Autism:
What Do Diet and Environment Have to Do With it?

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TRANSCEND

In order to understand why diet and environment could possibly matter to autism

- **It is necessary to think really carefully about what we think autism "is" and how autism "works"**
- **Critical to ask:**
  - **What is "behavior"?**
  - **What *generates* behavior?**
  - **How can we modulate the processes that generate behavior?**

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

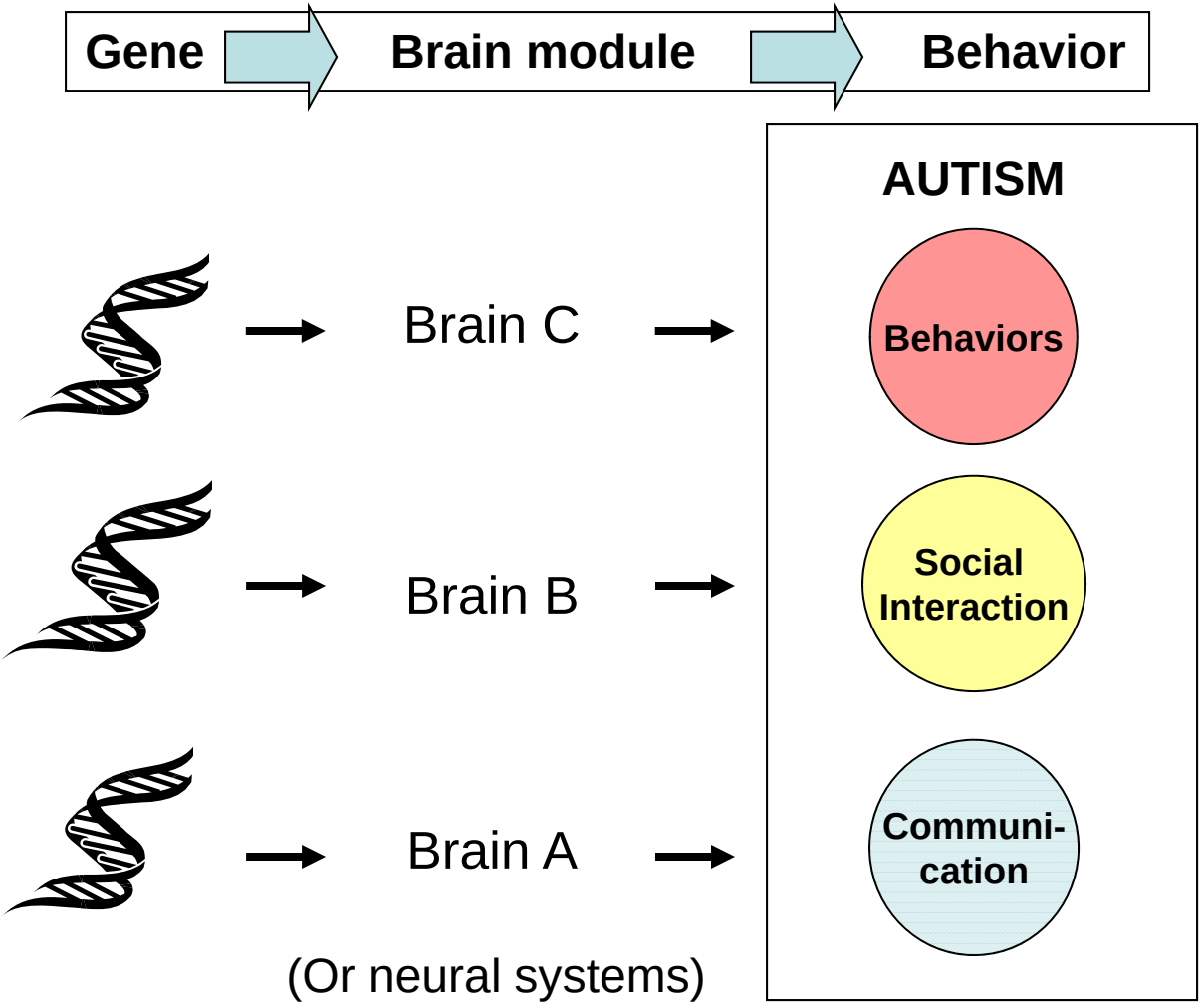
Seizures (~30%+), cognitive deficits, sensorimotor abnormalities, savant skills, immune impairments, GI distress(50-75%), food allergies (~50+%)

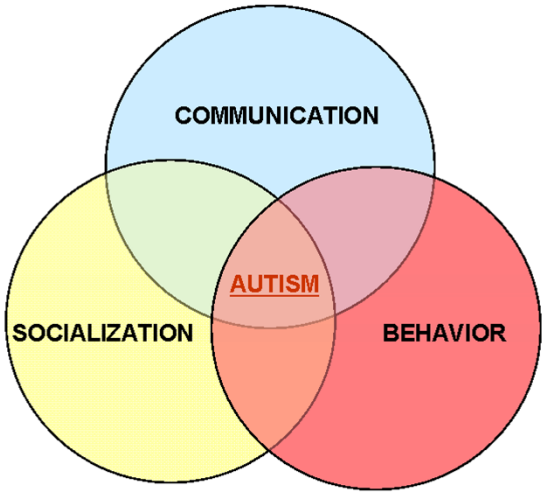
No biological markers exist to identify autism at this time

Autism is presumably *Heterogeneous biologically*

But autism is *biological*

From Definition to Model of Autism: Classic Modular Framework





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**

These assumptions are not supported by evidence.

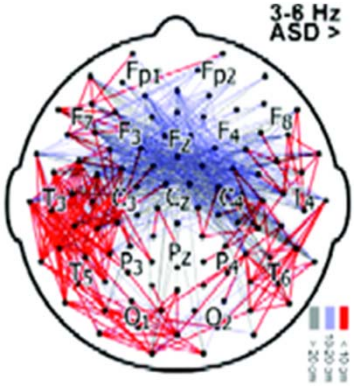
Emerging science contradicts them.

Beyond Genes

- **Not a Static Prevalence**
- **Not Just Genes: Environmental Contributors**
- **Not Just a Few High-Impact Genes: Hundreds of Mostly Lower-Impact Genes**
- **Not Just Inherited Genes: De Novo Mutations (that children have but their parents don't – where do they come from??)**
- **Not Even Mainly Genes: Substantial Environmental Contribution**
- **Not Just Mutations: Epigenetics**

Beyond the Brain

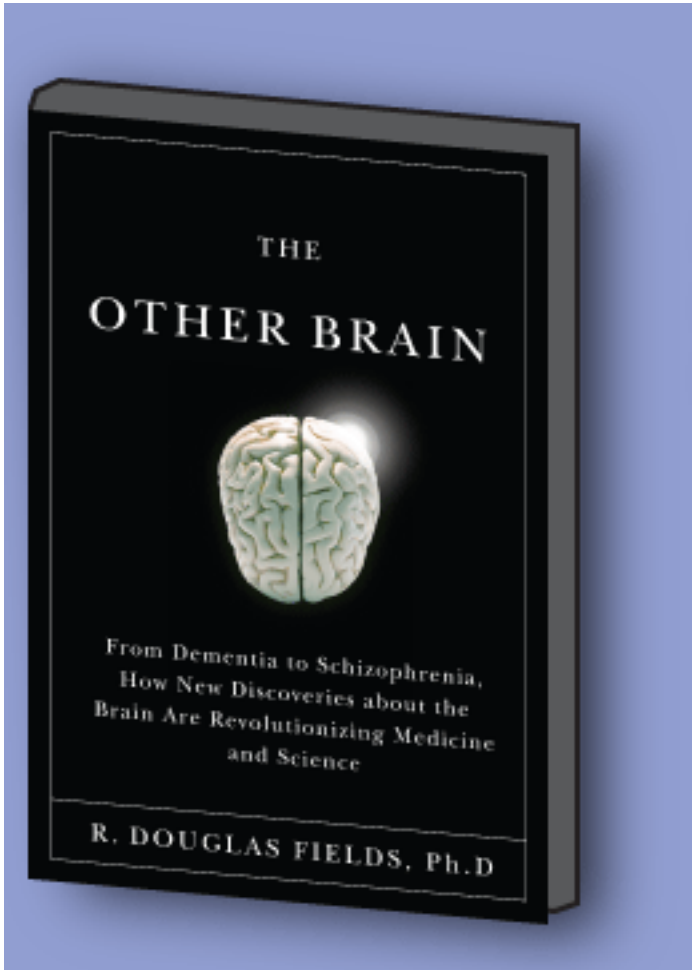
- **Not Just Brain Genes: Also expressed systemically**
- **Not Just Local, Modular Brain Disturbances: Whole Brain Involvement**
- **Not Just Regional Problems: Brain Coordination is Widely Challenged**
- **Not Just Brain Wiring: Active tissue pathophysiology in the brain (inflammation, oxidative stress,)**
- **Not Just the Brain – Whole Body, Whole System Involvement**



Beyond Neurons

- **Not Just Neurons: Glial Cells**
- **Not Just Brain Cells: Blood flow**
- **Not Just Brain Cells: maybe Even Extracellular Matrix**

THE OTHER BRAIN
by Douglas Fields, PhD, NIH scientist



ABOUT GLIAL CELLS

www.theotherbrainbook.com

Beyond
“Prenatally Programmed Deficit”

- **Not Just Deficit: Giftedness and High Intelligence.**
- **Not Just Prenatal**
- **Not Necessarily Present at Birth**
- **Not Just Behavior**

Beyond Hopelessness

- **Not a Life Sentence: Evidence of**
  - **Severity that varies, particularly in individuals with autism and mitochondrial disease**
  - **Transient marked reduction of severity in fever**
  - **Remission and loss of diagnosis (currently being studied at the NIMH)**

From Static to Dynamic Encephalopathy

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

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

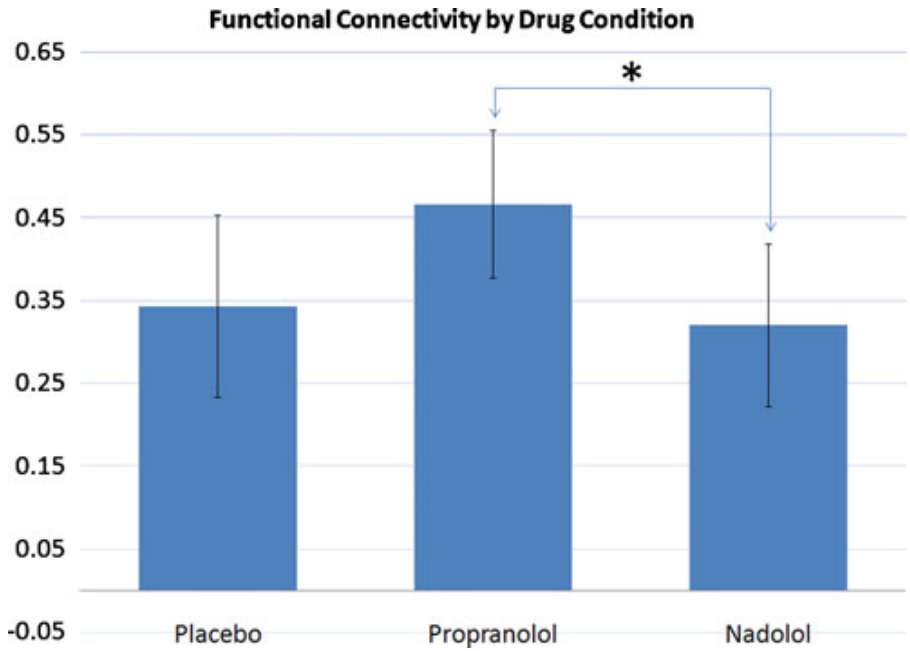
Behaviors Associated with Fever in Children with Autism Spectrum Disorders.
Curran et al, Pediatrics 2007

<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)**

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

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**

GENETIC EXPLANATIONS

Sense and Nonsense

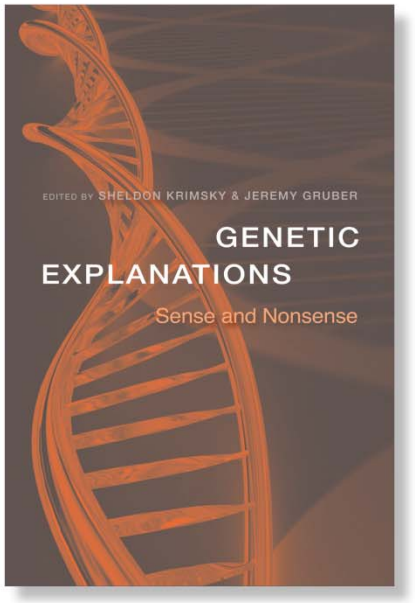
Edited by SHELDON KRIMSKY and JEREMY GRUBER

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

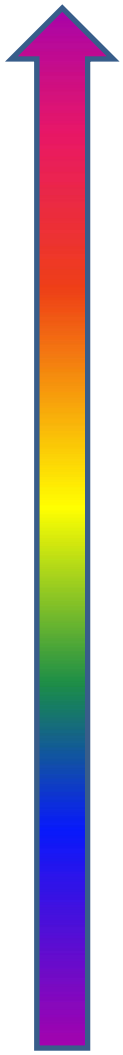
By Martha Herbert

Autism: WHY and HOW ?

www.autismWHYandHOW.org

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

Zoom through Autism's Complexity:
Levels that are all involved AT THE SAME TIME

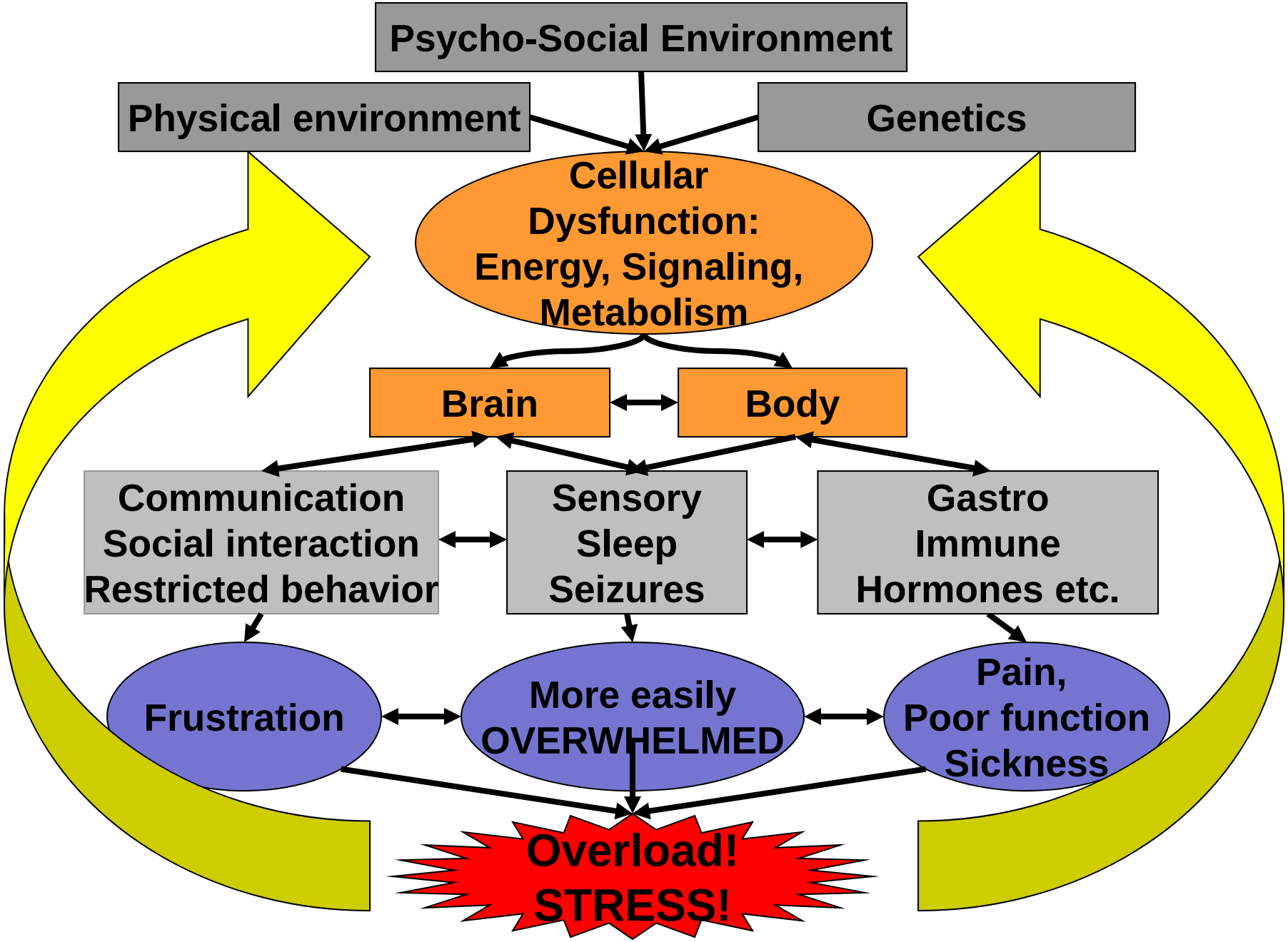


Creativity
Social interaction
Learning
Behavior
Brain as information system
Stress System
Brain as wet physical organ
Organs – GI, Immune
Cells
Chemistry
Genes and environment

Everything we do relies on our cells.

- Energy
- Moving things around
- Digestion
- Changing one chemical into another
- Taking out the trash
- Communicating
- Holding things together (structure)
- Protection

Whole Body Model: Vicious circles in brain and body



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**

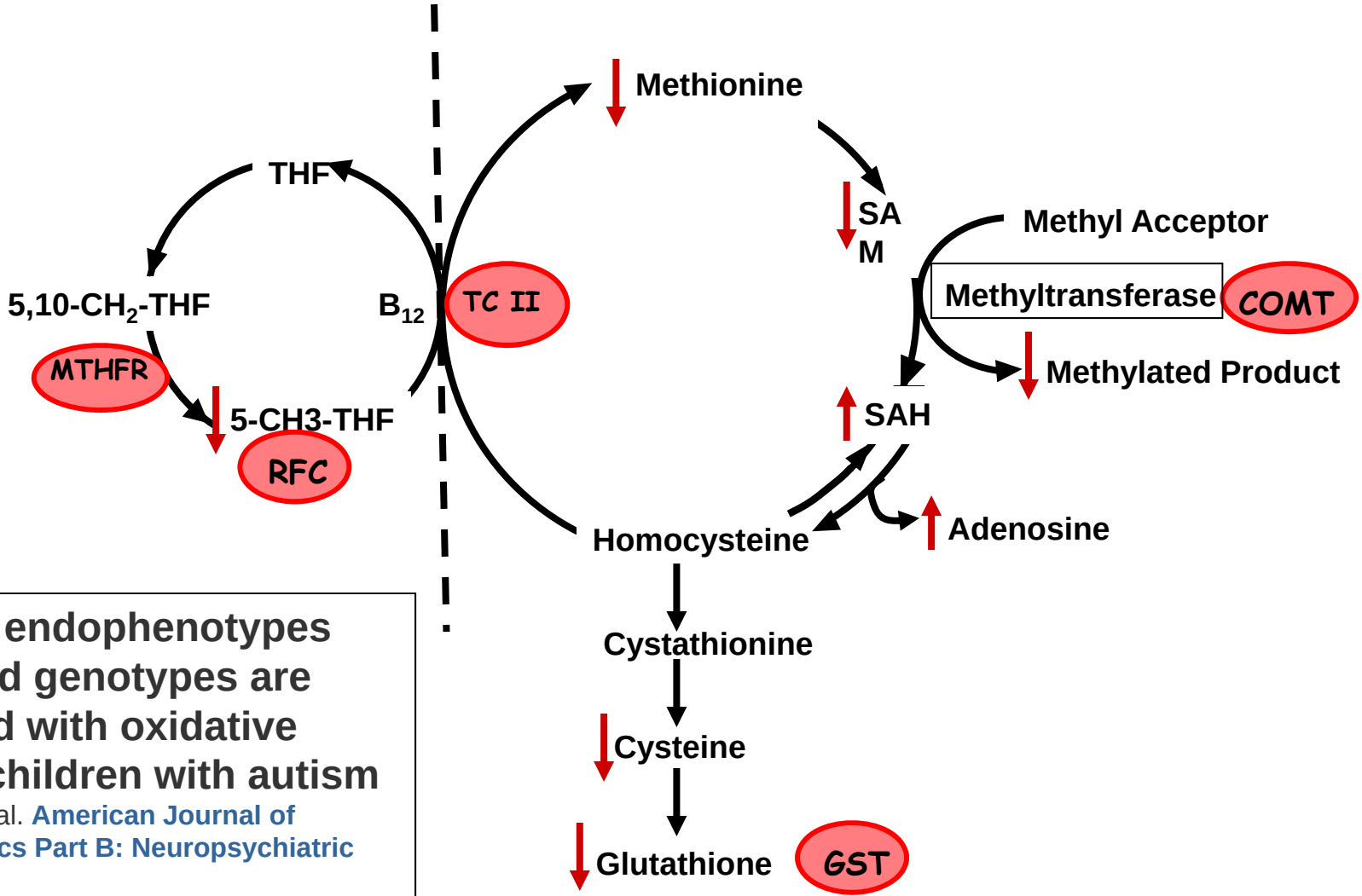
Sources include Hertz-Picciotto; van de Water; Patterson; Smith; others

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

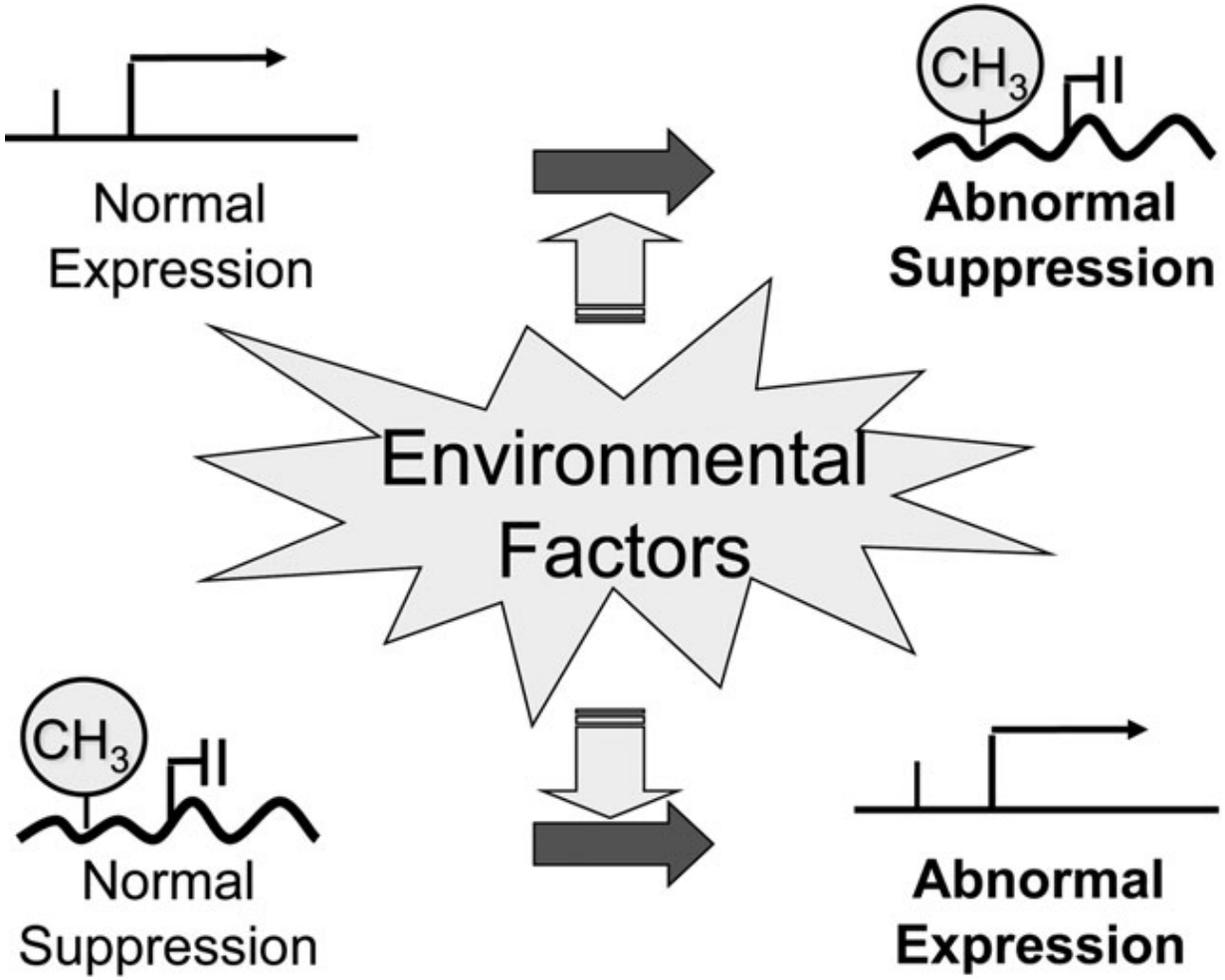
Metabolic Response to Genetic Polymorphisms in the Methionine Cycle



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.

Hypothesis: a Unifying Mechanism for Nutrition and Chemicals as Lifelong Modulators of DNA Hypomethylation

Environ Health Perspect. 2009 Dec;117(12):1799-802

– “alterations in methylation patterns due to background exposure to mixtures of chemical agents are plausible.

They may be more serious when nutritional deficiency or imbalance involved in the methylation cycle coexist.”

Hypothesis: a Unifying Mechanism for Nutrition and Chemicals as Lifelong Modulators of DNA Hypomethylation

Environ Health Perspect. 2009 Dec;117(12):1799-802

– “At present, there is a paucity of integrative human studies that consider both chemicals and nutrition. Therefore, future human studies will be needed to consider the influence of chemical exposures on DNA hypomethylation, accounting for dietary factors”

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?**

Canary in a Coal Mine

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

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

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.

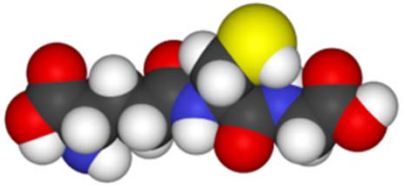
- Wendell Berry, Harper's, May 2008

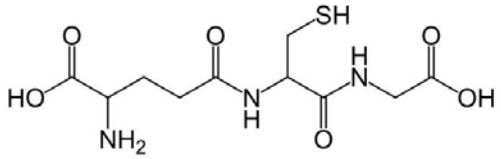
UN Report by 1360 scientists :

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

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



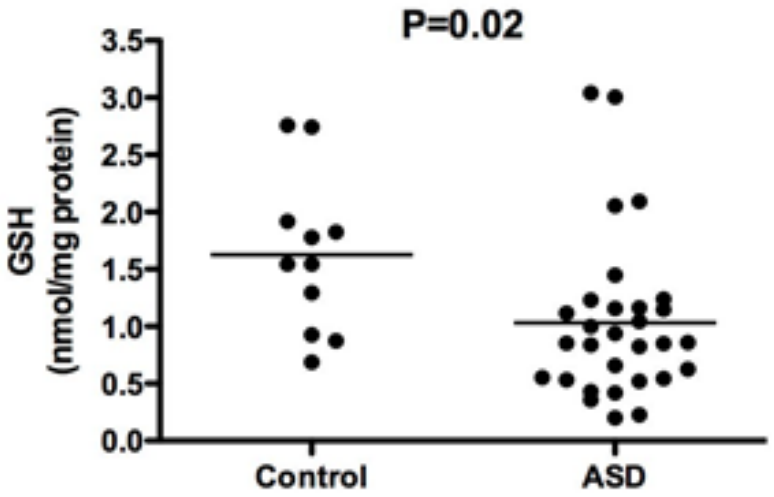


Made in the liver from three amino acids: Glutamate + Cysteine + Glycine

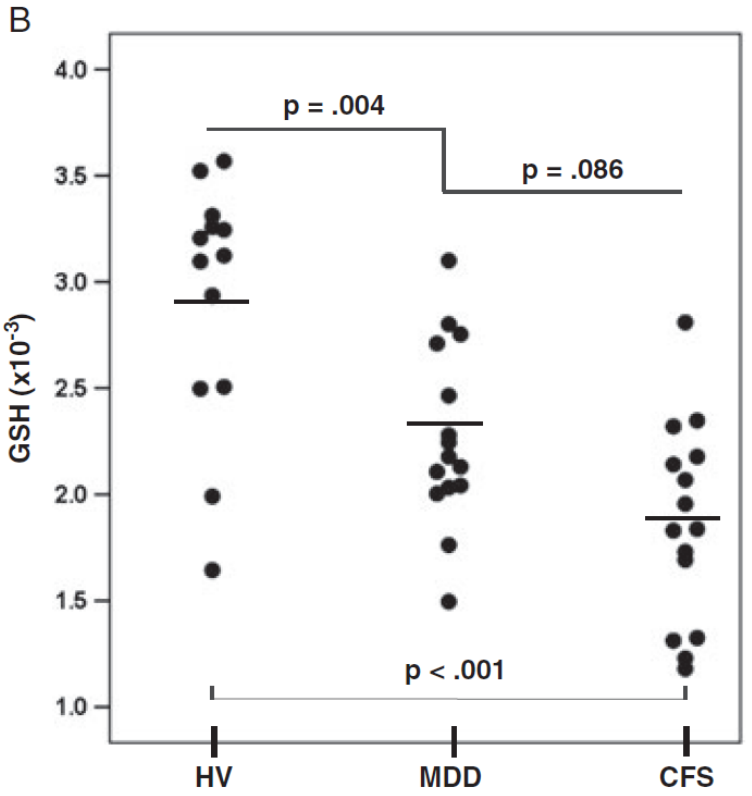
- **GLUTATHIONE (GSH) is vital for detoxification**
  - **Mops up toxins and free radicals**
- **The body's most potent anti-oxidant**
- **The most abundant antioxidant in the BRAIN**

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

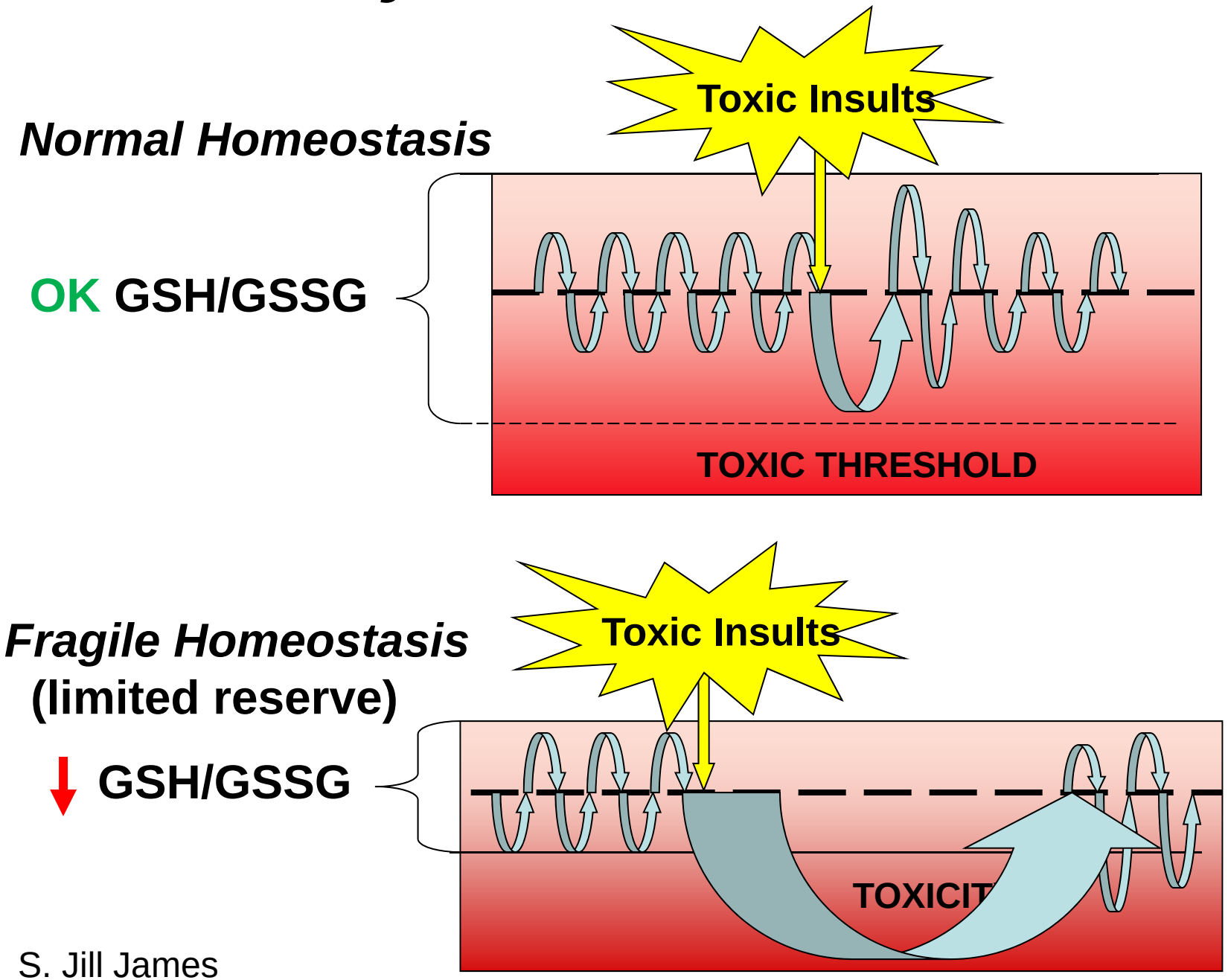


Suh, J., W. Walsh, et al. (2008). American Journal of Biotechnology and Biochemistry **4**(2): 105-113,



Shungu et al., 2012

Vulnerability with low GSH



S. Jill James

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**

- For reflection: "Glutathione: a novel treatment target in psychiatry" – *Trends Pharmacol Sci. 2008 Jul;29(7):346-51*

A must-read statement of a systems biology approach to complex illness:

From ‘omics’ to complex disease: a systems biology approach to gene-environment interactions in cancer

By Sarah S Knox: http://www.cancerci.com/content/10/1/11

Looks at cancer as accumulated ALLOSTATIC LOAD from diet and environment

Advocates a dynamic *transdisciplinary systems biology approach aimed at reversing multiple levels of dysfunction*.

JUST ABOUT EVERYTHING SHE SAYS

APPLIES TO AUTISM

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

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)

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

- **James SJ et al. *J Med Genet B Neuropsychiatr Genet. 2010 Sep;153B(6):1209-20.***
- **Confirmed previous findings plus found lower levels of plasma folate in case moms compared to controls.**

Magnesium findings in Autism

Magnesium Research 2006; 19(1): 53-62

- Lower RBC-Mg levels were found in both mothers andfathers
- – There was a statistically significant correlation of the mother's Mg to that of her child with autism
- Consistent with altered GSH/GSSG in autistic children and their mothers
- Behavioral improvement in the child with autism correlated with increases in RBC-Mg while on Mg supplements. Off supplement, behavior regressed as RBC-Mg fell to base-line.
- No difference in serum Mg was found

Oxidative Stress and Psychiatric Disorders

- **A meta-analysis indicates an association of oxidative stress in the majority of DSM-IV psychiatric disorders including: autism, Rett's, ADHD, schizophrenia, anxiety, and mood disorders.** *Full text available at:*

  http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2330073&blobtype=pdf

- **"…all these psychiatric disorders might benefit from a change to a whole-food plant-based diet."**

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

Nassim Zecavati, MD, MPH, and Sarah J. Spence, MD, PhD

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Current Neurology and Neuroscience Reports 2009, 9:129–136
Current Medicine Group LLC ISSN 1528-4042

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

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

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Tel: +1 617 724 5920;
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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.

Classes of Core Functions

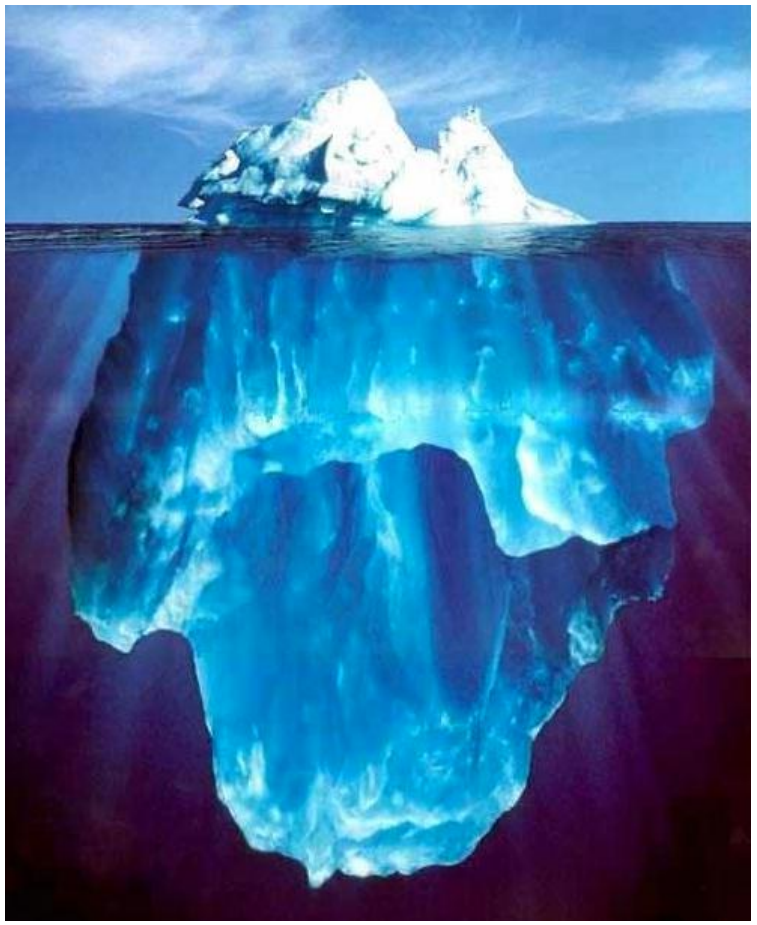
Abnormalities at all of these levels in autism— and many other major chronic diseases as well

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***

Whole Body systems Model: Symptoms Emerge from Problems with Underlying Functions

VISIBLE Social & Behavioral SYMPTOMS →

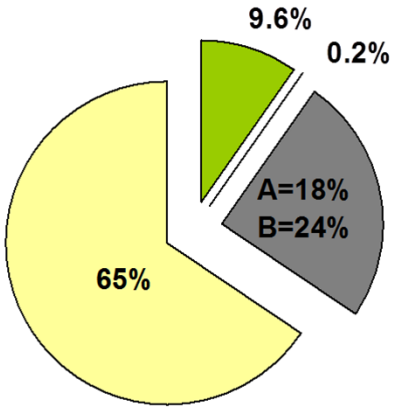
UNDERLYING SYSTEMIC FUNCTIONAL DISTURBANCES ↗



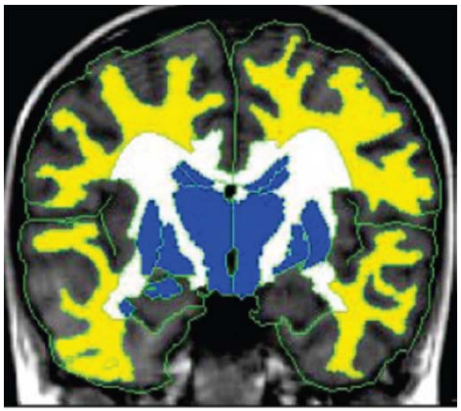
Ziggarut model: http://www.texasautism.com/

Not necessarily just prenatal

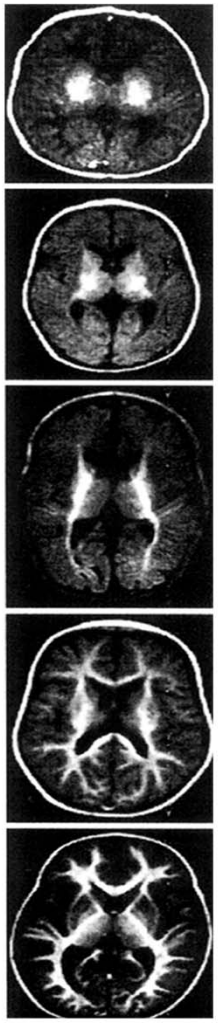
Location of white matter enlargement points to postnatal brain changes



White Matter Contributes Most to Autism Volume Increase



Radiate White Matter Enlargement



I- 1st Month

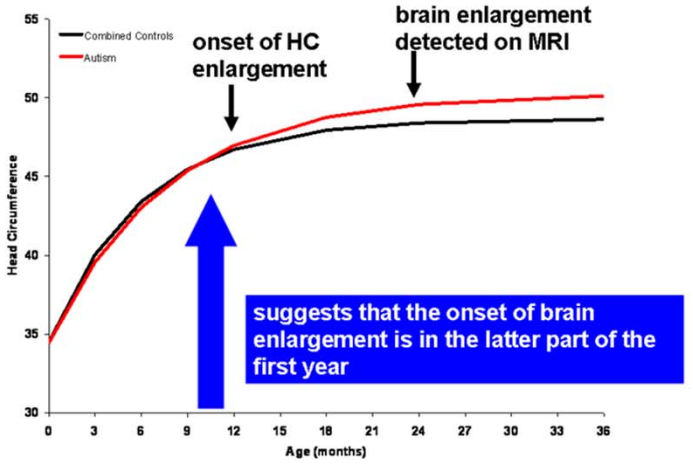
II- 2nd Month

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?

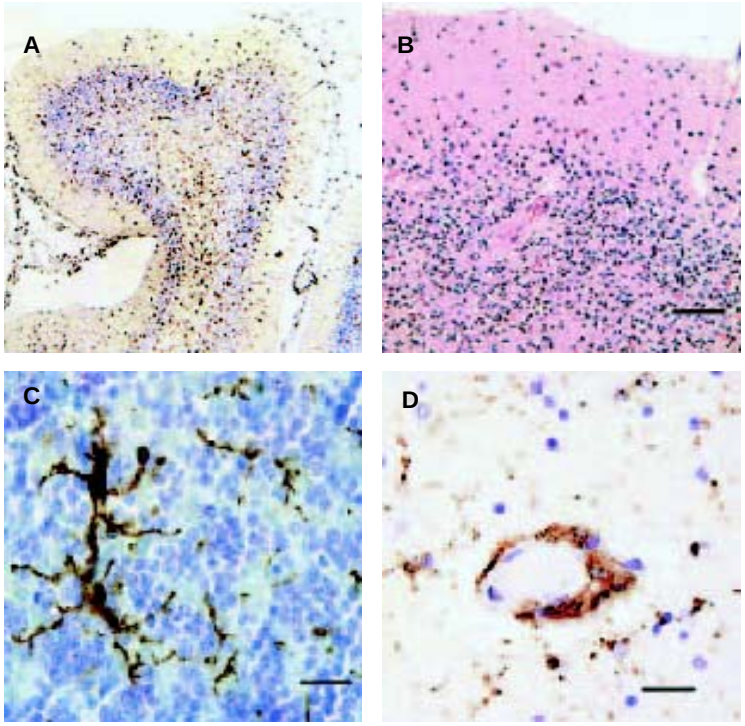
Not just genetically predetermined altered brain wiring diagram: Active Tissue Pathophysiology in Brain

- **Immune activation and other active pathophysiological processes in brain tissue**

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

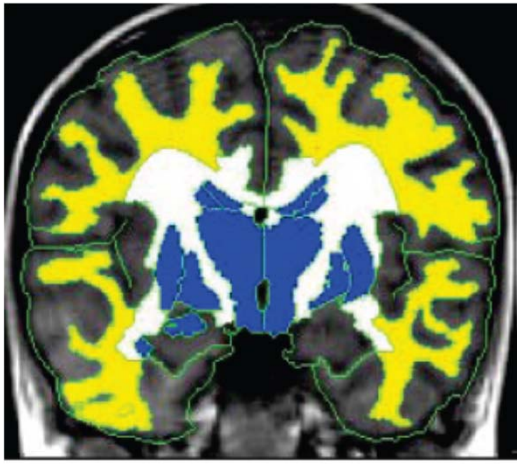


- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3-year old's brain

Pardo: Astrogliosis in Radiate White Matter

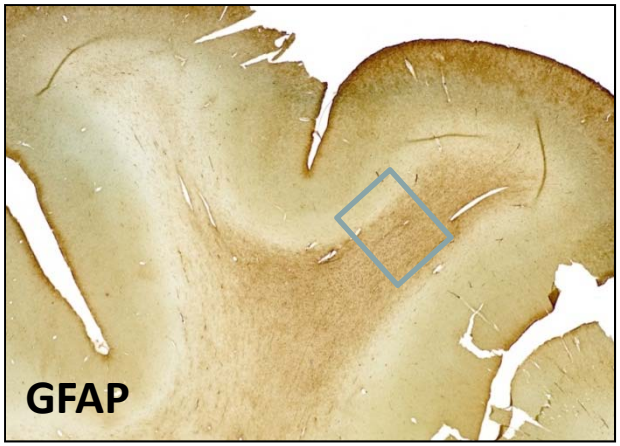
Astrogliosis

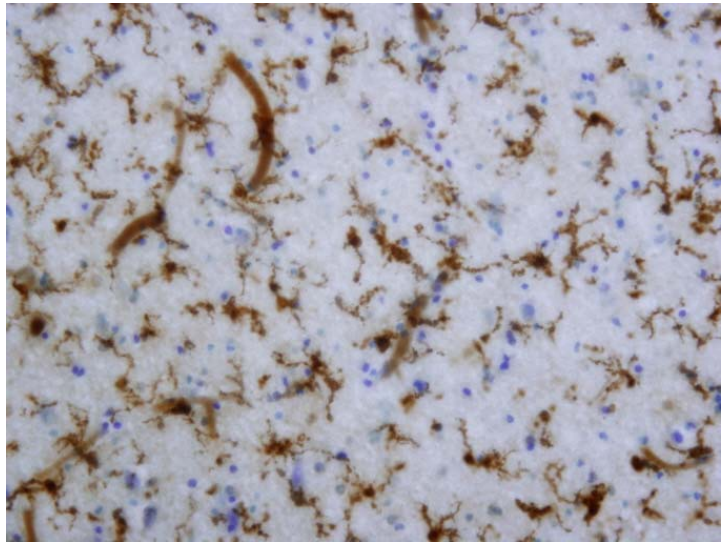
Microgliosis



Herbert:

Radiate White Matter Enlargement



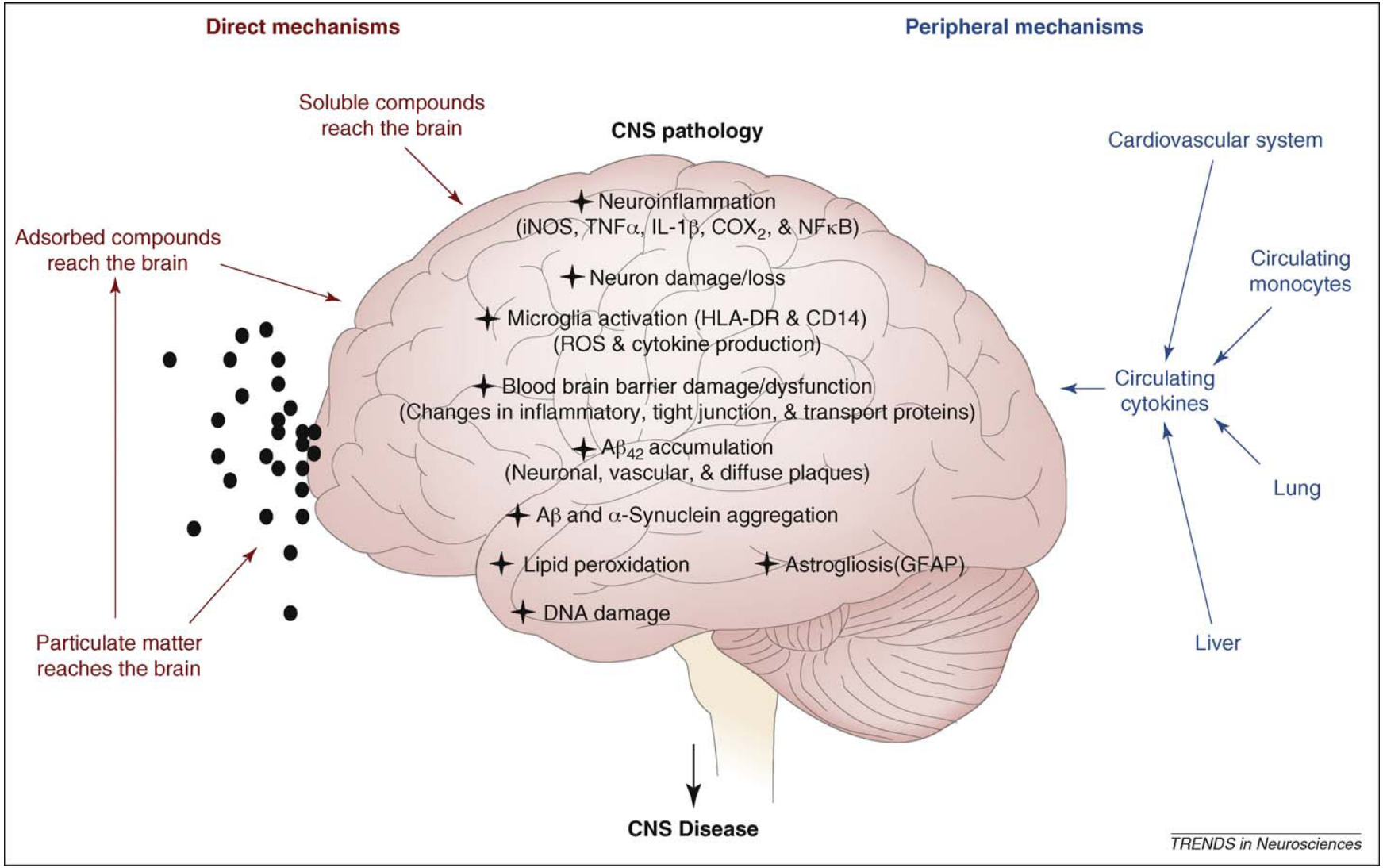


Pardo

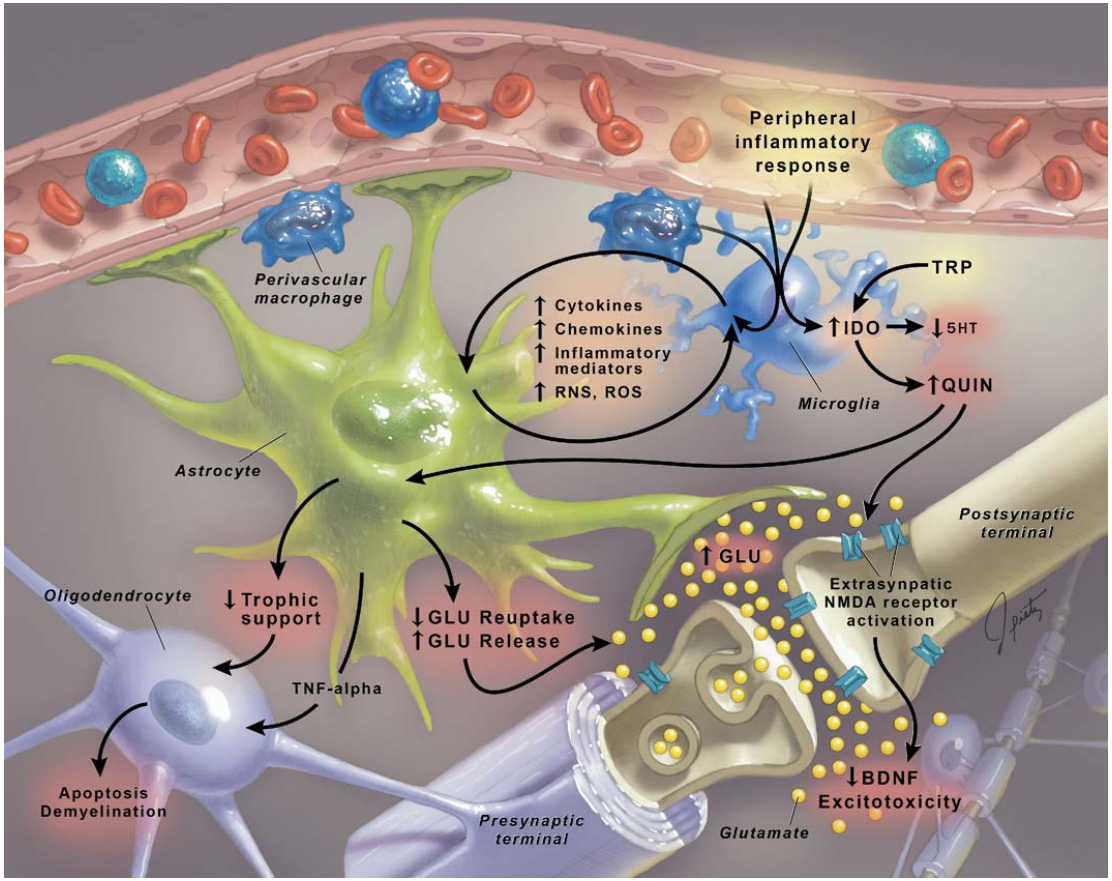
Air Pollution and Brain Inflammation

Block and Calderon-Gardicuenas, TNS, 2009

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



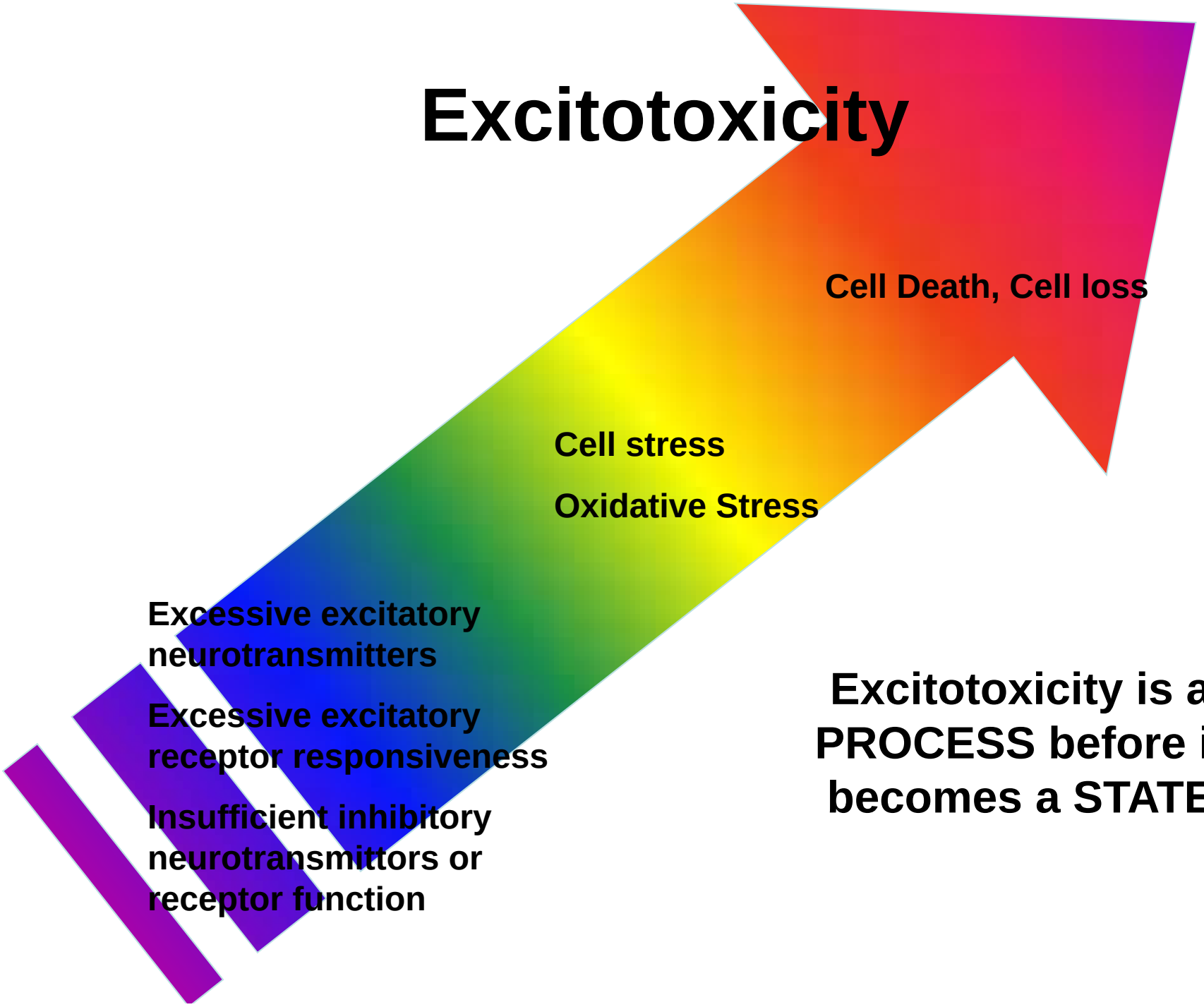
Brain cells in inflammation: What is the FUNCTIONAL IMPACT?



- **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

Excitotoxicity

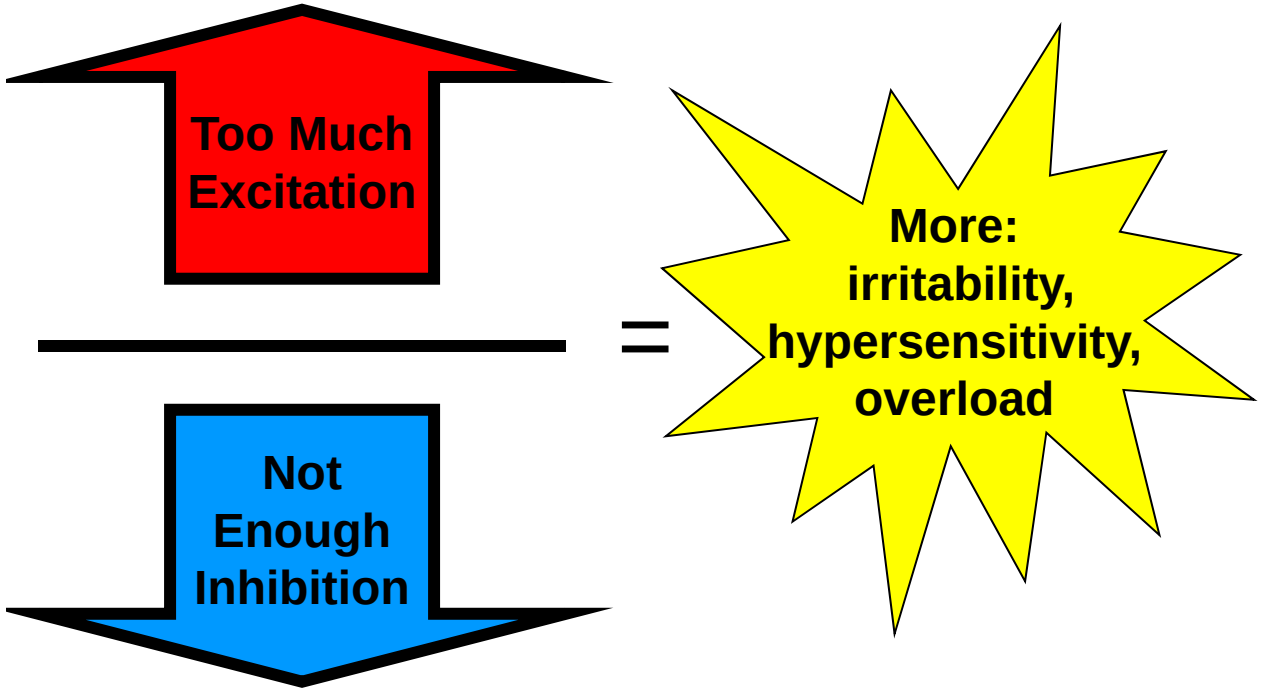


Excitotoxicity is a PROCESS before it becomes a STATE

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

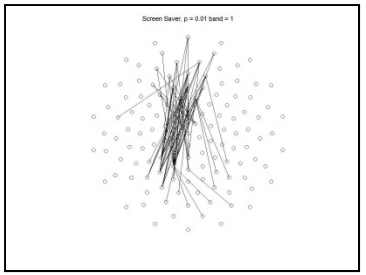
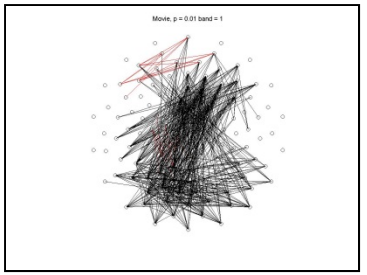
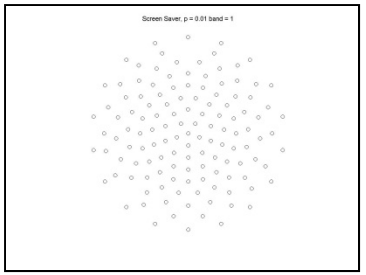
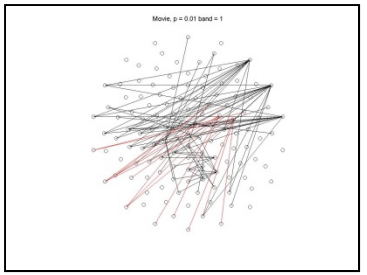
EEG of Sensory Responses

- **Sensory stimulation can be overwhelming**

➢ **Much more dysfunction when more stimulation**

➢ **Looks milder in older kids**

Prediction:
Improved connectivity with effective treatment

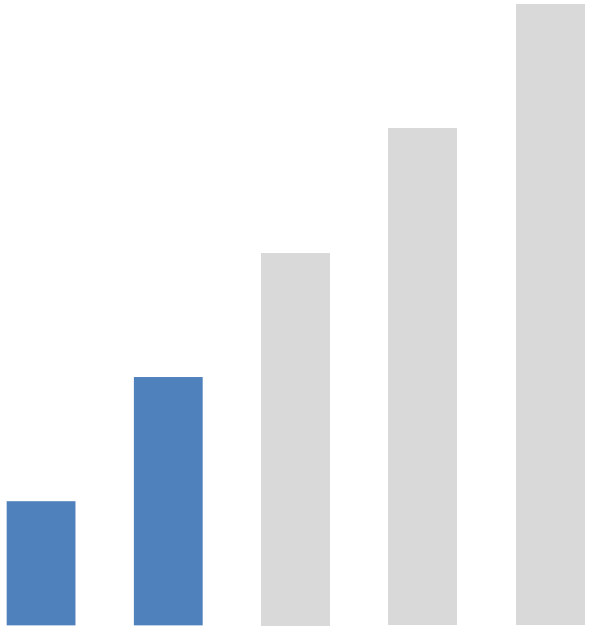
	Screen Saver: **Less Stimulation**	Movie: **More Stimulation**
5-8 years old		
9-11 years old		

Martien et al. 2008

Tissue pathophysiology REDUCES BRAIN BANDWIDTH

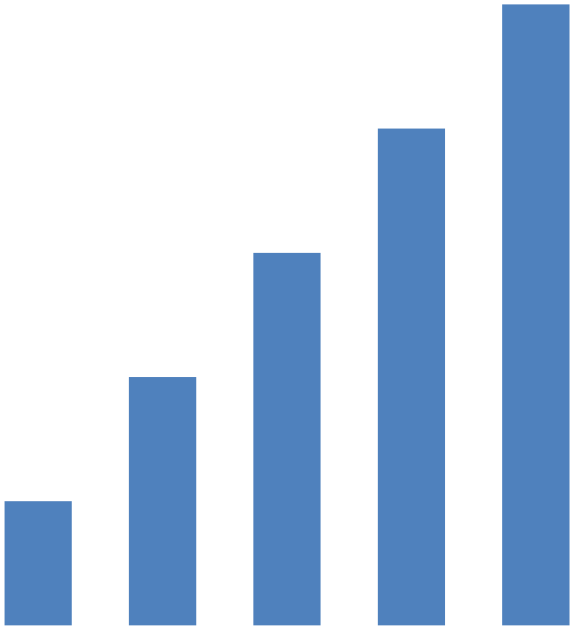
Poor Bandwidth:

Limited Reception



Lots of Bandwidth:

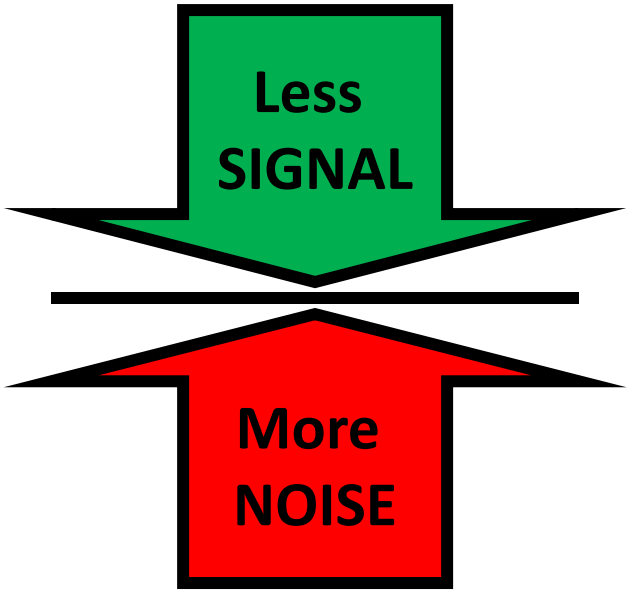
Good Reception



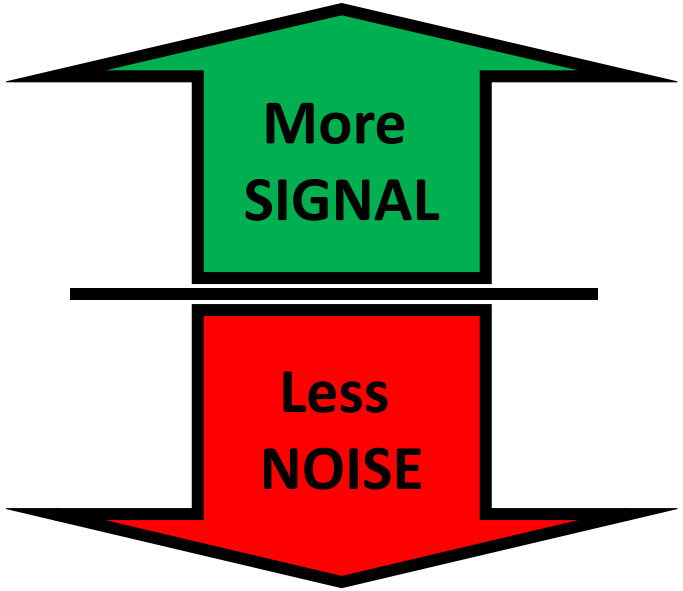
Better Reception Allows Better Discernment of Differences and More Spontaneous Learning

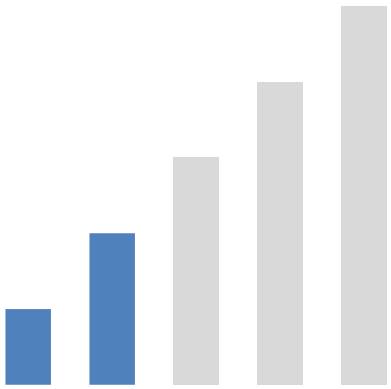
Worse SNR, Less Bandwidth

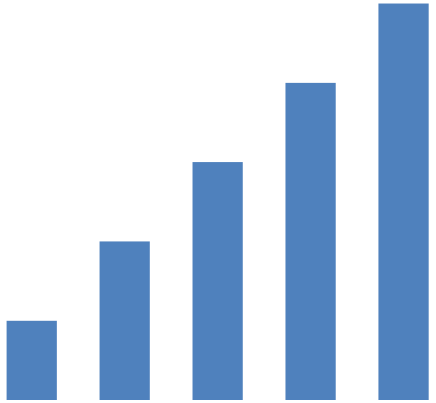
Better SNR, Better Bandwidth



SIGNAL to NOISE ratio (SNR) and BANDWIDTH







Better Reception Allows More Spontaneous Learning

The “Fluid Theory” of Connectivity Alterations in ASD

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

  Hendry 2005

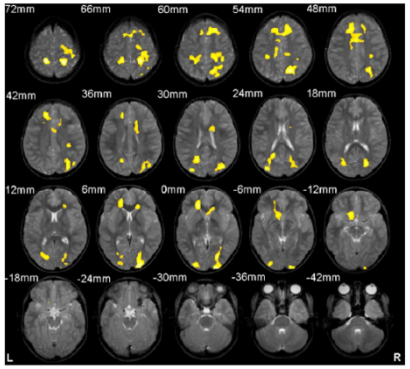
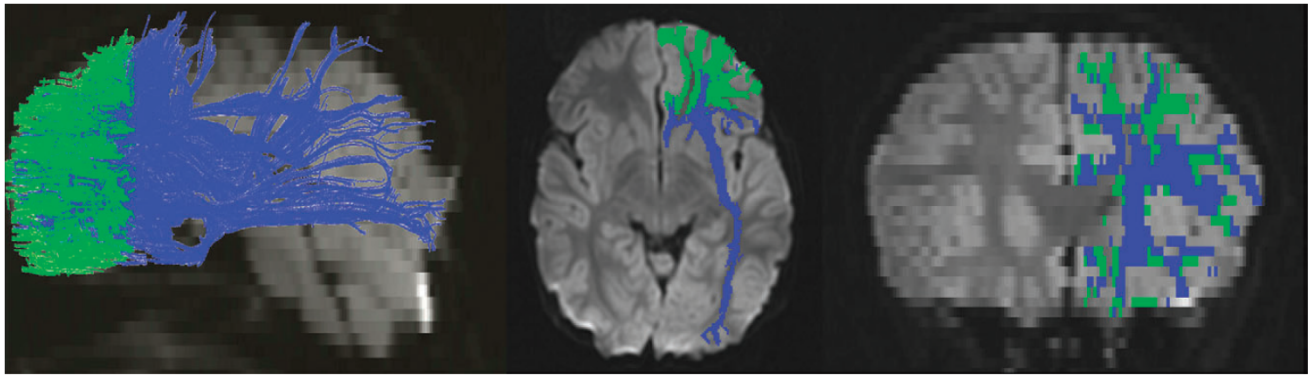


Fig. 2. Axial slices showing regions of increased T2 relaxation time in patients with autism compared to controls.

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

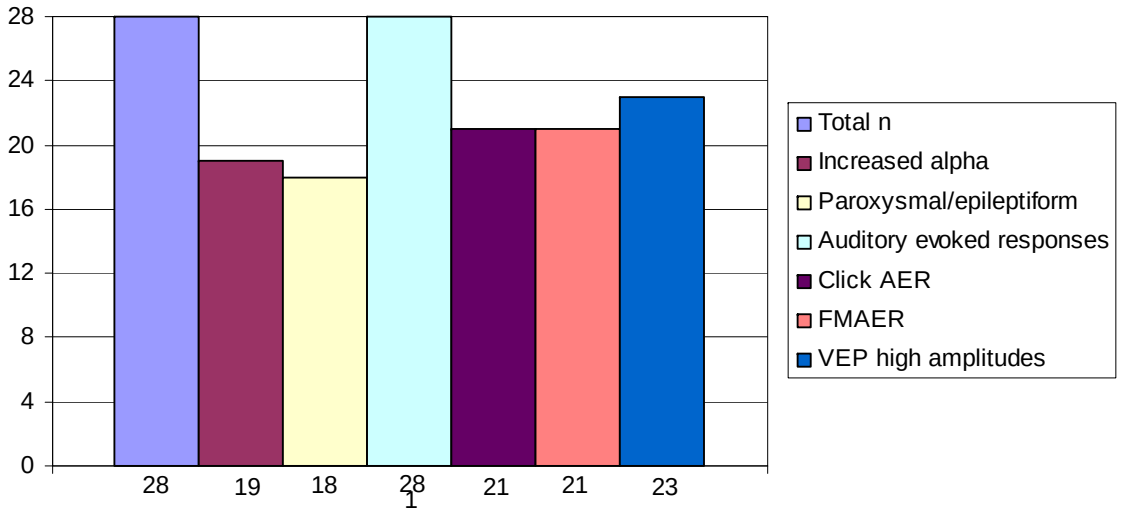
- **Lower perfusion in ASD brains (by many PET or SPECT studies) could impact brain function.**

How might this affect brain electrophysiology?

Lower 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

Autism Electrophysiological Abnormalities something in everyone, much in some



15 of these patients had no seizure history.

Visual Evoked Potential (VEP) amplitude was bigger: standard deviation was 2.42-8.92 SD (average 5.4 SD):

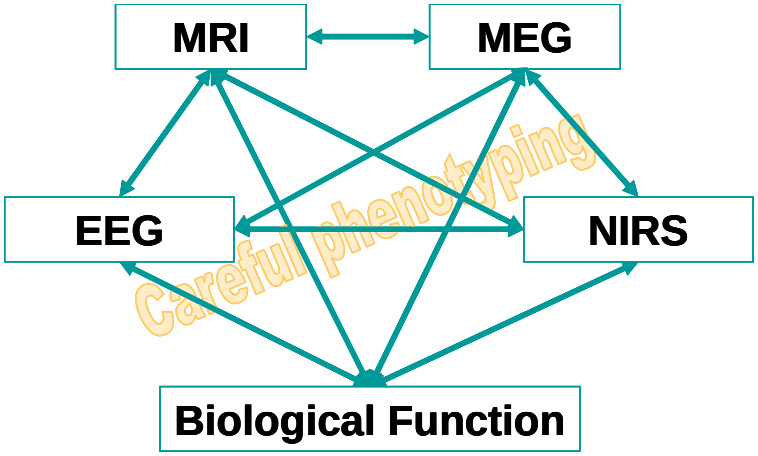
Same stimulus elicits larger response

Prediction: Less extreme sensory reactivity with effective treatment

Martien & Duffy

TRANSCEND Research Program

Treatment
Research
And
Neuro
SCience
Evaluation of
Neurodevelopmental
Disorders



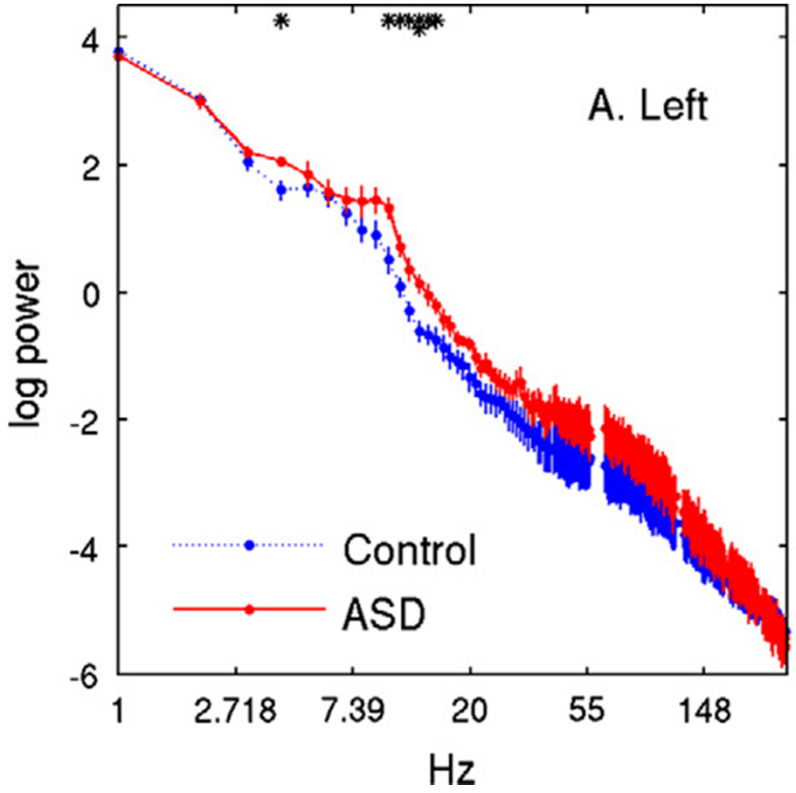
Integrative multimodal measurement platform
Optimization of measures that can detect change
In development, in regression, in improvement

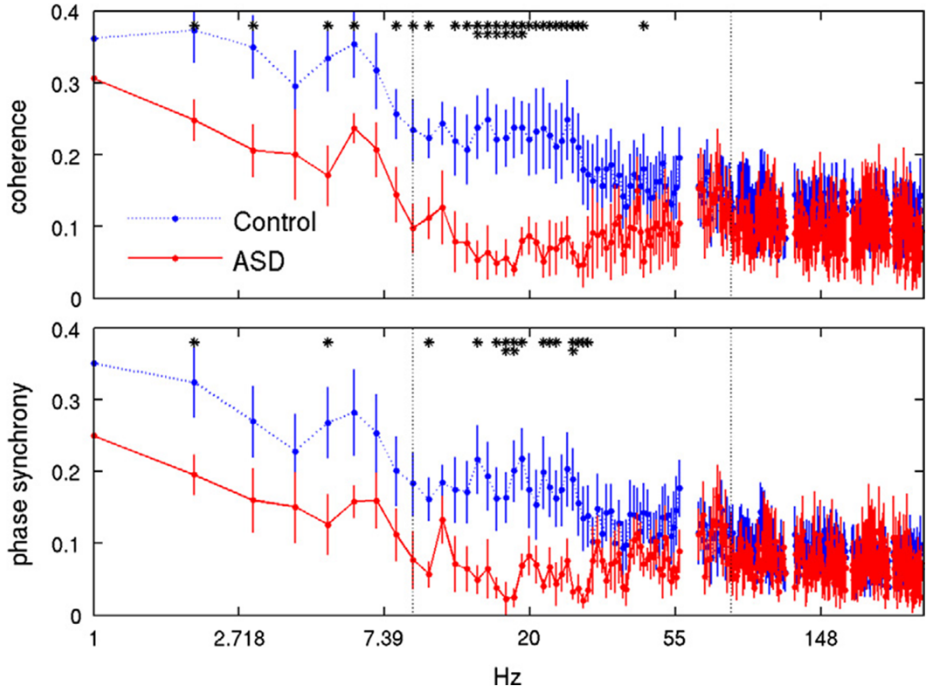
www.transcendresearch.org
transcend@partners.org

“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





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

<u>POOR SNR – Sound and Fury, signifying nothing</u>

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

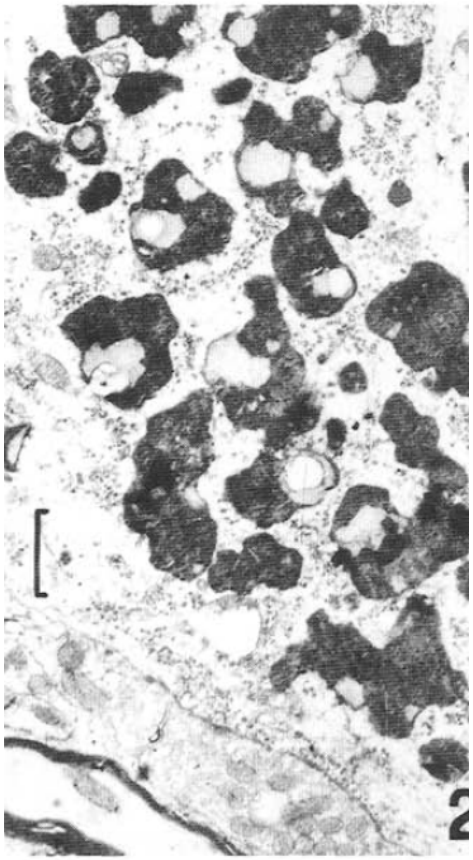
"Wild-type microglia arrest pathology in a mouse model of Rett syndrome"

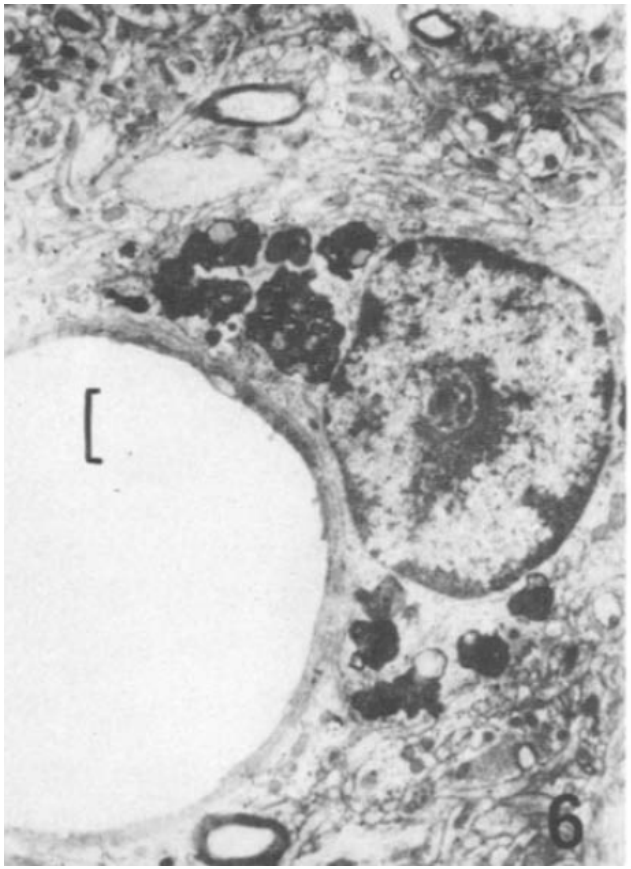
Derecki et al, Nature, 2012

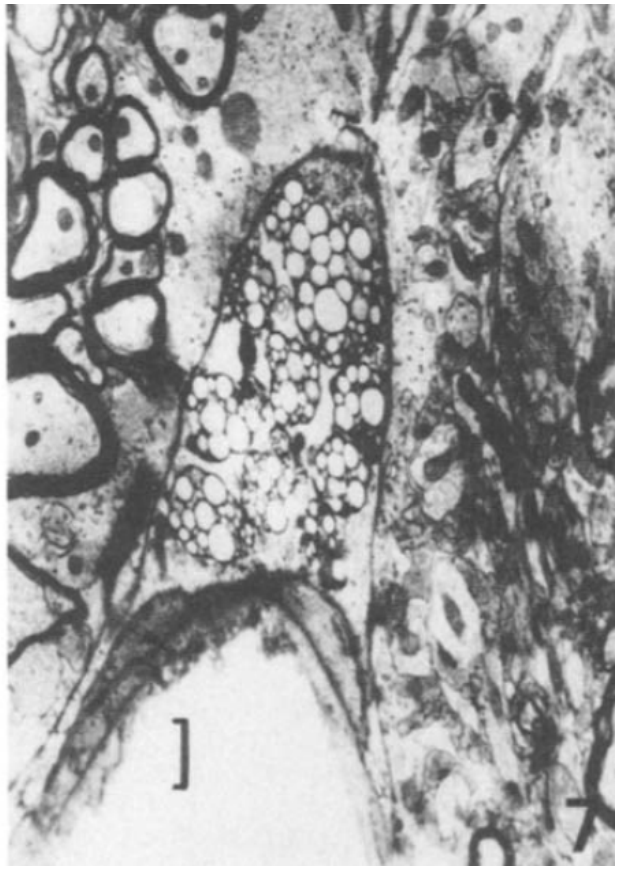
- **Rett features had been attributed to neuronal dysfunction**
- **Astroglial cells now known to contribute**
- **Now microglia shown to contribute as well: bone marrow transplant of wild type microglia**
  - **Increased lifespan, normalized breathing, increased body weight, improved locomotor activity**
  - ***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”

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







Why does garbage pile up?

TOO MUCH BAD STUFF

- **Toxicants**
- **Molecular debris from cellular stress and inflammation**

NOT ENOUGH GOOD STUFF

- **Not enough nutrients needed to run clean-up operations**
- **Blood flow that is less than it should be due to sickness or poor nutrition**

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**
  - **excellent food, green smoothies, bone broths**

Build Resiliency and Reduce "Total Load"

RESILIENCY

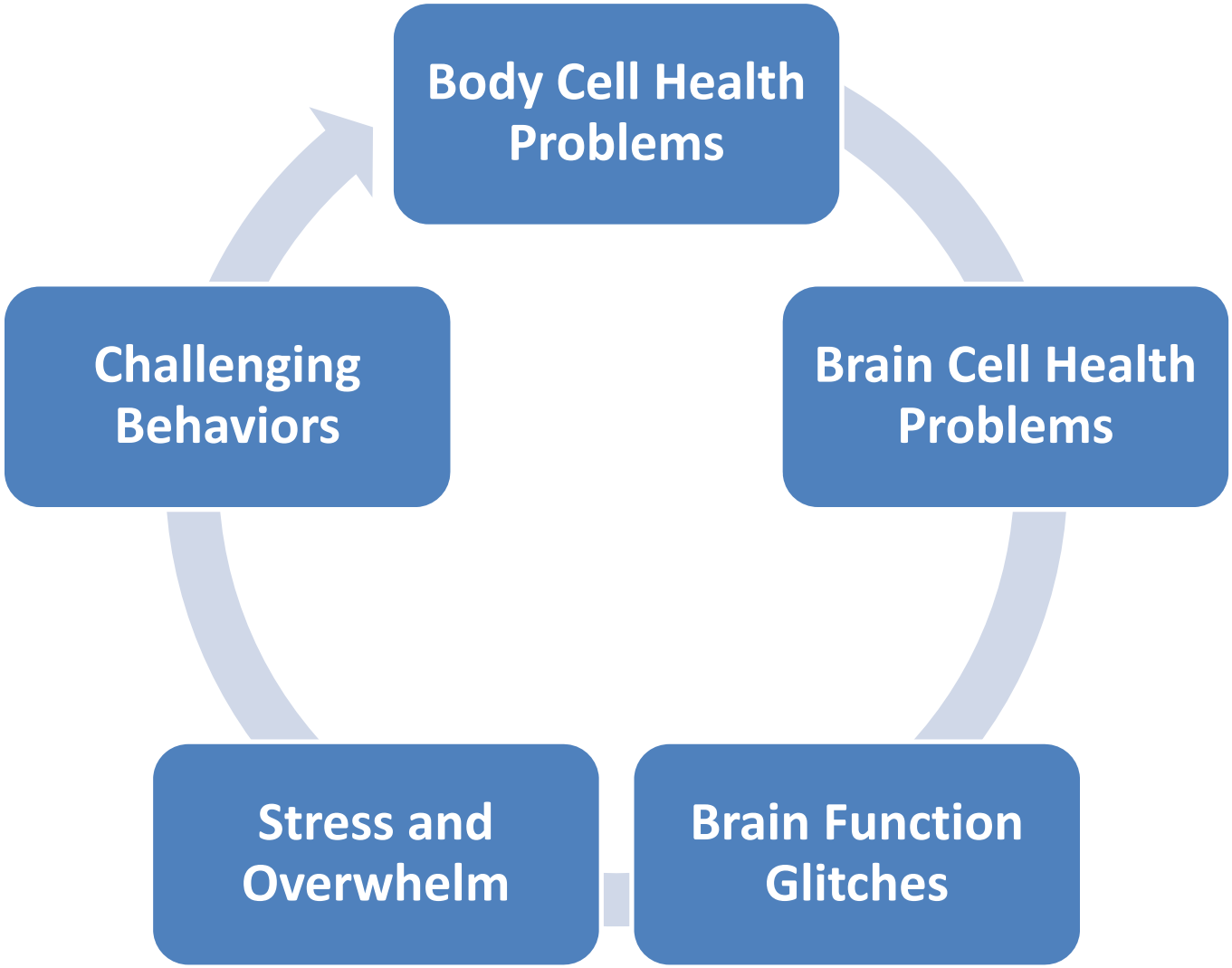
- The TOTAL SET of strengths, adaptations, skills, cell health, nutritional fortitude, exercise, community and more

"TOTAL LOAD"

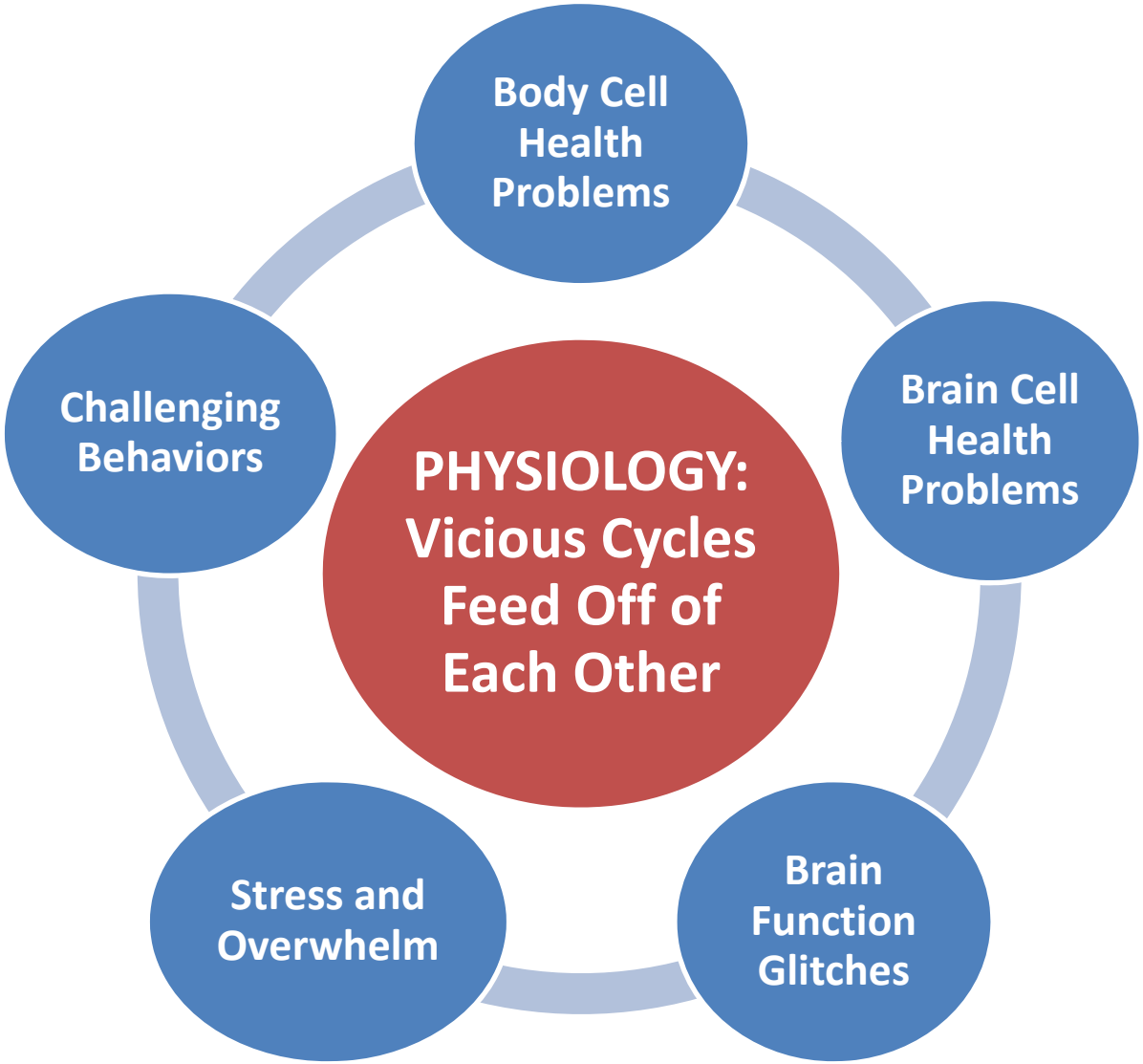
- The TOTAL BUILD-UP of noxious exposures, stressors and deficiencies

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

Physiology across levels: Interrelated



Problems in each area make trouble for the other areas



Toward the Pathophysiology of Autistic Regression

- ***Some combination of poor food, toxics, bugs and stress puts a load on body and brain. Maybe genetic weak points contribute too.***
- ***Cells are worn down and supplies to revive them are short.***
- ***The cells in brain and body get hypersensitive and overreactive because of oxidative stress and inflammation.***
- ***This just places more load on the cells.***
- ***At some point the "Total Load" gets too much and a tipping point is reached.***
- ***As body cells get more affected, they struggle and don't support the brain as well.***
- ***Brain glial cells poop out and don't keep up their housekeeping functions.***
- ***Brain energy production gets less efficient.***
- ***When brain cellular efficiency drops, brain networks get weaker and the child starts to disconnect from the world.***
- ***In this state the child's brain produces autistic behaviors.***
- **We used to think this was hopeless. Except it's not hopeless. It's a web. This web can be shifted at lots of different points, and these little shifts can add up to big changes.**

DoD Funded Study:
A MULTI-SYSTEM ASSESSMENT OF INFANTS AT HIGH RISK FOR AUTISM

Initiating PI: Martha Herbert
Partnering PI: Margaret Bauman

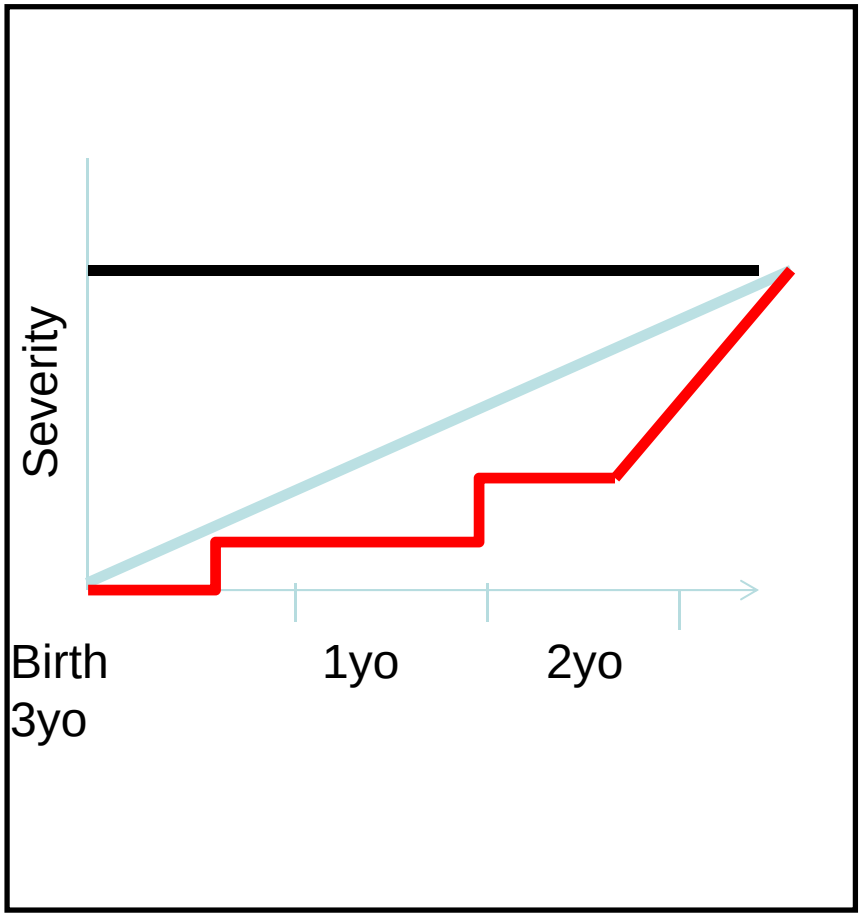
- **Longitudinal Multisystem assessment**
  - Metabolism, Immune, Toxics, Endocrine
  - Brain (EEG), Autonomics
  - Medical Comorbidities
  - Developmental/Behavioral Phenotyping

Infant EEG

Photos used with permission

Features of change we need to understand to help better

Regression



Improvement

- **Do systems improve all together?**
- **Or some before others (e.g. gut before immune?)**
- **Is it different for some than others?**
- **How can we predict this and use it to figure out the best approach for each individual?**

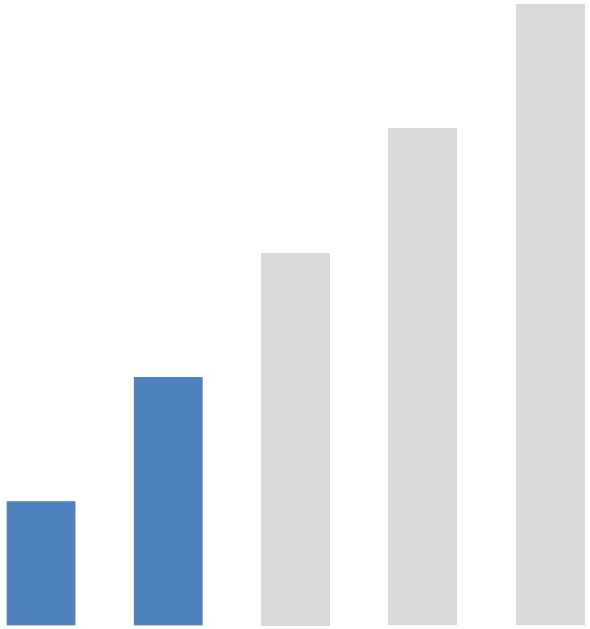
Hypothesis: Early correction or avoidance of abnormalities can be preventive

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

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

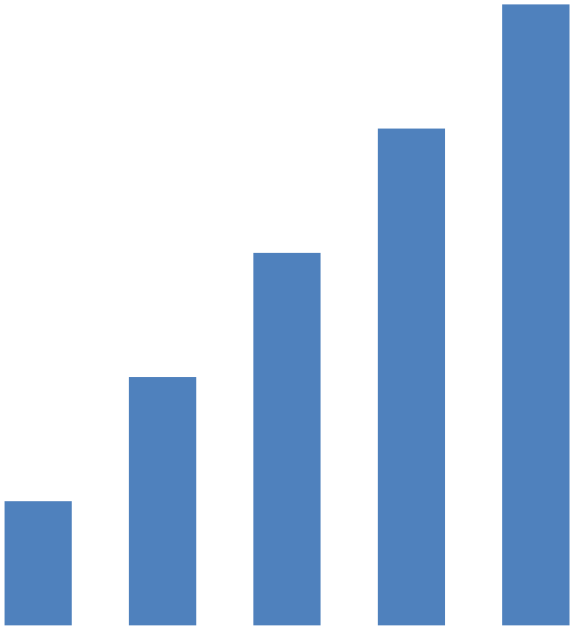
Poor Bandwidth:

Limited Reception



Lots of Bandwidth:

Good Reception



Better Reception Allows Better Discernment of Differences and More Spontaneous Learning

Recipe for Improvement: Two Basic Principles

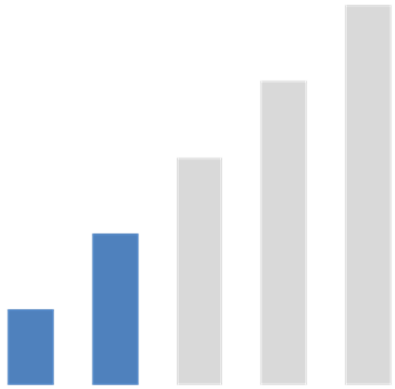
MAXIMIZE WHAT'S GOOD

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

REDUCE TOTAL LOAD

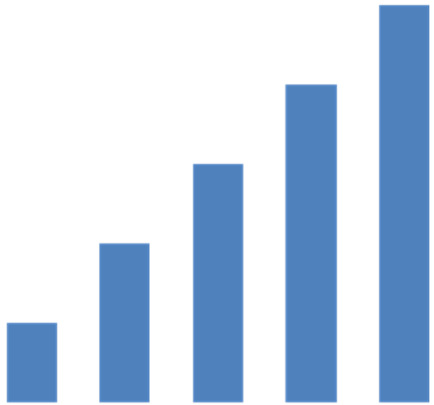
- Eliminate drag by
  - REDUCING TOXIC EXPOSURES AND ALLERGENS
  - GETTING ENOUGH SLEEP
  - PLENTY OF EXERCISE
  - BRAIN-BUILDING MOVEMENT
  - AVOIDING AND REDUCING INFECTION

RECIPE FOR IMPROVEMENT



POOR BANDWIDTH, LOTS OF CHAOS

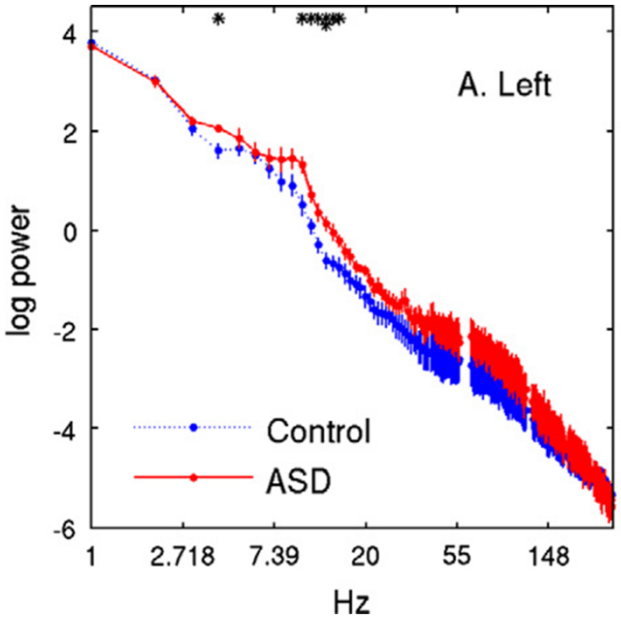
- Poor food: few nutrients, many allergens
- Lots of toxins and infectious issues
- Lots of stress, pressure, too much too fast

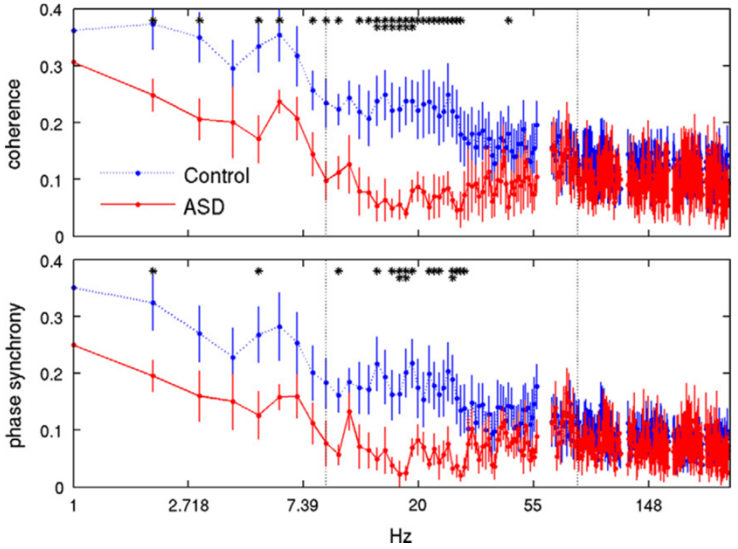


GOOD BANDWIDTH, RICH ORGANIZATION

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

TESTABLE, PLAUSIBLE HYPOTHESIS: Improving Diet and Environment Can Improve Brain Efficiency and Signal-To-Noise Ratio





PROPOSITION / ASSERTION:
We know enough <u>now</u> to promote health and hunt for and remove contributors to harm

Autism: WHY and HOW ?

www.autismWHYandHOW.org

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

Autism Revolution: Ten Tips

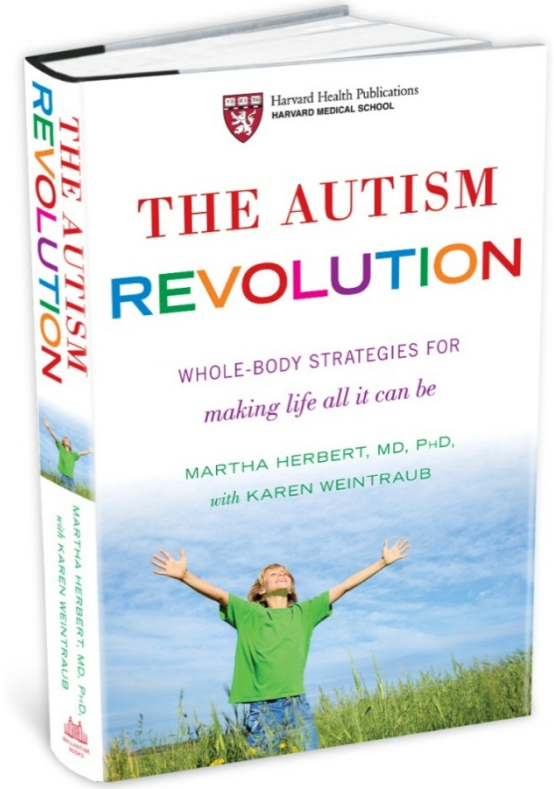
1. ***Go for the extraordinary.***
2. ***Know what you can't control — and what you can.***
3. ***Repair and support cells and cycles.***
4. ***Get gut and immune systems on your side.***
5. ***Build better brain health.***
6. ***Calm brain chaos***
7. ***Join your child's world.***
8. ***Love, rejoice,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

Systems biology of autism told through stories of people who get better:

The Autism Revolution:

Whole Body Strategies for Making Life All It Can Be

Ballantine – Harvard Health Publications, 2012



www.autismWHYandHOW.org

www.transcendresearch.org

TRANSCEND

www.AutismRevolution.org

www.marthaherbert.com