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Phase-Based Measures of Cross-Frequency Coupling in Brain Electrical Dynamics under General Anesthesia

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***Abstract*— The state of general anesthesia (GA) is associated with an increase in spectral power in scalp electroencephalogram (EEG) at frequencies below 40 Hz, including spectral peaks in the slow oscillation (SO, 0.1−1 Hz) and α (8−14 Hz) bands. Because conventional power spectral analyses are insensitive to possible cross-frequency coupling, the relationships among the oscillations at different frequencies remain largely unexplored. Quantifying such coupling is essential for improving clinical monitoring of anesthesia and understanding the neuroscience of this brain state. We tested the usefulness of two measures of cross-frequency coupling: the bispectrum-derived SynchFastSlow, which is sensitive to phase-phase coupling in different frequency bands, and modulogram analysis of coupling between SO phase and α rhythm amplitude. SynchFastSlow, a metric that is used in clinical depth-of-anesthesia monitors, showed a robust correlation with the loss of consciousness at the induction of propofol GA, but this could be largely explained by power spectral changes without considering cross-frequency coupling. Modulogram analysis revealed two distinct modes of cross-frequency coupling under GA. The waking and two distinct states under GA could be discriminated by projecting in a two-dimensional phase space defined by the SynchFastSlow and the preferred SO phase of α activity. Our results show that a stereotyped pattern of phase-amplitude coupling accompanies multiple stages of anesthetic-induced unconsciousness. These findings suggest that modulogram analysis can improve EEG based monitoring of brain state under GA.**

I. Introduction

General anesthesia (GA) is a drug-induced condition comprised of unconsciousness, analgesia, amnesia, and immobility, with maintanence of physiological stability [1]. Understanding changes in brain network dynamics induced by anesthetic drugs is crucial for tracking the state of the brain under GA and for gaining insights into how these drugs affect neuronal circuits. The electroencephalogram (EEG) is the method most commonly used in humans for tracking the state of the brain under GA. Spectral analysis of EEG recordings led to the discovery of systematic changes in the power in specific frequency bands associated with GA, including increases in δ (1-4 Hz), θ (5-8 Hz), α (8-14 Hz), β (12-30 Hz) and γ (30-80 Hz) [2], [3]. Such analysis treats oscillations within each frequency band independently, ignoring correlations in phase or amplitude between rhythms at different frequencies. Cross-frequency coupling is potentially an additional source of information about brain network dynamics that could be useful for identifying dynamical states [3].

Power spectral measures are invariant with respect to changes in the complex phase of a signal's Fourier transform. It is thus natural to consider measures that are sensitive to signal phase. Bispectral analysis measures correlation in the phases of oscillation at different frequencies. Bispectrum-based statistics have been used in quantitative clinical depth-of-anesthesia monitors, in a manner that compares the bispectrum across broad low- and high-frequency ranges [4]. A second type of cross-frequency correlation is phase-amplitude coupling, in which the amplitude of activity in one band depends systematically on the phase of a lower frequency rhythm [5]. Modulogram analysis measures phase-amplitude coupling in a time-resolved fashion.

We compared power spectral, bispectral and modulogram analyses for discriminating distinct brain states associated with GA. To capture the full range of dynamical states, we analyzed EEG recordings from study subjects anesthetized gradually, with progressively increasing concentrations of propofol over a period of ~ 75 min. We used a behavioral measure of responsiveness to auditory stimuli to track the subject's level of arousal with $\sim$10 s temporal resolution [6]. Our results reveal two distinct modes of phase-amplitude coupling corresponding to shallow and deep planes of GA, respectively. Modulogram analysis is thus a potentially valuable complement to power spectral and bispectral measures currently used to characterize depth of anesthesia.

II. Methods

A. Subjects and recordings

Following approval from the Massachusetts General Hospital Human Research Committee, we induced and allowed recovery from GA in healthy volunteers using the intravenous anesthetic propofol. For the anesthetic induction, we increased the targeted effect-site concentration of propofol in stepwise fashion to levels of 0, 1, 2, 3, 4, and 5 μg/ml every 14 minutes using a computer controlled infusion [7], [8]. Subjects listened to a series of pre-recorded sounds

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consisting of their name, affectively-neutral words, or a train of clicks, and responded to sounds from each category with a button press. We recorded button press times, and used the loss of button responses as an indicator of loss of consciousness (LOC). We referred to the propofol concentration where the subject lost consciousness as C_{LOC}. We then reduced the propofol concentration in a stepwise fashion to concentrations of $C_{LOC}-0.5$, $C_{LOC}-1.0$, and $C_{LOC}-1.5$ μg/ml, and 0 μg/ml, for 14 minutes each. We recorded 64-channel EEG continuously during this time (BrainAmp MRPlus, BrainProducts, GMBH). We used the resumption of button press responses to the ongoing auditory task as an indicator of return of consciousness (ROC). We analyzed the behavioral response data using a Bayesian approach to compute the instantaneous posterior distribution of response probability and corresponding confidence intervals [9], [6]. In this paper, we analyze a subset of the data including n = 3 subjects to demonstrate the application of bispectral and phase-amplitude modulation analysis methods, and their utility for discriminating between different states of GA.

B. SynchFastSlow analysis

We computed SynchFastSlow following the procedures in [4]. In brief, we divided the data set into epochs lasting 33 s, and further divided each epoch into 16 non-overlapping sub-epochs. In each sub-epoch, we estimated the signal Fourier transform in the range 1-47 Hz with 0.5 Hz resolution with a single taper using the Chronux routine `mtfftc` [10]. We estimated the bispectrum by averaging a third-order moment of the spectrum over all sub-epochs, $B(k_1,k_2) = |\langle X(k_1)X(k_2)X^*(k_1+k_2)\rangle|$. We then found SynchFastSlow $\equiv \log_{10}\frac{\sum_{\Omega_{fast}} B(k_1,k_2)}{\sum_{\Omega_{all}} B(k_1,k_2)}$, where

$$\Omega_{all} \equiv \{k_1,k_2|k_1>0, k_2>k_1, k_1+k_2 \leq 47\text{Hz}\},$$
$$\Omega_{fast} \equiv \{k_1,k_2|k_1>0, k_2>k_1, k_1+k_2 \in [40,47\text{Hz}]\}. \quad (1)$$

For purposes of comparison, we computed PowerFastSlow, a phase-free analog of SynchFastSlow that relies on power spectral information alone [11]: $PowerFastSlow \equiv \log_{10}\frac{\sum_{\Omega_{fast}} P(k_1,k_2)}{\sum_{\Omega_{all}} P(k_1,k_2)}$ where $P(k_1,k_2) \equiv \langle |X(k_1)|^2|X(k_2)|^2|X(k_1+k_2)|^2\rangle^{1/2}$. Our definition of PowerFastSlow differs slightly from that used in [11].

C. Cross-frequency coupling analysis

To characterize coupling between the phase of the slow oscillation (SO; $0.1-1$ Hz) and the amplitude of α ($8-14$ Hz) oscillations, we constructed a time-varying phase-amplitude modulogram, $M(t,\phi)$, which describes the relative α amplitude at a particular phase at each SO cycle. Given an EEG signal, $x(t)$, sampled at rate $F_s = 250$ Hz, we first removed ultra-low-frequency drift by subtracting a least-square-error spline fit to the signal with knots placed at 2 min intervals. Next we applied a band-pass filter to extract the rhythmic component within each frequency band of interest, $x_b(t), b \in \{\alpha, SO\}$. We used symmetric finite impulse response filters designed using a least-squares approach (SO: passband 0.1-1 Hz, transition bands 0.085-0.1 and 1-1.15 Hz, $\geq$ 17 dB attentuation in stop bands, order 2207 at 250 Hz; α: passband 8-13.9 Hz, transition bands 5.9-8 and 13.9-16 Hz, $\geq$ 60 dB attentuation in stop bands, order 513). Next we used a discrete Hilbert transform to compute the complex analytic signal, $z_b(t)$, satisfying $\text{Re}[z_b(t)] = x_b(t)$. The analytic signal provided the instantaneous α amplitude, $A(t) = |z_\alpha(t)|$, and SO phase, $\psi(t) = \arg[z_{SO}(t)]$.

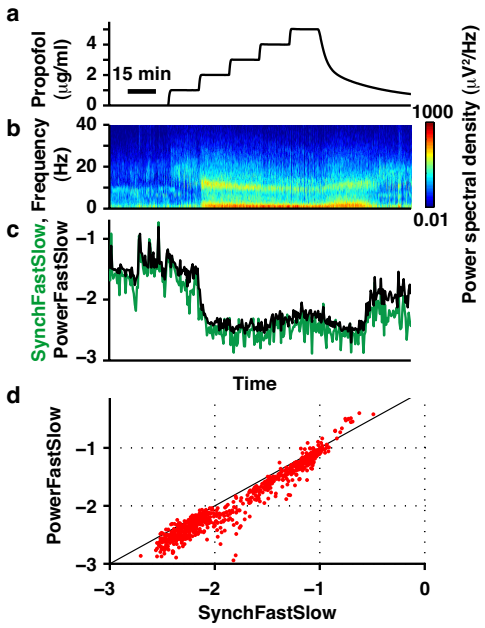

Fig. 1. (a) Predicted propofol effect-site concentration. (b) Time-frequency spectrogram from a frontal electrode. (c) SynchFastSlow (green) and PowerFastSlow (black) track the increase in low-frequency power at loss of consciousness. (d) Scatter plot showing strong correlation between SynchFastSlow and PowerFastSlow; points represent distinct 30 s epochs in three subjects.

We computed the modulogram by assigning each temporal sample to one of 18 equally spaced phase bins based on the instantaneous value of $\psi(t)$, then averaging the corresponding values of $A(t)$ within a 2-minute epoch:

$$M(t,\phi) = \frac{\int_{t-\frac{\delta t}{2}}^{t+\frac{\delta t}{2}}\int_{\phi-\frac{\delta\phi}{2}}^{\phi+\frac{\delta\phi}{2}} A(t')\delta(\psi(t')-\phi')d\phi'dt'}{2\pi\int_{t-\frac{\delta t}{2}}^{t+\frac{\delta t}{2}} A(t')dt'}, \quad (2)$$

where $\delta t = 120$ s and $\delta\phi = \frac{2\pi}{18}$. Note that $\int_{-\pi}^{\pi} M(t,\phi)d\phi = 1$, so that $M(t,\phi)$ is a normalized density of α amplitude over all SO phases.

To quantify the strength of modulation we defined the modulation index [5], $MI(t)$, as the Kullback-Leibler divergence, in bits, between $M(t,\phi)$ and a uniform phase distribution over the interval $[-\pi,\pi)$:,

$$MI(t) = \int_{-\pi}^{\pi} d\phi \frac{M(t,\phi)}{2\pi}\log_2 M(t,\phi). \quad (3)$$

We tested the statistical significance of the observed $MI(t)$ by a permutation test. We drew 200 random time shifts, Δt, from a uniform distribution on the interval $[-60, 60\ s]$. This

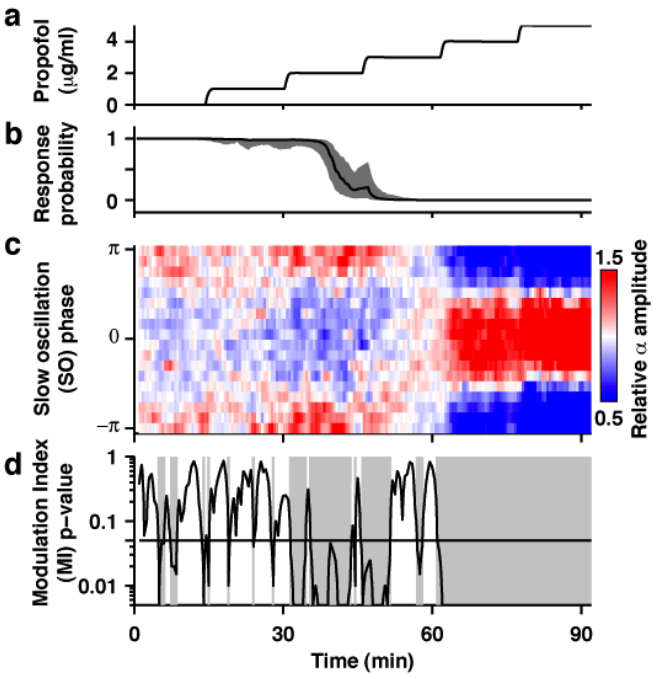

Fig. 2. (a) Time course of predicted propofol effect-site concentration. (b) Probability of response to an auditory stimulus, computed using a Bayesian method. Shaded region indicate 95% confidence interval. (c) Modulogram, $M(t,\phi)$, showing relative α band amplitude vs. SO phase within 2-min epochs. (d) P-value of the modulation index, $MI(t)$, determined by a shuffle control procedure; gray shading indicates statistically significant (p<0.05) epochs.

range of time shifts is longer than the coherence time of individual slow oscillations, but shorter than the duration of each experimental condition. We then used the above method to compute $MI_{perm}(t)$ using the original SO phase, $\psi(t)$, and the shifted α amplitude, $A(t-\Delta t)$. $MI(t)$ was judged significant if it was larger than 95% of the permuted values. We defined the preferred phase of the α rhythm as: $\Phi(t) \equiv \arg\left[\int_{-\pi}^{\pi} d\phi e^{i\phi} M(t,\phi)\right]$.

III. Results

A. Drug level-dependent changes in SynchFastSlow can be explained by changes in power alone, without phase

We compared the SynchFastSlow with a similar measure, PowerFastSlow, that is a function of the power spectrum and therefore completely insensitive to phase coupling. Following loss of consciousness, these measures decreased by 3.8 and 5.6 standard deviations, respectively, relative to their baseline value ($p < 10^{-15}$ Wilcoxon rank-sum test). However, we found the two measures were virtually identical to each other in terms of their full time course ($r = 0.98, p < 10^{-10}, n = 3$ subjects; Fig. 1d). Thus, although SynchFastSlow does reflect the increase in spectral power below 40 Hz under anesthesia, it does not contain significant additional information about non-trivial phase-phase coupling structure.

B. Modulogram analysis reveals phase-amplitude coupling

We reasoned that because both SO and α band EEG rhythms increase in power around the time of loss of consciousness, the two rhythms may share a neural mechanism. We tested this using modulogram analysis (see Methods) to visualize the time course of phase-amplitude coupling between these two frequency bands throughout our experimental recordings (Fig. 2). This analysis revealed strong modulation of the amplitude of α band oscillations by $> 60\%$ of its average amplitude on individual SO cycles after averaging over a 2-minute analysis window (Fig. 2c). Using a permutation control analysis (Fig. 2d) we found that the modulation index was statistically significant (magnitude larger than 95% of permuted controls) in 70% of unconscious epochs under GA, in which subjects did not respond to auditory stimuli ($MI = 0.048 \pm 0.076$ bits (mean $\pm$ s.d.), $n = 3$ subjects, 266 minutes total). The modulation was significant in only 17.3% of control epochs recorded before the onset of propofol ($MI = 0.0070 \pm 0.0034$ bits, $n = 3$, 64 minutes, $p < 10^{-8}$ for difference of medians, Wilcoxon rank-sum test).

At low propofol doses near the threshold for loss of consciousness, we noted an "Anti-Phase" pattern of coupling in which α band oscillations increased during the surface-negative phase of the slow oscillation. By contrast, at deeper anesthetic planes induced by increased propofol concentration, we observed an opposite pattern of phase-amplitude coupling. Here the α amplitude is largest at the surface-positive phase of the SO, and the coupling is thus "In-Phase."

C. Combined power spectral and modulogram analysis distinguishes three modes of brain electrical dynamics

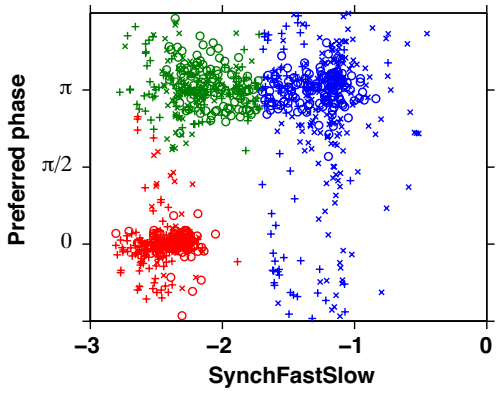

Fig. 3. Two-dimensional projection of EEG data in the space of modulation phase and SynchFastSlow for three subjects (Subject A: +; B: o; C: x). K-means clustering identified three separable states corresponding to baseline (blue), sedation/anti-phase coupling (green) and deep anesthesia/in-phase coupling (red).

The power spectrum and phase-amplitude coupling may be complementary sources of information about brain dynamics. Thus, a combination of both measures could reveal greater structure than either analysis alone. A two-dimensional projection of the EEG data in terms of SynchFastSlow and the preferred phase of the modulogram (Fig. 3) shows that these two measures capture distinct features of the EEG signal. In the baseline state phase-amplitude modulation is weak, and the preferred phase is broadly distributed. Under the

influence of propofol, both SynchFastSlow and PowerFast-Slow decline but subsequently remain constant throughout the period of anesthesia. Modulogram analysis distinguishes two states under GA, with modulation phase around 0 (In-Phase state) and $\pm\pi$ (Anti-Phase state), respectively. The In-Phase, Anti-Phase and Awake states form discrete clusters in the two-dimensional phase space (Fig. 3). We used k-means clustering to classify each time point for each subject into one of these three states.

IV. Discussion

We analyzed cross-frequency coupling in EEG recordings of brain electrical dynamics during propofol GA using measures of phase-phase and phase-amplitude coupling. The bispectrum derived SynchFastSlow, a component of clinical depth-of-anesthesia monitors, was highly correlated with an analogous power spectrum based measure that is insensitive to cross-frequency coupling. Several previous authors examined the usefulness of cross-frequency phase-phase coupling as an EEG correlate of anesthetic induced loss of consciousness [13], [11]. In agreement with studies that examined SynchFastSlow, we found that the contribution of cross-frequency coupling to this measure is negligible [11].

Using modulogram analysis, we found robust phase-amplitude coupling between SO (0.1-1 Hz) and α band (8-14 Hz) activity in GA. This coupling appeared in two distinct modes, with maximum α amplitude occurring at either the surface-postive or -negative phase of the underlying SO, respectively. The first mode, which we call In-Phase, occurs at the highest propofol concentrations when the subjects are completely unresponsive (unconscious). This pattern is analogous to modulation of broadband activity by slow oscillations or K-complexes recorded intracranially in sleeping subjects [14], [15]. By contrast, the Anti-Phase mode occurred during the transition into GA and was associated with increased α amplitude at the troughs of the SO. A recent study using electrocorticography (ECoG) from epileptic patients under propofol GA showed positive and negative correlations between the phase of low-frequency oscillations, including SO, and higher frequency power (1-200 Hz) [3]. EEG signals recorded in children under GA also reveal phase-amplitude coupling, including patterns similar to the In-Phase and the Anti-Phase modes described here [16]. Our results using modulogram analysis show that In-Phase and Anti-Phase coupling between SO and α activity are statistically significant, robust features of the EEG under GA, and they represent truly distinct modes of network activity.

To validate the usefulness of different measures for classifying EEG under GA, we applied k-means cluster analysis to the two dimensional feature space defined by SynchFastSlow and the modulation phase. Because the SynchFastSlow is very tightly correlated with PowerFastSlow, an equivalent classification could be obtained using power spectral information rather than the bispectrum. This analysis highlights the additional discrimination ability provided by incorporating phase-amplitude modulation in addition to the features considered in clinical depth-of-anesthesia monitors. More in-depth analyses using higher-dimensional feature spaces that include modulation analysis and different functions of the power spectrum and coherence might yield even greater discrimination among states. Future work should also examine the spatial distribution on the scalp of the phase-amplitude coupling reported here.

V. Acknowledgments

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