Using Brain State-dependent Transcranial Magnetic Stimulation for Investigating Causal Role of Cortical Oscillations in Functional States

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ABSTRACT: *Non-invasive brain stimulation is being used for manipulation of cortical oscillations in research and clinical context for development of possible therapeutic applications in brain disorders. Effects of brain stimulation show strong inter- and intra-individual variation. In general there are several sources of this variability, e.g. neuroanatomical and neurochemical factors. This article describes our work in the scope of EkoSMART consortium on development of peripheral sensing techniques. Here we focus on the rapidly varying neurophysiological factors – cortical oscillations. Current state of cortical oscillations can be continually recorded with peripheral sensors like EEG scalp electrodes and used online for continuous monitoring and adjustments of brain stimulation parameters. By adjusting the timing, intensity and frequency of transcranial stimulation to specific brain states it is possible to reduce variation in the treatment effects. However, since brain state-dependent stimulation (BSDS) requires online monitoring and analysis of neurophysiological data, it is technically demanding. BSDS has been made possible by recent technological advances and advances in analytical procedures. While EEG data has been traditionally analyzed in time- or frequency-domain only, time frequency analysis is being increasingly used and it offers better insight into neurophysiology of oscillations. BSDS is useful in the field of clinical neuroscience, where it can be used to personalize stimulation parameters, e.g. adjust deep brain stimulation depending on the severity in symptoms in Parkinson's disease. Because it enables manipulation of cortical oscillations when a specific brain state is detected, it allows stronger causal inferences about their role in behavior and brain states. Therefore, BSDS can be also used as a tool for verification or falsification of hypotheses in cognitive neuroscience.*

Keywords: Brain State-dependent Stimulation, Transcranial Magnetic Stimulation, Time-frequency Analysis, Electroencephalography, Cortical Oscillations

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1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method during which magnetic field in a coil induces an electric current in nearby conductive tissue – the brain – thereby inducing action potentials in neurons. It is a common technique for manipulating neuronal oscillations and is used for research and clinical purposes. Transcranial alternate or direct current stimulation (TACS / TDCS) is a similar, although much weaker technique for modulating neural activity.

Effects of the TMS treatment show strong inter- and intraindividual variability and are influenced by neuroanatomical, neurochemical and neurophysiological factors [10]. These factors can be trait-related and can be stable (e.g. cortical thickness, individual alpha rhythm frequency) or can vary intra-individually (e.g. circadian fluctuations). On the other hand, state-related determinants can vary strongly and rapidly within and between treatment sessions. For example, it has been shown that phase and amplitude of cortical oscillations influence corticospinal excitability as measured with motor evoked responses [1, 15]. In the case of trait-related factors, variability of TMS intervention can be reduced by pre-selection of individuals based on a certain trait or by homogenizing the influencing variable, e.g. applying the treatment at the same time of the day. However, cortical oscillations can also vary on a millisecond scale and to reduce the effects of these factors, brain-state dependent stimulation is needed.

2. Feasibility of Brain-state Dependent Stimulation

Brain-state dependent stimulation (BSDS) requires online monitoring and analysis of neurophysiological data (see Figure 1). Karabanov et al. [10] distinguish between (1) state-informed noninvasive transcranial stimulation (NTBS) and (2) adaptive, closed-loop1 NTBS. In the former, the timing, frequency or the intensity of stimulation is adjusted according to the predefined state (e.g. phase or power of cortical oscillations), whereas in the latter, stimulation is dynamically adjusted depending on the stimulation-induced state changes.

In recent years several studies have shown feasibility of both types of stimulation. An example of state-informed NTBS is a study by Bergmann et al. [2]. To answer the question how the phases of cortical oscillations affect cortical excitability, Bergmann et al. applied TMS during sleep while concurrently measuring electroencephalographic (EEG) signal. Single-pulse TMS was triggered by automatic detection of up- and down-states in slowoscillations during non-rapid eye movement sleep. It was shown that motor-evoked potentials (MEPs) and TMS-evoked potentials (TEPs) were larger during slow-oscillations up-states than during down-states. Similarly, Gharabaghi et al. [6] and Kraus et al. [11] showed that single-pulse TMS controlled by beta-band eventrelated desynchronization (ERD) during motor imagery resulted in an increase of corticospinal excitability whereas in the non- BSDS condition this effect was absent.

An example of an adaptive closed-loop stimulation is a study by Brittain et al. [4] who applied transcranial alternating current stimulation (TACS) over the motor cortex of patients with Parkinson's disease. Stimulation was delivered at tremorfrequency and adjusted in a way to produce phase-cancellation and thus achieving tremor-suppression up to 50%. Similarly, in a study by Little et al. [12] it was shown that deep brain stimulation in Parkinson's disease can be adjusted by providing feedback from local field potentials from the electrodes. This type of adaptive deep brain stimulation was more effective and efficacious than conventional continuous stimulation. While these studies provide proof-of-principle, it remains to be shown that EEG combined with non-invasive transcranial stimulation can also be used in a closed-loop, adaptive fashion [2].

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[1] In the literature, the term closed-loop stimulation is sometimes being used for both types of stimulation. However, Karabanov et al. [10] emphasize, that state-informed stimulation is not the same as "closed-loop" stimulation and that the latter term should only be used for a stimulation which adapts depending on stimulation effects in real-time.

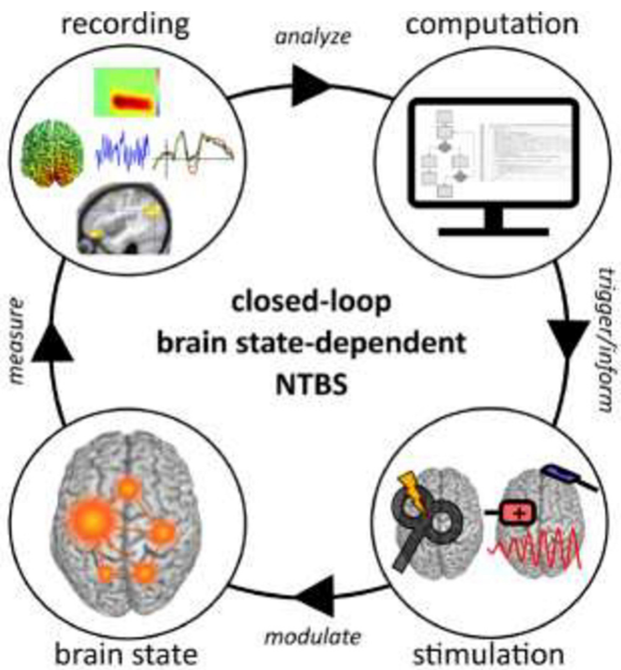
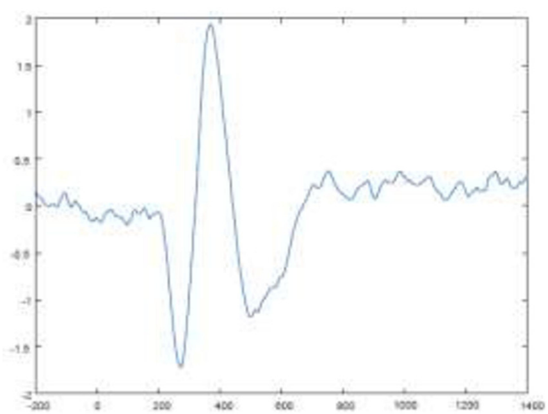


Figure 1. Closed-loop brain state-dependent non-invasive transcranial brain stimulation. Source: Bergmann et al., 2016 [3]. Originally published under CC BY license (https://creativecommons.org/licenses/by/4.0/)

Both neuroimaging (e.g. functional magnetic resonance) and electrophysiological methods (e.g. EEG) can be coupled with TMS for BSDS. TMS can be combined with fMRI for brain-states with slow fluctuations (e.g. resting state connectivity) and when spatial resolution and sensitivity to subcortical structures is important, whereas EEG is more appropriate when timing precision on sub-second level is more relevant.



2.1 Challenges in Online real-time Analysis of Brain-states

Traditionally, EEG data has been analyzed in time- or frequency domain. In time domain analyses (see Figure 2, top), data are typically averaged across epochs based on markers, which represent events (e.g. stimulus presentation or participants' response) by which event-related potentials (ERPs) are observed. This procedure is based on an assumption that signal is constant across trials, whereas all trial-to-trial variability is considered to be noise. One major disadvantage of ERP technique which originates from this assumption is that it requires a lot of trials to achieve acceptable signal-to-noise ratio. While this procedure is still being used, it is now known that this assumption is false since even temporally fluctuating potentials (so-called non-phase locked or induced activity) are averaged out from the signal and therefore cannot be reliably detected with ERP technique.

In frequency-domain analyses, EEG data is decomposed from time-domain into frequency-domain using Fourier transform. With

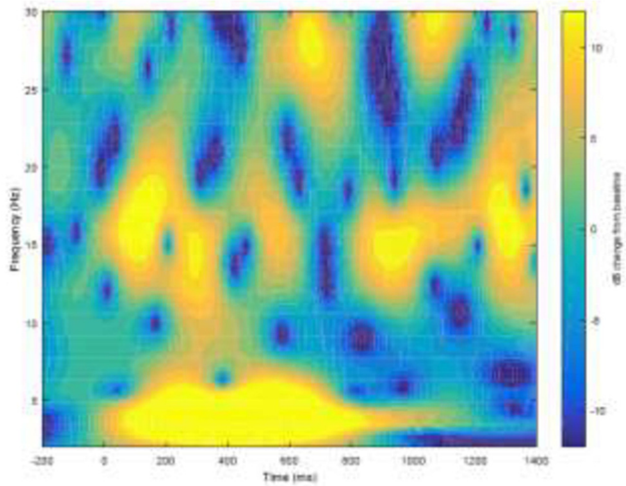


Figure 2. Same data analysed in time-domain (event-related potential, top) and with time-frequency analysis (bottom)

this procedure it can easily be estimated which frequencies constitute EEG signal, e.g. whether there is more activity in thetaband (4–7 Hz), beta-band (16–30 Hz), etc. This type of analysis is relatively simple and therefore widely used, e.g. for research on resting state EEG. However, the fact that brain is highly nonstationary renders results of frequency-domain analyses hard to interpret, especially when we are interested in how oscillations change in response to events. The third way to analyze EEG data is by means of time-frequency analysis. Time-frequency analysis offers good time and frequency resolution (although there exists a trade-off between them) [5]. Its results are closer to actual neurophysiology in comparison to the other two methods and therefore easier to interpret. Since it does not require a large number of trials to achieve acceptable signal-to-noise ratio and since it can be used to disentangle phase-locked and non-phaselocked activity, it is more appropriate for single-trial analyses. It also enables calculation of various connectivity measures based on phase, power, etc.

Although time-frequency analysis is more computationally consuming, it is more suitable for BSDS in comparison to time- or frequency-domain analyses. Besides usefulness in online monitoring of cortical oscillations in real-time, time-frequency analysis can also be used to generate hypotheses about the causal role of different types of oscillations and for evaluating the effects of transcranial stimulation.

Another important issue in BSDS with TMS are strong artefacts produced by stimulation lasting several milliseconds [16] and TEPs caused by stimulation. In state-informed open-loop stimulation a refractory period of several seconds can be used to avoid triggering of TMS by artefacts or TEPs, whereas for closedloop stimulation methods for online artefact reduction yet need to be developed.

3. Brain State-dependent Stimulation Enables Stronger Causal Inferences about Cortical Oscillations

Whereas the usefulness of BSDS in clinical context is evident as illustrated by examples described above, BSDS can also foster progress in cognitive neuroscience. Currently, dominant approach for investigating the role of cortical oscillations in cognition is to randomly present events and then observe changes in eventrelated potentials or event-related oscillations. In the case of investigation of effects of TMS on the brain, EEG is correlated with TEPs or MEPs. This approach is useful for generating hypotheses about relationship between brain and functional states, however, it is essentially a correlational approach. Stronger causal inferences are possible if events are triggered when a specific brain state is detected.

Besides BSDS where transcranial stimulation is adapted to the brain state, a stimulus presentation or task can also be adapted to the brain state, resulting in the so-called brain-state dependent task (BSDT) [8]. For example, Ngo et al. [13] applied auditory closed-loop stimulation in phase with slow oscillation up-states during sleep. This improved memory consolidation and enhanced declarative memory retention.

All three approaches can be used complementary: first, it can be shown that a specific oscillatory pattern is linked to behavior.

For example, Osipova et al. [14] have shown that stronger gamma and theta activity during visual stimuli presentation predicted subsequent retrieval. A hypothesis that gamma and theta activity is causally linked to memory encoding could further be tested using BSDS, where oscillations in gamma and theta spectra would be manipulated using transcranial brain stimulation. Further, using BSDT, if low theta or gamma power were detected during stimuli presentation, these stimuli could then be presented multiple times and in this way learning would be more efficient.

4. Conclusion

Computational advances and advances in statistical methods have in recent years enabled analysis of trial-to-trial variations in the field of neurophysiology. This has led to new hypotheses about the functional role of cortical oscillations. Brain state-dependent stimulation can be used as a tool for testing these hypotheses and thus enables making strong causal inferences about cortical oscillations. BSDS is a significant step towards optimizing noninvasive transcranial brain stimulation interventions, thus enabling more efficient stimulation adapted to the individual's brain and/or functional state. To conclude, research on brain state-dependent stimulation is still in its infancy and shows considerable promise in fostering progress in cognitive and clinical neuroscience.

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