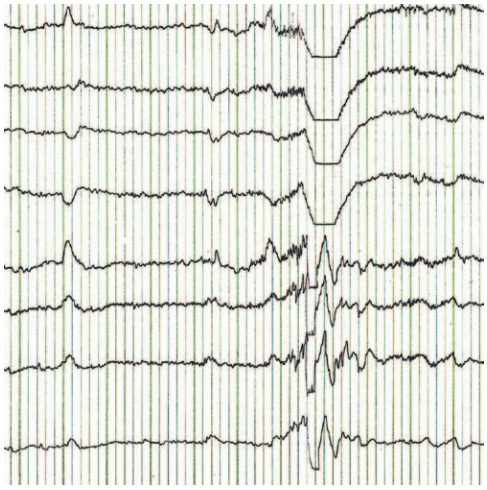
Integration and Information

Anesthetic Unconsciousness Finds a New Bandwidth

Andrew E. Hudson, M.D., Ph.D., Kane O. Pryor, M.D.

THE study of how anesthetic drugs reliably and reversibly cause unconsciousness provides insight not only into anesthetic mechanisms, but also into one of the great questions in all of science: how are humans conscious and what are the necessary and sufficient mechanistic features? One dynamical feature of anesthetic unconsciousness that has been repeatedly identified by multiple investigative groups using different anesthetics is the fragmentation or functional disconnection of cortical areas, whether assessed by electrophysiology or neuroimaging. Yet, upon recovery from anesthesia, we remain ourselves, with our memories, experiences, and personalities largely unchanged. This suggests that the underlying structural connectivity, in the sense of the point-to-point wiring of the brain, is stable during anesthesia, but it is reversibly rendered nonfunctional. How cortical computation becomes fragmented by anesthetics and then reconstitutes itself after recovery thus remains a vital question.



"How might disruption of the functional connection between cortical modules... be so crucial to inducing a state of unconsciousness?"

In a significant step toward linking the systems-theoretic level analysis of cortical fragmentation to candidate anesthetic mechanisms, the current issue of Anesthesiology contains a report by Pal *et al.*[1] that investigates the contribution of the cholinergic system to cortical fragmentation with anesthesia. In a rat model, the investigators simultaneously compared multiple electrocephalographic indices of cortical connectivity with microdialysate concentrations of cortical acetylcholine during wakefulness, two stages of sleep, and two different anesthetic regimens (propofol and sevoflurane). By including studies during rapid eye movement (REM) and slow-wave sleep (SWS), the investigators were able to compare anesthetic unconsciousness with contrasting physiologic states in which the absence of wakefulness is accompanied by either the presence (REM sleep) or absence (SWS) of increased cholinergic tone and cortical activation.

An earlier generation of studies evaluating anesthetic effects on connectivity emphasized the importance of first-order thalamocortical circuits and cross-regional coherence in the low γ range centered around 40 Hz. However, contemporary studies have provided persuasive evidence that cross-modal corticocortical networks and in particular frontoparietal networks may in fact be the most essential target for induced states of unconsciousness.

How might disruption of the functional connection between cortical modules, even when achieved *via* different mechanisms, be so crucial to inducing a state of unconsciousness? One conceptual framework is provided by integrated information theory (IIT), a mathematical characterization of consciousness first presented by Tononi in 2004, and recently updated.[2] In IIT, elements of a system that convey information (by possessing a large repertoire of flexible cause–effect states) can only contribute to consciousness if they are integrated such that the integrated whole contains more information than is possessed by the sum of its reduced parts. Integration requires connectivity. IIT has proven robust when tested experimentally and provides a parsimonious explanation for why brain regions can be highly active and yet not contribute to consciousness. The cerebellum, for example, contains far more neurons than the cortex and is highly interconnected with it, but according to IIT, it does not contribute to consciousness because it is made up of modules that have input–output processes that are highly independent. IIT also states that a system with a purely feedforward architecture cannot be conscious, even if it performs complex functions (the so-called "zombie

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Accepted for publication August 16, 2016. Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles, California (A.E.H.); and Department of Anesthesiology, Weill Cornell Medicine, New York, New York (K.O.P.).

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system"). Thus, a conscious system that contains both feedforward and feedback networks will become unconscious if those feedback processes are impaired. It is because of this prediction that the demonstrated loss of backward connectivity in anesthesia is so compelling,[3–5] just as it is in studies of the vegetative state.[6]

Experimentally, measures of fragmentation and functional disconnection required to assess the predictions of IIT are based on changes in correlation of activity, either spontaneous or evoked, between areas in the nervous system. These measures make various assumptions that correlation between two recorded signals can be interpreted as connectivity between two areas. Connectivity in this sense does not necessarily imply that anatomically site A projects to site B but that their activities are related. A and B are said to be "functionally connected" if there is statistical interdependence between them; it is often measured by spectral coherence or phase locking of oscillations in defined bandwidths. However, functional connectivity cannot infer directionality and is thus incomplete in addressing the questions posed by IIT. A is "effectively connected" to B if a causal relationship can be inferred; in other words, you can predict B from A. Experimental assessment of functional and effective connectivity uses different measures of coupling, including fixed-lag correlation or its frequency-domain analog, coherence. To assess directionality, Pal *et al.*[1] apply a highly sophisticated information theory–based technique, normalized symbolic transfer entropy, which has the advantage of being largely model free.

While the literature describing anesthetic effects on functional and effective connectivity is now quite developed, relatively little work has been attempted to link these system-level phenomena to mechanisms of anesthesia closer to the molecular level. Theoretically, several processes at different scales and at different locations could contribute to cortical fragmentation. Anesthetics have been shown to affect synaptic function and the way the postsynaptic neurons integrate information and alter populations that have long-range, relatively nonspecific projections that provide common inputs to large numbers of neurons. Anesthetic effects at the synapse could effectively decrease the coupling between depolarization of a presynaptic neuron and resulting depolarization of the postsynaptic neuron, as has been shown with halothane and isoflurane.[7] This appears to be an effect of disturbed presynaptic calcium signaling, as isoflurane inhibits presynaptic Ca^{2+} influx, resulting in a decrease in action potential–evoked exocytosis without affecting the vesicle pool size.[8] Within the postsynaptic neuron, the balance of tonic depolarization and hyperpolarization can shift the apparent width of a neuron's tuning curve (a description of the neuron's response to a particular stimulus attribute, which identifies the optimal value of that attribute and the width of the response curve around the peak). Extrasynaptic γ-aminobutyric acid–mediated tone, which can mediate such effects, appears to be a significant contributor to propofol and benzodiazepine anesthesia[9] and possibly isoflurane anesthesia.[10] Broader tuning curves imply that more neurons will fire simultaneously in response to the same stimulus, whereas narrower tuning curves make neuronal firing sparser, decreasing the amount of synchronized firing for a given stimulus. The effects of these alterations on information and integration are complex. Narrowing may increase information through increasing specificity but cause responses to be more localized and thus reduce integration. In contrast, broadening will lead to more global responses, but they will tend toward homogeneity and transfer less information.

Inhibition of populations that simultaneously project to two different cortical areas would remove a common input, again decreasing measures of effective connectivity. Candidate populations of interest include multiple circuits traditionally considered part of arousal and attention circuits, including noradrenergic cells in the locus ceruleus, dopaminergic cells in ventral tegmentum, glutamatergic cells in paramedian/nonspecific thalamus, and cholinergic nuclei in the pons and basal forebrain. It is to this latter population that Pal *et al.*[1] have turned their attention.

The acetylcholine neuromodulatory system is a natural candidate for explaining cortical fragmentation. Previous studies have shown that cholinergic levels in cortex are highest during REM sleep and wakefulness and are suppressed during non-REM sleep and anesthesia.[11] While cholinergic effects on cortex are complicated,[12] stimulation of basal forebrain results in cortical desynchronization, increased sensory responsiveness, and improved sensory processing—all of which are suppressed during general anesthesia. The projection anatomy of cholinergic neurons also offers an immediate connection to measures of cortical connectivity. By providing a widespread, synchronous input to multiple cortical areas, cholinergic signaling has the potential to synchronize different cortical areas, resulting in increased integration and information transfer.

A reductionist question addressed by Pal *et al.*[1] is whether anesthetic unconsciousness more closely mimics the signature of REM sleep, during which the cortex is engaged in complex activity and acetylcholine levels are high, or SWS, during which both complexity and acetylcholine levels are low. The answer is very much the latter. Consistent with previous reports, the investigators found that coherence and bidirectional connectivity in low γ bands (25 to 55 Hz) were present during wakefulness and disrupted during all states of nonwakefulness (REM sleep, SWS, and anesthesia). What Pal *et al.*[1] add to the anesthesia literature is a novel assessment of the high γ band (85 to 155 Hz), with findings that suggest that frontoparietal connectivity in this range may be an even more robust and universal marker of wakefulness. In distinction, coherence and directed connectivity in the θ band (4 to 10 Hz) were present during states of increased

cortical activation and acetylcholine levels (wakefulness and REM sleep) but not during SWS or anesthesia with propofol or sevoflurane. The investigators found no relationship between the cortical microdialysate concentrations of acetylcholine and the γ band effects.

The dissociations that Pal *et al.*[1] identify are highly informative. They suggest that the loss of wakefulness is closely and consistently associated with disruption of bidirectional connectivity in the γ band. As this γ fragmentation can be dissociated from acetylcholine levels, it is unlikely that the invariant mechanisms of anesthetic unconsciousness are dependent on cholinergic signaling, and for a similar reason, they cannot be dependent on effective connectivity in the θ band.

Just as the early 20th century astronomers exploring the solar system and local star clusters before relativity could have no comprehension of the questions facing modern cosmologists, the current models of human consciousness will inevitably evolve. Any plausible theory must be consistent with what is observed in experimental studies of anesthetic unconsciousness, and in this regard, the work presented by Pal *et al.*[1] contributes to the critical evaluation of models such as the IIT. But its impact in the anesthesia literature is greater. It adds important evidence to support the theory that the common, essential cause of anesthetic unconsciousness is related to the functional disruption of feedback systems and challenges the field to now seek bridges between systems- and cellular-level models.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Pryor: kap9009@med.cornell.edu

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