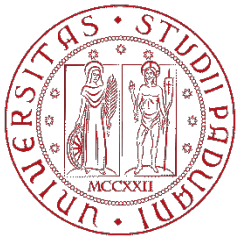

UNIVERSITY OF PADOVA

Department of General Psychology

Master Degree in Cognitive Neuroscience and Clinical Neuropsychology

Final dissertation

Optimization of Transcranial Magnetic Stimulation (TMS) parameters using concurrent TMS-EEG and TMS-fMRI

Supervisor

Professor: Antonino Vallesi

Co-supervisor

Professor: Till Ole Bergmann

Candidate: **Milad Amin Masouleh**

Student ID number: 1230501

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method that has shown diagnostic, therapeutic and research potential in the central nervous system (CNS), with research and clinical uses still evolving. Efficient TMS involves finding an optimal target location, i.e., coil position and orientation over a target brain region. Despite being an important procedure, there are no standard guidelines addressing the optimal procedure for TMS hotspot search. We used TMS evoked EEG potentials (TEPs) measured using concurrent TMS-EEG to propose a TMS hotspot search procedure. We also proposed the means to validate the TMS hotspot search procedure using TMS evoked BOLD response measured using concurrent TMS-fMRI. Although the presented TEPs evidence to characterize a genuine TMS hotspot is convincing, the TMS-fMRI-based evidence is insufficient and limited to claim any generalized validation of the proposed procedure. It reflects that future studies are needed to conduct further research validations.

Table of abbreviations/definitions

EEG	Electroencephalogram
EMG	Electromyogram
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
MSO	Maximum stimulator output
PES	Peripheral electrical stimulation
RMT	Resting motor threshold
TEPs	TMS-evoked EEG potential
TMS	Transcranial magnetic stimulation
TEBRs	TMS Evoked BOLD Responses

NIC	Neuroimaging Center
FDI	first dorsal interosseous muscle
E-field	Induced electric field
fMRI	functional MRI
MRI-B91	MagVenture TMS-Compatible coil
C-B60	MagVenture TMS Coil
X100	MagVenture TMS Stimulator
BEST	Brain Electrophysiological recording and Stimulation toolbox
Neuronavigation	MRI based Stereotactic Neuro-Navigation

Chapter one:

Introduction

Introduction

Non-invasive brain stimulation (NIBS) techniques are capable of neural modulation of specific brain areas and networks, primarily through induced electromagnetic or electric fields. NIBS tools have emerged as investigative means to explore brain functions and as therapies for neuropsychiatric conditions where the more conventional medications or therapies have not been effective (Reti, 2015). An increase in our knowledge of brain functions and their circuits and the development of state-of-the-art technologies to target more specific networks and regions focally has interested many researchers in the field of brain stimulation in the past decade. Beyond that, an increase in the proportion of neuropsychiatric disorders worldwide considers more innovative approaches parallel to the conventional psychotherapeutic or pharmacological treatments (Reti, 2015).

To better understand the effects of brain stimulation, we need to comprehend how brain circuits work, which somehow mediate functional and impaired brain activities. Brain stimulation triggers neural activation, which causes a cascade of events at the molecular level. The consequences of brain stimulation are typically transitory but, depending on the stimulation parameters and duration, and the number of sessions could also result in longer-lasting synaptic changes. These techniques include Transcranial Magnetic Stimulation (TMS), Cranial Electrotherapy Stimulation (CES), Transcranial Electrical stimulation (tES), deep brain

stimulation (DBS), Vagus nerve stimulation, and recently Transcranial Ultrasound Stimulation (TUS), amongst many other different techniques (Daramani et al. 2022, Reti et al. 2015)

Transcranial Magnetic Stimulation (TMS) is one of the most common non-invasive methods to modulate neural activities and have gained the attention of clinicians and researchers in the past decade. TMS is applied through a coil held over the head (on a specific cortical region of interest), which leads to an electromagnetic induction in the subject's brain. As a result, this current can pass through the skull, penetrate the cortex, and depolarize neurons, which can give rise to several neurophysiological and behavioural consequences based on the region that has been targeted and could modulate its activities (Horvath et al., 2011). On the other hand, one of the main limitations of this method is that TMS can only stimulate up to 3-5 cm in the depth of the cortical area and not in-depth tissue. However, TMS can indirectly induce the needed effects to modulate the neural activities even in the deeper areas via projection fibers and synaptic connections (Bergmann et al. 2020, Deng et al. 2012). Furthermore, the distribution of the manipulation depends on several parameters, such as the orientation of the coil, location of the coil, and stimulation intensity. Neurons on the cortex are mostly oriented perpendicular or parallel to the surface. Therefore, the orientation of the coil has an essential role in the brain's response to the stimulation. Besides that, because of the specific orientation of the TMS induced current, folding of the cortex also plays an important role in favoring stimulation of one or another neuronal sub-population (Hernandez-Pavon, Sarvas, Ilmoniemi, 2014). TMS can be applied to measure brain cortical excitability, connectivity, dynamics, and mapping to treat or study several neuropsychiatric disorders (Hernandez-Pavon, Sarvas, Ilmoniemi, 2014). Induced current results in Better excitation and inhibition activation or deactivation of brain networks

that leads to a top-down cascade of events and modulate the activities in the other regions in the same network. Investigation of this direct effect of TMS on the region of interest and registering brain response provides a great opportunity to study brain functions in a cause-and-effect paradigm.

Our understanding of the effect of TMS on the cortex mostly roots in studies applied to the primary motor cortex. Inducing stimulation in this region evokes activity in the contralateral muscles of the body. This activity can be measured using electrophysiological techniques, such as electromyography (EMG) or electroencephalography (EEG). On the other hand, delivering stimulation to most brain regions has no visible effects – except for the visual cortex, which can elicit phosphenes in the subjects and the primary motor cortex, which can elicit motor-evoked potentials and manifest movements. Therefore, combining TMS with other neuroimaging modalities such as EEG to investigate the brain's readout seems very promising (Hernandez-Pavon, Sarvas, Ilmoniemi, 2014).

TMS has been combined with magnetic resonance imaging (MRI) and computed tomography (CT) to measure the effect of TMS on the structural features of the brain (Schramm et al., 2020), functional magnetic resonance imaging (fMRI) to measure the blood-oxygen-level-dependent (BOLD) response to the TMS pulses (Bergmann et al., 2021), electroencephalogram to register the TMS elicited electromagnetic responses (Conde et al., 2019), as well as Positron Emission Tomography (Cuypers et al., 2021) and near-infrared spectroscopy (Park et al., 2013) as shown in a summarized **Figure 1**.

TMS combined with the aforementioned neuroimaging techniques can be used in an online or offline protocol. In an online method, TMS is applied during the neuroimaging data acquisition, which allows us to measure the immediate brain response (inhibition or facilitation). In an offline method, TMS applied before/after the neuroimaging data acquisition helps to evaluate the lasting changes in brain activity produced by rTMS. Based on the neuroimaging techniques, performing concurrent TMS in an online approach could be more challenging. In general, concurrent TMS and neuroimaging techniques can be useful to measure the immediate brain response or task-relevant activities and, in turn, as a tool to probe the brain responsiveness or brain mapping.

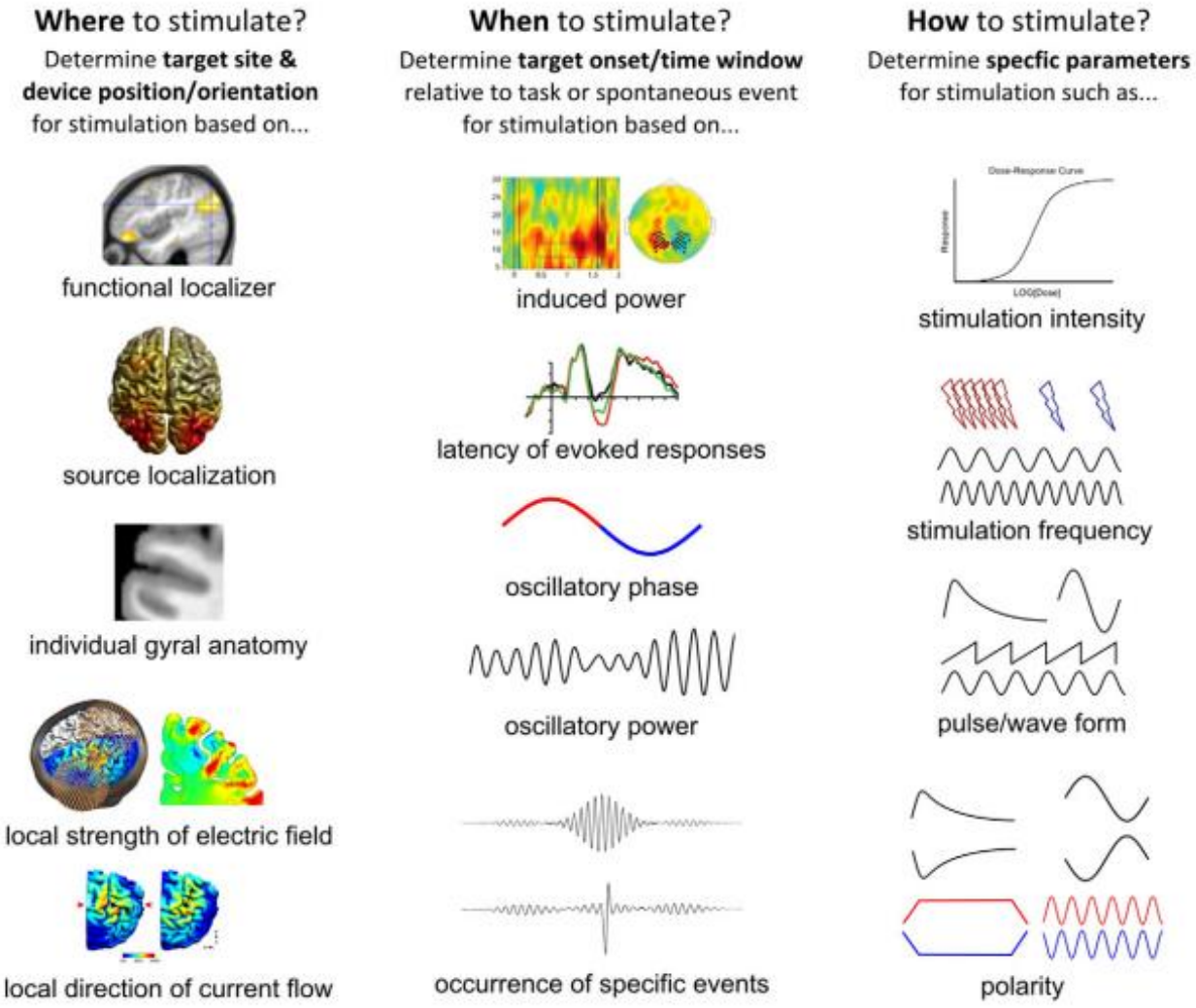

Figure 1: Neuroimaging methods help to know where, when, and how to stimulate (from Bergmann et al., 2016)

Due to the lack of solid knowledge about TMS effects on the less investigated brain regions and, at the same time, due to the need to optimize other constraints such as coil orientation, intensity, and frequency, more research on this area to find appropriate readouts seems essential. Many studies have investigated TMS effects using state of the art neuroimaging readouts such

as BOLD response and TMS evoked EEG potentials (TEPs). However, these results do not always present consistent results (Bergmann et al., 2016).

A single TMS pulse evokes a series of time-locked peaks and troughs in electroencephalographic (EEG) recordings of brain activity, which are commonly known as TMS-evoked EEG potentials (TEPs) (Rogasch & et al., 2018). Concurrent TMS with EEG is the only combination that allows getting millisecond time resolution and can help measure the immediate cortical responses to TMS. Recent studies have shown that some specific TMS-evoked potential (TEP) peaks are sensitive to a certain type of neurotransmission. For example, GABA-B receptor-mediated activity is associated with later peaks of TEP acquired from the primary motor cortex (for example, N100). The literature also discussed that earlier peaks in the TEPs acquired from the motor cortex (N45) are related to GABA-A receptors. These properties make TEPs a biomarker to investigate brain disorders and their causes, choose the best treatment for the patients, and monitor the treatment outcomes (Darmani et al., 2016; Manganotti et al., 2015; Premoli et al., 2014).

The first TMS-EEG studies were conducted at the beginning of the 1990s (e.g., Amassian et al., 1992a; Cracco et al., 1989), but this measurement suffered from several technical difficulties, such as artefacts caused by the TMS pulse. Hitherto, many of these problems have been resolved, and the TMS-EEG combination has become an important and very useful technique, for instance, to investigate functional connectivity.

Conde & colleagues (Conde et al. 2019) study showed that, even when considering the most advanced procedure to control peripheral activation during TMS, it still evokes serious off-

target excitations. These peripherally evoked potentials (PEPs) are very similar to TEPs, and it seems that a significant proportion of EEG signals are rooted in sensory inputs caused by TMS pulses. Therefore, it is still unclear if some TEPs necessarily reveal TMS-evoked cortical activities or other artefacts such as eye blinks, facial muscle activities, auditory evoked EEG potentials, sensory-evoked EEG potentials (SEPs) and issues arising from recording cables-electrodes interface, electrode-gel interface, gel-skin interface, and/or equipment.

The applicability of TMS techniques as a clinical tool for therapy, diagnosis, or mapping is limited by the variability of the TEP components. In general, this variability can be divided into three categories:

- inter-subject variability (e.g., muscle pre-activation level, current oscillatory rhythms, and arousal and attention level of the subjects)
- Intra-subject variability (e.g., caused by coil orientation, coil placement, coil shape, and stimulation intensity)
- Other parameters include somatosensory and auditory artifacts caused by TMS pulses (de Goede et al., 2018).

TEPs in general have several specific characteristics (Casarotto et al, 2010):

- TEPs are highly site-specific: If we stimulate two sites, for instance, left premotor and left parietal cortex, at the same intensity, we obtain different EEG responses (Rogasch et al., 2020).
- TEPs are orientation-dependent: If we stimulate the same site with the same intensity but with different coil orientations, we will obtain different EEG responses (Janssen et al., 2015).

- TEPs are intensity-dependent: If we stimulate the same target at different intensities, we will obtain a larger response after stronger stimulation (Conde et al., 2021).

Furthermore, it is not to be ignored that TMS coils have a highly specific predefined surface, but the human head shape is different. Therefore, placing a coil on the scalp surface does not always result in the tangential orientation between TMS induced current and target cortical surface. There is a need to optimize coil position and orientation based on a physiological read-out to overcome this problem. This process is called TMS hotspot search (Koponen, 2017; Stephani, 2016).

A similar hotspot search method is routinely applied, for instance, during ultrasound investigation. As shown in Figure 2, the operator empirically adjusts the location and orientation of the ultrasound transducer to get a proper echo before evaluating a target of interest or organ. Similarly, this approach is routinely applied in the TMS field based on a readout of the motor cortex, namely motor evoked potentials (MEPs). But TMS of non-motor brain regions does not produce an electromyographic evoked response. Such a hotspot searching procedure is only useful in cortical motor regions, but it does not advantage when TMS is employed outside the motor region. The problem of availability of a physiological readout in the non-motor cortical regions is addressed by TMS evoked EEG Potentials or TEPs. TMS activates cortical neurons at the stimulation site, inducing action potentials that cause downstream effects throughout the brain that, in turn, can be observed in EEG as evoked potentials (Casarotto, 2020).

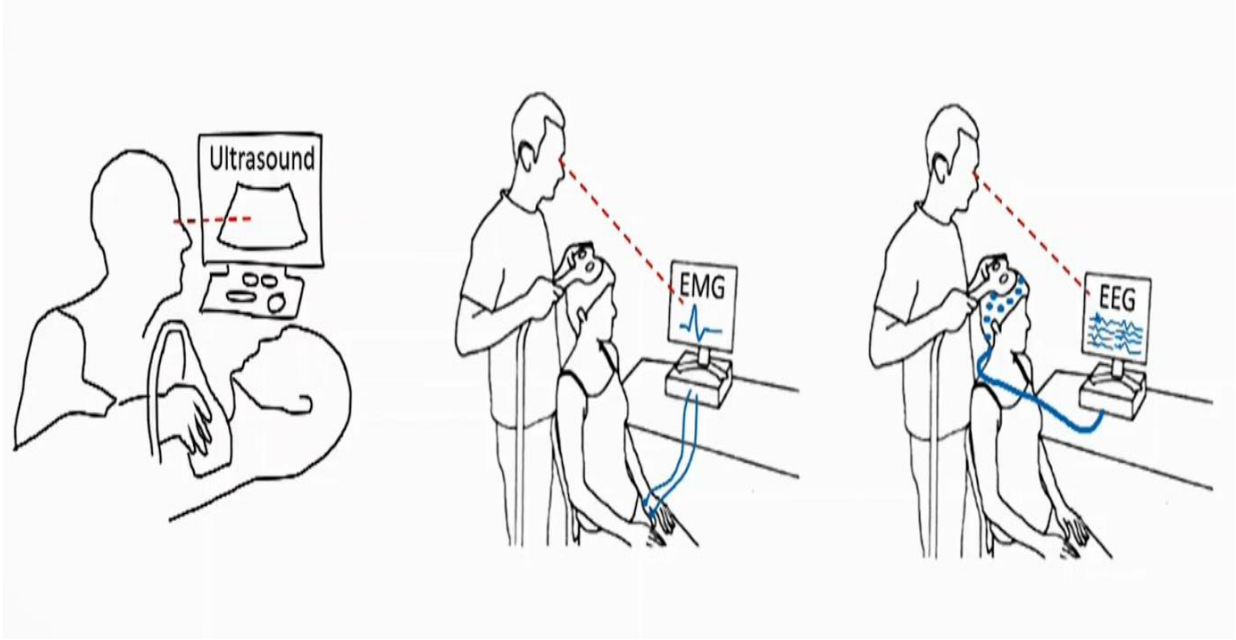

Figure 2: Comparison between ultrasound, EMG, and EEG hotspot search (Figure from Casarotto et al, 2010)

A concurrent combination of TMS with fMRI can also provide a powerful tool to explore the neural mechanisms of TMS effects and a method to investigate the effect of the stimulation on the specific region and the interconnected areas with proper spatial precision. In other words, the TMS-fMRI combination can assess similar properties of the brain as TEPs, but on different temporal and spatial scales (Bestmann & et al., 2008). TMS-fMRI combination can cover the whole brain, including subcortical and deep brain areas, which, in turn, helps explore the effect of TMS on the regional excitability and connectivity between remote areas. Although concurrent TMS-fMRI research started more than 20 years ago, the application of this method is limited to a few research centers, mostly due to the complexity and challenges in data collection. Like the TEPs, the concurrent TMS-fMRI method has some challenges, such as the

artifacts as well as peripheral sensory co-stimulation induced by the TMS coil (Bergmann & et al., 2021). It has also been proposed in review articles that, like for the MEP amplitude evoked by stimulation of the primary motor cortex, a slight rotation in the orientation of coil may result in a change in BOLD response amplitude, as shown in **Figure 3** (Bergmann & et al., 2021). Beyond that, gyral folding patterns, which differ substantially across subjects, and the anisotropy of white matter in the region of interest, can have a high impact on electric fields generated by TMS coils (Opitz & et al., 2013).

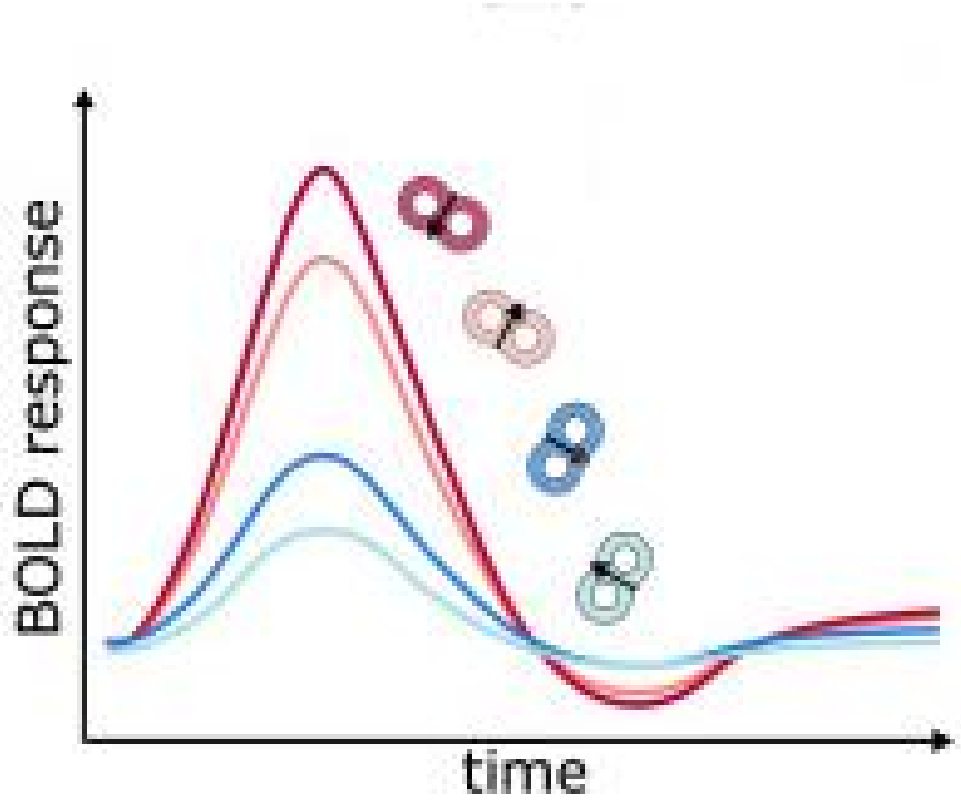

Figure 3: Speculated relationship between TMS coil relationship and TMS evoked BOLD response (Bergmann et al, 2021)

Overall, non-biological causes of intra-subject variability seem less challenging than controlling for the inter-subject variability of measures, which can be achieved through hotspot search optimization (de Goede & et al., 2018). The outcome from a hotspot could be used as a preferred target for TMS-fMRI, TMS-EEG, and TMS-EMG. Therefore, correct stimulation intensity, coil position, and orientation relative to the cortex at a good hotspot (herein after referred as a hotspot) or bad hotspot (herein after referred as a coldspot) are important to identify and isolate before actual stimulation/intervention experimental sessions.

In summary, regarding the similarity between both modalities (e.g., both signals demonstrate the direct or indirect result of synaptic activity instead of firing rate, and both are related to the local field potential), both TEPs and TMS Evoked BOLD response can be potentially advantageous tools for brain stimulation. However, they suffer from certain common challenges. For instance, at certain coil orientations within the same cortical region, the BOLD or EEG response to TMS is pronounced, whereas, at other locations, it is less pronounced or diminished. Currently, there are no standard guidelines addressing the optimal procedure for TMS hotspot search using both MEPs and/or TEPs. In addition, the optimal hotspot may also depend on the outcome measure of choice, i.e., depending on whether MEPs, TEPs, or TMS-evoked BOLD response are used to determine the hotspot and to measure the excitability or responsiveness of the stimulated cortex.

The literature discussed in the introduction covers briefly major topics important in today's non-invasive brain stimulation (NIBS) community. However, the scope of this work is limited and only includes the characterization of the TEPs from the MagVenture MRI-B91 TMS coil so that a TMS hotspot search procedure can be conducted using TMS-EEG and validated using

concurrent TMS-fMRI as first objectve. It is a novel aspect since no TEPs measurements have been reported using MRI-B91 TMS coil so far in the literature. The second objective was to minimize the somatosensory and auditory confounds so that a near genuine TEP can be isolated in real-time for the TMS hotspot search. The third aim was to conduct a meaningful TEP hotspot search, and the fourth to measure TMS evoked BOLD response at the TMS coil locations known as TEP hotspot and TEP coldspot so that the method to derive the hotspot and coldspot can be validated.

Chapter two:

Materials & Methods

Materials & Methods

Subject

The study population consists one male and healthy volunteers at the age of 33 that meet all inclusion and none of the exclusion criteria specified below. The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committee of the Landesärztekammer Rheinland-Pfalz. The participant was recruited based on an inclusion criterion that the MEP resting motor threshold (RMT) of the left primary motor cortex with an increased coil to cortex distance due to the EEG cap on the head and with relatively less powerful MRI-B91 TMS coil should be less than or equal to 100% maximum stimulator output (MSO)

Inclusion criteria

In order to be eligible to participate in this study, a participant met all of the following criteria:

- Participant is between 18 and 45 years old.
- Participant is right-handed.
- Participant is in good physical and mental health.
- Participant completely understands the study procedures, the risks, potential benefits and confirm to participate in the study by giving written informed consent before the experiments.
- Participant is willing to comply with the study restrictions

Exclusion criteria

A participant who met any of the following criteria excluded from participation in this study:

● Participant is under the age of legal consent.

● Participant is mentally or legally incapacitated, has significant emotional problems or has a history of a clinically significant psychiatric disorder (as defined by ICD-10). Participants who have had situational depression (i.e., an adjustment disorder with depressed mood) may be enrolled in the study at the discretion of the investigator.

● Participant has a history of any illness that, in the opinion of the study investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

● Participant has a history of stroke, seizures, or major neurological disorder.

● Participant has a history of significant head injury/trauma with loss of consciousness lasting for ≥15 minutes and one or more of the following:

a) Recurring seizures resulting from the head injury

b) Persistent neurological or cognitive sequels of the injury

c) Cognitive rehabilitation following the injury

● Participant has a family history of epilepsy.

● Participant has a cardiac pacemaker, implanted medication pump, intracardiac line, or acute, unstable cardiac disease.

● Participant has an intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head (excluding the mouth) that cannot be safely removed.

● Participant is currently a regular user (including “recreational use”) of any illicit drugs or has a history of drug (including alcohol) abuse.

● Participant has a known history of low blood pressure and/or a history of repeated hypotensive faints.

● Participant is pregnant or trying to get pregnant.

● Participant has any contra-indication to MRI or TMS.

● There is any concern by the investigator regarding the safe participation of the participant in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

Questionnaires

The participant filled all the questionnaire attached in the Appendix (The questionnaire were associated with handedness (Appendix 1) and TMS inclusion/exclusion criterion (Appendix 2).

Procedures and Experimental setup

The study consisted of two sessions, various preparation procedures and the actual experiment. In session one, structural MRI scans (T1 & T2 weighted MRI) of the subject were acquired for TMS neuronavigation. The rest of the preparation included right-hand FDI muscle EMG belly tendon montage and a 64 channel EEG cap readiness, as well as arrangements for MRI-based stereotactic neuronavigation. The subject was equipped with a modified foam earplug and a

headphone for TMS sound masking (please check the ‘TMS sound masking’ section below for more details). A thin layer (<5 mm) of foam was applied above the EEG cap, roughly covering the entire left pre-motor area, i.e., the study's cortical target site for stimulation. After the EEG cap preparation, the subject was bedded comfortably in supine position on a mattress so that the subsequent Motor evoked potentials (MEPs) and TEP measurements could be conducted in a setting similar to the experimental condition inside the MRI scanner (since the second session involves measurements inside MRI scanner in the supine position). The Session one consisted of initial MEP hotspot search and MEP resting motor threshold hunting and then TEP measurements including TEP hotspot and TEP coldspot search (i.e., searching for a location on the scalp in a particular brain region where the TEPs are expected to be less pronounced or completely absent despite effective stimulation), measurements of TEPs at the TEP hotspot and measurements of TEPs at the TEP coldspot separately. In Session two, the subject was lying in a supine position on the MRI scanner table, as shown in Figure 4, equipped with standard MR-compatible earplugs. A thick layer (50 mm) of foam was tapped on the inner surface of the TMS coil to maintain the coil to cortex distance as same as in session one since there was no EEG cap on the head during session two. Afterwards, the arrangements for MRI based stereotactic neuronavigation were completed. Subsequently, a TMS-fMRI measurement was conducted at the TEP hotspot, followed by another TMS-fMRI measurement at the TEP coldspot. The subject was instructed to keep their eyes open and minimize eye-blinks as much as possible during the TMS application periods in both sessions. The head of the subject was stabilized with a vacuum cushion to avoid movements and provide reliable conditions for TEP/TMS-fMRI measurements. Each session took approximately 90 minutes to complete.

Figure 4: Concurrent TMS-fMRI experimental setup in session two, dummy plastic head (left), real subject (right), MRI-B91 MagVenture TMS Coil (bottom)

Transcranial Magnetic Stimulation (TMS)

Single pulse TMS of the left pre-motor area was performed using a figure-of-eight shaped MagVenture MRI-B91 TMS coil connected to an MR-compatible MagPro X100 stimulator (MagVenture, Denmark). The coil was placed on the head in an anteromedial (coil handle) to posterolateral (coil transducer) direction and biphasic pulse with a reversed current direction induced posterolateral-to-anteromedial current in the brain tissue for the second, more effective, half-wave. In session one only, TMS was applied to the left primary motor cortex, and the BEST toolbox (www.best-toolbox.org) (Hassan et al., 2022) was used for MEP hotspot search and MEP resting motor threshold (RMT) hunting using the right hand FDI muscle EMG. The TMS coil was then moved to the left premotor area, and TEP hotspot and TEP coldspot search were conducted at an intensity of 90% RMT (89% MSO) to avoid contamination of TEPs due to possible re-afferent motor feedback and associated confounds. The same stimulation intensity was used in all the remaining TEPs/TMS-fMRI measurements. The TMS coil locations at the TEP hotspot and TEP coldspot were saved in the TMS neuronavigation system (Localite, Germany). The inter-trial interval (ITI) was 2-3 seconds and 18-22 seconds during the first and second sessions. A total of 100 TMS pulses were then delivered for each of the two spots (TEP hotspot/coldspot) during session one (TEPs measurements) and 45 TMS pulses for each of the two spots during session two (TMS-fMRI measurements). A total of 900 MRI volumes were acquired for each TMS coil location during session two (TMS-fMRI measurement).

EEG recording and analysis

EEG was recorded with a 64-channel cap built with TMS-compatible sintered Ag/AgCl electrodes (Multitrodes, EasyCap). EEG data were digitized at a sampling rate of 5 kHz with a TMS compatible 80-channel EEG/EMG system (NeurOne Tesla, Bittium, Finland) powered by an 8V MR compatible battery. Raw EEG data were post hoc analyzed in Matlab release 2017b by re-referencing it to the common average of all 64 EEG channels using standard Fieldtrip pipeline (www.fieldtriptoolbox.org) (Oostenveld et al., 2011). Artifact correction was applied manually by visual inspection of all the trials. Only 17 out of 200 trials were removed since muscle /movement artifacts contaminated them. The EEG data was then demeaned on a pre-stimulus baseline window of [-100 to -5] ms and averaged across all trials.

fMRI acquisition and analysis

The fMRI scans were acquired using a 3 Tesla Prisma MRI Scanner (Siemens, Germany) at the Neuroimaging Center (NIC), JGU Universitatsmedizin Mainz. The fMRI scanning was completed using an already established gradient-echo planar imaging (EPI) sequence optimized for TMS-fMRI measurements sensitive to detect blood-oxygenation-level dependent (BOLD) changes in tissue contrast. Standard spatial preprocessing was performed on the fMRI scans obtained during the second session. For all of the fMRI preprocessing and analysis, SPM12 (Welcome Department of Cognitive Neurology, London, UK) implemented in MATLAB

(MathWorks, Inc., Natick, MA) was used. After spatial registration of structural and functional images and slice timing correction, the data were realigned and normalized into standardized neuroanatomical space (MNI). Surface smoothing was applied with an 8 mm FWHM Gaussian kernel. Then, a general linear modeling (GLM) analysis of fMRI data was performed, modeling the TMS triggers as an event convolved with the canonical hemodynamic response function. Statistical contrast maps were constructed comparing brain response to the TMS pulses vs. brain activity during baseline (rest periods).

TMS sound masking

TEPs have the potential to reflect the response of the cortical neurons under the stimulation site if the confounds are properly controlled (Conde et al., 2019, Belardinelli et al., 2019). Some of the artifacts can be identified and minimized by optimizing the experimental procedures (Casarotto et al., 2022). For example, the TMS pulse produces a mechanical or tapping sensation when the TMS coil vibrates adjacent to the scalp surface. This problem can be attenuated by using a thin foam layer above an EEG cap. The TMS pulse also produces an audible instantaneous sound known as "TMS click," resulting in the auditory evoked EEG potentials or somatosensory activations (Conde et al., 2019, Rogasch et al., 2014, Miniussi and Thut, 2010; Nikouline et al., 1999). Isolation of a pure TEP from its confound is an essential step towards the correct interpretation of TEPs and, consequently, using them to optimize TMS parameters.

A novel TMS sound masking procedure was developed to allow safe and effective masking of the TMS click. First, two standard MR-compatible foam earplugs with silicon tubes were taken

(Figure 5A), and the extruding silicon tube from the foam earplugs was removed (Figure 5B). Next, both earplugs were joined together by applying a standard medical tape at the junction of the earplugs (Figure 5C). The joined earplugs were then also tapped to a standard wired audio earphone by ensuring that the silicon tube was properly aligned with the output surface of the audio earphone (Figure 5C). A standard audio headset was also used in the procedure (Figure 5D). Finally, the assembly with foam earplugs and audio earphones was equipped in the subject's ears (Figure5E).

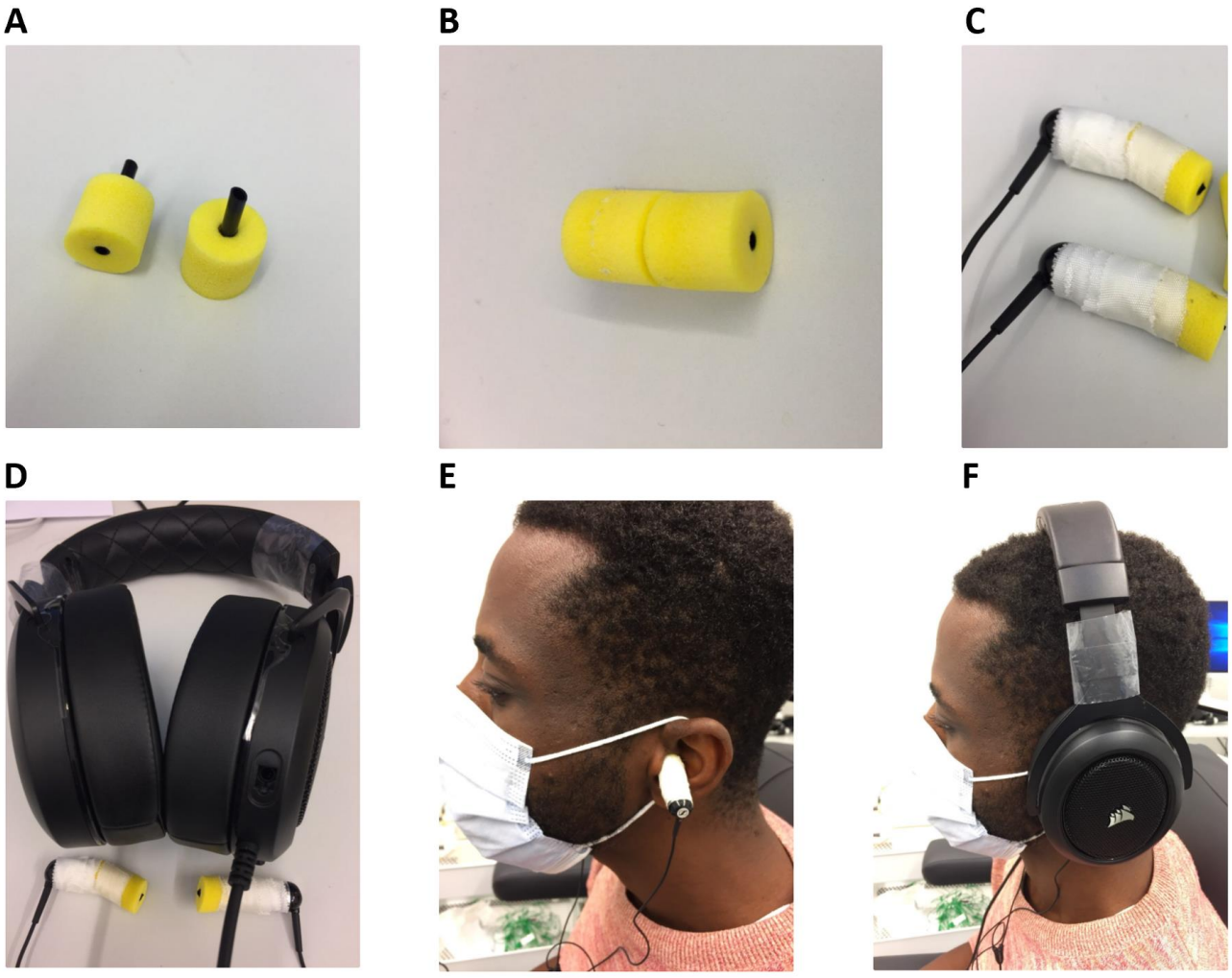

Figure 5: Different steps of setting up a novel 'TMS click sound' masking solution

The audio headsets were then superimposed on the foam earplugs and audio earphone assembly, as shown in Figure 5F. The sound of the TMS click at 100% MSO was sampled from the MagVenture MRI B91 coil and fed into the TAAC toolbox (Ruso et al., 2022). The same TMS click masking sound was then played by the TAAC toolbox (Ruso et al., 2022) on both audio inputs, i.e., audio headset and audio earphone-foam earplugs assembly. The sound intensity on both audio inputs was titrated separately (first inner earphone intensity and then external headset intensity) until the subject could not hear the TMS click. The experimenter ensured that the sound levels were under comfortable limits for the subject. TMS coil transducer was placed perpendicular to the scalp surface but in contact with the scalp surface during the sound titration procedure. The sound intensity on both audio inputs was at 50% of maximum sound intensity, and then an increasing step of 5% was taken until the subject was not able to identify any TMS click sound. An increment in the sound intensity of the audio input was stopped when the sound level crossed the comfortable sound limit, and the previous sound level (i.e., just 5% below the comfortable sound level threshold) was used eventually throughout session one.

BEST Toolbox

The BEST toolbox (www.best-toolbox.org) (Hassan et al, 2022) was used in TMS-EEG and TMS-fMRI measurement session. The Figure 6 below shows the snippets from real-time TEP hotspot search procedure mainly showing the butterfly plots, topographical pltos and multiplots of the EEG montages stated on the user interface.

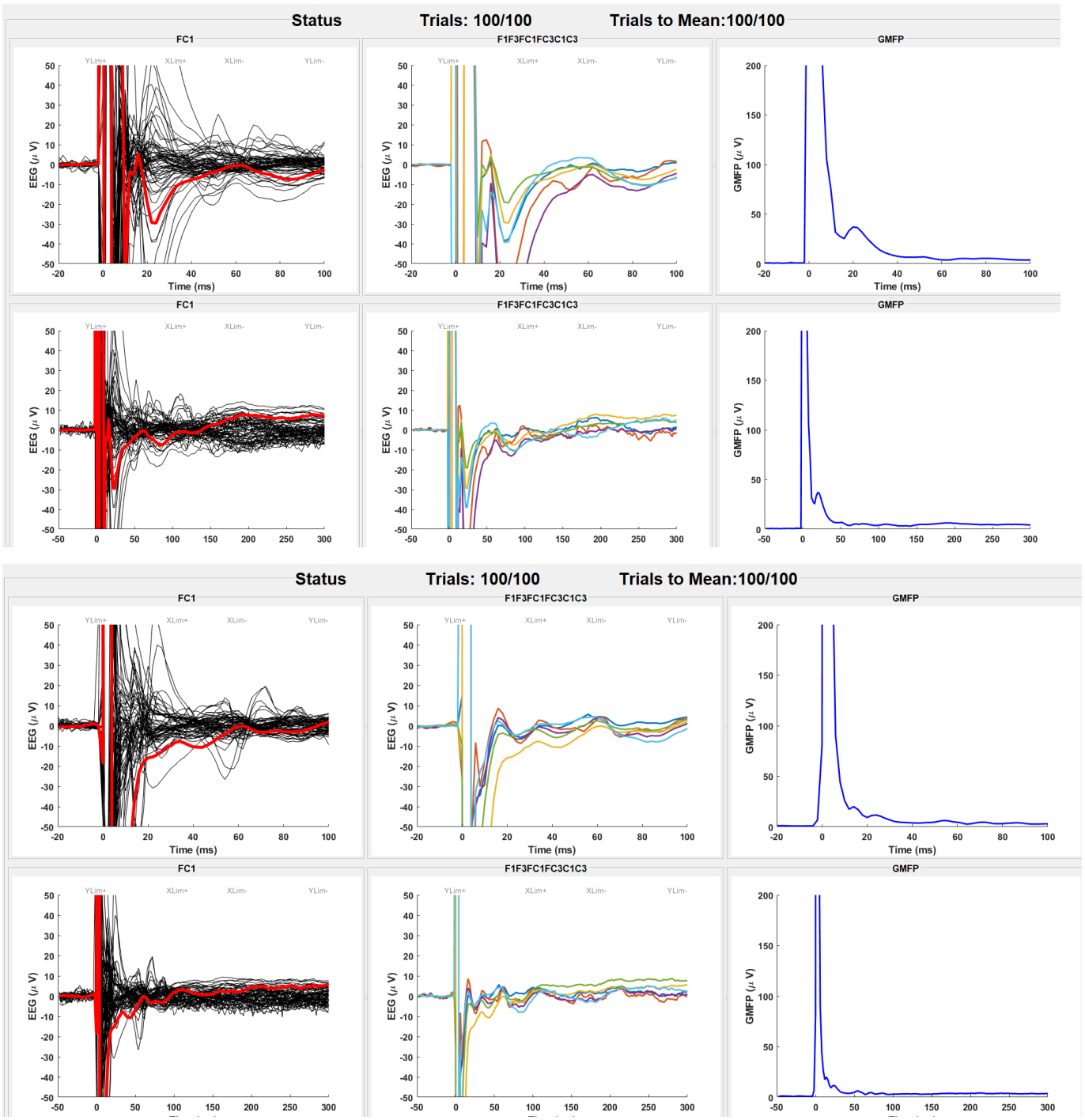

Figure6: Upper panel shows EEG butterfly plot, ertical plot and Global Mean Field Power at TEP Hotspot where as bottom one shows at TEP coldspot

Chapter Three:

Result and Discussion

Results & Discussion

Characterization of MRI-B91 TMS Coil TEPs

During the last decades, many groups have characterized the brain response to TMS by concurrent TMS-EEG using several TMS coils, including but not limited to MagVenture C-B60 (Steele et al., 2019), MagVenture Cool-B65 (Kerwin et al., 2018), MagStim 90mm external diameter figure of 8 shaped TMS coil (Gordon et al., 2021) and MagVenture MC-B70 (Reichenbach et al., 2011) (Please note that only one study per TMS coil has been cited here although many can be found in literature search). However, a novel aspect of this study design was to obtain the TEPs profile from the MagVenture MRI-B91 TMS coil. The MRI-B91 coil is a comparatively less powerful TMS coil and induces a lower current on the target cortical site. It was unknown if the stimulation from the MRI-B91 TMS coil at the maximum possible intensity (i.e., 100% MSO) would be able to evoke an EEG response at all. If it does, what would be its temporal and spatial characteristics? Would they be comparable to the results in the existing literature to claim any brain response to the stimulation?

A comparison of the TEPs using one of the commonly used TMS coils in the TMS-EEG studies, namely MagVenture C-B60 and the MR-compatible TMS coil used in this study, shows that the MR-B91 TMS coil evokes TEPs of similar temporal and spatial characteristics. **Figure 7** shows the TEPs obtained from two different TMS coils, i.e., C-B60 and MRI-B91, two different cortical locations, namely Cz and FC3, referenced against the common average of all 64 EEG channels when TMS is applied on the left premotor area using the respective coil in each session (100 trials each TMS coil, ITI of 2-3 s). The sufficient amplitude of evoked EEG response,

temporal characteristics, i.e., presence of P30, N45, P60, N100, P180, and N240 components, and spatial characteristics, i.e., across channels on surface EEG, shows similar profile. It assures that the MR-B9I TMS coil is equally capable of evoking TEPs compared with any other standard TMS coil.

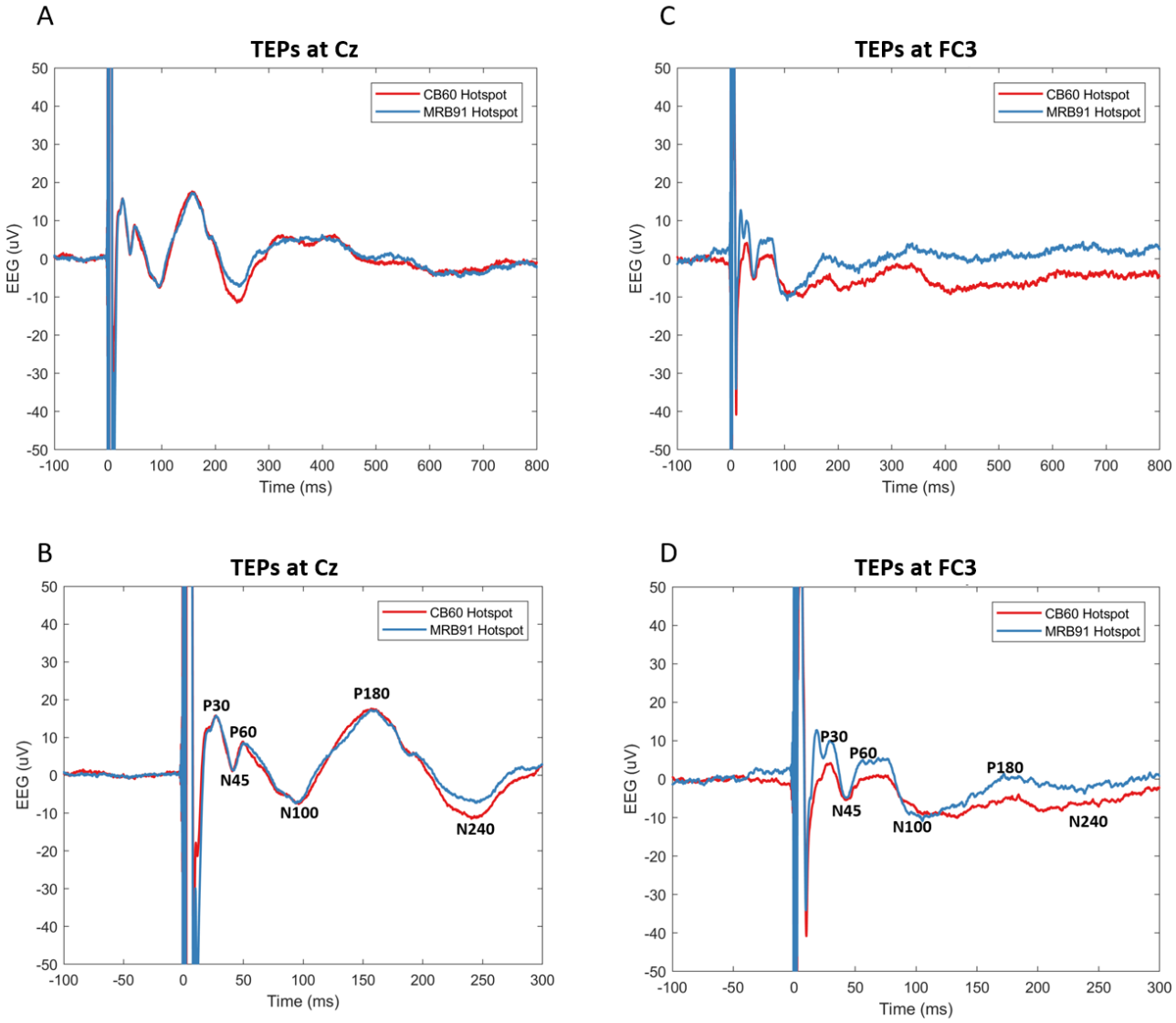

Figure 7: TEPs comparison between MagVenture CB60 TMS coil and MRI B91 TMS coil at Cz and FC3. Panel A&C shows the TEPs from -100 to 800 ms, whereas panel B&D shows the same TEPs from the -100 to 300 ms time scale.

Control of somatosensory confounds

Many confounding factors contaminate the brain response to the stimulation measured in TEP. These include the auditory evoked EEG potentials produced by an instantaneous and audible "click" sound whenever a TMS pulse is applied (de Goede et al.-, 2018). The leading cause of this evoked response is the auditory input to the brain through air and bone conduction. The application of TMS also produces a mechanical sensation on the scalp, which leads to sensory-evoked EEG potentials (SEPs) (de Goede et al., 2018) and contaminates the TMS-evoked EEG response. In addition, there are several artifacts produced by the magnetic field, namely, scalp muscles activation, movement artifacts arising from the startle response after an instantaneous click sound, microscale movements of the EEG electrodes and cables under the coil (de Goede et al., 2018). Control of somatosensory confounds is essential before determining a genuine TEP hotspot and TEP coldspot. A novel sound noise masking solution was developed and used in this work.

Additionally, an already available solution of using a thin foam layer between the scalp surface and the TMS coil was also incorporated in the experimental setup to reduce the somatosensory input to the brain. As a result, the auditory evoked EEG potentials can be mainly observed in the late components of TEPs, e.g., N100 and N240. However, the SEPs can be mainly observed in the early components of TEPs, e.g., P30. However, it is still tricky to access confounds in the very early components of TEPs, i.e., the ones that are within the first tens of milliseconds.

Manual feedback from the subject during the experiment assured that the subject could not hear the TMS click sound during all trials when the TMS coil transducer was placed perpendicular to the target cortical site. In addition, a subjective assessment of TEPs shown in **Figure 7** (panel A & D) reveals the attenuation of the N100 and N240 components and provides proof of sufficient control for the auditory evoked confounds.

Determination of TEP hotspot and TEP coldspot

The TEPs hotspot search procedure was initiated by randomly selecting a coil position at the target site with a 45 degrees coil orientation with respect to the medial-sagittal plane of the subject's head. The TEPs have been monitored in real-time at all possible coil orientations with a resolution of 10 degrees. The TEPs were also monitored by shifting the coil position by a factor of a few millimeters towards the lateral, medial, dorsal, and ventral sides of the left premotor area. The amplitude and spectral features (8-45 Hz) of early TEPs components [0 to 150 ms] were more profound at an angle of 90 degrees from the medial-sagittal plane at a certain position on the left premotor area of the subject, as shown on the red colored trace in **Figure 8** (panel A & D). Such a TMS coil position and orientation was declared as a TEPs hotspot. The location where TEPs amplitude was attenuated, but the spectral features remained unchanged, i.e., ~ 8-45 Hz, from 0 to 150 ms, as shown on the blue-colored trace in **Figure 8** (A & D), was declared as a TEP coldspot**. Figure 8** (B & E) shows butterfly plots of all the "raw" data collected from 64 EEG channels in the peristimulus period from -200 to 800 ms. The butterfly plot requires further preprocessing; however, a visual assessment of the plot shows a general attenuation in the TEPs of all EEG channels at the TEP coldspot compared to the TEP hotspot.

Previous research work on TEPs have also shown that spectral components in the range of alpha/beta/gamma (~8-45 Hz) frequencies are also observed in the early TEP components measured from different cortical sites, e.g., motor, prefrontal, premotor, parietal (Fecchio et al., 2017). Therefore, it can also be stated that the described procedure to determine TEP hotspot and TEP coldspot can be extended to search for a TEP hotspot or TEP coldspot in the other brain regions.

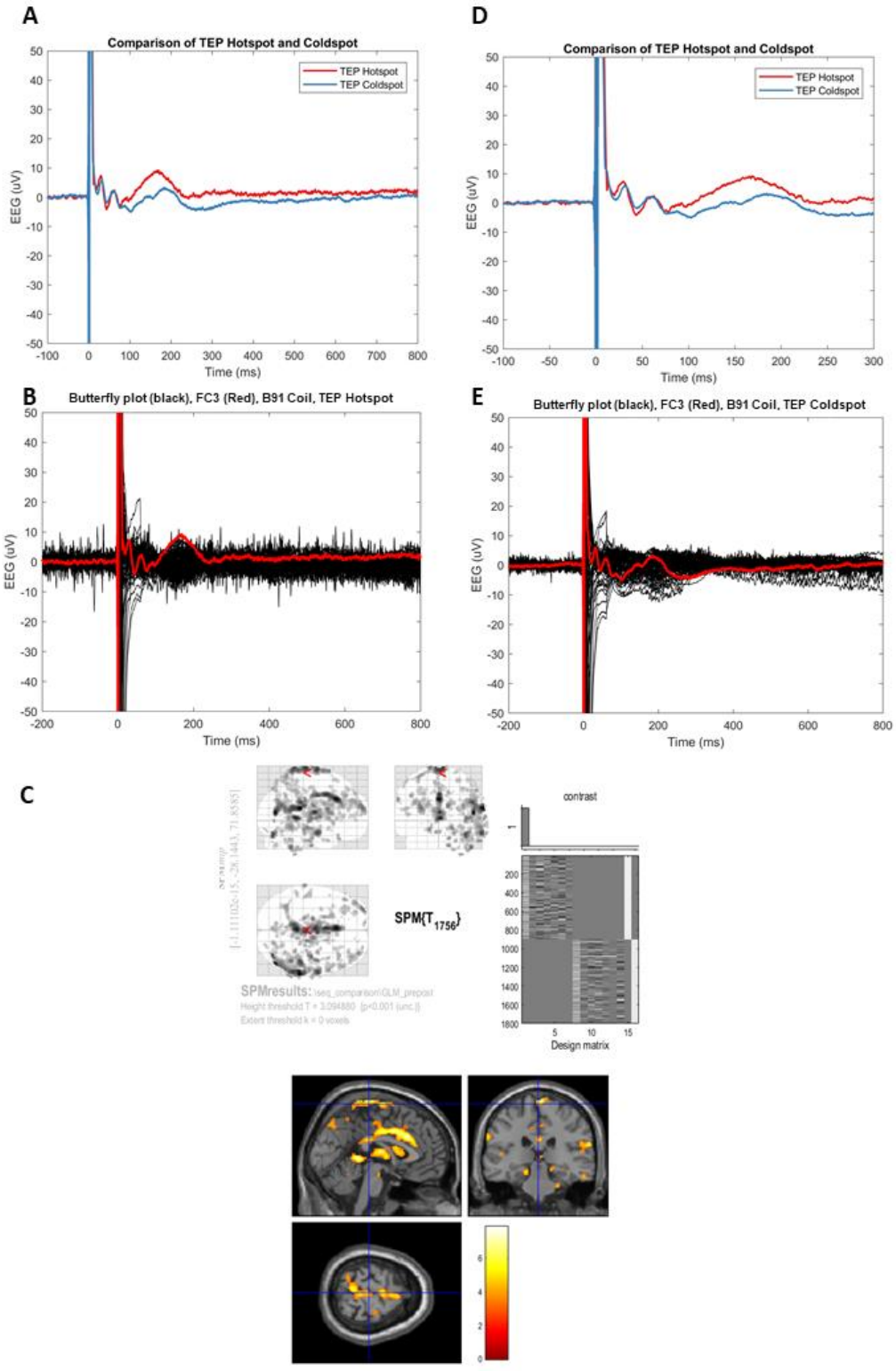

Figure 8: Comparison of TEP hotspot and TEP coldspot. A) Time-locked average of TEPs at FC3 from -100 to 800 ms on TEP hotspot vs. TEP coldspot; B) Butterfly plot of TEPs at 64 EEG channels (raw data)

on TEP hotspot; C) fMRI analysis of TEP hotspot condition; D) Time-locked average of TEPs at FC3 from -100 to 300 ms on TEP hotspot vs TEP coldspot; E) Butterfly plot of TEPs at 64 EEG channels (raw data) on TEP coldspot.

Validation of TEP hotspot and TEP coldspot

The validation of TEP hotspot and TEP coldspot using concurrent TMS-fMRI is a critical aspect of the study. To achieve the validation objective, MRI-B91 TMS coil locations for both hunted points (i.e., TEP hotspot and TEP coldspot) from session one were stored in the TMS neuronavigation system and were reproduced in the second session to perform TMS-fMRI and measure TMS-evoked fMRI response on both nearby sites. The fMRI analysis is shown in **Figure 8** (panel C) revealed an unfortunate measurement error during the hotspot TMS-fMRI measurement session. Similarly, the TEP coldspot TMS-fMRI measurement session also resulted in measurement error and could not be reported. The absence of a meaningful fMRI analysis is one of the limitations of the conducted study. However, the importance of the comparison between the TMS-evoked BOLD responses on the TEP hotspot and TEP Coldspot has been emphasized and will be an essential part of the subsequent refined procedure to optimize the TMS parameters using an advanced TEP hotspot search method.

Chapter Four:

Conclusion

Conclusion

The attenuation of amplitude but retention of spectral features of the TEPs obtained from the TEP hotspot vs. TEP coldspot identified through the described procedure assures that such a TMS optimization procedure can be extended to the next stage of a full-scale investigation and validation study. The study design can be improved by replacing or intermingling the event-related experimental procedure with a block design for TEPs and TMS-fMRI measurements. A faster event-related/block design comprising the ITI, e.g., every 1 second, may also be considered before finalizing the protocol to be used in a full-scale, more sophisticated validation investigation. A consistent ITI during both sessions (TEPs measurements & TMS/fMRI measurements) may also be considered compared to the varying ITI for this subject. The use of induced electric field modeling (E-field modeling) to guide the TEP hotspot and TEP coldspot search may also improve the procedure's effectiveness, and therefore it is highly recommended. Multiple different target cortical sites can also be selected for further investigation compared to the only cortical site (i.e., left premotor) considered in this work.

Limitations

Concurrent combination of TMS with EEG is a challenging field (Conde et al., 2019). Similarly, the simultaneous combination of TMS with fMRI to do online interventional protocols is also very recent development and difficult to practice (Bergmann et al. 2021). Therefore, we had to face several challenges associated with the meta combination of TMS-EEG and TMS-fMRI study design that results in many failed pilot and experimental sessions. All of the failed measurements have not been reported in the thesis; however, a single most successful measurement has been reported. The limitations of the experimental setup and confounds associated with the multimodal combination of these electrophysiological and neuroimaging methods have been a major factor of many failed measurements. Therefore, it was hard to complete one full subject without any measurement error. It is recommended that a better guideline and standard operating procedure for the experimental methods should be formulated and used in the upcoming studies.

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Appendix 1

Handedness Questionnaire

Händigkeits-Fragebogen

Anleitung

In diesem Fragebogen geht es darum, welche Hand oder Körperhälfte Sie bei bestimmten Tätigkeiten bevorzugen. In den meisten Fragen wird eine alltägliche Tätigkeit genannt. Bitte versuchen Sie sich vorzustellen, wie Sie diese Tätigkeit ausführen. Kreuzen Sie dann bitte an, ob Sie die Tätigkeit ...

... immer mit der linken Hand ausführen

... eher mit der linken Hand, aber manchmal auch mit der rechten ausführen

... mit beiden Händen gleich oft ausführen

... eher mit der rechten Hand, aber manchmal auch mit der linken ausführen

... immer mit der rechten Hand ausführen.

Die Fragen beziehen sich auf Situationen, in denen Sie prinzipiell die Möglichkeit haben, beide Hände zu benutzen. Wenn Sie zum Beispiel einmal einen Arm gebrochen hatten, dann beantworten Sie die Fragen bitte so, wie Sie es mit zwei gesunden Armen tun würden. Es geht darum, welche Körperhälfte Sie normalerweise bevorzugen.

Bei zwei Fragen geht es um die Bevorzugung eines Fußes oder eines Auges. Beantworten Sie auch hier, welche Körperhälfte Sie bei den jeweiligen Tätigkeiten bevorzugen.

Vielen Dank!

(1.) Welche Hand benutzen Sie zum Schreiben?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(2.) Welche Hand benutzen Sie zum Zeichnen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(3.) Welche Hand benutzen Sie zum Werfen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(4.) Welche Hand benutzen Sie, wenn Sie mit der Schere schneiden?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(5.) In welcher Hand halten Sie die Zahnbürste, wenn Sie sich die Zähne putzen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(6.) In welcher Hand halten Sie beim Essen das Messer, wenn Sie keine Gabel in der Hand halten?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(7.) In welcher Hand halten Sie den Löffel beim Essen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(8.) Welches ist die obere Hand, wenn Sie mit einem Besen fegen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(9.) In welcher Hand halten Sie ein Streichholz, wenn Sie es anzünden?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(10.) In welcher Hand halten Sie den Deckel, wenn Sie eine Schachtel öffnen?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(11.) Mit welchem Fuß treten Sie nach einem Ball?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(12.) Welches Auge benutzen Sie, wenn Sie nur eines benutzen dürfen (z.B. beim Fotografieren)?

immer die linke	eher die linke	beide	eher die rechte	immer die rechte

(13) Sind Sie von links auf rechts „umtrainiert" worden?

Ja	Nein

Wenn „Ja", wie alt waren Sie ungefähr, als Sie umtrainiert wurden? _____

(14.) Haben Sie aufgrund einer Verletzung oder Erkrankung die bevorzugte Hand oder Körperhälfte für längere Zeit oder dauerhaft gewechselt?

Ja	Nein

Wenn „Ja", ...

... wann war die Erkrankung oder Verletzung? _____

... unter welcher Erkrankung oder Verletzung litten Sie? _____

... haben Sie wieder zu ihrer ursprünglich bevorzugten Hand oder Körperhälfte zurückgewechselt?

Ja	Nein

(15.) Gab es Linkshändigkeit ...

... bei Ihrem Vater?	Ja	Nein	unbekannt
... bei Ihrer Mutter?	Ja	Nein	unbekannt
... bei Ihren Geschwistern?	Ja	Nein	unbekannt

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Screening-Fragebogen Transkranielle Hirnstimulation

Name, Vorname: _____ Geburtsdatum: _____
Geschlecht: weiblich männlich divers Händigkeit: rechts links beides

	ja	nein
1. Sind Sie minderjährig?		
2. Leiden Sie an einer Epilepsie oder haben Sie jemals einen Krampfanfall erlitten?		
3. Leidet jemand in Ihrer unmittelbaren Verwandtschaft (Eltern, Geschwister, Kinder) an Epilepsie oder hatte jemals einen Krampfanfall? Wenn ja, bitte spezifizieren Sie:		
4. Hatten Sie jemals einen Ohnmachtsanfall oder einen plötzlichen Bewusstseinsverlust (Synkope)? Wenn ja, beschreiben Sie bitte die jeweiligen Umstände.		
5. Haben Sie jemals an einer neurologischen oder psychiatrischen Erkrankung gelitten? Wenn ja, bitte spezifizieren Sie:		
6. Haben Sie eine Hauterkrankung oder eine Hautallergie? Wenn ja, bitte spezifizieren Sie:		
7. Haben Sie eine Hörminderung oder Pfeif-/Klingelgeräusche in Ihren Ohren (Tinnitus)?		
8. Nehmen Sie regelmäßig Medikamente ein (außer Kontrazeptiva)? Wenn ja, bitte listen Sie auf:		
9. Nehmen Sie regelmäßig Drogen ein? Wenn ja, bitte listen Sie auf:		
10. Hatten Sie jemals ein schweres Schädel-Hirn-Trauma (d.h. mit Bewusstseinsverlust)?		
11. Hatte Sie jemals eine Operation am Gehirn?		
12. Hatten Sie jemals eine Operation an Ihrem Rückenmark?		
13. Haben Sie Missbildungen im Bereich des Rückenmarks oder der Hirnventrikel?		
14. Haben Sie Implantate in Ihrem Gehirn/Schädel oder an einer anderen Körperstelle (z.B. Metallimplantat (Ausnahme: Titan), Metallsplitter/-fragmente, Gefäßclips, Cochlea-Implantat(e), Neurostimulator (z.B. Tiefenhirnstimulator, epidurale/subdurale Ableit-/Stimulationselektroden, Vagusnervstimulator))? Wenn ja, bitte spezifizieren Sie:		
15. Haben Sie einen Herzschrittmacher oder implantierte EKG-Elektroden?		
16. Tragen Sie eine medizinische Infusionspumpe in Ihrem Körper?		
17. Haben Sie Migräne oder eine andere Kopfschmerzerkrankung? Wenn ja, wie oft?_____		
18. Sind Sie schwanger oder versuchen Sie schwanger zu werden?		
19. Wurde bei Ihnen jemals eine transkranielle Magnetstimulation (TMS) durchgeführt? Wenn ja, wann war das letzte Mal?_____ Gab es Komplikationen? _____		
20. Wurde bei Ihnen jemals eine transkranielle Gleich- oder Wechselstrom-stimulation (TDCS/TACS) durchgeführt? Wenn ja, wann war das letzte Mal?_____ Gab es Komplikationen?		
21. Wurde bei Ihnen jemals eine Magnetresonanztomographie (MRT) durchgeführt? Wenn ja, gab es Komplikationen?		

_____ _____
Ort, Datum Unterschrift Proband

Dokument:	NIC-Formular: Screening-Fragebogen Transkranielle Magnetstimulation			
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