Postoperative Delirium

Disconnecting the Network?

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NETWORKS are central to life, a fact that becomes strikingly apparent when they become dysfunctional. We have all experienced a sense of frustration when the "net is down" or when trapped in an airport because some critical hub in another city has been debilitated by an unexpected snowstorm. Even seemingly minor disruptions in the transfer of information or people can lead to a surprising degree of disorganization. However, these relatively inconsequential annoyances of modern life pale in comparison with faltering or failing *brain* networks. Aberrant structural and/or functional connections across the brain account for numerous neurological conditions (such as apraxia or agraphia)[1] and have been hypothesized to mediate more complex cognitive disorders such as schizophrenia.[2] So why should a clinical anesthesiologist care about a neurologic or psychiatric "disconnection syndrome?" The answer is found in this issue of ANESTHESIOLOGY, where van Dellen *et al.*[3] present evidence to suggest that postoperative delirium is associated with abnormal patterns of functional and directional connectivity in the brain.

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Delirium is an acute cognitive disorder, which is typically characterized by a fluctuating course, inattention, disordered thinking, and altered level of consciousness.[4] With a reported incidence between 5 and 70% in patients older than 65 yr after various major surgeries,[5,6] delirium is arguably the most common neurologic complication of major surgery. Despite this, the pathophysiology of delirium is poorly understood.[7] Importantly, postoperative delirium is associated with increased morbidity, longer hospital or intensive care unit stay, cognitive decline, quality-of-life decrement, and death.[5,8–10] Patients with delirium can be hyperactive and agitated or hypoactive and lethargic. Interestingly, the hypoactive motor subtype is more common, is often undiagnosed, and has been associated with worse outcomes.[11] In short, delirium is a pathophysiologically obscure, underdiagnosed, common, and serious neurological complication of surgery. The field of anesthesiology should therefore prioritize its prevention, diagnosis, and treatment, while concurrently investigating its underlying mechanisms.

In the current study, van Dellen *et al.* conducted a postoperative assessment of patients aged 50 yr or older undergoing cardiac surgery who had no history of neurologic or psychiatric disease. Mental status was evaluated during a 5-day period after surgery (or after emerging from postoperative coma) using the confusion assessment method for the intensive care unit, a validated instrument for diagnosing delirium in intubated intensive care unit patients.[12] In addition, 21-channel electroencephalography was recorded in the postoperative period and later analyzed for functional connectivity, directional connectivity, and various network features (table 1). Clinical characteristics and connectivity and network measures were compared between patients with delirium and a matched cohort without delirium. The investigators found that, not surprisingly, patients with delirium (n = 25) were sicker and had longer surgical times compared with patients without delirium (n = 24). However, even controlling for these factors, there was a reduction of functional connectivity in the α bandwidth (8 to 13 Hz) and increased directional connectivity from central to anterior regions in the δ bandwidth (0.5 to 4 Hz). Furthermore, a number

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Table 1. Description of Network Properties

Network Property	Description
Phase lag index	A measure of functional connectivity based on phase relationships. This measure attempts to minimize the problem of volume conduction by ignoring zero-phase lag between brain activities.
Directed phase lag index	A measure of directional connectivity based on phase lead–lag relationship between two brain activities. A consistent phase lead or lag is posited to reflect information flow between the activities of two brain regions.
Average path length	A measure of *global* efficiency of information transmission in a brain network. It quantifies the average distance of shortcuts over all pairs of nodes. The shorter the path length, the faster the information transmission in the brain.
Clustering coefficient	A measure of *local* functional segregation of brain activities. If a node has a large clustering coefficient, it indicates its neighbors are highly interconnected.
Small worldness	A measure of the balance between global integration (path length) and local segregation (clustering coefficient). Diseased brains can lose the balance between global and local organization of information. Small-world characteristics are actually maintained during anesthetic-induced unconsciousness.

Adapted, with permission, from Lee H, Mashour GA, Noh GJ, Kim S, Lee U: Reconfiguration of network hub structure after propofol-induced unconsciousness. ANESTHESIOLOGY 2013; 199:1347–59. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of the copyright in the translation or adaptation.

of network properties (such as path length and clustering coefficient) were abnormal in patients who experienced delirium. The authors concluded that functional brain networks are less connected in association with postoperative delirium, suggesting that mechanistically it may be classified as a disconnection syndrome.

Before interpreting these results, it will be beneficial to consider some methodological points. There are four types of "connectivity" that are often measured in the brain: (1) *structural*, defined as the anatomic connections between brain regions, (2) *functional*, defined as the statistical covariations between the activity of brain regions, (3) *directional*, defined as coupled activity in which one brain region leads and another follows or lags (without, necessarily, having a causal influence), and (4) *effective*, defined as a causal relationship in which one brain region is influencing the activity of another. One well-known problem with measures of functional connectivity using electroencephalography is *volume conduction*. If the same source of activity is detected at two different electrodes, that activity artificially appears to be synchronized or coherent because it is merely common to both electrodes. To avoid this problem, Stam[13] (an author of the current study) and colleagues previously introduced phase lag index (PLI) as a measure of functional connectivity. PLI attempts to bypass the volume conduction problem by not "counting" zero-lag correlations (which, because there is *no* phase difference, could potentially come from the same source). Instead, PLI assesses consistent, nonzero phase lead–lag relationships that presumably reflect a functional connection between two sources of activity. Unlike this snapshot measure of instantaneous phase relationship, *directed* PLI (dPLI) is a measure of directional connectivity that assesses lead–lag relationships over time. dPLI has been studied in a neuroanatomically informed brain model and shows a tendency of α rhythm "flow" from anterior to posterior brain structures in the resting state,[14] which has been confirmed empirically in human volunteers.[15]

van Dellen *et al.* used PLI and dPLI in the current study. This means that their results regarding functional connectivity might be less likely to reflect volume conduction and also means that the findings may reflect longer-range connections in the brain (which would tend to have nonzero lag relationships). Of note, Lee *et al.* previously studied PLI and dPLI after induction with propofol, finding reduced PLI in the α bandwidth (8 to 13 Hz) during and after the period of anesthetic-induced unconsciousness. Furthermore, the abnormal dPLI may reflect changes in the topology of the network, as has also been suggested by the study of dPLI and propofol (although in the α rather than δ bandwidth).[15] In light of the current findings, it might be speculated that postoperative delirium reflects a failed recovery—or perhaps a fragile recovery—of functional connectivity, as manifested in the α bandwidth. This functional "disconnection" could prevent individual subsystems in the brain from properly interacting and integrating information, resulting in the cognitive deficits characteristic of delirium. Furthermore, electroencephalographic measures of connectivity may have diagnostic potential, especially in the case of hypoactive delirium when the phenotype is not clinically obvious.

There are a number of important points to consider before including postoperative delirium in the class of disconnection syndromes. First, a prior study of functional magnetic resonance imaging and delirium demonstrated an *increase* in functional connectivity between prefrontal cortex and posterior cingulate cortex, with decreases between cortical and subcortical structures.[16] These data need to be reconciled with the electroencephalographic study by van Dellen *et al.*, who found reduced corticocortical connectivity. Second, the differences in functional connectivity between the cohorts with and without delirium were small (PLI of 0.119 *vs.* 0.139). It is unclear what clinical meaning these statistically significant differences have in relation to overall network function, or whether they could be explained by more mundane reasons related to the processing of the electroencephalographic data. Third, unlike the past study of functional magnetic resonance imaging, this was not a within-subjects study design. In other words, we do not have data on individual subjects in periods of

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both lucidity and cognitive dysfunction and therefore cannot distinguish if the changes in functional connectivity are associated with delirium or some other brain property of these generally sicker patients. Finally, delirium has a complex etiology, so any potential relationship between the cognitive disconnections during anesthetic-induced unconsciousness[15,17] and those of the postoperative period is merely speculative.

Despite these limitations, it should be noted that the work by van Dellen *et al.* is the first to probe the electroencephalogram of patients with postoperative delirium beyond its spectral properties, pointing to the potential for functional disconnections and network abnormalities as the mechanism for disrupted cognition. Further work is required to reconcile these results with past investigations using functional magnetic resonance imaging and to establish robust connectivity measures that might reveal when the network is down.

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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