Syncopated Tempi of the Anesthetized Brain

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"…[C]ompare the function of the conscious brain to that of an orchestra making music."

In this issue of ANESTHESIOLOGY, there are two articles looking at changes in patterns of connectivity between different brain regions during general anesthesia.[1,2] These articles are full of the technical language of dynamics that might be somewhat daunting for clinicians. Can we make terms like "metastability," "spatiotemporal invariance," and even "connectivity" less abstract and more relevant to our day-to-day work? A common metaphor is to compare the function of the conscious brain to that of an orchestra making music. A symphony is made up of an evolving balance of synchrony and syncopation, harmony and dissonance, regularity and surprise. As the orchestra moves between fast and slow and loud and soft sections of music, so too does the brain move between fast waves and slow waves, high amplitude waves and low amplitude waves. There is no single fixed steady state, but conversely the brain activity is not completely unconstrained—therefore the brain is described as being "metastable." Similarly, the music sometimes requires that the flutes play synchronously with the violas, and sometimes half a step behind the trumpets. These papers use the weighted phase lag index as a measure of frontoparietal brain "connectivity." This index is simply quantifying whether the parietal lobe consistently activated *after* the frontal lobe. If it were to be applied to the symphony metaphor, it would give an estimate of whether the flutes tended to play after the trumpets on average.

In the first paper, Li *et al.* studied multichannel electroencephalograms in 30 volunteers who underwent a 3-hr administration of 1.3 minimum alveolar concentration isoflurane.[1] There were no nociceptive stimuli. They found that (unsurprisingly) a burst suppression pattern was common. More importantly, the subjects' brains were not in a single "anesthetized" state, but instead jumped around between a series of different states—even in the presence of an unchanging concentration of volatile anesthetic drug and without external stimuli. As is clearly seen in figures 3 and 4 of their article, the pattern of brain connectivity kept changing over short time scales of seconds to a few minutes. But they also found that the probabilities of the preferred states were different after an hour or two of isoflurane exposure, than they were near the beginning of anesthesia. For example, burst suppression was seen in almost half the time in the first hour, but was much less prevalent (only about 14%) during the last hour of the isoflurane. We can conclude that an hour of isoflurane has caused some sort of slow adaptation in underlying brain function. Is this a homeostatic protection against the deleterious effects of the burst suppression pattern? The neurobiological mechanisms of these slow secondary effects are largely unknown, but, having a time course of more than an hour, we might speculate about mechanisms involving changes in the neuromodulator milieu, long-term results of isoflurane-induced *N*-methyl-D-aspartate blockade, and changes in protein phosphorylation and expression. Experienced clinicians would agree that there is a subtle maturation in patient responses that occurs during the course of a long general anesthetic.

In the second study, Vlisides *et al.* looked at patients undergoing clinical general anesthesia (with the concomitant surgical noxious stimuli) to see if they showed similar patterns.[2] Because of the uncontrolled drug delivery and differences in data collection, a formal comparison is difficult. Nevertheless the results were broadly similar. Like the volunteer study, they found that the brains of surgical patients spontaneously shifted around between connectivity patterns over short and long time scales.

The other slightly confronting result in the surgical anesthesia study, was that they could not find a prolonged and reliable decrease in frontoparietal connectivity during maintenance phase of general anesthesia, when the patients were (apparently) unconscious. Their findings are in stark contrast to the prevailing view; that loss of frontoparietal connectivity is

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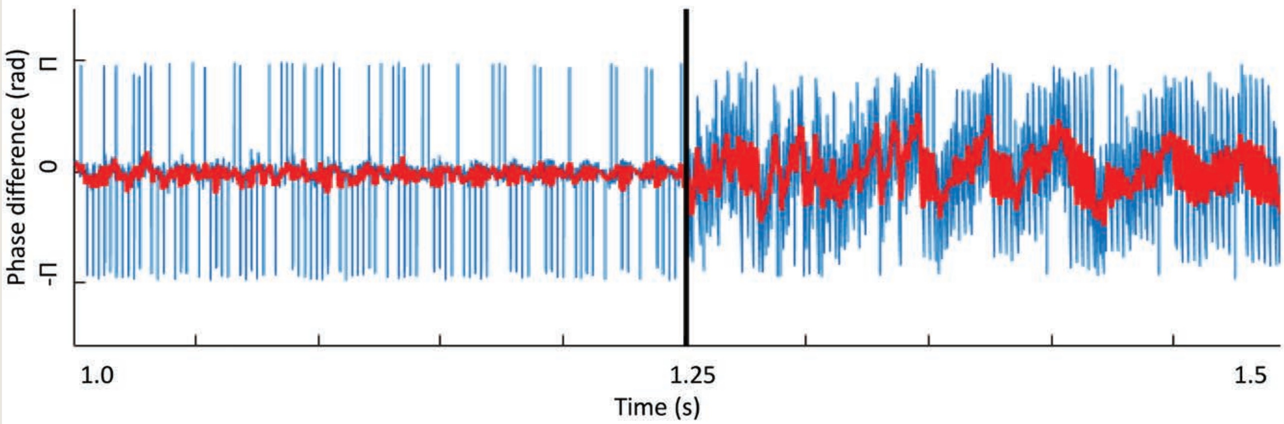

Fig. 1. The phase differences between bass and treble parts for the first section of Debussy's well-known piano piece, "Clair de Lune." It is noteworthy that the music moves between two clearly different states of phase structure (the transition is at the *vertical black line*), but the weighted phase lag index does not optimally capture this transition. (It is similarly close to zero, both before [-0.017] and after [0.0002] the transition.)

pathognomonic for loss of consciousness.[3,4] This is a question that opens up many subtle issues and needs further investigation. The methodology used in the current study necessarily involves massive reduction in the number of variables, which could introduce all sorts of hidden biases. The unconscious brain might indeed stop forming large neural assemblies, but perhaps our analysis methods just can't clearly see this process? As a whimsical but illustrative example, we present the phase lag differences between treble and bass for a section of piano music ("Clair de Lune") by Debussy in figure 1. We can see various different dynamics and transitions between the left and right hand on the piano, but these are not particularly well captured by the weighted phase lag index. There are many details in the analysis technique that could be debated and further refined. For example, the state pairs 7 and 8 (or 5 and 6) are somewhat overlapping and show many within-pair transitions. The clustering technique assumes an underlying multidimensional globular structure. If it allowed a cigar-shaped structure, then these pairs might be classified as a single state.

The authors also discuss the results in relation to the theories that anesthesia reduces the ability of the brain to integrate information; implying that level of consciousness depends on the size of the brain's potential repertoire of states, rather than any specific pattern. In this view, general anesthesia is causing unconsciousness by limiting the brain's repertoire of states, *i.e.,* forcing the brain to become like a country music station playing endless repeats of the song "Nine-to-Five," rather than a more diverse radio station featuring all varieties of music, news, weather, and talk shows, among others. Because the brain is continuously changing—even during deep general anesthesia—the authors suggest it is unlikely that any single measure of connectivity will correlate reliably with surgical anesthesia. To continue with the music metaphor, reducing the measurement of consciousness to a single number is like a music critic describing the success of a performance of a symphony by the loudness of the double basses. The optimal double bass volume did indeed contribute to the fleeting abstract beauty of the symphony, but it was not, in itself, a sufficient cause. The beauty of the music is a complex, high-level phenomenon that can emerge from all sorts of different pieces of music. If "consciousness" is more analogous to "beauty" than "loudness" or "phase synchrony," we need to be looking for more global and abstract indices of anesthesia effects; perhaps something like the brain's network topology?

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Advertising Abbott's Pentothal from Antarctica to Toledo: A Bolus for Bowlus?

Following Army service as a 23rd Infantry combat medic in the Southern Pacific Theater of World War II, Thomas P. Bowlus (1923 to 2014) earned his A.B. at Michigan State Normal College in 1947, the same year that the Australian National Antarctic Research Expedition (A.N.A.R.E.) launched. After earning his M.D. from the University of Michigan in 1951, Dr. Bowlus returned to his native northwest Ohio for internship and medical practice in Toledo (*upper left*). A decade later, Abbott, the makers of the Pentothal brand of sodium thiopental, began mass-mailing advertising postcards from exotic locations around the world. The postcard above (*bottom*) was postmarked (*upper right*) to Dr. Bowlus from an A.N.A.R.E. outpost in Wilkes Land in the Australian Antarctic Territory. For his minor surgical and office procedures, rather than bolus patients with intravenous Pentothal, Dr. Bowlus more likely resorted to the administration of local anesthetics or topical vapocoolants, or even to trichlorethylene by handheld inhaler. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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