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

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www.AutismRevolution.org
www.autismWHYandHOW.org
“LEGO” Modular Model:
Gene → Brain → Behavior
Determined before birth, fixed for life
Nothing you can do
New model – an Autism Revolution:
From genetic brain impairment to environmental, medical obstruction of brain function

Not just genetic:
- **Hundreds of genes, most modest impact**
- **Numbers going up**
- **Evidence for environmental factors**

Not just brain:
- **Systemic features – Whole Body**
- **Environmentally vulnerable physiology**

Not just brain modules:
- **Whole brain involvement**
- **Brain tissue changes**

Not necessarily hardwired:
- **Plasticity and recovery**
Gene → Brain → Behavior model

Genetics

Brain

Drugs

Communication
Social interaction
Restricted behavior

Behavior Therapy
Whole Body Systems Model: Vicious circles in brain and body

Psycho-Social Environment

Physical environment

Genetics

Cellular Dysfunction: Energy, Signaling, Metabolism

Brain

Body

Communication
Social interaction
Restricted behavior

Sensory
Sleep
Seizures

Gastro
Immune
Hormones etc.

Frustration

More easily
OVERWHELMED

Pain,
Poor function
Sickness

Overload!
STRESS!
Autism’s Symptoms Emerge from Problems with Underlying Functions

VISIBLE Social & Behavioral SYMPTOMS

UNDERLYING SYSTEMIC FUNCTIONAL DISTURBANCES

Ziggarut model: http://www.texasautism.com/
ENVIRONMENTALLY VULNERABLE PHYSIOLOGY

Current Opinion in Neurology, April, 2010

Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders
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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 genetic variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation.

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

Edited by SHELDON KRIMSKY and JEREMY GRUBER

Can genes determine which fifty-year-old will succumb to Alzheimer’s, which citizen will turn out on voting day, and which child will be marked for a life of crime? Yes, according to the Internet, a few scientific studies, and some in the biotechnology industry who should know better. Sheldon Krimsy 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, Krimsy 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 Krimsy 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.

New Book with Critiques of Genetic Overexplanation
Harvard U Press 2013

Ch.10 on Autism:
From Static Genetic Brain Defect to Dynamic Gene-Environment-Modulated Pathophysiology
By Martha Herbert
Autism: WHY and HOW?

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

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

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

- Reduced Glutathione = GSH (active form)
- Oxidized Glutathione = GSSG (used-up form)

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


Shungu et al., 2012
Vulnerability with low GSH

Normal Homeostasis

OK GSH/GSSG

Fragile Homeostasis (limited reserve)

↓ GSH/GSSG

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

Mitochondrial vulnerability to environmental influences

- Mitochondria are highly vulnerable in:
  - Their biochemistry – toxicants and oxidative stress can interfere
  - Their membranes - membrane damage both causes and results from mitochondrial dysfunction

- Their exquisite structural and functional characteristics provide a number of primary targets for toxicant-induced bioenergetic failure

Mitochondrial dysfunction and molecular pathways of disease
Exp Mol Pathol. 2007 Jan 17

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

“diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration”
Metabolic Findings in Parents of Children with Autism

• 86 autism parents differ from 200 controls in the following:

  – Higher homocysteine (Hcy)
  – Higher SAH (S-adenosylhomocysteine)
  – Lower GSH (glutathione)
  – Increased GSSG (oxidized glutathione)

(All markers of oxidative stress and inflammation)

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

• Many environmental exposures can contribute to
  – Inflammation
  – Reduction in brain perfusion
  – Compromise of the blood-brain barrier
Things that can open the Blood-Brain Barrier

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

Adapted from [http://faculty.washington.edu/chudler/bbb.html](http://faculty.washington.edu/chudler/bbb.html)
Location of white matter enlargement points to postnatal brain changes

What do we need to learn about the brain and about autism to understand this?
Inflammation and Oxidative Stress in Autism: chronic, ongoing postnatal medical problems, not confined to brain

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

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

  • These changes were found at similar intensities in brain aged 5-44 years
  • Greater intensity of inflammation in a 3-year old’s brain
Pardo: Astrogliosis in Radiate White Matter

Herbert:
Radiate White Matter Enlargement

Astrogliosis

Microgliosis

GFAP

HLA-Dr
Air Pollution and Brain Inflammation
Block and Calderon-Gardicuenas, TNS, 2009

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

Inflammation as a final common pathway
Brain cells in inflammation: What is the FUNCTIONAL IMPACT?

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

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Miller et al., BIOL PSYCHIATRY 2009;65:732–741
Environmental Stressors are contributing to an **ONGOING, CHRONIC** DEGRADATION OF BRAIN AND BODY **FUNCTION**

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


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Too Much Excitation

Not Enough Inhibition

= More:

- irritability,
- hypersensitivity,
- overload

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Reduced informational complexity and organization

Reduced signal to noise ratio

Increased chaos and confusion

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

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

Efrati et al., PLoS One, 2013
**EEG of Sensory Responses**

- Sensory stimulation can be overwhelming

- Much more loss of connectivity when more stimulation

- More tolerance of stimulation and less loss of coordination in older kids

Prediction: Improved connectivity with effective treatment

Lines indicate differences between ASD and age-matched controls

Martien et al. 2008
Metaphor: Tissue pathophysiology REDUCES BRAIN BANDWIDTH

Poor Bandwidth: Limited Reception

Lots of Bandwidth: Good Reception

Better Reception Allows Better Discernment of Differences and More Spontaneous Learning
SIGNAL to NOISE ratio (SNR) and BANDWIDTH

Worse SNR, Less Bandwidth

Less SIGNAL

More NOISE

Better SNR, Better Bandwidth

More SIGNAL

Less NOISE

Better Reception Allows More Spontaneous Learning
A Different Model of Autism: Autism as an emergent property of a system with altered parameters and challenged, struggling physiology

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

Herbert, 2009, “Autism: The centrality of pathophysiology and the shift from static to dynamic encephalopathy”
In Chauhan et al, Autism: Oxidative stress, inflammation and immune abnormalities
“Wild-type microglia arrest pathology in a mouse model of Rett syndrome”

• Rett features had been attributed to neuronal dysfunction
• Astroglial cells now known to contribute
• Now microglia shown to contribute as well: bone marrow transplant of wild type microglia
  – Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
  – *Improvement even without direct change to neurons*
  – Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited
Electron microscopy of therapeutically activated glia turning into “brain garbage collectors and transporters”

Glia collecting debris, and dumping it into blood vessel

Hypothesis regarding the Pathophysiology of Autistic Regression

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

Spelled out in more detail in Chapter 5 of THE AUTISM REVOLUTION (Herbert 2012)
Why does garbage pile up?

**TOO MUCH BAD STUFF**

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

**NOT ENOUGH GOOD STUFF**

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

• Abundant supplies allow the brain to
  – work at its best
  – protect it from being dragged down by inflammation and other health problems.
  – TAKE OUT THE GARBAGE!

• Better brain health will help restore the brain’s full powers.

• We can support brain health through “nutrient flooding” – high nutrient density diet
Build Resiliency and Reduce Allostatic or “Total Load”

RESILIENCY

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

“TOTAL LOAD”

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

Building RESILIENCY protects brain from the debilitating impacts of tissue pathophysiology
Physiology across levels: Interrelated

Body Cell Health Problems

Challenging Behaviors

Brain Cell Health Problems

Stress and Overwhelm

Brain Function Glitches

NOXIOUS EXPOSURES
Problems in each area make trouble for the other areas

**PHYSIOLOGY: Vicious Cycles Feed Off of Each Other**

- **Body Cell Health Problems**
- **Brain Cell Health Problems**
- **Stress and Overwhelm**
- **Brain Function Glitches**
- **Challenging Behaviors**
Dialing back the problems and Moving Toward Whole Body-Brain Health

PHYSIOLOGY: Build Resiliency to Create Virtuous Cycles

- Improve Cell Health
- Brain Health Improves
- Better Learning, Better Behavior
- Brain Functions Better
- Less Stress, More Bandwidth

HEALTHY EXPOSURES
PROPOSITION / ASSERTION:
We know enough now to promote health and hunt for and remove contributors to harm
Commentary

Molecular targets of dietary agents for prevention and therapy of cancer

Bharat B. Aggarwal, Shishir Shishodia

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Dietary agents with anti-cancer properties

Fig. 1 – Dietary agents with anti-cancer properties.
**Molecular Targets of Dietary Agents**

Vastly Rich – On Frontiers of Science

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**Fig. 3 – Molecular targets of dietary agents.**
Recipe for Improvement: Two Basic Principles

**MAXIMIZE WHAT’S GOOD**

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

**REDUCE TOTAL LOAD**

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

POOR BANDWIDTH, LOTS OF CHAOS

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

GOOD BANDWIDTH, RICH ORGANIZATION

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

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