Propofol Anesthesia: A Leap into the Void?

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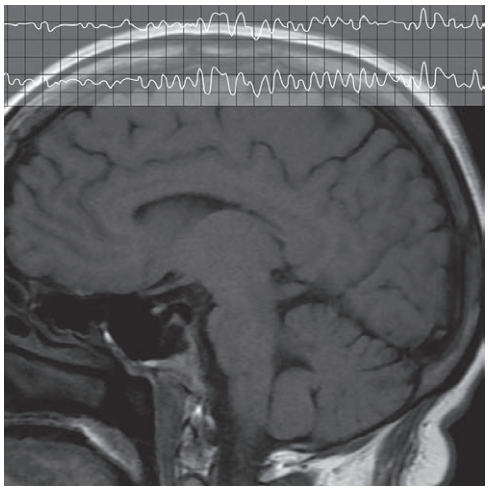
For the greater part of the 20th century, research into the mechanisms of general anesthesia focused on biomolecular targets such as lipids and proteins. In the mid-1990s, this approach was complemented by emerging studies of anesthetic mechanisms based on systems neuroscience, which has thus far been a major focus in the 21st century. This line of investigation extends beyond the molecular and biophysical focus to the study of neural circuits and the properties of large-scale brain networks, as assessed, for example, by functional magnetic resonance imaging and electroencephalography. For the past 15 yr, neuroimaging and neurophysiologic data during anesthetic state transitions have been increasingly analyzed with measures of functional connectivity (how activities of different brain regions co-vary), directional or effective connectivity (how activities in one brain region influence that of another), and global network properties (how interconnected nodes behave in terms of overall efficiency and organization).[1] Despite remarkable progress, questions remain, including how these various connectivity and network properties unfold during the induction of general anesthesia. Does the brain experience a smooth slide to the depths of oblivion? Or is there a kind of quantum leap into the void? In this issue of Anesthesiology, the study from Pullon, Warnaby, and Sleigh helps address this very quandary.[2] The investigators reanalyzed data from a study of 16 healthy human volunteers who underwent a slow induction of propofol anesthesia while multichannel electroencephalography was recorded. Behavioral responsiveness was assessed by a command and button-pressing; after general anesthesia was established, passive emergence (rather than a symmetrical down-titration of propofol) was permitted.



"[In anesthesia] does the brain experience a smooth slide to the depths of oblivion? Or is there a kind of quantum leap into the void?"

After the experiment, the investigators used the electroencephalographic data to assess functional connectivity, *i.e.*, how the neurophysiologic activity around one electrode relates to—or coheres with—that of a more distant electrode. By way of analogy, imagine the three authors of this Editorial singing in harmony. Our activity (singing) would be functionally connected (harmony) even if we were not influencing one another directly because we were all reading from a single musical score.

The investigators also measured a surrogate of shared information evident in the neurophysiologic signal and they analyzed network properties such as efficiency and clustering (*i.e.*, how many of a node's connections have connections with each other, like a close-knit group of friends). Finally, they analyzed complexity in the neurophysiologic signal, reflecting the diversity of activity across the brain. To complement these empirical studies, they also used a well-known computational model of oscillatory activity to link their empirical connectivity and complexity measures to an important dynamic feature of networks known as criticality. Criticality is when a system is poised on the boundary of order and disorder. In neurobiological terms, the advantage of dancing on this fine line is that the brain can flexibly respond to incoming stimuli without being entrenched in any one set of activities.

Although these analytic techniques have all been employed before in the context of anesthetic state transitions, what is new in the article from Pullon *et al.*[2] is the joint consideration of these network properties in the context of a slow, carefully controlled induction of propofol anesthesia. The gradual ramp-up of propofol infusion is important because a bolus dose would induce a rapid network change

Image: J. P. Rathmell.

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and thus mask the intrinsic nature of the state transition from consciousness to propofol-induced unresponsiveness. What the investigators found was evidence of a *phase transition* (*i.e.,* a jump from one state of the network to another). This quantum leap is of relevance to the history of the aforementioned anesthetic mechanisms research because such a phase transition cannot be reduced trivially to the sum of micro-level events at molecular targets. Rather, it reflects the emergent and collective dynamics of the system as a whole. This is of interest to us as clinicians because it suggests that the brain is not sliding down to general anesthesia in a way that could be readily measured by a smooth and linear index. Furthermore, the investigators found that the transition could not be reduced to brain activity being hypercoherent or decoherent. Rather, the state of coherence depended on the frequency under consideration, where alpha oscillations (around 10 Hz) were hypersynchronized and slow oscillations were fragmented. This was associated with a rapid decline in network efficiency, which would be inhospitable to information exchange across the brain. This is relevant to general anesthesia because information integration appears to be an important prerequisite for normal conscious experience.[1]

Consider that you and an attending surgeon get into a heated argument, speaking loudly to one another at the same time (we know this never happens, but just stretch your imagination). As a result, the rest of the staff in the operating room suddenly turn to their neighbors and break out into multiple local conversations. In this example, you and the surgeon would be abnormally synchronized (rather than healthily in sync), while the rest of the personnel would be desynchronized; at this point, the overall efficiency of the team would plummet, along with a disruption of information exchange among the team members. In other words, a dramatic shift in one set of events would have a host of attendant consequences at the same time. This is what Pullon, Warnaby, and Sleigh[2] suggest is happening in brain networks during the induction of general anesthesia.

Importantly, the investigators observed what is called "critical slowing down," which refers to a change in the state of criticality already discussed. This was an interesting finding for two reasons. First, critical slowing signals that the network has undergone a phase transition, which confirms the interpretation of the data. Second, systems that undergo critical slowing take longer to recover than they did to be disrupted. In terms of general anesthesia, that asymmetry would be manifested as hysteresis, in which forward and reverse processes are not the same. Hysteresis has, indeed, been observed in both animals and humans undergoing state transitions and can be attributed to the underlying network dynamics rather than solely to pharmacokinetic factors.[3–6]

As with all studies, this one had technical and analytical limitations, which the authors report clearly. Despite the limitations, the work of Pullon *et al.*[2] prompts further scientific and clinical investigation. Scientifically, we still need to understand the link between micro-level events related to anesthetic mechanisms (*i.e.,* molecular actions that might occur in a gradual manner) and macro-level events, which the authors argue happen in a sudden, discontinuous manner. Clinically, this work, along with that of others, makes us question the notion of a linear conceptualization of "depth of anesthesia," in which, for example, a neurophysiologic index would smoothly slide down along with a gradual descent in level of consciousness. In fact, this study makes us reconsider the proposition that consciousness is a graded phenomenon at all. Furthermore, the investigators provide evidence that there is a sudden change in network dynamics when humans become unresponsive; however, we remain ignorant as to whether they remain conscious but disconnected from the environment (such as in a dream state) or whether they have abruptly transitioned to a state of unconsciousness.[7] Is the electroencephalographic phase transition only a marker for loss of behavioral responsiveness, with the capacity for conscious experience continuing unperturbed? The next frontier is to understand whether unintended emergence from anesthesia is driven by a sudden reversal of these network dynamics, particularly when driven by nociceptive stimulation,[8] and whether these analytic techniques can be used to rapidly identify or predict periods of vulnerability and anesthetic state instability.

The authors are to be commended for highlighting how numerous network features that have been studied individually (hypersynchrony of alpha, decoherence of delta, and reduced efficiency, among others) appear to represent a constellation of properties that travel together as brain networks jump from the critical edge of consciousness into the void of anesthesia.

Competing Interests

Dr. Mashour is a consultant for TRYP Therapeutics (San Diego, California). The other authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Lee U, Mashour GA: Role of network science in the study of anesthetic state transitions. Anesthesiology 2018; 129:1029–44
2. Pullon RM, Warnaby CE, Sleigh JW: Propofol-induced unresponsiveness is associated with a brain network phase transition. Anesthesiology 2022; 136:420–33
3. Proekt A, Kelz MB: Explaining anaesthetic hysteresis with effect-site equilibration. Br J Anaesth 2021; 126:265–78

4. Warnaby CE, Sleigh JW, Hight D, Jbabdi S, Tracey I: Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. Anesthesiology 2017; 127:645–57
5. Kim H, Moon JY, Mashour GA, Lee U: Mechanisms of hysteresis in human brain networks during transitions of consciousness and unconsciousness: Theoretical principles and empirical evidence. PLoS Comput Biol 2018; 14:e1006424
6. Huang Z, Tarnal V, Vlisides PE, Janke EL, McKinney AM, Picton P, Mashour GA, Hudetz AG: Asymmetric neural dynamics characterize loss and recovery of consciousness. Neuroimage 2021; 236:118042
7. Sanders RD, Tononi G, Laureys S, Sleigh JW: Unresponsiveness ≠ unconsciousness. Anesthesiology 2012; 116:946–59
8. Gaskell AL, Hight DF, Winders J, Tran G, Defresne A, Bonhomme V, Raz A, Sleigh JW, Sanders RD: 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