HHS Public Access

Author manuscript

Conf Proc IEEE Eng Med Biol Soc. Author manuscript; available in PMC 2020 March 17.

Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2019 July ; 2019: 5808–5811. doi:10.1109/EMBC.2019.8856935.

Drug-Specific Models Improve the Performance of an EEG-based Automated Brain-State Prediction System

Kimia Kashkooli[1,2,*], **Sam L. Polk**[1,3,*], **Shubham Chamadia**[1], **Eunice Hahm**[1], **Breanna Ethridge**[1], **Jacob Gitlin**[1], **Reine Ibala**[1], **Jennifer Mekonnen**[1], **Juan Pedemonte**[1,4], **James M. Murphy**[3], **Haoqi Sun**[5], **M. Brandon Westover**[5], **Oluwaseun Akeju**[1,6]

[1]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[2]Tufts University School of Medicine, Boston, USA

[3]Department of Mathematics, Tufts University, Medford, USA

[4]División de Anestesiología, Pontificia Universidad Católica de Chile, Santiago, Chile

[5]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[6]Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA USA

Abstract

Maintaining anesthetic states using automated brain-state prediction systems is expected to reduce drug overdosage and associated side-effects. However, commercially available brain-state monitoring systems perform poorly on drug-class combinations. We assume that current automated brain-state prediction systems perform poorly because they do not account for brain-state dynamics that are unique to drug-class combinations. In this work, we develop a k-nearest neighbors model to test whether improvements to automated brain-state prediction of drug-class combinations are feasible. We utilize electroencephalogram data collected from human subjects who received general anesthesia with sevoflurane and general anesthesia with the drug-class combination of sevoflurane-plus-ketamine. We demonstrate improved performance predicting anesthesia-induced brain-states using drug-specific models.

I. Introduction

Anesthesiologists typically administer anesthetic-drugs to induce altered states of arousal that range from sedation to general anesthesia (GA). To induce these states, anesthetic-drugs are typically administered and adjusted empirically based on drug pharmacokinetic and pharmacodynamic properties as well as physiological variables such as changes in the heart rate or blood pressure. This current empirical approach to anesthetic-drug dosing has been associated with the inadvertent overdosing and underdosing of anesthetic-drugs. Overdosing

Corresponding author: kimia.kashkooli@tufts.edu.
*Equal Contribution

of anesthetic-drugs is associated with cardiovascular and respiratory side-effects and delayed recovery [1], while the underdosing of anesthetic-drugs is associated with unintended intraoperative awareness and post-traumatic stress disorder [2]. Thus, principled strategies for brain-state monitoring are expected to improve patient care directly.

In theory, electroencephalogram (EEG)-based brain-state monitoring is a principled strategy that may help limit drug overdosing and underdosing. However, the reliability of existing EEG-based brain-state monitoring devices has been called into question in numerous clinical scenarios [3]. One such scenario is during brain-state monitoring of anesthetic drug-class combinations [4]. Clinicians routinely administer the drug-class combination of gamma-amino-butyric acid A ($GABA_A$) receptor agonist drugs to maintain unconsciousness and N-methyl-D-aspartate (NMDA) receptor antagonist drugs as part of a balanced GA technique [5, 6]. Sevoflurane is an inhaled anesthetic vapor that is routinely administered to maintain unconsciousness in patients. The $GABA_A$ receptor is considered the principal receptor target for the neurophysiological dynamics associated with sevoflurane. These dynamics include increased slow (0.1–2 Hz) and beta (13–33 Hz) oscillation power during sedation and increased delta (2–4 Hz), theta (4.1–8 Hz) and frontal alpha (8.1–12 Hz) oscillation power during GA [7]. Ketamine is an intravenous anesthetic that is routinely administered with sevoflurane as an anesthetic-adjunct for anti-nociception and to decrease post-operative pain and opioid consumption. The NMDA receptor is considered to be the principal target receptor for the neurophysiological dynamics associated with ketamine. These dynamics include decreased alpha oscillation power and increased theta and beta-gamma (30–45 Hz) oscillation power at clinically-recommended drug doses for anti-nociception [5,8].

Recent studies of oscillations associated with anesthetic-drug-class combinations (e.g., $GABA_A$ agonist and NMDA antagonist drugs) provide a framework that may help foster improvements to current brain-state monitoring paradigms [5,6]. For example, high beta-gamma oscillation power is typically observed both in awake and active brain-states and during ketamine-induced GA [8]. Neurophysiologic changes like these may explain why current brain-state monitoring systems, which are designed using a one-model-fits-all-drugs approach, perform poorly when exposed to drug-class combinations. The administration of ketamine during sevoflurane GA causes current brain-state monitors to paradoxically interpret the patient's EEG as awake, even though the patient under GA. It is therefore not surprising that EEG-based brain-state monitors have not been incorporated into clinical standard-of-care practices due to their unreliability in relatively common clinical scenarios [3]. Moreover, the models underlying commercially available brain-state monitors are proprietary [3]. Therefore, the extent to which these models, when optimized for drug-class combinations, may improve brain-state monitoring remains unclear.

In this work, we developed an EEG-based automated brain-state prediction system using machine learning to classify the awake, sedated, and GA brain-states. We hypothesized that optimizing models for drug-specificity would improve model performance. We defined drug-specific models as those which were evaluated on data similar to that within the training set. We applied the *k*-nearest neighbors (KNN) classification algorithm to a uniform set of features to investigate whether improvements to current brain-state classification of a

drug-class combination routinely encountered in clinical practice is feasible. We demonstrated improved performance in our drug-specific models over our cross-test model.

II. Materials And Methods

A. Subject Selection and Data Recording

The Partners Human Research Committee approved our research study that was conducted at the Massachusetts General Hospital in Boston, MA, USA. A total of 12 healthy volunteers were recruited for this study (7 males; 5 females). Mean weight was 69.9 kg (SD, ±11.7) and mean BMI was 24.1 kg/m^2 (±3). Subject ages ranged from 20-34 years with a mean age of 25 (±4.8). We induced and allowed recovery from sevoflurane GA and the drug-class combination of sevoflurane-*plus*-ketamine GA in each of the 12 volunteers. Thus, each volunteer received both sevoflurane-induced GA and sevoflurane-*plus*-ketamine-induced GA on separate study days ranging 2 to 7 days apart. Sevoflurane was administered via tight-fitting face-mask. For the sevoflurane-induced GA visit, we increased the end-tidal sevoflurane concentration in a stepwise fashion from baseline (awake) to 1.1% (sedated), 2.1% (GA), and 2.8% (GA). Each concentration level was maintained for 15 minutes. For the sevoflurane-*plus*-ketamine-induced GA visit, after the baseline (awake) state, we increased the sevoflurane end-tidal concentration to 2.1% (GA) and maintained it for 15 minutes. Next, we administered a bolus of an anti-nociceptive dose of ketamine (0.75mg/kg) while maintaining the sevoflurane concentration for an additional 30 minutes (GA).

We recorded the EEG using the Waveguard system (ANT neuro, Netherlands) using a standard, high-density 64-channel EEG cap (ANT neuro, Netherlands). Data were down-sampled to 250 Hz and interpolated (for bad channels) using ASA-Lab software (ANT neuro, Netherlands). A nearest-neighbor Laplacian reference was applied to filter out features which were shared among neighboring electrodes. We extracted our features from the raw data of five frontal electrodes. The median of each feature across the five electrodes was evaluated to isolate frontal EEG dynamics. The multitaper approach for spectral analysis was used to obtain spectral estimates. The multitaper parameters are as follows: window length $T = 4$ s with no overlap, time-bandwidth product TW = 3, number of tapers K = 5, and spectral resolution = 1.5 Hz. We normalized spectral features by the median baseline (awake) slow power of each subject. We chose a window with no overlap so that each epoch would be independent from those preceding it, providing some theoretical guarantees to the machine learning algorithms we used [9].

B. Feature, Algorithm, and Hyperparameter Selection

For the sevoflurane visit, we selected 5-minute ECG epochs during the awake states (pre- and post-anesthesia) and after the sevoflurane reached the desired steady-state concentrations of 1.1%, 2.1%, and 2.8%. For the sevoflurane-*plus*-ketamine visit, we selected 5-minute EEG epochs during the awake states (pre- and post-anesthesia), after the sevoflurane reached a steady-state concentration of 2.1%, and approximately 2 minutes after the ketamine dose was administered. We classified a given 4 s epoch as one of three *a priori* defined anesthetic-states: GA (2.1% sevoflurane, 2.8% sevoflurane, or 2.1% sevoflurane-*plus*-ketamine), sedation (1.1% sevoflurane), or awake (pre- or post-anesthesia). We

combined the 2.1% and 2.8% sevoflurane states into one brain-state class, as they are both GA brain-states with similar spectral dynamics. For similar reasons, we ignored misclassifications between the sevoflurane-*plus*-ketamine-induced GA and sevoflurane-induced GA.

We considered a set of 100 spectral-domain, time-domain, and entropy-domain features to assess the performance of various classifiers (decision tree, random forest, KNN, subspace-KNN, and multinomial logistic regression) across an array of hyperparameter choices [9]. Through this exhaustive analysis, we found that the KNN classifier, endowed with the city-block metric, most accurately classified brain-states into our three *a priori* defined brain-states: awake, sedated, and GA. The city-block metric—also known as the ℓ^1 metric—emphasizes small component-wise differences [9]. Given a query point q, the KNN classifier finds the k points in its training set nearest to q, where distance is defined by the city-block metric. It then uses those k points' classifications to determine the most likely classification of q. KNN's simple construction makes it more interpretable than other common machine learning algorithms (e.g. support vector machines and neural networks) [9]. This allows for the careful selection of features which are catered to KNN and the problem of separating brain-state classes. The KNN algorithm is most successful when the data exists in clusters which can be separated by hyperplanes [10]. We defined this separation of clusters as linear separation. Linear separation of our classes would give a Bayes error of almost zero such that data can be separated with few disconnected components [10].

We extracted two curated lists of features. In the first list, we found seventeen features that linearly separated our *a priori* defined brain-states for the sevoflurane visit. In the second list, we found sixteen features that linearly separated our *a priori* defined brain-states for the sevoflurane-*plus*-ketamine visit. We selected the features that intersected both lists as our ultimate feature space (table I). We expected the selected features to differentiate both sevoflurane and sevoflurane-*plus*-ketamine GA from sedation and awake with high accuracy.

Keeping our carefully-selected feature set uniform, we varied the training and testing sets to measure the effect of drug-specificity on model performance. Cross-validation was performed using a leave-one-subject-out approach, which ensured that models were tested on "unseen" data [9]. To find the optimal hyperparameter choice k for our KNN models, we performed a grid-search and found the optimum to be $k = 6$. This optimization occurred before any analysis, and there was no further inner loop to vary k. The GA-specific (sevoflurane or sevoflurane-*plus*-ketamine) F_1 score was used as our performance metric. We defined this metric to the harmonic mean of GA specificity (true-negative rate) and GA sensitivity (true-positive rate). We performed ANOVA testing with post-hoc comparisons for all model pairs using the Tukey-Kramer Honest Significance Test (HSD). We chose a significance threshold of $p \leq 0.05$.

III. Results

A. Model Performances

First, we assessed performance when predicting GA in two drug-specific models. The performance of a model that was trained and tested on sevoflurane data (model 1) was 0.91

[95% CI, 0.84, 0.98], shown in table II. The performance of a model that was trained and tested on sevoflurane-*plus*-ketamine data (model 2) was 0.98, [0.94, 1.00], shown in table III. Next, we assessed model performance for a clinically relevant, cross-test model (model 3)—trained on a single drug-class (sevoflurane) and evaluated on a different drug-class combination (sevoflurane-*plus*-ketamine), shown in table IV. The performance of model 3 was 0.78, [0.62, 0.95]. In model 3, 10.8% of sevoflurane-*plus*-ketamine GA was misclassified as awake and 26.8% was misclassified as sedated. Fig. 1A illustrates the high performance of model 2, which was trained and tested on sevoflurane-*plus*-ketamine. Fig. 1B illustrates the lower performance of model 3, which was trained on sevoflurane but tested on sevoflurane-*plus*-ketamine.

B. Statistical Significance Testing

The drug-specific model (model 2) outperformed the cross-test model (model 3) by a margin of 0.20, [0.00, 0.39] in the GA-specific F_1 score, $p = 0.05$. Incorporating drug-specific training data did not significantly improve the performance on the awake state, which increased from model 3 to model 2 only by a margin of 0.03, [−0.07, 0.33], $p = 0.27$. Model 2 predicted the awake brain-state with an awake-specific F_1 score of 0.99, [0.96, 1.01] and model 3 predicted the awake state with an awake-specific F_1 score of 0.96, [0.90, 0.99].

IV. Discussion

A. Drug-Specific Brain-State Monitoring

Precisely targeting and maintaining anesthetic states using automated brain-state prediction systems is expected to reduce drug overdosage and associated side-effects, especially in patients for whom the current models fail such as the elderly or those with critical illnesses (i.e., sepsis) or during certain drug-class combinations. Commercially available brain-state monitoring systems perform poorly on drug-class combinations. This is likely because the models underlying these systems were developed under a one-model-fits-all-drugs assumption and trained solely on gabaergic drugs like sevoflurane [3]. In this work, we demonstrated improved performance of EEG-based brain-state classification when using drug-specific training sets. Importantly, this improvement was feature-independent, as we employed a uniform set of eight features across all of the models tested. Thus, a pragmatic, drug-specific training approach to models being developed for commercially available automated brain-state prediction systems may improve the performance of these systems.

Our finding that EEG data consistent with sevoflurane-*plus*-ketamine GA were misclassified as the awake or sedated brain-states in our cross-test model is consistent with previously published literature on the performance of commercially available brain-state prediction systems [15]. Sevoflurane at doses consistent with sedation is associated with beta oscillations [1]. Sevoflurane-*plus*-ketamine at doses consistent with GA is also associated with beta oscillations (Fig. 1C). We conjecture that EEG-based brain-state prediction systems ascribe high sedation and awake state prediction weights to beta oscillations. This could be the reason as to why these systems inaccurately misclassify GA states with beta oscillations (e.g. in sevoflurane-*plus*-ketamine) as either awake or sedation.

B. Study Limitations

Study limitations include the small sample size, narrow age range, lack of comorbidities, and single drug-class combination analyzed. EEG dynamics of the anesthetized brain changes systematically as a function of age [16, 17] and perhaps, critical illness. Thus, for generalizability and improved performance, models that account for various ages, comorbidities, and all clinically relevant drug-class combinations are necessary. We demonstrated that a drug-specific approach to brain-state monitoring may lead to improved performance using a limited set of features. However, model performance could also be improved with a more expansive feature set or with feature-independent models such as convolutional neural networks. Future studies that compare against a chance classifier may provide a better understanding as to whether the complexity of machine learning is warranted in the context of our brain-state prediction systems.

V. Conclusion

We conclude that EEG-based automated brain-state prediction systems based on drug-specific models result in improved performance compared to a one-model-fits-all-drugs approach. Improved brain-state monitoring systems are expected to foster widespread utilization and guidelines for patient monitoring.

Acknowledgment

Support: NIH-NIA R01AG053582 to O.A.

References

[1]. Campagna JA, Miller KW, and Forman SA, “Mechanisms of actions of inhaled anesthetics,” New England Journal of Medicine. vol. 348 no. 21 pp. 2110–2124. 2003. [PubMed: 12761368]

[2]. Whitlock EL et al., “Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials,” Anesth. and analg, Vol. 120, no. 1, pp. 87–95, 2015.

[3]. Kreuzer M, “EEG Based Monitoring of general anesthesia: Taking the Next Steps,” Front. in Comp. Neuro, vol. 11, pp. 11–56, 2017.

[4]. Sandler NA, “Additional clinical observations utilizing bispectral analysis,“ Anesthesia progress, vol. 47, no. 3, pp. 84–86, 2000. [PubMed: 11432161]

[5]. Akeju O, Hamilos AE, Song AH, Pavone KJ, Purdon PL, and Brown EN, “GABAA circuit mechanisms are associated with ether anesthesia-induced unconsciousness,” Clin. Neurophys, vol. 127, pp. 2472–81.2016.

[6]. Pavone KJ, Akeju O, Sampson A, Kelly L, Purdon PL, and Brown EN, “Nitrous oxide-induced slow and delta oscillations,” Clinical Neurophysiology, vol 127, pp. 556–564, 2016. [PubMed: 26118489]

[7]. Pavone KJ, Su L, Gao L, Eromo E, Vazquez R, Rliee J, Hobbs LE, Ibala R, Demircioglu G, Purdon PL, Brown EN, and Akeju O, “Lack of Responsiveness during the Onset and Offset of Sevoflurane Anesthesia Is Associated with Decreased Awake-Alpha Oscillation Power,” Front. in Sys. Neuroscience, vol. 11, pp.38, 2017.

[8]. Akeju O et al., “Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness.” Clinical neurophysiology, vol 127no. 6 pp. 2414–22. 2016. [PubMed: 27178861]

[9]. Friedman J, Tibshirani R, and Hastie T, The Elements of Statistical Learning: *Data Mining, Inference, and Prediction*. Springer Series in Statistics. New York: Springer-Verlag, 2009.

[10]. Vincent P, Bengio Y, “K-local hyperplane and convex distance nearest neighbor algorithms,” Adv. Neur.l Inf. Proc. Sys, pp.985–92, 2002.

[11]. Malarvili M, Mesbah M, and Boashash B, B. “Time-frequency analysis of heart rate variability for neonatal seizure detection,” EURASIP Journal on Applied Sig. Processing, vol. 1, pp.103–13, 2007.

[12]. Hjorth B, “EEG analysis based on time domain properties,” Electroen. and clinical neurophys, vol. 29, no. 3, pp. 306–310, 1970.

[13]. Bandtand C Pompe B, “Permutation entropy: a natural complexity measure for time series,” Physical review letters, vol. 88, no. 17, 2002.

[14]. Higuchi T, “Approach to an irregular time series on the basis of the fractal theory,” Physica D: Nonl. Phen, vol.31, no.2, pp. 277–283, 1988.

[15]. Hans P, Dewandre PY, Brichant JF, and Bonhomme V, “Comparative effects of ketamine in Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anesthesia,” British Journal of Anesthesia, vol 94, no. 3, pp. 336–340, 2005.

[16]. Purdon PL, et al., “The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia,” British journal of anaesthesia, vol. 115, pp. 46–57, 2015.

[17]. Lee JM et al.,“A Prospective Study of Age-dependent Changes in Propofol-induced Electroencephalogram Oscillations in Children,” Anesthesiology, vol 127, pp. 293–306, 2017. [PubMed: 28657957]

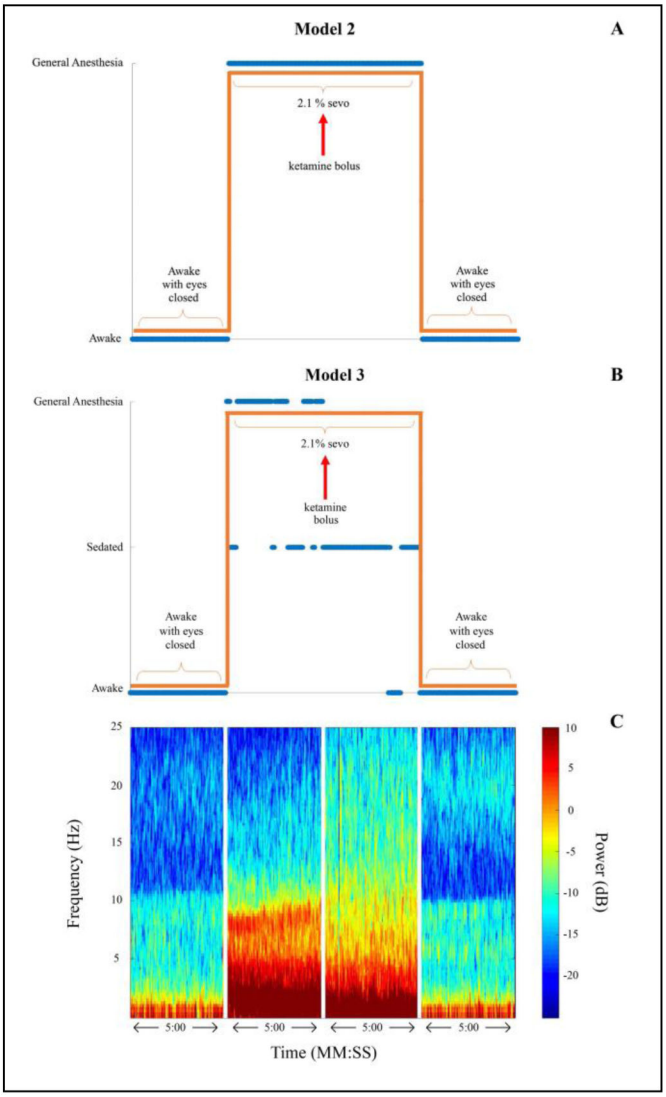

Figure 1. Performance of model 2 and model 3 in testing sevoflurane-*plus*-ketamine for an illustrative subject:

(A, B, C) Prediction performance of model 2 (top panel), prediction performance of model 3 (middle panel), and spectrogram of sevoflurane-plus-ketamine visit (bottom panel). Increased power in beta oscillations are associated with the administration of ketamine even though GA is maintained. Orange lines represent true brain-state classes and blue dots represent the class predictions.

TABLE I.

Feature set

Domain	Features
Spectral	Mean slow (0.1-2 Hz) power Mean theta (4.1-8 Hz) power Mean low-beta (12.5-15 Hz) power
Time	Instantaneous frequency mean [11] Instantaneous frequency kurtosis [11] Hjorth mobility [12]
Entropy	Permutation entropy [13] Higuchi fractal dimension [14]

TABLE II.

Model 1 – Average confusion matrix

		Predicted Class		
		Awake	***1.1% Sevoflurane***	***2.1 or 2.8% Sevoflurane***
True Class	***Awake***	99.4 %	0.6 %	0.0 %
	1.1% Sevoflurane	9.7 %	71.5 %	18.8 %
	2.1 or 2.8% Sevoflurane	0.0 %	7.4 %	**92.6 %**

TABLE III.

Model 2 – Average confusion matrix

		Predicted Class [b]		
		Awake	***2.1% Sevoflurane***	***2.1% Sevoflurane + Ketamine*** [a]
True Class	***Awake***	100.0 %	0.0 %	0.0 %
	2.1% Sevoflurane	6.3 %	71.4 %	22.3 %
	2.1% Sevoflurane + Ketamine [a]	0.0 %	**24.3 %** [c]	**75.7 %** [c]

[a] Subject 8 had missing sevoflurane-*plus*-ketamine data.

[b] Model 2 was limited by study design in that 1.1% sevoflurane was not administered during the sevoflurane-*plus*-ketamine visit.

[c] Misclassifications between sevoflurane GA and sevoflurane-*plus*-ketamine GA were ignored.

TABLE IV.

Model 3 – Average confusion matrix

		Trained Class		
		Awake	***1.1% Sevoflurane***	***2.1 or 2.8% Sevoflurane***
Tested Class	***Awake***	99.9 %	0.1 %	0.0 %
	2.1% sevoflurane	16.4 %	4.2 %	79.4 %
	2.1% Sevoflurane + Ketamine[a]	10.8 %	26.8 %	**62.4 %**

[a] Subject 8 had missing sevoflurane-*plus*-ketamine data.

TABLE V.

Summary Of Model Performance

	Train Data	Test Data	Mean GA F_1 score [CI] [c]
Model 1	Sevoflurane	Sevoflurane	0.91 [0.84, 0.98]
Model 2	Sevoflurane-*plus*-ketamine	Sevoflurane-*plus*-ketamine	0.98 [0.62, 0.95] [a, b]
Model 3	Sevoflurane	Sevoflurane-*plus*-ketamine	0.78 [0.94, 1.02] [a]

[a] Subject 8 had missing sevoflurane-*plus*-ketamine data and thus the mean and standard deviations in model 2 and 3 are performed using 11 subjects.

[b] Misclassifications between sevoflurane GA and sevoflurane-*plus*-ketamine GA were ignored.

[c] 95% confidence interval.