Another Brick in (Some Kind of) Wall

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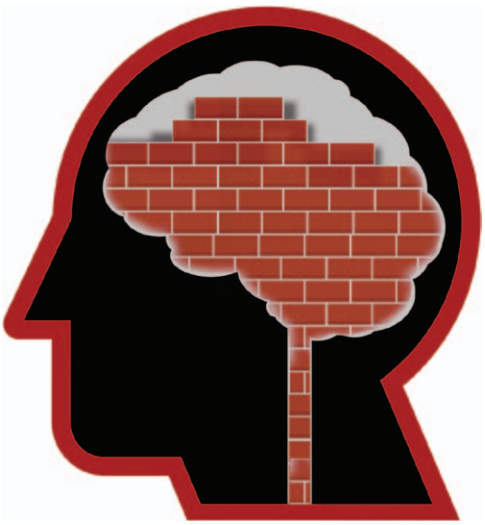
A COMMON metaphor for the scientific enterprise is that of building an edifice. Understanding of the natural world is painstakingly gained by new observations and interpretations, each of which builds on the foundations of previous work. Over the last decade, we have been quietly living through the construction of a new wing in the research-into-mechanisms-of-anesthesia mansion. This has been largely driven by the development of new experimental techniques in functional brain imaging. Functional magnetic resonance imaging (FMRI)—and at a coarser spatial resolution, the high-density electroencephalogram—have enabled us to see how general anesthetic drugs disturb the activity in precise anatomical regions of the brain. This is somewhat analogous to the impact of ultrasound on cardiology in the 1980s and 1990s. The underlying motivation behind these studies is to see if there are regions in the brain that are preferentially sensitive to and have pivotal roles in generating the state of general anesthesia and also how general anesthetic drugs disrupt the patterns of long-range brain coordination, which are presently believed to be necessary for the various components of normal wakefulness. To date, there are at least nine published FMRI studies and 14 high-density electroencephalogram studies. For practical reasons, most previous work has examined the FMRI effects of propofol. In this issue of Anesthesiology, Ranft *et al.*[1] describe a study looking at how medium (2%) and high concentrations (3%) of sevoflurane disturb the activity and interregional connectivity of the brain, as detected simultaneously by FMRI and high-density electroencephalogram. They found that sevoflurane showed comparable effects to those reported in previous propofol studies, namely, that at 2% concentrations of sevoflurane, there were clear decreases in electroencephalographic measures of information content and interregional information flux. In contrast, when measured by the FMRI, the overall brain connectivity showed surprisingly modest decreases in corticocortical and thalamocortical connectivity (figs. 3 and 4 and table 1, Supplemental Digital Content, in their article). Widespread decreases in brain connectivity only occurred at supraminimum alveolar concentration (greater than or equal to 3%) concentrations of sevoflurane. This is in agreement with other FMRI studies, which also show that most of the brain carries on business as usual under the usual clinical levels of anesthesia (minimum alveolar concentration, 0.5 to 1.2).[2] It is clear that, at these levels, general anesthesia does not dampen down activity in the brain uniformly—the so-called "wet blanket" theory of anesthesia.



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Instead, the study highlighted the differential effects of anesthesia on specific brain regions. Sevoflurane selectively impairs within-network cortical connectivity in anterior, higher order areas to a much greater extent than in the more posterior, parietal and primary sensory cortices, which are relatively robust to anesthesia (fig. 1). They also showed that local thalamic network connectivity is reliably depressed at 2% sevoflurane. However, depression of thalamocortical connectivity is very heterogenous.

The thalamic connectivity to the dorsolateral prefrontal cortex was most sensitive to anesthetic disruption. This area is a region of the cortex that is associated with higher order functions, such as working memory, and with networks that assess external sensory input. The finding is also in agreement with previous propofol studies.[3] Thus, there is growing evidence that a functioning dorsolateral prefrontal cortex

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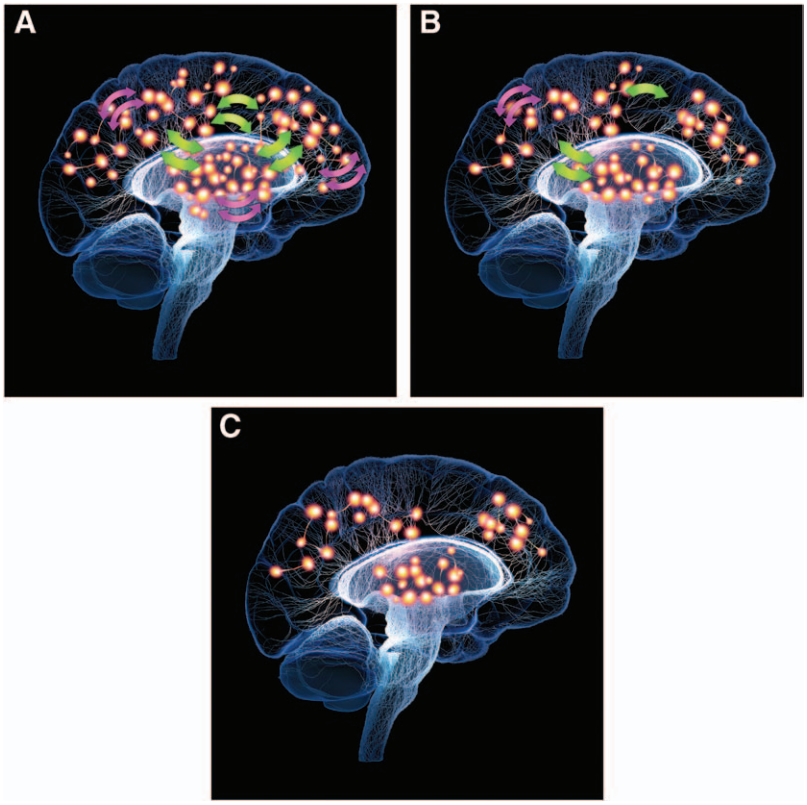

Fig. 1. Representations of the changes in functional magnetic resonance imaging (FMRI) connectivity between different brain regions with increasing sevoflurane concentrations. (*A*) FMRI connectivity in the waking state: there is widespread connectivity both between (*green arrows*) and within (*mauve arrows*) brain regions. (*B*) FMRI connectivity in the presence of medium concentrations of sevoflurane: connectivity is relatively maintained within the posterior networks, but connectivity has been lost between the dorsolateral prefrontal cortex with the thalamus and from the dorsolateral prefrontal cortex to the posterior cortex. (*C*) FMRI connectivity in the presence of high concentrations of sevoflurane: there is widespread loss of brain connectivity. Credit: © ThinkStock. Figure 1 was enhanced by ImagePower Productions.

might be necessary for the generation of a conscious state, which is able to perceive the outside world (so-called "connected consciousness"[4]). Presumably, the observed reduction in frontoparietal information flux seen in the electroencephalogram is also a manifestation of this sevoflurane-induced prefrontal cortical dysfunction.

There are significant methodological hurdles in the conduct and analysis of these sort of studies.[5] Many questions remain. The regional "connectivity" estimated by the electroencephalogram is mediated over time scales of around 20 to 80 ms, which are the time scales of nerve conduction around the brain. In contrast, the time scales for FMRI fluctuations are much longer—seconds to tens of seconds, probably reflecting different neurobiologic interconnection processes. When trying to analyze connectivity, the experimenter, typically, ends up with a connectivity matrix of many thousands of entries, each quantifying the correlation between each 1-mm^3 voxel and every other voxel in the brain. How do they make sense of this tsunami of data? In this article, the authors initially looked for patterns of highly connected groups of voxels (using a technique called independent component analysis) and how these networks altered with anesthesia. As a second method, they then chose a region of interest based on previous information (in this article, the thalamus was the region of interest) and investigated how that region changes its connectivity profile with the rest of the brain at different levels of anesthesia. The reader should be aware that in all these methods, it is necessary to apply a lot of skill and judgment, which may introduce bias to the interpretation of the experiments.

So how much confidence can we have in these results? The encouraging aspect of these studies is that largely similar results have been replicated in different laboratories around the world using quite different experimental protocols and analytic techniques. An ounce of replication is worth a ton of small *P* values. Even within this article, the region-of-interest analysis corroborated with the independent component method. It would seem that the new rooms in the research-into-mechanisms-of-anesthesia mansion look a bit odd but probably have a sound foundation. However, the real test of causation would be to actually selectively obtund the dorsolateral prefrontal cortex somehow and see if a state of anesthesia resulted. It is known that lesions in this part of the brain in animals seem to cause a state of disinterest in their surroundings rather than true anesthesia, implying

that impairment of other parts of the network (*e.g.*, cingulate cortex and intralaminar thalamus) is also necessary for anesthesia. We also have no idea why particular areas of the brain might show differential sensitivity to anesthesia. Do they have different interneuronal connection strengths or topologies, or do they have different types of neurons or just more, or different, receptors?

Clinicians may ask how could this knowledge help with the clinical management of patients? The widespread use of the FMRI techniques in the operating room is not likely in the near future, but the results of the work by Ranft *et al.*[1] do provide a rational basis for the development of a new generation of anesthesia monitors. For example, electrode placement and analysis should include some measures of frontoparietal interactions and perhaps aim to capture localized activity over the dorsolateral prefrontal cortex. It is instructive to look back in time. At the turn of the millennium, we had had only the most rudimentary understanding of the existence of the various cortical networks and their role in disorders of consciousness. The new wing is coming on well, perhaps almost ready for a roof, but we do not really have a connecting passage to the rest of the manor house.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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