Highways of the Brain, Traffic of the Mind

George A. Mashour, M.D., Ph.D.

HOW consciousness emerges from the coordinated activity of neural firing across the brain remains among the most important questions of twenty-first-century science. A related foundational question in the field of anesthesiology is how the anesthetic drugs we use on a daily basis reversibly suppress consciousness. There are many current approaches to this question, but whatever one's scientific perspective it is likely uncontroversial to suggest that we will need to understand the state of information in the brain during consciousness and anesthesia in order to achieve a satisfactory explanation. When considering such information processing, it might be helpful to consider the analogy of traffic. Streets and highways represent the structural basis that enables transport to and from various locations. Cars are the vehicles that carry the people and, collectively, traffic patterns emerge. We can imagine that, at certain times of the day, traffic can be dynamic, efficient, and complex. At other times, or under other conditions, there might be gridlock or the streets could be empty. On and off ramps along major highways help create the kinds of dynamic patterns that are observed in daily life.

"…constraining traffic to more inflexible patterns on the highways of the brain may be one reason why general anesthetics suppress consciousness."

In the brain, the anatomic connections between different regions are the structural highways, neural spikes across those highways are the vehicles, and information is the passenger being transported. Just as in the highway system, there can be dynamic patterns of traffic (such as in the waking state) or completely empty streets (such as in brain death). But what happens during the state of general anesthesia? In this issue of Anesthesiology, Uhrig *et al.* report a study of functional magnetic resonance imaging of the brain that evaluated the relationship between activity patterns (functional connectivity) and the highway system itself (structural connectivity).[1] By comparing these two forms of connectivity during consciousness and unconsciousness induced by various anesthetic drugs, they have identified a potentially agent-invariant signature of general anesthesia.

The investigators studied monkeys in a state of wakefulness, followed by general anesthesia with propofol, sevoflurane, or ketamine. They assessed the relationship between the functional magnetic resonance imaging signals in different parts of the brain, which is referred to as functional connectivity and which can be much more diverse than the structural connectivity highway itself.[2] In the waking state, they found that the repertoire of functional connectivity patterns was richer than the anatomic connections alone. In other words, they observed what appeared to be dynamic patterns of signals in the same way we can observe dynamic patterns of traffic, even assuming the same highway. What happened during anesthesia is that the repertoire of connectivity patterns contracted and the functional connectivity pattern more closely adhered to the structural connectivity. Returning to the analogy, you could imagine a variety of traffic situations in which your flexibility would be constrained and your travel much less efficient. Importantly, the specific restriction of flexibility in the functional connectivity patterns was a consistent finding across each of these molecularly and pharmacologically diverse anesthetics. Although Uhrig *et al.* did not study neural spike activity (the vehicle) or information (the passenger), their data suggest that constraining traffic to more inflexible patterns on the highways of the brain may be one reason why general anesthetics suppress consciousness.

To be more neuroanatomically specific, the investigators found that general anesthesia is dominated by brain states in which there is a disruption of correlated activity between the prefrontal, parietal, and posterior cingulate cortices. It was posited that this particular and consistent contraction of functional repertoire observed in the monkeys explains past observations in humans regarding the disruption of functional connectivity between the frontal cortex and more posterior cortex by the same three anesthetics (propofol, sevoflurane, and ketamine).[3,4] Although other brain areas were also affected—and subcortical regions were not evaluated—these brain regions are important nodes in a network that has been referred to as the global neuronal workspace.

Global workspace theory is a framework for explaining consciousness that originated in the field of psychology in

Image: A. Johnson/J. P. Rathmell.

Corresponding article on page 942.

Accepted for publication July 9, 2018. From the Center for Consciousness Science, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan.

 Anesthesiology 2018; 129:869-71

<zdoi;10.1097/ALN.0000000000002385>

the 1980s. In the past two decades, the theory has become increasingly informed by neuroscience and has thus metamorphosed into global neuronal workspace theory.[5] The basic idea is that information becomes conscious in the brain when it is broadcast and becomes available to a wide network that prominently involves prefrontal, parietal, and cingulate cortices.[6,7] Note that this theory attempts to explain the kind of conscious experience you are probably having right now, which includes not only experience but also the ability to hold that experience in working memory, talk about it, plan a course of action based on it, and more. This conscious experience is accessible to other cognitive systems and has thus been referred to as "access consciousness," in contrast to the more purely experiential "phenomenal consciousness."[8] Why should we in anesthesiology care about such a distinction? Clinically, it matters because access consciousness might be the consciousness that is going away when we administer general anesthetics. Since patients under general anesthesia can dream[9] and have isolated or disconnected fragments of experience,[10,11] access consciousness—in other words, accessible experience that is connected to a self and that can be reported, remembered, acted upon—might be the target of our drugs. Whether we should extinguish all forms of experience is a separate question, but what is actually suppressed during what we typically consider a successful general anesthetic could, in fact, be access consciousness. Scientifically, it matters because current thinking suggests that access consciousness requires more extensive involvement of the prefrontal cortex (in the front of the brain), whereas phenomenal consciousness, *i.e.*, the purer and more isolated experience, might be generated in what has been referred to as the posterior "hot zone" of consciousness (in the back of the brain).[12] Thus, if general anesthesia is to be considered the disruption of one or the other form of consciousness, we might search for its mechanisms in different parts of the brain. These clinical and scientific considerations converge on the question of brain monitoring, with some suggesting that general anesthesia should not be assessed by focusing on the frontal cortex,[13] as we have traditionally done. The consideration of access *versus* phenomenal consciousness, global neuronal workspace *versus* integrated information theories of consciousness, and anterior *versus* posterior neural correlates of consciousness is now an active debate in the neurosciences—anesthesiology surely has an important role to play in informing it and, possibly, resolving it.

In conclusion, Uhrig *et al.* have added further evidence that there is a neural correlate of anesthetic-induced unconsciousness that can be identified in the cortex and that is consistent across propofol, sevoflurane, and ketamine anesthesia. These data provide scientific support to studies showing agent-invariant disruption of functional connectivity in frontal-parietal networks during general anesthesia in humans,[3,14–17] studies demonstrating agent-invariant stabilization of cortical dynamics during general anesthesia in monkeys,[18] and theoretical frameworks proposing reduced network repertoire or efficiency as a driver of the anesthetized state.[19,20] The data also shift the conversation of anesthetic-induced unconsciousness from integrated information to the wider framework of access consciousness and global neuronal workspace theory. Additional studies clearly need to be conducted to understand how these cortical patterns relate to—or are driven by—the well-described effects of general anesthetics in subcortical regions, their causal significance, and the clinical relevance to the more complex perioperative environment that often includes a prolonged surgical anesthetic. The investigation of Uhrig *et al.* does, however, carry the field further on its journey by providing evidence that diverse general anesthetics constrain the traffic patterns of the mind to what might be lonely highways of the brain.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Mashour: gmashour@umich.edu

References

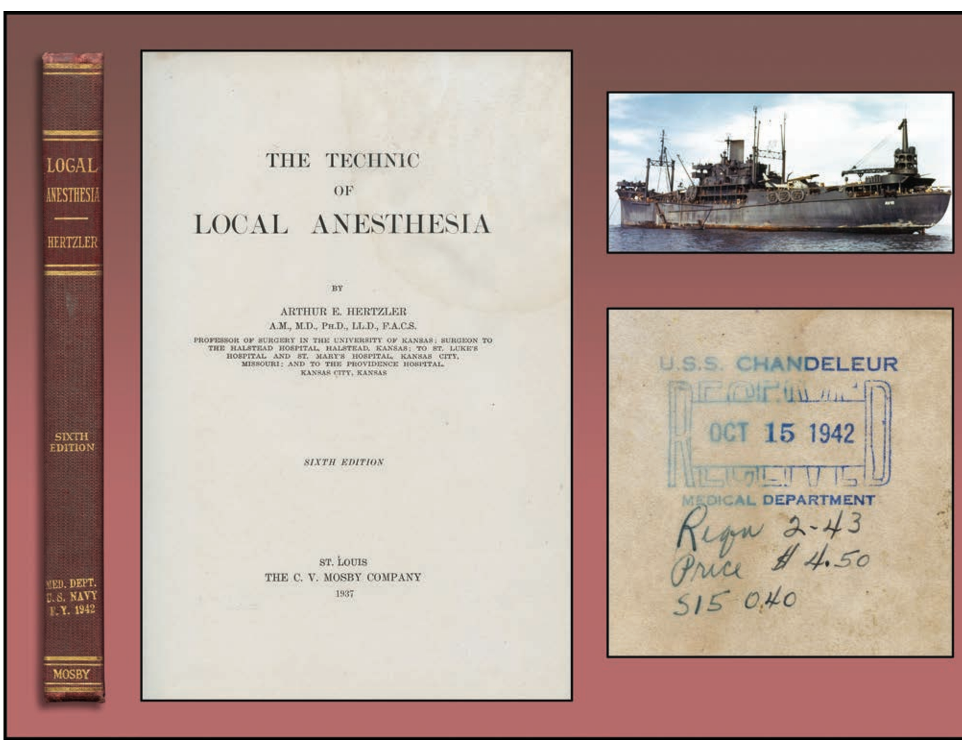
1. Uhrig L, Sitt J, Jacob A, Tasserie J, Barttfeld P, Dupont M, Dehaene S, Jarraya B: Resting-state dynamics as a cortical signature of anesthesia in monkeys. Anesthesiology 2018; 129:942–58
2. Barttfeld P, Uhrig L, Sitt JD, Sigman M, Jarraya B, Dehaene S: Signature of consciousness in the dynamics of resting-state brain activity. Proc Natl Acad Sci USA 2015; 112:887–92
3. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA: Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. Anesthesiology 2013; 118:1264–75
4. Mashour GA, Hudetz AG: Neural correlates of unconsciousness in large-scale brain networks. Trends Neurosci 2018; 41:150–60
5. Dehaene S, Changeux JP: Experimental and theoretical approaches to conscious processing. Neuron 2011; 70:200–27
6. Mashour GA: The controversial correlates of consciousness. Science 2018; 360:493–4
7. van Vugt B, Dagnino B, Vartak D, Safaai H, Panzeri S, Dehaene S, Roelfsema PR: The threshold for conscious report: Signal loss and response bias in visual and frontal cortex. Science 2018; 360:537–42
8. Block N: Two neural correlates of consciousness. Trends Cogn Sci 2005; 9:46–52
9. Leslie K, Skrzypek H, Paech MJ, Kurowski I, Whybrow T: Dreaming during anesthesia and anesthetic depth in elective surgery patients: A prospective cohort study. Anesthesiology 2007; 106:33–42
10. Warnaby CE, Seretny M, Ní Mhuircheartaigh R, Rogers R, Jbabdi S, Sleigh J, Tracey I: Anesthesia-induced suppression of human dorsal anterior insula responsivity at loss of volitional behavioral response. Anesthesiology 2016; 124:766–78
11. Sanders RD, Raz A, Banks MI, Boly M, Tononi G: Is consciousness fragile? Br J Anaesth 2016; 116:1–3
12. Koch C, Massimini M, Boly M, Tononi G: Neural correlates of consciousness: Progress and problems. Nat Rev Neurosci 2016; 17:307–21
13. 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

14. Jordan D, Ilg R, Riedl V, Schorer A, Grimberg S, Neufang S, Omerovic A, Berger S, Untergehrer G, Preibisch C, Schulz E, Schuster T, Schröter M, Spoormaker V, Zimmer C, Hemmer B, Wohlschläger A, Kochs EF, Schneider G: Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. Anesthesiology 2013; 119:1031–42
15. Ranft A, Golkowski D, Kiel T, Riedl V, Kohl P, Rohrer G, Pientka J, Berger S, Thul A, Maurer M, Preibisch C, Zimmer C, Mashour GA, Kochs EF, Jordan D, Ilg R: Neural correlates of sevoflurane-induced unconsciousness identified by simultaneous functional magnetic resonance imaging and electroencephalography. Anesthesiology 2016; 125:861–72
16. Bonhomme V, Vanhaudenhuyse A, Demertzi A, Bruno MA, Jaquet O, Bahri MA, Plenevaux A, Boly M, Boveroux P, Soddu A, Brichant JF, Maquet P, Laureys S: Resting-state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. Anesthesiology 2016; 125:873–88
17. Vlisides PE, Bel-Bahar T, Lee U, Li D, Kim H, Janke E, Tarnal V, Pichurko AB, McKinney AM, Kunkler BS, Picton P, Mashour GA: Neurophysiologic correlates of ketamine sedation and anesthesia: A high-density electroencephalography study in healthy volunteers. Anesthesiology 2017; 127:58–69
18. Solovey G, Alonso LM, Yanagawa T, Fujii N, Magnasco MO, Cecchi GA, Proekt A: Loss of consciousness is associated with stabilization of cortical activity. J Neurosci 2015; 35:10866–77
19. Hudetz AG, Humphries CJ, Binder JR: Spin-glass model predicts metastable brain states that diminish in anesthesia. Front Syst Neurosci 2014; 8:234
20. Lee U, Mashour GA: Role of network science in the study of anesthetic state transitions. Anesthesiology 2018 April 20 [Epub ahead of print]

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

How Hertzler's *Local Anesthesia* Saw More Than Local Military Action



A textbook authored at the University of Kansas by surgeon Arthur Hertzler, M.D., *The Technic of Local Anesthesia* was published in its 6th edition by 1937 (*left* and *center*). During the month before transferring the *Chandeleur* (*upper right*) from San Francisco's Western Pipe and Steel Company to the United States Navy, the seaplane tender received this copy of Hertzler's book for its Medical Department (*lower right*). Ferrying aviators, shipping cargo, and tendering seaplanes, the USS *Chandeleur* and this "local" book witnessed military action in the waters of the South Pacific and off the shores of the Philippines and Japan during World War II. Mothballed by 1947 in the Navy's Philadelphia reserve, the *Chandeleur* was scrapped in 1971. Fortunately, this book, this tiny piece of the USS *Chandeleur*, was recovered (not re-covered) recently for the Wood Library-Museum's military anesthesia collection. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.