Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Exploring the Neural Basis of Consciousness through Anesthesia

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Review of Boly et al. and Schröter et al.

Anesthetics are among the most widely used drugs affecting the CNS. While we have a reasonable understanding of the pharmacological effects of anesthetics (Brown et al., 2011), very little is known about the neural mechanisms by which this class of drugs brings about sedation and loss of consciousness (LOC). This is not surprising since our understanding of the phenomenon of consciousness itself is rudimentary at best. An understanding of the neural basis of anesthesia could thus prove to be a promising avenue for exploring the neural basis of consciousness. However, a few key impediments have stalled progress toward such an end. Anesthetics often have generalized excitatory/inhibitory effects on many regions of the brain and it is difficult to separate epiphenomenal effects from causal ones. A compounding factor is that many anesthetics have effects on the cardiovascular system, confounding the use of imaging methods relying on cerebral blood flow (like fMRI) for such investigations. Also, the logistics of monitoring and maintaining the physiology of the subject while simultaneously conducting investigations have been onerous.

Early investigations characterized changes in metabolism and blood flow in various parts of the brain under different anesthetics. Many of these studies reported an anesthesia-dependent decrease in activity in the thalamus, leading to suggestions that LOC results from a blockage of thalamocortical circuits at the level of the thalamus (Alkire et al., 2000). However, these same studies noted a concurrent decrease in activity across large swaths of cortex. Also, EEG recordings showed widespread spectral changes across many recording sites after administration of anesthetics. So currently it is unknown whether changes seen in thalamus reflect the primary site of action of anesthetics or are secondary to the action of the anesthetics on the cortex.

More recently, it has been proposed that LOC might occur from disruption of functional connectivity patterns among brain regions rather than from activation/inactivation of specific structures (Alkire et al., 2008). Two recent reports in *The Journal of Neuroscience* (Boly et al., 2012; Schröter et al., 2012) have investigated anesthesia-dependent changes in interareal functional connectivity, providing support for this hypothesis. In both studies, brain activity was monitored in healthy volunteers undergoing anesthesia with propofol, an intravenous agent that enhances neuronal inhibition by potentiating the action of GABA at $GABA_A$ receptors.

In the first study, Boly et al. (2012) recorded EEG signals from high-density electrode arrays as subjects slipped into propofol-induced LOC. The authors focused on signals reconstructed from two regions of interest, the anterior cingulate cortex (ACC) in the medial prefrontal region and posterior cingulate cortex (PCC) in the parietal precuneus, because these regions have previously been shown to contribute to the large changes in EEG spectral content seen under anesthesia. The authors then used dynamic causal modeling to reconstruct the observed response spectra under wakefulness, sedation, and LOC. Dynamic causal models are exquisitely detailed generative models that can predict EEG responses as a function of both intrinsic activity within model neuronal populations and the connectivity pattern between such populations. In this study, they considered three models, one including just the PCC and ACC and the other two including a model of the thalamus, either as two subpopulations independently connected to PCC and ACC or as a single population with shared connectivity to the two structures. Bayesian comparison between the three models indicated that the model with shared thalamic inputs accounted best for the data across subjects and states of consciousness. Exploration of the parameters of that model revealed that thalamic excitability increased during sedation and then stayed constant during LOC. On the other hand, backward connectivity from ACC to PCC stayed constant during sedation but decreased significantly during LOC. The authors suggest that such a suppression of prefrontal–parietal feedback could be the basis of LOC induced by propofol.

In the second study, Schröter et al. (2012) studied functional connectivity us-

Received Nov. 6, 2012; revised Dec. 5, 2012; accepted Dec. 6, 2012.
I thank Luke Woloszyn and Chris Fetsch for a critical reading of the manuscript; and Sara Hanrahan and Steve Nelson for helpful comments.
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DOI:10.1523/JNEUROSCI.5215-12.2013
 0270-6474/13/331757-02$15.00/0

ing fMRI signals recorded before and after propofol-induced LOC. They extracted time series of the fMRI signal from different brain regions and calculated the correlation in the 0.03–0.07 Hz band between pairs of regions. This frequency band was chosen to reduce confounds from non-neuronal physiological sources. Connectivity graphs were constructed by thresholding the matrix of correlations so as to restrict connection probabilities to 36–50%. The thresholds were set to prevent undue fractionation of networks while avoiding inclusion of random connections. The authors then characterized the connectivity graphs for before- and after-LOC conditions using various metrics from graph theory. As would be expected, they found a significant reduction in the strength of functional connectivity across many cortical and subcortical regions after anesthesia. There was a greater decrease in long-range connections after LOC, suggesting that global processing was affected more than local processing. In further support of this interpretation, the degree of clustering of connections increased with anesthesia. The authors then divided the brain regions into five subsystems—subcortical, limbic, paralimbic, primary sensory cortex, and association cortex—and analyzed functional connectivity between them. The most marked decrease in connectivity was between the subcortical regions and association cortex, which was greater than the decrease in connectivity within either of the subsystems, supporting a role for these networks in the maintenance of consciousness.

An important contribution of these studies is bringing to the forefront the idea that specific changes in the connectivity patterns between regions, rather than changes in activity of isolated brain structures, could be a basis of action of anesthetics. Both studies also reaffirm the importance of connectivity between subcortical structures like thalamus and areas in the association cortex like ACC and PCC in the maintenance of the conscious state. This dovetails with the idea from the fMRI literature that considers these frontal and parietal regions as forming important hubs of the "default network," a set of interconnected brain areas active during the resting state (Buckner et al., 2008).

So is the disruption of these cortical networks the mechanism by which anesthetics bring about LOC? Boly et al. (2012) suggest a primary role for feedback cortical connections in propofol-mediated LOC, deeming thalamic changes as necessary but not sufficient. While their model is rigorously detailed, they are hampered by the fact that EEG signals are mainly cortical in origin and, thus, the thalamus had to be modeled as a hidden source. Their assumptions for the thalamic population might disregard important properties of the thalamus and its interaction with the cortex that allow it to play a more central role in LOC. In fact, a major argument against a corticocentric theory for the basis of propofol-based anesthesia is the fact that birds, which lack an isocortex, are also susceptible to anesthesia by propofol (Gunkel and Lafortune, 2005). On the other hand, Schröter et al. (2012) observe that functional connectivity between subcortical regions and association cortices decreases more than the decrease in connectivity within association cortices. But the brain parcellation scheme they use precludes a more fine-grained comparison between thalamocortical connectivity and prefrontal–parietal connectivity that would have shed more light on this question.

Consciousness is not a unitary phenomenon but a catch-all term that includes wakefulness and awareness, among other phenomena (Shadlen and Kiani, 2011). While wakefulness is phylogenetically primitive and is a prerequisite for awareness, whether the two share a neural basis is unknown. Administration of propofol results in a progressive reduction and then loss of wakefulness and awareness. In contrast, dissociative anesthetics like ketamine, an NMDA receptor antagonist, have more complex effects: distorting perceptual awareness while influencing wakefulness to a lesser degree. Examining alterations of connectivity patterns under ketamine administration might prove informative in distinguishing these different aspects of consciousness. Other agents, like sufentanil, can reduce arousal by acting through receptors that are not present in the cortex; such agents might be useful for exploring the central roles of subcortical structures in the maintenance of the conscious state.

The established pharmacological safety and efficacy of anesthetics make them invaluable tools in exploring the neural basis of consciousness. Anesthetics form a large and diverse family of drugs, comprising multiple classes, each with its own preferred profile of molecular targets (Franks, 2008). While this affirms the complicated nature of the circuitry for the generation and maintenance of consciousness, it also offers avenues to selectively perturb different parts of the circuit, possibly enabling a deeper understanding of the phenomenon. Studies like the ones reviewed here attest to the utility of sophisticated data analysis techniques being used for exploring brain activity during anesthesia. Similar advances in data acquisition, like multielectrode recordings in human patients undergoing anesthesia (Hanrahan et al., 2011), promise exciting opportunities in the quest to understand the neural basis of consciousness through agents that cause its loss.

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