THE AUTISM REVOLUTION:

From a Static Brain Defect to a Chronic Systemic Dynamic TREATABLE Encephalopathy

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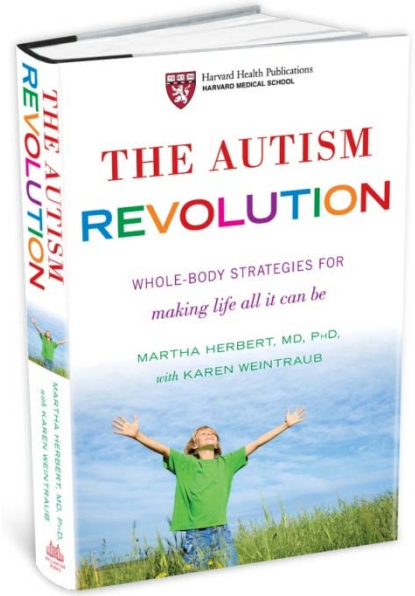
www.AutismRevolution.org

TRANSCEND



www.AutismRevolution.org

www.autismWHYandHOW.org

Autism: A *Behaviorally Defined* Syndrome

Biology is not part of the definition (and neither is prognosis)

DSM-IV Criteria for Autistic Disorder (299.0)

1. **Impaired social interaction**
2. **Impaired social communication**
3. **Markedly restricted repertoire of activities and interests**

Secondary Features of Autism

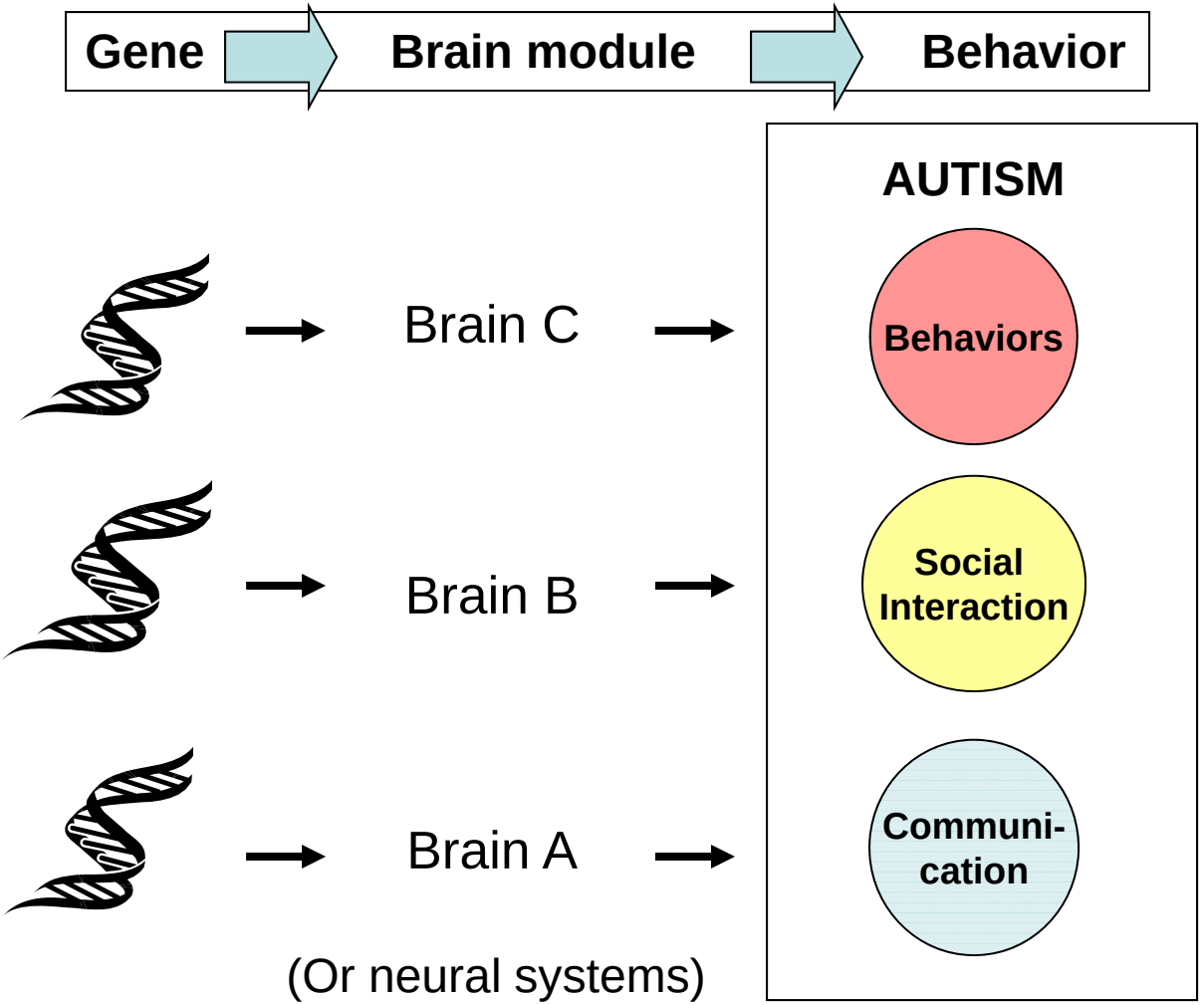
Seizures (~30%+), cognitive deficits, sensorimotor abnormalities, savant skills, immune impairments, GI distress(50-75%), food allergies (~50+%)

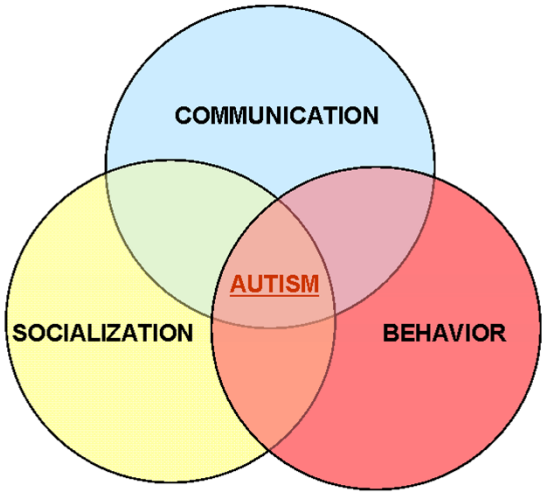
No biological markers exist to identify autism at this time

Autism is presumably *Heterogeneous biologically*

But autism is *biological*

From Definition to Model of Autism: Classic Modular Framework





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:

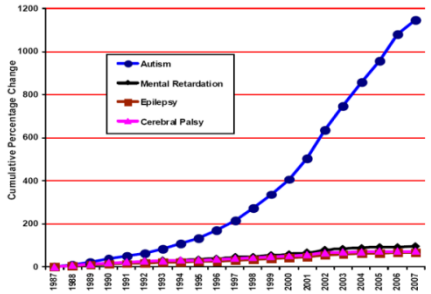
- ***Systemic features – Whole Body***
- ***Environmentally vulnerable physiology***

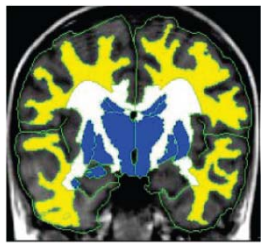
Not just brain modules:

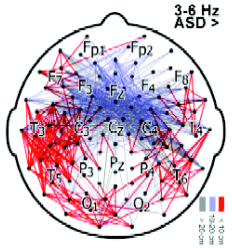
- ***Whole brain involvement***
- ***Brain tissue changes***

Not necessarily hardwired:

- ***Plasticity and recovery***







Is autism is really a hard-wired defect?

Research and clinical observations suggest otherwise:

- **Published transient improvement with fever**
  - **Reports of this under various other circumstances**
- **Documented recovery / remission in some cases**
- **Reversal of symptoms in autism-relevant animal models**

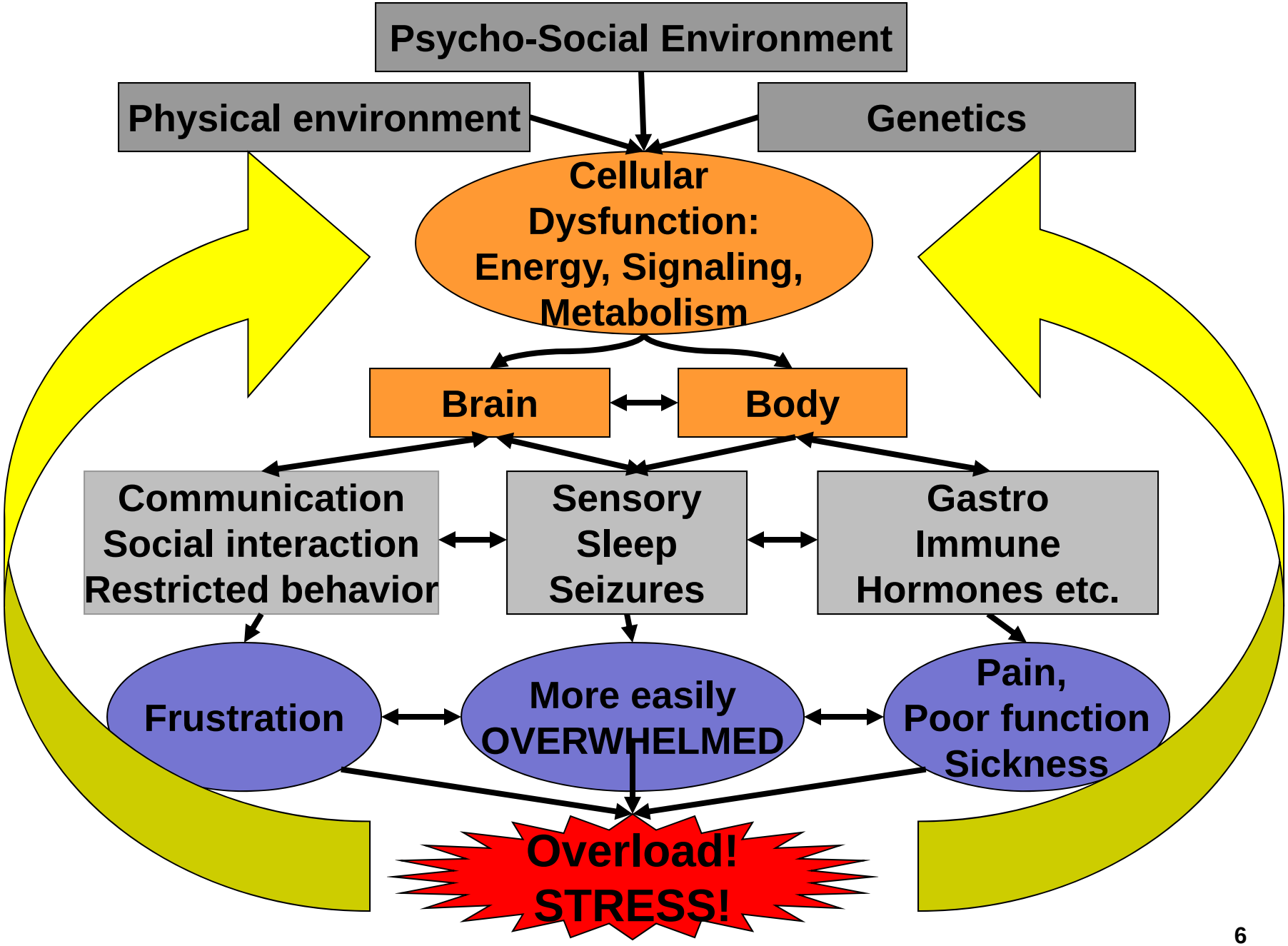
HOW CAN THE BRAIN IMPROVE LIKE THIS?

WHAT IS THIS TELLING US ABOUT AUTISM?

Hypothesis:

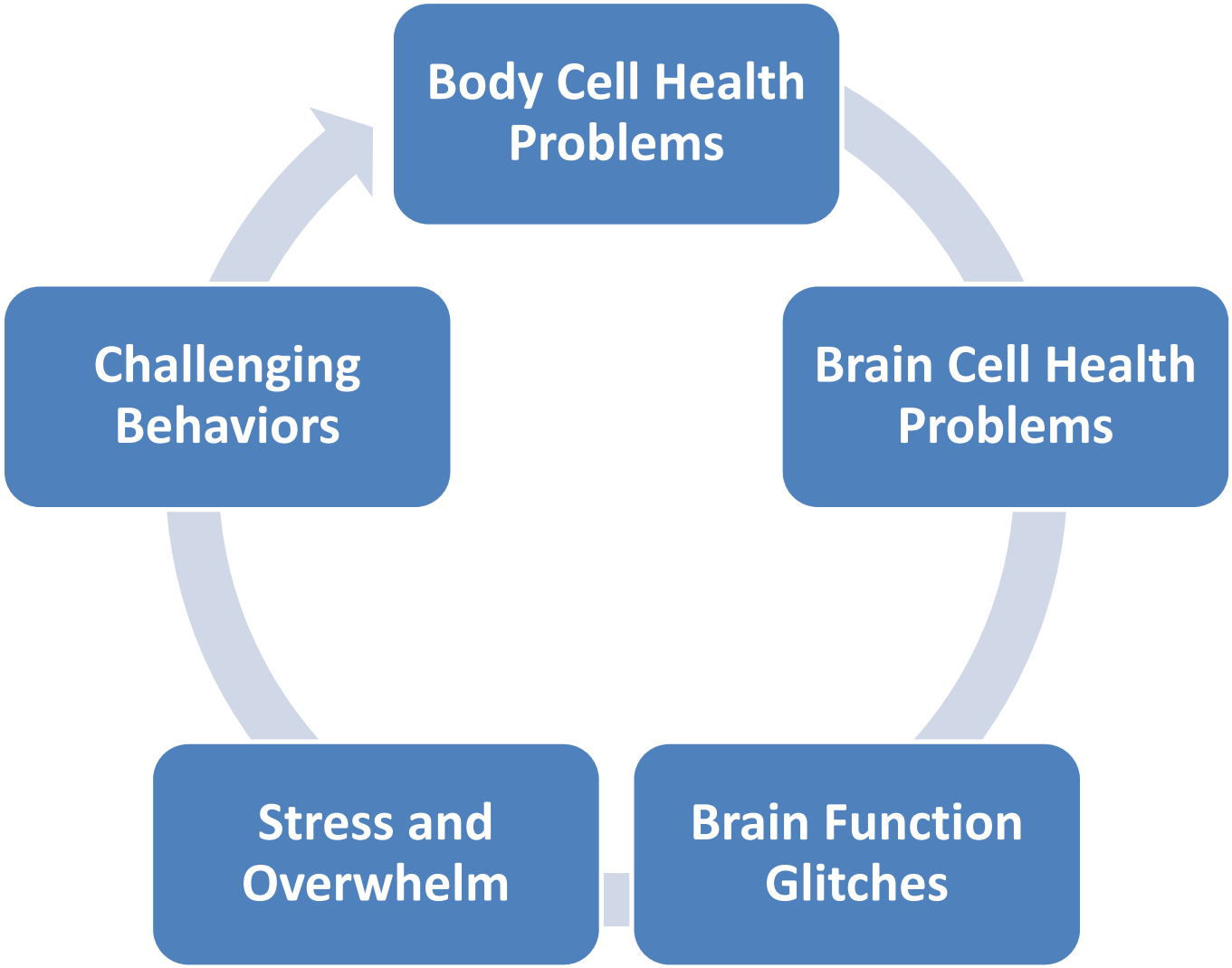
➔ASD: Not a STATIC but a DYNAMIC encephalopathy

Whole Body Model: Vicious circles in brain and body

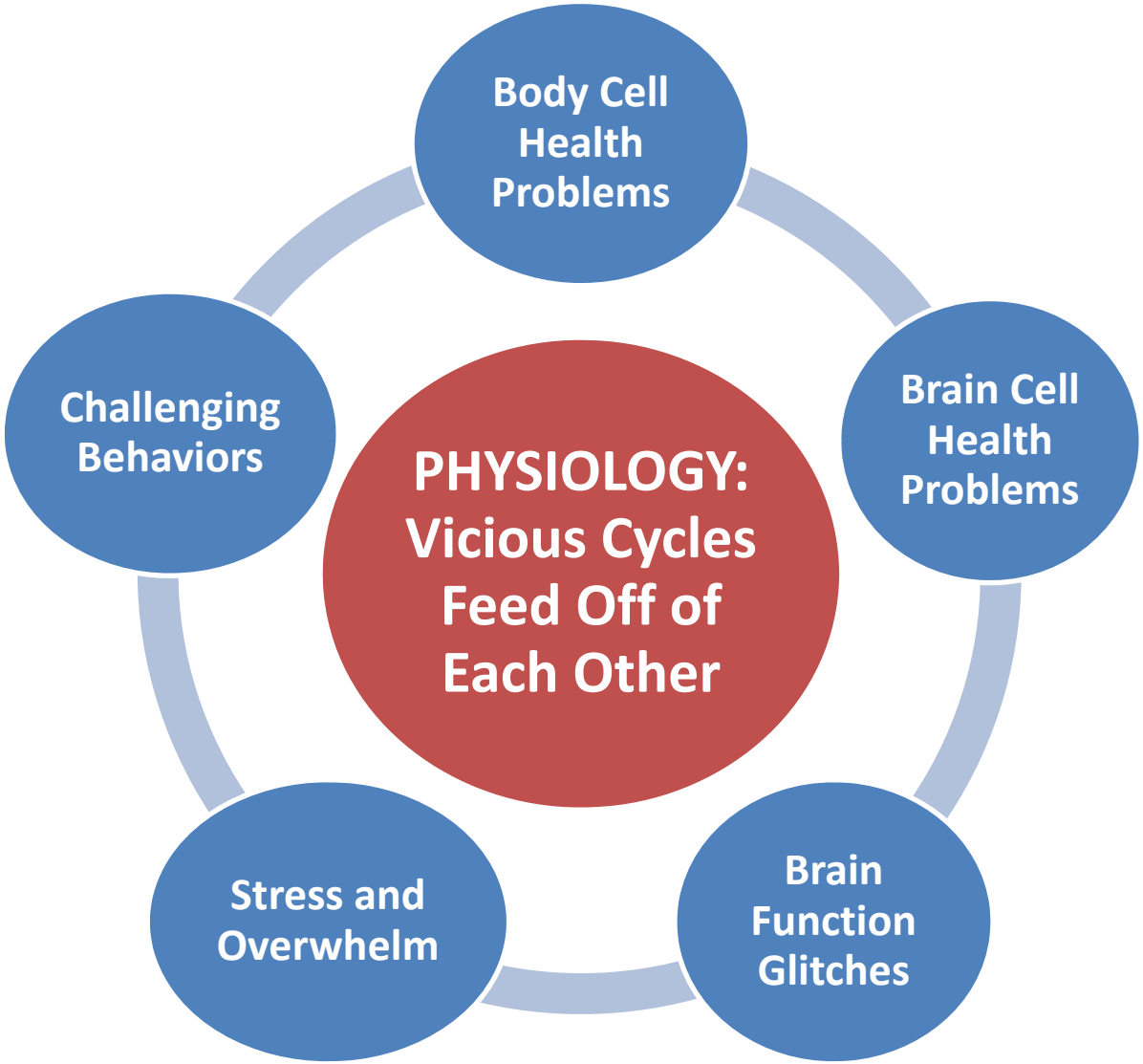


An Overview of Biomed

All the parts really influence each other

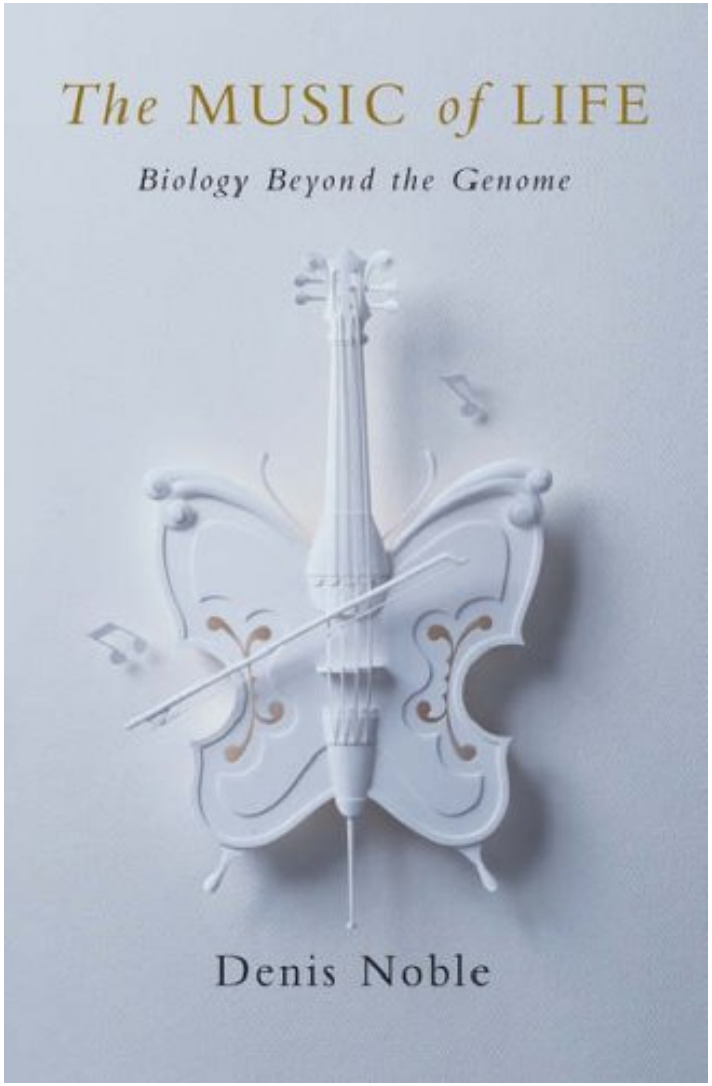


Problems in each area make trouble for the other areas



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

The Music of Life:
Biology Beyond the Genome

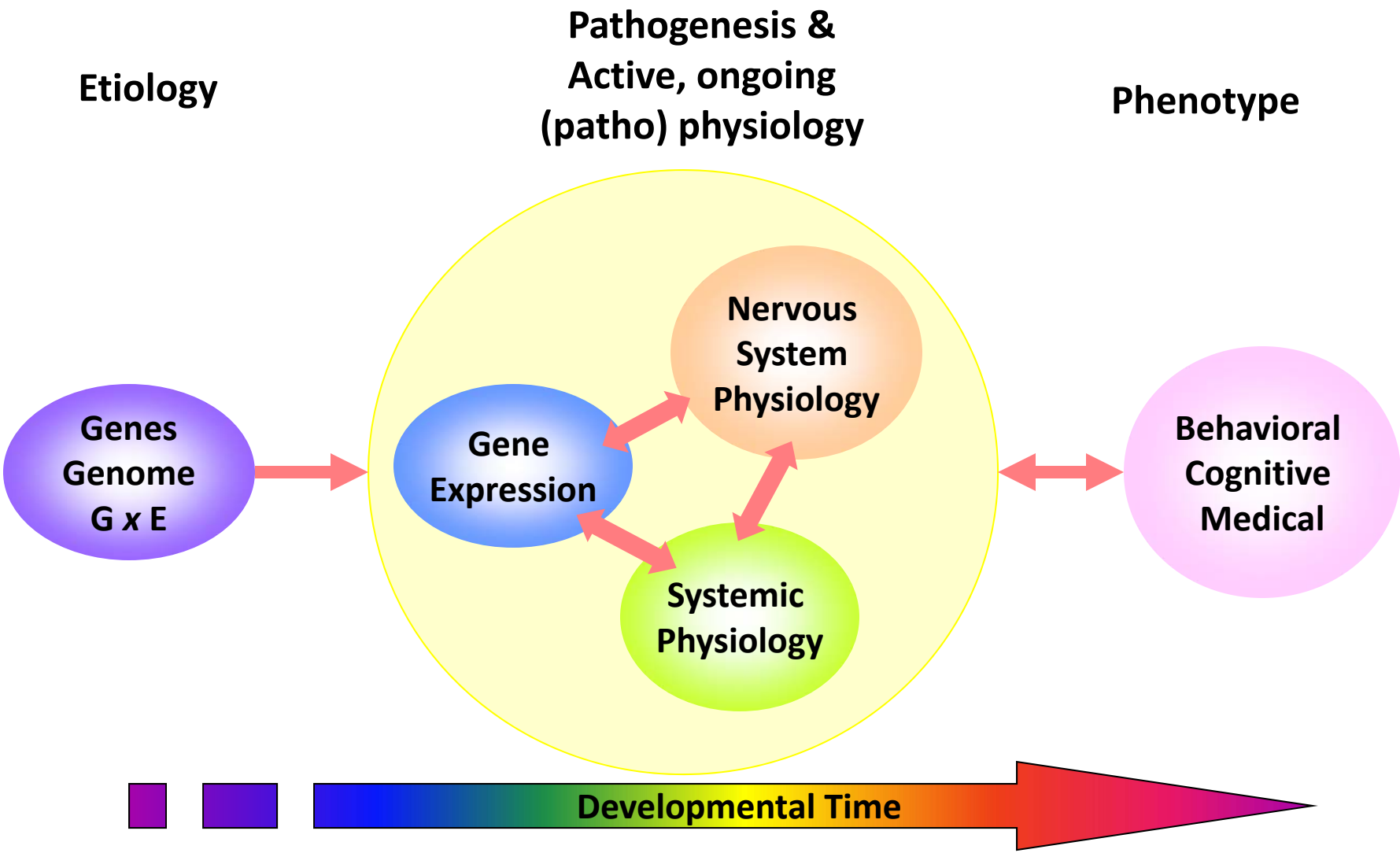


Beautiful readable book

Discusses physiology and the "middle→out" approach

http://www.musicoflife.co.uk/

A Middle-Out Approach to Autism: Physiology Centered



Assumption: Autism is a “developmental disorder”

This seems obvious.

But it carries a lot of extra baggage.

Assumption: Autism is a "developmental disorder"

What are the IMPLICATIONS of this assumption?

1. **It's all genetic and predetermined**
2. **The damage is done really early, probably before you are born**
3. **The brain is fundamentally and irretrievably differently structured and "broken"**
4. **Brain changes are the cause of ALL the problems**
5. **There is nothing you can do about it**

LET'S EXAMINE THE EVIDENCE

Not just genetic and predetermined: From Genetic to Gene x Environment, Epigenetics and Gene x Physiology x Environment

1. Are the numbers really going up?
2. Genes, environment and epigenetics can interact

GENETIC EXPLANATIONS

Sense and Nonsense

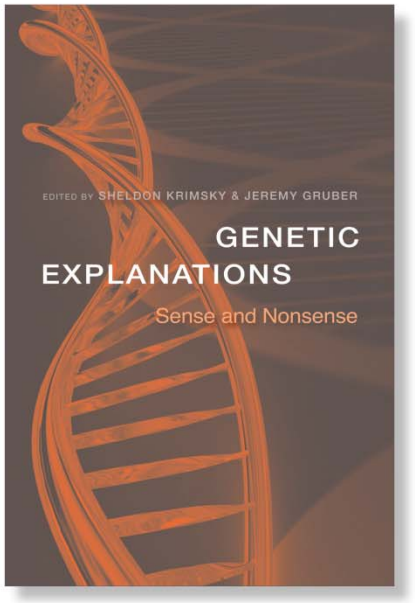
Edited by SHELDON KRIMSKY and JEREMY GRUBER

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

Ch.10 on Autism:

From Static Genetic Brain Defect to Dynamic Gene-Environment-Modulated Pathophysiology

By Martha Herbert

One-page summary and section headers posted on www.marthaherbert.org under publications – click link for this article

TITLE:

Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment Modulated Pathophysiology

AUTHOR:

Martha R. Herbert, PhD, MD

PUBLICATION:

Chapter 10 of *Genetic Explanations: Sense and Nonsense*. Krimsky, S. and Gruber, J. eds, Harvard University Press (2012).

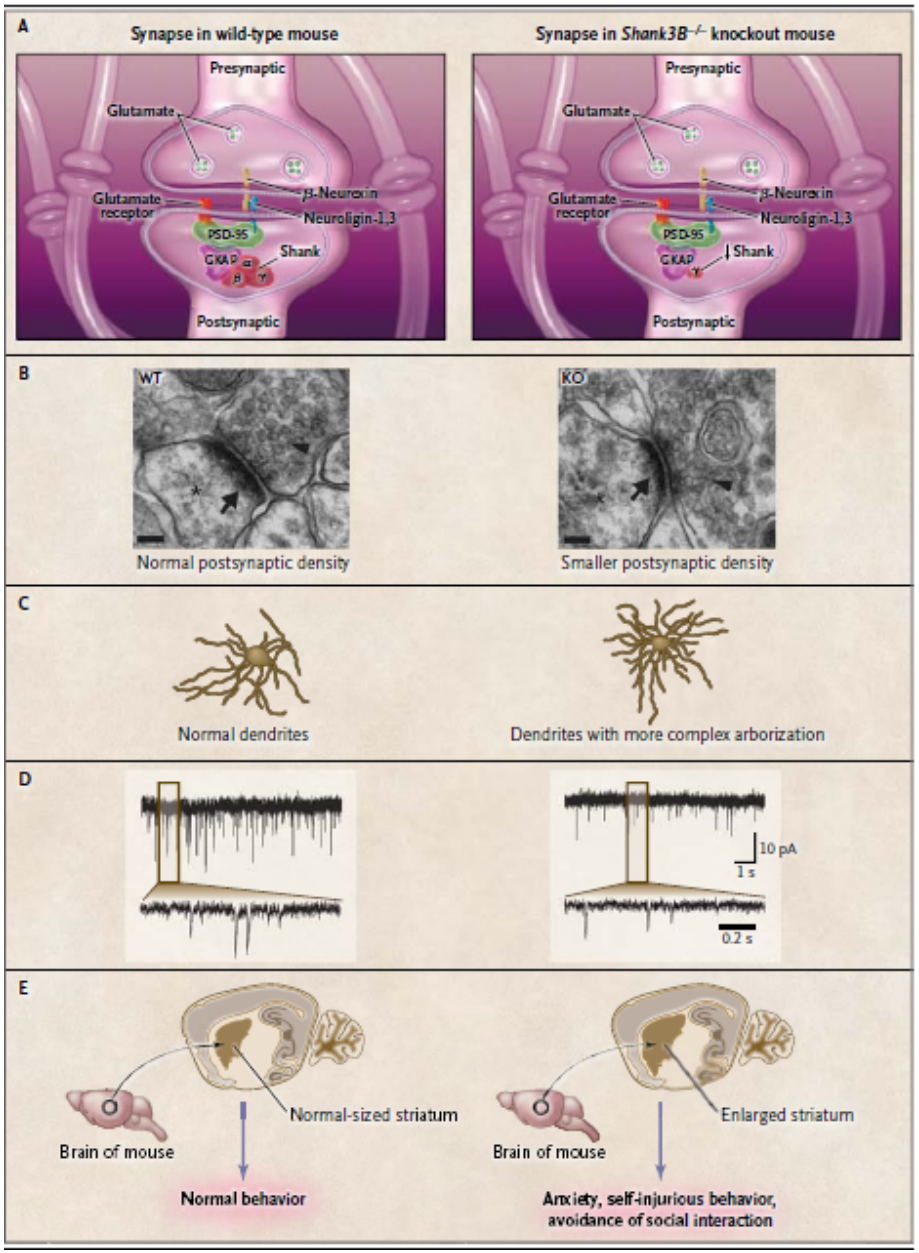
CHAPTER'S SECTION HEADERS:

A version of the above material written through stories, practically oriented and readable by the general public is **THE AUTISM REVOLUTION: Whole Body Strategies For Making Life All It Can Be**, by Martha R. Herbert with Karen Weintraub. Ballantine/Harvard Health Publications, 2012.

Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting

C. Betancur, Brain Res 2011 42-77

- **An exhaustive review of the clinical genetics and research genetics literature**
- **103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior.**
- **Commonalities with intellectual disability and epilepsy.**

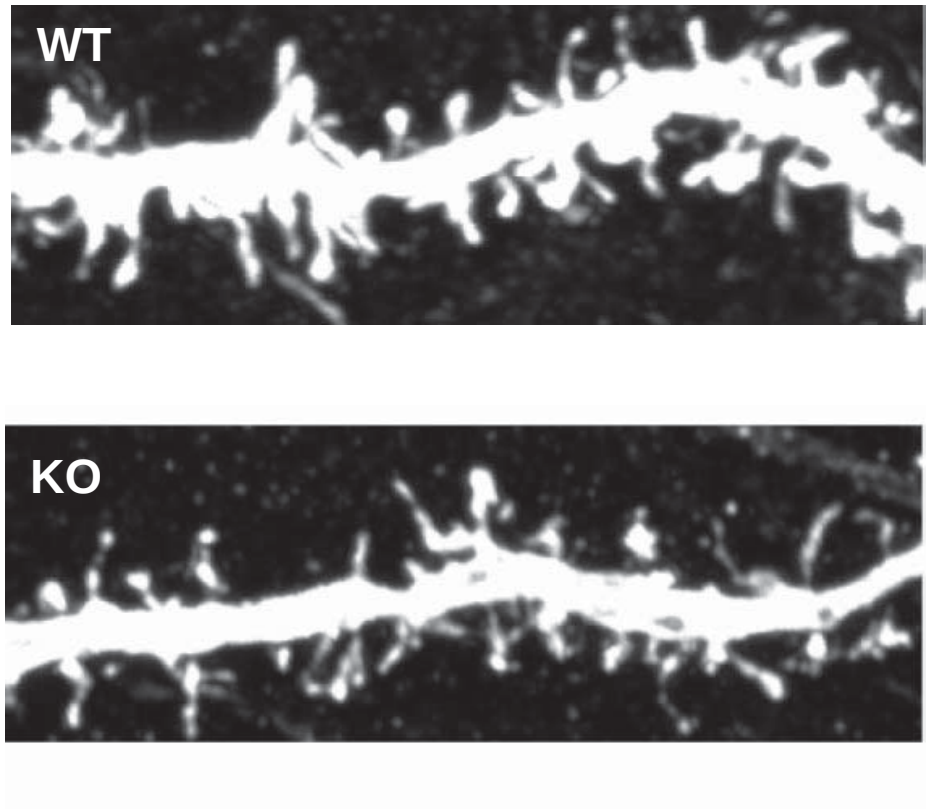


SHANK3, the Synapse and Autism

- **Altered postsynaptic density (PSD) proteins**
- **Smaller PSD**
- **Fewer dendritic spines**
- **More dendritic arborization**
- **Weaker signaling**
- **Larger striatum**
- **Autistic-like behaviors**

Herbert *NEJM* 2011 commenting on Peça et al., *Nature* 2011

Lower dendritic spine density



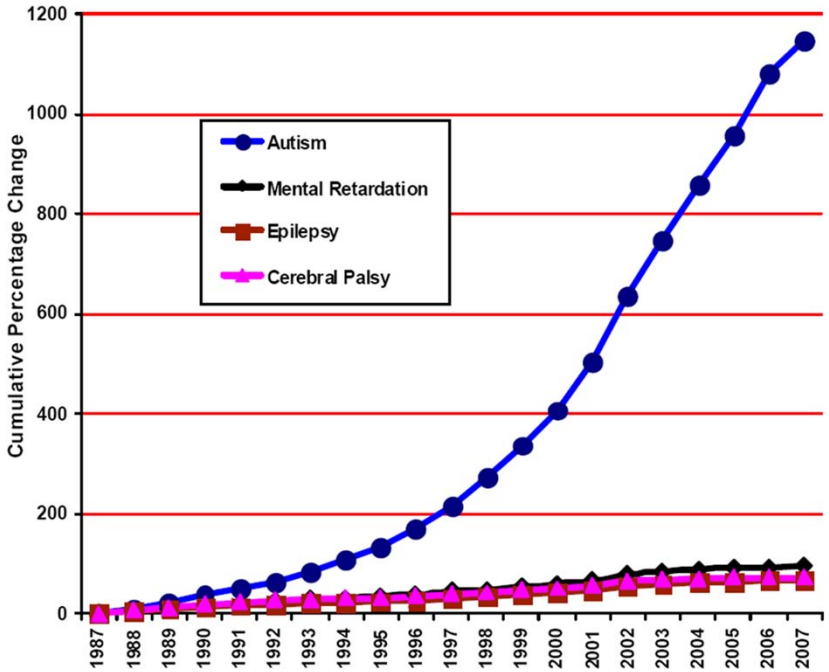
- **Spine density in striatal medium spiny neurons (MSNs) from *Shank3B*$^{-/-}$ mice is lower than that of wild-type MSNs**

Peça et al., *Nature* 2011

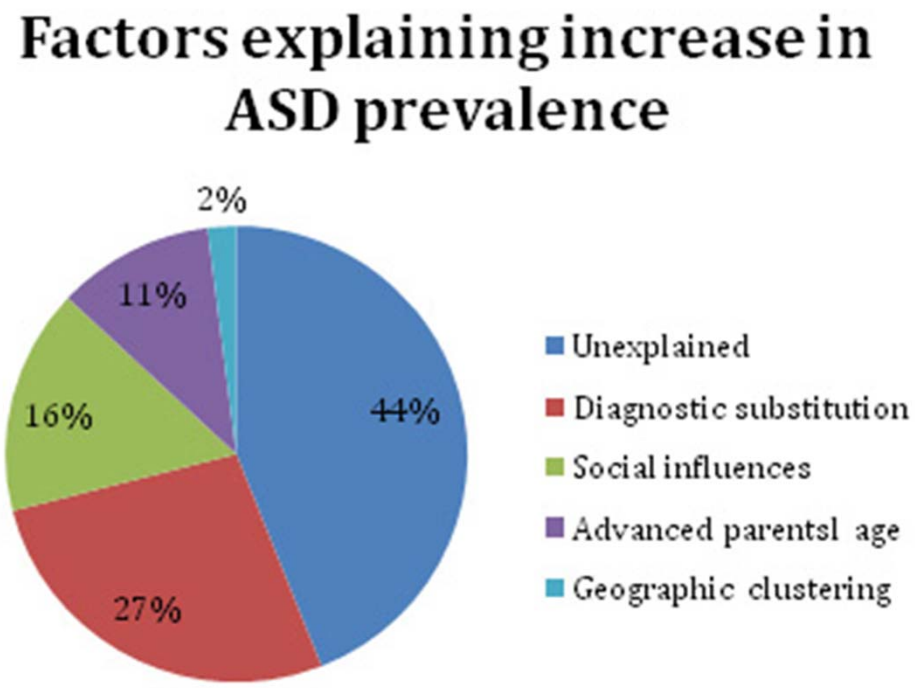
Complications

- **Well over 100 different genetic disorders involve an autistic phenotype (Betancur, *Brain Res,* 2011)**
- **These in turn comprise a small minority of cases with autism**
- **The synapse and PSD are highly complex**
- **Shank3 is expressed not just in brain but in gut and kidney, is involved in epithelial turnover and mucosal immune development, and is utilized by some gut pathogens in actin rearrangement. (Huett et al., *Exp Cell Res*, 2009)**

Environmental Role in Autism



2009 California report: http://www.dds.ca.gov/Autism/docs/AutismReport_2007.pdf



Growing body of associations of environmental exposures with autism risk and prevalence

Is autism really "all" genetic?

Twin studies and high recurrence support genetic influence, not genetic determination.

:

- **More identical than fraternal twin pairs are *concordant* (share an autism diagnosis)**
- **But concordance is only 60% for full autism**
- **90% concordance is for broad autistic spectrum (i.e., *milder)* in one of the twins**

What accounts for the incomplete concordance?

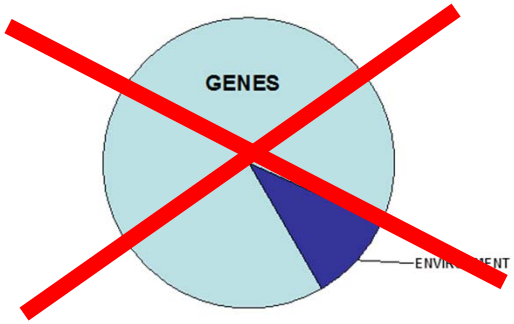
- **Conclusion of largest autism twin study to date:**
  - **Susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component.**
    - **Hallmayer et al, July 2011, Arch Gen Psych**

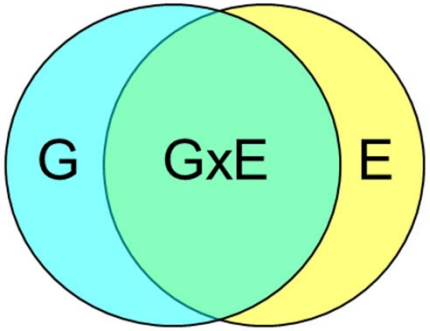
Intriguing question about concordance

- **Swedish study of schizophrenic identical twins**
  - ***Probable same placenta: 60% concordance***
  - ***Different Placentas: 11% concordance***

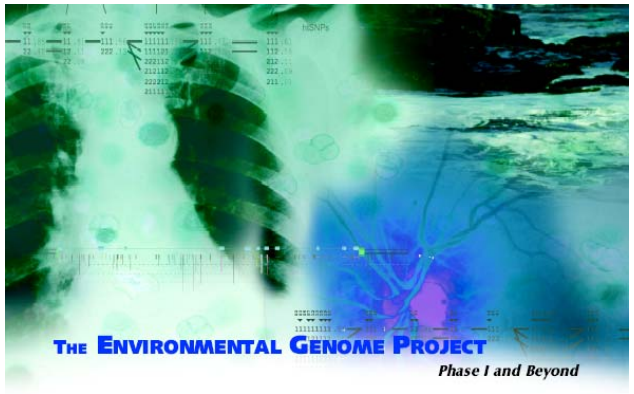
– Davis, Phelps, & Bracha, 1995

Gene-Environment Interactions: Not Either-Or but Both-And,





- G *and* E probably affect most cases
  - ASD can be 80% genetic AND 80% environment
  - Example: if everyone smoked, then who gets cancer is “genetic”
  - Population-attributable fractions do not have to add up to 100%



AUTISM AND ENVIRONMENTAL GENOMICS

Herbert MR, Russo JP, Yang S, Roohi J, Blaxill M, Kahler SG, McCoy L, Ziegler DA, Hatchwell E

Neurotoxicology, 2006

also

Autism and Environmental Genomics

Chapter in AUTISM, Amaral/Dawson,Geschwind, 2011

Defective/deficient GABAa Receptors in Autisms
+
Pesticides that antagonize GABAa Receptors
=
Gene *x* Environment Interaction
Increased Excitation/Inhibition Ratio

Pesticides that are Non-Competitive GABA antagonists

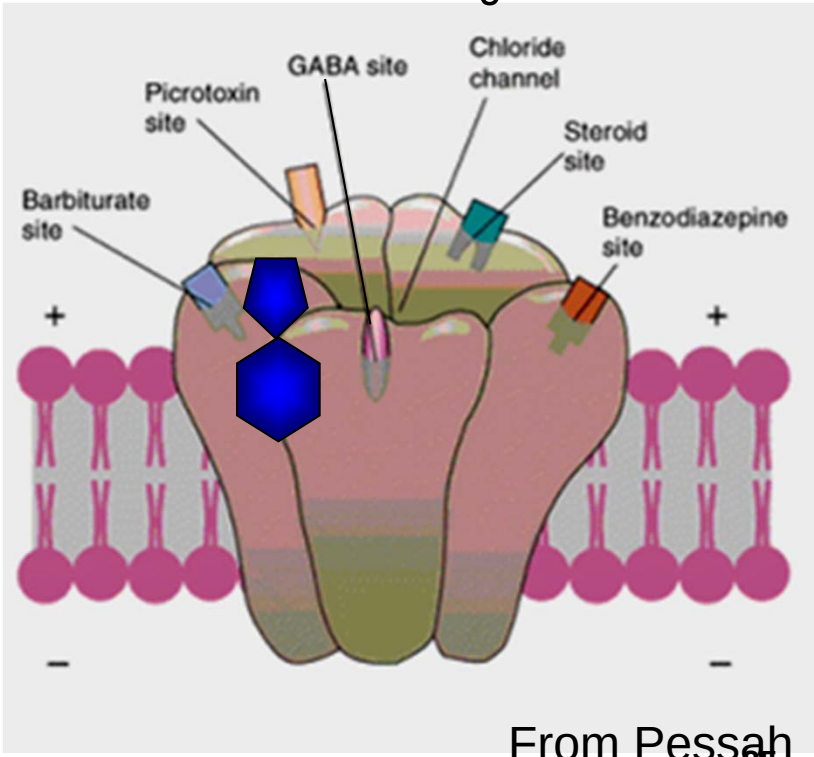
Fipronil (4-alkyl-1-phenylpyrazole)

>800 tons applied in 2000

Regent®
Goliath®
Nexa®
Adonis®

Chipco Choice®
Frontline®

Schematic illustration of a $GABA_A$ receptor with its binding sites



From Pessah

Factors that may increase autism risk

Environmental, Diet

- **Air pollution (Volk, 2011; Windham, 2006)**
- **Pesticides ((Roberts, EHP, 2007; Eskenazi, 2010)**
- **Low Vitamin D**
- **Flame retardants**
- **Antimicrobials in soaps**
- **Heavy metals**

Medical

- **Maternal obesity**
- **Maternal hypertension**
- **Maternal diabetes**
- **Maternal infection during pregnancy**
- **Familial autoimmune disease**
- **Antibiotics**

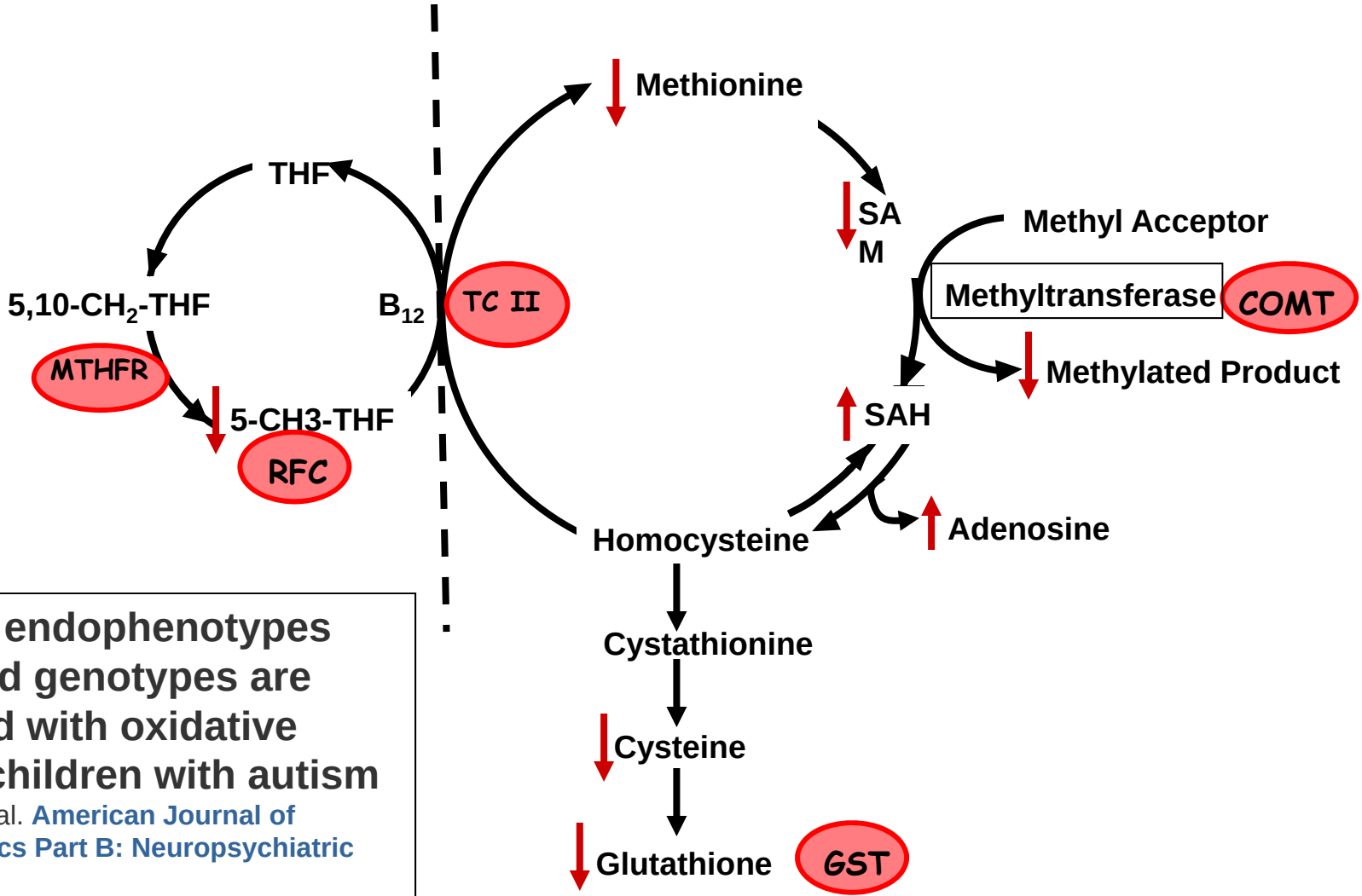
Sources include Hertz-Picciotto; van de Water; Patterson; Smith; others

Environmental factors that may reduce risk

- **Prenatal vitamins and One-Carbon Metabolism Gene Variants**
  - **Mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy (OR = 0.62 [95% confidence interval = 0.42-0.93]).**
  - **Significant interaction effects were observed for maternal MTHFR 677 TT, CBS rs234715 GT + TT, and child COMT 472 AA genotypes, with greater risk for autism when mothers did not report taking prenatal vitamins periconceptionally (4.5 [1.4-14.6]; 2.6 [1.2-5.4]; and 7.2 [2.3-22.4], respectively)**

Schmidt et al., *Epidemiology,* 2011

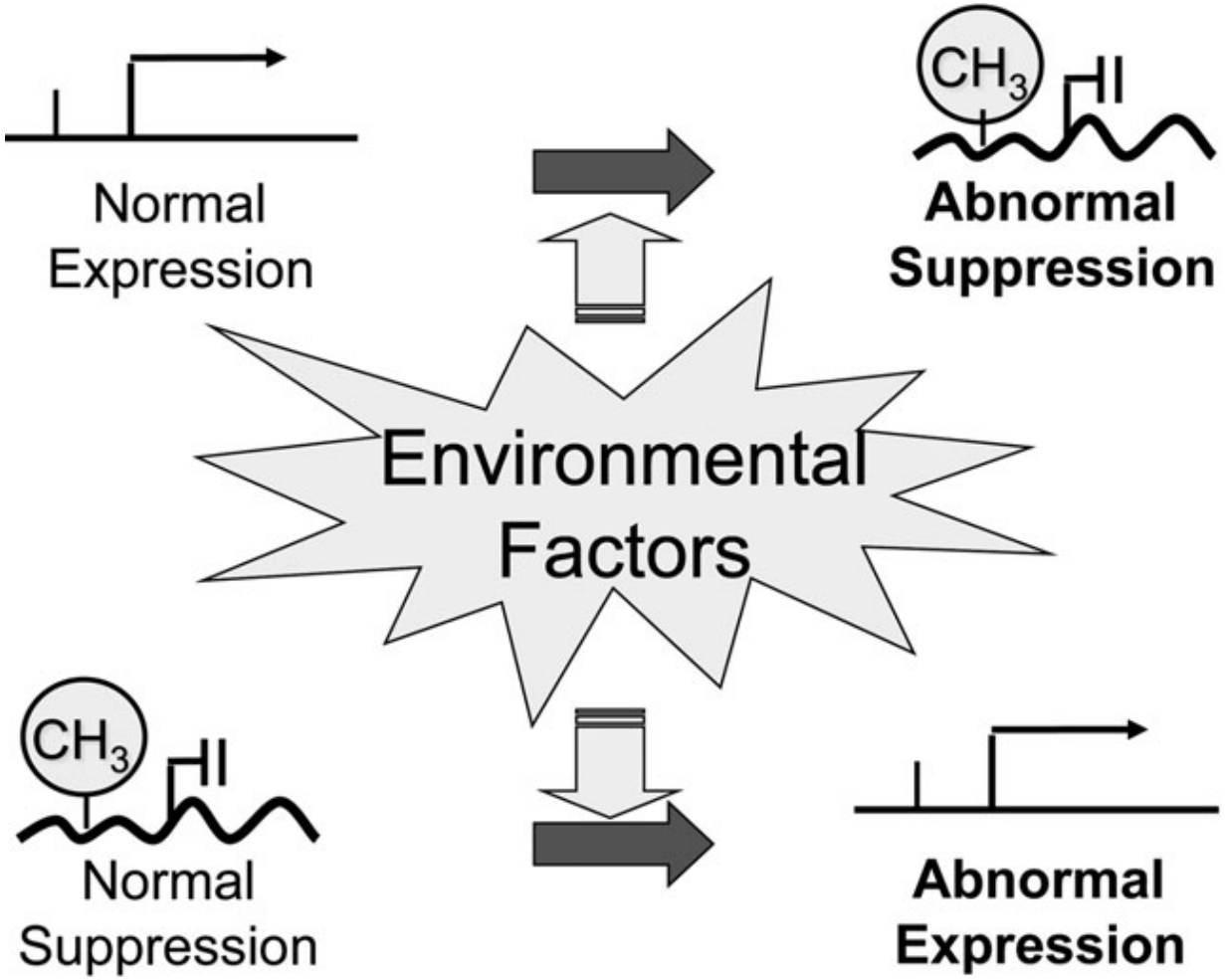
Metabolic Response to Genetic Polymorphisms in the Methionine Cycle



Metabolic endophenotypes and related genotypes are associated with oxidative stress in children with autism

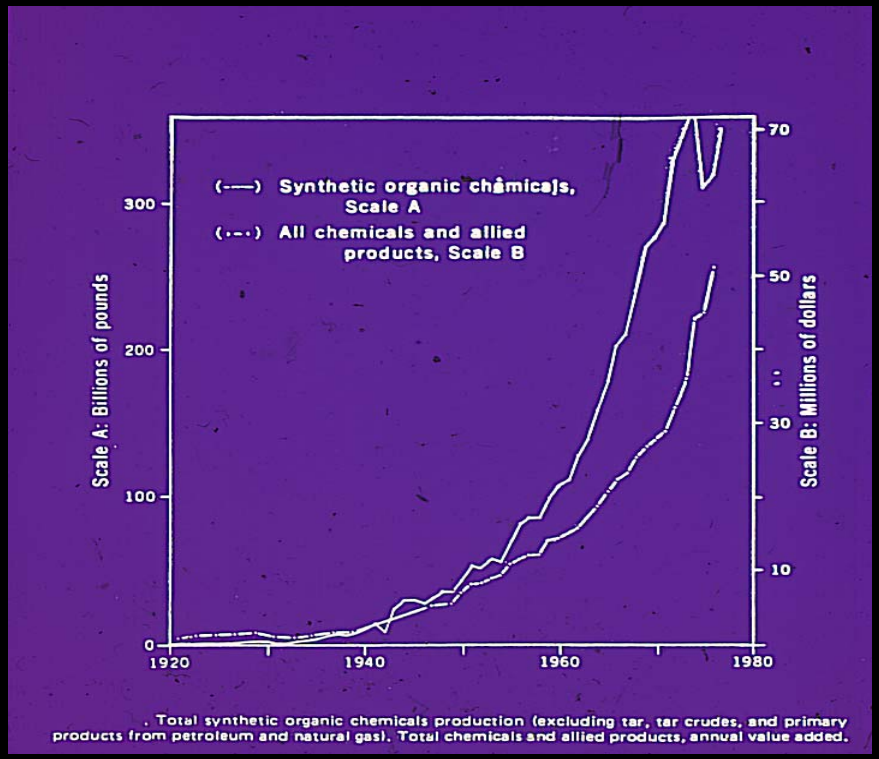
S. Jill James et al. **American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2006**

Epigenetics



Miyake, K., T. Hirasawa, et al. (2012). "Epigenetics in autism and other neurodevelopmental diseases." Adv Exp Med Biol **724**: 91-98.

"Environment" is not a constant: Unprecedented production of new-to-nature substances



Of the 287 chemicals detected in umbilical cord blood:

- **180 cause cancer in humans or animals**
- **217 are toxic to the brain and nervous system**
- **208 cause birth defects or abnormal development in animal tests**
- **Nearly 200 have been banned from the market for years**

www.bodyburden.org

The planet is not stable.

Our national faith so far has always been "There's always more." Our true religion is a sort of autistic industrialism.

- Wendell Berry, Harper's, May 2008

UN Report by 1360 scientists :

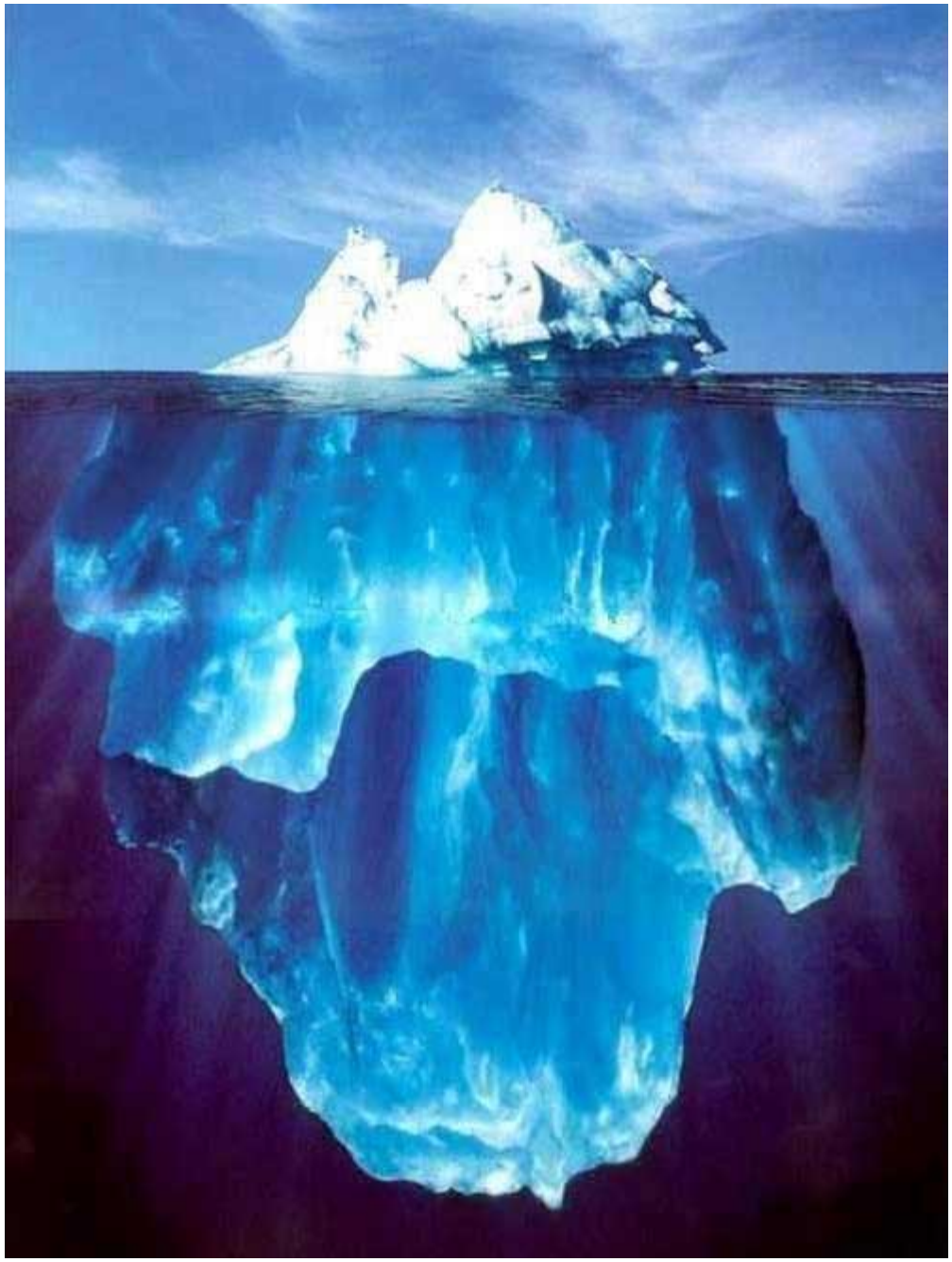
Ecosystem damage is so severe that we can no longer be confident that the Planet Earth can support human life for more than two generations.

http://www.millenniumassessment.org

Genomic instability

- **TOO MUCH**
  - **Toxic assaults on mitochondrial and cellular integrity**
- **TOO LITTLE**
  - **Nutrients in the diet that protect mitochondria, membranes and DNA repair mechanisms**
- **Inflammation, oxidative stress, hypomethylation**
  - **?increase in baseline mutation rate?**

The Autism Spectrum, the Tip of the Iceberg, and the Canary in the Coal Mine



Genomic Instability

Should autism be considered a canary bird telling that Homo sapiens may be on its way to extinction?

By Olav Albert Christophersen

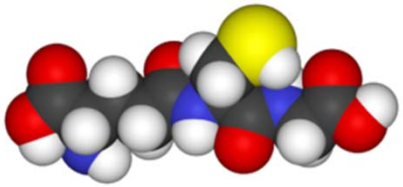
***Microbial Ecology in Health and Disease, 2012,* free online.**

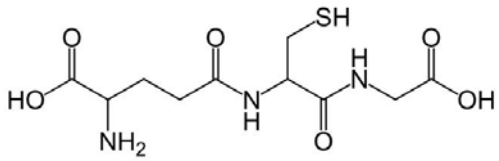
http://www.microbecolhealthdis.net/index.php/mehd/article/view/19008

IN OPEN SOURCE *NEW ISSUE* ON *MICROBIOME*:

http://www.microbecolhealthdis.net/index.php/mehd/issue/current

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



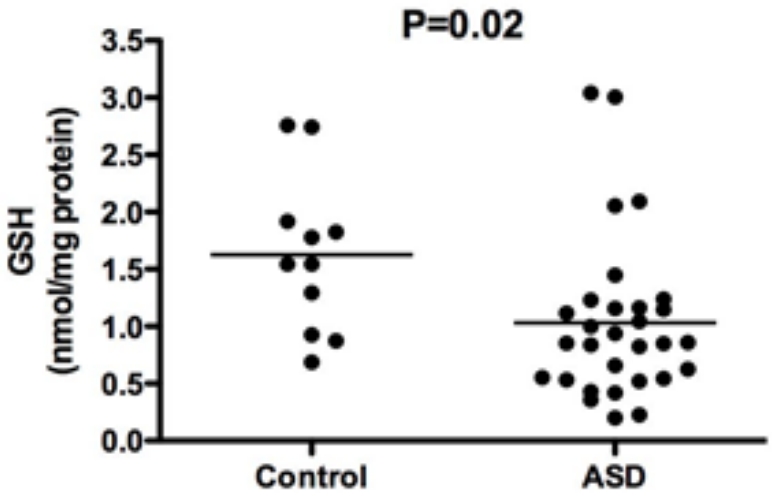


Made in the liver from three amino acids: Glutamate + Cysteine + Glycine

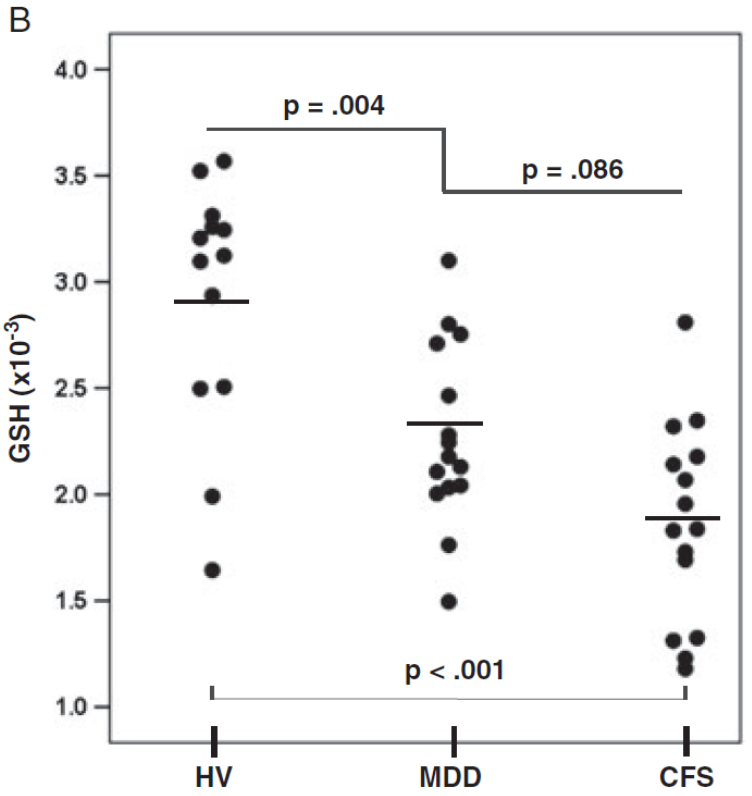
- **GLUTATHIONE is vital for detoxification**
  - **Mops up toxins and free radicals**
- **The body's most potent anti-oxidant**
- **The most abundant antioxidant in the BRAIN**
- ***Final common pathway:***
  - **Depleted by thousands of toxins, oxidative stress, infection, inflammation and nutrient-poor diet**

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,

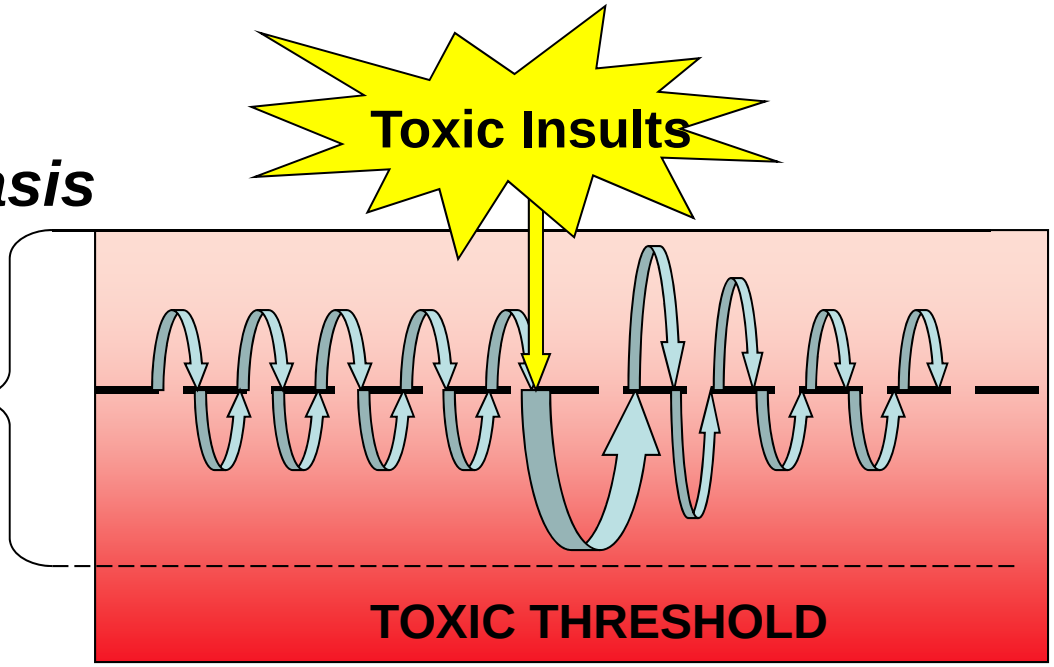


Shungu et al., 2012

Vulnerability with low GSH

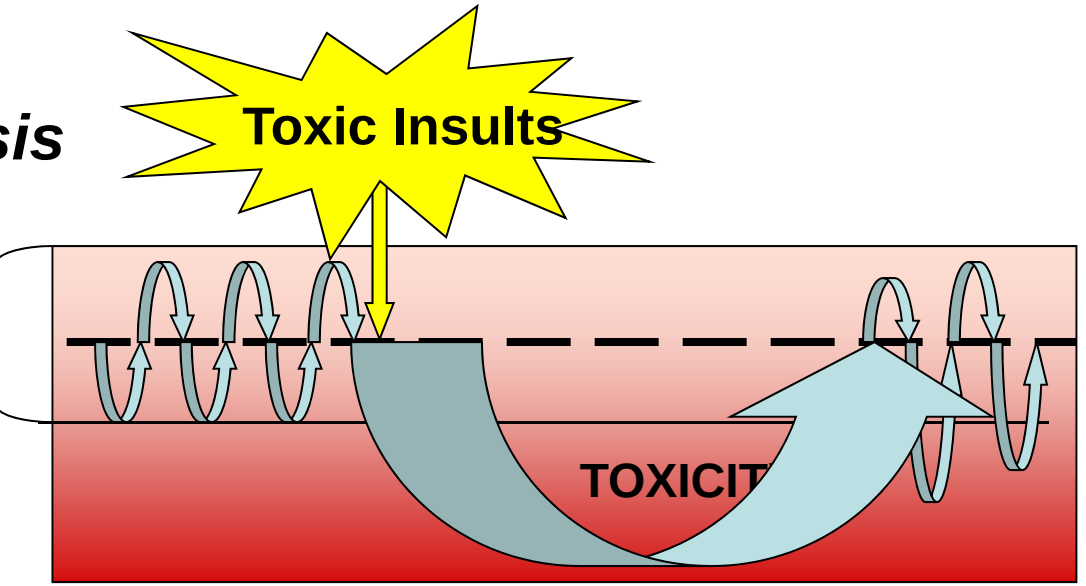
Normal Homeostasis

OK GSH/GSSG



Fragile Homeostasis
(limited reserve)

↓ GSH/GSSG



Environmental factors that may reduce risk

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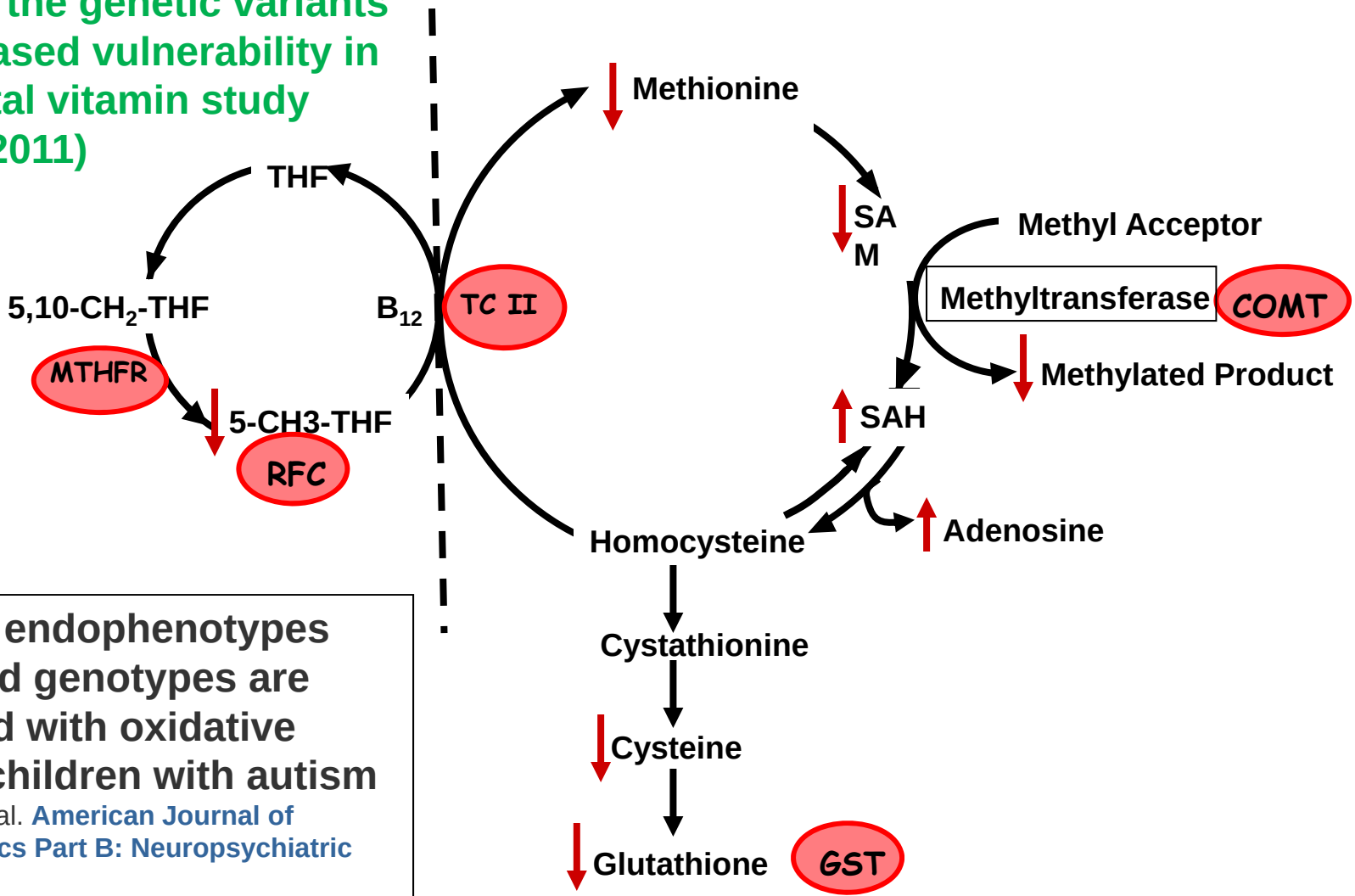
Schmidt et al., *Epidemiology,* 2011

Metabolic Response to Genetic Polymorphisms in the Methionine Cycle

These are the genetic variants that increased vulnerability in the prenatal vitamin study (Schmitz 2011)



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S. Jill James et al. **American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2006**

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.

Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders

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Current Neurology and Neuroscience Reports 2009, 9:129–136
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number of known neurometabolic disorders identified as having an autistic phenotype as well as theories related to other metabolic abnormalities thought to contribute to the development of autism. This is a particularly active area of autism research because a better understanding of these issues has implications both for discovery of the pathophysiologic underpinnings of the disorder and for the development of effective interventions.

- **The cause of autism remains largely unknown because it is likely** multifactorial, arising from the interaction of biologic, genetic, and environmental factors**. The specific role of metabolic abnormalities also is largely unknown, but current research may provide insight into the** pathophysiologic underpinnings of autism**,** at least in some patients**. We review a number of** known neurometabolic disorders **identified as having an autistic phenotype. We also discuss the** possible involvement of mitochondrial disorders and dysfunction as well as a theory regarding an increased vulnerability to oxidative stress, by which various environmental toxins produce metabolic alterations that impair normal cellular function**. Finally, we review various strategies for metabolic work-up and treatment. Accurate diagnosis of neurometabolic disorders and** a broader understanding of underlying metabolic disturbance even in the absence of known disease **have important implications both for individual patients and for research into the etiology of autism.**

Current Neurology and Neuroscience Reports 2009, **9:**129–136

Current Opinion in Neurology, **April, 2010**

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

Martha R. Herbert

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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

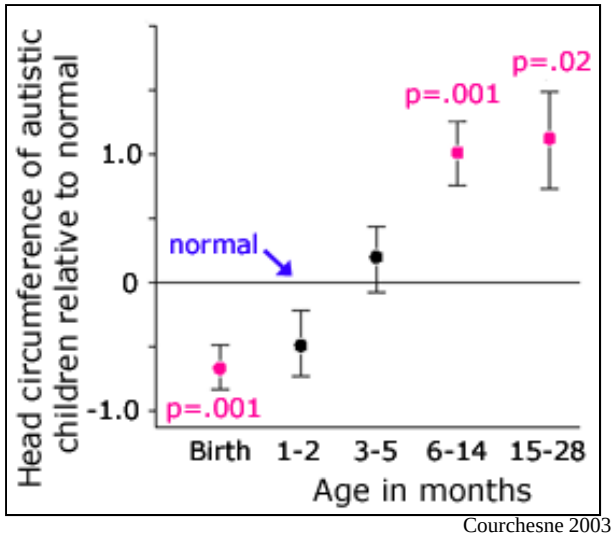
Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150 only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability 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

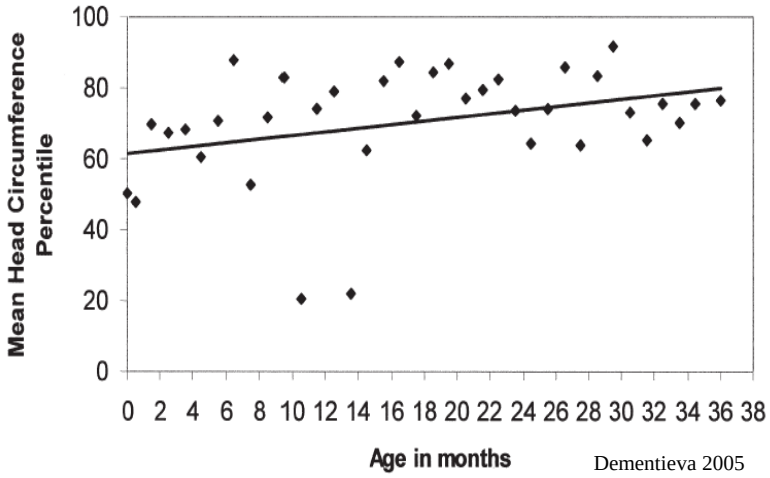
Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

Not necessarily just prenatal

TIMING OF POSTNATAL ATYPICAL BRAIN GROWTH: *EARLY RAPID GROWTH*

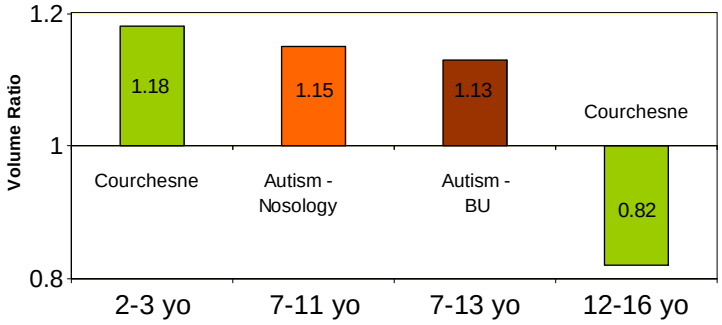


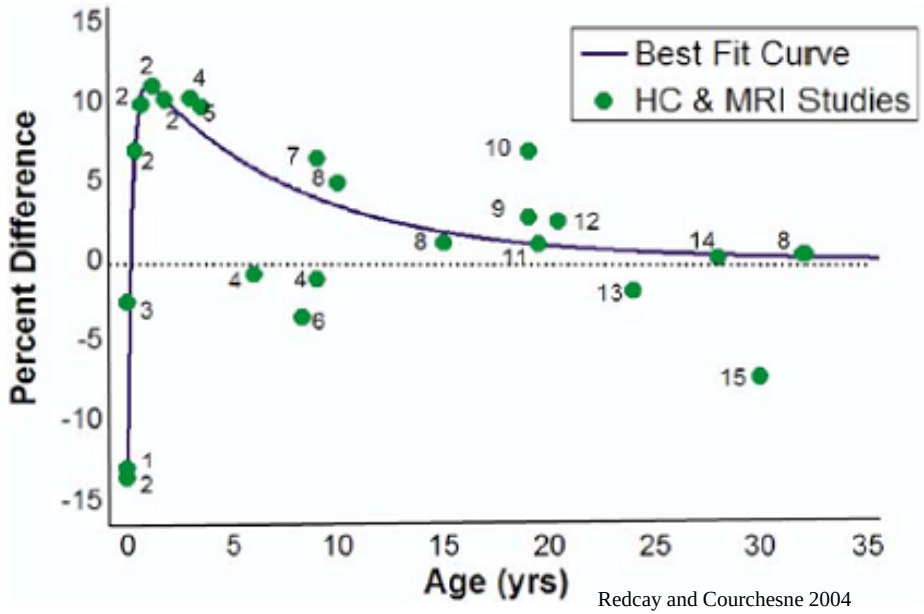
Courchesne 2003



Dementieva 2005

Tapering off after the first few years





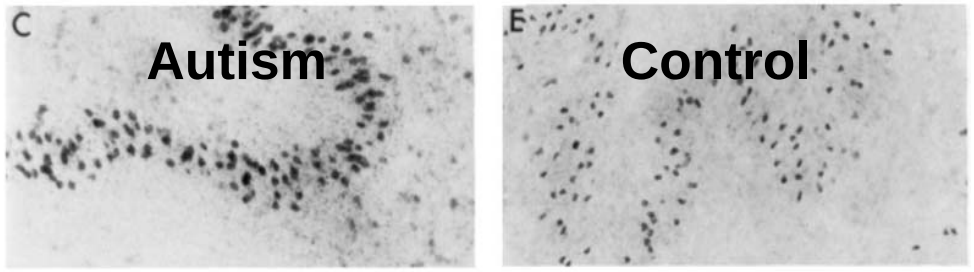
Redcay and Courchesne 2004

Ongoing postnatal cellular changes in the autistic brain

Neurons in autistic child:

- **larger than control**
- **normal in appearance**

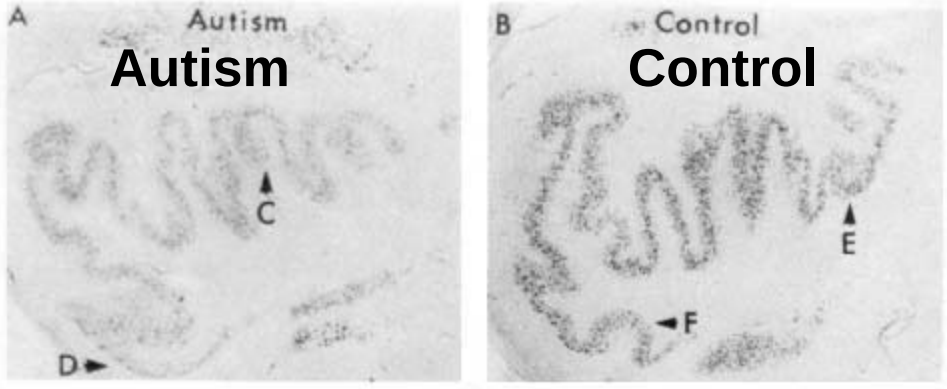
Child



Neurons in autistic adult male:

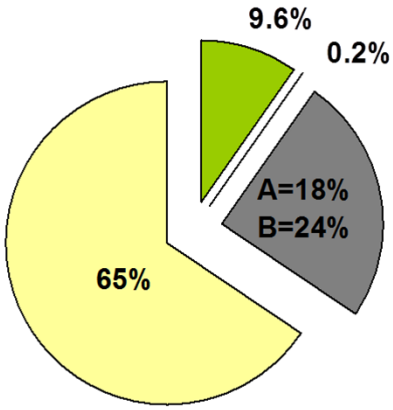
- **small in size**
- **adequate numbers**

Adult

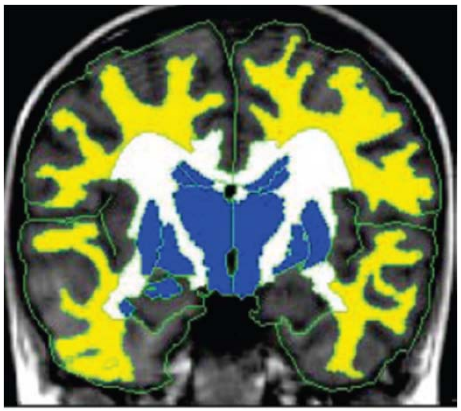


Kemper & Bauman 1992
Bauman and Kemper 2005

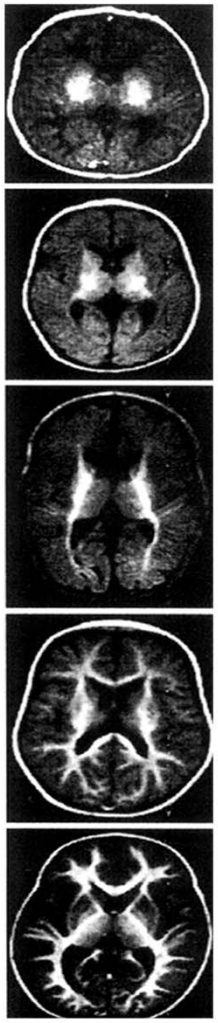
Location of white matter enlargement points to postnatal brain changes



White Matter Contributes Most to Autism Volume Increase



Radiate White Matter Enlargement



I- 1st Month

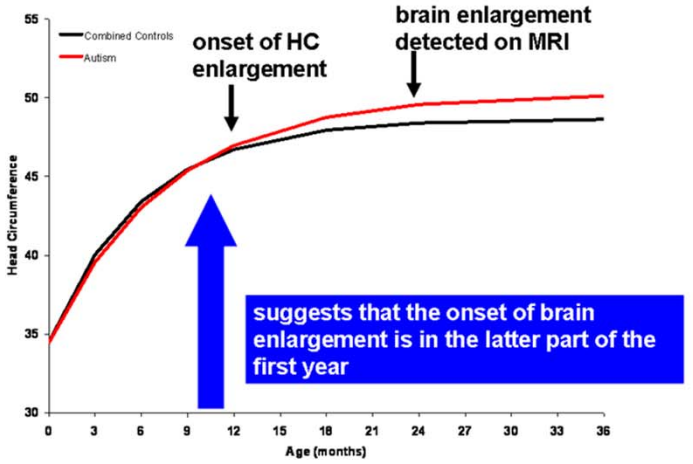
II- 2nd Month

III- 3rd-6th Month

IV- 7th-9th Month

V- > 9th Month

Inversion Recovery MRI Image
(Van der Knaap & Valk)



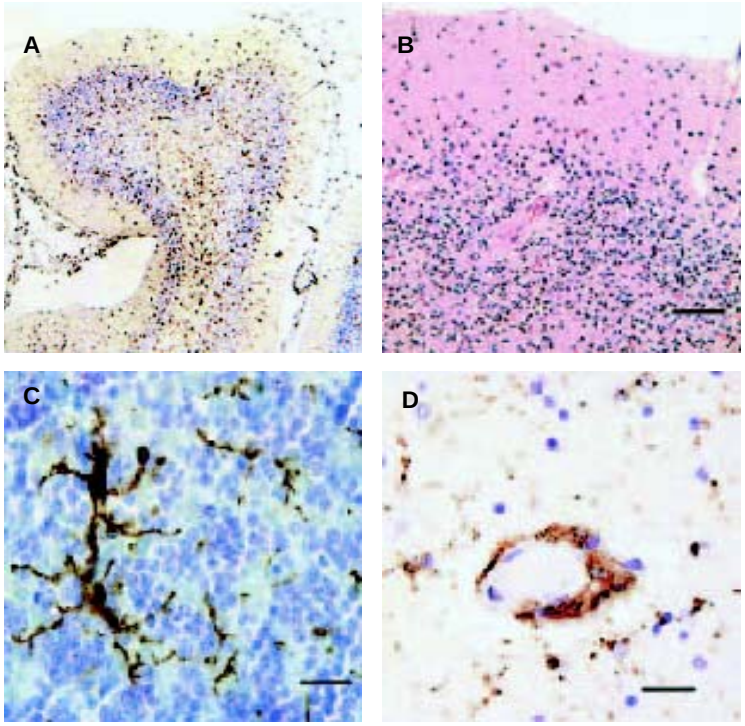
What do we need to learn about the brain and about autism to understand this?

Active Tissue pathophysiology in Brain

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

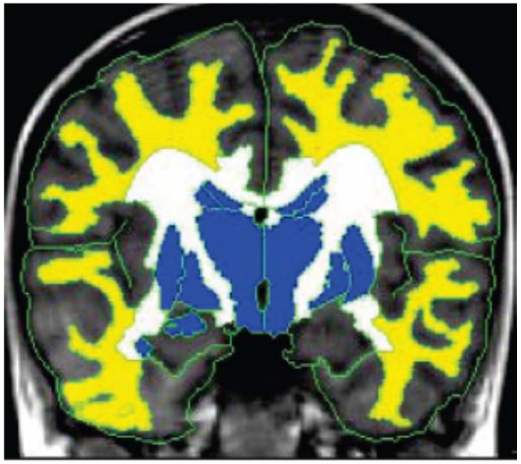


- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3-year old's brain

Pardo: Astrogliosis in Radiate White Matter

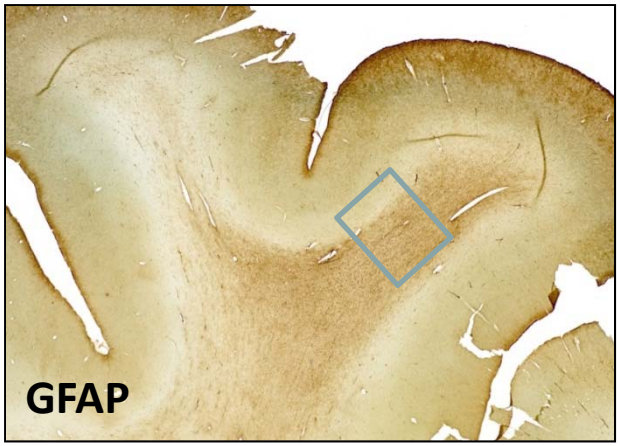
Astrogliosis

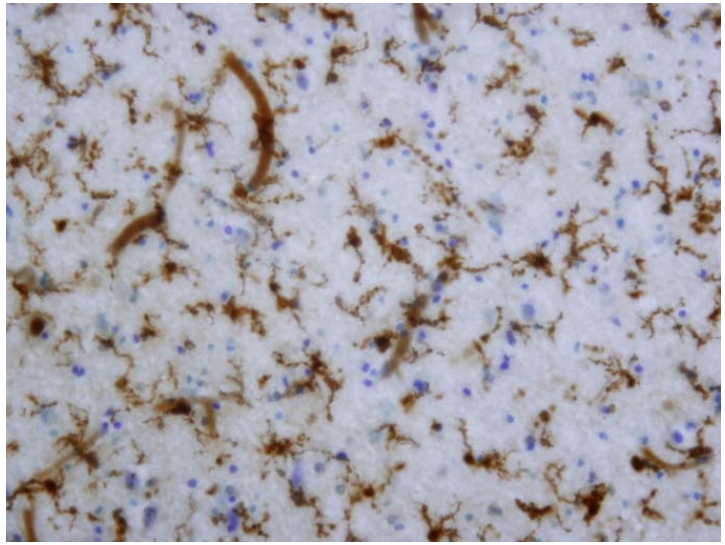
Microgliosis



Herbert:

Radiate White Matter Enlargement



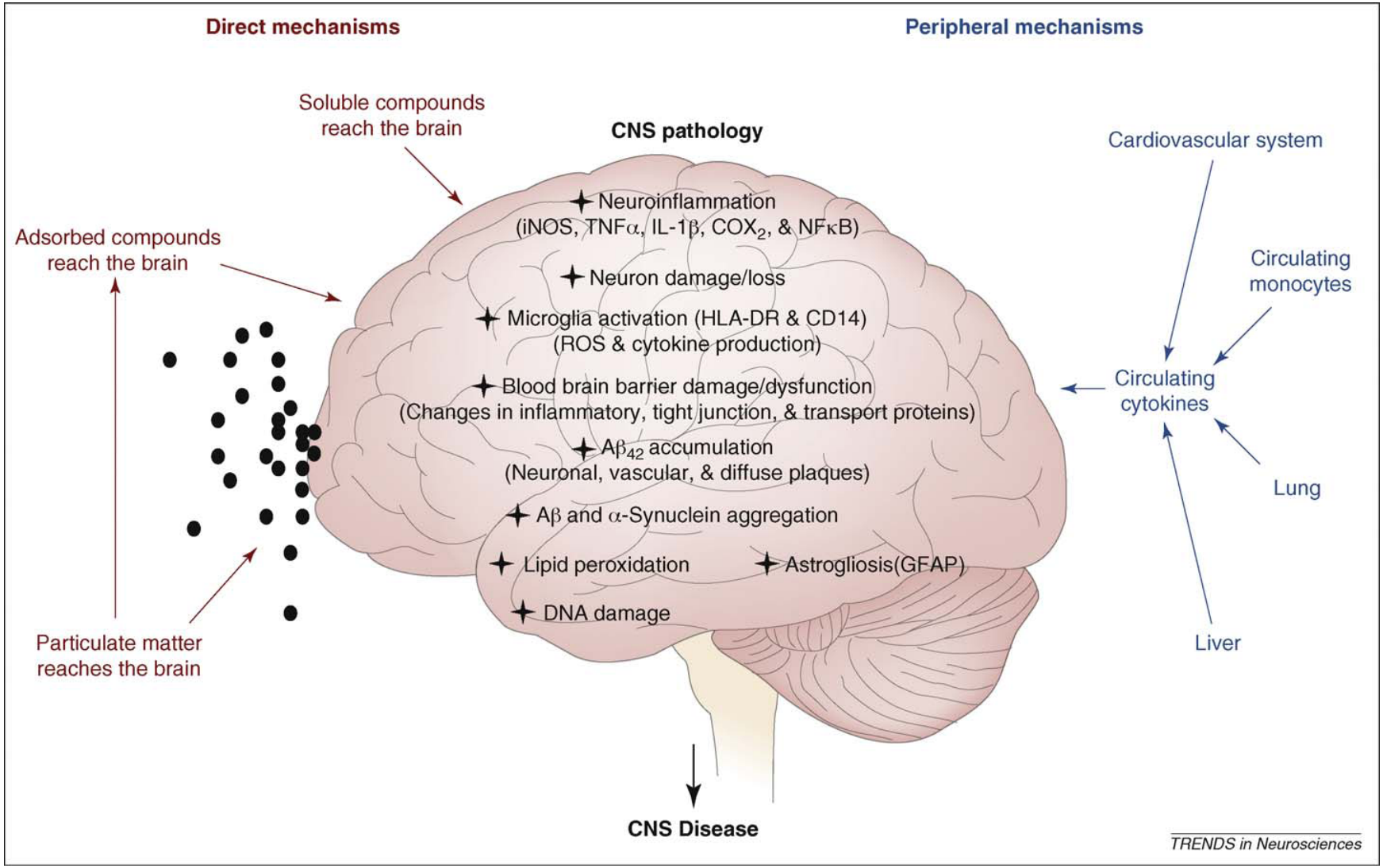


Pardo

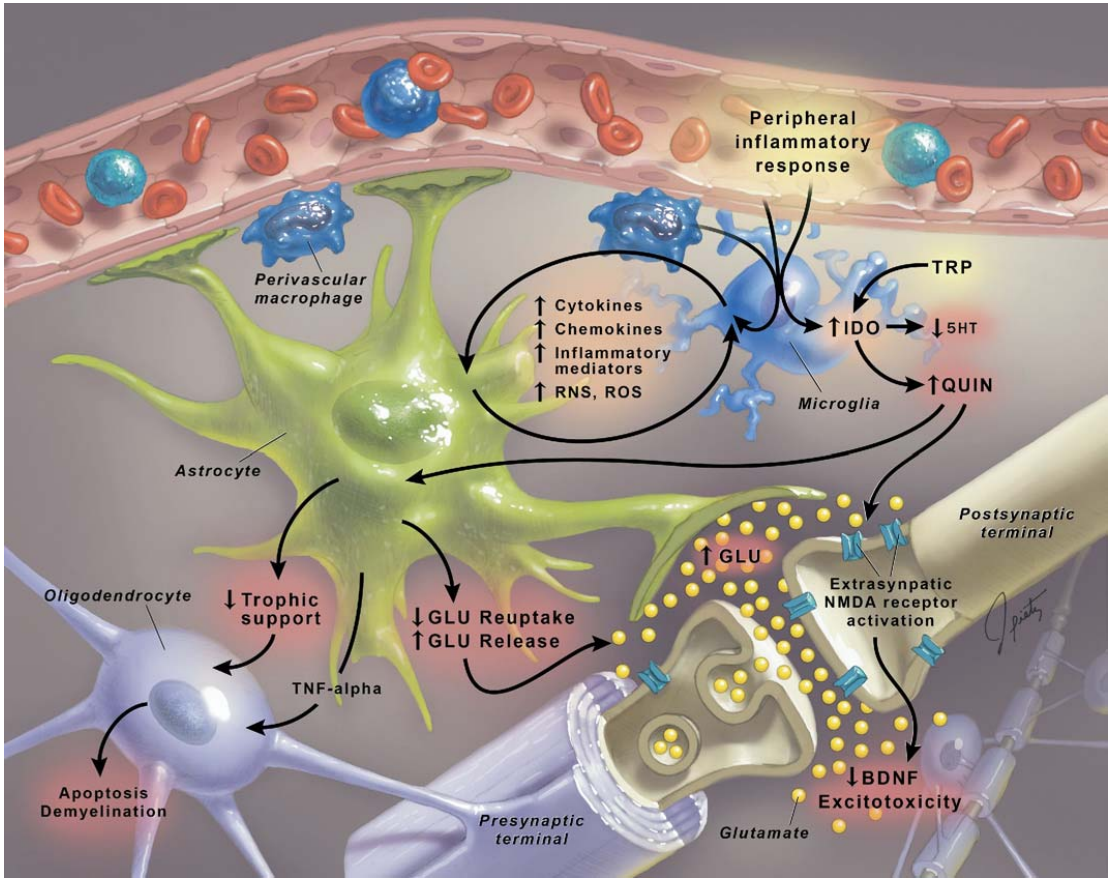
Air Pollution and Brain Inflammation

Block and Calderon-Gardicuenas, TNS, 2009

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



Brain cells in inflammation



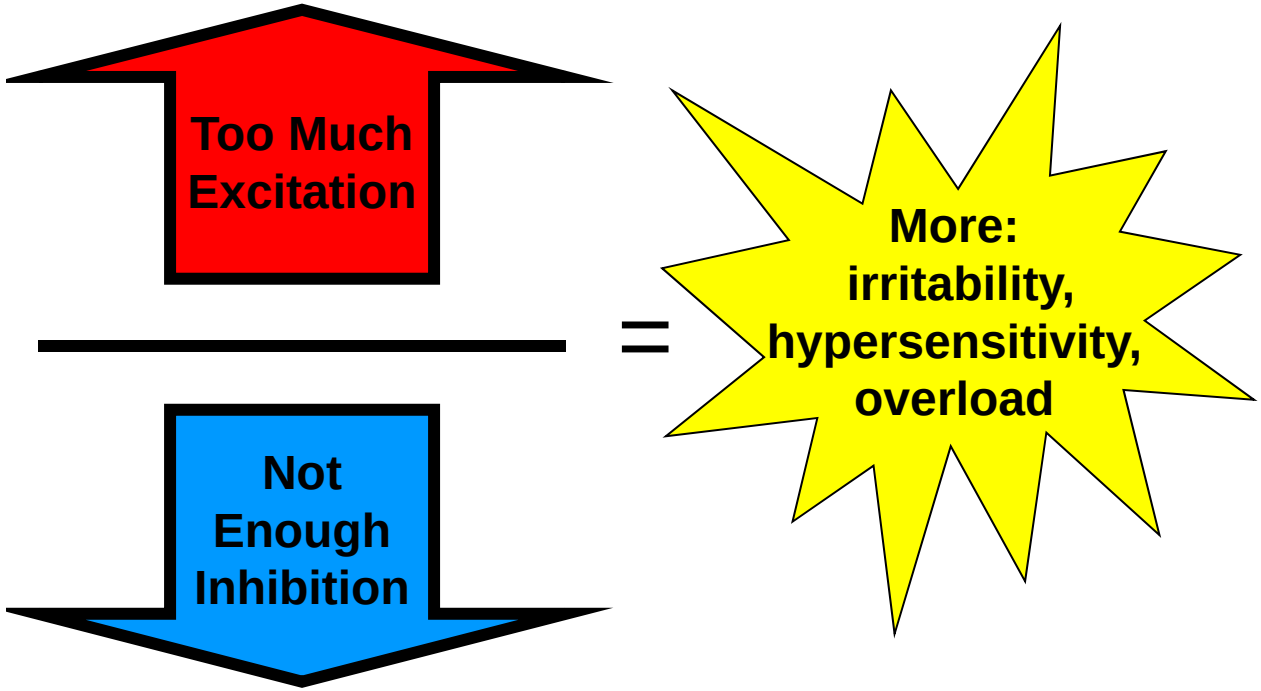
- **Excitatory chemicals created by activated glial cells**
- **Normal housekeeping functions of glial cells get neglected**
- **Chronic inflammation is irritating and promotes excitotoxicity**
- **Chronic inflammation can cause damage**

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

A FINAL COMMON PATHWAY?

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

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



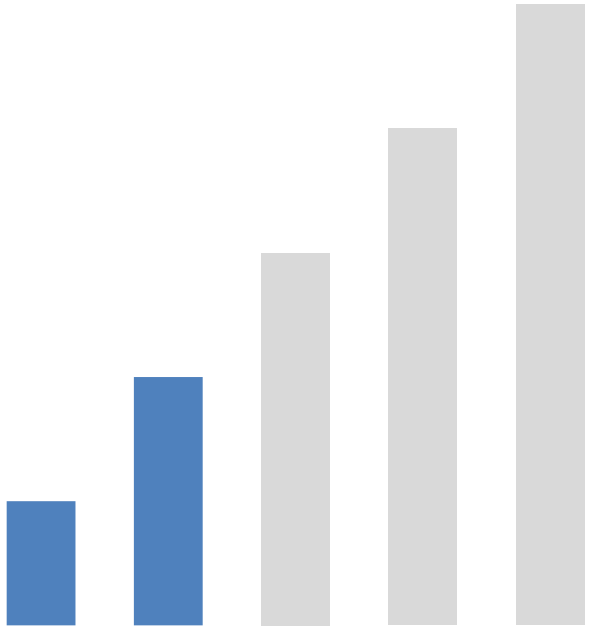
Loss of informational complexity and organization

Reduced signal to noise ratio

Reduce *Total Load* of Stressors to get Better Health, that will give Brains more "Bandwidth"

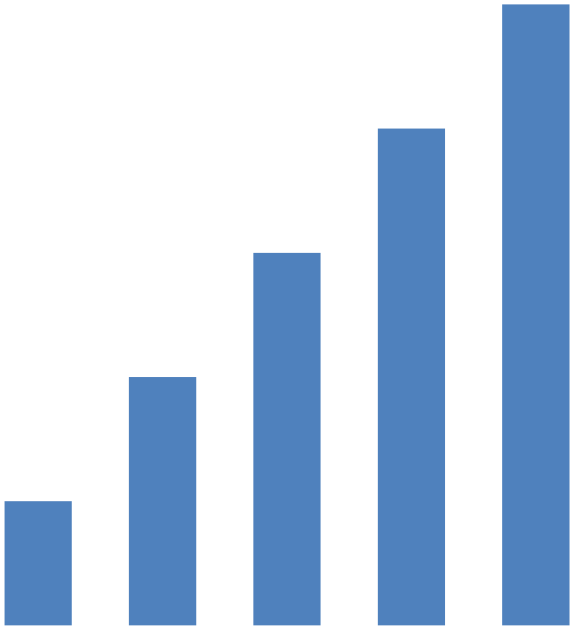
Poor Bandwidth:

Limited Reception



Lots of Bandwidth:

Good Reception



Better Reception Allows Better Discernment of Differences and More Spontaneous Learning

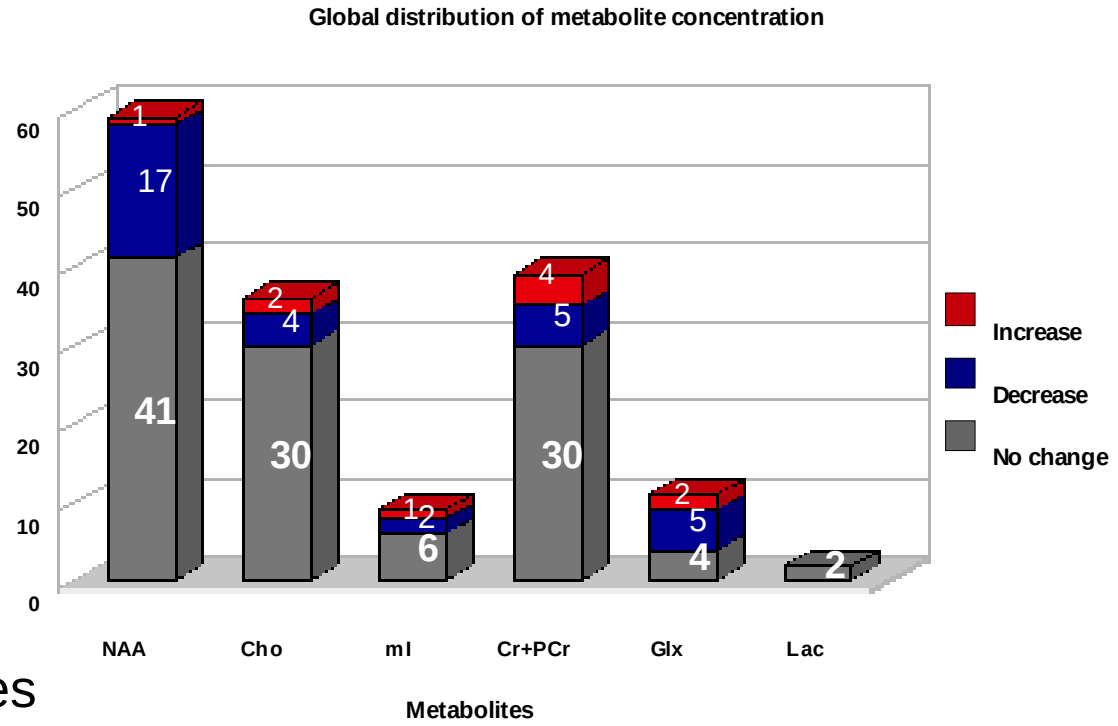
Active tissue pathophysiology undermines the idea that brain structure changes cause abnormal function

- **What if brain abnormal function led to abnormal structure?**
- **What if it is the PERSISTENCE OF THESE CELLULAR CHANGES that leads to the brain structure changes the brain scientists are measureing?**

Common explanation of brain enlargement in ASD: Failure of “pruning”

- **Testable through imaging: Failure of pruning implies**
  - **More fibers and fiber density**
  - **More cells**
- **Is this what we find?**

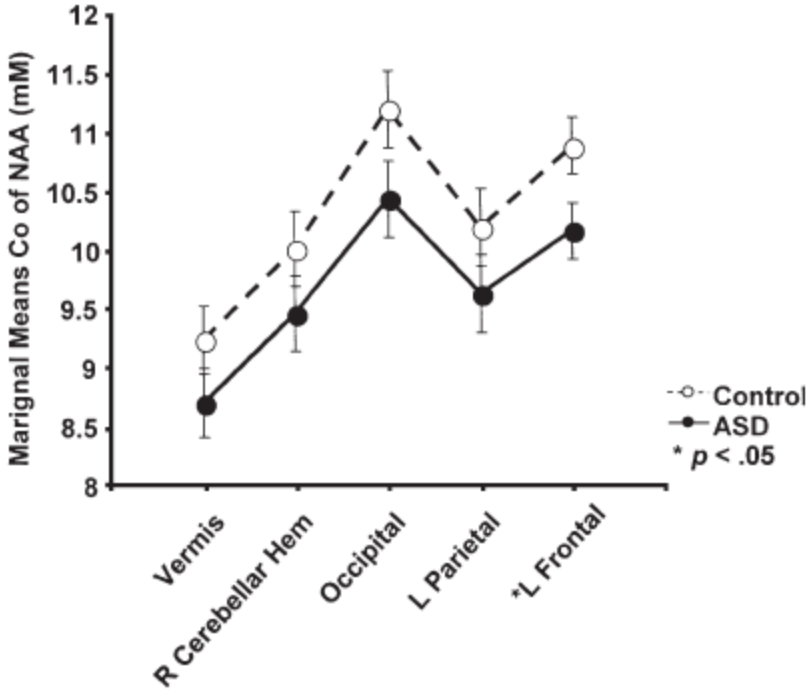
Brain magnetic resonance spectroscopy summary of findings in literature to date: Mostly lower density of metabolites

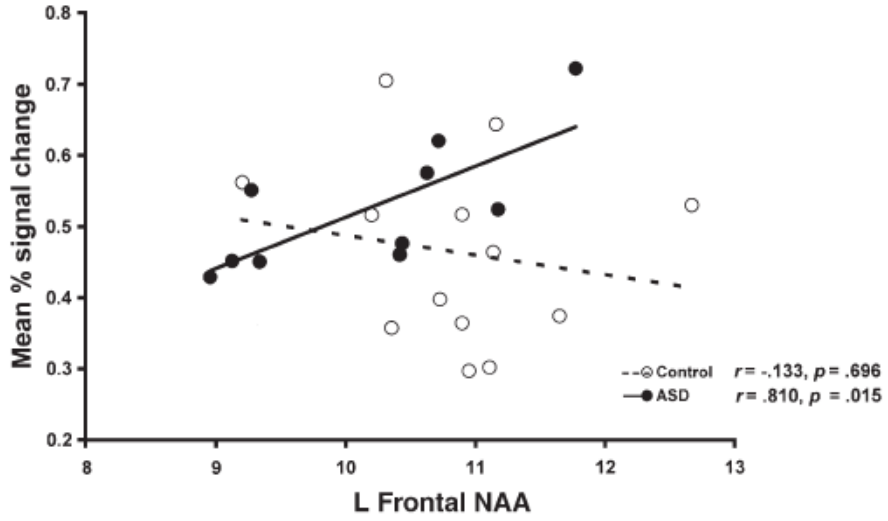


- Metabolites
  - Mostly reduced or no change; few reports of increase
  - Most studies done on 1.5T which has poor signal to noise ratio (only 1 of 22 done on 3T) and could miss differences

Shetty, Ratai, Ringer, Herbert, 2009

Dager review chapter 2008 and many papers





Kleinhans et al, 2007

Metabolite level correlating with brain activation

- More NAA in controls than in autism
- Linear correlation of amount of functional activation to amount of NAA
- NAA = N-acetylaspartate

The “Fluid Theory” of Connectivity Alterations in ASD

- **Water, not fiber changes in brain tissue**

  Hendry 2005

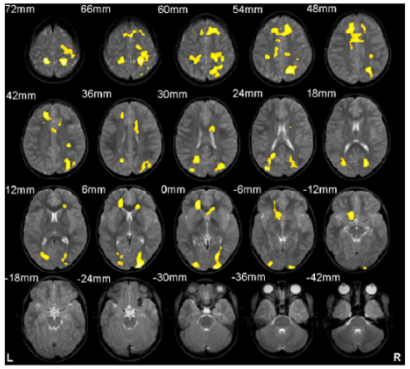
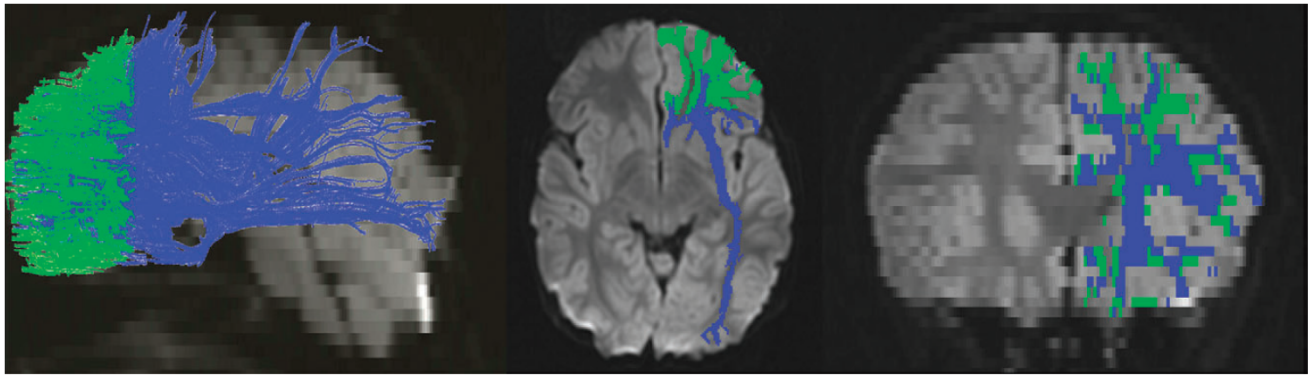


Fig. 2. Axial slices showing regions of increased T2 relaxation time in patients with autism compared to controls.

The idea that brain connectivity abnormalities arise from metabolic, immune and vascular disturbances that affect synaptic function.

- **Less white matter integrity**
- **Less restriction of water flow**
- **More diffusivity**



Sundaram 2008

- **Lower perfusion in ASD brains (by many PET or SPECT studies) could impact brain function.**

How might this affect brain electrophysiology?

Lower FA in key regions
Linked to higher (worse) diagnostic scores

- **White matter FA was significantly lower in key regions of prefrontal lobe and right ventral temporal lobe.**
- **Lower FA linked to higher (worse) diagnostic symptom scores**
- **Author interpretation:**
  In light of spectroscopy showing lower NAA ➔ less neuronal integrity or number, lower structural integrity *may be consistent with neuroinflammation*

Cheung et al., 2009

Lower perfusion in ASD brains could impact brain function. It could be maintained by active pathophysiology.

- 17 of 19 PET and SPECT studies showed low perfusion
- Those that showed areas of high perfusion still showed lower perfsuion more than higher
- Possible pathophysiology
  - Vasoconstriction
    - Oxidative stress acting on endovasculature
    - Astroglia swell when activated constricting capillary lumen
  - Blood viscosity
    - RBC lipid peroxidation (stiffer membranes → poor RBC deformability)
    - platelet activation (increased thromboxane)
    - increased nitric oxide (oxidative stress marker),
    - depressed glutathione peroxidase
    - depressed SOD
    - depressed catalase

Functional problems in the brain

- **Connectivity**
- **Sensory processing**

➢ **Are these caused by the large-scale structural problems?**

➢ **Or are they caused by cell metabolism problems?**

➢ **Most research has assumed the former, but not tested it as a hypothesis**

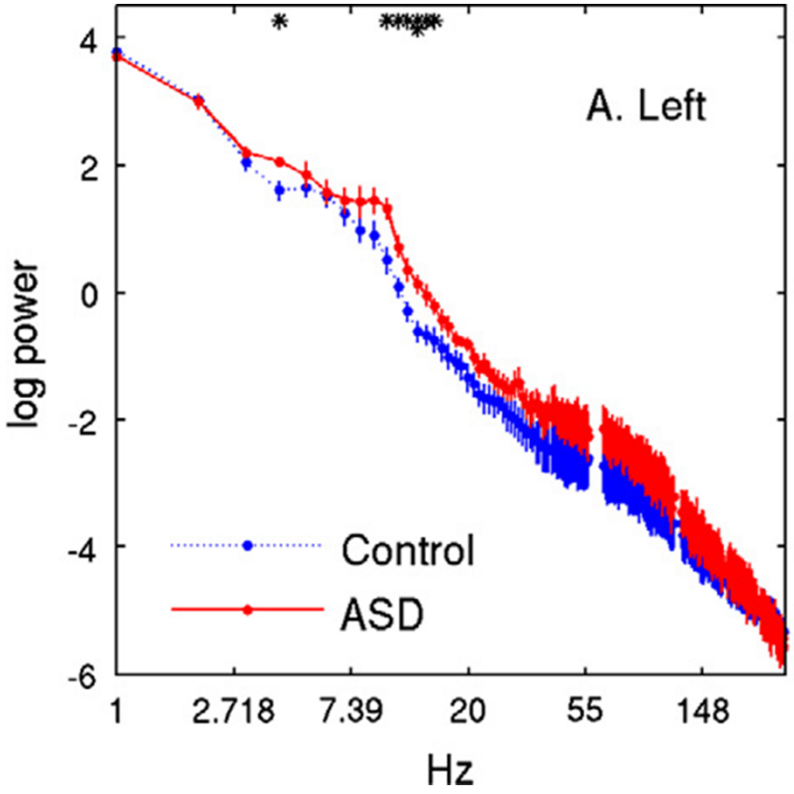
"Inefficiency" in brain signaling in autism

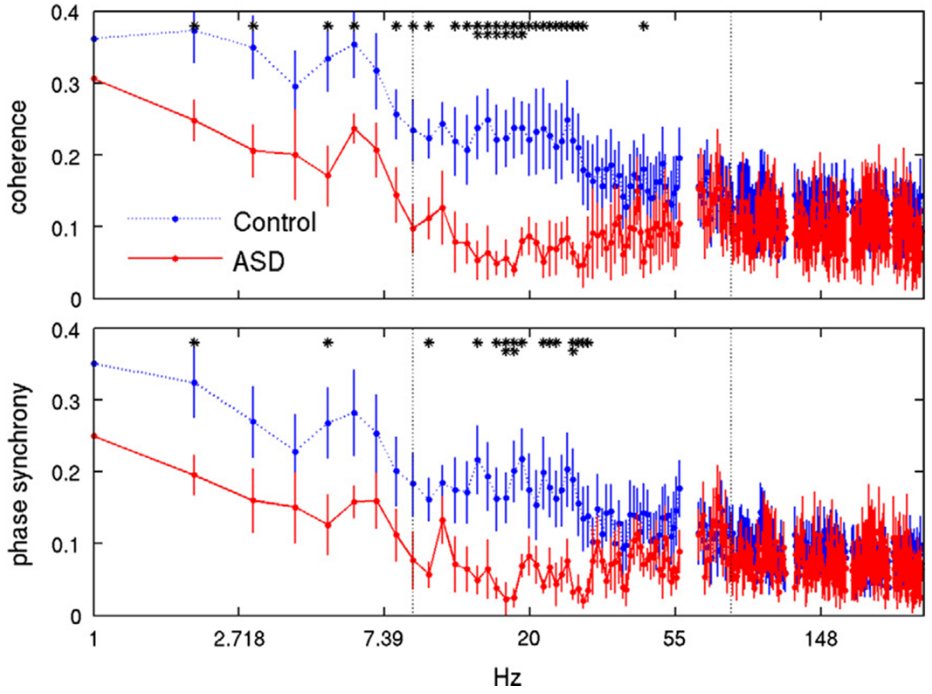
J.R. Isler, K.M. Martien, P.G. Grieve, R.I. Stark, M.R. Herbert

Clinical Neurophysiology 121 (2010) 2035–2043

Too much noise, not enough signal

BETTER BANDWIDTH SHOULD IMPROVE THIS



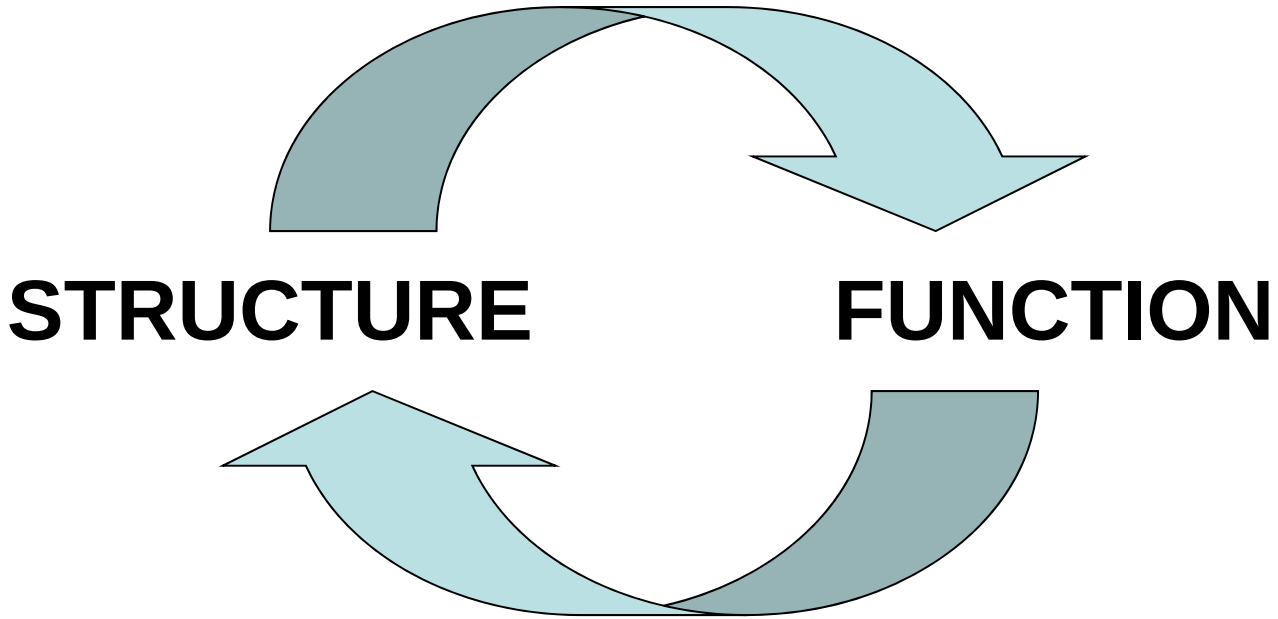


ASD has <u>more power</u> than controls… but *<u>less coherence</u>*

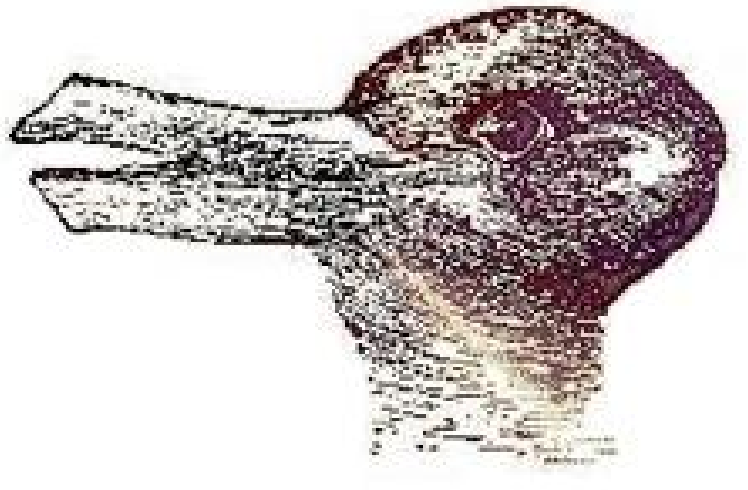
More <u>noise,</u> less <u>signal</u>

Structure ➔ Function?
Or Function ➔ Structure

or



Rabbit or duck?



Is autism a BRAIN DISORDER

or a

DISORDER THAT AFFECTS THE BRAIN?

Herbert, 2005

Multi-system from the start?
Kanner 1943 on ***body*** symptoms

Case 1: **"Eating has always been a problem ….." for him. He has never shown a normal appetite."**

Case 2: **"…large and ragged tonsils."**

Case 3: **diarrhea and fever following smallpox vaccination …. healthy except for large tonsils and adenoids.**

Case 4: **vomited a great deal during his first year… feeding formulas were changed frequently … tonsils were removed…**

Case 5: **nursed very poorly … quit taking any kind of nourishment at three months… tube-fed five times daily up to one year of age…At camp she slid into avitaminosis and malnutrition but offered almost no verbal complaints."**

Case 7: **vomited all food from birth through the third month….**

Case 8: **feeding formula caused …concern. … colds, bronchitis, streptococcus infection, impetigo…**

Case 9: **none of the usual children's diseases." [? Overactive immune system?]**

Case 10: **frequent hospitalizations because the feeding problem … repeated colds and otitis media**

Case 11: **was given anterior pituitary and thyroid preparations for 18 months**

Kanner's original paper, discussed in Jepson 2007

“The co-morbidity burden of children and young adults with autism spectrum disorders.”

- **The comorbidities of ASD encompass disease states that are significantly overrepresented in ASD with respect to even the patient populations of tertiary health centers.**
- **Significantly more: epilepsy, schizophrenia, inflammatory bowel disease, other bowel disorders, CNS/cranial anomalies, diabetes type 1, muscular dystrophy, sleep disorders**

Kohane, I. S., A. McMurry, et al. (2012). PLoS One 7(4): e33224.

HARVARD STUDY

Large Burden of Comorbidities in ASD
Requires Broad Multidisciplinary Management

In a study of co-morbidities for 14,000 ASD patients in the Harvard system under the age of 35, the authors concluded:

"The comorbidities of ASD encompass disease states that are significantly overrepresented in ASD with respect to even the patient populations of tertiary health centers. ***This burden of comorbidities goes well beyond those routinely managed in developmental medicine centers and requires broad multidisciplinary management that payors and providers will have to plan for."*** *[emphasis added]*

Source:
Kohane IS et al., (2012),
The Co-Morbidity Burden of Children and Young Adults with Autism Spectrum Disorders.
PLoS ONE 2012 (open access)

AAP Autism GI Consensus Reports January 2010

SUPPLEMENT ARTICLE

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report

AUTHORS: Timothy Buie, MD,[a,b,c] Daniel B. Campbell, PhD,[d] George J. Fuchs, III, MD,[e] Glenn T. Furuta, MD,[f,g] Joseph Levy, MD,[h] Judy Van de Water, PhD,[i] Agnes H. Whitaker, MD,[j] Dan Atkins, MD,[k,l] Margaret L. Bauman, MD,[b,m,n] Arthur L. Beaudet, MD,[o] Edward G. Carr, PhD,[p] Michael D.

abstract

Autism spectrum disorders (ASDs) are common and clinically heterogeneous neurodevelopmental disorders. Gastrointestinal disorders

SUPPLEMENT ARTICLE

Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASDs

AUTHORS: Timothy Buie, MD,[a,b,c] George J. Fuchs, III, MD,[d] Glenn T. Furuta, MD,[e,f] Koorosh Kooros, MD,[g] Joseph Levy, MD,[h] Jeffery D. Lewis, MD,[i] Barry K. Wershil, MD,[j] and Harland Winter, MD[a,c]

[a]*Department of Pediatrics, Harvard Medical School, Boston, Massachusetts;* [b]*Learning and Development Disabilities Evaluation and Rehabilitation Services, Lexington, Massachusetts;* [c]*Division of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts;* [d]*Division of Pediatric Gastroenterology*

abstract

Children with autism spectrum disorders (ASDs) can benefit from adaptation of general pediatric guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and gastroesophageal reflux disease. These guidelines help health care providers determine when gastrointestinal symptoms are self-limited and when evaluation be-

The Every Day of Some Autisms

What we need:
Clinical labs that will detect and report pertinent gut pathogens

Beyond the Human Genome to the Extended Genome: Host and gut-microbial co-metabolome interaction

J Nicholson, Nature Review Microbiology, 2005

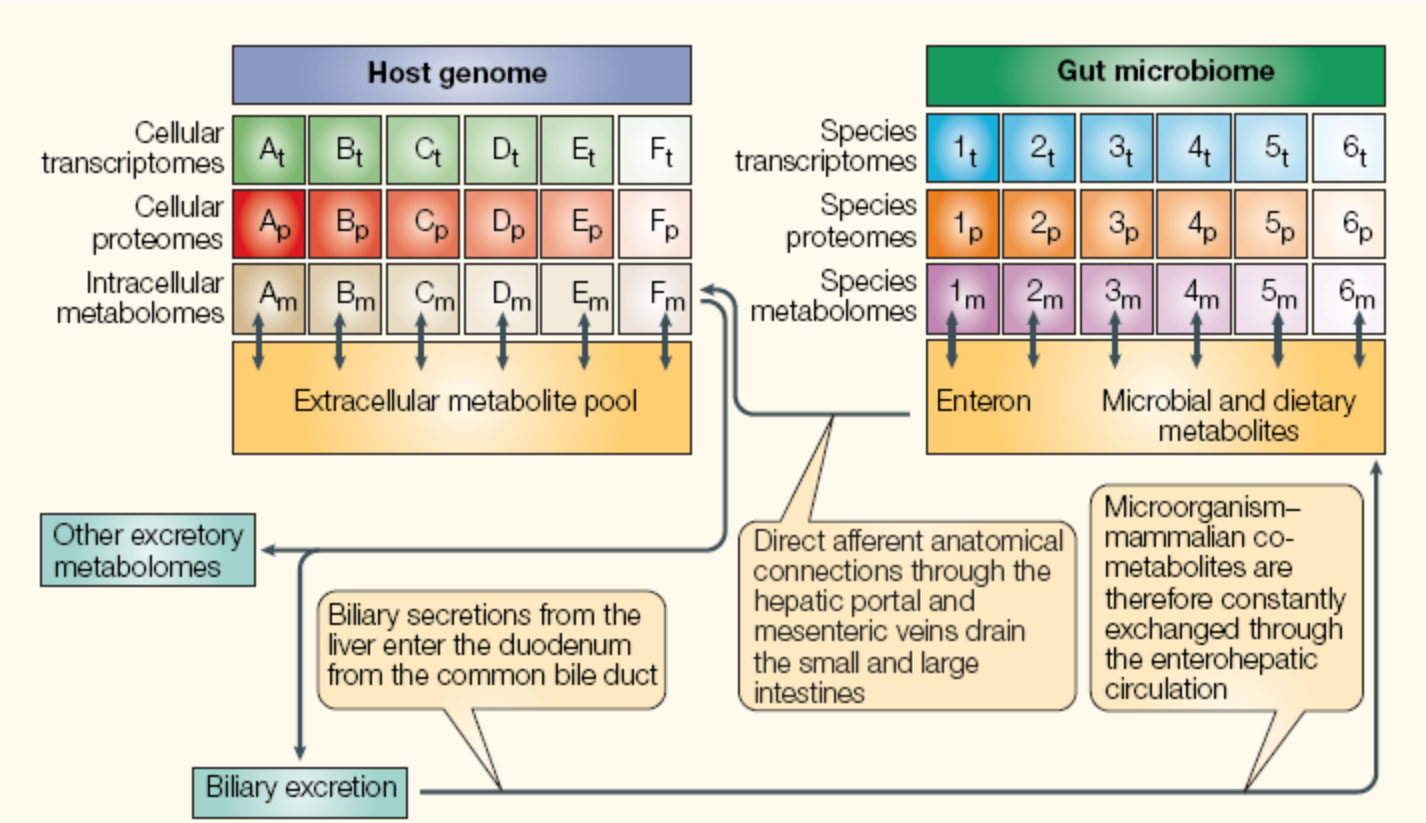


Figure 1 | **Visualizing the host and gut-microbial co-metabolome interaction.** In a series of six

Glial Cells in the Gut: Immune, Signaling and Barrier Function

Ruhl, 2005

Neurogastroenterol Motil (2005) 17, 777–790 doi: 10.1111/j.1365-2982.2005.00687.x

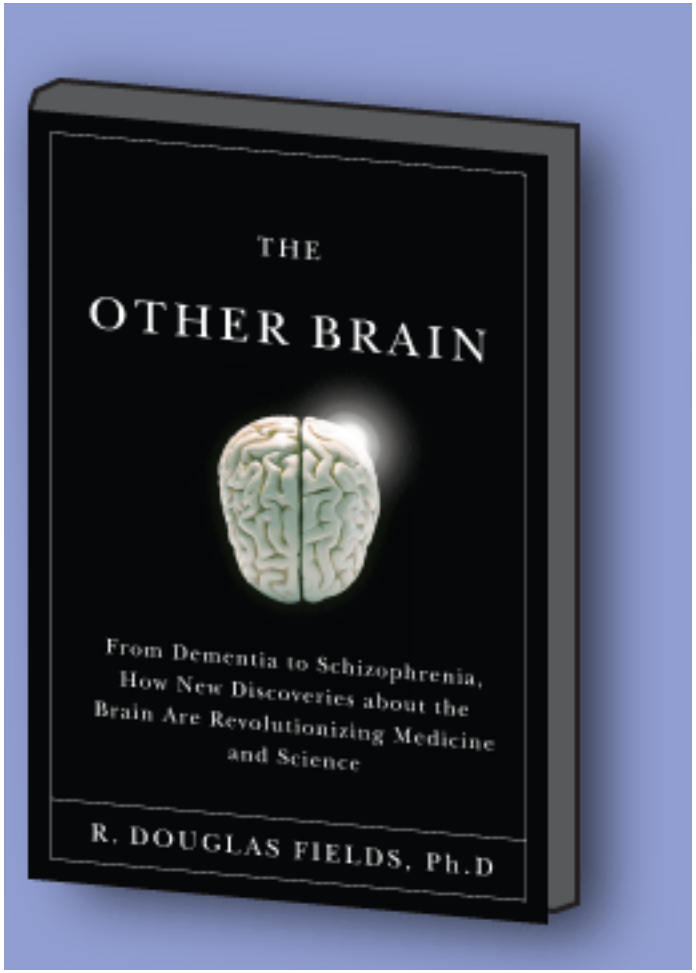
Glial cells in the gut

A. RÜHL

Department of Human Biology, Technical University of Munich, Germany

Abstract: The **enteric nervous system is composed of both neurons and glia**. Recent evidence indicates that enteric glia–which vastly outnumber enteric neurons–are actively involved in the control of gastrointestinal functions: they contain **neurotransmitter precursors**, have the machinery for **uptake and degradation of neuroligands**, and express neurotransmitter- receptors which makes them well suited as **intermediaries in enteric neurotransmission and information processing in the ENS**. Novel data further suggest that enteric glia have an important role in **maintaining the integrity of the mucosal barrier of the gut**. Finally, enteric glia may also serve as a ***link between the nervous and immune systems of the gut*** as indicated by their potential to **synthesize cytokines, present antigen and respond to inflammatory insults**. The role of enteric glia in human disease has not yet been systematically studied, but based on the available evidence it is **predictable that enteric glia are involved in the etiopathogenesis of various pathological processes in the gut, particularly such with *neuroinflammatory or neurodegenerative* components**.

THE OTHER BRAIN
by Douglas Fields, PhD, NIH scientist



ABOUT GLIAL CELLS

www.theotherbrainbook.com

Classes of Core Functions

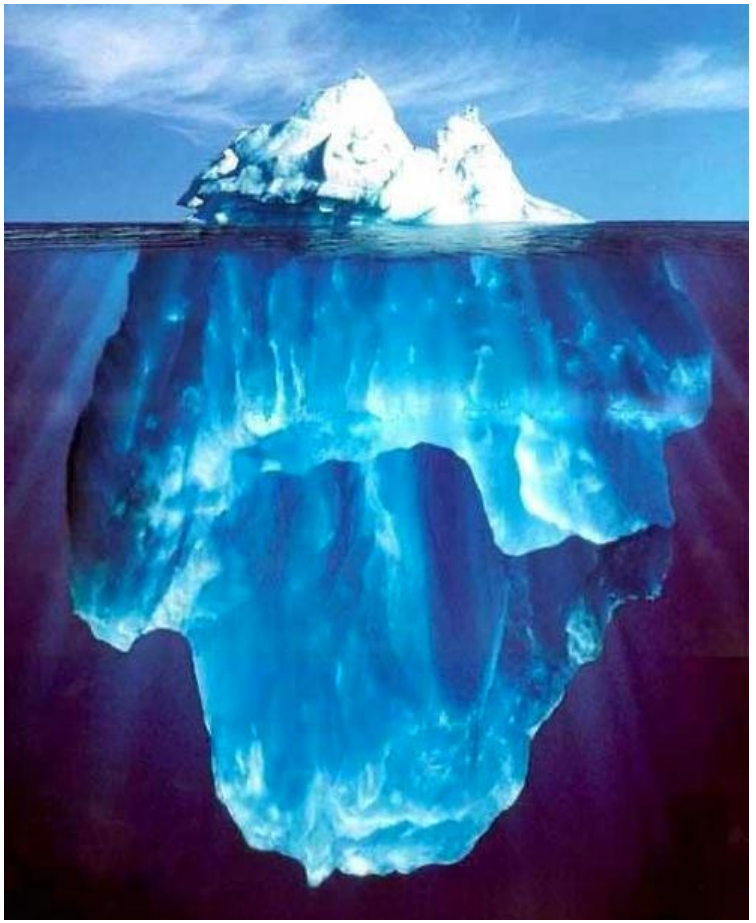
Abnormalities at all of these levels in autism— and many other major chronic diseases as well

Bioenergetics	• ***Mitochondrial dysfunction***
Biotransformation	• ***Metabolic dysfunction***
Transport, circulation	• ***Cerebral hypoperfusion***
Communication, inside and outside the cell	• ***Immune dysregulation*** • ***Neurotransmitters, hormones***
Structural integrity	• ***Hypotonia; cell membranes*** • ***Loss of bone density***
Protection and defense	• ***Immune and Autoimmune problems***
Elimination of waste	• ***Impaired intestinal function*** • ***Impaired detoxification***

Symptoms and function

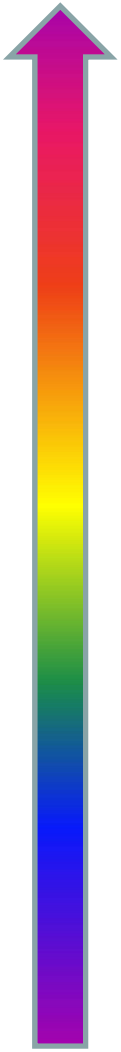
VISIBLE SYMPTOMS

UNDERLYING SYSTEMIC FUNCTIONAL DISTURBANCES



Ziggarut model: http://www.texasautism.com/

Autism is Complex:
Levels that are all involved AT THE SAME TIME



Creativity

Social interaction

Learning

Behavior

Brain as information system

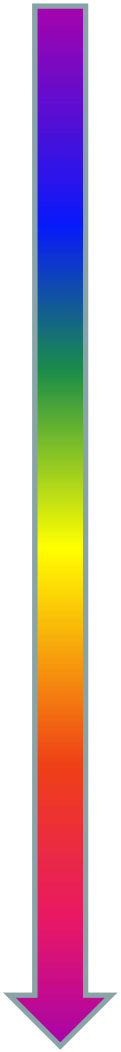
Brain as wet physical organ

Organs

Cells

Chemistry

Genes and environment



Chronic mechanisms can impact brain FUNCTION

Functional Vulnerabilities

❖ *Free Radicals*	→	• Energy Production
❖ *Calcium Upregulation*	→	• NMDA plasticity
❖ *Peroxidation*	→	• Lipid Membranes
❖ *Toxic Mediators*	→	• Transmitter Specificity
❖ *Chronic Inflammation*	→	• Glial Support

These are

- **Cellular**
- **Widespread**
- **Impact timing, signal intensity, coordination**

A Different Model of Autism: Autism as an emergent property of a system with altered parameters

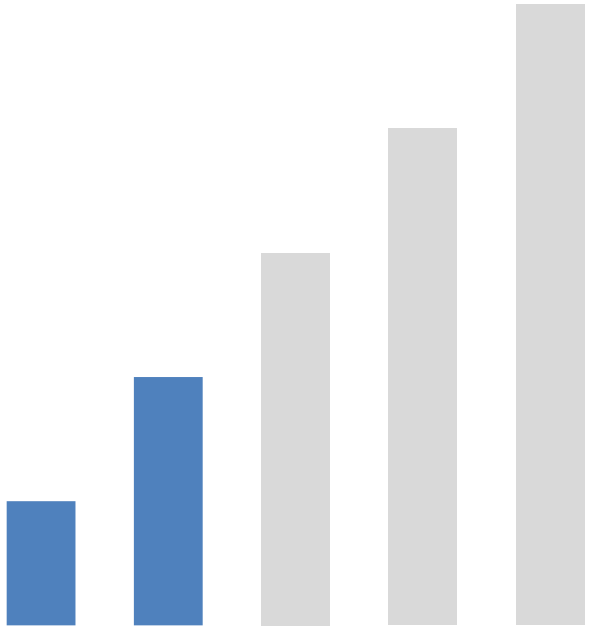
- **Autism could be a dynamic, active consequence of *challenges to cellular function throughout the body, including the brain***
- ***These cellular changes may be related to environmental insults***
- **Altered cellular response could be at the root of brain and body problems**
- **This could explain the dynamic features**
- ***Many cellular problems can be treated***

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

Reduce *Total Load* of Stressors to get Better Health, that will give Brains more "Bandwidth"

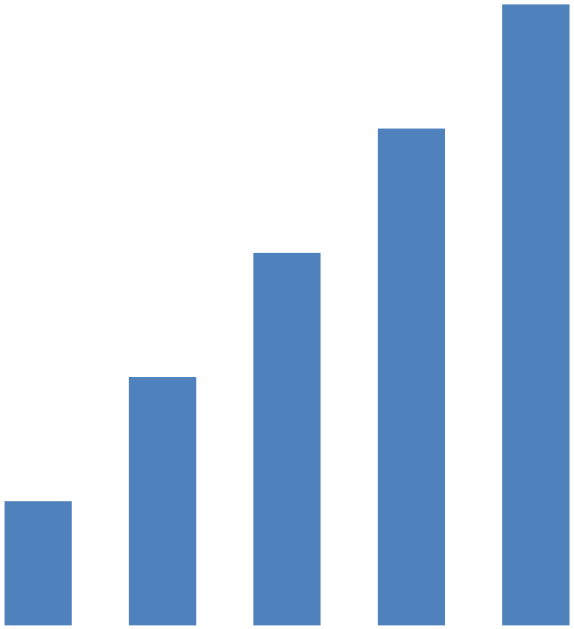
Poor Bandwidth:

Limited Reception



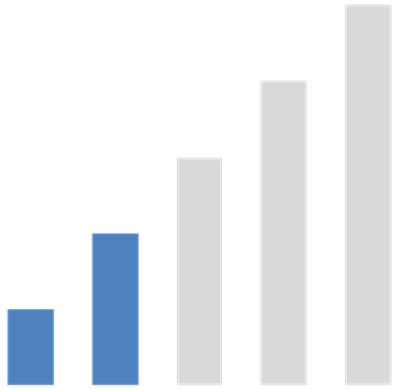
Lots of Bandwidth:

Good Reception



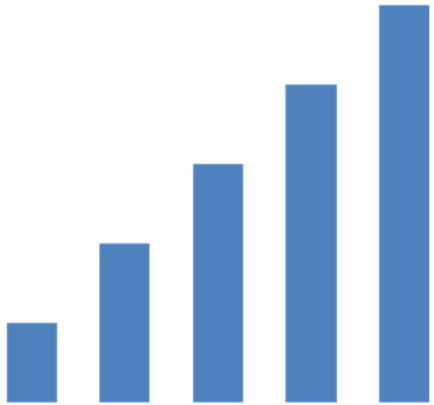
Better Reception Allows Better Discernment of Differences and More Spontaneous Learning

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

Toward a Physiological Model of Autistic Regression

A Theory of How Regression Happens: I: THINGS PILE UP

- **Demands are placed on the whole body by some combination of poor food, toxics, bugs and stress, maybe with genetic vulnerabilities in the mix.**
- **This degrades the support system of the brain – not enough antioxidants, essential fatty acids and other nutrients.**
- **Meanwhile the body and brain start to get hypersensitive and overreact with more inflammation and oxidative stress as the problems continue.**

A Theory of How Regression Happens: II: GLIAL CELLS GET SWAMPED

- **The astrocytes start falling behind in supporting and protecting the neurons.**
- **The astrocytes and microglia get further distracted by having to be “activated” as these toxics, bugs and stressors make bigger demands on the brain.**
- **This astrocyte and microglia activation produces oxidative stress, which degrades things more.**

A Theory of How Regression Happens: III: BLOOD AND ENERGY SUPPLY WEAKEN

- **The blood supply to the brain starts getting crimped – sticky blood passes through vessels that are squished by swollen astrocytes.**
- **Neuronal excitation gets out of control, and produces more oxidative stress, which only makes things worse.**
- **Glutathione and other repair mechanisms are not replenished and things keep getting worse.**
- **Mitochondrial efficiency drops.**

A Theory of How Regression Happens: IV: TIPPING POINT – *SWITCH TO LOWER DEMAND STATE*

- **At some point the "Total Load" is too much, and a tipping point occurs:**
  - **Astrocyte networks start to fall apart – gap junctions close, communication degrades. Glutamate piles up, irritating neurons and networks.**
  - **Brain networks get weaker and less extensive as cells go into a disorganized, distracted "idling" mode to protect their challenged resources.**
  - **The brain stops being able to coordinate complicated information processing. It starts getting overwhelmed and producing autistic experience and behaviors.**

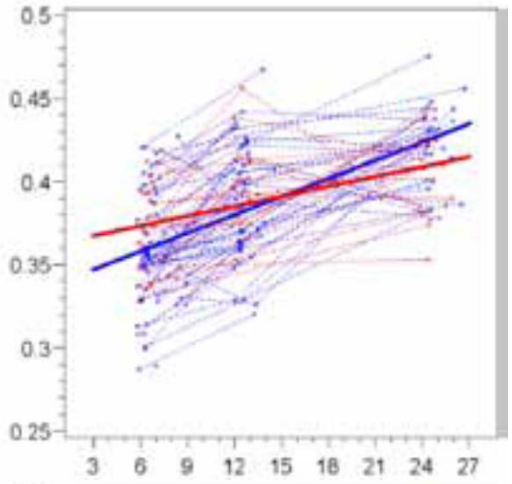
A Theory of How Regression Happens: V: VICIOUS CIRCLES CREATE STUCKNESS

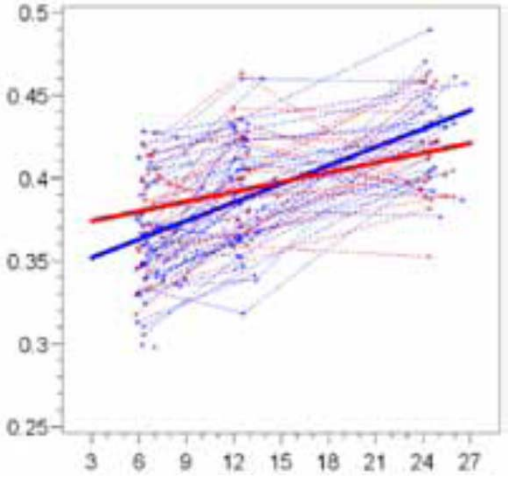
- **So many vicious circles are making each other worse that it is difficult to reverse the cycle by changing just one part of the web. It therefore looks hopeless.**
  - **Brain cells are challenged,**
  - **Body cells are challenged,**
  - **Organ function is challenged,**
  - **Behavior is disorganized and disconnected which only adds stress,**
  - **And diet is the opposite of what would help the system repair itself.**

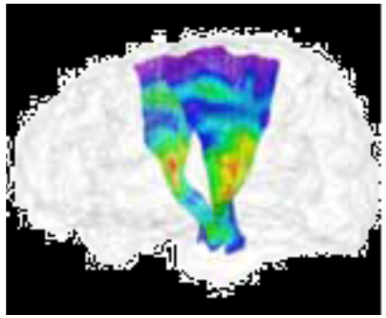
Autism: WHY and HOW ?

www.autismWHYandHOW.org

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







Wolff et al., 2012

BRAIN CHANGES IN INFANTS DEVELOPING AUTISM

- **From higher to lower “FA”**
  - **Decrease in fiber organization relative to controls**
- **This DEVELOPS over time**
- **It is probably DOWNSTREAM of the metabolic, cellular pileup of problems**

From “Why Aren’t We There Yet” Blog on Wolff Autism infant brain imaging - 1

www.autismWHYandHOW.org

1. ***Regarding "How autism is caused", it is dysfunction in the health of these many cellular, chemical and electrical functions that is <u>UPSTREAM</u> of the problems with FA development in infants with autism, and that if we <u>measure these upstream biological functions</u> we might get <u>more robust and clinically useful early brain indicators</u> of autism and autism risk.***

From “Why Aren’t We There Yet” Blog, Cont’d - 2

2. ***Regarding "what autism is", we might also understand autism better in terms of what I think are the ground zero mechanisms that intimately interrelate brain cell health problems with brain cell communication problems -- and that are disrupted by the extent to which the Total Load of exposures, insults, deficiencies and vulnerabilities overwhelms brain/body resilience***

From “Why Aren’t We There Yet” Blog, Concluded - 3

3. ***Regarding "how we can help," <u>looking at brain cell health problems in a whole body strategy context gives us a lot we can do</u> with what we know right now to improve the situation -- reducing “Total Load” and improving Resilience.***

THIS IS

THE AUTISM REVOLUTION

Not broken, and not so hardwired

Not cognitive impairment
But largely normal or superior intelligence

- **Wechsler Intelligence Scale vs. Raven's Progressive Matrices.**
  - **Wechsler requires greater communication skills.**
- **Raven's: ASD Children averaged 30 points higher (up to 70 points higher)**
- **Wechsler: 70 percent scored in the "retarded" range;**
- **Raven's showed just 20 percent in this range**

M. Dawson, I. Soulieres, M. A. Gernsbacher and L. Mottron
The level and nature of autistic intelligence. Psychol Sci 2007, 657-62

Improvement in core autism behaviors in setting of fever: not consistent with “hard-wired” cause

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

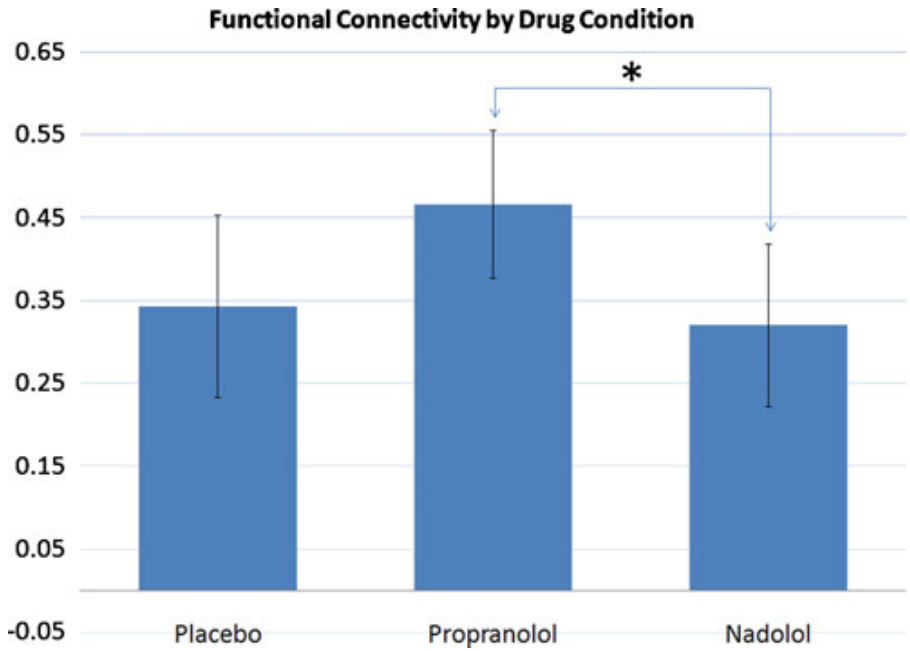
Behaviors Associated with Fever in Children with Autism Spectrum Disorders.
Curran et al, Pediatrics 2007

<u>Challenges posed by this study:</u>

- **This is not consistent with “static encephalopathy”**
- **What mechanisms might be consistent with this?**
  - **Proposed so far: locus ceruleus, environmental impact on glial gap junctions, cytokines, membrane lipids, dysfunctional electrophysiological oscillations**

- **Additional pertinent citations:**
  Helt / Fein et al, Neuropsychology Review, 2007; Herbert in Chauhan et al CRC Press late 2009, Mehler & Purpura 2009

Rapid IMPROVEMENT in brain connectivity suggests "state" not "trait"



Effect of Propranolol on Functional Connectivity in Autism Spectrum Disorder—A Pilot Study
Narayanan et al. (Beversdorf lab)
***Brain Imaging and Behavior*, 2010**

- **Functional connectivity, assumed to be a fixed trait, changed rapidly with drug that impacts brain stress level (propranolol)**

Neuropsychol Rev
DOI 10.1007/s11065-008-9075-9

Can Children with Autism Recover? If So, How?

Molly Helt · Elizabeth Kelley · Marcel Kinsbourne · Juhi Pandey · Hilary Boorstein · Martha Herbert · Deborah Fein

Received: 2 September 2008 / Accepted: 11 September 2008
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Abstract Although Autism Spectrum Disorders (ASD) are generally assumed to be lifelong, we review evidence that between 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills. Predictors of recovery include relatively high intelligence, receptive language, verbal and motor imitation, and motor development, but not overall symptom severity. Earlier age of diagnosis and treatment, and a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified are also favorable signs. The presence of seizures, mental retardation and genetic syndromes are unfavorable signs, whereas head growth does not predict outcome. Controlled studies that report the most recovery came about after the use of behavioral techniques. Residual vulnerabilities affect higher-order communication and attention. Tics, depression and phobias are frequent residual co-morbidities after recovery. Possible mechanisms of recovery include: normalizing input by forcing attention outward or enriching the environment; promoting the reinforcement value of social stimuli; preventing interfering behaviors; mass practice of weak skills; reducing stress and stabilizing arousal. Improving nutrition and sleep quality is non-specifically beneficial.

Keywords Autism spectrum disorders · Language development · Recovery · Stereotyped motor behavior

Introduction

Autism Spectrum Disorders (ASD) are a group of related developmental disorders that are characterized by impair-

Reversal in Mouse Models

PNAS

Inhibition of p21-activated kinase rescues symptoms of fragile X syndrome in mice

Mansuo L. Hayashi*†, B. S. Shankaranarayana Rao‡, Jin-Soo Seo§, Han-Saem Choi§, Bridget M. Dolan*, Se-Young Choi§, Sumantra Chattarji¶, and Susumu Tonegawa*‖

*The Picower Institute for Learning and Memory, Howard Hughes Medical Institute, RIKEN–Massachusetts Institute of Technology Neuroscience Research Center, and Departments of Biology and Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; ‡Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bangalore 560029, India; §Department of Physiology, College of Dentistry, Seoul National University, Seoul 110-749 Korea; and ¶National Center for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560065, India

Contributed by Susumu Tonegawa, May 29, 2007 (sent for review May 21, 2007)

Fragile X syndrome (FXS), the most commonly inherited form of mental retardation and autism, is caused by transcriptional silencing of the *fragile X mental retardation 1 (FMR1)* gene and conse-

ticity at glutamatergic synapses, such as long-term potentiation (LTP) in the cortex and long-term depression in the hippocampus, is abnormal in *FMR1* KO mice (11–13).

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Jacky Guy,[1] Jian Gan,[2] Jim Selfridge,[1] Stuart Cobb,[2] Adrian Bird[1]*

Rett syndrome is an autism spectrum disorder caused by mosaic expression of mutant copies of the X-linked *MECP2* gene in neurons. However, neurons do not die, which suggests that this is

om/naturemedicine

Reversal of learning deficits in a *Tsc2*$^{+/-}$ mouse model of tuberous sclerosis

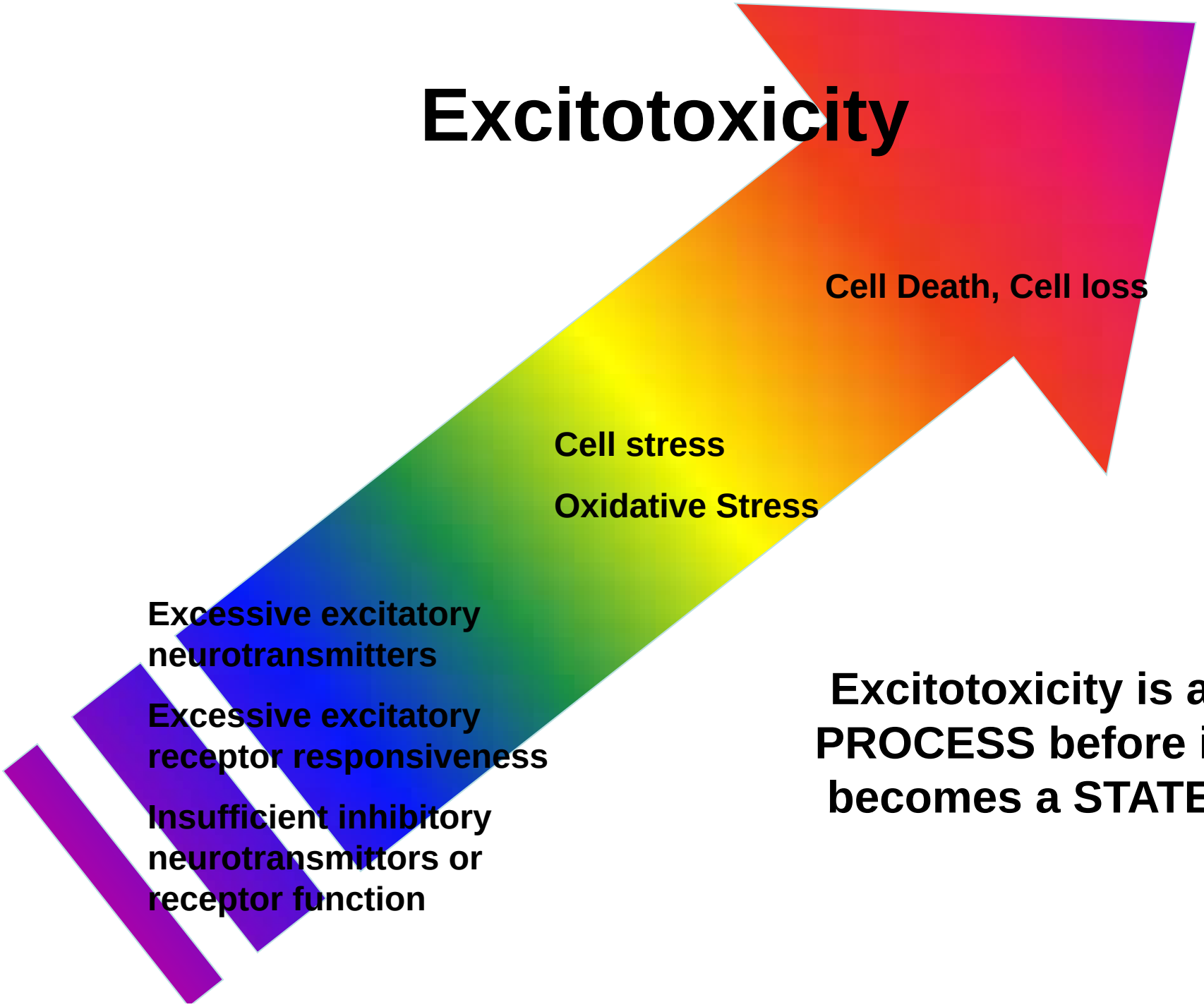
Dan Ehninger[1], Sangyeul Han[2], Carrie Shilyansky[1], Yu Zhou[1], Weidong Li[1], David J Kwiatkowski[3], Vijaya Ramesh[2] & Alcino J Silva[1]

"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**

Excitotoxicity



Excitotoxicity is a PROCESS before it becomes a STATE

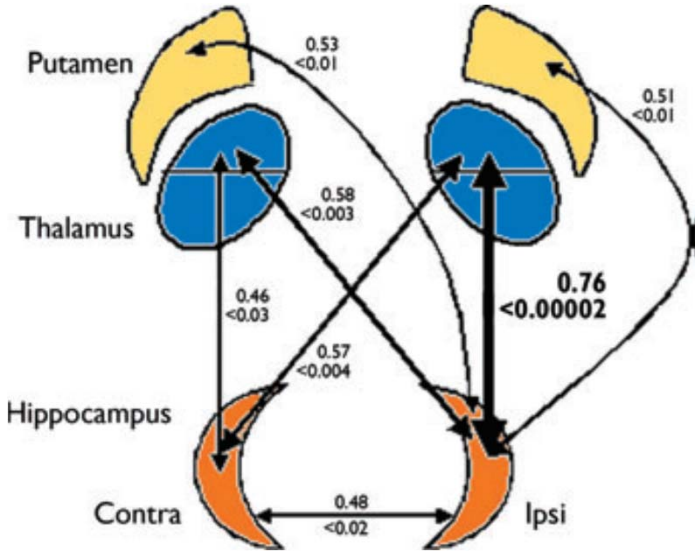
Short-term immune triggers cause long-term brain inflammation

- ***TNF-α* increases are triggered by bacterial and other exposures.** **(experiment used lipopolysaccharide (LPS) injection into gut cavity of rats)**
  - **In the bloodstream this *TNF-α* increase lasts 9 hours**
  - **In the liver it lasts 1 week**
  - ➢ **IN THE BRAIN IT LASTS 10 MONTHS**

This means that someone who gets exposed to a trigger of TNF-α every now and then could look like they have a chronic and untreatable brain problem.

Qin, *GLIA, 2007*

Reversibility of reduced NAA after epilepsy surgery



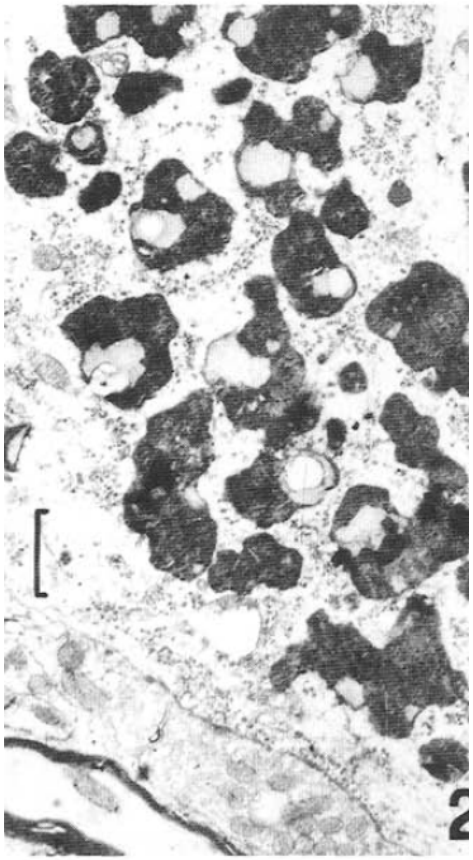
- **NAA (marker of neuronal density or function) reduced on the side opposite of a seizure focus**
- **After surgical resection of seizure focus, NAA on the other side returns to normal**
- **So – apparently those cells were not dead but "offline"**

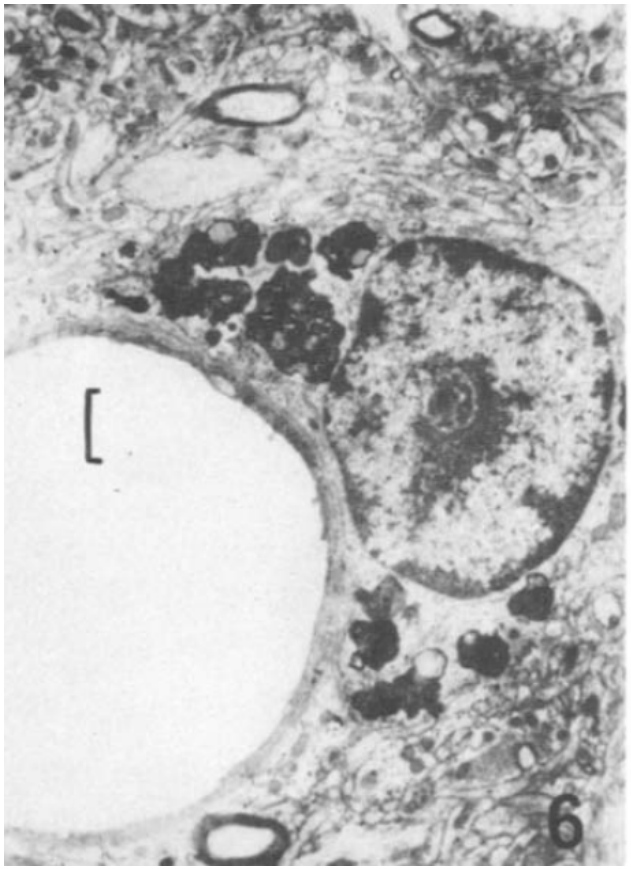
Pan, 2008
Neurometabolism in Human Epilepsy

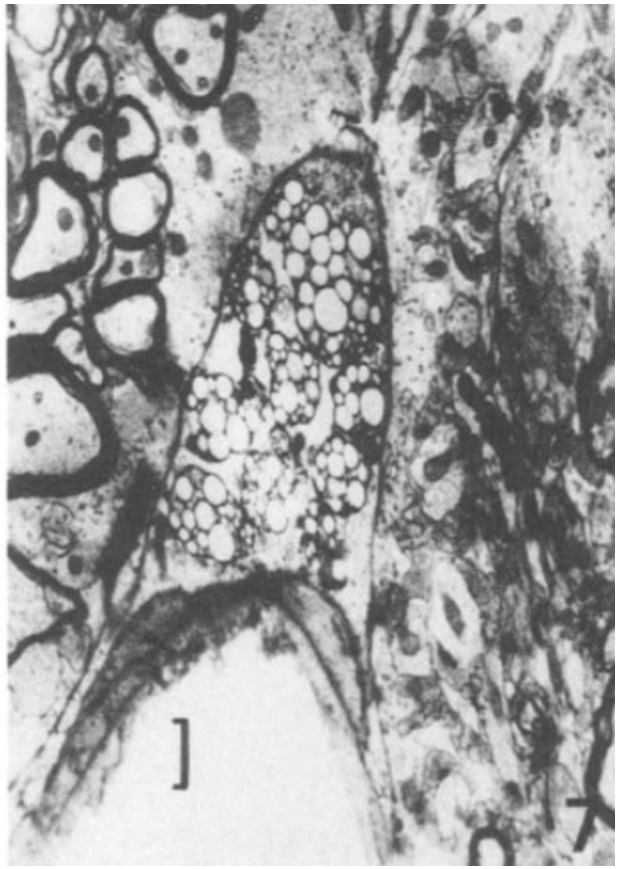
NAA = n-acetylaspartate

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

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

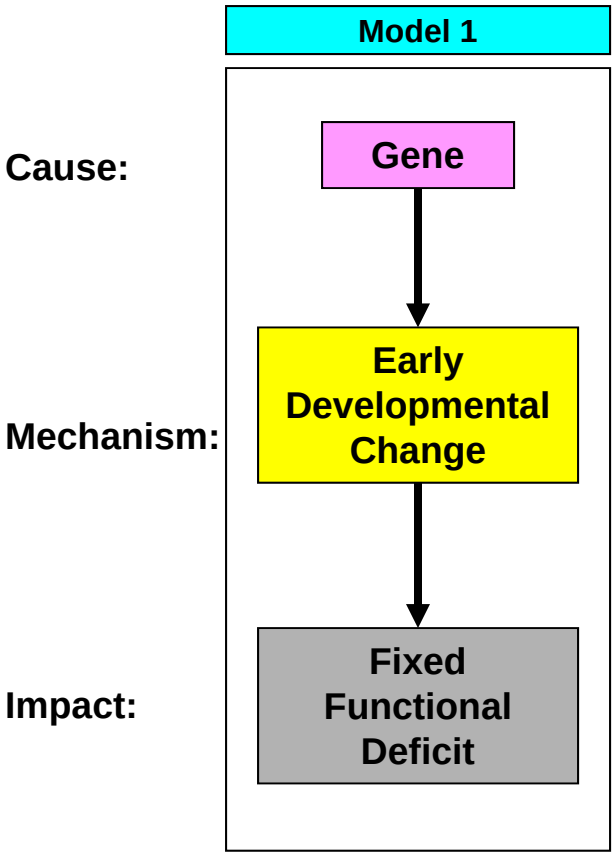






Expanding the Spectrum of Autism Mechanisms :

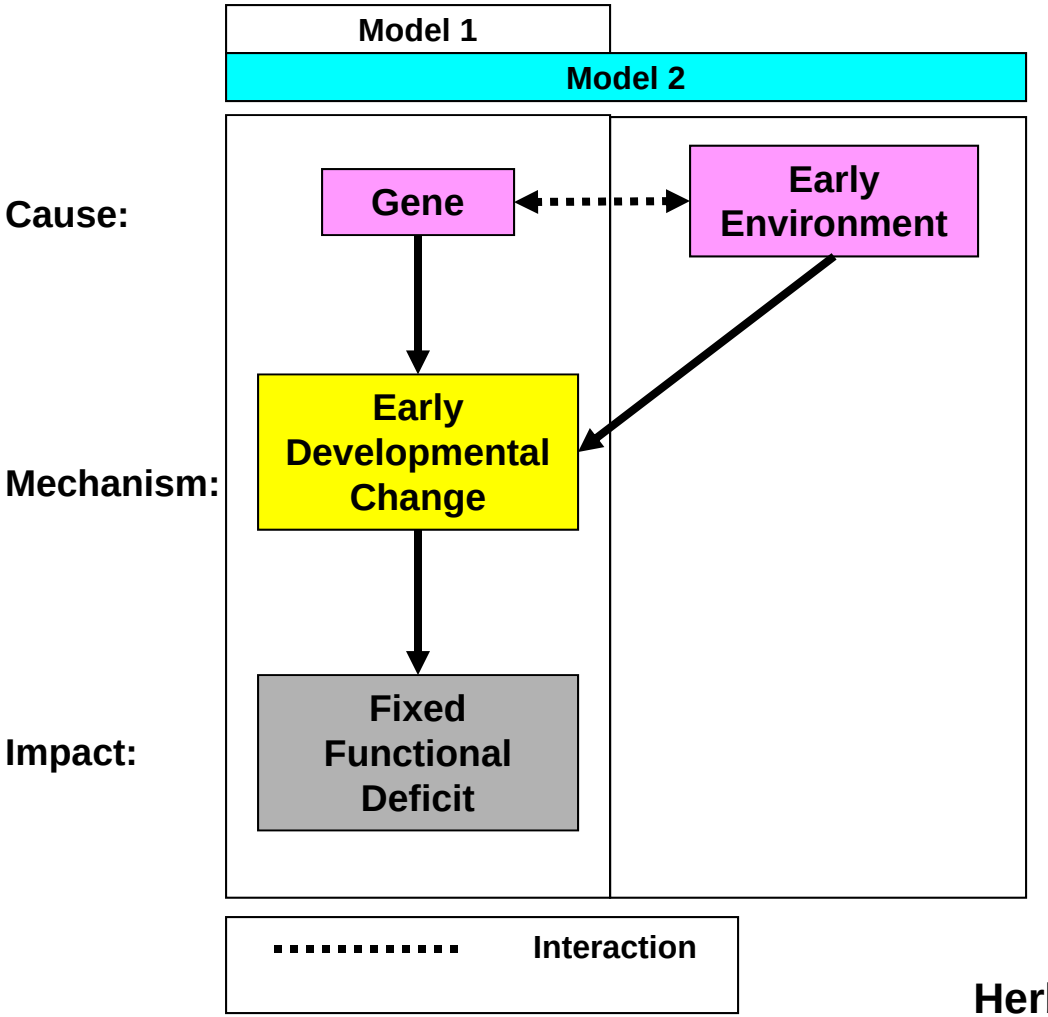
1. Genetically caused static encephalopathy



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms :

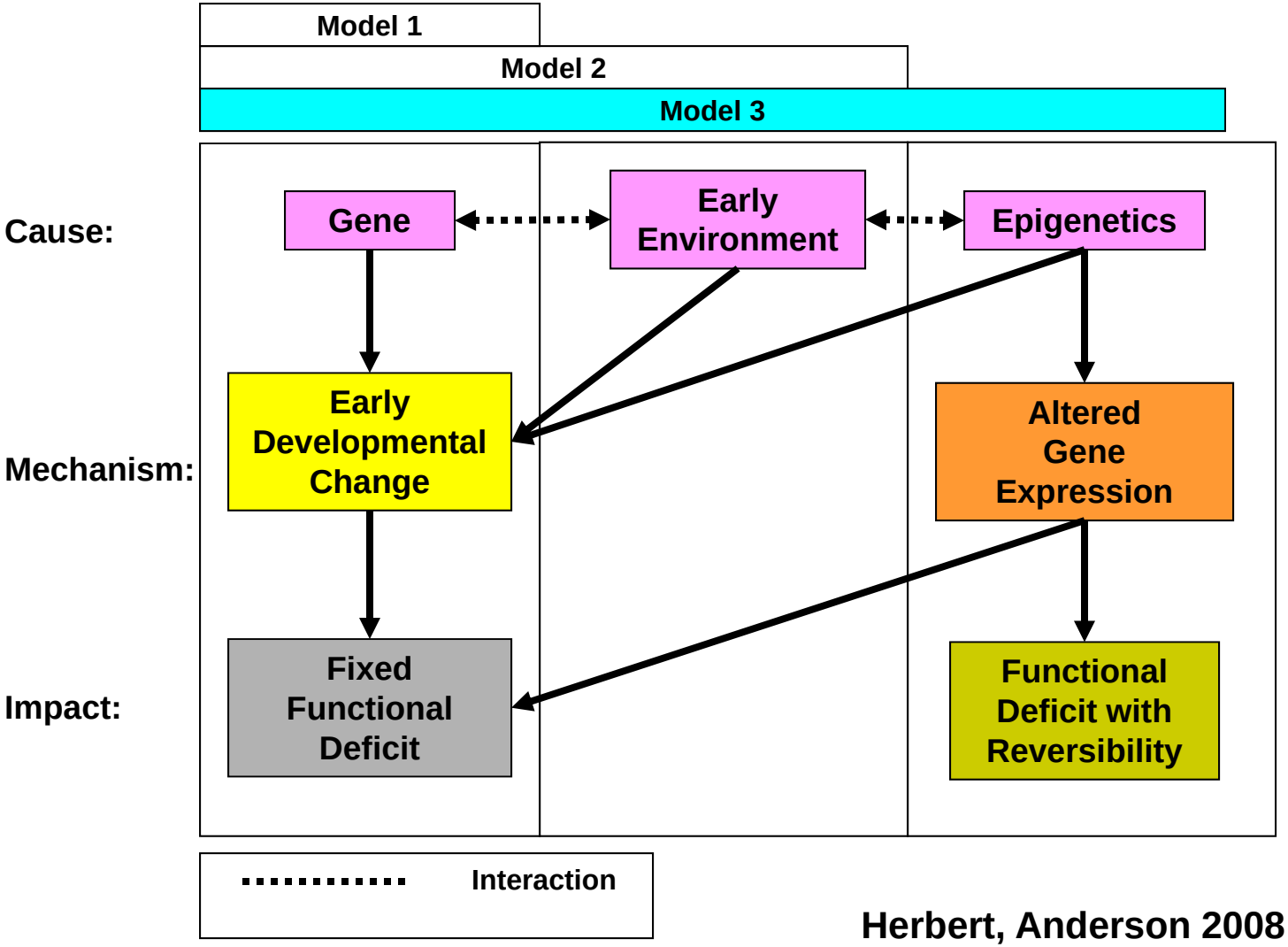
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms :

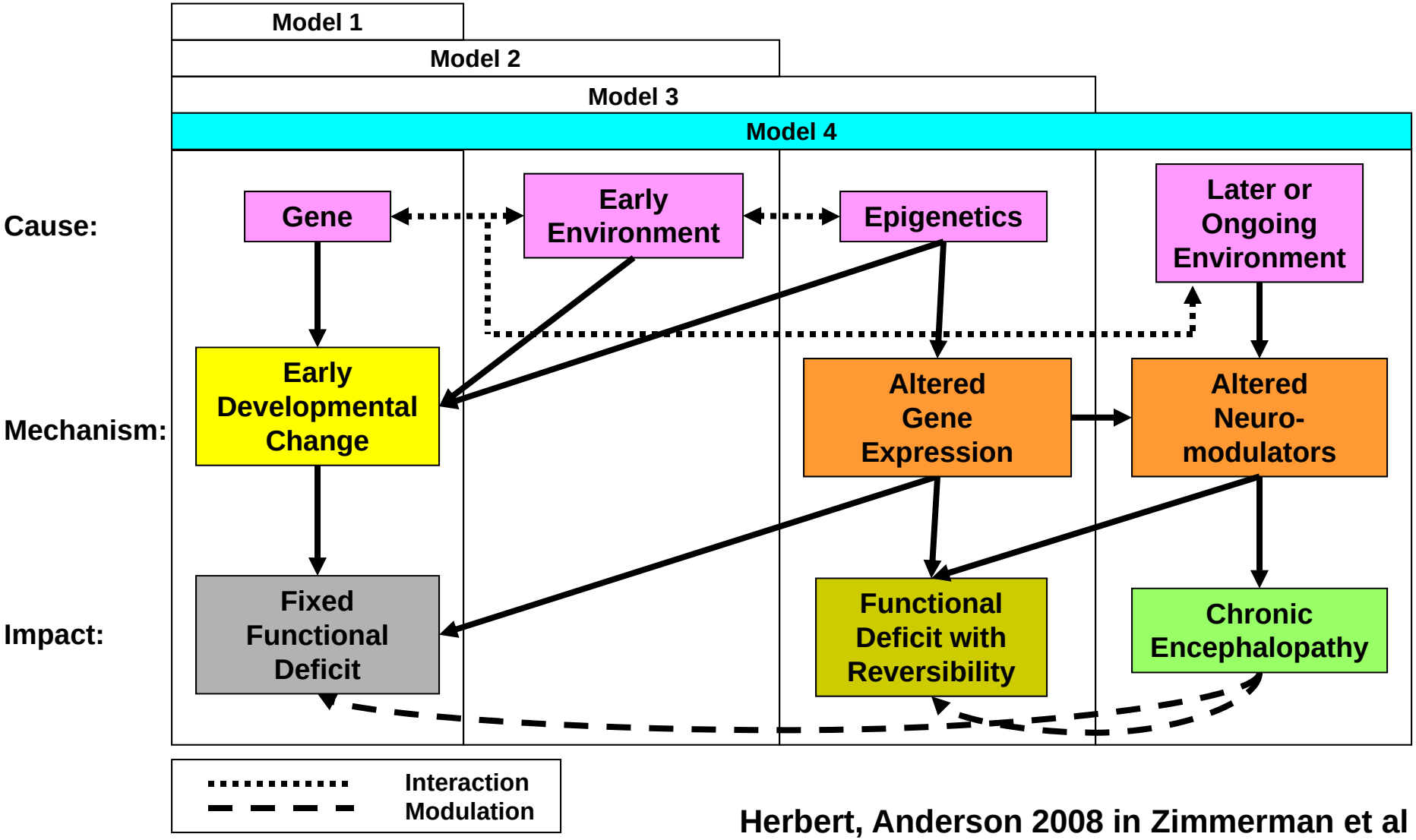
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. **Epigenetically altered gene expression**



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms:

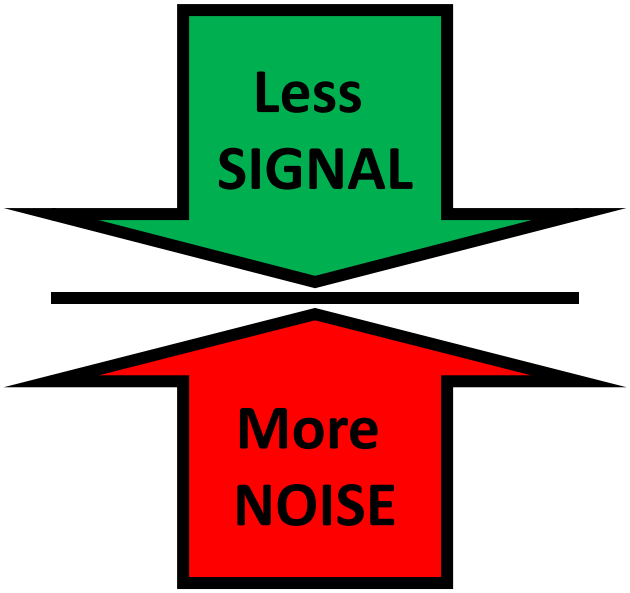
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. Epigenetically altered gene expression
4. **Later or ongoing environmental factors triggering chronic encephalopathy**



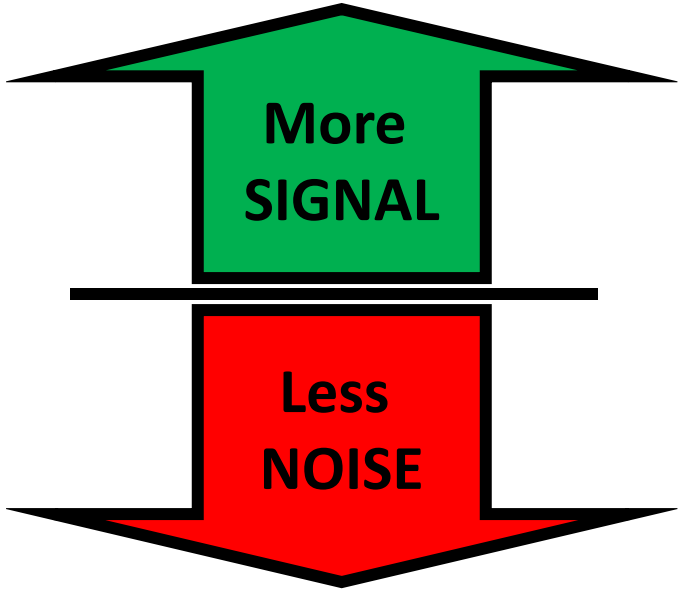
Herbert, Anderson 2008 in Zimmerman et al

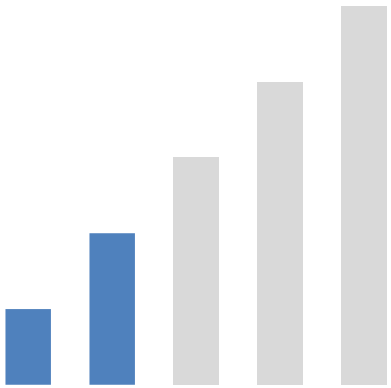
Worse SNR, Less Bandwidth

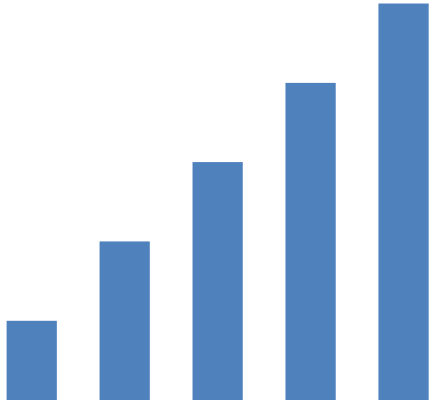
Better SNR, Better Bandwidth



SIGNAL to NOISE ratio (SNR) and BANDWIDTH

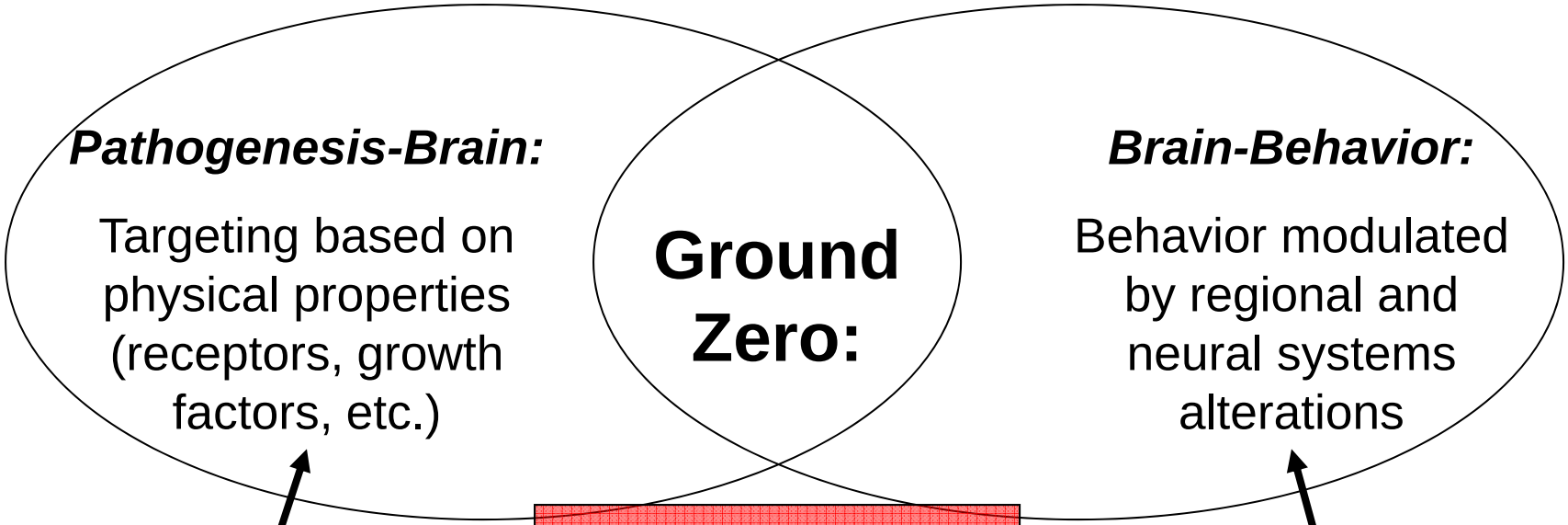






Better Reception Allows More Spontaneous Learning

Linkage needed between Pathophysiology and Cognitive Neuroscience



Pathophysiology

(including metabolism, immunology, metabolic imaging, neurology, neuropathology)

Interaction of metabolic and electro-physiological disturbance

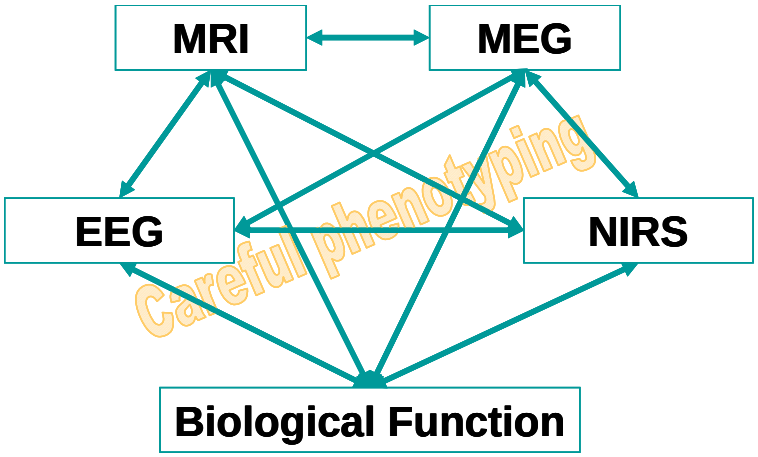
Cognitive Neuroscience

(including psychology, linguistics, functional neuroimaging, systems neuroscience)

Herbert & Ziegler, Neurotoxicology, 2005

TRANSCEND Research Program

Treatment
Research
And
Neuro
SCience
Evaluation of
Neurodevelopmental
Disorders



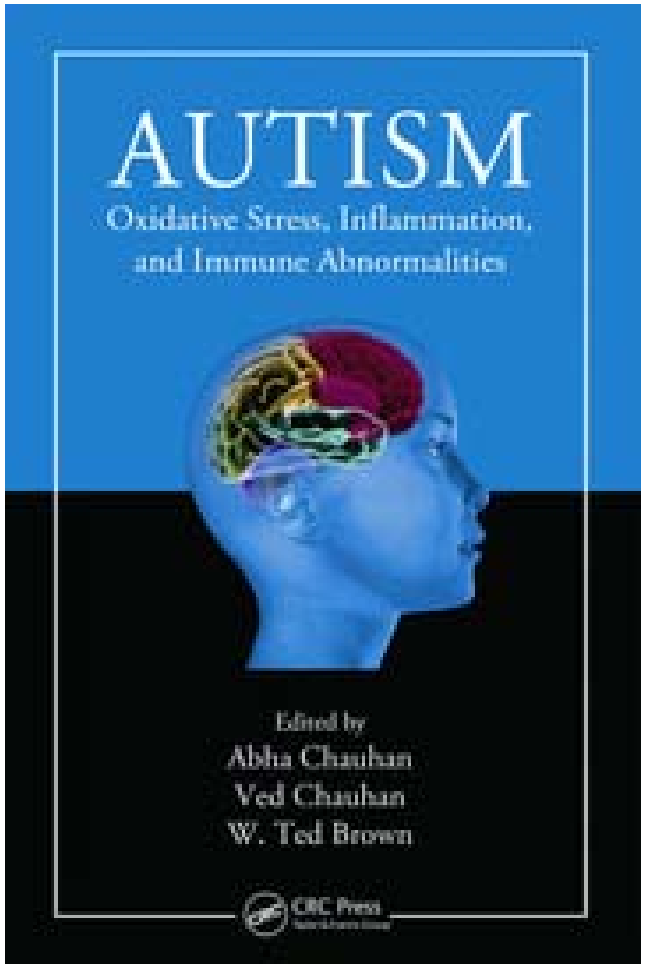
Integrative multimodal measurement platform

Optimization of measures that can detect change

- ***Pathophysiology interacting with neurophysiology***

In development, in regression, in improvement

www.transcendresearch.org
transcend@partners.org



Article detailing much content for this talk:

Autism: The Centrality of Active Pathophysiology and the Shift from Static to Chronic Dynamic Encephalopathy

By Martha R. Herbert, MD, PhD

2009

Autism:
Oxidative stress, inflammation and immune abnormalities

Chauhan A, Chauhan V, Brown T, eds., in press, 2009, Taylor & Francis/CRC Press.

GENETIC EXPLANATIONS

Sense and Nonsense

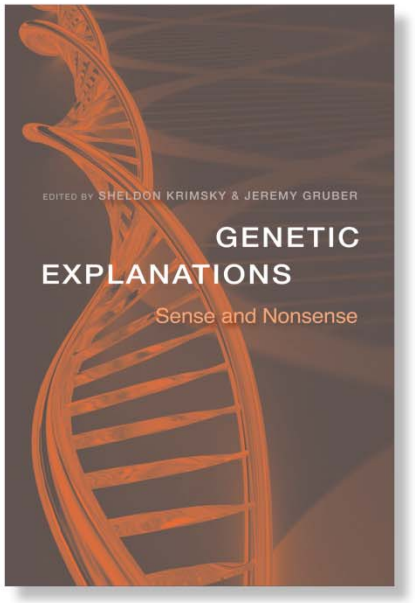
Edited by SHELDON KRIMSKY and JEREMY GRUBER

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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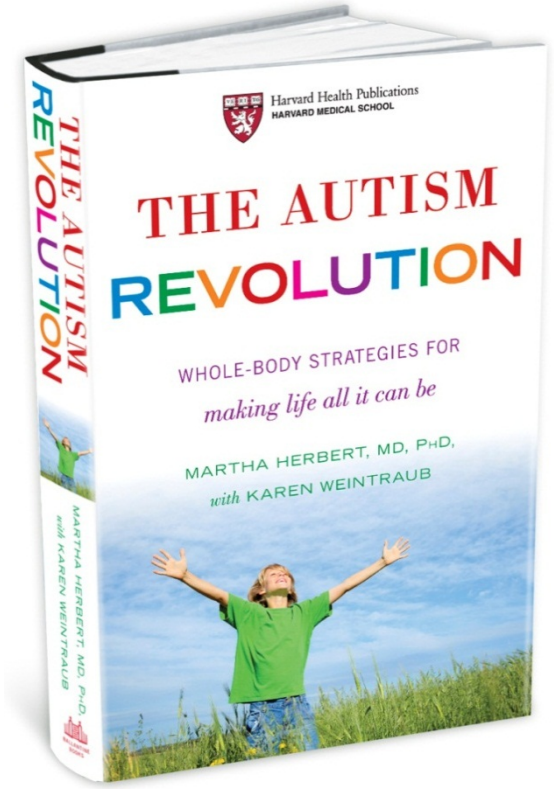

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