineskos[bx,by,bz], Steve Vucic[ca], Abraham Zangen[cb], Christoph Zrenner[bx,by,cc,cd], Risto J. Ilmoniemi[as]