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Using EEG Markers to Make Inferences about Anaesthetic-Induced Altered States of Arousal

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Gaskell and colleagues conducted a secondary analysis of a heterogeneous, multicenter database to study the relationship between the presence of frontal alpha-delta electroencephalogram (EEG) patterns and volitional responses assessed following anaesthesia induction using an isolated forearm technique.[1] The authors conclude that that neither the presence of the frontal alpha-delta EEG patterns nor any other EEG measure that they evaluated reliably correlated with the volitional responses. Based on the data the authors present, this statement is not correct.

Phase-Amplitude Modulation Discriminates Responsiveness from Unresponsiveness. The alpha and slow-delta oscillations that appear following the administration of a GABAergic anesthetic demarcate several states. There is a state of no modulation of the alpha oscillations by the slow-delta oscillations; a trough-max state during which the maximum amplitude of the alpha oscillation occurs at the nadir of the slow oscillations; the peak-max state during which the maximum amplitude of the alpha oscillations occurs at the peak of the slow oscillations; and the transition state, which marks the evolution of the peak-max modulation into burst suppression.[2] Purdon and colleagues showed that during induction and emergence from propofol-induced unconsciousness the presence of the trough-max pattern predicted a non-zero probability of response to auditory stimuli in each of 10 study subjects.[2] During the peak-max state all of the subjects were unresponsive.

Gaskell and colleagues analyzed EEG data from 86 subjects. They reported that of the 36 subjects who showed the either no modulation of the alpha oscillations by the slow-delta oscillations or the trough-max EEG pattern 6 had volitional responses. Hence, in the presence of the trough-max pattern or no modulation of the alpha oscillations by the slow-delta oscillations, the volitional response probability is 0.17 = 6/36 [0.08, 0.32].[3] The bracketed numbers are the 95% Bayesian credibility intervals based on a beta-binomial model (Fig. 1A, blue curve). This observation is completely consistent with a non-zero probability of response reported by Purdon and colleagues in the presence of trough-max dynamics.[2]

Gaskell and colleagues reported that no volitional response was elicited from any of the 50 patients who had either a peak-max or burst suppression pattern.[1] This gives a volitional

response probability of 0.0 = 0/50 [0, 0.06] (Fig. 1A orange curve). The probability that the response probability in the no modulation-trough-max group is greater than the response probability in the peak-max-burst suppression group is 0.9984, as computed by Monte Carlo convolution of the posterior densities from the two beta-binomial models (Fig. 1B).[3]

This reanalysis shows that, contrary to what the authors conclude, observing alpha and slow-delta oscillations and then assessing the state of phase-amplitude modulation (trough-max, peak-max, or no modulation) discriminates with high probability (effective certainty) between the unconscious and the conscious state in patients receiving a GABAergic induction agent or inhaled ether.[2] Source localization has helped identify the brain regions responsible for these modulation patterns.[4,5]. Mukamel and colleagues[4] localized the trough-max pattern to brain regions believed to mediate internal consciousness[6], and arousal from unconsciousness.[7] The peak-max pattern appears broadly across the cerebral cortex,[4] consistent with pronounced cortical OFF states in which neuronal firing is silent, and intracortical communications are likely fragmented.[5] Despite reporting 6 patients with volitional responses, no patient in the study had recall of intraoperative events following surgery.[1]

Some respondents had a neutral modulation pattern which we interpret to mean that there was no apparent phase-amplitude modulation either with the trough-max or the peak-max pattern. We presume that these subjects were patients D, E or F (Gaskell et al., Fig. 1D) or the patient in Figure 3. The lack of any modulation suggests that there was not a significant production of slow-wave oscillations despite what was perceived to be an appropriate induction dose of propofol. Absence of slow-wave modulation, a marker of decreased excitatory inputs from the brainstem to the thalamus and cortex and cortical OFF-states, makes it more likely that these patients could be conscious. Administered doses of anesthetics can be insufficient to induce unconsciousness despite apparent patient unresponsiveness. The presence of beta oscillations, absence of alpha and slow-delta oscillations and absence of burst suppression strongly suggest this state.

Ketamine Alters the Dynamics of and Alpha Oscillations. Formation of alpha oscillations is impeded by the administration of ketamine. This is because alpha oscillation production requires enhanced inhibitory activity among GABAergic inhibitory interneurons in the thalamus and cortex.[8,9] The GABAergic anesthetics enhance the activity of these interneurons whereas low-dose ketamine inhibits the activity of inhibitory neurons with NMDA receptors.[10,11] As a consequence, patients receiving ketamine will not form reliable alpha oscillations. Akeju and colleagues demonstrated this by showing that the initiation and maintenance of a ketamine infusion during sevoflurane and oxygen anaesthesia, shifted the alpha oscillations to beta oscillations (13-25 Hz).[12] Mashour and Avidian cite this observation in their commentary.[13] Figure 1D in the Gaskell paper shows that when the 3 ketamine patients (Patients D, E and F) were purportedly unconscious, each had peak power in the beta band and not in the alpha band. Furthermore, each of these 3 patients had diminished slow-delta power relative to the other patients in their cohort. These EEG features suggest that principled approaches are needed to monitor unconsciousness in patients receiving a combination of ketamine and a GABAergic anesthetic.

The Volitional Assessments Were Made With the Patients in a Dynamic Anaesthetic State. The authors state that anesthetic drugs were administered to "induce anaesthesia" without defining specific behavioral or neurophysiological endpoints, or fixed observational periods. The anaesthesiologists proceeded with the intubations after making their clinical assessments explicitly concluding that the anaesthetic state was adequate. Despite their clinical assessments, they found that the anaesthetic state was dynamic as 6 patients had volitional responses. That there could be a non-zero probability of response immediately following intubation is expected

because intubation is a potent nociceptive stimulus. In this study there is the added observational confound of the nociceptive stimulus due to the isolated forearm test. Hence, the findings from this reanalysis shows that the clinical assessment of the anaesthetic state based solely on a patient's appearance and vital signs is likely to be inaccurate immediately following intubation. Moreover, it points to a need to view anaesthesia-induced unconsciousness as a dynamic state that can be modulated by external stimuli.

Anaesthetic State Monitoring Should Combine the Clinical Assessment with EEG Monitoring and Knowledge of Neurophysiology. For a patient anesthetized with a GABAergic anesthetic alone or, with a GABAergic anesthetic combined with an opioid and a muscle relaxant, the presence of a slow-delta and alpha oscillation pattern offers a basis for assessing the level of unconsciousness. The presence of phase-amplitude modulation in the peak-max or trough-max states helps significantly to refine that assessment. In the operating room, we assess the spectral content of the EEG and the degree of phase-amplitude modulation by monitoring the spectrogram (density spectral array) and the raw EEG signal simultaneously.[14]

The findings of Gaskell and colleagues support the use of alpha and slow-delta oscillations to assess level of unconsciousness in anesthetized patients. Their study highlights the risks of drawing definitive conclusions from secondary investigations that lack prospective, systematic data collection, well-defined behavioral and neurophysiological endpoints and appropriate statistical analyses. Their work further highlights the importance of using spectral analysis coupled with more refined EEG measures and an understanding of the neurophysiology underlying anaesthetic-induced oscillations to evaluate accurately the arousal levels of patients receiving general anaesthesia.[10,11,14,15]

References

1 Gaskell AL, Hight D, Winders J, et al. Frontal alpha-delta EEG does not preclude volitional response during anaesthesia: prospective cohort study of the isolated forearm technique. *Br J Anaesth* 2017; **119**: 664-73

2 Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A* 2013; **110**: E1142-51

3 Chemali JJ, Van Dort CJ, Brown EN, Solt K. Active emergence from propofol general anesthesia is induced by methylphenidate. *Anesthesiology* 2012; **116**: 998-1005

4 Mukamel EA, Pirondini E, Babadi B, et al. A transition in brain state during propofol-induced unconsciousness. *J Neurosci* 2014; **34**: 839-45

5 Lewis LD, Weiner VS, Mukamel EA, et al. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. *Proc Natl Acad Sci U S A* 2012; **109**: E3377-86

6 Vanhaudenhuyse A, Demertzi A, Schabus M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. *J Cogn Neurosci* 2011; **23**: 570-8

7 Langsjo JW, Alkire MT, Kaskinoro K, et al. Returning from oblivion: imaging the neural core of consciousness. *J Neurosci* 2012; **32**: 4935-43

8 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

9 Flores FJ, Hartnack KE, Fath AB, et al. Thalamocortical synchronization during induction and emergence from propofol-induced unconsciousness. *Proc Natl Acad Sci U S A* 2017; **114**: E6660-E8

10 Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med* 2010; **363**: 2638-50

11 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

12 Akeju O, Hamilos AE, Song AH, et al. GABAA circuit mechanisms are associated with ether anesthesia-induced unconsciousness. *Clin Neurophysiol* 2016; **127**: 2472-81

13 Mashour GA, Avidan MS. Black swans: challenging the relationship of anaesthetic-induced unconsciousness and electroencephalographic oscillations in the frontal cortex. *Br J Anaesth* 2017; **119**: 563-5

14 Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology* 2015; **123**: 937-60

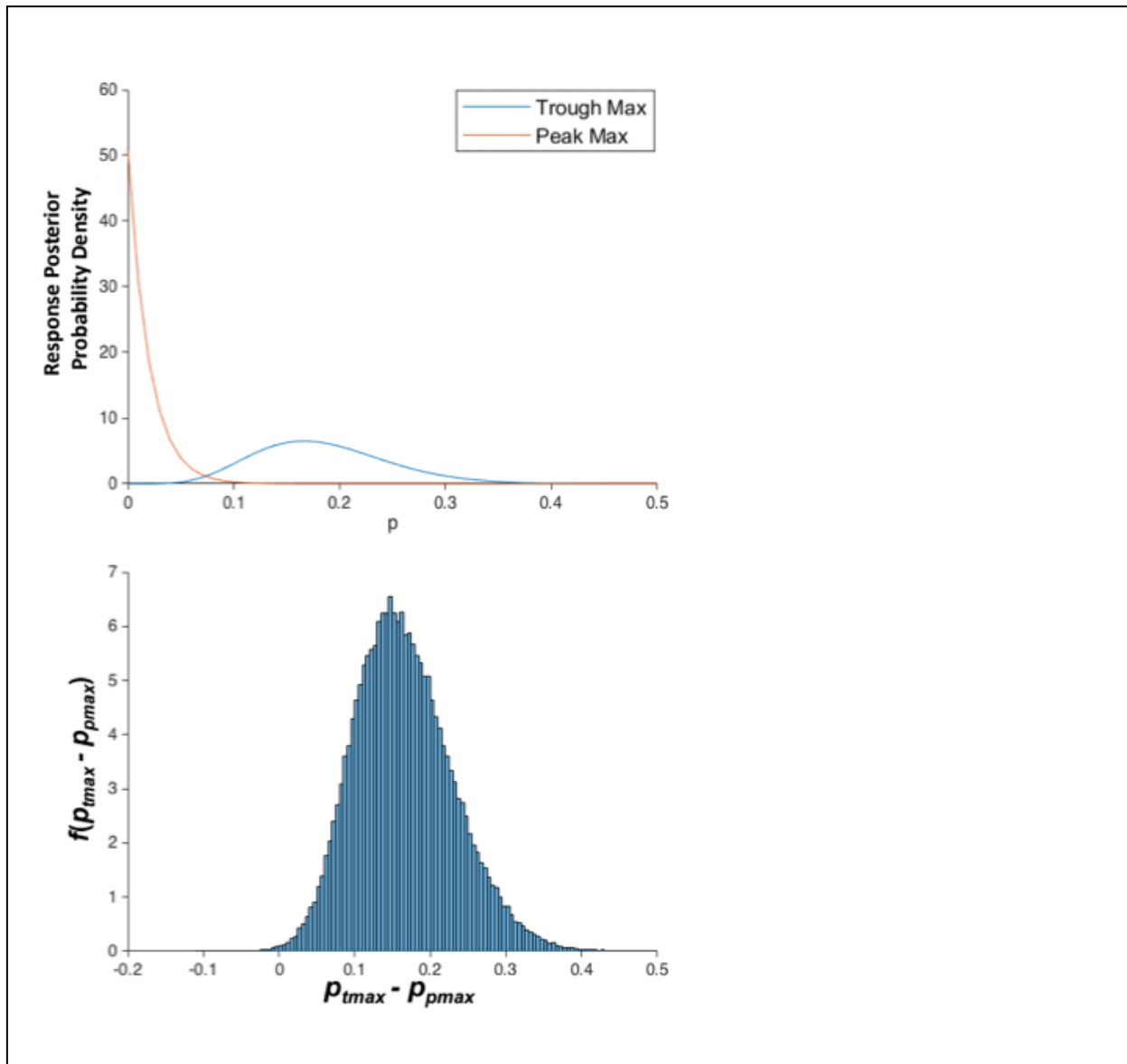15 Brown EN, Purdon PL. The aging brain and anesthesia. *Curr Opin Anaesthesiol* 2013; **26**: 414-9

Figure 1. Bayesian analysis of the probability of responding as a function of EEG signatures using a beta-binomial model.[3] **A.** Blue curve is $f(p_{t\max})$, the posterior probability density of responding during the isolated forearm test given a trough-max EEG pattern. Orange curve is $f(p_{p\max})$, the posterior probability density of responding during the isolated forearm test given a peak-max/ burst suppression EEG pattern. **B.** Probability density of the difference between the trough-max and the peak-max probability of responding computed by Monte Carlo convolution.[3] The probability density $f(p_{t\max} - p_{p\max})$, gives the probability that the trough-max probability of response is greater than the peak-max probability of response. The probability that the trough max response probability is greater than the peak-max probability is 0.9984 (area under the curve to the right of zero). Hence, the trough-max and peak-max groups can be distinguished with near certainty.