Pathophysiology of Delirium

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CRITICAL ILLNESS, BRAIN DYSFUNCTION, *and* SURVIVORSHIP (CIBS) CENTER

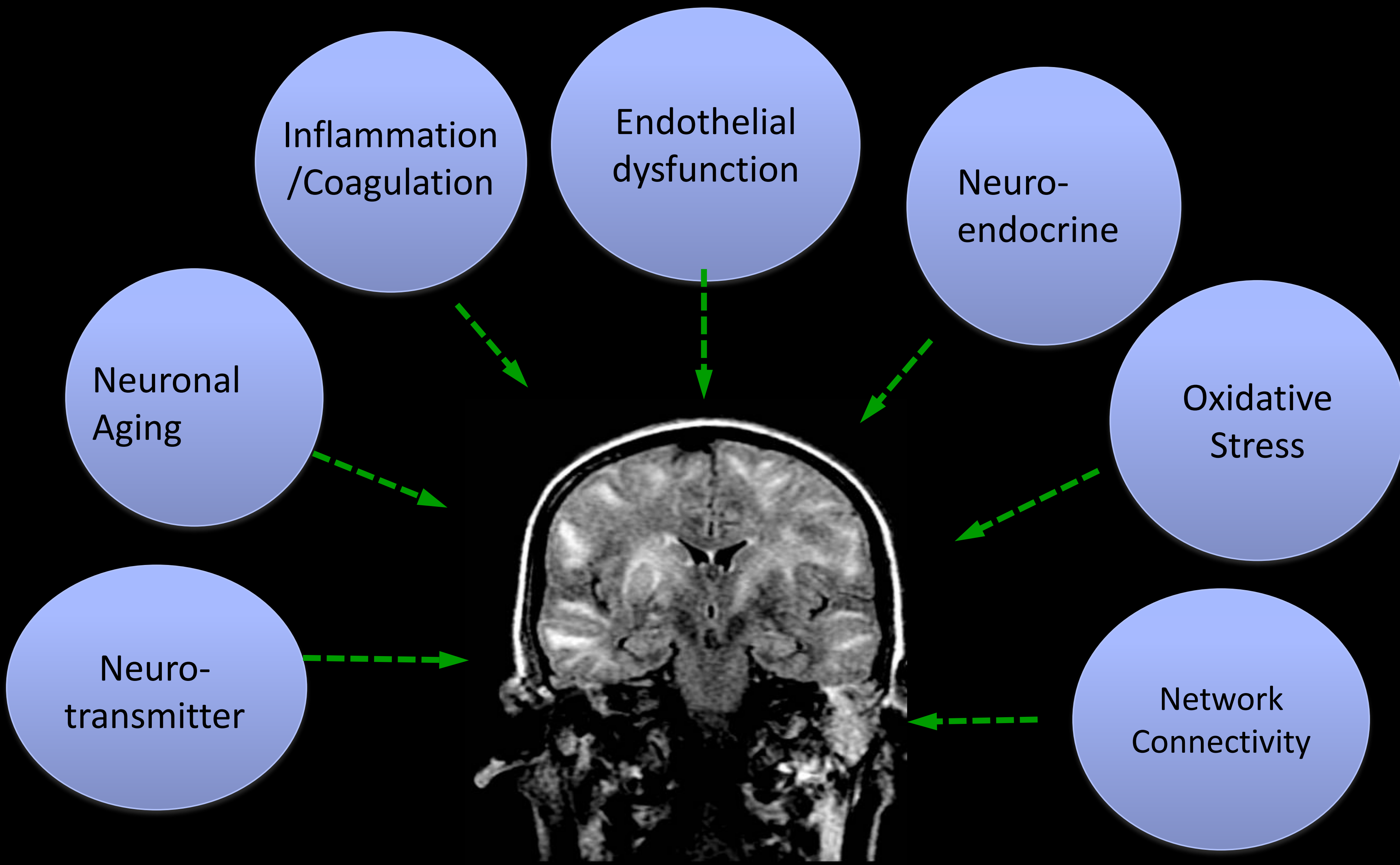
Disclosure

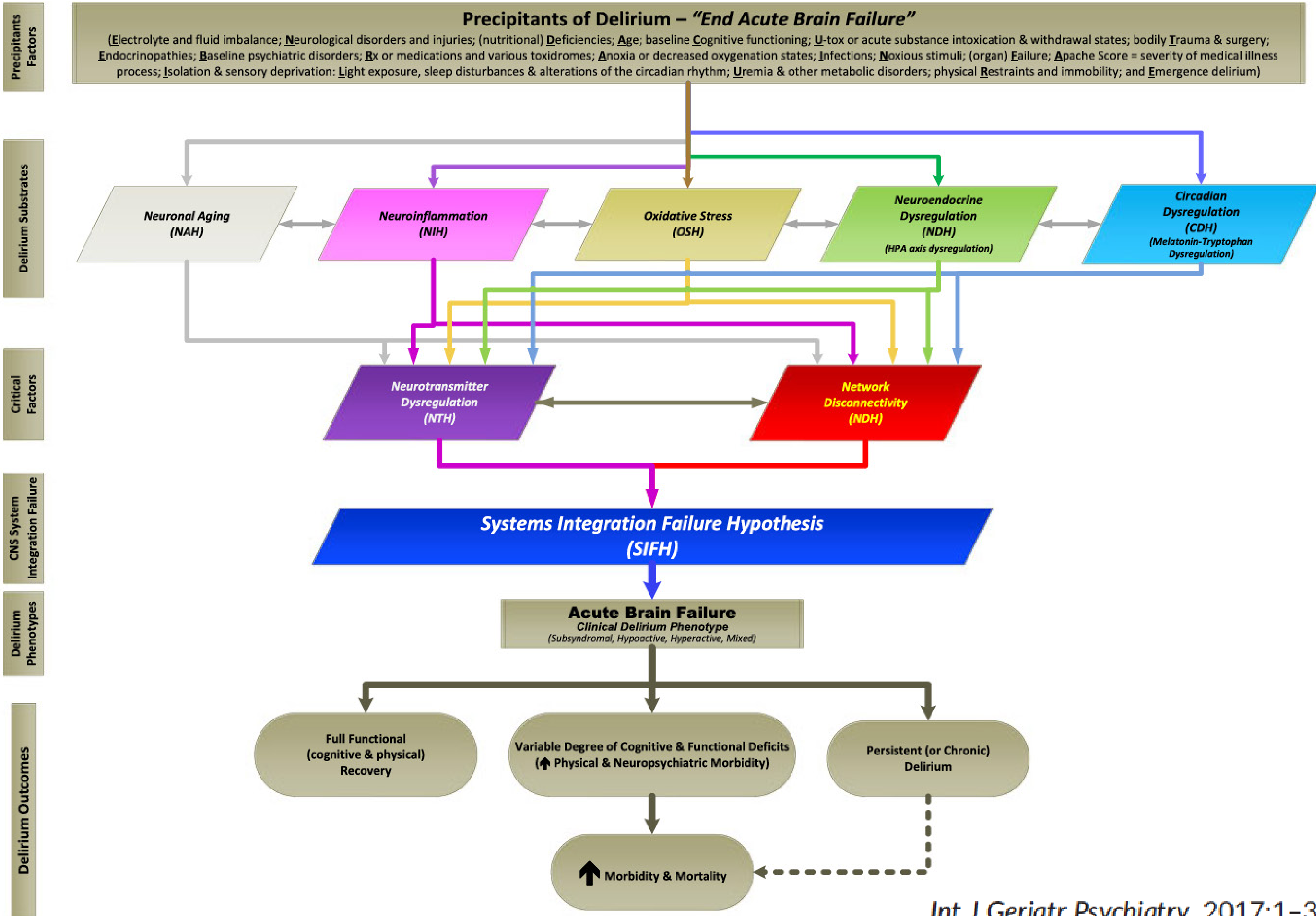
- Research grant from Hospira Inc. in collaboration with NIH
- Salary support
  - Vanderbilt Physician Scientist Award (2003-2005)
  - Foundation of Anesthesia Education and Research (2005-2007)
  - VA Career Development Award (2008-2011)
  - R01 NHLBI (HL111111), NIDUS

Focus

- Prevalent pathophysiological models
- Broad overview
- Focused on a critically ill population
- Supportive or circumstantial evidence through human research

Objectives: Mechanisms of Delirium





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

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Neurotransmitter Imbalances

- Monoamine Hypothesis (DA, Serotonin, NE)
- Cholinergic Hypothesis

The Monoamine Axis Hypothesis

- Serotonin, dopamine and norepinephrine may play an important role in the pathogenesis of delirium
- Bioavailability of amino acid precursors influence neurotransmitter synthesis by competing with the LAT-1 transporter in the blood brain barrier
  - Tryptophan → Serotonin
  - Tyrosine, Phenylalanine → Dopamine and Norepinephrine

Pardridge, WM (1998). Neurochem Res 23:635-644.
Wurtman, RJ, et al. (1980) Pharmacol Rev 32:315-335.

Amino Acids and Delirium

Psychopharmacology (2008) 200:243–254
DOI 10.1007/s00213-008-1201-0

OpenAccess

ORIGINAL INVESTIGATION

Acute tryptophan depletion dose dependently impairs object memory in serotonin transporter knockout rats

Am J Surg. 2008 November ; 196(5): 670–674. doi:10.1016/j.amjsurg.2008.07.007.

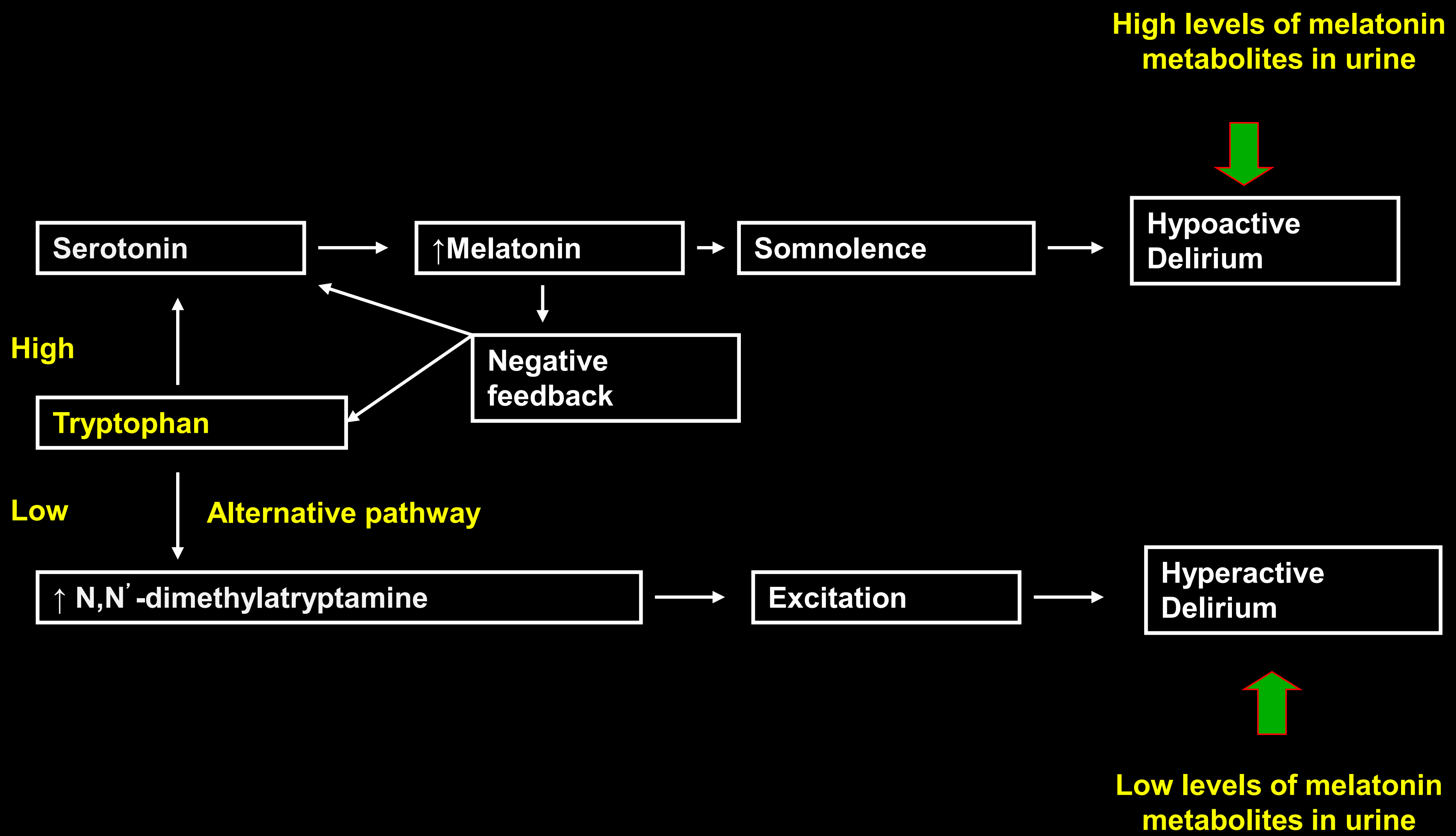
Low Tryptophan Levels Are Associated with Post-Operative Delirium in the Elderly

Thomas N Robinson, MD[1], **Christopher D Raeburn, MD**[1], **Erik M Angles, BS**[1], and **Marc Moss MD**[2]

Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. J Gerontol A Biol Sci Med Sci 2000;55(5):B249–B252. [PubMed: 10819312]discussion B53-4.

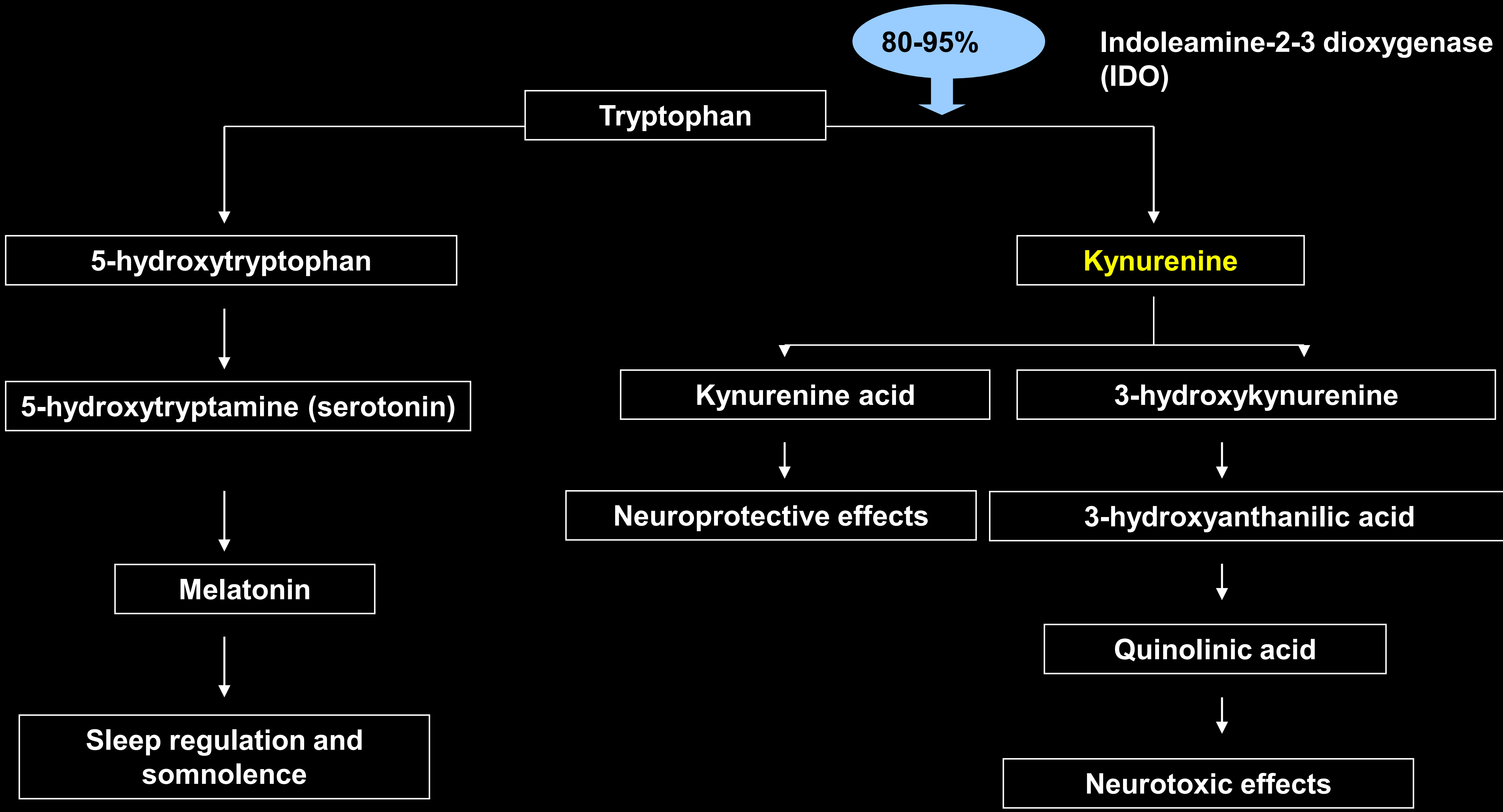
van der Mast RC, van den Broek WW, Fekkes D, et al. Is delirium after cardiac surgery related to plasma amino acids and physical condition? J Neuropsychiatry Clin Neurosci 2000;12(1):57–63.

Tryptophan and Delirium



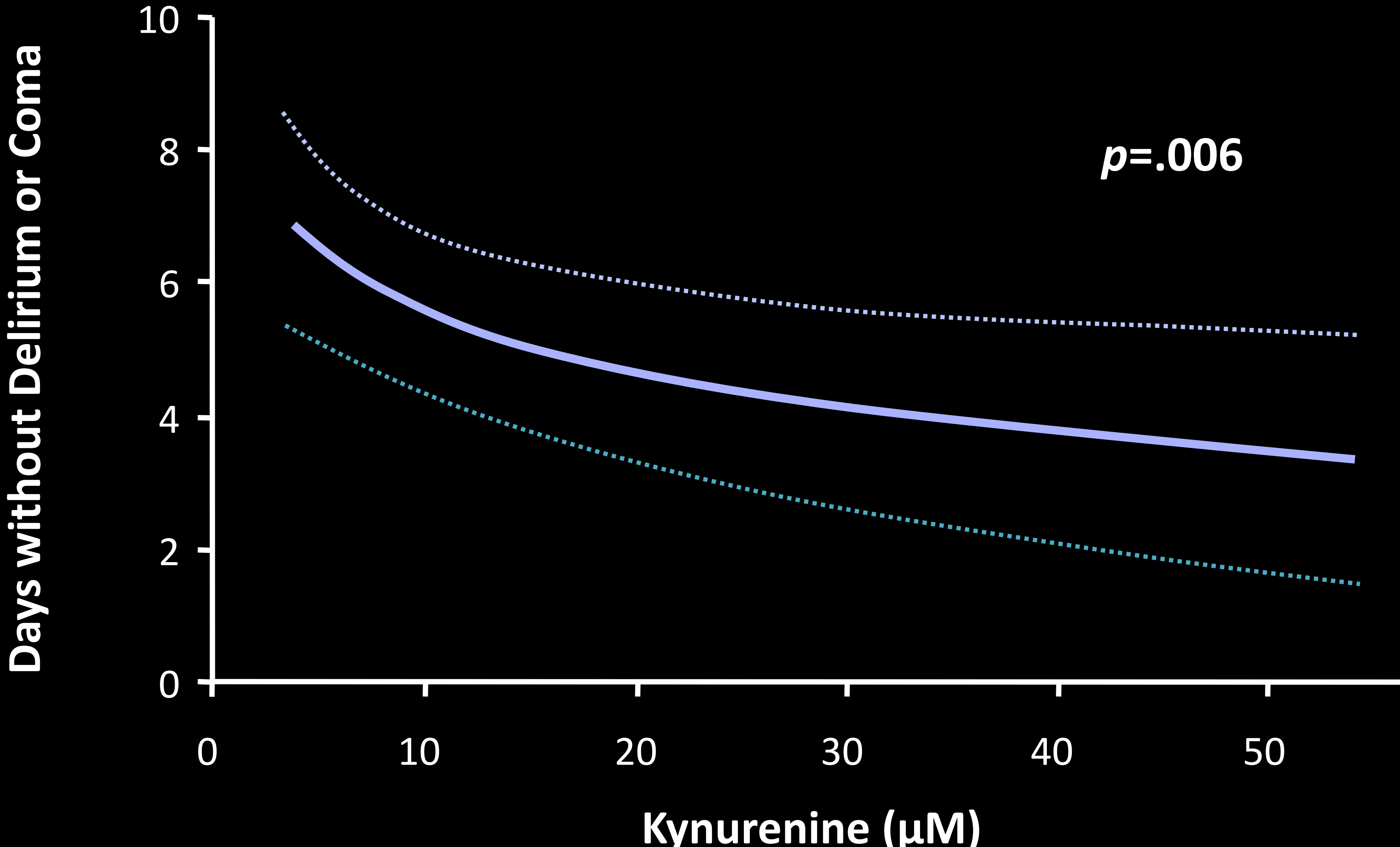
Lewis M, 2004 Medical Hypotheses;63;402-06

Tryptophan metabolites and delirium



Adams JR, et al. Crit Care Med 2012;40:835-41

Tryptophan Metabolites & Delirium



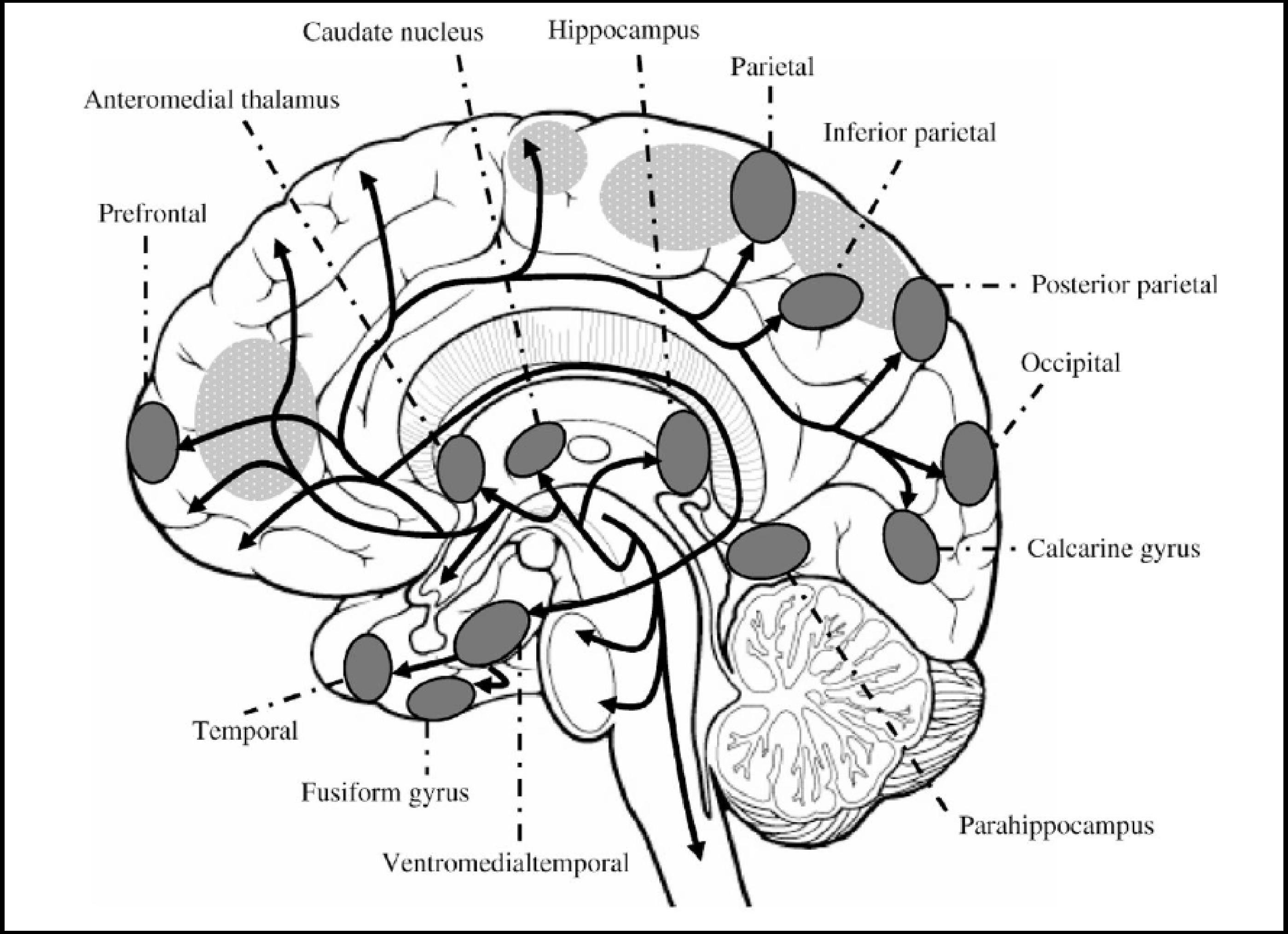
Adams JR, et al. Crit Care Med 2012;40:835-41

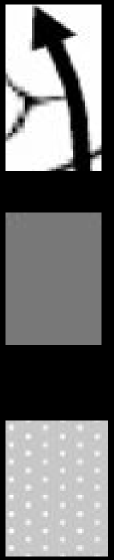
Role of cholinergic transmission

- Arousal/attention:
  - Cholinergic reticulothalamic pathway
    - Basal forebrain and PPT projections
  - Sensory gating for selective attention
  - Promotes fast, synchronized EEG activity
- Memory/cognition
  - Working, spatial memory
  - Executive function

Trzepacz. Semin Clin Neuropsychiatry. 2000 (2):132-48

Overlap of neuroimaging lesions and cholinergic pathways





Hshieh T et al. J Gerontol A Biol Sci Med Sci. 2008; 63(7): 764–772.

Clinical studies supporting cholinergic hypothesis

Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF, Coyle JT. Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2:651–653. [PubMed: 6116042]

Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161:1099–1105. [PubMed: 11322844]

Flacker JM, Cummings V, Mach JR Jr, Bettin K, Kiely DK, Wei J. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6:31–41. [PubMed: 9469212]

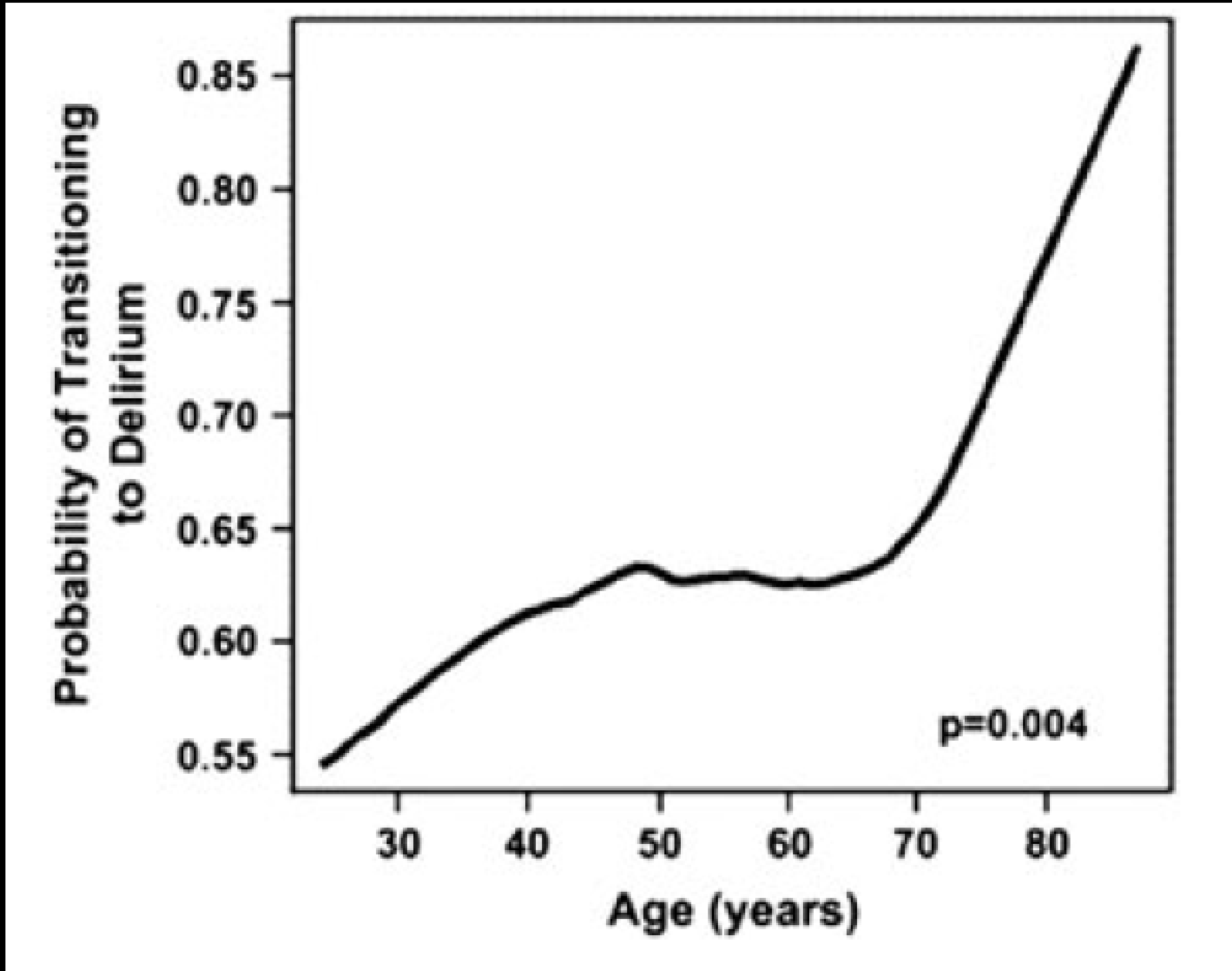
Cummings JL, Gorman DG, Shapira J. Physostigmine ameliorates the delusions of Alzheimer's disease. Biol Psychiatry 1993;33:536–541. [PubMed: 8513039]

2

Neuronal Aging

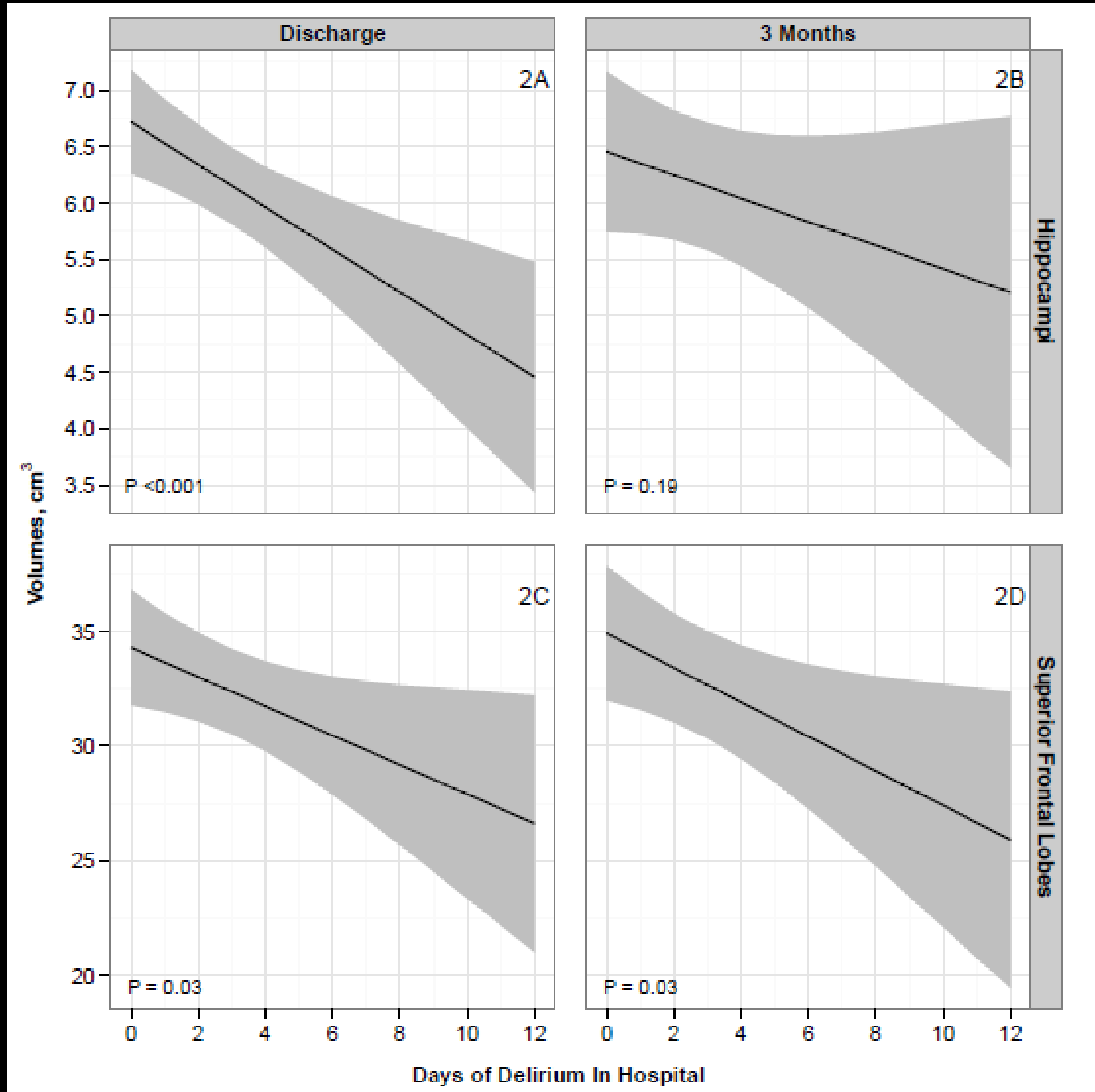
Changes with Aging

- Diminishing physiologic reserve
- Changes in the proportion of stress-regulating neurotransmitters
- Brain blood flow decline, decreased vascular density
- Neuron loss
- Decreased intracellular signal transduction systems



Anesthesiology. 2006;104(1):21-26.

The VISIONS MRI Studies



Gunther M et al. *CCM* 2012;40:2022-32.

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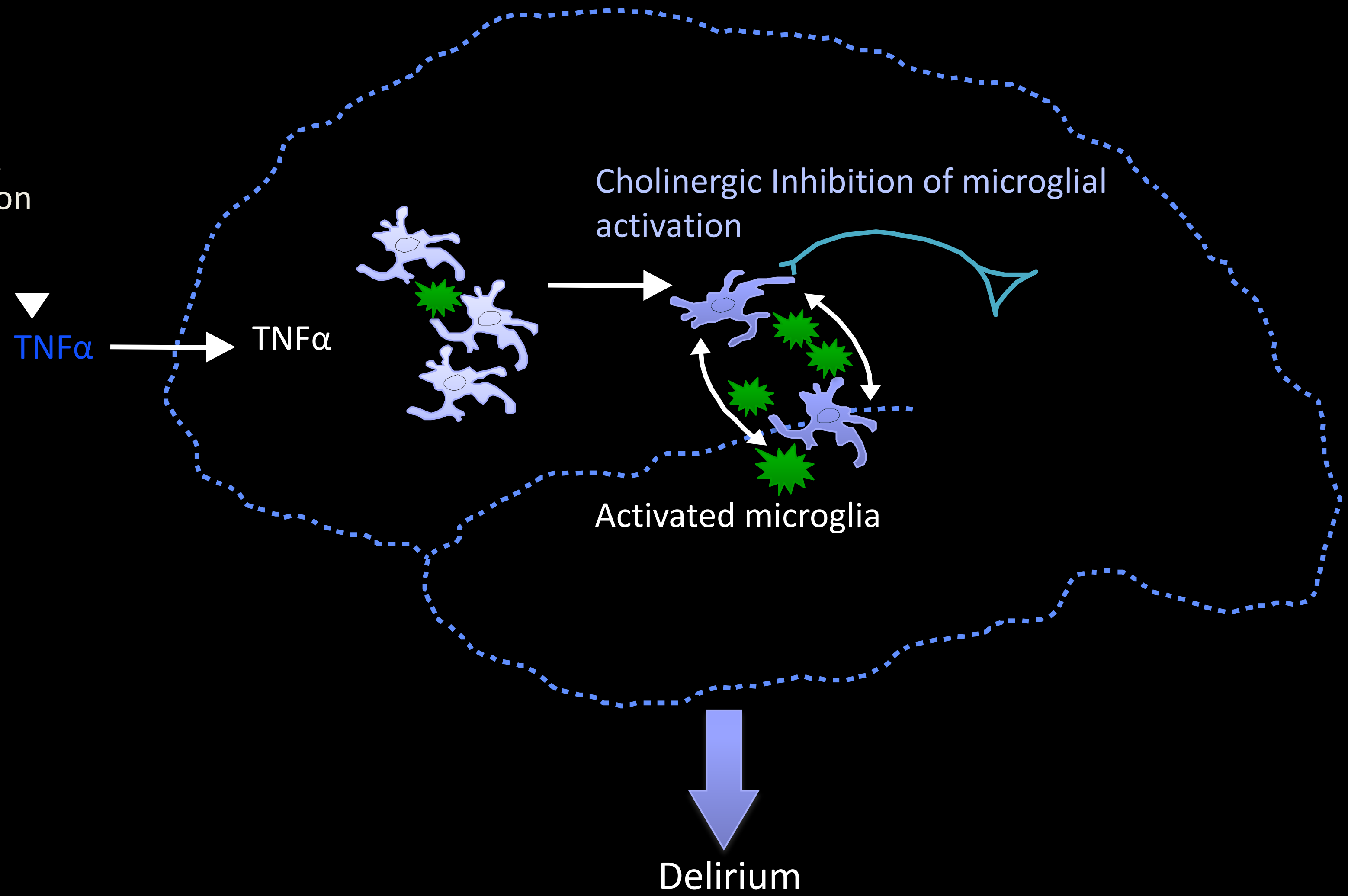
Systemic and Neuroinflammation

Cytokines, Acetylcholine, & Delirium/LTCI

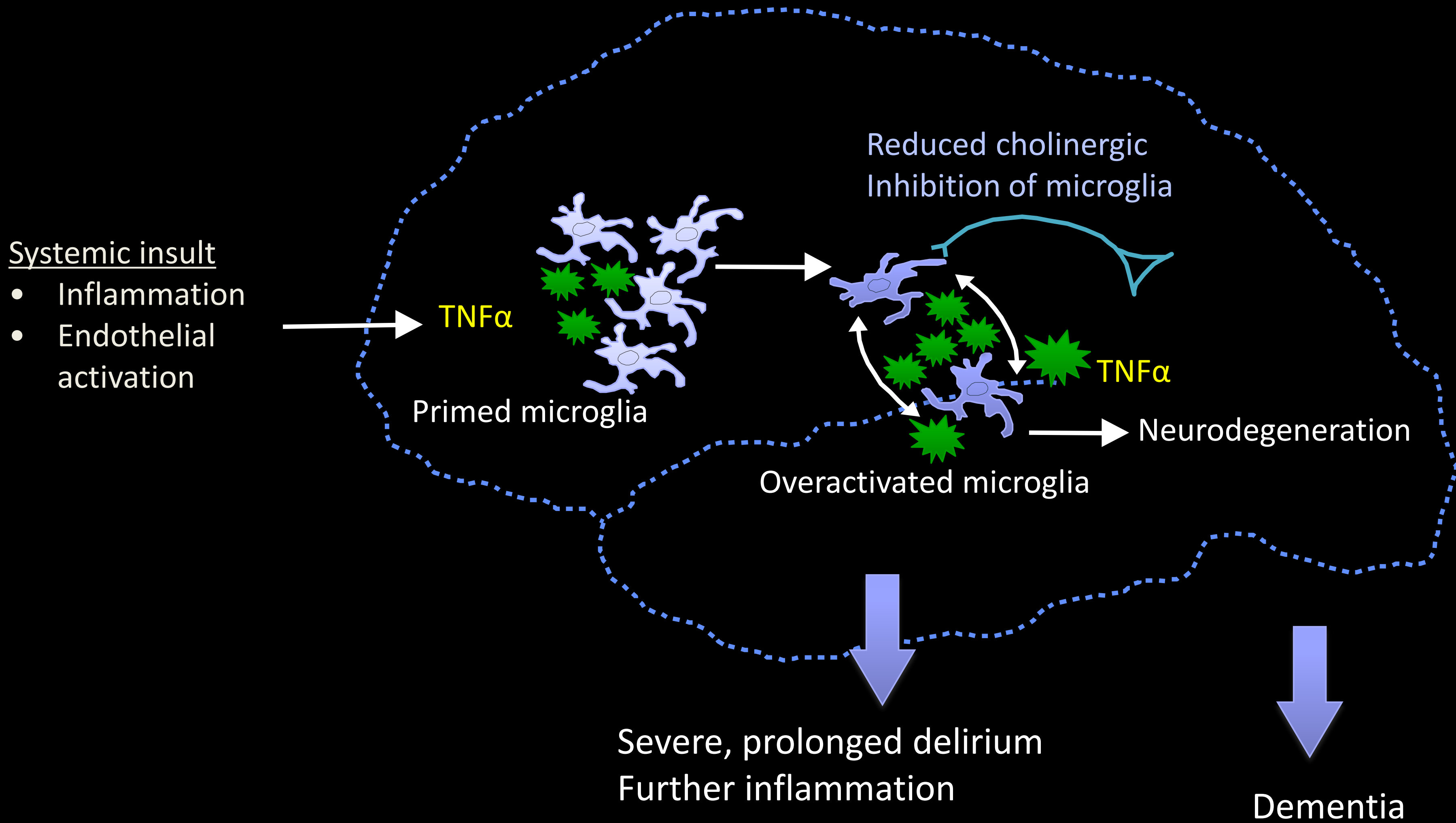
Systemic insult
- Inflammation
- Endothelial activation



Van Gool WA, et al. Lancet 2010;375:773-5

Inflammation and Delirium/LTCI

Old age, incipient neurodegenerative disease, or anticholinergics

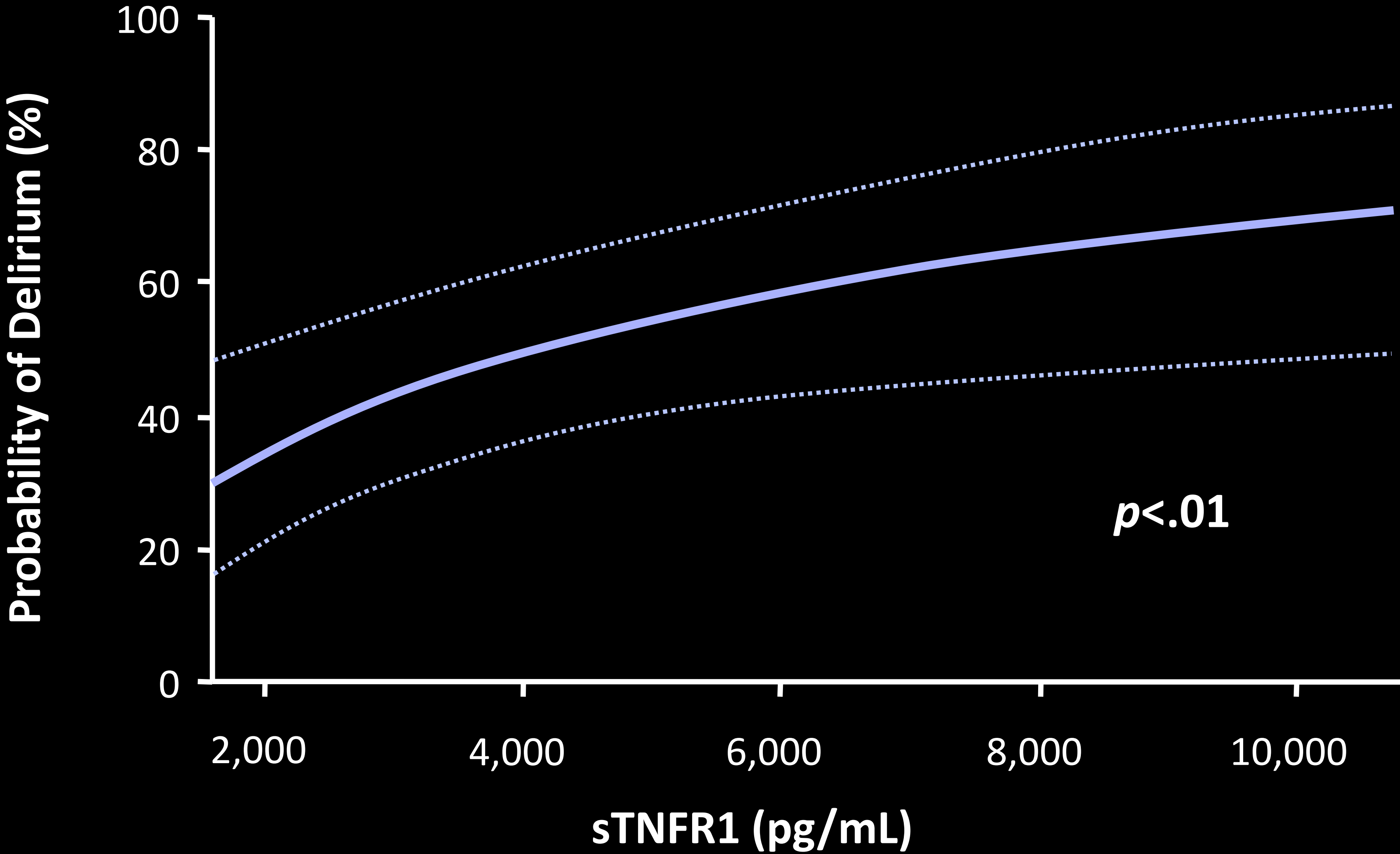


Van Gool WA, et al. Lancet 2010;375:773-5

Inflammatory markers and Delirium

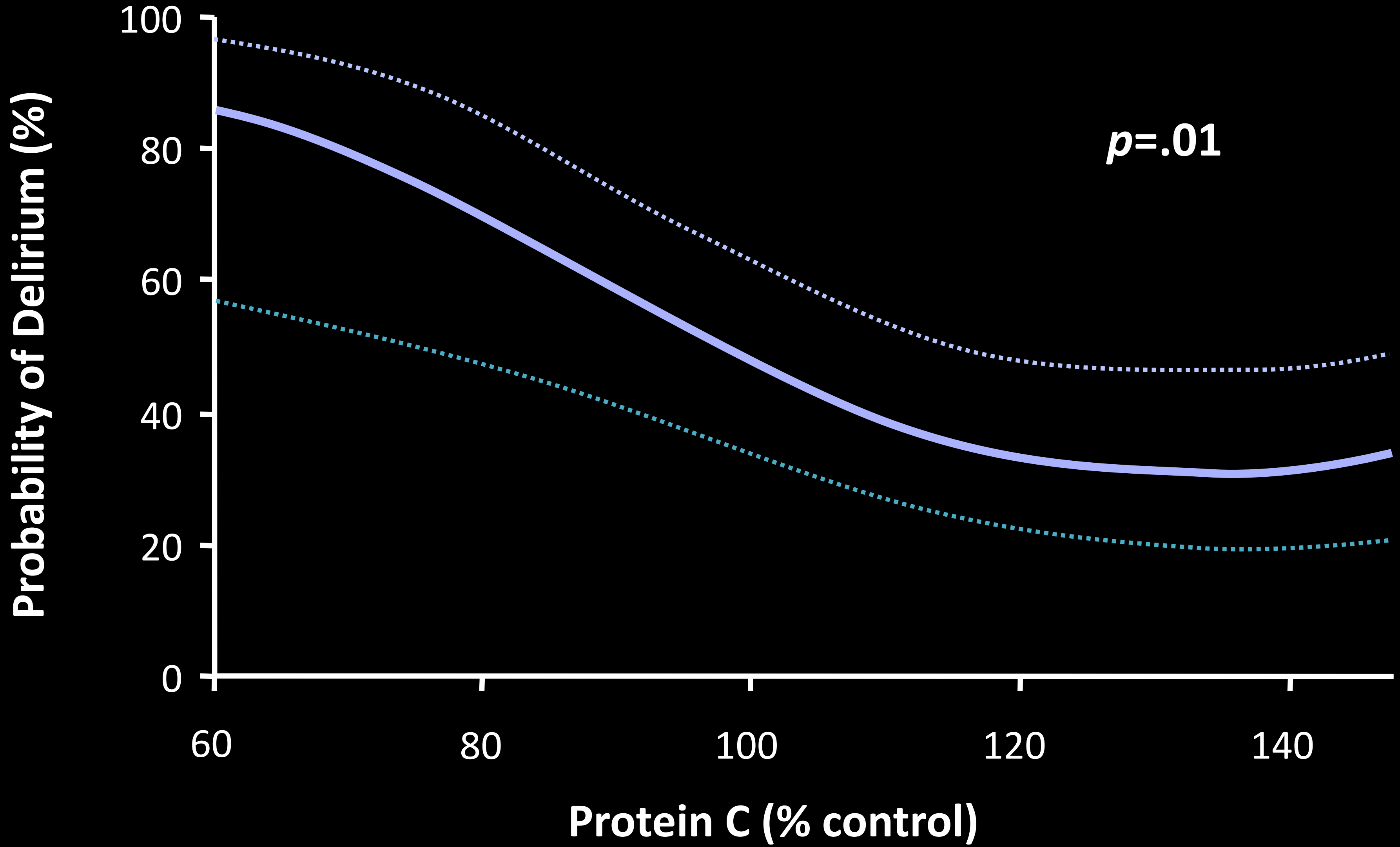
- 1.TNF
- 2. Interleukins (IL6, IL 8 etc)
- 3. Procalcitonin (PCT)
- 4. C-reactive protein (CRP)
- 5. Protein C

Soluble TNF Receptor-1 & Delirium



Girard TD, et al. Intensive Care Med 2012;38: 1965-73

Protein C & Delirium



Girard TD, et al. Intensive Care Med 2012;38: 1965-73

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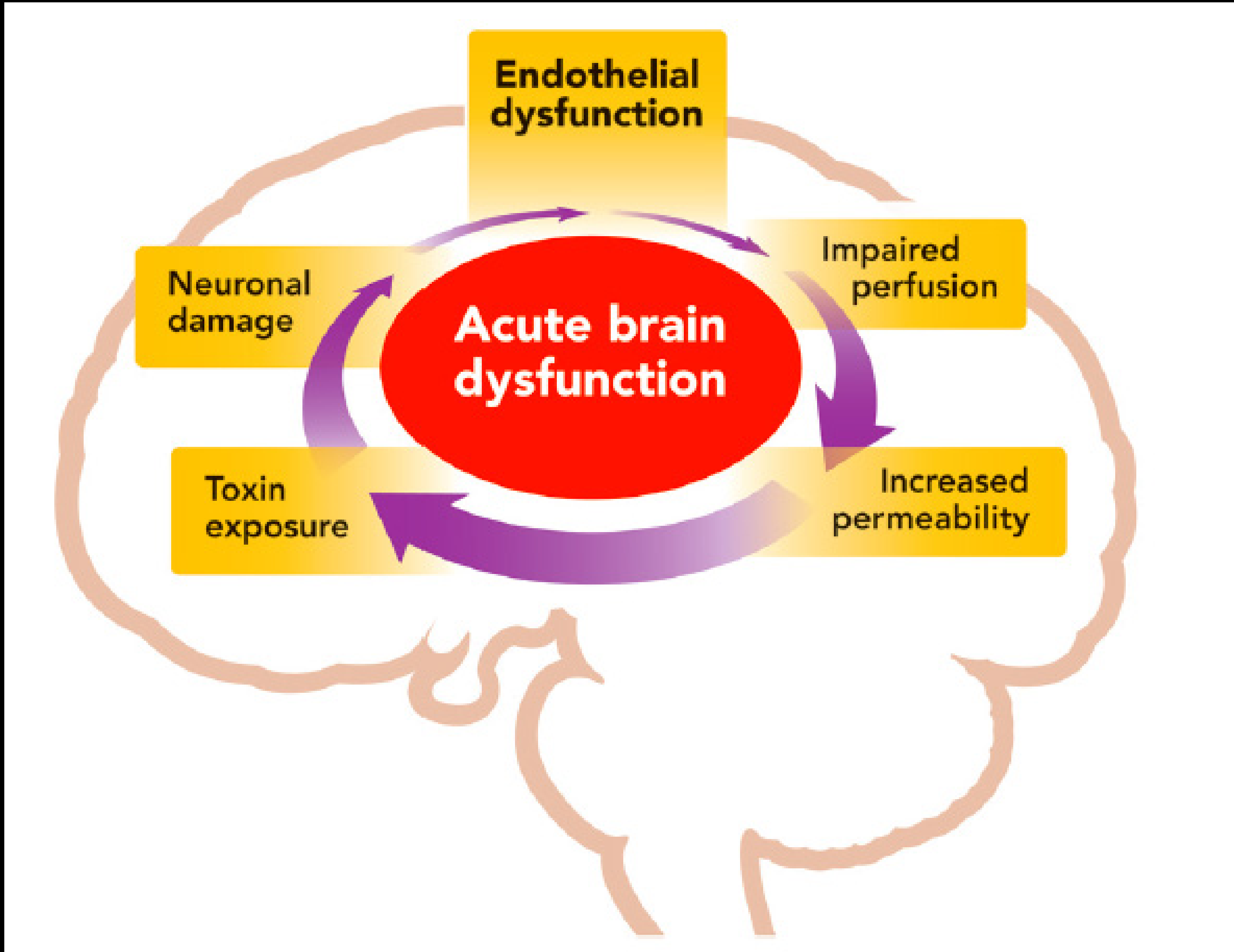
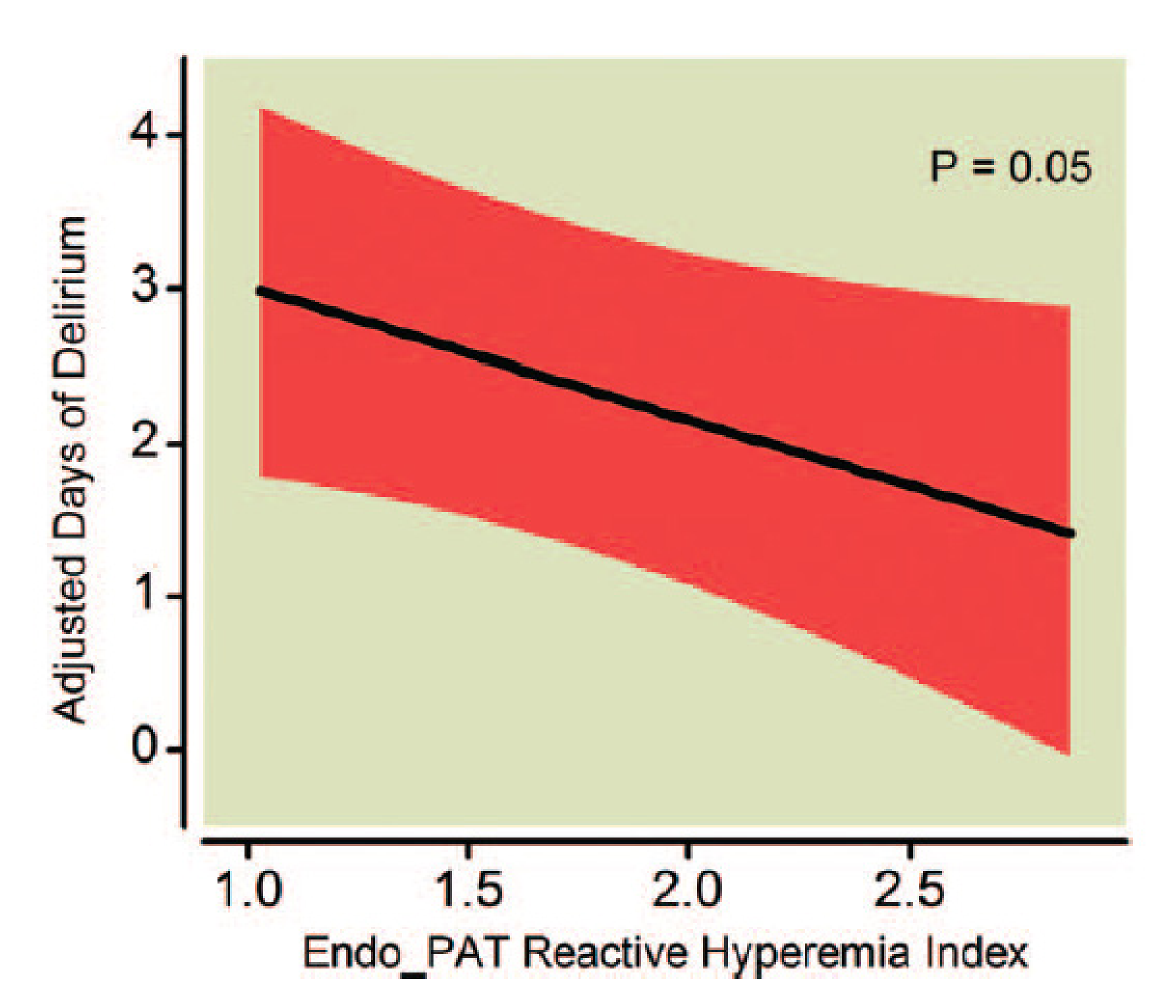
Endothelial Dysfunction, Blood Brain Barrier and Neuronal Injury



Hughes et al. Anesthesiology 2013; 118:631-9

Association between Endothelial Dysfunction and Acute Brain Dysfunction during Critical Illness

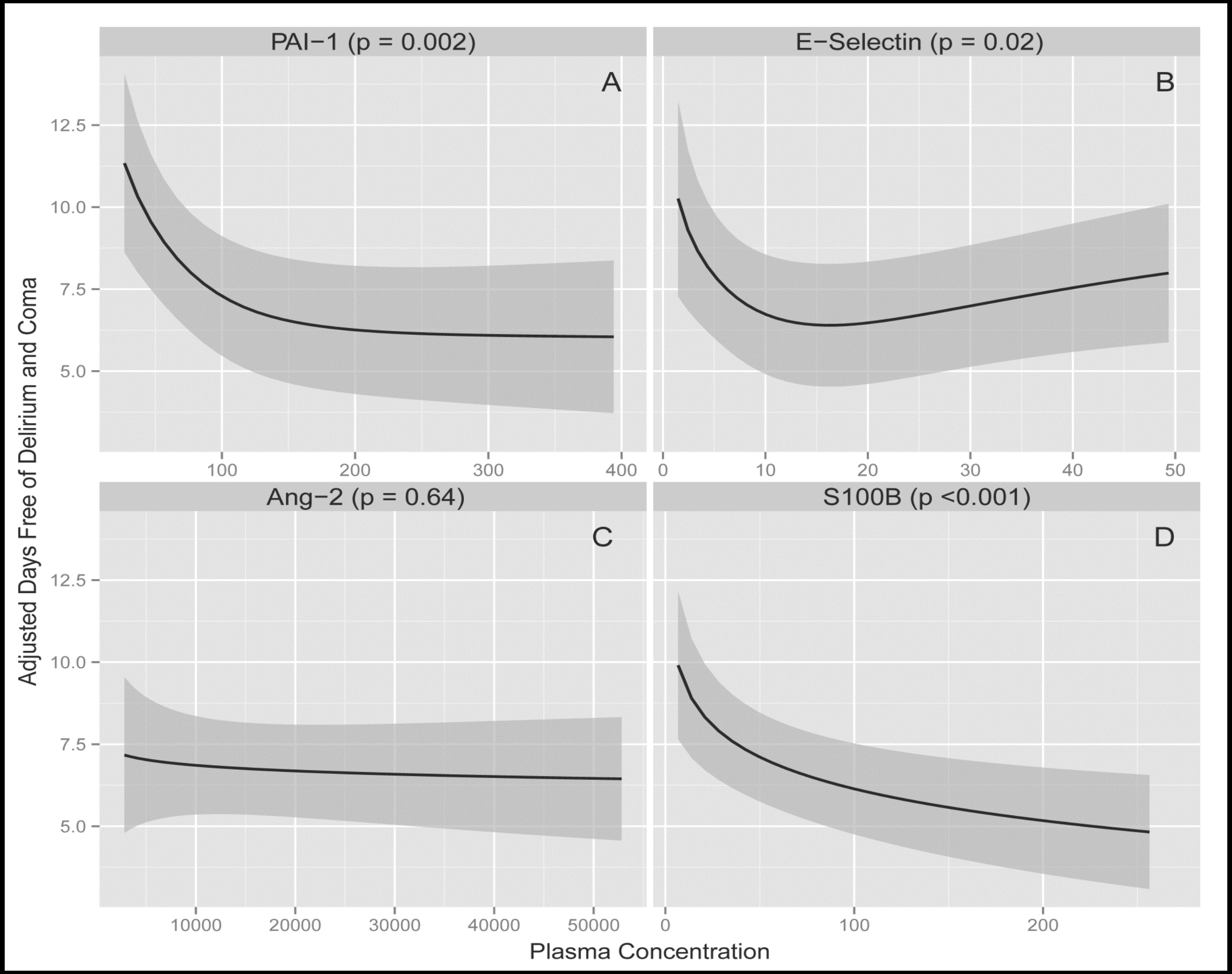
Christopher G. Hughes, M.D.,* Alessandro Morandi, M.D.,† Timothy D. Girard, M.D.,‡



- Adhesion molecules (E-Selectin)
- Coagulation molecules (PAI-1)
- Angiogenesis markers (Ang 1)
- Blood brain barrier injury (S100B)

Anesthesiology 2013; 118:631-9

Endothelial Dysfunction and Altered BBB Permeability/Neuronal Injury



Hughes CG et al. *Anesthesiology.* 2013; 118: 631-9
Hughes CG et al. *Crit Care Med*. 2016;

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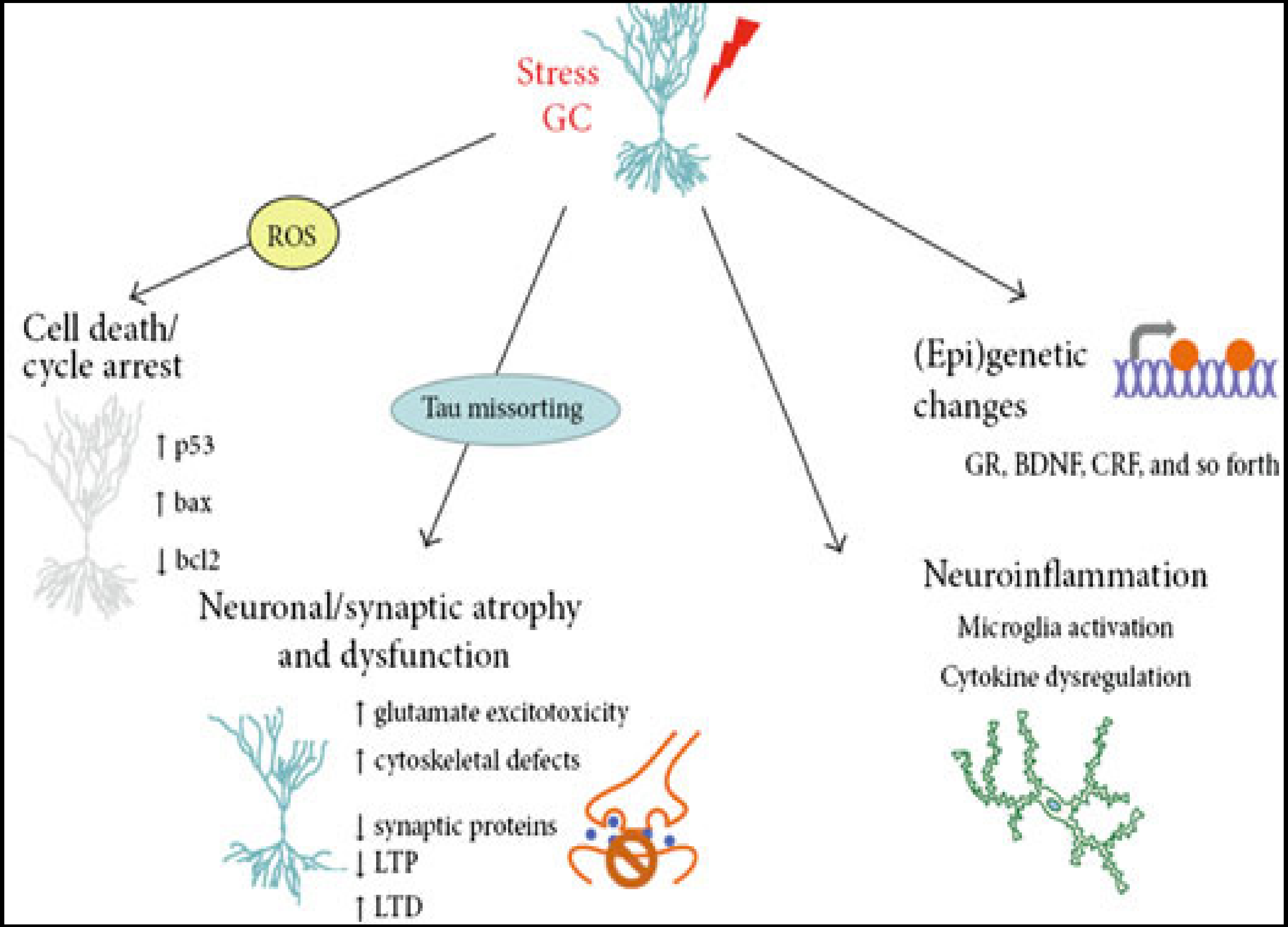
Neuroendocrine hypothesis

Neuroendocrine Hypothesis



Vyas et al. Neural Plas 2016

Kazmierski et al. Critical Care 2013, 17:R38
http://ccforum.com/content/17/2/R38

CRITICAL CARE

RESEARCH Open Access

Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study

Jakub Kazmierski[1*], Andrzej Banys[2], Joanna Latek[3], Julius Bourke[4] and Ryszard Jaszewski[5]

Table 5 Factors independently associated with delirium after CABG surgery revealed in multivariate stepwise logistic regression analysis[a]

Variable	Coefficient	Standard error	Odds ratio (95% CI)	*P* value
TMT-B[b]	0.016	0.004	1.02 (1.01 to 1.03)	< 0.0001
Creatinine concentration[b]	0.015	0.012	1.02 (0.99 to 1.04)	0.191
Dose of midazolam	0.081	0.028	1.08 (1.03 to 1.15)	0.005
Preoperative cortisol	0.005	0.002	1.005 (1.001 to 1.009)	0.025
Depression[b]	2.389	0.954	10.90 (1.68 to 70.67)	0.012
IL-2 concentration[c]	0.002	0.001	1.002 (1.001 to 1.004)	0.004
Constant	-12.964	2.725	-	< 0.0001

CI, confidence interval; TMT-B, Trial Making Test. [a]The regression model is statistically significant: $\chi^2 = 76.889$; $P < 0.001$. [b]Preoperative variable. [c]Postoperative variable.

Corticosteroids and Transition to Delirium in Patients With Acute Lung Injury*

Matthew P. Schreiber, MD, MHS[1]; Elizabeth Colantuoni, PhD[2,3]; Oscar J. Bienvenu, MD, PhD[3,4]; Karin J. Neufeld, MD, MPH[3,4]; Kuan-Fu Chen, MD, PhD[5]; Carl Shanholtz, MD[6]; Pedro A. Mendez-Tellez, MD[3,7]; Dale M. Needham, MD, PhD[3,8,9]

Measurements and Main Results: Delirium evaluation was performed by trained research staff using the validated Confusion Assessment Method for the ICU screening tool. A total of 330 of the 520 patients (64%) had at least two consecutive ICU days of observation in which delirium was assessable (e.g., patient was noncomatose), with a total of 2,286 days of observation and a median (interquartile range) of 15 (9, 28) observation days per patient. These 330 patients had 99 transitions into delirium from a prior nondelirious, noncomatose state. The probability of transitioning into delirium on any given day was 14%. Using multivariable Markov models with robust variance estimates, the following factors (adjusted odds ratio; 95% CI) were independently associated with transition to delirium: older age (compared to < 40 years old, 40–60 yr [1.81; 1.26–2.62], and ≥ 60 yr [2.52; 1.65–3.87]) and administration of any systemic corticosteroid in the prior 24 hours (1.52; 1.05–2.21).

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis
The HYPRESS Randomized Clinical Trial

Didier Keh, MD; Evelyn Trips; Gernot Marx, MD; Stefan P. Wirtz, MD; Emad Abduljawwad, MD; Sven Bercker, MD; Holger Bogatsch, MD; Josef Briegel, MD; Christoph Engel, MD; Herwig Gerlach, MD, PhD, MBA; Anton Goldmann, MD; Sven-Olaf Kuhn, MD; Lars Hüter, MD; Andreas Meier-Hellmann, MD; Axel Nierhaus, MD; Stefan Kluge, MD; Josefa Lehmke, MD; Markus Loeffler, MD; Michael Oppert, MD; Kerstin Resener, MD; Dirk Schädler, MD; Tobias Schuerholz, MD; Philipp Simon, MD; Norbert Weiler, MD; Andreas Weyland, MD; Konrad Reinhart, MD; Frank M. Brunkhorst, MD; for the SepNet–Critical Care Trials Group

Table 2. Primary and Secondary End Points[a]

End Point	Placebo (n = 176)	Hydrocortisone (n = 177)	Total (N = 353)	*P* Value
Primary				
Septic shock, No./total No. (%) [95% CI]				
ITT population	39/170 (22.9) [17.2-30.0]	36/170 (21.2) [15.6-28.1]	75/340 (22.1) [17.9-26.9]	.70
PP population	33/156 (21.2) [15.4-28.4]	29/155 (18.7) [13.3-25.7]	62/311 (19.9) [15.8-24.8]	.59
Secondary				
Mortality, No./total No. (%) [95% CI]				
28 d	14/170 (8.2) [5.0-13.4]	15/171 (8.8) [5.4-14.0]	29/341 (8.5) [6.0-12.0]	.86
90 d	28/168 (16.7) [11.8-23.0]	34/171 (19.9) [14.6-26.5]	62/339 (18.3) [14.5-22.8]	.44
180 d	37/167 (22.2) [16.5-29.0]	45/168 (26.8) [20.7-34.0]	82/335 (24.5) [20.2-29.4]	.32
ICU	14/172 (8.1) [4.9-13.2]	13/171 (7.6) [4.5-12.6]	27/343 (7.9) [5.5-11.2]	.85
Hospital	22/172 (12.8) [8.6-18.6]	23/171 (13.5) [9.1-19.4]	45/343 (13.1) [10.0-17.1]	.86
LOS, median (IQR), d				
ICU	9 (6-17)	8 (5-15)	8 (5-16)	.23
Hospital	25 (16-40)	26 (16-46)	26 (16-43)	.36
Mechanical ventilation, No./total No. (%) [95% CI]	103/172 (59.9) [52.4-66.9]	91/171 (53.2) [45.8-60.5]	194/343 (56.6) [51.3-61.7]	.21
MV-free time, median (IQR), d	5 (2-7)	4 (2-7)	4 (2-7)	.34
RRT, No./total No. (%) [95%CI]	21/172 (12.2) [8.1-17.9]	21/171 (12.3) [8.2-18.0]	42/343 (12.2) [9.2-16.1]	.98
RRT-free time, median (IQR), d	7 (4-14)	6 (4-12)	7 (4-13)	.35
SOFA score until day 14, median (IQR)[b]	5.0 (3.5-6.8)	4.7 (3.5-6.5)	4.8 (3.5-6.6)	.69
Delirium, No./total No. (%) [95% CI]	25/102 (24.5) [17.2-33.7]	11/98 (11.2) [6.4-19.0]	36/200 (18.0) [13.3-23.9]	.01

JAMA | Origina

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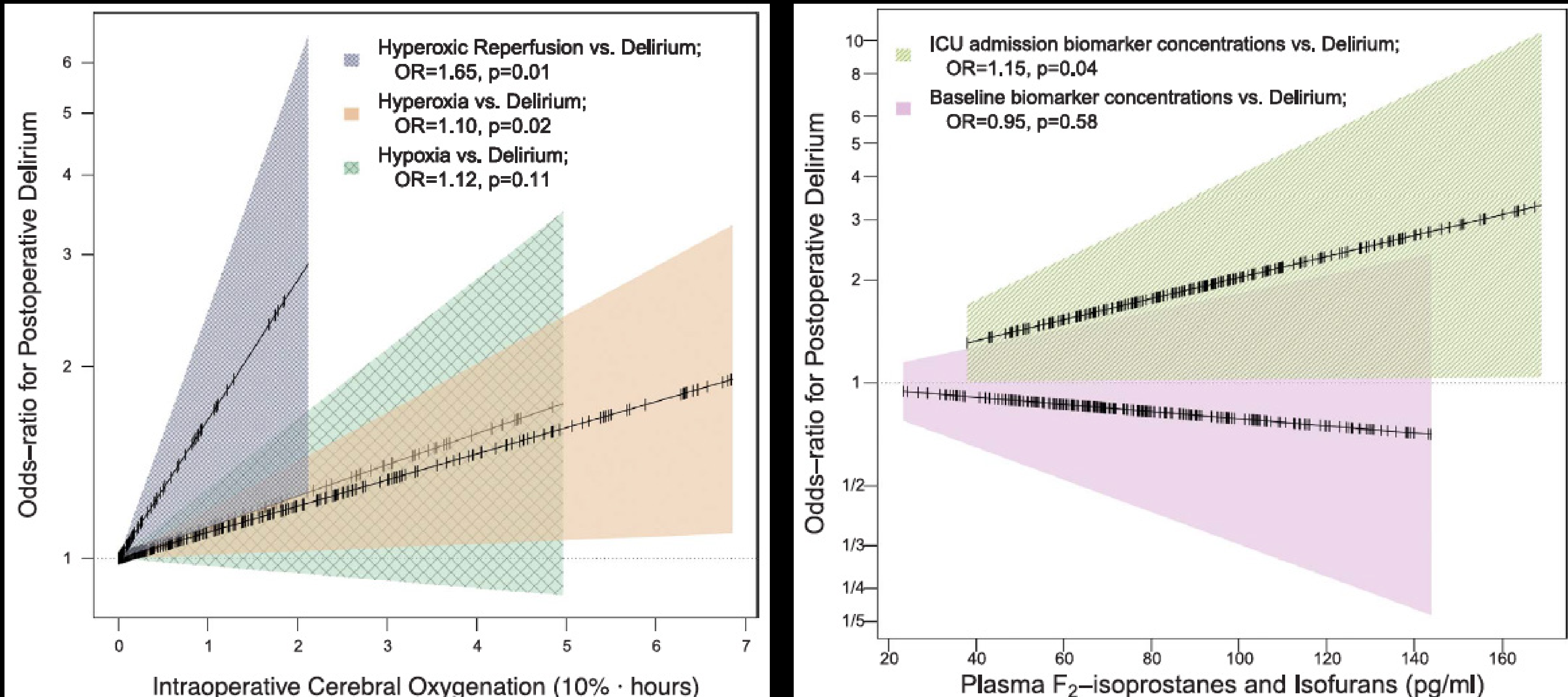
Didier Keh, MD; Eve … olger Bogatsch, MD;
Josef Briegel, MD; C … D; Lars Hüter, MD;
Andreas Meier-Hell … hael Oppert, MD;
Kerstin Resener, MD … eyland, MD;
Konrad Reinhart, M

6

Oxidative Stress

Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery

Marcos G. Lopez[a], Pratik Pandharipande[a], Jennifer Morse[c], Matthew S. Shotwell[c],



Partial mediation effect noted

Free Radical Biology and Medicine 103 (2017) 192–198

7

Network Connectivity

Network Disconnectivity Hypothesis

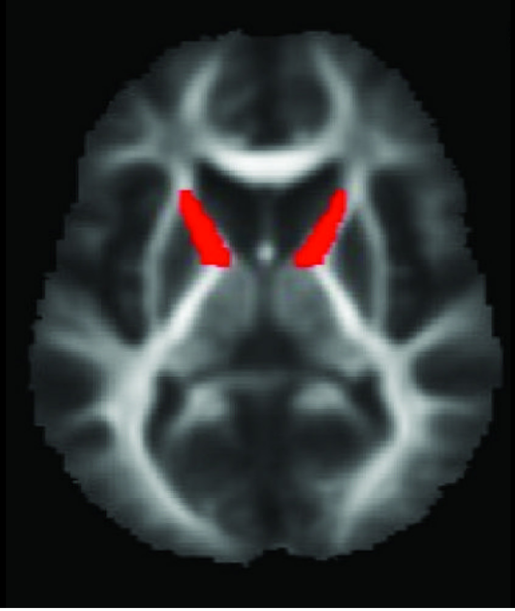
- Brain is highly organized and interconnected
- Complex integration of sensory information and motor responses
- Delirium represents a failure in integration and processing and an acute breakdown in network connectivity
- Baseline network connectivity (age, cognition) and inhibitory tone determined by neurotransmitter availability

Maldonando J. Int J Geriatr Psychiatry 2017

Decreased Functional Connectivity and Disturbed Directionality of Information Flow in the Electroencephalography of Intensive Care Unit Patients with Delirium after Cardiac Surgery

(ANESTHESIOLOGY 2014; 121:328-35)

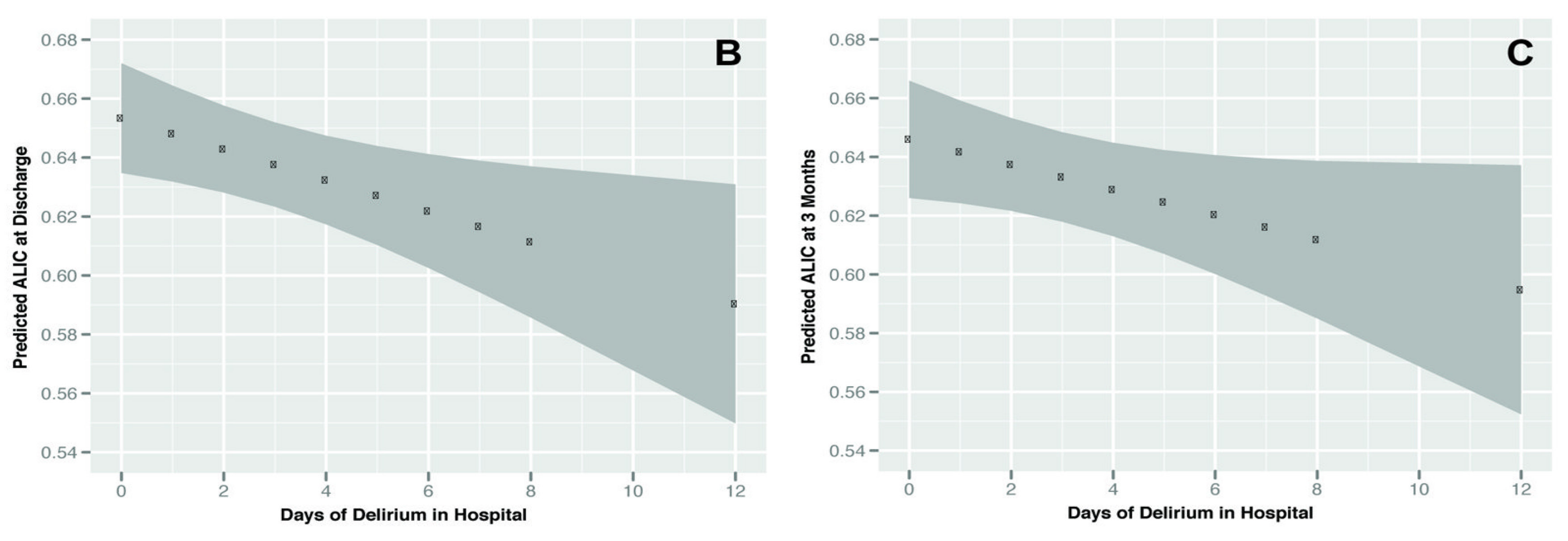
- Delirium associated with a decrease in alpha power and increase in δ power
- Measured Phase Lag Index (PLI)- estimates synchronization or the average connectivity strength between EEG channels for a particular band
- Mean phase lag index was lower in the α band (8 to 13 Hz) in patients with delirium
- δ Band–directed phase lag index was lower in anterior regions and higher in central regions in delirious patients indicating higher information flow toward anterior regions in the δ band.



White Matter Integrity and Delirium

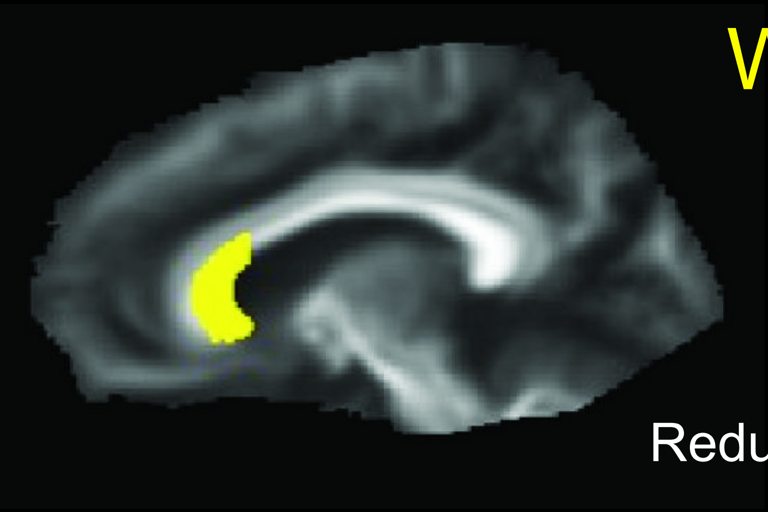
Anterior limb of the internal capsule

Reduced fractional anisotropy = white matter disruption



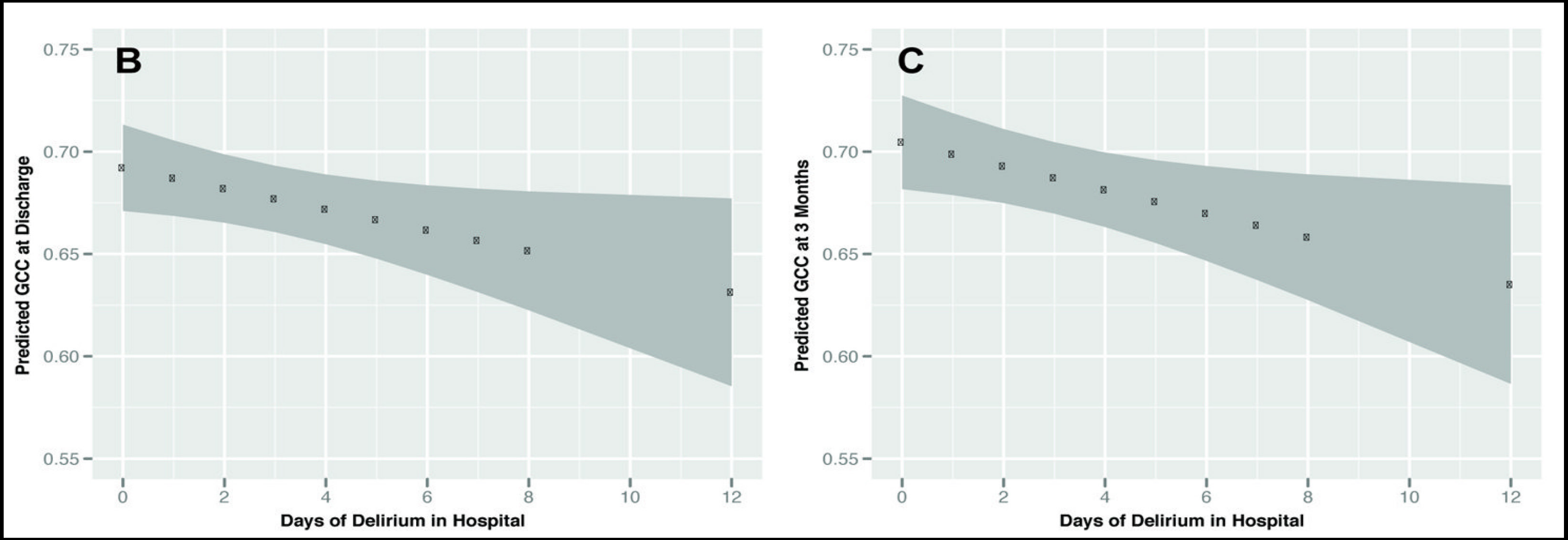
Morandi A M et al. *CCM* 2012;40:2182-9.

White Matter Integrity and Delirium



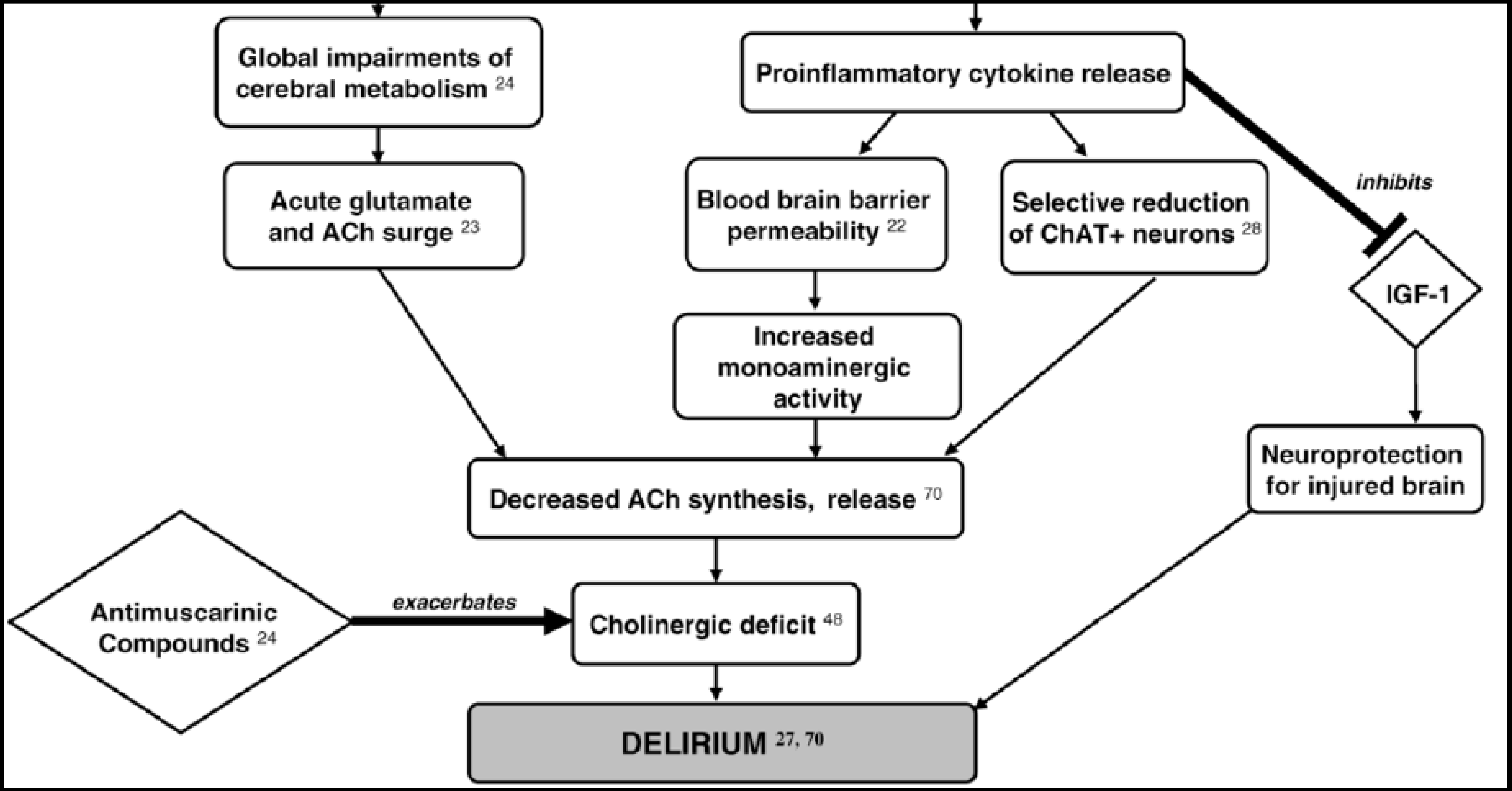
Genu of the corpus callosum

Reduced fractional anisotropy = white matter disruption



Morandi A M et al. *CCM* 2012;40:2182-9.

Delirium: Complex interplay of numerous mechanisms



Hshieh T et al. J Gerontol A Biol Sci Med Sci. 2008; 63(7): 764–772.

Questions?

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