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Metastability of Neuronal Dynamics during General Anesthesia: Time for a Change in Our Assumptions?

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There is strong evidence that anesthetics have stereotypical effects on brain state, so that a given anesthetic appears to have a signature in the electroencephalogram (EEG), which may vary with dose. This can be usefully interpreted as the anesthetic determining an attractor in the phase space of the brain. How brain activity shifts between these attractors in time remains understudied, as most studies implicitly assume a one-to-one relationship between drug dose and attractor features by assuming stationarity over the analysis interval and analyzing data segments of several minutes in length. Yet data in rats anesthetized with isoflurane suggests that, at anesthetic levels consistent with surgical anesthesia, brain activity alternates between multiple attractors, often spending on the order of 10 min in one activity pattern before shifting to another. Moreover, the probability of these jumps between attractors changes with anesthetic concentration. This suggests the hypothesis that brain state is metastable during anesthesia: though it appears at equilibrium on short timescales (on the order of seconds to a few minutes), longer intervals show shifting behavior. Compelling evidence for metastability in rats anesthetized with isoflurane is reviewed, but so far only suggestive hints of metastability in brain states exist with other anesthetics or in other species. Explicit testing of metastability during anesthesia will require experiments with longer acquisition intervals and carefully designed analytic approaches; some of the implications of these constraints are reviewed for typical spectral analysis approaches. If metastability exists during anesthesia, it implies degeneracy in the relationship between brain state and effect site concentration, as there is not a one-to-one mapping between the two. This degeneracy could explain some of the reported difficulty in using brain activity monitors to titrate drug dose to prevent awareness during anesthesia and should force a rethinking of the notion of depth of anesthesia as a single dimension. Finally, explicit incorporation of knowledge of the dynamics of the brain during anesthesia could offer better depth of anesthesia monitoring.

Keywords: metastability, isoflurane, rats, Sprague-Dawley, attractor networks, attractor dynamics

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INTRODUCTION

General anesthesia is a pharmacologically-induced, reversible state of unarousable unresponsiveness. As in other states of unconsciousness, such as absence seizure or the vegetative state, the brain is not necessarily electrically quiescent during general anesthesia. From the earliest days of electroencephalography (EEG), Gibbs et al. (1937) reported stereotypic shifts with