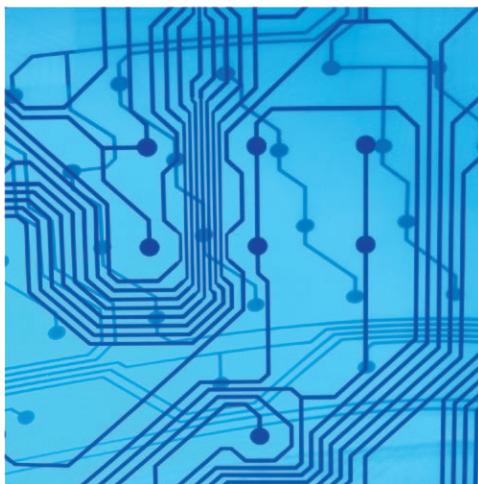


# Delirium, Neurotransmission, and Network Connectivity

## The Search for a Comprehensive Pathogenic Framework

THE acute confusional state of delirium remains a key problem in perioperative and critical care medicine.<sup>1</sup> Hampered by a lack of animal models, research is largely restricted to human studies that correlate biomarkers with the incidence and/or duration of delirium. Consequently, there is a lack of mechanistic studies to highlight novel therapies for the condition. Research into delirium is further limited by the lack of a comprehensive framework for its pathogenesis. Such a framework needs to link the features of delirium with two principal determinants of neural function: changes in neurotransmission and neural network connectivity.<sup>2</sup> Of course, studying these factors in the human is complex, particularly if the subject is delirious. These difficulties place even greater burden on clinical studies of sufficient size and rigor to identify pathogenic factors that *may* be manipulated to improve outcomes from delirium.

In this issue of ANESTHESIOLOGY, Hughes *et al.*<sup>3</sup> have provided evidence linking endothelial dysfunction to the risk of delirium. Among many functions, endothelial cells play an important role in controlling both vascular permeability and capillary blood flow. Hughes *et al.*<sup>3</sup> focused on blood flow using the Endo\_PAT device (Itamar Medical Ltd, Franklin, MA) to derive a “reactive hyperemia index,” where lower values reflect greater endothelial dysfunction. For this test, a cuff is inflated on one arm to 50 mmHg above systolic blood pressure, and the other arm serves as a reference. After 5 min of ischemia, the cuff is deflated and difference



**“... a [comprehensive conceptual] framework needs to link the features of delirium with two principal determinants of neural function: changes in neurotransmission and neural network connectivity.”**

in pulse wave amplitude between the two arms is used to calculate the reactive hyperemia index. The authors show that lower scores on the reactive hyperemia index were associated with an increased risk of acute brain dysfunction, including delirium.

The strengths of the study include the large sample size (147 critically ill patients enrolled with 134 completing the study), the clarity of data reporting, the duration of follow-up, and the diagnosis of delirium using a clinically useful test (the confusion assessment method-intensive care unit).<sup>4</sup> One weakness is that only a single measurement of the Endo\_PAT was taken, an apparent discordance with the long duration of follow-up. Thus, it is unclear whether endothelial function changes in a dynamic manner with the features of delirium. Furthermore, the study suffers from the pervasive problem of linking cause and effect—a difficulty plaguing the field of delirium research as residual confounding

may account for the differences observed. To the authors' credit, they attempt to adjust for confounding variables.<sup>3</sup> As underlying vascular disease may explain both endothelial dysfunction<sup>5</sup> and the risk of delirium,<sup>6</sup> the authors adjusted for the Framingham Stroke risk score.<sup>3</sup> Although this impacted on the results (and may not entirely account for the confounding of vascular disease), endothelial dysfunction was still associated with the acute brain dysfunction. Nonetheless, any causal link between endothelial dysfunction and delirium remains unproven. Furthermore, the authors point out that the Endo\_PAT device only measures a surrogate of endothelial function, and certainly not endothelial function at the blood brain barrier.<sup>3</sup> Therefore, this systemic measure of vascular reactivity may merely reflect the

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**Table 1.** Examples of Nonmodifiable and Modifiable Risk Factors for Delirium

Examples of Risk Factors	
Nonmodifiable (Patient Related)	Modifiable (Insult Related)
Age	Drugs
Cognitive impairment	Inflammation/Infection
Dementia	Metabolic abnormality
Vascular disease	Sleep deprivation

generalized illness or inflammation of critical care patients. Despite these concerns, impaired endothelial function may contribute to delirium.<sup>3</sup> An inability to meet the high metabolic demands of neurotransmission, through impaired autoregulation of cerebral blood flow, could lead to many of the neurologic symptoms of delirium.<sup>7</sup> Subsequent changes in neurotransmitter release and receptor expression may further affect neurologic function, especially when combined with other factors such as inflammation, sleep deprivation, or the impact of sedation.<sup>2,8–11</sup>

To provide a more coherent approach to the study of delirium, pathogenic frameworks that account for the cognitive disintegration of the delirium syndrome are required. To have validity, any framework must be consistent with the clinical data that have driven our understanding of the disorder, and it must address how brain function is perturbed at both the synaptic and neural network level. One such framework suggests that the risk of delirium is dependent on: (1) an acute change in inhibitory synaptic signaling, and (2) reduced connectivity of neural networks in the brain.<sup>2</sup> The proposal suggests that the delirium syndrome arises as increased inhibitory tone disintegrates neural networks. Acute (synaptic) changes in  $\gamma$ -aminobutyric acid inhibitory signaling in the brain may be driven by many modifiable risk factors for delirium, such as sedation (table 1). The theory also states that an important factor that determines the risk of delirium is the baseline (preinsult) connectivity in brain neural networks. This connectivity is influenced by many of the predisposing or nonmodifiable risk factors for delirium, such as age or dementia (table 1). For example, an increase in inhibitory tone (*e.g.*, with sedation) may not alone produce delirium, but when allied either with other factors that affect GABAergic signaling (*e.g.*, inflammation) or a predisposing risk factor that affects the baseline connectivity in the brain (*e.g.*, age or dementia), delirium may result.<sup>2</sup> This theory has been subsequently refined to suggest that a parallel increase in aminergic neurotransmission (such as norepinephrine or dopamine) may facilitate interaction with the environment at a reduced state of consciousness, as occurs during delirium.<sup>12</sup> Furthermore, it may be that the balance of excitatory and inhibitory neurotransmission is altered in delirium, hence understanding the role of key excitatory pathways, including those modulated by

acetylcholine,<sup>13</sup> is also required. Similarly, connectivity may be altered differentially between different brain regions with increases and decreases of connectivity possible,<sup>14</sup> perhaps leading to differing symptoms of delirium. Nonetheless, a central theme of altered neurotransmission and network connectivity is emerging. The data provided by Hughes *et al.*<sup>3</sup> may fit within this proposed framework for cognitive disintegration,<sup>2</sup> especially if we consider endothelial dysfunction as part of vascular disease. For example, acutely impaired endothelial function could contribute to changes in neurotransmission due to alterations in energetics,<sup>15,16</sup> whereas vascular disease may affect baseline connectivity in the brain<sup>17,18</sup>; it seems likely that both factors may be important to the pathogenesis of delirium.

Nonetheless, our understanding of delirium remains significantly limited. Importantly, the delirium syndrome comprises hyperactive, hypoactive, and mixed phenotypes; these phenotypes represent different forms of neurologic dysfunction. Until these forms are further dissected, both clinically and mechanistically, the development of therapies for delirium will be impaired. Although the study by Hughes *et al.*<sup>3</sup> has an appropriate sample size for the questions addressed, it is likely underpowered to look at subtypes of delirium. A critical step will be to study each subtype of delirium more closely and to analyze many factors such as comorbidities, endothelial function, sedation, and inflammatory burden in a single study. The critical care community will need to pull together to facilitate such a large, prospective study.

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