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An EEG-fMRI-TMS instrument to investigate BOLD response to EEG guided stimulation

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***Abstract*— Depression is a serious mental illness that is frequently resistant to a first round of pharmacotherapy. Electroconvulsive therapy (ECT) is effective even for such treatment resistant depression but is associated with significant adverse effects. Repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex in comparison causes only mild discomfort but is less effective than ECT. We hypothesize that TMS treatment efficacy could be improved by locking TMS onset to a specific, potentially subject specific phase of the prefrontal alpha rhythm in the electroencephalogram (EEG). Here, we present an instrument that can track and predict phase of the alpha rhythm in the EEG to precisely target TMS while concurrently recording functional magnetic resonance imaging (fMRI) to study local and distributed hemodynamic brain responses to stimulation. Tests of the instrument with three healthy adults indicate that EEG phase-locked TMS can be administered accurately enough to start testing systematically whether specific stimulation protocols can lead to clinically significant improvements in depression. To our knowledge, this is the first system that can deliver TMS phase-locked to the alpha rhythm while concurrently recording fMRI. For patients, such EEG guided TMS treatment could lead to better clinical outcomes and lower incidence of adverse effects.**

I. INTRODUCTION

Depression is reported to affect 19 % of US Americans at least once in their life time [1] with 50 to 60 % of the affected not fully responding to pharmacological treatment of adequate dose and duration (e.g. twelve weeks) [2]. For some individuals with such treatment resistant depression, electroconvulsive therapy (ECT) can be an effective therapy, but the adverse effects of ECT include memory loss and impairment of cognitive abilities [3].

Repetitive transcranial magnetic stimulations (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) on the other hand typically causes only localized, mild adverse effects like headache or discomfort but shows a comparably lower antidepressant effect relative to ECT, particularly if patients had previously failed to respond to more than one "adequate" antidepressant treatment before [4].

One idea to improve treatment efficacy of TMS is to analyze brain activity in real-time and to trigger TMS precisely when the brain is in a state where stimulation has a relatively stronger effect. This type of setup where endogenous signals are analyzed and results provided back to the user in real-time (here in form of stimulation) are referred to as "closed-loop" systems. In one example of such a closed-loop system, Zrenner and colleagues [5] showed that triggering rTMS over the motor cortex at the negative peak of the mu rhythm in the electroencephalogram (EEG) led to higher corticospinal excitability as evidenced by higher amplitude of the motor evoked potential. Triggering at the positive peak of the mu rhythm on the other hand had no effect on cortical excitability.

Fig. 1. Integrated EEG-fMRI-TMS instrument. Subject preparing to enter fMRI scanner wearing EEG cap while the TMS coil is positioned over left dorsolateral prefrontal cortex.

Analogous to the approach used by Zrenner et al., we reason that triggering rTMS over the left DLPFC at specific phases of an individual's alpha rhythm, derived from the same scalp location, may amplify treatment effect in depression. With inter-pulse-intervals corresponding to the subject's individual alpha cycle period, entrainment effects may also occur, where the phase of the alpha oscillation starts locking to the rTMS pulses [6].

To better study the effects of such closed-loop stimulation throughout the brain [7], we implemented an instrument

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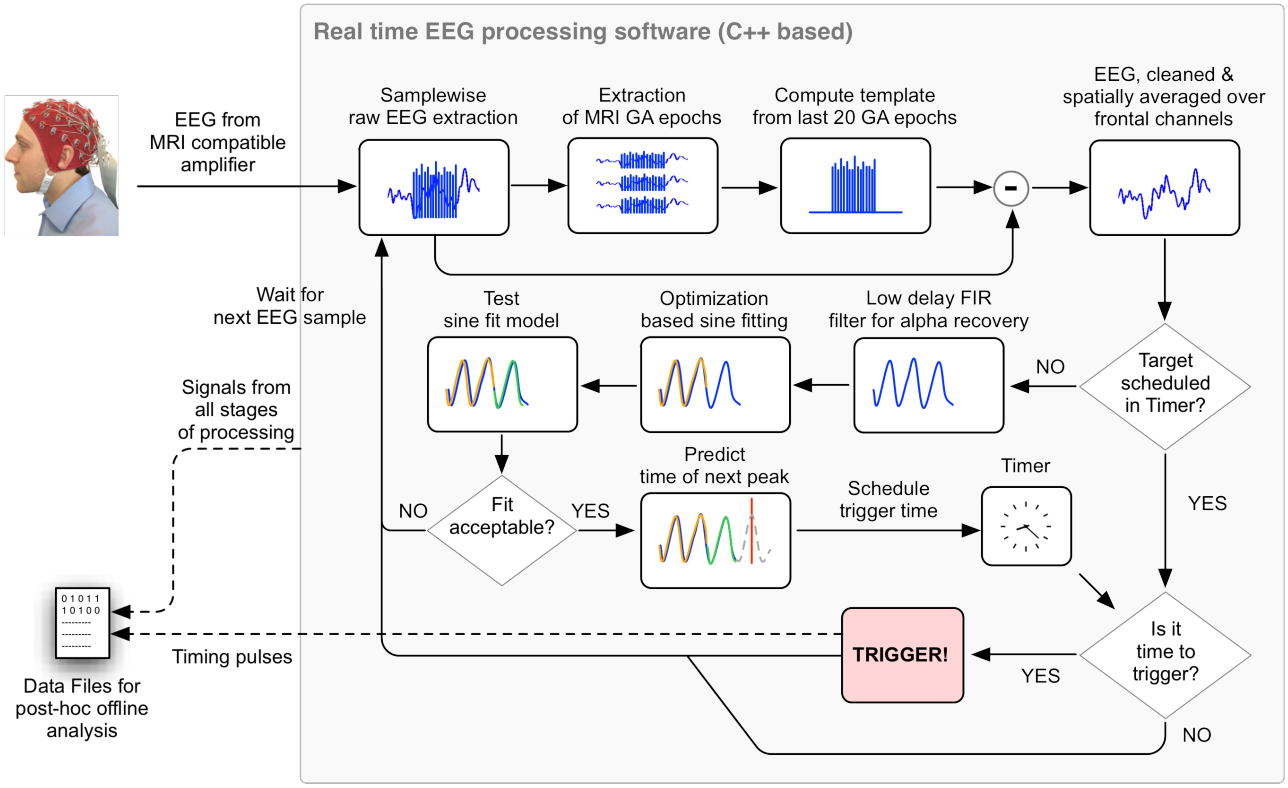

Fig. 2. Overview of the closed-loop processing of the EEG from sample-wise acquisition, over finite impulse response (FIR) based filtering, real-time gradient artifact (GA) removal, non-linear optimization based sine fitting and phase prediction to phase targeting.

that can concurrently record fMRI data, record the EEG, correct artifacts in the EEG based on an automatically updating gradient artifact template and track instantaneous phase of the EEG alpha rhythm for targeted TMS. From the perspective of building an EEG-based closed-loop system this is challenging for two reasons: (1) It requires an fMRI compatible amplifier that can deliver measured signals with minimal latency (<5 ms with our custom amplifier [8]) and (2) it requires removing artifacts that fMRI induces in the EEG in real-time.

We present preliminary results from tests outside and inside the scanner from three healthy study participants, which indicate that this instrument can target phase of the frontal alpha rhythm with a precision sufficient to systematically test whether specific closed-loop stimulation protocols can lead to clinically significant improvement in depression.

II. METHODS

A. Subjects

Three neurologically healthy, unmedicated adults (all male; ages 22, 31 and 31) participated in this study. Written informed consent was obtained from all subjects prior to the experiment and our experimental protocol was approved by the Institutional Review Board of the Medical University of South Carolina.

B. EEG-fMRI-TMS setup

Functional imaging was performed using a Siemens Prisma 3.0 T (Siemens, Erlangen, Germany) with a custom 12-channel head coil (Rapid MR International, LLC, Columbus, OH, USA) and a multi-echo multiband pulse sequence (multiband acceleration factor 2). We acquired whole-brain fMRI in 36 slices where voxel size was 3.2 x 3.2 x 3.2 mm. Repetition time (TR) was 1.6 s (TE1=11 ms, TE2=32 ms, TE3=53 ms and flip angle 58 degrees). The focus in this paper lies on EEG-guided stimulation and thus no fMRI results are reported. EEG was measured from a cap with 43 bipolar channels using a custom fMRI compatible amplifier [8] and sampled at 488 Hz. Impedances were kept below 25 kOhm and data acquisition was synchronized across signal modalities based on the 10 MHz clock of the fMRI scanner. The TMS coil (Magstim Rapid^2, Magstim Inc., Eden Prairie, MN, USA) was arranged to stimulate left DLPFC in single pulses and configured to a subject-specific intensity of 100 to 120 % of the motor threshold.

C. Phase tracking and prediction of the alpha oscillation

EEG is extracted sample-wise in real-time and subjected to template-based gradient artifact (GA) removal. Then the prefrontal alpha oscillation is recovered using a finite impulse response filter on the spatial average of four frontal EEG electrodes FP1, AF3, F3 and F7. A sine model is then fit onto the time window [-300 -100] ms by minimizing root

mean squared error (RMSE) via nonlinear optimization for the free frequency, phase and amplitude parameters. Provided that RMSE between model-based prediction and the actual signal on the test window [-100 0] ms are below specified thresholds, the time point for the next peak in the alpha rhythm is predicted and scheduled for future triggering of a timing pulse. Until the scheduled time-point is reached, the logic continues to pre-process data, but no new models are fitted. When the scheduled time point is reached, a timing-pulse is triggered and stored into a data file with all other signals for post-hoc offline verification of timing accuracy. Triggering is always followed by a refractory period of 5 s, in which new EEG data is preprocessed but sine fitting and hence triggering remain disabled (not depicted in diagram). An overview of this processing pipeline is shown in Fig. 2 and earlier additional tests were presented here [9].

D. Experimental protocol

In every session we first recorded 3 minutes of EEG data in order to determine the individual alpha frequency (i.e. center of peak in EEG). The signal processing steps involved in this procedure were as follows: First, the channels (FP1, AF3, F3 and F7) were spatially averaged. Then power spectral density was computed via the Welch periodogram (one second window, 0.5 s overlap). The individual alpha frequency was then determined as the maximum between 8 and 12 Hz and was 10 Hz for S01, and 9 Hz for S02 and S03. Subsequently, at least one run of 5 minutes was recorded for every one of the following three conditions: (1) Lying on MRI table, outside the bore, (2) inside bore during fMRI without TMS (3) inside bore during fMRI with TMS. For S03, condition 3 could not be recorded due to time constraints.

E. Post-hoc evaluation of stimulation accuracy

To evaluate targeting accuracy post-hoc, we calculated the phase difference between every pulse event marker and the phase in the alpha rhythm that was actually targeted in that instance. To recover the actual phase of the alpha oscillation as accurately as possible, EEG that was recorded concurrently with fMRI was first subjected to template-based suppression of gradient artifact and cardio ballistic artifact (also ballistocardiogram; BCG) [8]. For recordings where no TMS was pulsed, we then applied the same spatial averaging as in real-time, but afterwards used a strong bi-directional filter instead of the unidirectional filter that was used during real-time operation. For recordings where TMS was pulsed, we mitigated the distortive effects of the TMS artifact on the bidirectional filtering, by replacing the observed data in the 400 ms window following the TMS pulse with time-reversed data extracted from the 400 ms window before the TMS pulse (i.e. mirroring relative to TMS pulse). The phase at the TMS event was linearly interpolated from individual alpha frequency and phase 150 ms before the TMS pulse.

III. RESULTS

In three healthy adults, the presented closed-loop stimulation instrument was able to trigger between 1.4 and 5.5 pulse events per minute (despite 5 s refractory period) during concurrent fMRI recording, where 69.2 to 94.2 % of pulses were triggered within ± 90 degrees of the targeted phase (accuracy metric is the positive preditive value, PPV = True Positive / (True Positive + False Positive)). When the subjects were instead lying on the MRI table, while no pulse sequence was running, the instrument was able to trigger 2.6 to 7.3 pulse events per minute, where 74.4 to 95.5 % of pulses were triggered within ± 90 degrees of the targeted phase.

Overall, distributions of differences between targeted phases and actual pulse markers appear similar for when fMRI was recorded concurrently relative to outside the scanner bore (see Fig. 3).

IV. DISCUSSION

The findings from this preliminary study involving three healthy adults indicate that the presented closed-loop EEG-fMRI-TMS instrument can target a specific phase in the prefrontal alpha rhythm accurately and consistently enough (range of PPV inside scanner 69.2 to 94.2 %) to systematically test whether closed-loop stimulation can lead to clinically significant improvement in depression.

For the three subjects in this study, pulse rate and accuracy, were numerically lower during concurrent fMRI recording (3.6 pulses/min; PPV = 80.6 %), relative to operation outside the fMRI scanner (5.6 pulses/min; PPV = 88.1 %). With three participants, it is difficult to assess whether this effect is universal. Intuitively, we would expect performance to be lower when concurrently recording fMRI, where additional artifacts presumably decrease the SNR of the EEG relative to when the subject is lying outside the scanner. Visual inspection of the data, suggests that the real-time gradient artifact correction worked without obvious failures across the recordings of these three participants. Presently, the instrument implements no mechanism to suppress the BCG artifact during real-time operation. It is noteworthy that this type of artifact reduction poses a significant challenge, even during post-hoc analysis when acausal signal processing methods are applicable.

The most promising approaches to remove the BCG artifact use special EEG electrodes, where a second sensor, galvanically isolated from the scalp, records only noise and artifacts so that those can later be removed from the EEG [10]. To make sure there was no systematic assocation between the BCG artifact and the triggering mechanism we calculated the time difference between every pulse event marker and the closest R-spike. A systematic association between artifact phase and the triggering mechanism would be expected to manifest as significant non-uniformity in the distribution of these differences. No evidence for statistically significant non-uniformity has been found for any of the recordings within the scanner (Rayleigh test; p-values range from 0.109 to 0.948).

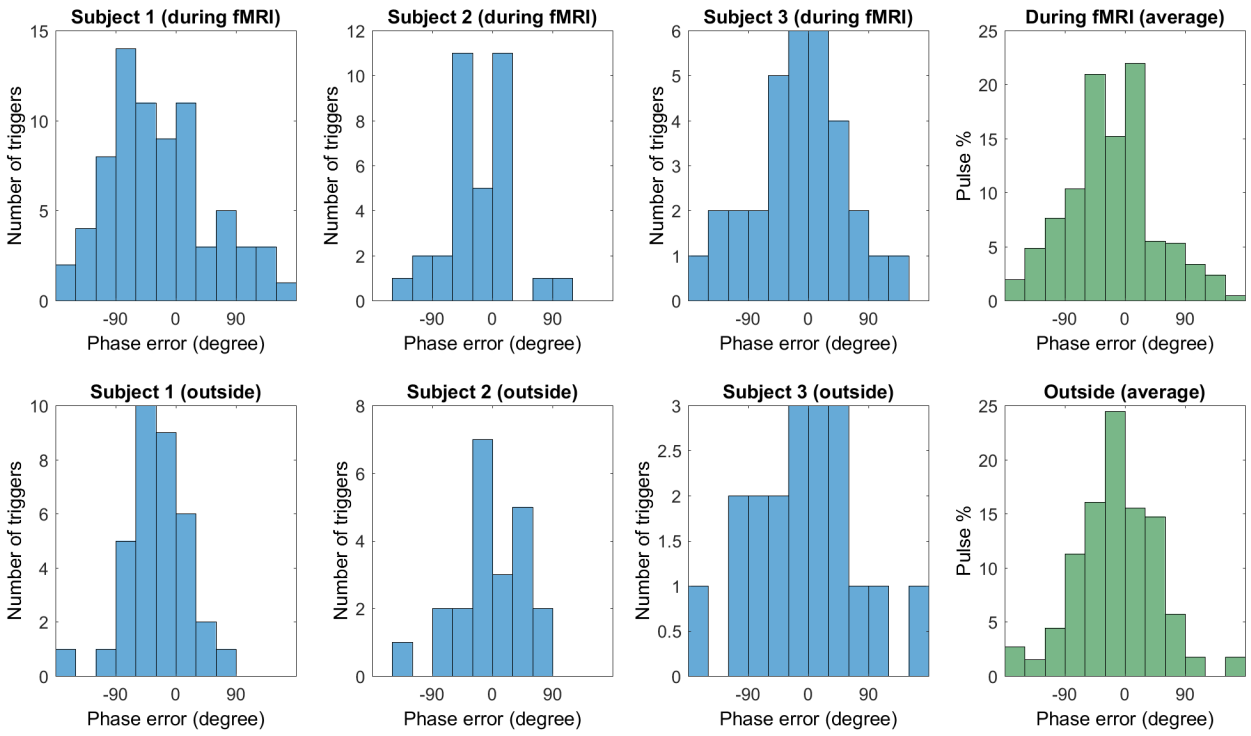

Fig. 3. Phase differences between pulse markers and target phase in the alpha rhythm in degrees. The blue histograms represent absolute numbers of pulses for individual subjects. For the green histograms on the right, individual histograms were first normalized by the total number of pulses for that individual and condition (inside or outside fMRI scanner) and then averaged across subjects.

In terms of stimulation reliability, Zrenner and colleagues [5] found a standard deviation of phase errors of overall 54.0 degrees, which is comparable to what we found in the present study where the standard deviation of phase errors outside the scanner was overall 58.4 degrees, inside, in the absence of TMS it was 73.1 and with TMS it was 44.3 degrees.

V. CONCLUSION

In summary, we interpret the results of this study as preliminary evidence that this EEG-fMRI-TMS instrument can administer phase-locked TMS accurately enough to systematically test whether certain closed-loop stimulation protocols can lead to clinically significant improvement in depression. At the same time the system allows us to study local and distributed hemodynamic responses of the brain to the stimulation.

REFERENCES

[1] R. C. Kessler and E. J. Bromet, "The epidemiology of depression across cultures," *Ann. rev. of public health*, vol. 34, pp. 119–138, 2013.

[2] M. Fava, "Diagnosis and definition of treatment-resistant depression," *Biological Psychiatry*, vol. 53, no. 8, 2003.

[3] The UK ECT Review Group, "Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis," *The Lancet*, vol. 361, 2003.

[4] S. H. Lisanby, M. M. Husain, P. B. Rosenquist, D. Maixner, R. Gutierrez, A. Krystal, W. Gilmer, L. B. Marangell, S. Aaronson, Z. J. Daskalakis, R. Canterbury, E. Richelson, H. A. Sackeim, and M. S. George, "Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial," *Neuropsychopharmacology*, vol. 34, pp. 522–534, 2009.

[5] C. Zrenner, D. Desideri, P. Belardinelli, and U. Ziemann, "Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex," *Brain stimulation*, vol. 11, pp. 374–389, 2018.

[6] G. Thut, T. O. Bergmann, F. Fröhlich, S. R. Soekadar, J.-S. Brittain, A. Valero-Cabré, A. T. Sack, C. Miniussi, A. Antal, H. R. Siebner, U. Ziemann, and C. S. Herrmann, "Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper," *Clinical Neurophysiology*, vol. 128, pp. 843–857, 2017.

[7] M. S. George, L. E. Stallings, A. M. Speer, Z. Nahas, K. M. Spicer, D. J. Vincent, D. E. Bohning, K. T. Cheng, M. Molloy, C. C. Teneback, and S. C. Risch, "Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely," *Human Psychopharmacology: Clinical and Experimental*, vol. 14, no. 3, pp. 161–170, 1999.

[8] P. Sajda, R. I. Goldman, M. Dyrholm, and T. R. Brown, *Signal processing and machine learning for single-trial analysis of simultaneously acquired EEG and fMRI.* K. Oweiss (Ed.), In Statistical signal processing for neuroscience and neurotechnology, Academic Press, 2010, pp. 311–334.

[9] Y. Lin, J. Faller, G. T. Saber, J. R. McIntosh, R. I. Goldman, M. S. George, P. Sajda, and T. R. Brown, "An EEG-fMRI-TMS system for investigating BOLD response to alpha phase-locked TMS," in *Society for Neuroscience Conference, San Diego, USA*, 2018.

[10] D. Steyrl, G. Krausz, K. Koschutnig, G. Edlinger, and G. R. Müller-Putz, "Reference layer adaptive filtering (RLAF) for EEG artifact reduction in simultaneous EEG-fMRI," *Journal of Neural Engineering*, vol. 14, no. 2, p. 026003, 2017.