

Complexity, Breaking Bad Tradeoffs, and the Evolution of Biological Failure

(1) GENERAL MODELS OF FAILURE

(2) FAILURE DUE TO COMPLEXITY AND COUPLING **Normal biological 'accidents'**

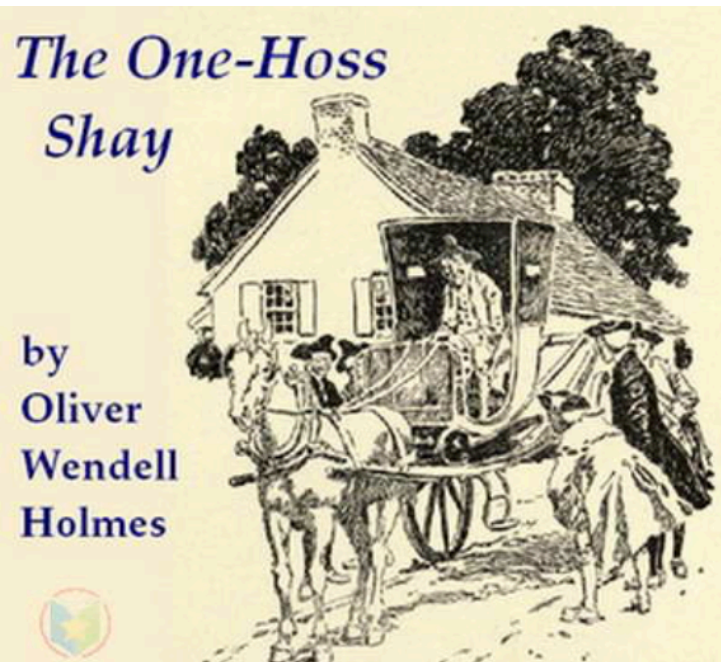
(3) FAILURE DUE TO BAD TRADEOFFS

Unbroken tradeoffs that weaken systems

Flexibility versus resilience

How break bad tradeoffs?



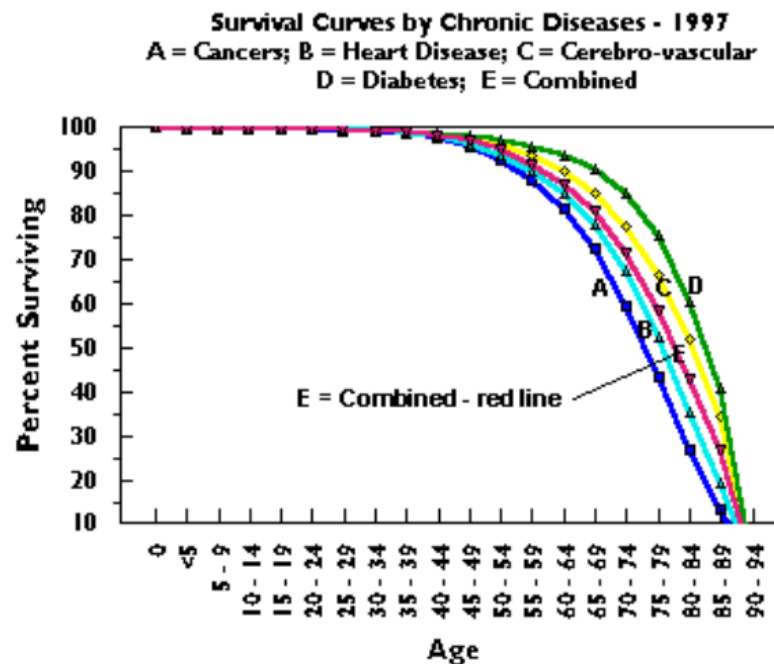


Have you heard of the wonderful one-hoss shay,
That was built in such a logical way
It ran a hundred years to a day,
And then, of a sudden, it...

... went to pieces all at once, —
All at once, and nothing first, —
Just as bubbles when they burst.
End of the wonderful one-hoss shay.
Logic is logic. That's all I say.

'ONE-HORSE SHAY' MODEL OF FAILURE

- Selection *stronger on weaker components*, makes them more robust
- All components become equally strong, equally likely to fail
- Slow, invisible weaknesses increase over time
- Then ALL components fail AT ONCE
- Does not account for weaker selection later in lifespan
- But may help explain exponentiality of increase in mortality with age, diversity of diseases





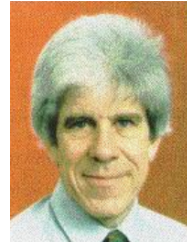
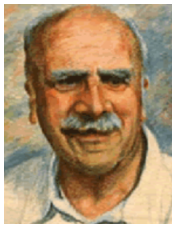
'Ling chi'

“DEATH BY 1000 CUTS” MODEL OF FAILURE

- Damage, mutations accumulate over time**
- Most mutations are deleterious**
- Tradeoff of cancer risk with losses of cellular function promotes (slow) senescence, if not die of cancer**
- Slow senescence inevitable**
- Supported by considerable molecular-genetic evidence**
- Supported by inverse comorbidities of cancer and neurodegenerative diseases (Alzheimer's, etc)**
- Are negative effects of cuts linear over time, or get worse?**

HALDANE, MEDAWAR, WILLIAMS, HAMILTON, MODEL OF FAILURE

WHY



**Strength of selection declines with age, due to
(1) smaller population, (2) less reproduction in future**

**Selection for genes with beneficial effects early in life,
deleterious effects later in life (antagonistic pleiotropy)**

+ early / - late

**Drift of genes with no effects early in life, deleterious
effects later in life (mutation accumulation)**

0 early / - late

- How translate into mechanistic patterns of failure?**
- Which systems fail first, later? At what levels? At what rates? Why?**
- Interdependence of systems during failure?**
- How reduce, delay failure rate? Role of defenses?**

<https://vigyanprasar.gov.in/haldane-john-burdon-sanderson/>

<http://www.greatthoughtstreasury.com/author/peter-medawar-fully-sir-peter-brian-medawar>

<http://www.evolution.unibas.ch/hamilton/index.htm>

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ABIOTIC MODEL OF FAILURE:

'**NORMAL ACCIDENTS**' (Charles Perrow, 1984, Yale sociologist)

Accidents (failures) are inevitable (normal) in complex systems



Risk of failures depends primarily on:

(1) Degree of Complexity relative to Linearity/Simplicity

(2) Tightness of Coupling between components
(weak/modular relative to tightly interactively linked)

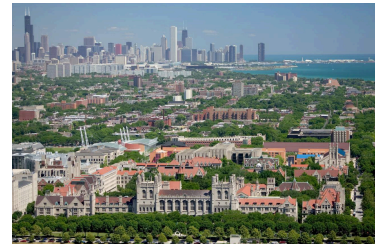
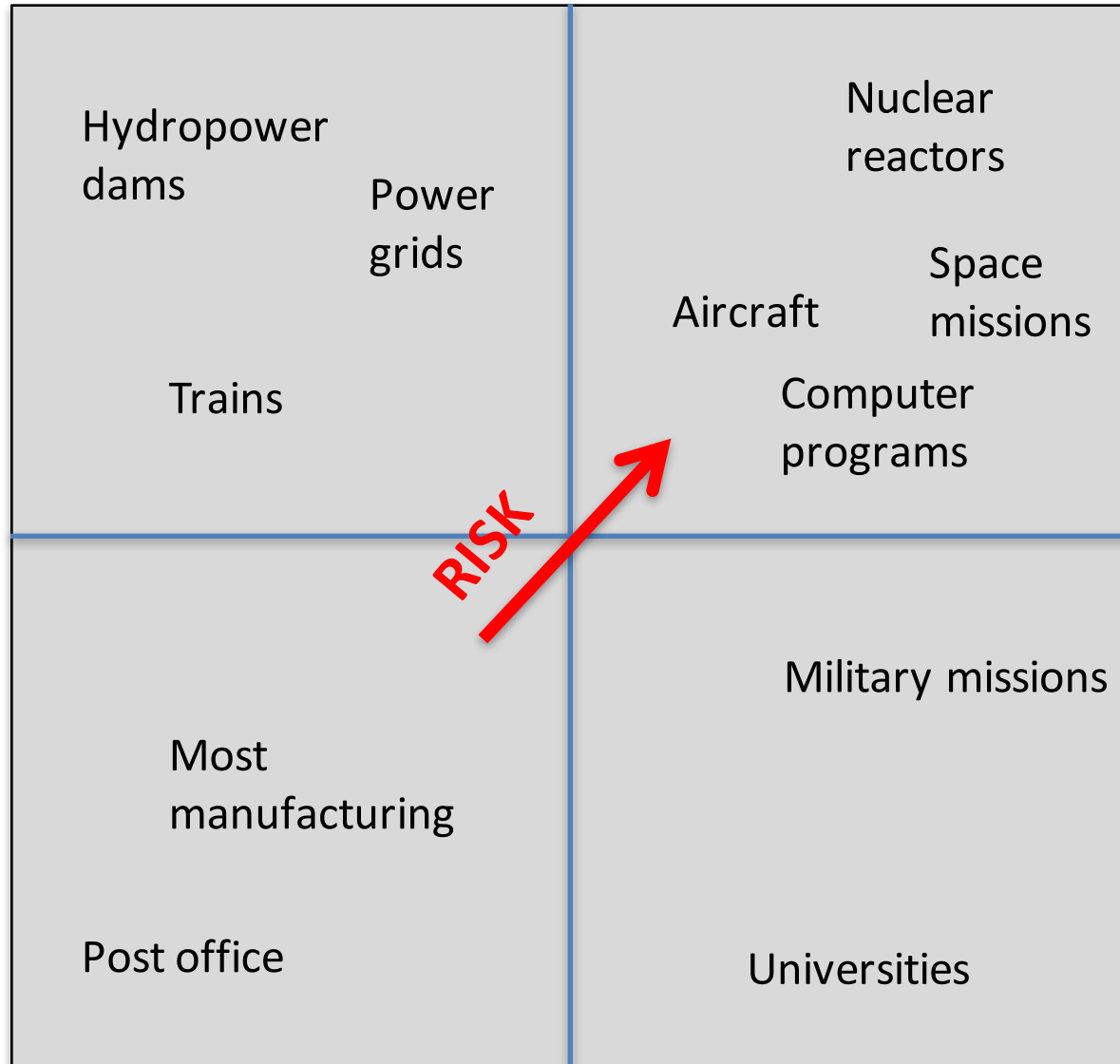
Applied to technological/managerial/non-biological systems

interaction
dependence
modularity

NORMAL ACCIDENT THEORY MATRIX OF RISK



LOOSE COUPLING TIGHT



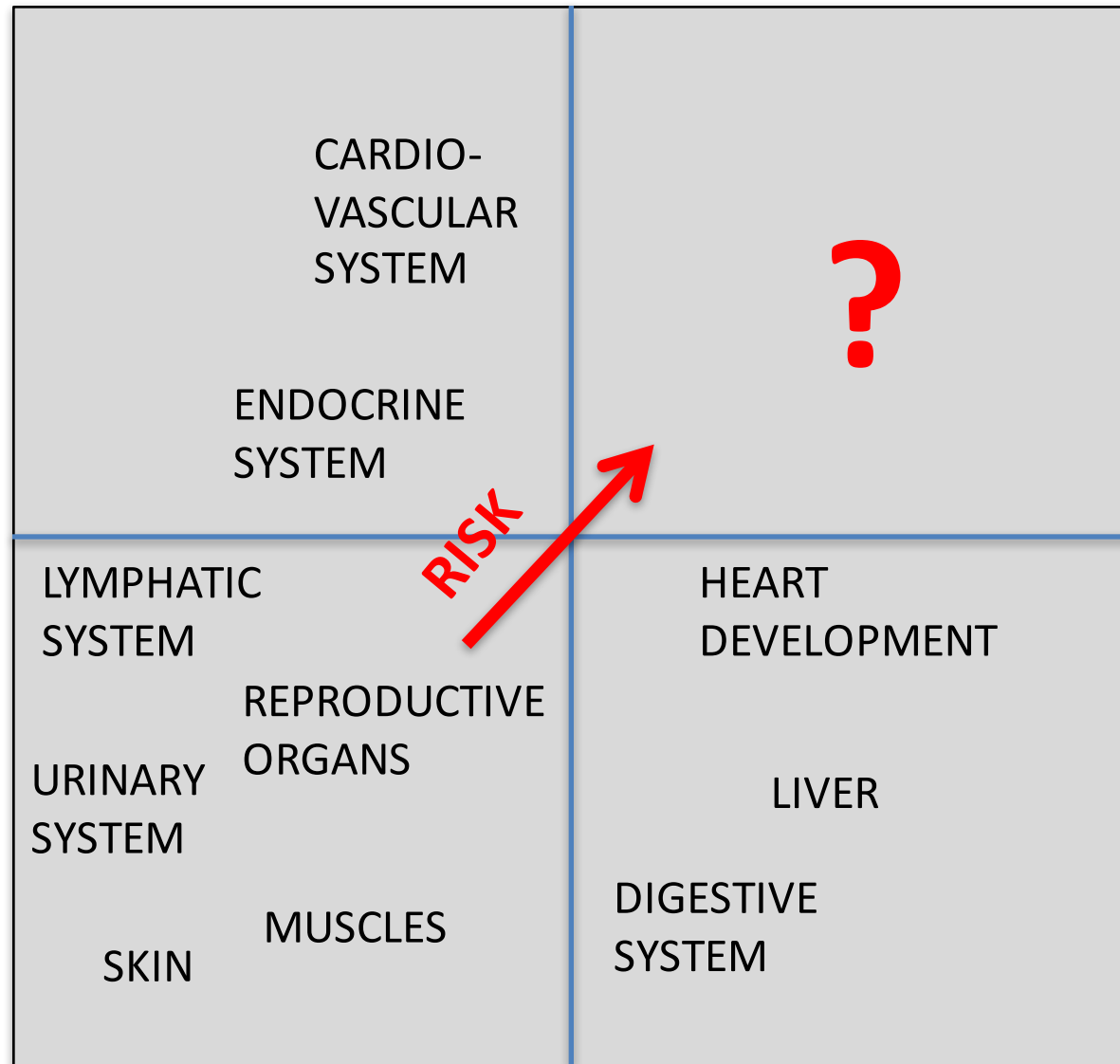
LINEAR/LOW COMPLEXITY HIGH



interaction
dependence
modularity

Normal **Biological** Failure Risk

LOOSE COUPLING TIGHT



→
+ AGEING

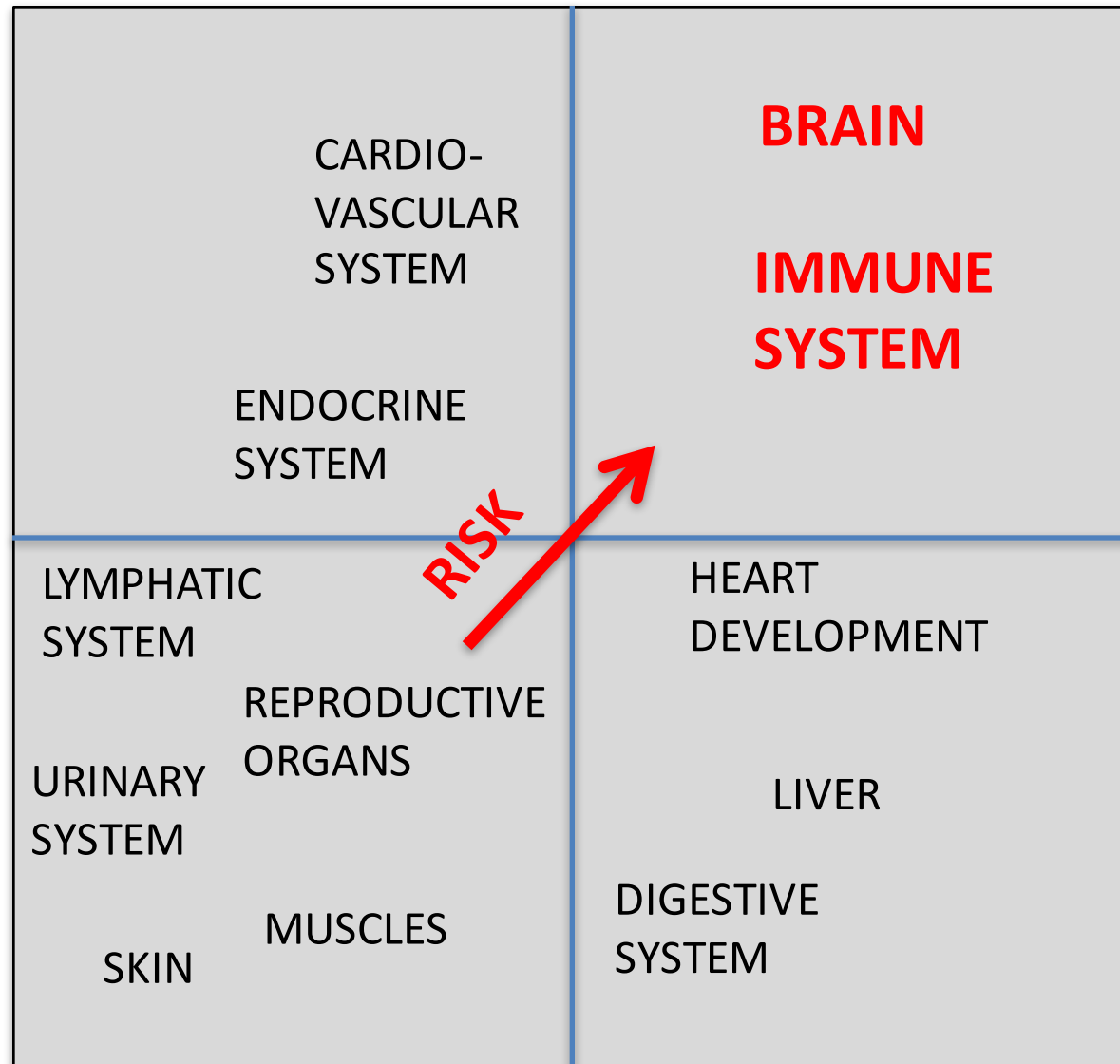
LINEAR/LOW COMPLEXITY HIGH

interaction
dependence
modularity

Normal **Biological** Failure Risk

SYSTEM-LEVEL

LOOSE COUPLING TIGHT



+ AGEING

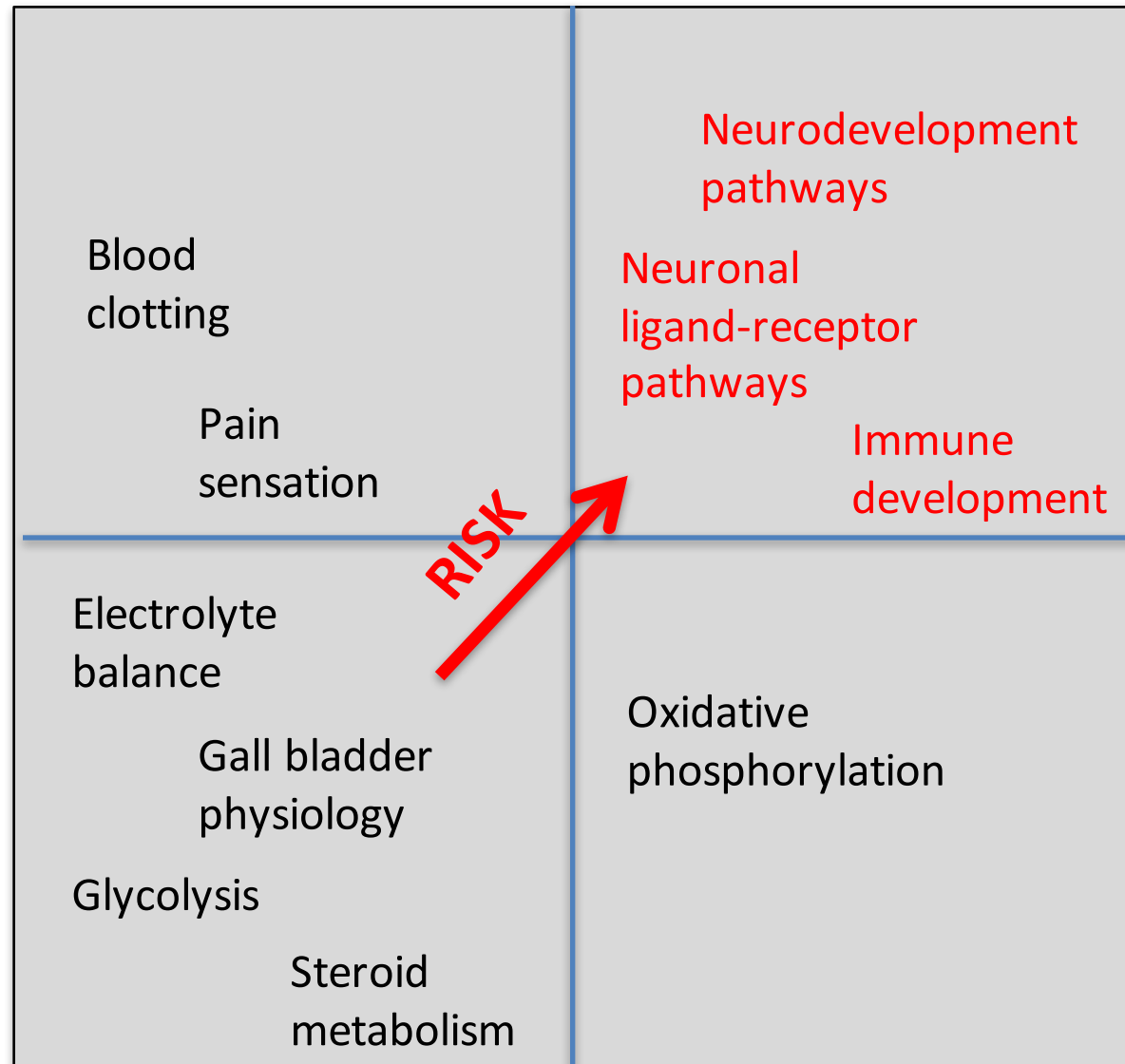
LINEAR/LOW COMPLEXITY HIGH

interaction
dependence
modularity

Normal **Biological** Failure Risk

PHYSIOLOGICAL LEVEL

LOOSE COUPLING TIGHT



→
+ AGEING

LINEAR/LOW COMPLEXITY HIGH

3rd, 4th
axes?

IS BIOLOGICAL FAILURE MEDIATED PREDOMINANTLY BY THE BRAIN AND THE IMMUNE SYSTEM?

Tight coupling + high complexity

BRAIN

Determines major components of **fitness** (sociality, intelligence...)->

Prioritized for energy, function

Controls other systems, more or less

Aerobic glycolysis (fast, simple, inefficient) early; OXPHOS late

Strong **selection** early in life

Mental disorders represent alternative '**attractors**' apparently
potentiated by **tight coupling** (e.g. schizophrenia, depression, mania, autism)

Clear **antagonistic pleiotropy** effects (e. g., APOE4, etc)

Alzheimer's, other dementias, cognitive declines mediate SENESCENCE

Cognitive senescence caused in part by OVER-DEFENSE (neurons long-lived, not replaced,
very high, inflexible energy needs)

2016

The association between intelligence and
lifespan is mostly genetic

Rosalind Arden,^{1,2,*†} Michelle Luciano,^{3†} Ian J Deary,³ Chandra A
Reynolds,⁴ Nancy L Pedersen,⁵ Brenda L Plassman,⁶ Matt McGue,^{7,8}
Kaare Christensen^{8,9} and Peter M Visscher¹⁰

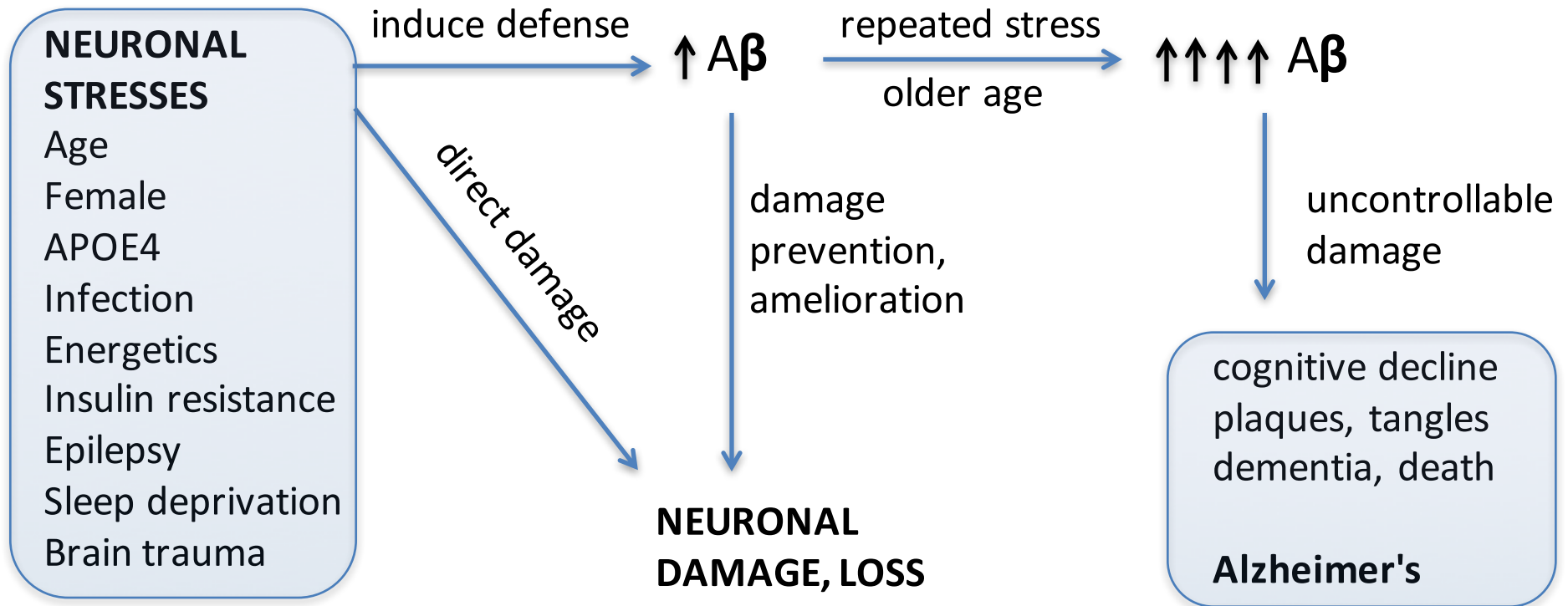
2017

Childhood intelligence in relation to major causes of death in 68 year
follow-up: prospective population study

[Catherine M Calvin](#), postdoctoral research assistant,^{1,2,3} [G David Batty](#), reader in epidemiology,^{2,4} [Geoff Der](#), senior
research fellow,^{2,5} [Caroline E Brett](#), lecturer in health psychology,^{2,6} [Adele Taylor](#), research assistant,¹ [Alison Pattie](#),
research associate,¹ [Iva Čukić](#), postdoctoral research assistant,^{1,2} and [Ian J Deary](#), professor of differential
psychology^{1,2}



The Amyloid Protection Hypothesis for Alzheimer's



**Senescence,
death by
dysregulated
'over-defense'**

IS BIOLOGICAL FAILURE MEDIATED PREDOMINANTLY BY THE BRAIN AND THE IMMUNE SYSTEM?

Tight coupling + high complexity

IMMUNE SYSTEM

Mediates major component of **fitness** (infection)

Pathogen defense

Prioritized for energy, function

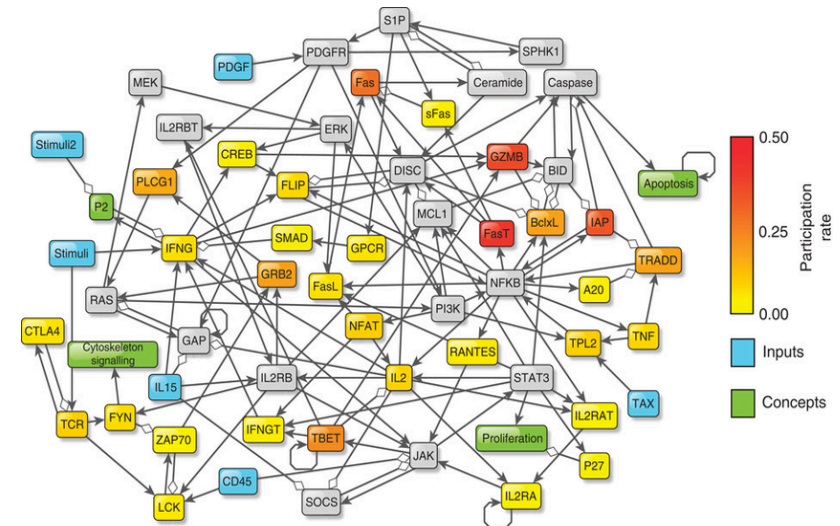
Very strong **selection** early in life

Cancer immunosurveillance throughout life

Autoimmunity, chronic inflammation, cytokine storms represent alternative **attractors** potentiated by tight coupling

Bodily senescence mediated in large part by **OVER-DEFENSE: INFLAMMAGING EFFECTS**

T cell signaling network



DO BRAIN AND IMMUNE SYSTEM PREFERENTIALLY MEDIATE SENESCENCE VIA HIGH COMPLEXITY AND TIGHT COUPLING?

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Normal biological 'accidents'

*brain and immune system do not play well with others
(do not trade off well with other systems)*

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FAILURE DUE TO (BAD) TRADEOFFS ('badaptations')

TRADEOFFS: *COMPROMISES BETWEEN ANTAGONISTIC FUNCTIONS*

life history theory

growth – differentiation – maintenance – reproduction

GROWTH vs DIFFERENTIATION (altricial vs precocial)

GROWTH vs DIFFERENTIATION (compensatory growth)

GROWTH vs MAINTENANCE (immune system, childhood)

&

GROWTH vs REPRODUCTION (early menarche, secular trend) FEMALES

MAINTENANCE vs REPRODUCTION (testosterone vs immune function) MALES

REPRODUCTION vs MAINTENANCE (child-bearing to menopause) FEMALES

&

DISEASE RISK 1 vs DISEASE/SENESCENCE RISK 2



Failures caused by:

-REDUCED INVESTMENTS IN MAINTENANCE, DUE TO TRADEOFFS

-FUZZINESS IN LIFE HISTORY TRANSITIONS

-TRADEOFFS IN DISEASE AND SENESCENCE RISKS



Diametrical diseases reflect evolutionary-genetic tradeoffs

Evidence from psychiatry, neurology,
rheumatology, oncology and
immunology

Bernard J. Crespi^{*1} and Matthew C. Go^{1,2,3}

Autism vs Psychotic-affective Disorders

Cancer vs Neurodegeneration

Infectious disease risk vs Autoimmunity

Osteoarthritis vs Osteoporosis

Anorexia vs Obesity

OPPOSITE:

Phenotypes
Comorbidities
Genetic risk factors
Mechanisms

Tradeoffs between **resilience** and **sensitivity**

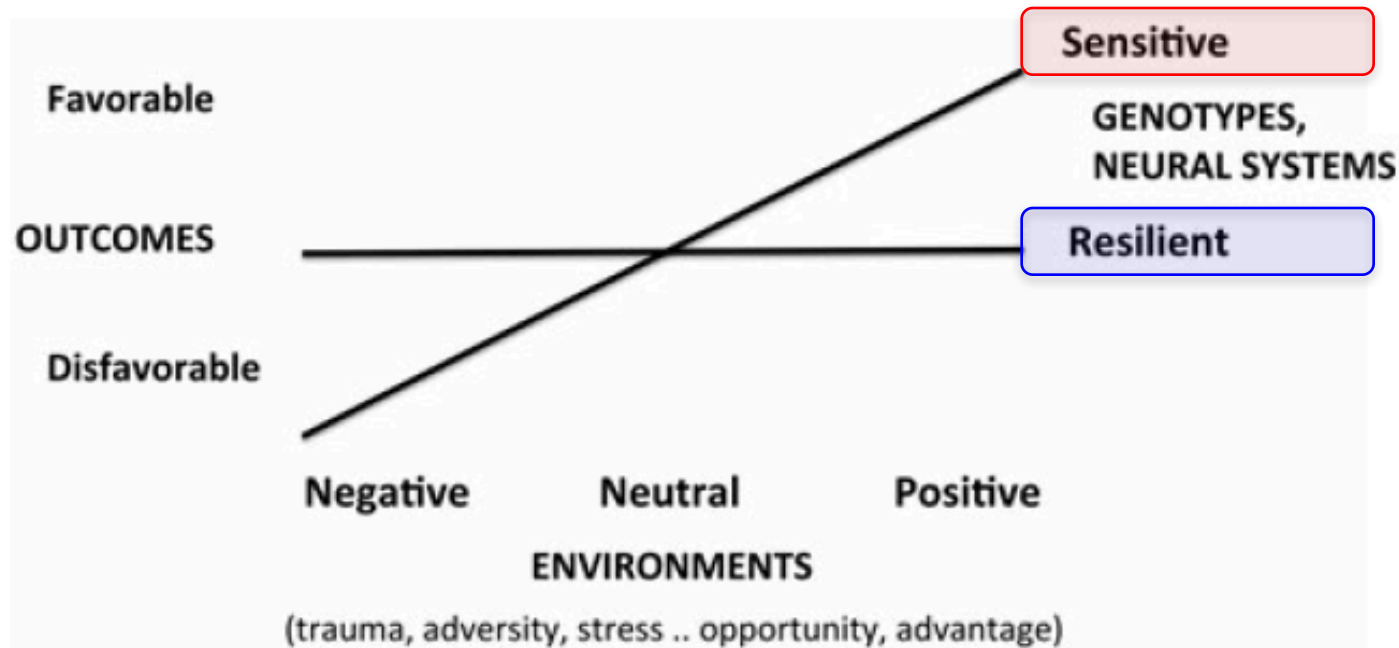


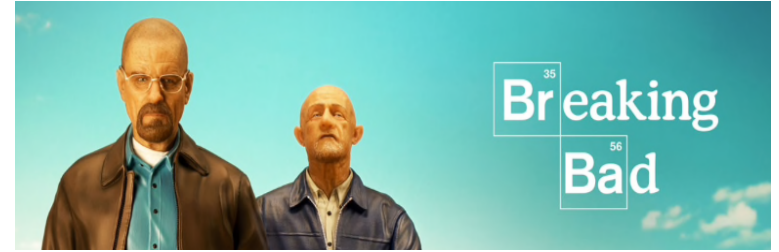
Figure 1 (Crespi). Cognitive trade-offs under a vantage sensitivity model, whereby resilience engenders benefits in poor environments but costs in good ones.



Jay Belsky
Michael Pleuss



BREAKING BAD TRADEOFFS: HOW?



(1) Increase investment in maintenance (immunity and brain, especially)
e. g., caloric restriction effects

(2) Promote less mutation and less-error-prone DNA repair
e. g., aerobic glycolysis, ketosis, etc

(3) Sharpen and optimize timing of life history transitions
infant->child, adrenarche, menarche, menopause

(4) Analyze mechanisms of antagonistic pleiotropy, tradeoffs
separate positive from negative effects

(5) Determine if most biological failures can be traced to the brain and the immune system

Is senescence due mainly to defense against death

...that (ultimately must) fail?