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Anesthesia as decoupling

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A cardinal effect of general anesthetics is loss of consciousness. Yet disruption of consciousness may be a happy accident; that is, the fundamental common mechanism of anesthetic drug effect may have nothing to do with a special targeting of conscious processing, as opposed to a generic effect on all neurons. After all, anesthetic drugs effect a remarkably wide range of organisms, incapacitating vertebrates, slowing organ movements of plants,[1] and even halting the environmental responsiveness of amoebae.[2] As organisms become simpler, it is hard to argue these organisms even have a consciousness to be disrupted, because we have difficulty with the very idea of such organisms having a subjective experience. But even these putatively non-conscious model organisms provide an opportunity to understand key features of the mechanisms of anesthetics. An emerging view is that the common effect of general anesthetics is to increase the modularity of communication networks – that is, anesthetics interrupt connections that normally exist between networks so that the networks are dominated by local activity – thereby disrupting the efficiency of information transfer through the organism and isolating the organism from its surroundings.[3]

In this issue of *Anesthesiology*, Awal and colleagues report the results of simultaneously recording neuronal activity in almost the entire head of the roundworm *Caenorhabditis elegans* at different depths of sevoflurane and isoflurane anesthesia.[4] In so doing, the authors are able to address a question which is currently unfeasible in mammalian models: whether general anesthetics equally disrupt relationships between all neurons, or whether connections between particular functional networks are critical vulnerable nodes that are responsible for the behavioral impact of general anesthetics. Imagine an organism had three neuronal networks: a sensory network that projects to a decision network that projects to a motor network. Severing any one of these connections would render the organism unresponsive to the environment, as the networks become more modular.[3] Or perhaps the effect of anesthetics on the nervous system is scrambled by the introduction of random fluctuations in all three networks, so that normal relationships between these three populations are decoupled.

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Awal et al.'s study depends upon two technical advancements in neurobiology over the last decade. The first is the development of fluorescent readouts of neuronal activity, which make electrical activity visible *in vivo*. The second is the rapid imaging of a 3 dimensional volume over time, which the authors addressed by utilizing light sheet microscopy.

Light sheet microscopy is so named because it simultaneously illuminates and captures an entire plane of the specimen (the "sheet" of light) simultaneously, rather than sequentially scanning a focused laser over each region of the sample in order, as a confocal microscope does.[5] By rapidly shifting the depth of the imaging plane, it becomes feasible to detect transient responses within a 3 dimensional volume. Interest in this imaging approach has exploded since it was reported in 2014 that it could be used to optically section specimens *in vivo*.[6]

Awal and colleagues found that the neurons in unanesthetized worms demonstrate stable global activity states that occasionally shift between different confirmations. While the worm is engaged in behavior, it defines a state in the nervous system. Because most of the time most neurons in *C. elegans* have slow, graded activity (rather than the more familiar all-or-none action potentials), the unanesthetized worm demonstrates very low frequency shifts in fluorescence levels, as neurons settle on stable intracellular calcium concentrations that persist until the next behavioral transition occurs. The introduction of 1.3 MAC equivalents of volatile anesthetic, either isoflurane or sevoflurane, rendered the worms behaviorally unresponsive. This so-called moderate anesthetic (i.e., a dose that prevents a behavioral response to a noxious mechanical stimulus, argued by the authors to be equivalent to a surgical plane in mammals) destabilized global activity states, such that neuronal activity became disorganized. The correlation between individual neurons broke down and individual neuron's calcium concentrations oscillated back and forth, shifting the resulting power spectrum of individual neurons to higher frequencies. Finally, at high concentrations of anesthetic (2.7 MAC equivalents), the activity in the network was globally suppressed.

In this experiment, activity persisted in the nervous system at moderate doses of anesthesia, just as it does in humans.[7] As a result, the authors argue that disruption of the normal coordination between neurons was the main effect observed with moderate anesthesia rather than suppression of neuronal activity. The authors report both raw correlation measures as well as more advanced techniques using principle components analysis to study ongoing dynamics, which showed that normal, stable activity patterns become much more complicated during moderate anesthesia, contrasting with previous reports of a stabilization of neuronal activity with anesthesia.[8] Yet, intriguingly, the loss of correlation between neurons left the power spectrum of the average of all 120 of the neurons in the head of *C. elegans* (the so-called "bulk signal") essentially unchanged, despite a significant shift in the spectra of individual neurons. That is, while the average of the total activity is not dramatically affected by anesthetic concentration, the neurons have stopped effectively coupling to each other and instead shift from high to low activity states and back again, so the structure of the activity is greatly perturbed.

This loss of organization of activity within a few hundred individual neurons, without a dramatic difference in the dynamics of the mean population activity, points at why it is difficult to monitor depth of anesthesia with electroencephalography (EEG) in the operating room. The voltage detected by a single EEG electrode is the summation of many thousands or millions of electrical dipoles from the neurons beneath that electrode. If the significant shift in network function is one of organization, then it is possible that activity sequences are disrupted during anesthesia while analysis of the average of ongoing activity would reveal only subtle differences.

These results also support the notion that anesthetics disrupt communication networks, decreasing the correlation between normally connected neurons thereby dissociating functional networks to isolate the worm from its surroundings. This seems to happen throughout the entire population of neurons, rather than being confined to a specific subset. Of course, the authors only tested two doses of anesthetics, so it is possible that they could have missed small differences in susceptibility between populations, but susceptibility differences between neurons are not major at sevoflurane or isoflurane doses consistent with those used in the operating room.

It remains to be seen how many of the lessons from this model apply to humans, but this work suggests that spinal cord function and cerebellar function might be as disturbed as cortical function by general anesthetics. The difference in dose responses observed for different behavioral endpoints – amnesia, hypnosis, loss of movement to sensory stimulation – might thus reflect differences in the robustness of the responsible networks to a given level of statistical disruption, rather than a selective dose-response relationship for suppression of the particular neuronal subpopulations involved in those functions – a provocative hypothesis to result from a simple model organism.

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