SPECIAL ARTICLE

Advancing the Neurophysiological Understanding of Delirium

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Delirium is a common problem associated with substantial morbidity and increased mortality. However, the brain dysfunction that leads some individuals to develop delirium in response to stressors is unclear. In this article, we briefly review the neurophysiologic literature characterizing the changes in brain function that occur in delirium, and in other cognitive disorders such as Alzheimer's disease. Based on this literature, we propose a conceptual model for delirium. We propose that delirium results from a breakdown of brain function in individuals with impairments in brain connectivity and brain plasticity exposed to a stressor. The validity of this conceptual model can be tested using Transcranial Magnetic Stimulation in combination with Electroencephalography, and, if accurate, could lead to the development of biomarkers for delirium risk in individual patients. This model could also be used to guide interventions to decrease the risk of cerebral dysfunction in patients preoperatively, and facilitate recovery in patients during or after an episode of delirium. **J Am Geriatr Soc 2017.**

Key words: delirium; electroencephalography; transcranial magnetic stimulation; connectivity; plasticity

Delirium is a common and costly problem, affecting up to 50% of hospitalized older adults, with estimated annual costs of $164 billion in the United States.[1,2] Delirium is associated with cognitive decline, loss of functional independence, and increased mortality.[1] Therefore, identifying individuals at risk for developing delirium, differentiating episodes of delirium likely to lead to lasting deleterious consequences, and minimizing the impact of delirium have assumed heightened importance. One central limitation preventing the achievement of these clinical goals is that current clinical definitions, such as the widely used Confusion Assessment Method (CAM[3]), are based on cognitive tests and bedside observations, and it is not completely clear how these signs and symptoms relate to the underlying brain dysfunction. Thus, a critical step is to understand, at a neurophysiologic level, why delirium happens in specific individuals. To this end, we begin by briefly reviewing the current literature on neurophysiologic investigations of delirium and other conditions that affect cognition, such as Alzheimer's disease (AD). We present a conceptual model advancing the hypothesis that delirium is due to a breakdown of normal brain function reflecting impairments in brain connectivity and plasticity. We explain how this model can be tested using the combination of Transcranial Magnetic Stimulation (TMS) and electroencephalograpy (EEG), and discuss some of the clinical implications of the model.

Neurophysiological Investigations of Delirium to Date

Neurophysiology during delirium has traditionally been studied using EEG, which measures the electrical fields produced by synchronized synaptic activity of cortical neurons. EEG activity is often divided into different spectral frequency bands, and changes in spectral band power (signal strength) have been reported in different disease states. The traditional spectral frequency bands evaluated during EEG recordings include delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) bands; alpha activity is the most prominent rhythm in the resting awake state (eyes-closed). More recently, techniques have been developed to assess statistical correlations in the EEG signals recorded from different electrodes, that indicate connectivity between different brain regions. Typically, these measures fall into two broad categories: measures of *functional* connectivity, which identify correlations in the

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statistical properties of brain signals from two or more regions, or measures of *effective* connectivity, which attempt to identify causal interactions between regions.

Changes in EEG spectral power and connectivity have been identified in patients with diseases that affect cognition such as Mild Cognitive Impairment (MCI) and AD. In these conditions, for example, loss of frontoparietal EEG connectivity is correlated with cognitive test results and disease progression over time.[4] Extending this work in MCI and AD, EEG measures may be useful in characterizing cerebral dysfunction in patients at risk for delirium. EEG is also useful in understanding the physiologic changes that occur *during* delirium, when the most consistent neurophysiological abnormality is a relative slowing of resting-state EEG rhythms, with abnormally decreased background alpha power and increased theta- and delta-frequency activity.[5,6] The degree of EEG slowing in delirium correlates with decline in performance on cognitive tests,[6] and both EEG slowing and cognitive dysfunction normalize when metabolic derangements leading to delirium (e.g., hypoxemia, hypoglycemia) resolve.[5] More recently, increased spectral variability,[7] decreased complexity of EEG activity,[7] and decreased EEG connectivity in the alpha band[8] have also been reported during delirium. EEG changes can differentiate individuals with delirium from those without delirium with an estimated sensitivity of 83.3% and specificity of 77.8% for visual analysis of EEG features,[9] up to a sensitivity of 100% and specificity of 96% for a quantitative measure of EEG spectral power.[10] Notably, EEG features may help differentiate patients with delirium and dementia from those with dementia alone with up to 83% accuracy.[11] However, in these studies the specific measures were retrospectively identified. Prospective studies validating these measures against reference standard delirium ratings are needed. In current clinical practice, EEG is used to distinguish delirium from nonconvulsive status epilepticus or an underlying psychiatric condition.

Another method useful for analysis of functional connectivity is resting-state functional magnetic resonance imaging (rs-fMRI). In this method, brain activity is measured while the subject sits in the MRI in a resting state (not doing any tasks, in contrast to active functional neuroimaging); different brain regions that show correlated changes in blood oxygenation are said to be "connected" into functional networks. rs-fMRI may play an important role in identifying abnormal brain networks during delirium. Patients with delirium show a positive correlation between activity in the dorsolateral prefrontal cortex (DLPFC) and the posterior cingulate, whereas a negative correlation between these regions is typically seen in patients without delirium.[12] Importantly, such abnormal correlations resolve after the episode of delirium ends. Abnormalities in brain resting-state connectivity have also been identified in hepatic encephalopathy, with improvements in brain connectivity seen after clinical improvement.[13] Furthermore, alterations in resting-state fMRI connectivity have been reported in many other neurocognitive disorders, ranging from AD to schizophrenia. Despite these intriguing findings, the neurophysiological relationship between pre-existing brain function, delirium risk, and the effects of delirium on brain activity and cognitive function have not been well-explored.

A Conceptual Neurophysiological Model of Delirium

Based on the above results, we propose a conceptual model (Table 1; Figure 1) that delirium is the consequence of the breakdown in brain network dynamics induced by insults or stressors in individuals with baseline low brain resilience due to low connectivity and/or deficient mechanisms of *neuroplasticity*, such as may be present in AD. Neuroplasticity, defined as the brain's ability to reorganize itself by forming new neural connections throughout life, allows the brain to compensate for injury and disease, and is often considered necessary for neurologic resilience (the ability to accommodate to or recover from a stressor).[14] Relevant brain stressors can include major surgery, general anesthesia, systemic inflammation, infections, and psychotropic drugs. Health conditions that might result in impaired plasticity include pre-existing neurodegenerative disorders, such as MCI and AD,[15] and comorbid conditions such as diabetes[16] or renal impairment. This model predicts that when individuals are confronted with acute insults, these stressors will alter brain connectivity (e.g., within the dorsal attention network[17]) and/or brain network dynamics (e.g., the relationship between dorsolateral prefrontal cortex activity and posterior cingulate activity[12]), resulting in symptoms of delirium such as inattention. This impact will be greater in individuals with pre-existing deficits in brain connectivity, specifically in the brain networks involved in resilience—which are linked to the construct of cognitive reserve.[18] Such alterations in brain connectivity and dynamics will be inadequately compensated in a brain with impaired plasticity, manifesting as the clinical syndrome of delirium. Supporting this model is the finding of altered connectivity and impaired plasticity in AD, which is established as a major risk factor for delirium.[1] This validity of this conceptual model can be assessed using the combination of Transcranial Magnetic Stimulation (TMS) and EEG.

Testing the Conceptual Model of Delirium with TMS-EEG

EEG and functional MRI passively record brain activity, and therefore are limited in their capacity for inferences about brain function. In contrast, TMS is a noninvasive brain stimulation technique that uses electromagnetic induction to produce changes in the activity of stimulated brain regions. When combined with simultaneous EEG recordings (TMS-EEG), TMS provides a powerful means to directly measure the cerebral response to an induced

Table 1. Relationship Between Connectivity, Plasticity and Delirium

	Plasticity	
	Preserved	Impaired
Connectivity		
High	No delirium	Acute delirium followed by compensation
Low	Acute delirium followed by compensation	Complicated delirium with sustained deficit

perturbation. TMS produces waves of activity that are reproducible and reliable[19] and that reverberate throughout the cortex.[20] To date, TMS-EEG has been used to assess cortical network properties in health and in a variety of neurologic and psychiatric diseases,[21,22] and detect alterations in cortical excitation/inhibition balance in diseases such as epilepsy.[23]

TMS-EEG provides a powerful means to measure the fundamental brain properties of *effective connectivity* and *neuroplasticity* (defined above). While TMS directly stimulates a relatively localized brain region, the evoked response propagates across brain regions over time[20] and can be used to determine the effective (causal) connectivity of the stimulated brain regions in individual subjects. When applied in repetitive trains, TMS produces persistent changes in cortical excitability that can be assessed using electromyography (EMG) and EEG, and can serve as measures of the integrity of neuroplasticity mechanisms.[24] Such TMS measures of neuroplasticity have been shown to be altered in diseases such as AD[25] and minimal hepatic encephalopathy.[26]

The conceptual model of delirium as a consequence of a breakdown in brain network dynamics is testable using TMS-EEG. Ideally, such a study should involve systematic and repeated assessments of brain structure, connectivity, neurophysiology and cognitive performance before patients enter the hospital (such as for scheduled elective major surgery), during hospitalization, and in the short- and long-term periods following hospitalization. The incorporation of neuroimaging and neurophysiologic approaches into longitudinal studies in vulnerable patients may ultimately help clarify the nature of the brain dysfunction that leads some patients to develop delirium in response to physiological stressors, and thus, identify physiological biomarkers for characterization of delirium risk. These biomarkers could also be assessed in animal models to enhance mechanistic insights and assess potential therapies.

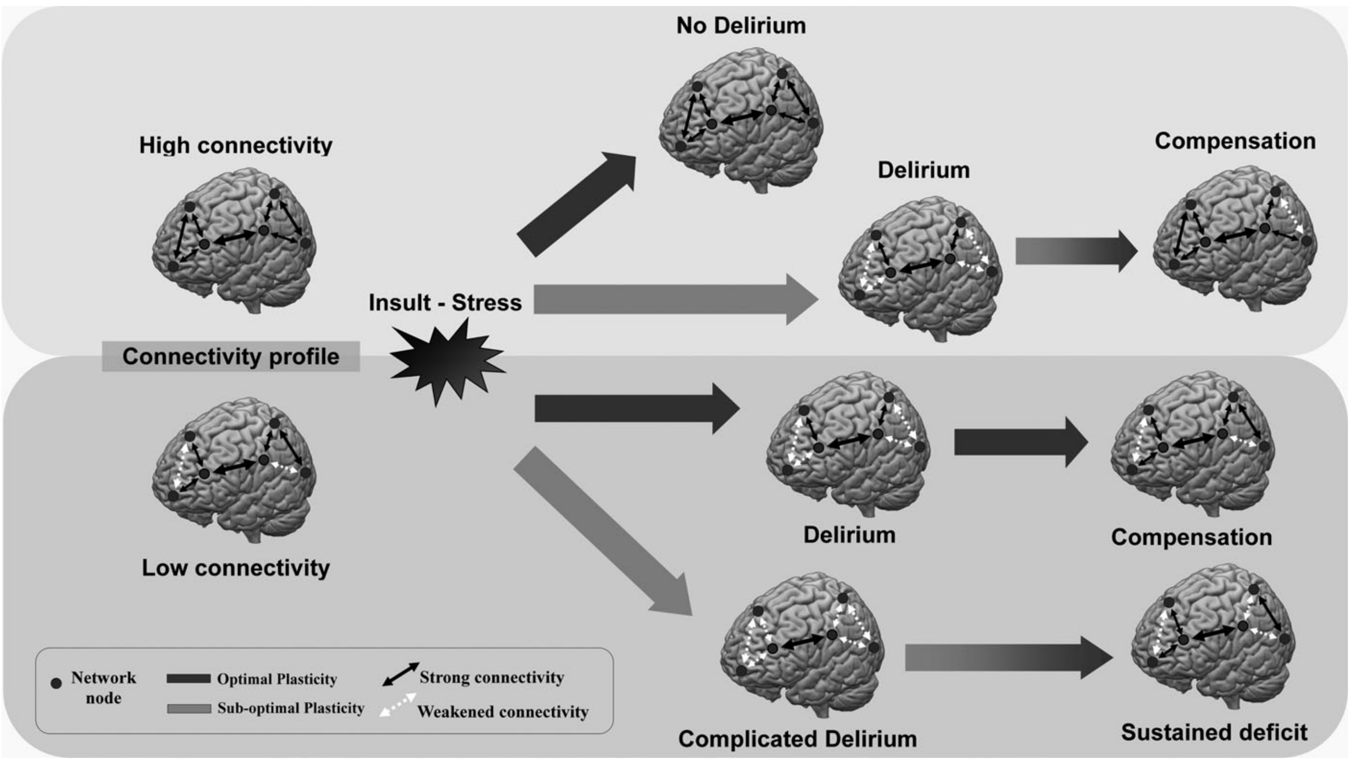

Figure 1. Conceptual model of brain connectivity, plasticity and delirium. The figure depicts a conceptual model illustrating how premorbid individual brain connectivity between brain regions (network nodes, grey circles) and the integrity of mechanism of brain plasticity (thick gray arrows) may relate to the susceptibility to delirium in response to exogenous (e.g., anesthesia) or endogenous (e.g., systemic infection) insults or stressors, and long-term outcome after recovery from delirium. Individuals with robust (high) baseline connectivity and preserved (optimal) cerebral plasticity (dark gray arrow, top) can accommodate stressors without changes in the integrity of brain networks, and thus do not experience delirium. Individuals with high baseline connectivity but impaired plasticity (light gray arrow, second row) cannot quickly accommodate to insults or stressors, and develop a significant decrease in connectivity and impairments in brain network integrity, which produce the symptoms of delirium. As the stressor resolves and normal brain connectivity is mostly reestablished, behavioral compensation occurs and normal cognitive function is restored. In individuals with low baseline connectivity but preserved plasticity (dark gray arrow, third row), insults/stressors acutely overwhelm normal plasticity processes, resulting in acute delirium. Over time, the baseline brain connectivity pattern is restored, and delirium resolves. In individuals with impairments in both baseline connectivity and plasticity (light gray arrow, bottom row), insults lead to severe disruptions in brain connectivity and function (complicated delirium). Brain network connectivity remains weakened even after resolution of the stressor, leading to sustained deficits.

Clinical Implications

The identification of specific features that mediate cerebral vulnerability to delirium may also lead to the development of brain-based interventions to reduce risk. For example, patients scheduled for major elective surgery who are found to have decreased cerebral connectivity might receive behavioral, pharmacologic or neurostimulatory interventions designed to increase connectivity[27–29] *prior* to surgery. Furthermore, patients already suffering from delirium could receive interventions to restore normal brain connectivity in affected networks, thereby facilitating recovery from delirium in situations when prophylaxis is not possible (such as after emergency surgery, when delirium incidence is particularly high.[30]) Such studies will also lead to an improved understanding of how delirium impacts the vulnerable brain, and may thus lead to interventions to mitigate the long-term effects of delirium on cognitive function.

More broadly, physiological stressors such as surgery or systemic infection can be viewed as a "stress test" for the brain. By systematically identifying the brain features related to connectivity and plasticity that lead some patients to "fail" this test and develop delirium, we may be able to operationalize and meaningfully test the concepts of brain health, brain vulnerability and brain reserve, with significant implications across a broad range of neuropsychiatric and cognitive diseases. As such, delirium provides a window of opportunity warranting detailed study not only in its own right, but for what it can teach us about brain function more generally.

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Conflict of Interest: APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync, and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI). None of the other authors report any conflicts of interest. All the other co-authors fully disclose they have no financial interests, activities, relationships and affiliations. The other co-authors also declare they have no potential conflicts in the three years prior to submission of this manuscript.

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