The Seven Bridges of Königsberg

THE business of the brain is the processing of information to produce mental representations, which are the building blocks of cognition. It is self-evident that networks of neurons must be somehow crucial to this process. However, it is not self-evident exactly how extraordinarily complex and dynamic cognitive functions actually emerge from the interactions of these networks. In this regard, the science of cognition—and the science of understanding how anesthetics impair cognition—has been constrained by the legacy of its previous success. The explosion in the use of functional magnetic resonance imaging over the past 15 yr has led to considerable progress in determining the brain locations associated with specific cognitive functions. One could be forgiven for believing that we could fully understand the underpinnings of human cognition…if only we knew exactly where everything was. Counterbalancing this bias is the incorporation of network-centered approaches to understanding cognitive function. Over recent decades the science of network topology has developed sophisticated methodology for the analysis and understanding of complicated network behavior. The paper by Lee *et al.* in this issue of ANESTHESIOLOGY describes how various network parameters of brain connectivity might be altered by propofol-induced loss of consciousness.[1] Anesthesiologists thus need to become familiar with the language of networks.

Graph theory (the precursor of modern network theory) was invented by the great mathematician Leonhard Euler. In 1735 he was able to prove that it was not possible to walk through the city of Königsberg (now Kaliningrad) crossing each of its seven bridges only once—because of the layout of islands in the Pregel River (fig. 1). Translating this finding to neural networks, neurons (or groups of neurons) are viewed as *vertices* or *nodes* (analogous to the islands in Königsberg), and the interactive connections between them are modeled as *edges* or *paths* (analogous to the bridges in Königsberg). The analysis of the topologic relationships between these simple elements continues to increase in mathematic and computational sophistication. These techniques are especially powerful because they are amenable to the fitting of empirically derived data. A summary of the application of network topology to neuroscience has been published recently.[2]

It is generally accepted that from worms to humans, animal brains tend to exhibit the so-called small-world type of network structure. This structure is characterized by clusters of strong local connectivity in conjunction with efficient long-range connections. Alteration of the topologic parameters has been shown to be associated with various neurologic disease processes such as epilepsy, schizophrenia, and dementia, and with drug modulation of the dopaminergic system.[3,4] Previous studies have used functional magnetic resonance imaging data to estimate the effects of anesthesia on network structure.[5] These techniques have good spatial but poor temporal resolution, and are better suited for evaluation of the ultralow frequency oscillations (less than 0.08 Hz) associated with the "default mode network" than they are to rapid cognitive dynamics. The current study by Lee *et al.* and its recent companion study[6] are the first to apply quantitative methods to the analysis of anesthesia-induced network topology, as estimated by cross-correlations obtained from multichannel electroencephalography. The authors do not attempt to map a detailed schematic of nodes and paths; instead, they use an elegant mathematic approach that compares the overall efficiency of the network with archetypal forms. The result is the ability to separate the anesthetic-induced loss of network function into two distinct components: one follows changes in the node—path architecture ("topologic transformation"), whereas the other results from diminished communication efficiency ("connection strength"), which is independent of changes in the network lattice. We are left none the wiser as to what the mechanistic underpinnings for these mathematic observations may be. But Lee *et al.* have introduced a novel quantitative method that promises to provide a framework for mechanistic studies over the coming years.

Three important results from this article must be mentioned. The first is that changes in consciousness are better correlated with general anesthetic-induced disruption of information processing in the parietal cortex than in the prefrontal cortex. Are we putting our electrodes in the wrong place to estimate depth of anesthesia? Although there may be some electromyography-related reasons for this observation, these data are in agreement with an increasing body of work arising from the study of pathologic coma states, which indicates that parietal cortical processing is a critical hub in the "seat of consciousness."[7] Furthermore, several recent diffusion tensor imaging studies have identified a prominent structural role for the precuneus region, which is densely interconnected and likely involved in several core network hubs.[8] Second, the authors apply random matrix theory to demonstrate that, at frequency ranges critical to the study of consciousness, a high degree of random "spurious" correlation will be found in the association matrix derived from the electroencephalogram. How are we to interpret other studies that do not incorporate a comparable sophisticated correction technique? Third, the authors identify a phenomenon

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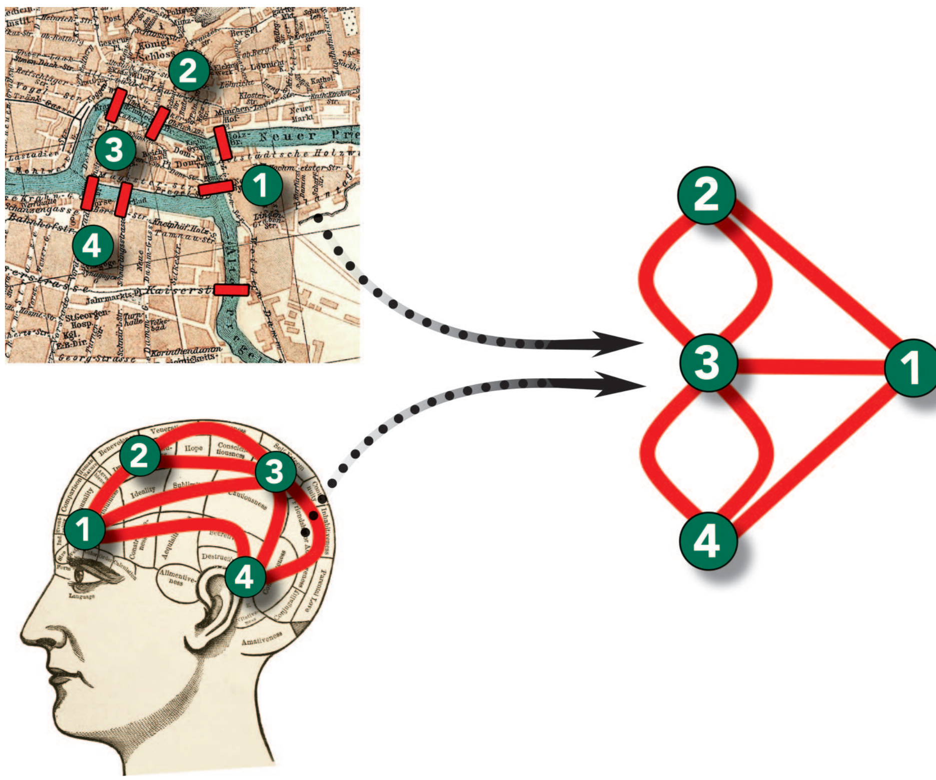

Fig. 1. A diagram to demonstrate the reductive approach of network topology. All of the physical details (distances, widths, gradients, surfaces, *etc.*) of the Königsberg city streets can be stripped away to leave only the important factors: four land masses (represented by *green circles* = "nodes " or "vertices " in modern parlance), and seven bridges (represented by *red lines* = "edges " or "connections"). Similarly, the complexity of the anatomic connections between different cortical areas is ignored, and only the functional connectivity of activity (as detected *via* the scalp electroencephalogram) is analyzed. For illustrative purposes only, we have arbitrarily chosen a cortical topology that is the same as that of the Königsberg bridges. (We have, however, made the important nodes in the temporoparietal area rather than in the frontal area—in accordance with Lee's results.)

that seems anecdotally self-evident to anyone who uses an anesthetic: emergence from anesthesia is not the mirror image of induction. Why this hysteresis occurs is poorly understood, and this study does not offer mechanistic insight. It does, however, suggest that a good place to start searching is to examine whether the brain emerging from anesthesia is able to recruit supranormal "bursts" of connection efficiency to overcome inertia in other elements of the network.

Electroencephalography has good temporal but poor spatial resolution. Many subtle issues arise from the use of such data. In principle, the measurement of synchronous networks across widespread areas of the cortex has the potential to usher in a new era of electroencephalogram analysis and understanding of "depth of anesthesia"; and perhaps to contribute to anesthetic models of pathologic states. Single-channel electroencephalogram recording will only ever be an indirect measure of the conscious state. By quantifying anesthetic-induced changes in the long-range cortical connection structure, the study by Lee *et al.* has moved us one step closer to directly measuring the neural substrate of consciousness.

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