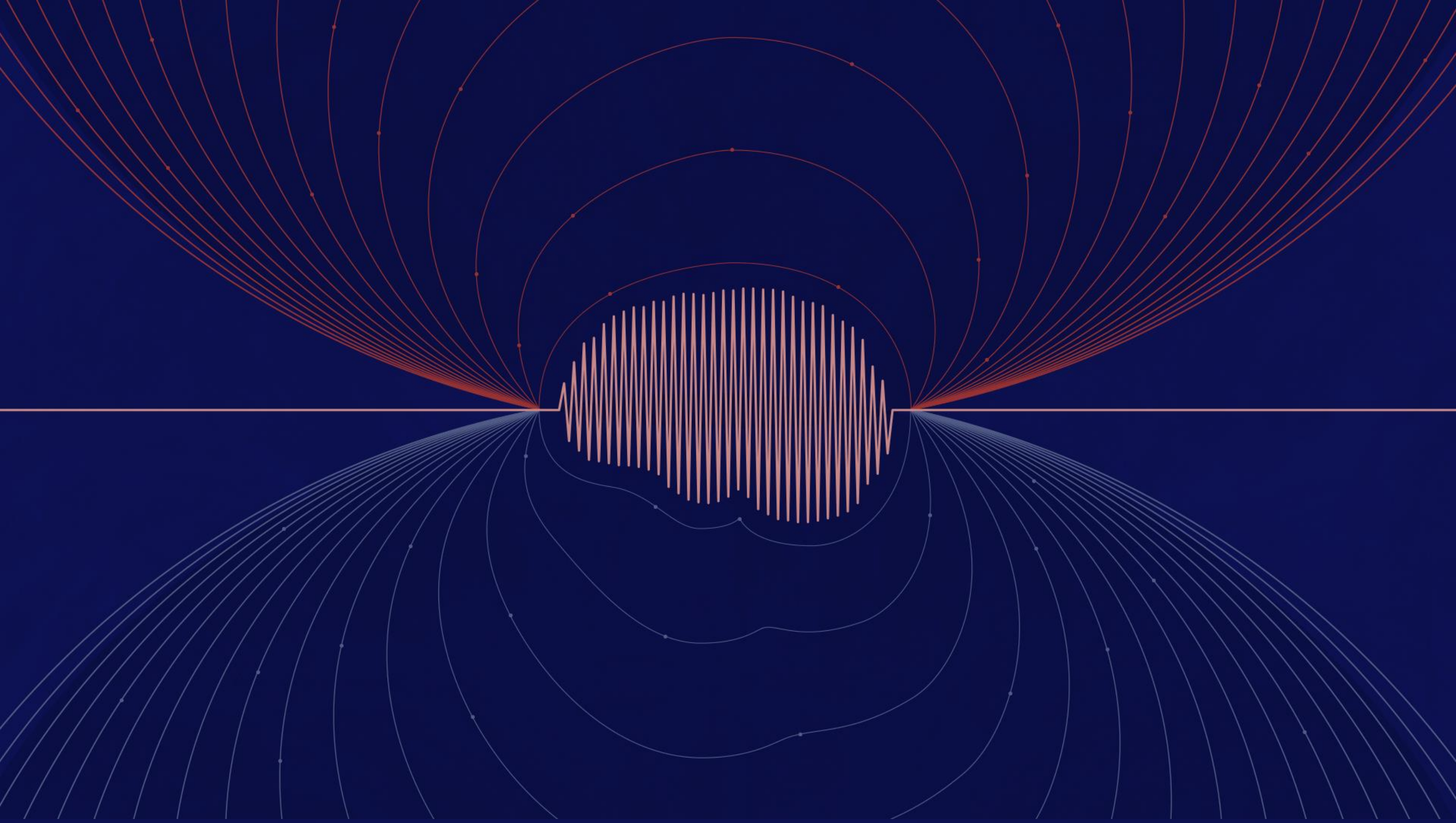

Book of Abstracts

6th Annual Brain Stimulation and Imaging Meeting

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The abstracts are listed in alphabetical order according to the last name of the presenting author.

Induction of late-phase LTP-like plasticity in the primary motor cortex with repeated anodal tDCS

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Introduction

Background: A single session of anodal tDCS induces LTP-like plasticity which lasts for about one hour, while repetition of stimulation within a time interval of 30 minutes results in late-phase effects lasting for at least 24 hours with standard stimulation protocols [1].

Objective: In this study, we explored if the after-effects of a recently developed intensified single session stimulation protocol [2] are relevantly prolonged in the motor cortex by repetition of this intervention.

Methods

16 healthy right-handed subjects participated in this study. The effects of an intensified (3mA-20min) and a standard anodal tDCS protocol (1mA-15min) with short (20 minutes) and long (3 hours) repetition intervals were compared with the effects of respective single session tDCS protocols (3mA-20min, 1mA-15min, and Sham). Cortical excitability alterations were monitored by single-pulse TMS-elicited MEPs.

Results

Compared to sham, both single session tDCS protocols (1mA-15min, and 3mA-20min) resulted in cortical excitability enhancements lasting for about 30 minutes after stimulation. The short repetition interval (20 minutes) resulted in a prolongation of after-effects for the standard protocol, which lasted for more than 24 hours after stimulation. For the intensified protocol, the prolongation of after-effects was limited to 90 mins after stimulation. The long repetition interval (3 hours) resulted in no excitability-enhancing after-effects for the intensified, and only trend-wise excitability enhancement for the standard protocol.

Conclusions

These results show a non-linearity of late-phase LTP-like plasticity induction, which depended not only on the interval of intervention repetition, but also on other protocol characteristics, including intensity, and duration of tDCS.

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Processing of structural and diffusion MRI for real-time tractography-based nTMS

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Introduction

Real-time information about the structural connections in the brain would be highly valuable when performing navigated transcranial magnetic stimulation (nTMS). This information can be obtained using diffusion MRI (dMRI) based tractography that can extract major structural connections in the brain, in-vivo and non-invasively. However, adapting tractography for nTMS has been challenging mainly because: (i) processing pipelines are time consuming (ii) obtaining reliable tractograms is difficult. In an effort to address these problems, we recently built a prototype real-time tractography-based nTMS system.

Methods

Our approach is to construct a modular framework that seamlessly integrates the output of preparatory (offline) analysis, into real-time (online) visualization. In the offline part, we first denosoise the dMRI [1] and correct distortions [2]. We then obtain local fiber orientation distributions (FOD) [3]. We also use Freesurfer recon [4] to obtain aseg+aparc labels which are used for anatomical contraints. The online part consists of three modules: (a) neuronavigation (b) fiber-tracking and (c) visualization. The neuronavigation module registers the TMS coil's location on the individual's MRI space. The fiber-tracking module does tractography using the location of the TMS coil. The visualization module displays the connections. We customized InVesalius for neuronavigation [5]. Fiber-tracking is done using our own algorithm [6,7] implemented in our Trekker software [8]. Our system allows the operator to change tracking parameters online and addresses the problem of uncertainty [9].

Results and conclusion

Real-time tractography-based nTMS holds great potential to improve TMS targeting, thereby helping to develop new treatments where connectivity plays a decisive role. Our work shows that this can be achieved by: (i) splitting the preprocessing part to be done offline and (ii) using a real-time tracker, enabling real-time adjustments for reliability.

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THE IMPACT OF ARTIFACT REMOVAL METHODS ON TMS-EEG SIGNAL: A COMPARATIVE STUDY

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Introduction

Recently, concurrent Transcranial Magnetic Stimulation and Electroencephalography (TMS-EEG) has gained popularity as a tool to study brain connectivity. The core concept of this technique is to use the millisecond precision of EEG to track the spread of the brain response following TMS stimulation within a specific network. However, the EEG signal after a TMS pulse is contaminated with TMS-related artifacts that often hide the neural response. To resolve this issue, different processing methods have been developed, with the aim of removing these artifacts, while keeping the brain signal. Despite having the same goal, these methods use fundamentally different strategies, which might lead to different results. In this study we aim at testing to what extent the choice of a different processing method can impact the final signal.

Methods

The same dataset from a TMS-EEG experiment (N=16) was processed with four recently published methods: (1) Automated artifact rejection for single-pulse TMS–EEG data (ARTIST) [1], (2) TMS–EEG signal analyzer (TESA, default pipeline) [2], (3) TMS–EEG graphical user interface (TMSEEG) [3], and (4) a pipeline consisting of source-estimate-utilizing noise-discarding algorithm (SOUND) and signal-space projection–source-informed reconstruction (SSP–SIR) [4].

Results

In both sessions, the resulting four TMS-evoked potentials (TEPs) showed differences in peaks amplitude and latencies. The Global Mean Field Amplitude (GMFA), which measures the standard deviation over channels, showed amplitude differences in late components (>100 ms), while early components (<100 ms) showed variability in both amplitude and latency (Fig 1).

Conclusion

The choice of the processing method impacts the final signal and might be a source of ambiguity when comparing results across different TMS-EEG studies. Our results highlight the urge for a shared and reliable processing method for contaminated TMS-EEG signal.

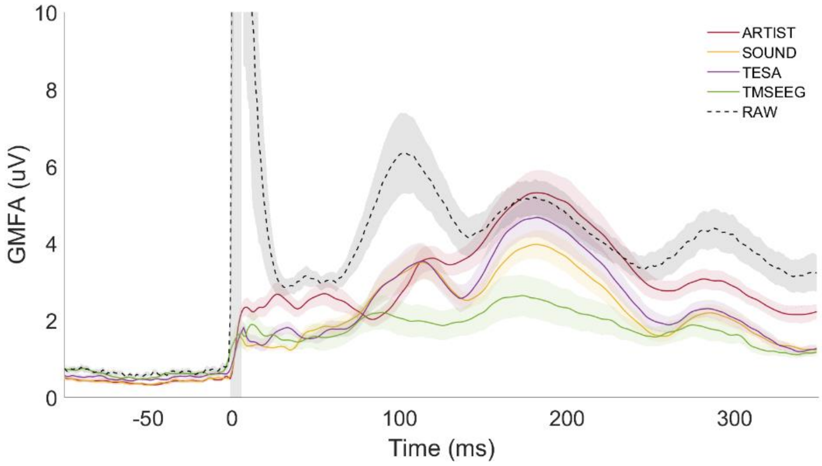

Figure 1: Global Mean Field Amplitude (GMFA). Each line represents the grand average of all subjects GMFA, after being processed with the four preprocessing pipelines (SOUND, ARTIST, TESA, TMSEEG). Dotted line represents the grand average GMFA of raw data. Shaded area around each line represents SEM. The grey area around zero on the time axis represents data removed and interpolated to deal with the TMS pulse artifact (-1 +6 ms).

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Brain changes due to a personalized neuromodulation against multiple sclerosis fatigue

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Introduction

A growing number of studies is beginning to outline a framework of altered brain features typical of multiple sclerosis (MS) fatigue mainly involving the primary sensorimotor and parietal networks [1]. In particular, a functional more than structural prevalence of these alterations supports the relevance of developing treatments aiming at compensating the neuronal electric communication dysfunctions.

Methods

A 5-day transcranial direct current stimulation (tDCS) targeting the somatosensory representation of the whole body (S1) delivered through an electrode personalized based on the brain MRI demontrated to be effiacious against MS fatigue (FaReMuS treatment) [2] [3]. We measured the brain activity at rest in 18 MS-patients through electroencephalography equipped with a Functional Source Separation algorithm and we assessed the neurodynamics state of the primary somatosensory (S1) and motor (M1) cortices via the Fractal Dimension and their functional connectivity via the Mutual Information before and after the treatment.

Results

The dynamics of the neuronal electric activity, more distorted in S1 than M1 before treatment, as well as the network connectivity, altered maximally between left and right M1 homologs, reverted to normal after FaReMuS. The intervention-related fatigue levels amelioration assessed by Modified Fatigue Impact Scale, correlated with changes of left S1 neurodynamics and with post-treatment M1 homologs functional connectivity, explaining 48% of fatigue reduction in the regression model.

Conclusion

A 5-day non-pharmacological neuromodulation tuned to specifc anatomo-functional features of the impaired regions can be effective against MS-fatigue, reverting the unbalanced functional connectivity among interconnected target networks underlying this symptom [4].

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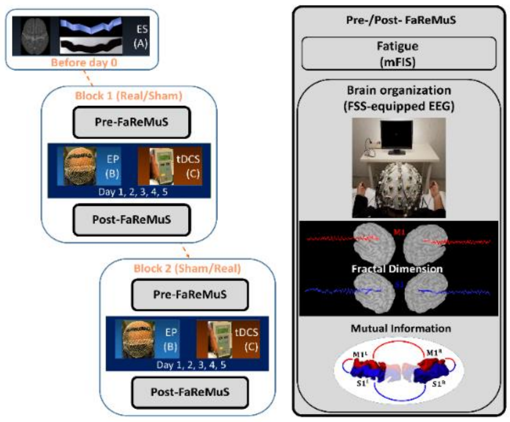

Figure 1: Experimental procedure in each person with MS undergoing FaReMuS.

Left: Individual brain MRI-based personalized electrode, blocks 1 and 2 schema. **Right**: Pre- and Post-FaReMuS we collected mFIS, and EEG-EMG. We represented the measures used for the resting state local activity (fractal dimension of the primary sensory and motor cortices) and the resting state functional connectivity between them (mutual information).

TMS-evoked potentials as a measure of transcallosal conduction delay in the motor system

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Conduction delay over long-range connections is a crucial feature of neural communication that impacts the efficacy of signal transmission between distant areas and thus influences the anatomo-functional architecture of the brain. For example, long transcallosal conduction delay (TCD) has been theorized to be the basis of hemispheric dominance. However, we lack a direct noninvasive measure of TCD to provide empirical support on the role of TCD.

In this work, we exploited the coregistration of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) to obtain a temporally precise cortical measure of transcallosal effective connectivity between primary motor cortices (M1-M1). Specifically, the amplitude and latency of TMS-evoked potentials (TEPs) can reflect the strength and conduction delay of connections, respectively.

We collected the following data from fifteen right-handed healthy participants: diffusion tensor imaging (DTI) of the corpus callosum; TEPs during an iSP paradigm in which the left and the right M1 were stimulated in separate blocks; performance, i.e. the difference in the timing of tapping between right and left hand (IHI), in an in-phase bimanual finger opposition task.

First, we aimed at individuating the TEP component that could represent the response of the contralateral primary motor cortex (M1) after signal transmission through callosal fibers. Regression analyses revealed that a positive component peaking on average at 15 ms, named P15, was predicted by the axial diffusivity of the body of the CC, which connects the motor cortices. Moreover, the amplitude of P15 positively predicted the ipsilateral silent period (ISP), a peripherical measure of inhibition.

Finally, asymmetric inhibition, i.e. the relative delay of inhibitory signal from the dominant (left) hemisphere over the delay of the inhibitory signal from the non-dominant (right) hemisphere, predicted better bimanual coordination performance.

Verb Network Strengthening Treatment Combined with tDCS in Non-fluent Chronic Aphasia

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Introduction

Verb network strengthening treatment (VNeST) is an aphasia therapy aimed at improving word and sentence production [1]. Transcranial direct current stimulation (tDCS) is a safe non-invasive brain stimulation method that can potentially enhance the effect of language therapy [2]. The present study is the first to test the added benefit of combining VNeST with tDCS in chronic post-stroke aphasia.

Methods

Data collection is ongoing. So far, four Russian-speaking people with chronic non-fluent aphasia participated in the study: IIM (f, 42); KEA (f, 45); SYaV (m, 61); ShAE (m, 68). Participants received two sessions of VNeST per day for ten days over the course of two weeks. TDCS was delivered for 20 minutes at the beginning of only the first session each day via two sponge electrodes at 1.5 mA, with the anode over the intact perisylvian cortex (target selected based on MRI). There were two experimental groups with regard to the cathode positioning: contralaterally to the anode (SYaV, ShAE) versus over the left shoulder (IIM). One of the participants (KEA) recieved sham stimulation. Outcomes were tested with a custom action naming and sentence production tests that included trained and untrained verbs and the Russian Aphasia Test (RAT) [3].

Results

All participants improved significantly in sentence production. One participant improved significantly in action naming (KEA). Others also showed a numerical improvement although it did not reach significance. The overall score on the RAT did not improve significantly following therapy.

Conclusion

A combination of VNeST with tDCS in Russian-speaking people with chronic non-fluent aphasia showed promising results. All participants improved in sentence production. However, as data collection is ongoing, it is yet impossible to distinguish between the benefits of behavioral language therapy and tDCS. Further analysis will also explore differences in performance on trained and untrained items.

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Acknowledgements

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TMS-EEG is sensitive to the brain's capacity for consciousness: a reproducibility study

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Introduction

Theoretically, consciousness relies on the brain's ability to sustain complex patterns of causal interactions independently of sensory and motor functions [1]. The Perturbational Complexity Index (PCI) jointly measures integration and differentiation in the Electroencephalographic (EEG) responses to Transcranial Magnetic Stimulation (TMS) [2]. In severely brain-injured patients, PCI showed unprecedented sensitivity in detecting minimal signs of consciousness and provided a reliable stratification of unresponsive patients with specific physiopathological implications [3]. Here we aim at reproducing previously reported results with a similar equipment in a different cohort of severely brain-injured patients with disorders of consciousness (DoC).

Methods

This study includes two unresponsive wakefulness syndrome (UWS) patients with severe metabolic encephalopathy, one post-anoxic UWS patient and one post-traumatic minimally conscious state (MCS-) patient. DoC was assessed with the Coma Recovery Scale (CRS-R) [4]. EEG was recorded with a 64-channel amplifier (BrainAmp DC, BrainProducts GmbH, Germany). TMS was delivered with a Rapid^2 stimulator (Magstim Ltd, UK) equipped either with D70 Alpha B.I. coil or with D70 Remote Coil. After TMS-EEG data preprocessing [2], the maximum PCI value (PCI_{max}) across stimulation sites in each patient was used for classification purposes according to a previous validation study [3].

Results

One metabolic UWS patient (CRS-R=5) (who died 5 days later) and the post-anoxic UWS patient (CRS-R=5) showed a severely abnormal, voltage-suppressed EEG background [5] and did not provide any significant EEG response to TMS (PCI_{max}=0). The other metabolic UWS patient (CRS-R=6) showed a marked slowing of background EEG (grade 3) [6] and low-complexity EEG responses to TMS (PCI_{max}=0.31). The MCS- patient (CRS-R=6, visual function subscale=2) showed a moderately abnormal EEG background [5] with a dominance of theta posterior rhythm and high-complexity EEG responses to TMS (PCI_{max}=0.45).

Conclusion

This study reproduces the results of previous large-scale validation [3] on a smaller sample size: specifically, PCI-based classification closely matched clinical diagnosis and correlated with qualitative EEG assessment. Two patients had the same total CRS-R score of 6: interestingly, the one diagnosed as MCS- based on his/her ability to fixate a bright object clearly showed high-complexity EEG responses to TMS. This result further highlights the sensitivity of PCI to the brain's capacity for consciousness, which may often go unseen when evaluating behavioral responsiveness.

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The impact of data length on real-time connectivity estimates

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Introduction

Non-invasive closed-loop EEG–TMS, in which EEG signals are analyzed in real-time to dynamically adjust stimulation settings, is receiving an increasing interest thanks to the experimental and therapeutic potential of brain-state dependent stimulation [1]. In this framework, a real-time analysis of EEG functional connectivity would allow for an appropriate characterization of brain states. However, real-time estimation of functional connectivity is challenging, since it requires short segments of data to allow for a fast tracking of spontaneous as well as stimulation-induced connectivity changes. This study aims to quantify through simulations the minimum data length required for a reliable estimation of functional connectivity.

Methods

We generated 3000 pairs of synthetic EEG recordings, with known connectivity structure in a given frequency-band of interest, F. The data length was expressed in terms of number of oscillation cycles at the center frequency of F. We assessed the capability of estimating functional connectivity for various data lengths (5–20 cycles), different levels of signal-to-noise ratio (SNR = 20, 10, 0 dB), and four connectivity metrics (phase-lag-index PLI [2], imaginary part of the phase-locking-value iPLV [3], orthogonalized amplitude-envelope correlation oAEC [4], and orthogonalized cross-correlation oCC). The accuracy of connectivity estimates was assessed in terms of fraction of statistically significant detections; specifically, a detection was considered as significant if it exceeded the 95th percentile of a null distribution.

Results

Fig. 1 shows the fraction of significant detections (FSD) as a function of the number of cycles, for different levels of SNR and connectivity measures. We found that at least 7 cycles are required by the iPLV and oCC to successfully detect the presence of connectivity in ≈100% of simulated pairs and with SNR=20 or 10 dB. Conversely, PLI and oAEC both require at least 10 cycles. An overall decrease of performance was observed for high noise contamination levels (SNR=0 dB).

Conclusion

Our findings suggest that a reliable real-time connectivity estimation is feasible using a relatively short data length (e.g., 350 ms for oscillations at ≈20 Hz). Hence, it can be effectively exploited in closed-loop neurofeedback stimulation systems.

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Acknowledgements

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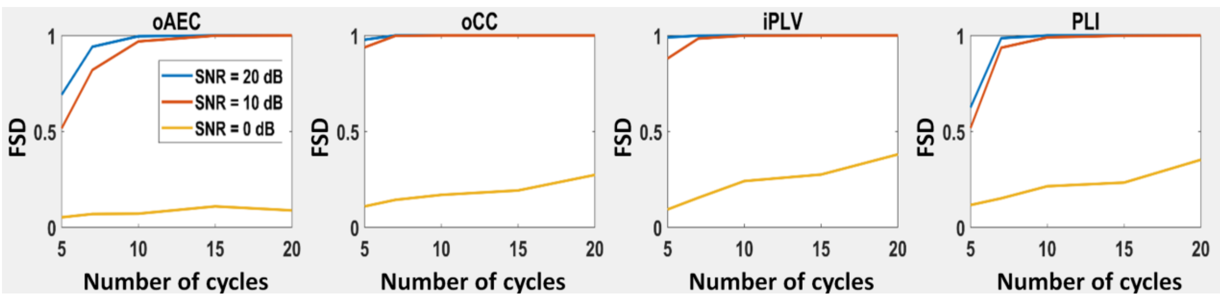

Figure 1: Fraction of significant detections (FSD) as a function of the number of cycles. Different panels refer to different connectivity measures (oAEC, oCC, iPLV or PLI). In each plot, different colors refer to different levels of SNR (20, 10 or 0 dB).

Variance in cortical depth across the brain surface

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Introduction

Non-invasive technologies that read or that stimulate the brain, such as EEG, TMS, or tDCS, frequently make assumptions about the anatomical structure of the brain. This is necessary as, in most cases, the structure of the brain is not visible. One example is the projection of a tDCS-derived computed electric field onto a standard brain model. But to what extent can we rely on a standard brain image in understanding effects in an individual person? Are there particular regions of the brain where a standardised analysis is inadvisable? This study examines the variance in cortical depth, a key factor in dose-setting for TMS/tDCS, across a wide sample of healthy adults.

Methods

94 structural (T1) brain images from right-handed men and women aged 25-60 were downloaded from the OASIS series [1]. SPM12b segmented the images into grey matter and the soft tissues. A convex hull was applied to the soft tissue to give the scalp surface. For each point in the grey matter, the euclidean distance from that point to the closest point on the scalp was determined, which defined the scalp-to-brain distance for that point. Each brain image was then transformed to the MNI template to allow for comparisons between images. Previous studies [e.g. 2] have used the mean scalp-brain distance, however the variance of this measure depends on the depth; therefore the coefficient of variation (CoV : standard deviation divided by the mean) was used as a scale-free measure of variance. Five ROIs from the AAL atlas [3] were used to illustrate regional CoV.

Results

Figure 1A shows the CoV for the sample. Figure 1B idenitifies five areas from the AAL atlas that are common targets for brain stimulation, and the mean CoV in those areas is shown in 1C. Regions with high CV include the occipital and precentral areas, while the prefrontal ROI shows relatively low CoV.

Conclusion

This study has shown that some regions of the brain have a greater variance in depth than others. This has important implications for the use of standardised head models in targeting non-invasive brain stimulation. For example, the use of scalp-to-surface depth as a means of setting intensity is suspect in brain regions with high variance. High CoV in the motor (PreC) and visual (Occ) areas has implications for the use of motor or visual evoked potentials in setting stimulation intensity for other brain areas. Lower CoV in prefrontal cortex means it is a suitable target for unsupervised stumulation by home users.

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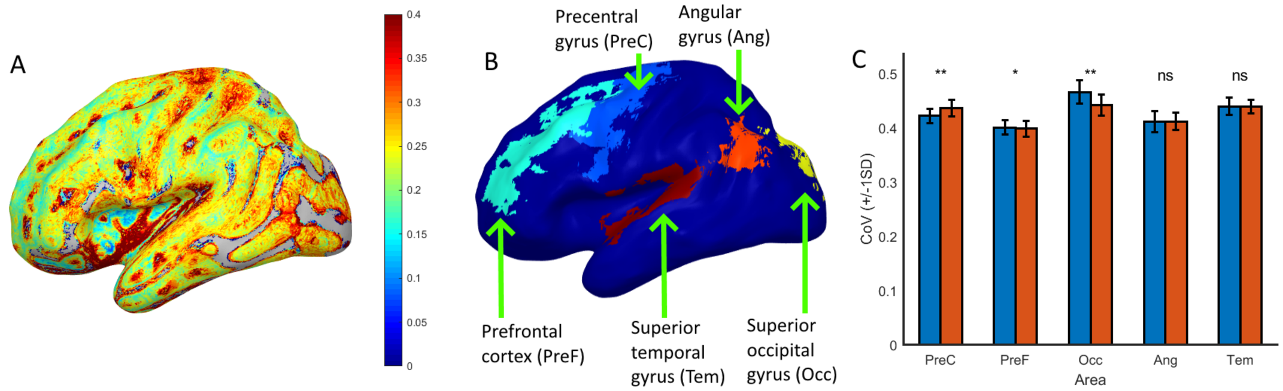

Figure 1A: CoV across the whole brain. B: Selected ROIs based on the AAL atlas. C: CoV in those ROIs. Stars indicate regions where CoV for the left hemisphere (blue) differs from the right (red).

TMS-EEG as a measure of the intermittent theta-burst stimulation's mechanism in prefrontal cortex.

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Introduction

Since the emergence of the combination of transcranial magnetic stimulation (TMS) with electroencephalography (TMS-EEG), it is possible to assess cortical plasticity in any defined cortical region[1]. Therefore, it is possible to record the effect of intermittent theta-burst stimulation (iTBS) to the left dorsolateral prefrontal cortex (DLPFC). Indeed, iTBS is used as a functional treatment of depression with promising advantages including a reduced stimulation time compared to the classical repetitive TMS (rTMS) treatment[2]. Although iTBS is already used in clinical practice, the optimal duration of stimulation is unknown. This TMS-EEG study aimed to determine the optimal iTBS duration to activate the left DLPFC, out of the 3 most commonly used durations: 600, 1200 and 1800 pulses.

Methods

A total of 14 healthy participants were enrolled to each undergo 3 different durations, which were administered at 3 different sessions (counterbalanced order; 7 days between sessions). TMS-EEG was performed before and after each iTBS session to assess both TMS-evoked potentials (TEP) and TMS-evoked oscillations. More specifically, we focused on 5 EEG components (P30, N45, P60, N100 and P200) and 4 frequency bands (theta, alpha, beta and gamma).

Results

Linear mixed models were performed. TEP results shows that all iTBS conditions induced a significant reduction of the amplitude of TMS-EEG indexes of cortical excitability (P30, P60 and P200) and an increase in measures of cortical inhibition (N45), but suggest no difference between the 3 iTBS durations on the modulation of cortical excitability. Similarly, that the power of theta and alpha frequency bands significantly changed after iTBS, but resulted in no difference between the 3 iTBS durations.

Conclusion

Results show no difference between the 3 iTBS durations on the modulation of cortical excitability suggesting the absence of a linear effect between iTBS duration and modulation of brain excitability in the left DLPFC.

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Direct activation of cortical neurons using focused ultrasound in the primary somatosensory cortex of the rat *in vivo*

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Introduction

There is controversy if focused ultrasound (FUS) can directly activate cortical neurons. Earlier publications report this to be the case, more recent ones indicate that FUS may act indirectly via auditory pathways. We compared the response to FUS on the local field potential (LFP) in living rats with that evoked by other stimuli. We obtained evidence for direct activation.

Methods

We used 21 adult Sprague Dawley rats (250-350g) for the study. Three types of stimulation were applied: Whisker stimulation, Direct cortical stimulation (DCS) and FUS. Whisker stimulation was done with a device attached to a step motor activated by a trigger to synchronize stimulation and recording. The whiskers map onto corresponding cortical barrel columns. DCS and FUS stimulation were applied to an exposed brain surface after removing the skull. For DCS said barrel column was directly stimulated epidurally with an electrode. FUS stimulation was applied at different depths in the same location, using an in-house built transducer with a narrow linear beam of FUS (4 MHz) with a full width half maximum (FWHM) of <1 mm. Intensity was in the allowed range for humans as recommended by FDA.

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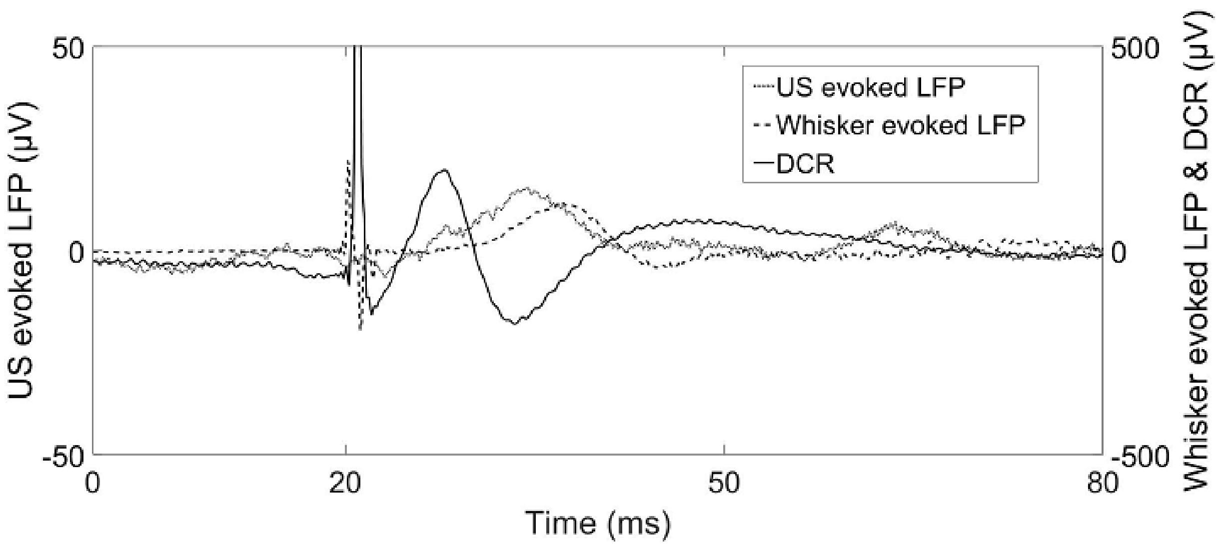
Conclusion

The FUS-evoked LFP reversed polarity beetween 1 and 1.5 mm along the depth of the cortex, the waveforms being mirror images of each other. This profile demonstrates that the FUS was able to generate neuronal responses in the grey matter of the cortex below the transducer.
We compared latency of the onset of the LFP for the three methods, see Figure.The FUS-evoked LFP arrived with a latency between those of the DCR and whisker-evoked LFP. This also supports the conclusion of direct stimulation.



Functional connectivity of the motor system and the resting motor threshold: A replication study.

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Introduction

Recent evidence suggests an impact of functional connectivity (FC) of the motor system on the RMT [1]. The aim of this study was to validate these findings on the impact of FC between the primary motor cortex (M1) and dorsal premotor cortex (PMd) as well as other motor areas on the RMT. The impact of the above-mentioned predictors is compared to the coil-to-cortex distance (CCD) as a known predictor of the RMT.

Methods

The RMT was measured bi-hemispherically in 38 healthy right-handed subjects (37.5 ± 13.8 years, 21 females) using navigated TMS. Resting-state FC was assessed inter-hemispherically on M1 and intra-hemispherically between M1 in relation to primary somatosensory cortex (S1), dorsal and ventral premotor cortex (PMd, PMv), supplementary motor area (SMA) and pre-SMA. Other factors included in the analysis were age, sex and CCD. The relationship between each predictor and the RMT was assessed with a linear mixed model to account for non-independence of observations within the same subjects. Further, we evaluated the previously proposed model [1] for the dominant hand using age, sex, CCD and FC between M1 and PMd.

Results

FC between M1 and PMd did not significantly predict the RMT ($b = -0.05$, $t(37) = -0.02$, $p = 0.986$). In addition, FC between further regions did not predict the RMT either. Singularly CCD showed a significant impact on the RMT ($b = 1.45$, $t(37) = 5.38$, $p < .001$). This model explained 42% of the variance of the RMT and was advantageous over a simpler model containing only the random effect for subjects ($x^2(1) = 23.68$, $p < 0.001$). Further, the model for the dominant hemisphere only showed a significant effect only for the CCD ($b = 1.56$, $t(34) = 4.76$, $p < 0.001$).

Conclusion

We could not replicate previous findings on the impact of FC to non-primary motor areas on the RMT in a larger sample. The distance between stimulation coil and cortex remains the most important and well-established predictor for the RMT.

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Effects of 8-weeks of Aerobic Exercise Intervention on Fitness and Neuroplasticity in Aging Adults

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Introduction

Aerobic exercise is known to promote cognitive function and mental well-being in aging adults, but the exact mechanisms are not fully elucidated [1]. Studies in animal models and humans have attributed exercise-mediated cognitive improvements to two main mechanisms: neuroplastic changes in the nervous system resulting in enhanced synaptic activity; and increased cardiovascular fitness, which may optimize cerebral blood flow, release of trophic factors and promote structural changes [2,3]. The objective is to assess both neuroplasticity and cardiovascular fitness in sedentary aging individuals who participated in an 8-week progressive exercise intervention.

Methods

Twelve (≥55 years; mean age=59.5±3.7; 58.3% females) cognitively healthy (MoCA≥24; mean=25.9) sedentary individuals have completed the intervention to date. Participants engaged in a supervised aerobic exercise intervention 3x/week over the course of 8 weeks for a total of 24 exercise visits. Aerobic exercise sessions were 60 min of steady-state on either a treadmill, elliptical, or bike, delivered at moderate intensity (55-64%) for the first 4 weeks and high intensity (65%-90%) for the subsequent 4 weeks. At baseline and post-intervention, participants underwent a neuroplasticity assessment utilizing transcranial magnetic stimulation (TMS), and an Incremental Shuttle Walking Test (ISWT) to assess cardiovascular fitness. The neuroplasticity assessment consisted of measuring the amplitude of motor evoked potentials (MEPs) at baseline (T0), and following intermittent theta-burst stimulation (iTBS), at regular intervals (T5, T10, T20, T30) and then quantifying the iTBS-induced modulation of MEPs as percent change from baseline to post iTBS across each time point (%Δ). The cardiovascular fitness measures derived from the ISWT was the walking distance and Heart Rate Recovery (HRR), which was used to estimate VO2.

Results

We found significant correlations between cardiovascular fitness (HRR1-min) and neuroplasticity at baseline (%Δ post-iTBS at T5, p=0.016, r=.733; and T10, p=.009,r=.743). In the pre to post comparisons, there was an increase in neuroplasticity (%Δ pre to post-iTBS at T5, mean=40.86%, p=.010) and cardiovascular fitness (HRR 2-min, mean diff= 10.73, p=.038). A positive strong correlation was found between the change in neuroplasticity (%Δ pre to post-iTBS at T5) and the change in cardiovascular fitness (HRR at 1-min,p=0.016,r=.765).

Conclusion

In the preliminary results, we found correlations between the efficacy of the mechanism of plasticity as measured by iTBS and cardiovascular fitness at baseline, and improvements in both measures from pre to post the 8 week physical exercise intervention.

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Stimulating the VLPFC Modulates Frustration-Induced Aggression: A tDCS Experiment

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Introduction

The prefrontal cortex is crucial for top-down regulation of aggression, but the neural underpinnings of aggression are still poorly understood. Past research showed the transcranial direct current stimulation (tDCS) over the ventrolateral prefrontal cortex (VLPFC) modulates aggression following exposure to risk factors for aggression (e.g., social exclusion, violent media). Although frustration is a key risk factor for aggression, no study to date has examined the modulatory role of tDCS on frustration-induced aggression. By exploring the VLPFC involvement in frustration-aggression link, we tested the hypothesis that the anodal tDCS over right and left VLPFC modulates frustration-induced aggression. We also explored whether tDCS interacts with gender to influence frustration-induced aggression.

Methods

90 healthy participants (45 men) were randomly assigned to receive anodal or sham tDCS over the right or left VLPFC before being frustrated by an accomplice. To increase reliability, several tasks were used to measure aggression.

Results

We found that anodal tDCS over the left VLPFC, compared to sham stimulation, increate aggression. Unexpectedly, no main effect was found following tDCS of right VLPFC. However, we also found a significant interaction between gender and tDCS, showing that males were more aggressive than females following sham stimulation, but females became as aggressive as males following active tDCS.

Conclusion

Overall, these results shed light on the neural basis of frustration-induced aggression, providing further evidence for the involvement of VLPFC in modulating aggressive responses, and on gender differences in aggression. Future research should further investigate the role of stimulating the VLPFC on frustration-induced aggression.

FaReMuS modifies the control of everyday movements

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Introduction

Fatigue in multiple sclerosis (MS) occurs together with impairment of motor control strategy, as reflected in previously observed altered central-peripheral communication [1]. In the management of this debilitating symptom, beyond pharmacological approaches that still lack specificity, it appears promising the personalized neuromodulation called FaReMuS [2], [3]. We tested the working hypothesis that FaReMuS reduces the fatigue related alteration of the central-peripheral synchronization.

Methods

In mildly disabled MS patients, for whom fatigue symptom is crucially bothersome, we measured the cortico-muscular coherence (CMC) between simultaneous electroencephalographic and surface electromyographic signals during a weak handgrip before and after FaReMuS. This consisted of 5-day tDCS over the whole body somatosensory representation areas. We assessed the variations of motor strategy induced by FaReMuS, while testing their association with the effectiveness of the treatment as expressed by the reduction of fatigue.

Results

In the pre-treatment phase, the CMC was observed at a mean frequency of 31.5±1.6 Hz (gamma-band) and positively correlated with the level of fatigue (p=.027). After treatment, the CMC frequency reduced to 26.6±1.5 Hz (p=.022), thus forthcoming the physiological beta-band as observed in healthy people.

Conclusion

FaReMuS, a personalized neuromodulation treatment efficacious against MS-fatigue, was able to normalize the central- peripheral communication subtending simple everyday movements.

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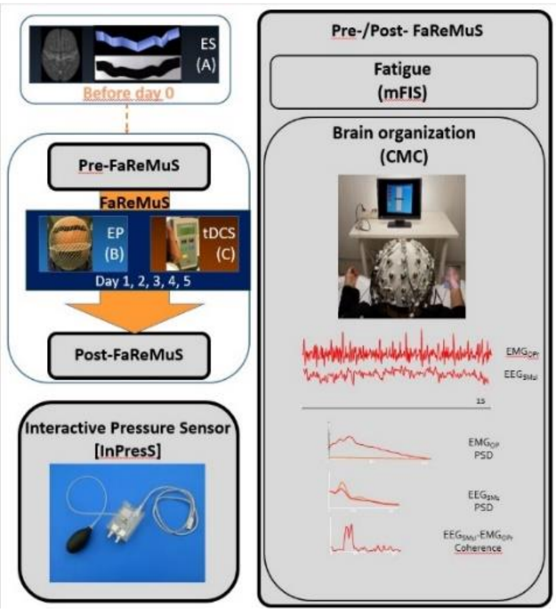

Figure 1: Experimental procedure in each person with MS undergoing FaReMuS.

Left: Individual brain MRI-based personalized electrode, study design schema, Interactive Pressure Sensor (InPresS) for motor task control providing visual feedback. **Right**: Pre- and Post-FaReMuS we collected mFIS, and EEG-EMG. We represented the measures used for the upstream and downstream nodes activities (Cortical and muscular Power Spectral Density, PSD) and the functional connectivity between them (cortico-muscular coherence).

The role of pre-stimulus cortical oscillations for signal propagation after a TMS pulse

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Introduction

Oscillatory brain activity is thought to modulate excitability changes in neural populations, serving as a mechanism for coordinated functions and synchronization in the central nervous system. These oscillations can be influenced by transcranial magnetic stimulation (TMS) and studied by combining it with electroencephalography (EEG). The phase of the mu rhythm preceding stimulation has been found to affect corticospinal responses to TMS [1]. We hypothesized that the phase of the spontaneous oscillations prior to TMS may play a role in signal propagation between cortical areas.

Methods

We applied TMS to the left primary motor cortex and right pre-motor areas of three subjects. After pre-processing [2], we estimated the phase of the EEG signal prior to the TMS pulse for the mu- and beta-rhythm frequency bands (7–13 and 13–30 Hz, respectively) for each trial with a sliding-window narrow-band Hilbert transform method. We then divided the trials into two classes based on the phase (negative or positive peaks of oscillatory activity) of the EEG signal just before the TMS pulse. Within each subject, we compared the TMS–EEG responses of the two trial classes for both rhythms with cluster-based statistics [3].

Results

The propagation of the EEG potentials after TMS differed between the two classes, for both rhythms, for all subjects at different time and scalp points (Fig. 1). For each subject, a few clusters of significant differences were found. The pre-stimulus mu rhythm had a larger effect on propagation than beta rhythm for these two stimulated cortical regions.

Conclusion

These preliminary findings provide further evidence on the influence of spontaneous cortical oscillations in shaping the neuronal response to a TMS pulse. Understanding how spontaneous activity affects TMS-evoked responses will help in designing future activity-dependent cortical stimulation protocols, which reduce variability in responses and increase specificity in studying cortical networks.

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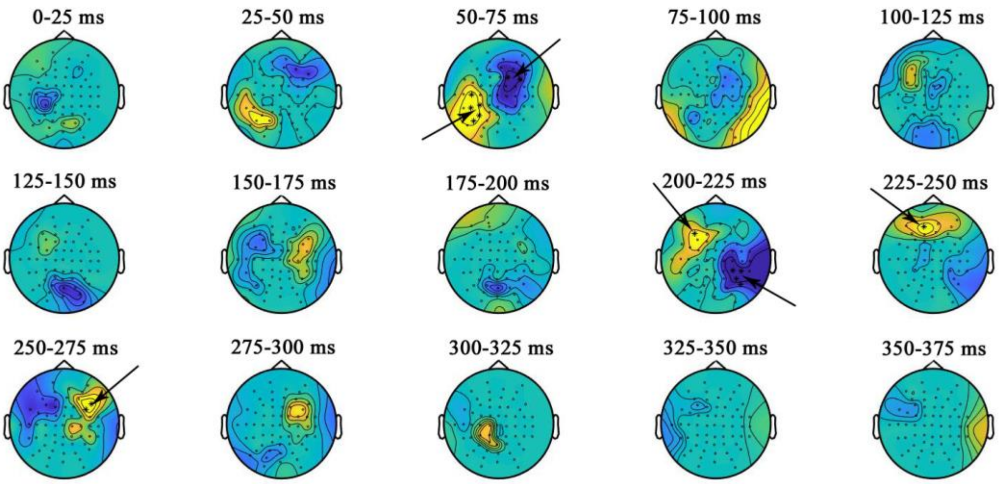

Fig. 1. Data of a subject with four significant clusters at time windows 50–75 and 200–275 ms for the μ-rhythm at M1. The arrows show the significant clusters at various time and scalp points.

The more excited the better?

Occipital cortex TMS and visual perception

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Introduction

Can we temporarily manipulate visual perception? How occipital cortex excitability influences it? Those research questions are based on the assumption that phosphene threshold (PT) represents occipital cortex excitability and that occipital cortex excitability determines the quality of visual perception. However, there is a lack of evidence on the relationship between PT and visibility measures. Moreover, the results concerning the influence of occipital continuous Theta Burst Stimulation (cTBS) on visual perception are inconclusive. The study aims were: (1) investigating the relationship between the occipital cortex excitability and visibility measures, (2) verifying how cTBS affects participants' visual perception and (3) determining how cTBS-visual task interaction influences PTs.

Methods

We used stimulus awareness ratings in combination with a visual identification task. Participants (n=40) underwent phosphene recognition training and PT estimation prior to completing the visual task on the first day of the study. On the consecutive two days, either active or sham cTBS was applied and pre-cTBS-task and post-cTBS-task PT were estimated. By changing the neural excitability of the occipital cortex we aimed to manipulate participants' visual task performance. Additionally, we looked for correlations between these visibility measures and participants' PTs.

Results

cTBS resulted in a decrease in identification task accuracy but influenced neither awareness ratings distribution nor metacognitive efficacy. We did not find any correlation between PT and visibility measures. PTs significantly increased following sham but not cTBS.

Conclusion

The study provides new evidence regarding occipital cTBS influence on visual perception. Moreover, it challenges the common assumption about the relationship between occipital cortex excitability and visual perception. It may suggest no direct relationship between visual perception and occipital cortex excitability or that PT is not an adequate measure of it. We hypothesise that relationship between PTs and occipital cortex excitability is non-linear. Furthermore, we discuss methodological aspects of using TMS in visual perception studies.

Phase-synchronized 6 Hz rTMS with tACS induces sustained increase in 6 Hz Oscillations

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Introduction

Neural oscillations are associated with many cognitive functions and disorders. Modulating oscillatory activity using non-invasive brain stimulation (NIBS) may be a viable approach for exploring causality of oscillatory rhythms in cognition, and developing treatments for patients with cognitive disorders. We recently developed a NIBS protocol whereby repetitive transcranial magnetic stimulation (rTMS) was phase-synchronized with transcranial alternating current stimulation (tACS) in order to induce frontal 10Hz oscillations. Here, we aim to optimize and extend this protocol to induce and sustain 6Hz oscillations, given their functional relevance in critical cognitive functions.

Methods

A custom electrical circuit was designed to elicit rTMS pulses at precise phases of the tACS sinusoidal waveform. We then investigated whether applying 20 min of "peak-synchronized" rTMS (80% AMT) and tACS (1mA) at 6Hz over the prefrontal cortex (PFC) could induce and sustain 6Hz oscillations in the resting state EEG. tACS was applied through four bilateral electrodes (F3/F4, TP9/TP10) with rTMS delivered over the F3 and F4 tACS electrodes. 25 healthy participants took part in 5 randomized sessions: rTMS+tACS, rTMS only, tACS only, and, sham rTMS+sham tACS, as well as an additional experiment where tACS was continued for a longer duration after the initial block. EEG was recorded before, immediately after, and every 10 min for up to 60 min after stimulation, in eyes-open (EO) and -closed (EC) conditions.

Results

The rTMS+tACS protocol significantly enhanced 6Hz EEG power for up to 60 min compared to sham, in both EO and EC ($p<0.001$ for both). Moreover, with the rTMS+tACS+longer tACS protocol, effects were greater and sustained for a longer duration. Lesser effects were observed with the tACS only protocol in EO and EC ($p<0.05$), while rTMS alone and sham stimulation did not result in any effect.

Conclusion

Our findings show the feasibility of phase-synchronizing NIBS for inducing, and stabilizing neural oscillations. Further studies will be needed to ascertain the precise mechanisms underlying the observed effects. Our findings open promising potential for exploring and modulating relevant cognitive functions and clinical applications.

Keywords: tACS, rTMS, EEG, theta power, connectivity.

Focality of the Excitatory and Inhibitory pp TMS phenomena

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Introduction

Paired pulse transcranial magnetic stimulation (ppTMS) is used for evaluating cortical excitatory and inhibitory processes.[1] ppTMS paradigms depending on the length of the interstimulus interval (ISI) can be classified into (1) long-interval ppTMS phenomena (such as intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI)) and (2) short-interval ppTMS phenomena (such as short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF)). The goal of this study was to investigate the focality of ppTMS phenomena in different upper limb muscles. We hypothesized that the length of the ISI would predict the correlation strength of ppTMS phenomena among different upper limb muscles.

Methods

20 healthy right-handed participants were enrolled in the study (10 females, 18-30 y.o.). All ppTMS phenomena were probed using MRI-navigated TMS applied to the abductor pollicis brevis (APB) hotspot in the left primary motor cortex. Motor evoked potentials (MEPs) were recorded from the right upper limb muscles: APB, extensor digitorum communis (EDC), abductor digiti minimi (ADM) and biceps brachii (BB). Each ppTMS paradigm include 15 trains repeated 3 times. Mean values were calculated for each ppTMS phenomenon and muscle, except for the inhibitory phenomena (SICI and LICI) in the BB muscle, as MEPs in it to single-pulse TMS were lower than 150 μV Mean of each ppTMS was calculated and normalized by single pulse TMS responses.

Spearman's rank correlation coefficient was calculated in order to assess the associations in inter-muscle ppTMS phenomena, FDR correction was used.

Results

Mean effects of ppTMS phenomena were as following: SICI APB - 1.04 (0.75-1.31), ADM - 1.04 (0.71-1.37), EDC - 1.15 (0.86-1.43); SICF APB - 1.94 (1.63-2.23), ADM - 2.02 (1.63-2.40), EDC - 1.75 (1.38-2.11), BB - 1.67 (1.36-1.97); ICF APB - 3.18 (2.05-4.31), ADM - 4.01 (2.52-5.50), EDC - 2.97 (2.15-3.79), BB - 2.41 (1.81-3.01); LICI APB - 0.40 (0.11-0.68), ADM - 0.54 (0.27-0.81), EDC - 0.50 (0.29-0.70).

Significant correlations among the muscles were obtained for SICI ($r = .64$, $p = .01$), ICF ($r = .60$, $p = .01$) and LICI phenomena ($r = .77$, $p < .001$). At the same time, there were no significant correlations among the muscles for the SICF phenomenon.

Conclusion

Our results show no direct link between the duration of the ISI and the focality of ppTMS phenomenon. The lack of the correlations among muscles for SICF might be explained by its specific mechanism, which involves the superposition of D-and I-waves on a single neuron. [2] Such understanding of the TMS phenomena focality is important both in a fundamental way and for practical reasons for developing new TMS approaches.

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Intermittent photic stimulation in healthy controls in MEG

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Introduction

Intermittent photic stimulation (IPS) is commonly used in clinical electroencephalography (EEG) in eyes open (EO) and eyes closed (EC) conditions [1]. IPS enhances the diagnostic sensitivity of EEG and cause epileptic seizures in patients suffering from photosensitive epilepsy [2]. In contrast to EEG, IPS has not been included in clinical magnetoencephalography (MEG) practice guidelines [3,4] due to the lack of MEG compatible stimulators.
We have developed an MEG-compatible *Euphotic* IPS stimulator (PCT patent pending/Aalto University) providing diffuse IPS through the eye lid both in EO and EC conditions. Here we present results in healthy controls.

.Methods

We used *Euphotic* IPS stimulator utilizing a LED light source, controlled with TTL pulses, and multifilament optic fibres. The cortical responses elicited by IPS stimulation were measured by MEG (Elekta Neuromag TRIUX™; Elekta Oy, Helsinki Finland) inside a two-layer magnetically shielded room (Vacuumschmelze GmbH & Co. KG, Hanau, Germany). Magnetic resonance images (MRIs) were collected with a 3 T MRI scanner (Siemens 3T MAGNETOM Prisma, Erlangen, Germany). The measurements were carried out at the Cognitive Neuroimaging Centre (CoNiC) at Nanyang Technological University (NTU), Singapore. The study has been approved by NTU Institutional review board (IRB).
We measured six subjects without a history of epilepsy or problems associated with IPS. The MEG measurements included the preparation of the subject and digitization of the landmarks and head position coils for the co-registration between MEG and MRI. Resting state MEG signals and MEG signals during IPS stimulation measured and compared in EO and EC conditions. The sources contributing to the averaged MEG signals coinciding with the IPS were modeled with equivalent current dipoles (Elekta Oy, Helsinki, Finland) and superimposed with co-registered MRIs.

Results

The *Euphotic* IPS stimulator did not produce any artefacts in MEG recordings. All the subjects tolerated the IPS well. The MEG responses elicited with IPS were easily detectable and reproducible. The corresponding sources were located mostly at V6 area both in EO and EC conditions

Conclusion

The present work emphasizes MEG responses to IPS stimuli in control subjects. Elicited responses can be easily modeled and localized using equivalent current dipoles. "*Euphotic*" IPS stimulator wit diffuse light can be used in humans for both basic and clinical research projects. We consider *Euphotic* IPS as a potential tool to study non-invasively cortical excitability and, e.g., neuromodulation [5] in humans.

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Acknowledgements

Euphotic Core team members Pia Kemppainen-Kajola and Jani Issakainen at Aalto University.

Modelling of brain states using a coarse-grained Kuramoto model in TMS-EEG

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Introduction

Measurement of brain activity by EEG and application of transcranial magnetic stimulation (TMS) in a closed-loop setup has potential as a treatment for many brain conditions, such as Alzheimer's disease and depression. However, the requirement for the delay between the measurement of brain state and the consequent application of stimulation is stringent; a delay of 0.5 s is already too long in terms of treatment [1]. To reduce the delay caused by analysis and prediction algorithms, novel concepts need to be introduced. We propose to use a Kuramoto model in connection with EEG measurements as a potentially fast method for brain state prediction. Our first aim was to determine how many oscillators should be included to model realistic EEG dynamics and still keep computations efficient.

Methods

We simulated a Kuramoto model on an anatomically accurate EEG source model, consisting of 20001 cortical nodes, each representing one focal current source. We coarse-grained the source space by grouping together the primary nodes. The maximum number of primary nodes that could be represented by one coarse-grained node was determined by the criterion that the resulting topography must be essentially identical to the one obtained by direct forward transformation of the original nodes. In the model, a Kuramoto oscillator then represents each of these coarse-grained nodes. The basic Kuramoto model can be used as a model to predict effects in brain stimulation [2]. A modification to this model allows inclusion of spatial information [3].

Results

We show that correspondence between an implemented coarse-grained model and selected brain states can be achieved. Extraction of model parameters from EEG measurement data is demonstrated.

Conclusion

Kuramoto model combined with spatial course-graining of the source space was shown to be a feasible method for modelling and prediction of brain states and also for generating simulated data. The feasibility of learning model parameters, primarily coupling strengths, from the data will be investigated in the follow-up work.

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Gender effects in a subsample of the S1200 HCP cohort – a simulation study

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Introduction

In our previous studies (1, 2, 3) we have used specific frontal ROIs of the DLPFC atlas by Sallet et al. (4) for our studies. In this simulation study we focused on the analysis of gender and age variability of transcranial Direct Current stimulation at electrode positions F3 and F4 on a left DLPFC ROI.

Methods

125 subjects (mean age=28.86, age range=22-35, 71 women, 54 men) of the S1200 cohort (Wu-Minn HCP Data) were used and calculated at the Leibnitz Supercomputing Centre (LRZ, Garching, Germany) using slurm and freesurfer 6. This data was then post-processed on a local cluster with SIMNIBS integrated in the NAMNI scripts [5] and following parameters: Anode, F3, 0.002A and cathode, F4, 0.002A, electrode size 50x70mm, electrode thickness=4mm. The electric fields were determined for the top field norm for vector field (normE) 95.0%, 99.0% and 99.9%. Additionally, the mesh area was extracted with a field equal to or greater than X% of the 99.9th perecntile for the efields of 50% and 75%. From 76 subjects of this sample an additional ROI analysis (sphere, radius of 18mm, MNI xyz-coordinate -32, 45, 19) was performed. This DLPFC ROI covers the central areas of the Sallet atlas. An independent Student's t-test was calculated for the grouping variable gender and the mean values of the ROI analysis. In addition, correlations between age and intracranial volume ICV and ROI efields were calculated. The whole brain fields for the perecntile 95%, 99% and 99.9% are given descriptively. Software used: freesurfer 6.0.1, FSL 5.0.9, SIMNIBS 3.1.0.

Results

The independent Student's t test showed a significant difference ($p=0.006$) for the factor gender (female vs. male) for the ROI analysis of the mean normE values ($t=-2.812$, $df=74$, $CI=-0.063, -0.011$, Cohen's $d=-0.66$). The correlation between the DLPFC ROI normE results and age was not significant (Pearson's $r=-0.176$, $p=0.13$). The correlation between the DLPFC ROI normE and the ICV showed a significant correlation (Pearson's $r=0.483$, $p<0.001$).

Conclusion

In this simulation study clear gender influences on the simulated efileds in a brain area relevant for prefrontal tDCS were found. The efields correlated significantly with the ICV, which could be a relevant factor for the specification and individualization of tDCS in future research and clinical application.

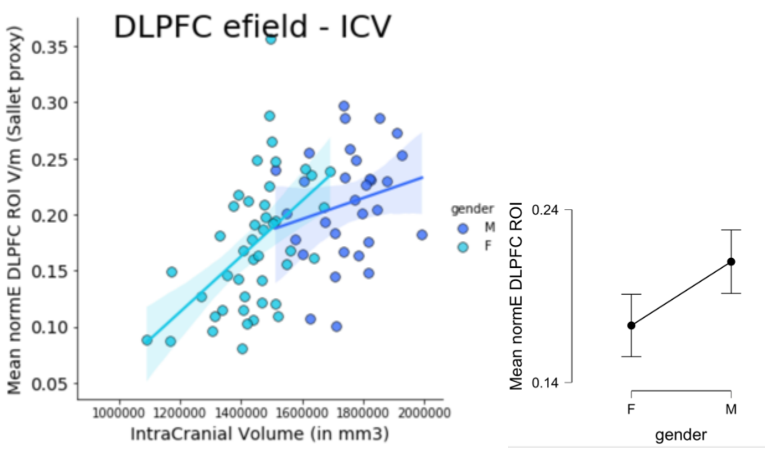

Figure 1: Regression plot between the mean normE DLPFC ROI values (in V/m) and the ICV, shown for gender (turquoise= women, purple=M men). There are significant differences between women and men in this brain area.

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Peersourced TMS–EMG MEP annotation tool for algorithm development and open research

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Introduction

The development and use of machine learning algorithms face an obstacle: how to find large quantities of reliably labelled data for training? Similarly, comparing between algorithms can prove challenging, due to lack of standardization and transparency. At the same time, researchers using electromyography (EMG) with transcranial magnetic stimulation (TMS) are in need of algorithms that reliably detect the onset interval between the TMS stimulus and the motor evoked potential (MEP) response. To tackle these challenges we developed an online tool for manually annotating the latency of MEPs. The platform allows rapid labelling the response onset and to mark issues. The data annotations enable their use as training and testing datasets for machine learning algorithms. All data on the platform are donated by individual researchers, or institutions. The data are placed under a permissive license and made publicly available. After an initial testing period, also aggregated data will be provided for analysis and development purposes freely and we plan to implement analysis tools directly onto the platform.

Methods

Platforms for sharing and analyzing a multitude of neuroscience data already exist. Particularly OpenNeuro [1] is a successful example of a popular service. In contrast to OpenNeuro, our platform specifically targets a specific research problem, which is to create a large, manually annotated, dataset for analysis and algorithm development.

Crowdsourcing and *citizen science* [2] can refer to non-scientists taking part in analyzing large quantities of data that scientists themselves cannot tackle. Our platform resembles both of these methods but differs by employing specifically experienced researchers instead of the general public. We refer to this method as *peersourcing*.

The data labelling tool shown in Figure 1, is built using a microservice model and deployed on a cloud platform. This allows for scalability, ease of access, and a rapid development cycle. The tool operates in web browsers on both smart phones and computers regardless of operating system.

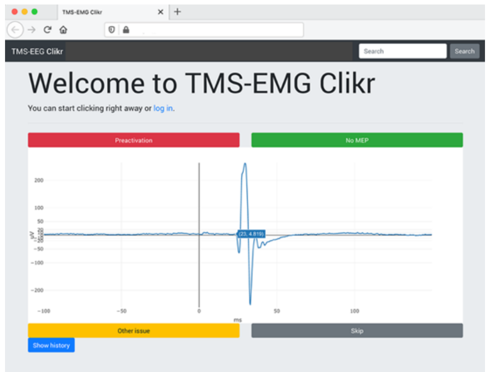

Figure 1. Screenshot of data labelling interface early prototype.

As the first realization of the potential of the tool, we are studying the inter-researcher variance in the ways in which they manually annotate the MEP onset position.

Results

Preliminary user research tests indicate that during a TMS–EMG data labelling task, the user can reach a rate of 500–750 annotations per hour. This result in itself is an improvement compared to, for example, many offline workflows.[3] Publicly available annotated datasets for TMS-EMG experiments have not yet been in this extent.

Conclusion

The first functional prototype for manually annotating TMS–EMG experiment data with MEP latencies is undertaking its first testing phase. Next, we plan to extend data gathering and gradually make the platform more open. Ultimately, our goal is to generalize the platform for annotating, testing, and analyzing other neuroscience data as well.

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Transcranial magnetic stimulation of prefrontal cortex for modulation of insight problem solving

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Introduction

Insight is the sudden and unpredictable appearance of a problem’s solution. This phenomena is intensively studied due to its probable association with creative thinking and creativity. Several studies showed the effects of anodal tDCS over left premotor cortecs on the insight solution frequency (Cerutti et al., 2009, Metuki N et al., 2012). Online repetitive transcranial magnetic stimulation (rTMS) applying during the task performance is widely used approach to disrupt brain regions that are involved it task processing and investigate causal role of stimulated brain area. Our aim was to assess the effects of online rTMS over right and left DLPFC on insight problem solving.

Methods

10 healthy right-handed adults (7 women, mean age - 18.0 [18.0; 21.5] years) were included. rTMS was performed on neuronavigated system NBS eXimia (Nexstim). All participants underwent 1 session of online-rTMS of left/right DLPFC and Vertex in randomized order with intersession’s interval not less than 48 hours. Online paradigm included presentation of an anagram for 9 sec followed by 4 sec train of 10 Hz rTMS; after the end of stimulation the subject has additional 4 sec to solve the anagram. If the anagram was solved during the rTMS train stimulation or within 4 seconds after the participant was asked if he experienced insight or non-insight solution. During each session 35 anagrams were presented. We assessed the total number and frequency of insight problem solving. Statistical analysis was performed on MATLAB R2018a.

Results

One person experienced 3 insights during the rTMS session. No significant difference was found in total number (Friedman test, $p = 0.34$) and frequency of insight solving (Friedman test, $p = 0.56$) depending on stimulating area.

Conclusion

We did not find any effects of rTMS of left and right DLPFC on insight problem solving. We plan to continue the study to increase the statistical power.

Acknowledgements

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Double facilitating triple pulse in clinical MEP-exams

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Introduction

Motor evoked potential (MEP) exams can be used to assess the central conduction time (CCT) of a patient's motor pathway. With a paired pulse TMS it is possible to also assess the patient's short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), depending on the interstimulus interval (ISI) [1]. An added benefit to the facilitating paired pulse method is that it can also be used to elicit MEP-responses when single pulse stimulation is unable to do so. However, even with paired pulse stimulation it is sometimes difficult to elicit MEP-responses reliably in patients, particularly from the lower extremities [2]. A proposed solution would be to use a triple pulse method with two facilitating pulses, to increase the likelihood and amplitude of MEP responses.

Methods

We analyzed a sample of 50 healthy volunteers participating in collection of reference values for MEP exams in the Meilahti hospital. Test subjects were aged between 24-70 years and had no known epilepsy, CNS affecting medications, or pathologies of the motor pathway. Equipment: Magstim 3 into 1, round 90 mm coil, monophasic pulses. Target muscles: abductor pollicis brevis (APB) & tibialis anterior (TA).

Measurements done only to dexter side of test subjects:

- Resting motor threshold (MT) determined as > 5/10 MEP-responses ≥ 50 µV
- 5 x Single pulse (120% MT)
- 5 x Paired pulse (90 % + 120 % MT, ISI 13 ms)
- 5 x Triple pulse (90 % + 90 % + 120 % MT, ISI 13 ms)

Mean amplitude calculated from each 5 measurements, including 0 amplitude ones.

Results

Triple pulse TMS elicited MEPs of higher mean and median amplitude than either single pulse or paired pulse TMS in both APB and TA muscles; the increase in amplitude was more substantive in the TA. There were two instances where a single or paired pulse failed to elicit reliable MEP responses, but triple pulse succeeded.

Conclusion

Facilitating paired pulse TMS is more reliable in producing MEP responses than single pulse TMS, especially in the lower extremities. Double facilitating triple pulse TMS might be an even more reliable method, and could possibly offer new diagnostic correlations as well, but further clinical testing on patients is needed to study this.

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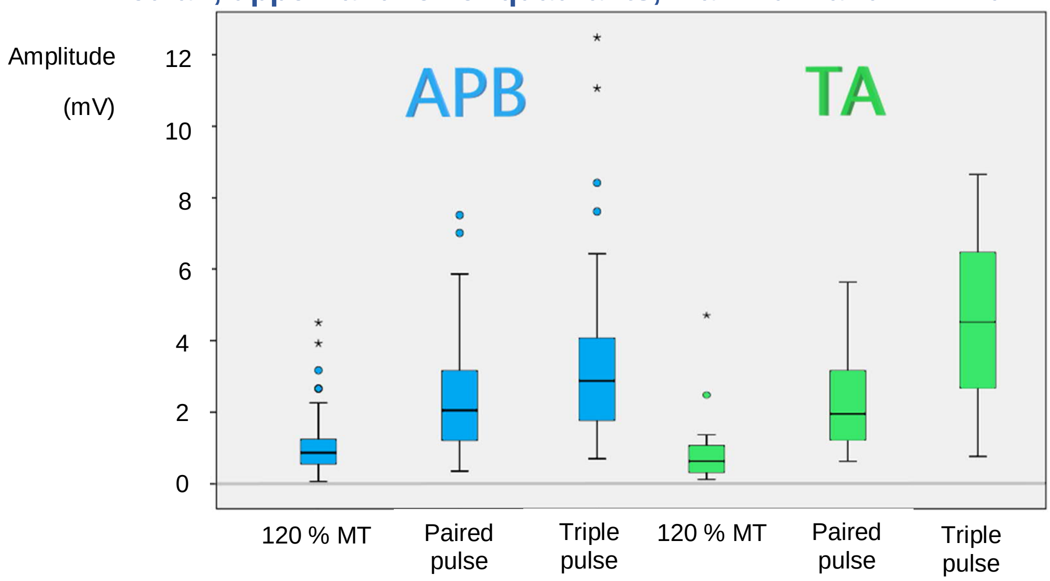
Figure: distribution of MEP amplitudes in APB and TA muscles: median, upper- and lower quadrants, maximum and minimum values



Design and production of a 5-coil multi-locus TMS transducer

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Introduction

Recently, a multi-locus TMS (mTMS) optimization method and a system with a set of five overlapping coils [1] to electronically adjust the stimulation site were proposed. However, this 5-coil design was not fully developed or assessed for practical use or manufacturing. To continue, we designed and built a transducer using the proposed optimization process.

Methods

The coil windings were designed with the minimum-energy optimization algorithm [1] and varying the initial parameters, such as the transducer dimensions, number of winding turns, coil stack order, and the area under the coil where stimulation location can be controlled. Coils were then wound using Litz wire in 3D-printed formers that were designed to match the optimized coil windings. With an electric field characterization device [2], we measured the electric field distributions of the built coils in a spherical head geometry.

Results

The mTMS transducer consists of two orthogonal four-leaf clover coils, two perpendicular figure-of-eight coils, and one round coil stacked on top of each other from closest to furthest from the head. The rectangular transducer is 2.6-cm thick and has a side length of 30 cm. The measured electric field distributions of all five coils resemble closely the simulated distributions. The coils were able to produce TMS pulses up to the maximum capacitor voltage of our electronics.

Conclusion

The results from the constructed mTMS transducer suggest that it can electronically control the stimulation location and orientation in a 3-cm-diameter circular region. The device will allow moving the stimulation site faster and more precisely than a human or a robot could do when physically moving a conventional TMS coil. The system will be useful, e.g., for studying brain networks and compensating for head movements.

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Exploring the role of prefrontal regions in executive control and conscious perception

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Introduction

The executive control network is involved in novel or complex situations or those in which prepotent responses need to be overridden [1]. When executive control is exerted, conscious perception is impaired [2]. This behavioral interaction is hypothesized to be sustained by shared neural resources in frontal regions for executive control and conscious perception.

Methods

A dual task paradigm was employed, in which participants responded to a Stroop task concurrently to a detection task of near-threshold Gabor stimuli [3]. In experiment 1, an event related functional magnetic resonance design was employed. In experiment 2, the right supplementary motor area (SMA) or a control region (vertex) were stimulated by using online transcranial magnetic stimulation (TMS) while participants responded to the same task. Diffusion weighted imaging tractography was used to explore the contribution of the different branches of the superior longitudinal fasciculus (SLF I, II, III) to the interactions between executive control and conscious perception.

Results

Experiment 1 demonstrated a neural interaction between executive control and conscious perception in the functional connectivity of fronto-parietal regions. This neural interaction was associated to the microstructural characteristics of the left SLF II. Experiment 2 demonstrated that TMS over the SMA (as compared with the vertex condition) impaired conscious perception but only for incongruent Stroop trials. However, this effect was mainly observed in participants with low integrity values of the right SLF III.

Conclusions

Results suggest partially shared neural resources for executive control and conscious perception in frontal regions. This interaction is associated with microstructural properties of long-range white-matter tracts, such as the SLF. However, it is plausible that the overlap between regions or neural mechanisms supporting executive control and conscious perception is less massive than the observed with other attentional systems (orienting and alerting), resulting in a less consistent neural and behavioral interaction.

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No effect of inter-pulse interval for TMS motor evoked potentials in active muscles

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Introduction

The interval between the stimulation pulses affects the muscle responses measured using transcranial magnetic stimulation (TMS) when the targeted muscle is resting [1, 2]. This necessitates the use of sufficiently long inter-pulse intervals (IPIs), which considerably increases the measurement time in TMS motor mapping studies. However, there is some evidence that the IPI has no effect on the responses evoked in active muscles [3]. If using the active muscle removes the effect of IPI, TMS pulses could be delivered faster reducing the measurement time. Thus, the purpose of this study is to find out if IPI affects the TMS motor evoked potentials (MEPs) during active muscle contraction.

Methods

We studied the MEPs from the first dorsal interosseous (FDI) muscle of the right hand in eight subjects during the TMS of the primary motor cortex. Three different IPIs (2 s, 5 s, and 10 s) with two different conditions, active (N=8) and resting (N=4) muscles, were used. 30 pulses were delivered for each IPI for both conditions at the intensity of approximately 20% above the threshold intensity. The location of the stimulation was determined as the hotspot for the measured FDI muscle. For analysis, a mixed linear regression was used to predict MEP amplitudes based on IPIs.

Results

For the active muscle (N=8), the IPI had no significant effects. The only variable affecting the MEP amplitudes during active muscle contraction was the baseline EMG magnitude before the pulse, higher baseline producing higher MEP amplitudes. For the resting muscle (N=4), the 5 s IPI had a significant positive effect on the measured MEP amplitudes.

Conclusion

The results for resting muscle support the findings in previous studies, in which shorter IPIs increased the MEP amplitude [1,?]. For active muscle contraction, the IPI had no effect. The results indicate that IPIs as short as 2 s can be used to speed up TMS motor mapping in active muscles.

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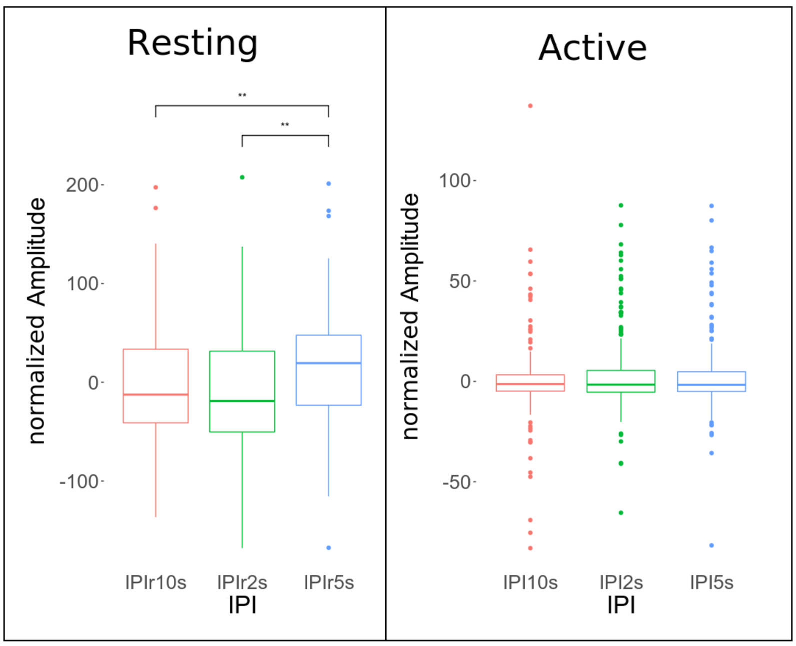

Figure 1: The effect of different IPIs on MEP amplitudes for resting and active muscles. The effect of baseline is removed from the amplitudes and they are normalized by subjects.

Defining brain excitability states from EEG by data-driven spatio-temporal filtering

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Introduction

Transcranial magnetic stimulation (TMS) -elicited motor-evoked potentials (MEPs) show large inter-trial variability. Based on pre-stimulus EEG, it is possible to derive brain state estimates, which reflect the instantaneous excitability and, thus, can predict the MEP amplitude [1]. We aim to optimize individualized EEG filters by machine learning to enhance the identification of brain states.

Methods

Five healthy subjects participated in this study where 800-1200 single stimuli were delivered on the left primary motor cortex, while simultaneously recording 128-channel EEG, and EMG from a contralateral hand muscle.

In the preprocessing, bad EEG channels and trials were automatically removed with the help of the SOUND algorithm [2]. ICA was used to remove artifacts. Each recorded response was labeled according to the peak-to-peak MEP amplitude to represent either low or high excitability state.

A linear classifier was trained to identify the brain by logistic regression. We iteratively optimized spatial and temporal filters to extract the brain state estimate from the EEG recorded during the chosen time window. After obtaining the filters, we estimated the corresponding temporal and spatial patterns, which represented the different states.

We compared logistic regression with several time windows, and variable numbers of filters. The results were also compared to the predefined spatial filter (C3 Hjorth) and circular-to-linear regression, which can be used to capture the optimal phase for excitability at a given frequency.

Results

The data-driven classifier was able to predict excitability states in all subjects (Kappa 0.16–0.44), whereas the C3-Hjorth filter combined with circular-to-linear regression was able to find a predictive phase in two subjects (Kappa 0.22–0.48). The predictive temporal patterns had greatest power within μ frequency band, whereas the predictive topographies had variable distributions.

Conclusion

With machine learning, it is possible to optimize spatio-temporal EEG filters, which can identify changes in brain excitability without prior information. On the other hand, the results can help us to build priors for further experiments. The filters can be also used online in closed-loop EEG–TMS measurements, e.g., to improve TMS therapy.

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Phase-specific modulation of endogenous low-frequency oscillations with direct electrical stimulation of the human cortex

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Introduction

Low frequency oscillations across the cortex underly coordination of brain networks in humans and play a critical role in cognition. Researchers have used direct electrical brain stimulation to treat a range of neurological and psychiatric disorders in which these oscillations function abnormally [1,2]. Direct electrical stimulation holds the potential to modulate these cortical oscillations [2-5]; however, we do not yet have a detailed understanding of how stimulation alters narrowband low frequency oscillations. Therefore, to fill this gap in our understanding, we investigated the effects of stimulation timing and location on narrowband low frequency oscillations.

Methods

We collected human electrocorticographic recordings from 106 neurosurgical epilepsy patients while systematically delivering stimulation at different combinations of frequency and amplitude at specific locations while patients were at rest. In order to understand how stimulation affects low frequency oscillations, we measured the amplitude and frequency of narrowband oscillations before and after stimulation was delivered. We identified stimulation trials where low frequency oscillations were ongoing prior to stimulation onset and measured the phase of these oscillations at which stimulation was first delivered. We then compared changes in amplitude and frequency of oscillations following stimulation between trials categorized by the phase of stimulation onset.

Results

Here, we show that stimulation-related amplitude changes in low-frequency oscillations depend on the phase and frequency of an ongoing oscillation at which stimulation is delivered. We found that ongoing theta, alpha, and beta oscillations show different levels of amplitude change when stimulation is delivered at their peak or trough. Additionally, we investigated how phase-specific modulations depend on stimulation location and recording regions. When stimulation was delivered at specific MTL and LTL locations with ongoing low-frequency oscillations, changes in activity at nearby recording sites following stimulation depended the phase at which stimulation was delivered.

Conclusion

Whereas our previous work shows that excitation and inhibition depend on stimulation frequency, these results show that phase-specific stimulation also plays an important role in modulating specific features of narrowband oscillations. Taken together, these results imply that the impact of brain stimulation on cortical activity is much more nuanced than excitatory and inhibitory effects. By characterizing the effects of brain stimulation delivered at specific phases of low frequency oscillations, our results provide insight into how brain stimulation protocols may be timed and precisely targeted to modulate specific features of endogenous network oscillations.

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New open-source tools for cleaning artifactual TMS–EEG data

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Introduction

Although combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) is a powerful method to study cortical effective connectivity, TMS–EEG signals often suffer from noise and artifacts. In practice, TMS–EEG data analysis is based on visual rejection of contaminated data segments or noisy independent components [1], although theory for more objective data cleaning methods has been developed.

Methods

We implemented the source-utilized noise discarding algorithm (SOUND) [2] and the signal-space projection–source-informed reconstruction (SSP–SIR) [3] in TESA [1], an extension to the popular EEGLAB toolbox. SOUND and SSP–SIR are spatial filtering methods that target the general EEG noise and the TMS muscle artifacts, respectively. We provide graphical user interfaces (GUIs) and detailed documentation that aid in implementing these methods. For using SOUND/SSP–SIR, an EEG forward model needs to be constructed. The published tools allow to automatize this process. All code is available open source through TESA.

Results

The SOUND and SSP–SIR functions worked as expected in all the tests, clearly improving data quality. The SSP–SIR function was also tested in rejecting the multisensory responses to TMS [4]; the TESA manual provides detailed instructions to replicate this process. With a standard research computer and standard TMS–EEG data, the computation time for SOUND and SSP–SIR were ~2 s and ~3s, respectively.

Conclusion

We have implemented the first user-friendly versions of SOUND and SSP–SIR, which have shown to be effective in removing disturbances from TMS–EEG data. The short computation times, GUIs, and detailed user manuals make SOUND and SSP–SIR useful for various TMS–EEG researchers. The current SOUND and SSP–SIR functions can be easily included in EEGLAB- or Fieldtrip-based data-analysis pipelines.

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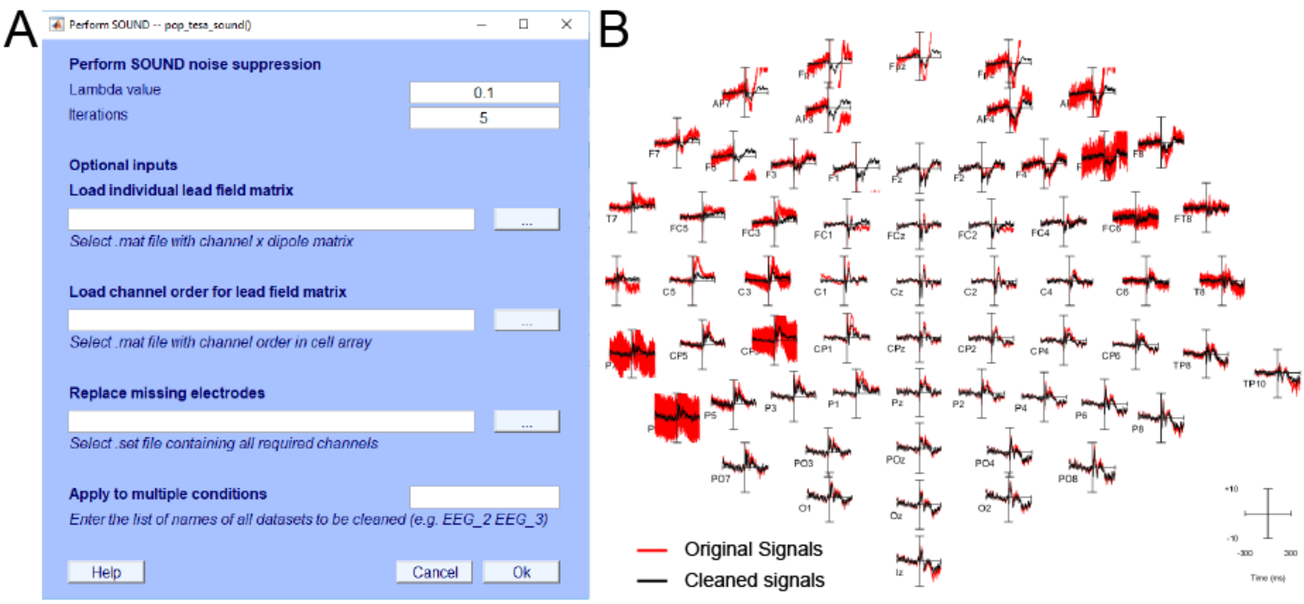

Figure 1: **A:** Screenshot of the SOUND GUI. **B:** A representative example of the SOUND cleaning outcome.

Feature variability in motor evoked potential in single-pulse transcranial magnetic stimulation

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Introduction

Motor-evoked potential (MEP) is the main evaluation of transcranial magnetics stimulation (TMS) [1]. Our aim is to identify constant and varying MEP features in single-pulse TMS in relation with the stimulation coil rotation, in order to further understand the TMS-induced motor activation and the generated MEP morphology.

Methods

Nine normal subjects participated in this study. The experiment was performed with navigated single-pulse TMS, in which the stimulation coil placed over the subject's primary motor cortex. The stimulation coil was rotated from -135 to 135 degree, by 5-degree step. MEPs was recorded at the first dorsal interosseous by electromyography (EMG), which was offline-analyzed by Matlab. Nine MEP features were calculated from each dataset, and then investigated [2].

Results

The results shows that as the stimulation coil rotation approaches the optimal angle, the MEP shape is unchanged, while its size is increasing. Figure 1 shows that the amplitude follows Gaussian function, *i.e.* the amplitude reach maxima if the coil rotation is at the optimal angle. However, the features relate to the MEP morphology, such as turns and phases, are mostly constant at 2 and 3, respectively; MEP thickness, which is the ratio of AUC to amplitude, stays constant between 2 and 4. MEP latency keeps constant, in contrast with previous researches [3]. In addition, the MEP average of normalized MEPs of one dataset, where it holds 79.3% of total variation of the whole dataset.

Conclusion

These results would provide additional understanding of the cortical activation mechanisms under the effect of TMS, particularly on the activation based on the cortical neuronal arrangement. Based on these findings, it appears that the MEP morphology is not affected by the rotation of the stimulation coil, while its amplitude is heavily affected.

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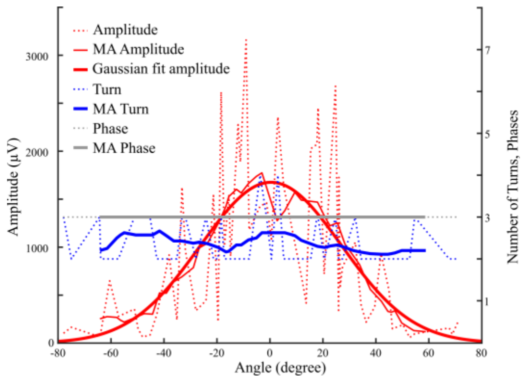

Figure 1: Amplitude, turns and phases versus stimulation coil. The amplitude, as size measurement, increase according to the Gaussian function as the coil rotation approaches the optimal angle (0 degree). In contrast, the turn and phase, which define the MEP morphology, remain constant at 2 and 3.

SMA as a target for repetitive TMS: a systematic review of clinical and fundamental approaches

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Introduction

Supplementary motor area (SMA) is a multifunctional cortical region [1], that is a promising target for neuromodulation in a wide range of neuropsychiatric disorders, affecting motor and cognitive domains [2]. Repetitive TMS (rTMS) of the SMA has been shown to improve motor symptoms in Parkinson's Disease, Obsessive-Compulsive Disorder, Tourette's syndrome etc. [3,4,5]. However, no systematic review has been conducted on this topic. A current study is dedicated to cover this lack of knowledge and to provide an overview of the SMA functional properties that were examined with rTMS.

Methods

This systematic review was conducted and reported according to the Cochrane and PRISMA guidelines (PROSPERO ID - 141289). All original articles published up to 27 July 2019, considering SMA rTMS were extracted from PubMed, Cochrane and Scopus databases. Three investigators assessed the studies' quality with the Cochrane risk of bias tool [6]. 92 articles were divided into two categories: (1) studies in healthy volunteers and (2) studies including patients. The qualitative analysis was performed with narrative textual synthesis.

Results

Literature analysis revealed the effect of SMA rTMS neuromodulation on a wide range of the motor control aspects (movement preparation, sequence processing, breathing control), emotions and time processing. SMA is reported to have strong functional connectivity with the primary motor cortex, prefrontal cortex, secondary somatosensory cortex, insula, and cerebellum. rTMS of the SMA caused clinical improvement in Parkinson's Disease, Obsessive-Compulsive Disorder, and Tourette's Syndrome patients (Fig.1).

Conclusion

Analysis of the SMA rTMS studies showed that SMA is critically involved in motor and cognitive processes. In a clinical setup, SMA seems to be an effective target for neuromodulation in patients with affected motor system (Fig.1). This review will be in help for the invention of new neuromodulatory protocols targeting SMA (e.g. catatonia).

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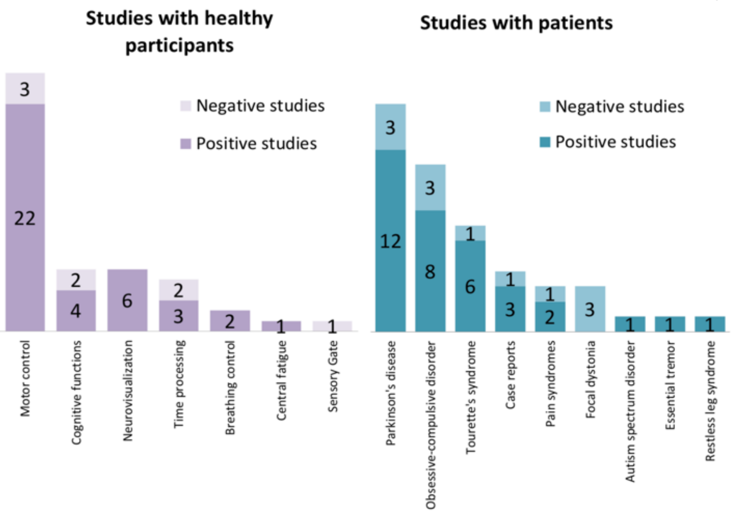

Figure 1: Representation of the SMA rTMS studies, with healthy volunteers and patients, reflecting number of studies examined function/disease, positive/negative outcomes

TPS (Transcranial Pulse Stimulation) reduces significantly Alzheimer's disease symptoms

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Introduction

Low intensity shock waves proofed to be efficient for the treatment of non-unions, tendon and muscular pain, wound healing, heart insufficiency, erectile dysfunction, aesthetic and finally neurological indications. The working principle is the mechanical stimulation of biological processes called mechanotransduction resulting in increased cell metabolism, release of nitric oxide (eNO) and numerous growth factors. There is also an anti-inflammatory effect, stimulation of stem cells and the innate immune system.

Alzheimer's disease or dementia in general is multi modal disease resulting from different causes like deposition of dedicated proteins (tau, beta-amyloid), inflammation, reduced blood supply and others.

Methods

Transcranial Pulse Stimulation (shockwave pulses) was applied to patients suffering from minor Alzheimer's disease in two centers. 35 patients were treated in this multicenter clinical pilot study. The treatment consisted of 6 sessions in 2 weeks, with 6000 pulses per session, energy flux density of 0.2 mJ/mm^2 at 5Hz. It was performed with an unshaved head through the hair. The treatment is painless and very well tolerated by the patients.

Results

The patients showed a significant improvement of the Alzheimer's disease symptoms of over 10% measured with CERAD Plus battery of tests. The improvement was maintained until 3 months follow-up. No side effects have been observed.

Conclusion

In spite of the unique positive results, further clinical evaluations are needed. Placebo controlled, randomized trials are ongoing. The device (Neurolith) has meanwhile the CE mark clearance in Europe and there are regulatory activities in further regions.

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Figure 1: Cortex regions treated with TPS as documented by BodyTrack system

Fast motor mapping with a 2-channel multi-locus TMS

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Introduction

Motor mapping with transcranial magnetic stimulation (TMS) is a time-consuming procedure, requiring good manual skills of an operator. Here, we investigated the possibility of using a two-channel multi-locus TMS (mTMS) device to perform fast multi-muscular TMS motor mapping with 1-mm resolution in the lateral–medial direction.

Methods

We used an mTMS transducer that allows targeting of the electric field (EF) in the cortex with 1-mm resolution along a line ranging from –15 to 15 mm from the physical center of the transducer. Three healthy subjects (32–34 years old, one female) participated in the study. mTMS was applied to the left primary motor cortex (Fig. 1B). Motor evoked potentials (MEPs) were recorded from four hand muscles: abductor pollicis brevis, abductor digiti minimi, extensor digitorum communis, and first dorsal interosseous. The orientation of the induced EF was perpendicular to the central sulcus for all pulses. Stimuli were delivered in 3 to 5 sequences, 155 pulses in each; after each sequence, the transducer was moved by 10–15 mm along the posterior–anterior direction (Fig. 1B). Each location was stimulated five times in random order; the distance between consecutive locations was at least 10 mm. The interstimulus intervals were pseudorandomized in the range of 1.5–2 s.

Results

Each mapping procedure lasted only 14–23 minutes (3- or 5-line designs) plus a two-minute break after completing the stimulation of each line. We covered up to 18 cm^2 of the primary motor cortex with 1-mm lateral–medial resolution. MEP amplitudes from all the investigated muscles were visualized in real-time, according to the location of the induced EF maximum (Fig. 1C). The distribution of MEP amplitudes was approximately Gaussian, with a maximum in the hotspot.

Conclusion

These preliminary results demonstrate that with an mTMS device the time of TMS mapping procedure can be considerably shortened without sacrificing its spatial accuracy.

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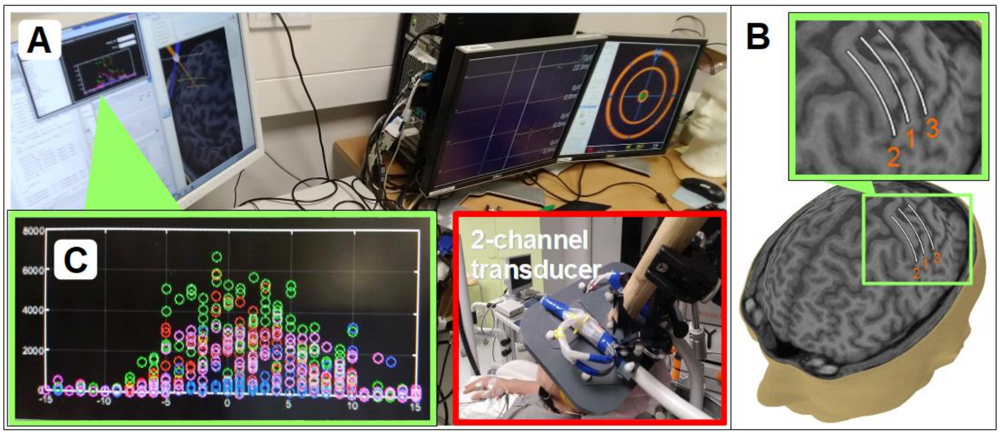

Figure 1: (A) Setup view. (B) Example of 3 lines coil positioning. (C) Real-time motor evoked potential (MEP) amplitudes during the motor mapping along one of the lines: different colors represent different muscles, the *x*-coordinate: distance from the hotspot in lateral-medial (LM) orientation (–15 to 15 mm), the *y*-coordinate: response amplitude in µV.

The impulse noise of TMS inside a 3T MRI scanner

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Introduction

The operation of transcranial magnetic stimulation (TMS) coil produces high intensity impulse sounds in the form of clicking. In a typical operation environment, the sound pressure levels (SPL) of the click sounds generated by a TMS coil can be more than 120 dB [1]. When placed in a strong magnetic field, the interaction of the magnetic field and the current in the TMS coil can cause a strong force exerted on the TMS coil [2] and produce acoustic noise. In order to perform a concurrent TMS-functional magnetic resonance imaging (fMRI) experiment safely, the SPLs generated by the TMS coil must be quantitatively characterized. In this study, we present the method and results of measuring the SPLs of a commercial MRI-compatible TMS coil inside a 3T MRI scanner.

Methods

We built a system allowing for the transmission of sounds generated inside an MRI scanner (Skyra, Siemens, Erlangen, Germany) to the outside of the shielded MRI room through a non-elastic tube (Stress Nobel 40 bar). The sounds were measured at different positions and stimulation intensities by a microphone (MKE-PC2, Sennheiser electronic GmbH & Co. KG, Germany) firmly attached to the end of the tube outside the shielded room and recorded using high quality audio interface (RME Babyface Pro, Audio AG, Germany). The measurements where done with two TMS coil orientations compared to the magnetic field (Figure 1). The measurement system was calibrated in the Aalto acoustics laboratory as the acoustic noises changed the intensities and spectra after passing through.

Results

The measurement locations and SPL results of MRI-compatible TMS system with both coil orientations compared to the magnetic field are presented in Figure 1. The maximum measured SPL was 141.0 dB(C).

Conclusion

Based on the measured SPL, we concluded that hearing protection is obligatory during concurrent TMS-fMRI experiments. Separating the scalp and the TMS coil by an air space or porous materials is highly recommended.

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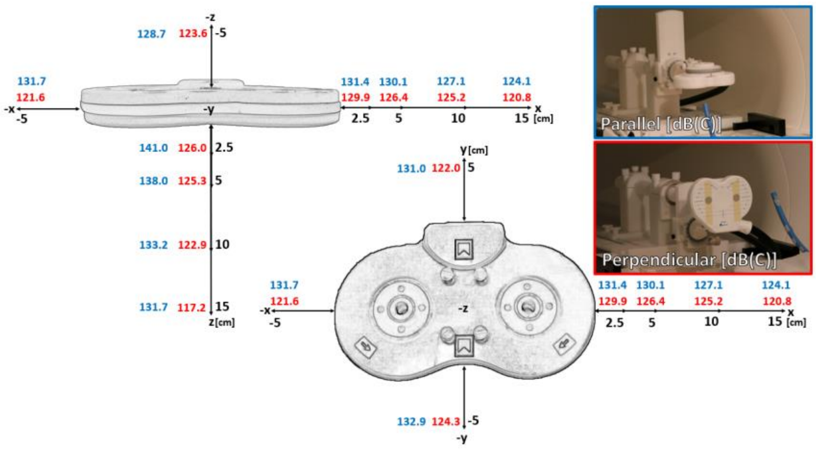

Figure 1: Measurement locations, coordination system, and the SPLs of MagPro R30 stimulator and MRi-B91 TMS-coil in 3T MRI with two TMS coil orientations compared to the magnetic field. Stimulation intensity was 100 V/m = 93% maximum stimulator output that was measured by a dedicated device [3].

Deep learning -based forecasting of EEG time series for brain state dependent TMS

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Introduction

Transcranial magnetic stimulation (TMS) has shown great promise in treating neurological disorders, such as stroke or depression [1]. However, treatment outcomes have been modest and variable [1], possibly because the response to TMS depends on the instantaneous state of the brain [2]. One solution is to trigger TMS based on real-time EEG, but this is challenging because of the time spent in algorithmic decision making. Until now, only autoregressive forward prediction has been employed for TMS timing [2]. To improve on this, we propose a deep learning model for predicting EEG time series.

Methods

A convolutional neural network (CNN) model was developed for forecasting resting-state EEG time series. The model architecture (Fig. 1A) is a close adaptation of the raw audio generating model Wavenet [3] - a key difference being that we map the input to the output sequence directly with a dense layer. The model was trained on band-pass-filtered (8–12 Hz) eyes-open 60-channel EEG data from one subject. The training and label sequences consisted of 1500 and 150 ms worth of subsequent time stamps, respectively.

Results

Mean absolute error of 0.57 μV for 150 ms predictions was achieved in the test set (Fig. 1B).

Conclusion

We found that CNNs are promising for forecasting EEG time series for brain state dependent TMS. We will extend this methodology into a multivariate model, in which the relationships between concurrent signals of all channels are included in the predictions. Furthermore, these models will be trained for predicting the cortical responses to TMS.

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Acknowledgements

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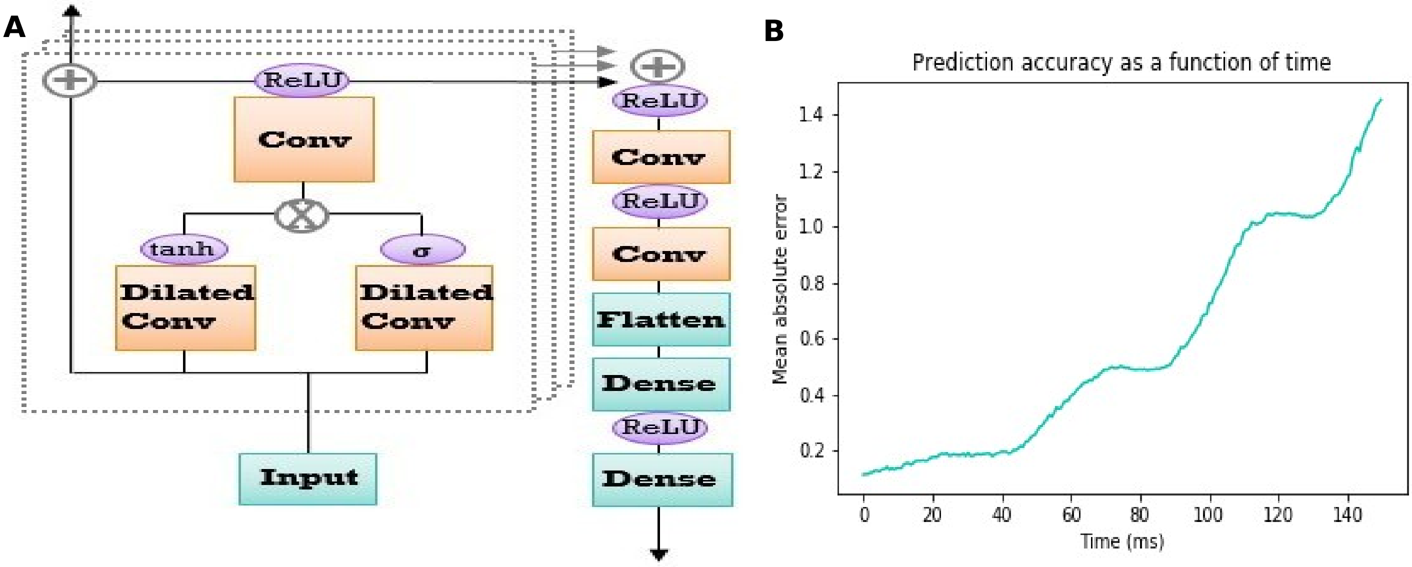

Figure 1A) Deep learning model architecture, inspired by Wavenet, B) Mean absolute error of forward predictions as a function time for the test set (1920 test instances, 150 ms each)

Modulation of working memory and resting state fMRI by tDCS of the right fronto-parietal network

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Introduction

We targeted right fronto-parietal network by tDCS to induce behavioral changes upon visual object matching task (VOMT, [1]) with two difficulty levels in a double-blind cross-over trial. We further explored neural underpinnings of induced changes by resting-state fMRI (rs-fMRI).

Methods

Twenty-seven healthy volunteers (mean age: 27 ± 4.1 years) participated in the behavioral testing and a subgroup (n=22) underwent rs-fMRI prior to and after each tDCS condition (active or sham; tDCS: 2 mA, 20 minutes). The anode was positioned over the right orbitofrontal cortex (rOFC) with the cathode over the right posterior parietal cortex (rPPC). Paired t-tests compared differences in reaction times (RT) in VOMT performance between stimulation conditions. Seed-based voxel-wise whole brain functional connectivity (FC) analysis with seeds located at stimulation sites was performed. In addition, resting-state functional connectivity between stimulation seeds and the default mode network (DMN) was analyzed.

Results

We observed a significant difference in RT change after real stimulation as compared to sham (p=0,049) for higher difficulty. Seed based analysis produced no significant results. We observed increased connectivity between the stimulated rOFC and the DMN (p = 0,042) only after sham stimulation. We found significant positive correlation of rOFC-DMN connectivity with tDCS-induced behavioral changes (r=0.391; p=0.009). This means that quicker responses in the task were connected with higher connectivity between the stimulated seed rOFC and DMN.

Conclusion

Our results demonstrate that targeting the right fronto-parietal network by tDCS leads to positive cognitive aftereffects of active vs. sham stimulation that is observed already in young healthy subjects in VOMT. Specific tDCS-induced changes in cognitive outcomes are associated with changes in resting state functional connectivity between the task-positive (fronto-parietal) and the task-negative (DMN) networks.

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Acknowledgements

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Enhancement of speech-in-noise comprehension through transcranial alternating current stimulation

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Introduction

Auditory cortical activity tracks speech rhythms, in particular at the rate of words (1 - 4 Hz, delta band) and at the rate of syllables (4 - 8 Hz, theta band). The modulation of this cortical tracking through alternating current stimulation with the speech envelope has been found to influence the comprehension of speech in noise [1–3]. However, the stimulation can be performed with different parameters, such as temporal delay, particular frequency band and a potential phase delay. The influence of these stimulation parameters on speech comprehension remains insufficiently understood.

Methods

We presented human volunteers with single sentences that were embedded in noise to assess their speech comprehension. Simultaneously we stimulated the subject's auditory cortices through transcranial alternating current. The current waveforms were obtained from the speech envelope and were shifted by different temporal delays as well as phases. We also explored currents that were obtained from the speech envelope filtered in the delta and in the theta frequency bands.

Results

We first investigated two characteristic delays that emerge in the cortical tracking of speech rhythms, a short delay of 100 ms and a longer delay of 250 ms. We found that current stimulation at both delays influenced speech comprehension [4]. Moreover, stimulation with a distractor envelope rendered speech harder to understand. Next, we applied current waveforms that followed either the delta- or the theta-band portion of the speech envelope. The theta-band current stimulation had a significant effect on speech comprehension, while the delta-band stimulation did not [5]. Last but not least, we investigated the influence of different latencies of the theta-band stimulation on the comprehension of speech in noise. We found that no latency yielded the highest speech comprehension, which was higher than under a sham stimulus.

Conclusion

Our results show that the modulation of speech comprehension through transcranial alternating current stimulation is driven by the theta- but not by the delta band. Speech-in-noise comprehension can be enhanced when the current waveform is temporally aligned to the speech signal.

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Connecting to the networks of the human brain with multi-locus transcranial magnetic stimulation

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Introduction

Non-invasive neuromodulation with transcranial magnetic stimulation (TMS) has demonstrated moderate to good results and has been approved widely for clinical use [1]. However, network studies have suggested that the brain is extremely difficult to control via a single site [2], which may contribute to the small effect size of the current single-coil techniques in therapeutic applications [1]. The goal in the multinational ConnectToBrain project is to develop for research, diagnostics, and therapy a feedback-controlled multi-locus TMS (mTMS) technique (Fig.1).

Methods

The project includes three main development areas: 1) Multi-locus TMS array [3] covering most of the cortical mantle and allowing real-time control over the locus, direction, intensity, and timing of the stimulation; 2) Real-time analysis of brain activity and connectivity by using high-density electroencephalography and *a priori* information from magnetic resonance imaging and magnetoencephalography for brain-state-dependent and closed-loop stimulation; 3) Demonstration of feasibility, safety, and effects of the developed techniques, and their therapeutic utility in dysfunctional brain networks in Alzheimer's disease and motor stroke.

Results

We have performed feedback-guided motor-hotspot determination with a two-coil mTMS prototype, which is more reliable, less user-biased, and requires fewer pulses than the conventional manual approach. We are currently developing a five-coil prototype, and algorithms for brain-state-dependent stimulation.

Conclusion

We expect to develop new technology capable of correcting dysfunctional brain networks in several brain disorders with better therapeutic efficacy than current state-of-the-art techniques and the potential to induce a major paradigm shift in therapeutic neuromodulation. If successful and widely used in clinical applications, ConnectToBrain will eventually lead to a substantial reduction in the suffering and economic burden caused by brain disorders.

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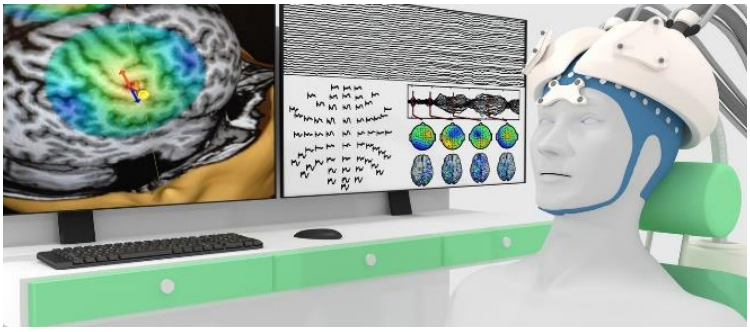

Figure 1: Illustration of the feedback-controlled multi-locus transcranial magnetic stimulation system allowing real-time control over the locus, direction, intensity, and timing of the stimulation, and feedback-controlled and brain-state-dependent stimulation based on real-time analysis of brain activity and connectivity.

New Insights into Sentence Comprehension from a Condition-and-Perturb TMS-EEG Study

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Introduction

A large-scale network including the posterior inferior frontal gyrus (pIFG) and posterior superior temporal gyrus/sulcus (pSTG/STS) supports speech comprehension, a process that unfolds rapidly over time. Therefore, previous context information is used to make predictions about upcoming input. The event-related potential that is sensitive to fulfilled semantic predictions is the N400. Words that follow a less predictive (e.g. He sees the beer) relative to a highly predictive (e.g. He drinks the beer) context elicit a larger N400. A recent study combined electroencephalography (EEG) with transcranial magnetic stimulation (TMS) to investigate the role of the left pIFG and pSTG/STS in sentence comprehension [1]. TMS applied at verb onset had short-lasting effects on the N400. The sentence final noun, however, showed no effect. The authors suggested that the semantic network might have compensated for the perturbation, in particular by the left angular gyrus (AG). The present study used a condition-and-perturb TMS-EEG approach to probe the contributions of the left pIFG and pSTG/STS after excitability in the left AG was temporarily reduced using continuous theta-burst stimulation (cTBS).

Methods

We applied cTBS at the AG and triple-pulse TMS (10 Hz) at verb onset during auditorily presented sentences over either pIFG, pSTG/STS, or sham.

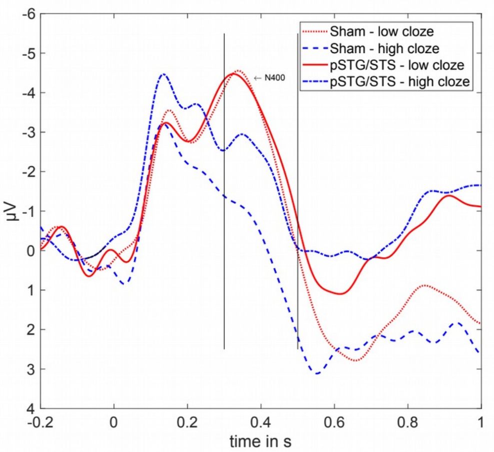
Results

The effect of pSTG/STS TMS outlasted the stimulation duration at the verb and affected processing of highly predictable nouns, as indexed by changes in the N400 amplitude when compared to sham. We infer that conditioning AG with cTBS caused a dysfunction in this area, which increased the functional relevance of the left pSTG/STS for sentence-based semantic processing and sensitized the semantic network to the disruptive TMS effects. The ERP data of pIFG TMS is still under analysis.

Conclusion

The functional significance of the left pSTG/STS within the semantic network depends on the functional integrity of the left AG.

Figure 1 (electrode Cz)



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TMS-evoked potentials in Dravet syndrome – fewer components

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Introduction

Transcranial magnetic stimulation coupled with EEG (TMS/EEG) may allow better understanding of abnormal cerebral function in neurological conditions. Dravet syndrome is caused by loss-of-function variants in *SCN1A*, encoding the type 1 voltage-gated sodium channel. Individuals with Dravet syndrome were shown to lack short-interval intracortical inhibition, a GABA$_A$ergic TMS-EMG measure [1]. We hypothesized that individuals with Dravet syndrome might show changes in TMS-evoked potential (TEP) components, such as those linked with GABAergic neurotransmission.

Methods

Three people with genetically-confirmed Dravet syndrome due to pathogenic variants in *SCN1A* underwent neuronavigated TMS-EEG, using a navigation tracking system, monophasic stimulator (Magstim 200) and a BrainAmp hd-EEG (64 electrodes). The stimulation site was the dominant premotor area. The exact coil position and stimulus intensity were individualised based on online visualisation of the TEPs. Data preprocessing, global mean field power (GMFP) and spectral analysis were computed using customized Matlab-scripts using EEGLab functions. Results were compared with those from five healthy controls.

Results

Both patients and controls showed an evoked cortical response. We show a reduction in the number of components of the evoked response to TMS compared to healthy subjects, as confirmed by GMFP analysis. In line with our hypothesis, there was a mismatch between patients and controls in the GABAergic components, such as N45 and N100. Moreover, the power spectral analysis showed a decrease in natural frequencies [2] of the premotor area in individuals with Dravet syndrome compared to our healthy controls and literature.

Conclusion

In individuals with Dravet syndrome, TEPs may be highly abnormal. This may reflect functional and structural changes in the brain circuitry as well as a different level of excitability. Apart from the underlying genetic condition, differences may reflect effects of seizure activity and medications. Further work should be conducted to assess whether TEP complexity could serve as a biomarker in Dravet syndrome and other epileptic encephalopathies.

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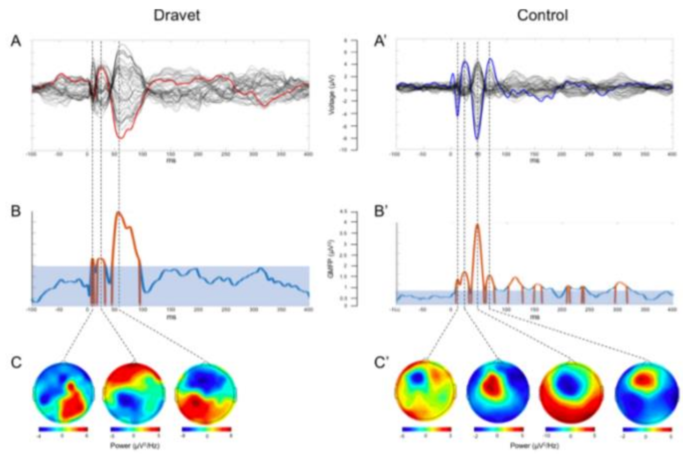

Figure 1: All panels refer to a representative patient on the left and a healthy control on the right. A and A': Butterfly plot of the average response to left premotor stimulation for each EEG channel between -100ms and +400ms post stimulus, red and blue lines show the channel F1 under the stimulation coil; B and B': Global mean field power of the TEPs, the statistically significant components of the response shown in orange; C and C': Topographical distribution of the average voltages.

Enhancement of visual cognition in healthy seniors using anodal prefrontal tDCS

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Introduction

Visual cognition deficits are common in mild cognitive impairment (MCI) (Nemcova Elfmarkova et al. 2017). In this pilot study, we investigated the acute effects of transcranial direct current stimulation (tDCS) on visual attention in healthy seniors. Our main objective was to identify the tDCS protocol with a beneficial effect on visual cognition that could be further applied to MCI patients and assessed in a multi-session tDCS regimen.

Methods

In this double-blind crossover study, anodal tDCS was applied over the left dorsolateral prefrontal cortex in 25 older adults (68.4 ± 5.6 years of age). T1 MRI image-based neuro-navigation was used to precisely target the center of the electrodes on the scalp. To test visual cognition, a visual-matching task (VMT) with objects in conventional and unconventional view was used. Baseline performance in VMT was determined as the average performance of all sessions prior to tDCS. The improvement in VMT performance for each session (active or sham) was calculated as a difference between post vs. prior tDCS performance. Paired sample repeated parametric measures were used to test statistical differences in performance improvements between conditions (active vs. sham).

Results

Based on our behavioral analysis, the performance gains from tDCS relative to baseline differed significantly between the active vs. sham condition favoring active stimulation in both the conventional viewing condition ($t(24)=-2.25$, $p<0.034$) and the unconventional viewing condition ($t(24)=-2.28$, $p<0.031$) indicating a beneficial effect of tDCS on visual attention at both, low and higher cognitive loads.

Conclusion

Our preliminary results indicate that anodal tDCS of prefrontal cortex may enhance visual cognition in the aging population. Functional connectivity analysis using resting state fMRI before and after tDCS stimulation is ongoing with the potential to elucidate underlying neural mechanisms behind tDCS-induced enhancement of visual processing.

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Controlled pulse waveforms for TMS

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Introduction

Multi-locus transcranial magnetic stimulation (mTMS) exploits the superposition of electric fields to adjust the location of stimulation electronically without physical coil movement [1]. This is achieved by multiple stimulation coils that are controlled individually. However, if a subsequent pulse requires a lower capacitor voltage than a preceding pulse, a long wait period (on the order of a second) may be needed for the capacitor voltage to drop to a sufficient level.

Methods

We have developed an mTMS system including power-electronics modules for five overlapping coils. As each module, driving current to a single coil, is based on an H-bridge, the topology of the power circuit can be altered on the fly to control the current flowing through the coil windings, similar to pulse-width modulation (PWM). This allows controlling the effect of the electric field. By appropriately controlling the bridge, it is possible to drive the current from a given capacitor voltage in such a way that the effective pulse intensity matches that of a traditional lower-voltage pulse.

We developed an algorithm to determine the control sequences necessary to mimic a given conventional lower-voltage pulse. To overcome waveform distortions caused by numerous reactive components in the system, we have planned an automated instrumentation setup that drives pulses through the coils, measures the responses and compares them with the desired outputs, and adjusts the control sequences correspondingly. This allows generating pulses that accurately match the desired electric field waveforms.

Results

Preliminary tests with two subjects suggest that the brain activation due to a PWM-based pulse is similar to that due to a conventional pulse being approximated. The equivalence of PWM-based pulses with conventional ones is based on the fact that charge leakage through neuronal membranes is a relatively slow process and, therefore, the membrane voltages produced by the new pulses can be made to match those produced by conventional means.

Conclusion

The algorithm and instrumentation seem promising for fast adjustment of mTMS pulses. An additional benefit of the proposed high-voltage drive is reduced heat generation, as the capacitors do not need to be discharged to generate weaker pulses.

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Biophysical neural modeling of EEG to interpret the impact of TMS on brain dynamics

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Introduction

Interpreting the neural response to TMS in humans is challenging but crucial to develop maximally impactful stimulation paradigms. Simultaneous TMS-EEG is a promising non-invasive method to study brain dynamics evoked by neurostimulation, however recent evidence suggests that TMS-evoked potentials (TEPs) reflect peripheral sensory responses rather than focal perturbations [*1*]. To address this potential confound, we characterize distinct EEG signatures of direct cortical and peripheral sensory stimulation, and use biophysically principled neural modeling to guide the mechanistic interpretation of these signals.

Methods

We applied single- and triple-pulse TMS over primary somatosensory cortex using a Magstim Rapid[2] biphasic stimulator with MRI-based neuronavigation (Brainsight). EEG was recorded with a sampling rate of 25 kHz using 63 passive electrodes (BrainProducts actiChamp Plus). To interpret TEPs, we used the Human Neocortical Neurosolver software (HNN; hnn.brown.edu; [*2*]). HNN simulates the currents that generate macroscale EEG signals based on their biophysical origin. Building upon previous work which identified neural mechanisms underlying tactile evoked responses [*3*], we modeled the TEP, including early components interpreted as a direct response to induced currents [*4*], and later components mainly reflecting peripherally evoked potentials [*5*].

Results

We demonstrate that early components of the TEP can be resolved within <5 ms of the TMS pulse, providing a basis for characterizing EEG signals that may reflect direct cortical activation from induced currents. We also observe that later components of the TEP are remarkably similar to previously characterized tactile evoked responses.

Conclusion

Although peripherally induced responses contribute to the waveform shape of the TEP, conscientious data collection and neural modeling can aid in the interpretation of mechanisms underlying direct cortical and peripheral stimulation by simulating the biophysical mechanisms underlying distinct components of the recorded EEG signal.

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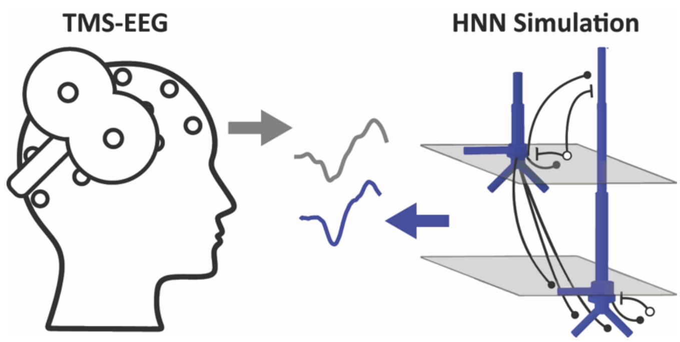

Figure 1: To gain a better understanding of the biophysical mechanisms underlying TMS-evoked brain dynamics, we record simultaneous EEG-TMS and use the neural modeling software 'Human Neocortical Neurosolver' (hnn.brown.edu) to interpret our recorded EEG signals.

Towards concurrent multi-locus TMS and functional MRI for rats

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Introduction

Concurrent transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) in animal models is a powerful technique to monitor functional changes combined with anatomical information [1]. However, TMS–fMRI poses significant technical challenges, such as restricted space for accurately targeting TMS on the small brain inside the bore and high mechanical stress on the transducer due to the interaction between the magnetic field and the stimulation current. To overcome these challenges, we developed an MRI-compatible multi-locus TMS (mTMS) transducer optimized for rats that allows electronic control of the stimulus orientation inside the scanner.

Methods

The mTMS transducer was designed with the help of a minimum-energy optimization algorithm [2]. The surface current distributions were computed on 95-mm diameter planes 5- and 7-mm distant from a spherical cortex model. Coils were wound using Litz wire in a 3D-printed former. The transducer and a surface transmit–receive radio-frequency coil were placed on top of a gel phantom with a rat brain. Imaging was conducted in a 9.4-T MRI scanner using Multi-Band SWIFT (MB-SWIFT) sequence [3] while delivering TMS pulses at capacitor voltages up to 1000 V.

Results

The mTMS transducer comprised two stacked perpendicular figure-of-eight coils. SWIFT revealed no passive artefacts due to the presence of the mTMS transducer. The TMS pulse destroyed only 4/2000 spokes in k-space leading to negligible artefact in the SWIFT image. The former fractured at 1000-V stimulation with the bottom coil due to excessive mechanical forces generated by the wires.

Conclusion

The developed transducer is MRI-compatible (except for the fracturing at the highest voltage), can be placed in a 120-mm diameter bore for small-animal studies, and allows changing the stimulus orientation without mechanical movements. Stronger materials will be tested so that the transducer case would withstand the mechanical forces.

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A common framework for modelling electroencephalography and transcranial magnetic stimulation

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Introduction

In electroencephalography (EEG), the brain is studied by measuring the differences of electric potential on the scalp, while in transcranial magnetic stimulation (TMS) the brain is stimulated with electric field (E-field) induced by a changing magnetic field caused by current pulses in a coil outside the head. In TMS–EEG, one measures the effect of stimulation and/or triggers the stimulation using EEG. The conductivity structure of the head affects both EEG and TMS.

To interpret an EEG measurement in the brain frame-of-reference, or to estimate the strength of the TMS-induced E-field in the brain for dosing the stimulation, we need forward field models. Building realistic forward models involves manual work and specialized software; the most of effort and computation time go for making the volume conductor model of the head. The models used for EEG and TMS are typically generated independently. Here, I present a framework in which the EEG model is a part of a TMS model.

Methods

The cortical generator of EEG signal is modelled as a source current distribution, discretized into current dipoles. In EEG forward problem, we solve the surface potential due to those dipoles. Using reciprocity theorem (1), the TMS-induced E-field in a location in the cortex is expressed in terms of magnetic flux generated by a current dipole in the corresponding location. To compute the magnetic flux, we need to model the total current driven by the dipole in the head; this current depends on the electric potential on conductivity boundaries (2), including the scalp. In other words, to compute the TMS-induced E-field in the cortex, we first solve the EEG forward problem. This part of the problem is independent of the TMS coil.

Results and Conclusion

I demonstrate the framework with a series of examples, from simple and conceptual to a highly realistic, solved using the tools presented in (3). The common framework considerably facilitates the construction of EEG and TMS models.

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TMS-EEG: a promising tool to study the tDCS effects on cortical excitability

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Introduction

Although transcranial Direct Current Stimulation (tDCS) is increasingly used in experimental and clinical settings, the neurophysiological underpinnings of its effects remain unclear.
Accordingly, in the last years, there has been a keen interest in understanding its mechanisms of action, and recently a series of studies on anodal tDCS (a-tDCS) show a rise of cortical excitability in a bilateral frontoparietal network, following structural connections [1,2]. To further address this issue, we started from these results on a-tDCS to explore cortical plasticity modulation induced by cathodal tDCS (c-tDCS) on healthy subjects.

Methods

We carried out two different studies applying c-tDCS on the right posterior parietal cortex (PPC): the first during resting state; and the second while participants were involved in the Posner Cuing Task. In both the studies, we used Transcranial Magnetic Stimulation and the co-recording of Electroencephalography (TMS-EEG), which allows for tracking tDCS-induced changes on cortical excitability and effective connectivity. Using TMS, we targeted the left PPC while the EEG was concurrently recorded from 60 channels. Each participant underwent an additional control session in which sham tDCS was delivered. At sensors, indexes of global and local cortical excitability were obtained. A source modelling analysis was also performed, computing global and local current density at the cortical level, to assess the tDCS effects, avoiding the potential confound of volume conduction.

Results

At resting state, both sensors and cortical sources results show no differences during and after c-tDCS, compared to pre-stimulation session, both at global and local level. At an active state, both polarity tDCS stimulations induced modulation of cortical excitability only in the task-relevant brain regions [3].

Conclusion

These data highlight a non-linear impact of anodal and cathodal tDCS on cortical excitability and how different states (resting vs active) can modulate the effects, in line with “activity-selectivity” hypothesis. These results hold relevant implications for tDCS setups both in cognitive neuroscience experiments and rehabilitation protocols.

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Anodal tDCS over the left or right DLPFC differentially influences memory performance

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Introduction

The generation of a new memory first requires encoding. The level to which new information is encoded influences how well it is remembered later; that is, deeper encoding (rather than shallow) leads to stronger memory traces and facilitates retrieval [1]. Positively or negatively valenced information even further facilitates retrieval compared to neutral information [2]. For encoding [3] as well as for the processing of emotionally valenced material [4], the dorsolateral prefrontal cortex (DLPFC) is functionally relevant. In the current study, we modulated the excitability of the DLPFC via anodal transcranial direct current stimulation (tDCS) during three levels of encoding (i.e., shallow, deep, and emotional). We stimulated either the left or the right DLPFC, since in healthy young adults, the left DLPFC may be particularly involved during encoding, while the right DLPFC is more important during retrieval of information. We hypothesized that tDCS to the left DLPFC would specifically increase memory performance, while stimulation to the right DLPFC would not. In addition, we hypothesized that stimulating the left or right DLPFC at encoding would differentially modulate the later retrieval of emotionally valenced content.

Methods

In this double blind, placebo-controlled, and parallel group study, we randomly assigned participants to one of three encoding conditions and delivered either sham or 20 minutes of 1mA anodal tDCS during an incidental learning task of 40 words. We placed the anode over the left (n=126, age 23.6 ± 2.6, 64 male) or right DLPFC (n=135, age 23.0 ± 3.0, 58 male) and the cathode over the contralateral supraorbital region (Figure 1). We tested retrieval performance with a free recall test.

Results

Stimulating the left DLPFC during shallow and deep encoding significantly enhanced free recall performance, while stimulating the right DLPFC did not. For positively valenced material, stimulation of both left and right DLPFC at encoding increased retrieval performance. For negative content, stimulation to the left DLPFC significantly decreased later retrieval performance, while stimulation to the right DLPFC increased subsequent retrieval performance (Figure 1).

Conclusion

Stimulating the left DLPFC during incidental encoding significantly enhances memory performance and participants focus significantly less on negative content. Modulating the left DLPFC may have strengthened brain activity patterns during encoding and thereby facilitated later reactivation of those patterns. For emotionally valenced material, stimulation to the left may have influenced hippocampal-amygdala coupling. In the future, we plan to apply a similar protocol in a clinical cohort (i.e., patients with depression) and to acquire imaging data to unravel the underlying neural mechanisms of memory enhancement via tDCS.

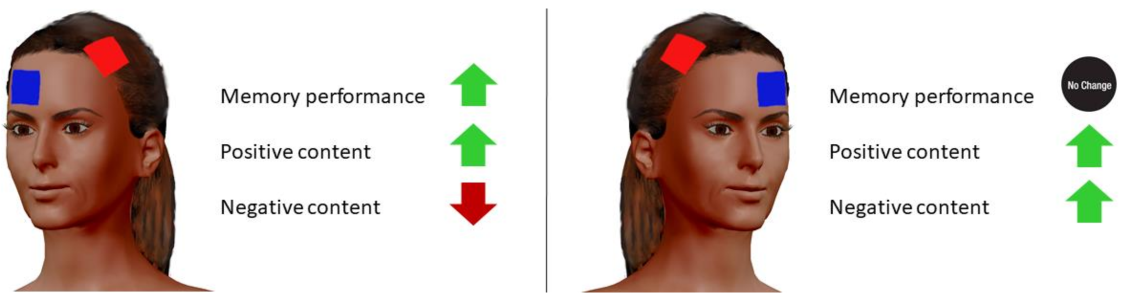

Figure 1. Summary of our results.

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The effects of frontal tACS on reversal learning

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Introduction

In the frontal cortex both theta and beta oscillations are associated with learning of reward and punishment contingencies [1]. Furthermore, the ratio between theta and beta oscillations has shown to be a predictor for reversal learning performance [2]. However, the specific role of these frequencies and is still unknown. In two experiments we applied transcranial alternating current stimulation (tACS) at the theta and beta frequency and investigated the effects on reversal learning as well as on endogenous theta and beta oscillations and the theta/beta ratio in resting state electroencephalogram (EEG).

Methods

In experiment 1 participants received 1 mA theta-tACS (6 Hz) over left and right frontal cortex while performing a reversal learning task. In experiment two, the same task was used, using two tACS montages, one applying currents within the left and right frontal cortex, whereas the other applied currents interhemispherically, at the beta frequency (20 Hz). In both experiments resting-state EEG was measured before and after stimulation.

Results

Experiment 1: Compared to sham, participants who received theta-tACS learned a reversal significantly faster. However, the implementation of the rule, i.e. taking high risk when this is the best option, worsened. The EEG results showed a decrease in left frontal cortex theta/beta ratio activity.
Experiment 2: Compared to sham, participants who received beta-tACS showed better rule implementation. The EEG results showed a significant decrease in left and right frontal cortex theta/beta ratio activity.

Conclusion

Although both theta- and beta-tACS improved reversal learning, they affected different aspects of the task, that is rule learning versus rule implementation. Furthermore, after both theta- and beta-tACS frontal theta/beta oscillation were significantly decreased. This suggests an interaction between oscillations of both frequencies in the frontal cortex underlying the processing of rewards and punishments.

References

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Figure

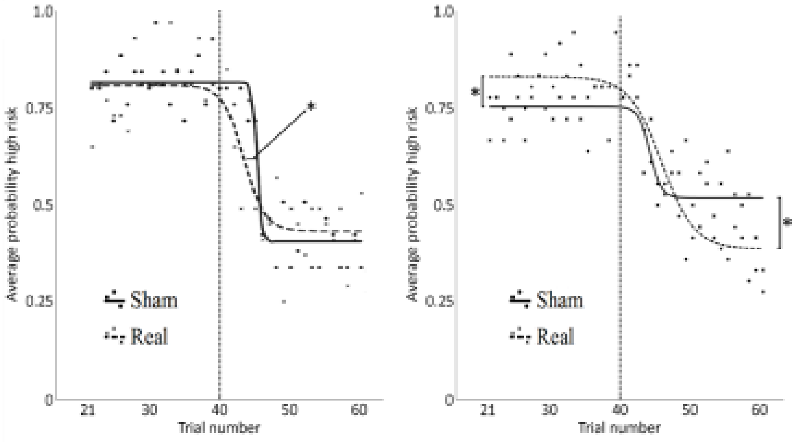

Figure 1. Reversal learning performance during real and sham theta tACS (left) and beta tACS (right). During theta tACS participants needed fewer trials to reverse behavior, compared to sham, suggesting faster learning. During beta tACS participants took more risk in high risk blocks and less risk in low risk blocks, compared to sham, suggesting better rule implemenetation.

Open hybrid MEG–MRI scanner and combining it with transcranial ultrasound stimulation

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Introduction

While conventional MRI uses increasingly high magnetic fields, unconventional approaches have emerged, e.g. with the signal detected in an ultra-low field (ULF) on the order of Earth's field. ULF-MRI differs from high-field MRI in several interesting ways. In this scheme, the pulsed magnetic fields can be applied silently and with an open-geometry coil system. The detected kHz-range signal can be modeled from theory with high accuracy. The unique possibilities of ULF-MRI also include the combination of MRI and magnetoencephalography (MEG), the measurement of millisecond-scale magnetic-field signals generated by the electrical activity of the brain. ULF-MRI and associated methods such as current-density imaging (CDI) can significantly improve the spatial characterization and localization of brain activity.

In addition to developing a hybrid MEG–MRI system, we are working towards an *in vivo* combination of transcranial ultrasound stimulation and hybrid MEG–MRI. Recent research shows that ultrasound has potential in noninvasively modulating brain activity or even direct neuronal activation.

Methods

The instrumentation for ULF MRI differs from conventional MRI in all parts, including coil design, detection, pulse-sequence electronics, dewar, reconstruction and software. For example, in a shared liquid-helium bath at 4.2 K, we have a rapidly pulsable magnet for prepolarizing the spins in the target tissues, as well as a sensor array based on superconducting quantum-interference devices (SQUIDs) for highly parallel imaging. In addition to the MRI signals, the same sensors also detect MEG, providing brain-activity data at millisecond resolution. Furthermore, with an accurate spatial calibration technique, ULF MRI provides vital information for localizing brain activity and submillimeter registration for MEG–MRI. With dedicated ultra-low-noise amplifiers, it is possible to switch off even the main field B_0 during an imaging sequence. This enables encoding three-dimensional information for current-density imaging (CDI) using novel techniques.

For ultrasound experiments, we employ a phantom setup with 1-MHz transducer signals fed into the imaging setup using a noise decoupler system in order to retain the ability to make sensitive magnetic field measurements.

Results

We present, to our knowledge, the first functioning ULF MRI system with full coverage of a helmet-shaped sensor arrangement around the head, exposing 120 magnetometers to MRI pulses in all directions. We describe improvements to different parts of the technology with the aim of, one by one, solving the problems that limit the possibilities of ULF-MRI. The techniques include Dynamical Coupling for Additional dimensioNs (DynaCAN), a method using specifically designed pulse waveforms to couple to complex dynamics that have memory of their past. We describe our progress in determining whether MEG–MRI can be successfully combined with transcranial ultrasound stimulation without hampering the magnetic measurements.

Conclusion

We have designed and constructed a brain-scanner prototype with 120 receiving channels around the head, enabling the joint reconstruction of data from parallel magnetic resonance and biomagnetic signals. We further aim to achieve *in vivo* transcranial focused ultrasound stimulation combined with MEG–MRI. We present first results obtained with the prototype. The long-term goal is to bring imaging of electrophysiology to the next level as well as to allow combinations with other techniques based on e.g. magnetic resonance and ultrasound.