Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness

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AUTHOR SUMMARY

General anesthesia involves rapidly inducing a reversible coma by administering a large dose of a fast-acting drug, such as propofol. Previous research has demonstrated that propofol enhances inhibitory input to neurons throughout the spinal cord, brainstem, thalamus, and cortex (1). However, how these effects in single cells translate to larger-scale neural circuits and cause unconsciousness is not well understood. We recorded spiking activity from ensembles of single neurons and intracranial electrical activity during the induction of propofol general anesthesia in human subjects undergoing surgery. We found that loss of consciousness (LOC) corresponds to the abrupt onset of a slow cortical oscillation that marks a fragmentation of neuronal networks. These results identify the slow oscillation as a dramatic neural correlate of LOC and demonstrate that slow oscillation marks the transition into a brain state in which local neuronal networks are isolated, impairing both temporal and spatial communication throughout the cortex.

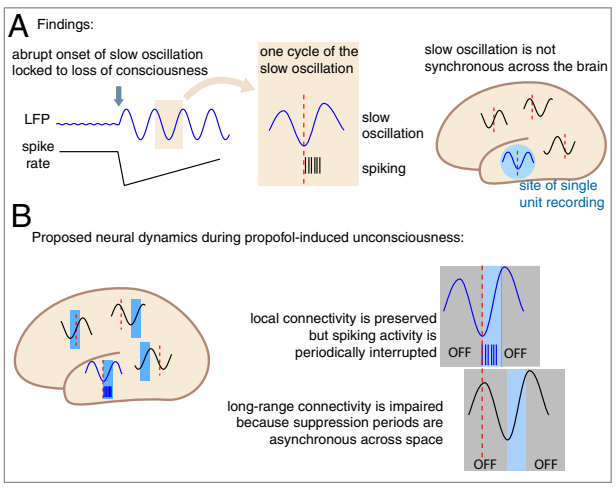

Fig. P1. Propofol-induced loss of consciousness occurs at the onset of a slow oscillation that is associated with fragmented neuronal networks. (*A*) Loss of consciousness occurs simultaneously with the onset of the slow oscillation. Unconsciousness is not associated with consistent changes in mean spike rates. Instead, spiking is grouped into short windows locked to the trough of the slow (<1 Hz) oscillation. These troughs occur at different times in different cortical regions, thereby fragmenting activity in different brain regions into distinct, asynchronous windows. LFP, local field potential. (*B*) Slow oscillation marks a state in which functional connectivity can be preserved within small (<4 mm) neuronal networks; however, processing within a local network is interrupted periodically by suppression of spiking. Global communication between brain regions also is impaired, because these suppressions occur at different times across cortical areas.

How general anesthetic drugs produce unconsciousness remains an open question in neuroscience. One current hypothesis is that unconsciousness is the result of a breakdown of information integration in the cortex (2, 3). However, the mechanism by which this breakdown might occur is not known. Most studies have used deeply anesthetized animals to probe this question, but they were unable to identify the neural changes corresponding to LOC because of the difficulty of continuously monitoring animal consciousness. To address this question, we measured neuronal and network-level electrophysiological signals in three human subjects during planned neurosurgery to remove electrodes implanted to diagnose medically refractory epilepsy. These recordings included intracranial electrocorticograms spanning up to 8 cm of the cortex, local field potentials, and ensembles of single neurons (n = 198). The subjects received propofol and were instructed to perform a simple task in which they responded to sounds by pressing a button; the 5-s window in which they stopped performing the task was defined as the time of LOC.

We first examined spike rates in single neurons to test whether propofol's inhibitory effects caused widespread suppression of neuronal activity. We found that spike rates dropped significantly after LOC, but this decrease occurred 0–30 s after LOC, rather than simultaneously with the change in behavioral state. In addition, we observed large fluctuations in spike rates during the unconscious period that varied between 30% and 115% of the baseline rate during the conscious state. Therefore we concluded that unconsciousness is not strictly associated with a reduction in mean neuronal activity.

Given that neuronal activity was not necessarily suppressed during unconsciousness, we next examined whether a change in the network structure of spiking occurred at LOC. We found that LOC occurred simultaneously with the onset of a slow (<1 Hz) oscillation in the local field

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potential. Changes in other frequency bands also occurred, including a decrease in theta (3–8 Hz power) and increases in alpha (~10 Hz) and gamma (25–40 Hz) power (4), but these features fluctuated after LOC, most likely in relation to propofol drug level. In contrast, slow oscillation power increased abruptly at LOC and remained elevated throughout the recording. Previous studies in deeply anesthetized animals have shown that this oscillation is associated with neurons alternating between UP (activated) and DOWN (inactivated) states (5). The extracellular recordings collected here demonstrate an analogous alternation between ON (activated) and OFF (inactivated) states during unconsciousness. We found that this alternation occurred in nearly all single units and developed within seconds of LOC. Neuronal processing therefore was limited to intervals of a few hundred milliseconds, which were interrupted periodically by suppression lasting several hundred milliseconds.

We next analyzed how these periods of suppression were distributed across the brain. We analyzed the slow oscillation phase and found that distant cortical areas frequently were at different phases. Because the phase was strongly associated with periods of suppressed activity, this finding implied that different brain regions were active at different times. These asynchronous periods of suppression therefore would be expected to impair global cortical communication, because active neurons in one area would be unable to propagate information effectively to a distant, inactivated brain region.

Given that neuronal communication was impaired over large timescales and across distant cortical regions, we next investigated whether connectivity in local (<4 mm) networks was impaired. Unexpectedly, we found that millisecond-scale connectivity between pairs of units was preserved during general anesthesia, suggesting that relationships between nearby neurons were not disrupted substantially during unconsciousness. In addition, we found that the history of ensemble unit spiking was useful for predicting future spiking, indicating that significant structure remained in the units during unconsciousness. These results suggest that significant aspects of local functional connectivity were preserved during general anesthesia, although for short timescales. However, neuronal activity was fragmented into brief temporal windows, thereby preventing both temporal and spatial information processing.

We conclude that although propofol produces a broad range of oscillatory and neuronal dynamics, slow oscillation is correlated most specifically with LOC. We show that slow oscillation marks a fragmented brain state that impairs communication between distant cortical areas and over long timescales, despite preserved structure in small neuronal networks (Fig. P1). Because slow oscillations can be observed in normal sleep, certain types of coma, and complex-partial seizures, it is possible that specific types of slow oscillation dynamics are associated with different arousal states. One limitation of our study is that the subjects had epilepsy; the consistency of our results across subjects suggests that their underlying pathology did not affect their neural response to propofol, but future experiments could investigate this question further in patients with different pathologies. Future studies also could investigate the relationship between specific types of slow oscillations and behavioral states and test whether they can be used clinically to monitor patient consciousness during surgical procedures. Our results are consistent with the hypothesis that unconsciousness during general anesthesia is caused by a breakdown of cortical integration (2, 3) and suggest a mechanism for how propofol could induce this state.

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