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The electroencephalogram: a missing piece in personalized anesthesia care

Patrick L. Purdon, Ph.D., David W. Zhou, M.S., Oluwaseun Akeju, M.D., M.M.Sc., and Emery N. Brown, M.D., Ph.D.

Massachusetts General Hospital, Boston, Massachusetts (P.L.D.)

Patrick L. Purdon: patrickp@nmr.mgh.harvard.edu

In Reply

We thank Drs. Saraiva and Lobo for their thoughtful analysis of our work. We point out that in our ANESTHESIOLOGY article, Akeju *et al.*,¹ we took care to indicate that the propofol data came from a previous study, Purdon *et al.*,² in which we cited the classic paper by Schnider *et al.*³ (see page 2, paragraph 2, of Purdon *et al.*²). In Purdon *et al.*,² we used the Schnider model to administer propofol at target effect-site concentrations from 0 through 5 µg/ml to subjects executing an auditory task at 4-s intervals. The probability of response to these sounds was used to identify in each subject time points for loss and recovery of consciousness, which were used to identify electroencephalogram signatures of propofol-induced unconsciousness and sedation.^{2,4,5}

We analyzed the pharmacokinetic/pharmacodynamic (PK/PD) models used in target-controlled infusions and the electroencephalogram studies we have conducted over the past several years. As the authors suggested, we reexamined the effect-site concentrations associated with loss of consciousness for the subjects (18 to 36 yr of age) studied in Purdon *et al.*² The effect-site concentrations from our subjects (fig. 1) reflect what we see everyday in the operating room: the doses required to induce unconsciousness with propofol vary widely from person to person. In this case, the propofol effect-site concentrations associated with loss of consciousness ranged from 1 to 4 µg/ml. Our data are consistent with previous studies. For instance, Iwakiri *et al.*,⁶ cited by Drs. Saraiva and Lobo, showed that patients lost consciousness at propofol effect-site concentrations between 0.7 and 4.8 µg/ml. The strategy underlying target-controlled infusion is that if we cannot observe a patient's response to propofol, we use a population-based PK/PD model to select a dose that is approximately correct. These data show that the PK/PD estimate is likely to be inaccurate in an individual patient. Expecting a population-based measure of anesthetic effect to produce exactly the same effect in every patient is analogous to expecting 80 µg of phenylephrine to raise every patient's systolic blood pressure by 15 mmHg.

Competing Interests

Drs. Purdon, Akeju, and Brown have submitted patent applications describing the use of the electroencephalogram for monitoring sedation and general anesthesia. Some of these patents have been licensed to Masimo Corporation (Irvine, California) by Massachusetts General Hospital (Boston, Massachusetts). Drs. Purdon, Akeju, and Brown are due to receive institutionally distributed royalties under this licensing agreement. Drs. Purdon and Brown have consulting agreements with Masimo Corporation. Mr. Zhou declares no competing interests.

What if instead the anesthesiologist could track in real time a marker of an individual patient's propofol-induced brain state? Recent work suggests that this is highly tractable using the electroencephalogram. In Purdon *et al.*,² we show the electroencephalogram signatures associated with unconsciousness: a combination of slow (< 1 Hz) oscillations and alpha (8 to 14 Hz) oscillations (fig. 2, reproduced with permission). Although it is possible to recognize these oscillations in unprocessed electroencephalogram recordings,⁷⁻⁹ they are clearly evident in the spectrogram, which is the frequency distribution of the electroencephalogram power displayed as a function of time (fig. 2). We observe this propofol-induced signature of unconsciousness every day in the operating room.¹⁰ These propofol-induced electroencephalogram oscillations are among the largest neurophysiological signals seen in neuroscience,¹ have been reported by a number of other researchers,¹¹⁻¹⁴ and relate fundamentally to the neurophysiological mechanisms by which propofol produces unconsciousness.^{2,15-20}

The pharmacodynamics component of the Schnider model is informed by an electroencephalogram representation that quantifies power within different frequency bands.³ In the Schnider model, the most significant indicators of propofol's drug effect correspond to the alpha oscillation (fig. 3).³ This observation is completely consistent with the fact that the alpha oscillation is one of the two electroencephalogram oscillations associated with propofol-induced unconsciousness.^{2,11,12,16*} However, it further suggests that we could administer propofol with much greater accuracy in individual patients by simply monitoring the electroencephalogram and titrating the anesthetic to the desired electroencephalogram signature. We have shown that like propofol, each anesthetic has a distinct electroencephalogram signature.^{1,10,21-23}

In anesthesiology, the electroencephalogram is often viewed synonymously with processed electroencephalogram indices designed to indicate "depth of anesthesia" using a single number between 0 and 100. These indices have been designed with a one-size-fits-all approach in which the same index value is meant to represent the same state of unconsciousness, regardless of the anesthetic being administered, and without regard to significant age-dependent differences in anesthesia-induced electroencephalogram features.²⁴⁻²⁶ Anesthesiologists have learned over the years that their use does not reduce the incidence of awareness²⁷ and that patients' underlying brain states can vary substantially despite being maintained within the recommended index range.^{26,28,29} Alternatively, the unprocessed electroencephalogram and its spectrogram make it possible to view directly the patient's brain states under general anesthesia.²³ Over the past several years, we have been teaching anesthesiologists at our institution to read the unprocessed electroencephalogram and its spectrogram. The spectrogram makes the electroencephalogram easier to read and relate to underlying systems neuroscience mechanisms. Our course, "Clinical Electroencephalography for the Anesthesiologist," can be accessed online, free of charge, at www.AnesthesiaEEG.com. A significant challenge in teaching the electroencephalogram has been the perceived complexity of the signal, but with appropriate application of modern signal processing methods,^{1,2,10,30} the structure of anesthesia-induced electroencephalogram

*We conjecture that the slow oscillation may have been absent in Schnider *et al.*³ due to the choice of the frequency bands for the "canonical univariate parameter" or perhaps due to the choice of electroencephalogram filtering parameters.

oscillations becomes much easier to discern. It is not surprising that these electroencephalogram signatures may have been overlooked previously in the absence of appropriate methods to visualize them. Using the unprocessed electroencephalogram and its spectrogram, electroencephalogram signatures associated with brain states during general anesthesia and sedation are easy to discern and interpret.

In the United States, we are eagerly awaiting newly proposed programs to support research on personalized medicine,³¹ with the hope that at some point in the future, we can administer therapies tailored uniquely to each patient's specific needs. An example would be choosing the correct dose of medication for every individual. In anesthesiology, we can move toward personalized anesthesia care by using a "missing piece" of information that has been hiding in plain sight all along: the electroencephalogram.

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Fig. 1. Histogram of predicted propofol effect-site concentrations associated with loss of consciousness, from subjects studied in Purdon *et al.*² administered using the Schnider model.³

Fig. 2.

Electroencephalogram signature of propofol-induced unconsciousness. (A) Probability of response curves for less salient auditory click stimuli (*blue*, P_{clicks}) and more salient verbal stimuli (*red*, P_{verbal}), pooled across the cohort of subjects. Time points for loss of consciousness (LOC) and recovery of consciousness (ROC) were identified for each subject using the individual subject response curves. (B) Baseline-normalized spectrograms from a frontal channel aligned with respect to LOC and ROC. The spectrogram quantifies the power in the electroencephalogram as a function of time (x-axis) and frequency (y-axis). The white contour circumscribes the regions where power differs significantly from baseline ($P < 0.05$, sign test) and indicates significant increases in power spanning low frequency (0.1 to 1 Hz) through gamma (25 to 35 Hz) bands. The largest oscillations are in the slow (0.1 to 1 Hz) and alpha (8 to 14 Hz) bands. Adapted from Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN: Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A* 2013; 110:E1142–51. (Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.)

Fig. 3.

Coefficients of the “canonical univariate parameter” (CUP) used in Schnider *et al.*³ to characterize propofol pharmacodynamics. The largest coefficients correspond to the alpha oscillation, one of the electroencephalogram signatures of propofol-induced unconsciousness, shown in figure 2.