Combining TMS and EEG

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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

Outcome Measures

 MEP Amplitude
This is cool, But ...

What Is Missing?

- Cortical origin?
- Non-motor regions?
- State-Dependency?
- Changing brain activity states in disease conditions?

Motor Responses
MEPS
EEG to the rescue?

Berger’s Waves

EEG in humans introduced by Hans Berger in 1920s
EEG: What are we recording?

Mostly captures the synaptic activity at the surface of the cortex.

EPSP + IPSP generated by synchronous activity of neurons.

Interplay between excitatory pyramidal neurons and inhibitory interneurons.
EEG language?

- **Amplitude (or Power)**
  - Strength $(\mu V \text{ or } \mu V^2)$

- **Frequency**
  - # of Cycles/Second (Hz)

- **Phase**
  - (Radians)

**Graphs:**
- 10Hz
- 20Hz
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 $X_i(f)$

- Imag
- Real

Magnitude

Phase

- Delta
- Theta
- Alpha
- Beta
- Gamma

$10 \log(\mu V^2/Hz)$

- Frequency ~ 10 Hz
- Instantaneous Phase ~ $\pi/2$
- Instantaneous Amplitude ~ 24 $\mu V$

- Frequency ~ 20 Hz
- Instantaneous Phase ~ $\pi/2$
- Instantaneous Amplitude ~ 5 $\mu V$

EEG Signal

0.5 Sec

$10 \mu V$
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 Desynchronization (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?

1 – EEG is a summation of excitatory and inhibitory synaptic activity.

2 – EEG has different spatial, spectral and temporal architecture under anesthesia, during sleep, in resting wakefulness, or during sensory processing or higher order cognitive performance.

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
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Marrying TMS with EEG ... the problems ...
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
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

Virtanen et al., 1999

- Temp \sim r^2
- Temp \sim B^2
- Temp \sim \text{metal electrical conductivity (}\sigma\text{)}
There were all kinds of other issues too...

- We learned that TMS induces a secondary current (eddy current) in nearby 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;
Other problems

**TMS click is loud!**

~ 100 dB 5 cm of the coil

**TMS induces auditory evoked potentials**

Air & Bone Conducted

- Normal TMS
- 2 cm & plastic
- 2 cm above the scalp

Some Solutions

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

Nikouline 1999

Massimini 2005
And some remain problematic...

TMS may cause motor responses in scalp muscles

Some Solutions

Changing the coil angle to stimulate muscles less

EMG artifact removal after recording

Independent Component Analysis
Site of stimulation is critical
Other difficulties

TMS may induced eye blinks

Some Solutions

- EOG Calibration Trial
- Delete Contaminated Trials
- Independent Component Analysis (ICA)
Some Tricks!!

Minimize residual artifact online (i.e., during recording)

Removing artifact offline (i.e., after the fact)
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
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

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

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
ICA can remove artifactual components

Rogasch et al. *NeuroImage* 2014: Used ICA to remove components that are likely muscle and decay artifacts related to stimulation
**Clean**

Rogasch et al., *NeuroImage*, 2014
Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software

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

Sravya Atturi\textsuperscript{1,2,} Matthew Frehlich\textsuperscript{1,2,} Ye Mei\textsuperscript{4}, Luis Garcia Dominguez\textsuperscript{1,} Nigel C. Rogasch\textsuperscript{4}, Willy Wong\textsuperscript{2,3}, Zafiris J. Daskalakis\textsuperscript{5,6} and Faranak Farzan\textsuperscript{1,6*}
Take Home Message
What do I need to do if I want to go back home and try this?
Step-by-Step Guideline:

1. Select an Input [Figure 2 Input]
   - TMS protocol
   - TMS input location
   - TMS time of administration

2. Control for the Brain State [Figure 2 Brain State]
   - Developmental, behavioral, disease states, brain dynamics (if applicable)

3. Use a TMS Compatible EEG System
   - Appropriate hardware
   - Appropriate amplifier set-up

4. Prepare the EEG CAP
   - Minimize sensor and skin impedance
   - Proper placement and arrangement of sensors and wires
   Caution: Avoid direct contact between the TMS’ coil and the reference electrode

5. Select Control Conditions
   - Placebo or no-task conditions
   - Auditory masking
   - Coil orientation
   - Calibration trials

6. Data Collection
   - Appropriate number of trials per condition accounting for potentially substantial bad trials
   - Impedance monitoring
   - Online neuronavigation
   - Layer of foam between coil and electrodes

7. Data Processing
   - Remove bad sensors/trials
   - Remove large amplitude TMS pulse artifact or large EMG
   - Offline filters to remove frequency-specific noise
   - ICA or other approaches to remove general and TMS-related EOG, EMG, ECG or electrode movements
   - Interpolate deleted sensors (optional)
   - Re-referencing (optional)
   - Source Localization (optional)

8. Data Analysis [Figure 2 Output]
   - Select EEG outcome measures
   - Select output locations
   - Select time windows

9. Statistical Analysis

What then?

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What is the added value?

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

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And understand relationship between brain and behavior

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And possibly ...

EEG-gated TMS!

Concurrently Stimulate & Record

Manual Adjustment

Recording (output)

Stimulation (input)

Adjust Stimulation Parameters Based on the Recording
# Added Value of TMS+EEG

<table>
<thead>
<tr>
<th>Advanced Technology</th>
<th>Monitor cortical activation with <strong>high temporal resolution</strong></th>
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<td>A more <strong>direct</strong> measure of TMS effect</td>
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<table>
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<tr>
<th>Neuroscience</th>
<th>Examine physiology of <strong>motor AND non-motor</strong> regions at various mental states of sleep, rest, cognitive processing</th>
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<tr>
<td></td>
<td>- Local excitation, inhibition &amp; plasticity</td>
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<td></td>
<td>- Functional connectivity between regions</td>
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<td>- Disrupt behavior to examine causality</td>
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<tr>
<th>Clinical Application</th>
<th>Improve diagnosis</th>
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<td>Investigate the mechanism of actions of rTMS therapy</td>
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<td></td>
<td>Safety monitoring during rTMS (e.g., in epilepsy)</td>
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Single Pulse TMS-EEG
In 1989, Cracco et al., examined transcallosal responses by applying TMS to one side and recording EEG from the other side.

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, *Electroencephalograph Clin Neurophysiol*
Temporal Evolution of TMS induced Potentials

Motor Cortex

Visual Cortex

Ilmomiemi et al., Neuroreport 1997
TMS Induces Several EEG Peaks

**N15–P30; N45; P55; N100; P180**

Komssi, Human Brain Mapping, 2004

Other Earlier or Later References: Paus 2001; Komssi, 2002; Ferreri 2010;
TMS Induced Cortical vs. Motor Response

The N15-P30 correlated with the amplitude of MEP at the periphery

Maki & Ilmoniemi 2010

N100 may be related to inhibitory mechanism

Bender et al., 2005; Bonato et al., 2006
Farzan et al., 2013
Stimulation of non-motor regions

Potentials produced by DLPFC stimulation are correlated with, but smaller than, potentials produced by motor cortex stimulation. Motor cortex TEPs increase faster with higher intensity of stimulation than DLPFC TEPs

Kahkonen 2004
TMS generates a clear EEG response even below motor threshold!

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

Komissi et al, Human Brain Mapping, 2004

Kahkonen 2005
Single-pulse TMS produces waves of activity in spatially separate locations in awake subjects

Massimini 2005
**Power of spontaneous alpha oscillations** in the sensorimotor cortex immediately prior to administration of TMS is negatively correlated with TMS-evoked MEP amplitudes (Sauseng 2009; Zarkowski 2006)

The amplitude and phase of the mid-range beta oscillations recorded distally over the occipital cortex correlated with subsequent TMS-evoked MEP amplitudes (Maki & Ilmoniemi 2010)
Natural Frequency of Human Thalamocortical Circuits

“Natural frequency may provide information about the structure, state and property of the underlying tissue.”

Rosanova et al, JNeuroscience, 2009
Reduced in psychiatric dz

Canali 2015 J Affective Do
Paired Pulse TMS-EEG
TMS-EEG used to assess LICI in Motor and Prefrontal Cortex

Daskalakis 2008
Prefrontal LIC is correlated with WM

Rogasch 2015 Cortex
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 et al, in preparation
Neuroscience Applications
Breakdown of effective connectivity during sleep and with anesthesia

Massimini 2005

Ferrarelli 2010
Task-specific signal transmission from PFC in visual selective attention

Morishima 2009: TMS applied to FEF during performance of a visual discrimination task for motion direction or visual gender.
Use EEG and rTMS to Induce Natural Brain Oscillations Observed During Cognitive Tasks

Thut 2011: Showed that alpha-TMS targeted to the source of EEG alpha activity can upregulate the targeted alpha-oscillations in the attention network.

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
And assess whether EEG or MRI connectivity measures predict propagation.

Vink et al, in preparation
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But first ... Are TMS-EEG Indices Valid & Reliable?
Validity and Reliability of TMS-EEG: Hopeful Signs of Progress

**Validity**: Often comparing conventional TMS-EMG measures with TMS-EEG measures to establish validity

Reference(s): Farzan 2010; Maki 2010 & 2011; Ferreri 2011

**Test-retest reliability**: E.g., temporal characteristics such as EEG peaks evaluated in PFC and MC or LICI induced modulation of cortical oscillations.

Reference(s): Lioumis 2009; Farzan 2010; Casarotto 2010
Example of Validation

Farzan 2010

% EEG inhibition at motor cortex

% EMG inhibition at right APB

r = 0.85
p<0.0001

100ms

EMG

Computer

EEG

EEG Computer

EEG at C3 (µV)

Time (ms)

M/F

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Example of Reliability

Retest after one week

A high overall reproducibility ($r > 0.80$) was observed for both motor and prefrontal cortex

Lioumis et al., 2009
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
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
Diagnosis of Schizophrenia vs. Bipolar Disorder

NO difference in EMG measure of LICI. Only selective deficit when LICI measured for gamma oscillations in the DLPFC. Increased delayed activity with motor cortex stimulation in schizophrenia patients versus healthy subjects.

Farzan 2010 Brain

Other TMS-EEG in SCZ: Ferrerali 2009
Regional cortical hyperexcitability 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.

Shafi, 2015 Ann Neurol
That may correlate with seizure focus!

Sources of abnormal delayed activity (A, B) spatially colocalized with interictal discharge (C, E) and seizure onset zones (D, F) even though stimulation site was far away (red dot in above figure)

Shafi 2015 Ann Neurol
EEG-Guided TMS

**Selection of Location of Stimulation Target**
- Anatomic focus of abnormal EEG activity (e.g. epileptic focus; Rotenberg 2009)
- Cortical source of EEG rhythm of interest (Thut 2011)

**Titration of strength, frequency or length of stimulation**
- To individual brain frequencies (Klimesch 2003); Jin 2012 (schizophrenia); Leuchter 2015 (depression)
- To specific size of TEP response, or to specific evoked brain responses (e.g. slow waves; Massimini 2007)

**Timing of delivery of TMS stimulation**
- To administer stimulation when the underlying cortical state is more uniform, or when stimulation is more likely to achieve a specific result (Romei 2008, Sauseng 2009)
- To administer TMS at specific phases of ongoing cortical rhythms (Maki and Ilmoniemi 2010; Dugue 2011)

**Identification of subjects**
- Subjects with expected behavioral response to a particular TMS protocol (Rizk 2013)
- Patients likely to respond to a specific rTMS treatment protocol

**Duration of stimulation**
- Administration of TMS treatment until specific EEG biomarkers are achieved
Rotenberg et al, 2009: rTMS may have beneficial effects in treatment of Epilepsia Partialis Continua
And in refractory status

- 24M develops new onset refractory status epilepticus from left occipital region
  - Recurrent hospitalizations over 6 month period for 5-30 seizures per day despite multiple antiseizure medications, burst-suppression

VanHaerents et al, Clin Neurphys 2015
rTMS to seizure source leads to control

VanHaerents et al, Clin Neurphys 2015
rTMS to EEG source in tinnitus

Wang 2015 PLOS One
rTMS at IAF for Depression

ITT Analysis Population
n = 202
Active n=103  Sham n=99

Excluded from PP Analysis Population
Active n=44  Sham n=38
17 – Premature Discontinuation
16 – Did not receive 80% of treatments in 60 days
11 – Incorrect IAF

PP Analysis Population
n = 120
Active n=68  Sham n=61

Leuchter 2015 Br Stim

* P < 0.033
Summary

### Input Location
- **Anatomically guided**: Scalp landmark, Brain atlas, MRI, DTI
- **Functionally guided**: fMRI, TMS, EEG

### TMS Input Protocol
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Mechanism</th>
<th>Neurobiology</th>
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<tbody>
<tr>
<td>Single pulse</td>
<td>Excitation, Inhibition</td>
<td>NMDA, GABA</td>
</tr>
<tr>
<td>Paired Pulse</td>
<td>Local &amp; Long-range Excitation, Inhibition, Connectivity</td>
<td>NMDA, GABA, Acetylcholine, GABA</td>
</tr>
<tr>
<td>Repetitive TMS</td>
<td>Plasticity</td>
<td>NMDA</td>
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### Output Location
- Selected sensors or sources
  - All sensors (topography)
  - All sources (tomography)

### EEG Output Measures

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

### 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

### Input Time
- Guided with respect to a brain state

### Output Time
- Relative to input time
- Relative to a brain state

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Develop
In Vivo Techniques

Understand the Physiology of Healthy Human Brain

Prevention Diagnosis Rehabilitation Treatment

Technology
Neuroscience
Clinical Application

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