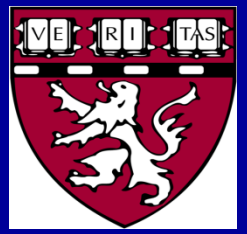

Delirium: What is it, and what do we (not) know about it?

Edward R. Marcantonio, M.D., S.M.

Professor of Medicine

Harvard Medical School

Beth Israel Deaconess Medical Center

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Plan

- Delirium: What is it?
  - Historical Perspective
  - Geriatric syndrome
- What do we (not) know about it?
  - Assessment and Diagnosis
  - Epidemiology
  - Mechanisms
  - Interventions

Delirium: What is it?

Historical perspective

Delirium: early descriptions

Celsus, 1st Century:

> “Sick people, sometimes in a febrile paroxysm, lose their judgment and talk incoherently… when the violence of the fit is abated, the judgment presently returns…”

Synonyms: Peer-reviewed literature

- Acute confusional state
- Acute mental status change
- Altered mental status
- Toxic/metabolic encephalopathy
- Sundowning
- Subacute befuddlement

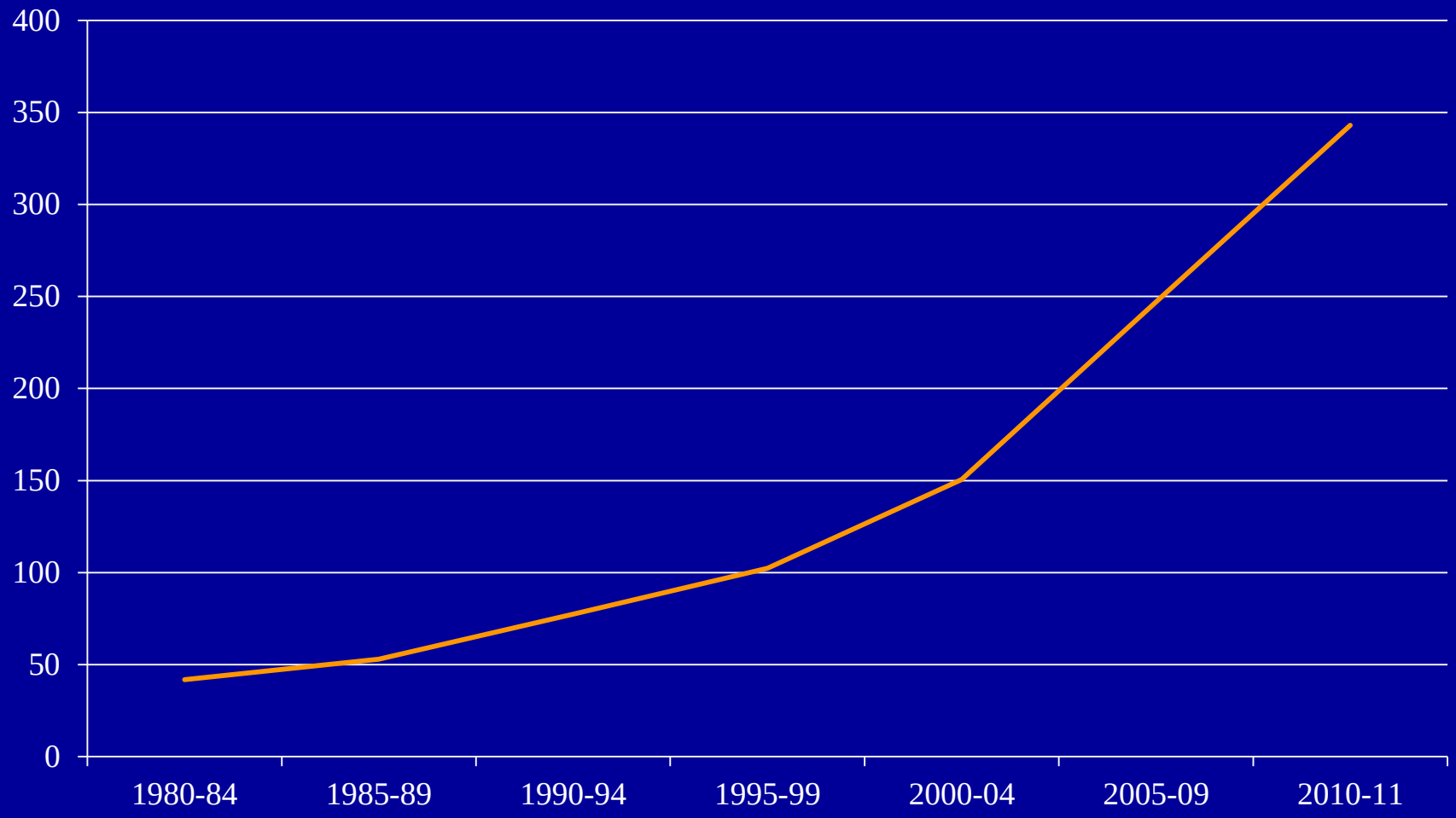
Multiple names still cause confusion across disciplines

Francis et. al., JGIM, 1990

Delirium Timeline

Years	Event
1980	Delirium first appears in DSM 3
1980's	Delirium research takes off
1990	Publication of the CAM
Early 1990's	Publication--predictive models
Late 1990's	Publication--intervention studies
2000's	ICU Delirium, Long term effects
2010's	First NIH P01, ADS founded, Several intervention trials launch

Articles Published on Delirium Per Year



What is delirium in DSM5?

- Disturbance in attention and awareness (reduced orientation to the environment)
- Develops acutely and tends to fluctuate
- An additional disturbance in cognition, (e.g., memory deficit, language, visuoperceptual)
- Not better explained by a preexisting dementia
- Not in face of severely reduced level of arousal or coma
- Evidence of an underlying organic etiology or etiologies

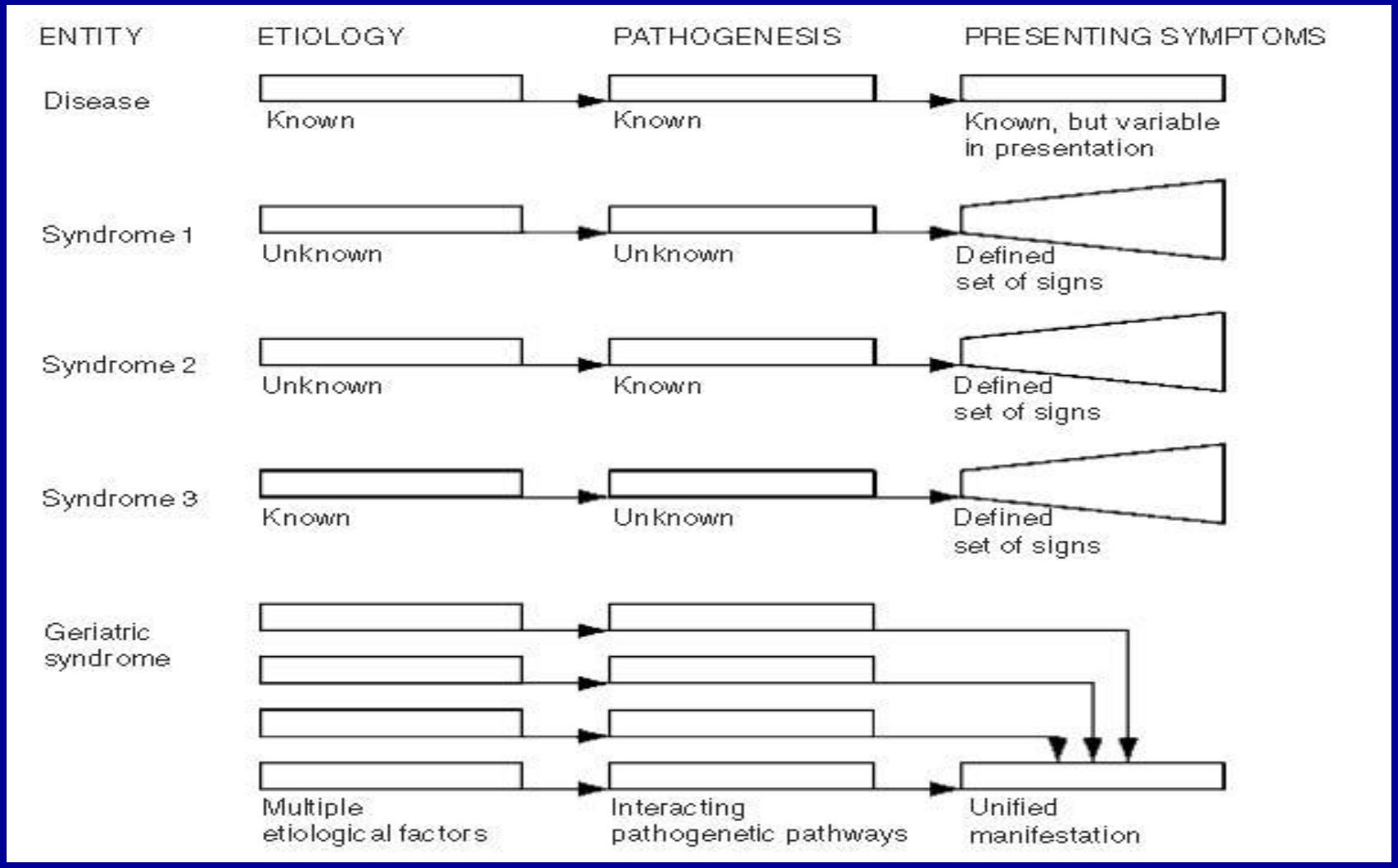
Delirium

Geriatric Syndrome

Delirium=Acute brain failure

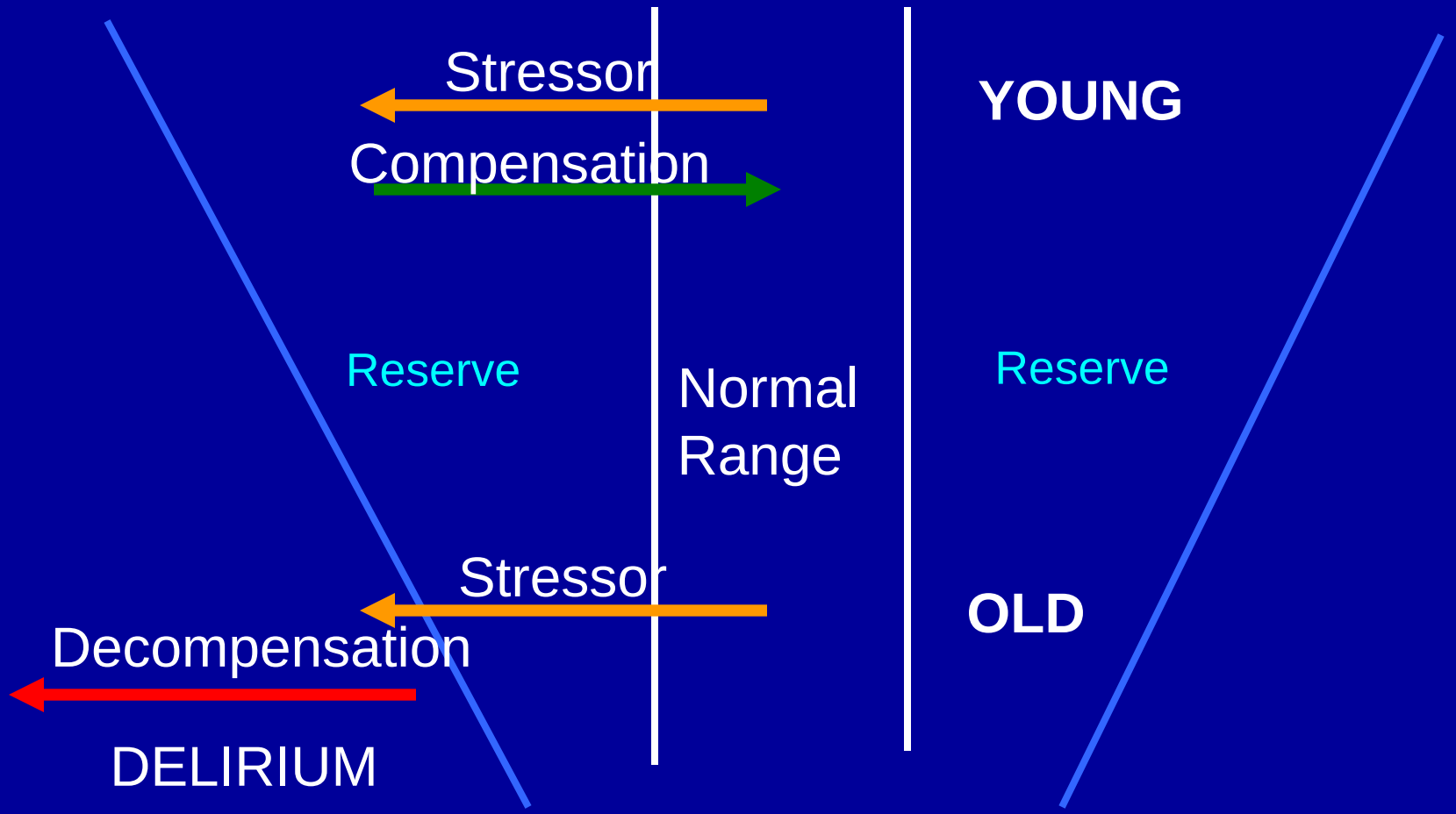
- Caused by exceeding reserve
- Under stress, brain is “weakest link”
  - In others, falls, U.I., may occur
- Multiple contributing etiologies
- Final common pathway of multiple mechanisms

Delirium → Geriatric Syndrome



Inouye, Kuchel et. al., JAGS, 2007

Delirium: ↑ Risk with Aging



Delirium Assessment and Diagnosis

What we know

Delirium Measures

- CAM: Diagnostic Algorithm, Long CAM
- CAM-ICU (B-CAM)
- Symptom checklists: NEECHAM, DOS
- Delirium Severity Measures
  - DRS-98, MDAS, CAM-S

Inouye et. al. Ann Int Med, 1990, Ely et. al., JAMA, 2001, Han et. al., Ann Emerg Med 2013,Neelson, et. al., Nurs Res, 1996, Trzepacz et. al., J Neuropsych 2001, Breitbart et. al. , J Pain Symp Manag, 1996, Inouye et. al, In Press.

CAM Diagnostic Algorithm

- Feature 1: Acute change, fluctuating course
- Feature 2: Inattention
- Feature 3: Disorganized thinking
- Feature 4: Altered level of consciousness

Diagnosis of Delirium: requires presence of Features 1 and 2 and either 3 or 4.

Inouye et. al., Ann Int Med, 1990.

Bedside Delirium Evaluation

- Patient Interview:
  - Symptoms: confusion, perceptual disturbances
  - Cognitive testing: orientation, attention
- Interviewer observations:
  - Altered Level of Consciousness
  - Psychomotor agitation, retardation
- Family/caregiver: time course, acuity
- CAM puts it all together

Phenomenology

- Psychomotor variants:
  - Hyperactive, Mixed: 25%
  - Hypoactive, normal: 75%
- Abnl LOC: Prevalence varies widely
  - Higher in ICU, PACU
- Hallucinations, delusions rare (~10%)
- Delirium superimposed on dementia
  - May account for 50% in some settings

What we don't know

- Which assessments are best suited to which populations?
- Can we use modern measurement theory to improve assessment?
- How to implement case finding on a broad "population" level?
- How to improve documentation?
  - ICD-9 (10) billing codes, EMRs
  - Facilitate large scale QI efforts

Delirium Epidemiology

What we know

Delirium Incidence/Prevalence

Population	Prevalence or Incidence	Rate (%)
Medical Inpatients >70 yrs	Mixed (50:50)	30-40%
Major surgery > 70 yrs	Incidence	15-25%
Hip Fx, CABG > 65 yrs	Incidence	45-55%
Intensive Care Unit > 18 yrs	Mixed	75-80%
Post-acute admits > 70 yrs	Prevalence	15-20%

Inouye et. al., Ann Int Med, 1993; Marcantonio et. al., JAMA, 1994; Marcantonio et. al., JAGS, 2000; Ely et. al., JAMA, 2004; Marcantonio et. al., JAGS, 2010

Delirium Risk Model

Predisposing factors:

- advanced age
- pre-existing dementia
- other CNS diseases
- functional impairment
- multiple comorbidities
- multiple medications
- imp. vision/hearing

Precipitating factors:

- new psychoactive med
- acute medical problem
- exacerbation of chronic medical problem
- stroke
- surgery
- pain

Inouye et. al., JAMA, 1996

Implications of Risk Model

- More baseline vulnerability, less acute precipitants needed
- Acute precipitants rarely in the CNS
- “Law of Parsimony” rarely applies:
  - There is rarely a single cause of delirium
  - C/w geriatric syndrome

Validated Clinical Prediction Rules

Population	Risk Stratification
General Medicine	18X low-high
Non-cardiac surgery	22X low-high
Hip Fracture	10X low-high
Cardiac Surgery	5X low-high

Inouye et. al., Ann Int Med, 1993, JAMA 1996, Kalisvaart, J Am Geriatr Soc, 2006
Marcantonio et. al., JAMA, 1994, Rudolph et.al., Circulation, 2009

Outcomes after Delirium

Short Term Outcomes

- Nosocomial complications: RR=2-5
- In-hospital death: RR=2-20
- Increased LOS: 2-5 days
- Post-acute facility placement: RR=3-5

*Adjusted for age, sex, cognitive impairment, functional impairment, comorbidity, admitting diagnosis

Marcantonio et. al, JAMA, 1994 and others

Long term outcomes

Meta-analysis showed delirium was independently* associated with:

- Mortality for up to 2 years
- Institutionalization for up to 14 months
- New dementia for up to 4 years

*Adjusted for age, sex, cognitive impairment, functional impairment, comorbidity

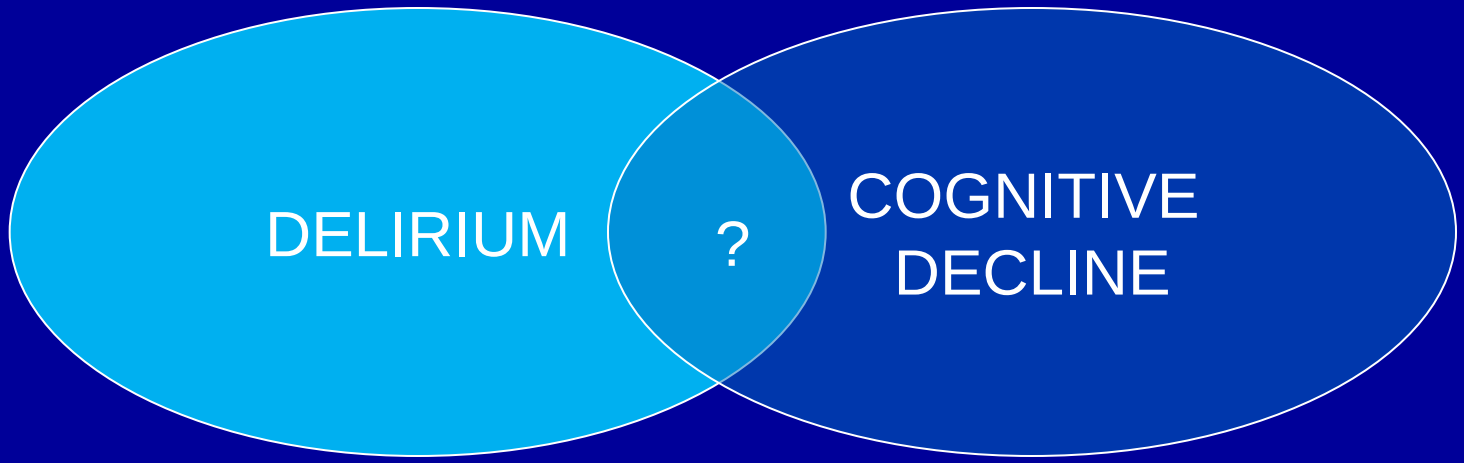
Witlox et. al., JAMA, 2010

Costs

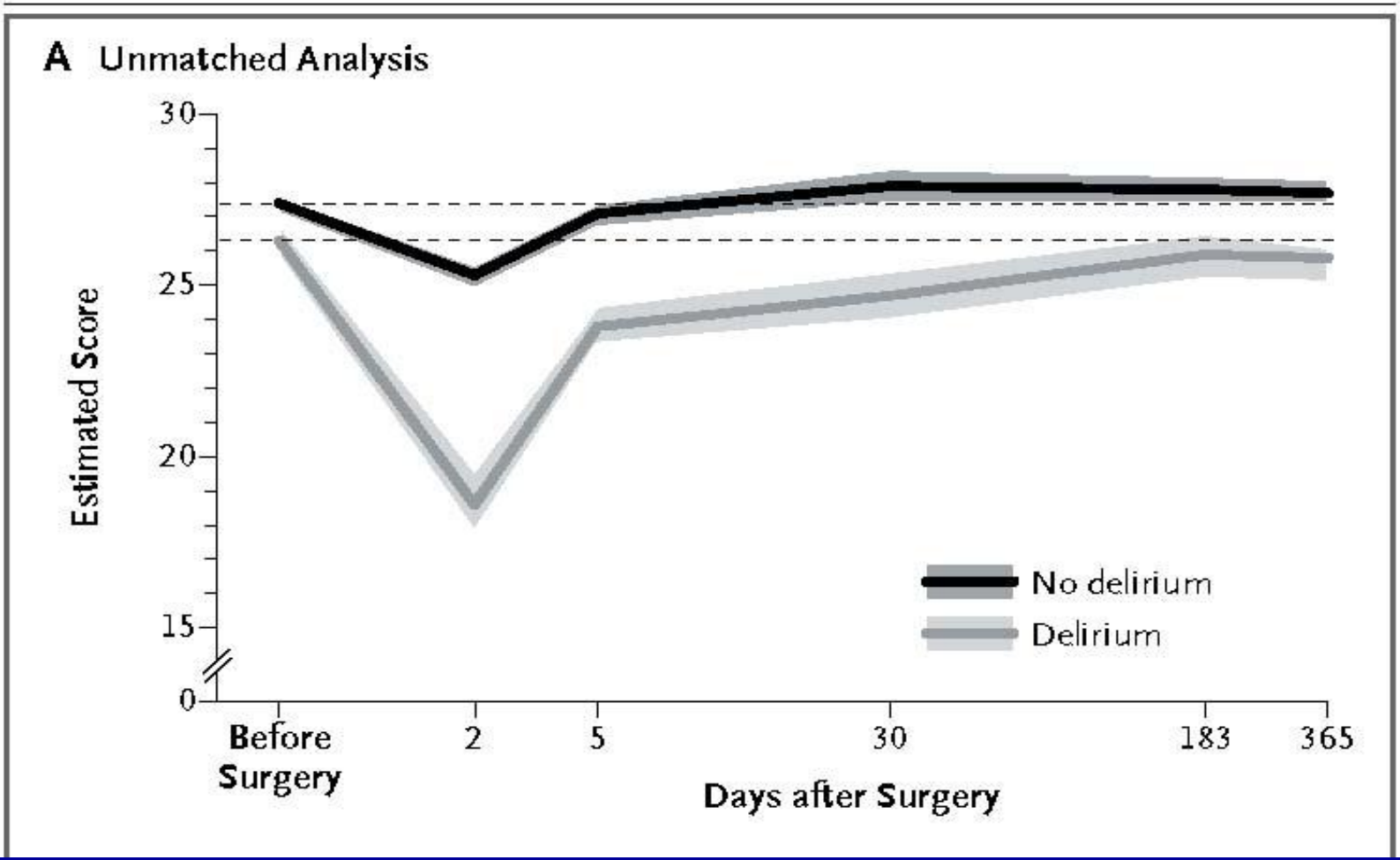
- Delirium → $60,000 incremental costs per patient over subsequent 12 months
- Translates to over $100 billion annually
- Most of these costs after hospitalization
- Increasing importance in ACO era

Leslie, Marcantonio et. al. Medical Care, 2008

Relationship to long term cognition

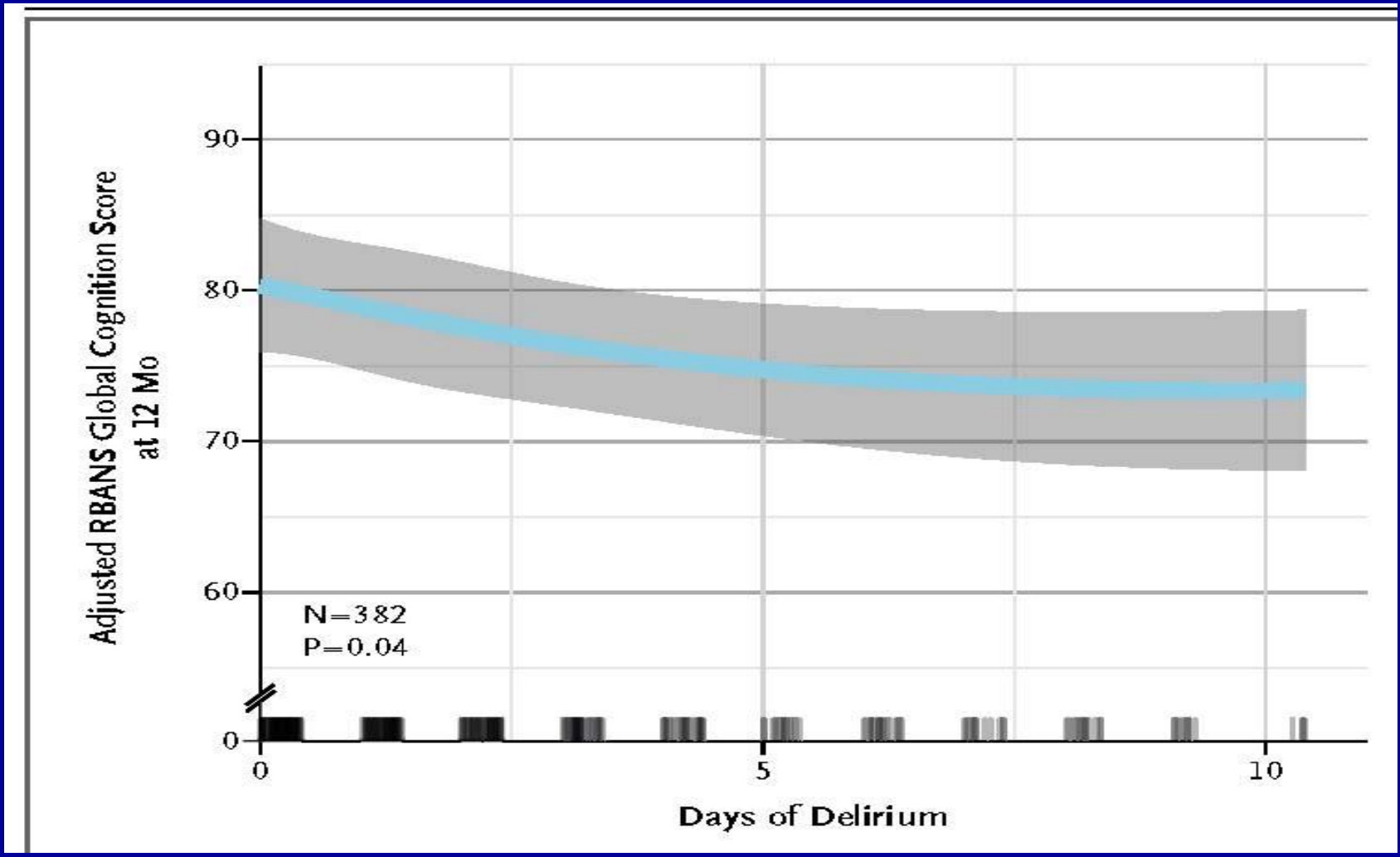


TRACS: Thinking and Recovery after Cardiac Surgery--Delirium, Cognition



Saczynski, Marcantonio et. al., NEJM, 2012

BRAIN-USA: Cognition 12 mos. after ICU



Pandharipande et. al, NEJM, 2013

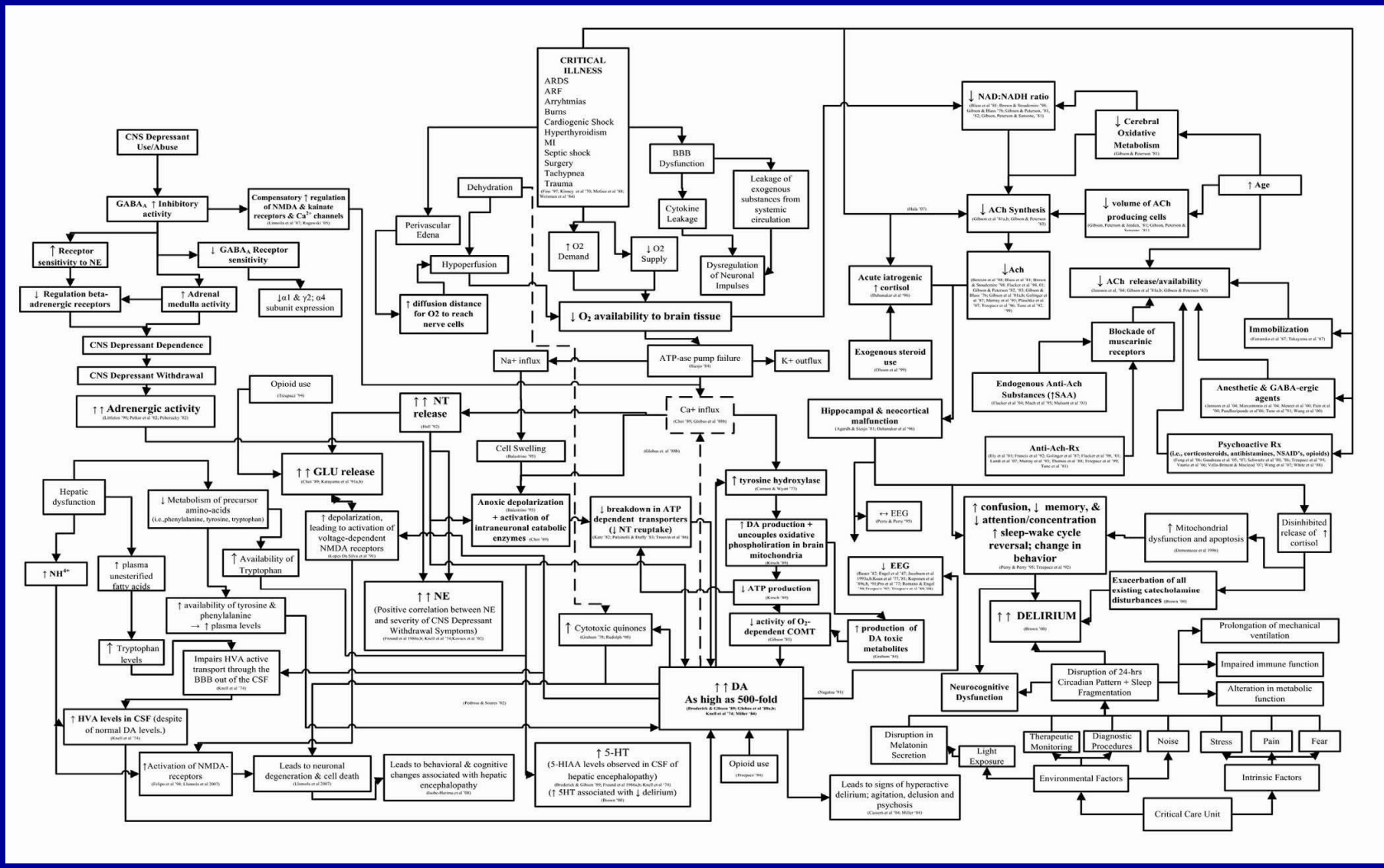
What we don’t know

- Can we implement risk factor models at “point of care” to impact outcomes?
- Can we further improve risk stratification with biomarkers, genes, or imaging?
- What are the mechanisms by which delirium is linked to long term outcomes?
- What is the true relationship between delirium and dementia?

Delirium Mechanisms

What we know

Schematic of Delirium Mechanisms



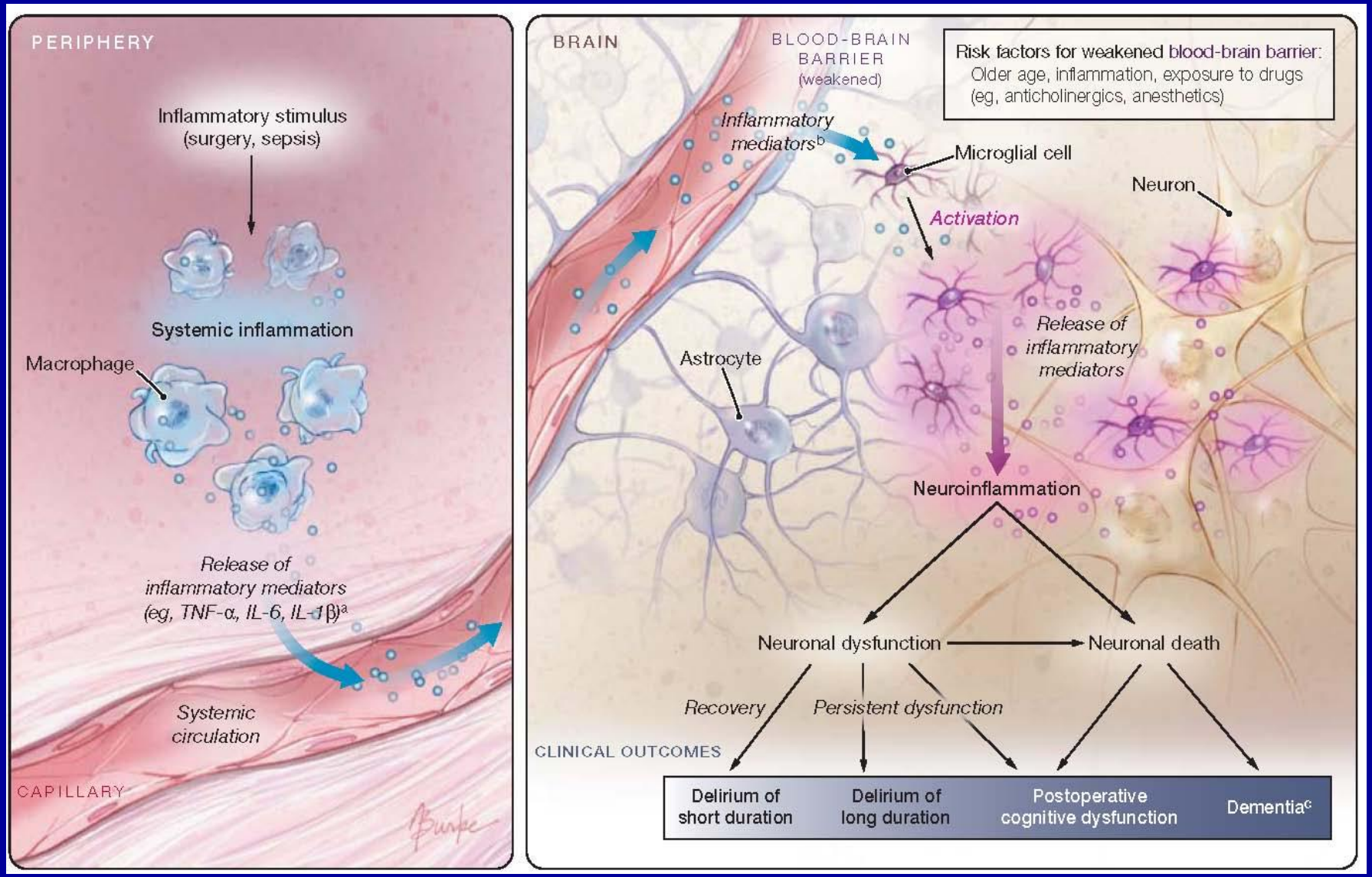
Maldonado, Am J Geri Psych, 2013

Major Mechanistic Models

- Neuro-inflammation
- Neuro-aging (homeostenosis)
- Neuro-endocrine (aberrant stress)
- Neurotransmitter dysregulation
- Oxidative stress
- Sleep/wake dysregulation (melatonin)
- Network disconnectivity

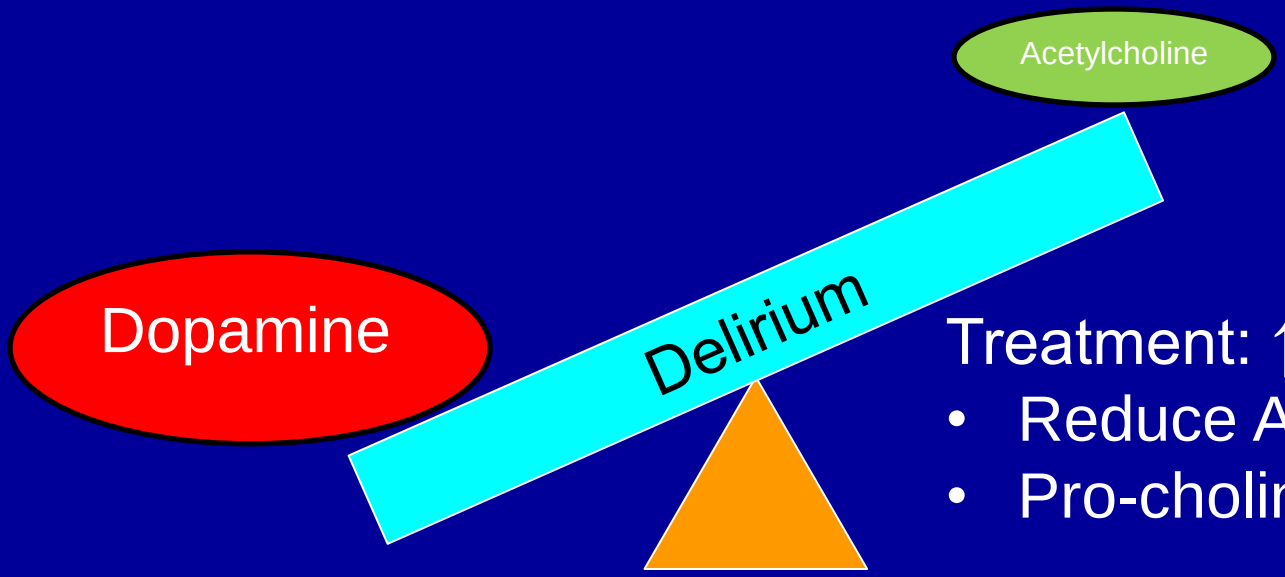
Maldonado, Am J Geri Psych, 2013

Neuroinflammation Hypothesis



Marcantonio et. al. JAMA, 2012

Neurotransmitter Hypothesis (simplified)



Treatment: ↑ Acetylcholine

- Reduce Anti-cholinergics
- Pro-cholinergic drugs

Treatment: ↓ Dopamine

- Reduce dopaminergic drugs
- Antipsychotics

Animal Models

- Necessary to advance basic research
- Several models now developed
- Delirium: “sickness behavior syndrome”

Cons/Caveats:

- Can we truly replicate delirium in an animal?
- Is it possible to create a single model for such a complex syndrome?
- Need to consider issues of aging

What we don’t know

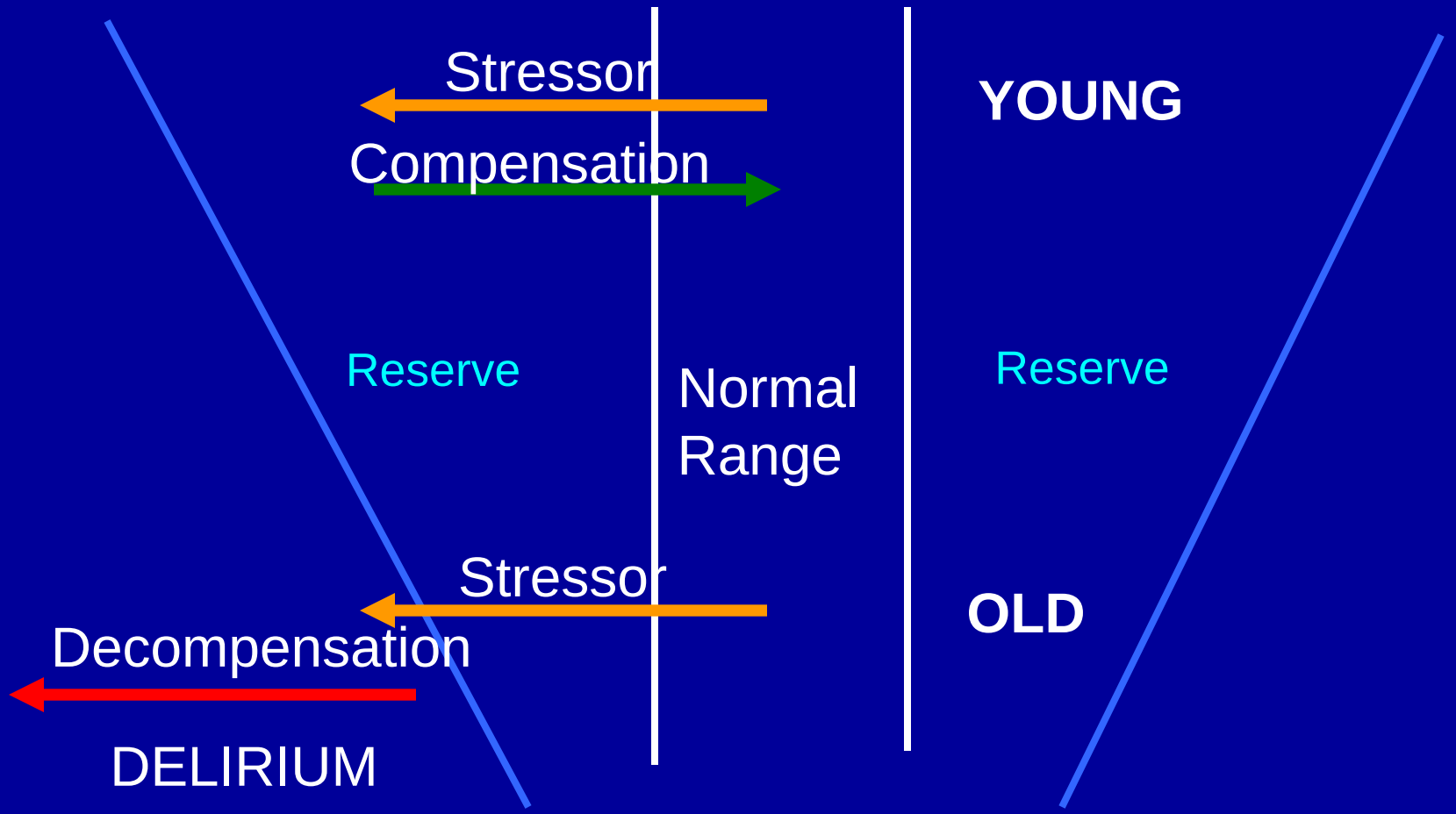
- Of all the postulated mechanisms, are some more prevalent/pertinent?
- Can we match mechanisms to delirium phenotypes?, to patients?
- Can we create animal models that inform the human condition?
- Given its complexities, can a coherent picture of the “whole elephant” emerge?

Delirium Interventions

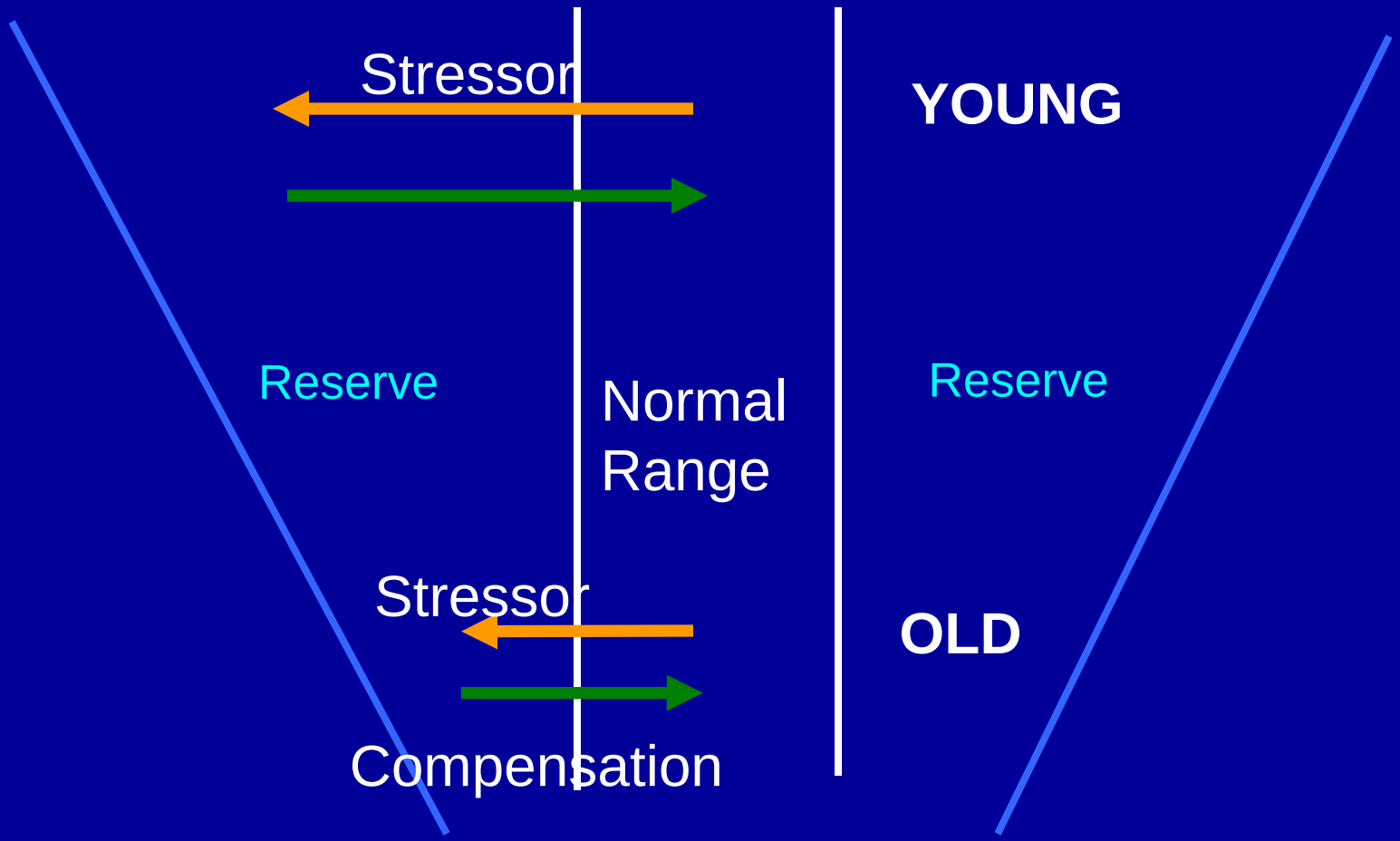
What we know

Delirium Prevention

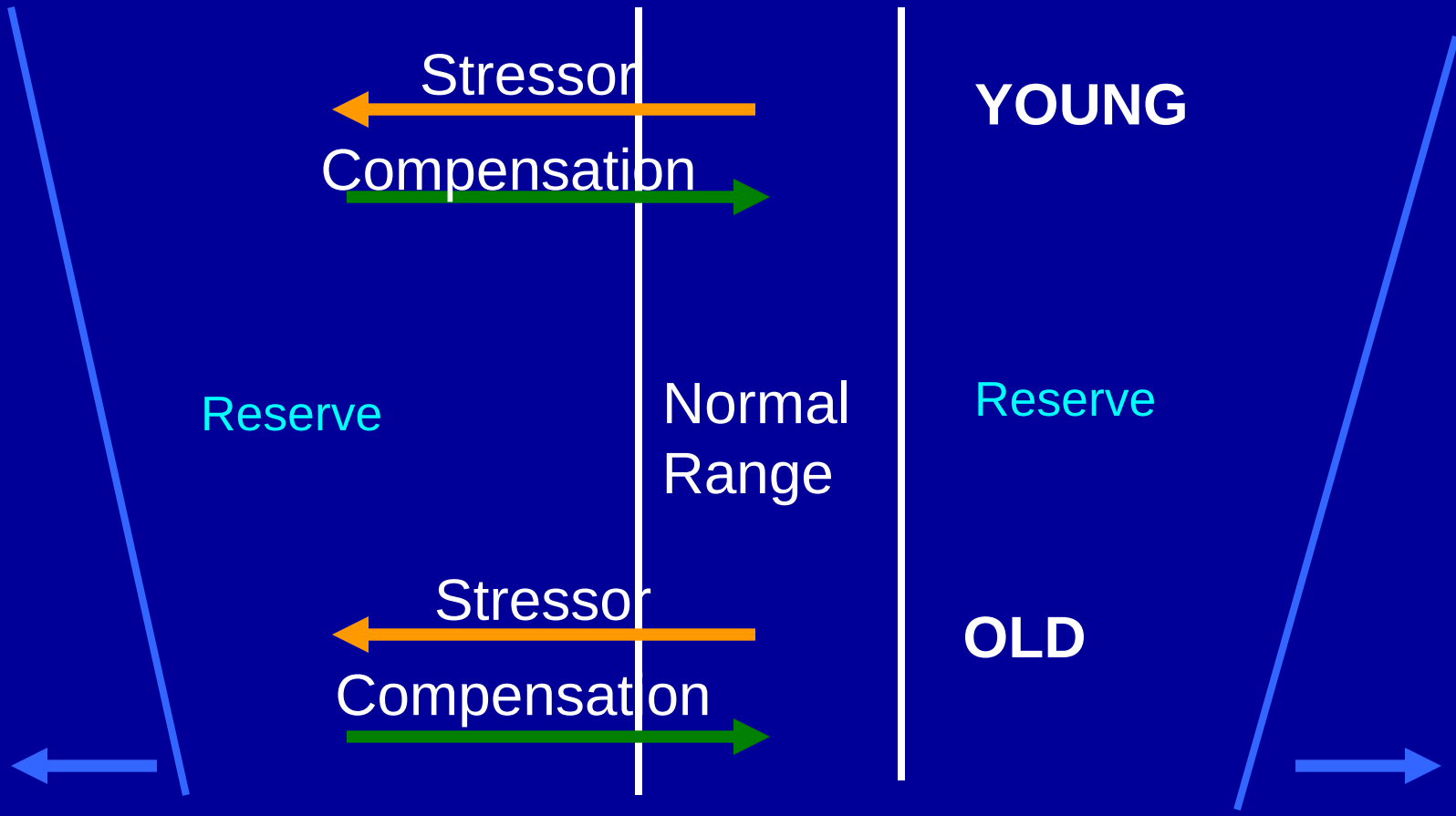
Homeostenosis: Implications for Prevention



Reduce Stressors



Increase Reserve



Multicomponent Prevention

Approach	Evidence
HELP	Targeted 6 Delirium Risk Factors Reduced delirium by 40% Disseminated (>100 centers)
Proactive Consultation	10 Modules targeting Delirium Risk Reduced delirium by 36%
Patient Centered Care	Care: task allocation→ individualized Reduced delirium duration, LOS

Inouye et. al. NEJM, 1999, Rubin et. al. JAGS 2011, Marcantonio et. al. JAGS, 2001, Lundstrom et. al., JAGS, 2005

Single Component Prevention

Approach	Evidence
Antipsychotics (low dose)	Mixed (benefit/harm)
Dementia Drugs	No benefit
Reducing sedation, surgery	Preliminary benefit
Reducing sedation, ICU	Benefit
Blood transfusion, Hgb=10	No benefit

Kalisvaart et. al., JAGS, 2005, Larsen et. al., Psychosomatics, 2010; Wang et. al., Crit Care Med. 2012; Hshieh et. al, J Gerontol Med Sci. 2008; Liptzin et. al. Am J Geriatr Psych. 2005; van Eijk, et. al., Lancet, 2010; Marcantonio, et. al., J Am Geriatr Soc., 2011; Seiber et. al, Mayo Clin Proc., 2009; Pandaharipande et. al. JAMA. 2007; Riker et. al. JAMA. 2009; Maldonado et. al., Psychosomatics 2009; Schweickert et. al., Lancet, 2009, Needham et. al., Arch Phys Med Rehab, 2010, Gruber-Baldini et. al., JAGS, 2013.

Summary of Prevention

- Multifactorial strategies work
  - Multiple small interventions yield big results
  - Key: fidelity to intervention program
  - Little ongoing work in this area (why?)
- Single component interventions
  - ↓ drugs: effective
  - Other single mechanism targets: mixed
- Little work: ↑ Reserve

Delirium Treatment and Rehabilitation

Multicomponent Treatment (Acute)

Intervention	Results
Systematic detection of delirium, Specialized care	Trend toward quicker cognitive improvement
Comprehensive Geriatrics Assessment, Specialized Management	Reduced delirium severity and duration
“Delirium Room”	Reduced use of sedating meds; equally safe outcomes

Cole et. al. CMAJ. 2002; Pitkala et. al. J Gerontol Med Sci. 2006; Flaherty et. al., J Am Geriatr Soc, 2003.

Single Component (Drug) "Treatment"

- What (and who) are we treating?
- Existing literature:
  - Antipsychotics pref. to benzodiazepines (most cases)
  - Atypicals: equivalent to haloperidol
  - Reduced delirium severity: hyperactive → hypoactive?
- New placebo controlled trials:
  - Several ongoing, primarily in the ICU
  - First just published: "haloperidol did not modify duration of delirium in critically ill patients"

Lacasse et. al., Ann Pharm, 2006; Multiple Cochrane systematic reviews; Page, et. al. Lancet Resp Med, 2013

Commonly used drugs
(all “off label”)

Drug/Route	Starting Dose	Sedation	EPS
Haloperidol PO, IV	0.25-2 mg	+	++++
Risperidone PO, IV	0.25-2 mg	+	+++
Olanzapine PO, SL, IM, IV	2.5-10 mg	++	++
Quetiapine PO	12.5-50 mg	++++	+

Marcantonio, Ann Int Med, 2011

Delirium Rehabilitation

- Substantial fraction of delirium persists
- Even if resolved, cognitive deficits persist
- Goal of programs:
  - Assess delirium perpetuating factors and eliminate as possible
  - Cognitive rehabilitation
  - Physical rehabilitation
- Several trials ongoing in post-acute and outpatient settings

What we don't know

- How can we more effectively disseminate proven multifactorial strategies?
  - Adding effective single component interventions
- Can we design/test new interventions?
  - to improve reserve?
  - for delirium rehabilitation?
- Can we create research networks to facilitate testing of complex interventions?
- How do we get delirium on the radar screen of large healthcare organizations?

U13 Conference Sessions

- Delirium as a Geriatric Syndrome
  - Parallels to Sleep, Voiding Dysfunction
- Psychoneuroimmunology
- Delirium and dementia: same or different?
- Delirium in vulnerable older adults: frailty, multi-morbidity, anesthesia
- Interventional research

U13 Conference Structure

- Large groups:
  - 20 minute talks
  - 5 minutes for questions
- Discussion time: large and small group
- Mentoring program
- Make connections: move the field forward