Clinical Neurophysiology 158 (2024) 196–203

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Opinion Paper

Towards real-time identification of large-scale brain states for improved brain state-dependent stimulation

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1. Neuroimaging evidence for network-level brain states

In the last decades, system neuroscience has provided evidence for the dependence of human cognition and behavior on the formation of neuronal networks that transiently link distributed brain regions in response to external stimuli and or task demands (Gonzalez-Castillo and Bandettini, 2018), closely resembling networks observed also during the resting state (Deco and Corbetta, 2011). Yet, more recently, evidence has been provided for the idea that the internal state, i.e., the latent properties or activity of the brain when an external input is delivered, influences how the brain processes a task (Bradley et al., 2022). Seemingly, response and task performance are the result of a nonlinear interaction between the ongoing latent brain state and stimulus processing (Huang et al., 2017), with the fluctuation between different states in both time and space determining the variable responses of the brain in relation to behavior (Zagha and McCormick, 2014). A relevant example in this framework is the work by (Taghia et al., 2018), using functional Magnetic Resonance Imaging (fMRI) on a second/sub-second temporal scale, proposing a computational approach to identify large-scale latent brain states, and to determine their relation to working memory task conditions. Several studies using non-invasive electrophysiology, i.e., ElectroEncephaloGraphy (EEG) and MagnetoEncephaloGraphy (MEG), have also shown that perception and task performance depend on the *current state* of the brain before the stimulus, e.g., (Shin et al., 2017; VanRullen et al., 2011; Weisz et al., 2014), showing also that the duration of such latent brain states is in the order of tens of milliseconds.

2. Brain state-dependent stimulation

The integration of Transcranial Magnetic Stimulation (TMS) with techniques able to non-invasively measure neuronal activity, such as EEG (Bergmann, 2018; Bergmann et al., 2016; Ilmoniemi and Kičić, 2010; Silvanto and Pascual-Leone, 2008), has made it possible to detect the state of the brain right before the stimulation (Bai et al., 2022; Zrenner et al., 2018). This has been mostly assessed by looking at the temporal and spectral characteristics of the EEG signal at the channels near the brain region being stimulated (Mäki and Ilmoniemi, 2010). As a paradigmatic example, the phase and power of the sensorimotor 9–13-Hz mu rhythm have been considered as indicators of cortical excitability that determines the response to TMS in the sensorimotor system (Desideri et al., 2019; Karabanov et al., 2021; Madsen et al., 2019; Schaworonkow et al., 2019; Zrenner et al., 2018). By considering the phase and power of the mu rhythm to trigger the stimulation, it might be possible to reduce inter- and intra-subject variability (Ziemann and Siebner, 2015). Nevertheless, these studies, differently from neuroimaging-based evidence for network-level brain states, have relied on local features of brain activity rather than on large-scale properties of brain dynamics.

Abbreviations: CSP, Common Spatial Pattern; EEG, electroencephalography; ER-FLBS, Endpoint-Related Fast-dynamic Large-scale Brain States; FLBS, Fast-dynamic Large-scale Brain States; fMRI, functional Magnetic Resonance Imaging; HMM, Hidden Markov Model; M1, primary motor cortex; MEG, magnetoencephalography; MEP, Motor Evoked Potential; MRI, Magnetic Resonance Imaging; mTMS, multi-locus TMS; SMA, supplementary motor area; TEP, Transcranial Evoked Potential; TMS, Transcranial Magnetic Stimulation.

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https://doi.org/10.1016/j.clinph.2023.09.005

3. Proposed conceptual definition of large-scale brain states

While in all the above-mentioned studies, brain states are implicitly defined as recurring and continuously evolving sets of neural dynamics that are stable for a behaviorally significant period (Zagha and McCormick, 2014), we want to further clarify a few more aspects that are crucial to the definition of brain states that we will refer to in this paper.

First, the duration of brain states we aim at identifying here must be compatible with that of behavior, i.e., fast dynamic brain states with temporal frequencies in the range 0.1–100 Hz. This makes us exclude from the present paper any reference to other common definition of brain states such as wakefulness compared to sleep, consciousness compared to unconsciousness or, for example, meditative or transcendental states (Bradley et al., 2022). The rationale for this choice does not come from the idea that these alternative definitions of brain states do not impact the effects of the stimulation (Massimini et al., 2005); it rather stems from our overarching goal to identify brain states that can be a reference for triggering the stimulation in real time.

Second, we want to identify large-scale brain states, as opposed to local properties used so far in EEG–TMS for brain state-dependent stimulation. The idea that we want to promote is to rely on large-scale properties of the brain for the identification of such a recurring set of neural dynamics, similarly to what was done in the neuroimaging studies we referred to in the first paragraph. Indeed, this paper is framed in the context of the ConnectToBrain project (connecttobrain.eu), which develops multi-locus TMS systems capable of stimulating multiple brain locations at once or in rapid spatiotemporal sequences (see section Towards large-scale stimulation of Fast-dynamic Large-scale Brain States). With this vision in mind, it is clear that a dynamic large-scale definition of brain state can be optimally exploited by the multi-locus TMS system (Koponen et al., 2018; Nieminen et al., 2022; Souza et al., 2022), or any other system able to target multiple brain regions, with regard to when and where the network-like stimulation should be delivered. Brain states with the above properties will be referred to as Fast-dynamic Large-scale Brain States (FLBS).

Third, the identified FLBS must be such that when TMS is applied, this results in an improvement in the targeted endpoint of the stimulation (see Fig. 1 for a graphical representation of this concept). In this context, the endpoint is a feature in neural, behavioral, or peripheral responses to stimulation that changes, on a short term or in the longer run, as a consequence of TMS. Possible endpoints may relate to: EEG features (e.g., amplitude of Transcranial Evoked Potentials or TEPs, functional and effective connectivity), behavioral responses (e.g., task response accuracy), peripheral responses (e.g., amplitude of Motor Evoked Potentials, MEPs), and clinical scores (e.g., Upper Extremity Fugl-Meyer Assessment scale for determination of arm-/hand function in motor stroke, (Fugl-Meyer et al., 1975)). Overall, the concept of endpoint improvement is broad, since it depends on the nature of the endpoint and may cover, for example, increased strength of a specific feature (e.g., larger TEPs, larger motor network connectivity) as well as a smaller variability of a specific feature (e.g., amplitude of MEPs) across stimulation repetitions or subjects. In the following, we will refer to FLBS with the latter property as Endpoint-Related Fast-dynamic Large-scale Brain State (ER-FLBS). In this paper, we will introduce a series of methods to identify ER-FLBSs from off-line EEG data in the time interval before the stimulation. For specific examples, we will also show that the identified brain states are actually related to a specific endpoint, which for the sake of clarity, will be, through this paper, the amplitude of the MEP. Finally, we will also provide theoretical evidence for the identification and targeting of ER-FLBSs during an on-line experiment.

4. Types of endpoint-related fast-dynamic large-scale brain-state and methods for their off-line identification

In this paragraph, we will first introduce methods to identify FLBSs from off-line data according to different metrics. Then, we will describe how these FLBSs can be put in relation with the target endpoint, thus being identified as ER-FLBS, and, finally, we will provide an example of off-line analysis of ER-FLBSs.

A large-scale brain state with fast dynamics can be identified off-line from electrophysiological data as a pattern of frequency-specific whole-brain activity or signal power. A popular method to this end is EEG microstate analysis, which aims to identify dynamical sequences of stable large-scale spatial topographies on the scalp (Britz et al., 2009; Croce et al., 2020; Murray et al., 2008) using an unsupervised learning approach such as k-means (Bishop, 2006) to cluster scalp topographies based on their similarity measured using Euclidean distance. More recently, alternative methods to identify patterns of activity and their dynamics based on Hidden Markov Models (HMMs) have been proposed (Vidaurre et al., 2018). HMM serves as a statistical tool for depicting a sequence of hidden data distributions, in which the likelihood of occurrence of each state solely depends on its antecedent occurrence. Differences between microstates and HMM states arise both spatially and temporally. Microstates have been related to sharp events of neural synchronization, i.e., peaks in the Global Field Power, whereas HMM states disclose network-level activity with 100–200-ms lifetimes. Both microstate and HMM analyses can, thus, be used to identify neural events occurring at different temporal scales, representing the fast, sub-second scale electrophysiological dynamics (Coquelet et al., 2022). In the following, we will provide an exemplary application of the HMM approach to derive this type of brain states from TMS–EEG data. Another method of separating spatial patterns of activity from the multivariate signal—Common Spatial Patterns (CSPs)—is tailored to extract EEG components that maximally distinguish between given discrete classes of data or experimental conditions (Koles et al., 1990). CSP is designed to isolate signal components based on covariances in the spatial distribution of oscillatory power (when applied to real-valued signals) and phases (when applied to complex signals, Falzon et al., 2012) across EEG sensors. The spatial filters for component extraction are created via generalized eigenvalue decomposition of channel covariance matrices. Thus, the time resolution of the derived patterns is conditional on the choice of the time window for covariance estimation. In principle, signal components uncovered by CSP represent neuronal activity most distinct between provided experimental conditions, and as such, can detect neuronal processes that predict the outcome of TMS.

FLBSs can be also defined from functional connectivity approaches which capture interactions between brain regions. Common strategies to assess functional connectivity by MEG and EEG relying either on coupling of slow signal fluctuations in the range 0.1–1 Hz (e.g., de Pasquale et al., 2010) or on phase coupling of fast neuronal oscillations in the range 1–100 Hz (e.g., Marzetti et al., 2013). See (Engel et al., 2013) for a review on brain coupling modes. Here, we will consider only bivariate phase-coupling metrics as a measure of functional connectivity (Basti et al., 2020; Marzetti et al., 2019) under the hypothesis that phase coupling of neuronal oscillations is a proxy for communication between brain regions (Fries, 2005). More specifically, we will consider the temporal evolution of such phase coupling between pairs of regions, i.e., dynamic functional connectivity, which, if sustained for a behaviorally relevant time period (Ermolova et al., 2021), may represent connectivity-based FLBSs. Of note, dynamic functional connectivity calculation is prone to false detections; thus, several theoretical and practical aspects must be considered for a

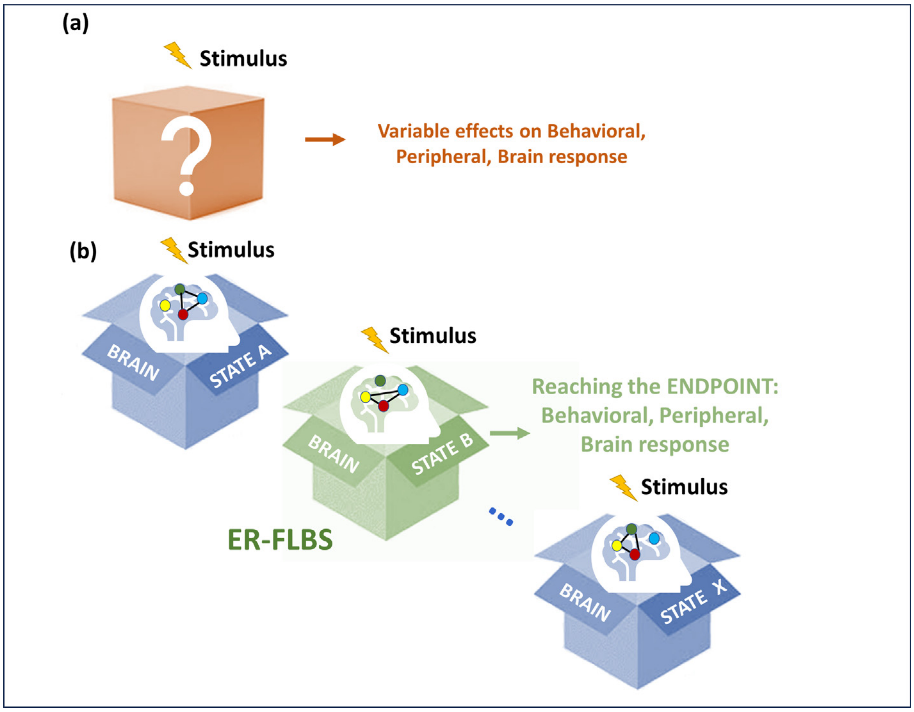

Fig. 1. The idea of brain state-dependent stimulation. (a) A stimulus delivered without taking into account the current brain state can lead to variable outcomes for all the considered endpoints (e.g., Behavioral, Peripheral, Brain response); (b) Only when the Endpoint-Related Fast-dynamic Large-scale Brain-state (ER-FLBS) is targeted, an improved impact can be gained.

reliable analysis. In brief, we will rely on high-density EEG montages, eventually in combination with spatial filters (e.g., Laplacian montages or inverse estimators) to increase EEG spatial focality. In addition, we will base our functional connectivity estimation on time-lagged quantities, thus minimizing volume conduction effects (Marzetti et al., 2019). The duration of the data segment to be considered for the dynamical analysis will be also chosen in accordance with our previous results (Sommariva et al., 2019; Basti et al., 2022).

To facilitate the interpretation of the connectivity-based FLBSs, neuroimaging and neurophysiological works have relied on graph theory (Bullmore and Sporns, 2009). Indeed, MEG and EEG studies identified cortical hubs, which ensure the balance between functional specialization and dynamic integration in the brain (Kabbara et al., 2017; de Pasquale et al., 2018) as well as highlight different degrees of dynamic brain modularity (Kabbara et al., 2019). However, the relationship of time-evolving graph theoretical properties and the TMS-evoked responses has not been studied. Structural brain connectivity networks estimated with diffusion MRI-based streamlines tractography have been shown to be reproducible (Roine et al., 2019) although often contaminated with false positive connections (Maier-Hein et al., 2017). Our preliminary data showed that the structural connectivity of the stimulation locus is related to the TMS-evoked significant current density (Casali et al., 2010; Ukharova et al., 2022). In addition, functional MRI has been used to detect resting-state and task-based networks in the brain (Cole et al., 2021), which may be useful a priori information for brain state identification. Taking structural and functional MRI connectivity into account may be able to constrain the source estimation problem and increase reliability for EEG-based connectivity metrics. For instance, strategies that incorporate individual task or resting-state fMRI networks in the EEG inverse problem solution can be implemented to ameliorate the low EEG spatial resolution in source space. One of such strategies would be to impose a loose spatial constraint based on the fMRI network results to the EEG source activity (Liu et al., 1998; Mantini et al., 2010).

Once FLBSs have been identified, an important point is the assessment of possible relations between FLBSs and the targeted endpoint. As already mentioned in the previous paragraphs, a variety of endpoints can be of interest depending on the specific scientific or clinical questions at hand. Thus, depending on the nature of the endpoint, as well as on the method used to identify the FLBSs, different approaches can be used to assess their putative relations to the target endpoint and, thus, assess their ER-FLBS status. We will here provide examples for two different approaches used to identify FLBSs, namely functional connectivity and HMM, and for one target endpoint, i.e., the amplitude of the MEP.

For the connectivity approach, it is conceivable that a change in the endpoint is related to a change in the connectivity state of the motor network before the stimulation eliciting the MEP. More specifically, we can consider different nodes in this network and define as different FLBSs the distinct connectivity configurations among these nodes. For the sake of simplicity, we will here consider only the two-node case (e.g., left primary motor cortex – left M1 – and ipsilateral supplementary motor area – SMA) and, thus, two FLBSs, namely the FLBS characterized by either a high or low connectivity between these two nodes. These two FLBSs will alternate across trials and, to investigate whether these FLBSs have a relation to the MEP amplitude, we consider the MEP values in the high-connectivity trials and compare them to the MEP values in the low-connectivity state, at group level or at single subject level. If a clear relation is observed, e.g., larger MEP values in trials characterized by a high-connectivity state (Marzetti et al., 2023), we conclude that the high-connectivity FLBS is an ER-FLBS for the MEP amplitude endpoint.

With the HMM approach, a data-driven identification of brain states can be obtained. HMM analysis reveals discrete states specified by their topography and time course, as well as the dynamics of the occurrence of these states in time. Brain states identified by

HMM are FLBSs, as evident from the empirical observation about their topography and their duration for EEG and MEG data. Finally, the relation to the target endpoint can be assessed by establishing a correspondence between the MEP amplitude and a specific feature of FLBS dynamics in that trial, for example, the spatiotemporal characteristics of the last state occurring before the stimulation or of the most represented one in that trial. An example of the off-line identification of ER-FLBSs is provided in Fig. 2. Fig. 2a and b show the topographies and the power spectra, respectively, of the six identified FLBSs; Fig. 2c their duration and Fig. 2d the relative MEP amplitude (i.e., median MEP amplitude percentage change with respect to global median across all states) corresponding to the trials associated with each state present at the time of stimulation. Overall, these results suggest that State 4 is an ER-FLBS for the MEP high-amplitude endpoint.

Endpoint-Related Fast-dynamic Large-scale Brain-states can be identified also with supervised learning approaches, such as classification or regression algorithms. By these approaches, we can train a model that directly predicts the endpoint variable given the signal. For example, Metsomaa et al. (2021) used a logistic regression classifier to separate high and low cortical excitability states from the pre-stimulus EEG spatiotemporal signal. The algorithm learns a set of spatiotemporal filters, which can be used to identify the excitability state. These approaches can be used not only with raw EEG signals but also with functional connectivity signals, for example (Syrjälä et al., 2021). Supervised learning approaches can also be used to identify patterns of activity, which will be then related to a behavioral endpoint (Guidotti et al., 2015), for example by correlating the accuracy of classification with the endpoint, thus establishing a relationship between the discrimination ability and the expected response. In this framework, another possible approach is to leverage on the high temporal resolution of EEG signals to train a classifier in each timepoint and localize when (and where) brain states differ and the span of this distinction (Grootswagers et al., 2017). This technique has been applied to decode the dynamics of grasping (Guo et al., 2021) and of object recognition (Cichy et al., 2014) using the EEG activity from all channels; the technique can also be extended to other time-varying measures such as dynamic functional connectivity.

In conclusion, the output of the off-line analysis will be, independently of the approach, one (or more) *reference* ER-FLBSs (Fig. 3a) linked to a given target endpoint. For the sake of simplicity and without loss of generality, we will in the following assume that only one *reference* ER-FLBS has been identified by the adopted off-line analysis.

5. Towards real-time identification of endpoint-related fast-dynamic large-scale brain-states

Once the *reference* ER-FLBS has been (off-line) identified, a real-time brain state-dependent stimulation protocol can be established. As stated in the "**Proposed conceptual definition of large-scale brain states**" section, all ER-FLBSs, and thus the *reference* ER-FLBS, must be such that when TMS is applied at their occurrence, this results in an improvement in the targeted endpoint. In fact, repeated TMS during presence of the *reference* ER-FLBS in the real-time measurement will change in line with that observed off-line.

As a paradigmatic example, we consider the case, already discussed in the off-line analysis section, in which the target endpoint is the amplitude of MEP and the *reference* ER-FLBS is a state of high functional connectivity between regions in the motor network (e.g., left M1 and SMA), as depicted in Fig. 3a. Thus, we expect higher MEP amplitude values when TMS at left M1 is delivered at the ER-FLBS. To detect such ER-FLBS in the data stream, algorithms to calculated dynamic functional connectivity in real time are required (Basti et al., 2022) together with an appropriate data preprocessing step. As raw streaming EEG data have an inherently low signal-to-noise ratio, the noise can easily become a bottleneck for efficient ER-FLBS detection. The non-neuronal noise can be suppressed efficiently with appropriate spatial filters, which can either be estimated directly from the streaming EEG data in an asynchronous parallel process (Mutanen et al., 2022) or adapted from pre-recorded training data, e.g., using independent component analysis and beamforming (Hernandez-Pavon et al., 2022). The streaming data is also a mixture of brain signals of interest and other activity that can be considered as neuronal noise. To highlight the ER-FLBS-relevant brain signals from the cortical nodes of interest, either anatomy-based (Hauk and Stenroos, 2014; Madsen et al., 2019) or functional-data-driven (Metsomaa et al., 2021; Nikulin et al., 2011) spatial filters could be applied to the multichannel data.

In Fig. 3b, we envision a pipeline to recognize the *reference* ER-FLBS in real time. In this pipeline, we assume that a spatial filter has been applied to sensor level (high-density, i.e., 128 channels or more) EEG data to derive brain-level signals (Fig. 3b bottom right). In practice, most brain state-dependent stimulation studies rely on sensor-level signals to extract brain-state information. Nevertheless, since the estimation of source activities from sensor-space data in real time can be performed with fast processing (Li et al., 2019), it is advisable considering source-level data to estimate functional connectivity. Indeed, source space data can alleviate some of the potential confounds of the sensor space analysis, e.g., assumptions that might not always hold due to inter-individual variability. Dynamic functional connectivity is thus estimated, and its time course (Fig. 3b bottom left) is used to compare it to the *reference* ER-FLBS, e.g., by adaptive threshold-based algorithms, and target the stimulation. The comparison can also be performed using a similarity metric, such as spatial correlation, between the current and the *reference* ER-FLBS, so that if the current state is similar to the *reference*, i.e., correlation is above a certain threshold, the stimulation is triggered. In the case of a machine-learning-based approach, the current signal will be the input of the trained machine-learning model, which will classify it as *reference* ER-FLBS or not, using the parameters fitted online, and then trigger the stimulation when the current datapoint is labeled as *reference* ER-FLBS.

An important aspect of the real-time detection of ER-LFBSs is whether the above pipeline, or similar ones that can be conceived to recognize the *reference* ER-FLBS with other methods, introduce any delay between the time at which the current brain state is being evaluated and the TMS-trigger timing. Usually, if the real-time analysis (or at least part of it) is performed by a standard computer, a variable delay of about 80 ms can be observed between the data segment used to estimate functional connectivity and the stimulation time (Vetter et al., submitted). This increases the risk for the network's connectivity to have already changed to another state when the stimulus is delivered. Therefore, to accurately target a specific brain state, the real-time *reference* ER-FLBS detection pipeline should run on a device optimized for real-time EEG processing. Furthermore, since small delays will always be observed, dedicated algorithms should predict the future evolution of the signal from its past in order to be able to estimate the *reference* ER-FLBS also in the near future. For this purpose, we have developed an algorithm based on deep learning (Pankka et al., 2021) that outperforms the autoregressive models traditionally used for the prediction (e.g., in Zrenner et al., 2018).

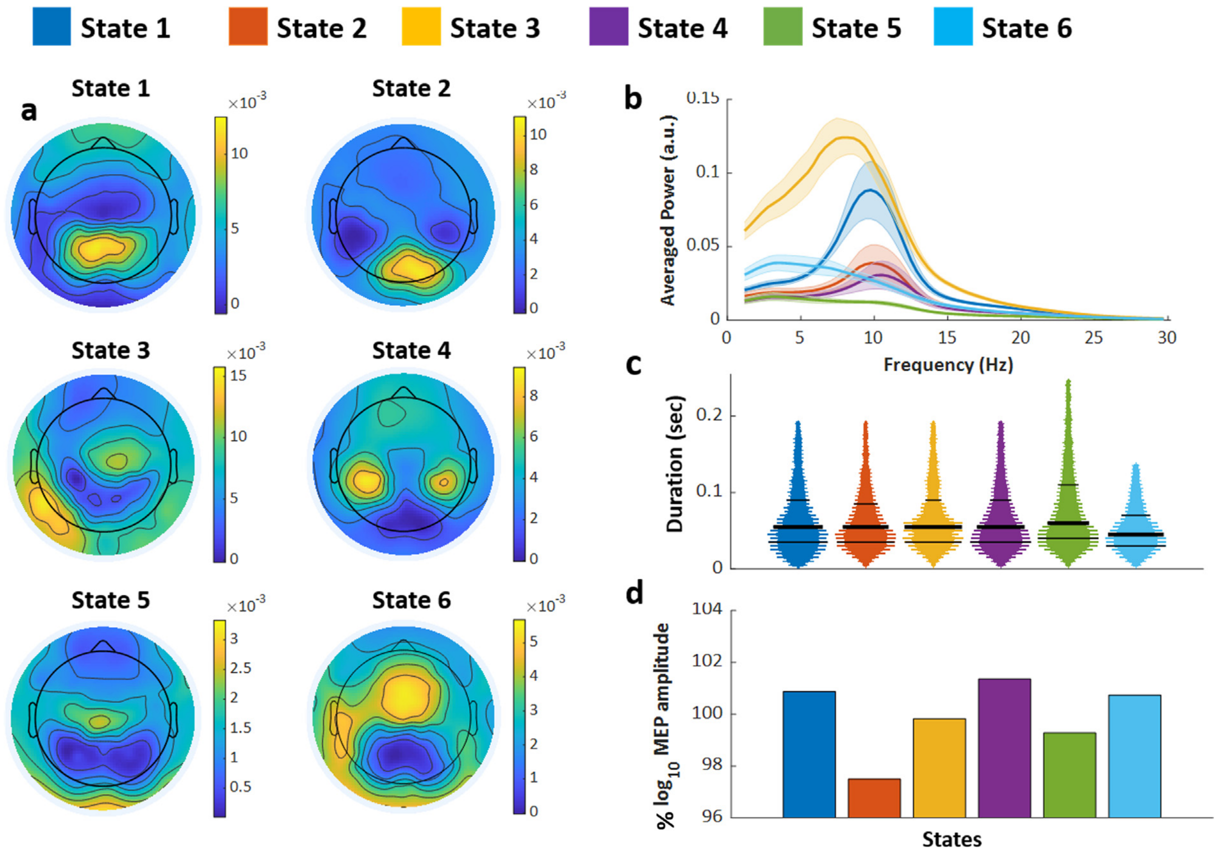

Fig. 2. Hidden Markov model approach to extract Endpoint-Related Fast-dynamic Large-scale Brain-states. Endpoint-Related Fast-dynamic Large-scale Brain States (ER-FLBSs) as identified by a time-delayed embedded Hidden Markov Model approach (Vidaurre et al., 2018) on a group of 8 healthy volunteers (data described in Metsomaa et al., 2021). (a) Topography of the power spectrum of the different states at the state peak frequency; (b) Averaged power spectrum of the states; (c) Distribution of duration of the states; (d) Relative percentage of median Motor Evoked Potential (MEP) amplitude (with respect to global median of MEP amplitudes) for the different states. State 4 shows statistically higher MEP amplitudes in comparison to states 2, 3, 5 and 6 (Wilcoxon Rank Sum, one star indicates $p < 0.05$ and two stars indicate $p < 001$; Bonferroni Correction for multiple comparisons).

6. Towards large-scale stimulation of Endpoint-Related Fast-dynamic Large-scale Brain-states

The application of real-time identification of ER-FLBSs in non-invasive neuromodulation protocols needs to be supported by the development of novel neurostimulation technologies. For instance, delivering complex sequences of stimuli to follow the rapidly changing neuronal dynamics across multiple brain sites is currently unattainable using traditional TMS devices. A promising new tool to overcome this limitation is the multi-locus TMS system (mTMS) (Koponen et al., 2018). mTMS is a magnetic stimulator capable of electronically changing the intensity, the location, and the orientation of the induced electric field in the brain without physically moving the coil set (coil set is sometimes referred to as transducer) (Nieminen et al., 2022; Souza et al., 2022). Such electronic control is achieved by simultaneously combining the electric fields generated on the cortical surface by multiple overlapping coils. With mTMS, it is possible to target nodes of a neural circuit with different parameters and within sub-millisecond intervals (Nieminen et al., 2019; Souza et al., 2021; Tugin et al., 2021). Electronic targeting also enables closed-loop automated stimulation protocols based on physiological feedback from EMG (Tervo et al., 2020) and EEG (Tervo et al., 2022) as endpoints. This demonstrates the applicability of flexible targeting for refining the understanding of ER-FLBSs in an offline mode, as well as for an online detection of the *reference* ER-FLBSs. For example, with mTMS, an FLBS alteration could be addressed in context of sensitivity of neuronal populations to the orientation of the induced electric field (Pieramico et al., 2023; Souza et al., 2022). Inversely, recruitment of larger number of neurons can be achieved by applying the TMS pulses with rotational fields (Roth et al., 2023), possibly reducing the variability in estimation of reference ER-FLBS.

7. Conclusion and future directions

In this paper, we introduce the conceptual definition of Endpoint-Related Fast-dynamic Large-scale Brain States (ER-FLBS) as brain states exhibiting fast temporal dynamics and a large-scale spatial distribution, together with being related to a targeted endpoint. While the aspects concurring to define ER-FLBS are not new in neuroimaging, binding them together in a unified concept opens new perspectives for advancing brain state-dependent stimulation. ER-FLBSs can reliably be derived from off-line analysis of EEG–TMS data and their definition is sufficiently broad to accommodate different methodological approaches for their identification with respect to several possible endpoints. A *reference* ER-FLBS can thus be off-line defined and, importantly, be detected in an on-line experiment such that its occurrence can be considered as a landmark in time (and space) to trigger brain stimulation. The specific on-line approach for the detection of the *reference* ER-FLBS depends on the type of ER-FLBS and on the strategy for its off-line identification. In any case, to ensure on-line data processing, a dedicated real-time hardware must be employed. The required

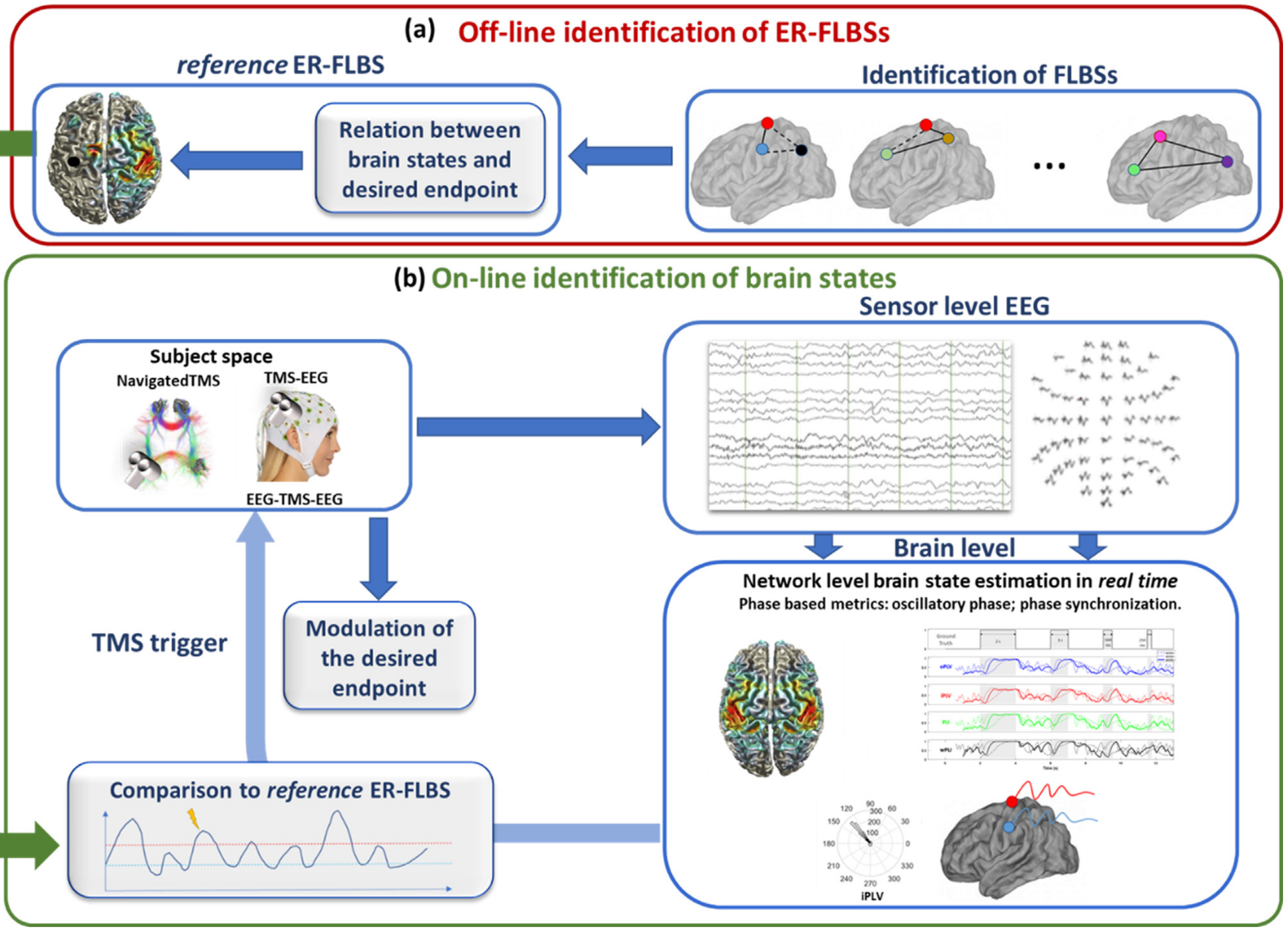

Fig. 3. Exemplary pipeline for the integration of off-line and on-line identification of Endpoint-Related Fast-dynamic Large-scale Brain-state. The pipeline considers Endpoint-Related Fast-dynamic Large-scale Brain-states (ER-FLBSs) identified by means of the functional connectivity approach. (a) Off-line identification: identify specific functional connectivity patterns as Fast-dynamic Large-scale Brain-states and assess which of them are related to the desired targeted endpoint to define one or more *reference* ER-FLBSs that we aim at targeting on-line. (b) On-line identification: estimate dynamic functional connectivity from electroencephalography (EEG) in real time and identify the presence of the *reference* ER-FLBS, deliver TMS when the *reference* ER-FLBS is present in order to enhance the probability of eliciting the desired endpoint (e.g., behavioral, peripheral, brain response).

temporal resolution of this hardware must be such that the *reference* ER-FLBS is detected within a timeframe smaller than its duration, which we hypothesize here to be at least tens of milliseconds. This will ensure that the stimulation is delivered when the *reference* ER-FLBS is still the ongoing brain state. Although not strictly necessary, it might be useful to also employ a dedicated software for on-line visualization of ongoing brain states. Ultimately, the real-time identification of the *reference* ER-FLBSs should inform adaptive closed-loop algorithms (described in detail in a companion paper Rösch et al.) which deliver complex neuromodulation protocols through an mTMS system for the large-scale modulation of FLBSs.

To determine the impact of the ER-FLBS-based strategy on brain state-dependent stimulation, further studies are needed in basic and clinical neuroscience. In this framework, this approach needs to be tested with other brain networks (outside motor cortex) and other endpoints (including behavioral endpoints). It will also be relevant to investigate whether a combination of local and long-range brain states or the co-occurrence of different ER-FLBS can be considered to be second-level brain states that can further improve the stimulation impact.

Finally, a new frontier for state-dependent stimulation could be to leverage network physiology approaches to expand the concept of ER-FLBS to brain–body states rather than just brain states.

Disclosures

RI has patents and patent applications on TMS technology. All other authors have no conflicts of interest.

Acknowledgements

This study is part of the ConnectToBrain project that has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant agreement No. 810377). VHS has received funding from the Academy of Finland (decision No. 349985). This concept paper should be considered in conjunction with the other three concept papers (Rissanen, Sinisalo et al., under review; Rösch et al., under review; Humaidan, Xu et al., under review) illustrating the ongoing activities that are carried out and that, altogether, constitute the overall investigation of the ConnectToBrain project.

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