Fragmenting consciousness

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The mechanism of human consciousness persists as a fundamental question in science and philosophy. As English biologist T. H. Huxley noted, "how it is that anything so remarkable as a state of consciousness comes about as the result of irritating nervous tissue, is just as unaccountable as the appearance of the Djin when Aladdin rubbed his lamp." Although the neurobiological basis of phenomenal experience has yet to be fully elucidated, anesthesiologists are nonetheless adept at coaxing the genie of consciousness back into the lamp—usually within a matter of seconds. In PNAS, Lewis et al. (1) demonstrate the spatiotemporal fragmentation of neural networks at the onset of propofol-induced unconsciousness and provide support for the hypothesis that anesthetic agents act by unbinding neural activity rather than merely suppressing it.

The Unity of Consciousness

Before a discussion of the article itself, it will be helpful to provide a context for the work of Lewis et al. (1) with respect to a central feature of phenomenal experience referred to as the "unity of consciousness." Our perception of the world is complex and multimodal, but the elements of experience nonetheless cohere in a seemingly seamless unity. If you are sitting on a beach enjoying a sunset, the explosion of orange, the salt on your lips, the whoosh of the wind, and the grainy sand between your toes all arrive as a single experience, despite the fact that they are processed as distinct modalities in spatially discrete sensory cortices. This unity was considered to be of paramount importance by the German philosopher Immanuel Kant, whose *Critique of Pure Reason* from the late 18th century provides a philosophical account of how consciousness is determined by the segregation of functionally distinct faculties that are subject to a fundamental principle of global integration (2). Kant's framework anticipated current network theory (3) and was the modern origin of the idea that consciousness is critically dependent on cognitive synthesis. In the 19th century, neurologists began to correlate anatomically discrete lesions with specific neurological deficits, providing clinical evidence for functional segregation as well as motivating connectionist models of cognition (4). Moving forward to the late 20th century, the question of how specialized cognitive activities of discrete neuronal subpopulations are bound together to generate a unified experience became known as the "cognitive binding problem" (5). Two main solutions emerged: binding by synchrony, in which the outputs of spatially remote cognitive modules in the brain are temporally correlated to unify diverse features of an object into a single representation; and binding by convergence, in which sensory processing from different areas is synthesized by yet another and higher-order neuronal population. In the 21st century, this line of

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inquiry evolved to information integration theory (6), which suggests that the capacity for a system to be conscious is directly proportional to its ability to synthesize the activity of functionally specialized brain regions. A theoretical approach to quantifying this capacity has been described (denoted as ϕ), but the current experimental surrogate for information integration in the brain relates to measures of effective connectivity. Effective connectivity reflects the causal influences of one brain area on another, rather than the mere statistical covariation characteristic of functional connectivity.

The Disunity of Anesthesia

In the past decade, several theories of anesthetic mechanism have been based on the unity of consciousness (7–9). The underlying theme is the same: if the binding or integration of neural processing is a necessary mechanism for consciousness, the unbinding or disintegration of this processing should be a sufficient mechanism for unconsciousness. This paradigm predicts that sensory or other cognitive processing can occur during general anesthesia, but anesthetic inhibition of neural synthesis prevents that processing from becoming conscious. Neuroimaging studies during the past 5 y have largely validated this prediction by demonstrating that primary sensory networks are maintained during anesthetic-induced unconsciousness, whereas multimodal associa-

tion areas and internetwork connectivity appear differentially susceptible to the effects of anesthetic agents (10–13). Neurophysiological studies have furthermore revealed that cortical effective connectivity is reduced during benzodiazepine-induced unconsciousness (14), and multiple anesthetic agents have been shown to disrupt the anterior-to-posterior feedback connectivity that is thought to be critical for consciousness (15, 16). Of note, many of these neurophysiological findings have parallels in sleep and vegetative states (17, 18).

Unfortunately, neuroimaging does not have the temporal resolution to capture state transitions that occur on the order of seconds, and scalp electroencephalography is limited in terms of spatial resolution. Lewis et al. (1) have advanced the field with a multiscale neurophysiological study of humans undergoing transitions from consciousness to general anesthesia induced by the i.v. drug propofol. Three patients with medically refractory epilepsy were implanted with cortical electrode grids (for clinical purposes) as well as a 96-channel microelectrode array (for research purposes), collectively enabling the recording of single unit activity, local field potentials, and electrocorticograms. These patients were administered bolus doses (as opposed to steady-state infusions) of propofol as part of routine clinical care and received auditory stimuli every 4 s. Loss of consciousness was defined as the cessation of button pressing in response to the auditory prompts; neural spikes, spectral features, and phase relationships were subsequently analyzed. By using these methods, Lewis et al. (1) identified a dramatic spatial and temporal fragmentation of neural networks in association with propofol-induced unconsciousness.

At loss of consciousness, there was a precipitous increase in the power of slow oscillations, characterized by a frequency of 0.1 to 1 Hz. Importantly, the increase was observed within a 5-s epoch in which the transition from consciousness to unconsciousness occurred. Despite additional spectral alterations in other bandwidths (e.g., α or θ), it was the stably increased power of the slow oscillation that was most closely associated with propofol-induced unconsciousness. Mean

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neuronal spike activity was markedly suppressed after loss of consciousness, but activity subsequently returned to baseline in some cases—and above baseline in others—despite the fact that the patients were still unconscious. This strongly suggests that it is not the suppression of neuronal activity, per se, that mediates anesthetic-induced unconsciousness. Rather, Lewis et al. (1) found that spike activity was temporally fragmented, with periods of high activity interrupted by quiescence. Of critical importance, neuronal spiking became coupled to the phase of the slow oscillation at loss of consciousness, but the phase coupling of these slow oscillations across different areas of the cortex dropped significantly as the distance increased. To summarize, spike activity was coupled to the slow oscillation but fragmented into "on" and "off" states, while the slow oscillations became uncoupled with increasing cortical distance. Thus, neuronal activity in one cortical area (spiking "on") could be occurring while neuronal activity in another cortical area is suppressed (spiking "off") as a result of the variable phase relationship of the slow oscillation. These neurophysiological conditions would preclude the temporal co-ordination and effective communication

currently believed to be required for consciousness and suggest that the slow oscillation is a critical mediator of anesthetic-induced unconsciousness.

Although the data of Lewis et al. (1) are compelling, more questions remain. First, the study was conducted in three patients with epilepsy who (because of antiepileptic drug use) may potentially have alterations of γ-aminobutyric acid receptors, the molecular target of propofol. Further support of these exciting findings is warranted. Second, because the patients were being anesthetized for a surgery in which the cortical electrodes were being removed, the investigators were not able to gather data on the return of consciousness. The reversal of the phase–spike and phase–phase relationships in association with recovery of consciousness will be important confirmation. Third, the observed disruption of neural coordination must be considered in light of emerging data regarding the reorganization of networks after anesthetic-induced unconsciousness (19–21), in which global properties (e.g., small-worldness) appear to be maintained despite local changes. Such flexible re-configuration and adaptation may be relevant to the reversibility of cognitive function after discontinuation of general

anesthetic agents, in contrast to the persistent network breakdowns observed with chronic disorders of consciousness. Fourth, the phase–spike and phase–phase relationships identified in this study (1) should be explored in other physiologic or pathologic states of unconsciousness to facilitate a more nuanced appreciation of state and trait distinctions. Finally, additional studies are required to assess whether the observed fragmentation of networks through uncoupled slow oscillations is specific to propofol-induced unconsciousness, or whether other anesthetic agents with distinct molecular mechanisms have similar effects.

In conclusion, Lewis et al. (1) provide compelling data in humans that the slow oscillations induced by propofol are associated with neurophysiological conditions that dramatically reduce the probability of information synthesis across the cortex. The unity of consciousness becomes so disrupted under general anesthesia that, as Kant might have predicted, there ceases to be consciousness at all. Perhaps Huxley did not get it quite right. The genie of consciousness appears to be fragmented among many magic lamps, the spirit being fused or rent as it is summoned into and out of existence.

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