**EEG complexity during anesthesia predicts consciousness recovery in disorders of consciousness: a machine learning approach**

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**Introduction**: Complexity measures of electroencephalography (EEG) signals have been strongly associated with anesthesia-induced loss of consciousness, as well as psychedelic-induced altered states of consciousness.1,2 Multiple versions of the Lempel-Ziv complexity algorithm (LZC), a measure of signal compressibility and usually calculated on the 0.1-45 Hz frequency range,3 have been found to consistently track the depth of anesthesia4 and to outperform other measures of signal entropy as a discerning feature in the classification of conscious versus unconscious healthy brains.5 Furthermore, our group recently showed that the functional reconfiguration of the alpha EEG network in response to anesthesia could predict recovery of consciousness in brain-injured patients in disorders of consciousness (DOC),6 and that the anesthesia EEG alone may contain relevant properties capable of identifying patients with the capacity for consciousness recovery.7 This study aimed to determine whether EEG LZC could train machine learning models capable of predicting consciousness recovery in DOC.

**Methods**: In fourteen (n = 14) DOC patients (40 ± 16 years old; 9 females), we recorded 5 minutes of high-density EEG (128 channels) during a resting baseline state (*Baseline)* and 5 minutes during propofol anesthesia (*Anesthesia*)at 2.0 mcg/ml target effect site concentration. Cleaned EEG signals were filtered in the 0.1-45Hz frequency range and were used to calculate the normalized multivariate LZC8 for each participant, for both *Baseline* and *Anesthesia* states. Alpha LZC was compared between patient groups based on recovery outcome (whether or not consciousness was recovered within 3 months post-sampling), using independent samples t-tests. Normalized alpha LZC scores (one per participant, per state including *Reconfiguration*: the difference between *Anesthesia* and *Baseline*) and recovery outcome were used respectively as features and ground-truths to train machine learning models using leave-one-out cross-validation implemented within scikit-learn.9 Multiple machine learning models (logistic regression, support vector machine, linear discriminant analysis and decision tree [DT] classifiers) were trained with either *Baseline,* *Anesthesia* or *Reconfiguration* alpha LZC andrecovery outcome.

**Results**: Patients who recovered consciousness within 3 months post-sampling (n = 6) had significantly higher LZC during *Anesthesia* than those who did not recover (n = 8) (t(12) = 4.27, p= 0.002). No group difference was found for *Baseline* (t(12) = 0.61, p = 0.554) or *Reconfiguration* alpha LZC (t(12) = -1.9, p=0.08). DT classifiers were the most performant. When trained using *Baseline* and *Reconfiguration* LZC, mean accuracies of 35.71% and 57.14% were achieved, respectively. Conversely, the DT classifier trained using *Anesthesia* LZC obtained a mean accuracy, sensitivity and precision of 100%.

**Conclusion**: EEG signal complexity under anesthesia was higher in DOC patients who recovered consciousness within 3 months post-sampling. Although *Baseline* and *Reconfiguration* alpha LZC were not informative, *Anesthesia* alpha LZC was sufficient to train a machine learning model capable of discerning those with the capacity for recovery of consciousness with 100% accuracy. Considering that behavior-dependent tools for the prognostication of consciousness recovery in DOC do not exceed 75-80% accuracy,10 brain imaging features such as the alpha LZC complexity could be promising discerning factors to train machine learning classifiers capable of surpassing expert-level performance.

**References**

1. Frohlich, J., Toker, D., Monti, M.M. (2021), ‘Consciousness among delta waves: A paradox?’, *Brain*, **vol. 144**, pp. 2257–2277.
2. Toker, D., Pappas, I., Lendner, J. D., Frohlich, J., Mateos, D. M., Muthukumaraswamy, S., Carhart-Harris, R., Paff, M., Vespa, P. M., Monti, M. M., Sommer, F. T., Knight, R. T., & D'Esposito, M. (2022), ‘Consciousness is supported by near-critical slow cortical electrodynamics’, *Proceedings of the National Academy of Sciences of the United States of America*, **vol. 119**, no. 7.
3. Lempel, A., Ziv, J. (1976), ‘On the complexity of finite sequences’, *IEEE Transactions on Information Theory*, **vol. 22**, no. 1, pp. 75-81.
4. Viertiö-Oja H., Maja V., Särkelä M., Talja P., Tenkanen N., Tolvanen-Laakso H., Paloheimo M., Vakkuri A., Yli-Hankala A., Meriläinen P. (2004), ‘Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module’, *Acta Anaesthesiol Scand*. **vol. 48**, no. 2, pp.154-61.
5. Schartner, M., Seth, A., Noirhomme, Q., Boly, M., Bruno, M. A., Laureys, S., Barrett, A. (2015), ‘Complexity of Multi-Dimensional Spontaneous EEG Decreases during Propofol Induced General Anaesthesia’, *PloS one*, **vol. 10**, no.8.
6. Duclos, C., Maschke, C., Mahdid, Y., Nadin, D., Rokos, A., Arbour, C., Badawy, M., Létourneau, J., Owen, A. M., Plourde, G., Blain-Moraes, S. (2022), ‘Brain Responses to Propofol in Advance of Recovery from Coma and Disorders of Consciousness: A Preliminary Study.’, *American journal of respiratory and critical care medicine*, **vol. 205**, no. 2, pp. 171–182.
7. Maschke C., Duclos C., Owen A.M., Jerbi K., Blain-Moraes S. (2022), ‘Aperiodic brain activity and response to anesthesia vary in disorders of consciousness’, *bioRxiv*. 2022.04.22.489199.
8. Zozor, S., Ravier, P., Buttelli, O. Buteeli. (2005), ‘On Lempel-Ziv complexity for multidimensional data analysis’, *Physica A: Statistical Mechanics and its Applications*, **vol. 345**, pp. 285–302.
9. Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., Duchesnay, E. (2011), ‘Scikit-learn: Machine Learning in Python’, *J. Mach. Learn. Res*, **vol. 12**, pp. 2825–2830.
10. Magliacano, A., Liuzzi, P., Formisano, R., Grippo, A., Angelakis, E., Thibaut, A., Gosseries, O., Lamberti, G., Noé, E., Bagnato, S., Edlow, B.L., Lejeune, N., Veeramuthu, V., Trojano, L., Zasler, N., Schnakers, C., Bartolo, M., Mannini, A., Estraneo, A. (2023), ‘Predicting Long-Term Recovery of Consciousness in Prolonged Disorders of Consciousness Based on Coma Recovery Scale-Revised Subscores: Validation of a Machine Learning-Based Prognostic Index’, *Brain Sciences*, **vol. 13**, no. 51.