Introduction : **Psychoneuroimmunology and Delirium**

Stress and medical/surgical illness and Sickness Syndrome

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DISCLOSURES

Funding from National Institutes of Health

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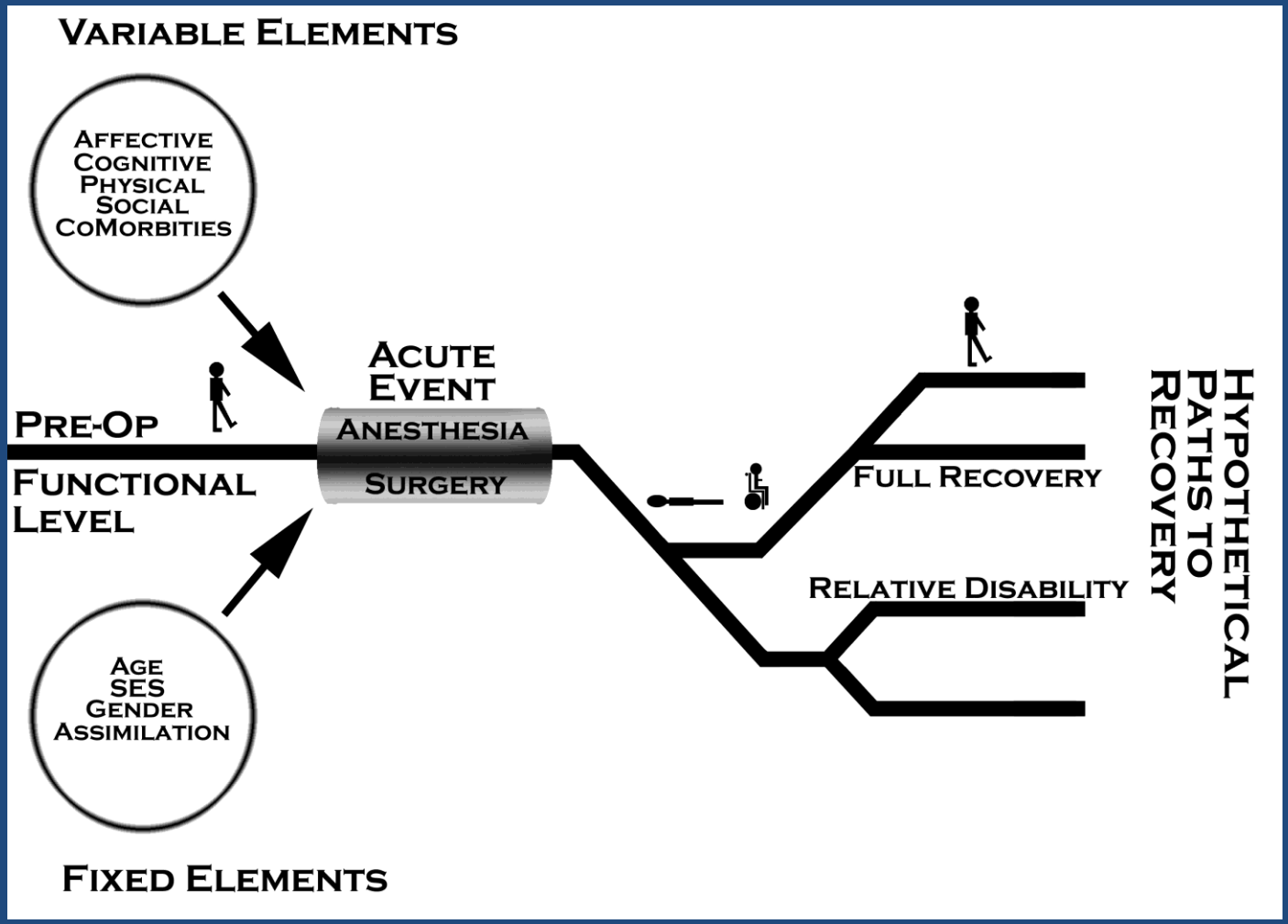
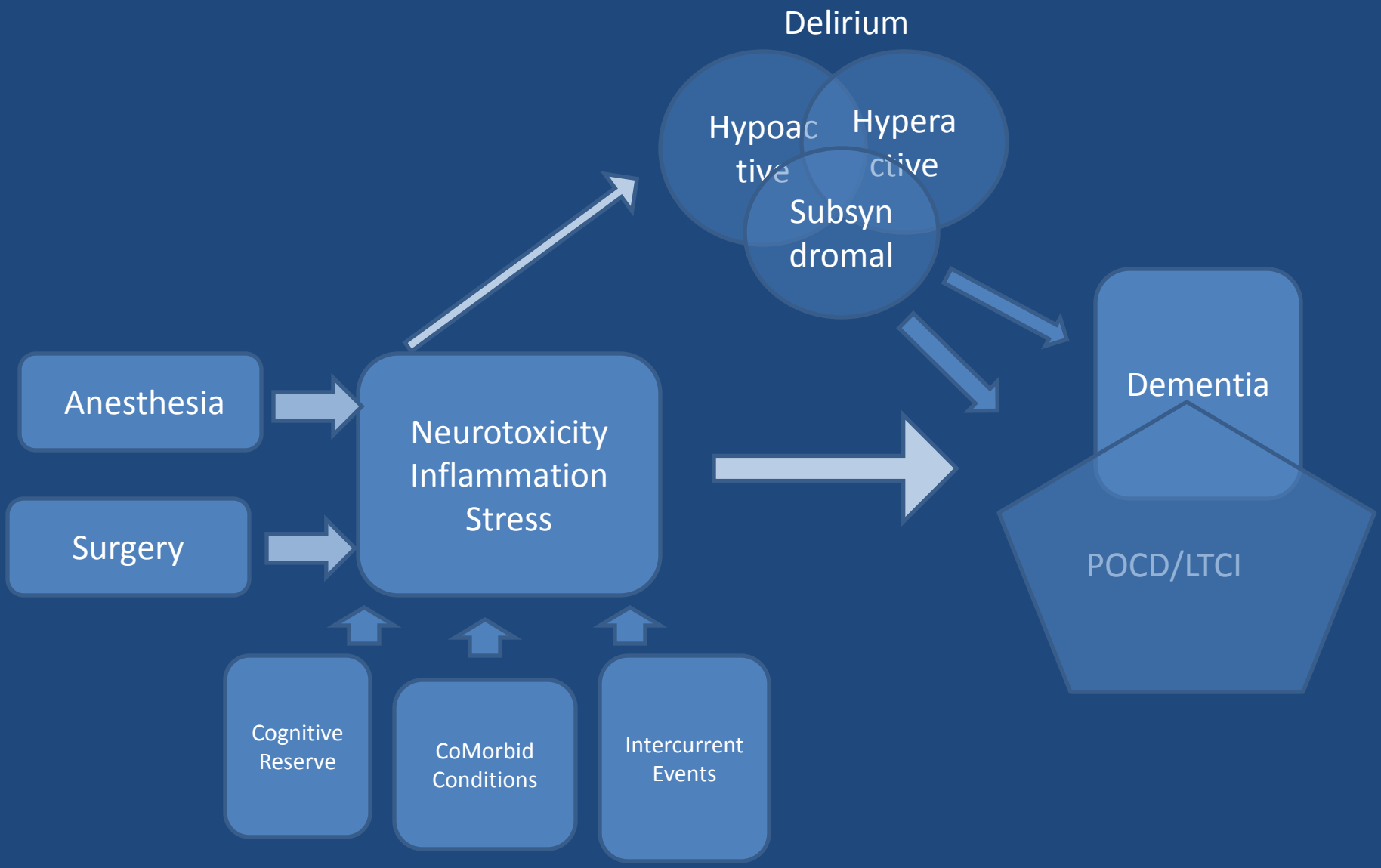
Drug from Hospira, Inc
Monitors and probes from CasMed
Monitors and probes from Covidean

S. Deiner, MD

Model of Functional Recovery Following Anesthesia and Surgery




Delirium
Hypoac
tive
Hypera
ctive
Subsyn
dromal
Anesthesia
Surgery
Neurotoxicity
Inflammation
Stress
Dementia
POCD/LTCI
Cognitive
Reserve
CoMorbid
Conditions
Intercurrent
Events

Setup

- History
- Caveats
- Background

Claude Bernard (1813 – 1878)

- Blind experiments
- When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted.

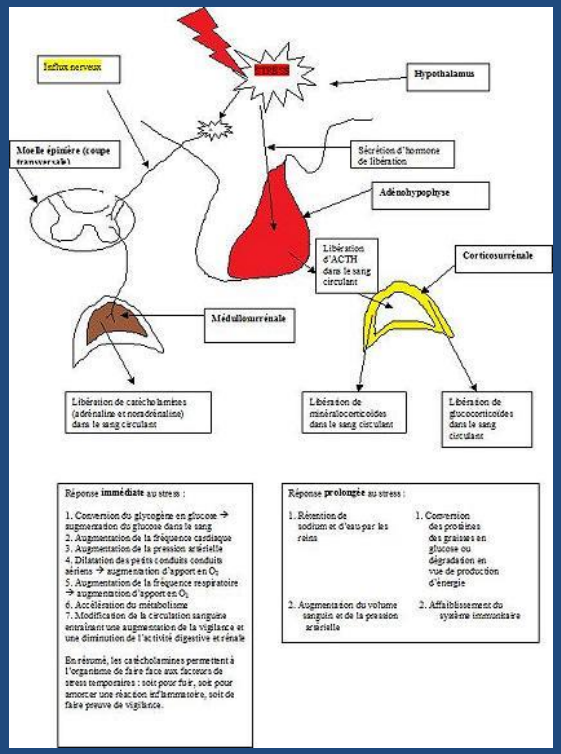
- *milieu intérieur*
- The stability of the internal environment is the condition for the free and independent life.
- Sickness and death are only a dislocation or perturbation of that mechanism

Walter Bradford Cannon (1871-1945)

- In his work with animals he observed that any change of emotional state in the beast, such as anxiety, distress, or rage was accompanied by total cessation of movements of the stomach
- Terms:
  - Fight or flight
  - homeostasis

Hans Hugo Bruno Selye (1907-1982)

- **General Adaptation Syndrome**.
- This syndrome consists of an enlargement of the adrenal gland, atrophy of the thymus, spleen and other lymphoid tissue, and gastric ulcerations.
- **Its not stress that kills us, it is our reaction to it.**



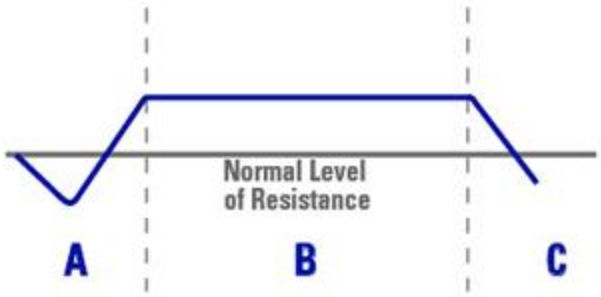


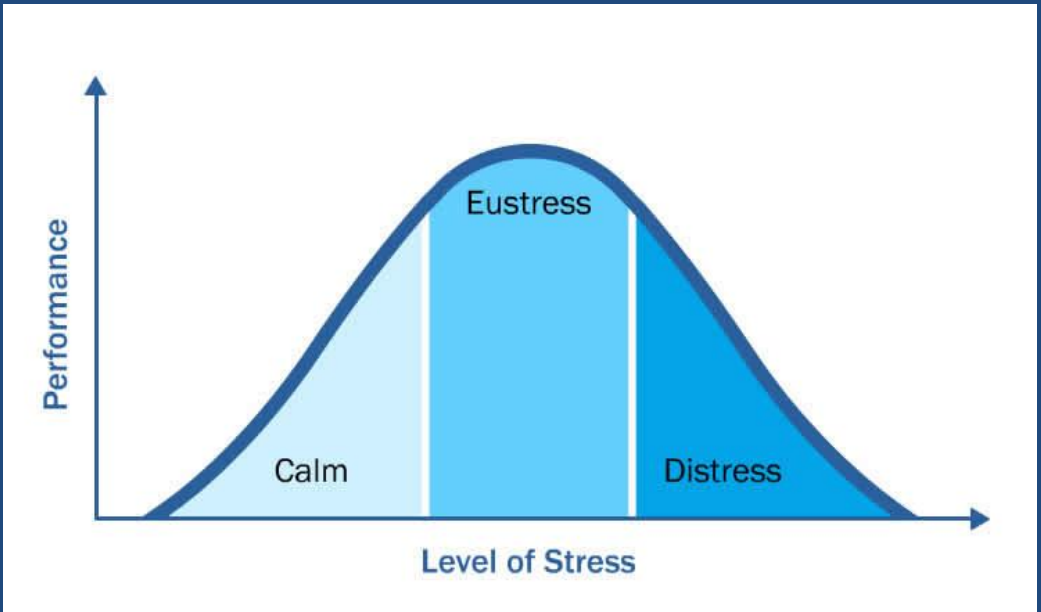
Figure 1. The three phases of the general adaptation syndrome (GAS) (Selye, 1974).

A. Alarm reaction. The body shows the changes characteristic of the first exposure to a stressor. At the same time, its resistance is diminished and, if the stressor is sufficiently strong (severe burns, extremes of temperature), death may result.

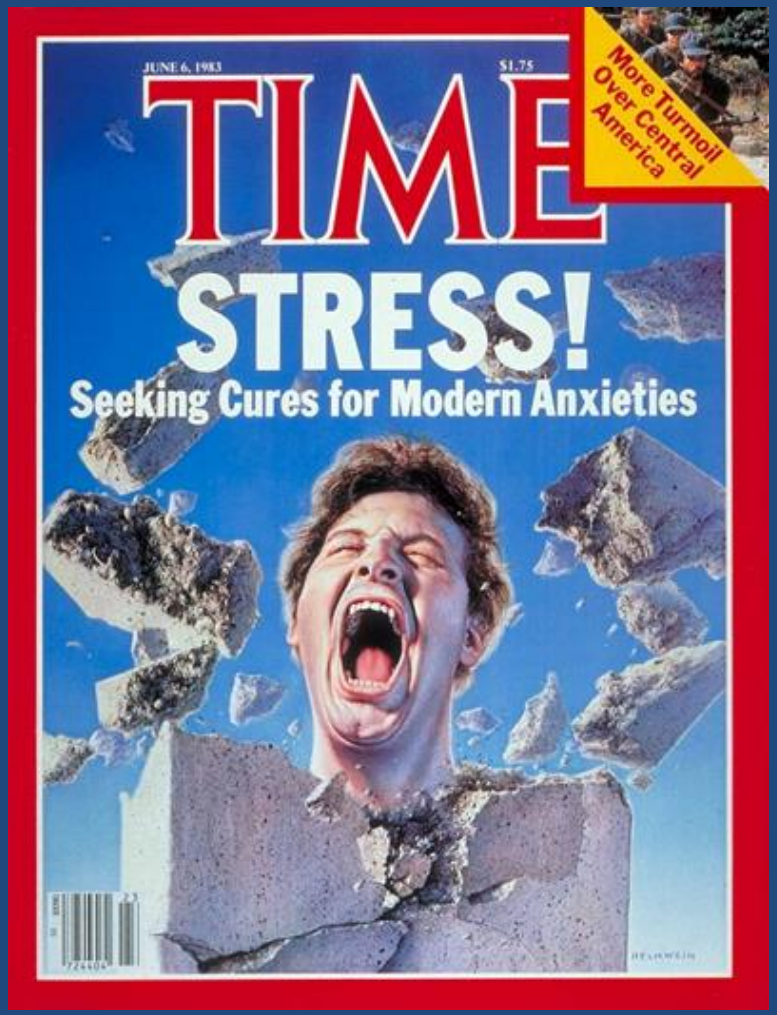
B. Stage of Resistance. Resistance ensues if continued exposure to the stressor is compatible with adaptation. The bodily signs characteristic of the alarm reaction have virtually disappeared, and resistance rises above normal. If this stage is prolonged, hyperadaptosis occurs.

C. Stage of Exhaustion. Following long-continued exposure to the same stressor, to which the body had become adjusted, eventually adaptation energy is exhausted. The signs of the alarm reaction reappear, but now may be irreversible, and the individual may experience symptoms of adrenal failure.

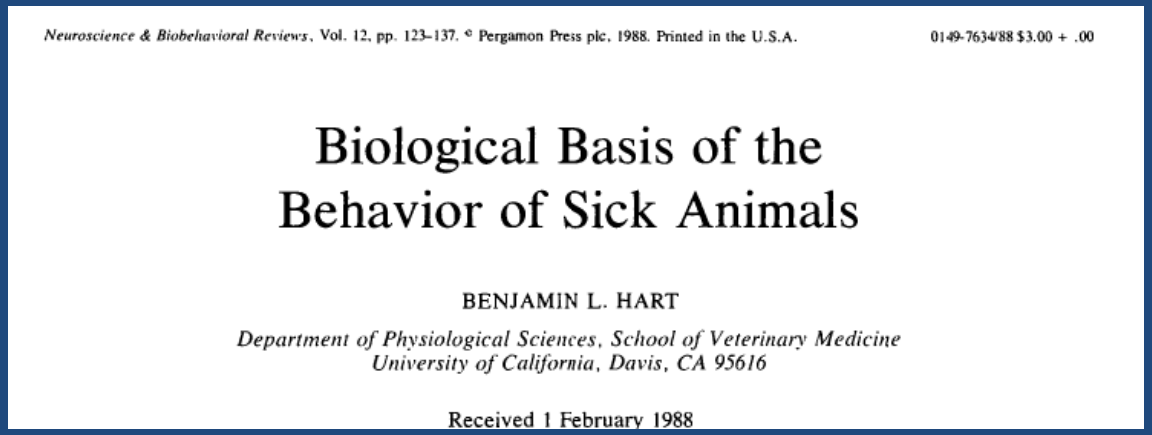
Stress



June 6, 1983


JUNE 6, 1983
$1.75
TIME
More Turmoil Over Central America
STRESS!
Seeking Cures for Modern Anxieties

Sickness Behavior



Neuroscience & Biobehavioral Reviews, Vol. 12, pp. 123–137. © Pergamon Press plc, 1988. Printed in the U.S.A. 0149-7634/88 $3.00 + .00

Biological Basis of the Behavior of Sick Animals

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University of California, Davis, CA 95616

Received 1 February 1988

The most commonly recognized behavioral patterns of animals and people at the onset of febrile infectious diseases are **lethargy, depression, anorexia, and reduction in grooming**. Findings from recent lines of research are reviewed to formulate the perspective that the behavior of sick animals and people is not a maladaptive response or the effect of debilitation, but rather an organized, evolved behavioral strategy to facilitate the role of fever in combating viral and bacterial infections. The sick individual is viewed as being at a life or death juncture and its behavior is an all-out effort to overcome the disease.

Coordinated Physiologic Processes

- Fever
- Pain (hyperalgesia)
- Fatigue
- Cognitive loss
- Anorexia
- Anhedonia
- Social withdrawal

Psychoneuroimmunology

- 1975 Robert Ader and Nicholas Cohen University of Rochester
  - a signal via the nervous system (taste) was affecting immune function.
- 1981 David Felten, Indiana University
  - discovered a network of nerves leading to blood vessels as well as cells of the immune system.
- *Psychoneuroimmunology* - 1981

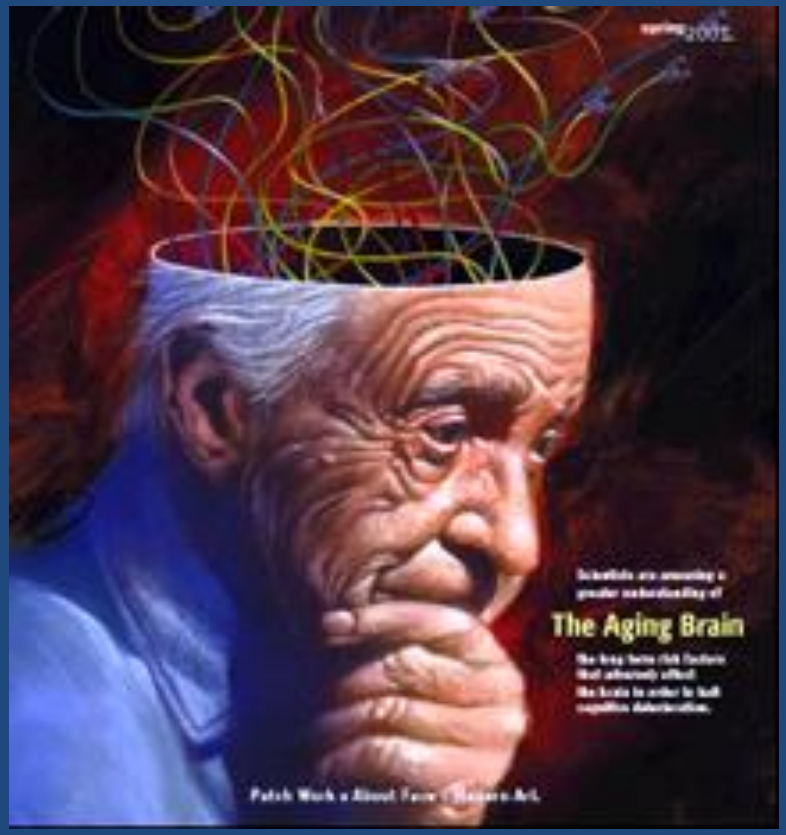
Links to immune function

- Herbert and Cohen in 1993, they examined 38 studies of stressful events and immune function in healthy adults.
  - acute laboratory stressors (e.g. a speech task),
  - short-term naturalistic stressors (e.g. medical examinations)
  - long-term naturalistic stressors (e.g. divorce, bereavement, caregiving, unemployment).
  - Consistent stress-related increases in numbers of total white blood cells, as well as decreases in the numbers of helper T cells, suppressor T cells, and cytotoxic T cells, B cells, and Natural killer cells (NK).

- Zorrilla et al. in 2001, replicated Herbert and Cohen's meta-analysis.
  - analyzed 75 studies of stressors and human immunity.
  - Naturalistic stressors were associated with increases in number of circulating neutrophils, decreases in number and percentages of total T cells and helper T cells, and decreases in percentages of Natural killer cell (NK) cells and cytotoxic T cell lymphocytes.
  - replicated Herbert and Cohen's finding of stress-related decreases in NKCC and T cell mitogen proliferation to Phytohaemagglutinin (PHA) and Concanavalin A (Con A).

Long Term Stress

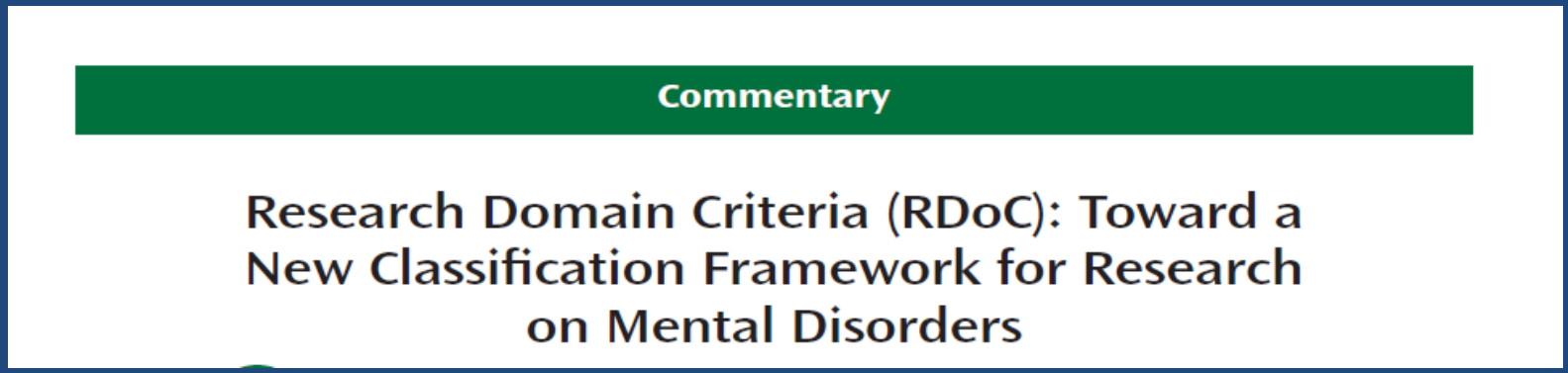
- Sapolsky – glucocorticoid effects on aging brain
- McEwen and Stellar (1993)
  - **allostatic load** : "the wear and tear on the body" which grows over time when the individual is exposed to repeated or chronic stress
  - explains how frequent activation of the body's stress response, essential for managing acute threats, can in fact damage the body in the long run



- History
- Caveats to application in delirium
- Theory of Delirium
- Introduction to context of Sickness and Delirium

Caveats

- Immunoneuropsychiatry ?
  - bi-directional associations between psychological and biological processes
- Limitations of animal models
  - Species differentiation
  - M7
- Diagnostic issues
  - DSMs, different instruments
  - NIMH rejection of DSM V in favor of RDoC
  - Sepsis associated encephalopathy (SAE) and ICD
  - Motoric subtypes? ICU vs. postoperative vs. general?
- Role of Normal (successful) Aging vs. Dementia



Am J Psychiatry 2010;167:748-751. d

- Research approaches for the RDoC project will differ from current practice, which typically constrains study designs not only to a single DSM/ICD patient group but also to particular clinical features.
- The primary focus for RDoC is on neural circuitry, with levels of analysis progressing in one of two directions: upwards from measures of circuitry function to clinically relevant variation, or downwards to the genetic and molecular/cellular factors that ultimately influence such function.
- Research for RDoC can be conceived as a matrix in which the rows represent various constructs grouped hierarchically into broad domains of function (e.g., negative emotionality, cognition).

Encephalopathy pays better than Delirium

Making a clinical distinction between delirium and encephalopathy is very important but can be confusing. From a coding perspective, delirium is classified as a mental disorder or as a symptom; encephalopathy is recognized as a specific neurologic diagnosis that identifies toxic and metabolic states affecting the brain.

For precise documentation and correct coding, the diagnostic term encephalopathy is preferred for describing mental status alteration when due to toxic or metabolic causes. The term delirium is best reserved for psychiatric conditions unrelated to underlying systemic conditions.

"Delirium" (293.0) is considered a nonspecific code by Medicare (and thus, most other payors). Clinically, it is the same as encephalopathy, whether metabolic (348.31) or toxic (349.82). Toxic encephalopathy is secondary to drugs (eg, prednisone, fentanyl, lithium OD, alcohol), while metabolic is pretty much everything else.

Metabolic encephalopathy and toxic encephalopathy are considered more specific diagnoses, meaning you have a better idea of what is causing the pt's delirium. I rarely use the term "delirium" in the chart unless I don't know what is causing it (or I might use the term "encephalopathy" without the qualifier).

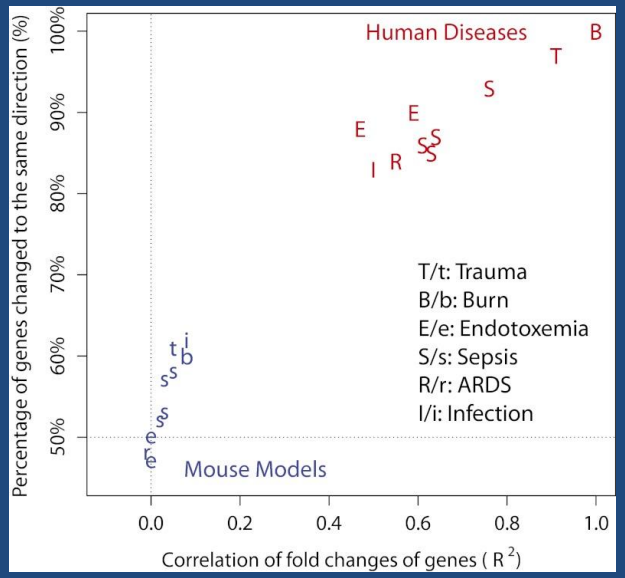
Some payors will not pay for 293.0 because it is considered a "mental disorder", due to its being in the 290-319 ICD-9 range, which are considered Mental Disorders. Like, if they contract with a carve-out company to handle psychiatric claims, then the payor may require the bill goes thru the carve-out.

Finally, in states which use the newer APR-DRGs to pay for inpatient hospital claims, a secondary diagnosis of 348.31 or 349.92 will, in some cases, result in a higher severity level... and thus a higher payment. 293.0 almost never results in a higher severity level.

An inherent assumption in the use of murine models to mimic human systemic inflammation is that the time course of injury and repair between the species is similar. Decisions about timing of sample acquisition, endpoints for analysis, or dosing of drugs are dependent on this assumption.

Genomic responses in mouse models poorly mimic human inflammatory diseases

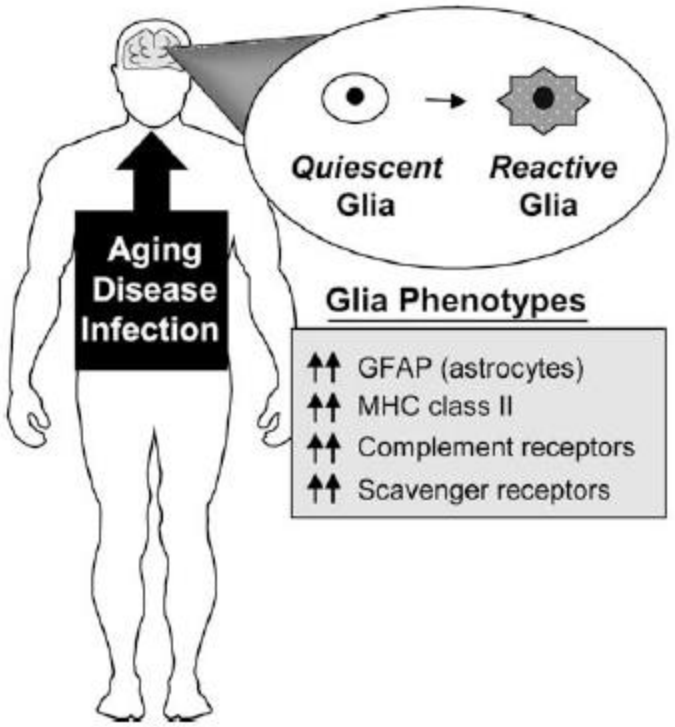
PNAS | February 26, 2013 | vol. 110 | no. 9 | 3507–3512

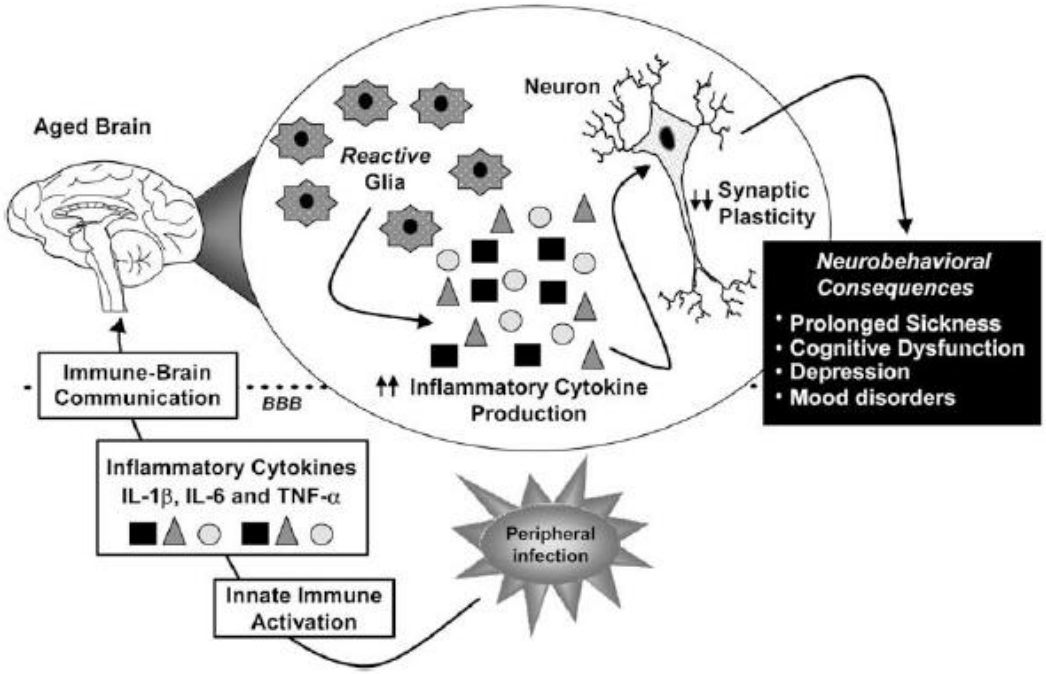


Age and Neuroinflammation: A Lifetime of Psychoneuroimmune Consequences

Jonathan P. Godbout, PhD[a,b,*], Rodney W. Johnson, PhD[c]

Immunol Allergy Clin N Am 29 (2009) 321–337





Brief Communications

Interactive Effects of Stress and Aging on Structural Plasticity in the Prefrontal Cortex

Erik B. Bloss,[1] William G. Janssen,[1] Bruce S. McEwen,[3] and John H. Morrison[1,2]

[1]Fishberg Department of Neuroscience and Kastor Neurobiology of Aging Laboratories, and [2]Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, New York 10029, and [3]Laboratory of Neuroendocrinology, Rockefeller University, New York, New York 10021

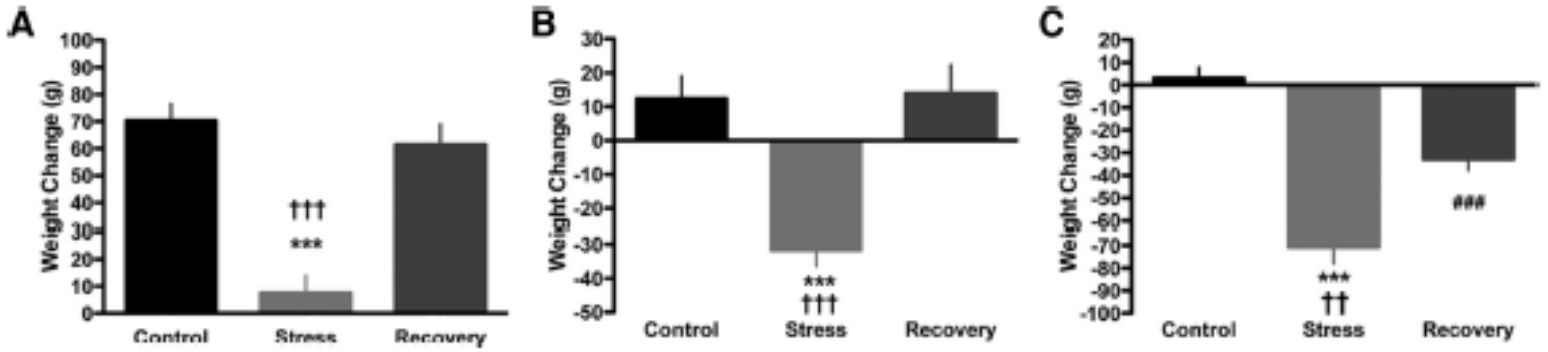


Figure 1. Stress causes body weight alterations at all ages. ***A***, In 3-month-old rats, stress reduced weight gain over the course of the paradigm, which normalized with 3 weeks of recovery. ***B***, In 12-month-old rats, stress caused weight loss that normalized with recovery. ***C***, In 20-month-old rats, stress caused robust weight loss that did not normalize with 3 weeks of recovery. $^{***}p < 0.001$, control versus stress; $^{\dagger\dagger}p < 0.005$, stress versus recovery; $^{\dagger\dagger\dagger}p < 0.001$, stress versus recovery; $^{\#\#\#}p < 0.001$, control versus recovery. Data presented represent group mean ± SEM.

Medical Hypotheses 77 (2011) 140–143

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hypothesis for the pathophysiology of delirium: Role of baseline brain network connectivity and changes in inhibitory tone

Robert D. Sanders *

Baseline Network Connectivity

Inhibitory Tone

Inhibitory Tone

Arousal Tone

Network Connectivity

Baseline

New Injury – decreased adaptability

Inhibitory Tone

- Baseline – changes with age
  - Cognitive Reserve
  - Early or developed dementia
- Alteration of inhibitory tone
  - Anesthetics and other drugs (GABA)
  - Inflammation
  - Sleep disruption
  - Metabolic abnormalities

Cytokine Dysregulation, Inflammation and Well-Being

Ilia J. Elenkov[a, d] Domenic G. Iezzoni[b] Adrian Daly[e] Alan G. Harris[b]
George P. Chrousos[c]

[a]Division of Rheumatology, Immunology and Allergy, Georgetown University Medical Center, Washington, D.C.,
[b]Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough Co., Kenilworth, N.J., and
[c]National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md., USA;
[d]San Raffaele Research Center, Rome, Italy; [e]University of Liege, Liege, Belgium

Review

Neuroimmunomodulation 2005;12:255–269
DOI: 10.1159/000087104

Received: March 17, 2005
Accepted after revision: April 7, 2005

- the acute-phase reaction
- Sickness behavior
- the pain program
- the stress response

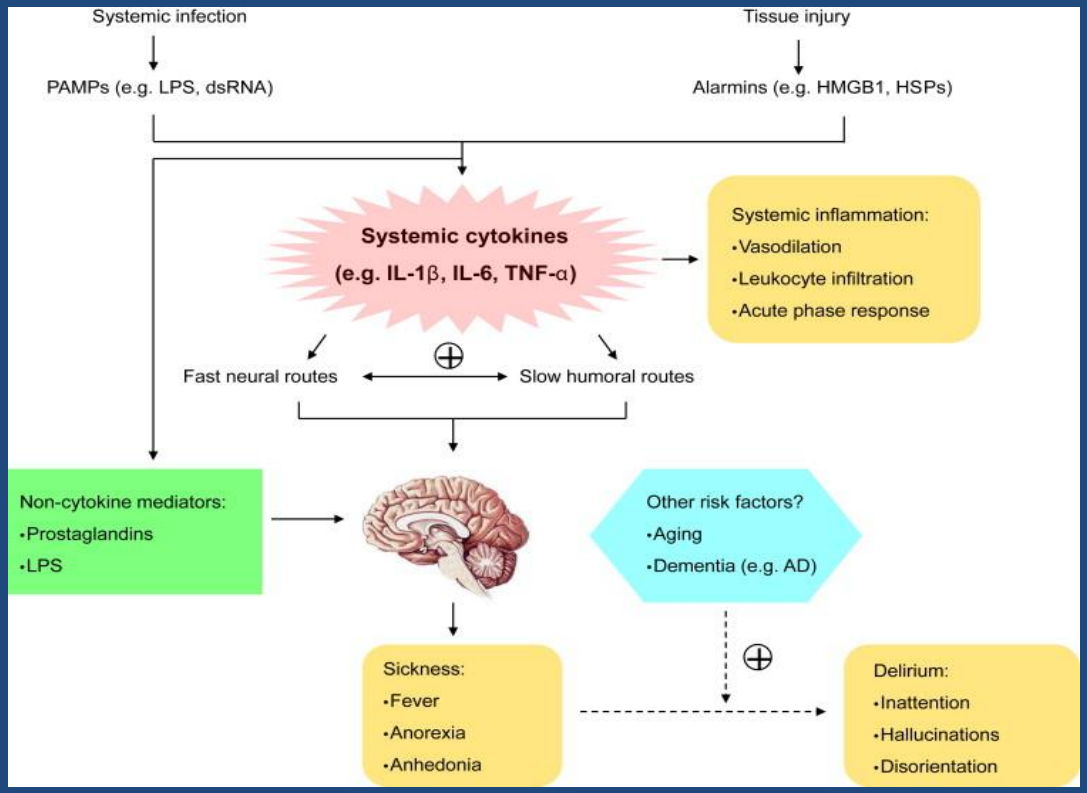
Review

Cytokines: How important are they in mediating sickness?

David Chun-Hei Poon[a], Yuen-Shan Ho[a], Kin Chiu[a], Raymond Chuen-Chung Chang[a,b,c,*]

Neuroscience and Biobehavioral Reviews 37 (2013) 1–10

- Cytokines are induced centrally and peripherally during systemic inflammation



Brain, Behavior, and Immunity 28 (2013) 1–13

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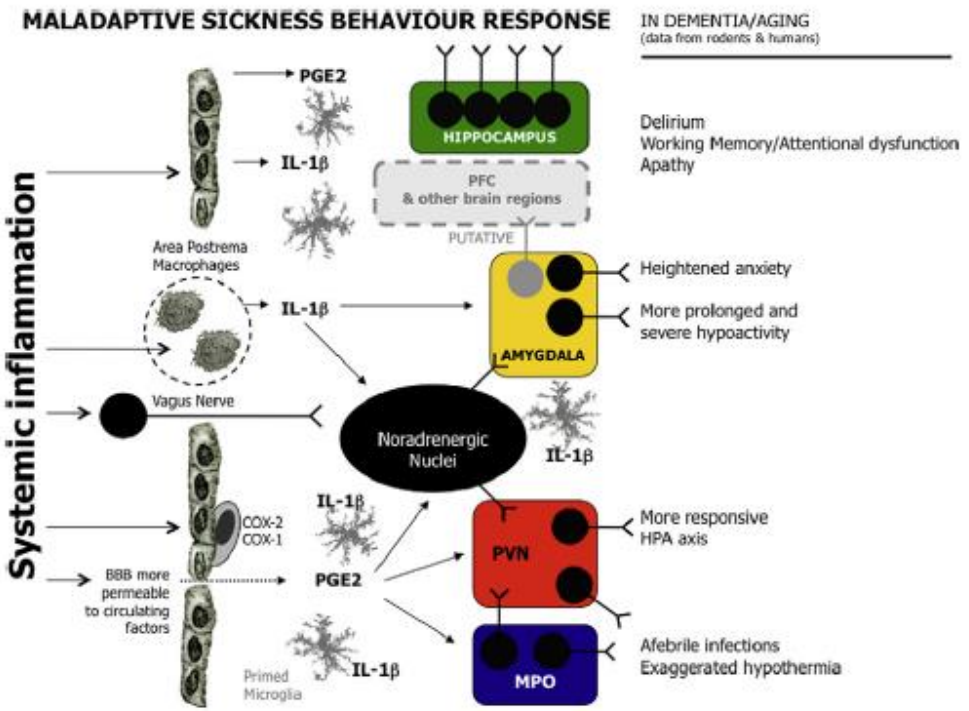
Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Invited Review

At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response

Colm Cunningham [a,*], Alasdair M.J. MacLullich [b]



Inhibitory Tone

Arousal Tone

Network Connectivity

Baseline

New Injury – decreased adaptability

American Delirium Society

- **4th Annual Meeting: American Delirium Society Historic Tremont Hotel**
- **Baltimore, Maryland, June 1 - 3, 2014**

- http://www.americandeliriumsociety.org/

Inflammatory mediators in delirium: Where the neural circuitry of sickness syndrome and dementia meet

Dr. Colm Cunningham, Trinity College, Dublin Ireland

Blood Brain Barrier

Dr. Christopher Hughes, Vanderbilt University

Resilience – implicatiions for delirium onset and recovery

Dr. Dilip Jeste, UCSD

Manipulation/management of peri-illness stress (inflammation)

Dr. Laura Dugan, UCSD

Small Group Discussion with Lunch