



Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2009 ; 1: 4719–4722. doi:10.1109/IEMBS.2009.5334195.

Estimation of Brain State Changes Associated with Behavior, Stimulation and Epilepsy

Catherine Stamoulis^{*}, Elke Praeg, Bernard S. Chang, Shahid Bashir, and Alvaro Pascual-Leone

Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston MA 02215

Abstract

Brain state dynamics vary at different spatio-temporal scales with behavior, stimulation, and disease, and may be unobserved (latent). Using a state-space model framework and subspace identification, we estimated spatio-temporally localized, latent state changes associated with the application of transcranial magnetic stimulation (TMS), to assess the effect of stimulation on brain state dynamics. State appeared to be modulated by behavior in a spatially-specific manner and small-amplitude state fluctuations were temporally locked to stimulus presentations. In addition, during and following TMS, an overall, bilateral and spatially non-specific decrease in brain state was observed. We also estimated brain state changes during seizure evolution (independent of TMS), in focal and generalized seizures, which have very different epileptogenesis and propagation mechanisms, possibly resulting also in distinct spatio-temporal dynamics. Indeed, our preliminary results showed that in focal seizures, temporally localized dynamic state changes occur at least 1 min prior to seizure onset, with a decrease in steady-state followed by an increase which reaches a maximum during the ictal interval. In contrast, no such dynamic pattern was evident in state estimates during generalized seizures.

I. INTRODUCTION

The scalp electroencephalogram (EEG) provides large-scale information on brain activity and its modulation with behavior, disorders or disease, e.g., epilepsy, and stimulation, e.g., transcranial magnetic stimulation (TMS). All represent a type of perturbation to the steady-state brain activity and induce spatio-temporal state changes in the brain at different scales. For example, a visual task may result in localized state changes primarily in visual areas, whereas sleep results in a global change in brain state. Thus, in addition to the large-scale or global Up and Down state of the brain, there are also changes at smaller temporal and spatial scales. Some are observable in EEG recordings, e.g., eyes closed or inter-ictal versus ictal states in epilepsy, but there are also latent (unobservable) states. For example, epilepsy-related changes in brain activity may occur long before seizure onset, possibly due to an unobservable change in brain dynamics, including network synchronization or neuronal excitability.

There is significant interest in the estimation of dynamic changes in brain state associated with disease or stimulation, both for diagnostic purposes and for optimizing therapeutic stimulation. Specifically, in epilepsy brain state changes possibly occurring long before seizure onset, and potentially triggering a seizure, are not well understood. In order to predict a seizure and prevent its initiation, it is critical to estimate such precursive dynamic state changes. In the context of therapeutic stimulation, TMS is a well-established, non-invasive method for stimulating the

^{*}Corresponding author: cstamoul@bidmc.harvard.edu.

brain and modulating neuronal networks. It is increasingly used to study basic brain function, and to treat a wide range of brain disorders, from epilepsy to psychiatric conditions [3][8]. Its spatio-temporal optimization using EEG, to assess its effect on brain function and maximize its therapeutic potential, is relatively new but critical, since long-term effects and efficacy depend on the location and timing of TMS delivery. In this study, we present preliminary results on the estimation of brain state dynamics in healthy subjects undergoing TMS and in patients with focal and generalized seizures. We demonstrate that behavior, stimulation and epilepsy modulate state in a specific spatio-temporal manner, not directly observable in EEG signals.

II. METHODS

A. EEG Data and TMS Paradigm

All data were collected at Beth Israel Deaconess Medical Center. Scalp EEG recordings from 4 patients with focal seizures and one patient with generalized seizures were analyzed. The data were collected using a 42-channel system (20 cerebral channels), in the International 10–20 System Configuration, and were sampled at 500 Hz. Scalp EEG data from 4 healthy subjects undergoing TMS were collected at the Berenson Allen Center for Noninvasive Brain Stimulation. Data were collected with a 32-channel system (29 cerebral channels), in the 10-10 configuration, sampled at 1000 Hz. Baseline EEG recordings were obtained during the presentation of various visual stimuli, including pictures and a checkerboard, to establish a subject-specific baseline. Pseudorandomly timed TMS pulses were delivered over left primary motor cortex (M1), for motor and baseline conditions, and at approximately the location of channel P3 for visual conditions, at areas of highest motor response of contralateral M. abductor pollicis brevis, with the lowest stimulation intensity. TMS was delivered by means of a Magstim machine, and a figure eight 70 mm coil [9]. EEG recordings were obtained continuously for approximately 60 min (30 min pre-TMS delivery and 30 min during TMS). The intensity of the TMS pulses were subject-specific, based on the TMS motor threshold for each subject (for eyes open/closed, intensity was at 120% of the motor threshold, for all other visual and motor conditions at 90% of the motor threshold). The 60 Hz noise and its harmonics typically seen in EEG signals was filtered out in all data, using a 2nd order elliptical stopband filter with 1.5 Hz bandwidth. The data were filtered in both directions to eliminate potential phase shifts associated with the non-zero phase of the filter. The muscle artifact often seen in EEG signals during seizures were suppressed using matched-filtering, when independent artifact signatures were available from quiescent periods, or by eliminating the highest frequency mode, when the artifact was coupled to the seizure signal [15].

B. TMS Artifact Suppression

Application of TMS results in high-amplitude artifacts in EEG recordings, unrelated to normal brain activity, for approximately 20–30 ms following stimulation [13]. In this study we estimated the duration of the TMS effect to be approximately 20 ms. The TMS-induced current saturates the EEG amplifiers, resulting in artifacts coupled to the true brain activity. Conventional filtering is inefficient since the TMS pulse is approximately a delta function and thus band-limited only by the amplifier bandwidth. Therefore, the contribution of the TMS pulse to the EEG signal cannot be decoupled through bandpass filtering. Other off-line techniques have been proposed, including the application of a Kalman filter [13]. In that study, the EEG signal was modeled as a linear superposition of a deterministic TMS-related component, and a decoupled true brain activity component. Here, to eliminate the TMS artifact, we followed a similar approach to [13], included the TMS signal as an impulse input term in the dynamic state model (Equation 2) and modeled the time-dependent stochastic effect of TMS as a temporally localized change in the variance of the output noise term $\vec{e}(t)$, i.e., assuming a 20 ms TMS effect. However, we estimated the state of the system $\hat{x}(t)$ and

subsequent artifact-free estimate of the EEG signal $\hat{y}(t)|\hat{x}(t)$ using subspace identification. An example of the artifact-free signal is shown in Figure 5.

C. State-Space Estimation

The state-space model is widely used to estimate the unobserved (latent) *state* of a system, given a set of observations and an assumed initial state. The model is described by two equations, the state and the observations equations:

$$\begin{aligned}\vec{x}(t+1) &= \mathbf{F}\vec{x}(t) + \mathbf{G}\vec{u}(t) + \vec{w}(t) \\ \vec{y}(t) &= \mathbf{H}\vec{x}(t) + \mathbf{D}\vec{u}(t) + \vec{e}(t)\end{aligned}\quad (1)$$

where for N sensors, $\vec{x}(t) = [x_1(t), x_2(t), \dots, x_N(t)]$ is the system state at time t , $\vec{y}(t)$ is the corresponding measurement vector, $\vec{u}(t)$ is the system input, and $w(t)$, $e(t)$ are independent system and measurement noise terms, respectively, assumed to be zero-mean and with

covariance matrices \sum_w^2 and \sum_e^2 , respectively. State is assumed to be a continuous, neurophysiologically relevant but unobserved parameter. To model the stochastic, but temporally localized effect of TMS on the EEG signal, we assumed the approach in [13] and included an additional term in the measurement noise covariance for the assumed duration of the TMS effect (20 ms), i.e.,

$$\sum_e^2(t) = \begin{cases} \sum_e^2(t), & t > t_{TMS} + 0.02, t < t_{TMS} \\ \sum_e^2(t) e^{-\gamma(t-t_{int})}, & t_{int} \in [t_{TMS}, t_{TMS} + 0.02] \end{cases}$$

where γ , the decay coefficient was directly estimated from the EEG data and t_{int} the assumed duration of the TMS pulse. Matrices \mathbf{F} , \mathbf{G} , \mathbf{H} , and \mathbf{D} are the model matrices to be estimated. In seizure-induced EEG signals, for simplicity we assumed $\vec{u}(t) = 0$, although one may assume that some unknown non-zero input, such as an external auditory or visual stimulus may trigger a seizure. In the case of repeated TMS stimulation, the input $\vec{u}(t)$ was assumed to be an impulse, i.e., a delta function such that:

$$\vec{u}(t - t_{TMS,n}) = \begin{cases} 1, & \text{if } t = t_{TMS,n}, n = 1, 2, \dots, N_p \\ 0, & \text{otherwise} \end{cases}$$

where $t_{TMS,n}$ is the time at which a TMS pulse is applied, and N_p is the total number of pulses. There is a wide range of methods used to estimate the state vector [7][10][18]. In this study we used subspace identification (the N4SID algorithm) to solve for the matrices in the state space model, directly from input-output data using linear algebra tools [18]. Another requirement of this estimation is to choose the order of the state space model. There are several studies that address the problem of model order, using several criteria and error measures to assess the adequacy of the selected model [16][6]. Using the Akaike Information Criterion (AIC), we estimated that order 3 and 5 models for the seizure and TMS data, respectively, were adequate at least for preliminary analysis. Finally, given that we expect that both seizure evolution, (particularly focal seizures) and area-specific TMS result in differential activation of the brain, we estimated the state vector for each channel separately, instead of assuming a single-input (or zero-input), multiple-output system.

III. ANALYSIS

A. Seizure data analysis

Estimation of dynamic state during seizure evolution, provides additional information not necessarily evident from the raw EEG signals (latent). Figure 1 shows an example of EEG and estimated state signals at 4 channels in different areas of the brain, during a 4 min pre- to post-ictal segment. The lowest order state vector (order 1) is shown. There is a temporal correlation between the seizure and the dynamic brain state, particularly in frontal areas, where there is a specific state signature, bilaterally (channels F7 and F8 are in opposite hemispheres) with a clearly defined decrease in state at about 50 s and gradual increase, reaching a maximum during the ictal interval. Interestingly, this signature is not as well defined in distant from the focus areas, as seen in the state variability in the occipital areas (channel O2). In this channel, there is an overall state increase pre-ictally and during the ictal interval, which decreases after seizure termination. In contrast, the decrease in state in frontal channels starts during the ictal interval. Similar results were obtained for all analyzed focal seizures. State may represent different parameters, including a measure of desynchronization/hypersynchronization of neuronal activity, non-stationarity and thus time-dependent frequency content; of brain oscillations, and even a measure of randomness or entropy in neuronal networks. Depending on the order of the model, several state parameters can be estimated simultaneously. In the case of seizures this estimate may represent the progressive increase in abnormal network and brain activity hypersynchronization.

We also examined potential differences in state dynamics during generalized seizures. Mechanisms of epileptogenesis are quite different for the two seizure types. Figure 2 shows the estimated state vector for a generalized seizure.

In contrast to focal seizures, there was no area-specific or pattern-specific signature of state change during either of the two analyzed generalized seizures. Instead, an overall increase in state was observed starting ~100 s prior to seizure onset in the left hemisphere and ~90 s in the right hemisphere, which persisted following seizure termination. The difference in state dynamics may reflect the onset, localization and propagation differences between the two types of seizures.

B. TMS-EEG data analysis

We estimated changes in dynamic state during the presentation of visual stimuli, in baseline recordings and during TMS. An example of the estimated state vector from baseline EEG is shown in Figure 3. An overall, area-specific variation in state during the pre-TMS 23 min recordings, was observed. Also, small-amplitude state changes were estimated, particularly in frontal areas, which appeared to be temporally locked to the presentation of visual stimuli.

We also compared the estimated state at neighboring channels, as shown in Figure 4, as a function of hemisphere and brain area. Results were averaged over subjects.

State correlations within a particular brain area was highest during the presentation of visual stimuli and decreased in their absence, particularly towards the last 3–4 min of the recording session. The temporally-averaged state correlation coefficient varied in different brain areas and between the two hemispheres, with higher correlations between state signals in left centro-parietal channels ($\rho = 0.753$, CI:[0.697,0.775]) and lower correlations between corresponding states in right centro-parietal and parietal channels ($\rho = 0.418$, CI:[0.387,0.518]). We finally compared state estimates to corresponding state vectors during TMS delivery. An example is shown in Figure 5. Baseline and TMS-modulated state vectors are compared in Figure 6.

There is a consistent large-scale decrease in brain state during TMS application, bilaterally and non-specifically at different brain areas. However, in right frontal and fronto-central areas, state reaches a minimum approximately 450 s following the delivery of the first TMS pulse and subsequently slowly increases. This trend is less evident and occurs later in parieto-central and parietal areas. It also occurs later in corresponding areas of the left hemisphere, although there was significant variability in the location of this minimum among subjects, in the range 400–650 s.

IV. DISCUSSION

We have presented preliminary results on the estimation of dynamic brain state, at the second/minute temporal scale, in baseline EEG recordings and during TMS delivery, in healthy subjects, and during focal and generalized seizure evolution in epilepsy patients. State was assumed to be an unobserved parameter of brain dynamics and could represent a number of neurophysiological parameters, including network synchronization, excitability, temporally-varying frequency of brain oscillatory activity, etc. Stimulation resulted in a global decrease in brain state and progressive recovery of baseline state started at different times depending on the brain region, but typically at least 7–8 min following the initial delivery of TMS. In baseline EEG recordings, small-scale state fluctuations were temporally locked to the stimulus presentation. In epilepsy patients, state could represent a different parameter of brain dynamics, such as hypersynchronization of neuronal activity. In both focal and generalized seizures state increased prior to seizure onset. In focal seizures, state reached a maximum during the ictal interval and subsequently decreased. In contrast, in generalized seizures, state progressively increased past the seizure termination, possibly reflecting different onset or propagation mechanisms. These results suggest that information on the modulation of brain dynamics by behavior, disease and stimulation is encoded in the EEG signal beyond its amplitude and spectrum, and may be estimated using a state-space framework.

References

1. Carmeli C, Knyazeva MG, et al. Assessment of EEG Synchronization Based on State-Space Analysis. *Neuroimage* 2005;25:339–354. [PubMed: 15784413]
2. Contreras D, Steriade M. Cellular Basis of EEG Slow Rhythms. *J Neurosci* 1992;15:604–622. [PubMed: 7823167]
3. Hallett M. Transcranial Magnetic Stimulation and the Human Brain. *Nature* 2000;406(6792):147–150. [PubMed: 10910346]
4. Iasemidis LD, Shiau DS, Sackellares C, Pardalos PM, Prasad A. Dynamical Resetting of the Human Brain in Epileptic Seizures. *IEEE Trans Biomed Eng* 2004;51(3):493–506. [PubMed: 15000380]
5. Iramina K, Maeno T, Kowatari Y, Ueno S. Effects of Transcranial Magnetic Stimulation. *IEEE Trans Magn* 2002;38(5):3347–3349.
6. Isaksson A, Wennberg A, Zetterberg LH. Computer Analysis of EEG Signals with Parametric Models. *Proc IEEE* 1981;69:451–461.
7. Kalman RE. A New Approach to Linear Filtering and Prediction Problems. *Trans, of the ASMEJ of Basic Engineering* 1960:33–45.
8. Kobayashi M, Pascual-Leone A. Transcranial Magnetic Stimulation in Neurology. *Lancet In Neurology* 2003;2(3):1450–1456.
9. Kobayashi M, Theoret H, Pascual-Leone A. Suppression of Ipsilateral Motor Cortex Facilitates Motor Skill Learning. *European Journal of Neuroscience* 2009;29(4):833–836. [PubMed: 19200062]
10. Ljung, L.; Soderstrom, T. *Theory and Practice of Recursive Identification*. MIT Press; 1986.
11. Lo P, Chung W. An Approach to Quantifying the Multi-Channel EEG Spatial-Temporal Feature. *Biom Journal* 2000;42(7):901–916.
12. Meier R, Kumar A, Schulze-Bohage A, Aertsen A. Comparison of Dynamical States of Random Networks with Human EEG. *Neuro-computing* 2007;70:1843–1847.

13. Morbidi F, Garulli A, Prattichizzo D, Rizzo C, Rossi S. Application of Kalman Filter to Remove TMS-Induced Artifacts from EEG Recordings. *IEEE Trans Control Sys Tech* 2008;16(6):1360–1366.
14. Pardalos PM, Yatsenko V, Sackellares JC, Shiao DS, Chaoval-itwongse W, Iasemidis L. Analysis of EEG Data Using Optimization, Statistics, and Dynamical System Techniques. *Computational Statistics and Data Analysis* 2003;44(1–2):391–408.
15. Stamoulis, C.; Chang, BS. Application of Matched-Filtering to Extract EEG Features and Decouple Signal Contributions from Multiple Seizure Foci in Brain Malformations. *IEEE Proc. 4th International Conference on Neural Engineering*; 2009.
16. Steinberg HW, Gasser T, Franke J. Fitting AR Models to EEG Time Series: An Empirical Comparison of Estimates of the Order. *IEEE Trans Acoust Speech, Signal Process* 1985;ASSP-33(1):143–150.
17. Tarvainen MP, Hiltunen JK, Ranta-aho PO, Karjalainen PA. Estimation of Nonstationary EEG with Kalman Smoother Approach. *IEEE Trans Biomed Eng* 2004;51(3):516–524. [PubMed: 15000382]
18. Van Overschee, P.; De Moor, B. *Subspace Identification of Linear Systems*. Kluwer Academic Publishers; 1996.

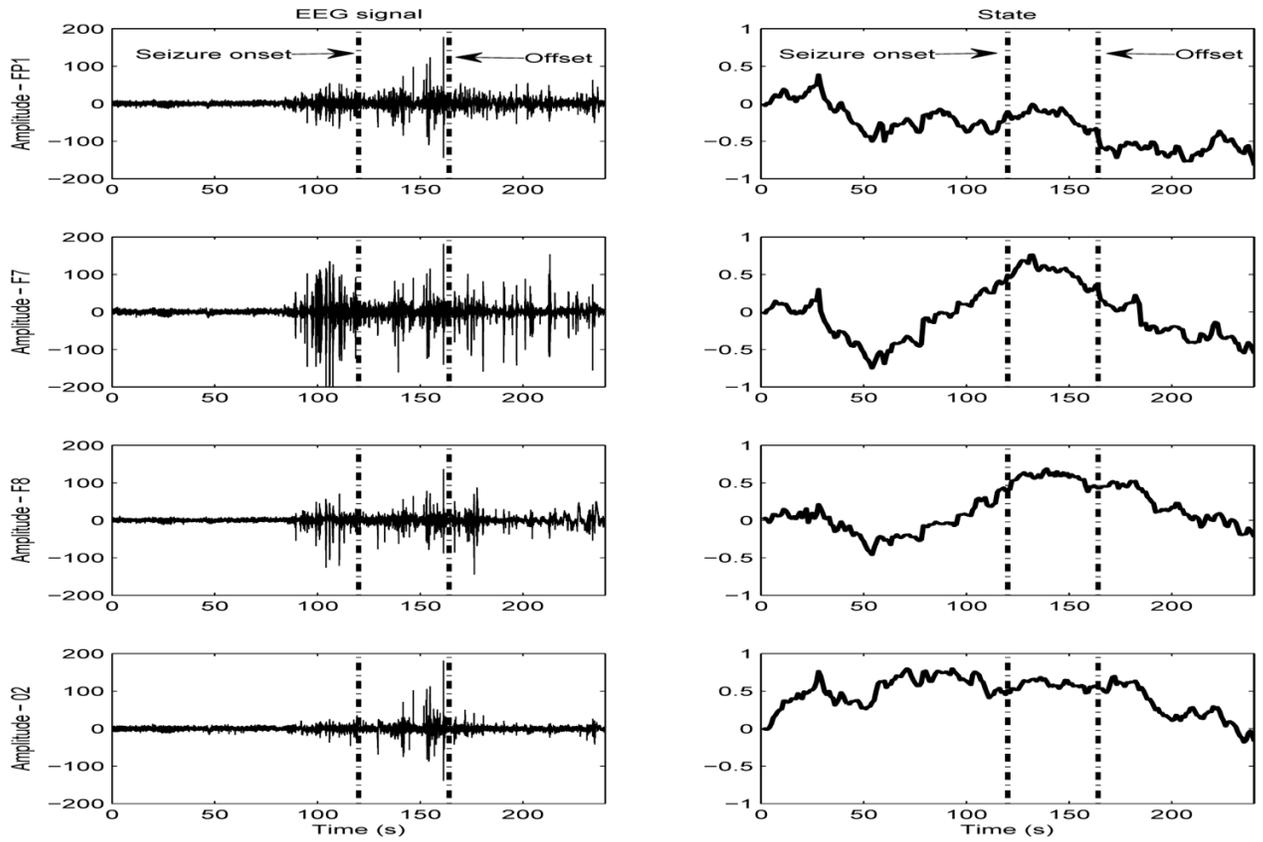


Fig. 1. EEG recordings at 4 channels (FP1, F7, F8, O2) and corresponding normalized state vectors during a seizure with a visually identifiable focus.

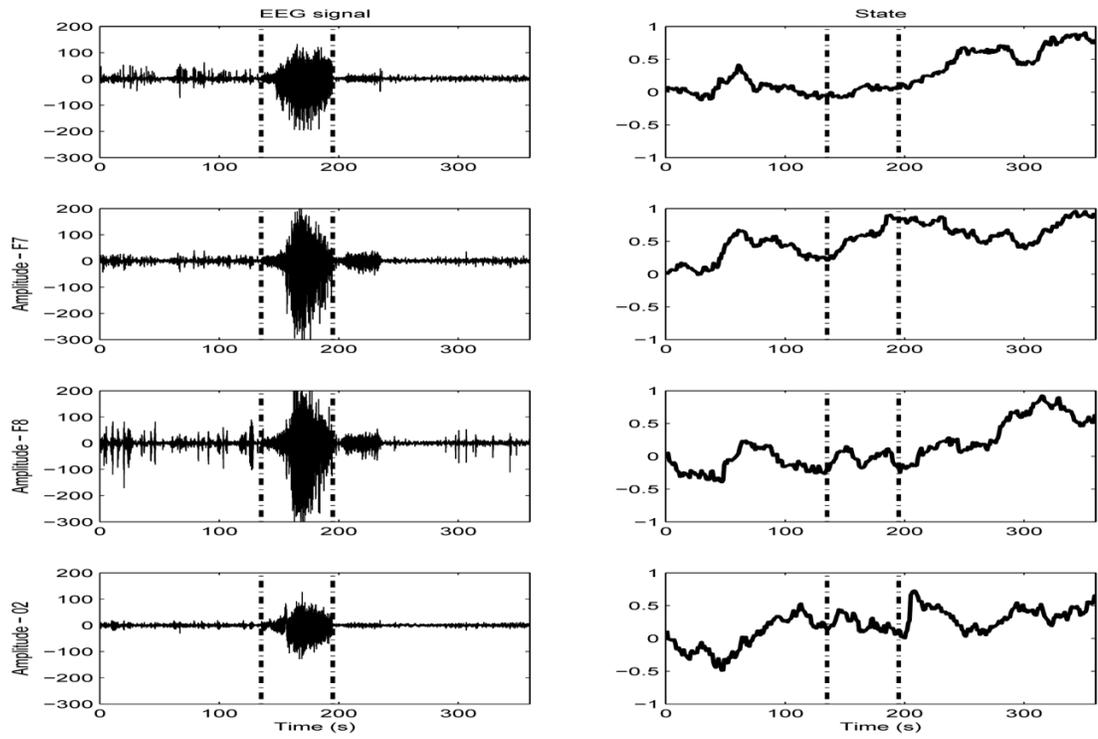


Fig. 2.
EEG recordings and corresponding state vector during a generalized seizure.

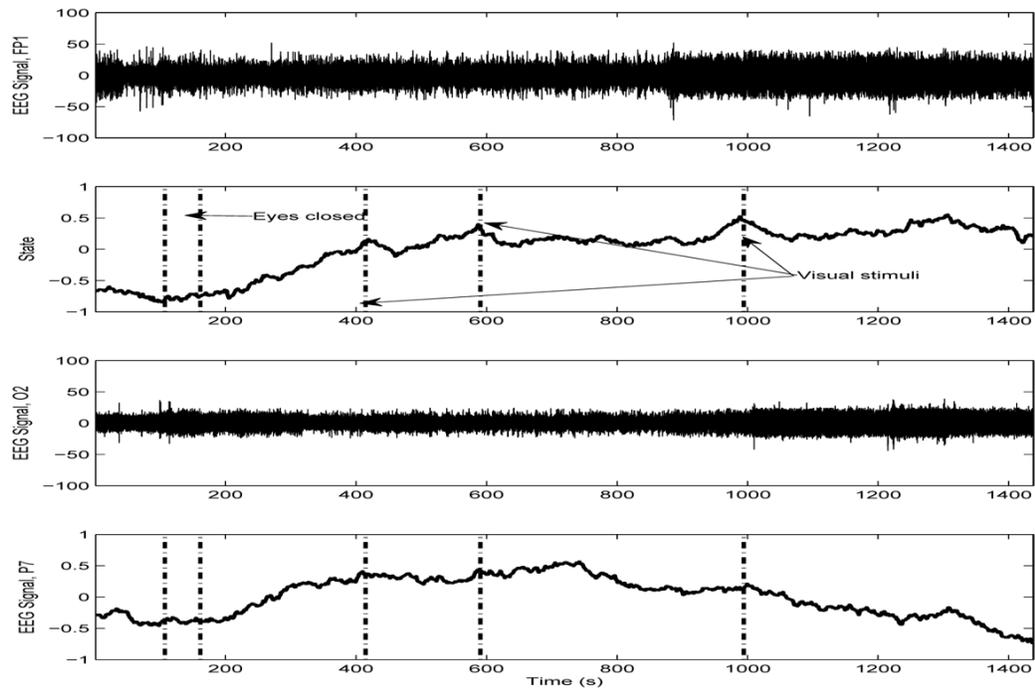


Fig. 3. Pre-TMS EEG recordings and respective estimated dynamic state vectors, at channels FP1 and P7, i.e., in frontal and parietal areas. Brain state vectors differ significantly in the latter 400 s of the recording.

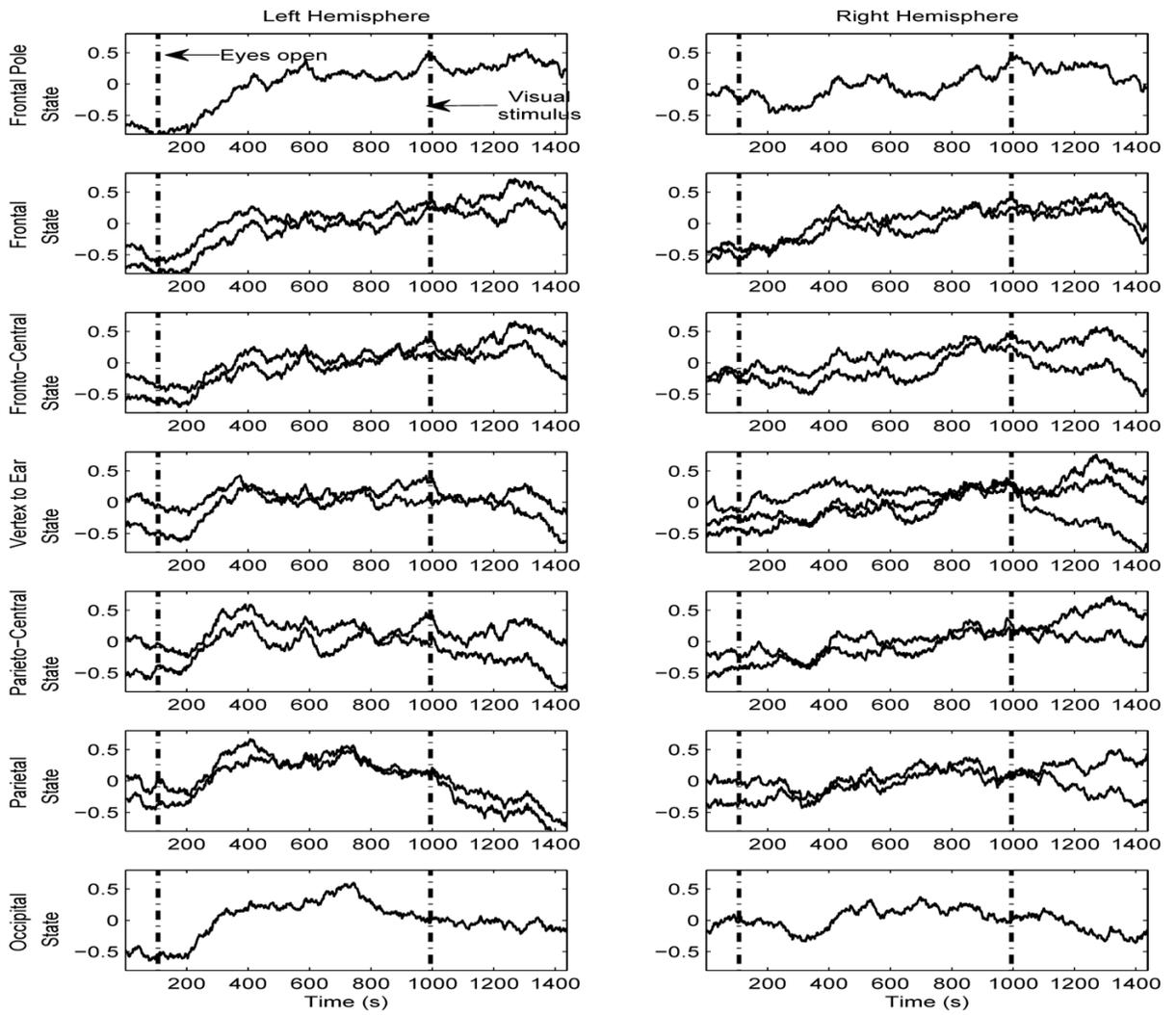


Fig. 4. State variability at different brain areas, for left and right hemispheres.

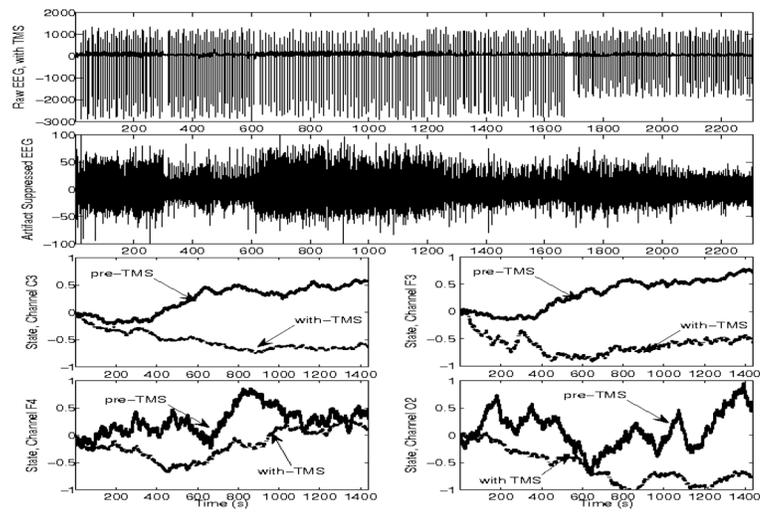


Fig. 5. Raw EEG signal during TMS, artifact-suppressed signal, and state estimates pre-TMS and during TMS at different channels and brain areas. The raw and TMS-suppressed signals are at different scales (20:1).

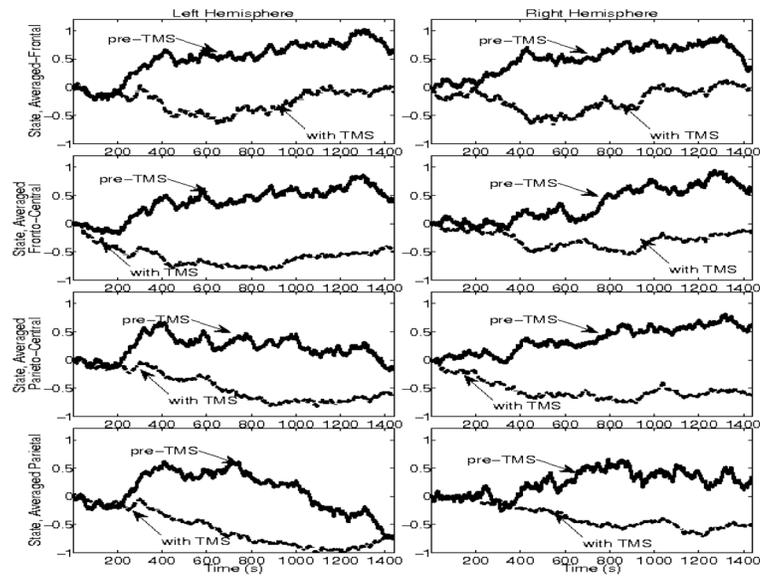


Fig. 6. Brain state estimates pre-TMS (solid) and during TMS (dashed), averaged over all subjects and channels in particular brain areas, for left and right hemispheres, respectively.