changes with the predicted ES concentration and the total administered propofol (*e.g.*, at what ES concentration should we expect the occurrence of alpha band?), especially because previous evidence showed a poor correlation between predicted ES concentration calculated by the Schnider model and processed electroencephalogram–derived indices of consciousness.[8]

For a possible average patient (male, age 36, weight 70 kg, and height 170 cm), we simulated with Tivatrainer® software (Gutta BV, The Netherlands, software available for download at http://www.eurosiva.eu, accessed April 22, 2015) two possible ES TCIs of propofol according to the scheme reported by the authors, using the two more common pharmacokinetic models for ES control[3,4,9] (figs. 1 and 2). The concentrations calculated by these two models have different time courses with different total administered doses of propofol: during the experimental period of 14 × 5 min, the total dose administered by the Schnider model is 659 mg of propofol while the Modified Marsh Model administers a total dose of 742 mg of propofol, as a result of different infusion rates, which seem to us to be low to induce the characteristic spectrogram for propofol.

Thus, we consider that a full spectrogram as the one resulting from dexmedetomidine infusion would be valuable information for a better comprehension of the electroencephalographic changes resulting from a stepwise approach of propofol-induced LOC: especially for those who use TCI of propofol, it would be extremely useful to know at which calculated ES concentration by a particular pharmacokinetic model is expected to occur the through-max and peak-max changes.

Competing Interests

The authors declare no competing interests.

Alexandra P. Saraiva, M.D., Francisco A. Lobo, M.D.
Centro Hospitalar do Porto, Hospital Geral de Santo António, Porto, Portugal (F.A.L.). francisco.lobo@me.com

References

1. Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K, Gao L, Lei G, Pierce ET, Walsh JL, Brown EN, Purdon PL: A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014; 121:978–89
2. 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
3. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998; 88:1170–82
4. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90:1502–16
5. Nunes CS, Ferreira DA, Antunes L, Lobo F, Santos IA, Amorim P: Individual effect-site concentrations of propofol at return of consciousness are related to the concentrations at loss of consciousness and age in neurosurgical patients. J Clin Anesth 2009; 21:3–8
6. Lobo F, Beiras A: Propofol and remifentanil effect-site concentrations estimated by pharmacokinetic simulation and bispectral index monitoring during craniotomy with intraoperative awakening for brain tumor resection. J Neurosurg Anesthesiol 2007; 19:183–9
7. Iwakiri H, Nishihara N, Nagata O, Matsukawa T, Ozaki M, Sessler DI: Individual effect-site concentrations of propofol are similar at loss of consciousness and at awakening. Anesth Analg 2005; 100:107–10
8. Barakat AR, Sutcliffe N, Schwab M: Effect site concentration during propofol TCI sedation: A comparison of sedation score with two pharmacokinetic models. Anaesthesia 2007; 62:661–6
9. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment *versus* two methods for effect compartment–controlled target-controlled infusion for propofol. Anesthesiology 2000; 92:399–406

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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

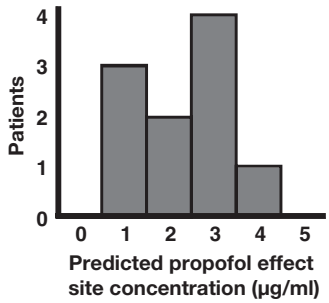

Fig. 1. Histogram of predicted propofol effect-site concentrations associated with loss of consciousness, from subjects studied in Purdon *et al.*[2] administered using the Schnider model.[3]

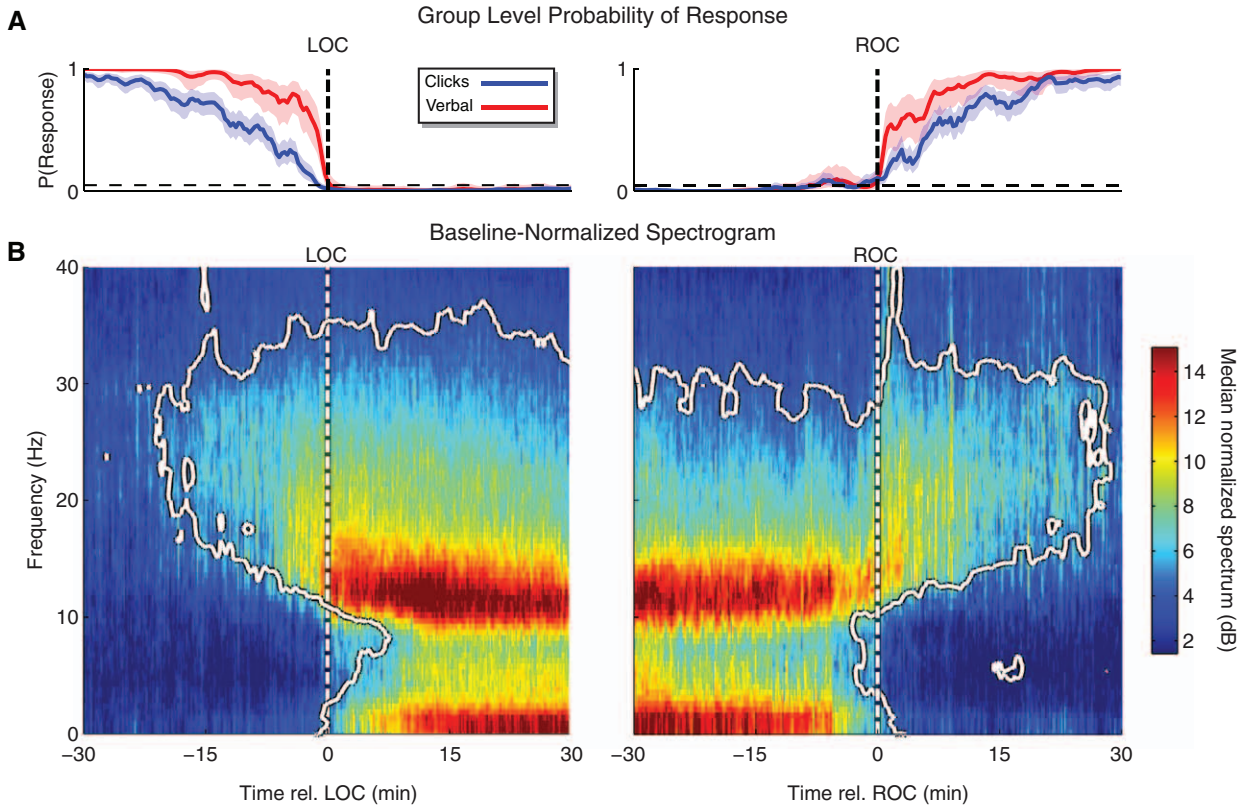

Fig. 2. Electroencephalogram signature of propofol-induced unconsciousness. (*A*) Probability of response curves for less salient auditory click stimuli (*blue*, P_{clicks}) and more salient verbal stimuli (*red*, P_{verbal}), pooled across the cohort of subjects. Time points for loss of consciousness (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.)

Frequency Bin (Hz)	Coefficient
27.5 - 30	0.003469
24.5 - 27	-0.022001
21.5 - 24	0.027539
18.5 - 21	0.024896
15.5 - 18	0.012265
12.5 - 15	0.424367
9.5 - 12	0.218774
6.5 - 9	0.012887
3.5 - 6	0.003227
0.5 - 3	0.000659

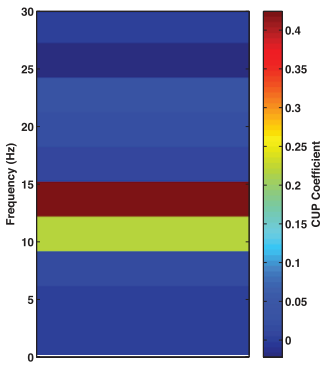

Fig. 3. Coefficients of the "canonical univariate parameter" (CUP) used in Schnider *et al.*[3] to characterize propofol pharmacodynamics. The largest coefficients correspond to the alpha oscillation, one of the electroencephalogram signatures of propofol-induced unconsciousness, shown in figure 2.

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.

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 awareness[27] 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 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.

* 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.

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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.

Patrick L. Purdon, Ph.D., David W. Zhou, M.S., Oluwaseun Akeju, M.D., M.M.Sc., Emery N. Brown, M.D., Ph.D. Massachusetts General Hospital, Boston, Massachusetts (P.L.D.). patrickp@nmr.mgh.harvard.edu

References

1. Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K, Gao L, Lei G, Pierce ET, Walsh JL, Brown EN, Purdon PL: A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014; 121:978–89
2. 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
3. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90:1502–16
4. Wong KF, Smith AC, Pierce ET, Harrell PG, Walsh JL, Salazar-Gomez AF, Tavares CL, Purdon PL, Brown EN: Statistical modeling of behavioral dynamics during propofol-induced loss of consciousness. J Neurosci Methods 2014; 227:65–74
5. Smith AC, Wirth S, Suzuki WA, Brown EN: Bayesian analysis of interleaved learning and response bias in behavioral experiments. J Neurophysiol 2007; 97:2516–24
6. Iwakiri H, Nishihara N, Nagata O, Matsukawa T, Ozaki M, Sessler DI: Individual effect-site concentrations of propofol are similar at loss of consciousness and at awakening. Anesth Analg 2005; 100:107–10
7. Bennett C, Voss LJ, Barnard JP, Sleigh JW: Practical use of the raw electroencephalogram waveform during general anesthesia: The art and science. Anesth Analg 2009; 109:539–50
8. Martin JT, Faulconer A Jr, Bickford RG: Electroencephalography in anesthesiology. Anesthesiology 1959; 20:359–76
9. Gibbs FA, Gibbs EL, Lennox WG: Effect on the electroencephalogram of certain drugs which influence nervous activity. Arch Intern Med 1937; 60:154–169
10. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL: Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014; 121:990–8
11. Feshchenko VA, Veselis RA, Reinsel RA: Propofol-induced alpha rhythm. Neuropsychobiology 2004; 50:257–66
12. Supp GG, Siegel M, Hipp JF, Engel AK: Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. Curr Biol 2011; 21:1988–93
13. Murphy M, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M: Propofol anesthesia and sleep: A high-density EEG study. Sleep 2011; 34:283–91A
14. Ní Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I: Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. Sci Transl Med 2013; 5:208ra148
15. Lewis LD, Weiner VS, Mukamel EA, Donoghue JA, Eskandar EN, Madsen JR, Anderson WS, Hochberg LR, Cash SS, Brown EN, Purdon PL: Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci U S A 2012; 109:E3377–86
16. Cimenser A, Purdon PL, Pierce ET, Walsh JL, Salazar-Gomez AF, Harrell PG, Tavares-Stoeckel C, Habeeb K, Brown EN: Tracking brain states under general anesthesia by using global coherence analysis. Proc Natl Acad Sci U S A 2011; 108:8832–7
17. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ: Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. Proc Natl Acad Sci U S A 2010; 107:22665–70
18. Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–50
19. Brown EN, Purdon PL, Van Dort CJ: General anesthesia and altered states of arousal: A systems neuroscience analysis. Annu Rev Neurosci 2011; 34:601–28
20. Mukamel EA, Pirondini E, Babadi B, Wong KF, Pierce ET, Harrell PG, Walsh JL, Salazar-Gomez AF, Cash SS, Eskandar EN, Weiner VS, Brown EN, Purdon PL: A transition in brain state during propofol-induced unconsciousness. J Neurosci 2014; 34:839–45
21. Brown EN, Solt K, Purdon PL, Akeju O: Monitoring brain state during general anesthesia and sedation, Miller's Anesthesia, 8th edition, edited by Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, Elsevier, 2014, pp 1524–40
22. Purdon PL, Brown EN: Clinical Electroencephalography for Anesthesiologists the Anesthesiologist. Boston, Partners Healthcare Office of Continuing Professional Development, 2014. Available at: AnesthesiaEEG.com. Accessed July 17, 2015
23. Purdon PL, Sampson AL, Pavone KJ, Brown EN: Clinical electroencephalography for anesthesiologists, part I: Background and basic signatures. Anesthesiology 2015; in press
24. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, Zhou DW, Solt K, Brown EN: The aging brain: An age-dependent analysis of the electroencephalogram during propofol and sevoflurane general anesthesia. Br J Anaesth 2015; in press
25. Akeju O, Pavone KJ, Thum JA, Firth PG, Westover MB, Puglia M, Shank ES, Brown EN, Purdon PL: An age-dependent analysis of sevoflurane-induced electroencephalogram dynamics in children. Br J Anaesth 2015; (in press)
26. Besch G, Liu N, Samain E, Pericard C, Boichut N, Mercier M, Chazot T, Pili-Floury S: Occurrence of and risk factors for electroencephalogram burst suppression during propofol-remifentanil anaesthesia. Br J Anaesth 2011; 107:749–56
27. Avidan MS, Jacobsohn E, Glick D, Burnside BA, Zhang L, Villafranca A, Karl L, Kamal S, Torres B, O'Connor M, Evers AS, Gradwohl S, Lin N, Palanca BJ, Mashour GA; BAG-RECALL Research Group: Prevention of intraoperative awareness in a high-risk surgical population. N Engl J Med 2011; 365:591–600
28. Whitlock EL, Villafranca AJ, Lin N, Palanca BJ, Jacobsohn E, Finkel KJ, Zhang L, Burnside BA, Kaiser HA, Evers AS, Avidan MS: Relationship between bispectral index values and volatile anesthetic concentrations during the maintenance phase of anesthesia in the B-Unaware trial. Anesthesiology 2011; 115:1209–18
29. Sleigh JW: Depth of anesthesia: Perhaps the patient isn't a submarine. Anesthesiology 2011; 115:1149–50
30. Babadi B, Brown EN: A review of multitaper spectral analysis. IEEE Trans Biomed Eng 2014; 61:1555–64
31. Dennis B: Obama touts 'lifesaving' potential of personalized medicine, Washington Post, 2015

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Perioperative Care of the Elderly Patient with Hip Fracture

To the Editor:

We were very encouraged to read Boddaert *et al.*'s review[1] and Colquhoun *et al.*'s accompanying editorial[2] on the contemporary management of elderly patients with hip fracture, an international health problem that would benefit hugely