DELIRIUM

Session 112

Managing Delirium in Post-acute and Long Term Care

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Disclosure

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Summaries, recommendations, and claims made hereafter represent the personal opinion of the presenter as based upon an assessment of the salient literature. Unless otherwise explicitly stated, the contents of this presentation do not represent the opinion of either the Veteran's Health Administration or the University of South Florida.

There are no relevant financial relationships to disclose.

Objectives

- Summarize the most common clinical presentation of delirium
- Identify both common and rare contributors to the development of delirium
- Describe the role of structured delirium screening instruments in PALTC
- Review pharmacologic and non-pharmacologic management of delirium

Delirium defined

"...an acute neuropsychiatric disorder... of impaired consciousness... characterized by generalized impairment of cognition, with inattention as its cardinal feature, but also involves a range of noncognitive symptoms affecting motor behavior, sleep-wake cycle, thinking, language, perception, and affect." [1]

Other terms used

- Acute…
  - …brain failure
  - …brain syndrome
  - …dementia
  - …organic psychosis
  - …organic reaction
  - …organic syndrome
  - …reversible psychosis
  - …secondary psychosis
- Cerebral insufficiency
- Confusional state
- Dysergastic reaction
- Encephalopathy
- Exogenous psychosis
- Infective-exhaustive psychosis
- ICU psychosis
- Metabolic encephalopathy
- Oneiric state

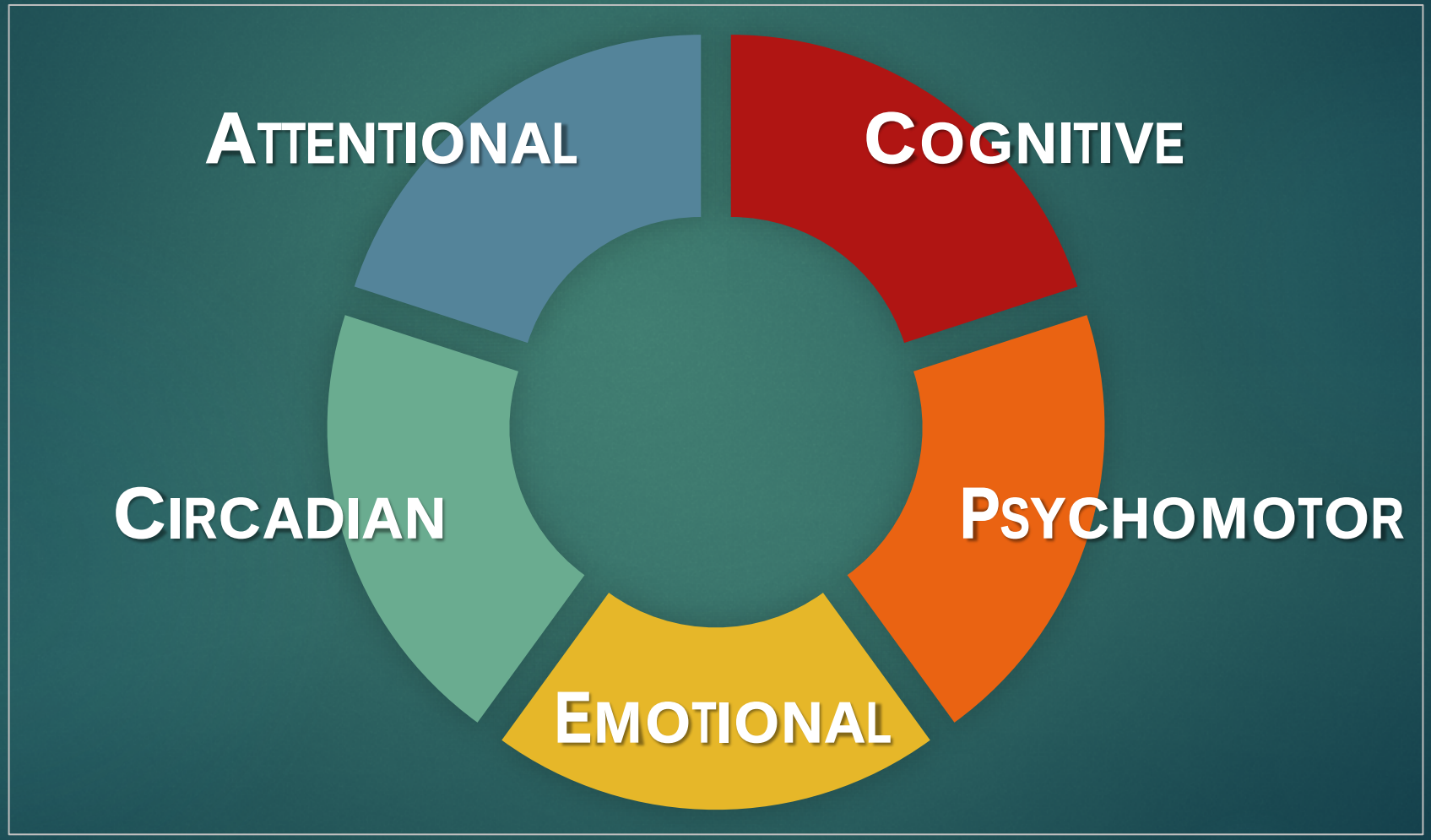
DSM-5 Diagnostic Criteria

- A **disturbance in attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) **and awareness** (reduced orientation to the environment).
- The disturbance **develops over a short period of time** (usually hours to a few days), **represents a change from baseline** attention and awareness, and **tends to fluctuate** in severity during the course of a day.
- An **additional disturbance in cognition** (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
- The disturbances in Criteria A and C are **not better explained by another preexisting, established, or evolving neurocognitive disorder** and do not occur in the context of a severely reduced level of arousal, such as coma.
- There is **evidence** from the history, physical examination, or laboratory findings **that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal** (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Phenomenology (DRS-98)[3]

Core deficits:	Attention	97-100%
	Orientation	76-96%
	ST memory	88-92%
	LT memory	89-96%
	Sleep-wake	92-97%
	Thought proc.	54-79%
	Visuospatial	87-96%
	Motor	24-94%
	Language	57-67%
Non-core	Perception	50-63%
	Delusion	21-31%
	Affect	43-86%

Delirium: 5 Core Domains[2]



Motor subtypes: [1]

- **Hyperactive** (Greek *phrenitis*)
  - DSM-5: "…hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care."
  - Excited catatonia sometimes thought to be an extreme variant
- **Hypoactive** (Greek *lethargicus*)
  - DSM-5: "…hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor."
  - Retarded catatonia sometimes thought to be an extreme variant
- **Mixed**
  - Identified as a subtype in the 1990s, so no fancy Greek phrase
  - DSM-5: "…normal level of psychomotor activity even though attention and awareness are disturbed. Also includes individuals whose activity level rapidly fluctuates."

Consequences in Acute Care [2]

- Mortality rates 4-65% during the index hospitalization
- Number of delirious days predicts mortality
- Implications of persistent cognitive difficulties

Consequences in PALTC [6]

- Delirium may be present in up to 70% of LTC patients
- Mean duration of delirious episodes 1.5 +- 1.4 weeks
- Increased mortality rate
- Increased fall rates
- Increased polypharmacy for management
- Rehospitalization and extended PA LOS

Risk Factors in PALTC: **Cognition** [7]

MMSE 10+		MMSE < 10
3.4%	Baseline Prevalence	33.3%
1.6	Incidence per 100 person-weeks	6.9

Causes: Acute Care

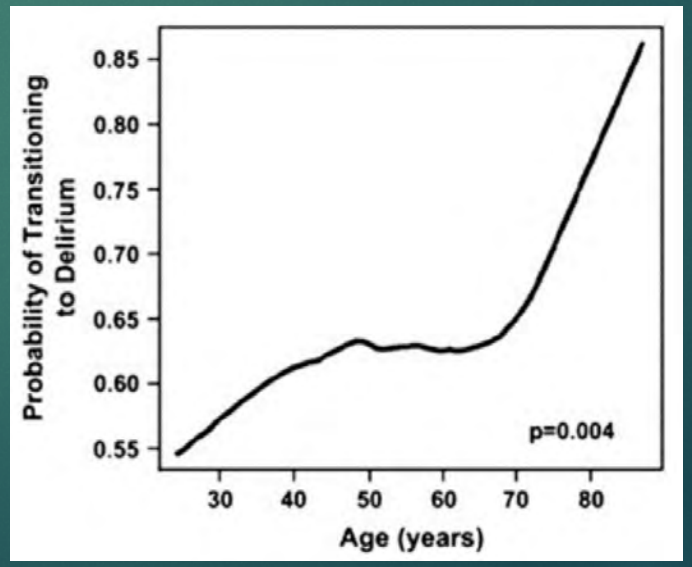
I	Infection / Iatrogenic
W	Withdrawal
A	Acute metabolic (acidosis, alkalosis, electrolytes)
T	Trauma (closed head injury, CVA)
C	CNS pathology (seizure, stroke, encephalitis)
H	Hypoxia, Hypercarbia
D	Deficiencies (thiamine, niacin, B12, folate)
E	Endocrinopathies (thyroid, glucose, adrenal)
A	Acute vascular (HTN crisis, arrhythmia)
T	Toxins/drugs
H	Heavy metals

Causes: PALTC

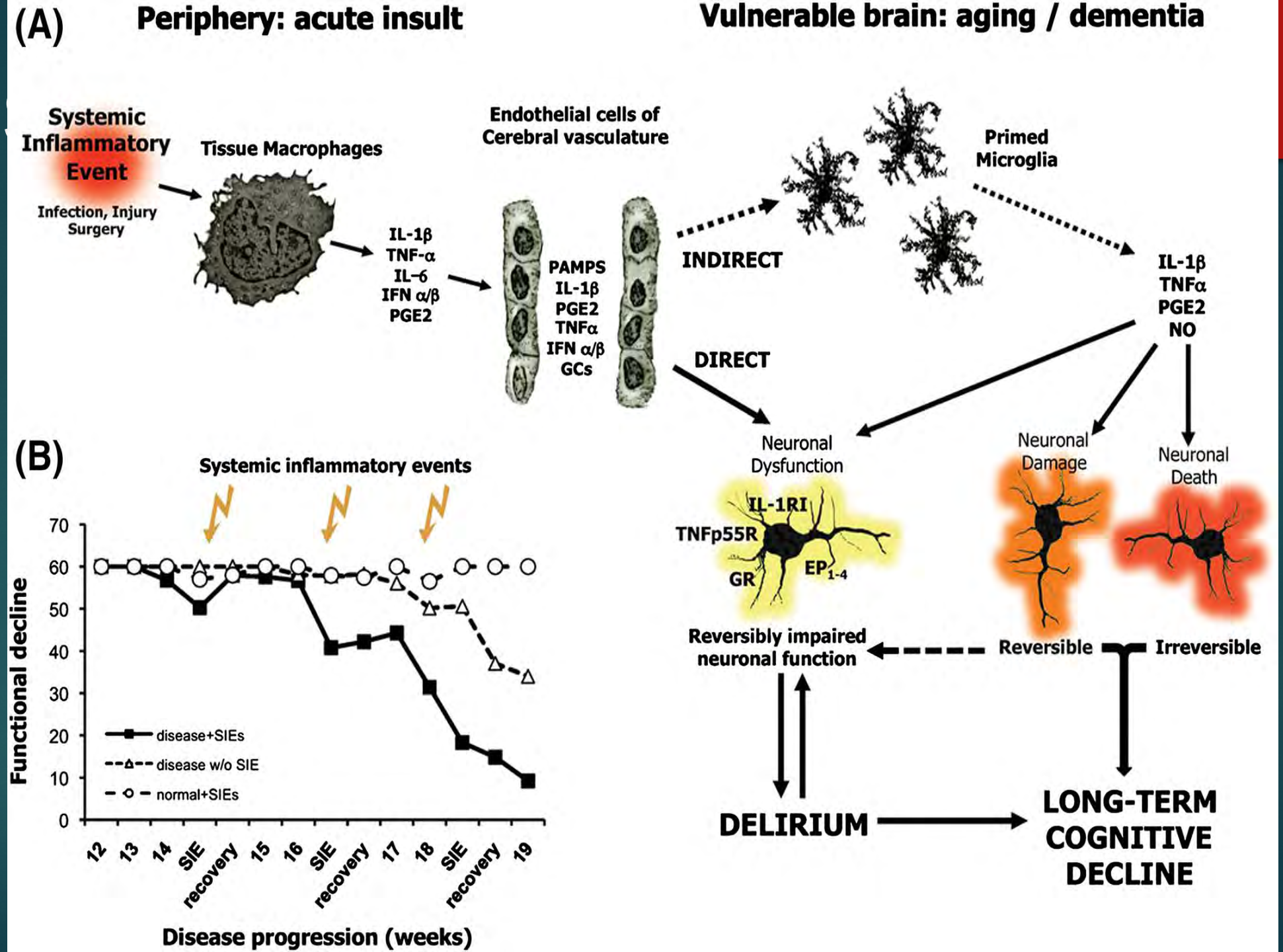
D	Drugs
E	Eyes, ears, other sensory deficits
L	Low O2 states (MI, CVA, PE)
I	Infection
R	Retention (urine, stool)
I	Ictal state
U	Under-hydration / under-nutrition
M	Metabolic (DM, Electrolyte derangement)
(S)	Subdural Hematoma

SIHS: Neuronal Aging

- Diminishing physiologic reserve associated with aging
- Changes in proportion of stress-regulating neurotransmitters
- Relative changes in brain blood flow, vascular density
- Blood-brain barrier permeability disruption
- Neuronal loss



SIH

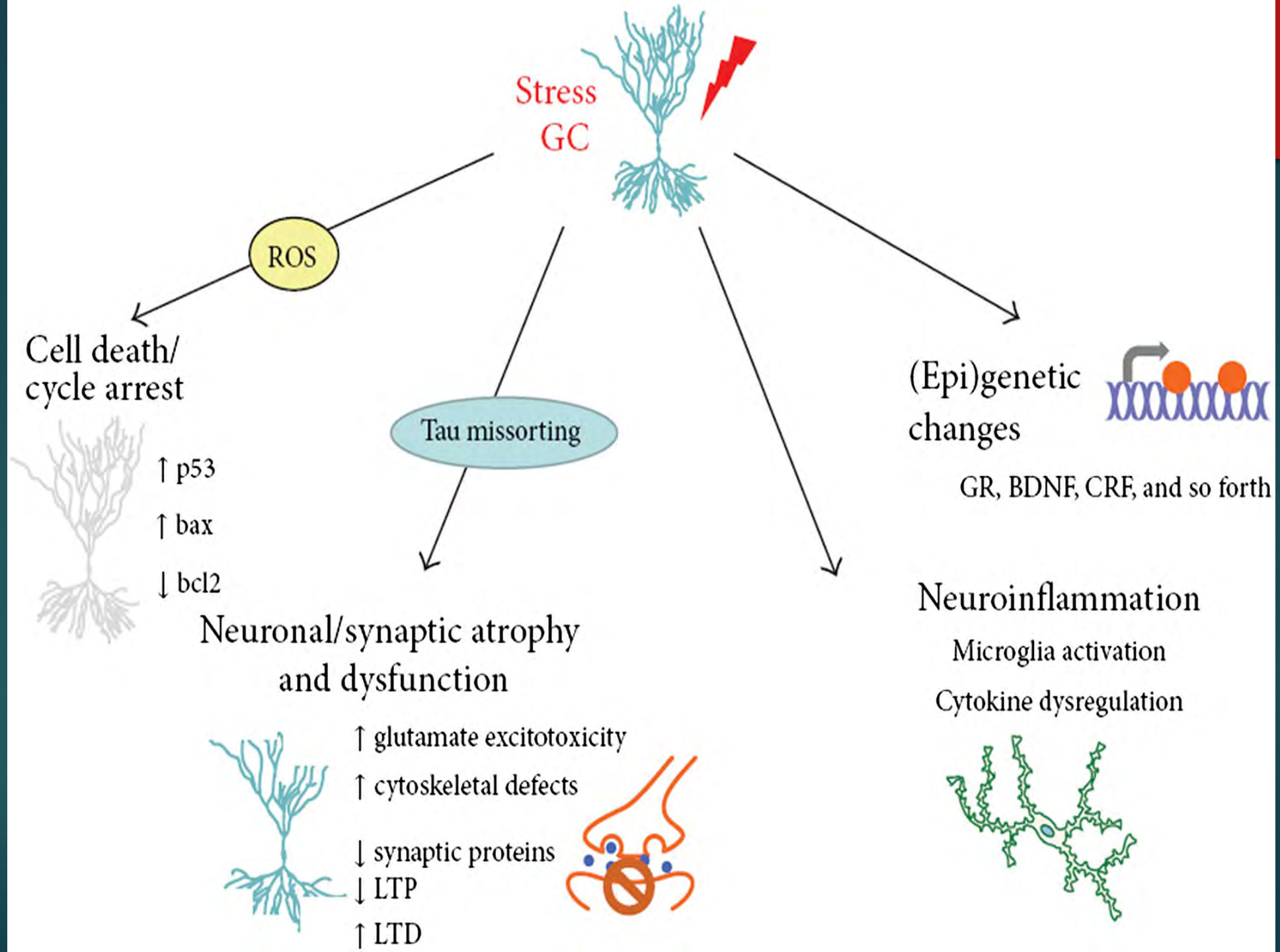

(A)
Periphery: acute insult
Vulnerable brain: aging / dementia
Systemic Inflammatory Event
Infection, Injury Surgery
Tissue Macrophages
IL-1β
TNF-α
IL-6
IFN α/β
PGE2
Endothelial cells of Cerebral vasculature
PAMPS
IL-1β
PGE2
TNFα
IFN α/β
GCs
INDIRECT
DIRECT
Primed Microglia
IL-1β
TNFα
PGE2
NO
Neuronal Dysfunction
Neuronal Damage
Neuronal Death
IL-1RI
TNFp55R
GR
EP1-4
Reversibly impaired neuronal function
Reversible
Irreversible
DELIRIUM
LONG-TERM COGNITIVE DECLINE
(B)
Systemic inflammatory events
Functional decline
70
60
50
40
30
20
10
0
disease+SIEs
disease w/o SIE
normal+SIEs
12
13
14
SIE
recovery
15
16
SIE
recovery
17
18
SIE
recovery
19
Disease progression (weeks)

SIHS: Oxidative Stress

- “Clinical expression of a cerebral metabolic defect”
- Reactive oxygen and nitrogen species cause damage to cell structures, proteins, and DNA
- Brain is highly susceptible due to high lipid content (myelin sheaths), high rates of oxidative metabolism, and low antioxidant capacity
- May reduce ionic gradients thus resulting in cortical spreading depression
- Influx of sodium, calcium; efflux of potassium results in a dramatic release of glutamate and dopamine

SIHS: Neuroendocrine

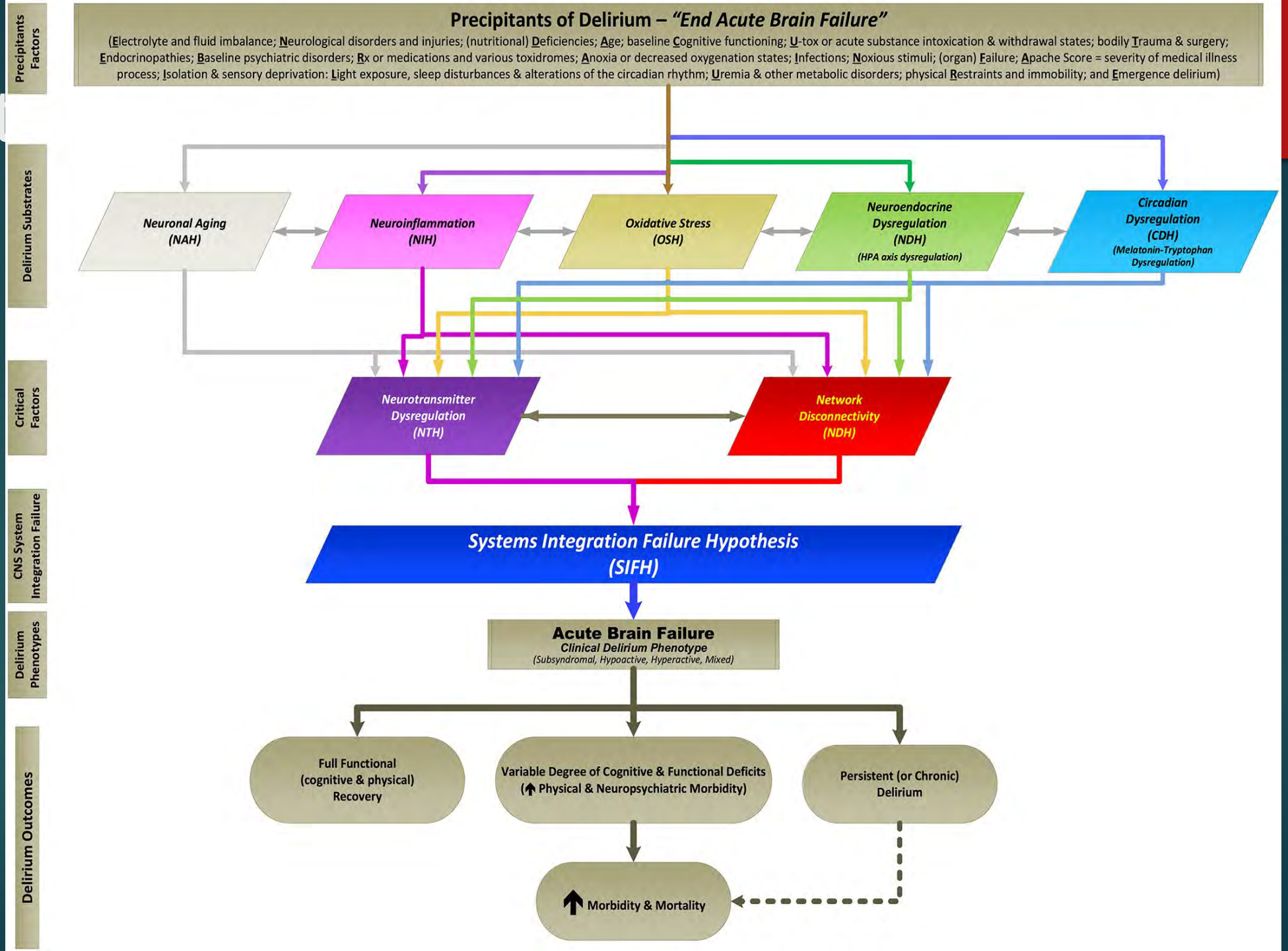
- Glucocorticoids (GC) in the normal stress response mobilize energy stores and suppress nonvital functions in an effort to facilitate adaptation and maintain homeostasis
- Dysregulation of the limbic hypothalamic-pituitary-adrenal axis may cause chronic activation of GC receptors
- Highest concentration of GC receptors in the brain is in the hippocampus
- Also creates reactive oxygen species and tau hyperphosphorylation

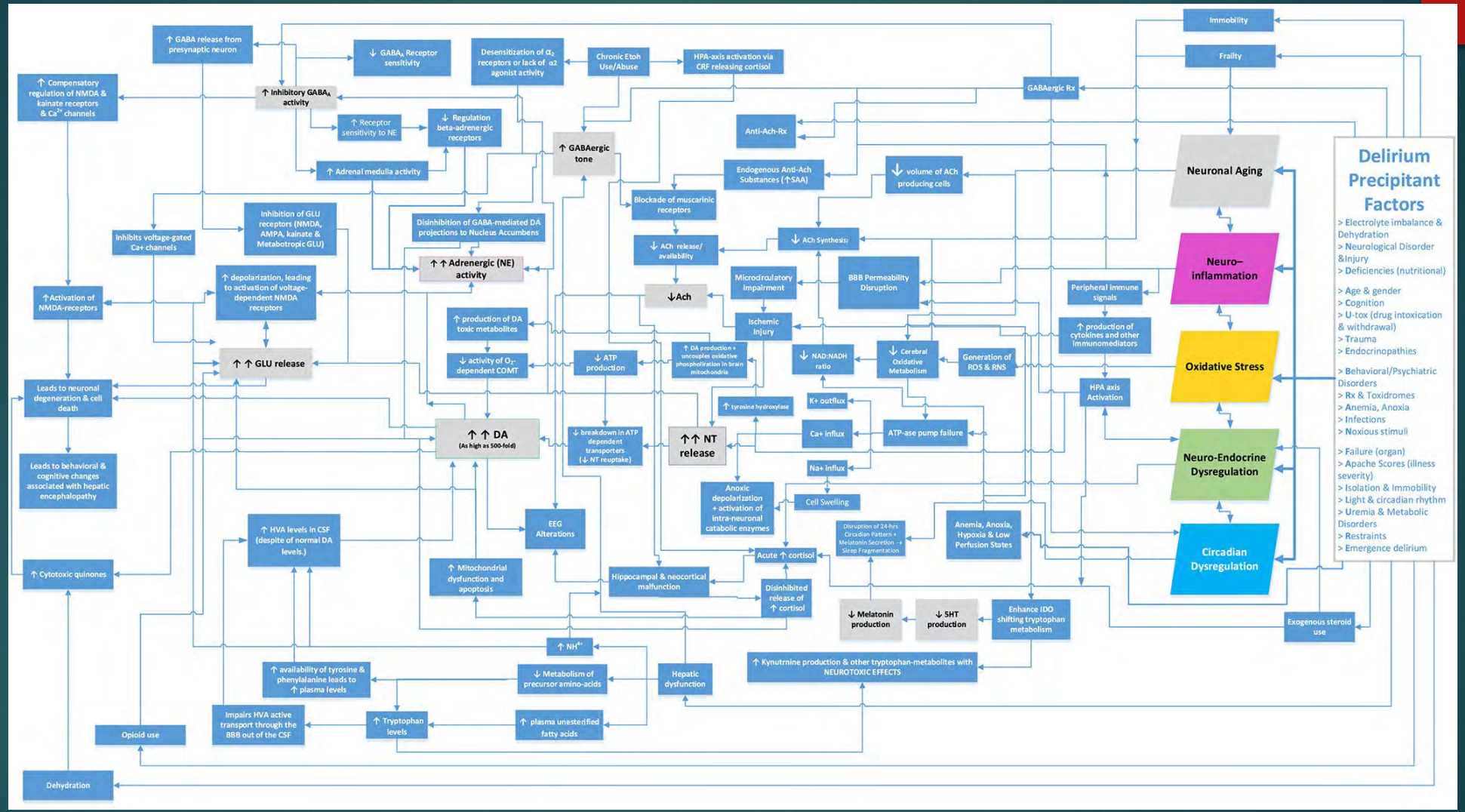

Stress
GC
ROS
Cell death/
cycle arrest
↑ p53
↑ bax
↓ bcl2
Tau missorting
(Epi)genetic
changes
GR, BDNF, CRF, and so forth
Neuronal/synaptic atrophy
and dysfunction
↑ glutamate excitotoxicity
↑ cytoskeletal defects
↓ synaptic proteins
↓ LTP
↑ LTD
Neuroinflammation
Microglia activation
Cytokine dysregulation

SIHS: Circadian dysregulation

- Melatonin production impaired by inflammation
- Deprivation increases both homeostatic and allostatic loads
  - Homeostatic: Buildup of metabolic byproducts
  - Allostatic: Increased sympathetic tone
- Decreased levels of melatonin metabolites found in hyperactive delirium, elevated levels in hypoactive

Pat


Precipitants Factors
Precipitants of Delirium – "End Acute Brain Failure"
(Electrolyte and fluid imbalance; Neurological disorders and injuries; (nutritional) Deficiencies; Age; baseline Cognitive functioning; U-tox or acute substance intoxication & withdrawal states; bodily Trauma & surgery; Endocrinopathies; Baseline psychiatric disorders; Rx or medications and various toxidromes; Anoxia or decreased oxygenation states; Infections; Noxious stimuli; (organ) Failure; Apache Score = severity of medical illness process; Isolation & sensory deprivation: Light exposure, sleep disturbances & alterations of the circadian rhythm; Uremia & other metabolic disorders; physical Restraints and immobility; and Emergence delirium)
Delirium Substrates
Neuronal Aging (NAH)
Neuroinflammation (NIH)
Oxidative Stress (OSH)
Neuroendocrine Dysregulation (NDH)
(HPA axis dysregulation)
Circadian Dysregulation (CDH)
(Melatonin-Tryptophan Dysregulation)
Critical Factors
Neurotransmitter Dysregulation (NTH)
Network Disconnectivity (NDH)
CNS System Integration Failure
Systems Integration Failure Hypothesis (SIFH)
Delirium Phenotypes
Acute Brain Failure
Clinical Delirium Phenotype
(Subsyndromal, Hypoactive, Hyperactive, Mixed)
Delirium Outcomes
Full Functional (cognitive & physical) Recovery
Variable Degree of Cognitive & Functional Deficits (↑ Physical & Neuropsychiatric Morbidity)
Persistent (or Chronic) Delirium
↑ Morbidity & Mortality


↑ GABA release from presynaptic neuron
↓ $GABA_A$ Receptor sensitivity
Desensitization of α_2 receptors or lack of α2 agonist activity
Chronic Etoh Use/Abuse
HPA-axis activation via CRF releasing cortisol
↑ Compensatory regulation of NMDA & kainate receptors & Ca^{2+} channels
↑ Inhibitory $GABA_A$ activity
↑ Receptor sensitivity to NE
↓ Regulation beta-adrenergic receptors
↑ Adrenal medulla activity
↑ GABAergic tone
Anti-Ach-Rx
GABAergic Rx
Endogenous Anti-Ach Substances (↑SAA)
↓ volume of ACh producing cells
Blockade of muscarinic receptors
Inhibits voltage-gated Ca+ channels
Inhibition of GLU receptors (NMDA, AMPA, kainate & Metabotropic GLU)
Disinhibition of GABA-mediated DA projections to Nucleus Accumbens
↓ ACh release/ availability
↓ ACh Synthesis
↑ ↑ Adrenergic (NE) activity
↓Ach
Microcirculatory impairment
BBB Permeability Disruption
↑Activation of NMDA-receptors
↑ depolarization, leading to activation of voltage-dependent NMDA receptors
↑ production of DA toxic metabolites
Ischemic Injury
↑ production of cytokines and other immunomediators
Peripheral immune signals
↑ ↑ GLU release
↓ activity of O_2-dependent COMT
↓ ATP production
↑ DA production + uncouples oxidative phospholiration in brain mitochondria
↓ NAD:NADH ratio
↓ Cerebral Oxidative Metabolism
Generation of ROS & RNS
HPA axis Activation
Leads to neuronal degeneration & cell death
↑ tyrosine hydroxylase
K+ outflux
Ca+ influx
ATP-ase pump failure
Na+ influx
↑ ↑ DA (As high as 500-fold)
↓ breakdown in ATP dependent transporters (↓ NT reuptake)
↑↑ NT release
Leads to behavioral & cognitive changes associated with hepatic encephalopathy
Anoxic depolarization + activation of intra-neuronal catabolic enzymes
Cell Swelling
↑ HVA levels in CSF (despite of normal DA levels.)
EEG Alterations
Disruption of 24-hrs Circadian Pattern + Melatonin Secretion → Sleep Fragmentation
Anemia, Anoxia, Hypoxia & Low Perfusion States
↑ Cytotoxic quinones
↑ Mitochondrial dysfunction and apoptosis
Acute ↑ cortisol
Hippocampal & neocortical malfunction
Disinhibited release of ↑ cortisol
↓ Melatonin production
↓ 5HT production
Enhance IDO shifting tryptophan metabolism
Exogenous steroid use
↑ NH^+
↑ availability of tyrosine & phenylalanine leads to ↑ plasma levels
↓ Metabolism of precursor amino-acids
Hepatic dysfunction
↑ Kynutrnine production & other tryptophan-metabolites with NEUROTOXIC EFFECTS
Impairs HVA active transport through the BBB out of the CSF
↑ Tryptophan levels
↑ plasma unesterified fatty acids
Opioid use
Dehydration
Immobility
Frailty
Neuronal Aging
Neuro–inflammation
Oxidative Stress
Neuro-Endocrine Dysregulation
Circadian Dysregulation
Delirium Precipitant Factors
> Electrolyte imbalance & Dehydration
> Neurological Disorder &Injury
> Deficiencies (nutritional)
> Age & gender
> Cognition
> U-tox (drug intoxication & withdrawal)
> Trauma
> Endocrinopathies
> Behavioral/Psychiatric Disorders
> Rx & Toxidromes
> Anemia, Anoxia
> Infections
> Noxious stimuli
> Failure (organ)
> Apache Scores (illness severity)
> Isolation & Immobility
> Light & circadian rhythm
> Uremia & Metabolic Disorders
> Restraints
> Emergence delirium

Recognizing Delirium

- Cole, et al. graphic

Screening assessment

- CAM: Most widely used instrument, based on DSM criteria
  - CAM-ICU: Modified for critically ill, nonverbal patients
  - bCAM: Modified from CAM-ICU for wider validation
- DRS-R-98
- MDAS
- Helfand, et al. 11/02/2020*

4AT

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	**0**
Mild sleepiness for <10 seconds after waking, then normal	**0**
Clearly abnormal	**4**

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	**0**
1 mistake	**1**
2 or more mistakes/untestable	**2**

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December."
To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	**0**
	Starts but scores <7 months / refuses to start	**1**
	Untestable (cannot start because unwell, drowsy, inattentive)	**2**

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	**0**
Yes	**4**

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4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

Clinical examination

- Physical examination
- Neurologic examination
  - Includes sensory examination
  - Assessing for focal neurologic injury
  - Prospective trial in 2011 proposed that the presence of >1 primitive release sign pre- and post-operatively may suggest a higher likelihood of progressing to delirium
  - Myoclonus
    - Positive: muscular contraction
    - Negative: interruption of muscular activity

Management: Environmental

- Sleep-wake support
- Prominent role of ambulation
- Social engagement
- Environmental reorientation
- Responding to

Management: Pharmacologic

- Every class associated with benefits and risks
  - Sedative-hypnotics
    - Benzodiazepines
    - Non-benzodiazepine sleep aids
  - Antipsychotics

New Strategies in Pharmacologic Management?

- Alpha 2 agonism

Prevention of Delirium in PALTC

- Recognition of delirium on admission
- Identification of risk factors at every stage
- Systematic approaches to proactive screening
- Structured responses to medical evaluation
- Proactive support to prevent decompensation

Prehabilitation Expanded

- Automated identification algorithms
- Structured protocol responses

- Hospital Elder Life Program - LTC

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Thank you!

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