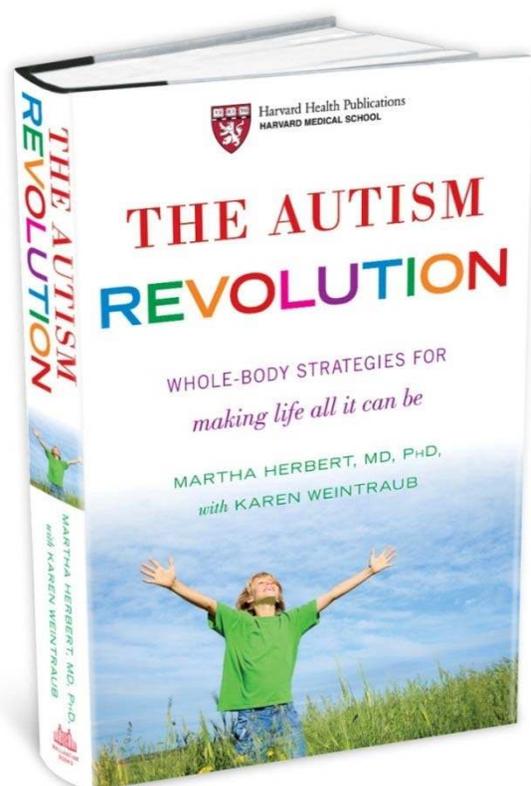
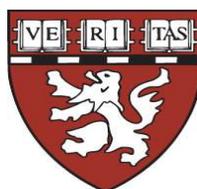


Environmental Exposures and Autism: The Interplay Between Genes, Environment and Health Status



Martha Herbert, MD, PhD
www.marthahebert.com
TRANSCEND Research Program
www.transcendresearch.org
Pediatric Neurology
Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Harvard Medical School



www.AutismRevolution.org

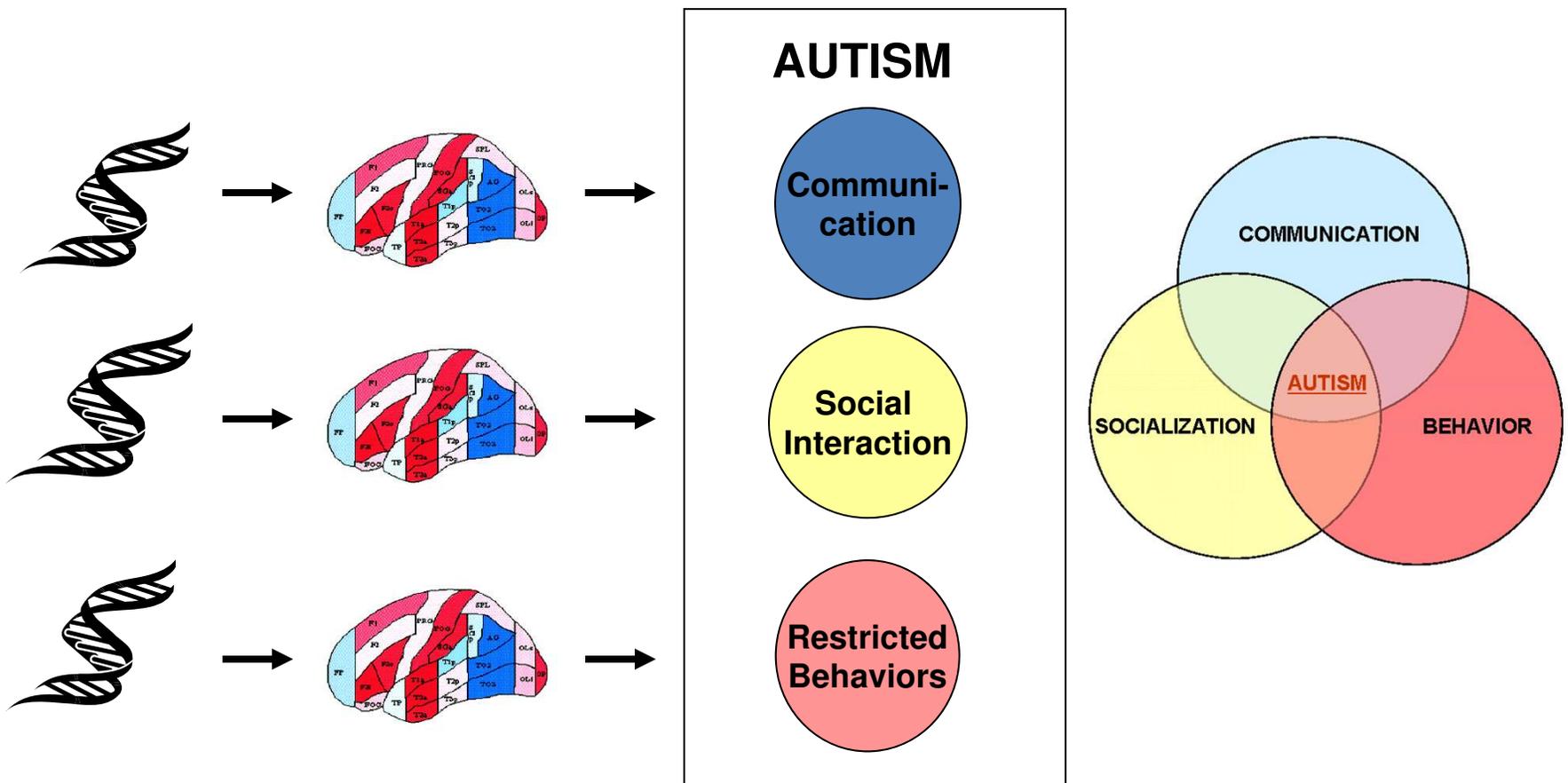
www.autismWHYandHOW.org

“LEGO” Modular Model:

Gene → Brain → Behavior

Determined before birth, fixed for life

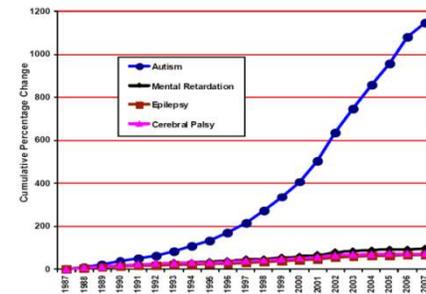
Nothing you can do



New model – an Autism Revolution: From genetic brain impairment to environmental, medical obstruction of brain function

Not just genetic:

- *Hundreds of genes, most modest impact*
- *Numbers going up*
- *Evidence for environmental factors*



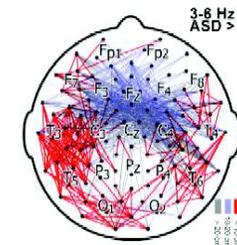
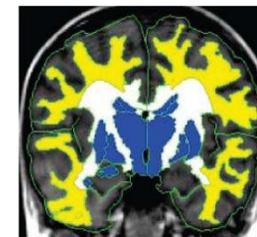
Not just brain:

- *Systemic features – Whole Body*
- *Environmentally vulnerable physiology*



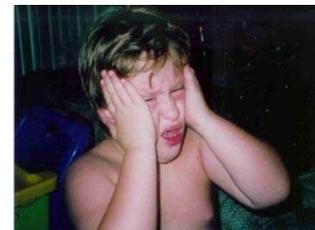
Not just brain modules:

- *Whole brain involvement*
- *Brain tissue changes*

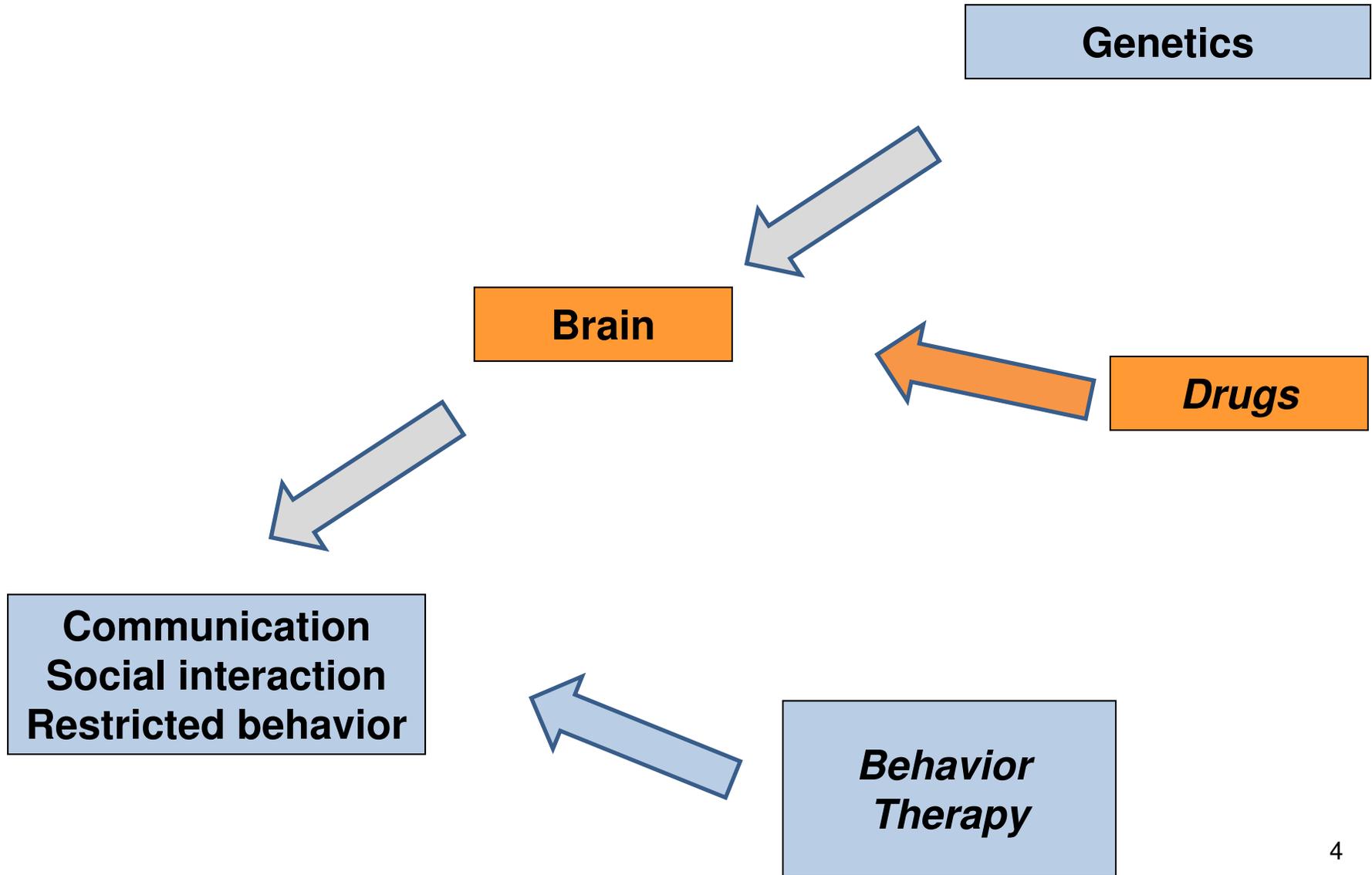


Not necessarily hardwired:

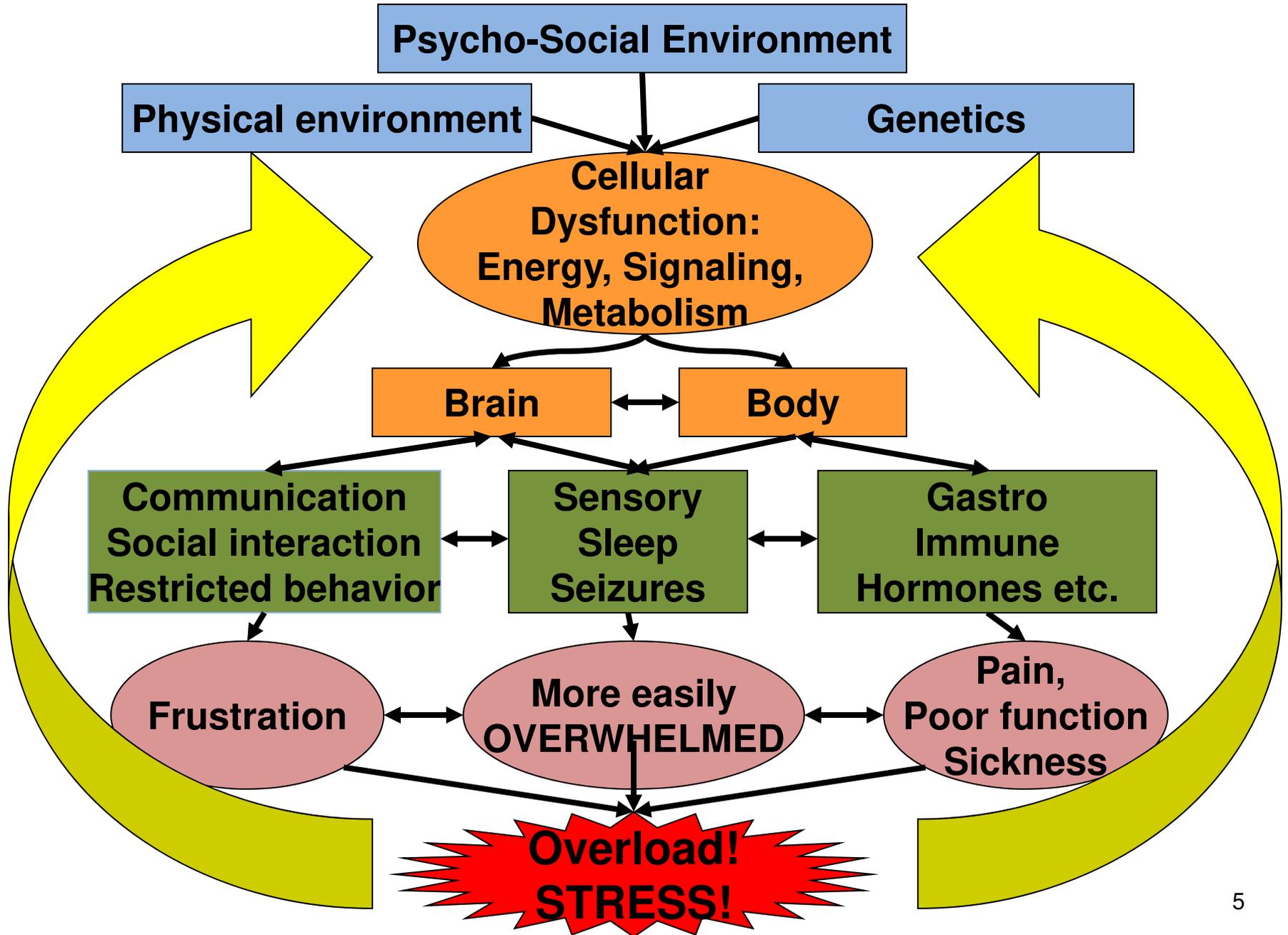
- *Plasticity and recovery*



Gene → Brain → Behavior model

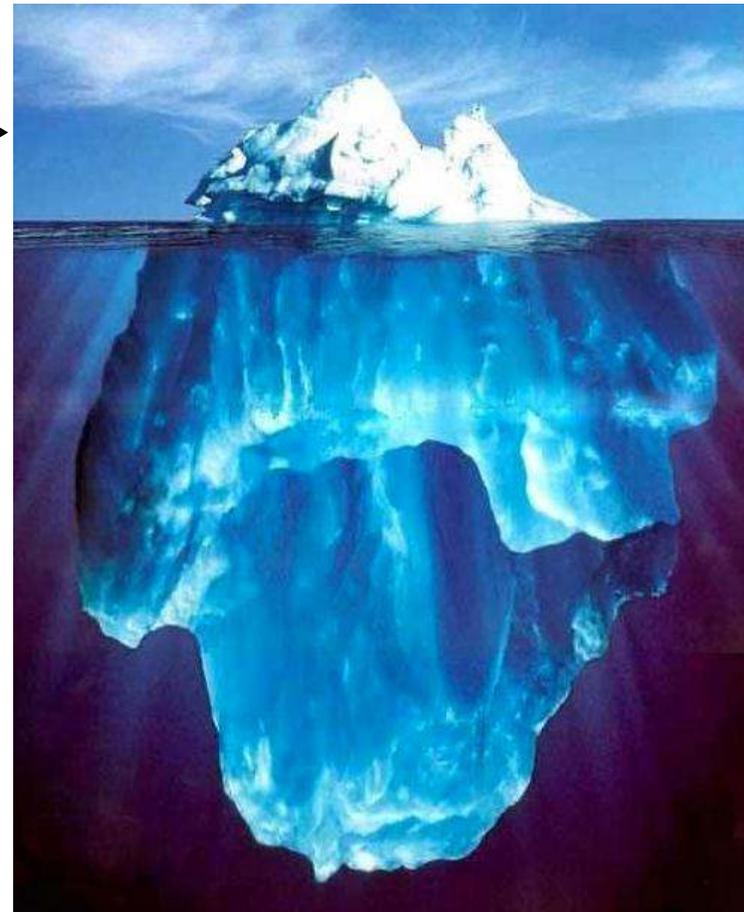


Whole Body Systems Model: Vicious circles in brain and body



Autism's Symptoms Emerge from Problems with Underlying Functions

**VISIBLE Social
& Behavioral
SYMPTOMS**



**UNDERLYING
SYSTEMIC
FUNCTIONAL
DISTURBANCES**



ENVIRONMENTALLY VULNERABLE PHYSIOLOGY

Current Opinion in Neurology, April, 2010

Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders

Martha R. Herbert

TRANSCEND Research Program, Pediatric Neurology,
Massachusetts General Hospital, Charlestown,
Massachusetts, USA

Correspondence to Martha R. Herbert, TRANSCEND
Research Program, Pediatric Neurology,
Massachusetts General Hospital, 149 13th Street,
Room 10.018, Charlestown, MA 02129, USA
Tel: +1 617 724 5920;
e-mail: mherbert1@partners.org

Current Opinion in Neurology 2010, 23:000–000

Purpose of review

To present a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs).

Recent findings

Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150 only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation.

Summary

Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

GENETIC EXPLANATIONS

Sense and Nonsense

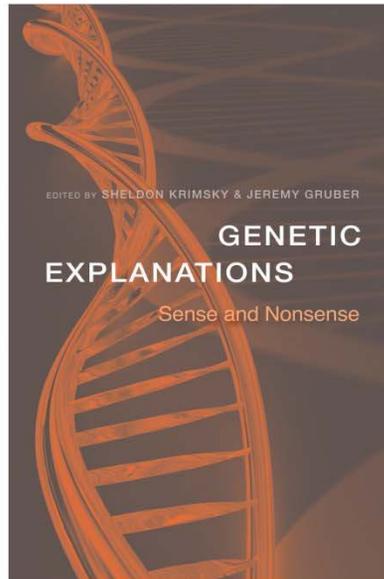
Edited by **SHELDON KRIMSKY** and **JEREMY GRUBER**

Can genes determine which fifty-year-old will succumb to Alzheimer's, which citizen will turn out on voting day, and which child will be marked for a life of crime? Yes, according to the Internet, a few scientific studies, and some in the biotechnology industry who should know better. Sheldon Krimsky and Jeremy Gruber gather a team of genetic experts to argue that treating genes as the holy grail of our physical being is a patently unscientific endeavor. *Genetic Explanations* urges us to replace our faith in genetic determinism with scientific knowledge about how DNA actually contributes to human development.

The concept of the gene has been steadily revised since Watson and Crick discovered the structure of the DNA molecule in 1953. No longer viewed by scientists as the cell's fixed set of master molecules, genes and DNA are seen as a dynamic script that is ad-libbed at each stage of development. Rather than an autonomous predictor of disease, the DNA we inherit interacts continuously with the environment and functions differently as we age. What our parents hand down to us is just the beginning. Emphasizing relatively new understandings of genetic plasticity and epigenetic inheritance, the authors put into a broad developmental context the role genes are known to play in disease, behavior, evolution, and cognition.

Rather than dismissing genetic reductionism out of hand, Krimsky and Gruber ask why it persists despite opposing scientific evidence, how it influences attitudes about human behavior, and how it figures in the politics of research funding.

Sheldon Krimsky is Professor of Urban & Environmental Policy & Planning in the School of Arts and Sciences and Adjunct Professor of Public Health and Community Medicine in the School of Medicine at Tufts University. **Jeremy Gruber** is President and Executive Director of the Council for Responsible Genetics.



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New Book with Critiques of Genetic Overexplanation

Harvard U Press 2013

Ch.10 on Autism: *From Static Genetic Brain Defect to Dynamic Gene- Environment- Modulated Pathophysiology*

By Martha Herbert

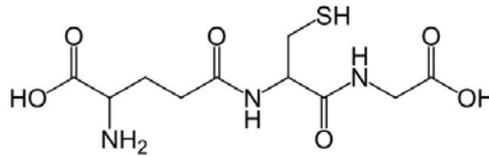
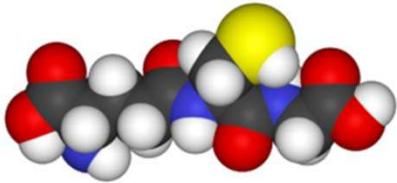
Autism: WHY and HOW ?



www.autismWHYandHOW.org

- A website reviewing multiple viewpoints and their intersections
- A literature repository
- A framework for reflective discourse

GLUTATHIONE PROTECTS CELLS from environmental stress, but is often low in **ASD** (and many other chronic conditions)

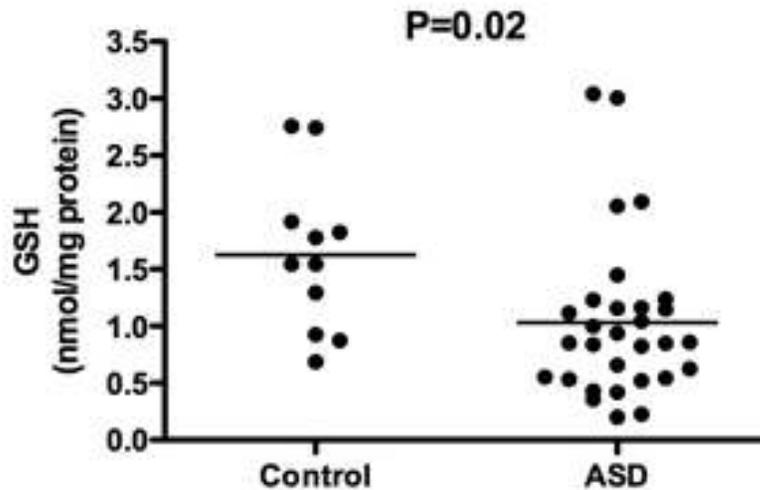


Made in the liver from
three amino acids:
**Glutamate + Cysteine +
Glycine**

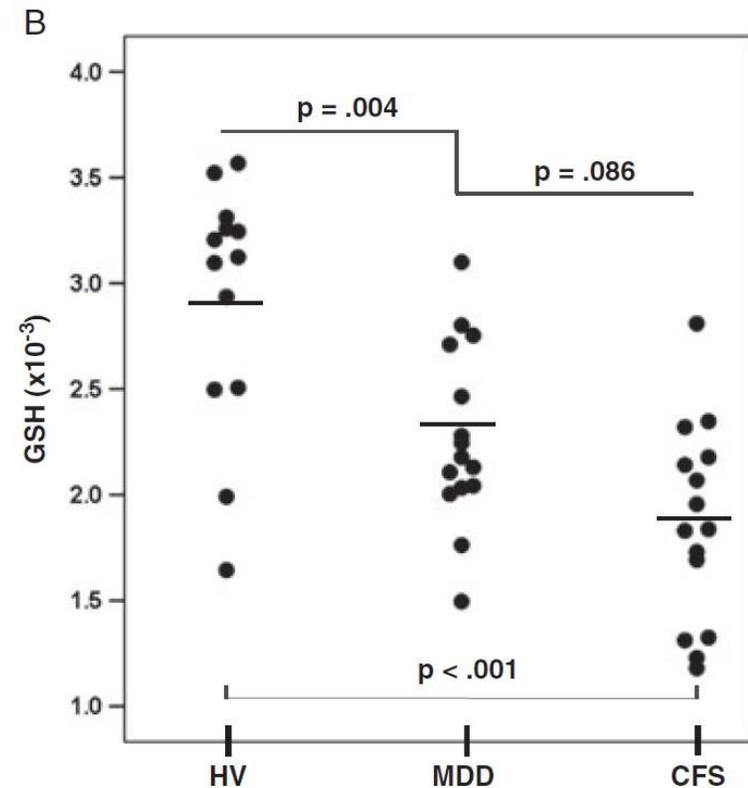
- **GLUTATHIONE (GSH) is vital for detoxification**
 - Mops up toxins and free radicals
- The body's most potent anti-oxidant
- **The most abundant antioxidant in the BRAIN**
 - Reduced Glutathione = GSH (active form)
 - Oxidized Glutathione = GSSG (used-up form)

LOW GLUTATHIONE

Glutathione - critical antioxidant and detox chemical - low levels in brains of depressed patients, lower in brains in Chronic Fatigue Syndrome – And low systemically in Autism



Suh, J., W. Walsh, et al. (2008). American Journal of Biotechnology and Biochemistry 4(2): 105-113,

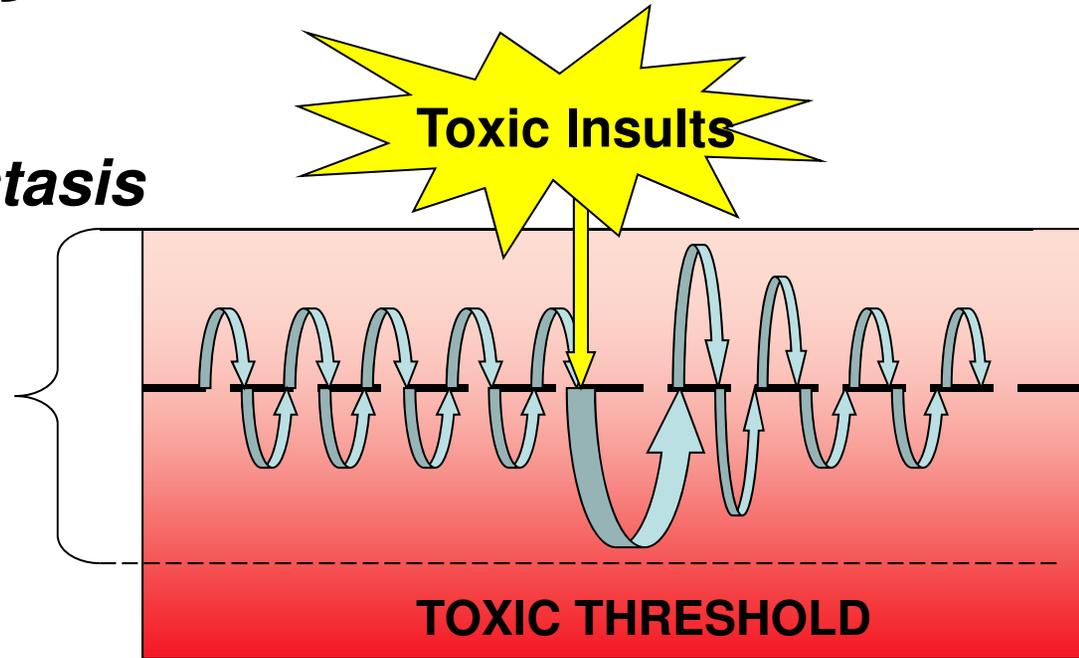


Shungu et al., 2012

Vulnerability with low GSH

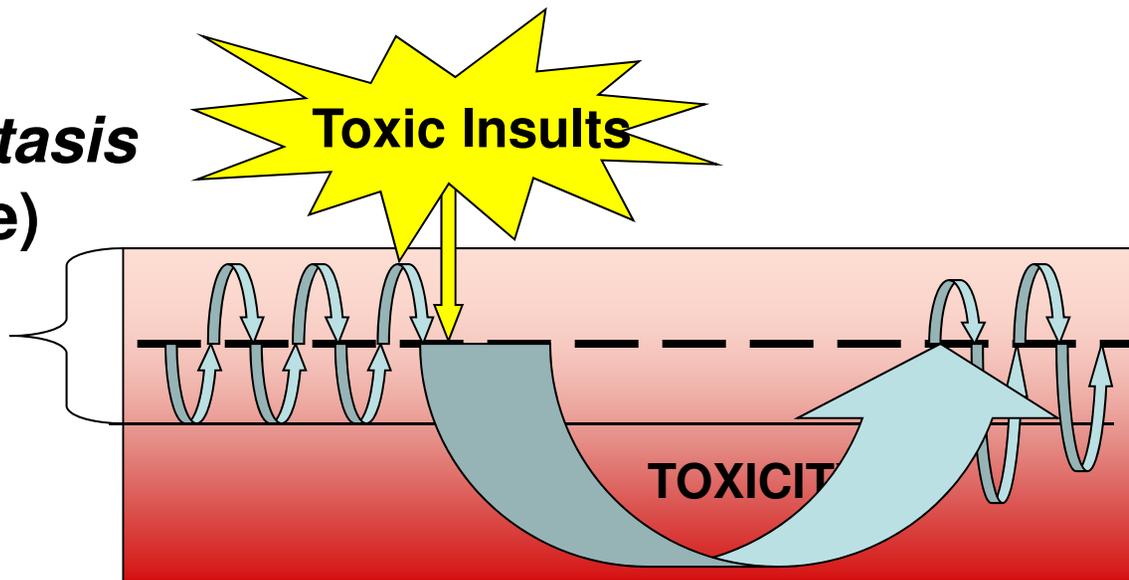
Normal Homeostasis

OK GSH/GSSG



Fragile Homeostasis
(limited reserve)

↓ GSH/GSSG



Glutathione as a “Final Common Pathway”

- **GSH is depleted by thousands of toxins, oxidative stress, infection, inflammation, EMF and nutrient-poor diet**
- **Small exposures of any one thing can still add up to a substantial depletion of antioxidant resilience**
- **Lee, D. H., D. R. Jacobs, Jr., et al. (2009).
“Hypothesis: a unifying mechanism for nutrition and chemicals as lifelong modulators of DNA hypomethylation.” Environ Health Perspect 117(12): 1799-1802.**

Mitochondrial vulnerability to environmental influences

- **Mitochondria are highly vulnerable in:**
 - **Their biochemistry – toxicants and oxidative stress can interfere**
 - **Their membranes - membrane damage both causes and results from mitochondrial dysfunction**
- **Their exquisite structural and functional characteristics provide a number of primary targets for toxicant-induced bioenergetic failure**

Wallace and Starkov, *Mitochondrial targets of Drug Toxicity*, Annu Rev Pharmacol Toxicol, 2000. 40:353-99

Mitochondrial dysfunction and molecular pathways of disease

Exp Mol Pathol. 2007 Jan 17

– “A wide range of **seemingly unrelated disorders**, such as **schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis**, have **underlying pathophysiological mechanisms** in common, namely **reactive oxygen species (ROS) production, the accumulation of mitochondrial DNA (mtDNA) damage**, resulting in **mitochondrial dysfunction**. Antioxidant therapies hold promise for improving mitochondrial performance.”

“diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration”

Metabolic Findings in Parents of Children with Autism

- **86 autism parents differ from 200 controls in the following:**
 - **Higher homocysteine (Hcy)**
 - **Higher SAH (S-adenosylhomocysteine)**
 - **Lower GSH (glutathione)**
 - **Increased GSSG (oxidized glutathione)**

(All markers of oxidative stress and inflammation)

J Autism Dev Disord. 2008 Nov;38(10):1966-75

Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome

Lintas et al., *Neurobiol Dis*, 2010

...Our results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. **A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders.** This conclusion may be important for the definition of pharmacological therapies able to ameliorate clinical symptoms across these disorders.

Environment and Brain tissue vulnerability

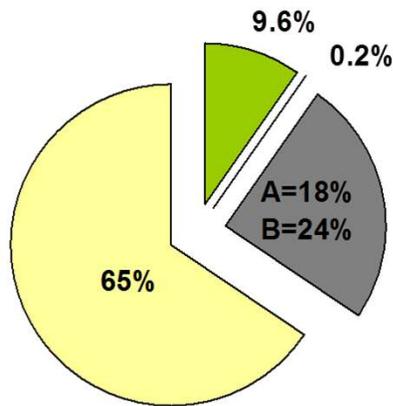
- **Many environmental exposures can contribute to**
 - **Inflammation**
 - **Reduction in brain perfusion**
 - **Compromise of the blood-brain barrier**

Things that can open the Blood-Brain Barrier

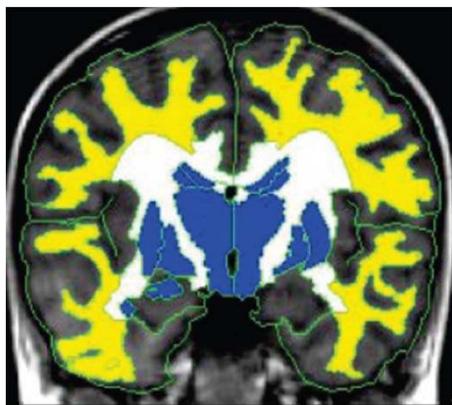
- **Hypertension (high blood pressure)**
- **Hyperosmolality (a high concentration of a substance in the blood)**
- **Microwaves**
- **Radiation**
- **Infection**
- **Inflammation; mast cells from gut**
- **Ischemia (insufficient oxygen)**
- **Injury, Trauma, Pressure**
- **Deficient Vitamin C or flavonoids**

Adapted from <http://faculty.washington.edu/chudler/bbb.html>

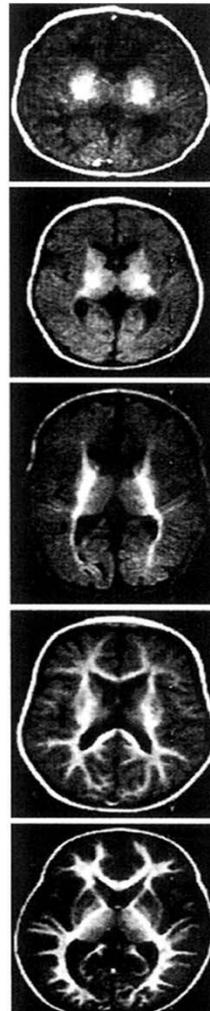
Location of white matter enlargement points to postnatal brain changes



White Matter Contributes Most to Autism Volume Increase



Radiate White Matter Enlargement



I- 1st Month

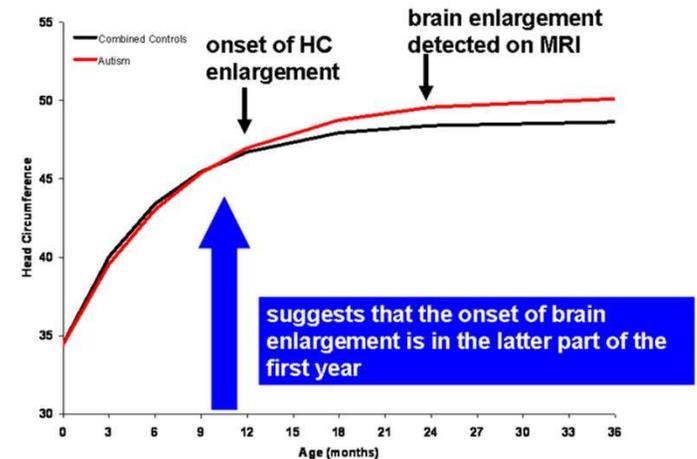
II- 2nd Month

III- 3rd-6th Month

IV- 7th-9th Month

V- > 9th Month

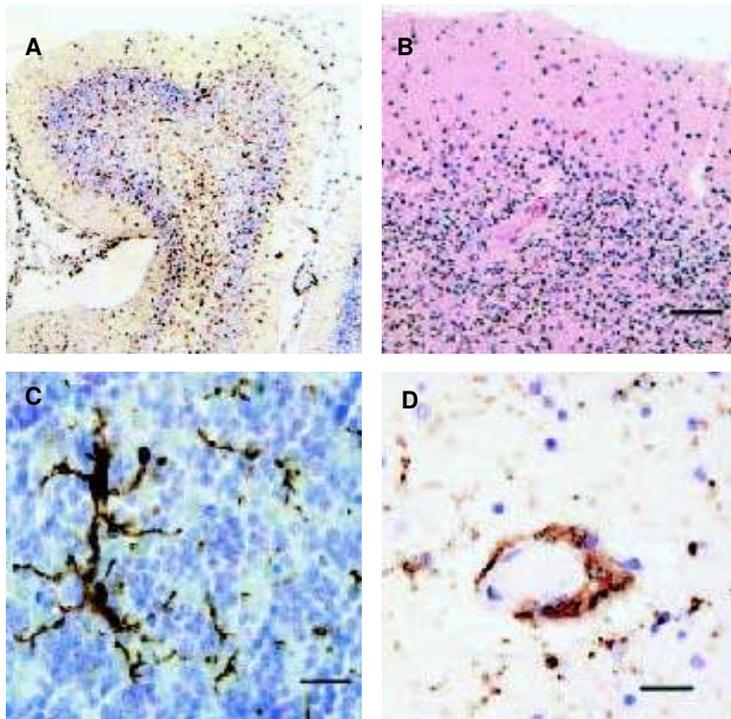
Inversion Recovery MRI Image (Van der Knaap & Valk)



What do we need to learn about the brain and about autism to understand this?

Inflammation and Oxidative Stress in Autism: chronic, ongoing postnatal medical problems, not confined to brain

Neuroglial activation and neuroinflammation in the brain of patients with autism
Vargas et al, 2005, Annals of Neurology



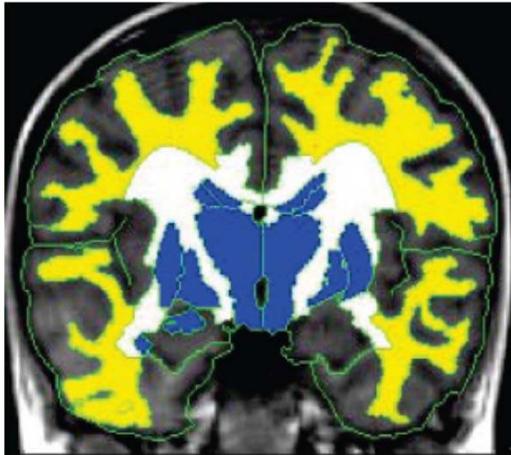
Oxidative stress in brain tissues from autistic patients Increased concentration of isoprostanes
Vargas et al, 2005, Annals of Neurology

- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3-year old's brain

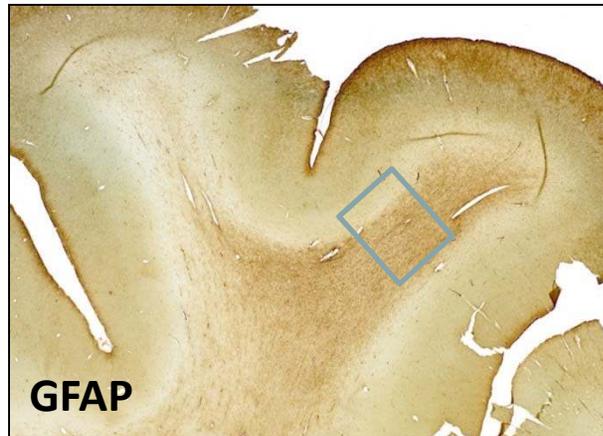
Pardo: Astrogliosis in Radiate White Matter

Astrogliosis

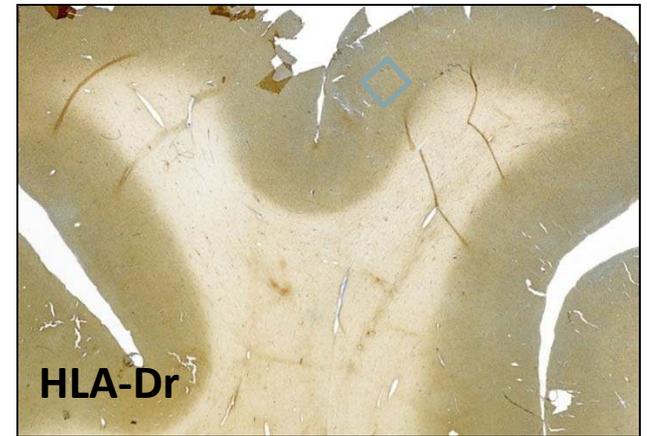
Microgliosis



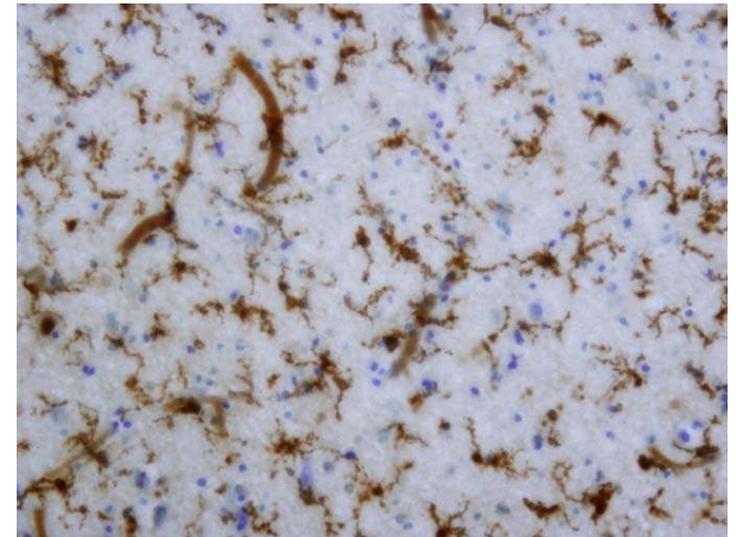
Herbert:
Radiate White
Matter Enlargement



GFAP



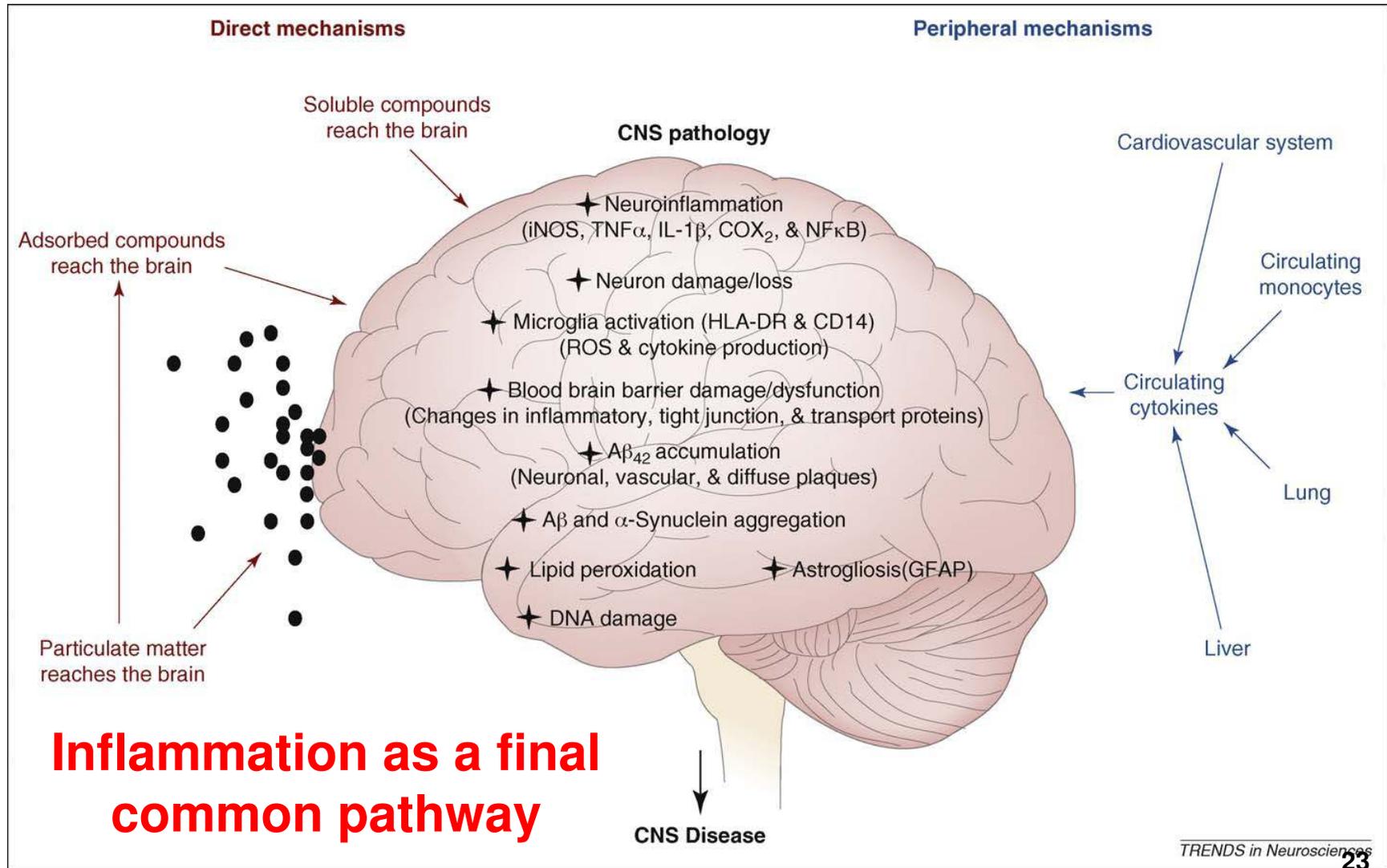
HLA-Dr



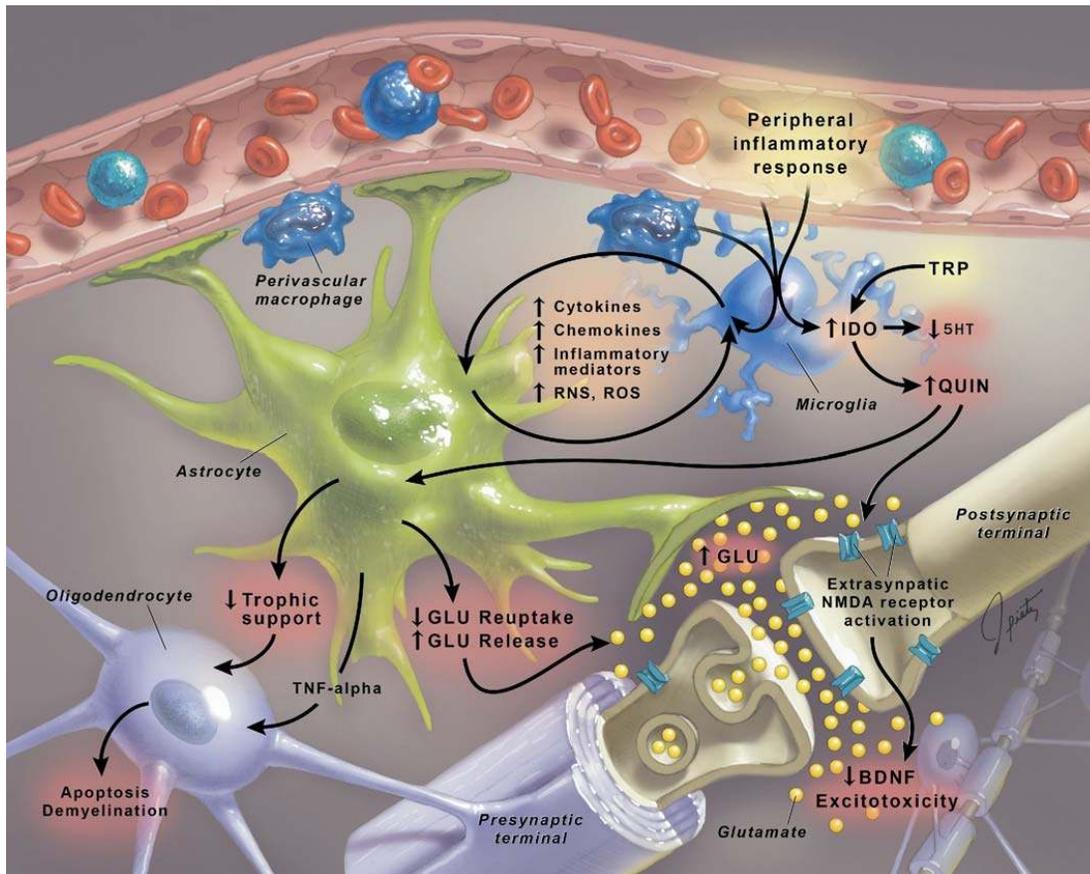
Air Pollution and Brain Inflammation

Block and Calderon-Gardicuenas, TNS, 2009

Air pollution already linked to autism
(e.g. Palmer 2006; Windham 2006; Volk 2011)



Brain cells in inflammation: What is the FUNCTIONAL IMPACT?



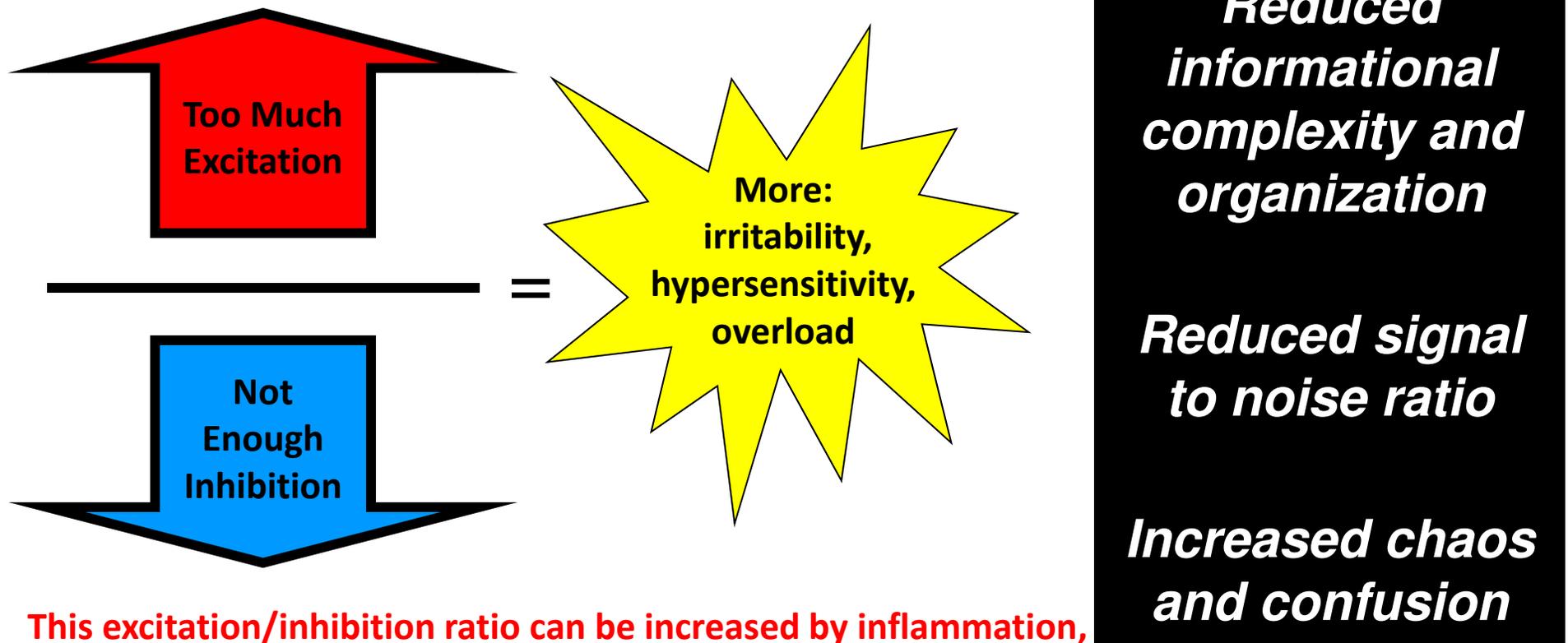
- Excitatory chemicals created by activated glial cells
- Normal housekeeping functions of glial cells get neglected
- Chronic inflammation is irritating and promotes excitotoxicity
- Chronic inflammation can cause damage

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression.
Miller et al., BIOL PSYCHIATRY 2009;65:732–741

Environmental Stressors are contributing to an ONGOING, CHRONIC DEGRADATION OF BRAIN AND BODY FUNCTION

Model of autism: Increased ratio of excitation / inhibition in key neural systems

Rubenstein & Merzenich, *Genes, Brain and Behavior* (2003) 2: 255-267



This excitation/inhibition ratio can be increased by inflammation, oxidative stress and toxicants, as well as genetic dysfunction

Mitochondrial Dysfunction and Synapses

- **Neurons impacted by metabolic dysfunction have the energy to stay alive,
→ *but not always enough to fire electric signals***

Efrati et al., PLoS One, 2013



EEG of Sensory Responses

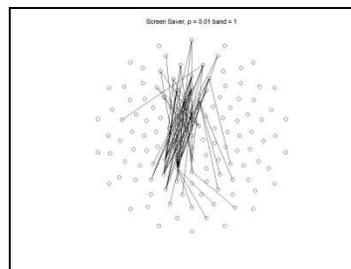
- **Sensory stimulation can be overwhelming**

- **Much more loss of connectivity when more stimulation**
- **More tolerance of stimulation and less loss of coordination in older kids**

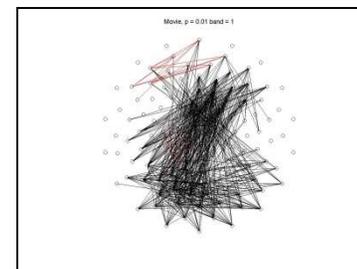
**Prediction:
Improved connectivity
with effective treatment**

5-8
years old

Lines indicate differences between
ASD and age-matched controls

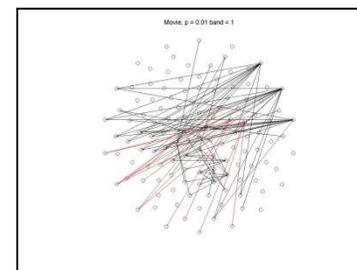
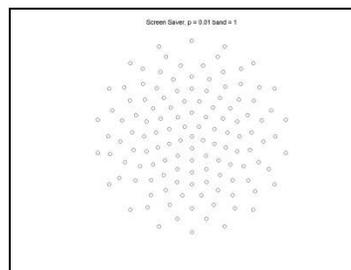


Screen Saver:
Less Stimulation



Movie:
More Stimulation

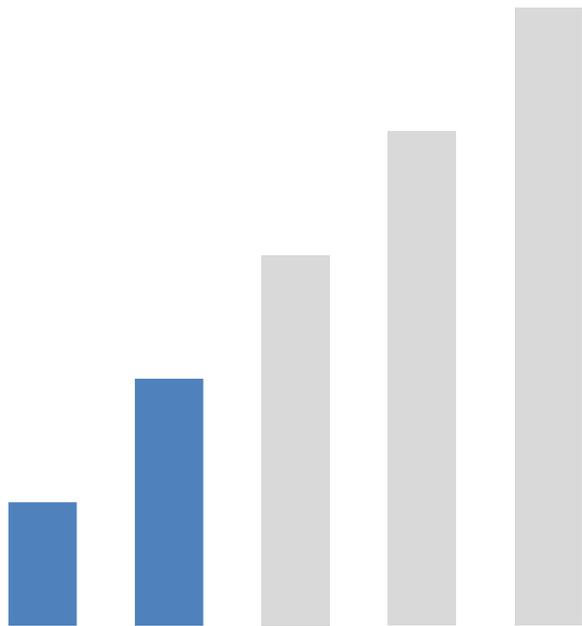
9-11
years old



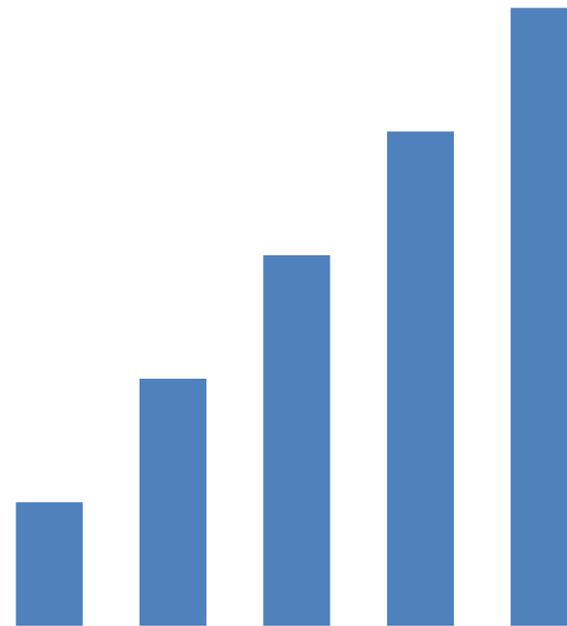
Martien et al. 2008

Metaphor: Tissue pathophysiology **REDUCES BRAIN BANDWIDTH**

**Poor Bandwidth:
Limited Reception**



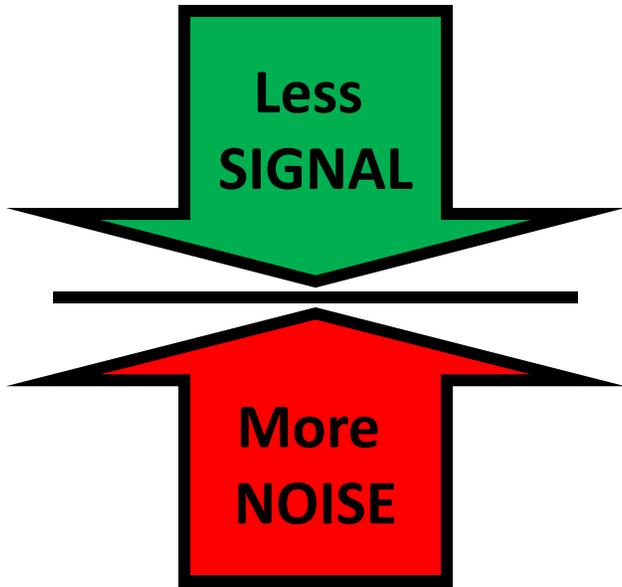
**Lots of Bandwidth:
Good Reception**



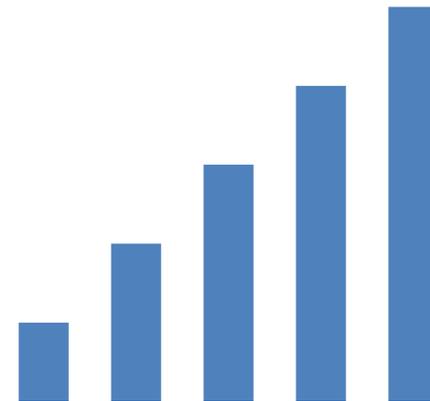
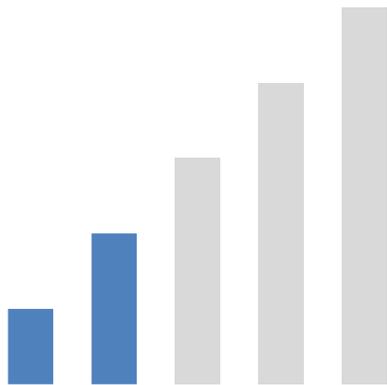
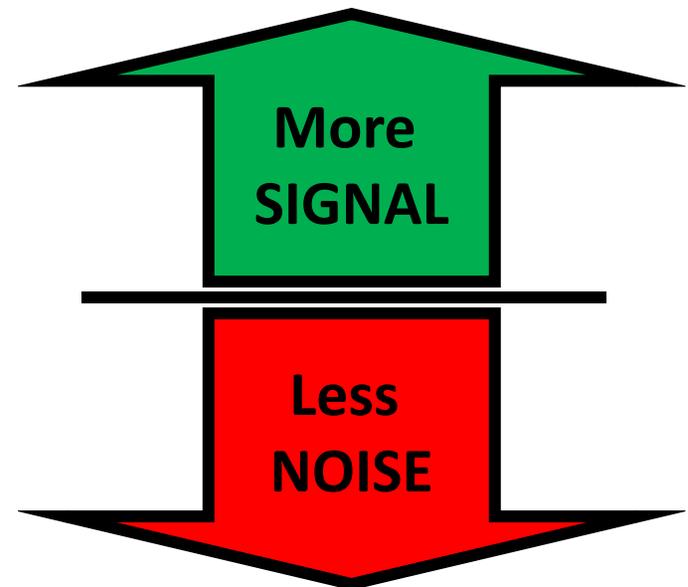
**Better Reception Allows Better Discernment of
Differences and More Spontaneous Learning**

Worse SNR, Less Bandwidth

Better SNR, Better Bandwidth



**SIGNAL
to
NOISE
ratio
(SNR)
and
BANDWIDTH**



Better Reception Allows More Spontaneous Learning

A Different Model of Autism: *Autism as an emergent property of a system with altered parameters and challenged, struggling physiology*

- Autism is not just a “developmental disorder” that’s hardwired into the brain before you’re born
- Autism is *created moment by moment* by *how the cells in the brain function*
- The cells of the brain function differently depending on their health
- The health of brain cells depends on the health of the whole body – and on the health of the earth

*Herbert, 2009,
“Autism: The centrality of pathophysiology and the shift from static to dynamic encephalopathy”
In Chauhan et al, Autism: Oxidative stress, inflammation and immune abnormalities*

“Wild-type microglia arrest pathology in a mouse model of Rett syndrome”

Derecki et al, Nature, 2012

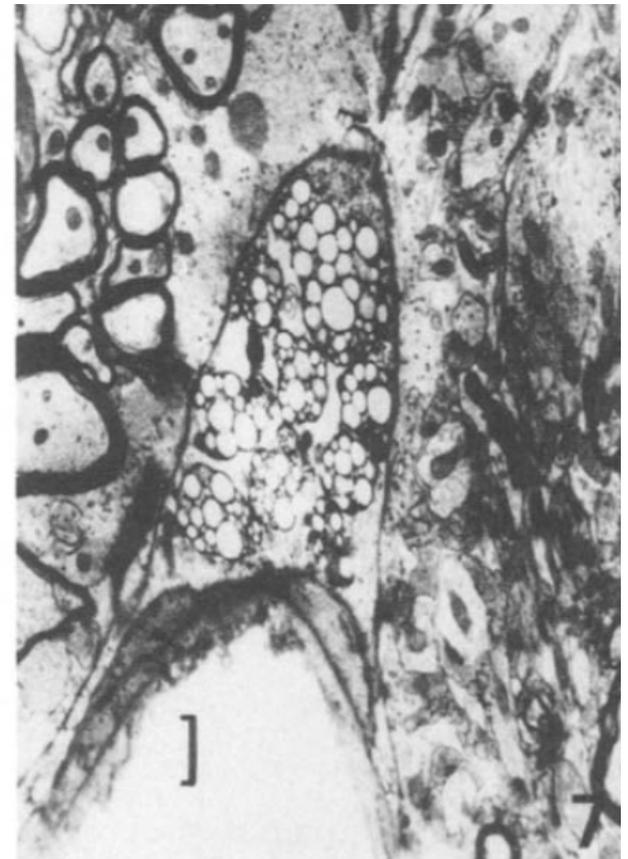
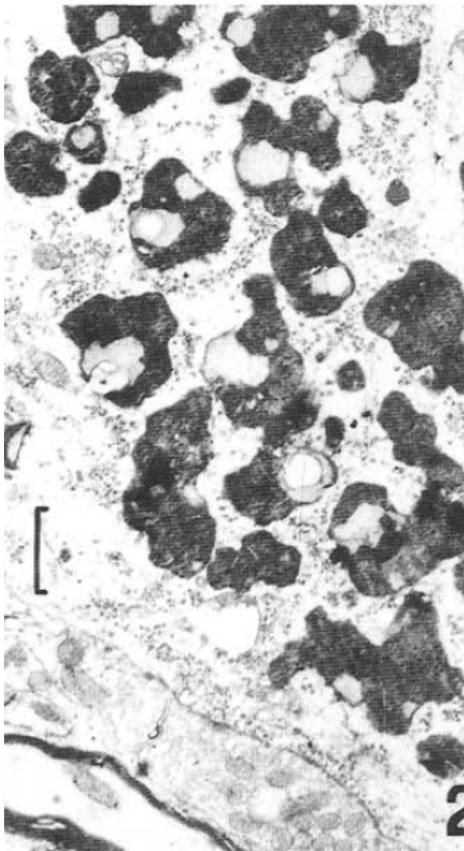
- Rett features had been attributed to neuronal dysfunction
- Astroglial cells now known to contribute
- **Now microglia shown to contribute as well: bone marrow transplant of wild type microglia**
 - Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
 - *Improvement even without direct change to neurons*
 - **Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited**

**Electron microscopy of
therapeutically activated glia turning into
“brain garbage collectors and transporters”**

Glia collecting debris, and dumping it into blood vessel

RIGA, S. et al., *Ann. N.Y. Acad. Sci.* 1067: 383–387 (2006)

RIGA, S. et al., *Arch. Gerontol. Geriatr.* suppl. 4 (1994) 227-234



Hypothesis regarding the Pathophysiology of Autistic Regression

- *Too much allostatic load plus genetic and environmental weak points.*
- *Oxidative stress and inflammation*
- *Cells become hypersensitive and overreactive*
- *Tipping point is reached.*
- *Brain glial cells poop out and don't keep up their housekeeping functions.*
- *Brain energy production gets less efficient.*
- *Brain networks get weaker*
- *Weaker brain networks produce weaker interactions with world*
- *This produces behaviors we call “autistic.”*

Spelled out in more detail in Chapter 5 of
THE AUTISM REVOLUTION (Herbert 2012)

Why does garbage pile up?

TOO MUCH BAD STUFF

- Toxicants that actively interfere with cellular processes
- Molecular debris from cellular stress and inflammation

NOT ENOUGH GOOD STUFF

- Not enough nutrients needed to run clean-up operations and keep things working
- Blood flow that is less than it should be due to sickness, poor nutrition, inflammation or oxidative stress

The brain needs energy and nutrition supplies

- **Abundant supplies allow the brain to**
 - work at its best
 - protect it from being dragged down by inflammation and other health problems.
 - **TAKE OUT THE GARBAGE!**
- **Better brain health will help restore the brain's full powers.**
- **We can support brain health through “nutrient flooding” – high nutrient density diet**

Build **Resiliency** and Reduce Allostatic or “**Total Load**”

RESILIENCY

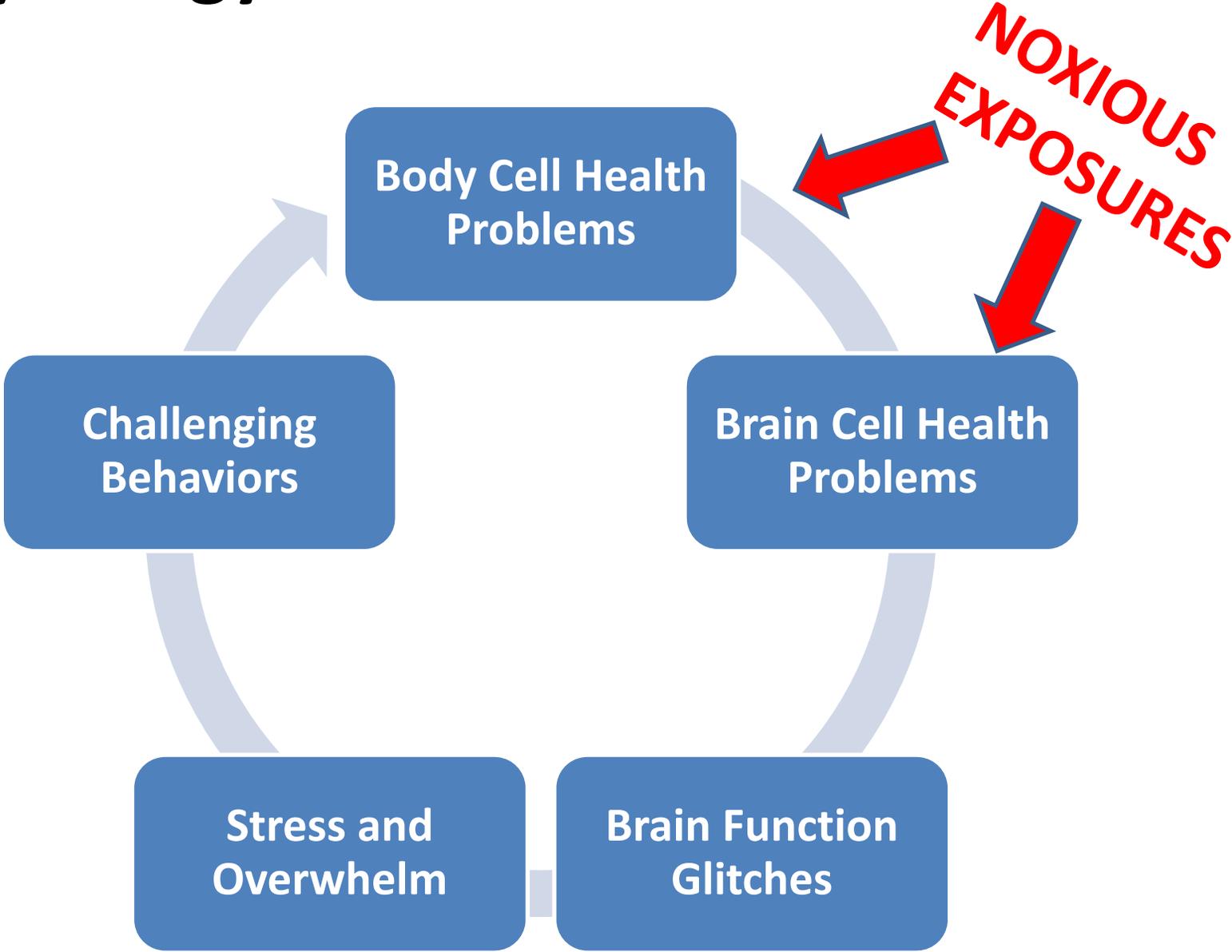
- The TOTAL SET of strengths, adaptations, skills, cell health, nutritional fortitude, exercise, community and more

“TOTAL LOAD”

- The TOTAL BUILD-UP of noxious exposures, stressors and deficiencies

Building **RESILIENCY** protects brain from the debilitating impacts of tissue pathophysiology

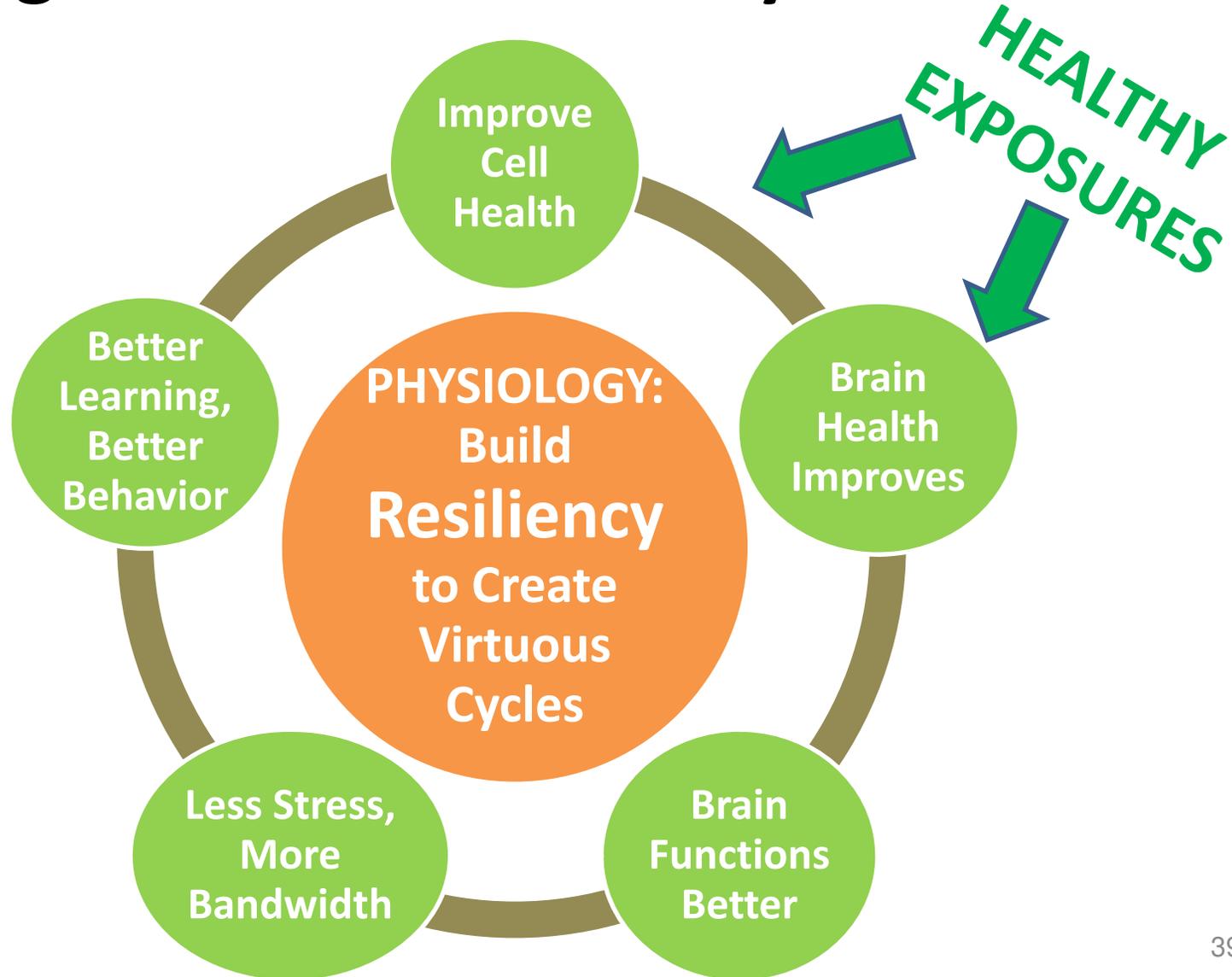
Physiology across levels: Interrelated



Problems in each area make trouble for the other areas



Dialing back the problems and Moving Toward Whole Body-Brain Health



PROPOSITION / ASSERTION:

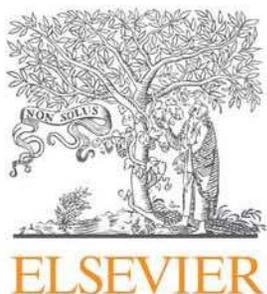
**We know enough now to
promote health and hunt for and
remove contributors to harm**

FOOD CAN PROTECT FROM TOXICITY

Biochemical Pharmacology

72(2006) 1397 – 1421

BIOCHEMICAL PHARMACOLOGY 71 (2006) 1397–1421



available at www.sciencedirect.com



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



Commentary

Molecular targets of dietary agents for prevention and therapy of cancer[☆]

Bharat B. Aggarwal^{a,*}, Shishir Shishodia^b

^a Cytokine Research Laboratory, Department of Experimental Therapeutics,
The University of Texas M.D. Anderson Cancer Center, Box 143, 1515 Holcombe Boulevard, Houston, TX 77030, USA

^b Department of Biology, Texas Southern University, 3100 Cleburne Street, Houston, TX 77004, USA

ARTICLE INFO

ABSTRACT

Dietary agents with anti-cancer properties

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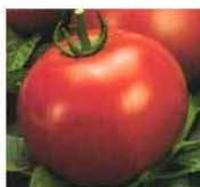
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Artichoke
(Silymarin)



Oleander
(Oleanderin)



Tomato
(Lycopene)



Garlic
(Diallyl sulfide, ajoene,
S-allyl cysteine, allicin)



Carrots
(β -carotenes)



Tea
(Catechins)



Red grapes
(Resveratrol)



Red chilli
(Capsaicin)



Turmeric
(Curcumin)



Cloves
(Eugenol &
isoeugenol)



Honey-bee propolis
(Caffeic acid, CAPE)



**Cruciferous
vegetables**
(Sulforaphane)



Pomegranate
(Ellagic acid)



Ginger
(6-Gingerol)



Basil
(Ursolic acid)



Fennel,
(Anethol)



Soybean
(Genistein)



Aloe
(Emodin)

Fig. 1 - Dietary agents with anti-cancer properties.

Molecular Targets of Dietary Agents Vastly Rich – On Frontiers of Science

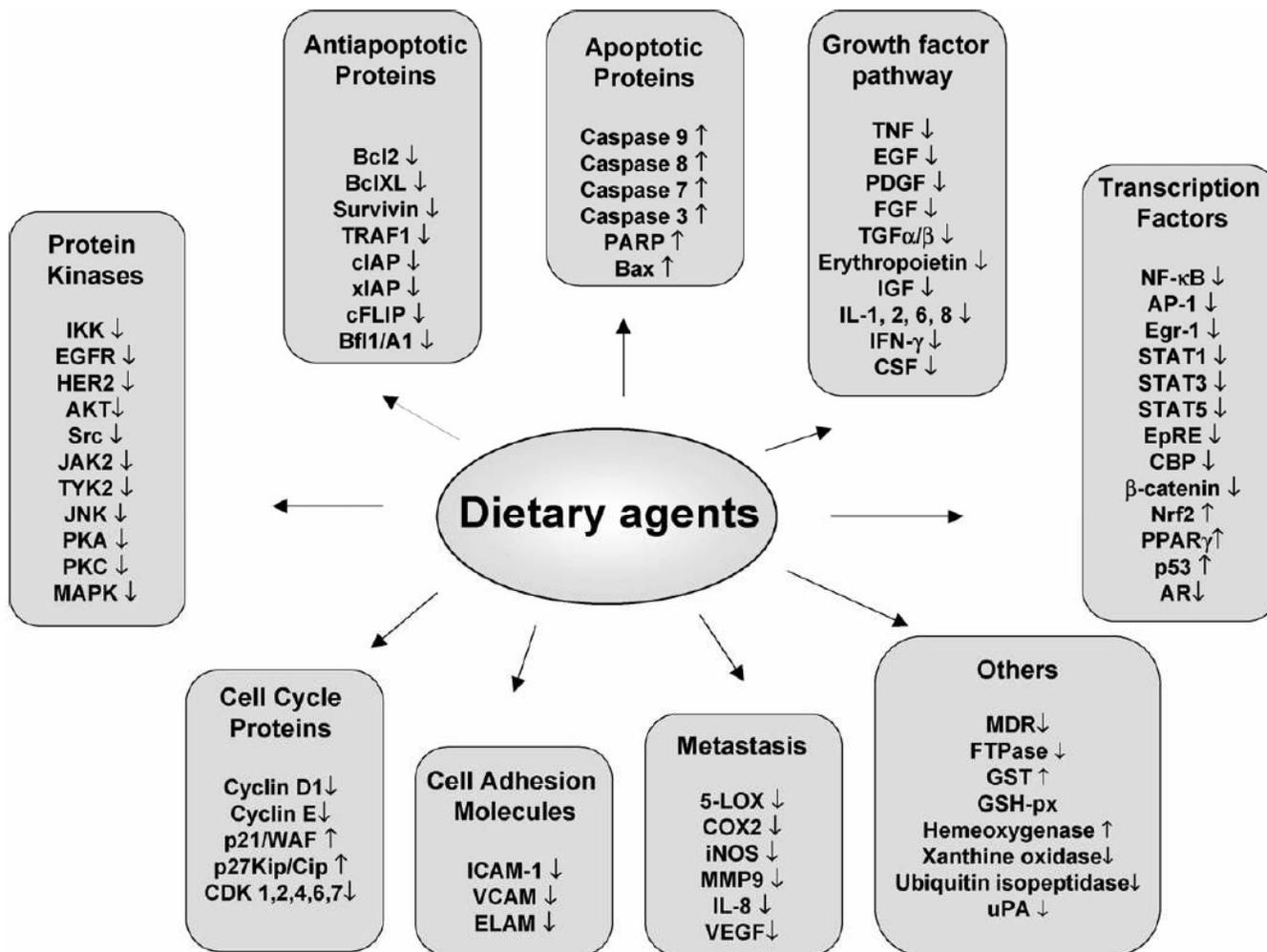


Fig. 3 – Molecular targets of dietary agents.

Recipe for Improvement: Two Basic Principles

MAXIMIZE

WHAT'S GOOD

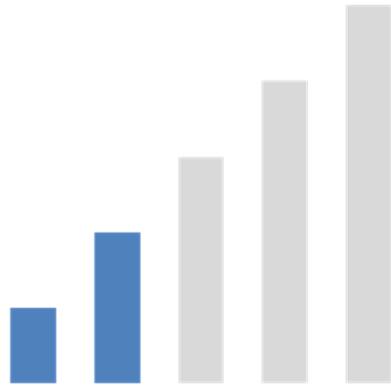
- **Build resilience through**
 - FOOD
 - ACTIVITY
 - BALANCE
 - OPTIMAL INFORMATION INPUT
 - KEEPING GUT BUGS HEALTHY

REDUCE

TOTAL LOAD

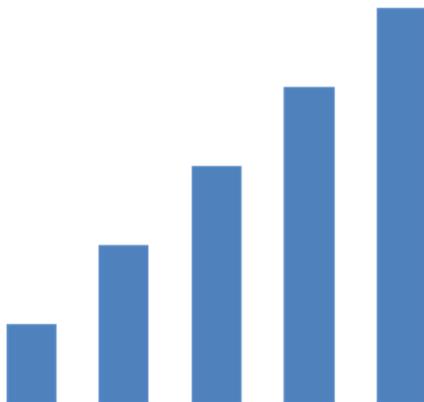
- **Eliminate drag by**
 - REDUCING TOXIC EXPOSURES AND ALLERGENS
 - GETTING ENOUGH SLEEP
 - PLENTY OF EXERCISE
 - BRAIN-BUILDING MOVEMENT
 - AVOIDING AND REDUCING INFECTION

RECIPE FOR IMPROVEMENT



POOR BANDWIDTH, LOTS OF CHAOS

- Poor food: few nutrients, many allergens
- Lots of toxins and infectious issues
- Lots of stress, pressure, too much too fast



GOOD BANDWIDTH, RICH ORGANIZATION

- Excellent food: high nutrient density, minimal allergens
- Minimal toxic and infectious burden
- Love, learning, respect, sensitive sensory input, savor each moment

Autism Revolution: Ten Tips

- 1. Go for the extraordinary.**
- 2. Know what you can't control (genetic code) — and what you can (gene expression, environment).**
- 3. Repair and support cells and cycles.**
- 4. Get gut and immune systems on your side.**
- 5. Build better brain health.**
- 6. Calm brain chaos**
- 7. Join your child's world.**
- 8. Love, rejoice, and make breakthroughs.**
- 9. Lead the revolution!**
- 10. Do it for yourself, your next baby, your family, and your world.**

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