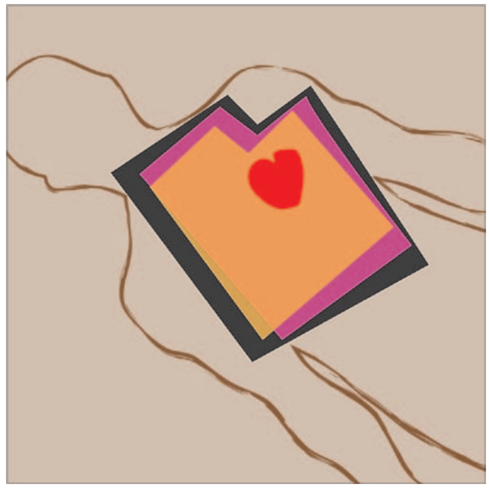
Consciousness and the 21st Century Operating Room



DURING discussions of intraoperative monitoring with our anesthesiology residents, I like to describe the following clinical scenario involving a new patient and a rather unusual cardiologist. After waiting months for an appointment, Mrs. Jones is befuddled that her "heart doctor" performs only a neurologic examination and, on the basis of that examination, has ordered a stress test. She is flabbergasted to discover that this test consists of a brisk run on the treadmill followed by diagnostic evaluations with electroencephalography and brain scanning. Why is Mrs. Jones confused and upset? The residents—and you—can easily identify the problem: the cardiologist is making inferences about the cardiovascular system based on data from the nervous system, despite the fact that the target organ of cardiology is the heart. The good news, of course, is that real-life cardiology does not work this way… the bad news is that real-life anesthesiology does. In operating rooms around the world, anesthesia providers are making inferences about the nervous system based on data from the cardiovascular system, despite the fact that—for general anesthetics—the target organ of anesthesiology is the brain. In this issue of Anesthesiology, Jordan *et al.*[1] take multiple approaches to assess brain function during propofol anesthesia in humans and pave the way for the neurobiology of consciousness to inform our clinical practice.

"In operating rooms around the world, anesthesia providers are making inferences about the nervous system based on data from the cardiovascular system, despite the fact that—for general anesthetics—the target organ of anesthesiology is the brain."

In brief, Jordan and his coinvestigators found that propofol-induced unconsciousness is associated with a reduction of directed connectivity from anterior to posterior brain structures (fig. 1 for summary). They derived this conclusion from the analysis of electroencephalography using the technique of symbolic transfer entropy, a method based on information theory. This has neurobiological significance because such "top-down" or "feedback" processing from the prefrontal cortex is thought to be particularly important for human consciousness.[2] Impairment in feedback connectivity from frontal to parietal areas of the brain has previously been associated with induction of unconsciousness using propofol, sevoflurane, and ketamine in humans (table 1 for review of relevant studies)[3–9] as well as isoflurane in rats.[10] The current study is unique because it extended investigation in two directions. First, in addition to using electroencephalography, Jordan *et al.* used functional magnetic resonance imaging to assess underlying brain connectivity. Second, they conducted a separate analysis of their high-density electroencephalography recordings and identified selective changes in the frontal region that could be amenable to intraoperative monitoring. As such, they have helped bridge a translational gap and advanced our understanding of anesthetic mechanisms as well as anesthetic monitoring. Based on their neuroimaging findings, we now know that the loss of top–down (feedback) processing observed in previous studies is associated with functional disconnections between anterior and posterior brain structures, as opposed to some epiphenomenal marker identified by electroencephalographic analysis. This is important because of certain discrepancies among studies using only electroencephalography (table 1; although a past neuroimaging

Illustration: J. P. Rathmell.

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◆ This Editorial View accompanies the following article: Jordan D, Ilg R, Riedl V, Schorrer 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.

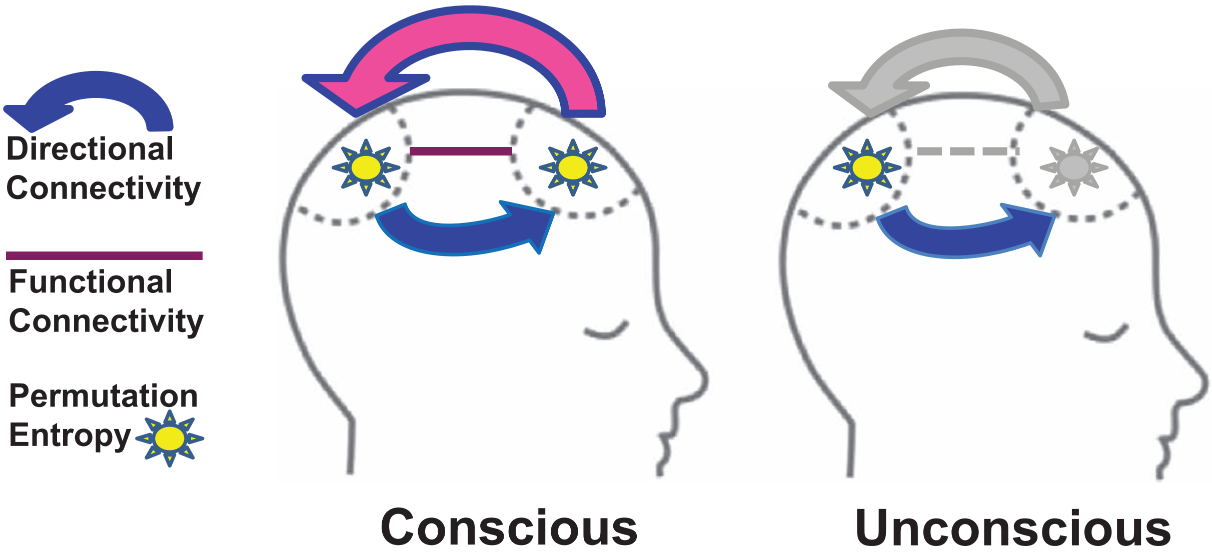

Fig. 1. Schematic that summarizes the findings of Jordan *et al.*[1] The authors used simultaneous electroencephalography and functional magnetic resonance imaging to study propofol-induced unconsciousness. They identified a decrease in (1) anterior-to-posterior directional connectivity (symbolized by *arrows*, with *gray* color indicating a reduction), (2) anterior–posterior functional connectivity (symbolized by *lines*, with *gray color/dash* indicating a reduction), and (3) frontal permutation entropy (symbolized by *stars*, with *gray* color indicating a reduction).

study also identified functional disconnections between anterior and posterior networks,[9] it did not have simultaneous electroencephalography). Just as importantly, we now know that we might be able to capture a glimpse of that neurobiological picture with a more readily calculated measure (permutation entropy) that can be used intraoperatively. Fortunately, the neurophysiologic relevance of the frontal lobes to consciousness and anesthesia fits well with the practical realities of the brain activity that we can actually monitor in the operating room.

Table 1. Electroencephalographic Studies of Directional (Anterior–Posterior) Brain Connectivity during Consciousness and Anesthesia in Humans

Study	Participants	Anesthetic	Analytic Technique	Comments
Lee *et al.*[3]	Healthy volunteers	Propofol	Evolution map approach	Disrupted frontoparietal feedback connectivity
Ku *et al.*[4]	Surgical patients	Propofol, sevoflurane	Evolution map approach, symbolic transfer entropy	Disrupted frontoparietal feedback connectivity, return of feedback during recovery of consciousness
Barrett *et al.*[5]	**Healthy volunteers**	**Propofol**	**Granger causality**	**Increased bidirectional connectivity**
Nicolaou *et al.*[6]	**Surgical patients**	**Routine surgical anesthetic regimens**	**Granger causality**	**Increased frontoparietal connectivity, return to baseline with recovery of consciousness**
Boly *et al.*[7]	Healthy volunteers	Propofol	Dynamic causal modeling	Disrupted frontoparietal feedback connectivity
Lee *et al.*[8]	Surgical patients	Ketamine, propofol, sevoflurane	Normalized symbolic transfer entropy	Disrupted frontoparietal feedback connectivity
Jordan *et al.*[1]	Healthy volunteers	Propofol	Symbolic transfer entropy	Disrupted anterior–posterior feedback connectivity; confirmation with simultaneous fMRI

Note that the two studies highlighted in **bold**, which used Granger causality as a measure of directional connectivity, had opposite results compared with the other investigations. The use of simultaneous fMRI by Jordan *et al.*[1] supports the reduction of frontal–parietal connectivity found in the majority of electroencephalographic studies, but further work is required. The magnetic resonance imaging results are consistent with those of Boveroux *et al*.[9]

fMRI = functional magnetic resonance imaging.

Despite the compelling findings of this study, there are many questions that have yet to be answered. On the mechanistic level, why should there be a *preferential* interruption of top–down information processing in the brain? How do molecularly and pharmacologically diverse anesthetics achieve this potentially common endpoint?[8] How do we link the events at the "top" of the brain (prefrontal cortex) with the influence of subcortical structures (brainstem, diencephalon) controlling arousal states and mediating anesthetic endpoints?[11] In terms of the implications for monitoring, we know that this loss of top–down/feedback connectivity from frontal to parietal areas consistently occurs with loss of consciousness, but what about the recovery phase? Does feedback connectivity return in advance of or in association with returning consciousness? If so, will we be able to detect it in real time in the real-world intraoperative setting? The data presented by Jordan *et al.* encourage future research into both anesthetic mechanism and anesthetic monitoring.

The current study is among a handful of emerging investigations that are combining magnetic resonance imaging with electroencephalography. Although no one would suggest that real-time neuroimaging is practical for the operating room, the data derived from these studies will help establish a scientifically grounded basis for new metrics of anesthetic depth. These technological advances, in conjunction with hypotheses based on the cognitive neuroscience of consciousness, will hopefully usher in an era of brain monitoring techniques that have a clear neurobiological basis. Without such a basis, it is unlikely that we will ever adopt a standard monitor for the brain… this is because anesthesiologists are compelled not only by the numbers on their monitors but also more fundamentally by the underlying physiology. Studies similar to that of Jordan *et al.* will help advance the field toward routine monitoring of a key target of general anesthetics by making the assessment of consciousness a practical and mechanistically grounded tool for the 21st century operating room.

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