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Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure

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Background: Delirium is the most common neuropsychiatric syndrome encountered by clinicians dealing with older adults and the medically ill and is best characterized by 5 core domains: cognitive deficits, attentional deficits, circadian rhythm dysregulation, emotional dysregulation, and alteration in psychomotor functioning.

Design: An extensive literature review and consolidation of published data into a novel interpretation of known pathophysiological causes of delirium.

Results: Available data suggest that numerous pathological factors may serve as precipitants for delirium, each having differential effects depending on patient-specific patient physiological characteristics (substrate). On the basis of an extensive literature search, a newly proposed theory, the systems integration failure hypothesis, was developed to bring together the most salient previously described theories, by describing the various contributions from each into a complex web of pathways—highlighting areas of intersection and commonalities and explaining how the variable contribution of these may lead to the development of various cognitive and behavioral dysfunctions characteristic of delirium. The specific cognitive and behavioral manifestations of the specific delirium picture result from a combination of neurotransmitter function and availability, variability in integration and processing of sensory information, motor responses to both external and internal cues, and the degree of breakdown in neuronal network connectivity, hence the term acute brain failure.

Conclusions: The systems integration failure hypothesis attempts to explain how the various proposed delirium pathophysiologic theories interact with each other, causing various clinically observed delirium phenotypes. A better understanding of the underlying pathophysiology of delirium may eventually assist in designing better prevention and management approaches.

KEYWORDS

acute brain failure, delirium, delirium pathophysiology, encephalopathy, metabolic derangements, system integration failure hypothesis

1 | WHAT IS DELIRIUM?

Delirium is the most common neuropsychiatric syndrome encountered by clinicians dealing with older adults and the medically ill.[1,2] Delirium is an acute or subacute disorder, usually developing within hours to days, which represents a change from the patient's baseline cognitive functioning, characterized by disturbances in attention, awareness, and multiple aspects of cognitive functioning, not better explained by a preexisting or other neurocognitive disorder.[3]

The phenomenon of delirium is best understood as having 5 core domains (Figure 1): *cognitive deficits* (characterized by perceptual distortions, impairment in memory, abstract thinking and comprehension, executive dysfunction, and disorientation); *attentional deficits* (characterized by disturbances in consciousness and a reduced ability to direct, focus, sustain, and shift attention); *circadian rhythm dysregulation* (characterized by fragmentation of the sleep-wake cycle); *emotional dysregulation* (characterized by perplexity, fear, anxiety, irritability, and/or anger); and *psychomotor dysregulation* (which confers the various phenotypic presentations).

2 | DELIRIUM PHENOTYPE

Phenotypically, there are at least 5 types of delirium, based on their clinical manifestations (Figure 2).[2] Most delirium presentations seem to be preceded by a prodromal phase, usually marked by restlessness, anxiety, irritability, and sleep disturbances, which usually develop over a period of hours to days.

Subsyndromal delirium represents an incomplete presentation of the syndrome. Medically ill patients with subsyndromal delirium experienced longer intensive care unit (ICU) length of stay and longer overall hospital stay, lower cognitive and functional outcomes, and increased postdischarge mortality[4] and have the same set of risk factors and experience similar outcomes as patients experiencing *Diagnostic and Statistical Manual of Mental Disorders* (DSM)–defined delirium.[5]

The 3 classic motoric presentations include the hyperactive, hypoactive, and mixed delirium types.[6] Among the older medically ill population, the hypoactive-type delirium is the most common (65%), as compared with hyperactive (25%) or mixed (10%).[7]

More recently, 2 "variants" of delirium have been described: the "catatonic variant," which represents an extreme form of hypoactive delirium, and the "excited variant," which represents an extreme form of hyperactive delirium (Figure 3). The latter is associated with the use of sympathomimetic drug abuse (eg, psychostimulants, designer drugs [like the synthetic cathinone 3,4-methylenedioxymethamphetamine], or "bath salts"), which may lead to a hypermetabolic syndrome and potentially death, if not promptly recognized and treated.

Although the DSM defines delirium as a transient syndrome, "chronic" or persistent delirium forms may be seen in a number of scenarios, such as those with baseline cognitive impairment or experiencing delirium as sequelae to new intracranial processes or the effects of acute substance intoxication or withdrawal.

3 | DELIRIUM PRECIPITANT FACTORS

A number of clinical and pathophysiological factors have been associated with the onset of delirium, referred to here as *precipitant factors*. We use the mnemonic "End Acute Brain Failure" to help recall 20 of the most clinically relevant risk factors associated with the appearance of delirium, which are described in Table 1 in detail.[1,2,8]

4 | SUBSTRATES OF DELIRIUM

There are a number of patient-specific physiological characteristics that serve as substrate to the development of delirium (Figure 4). Table 2 highlights the areas of intersections between the various substrates of delirium.

4.1 | Age: neuronal aging hypothesis

According to the neuronal aging hypothesis, the changes accompanying the aging process are associated with diminishing physiologic reserve, making us increasingly vulnerable to physical stress and illness.[10] Aging is associated with a number of age-related cerebral changes including changes in the proportion of stress-regulating neurotransmitters, brain blood flow decline, decreased vascular density, neuron loss, and intracellular signal transduction systems.[11-15] Multiple studies have found older age to be an independent risk factor for delirium among hospitalized, medically ill older adult patients,[16] with an increased delirium risk from 3% for those less than 65 years old to 14% for those 65 to 74 years old and 36% for patients 75 years and older ($P < .0001$).[17] Others have found that in older adult ICU patients, the probability of developing delirium increases by 2% per year after age 65 (Figure 5).[18]

Even mild impairment in higher-order cognitive functions is predictive of postoperative delirium (POD) even in the absence of frank cognitive impairment.[19] Among nondemented older adults undergoing elective orthopedic surgery, subtle preoperative attention deficits predicted a 4- to 5-fold increased risk of POD for subjects with more than 1 standard deviation above the sample means.[20] Similarly, among older subjects undergoing orthopedic surgery, the incidence of POD increased from 32% in nondemented patients to 100% for those with dementia.[21]

There are ample data to suggest a reciprocal relationship between delirium and cognitive decline: that is, among older adults, dementia is the strongest risk factor for delirium[22,23]; and the development of delirium significantly increases the risk of subsequent cognitive decline, including dementia.[24] Similarly, in older, adult ICU patients, after an episode of delirium, there is a 63% probability of developing dementia at 48 months, compared with 8% in patients without delirium.[25] Table 3 contains a list of potential mechanisms associated with the increased risk of delirium in older adults.

4.2 | Inflammation: neuroinflammatory hypothesis

According to the neuroinflammatory hypothesis (NIH), delirium represents the central nervous system (CNS) manifestation of a systemic disease state that has crossed the blood-brain barrier (BBB).[26,27]

Key points

- Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances.
- The phenomenology of delirium is characterized by 5 core domains: cognitive deficits, attentional deficits, dysregulation in circadian rhythm, emotional dysregulation, and alteration in psychomotor functioning.
- The SIFH proposes that the specific combination of neurotransmitter dysfunction and the variability in integration and appropriate processing of sensory information and motor responses, as well as the degree of breakdown in cerebral network connectivity directly, contribute to the various cognitive and behavioral changes, as well as the clinical motoric phenotype observed in delirium.

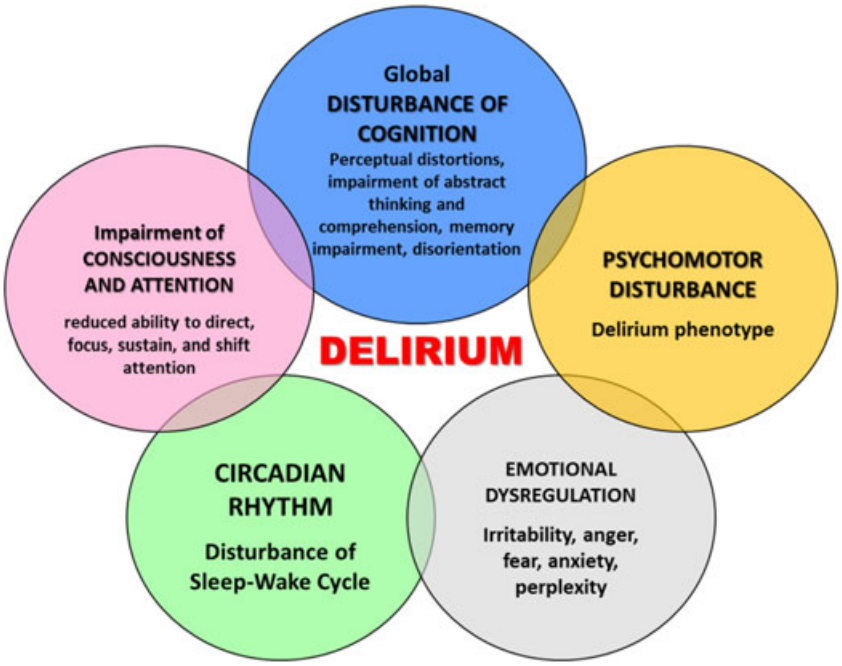

FIGURE 1 Delirium core domains. The phenomenon of delirium has 5 core domains: cognitive deficits (characterized by perceptual distortions, impairment in memory, abstract thinking and comprehension, executive dysfunction, and disorientation), attentional deficits (characterized by disturbances in consciousness and a reduced ability to direct, focus, sustain, and shift attention), circadian rhythm dysregulation (characterized by fragmentation of the sleep-wake cycle), emotional dysregulation (characterized by perplexity, fear, anxiety, irritability, and/or anger), and psychomotor dysregulation (which confers the various phenotypic presentations) [Colour figure can be viewed at wileyonlinelibrary.com]

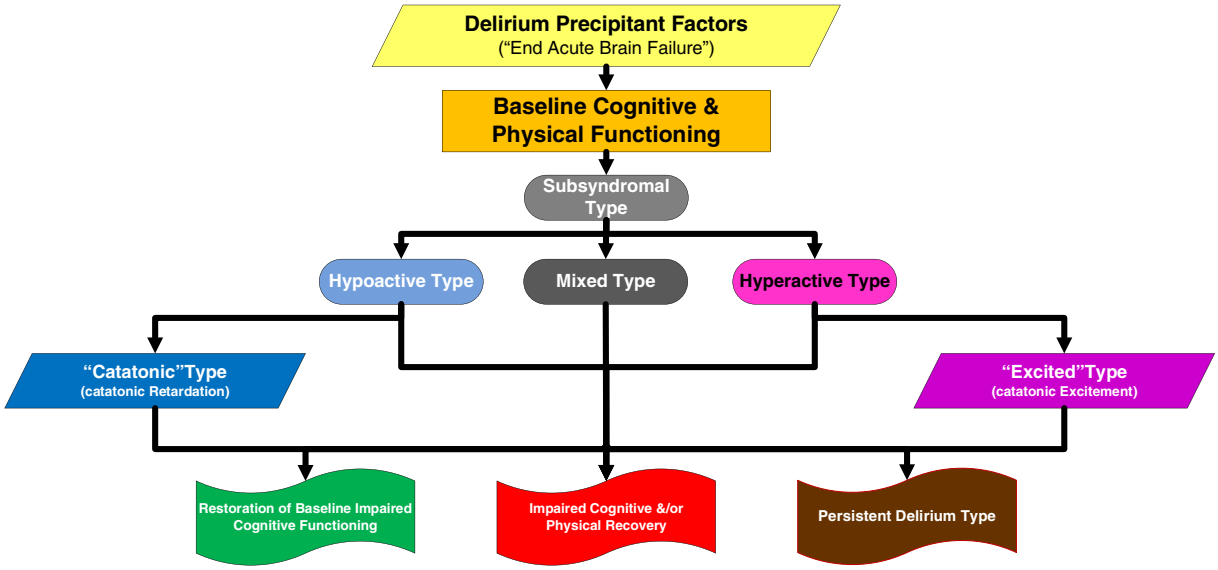

FIGURE 2 Delirium phenotypes and clinical outcomes. Phenotypically, there are at least 5 types of delirium, based on their clinical manifestations: the prodromal phase usually marked by restlessness, anxiety, irritability, and sleep disturbances, which usually develop over a period of hours to days; the traditional hypoactive, hyperactive, and mixed motoric types (with the extremes of catatonic retardation and catatonic excitement); and a potential chronic or persistent delirium type [Colour figure can be viewed at wileyonlinelibrary.com]

Inflammation has long been recognized as a trigger for episodes of delirium, particularly in older adults,[22,28-32] with a correlation between the severity of the patient's underlying medical problem and the development of delirium.[18,33]

The NIH proposes that peripheral inflammatory processes (eg, infections and surgery) induce activation of brain parenchymal cells, which express inflammatory cytokines and other inflammatory mediators in the CNS (eg, C-reactive protein, interleukin [IL]-6, tumor necrosis factor alpha, IL-1RA, IL-10, and IL-8),[34,35] leading to neuronal and synaptic dysfunction and subsequent neurobehavioral and cognitive symptoms characteristic of delirium (Figure 6).[31,36-38] Studies have demonstrated that microglia can be primed by prior

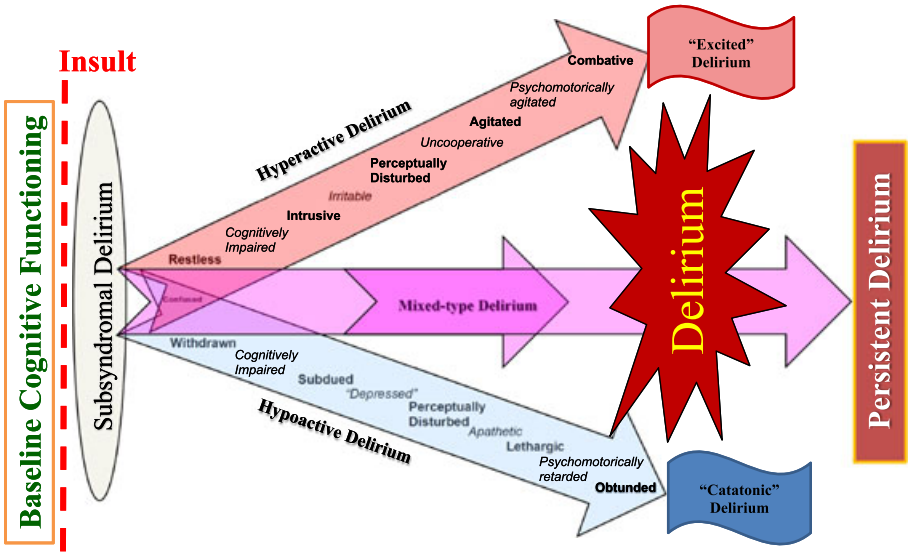

FIGURE 3 Delirium phenotypes, symptom progression [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Delirium: predisposing and precipitating risk factors—"end acute brain failure"

Risk factors	Examples
Electrolyte abnormalities and fluid imbalance	Electrolyte disturbances (eg, hyperammonemia, hypocalcemia/hypercalcemia, hypokalemia/hyperkalemia, hypomagnesemia/hypermagnesemia, hyponatremia/hypernatremia, hypophosphatemia/hyperphosphatemia, hypochloremia/hyperchloremia); hypovolemia (eg, dehydration, bleeding, and emesis); hypervolemia (eg, volume overload due to excessive fluid supplementation, hepatic failure, renal failure, and heart failure)
Neurological disorders and injuries	All neurological disorders (eg, central nervous system [CNS] malignancies, abscesses, cerebrovascular accident, intracranial bleed, meningitis, encephalitis, neoplasms, vasculitis, multiple sclerosis, epilepsy, Parkinson disease, normal pressure hydrocephalus, traumatic brain injury, diffuse axonal injury, paraneoplastic syndrome
Deficiencies (nutritional)	Nutritional deficiencies (eg, malnutrition, low serum protein/albumin, low caloric intake, and "failure to thrive"), malabsorption disorders (eg, celiac disease), and hypovitaminosis, specifically deficiencies in cobalamin (B12), folate (B9), niacin (B3, leading to pellagra), thiamine (B1, leading to beriberi and Wernicke disorder)
Age and gender	Age (>65) and gender (m > f). Old age is likely a contributor because of increased number of medical comorbidities; ↑ overall frailty, ↓ volume of acetylcholine-producing cells; ↓ cerebral oxidative metabolism; ↑ cognitive deficits; ↑ risk of dementia; ↑ age-related cerebral changes in stress-regulating neurotransmitters and intracellular signal transduction systems; chronic neurodegeneration with an increased production of inflammatory mediators, including cytokines and acute phase proteins
Cognitive functioning	Baseline cognitive deficits, even subtle ones, have been associated with an increased risk of developing delirium. The presence of dementia, more than double the risk for postoperative delirium
U-Tox or acute substance intoxication and withdrawal states	Acute illicit substance intoxication (eg, cocaine, phencyclidine, lysergic acid diethylamide, and hallucinogens) and substance withdrawal states, particularly abstinence syndromes from CNS depressant agents (eg, alcohol, benzodiazepines, barbiturates, muscle relaxants, and opioids)
Trauma	Physical trauma and injury, heat stroke, hyperthermia and hypothermia, severe burns, surgical procedures
Endocrinopathies	Endocrine disturbances such as hyperthyroidism/hypothyroidism, hyperparathyroidism/hypoparathyroidism, hyperadrenalism/hypoadrenalism, exogenous corticosteroid use (eg, Cushing syndrome), hyperglycemia/hypoglycemia, hyperpituitarism/hypopituitarism, carcinoid syndrome, porphyria
Behavioral-psychiatric disorders	Certain psychiatric diagnoses, including undue emotional distress, a history of alcohol, and other substance abuse, as well as depression, schizophrenia, and bipolar disorder have been associated with a higher incidence of delirium
Rx: medication use and other toxidromes	Several pharmacological agents are highly deliriogenic. Among the most common agents are sedative hypnotics (eg, GABAergic agents, such as benzodiazepines, barbiturates, and propofol), anticonvulsants, anticholinergic agents, analgesics (eg, opioids, ketamine, and nonsteroidal anti-inflammatory drugs), antihistaminic agents (usually first generation and H2 blockers), antibiotics (eg, fluoroquinolones), cardiac and pulmonary agents (eg, digitalis, warfarin, sympathomimetic agents, diuretic, antiarrhythmic, and antihypertensive agents), psychotropic agents, steroids, dopamine agonists, muscle relaxant agents, immunosuppressant agents, and antiviral agents. There are a number of over-the-counter agents, especially those with anticholinergic (eg, henbane, jimson weed, datura, and mandrake) and psychoactive qualities (eg, dextromethorphan, ephedrine, and pseudoephedrine). Also must consider the toxic effects of pharmacological agents (eg, serotonin syndrome, neuroleptic malignant syndrome, and anticholinergic states) and the deleterious effects of toxic levels of various therapeutic substances (eg, lithium, tricyclic antidepressant agents, anticonvulsant agents, and immunosuppressant agents). Various toxins including carbon dioxide and monoxide poisoning, solvents, exposure to heavy metals (eg, lead, manganese, and mercury), insecticides, pesticides, poisons, and biotoxins (animal poison) can also manifest with delirium.

(Continues)

TABLE 1 (Continued)

Risk factors	Examples
Anemia, anoxia, hypoxia, and low perfusion/oxygenation states	Any state that may contribute to decreased oxygenation (eg, pulmonary or cardiac failure, hypotension, anemia, hypoperfusion, intraoperative complications, hypoxia, anoxia, carbon monoxide poisoning, and shock)
Infections	Pneumonia, urinary tract infections, sepsis, viral infections, encephalitis, meningitis, malaria, cerebral abscess, and HIV/AIDS
Noxious stimuli (pain)	Data suggest that both pain and medications used for the treatment of pain have been associated with the development of delirium. Studies have demonstrated that the presence of postoperative pain is an independent predictor of delirium after surgery. On the other hand, the use of opioid agents has been implicated in the development of delirium
Failure (organ)	End organ failure (eg, hepatic, cardiac, and renal failure) may lead to a delirious state
Apache score (severity of illness)	Evidence shows that the probability of transitioning to delirium increases dramatically for each additional point in the Acute Physiology and Chronic Health Evaluation II severity of illness score
Isolation and sensory deprivation	Social isolation, decreased intellectual stimulation; this includes sensory impairments, such as decreased visual and auditory acuity and increased functional dependence (eg, requiring assistance for self-care and/or mobility)
Light, sleep, and circadian rhythm	Sleep disturbances and alterations of the circadian rhythm: sleep deprivation, sleep disorders (eg, obstructive sleep apnea and narcolepsy), and disturbances in sleep-wake cycle
Uremia and other metabolic disorders	Metabolic disorders: acidosis, alkalosis, hyperammonemia, hypersensitivity reactions, glucose disturbances (eg, hypoglycemia or hyperglycemia), and acid-base disturbances. Other disorders to consider include fecal impaction and urinary retention
Restraints and immobility	The use of physical restraints (ie, soft or leather restraints) and other externally immobilizing technologies (eg, endotracheal tubes [ventilator], cardiac and pulmonary assistive devices and technologies [ventricular assist device and extracorporeal membrane oxygenation]), intravenous lines, bladder catheters, intermittent pneumatic leg compression devices, casts, and traction devices all have been associated with an increased incidence of delirium. Physical immobility and increased functional dependence (eg requiring assistance for self-care and/or mobility) have been associated with increase delirium rates
Emergence delirium	Emergence from medication-induced sedation, coma, or paralysis, which may be associated with CNS depressant withdrawal, opioid withdrawal, rapid eye movement rebound, and sleep deprivation

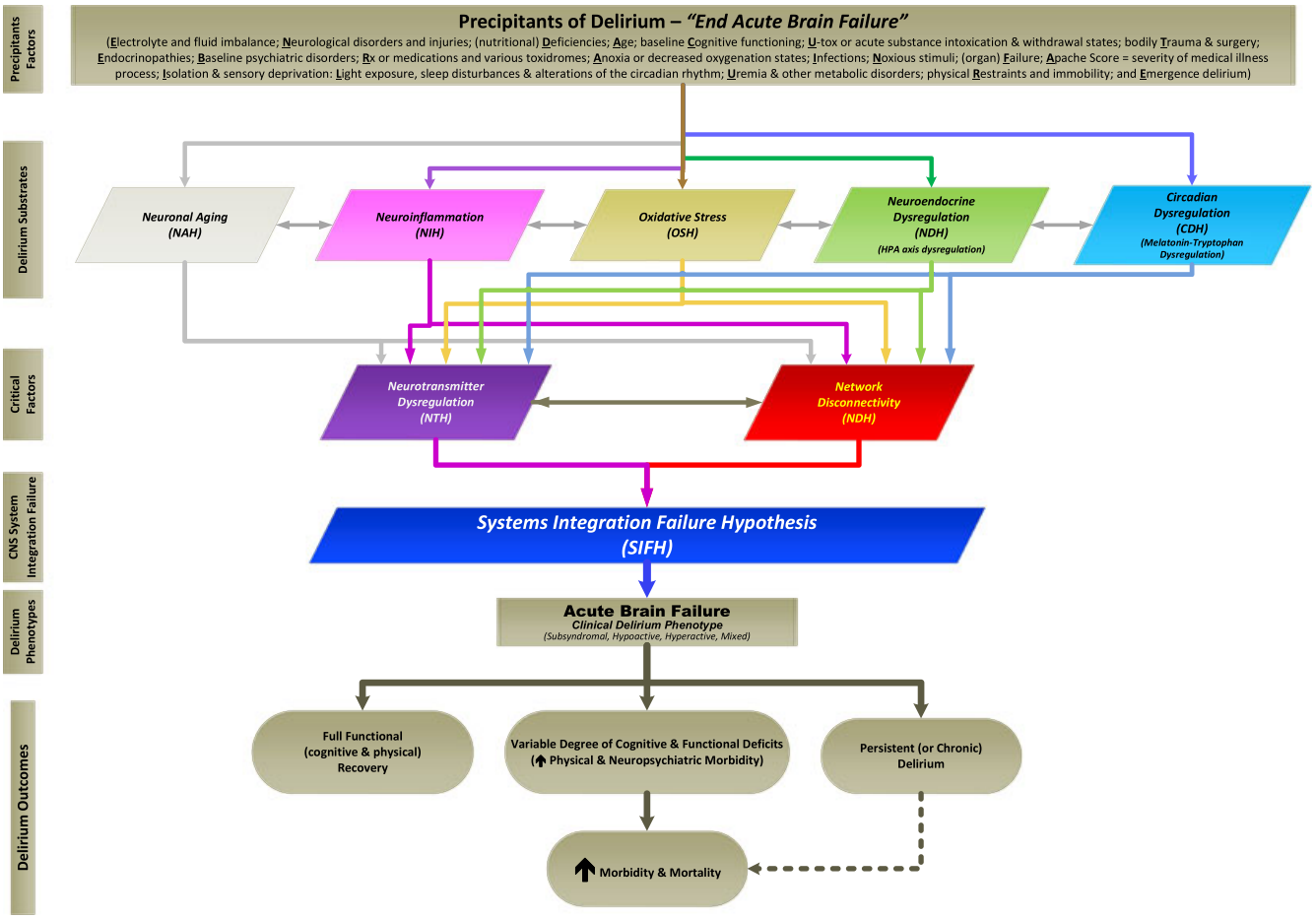

FIGURE 4 The system integration failure hypothesis of delirium [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Intersection between the various delirium substrate hypotheses

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
Neuronal aging hypothesis		Aging is associated with an increase in baseline levels of circulating inflammatory mediators including cytokines and acute phase proteins. Aging and neurodegenerative disorders exaggerate microglial responses by systemic immune stimuli, such as peripheral inflammation and/or infection, with evidence that activation of the peripheral innate immune system leads to exacerbated neuroinflammation in the aged brain. Chronic neurodegeneration is accompanied by an inflammatory response characterized by a selective activation of CNS microglial cells which are "primed" to produce exaggerated inflammatory responses to immunological challenges.	The aging process is the accumulation of oxidative damage to cells and tissues, also known as the "free radical theory of aging." In both the aging and delirious brains, there is a decline in the normal antioxidant defense mechanisms, which increases the vulnerability of the brain to the deleterious effects of oxidative damage. In fact, free radicals of mitochondrial origin may be among the primary causes of mitochondrial DNA damage. The production of cytokines in the CNS, partly mediated by Aβ, is accompanied by ROS production by activated microglia, which then leads to the release of proinflammatory molecules.	Cumulative exposure to high levels of GCs can be particularly detrimental for the aged hippocampus, a brain structure involved in learning and memory in both animals and humans. Aging itself is associated with age-related cerebral changes in stress-regulating hormones and intracellular signal transduction systems. Aging reduces the tolerance of GC stress hormones. Meanwhile, studies have shown that exposure to stress increased the levels of GCs, reduced GC receptor expression, and promoted senile plaque deposition, neuronal injury, and cognitive impairment.	Aging is associated with several well-described changes in patterns of sleep: (*a*) phase advance in the normal circadian sleep cycle (ie, go to sleep earlier in the evening but also to wake earlier) and (*b*) increased prevalence of many sleep disorders (ie, insomnia, rapid eye movement sleep behavior disorder, narcolepsy, periodic leg movement disorder, restless legs syndrome, obstructive sleep apnea). The decline in melatonin production in aged individuals may be one of the primary contributing factors for the development of age-associated neurodegenerative diseases.	Age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems. The aging process is associated with changes in the activity (eg synthesis, storage, release, receptor action, reuptake, and biotransformation or degradation) of several neurotransmitters in the CNS, especially DA, NE, 5HT, ACh, and GABA. Aging is also associated with a decreased volume of ACh-producing cells.
Neuroinflammatory hypothesis	Brain inflammation, characterized by increased microglia and astrocyte activation, increases during aging and is a key feature of most neurodegenerative diseases. Glial activation results in the sustained production of proinflammatory cytokines and ROS, giving rise to a chronic inflammatory process.		A major defense mechanism provided by mononuclear phagocytes (monocyte, tissue macrophage, and dendritic cell) is the production of free radicals and reactive molecular species, all potentially toxic to invading organisms. Among neurons, astrocytes and microglia of the CNS, the microglia are, in large measure, responsible for generating free radicals. Microglia possess the	Hormones help coordinate an animal's physiology and behavior to match its environment and maximize survival; and among the most important processes influenced by endocrine hormones are the immunological and behavioral responses to infection and inflammation. While microglia normally serve a housekeeping function in the brain (eg, removal of cellular debris) to maintain homeostasis,	Through their ability to promote sleep, cytokines are involved in the generation of an inner rhythm that controls the secretion of growth hormone, prolactin, and cortisol. Activation of the immune system counteracts infection and increases resistance to pathogens by inducing slow wave sleep, presumably via the production of inflammatory cytokines such as tumor necrosis factor alpha, IL-2, or	Acute systemic inflammation is a major trigger for cholinergic hypoactivity, which mediates the cognitive dysfunction observed during delirium. Acetylcholine deficiency further explains the relationship between the occurrence of delirium, critical care illness, and the development of cognitive impairment. Research data have demonstrated that ACh

(Continues)

TABLE 2 (Continued)

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
			nicotinamide adenine dinucleotide phosphate oxidase complex, which when assembled and activated, produces free radicals in abundance on the external cell surface; which can lead to tissue damage. Mitochondrial metabolism is a secondary producer of these destructive oxidants, via oxidative phosphorylation. Neuroinflammation leads to loosening of the blood-brain barrier's intercellular tights, allowing for extravascular fluid shift and formation of perivascular edema, and decrease of nutritive and oxygen perfusion leading to oxidative stress.	when subsequently exposed to a proinflammatory immune challenge, a primed microglia (eg, exposed to stress or exogenous GCs), becomes activated, resulting in activation of caspase 1, which cleaves pro-IL-1 to mature IL-1. Interleukin 1 is then released to induce a cascade of proinflammatory events resulting in neuroinflammation.	interferon gamma. Conversely, when the circadian rhythm is disrupted by an external change in the light-dark cycle, immune cells exhibit enhanced proinflammatory responses and lipopolysaccharide-induced IL-6 release.	reduces, while DA increases, inflammation-induced cytokine secretion by macrophages. Proinflammatory cytokines that induce sickness behavior also enhance activity of the ubiquitous indoleamine-2,3-dioxygenase, which leads to a shift in the metabolism of tryptophan away from the production of 5HT and melatonin (contributing to sleep and mood disturbances), while increasing the production of kynurenine and other neurotoxic by-products. Activated microglia participate in inflammatory processes linked to neurodegeneration by producing neurotoxic factors including quinolinic acid, superoxide anions, matrix metalloproteinases, nitric oxide, AA and its metabolites, chemokines, proinflammatory cytokines, and excitotoxins including GLU.
Oxidative stress hypothesis	Aging is accompanied by changes in membrane fatty acid composition, including a decrease in the levels of polyunsaturated fatty acids, such as AA, which	The abnormal production by glial cells of proinflammatory cytokines, chemokines, and the complement system, as well as ROS and reactive nitrogen		Psychological stress increases the circulating levels of the stress hormones (ie, GCs) and NE, in part through the production of ROS/reactive nitrogen	Research and clinical data suggest that the circadian regulation of protein expression plays a significant role in the cellular response to oxidative stress. Many	Oxidative stress affects the synthesis and release of multiple neurotransmitters, including ACh, DA, 5HT, and NE; see also Figure 10.

(Continues)

TABLE 2 (Continued)

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
	are abundant in the aging brain and highly susceptible to free radical attack. There is a correlation between the concentration of AA and long-term potentiation, suggesting that oxidative depletion of AA levels may relate to cognitive deficits. Oxidative damage to lipids can also occur indirectly through the production of highly reactive aldehydes. Peroxidation of AA forms malondialdehyde, which induces DNA damage by reacting with amino acids in protein to form adducts that disrupt DNA base pairing. Increased levels of malondialdehyde have been found in the aged human brain. The Aβ-induced oxidative stress hypothesis postulates that the oligomer Aβ is inserted into the membrane systems to initiate much of the oxidative stress observed in the brain during the progression of various neurocognitive disorders. Under normal circumstances, astrocytes are important for Aβ clearance and degradation and for forming a protective barrier between Aβ deposits and neurons. Astrocytes also provide neuronal support. Yet, in response to chronic stress, they could also be	species, can disrupt nerve terminal activity, causing dysfunction and loss of synapses, which correlate with memory decline; these are phenomena preceding neuronal death.		species. Studies have demonstrated that the brain is the organ most susceptible to GC-induced oxidative stress. The administration of exogenous GCs, mimicking a condition of physiological stress, is associated with increased levels of oxidative stress in the brain because the hypothalamic-pituitary-adrenal axis is mainly controlled by the mineralocorticoid and GC receptors located in the brain, also because brain cells have high metabolic intensities, low antioxidant defenses, and high contents of polyunsaturated fatty acids, which are targets of lipid peroxidation. Dexamethasone induces the overproduction of ROS, causing dysregulation of physiological processes.	antioxidants and enzymes that protect the cell from oxidative stress exhibit daily cycles (ie, circadian rhythm) in their expression or activity levels. Circadian rhythms and oxidative stress are also linked through the activity of at least 2 known factors that play a significant role in both processes: melatonin and the coenzyme nicotinamide adenine dinucleotide. Melatonin also enhances the antioxidant potential of the cell by stimulating the synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase and by augmenting glutathione levels.	Abnormalities in neurotransmitter concentration or receptor sensitivity may be caused by alterations in cerebral oxidative metabolism. Glutamate is released under neuroinflammatory conditions. Part of the neuroprotective action of astrocytes is associated to their capacity to take up excess GLU, convert it to glutamine, and recycle it to neurons. Similarly, Aβ decreases the uptake of GLU, increases oxidative stress, and activates the mitogen-activated protein kinase pathways. There is also a strong association between hypoxia and related states and impairment in the synthesis of amino acids, leading to ACh decline, suggesting a potential common mechanism in the occurrence of delirium.

(Continues)

TABLE 2 (Continued)

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
	a source for Aβ, owing to their overexpression of BACE1.					
Neuroendocrine hypothesis	Excessive exposure to these hormones can damage the brain and make neurons more vulnerable to neurological insults. Repeated or prolonged exposure to GCs has a deleterious impact on brain function and may likely contribute to some of the age-related decline in brain function. In addition, elevated cortisol in stress and aging is postulated to accelerate cognitive and physiological decline.	Glucocorticoids may have proinflammatory effects in the brain and can even enhance neuroinflammation at multiple levels in the pathway linking lipopolysaccharide exposure to inflammation. In addition, GCs can increase proinflammatory cell migration, cytokine production, and even transcription factor activity in the brain.	Meta-analysis has demonstrated that the brain is the most susceptible tissue to GC-induced oxidative stress. Glucocorticoid receptor signaling represses the antioxidant response by inhibiting histone acetylation mediated by the transcriptional activator nuclear factor erythroid 2–related factor 2. Glucocorticoids endanger hippocampal neurons by exacerbating the excitotoxic GLU-calcium-ROS cascade; with clinical and research data demonstrating that excess GCs cause hippocampal damage by regulating genes involved in ROS generation. Glucocorticoids exacerbate hypoxic hippocampal injury associated with seizure activity.		Glucocorticoids participate in sustaining circadian energy levels in mammals. Glucose tolerance was lower in the sleep-debt condition than in the fully rested condition, as were thyrotropin concentrations. Sleep deprivation is associated with increased evening cortisol concentrations and increased activation of the sympathetic nervous system.	The stress-induced release of GCs induces changes in GLU neurotransmission (including effects on GLU release, GLU receptors, and GLU clearance and metabolism) in the prefrontal cortex and the hippocampus, thereby influencing some aspects of cognitive processing. An indirect way by which GCs can influence neurotransmission (glutamatergic, as well as GABAergic, cholinergic, noradrenergic, and serotonergic) is through crosstalk with the endocannabinoid system. They rapidly stimulate endocannabinoid production in the brain, whereupon endocannabinoids bind to cannabinoid receptor 1 and transient receptor potential cation channel subfamily V member 1 and inhibit neurotransmitter release.
Circadian rhythm dysregulation hypothesis	Melatonin also inhibits the aggregation of the Aβ protein into neurotoxic microaggregates responsible for the neurofibrillary tangles characteristic of Alzheimer disease, and it	Sleep deprivation has been associated with decreased proportions of natural killer cells, reduced lymphokine-activated killer activity, and reduced IL-2 production.	Oxygen and circadian rhythmicity are essential in a myriad of physiological processes to maintain homeostasis, from blood pressure and sleep-wake cycles, down to cellular signaling	Sleep deprivation may alter endocrine and metabolic functions, altering the normal pattern of cortisol release and contributing to alterations of "GC feedback regulation,"		In the daytime, light-initiated signals are transmitted via the suprachiasmatic nucleus to the pineal gland through the upper cervical ganglion. Melatonin is produced

(Continues)

TABLE 2 (Continued)

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
	prevents the hyperphosphorylation of the tau protein.		pathways that play critical roles in health and disease. The cellular concentrations or activity levels of many antioxidants and protective small molecules (eg, melatonin) have been found to have circadian rhythmicity. Numerous study data suggest that the circadian regulation of protein expression plays a significant role in the cellular response to oxidative stress.	glucose tolerance, and insulin resistance.		by the pineal gland at night. Light stimulus causes an increase in the secretion of cortisol, 5HT, and DA, while suppressing melatonin, NE, and ACh. Serum melatonin levels are normally undetectable in the daytime but are significantly higher during the night. Circadian disruption, sleep onset insomnia, and difficulties in maintaining sleep in delirious patients could be partly related to a presumed hyperactivity of the dopaminergic system and dysfunction of the GABAergic system, both associated with core features of delirium and with signaling in sleep- and wake-promoting brain regions.
Neurotransmitter hypothesis	Multiple studies have demonstrated that there are changes in the synthesis, storage, release, receptor action, reuptake and metabolism of various transmitters in the aging brain. There is also evidence suggesting that there are (brain) regional variations depending on the transmitter involved.	Acetylcholine deficiency further explains the relationship between the occurrence of delirium, critical care illness, and the development of cognitive impairment. These factors may be related given that ACh reduces while DA increases inflammation-induced cytokine secretion by macrophages. Microglia express receptors for various neurotransmitters (eg, adenosine triphosphate, adenosine, GLU, GABA, ACh, DA, and	Abnormalities in neurotransmitter concentration or receptor sensitivity may be caused by alterations in cerebral oxidative metabolism. There is a strong association between hypoxia and related states and impairment in the synthesis of amino acids, leading to ACh decline, suggesting a potential common mechanism in the occurrence of delirium. The nervous system is especially vulnerable to ROS-mediated injury.	Neurotransmitters, including catecholamines and serotonin, play a crucial role in maintaining homeostasis in the human body. There are multiple areas of interaction between GCs and various neurotransmitters. The interaction of GCs with NE and DA affects arousal and the individual's ability to orient, focus, and sustain attention on perceived events and mobilize resources for necessary decision making and action. Glucocorticoids	The sleep/circadian timing systems are the product of complex interactions among multiple brain regions, neurotransmitter systems, and modulatory hormones. Thus, abnormalities in any key neurotransmitter system will impinge on the sleep/circadian timing systems at multiple levels.	

(Continues)

TABLE 2 (Continued)

Hypothesized areas of intersections	Neuronal aging hypothesis	Neuroinflammatory hypothesis	Oxidative stress hypothesis	Neuroendocrine hypothesis	Circadian rhythm dysregulation hypothesis	Neurotransmitter hypothesis
		adrenaline). Conversely, activation of various neuroreceptors (ie, Ach, GABA, and NE) suppresses microglial responses, whereas activation of adenosine triphosphate or adenosine receptors activates them, via activation of a Ca(2+) signaling pathway, which results in activation of mitogen-activated protein kinases and nuclear factor kappa B proteins with the release of proinflammatory factors. It is important to note that both GLU and DA have both proinflammatory and anti-inflammatory properties depending on the receptor subtypes expressed in a particular microglia.	Glutamate exocytosis is a major cause of oxidative stress. In addition, the high Ca^{2+} traffic across neuronal membranes and interference of ion transport increase intracellular Ca^{2+}, often leading to oxidative stress. Finally, activated microglia produces ROS and cytokines in a perpetual process.	participate in attention and emotional memory processes through interactions with NE, while decision making based on salience requires GCs and DA. Cortisol can potentiate the experience of fear and anxiety through the activation of extrahypothalamic corticotropin-releasing hormone. Chronic high cortisol levels are detrimental to a number of cognitive domains, and this has implications for cognitive/emotional processing and behavior. Overactivation of the amygdala and associated cortical areas may alter the experience of these patients across a number of cognitive domains, involving attention, perception, and memory systems normally recruited by cortisol.		

Abbreviations: AA, arachidonic acid; Aβ, amyloid beta; ACh, acetylcholine; CNS, central nervous system; DA, dopamine; 5HT, 5hydroxytryptamine or serotonin; GABA, gamma-aminobutyric acid; GCs, glucocorticoids; GLU, glutamate; IL, interleukin; NE, norepinephrine; ROS, reactive oxygen species.

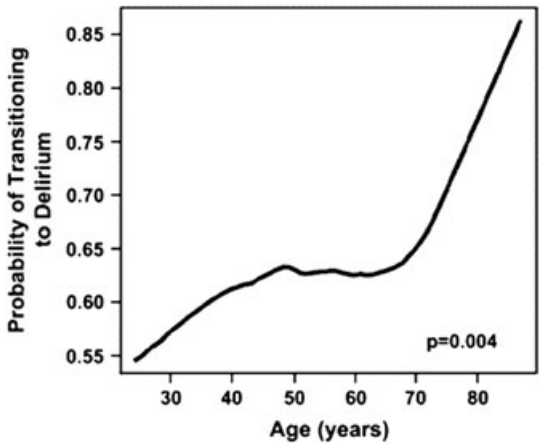

FIGURE 5 Age and transition to delirium. This figure shows an estimation of the probability of transitioning to delirium by age and indicates that the incremental risk is large for patients 65 years and older. The probability of transitioning to delirium increased dramatically (by 2%) for each year of life after 65 years. Adjusted odds ratio, 1.01 (1.00, 1.02), P = .03. Source: Pandharipande et al[18]

neurodegenerative processes, thus triggering an exaggerated response to systemic inflammatory signals.[39,40] See Table 4 and Figure 7 for a summary of proposed pathways by which peripheral factors elicit a neuroinflammatory response.[41]

During various disease states (eg, inflammation), leukocytes adhere to the BBB endothelial cells, leading to disruption of cell-cell adhesions and increased endothelial permeability, decreased perfusion and longer diffusion distance for oxygen,[30,42] and enhanced infiltration of leukocytes and transport of cytokines into the CNS, producing ischemia and neuronal apoptosis.[36,43] Studies have suggested that various anesthetic agents (eg, sevoflurane and isoflurane) can cause marked disruption of BBB-associated tight junctions, leading to increased BBB permeability (Figure 8).[44,45] The frequency and magnitude of this effect increase with age, thus potentially serving as a mechanism to mediate POD.

4.3 | Oxidation: oxidative stress hypothesis

Mounting clinical and experimental evidence indicates that reactive oxygen species and reactive nitrogen species (eg nitric oxide, NO[*]) play important roles in many physiological and pathological conditions,[46] resulting in oxidative stress, an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA.[47] The brain is particularly susceptible because it has a large lipid content of myelin sheaths, a high rate of brain oxidative metabolism, and a low antioxidant capacity.[48] Data suggest that oxidative stress and/or antioxidant deficiencies may increase the damage to cerebral tissue, leading to cognitive decline and possibly irreversible cerebral

TABLE 3 Potential mechanisms associated with the increased risk of delirium in the elderly

○ Neuronal loss (particularly in locus coeruleus and substantia nigra.
○ Changes in various neurotransmitter systems.
○ Age-related decline in white matter integrity, observed as increases in water diffusion and volume of hyperintense white matter lesions, intergyral spans, and reduction in fractional anisotropy of water diffusion, correlated with a decline in the global and regional cerebral glucose uptake.
○ Age-related decline in regional cerebral blood flow, particularly in the anterior cingulate gyrus, bilateral basal ganglia, left prefrontal, left lateral frontal, and left superior temporal and insular cortex, as measured by single-photon emission tomography.
○ Age-related changes in cerebral blood flow, likely associated with brain microvascular pathologies
• rarefaction of the microvasculature in some regions of the brain
• decreased vascular density
• damaged microvessels, with associated microinfarcts and microhemorrhages, likely due to peripheral arterial aging leading to stiffening and dilation of the proximal aorta with transmission of flow pulsations downstream into the brain
• decline in cerebrovascular angiogenesis
• impaired cerebral blood flow due to tortuous arterioles and deposition of excessive collagen in veins and venules
○ Age-related decline in cerebral metabolic rate of oxygen more markedly in bilateral putamen, left supratemporal, left infrafrontal, and left parietal cortices.
○ Decreased oxygen supply (eg, hypoxia) leading to a decrease in redox activity, resulting in decreased acetylcholine (ACh) production (oxidative stress).
○ Decreased cerebral oxidative metabolism.
○ Age-related changes in brain neurochemical activity:
• There is a significant increase in soluble hexokinase activity with age, due to an increased release of mitochondrial-bound hexokinase.
• There is a negative correlation of the activity of fructose-6-hosphate kinase with age, particularly in the brain cortex and putamen.
• There is a significant decline of carbonic anhydrase (important in the regulation of the pO_2/pCO_2 ratio in the brain tissue) with increasing age. Thus, pCO_2-dependent regulation of tissue pH, ionic transport processes, and cerebral blood flow regulation have the tendency to become more and more unstable.
• There is a progressive, age-dependent decline in cyclic adenosine monophosphate–dependent activity, most significantly in the brain cortex and thalamus, followed by the hippocampus, amygdala, and globus pallidus.
○ Age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems (neurotransmitter hypothesis).
○ Decreased ACh levels in plasma and cerebrospinal fluid, which may lead to
• Decreased volume of ACh-producing cells associated with normal aging (neurotransmitter).
• Decreased ACh synthesis associated with aging.
• Increase in baseline levels of circulating inflammatory mediators including cytokines and acute phase proteins (neuroinflammation).

Source: Modified from Maldonado.[26]

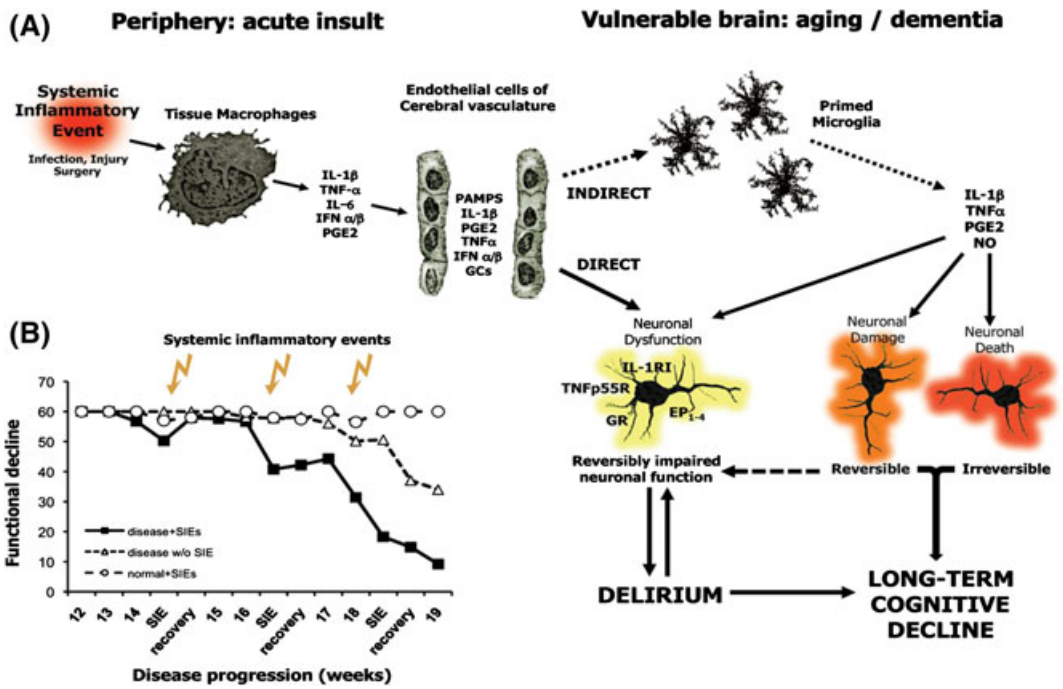

FIGURE 6 Neuroinflammatory hypothesis. A, Systemic inflammatory events trigger the release of inflammatory mediators by tissue macrophages and brain vascular endothelial cells. These mediators may affect neuronal function directly or via the activation of microglial cells that have become primed by neurodegenerative disease or aging. Inflammatory mediators may cause reversible disruption of neuronal function, as in the case of delirium; they may be irreversible and contribute to long-term cognitive decline or may bring about neuronal death and contribute to the accumulating damage and neuropathological burden. B, Successive systemic inflammatory insults induce acute dysfunction, which is progressively less reversible each time, but also contribute to the progression of permanent disability. Abbreviations: EP1-4, prostaglandin receptors 1-4; GCs, glucocorticoids; GR, glucocorticoid receptor; IFNα/β, interferon α/β; IL-1RI, interleukin 1 receptor type I; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; SIEs, systemic inflammatory events; TNFp55, TNFp55 receptor. Source: Cunningham[31] [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Potential pathways by which peripheral or systemic factors may elicit a central neuroinflammatory response

There are at least 4 known forms of immune brain communication pathways
(*a*) The "neural pathway"—peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines activate primary afferent nerves, such as the vagus nerve (Figure 6).
(*b*) The "humoral pathway" involves circulating PAMPs that reach the brain at the level of the choroid plexus (CP) and the circumventricular organs where PAMPs induce the production and release of proinflammatory cytokines by macrophage-like cells expressing toll-like receptors (Figure 7).
(*c*) An active transport system across the blood-brain barrier (BBB)
(*d*) A "leaky" BBB—neuroinflammation causes BBB permeability disruption, as suspected by elevations of S100 beta (a calcium-binding protein with cytokine-like properties) and changes in synaptic transmission, neural excitability, and cerebral blood flow, leading to the neurobehavioral and cognitive symptoms characteristic of delirium (eg, disruption in behavior and cognitive functions). Many of delirium's precipitant factors (eg, infections, intraoperative anesthesia, and postoperative sedation) are themselves associated with potential BBB integrity compromise. For example, it has been found that the BBB is disrupted in cases of septic encephalopathy, which allows for increased blood-brain transport of neutral amino acids.

degeneration, potentially leading to the development of persistent delirium.[49]

The oxidative stress hypothesis (OSH) suggests that delirium is "the clinical expression of a cerebral metabolic defect, [leading] at the clinical level, [to] the characteristic disturbance in cognitive functions" (Figure 9).[50,51] Thus, according to the OSH, decreased brain oxidative metabolism leads to abnormalities of various neurotransmitter systems, causing cerebral dysfunction and the behavioral symptoms of delirium.[8,26] Inadequate oxidative metabolism may be one of the underlying causes of the metabolic problems initiating the cascade that leads to the development of delirium, namely, the inability to maintain ionic gradients, causing cortical spreading depression (ie, spreading of a self-propagating wave of cellular depolarization in the cerebral cortex)[52]; abnormal neurotransmitter synthesis, metabolism, and release[53-57]; and free radical production and a failure to effectively eliminate neurotoxic by-products.[53,54] In fact, many have found a strong correlation between intraoperative O_2 saturation and postoperative cognitive dysfunction.[48,58,59] Even healthy control subjects may exhibit symptoms of delirium after experiencing a drop in their PaO_2 to 35 mm Hg.[60] Similarly, among a group of patients undergoing cardiac surgery, those who developed POD had lower preoperative and intraoperative cerebral oxygen saturation (ScO_2) levels, were older, and had lower preoperative hemoglobin levels compared with non-POD patients.[61]

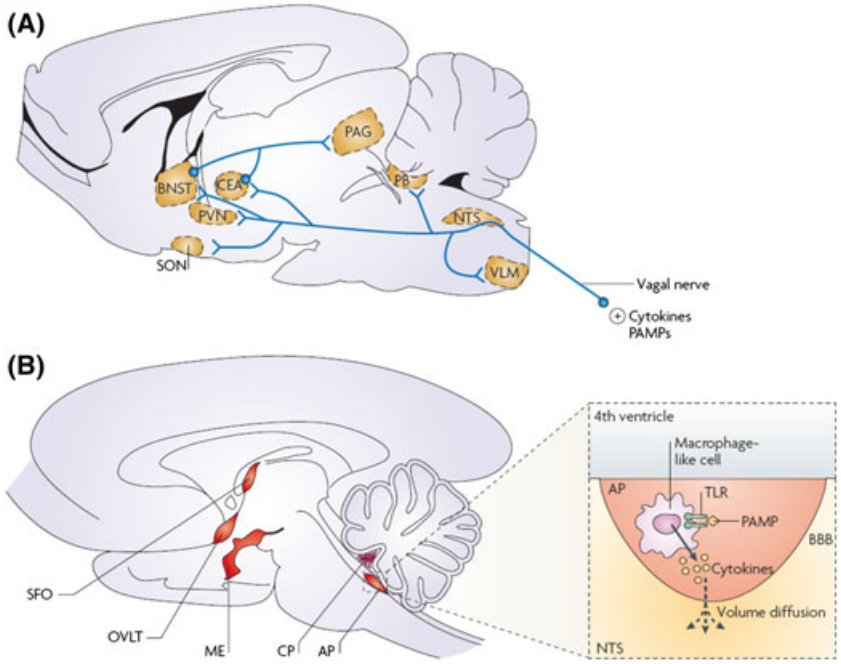

FIGURE 7 Pathways that transduce immune signals from the periphery to the brain. A, The *neural pathway* peripherally produced pathogen-associated molecular patterns (PAMPs), and cytokines activate primary afferent nerves. Vagal afferents project to the nucleus tractus solitarius (NTS), and from there to the parabrachial nucleus (PB), the ventrolateral medulla (VLM), the hypothalamic paraventricular and supraoptic nuclei (PVN and SON, respectively), the central amygdala (CEA), and the bed nucleus of the stria terminalis (BNST). These last 2 structures form part of the extended amygdala, which projects to the periaqueductal gray (PAG). B, The *humoral pathway* involves circulating PAMPs that reach the brain at the level of the choroid plexus (CP) and the circumventricular organs, including the median eminence (ME), organum vasculosum of the laminae terminalis (OVLT), area postrema (AP), and suprafornical organ (SFO). In the circumventricular organs, PAMPs induce the production and release of proinflammatory cytokines by macrophage-like cells expressing toll-like receptors (TLRs). Source: Dantzer et al[41] [Colour figure can be viewed at wileyonlinelibrary.com]

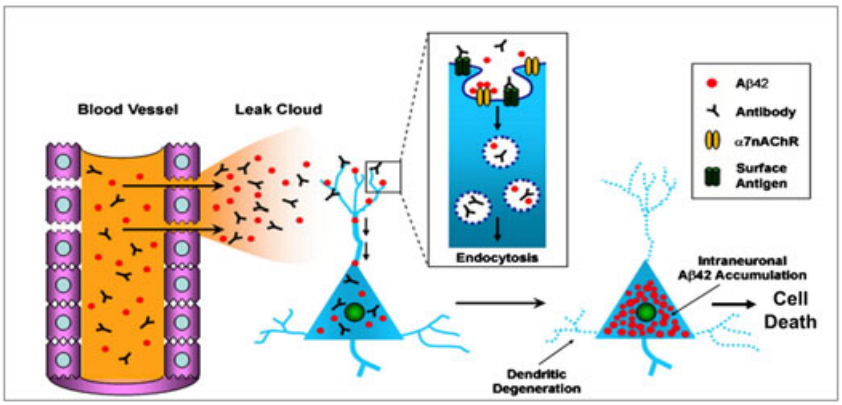

FIGURE 8 Proposed mechanism for the link between postoperative delirium and subsequent cognitive decline. Exposure to anesthetics may cause an immediate, short-term breakdown of blood-brain barrier (BBB) integrity, which leads to an influx of plasma components into the brain tissue that causes disruption of brain homeostasis and neuronal misfiring, all culminating into the array of symptoms that hallmark delirium. Failure to completely restore BBB integrity (most common in older people) may trigger long-term BBB breakdown, which can drive chronic plasma influx, more permanent disruption of brain homeostasis, and impairment of neuronal function. Chronic binding of blood-borne brain-reactive autoantibodies and soluble amyloid peptide (Aβ42) to neurons, and their internalization via endocytosis, are essential features of subsequent cognitive decline and early Alzheimer disease pathology. Source: Forsberg et al[44] [Colour figure can be viewed at wileyonlinelibrary.com]

The OSH intersects with the neurotransmitter hypothesis (NTH)[27] as decreased oxygenation causes a failure in oxidative metabolism, which leads to a failure of the adenosine triphosphatase pump system.[62] When the pump fails, the ionic gradients cannot be maintained, leading to significant influxes of sodium (Na^+) and calcium (Ca^{2+}), while potassium (K^+) moves out of the cell.[62,63] The influx of Ca^{2+} during hypoxic conditions is associated with a dramatic release of several neurotransmitters, particularly glutamate (GLU) and dopamine (DA).[57,62-65] Glutamate stimulates the influx of Ca^{2+}, thus potentiating its own release,[66,67] which accumulates in the extracellular space as its reuptake and metabolism in glial cells are impeded by the adenosine triphosphatase pump failure.[62] In addition, at least 2

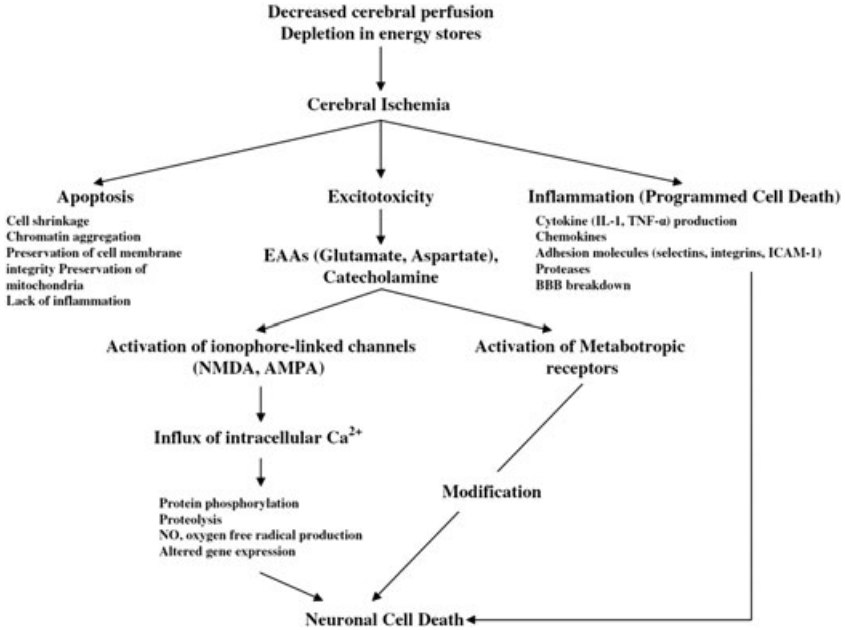

FIGURE 9 Mechanisms of brain injury after global cerebral ischemia. During cerebral ischemia, excess glutamate exits into the extracellular compartment owing to cellular depolarization, coupled with its impaired uptake, which results in increases in intracellular Ca^{2+}. The cascade of events responsible for glutamate excitotoxicity includes 3 distinct processes: (1) induction, whereby extracellular glutamate efflux is transduced by receptors on the neuronal membrane to cause intracellular Ca^{2+} overload, which leads to lethal intracellular derangements; (2) amplification of the derangement, with an increase in intensity and involvement of other neurons; and (3) expression of cell death triggered by cytotoxic cascades. Excess release of Ca^{2+} and its intracellular influx is thought to be the primary trigger for a variety of complex, deleterious intracellular processes that result from activation of catabolic enzymes such as phospholipases (leading to cell membrane breakdown, arachidonic acid, and free radical formation) and endonucleases (which lead to fragmentation of genomic DNA and energy failure due to mitochondrial dysfunction). Source: Harukuni and Bhardwaj[50]

factors facilitate dramatic increases in DA: diminished conversion of DA to norepinephrine (NE), which is oxygen dependent, and hypoxic inhibition of the catechol-*o*-methyl transferase enzymes, required for degradation of DA, leading to even greater accumulation of DA.[68] At the same time, 5-hydroxytryptamine (5HT) levels fall moderately in the cortex, increase in the striatum, and remain stable in the brainstem.[69] Hypoxia also leads to a reduced synthesis and release of acetylcholine (ACh), especially in the basal forebrain cholinergic centers.[70] Indeed, cholinergic neurotransmission is particularly sensitive to metabolic insults, such as diminished availability of glucose and oxygen.[71] Reduction in cerebral oxygen and glucose supply and deficiencies in enzyme cofactors such as thiamine may induce delirium by impairing ACh production.[72,73] These changes have been extensively reviewed elsewhere.[27]

4.4 | Glucocorticoids: neuroendocrine hypothesis

Under normal circumstances, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which through inputs from the brainstem nuclei and the amygdala, activates the paraventricular nucleus of the hypothalamus, resulting in the release of corticotropin-releasing hormone, and then through the hypophyseal portal system acts on the pituitary gland, inducing the release of adrenocorticotropic hormone, which promotes glucocorticoid (GC) release from the adrenal cortex, including cortisol. Glucocorticoid physiological function is to aid the body in coping with the demands imposed by stressful events, mobilizing energy stores, suppressing nonvital body functions, facilitating physiological and behavioral adaptation, and maintaining homeostasis.[74-77] The normal physiologic response would require a prompt poststress return of GCs to basal levels, leaving GC receptors mostly unoccupied through inhibitory feedback loops involving the medial prefrontal cortex, the hippocampus, and the limbic HPA (LHPA) axis.[78-80] A dysregulation of the LHPA axis may lead to chronic activation of low-affinity GC receptors, which may lead to serious adverse CNS injury.[81] The hippocampus, which contains the highest concentration of GC receptors of any brain region, is a major target for the negative effects of excessive GC levels,[82] with data demonstrating that hippocampal malfunction occurs relatively early during the metabolic stress environment leading to delirium.[74,76,81,83-89]

The neuroendocrine hypothesis proposes that delirium represents a physiological reaction to acute or chronic stress, mediated by abnormally high GC levels. Glucocorticoids exert widespread actions in the CNS, ranging from the regulation of gene transcription, cellular signaling, modulation of synaptic structure, and transmission and glial function to behavior.[9] The neuroendocrine hypothesis proposes that, over time, repeated or prolonged high GC levels impair the ability of neurons to survive after various metabolic insults, leading to a general vulnerability in brain neurons,[83,90] also known as the "aberrant stress response."[84]

There is plenty of scientific evidence demonstrating that repeated or prolonged exposure to stress and elevated GCs may have a negative impact on brain function, leading to neuronal injury and psychopathology (Figure 10),[9,77] Particularly, older adults who experience POD had higher postoperative cortisol levels (P = .002) with enhanced

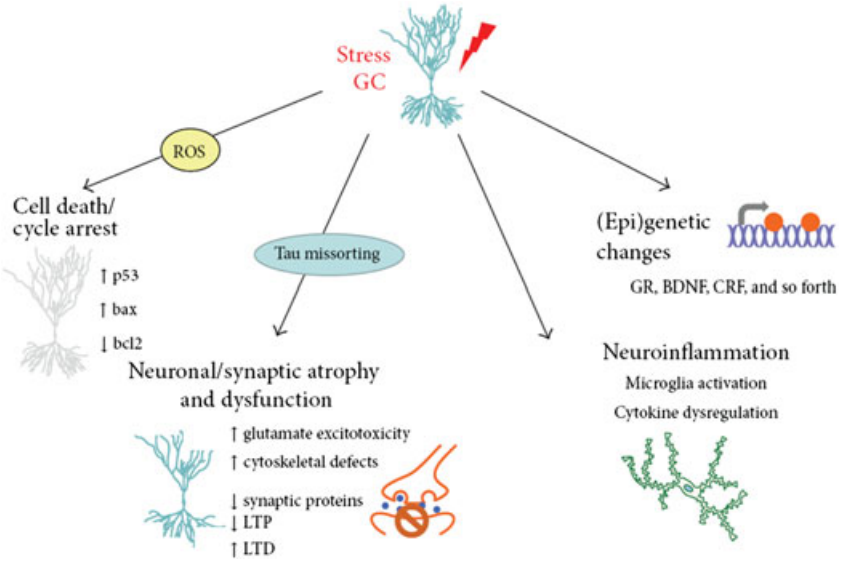

FIGURE 10 Neuroendocrine circuits in delirium. Glucocorticoids (GCs) are secreted under conditions of stress; neuronal damage and brain pathologies are a common consequence of persistently elevated GC secretion. Glucocorticoid can trigger mitochondrial dysfunction and the apoptotic machinery, as well as cell cycle arrest and cell death. In addition, stress/GC may induce neuronal atrophy and synaptic dysfunction/loss by stimulating hyperphosphorylation of the cytoskeletal protein Tau, thus disturbing the integrity of the cytoskeleton and missorting Tau at synapses. Together, these events may eventually result in the degradation of synaptic proteins and decreased synaptic plasticity. Stress and GC are also established as modulators of microglial activation and neuroinflammatory processes and may influence neuronal structure and function through epigenetic mechanisms. Source: Vyas et al[9] [Colour figure can be viewed at wileyonlinelibrary.com]

postoperative elevation in relation to baseline (P = .004).[15] The mechanisms linking excess GC release and neuronal injury and/or exacerbate cell death have been described elsewhere (Table 5).[26] The loss of normal inhibition of adrenal steroidogenesis results in continuous secretion of peak amounts of corticosteroids. A relationship between dexamethasone nonsuppression and various neuropathological states has been described in dementia[91-93] and delirium.[83,94-96] Those at higher risk for delirium (eg, older adults with baseline cognitive impairment) exhibited sustained high cortisol levels after major stressors likely due to impaired feedback regulation of the LHPA axis.[78,96-99] Cortisol nonsuppression after dexamethasone administration has been associated with delirium in 78% of subjects experiencing lower respiratory tract infection.[83] Among postoperative[100] and poststroke[95,101] patients, increased cortisol levels and/or HPA axis dysregulation has been associated with the development of delirium. The increased GC availability associated with illness and trauma and/or exogenous steroid administration may further contribute to sustaining high levels of circulating cortisol,[102] and that may cause resistance to cortisol feedback inhibition mediated by receptor loss in the hippocampus.[75,103] Glucocorticoids rapidly induce GLU release in the hippocampus through a mechanism that may involve a membrane-associated form of the mineralocorticoid receptor. An indirect way by which GCs can influence neurotransmission (glutamatergic, as well as GABAergic, cholinergic, noradrenergic, and

TABLE 5 Glucocorticoids and delirium

Demented patients with delirium exhibited significant differences in basal cortisol levels compared with demented, nondelirious patients. Furthermore, there was a strong linear relationship between delirium and dexamethasone suppression test pathology irrespective of age and severity of dementia, that is, the greater the intensity of delirium, the greater the level of nonsuppression.
Potential mechanisms to explain how excess glucocorticoid (GC) release can compromise neuron's ability to survive neurologic insults, which may lead to or exacerbate cell death
• Inhibiting glucose transport into neuron, thus inducing metabolic vulnerability
• Increase proinflammatory cell migration, cytokine production, and even transcription factor activity in the brain
• Amplifying the damaging cascade of glutamate excess, calcium (Ca^{2+}) mobilization, and oxygen radical generation
• Inducing spine loss and dendritic atrophy, thus decreasing neuroplasticity
• Enhancing oxygen radical-mediated neurotoxicity
• Exacerbating the toxicity of other neurotoxins (eg, doxorubicin) whose mechanisms of action overlap GC pathways
• Impairing long-term potentiation (LTP)
• Reducing hippocampal glial cell activation and proliferation
• Altering the expression and signaling of neurotrophins, particularly brain-derived neurotrophic factor (BDNF)
• Exacerbating the breakdown of cytoskeletal proteins (ie, tau)
• Impairing neurogenesis

Source: Modified from Maldonado.[26]

serotonergic) is through cross-talk with the endocannabinoid system (Figure 11).[104]

Systemic corticosteroid use is a recognized risk factor for the development of delirium and other psychiatric phenomena in hospitalized patients.[15,105-109] In fact, the use of exogenous steroids has been associated with the development of various neuropsychiatric disorders, including delirium, depression, mania, psychosis, and cognitive/memory impairment in up to 60% of those taking corticosteroids.[110] In older adults, systemic GC use may be a contributor to cognitive dysfunction[111] and delirium.[112,113]

4.5 | Sleep: circadian rhythm dysregulation or melatonin dysregulation hypothesis

Secreted by the pineal gland, melatonin is primarily responsible for the organization of circadian rhythms, especially core temperature and sleep-wake rhythms, and multiple other physiological functions, such as immune response, antioxidative defenses, hemostasis, and glucose regulation.[114] The circadian pattern of pineal melatonin secretion is regulated by the biological clock that resides within the hypothalamic suprachiasmatic nucleus,[115] synchronized to the environmental light-dark cycle (Figure 12).[116,117] Figure 13 details the relationship between inflammation and the metabolism of tryptophan, 5HT, melatonin, and kynurenic and quinolinic acid. Table 6 contains a summary of melatonin's physiological effects, which may be protective against delirium.[118]

The circadian rhythm dysregulation hypothesis suggests that disruptions to the 24-hour circadian cycle, the usual stages of sleep, and variations in natural light exposure may lead to disturbances in the physiological sleep architecture that may contribute to the development of delirium.[26,27,119] There is evidence suggesting that chronic sleep deprivation is a physiological stressor, resulting in an allostatic load contributing to cognitive problems and delirium, likely via increased levels of proinflammatory cytokines, decreased parasympathetic and increased sympathetic tone, increased blood pressure, increased evening cortisol levels, and elevated insulin and blood glucose.[120,121] Ongoing sleep deprivation can lead to cumulative sleep debt, which in turn, may be a contributing factor of delirium and its associated cognitive deficits.[122-124] In fact, circadian disruptions have long been recognized as a potential pathologic mechanism of the increased risk for multiple medical conditions, including delirium.[125] Sleep deprivation consistently precede the onset of delirium in postsurgical cardiac patients.[126,127] Studies have demonstrated a relationship between abnormally low melatonin serum levels and POD.[128] Similarly, ICU delirium was significantly more likely among sleep-deprived patients.[129,130]

Various studies have demonstrated a relationship between melatonin levels and delirium motoric phenotypic presentations. Among hospitalized medically ill older adults, decreased levels of urinary 6-sulfatoxymelatonin (the chief metabolite of melatonin) were

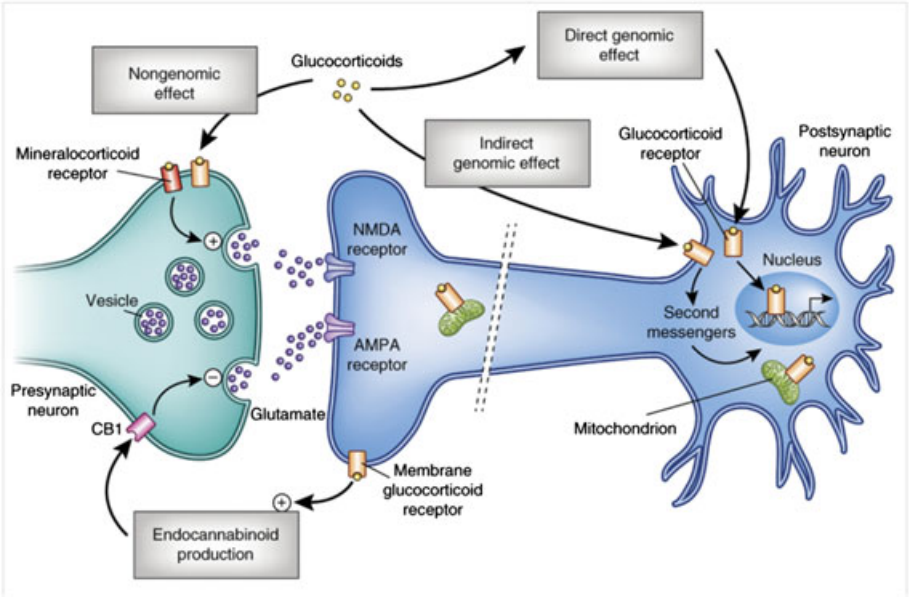

FIGURE 11 Steroid effects in neurotransmission. Glucocorticoids can bind, with different affinities, to glucocorticoid and mineralocorticoid receptors, which are expressed throughout the brain. Adrenal steroids can have both rapid and delayed effects, resulting from nongenomic mechanisms (mediated by membrane receptors), indirect genomic mechanisms (mediated by membrane receptors and second messengers) and genomic mechanisms (mediated by cytoplasmic receptors that move to the nucleus and act as transcription factors). Although mineralocorticoid and glucocorticoid receptors seem to mediate many of these effects, other membrane-associated receptors, including G protein–coupled receptors, may also be involved in some of these actions. Glucocorticoids rapidly induce glutamate release in the hippocampus through a mechanism that is absent when the mineralocorticoid receptor is deleted and that may involve a membrane-associated form of the mineralocorticoid receptor. An indirect way by which glucocorticoids can influence neurotransmission (glutamatergic, as well as GABAergic, cholinergic, noradrenergic, and serotonergic) is through crosstalk with the endocannabinoid system. They rapidly stimulate endocannabinoid production in the brain, whereupon endocannabinoids bind to cannabinoid receptor 1 (CB1) and transient receptor potential cation channel subfamily V member 1 (TRPV1) and inhibit neurotransmitter release. Although a G protein–coupled receptor is implicated in endocannabinoid production, there is also evidence for a mechanism blocked by Ru486—a selective antagonist of the classical cytoplasmic glucocorticoid receptor—in the rapid actions of glucocorticoids in prefrontal cortex. Source: McEwen et al[104] [Colour figure can be viewed at wileyonlinelibrary.com]

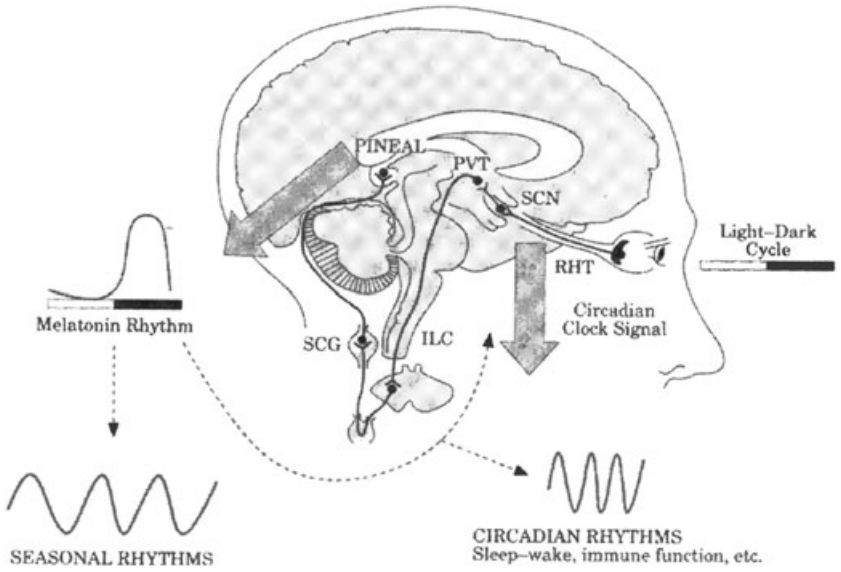

FIGURE 12 Control of melatonin secretion. Photic information is conveyed to the suprachiasmatic nuclei (SCN), principally through the retinohypothalamic tract (RHT), where it synchronizes the activity of the circadian oscillator to exactly 24 h. Neuronal efferent pathways from the SCN directly distribute circadian information to different brain areas, including the pineal gland, which generates the melatonin rhythm. The generated melatonin rhythm might be used by the SCN to distribute its rhythmic information. Reprinted from Cardinali and Pevet[116]

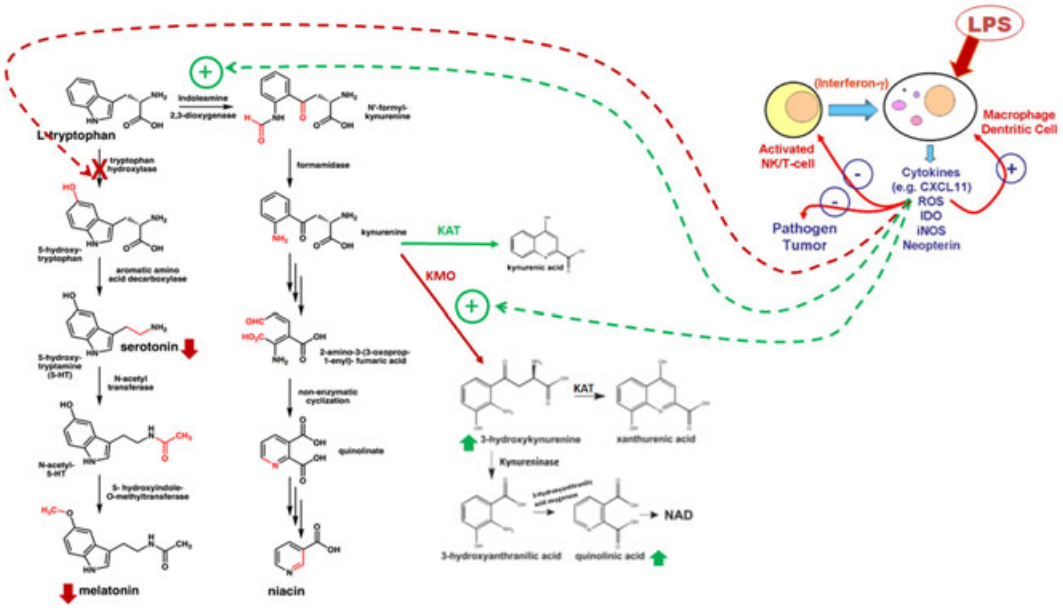

FIGURE 13 Metabolic pattern of tryptophan (TRP), 5-hydroxytryptamine, melatonin, and kynurenic and quinolinic acid. Evidence suggests that some proinflammatory cytokines not only can induce sickness behavior but also can enhance activity of the ubiquitous indoleamine-2,3-dioxygenase, leading to deficient TRP levels, thus a reduction in 5-hydroxytryptamine and melatonin production and a shift to the production of kynurenine and other neurotoxic TRP-derived metabolites. Source: Modified from Stone et al[118] [Colour figure can be viewed at wileyonlinelibrary.com]

found during periods of hyperactive delirium, while patients with hypoactive delirium had raised 6-sulfatoxymelatonin levels.[131] Studies have demonstrated that the administration of melatonin may improve the quality of sleep and prolong sleep time[132] among ICU patients, while others have found that the prophylactic administration of low-dose, exogenous melatonin may decrease the incidence of delirium.[133,134] A meta-analysis of randomized controlled trials of studies using exogenous melatonin for delirium prevention found that melatonin supplementation had a significant preventive effect in decreasing the incidence of delirium in medically ill older adults.[135]

5 | CRITICAL ETIOLOGICAL FACTORS IN THE DEVELOPMENT OF DELIRIUM

The critical etiological factors in the development of delirium include the 2 proximal steps leading to the ultimate failure of system integration, and likely the factors contributing to the phenotypic presentation of delirium: an alteration in neurotransmitter synthesis, function and/or availability, and a failure in the balanced and integrated function of multiple neuronal networks that normally would work in sync to maintain adequate processing of sensory information and motor responses.[26]

TABLE 6 Physiological effects of melatonin and deliriolytic effects

Melatonin play important roles in multiple bodily functions, which may have potential implications regarding the development of delirium in the medically ill
○ Chronobiotic effect (affecting aspects of biological time structure)
○ Sleep-wake cycle regulatory effects
○ Helps reset circadian rhythm disturbances
○ Effective free radical scavenger with extensive antioxidant activity (with a particular role in the protection of nuclear and mitochondrial DNA) with strong antiapoptotic signaling function
○ Extensive anti-inflammatory activity
○ Melatonin scavenges hydroxyl, carbonate, and various organic radicals as well as a number of reactive nitrogen species
○ Melatonin also enhances the antioxidant potential of cells by stimulating the synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase and by augmenting glutathione levels
○ Melatonin preserves mitochondrial homeostasis, reduces free radical generation and protects mitochondrial adenosine triphosphate synthesis by stimulating complexes I and IV activities
○ Antinociceptive and analgesic effects
○ Melatonin receptors appear to be important in mechanisms of learning and memory
○ Inhibits the aggregation of the amyloid beta protein into neurotoxic microaggregates responsible for the neurofibrillary tangles characteristics of Alzheimer's disease and it prevents the hyperphosphorylation of the tau protein; protect against the neurotoxicity of Abeta and glutamate.
○ Reduces the affinity of glucocorticoid (GC) receptors, prevents GC inhibition of cell proliferation, and reduces the GC-induced neurotoxicity and apoptosis

5.1 | Neurotransmission: NTH

The NTH suggests that the most commonly described neurotransmitter changes associated with delirium are reduced availability of Ach (↓Ach); excess release of DA (↑DA), NE (↑NE), and/or GLU (↑GLU); and alterations (eg, both a decreased activity and an increased activity depending on circumstances and etiological factors) in serotonin (↓↑5HT), histamine (↓↑H1&2), and/or gamma-aminobutyric acid (↓↑GABA), as previously reviewed by others (Table 7; Figure 10).[1,26,27,136,137] The NTH stresses the fact that the cholinergic and dopaminergic systems not only interact with each other also exert influence on other significant neurotransmitter systems: the glutamatergic (GLU; the primary excitatory neurotransmitter) and GABA (the primary inhibitory neurotransmitter) pathways.[138] Furthermore, some pharmacological agents (eg, opioids) may cause delirium by increasing DA and GLU activity, while decreasing ACh availability[139] or altering GABAergic

TABLE 7 Confirmed or suspected neurotransmitter alterations associated with delirium

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Mel	Phe	His	Cytok	HPA axis	Cort	NMDA activity	RBF Δ	Inflam	EEG
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↓	↑	↑,↓	±↑	±	↑	↑	±	↑	↓
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	±↑	±	↑	↓	±	↑	↓
TBI	↑	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑±	↑	↑	↑	↑	↑±	↓
CVA	↓	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑±	↑	↑	↑	±	↑±	↓
Hepatic Encephalopathy	⇔	↓	↑	↑↑	↑	↓	↑	↓	↑	↑	↑±	±	↑	↑	±	↑	↓
Sleep deprivation	↓	↓	±	↑	↑	↑	↓	↓±	↑	↑	↑	±	↑	↑	↑	↑±	↓
Trauma, Sx, & Post-op	↓	↑	↑	↑	↓	↑	↓	↓	↑	↑	↑	↑	↑	↑	±	↑	↓
ETOH & CNS-Dep Withdrawal	↑	↑	↑	↓	↑	↑	↓	↓	↑	↑	↑	↑±	↑	↑	↓	↑	↑
Infection/Sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↓	↑	↑±	↑	↑±	±	↑	↓
Dehydration & Electrolyte Imbalance	⇔	↑	↑	↑	↓	↑	?	↓	?	↑	↑	±	↑	↑	↓	±↑	±
Medical Illness	↓	↑	↑	±	↓	↑	↓	↓	↑	↑	↑	↓	↑	↑	±	±	±

Abbreviations: ↑, likely to be increased or activated; ↓, likely to be decreased; ↔, no significant changes; ( ), likely a contributor, exact mechanism is unclear; (–), likely not to be a contributing factor; ACH, acetylcholine; CNS-Dep, central nervous system depressant agent; Cort, Cortisol; CVA, cerebrovascular accident; Cytok, cytokines; DA, dopamine; EEG, electroencephalograph; Etoh, alcohol; 5HT, 5-hydroxytryptamine or serotonin; GABA, gamma-aminobutyric acid; GLU, glutamate; His, histamine; HPA axis, hypothalamic-pituitary-adrenal axis; Inflam, inflammation; Mel, melatonin; NE, norepinephrine; NMDA, *N*-methyl-D-aspartic acid; Phe, phenylalanine; Trp, tryptophan; RBF, regional blood flow; Sx, surgery.

effects.[27] Table 8 contains a summary of the neurotransmitter alterations associated with delirium.

5.2 | Functional connectivity: network disconnectivity hypothesis

Criterion A of the DSM-5 for delirium describes it as a disturbance in attention and awareness.[3] Recent advances in diffusion-weighted magnetic resonance imaging and tractography methods have greatly facilitated the noninvasive mapping of structural networks in the human brain (see Figure 14).[140,141,143,144]

The network disconnectivity hypothesis (NDH) recognizes that the brain is intrinsically organized into dynamic, anticorrelated functional networks[145] and that reduced network anticorrelation may explain the attentional deficits observed in delirious patients (see Figure 15).[146] Intact consciousness requires integrity of functional networks and their connectivity, based on a cooperative but mutually exclusive paradigm of introspection (ie, default mode network [DMN]) versus external awareness (ie, task positive network).

The DMN is a group of brain regions that is preferentially more active at rest than during attention-demanding tasks and characterized by a high degree of functional connectivity.[147-151] Anatomically, it includes the posteromedial cortex (including the posterior cingulate cortex), the anteromedial cortex, and temporoparietal junctions.[145,151-154] The DMN in the healthy brain is associated with stimulus-independent thought and self-reflection and that greater suppression of the DMN is associated with better performance on attention-demanding tasks.[155]

In contrast, the task positive network is mostly active during external focused attention and goal-directed task performance. Anatomically, the task positive network encompasses regions of the dorsal attention system, the dorsolateral and ventrolateral prefrontal regions, the insular cortex, and the supplementary motor area and the pre–supplementary motor area.[145]

The NDH suggests that the brain is a highly organized and interconnected structure functioning to allow complex integration of sensory information and motor responses and suggests that delirium represents a variable failure in the integration and appropriate processing of sensory information and motor responses.[26] Thus, the NDH proposes that delirium results from an acute breakdown in network connectivity within the brain.[156]

According to the NDH, 2 important determinants predict a subject's vulnerability to delirium: (*a*) the baseline network connectivity (defined as the connectivity of neural networks within the brain before the precipitating insult provoking delirium), which is influenced by most recognized "nonmodifiable delirium risk factors" (eg, age and baseline level of cognitive functioning), and (*b*) the level of inhibitory tone, which will determine the degree of change in network connectivity and is influenced by a number of factors, including neurotransmitter functionality and availability.[156] This model suggests that these 2 determinants affect separate neuronal networks to variable degrees, thus leading to the various clinically observed deliria motoric phenotypes (eg, hyperactive, hypoactive, and mixed). The form of delirium that ensues will depend upon how and which networks break down, influenced by both the individual's baseline network connectivity and the degree change in inhibitory tone produced.

Resting state functional magnetic resonance imaging scans, obtained during and after the resolution of delirium, have demonstrated a long-lasting disruption in reciprocity of the dorsolateral prefrontal cortex with the posterior cingulate cortex and a reversible reduction of functional connectivity of subcortical regions (eg, thalamus) with the reticular activating system and with nuclei responsible for forebrain ACh (ie, the midbrain nucleus basalis) and DA innervation (ie, the midbrain ventral tegmental area).[146] The persistence of these physiological disruptions, beyond the resolution of acute delirious symptoms, may account for reported cognitive problems, which often outlast the acute episode of delirium. Electroencephalographic and evoked potential data may provide further support for this theory by suggesting that the pathophysiology of at least some forms of delirium may have a subcortical component.[157]

The NDH intersects with the NTH as studies have demonstrated that some core symptoms of delirium likely involve changes in dynamic aspects of neuronal activity affecting the brain's ability to integrate information through functional disconnection between different anatomical structures[158]; also see Figure 16. In fact, consciousness-altering anesthetic agents (eg, propofol, benzodiazepines, and ketamine) achieve their effect by disturbing the connectivity between brain regions composing the resting-state consciousness networks, including the DMN, executive control network, salience network, auditory network, sensorimotor network, and visual network sustain mentation.[161] Altered GABAergic neurotransmission is implicated in increasing the CNS's inhibitory tone, which may contribute to the development of delirium.[156] Furthermore, GABAergic agents may further destabilize the sleep-wake cycle, as they suppress orexinergic neural firing in the perifornical nucleus,[162] whose function is to prevent inappropriate transition into sleep.[163-166]

The NDH also relates to the NIH as acute neuroinflammation affects physiological processes implicated in neuronal and synaptic functions with consequent neurochemical disturbances and functional disconnection between different anatomical structures.[36] In fact, systemic inflammation drives an upregulation in expression of $GABA_A$ receptors and an increased in GABA synthesis[167] and suppresses orexinergic neuronal activity during the wakeful period.[168]

This model also intersects with the neuronal aging hypothesis as it suggests that aging is accompanied by disruptive alterations in the coordination of large-scale brain systems that support high-level cognition.[156,169] A study assessing white matter (WM) integrity using diffusion tensor imaging suggested that abnormalities in the deep WMs and thalamus could have accounted for the patients' vulnerability to developing delirium after cardiac surgery, compared with nondelirious subjects.[170] A more recent study, also conducted among older cardiac surgery patients, demonstrated that the prevalence of severe cerebral WM hyperintensities on magnetic resonance imaging was significantly higher in delirious patients and similarly concluded that these lesions were likely one of the most important risk factors for the development of delirium after cardiac surgery.[171]

Finally, aging is also associated with a reduction in GABAergic tone, thus allowing for increased neuronal activity in certain brain regions,

TABLE 8 Neurotransmitter changes associated with delirium

Neurotransmitter	Changes
Acetylcholine (↓Ach)	The *cholinergic system* is one of the most important modulatory neurotransmitter systems in the brain, controlling activities that depend on selective attention, which themselves are an essential component of conscious awareness (the 2 key components in the criteria of *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, for diagnosing delirium). Adequate acetylcholine (ACh) levels are also essential for the regulation of multiple neuropsychiatric functions, including rapid eye movement sleep, memory, and synchronization of the electroencephalogram, all of which are somehow impaired in delirium. An *impairment of central cholinergic transmission* is often considered "a common denominator" in delirium, with multiple studies documenting low levels of ACh in plasma and cerebrospinal fluid of delirious patients. Cortical ACh deficiencies allow irrelevant intrinsic and sensory information to enter conscious awareness and may explain the impairments in cognition, attention, emotional dysregulation, and disturbance in circadian rhythm at the core of delirium. Finally, high levels for serum anticholinergic activity (SAA) have been associated with an increased likelihood of delirium among medically ill patients as well as in postoperative delirium (POD), consistent with the clinical relationship observed between a drug's anticholinergic potential and its deliriogenic effects. Evidence suggests that an elevation in SAA levels predicts the development of delirium, while a resolving delirium is correlated to normalizing SAA levels. It also explains why the use of physostigmine, a reversible cholinesterase inhibitor, is effective in reversing the prolonged coma, myoclonus, and delirium induced by anticholinergic drugs.
Dopamine (↑DA)	Elevations of *dopamine* (DA) have long been suspected in the development of delirium and often seen as "the other side of the coin," opposite to ACh deficiency. Cerebral ischemia animal models have found an up to 500-fold increase in extracellular DA levels. Studies have found elevation of DA's metabolites (ie, homovanillic acid) in the cerebrospinal fluid of patients with fulminant hepatic encephalopathy (HE). The mechanisms mediating the dramatic rise in DA levels among delirious patients have been reviewed elsewhere.[26] Dopamine may exert its deliriogenic effect by 1 of 3 mechanisms: direct excitatory activity of DA (eg, toxicity with substances known to increase DA release or availability, such as amphetamines, cocaine, and L-3,4-dihydroxyphenylalanine), Dopamine-mediated potentiation of glutamate (GLU)–mediated exocytotic injury, and/or induction of apoptosis by mechanisms independent of oxidative stress, which may explain why DA depletion by alpha-methyl-paratyrosine may have a neuroprotective effect against hypoxic stress and injury and why DA blockade can be used to reduce hypoxic damage in the hippocampus. Data suggest that DA administration is associated with nearly a tripling of the odds of the subsequent need of the antipsychotic drug for management of delirium and associated behavioral disturbance. Others have found both DA administration ($P < .001$) and the amount of DA administered ($P < .001$) as independent risk factors for delirium along with older age ($P = .03$). It is also important to note the growing body of evidence demonstrating that antipsychotic agents are effective not only as treatment of delirium, in delirium prevention. Studies have revealed that there are no significant differences in efficacy among antipsychotic agents, with no major differences in response rates between clinical subtypes of delirium. Thus, it is possible that not only are antipsychotic agents effective in the symptomatic management of the symptoms of delirium, but they also address the underlying massive DA surge associated with all delirial phenotypes, even the hypoactive type.
Norepinephrine (↑NE)	Excess *norepinephrine (NE) release* secondary to hypoxia or ischemia leads to further neuronal injury and the development or worsening of delirium. Delirium has long been speculated to be associated with excess release of NE. Studies have found that increased epinephrine and NE urinary levels predicted the incidence of delirium among hospitalized, older patients. Specifically, in cases of alcohol withdrawal syndromes (AWSs), excess noradrenergic activity drives most of the symptoms (eg, diaphoresis, tachycardia, increased blood pressure, restlessness, anxiety, agitation, and tremors). Upon abrupt cessation of alcohol consumption, there is evidence of decreased signaling at the α_2 receptor, resulting in an inability of the noradrenergic system to regulate its firing leading to AWS. In addition, alcohol withdrawal causes an upregulation of glutamate transmission in the locus coeruleus (the major noradrenergic nucleus of the brain), increasing the activity of the noradrenergic system. This may contribute to the autonomic instability, behavioral agitation, and psychosis seen during alcohol withdrawal delirium or delirium tremens. Furthermore, catecholamines can enhance the activity of the bed nucleus of the stria terminalis neurons, which may, in turn, increase the excitability of glutamatergic bed nucleus of the stria terminalis neurons that project to the ventral tegmental area. In fact, there is evidence of a normalization in plasma concentration of epinephrine as AWS improved. Randomized clinical trials have demonstrated that selective alpha-2 agonist agents (eg, dexmedetomidine [DEX]) substantially decreased the incidence of POD compared with GABAergic agents, particularly among older people; decreased incidence of delirium tremens upon alcohol cessation; shorter mechanical ventilation times; and reduced the incidence of emergence delirium. Similarly, alpha-2 agonist agents have shown neuroprotective qualities by suppressing circulating catecholamine levels during cerebral ischemia. Some have found that DEX-based sedation is associated with a lower risk of neurocognitive dysfunction and is associated with improved sleep quality in elderly intensive care unit patients, while others have found that the use of DEX may decrease neuroinflammation via inhibition in the expression of monocyte chemoattractant protein 1 messenger RNA ($P < 0.001$), one of the key chemokines that regulate migration and infiltration of monocytes/macrophages.
Glutamate (↑GLU)	*Glutamate* is the brain's principal excitatory neurotransmitter, and excessive activation of *N*-methyl-D-aspartate receptors may lead to neuronal degeneration and cell death. Excess excitotoxicity resulting from glutamate hypertransmission is one of the proposed theories to explain the abnormal neuronal responses to acute medical insults, such as delirium. Animal models have found that cerebral ischemia may be associated with an up to 7-fold increase in extracellular GLU levels, significantly correlated with infarct size. Studies have suggested that the neurotoxicity of beta-amyloid peptide may be related to the overactivation of glutamatergic transmission and excitotoxicity, which may serve as a potential explanation to the increased rate of delirium in patients with baseline cognitive dysfunction and may further explain the long-term cognitive impairment following episodes of delirium. The mechanisms mediating the dramatic rise in GLU levels among delirious patients have been reviewed elsewhere. Glutamate's and DA's actions are interdependent, as it appears that GLU requires the presence of DA to exert some of its toxic effects, namely, Ca^{2+}-induced neuronal injury. At high levels, DA may cause enough depolarization of neurons to activate the voltage-dependent *N*-methyl-D-aspartate receptor, therefore facilitating GLU's neurotoxic effects. A number of agents known to modulate glutamatergic neurotransmission have demonstrated effectiveness in the management of some forms of delirium, particularly the hyperactive and mixed types—such as valproic acid. Valproic acid's complex effects on the various neurotransmitters involved in development and manifestations of

(Continues)

TABLE 8 (Continued)

Neurotransmitter	Changes
	delirium have been discussed elsewhere. There is reason to believe that other antiepileptic agents with similar effects in GLU transmission may also have a beneficial effect in the management of hyperactive- and mixed-type delirium.
Serotonin (↓↑5HT)	Both elevation and deficiencies in *5-hydroxytryptamine (serotonin; 5HT)* activity have been linked to the development of delirium. Normal 5HT synthesis and release in the brain are dependent on the availability of its precursor tryptophan (TRP). Please see Figure 13 for a relationship between TRP, 5HT, and kynurenic acid metabolism. Reduced 5HT levels have been identified in patients suffering from delirium associated with AWS, catabolic states, hypoxia, immobility, infections, ischemia, and postoperative states among others. In fact, the sudden discontinuation of 5HT reuptake inhibitors has been associated with various neuropsychiatric syndromes, including delirium. Similarly, decreased TRP availability may lead to a reduction in 5HT. All large neutral amino acids (LNAA; ie, phenylalanine [PHE], TRP, leucine, isoleucine, methionine, tyrosine, and valine) compete to enter the brain through the same saturable carrier. Therefore, as the concentration of one increases, central nervous system entry of other LNAAs conversely decreases. Phenylalanine has the additional interesting property of conversion to neurotoxic metabolites and competes with TRP for entry into the brain. Once it enters the brain, PHE competes with TRP and tyrosine for metabolism, via hydroxylation. Studies have demonstrated that elevations of the PHE/LNAA ratio are independently associated with POD. Studies of older medically ill patients suggest that an elevated plasma PHE/LNAA ratio during acute febrile illness is associated with delirium. Patients with hepatic and septic encephalopathy have also been found to experience increased levels of PHE and PHE metabolites in the plasma and cerebrospinal fluid. Similarly, hepatic dysfunction may lead to decreased metabolism of precursor amino acids (ie, PHE and tyrosine), which may lead to increases in TRP availability, which leads to increases in 5HT. In fact, elevation in 5-hydroxyindoleacetic acid levels has been associated with HE and in patients suffering from hypoactive delirium. Studies have found that an increased ratio of free to bound TRP enhances its availability to brain tissue, which in turn increases 5HT synthesis, thus precipitating HE. Conversely, elevated 5HT levels have been described among patients suffering from delirium associated with clozapine toxicity, HE, and 5HT syndrome. In fact, in a recent study of delirium in the intensive care unit, investigators found that 72% of those experiencing delirium were receiving drugs potentially contributing to serotonergic toxicity. Some have reported that the stereotactic injection of WAY-100635, a 5HT-1A antagonist, improved the delirium-like behavior in animal models; and at least 3 reports have suggested that selective 5HT 5HT3-type receptor antagonists may be effective in the treatment of agitated POD.
Histamine (↓↑H1&2)	There is evidence suggesting that both increased and decreased *histamine (HA) levels* may lead to delirium. Histamine receptors A1 (HA1) and A2 (HA2) are known to affect the polarity of cortical and hippocampal neurons and that it is well known that pharmacological antagonism of either receptor is sufficient to cause delirium. Clinical data have demonstrated that the use of H1 blockers (eg, diphenhydramine and promethazine) and H2 blockers has been associated with a significant increase in the occurrence of delirium, especially among older adults and those with chronic kidney disease. Excessive release of HA, like during surgical stress and hypoxia, may lead to delirium, with data suggesting that the first-generation anti-HA agent cyproheptadine can be a potential option for the prevention of POD.
Gamma-aminobutyric acid (↓↑GABA)	γ-Aminobutyric acid (GABA) is the brain's principal inhibitory neurotransmitter and plays a role in regulating neuronal excitability throughout the nervous system. Evidence suggests that GABA activity is increased in some types of delirium (eg, cerebral ischemia and HE), while decreased in others (eg, antibiotic-induced delirium and alcohol or central nervous system depressant withdrawal). The mechanisms mediating GABAergic agents' deliriogenic effects have been reviewed elsewhere.[26] Evidence also suggests that endogenous GABA causes tonic inhibition of ACh release in the ventral hippocampus via septal GABA(A) receptors and, to a lesser extent, via GABA(B) receptors in the medial septum and hippocampus. A systematic review including 68 drug trials found that benzodiazepine drugs consistently induced both amnestic and nonamnestic cognitive impairments, with evidence of a dose-response relationship.

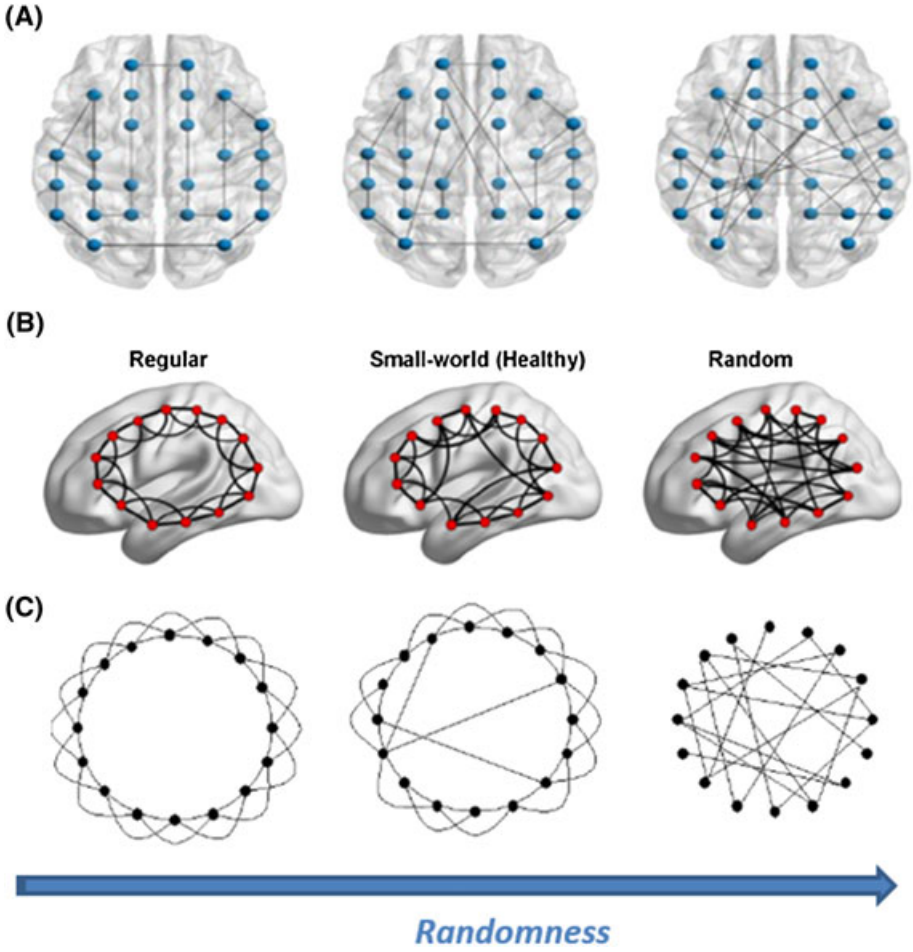

FIGURE 14 Network disconnectivity hypothesis. Recent advances in diffusion-weighted magnetic resonance imaging and tractography methods have greatly facilitated the noninvasive mapping of structural networks in the human brain. Specifically, white matter pathways can be mapped through inferring the spatial orientations and trajectories of bundles of myelinated axons traversing the brain, on the basis of measurements of diffusion anisotropy of water or other small molecules within biological tissue.[140-142] Source: A, Liu et al[143]; B, Cao et al[141]; C, Watts and Strogatz[144] [Colour figure can be viewed at wileyonlinelibrary.com]

primarily the prefrontal cortex.[172] With advanced age, there is a down-regulation of several subunits of the $GABA_A$ receptors (ie, α1, α5, β3, and γ2); therefore, a stimulus that increases the level of inhibitory tone may have a greater effect and further break down network connectivity.[173] The aged brain also experiences reductions in orexin signaling,[174,175] which may contribute to the fluctuating arousal level seen in delirious states when exposed to various noxious stimuli (eg, infection, GABAergic agents, and sleep deprivation). Similarly, it intersects with the NTH as it specifically implicates the GABA system (eg, benzodiazepine or hepatic encephalopathy–induced delirium) and the cholinergic system (eg, anticholinergic delirium) as likely principal culprits.

6 | DELIRIUM AS A FAILURE OF CNS SYSTEM INTEGRATION: TOWARDS A UNIFYING HYPOTHESIS OF DELIRIUM

The systems integration failure hypothesis (SIFH) brings together the most salient, previously described theories contributing to the development of delirium into one cohesive paradigm (Figure 17), describing the various contributions from each into a complex web of pathways, while explaining the mechanism for delirium's various phenotypic presentations (Figure 4). The SIFH highlights areas of intersection and commonalities and explains how the variable contributions of these lead to the development of the various cognitive and behavioral dysfunctions characteristic of delirium. The SIFH proposes that alterations in neurotransmitter function combined with a failure of the complex, highly organized and interconnected brain systems lead to a failure in the CNS's functional integration and appropriate processing of information and response mechanisms. The SIFH is a way of understanding that most of the previously available theories of delirium pathophysiology are complementary, rather than mutually exclusive, with many areas of intersection and reciprocal influence, which is more akin to the complexities of the human brain.

Thus, the SIFH suggests that at any given time, a number of precipitant factors may serve as triggers for the development of delirium or acute brain failure. The mnemonic "end acute brain failure" (see Table 1) summarizes the set of precipitant insults long recognized as acute proximate factors to the development of delirium.

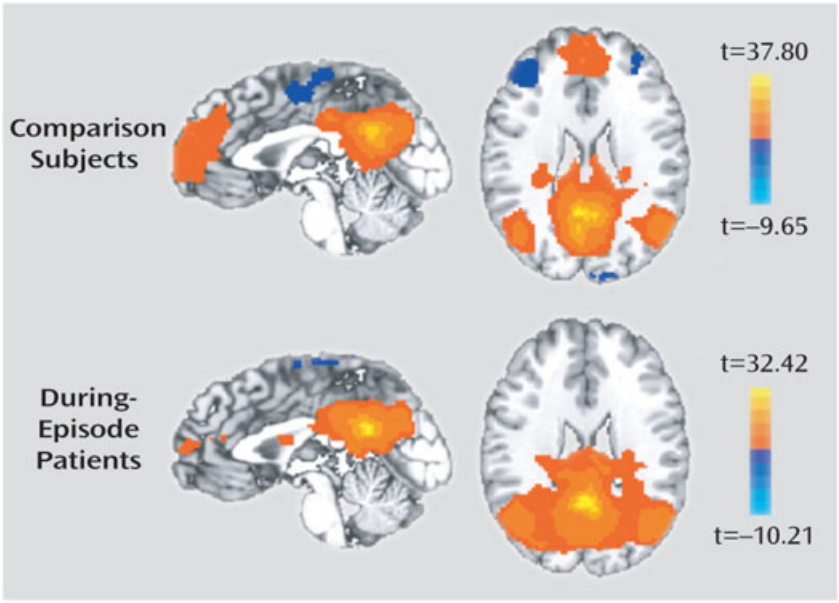

FIGURE 15 Network disconnectivity hypothesis of delirium. Activity of the seed region in comparison subjects showed positive correlations (red) with the posteromedial/anteromedial cortices and the temporoparietal junctions and a negative correlation (blue) with the frontolateral cortices. These correlations disappeared in the anteromedial and cortices and were enhanced in the posteromedial cortices during an episode of delirium. Source: Choi et al[146] [Colour figure can be viewed at wileyonlinelibrary.com]

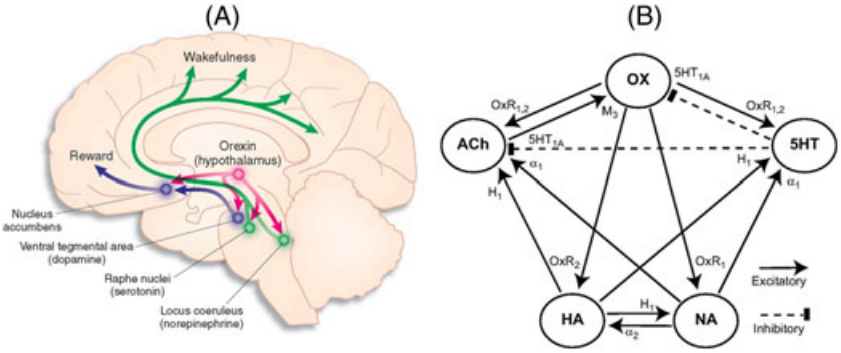

FIGURE 16 Network influencing alertness vs somnolence. Relationship between acetylcholine (ACh; necessary for the initiation of rapid eye movement [REM] sleep), noradrenaline (NA; its activity in the locus coeruleus [LC; the main is involved in arousal] is the most important regarding the sleep-wake cycle), dopamine (DA; seems to regulate sleep-wake states and helps control when we enter each and can also can downregulate melatonin), melatonin (MEL; helps regulate circadian rhythms in the body as a reaction to environmental lighting conditions), 5-hydroxytryptamine (5HT; helps to maintain arousal and cortical responsiveness as well as inhibit REM sleep), and orexin (OX, hypocretin; produced in the hypothalamus and is responsible for regulating many different systems involved with sleep and stabilizing both awake and sleep states). The OX system regulates DA, NA, histamine (HA), and ACh systems. It is also responsible for integrating different metabolic demands, circadian rhythms, and sleep debt to decide what state the body should be in (asleep or awake); GABA, the main inhibitory neurotransmitter (NT), induces sleep by downregulating activity in the posterior hypothalamus (thus inducing sleep). Glutamate, the primary excitatory NT, is also the most common NT in the brain. Glutamatergic inputs in the posterior hypothalamic region help regulate both REM sleep and wakefulness. Source: A, Scammell and Saper[159]; B, Brown et al[160] [Colour figure can be viewed at wileyonlinelibrary.com]

These precipitant factors have a differential effect in each individual depending on the varying degrees of immutable factors or neurophysiological substrate upon which they occur (eg, age, the presence [past and/or present] of inflammation, oxidative stress, endocrine abnormalities, and/or circadian dysregulation). The more substrate elements affected, the more likely it is that a patient will develop further deterioration of central organization. Thus, an individuals' baseline substrate and psychophysiological functional reserve will determine the robustness or frailty of the overall system in an inverse relationship with acute precipitant factors; that is, the more compromised the substrate, the less severe the precipitant factor needs to be to lead to significant disruption of the overall system (Figure 4). This may explain why frail and/or cognitively impaired older adults experience brain dysfunction with relatively mild insults (eg, urinary tract infection, dehydration, and pneumonia), while a healthier individual may withstand the insult with minimal ill effects.

The effect of an acute insult (precipitant factors) upon the chronic neurophysiological state (substrate) leads to a cascade of events that cause a temporary neuropsychiatric disorder primarily resulting in a metabolic derangement leading to alterations in neurotransmitter dysfunction (Figure 17). Alterations in ACh and DA affect glutamatergic and GABAergic pathways, as well as multiple critical cerebral systems

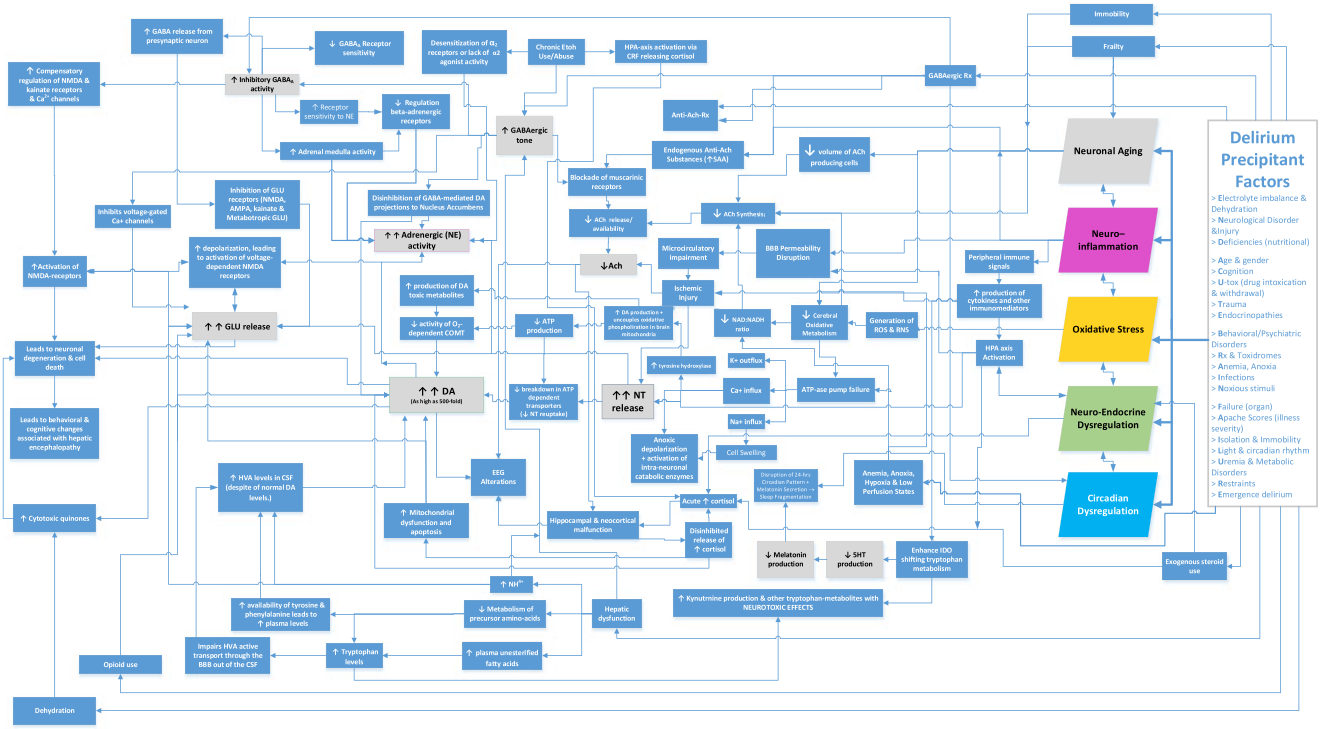

FIGURE 17 Pathophysiology of delirium: the systems integration failure hypothesis [Colour figure can be viewed at wileyonlinelibrary.com]

including the striatum, the substantia nigra/ventral tegmental area, and the thalamus. The thalamus acts as a filter, allowing only the relevant information to travel to the cortex. It is here that we find the significant role of the cortical cholinergic system and associated projections in mediating specific attentional processing (ie, sustained, selective, and divided attention performance), arousal, and rapid eye movement sleep-associated dreaming.[176,177] Under normal circumstances, cholinergic activity in the prefrontal regions facilitates the activation of the anterior attention system and associated executive functions.[176] Besides deficits in ACh and excess of GLU, NE, and DA, other neurotransmitter systems may also be involved, adding to the phenotypic presentation and pattern of behavior and cognitive deficits.

According to the SIFH, there are multiple important determinants that eventually predict a subject's vulnerability to delirium: (*a*) the presence of physiological vulnerabilities (the substrate) and (*b*) an acute insult (precipitant) further taxing an already fragile system with limited functional reserves. The various vulnerabilities make it more likely that a patient may experience a derangement in functional metabolism leading to (*c*) an alteration in neurotransmitter synthesis, function, and/or availability and (*d*) a dysregulation of neuronal activity and connectivity secondary to systemic disturbances, which mediates the complex phenotypic and neurocognitive changes observed in delirium (see Figures 13 and 17; Table 7).

The interplay between the alterations in neurotransmitter integrity (ie, neurotransmitter availability and receptor function) and which network emerges as dominant or unchecked and the variability in integration and appropriate processing of sensory information and motor responses, mediated by an acute breakdown in brain network connectivity, give rise to the various clinical manifestations observed in the various delirial motoric phenotypes (eg, hyperactive, hypoactive, and mixed). In other words, the form of delirium that ensues will depend upon how and which networks break down, influenced by both the individual's baseline network connectivity and the degree change in inhibitory tone produced (see Figures 16 and 17).

Furthermore, the SFIH suggests that the lack of systems integration and alteration in neurotransmitter homeostasis leads to the aberrant activation of parasympathetic control, triggered by a number of physiological signals associated with illness processes (eg, mechanical ventilation), leading to pathological signaling activation of neuroreceptors, which ultimately triggers apoptosis in various brain areas, independent of hypoxia, oxidative stress, or inflammatory responses. Ultimately, this aberrant signaling can trigger both early and late apoptotic triggers, which may mediate both the acute changes classically associated with acute delirium, as well as the more prolonged cognitive changes we associated with persistent delirium. Thus, the SIFH suggests that the various phenotypic presentations of delirium (eg, hypoactive, hyperactive, mixed, or subsyndromal) may be better explained by the action of various factors acting on specific brain neurochemical systems,[178] placing an already fragile and disconnected system at risk of malfunction, thus leading to the symptoms of acute brain failure.

7 | CONCLUSIONS

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity, mediated by alterations in the neurotransmitter and dysfunction of neuronal networks, secondary to systemic disturbances. The combined effect of precipitant and substrate factors leads to final common pathways associated with the behavioral and cognitive changes observed in delirium, including the various phenotypic presentations.

The SIFH integrates and explains how the most salient etiological theories converge into an integrated web of pathways—highlighting

areas of intersection and commonalities and explaining how the variable contribution of these hypotheses may lead to the development of various cognitive and behavioral dysfunctions characteristic of delirium. The SIFH proposes that alterations in neurotransmitters synthesis and availability, combined with a failure of the complex, highly organized and interconnected brain systems (ie, disruption in network connectivity), lead to a failure in the CNS's functional integration and appropriate processing of information and response mechanisms and mediating the 5 core clinical domains of delirium. The SIFH proposes that individuals have varying degrees of specific physiological characteristics (ie, substrates) and that this "load" will determine the basic fragility of the system in an inverse relationship with acute precipitant factors (eg, infection and inflammation, sleep deprivation, trauma, surgery, hypoxia, medication use, substances of abuse, organ failure, electrolyte imbalance, and metabolic derangement).

A better understanding of the underlying pathophysiology may eventually assist us in designing better delirium prevention and management approaches.

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