Autism & Environmental Vulnerability
Martha Herbert, MD, PhD

Autism & Environmental Vulnerability: Whole Brain, Whole Body, Whole Planet

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1

Overview: Autism as a Warning for All of Us

- Autism has been defined behaviorally
- But it is a whole-body condition
- Many of its core biological features are found in a wide range of other chronic childhood and adult illnesses
- Many of its features strongly suggest environmental insults
- Many of its features are treatable through easily available environmental changes, i.e. diet and nutrition
- Preventing and treating autism open doors to helping many millions of others as well

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Autism: A *Behaviorally Defined* Syndrome

DSM-IV Criteria for Autistic Disorder (299.0)

1. Impaired social interaction
2. Delayed and disordered 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+%)

3

Autism: A *Behaviorally Defined* Syndrome
Biology is not part of the definition
(and neither is prognosis)

DSM-IV Criteria for Autistic Disorder (299.0)

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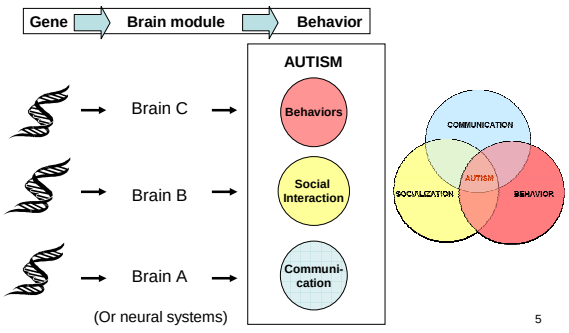
No biological markers exist to identify autism at this time

Autism is presumably *Heterogeneous biologically*

But **autism is *biological***

4

From Definition to Model of Autism: A Common Modular Framework



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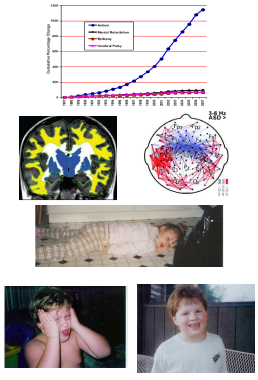
Anomalies

- Not just genetic:
  - *Numbers going up*
  - *This suggests environment*
- Not just brain modules:
  - *Whole brain involvement*
  - *Brain tissue changes*
- Not just brain:
  - *Systemic features – Whole Body*
- Not necessarily hardwired:
  - *Plasticity and recovery*
  - *Treating body with diet and nutrition can help brain*



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What could make numbers go up?

- Factors in the environment
- Differences in vulnerability

Or both:

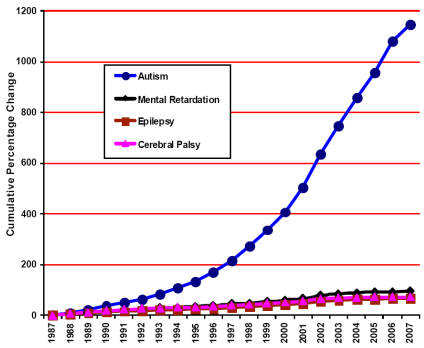
- Things in the environment that make vulnerability worse

7

Cumulative Percentage Change of Autism, Cerebral Palsy, Epilepsy, and Mental Retardation over Two Decades

AUTISM UP 1200%

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



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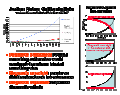
No proof that these arguments explain away ALL the increase



New paper from UC Davis (*Epidemiology*,Hertz-Picciotto and Delwiche, 2009)

- **600% increase in reported cases 1990 → 2001**
  - **200% can be explained by non-environmental factors:**
    - **24%: age at diagnosis**
    - **56%: inclusion of milder cases**
    - **120%: Change in DSM diagnostic criteria (DSM-III to DSM-IV)**
  - **The rest of the increase (400%) may have been from environmental contributors**
  - **Even some of the earlier cases could have been "environmental"**

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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?

- Swedish study of schizophrenic identical twins
  - *Probable same placenta: 60% concordance*
  - *Different Placentas: 11% concordance*
    - *Davis, Phelps, & Bracha, 1995*

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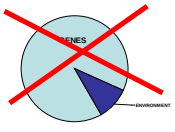
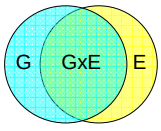
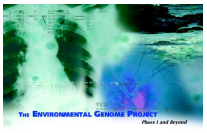
Gene-Environment Interactions: Not Either-Or but Both-And,





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



AUTISM AND ENVIRONMENTAL GENOMICS

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

Neurotoxicology, 2006

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Rise in Autism Prevalence v. Other Major Chronic Conditions in US

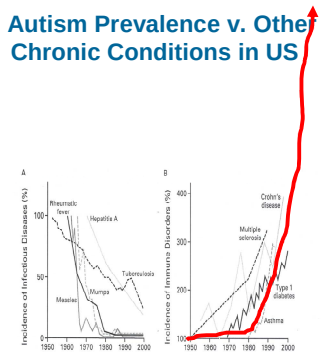

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Jousimies et al.[7] In Panel B, data on immune disorders are derived from Swanbrick et al.,[8] Dubois et al.,[9] Tuomilehto et al.,[10] and Pugliatti et al.[11]

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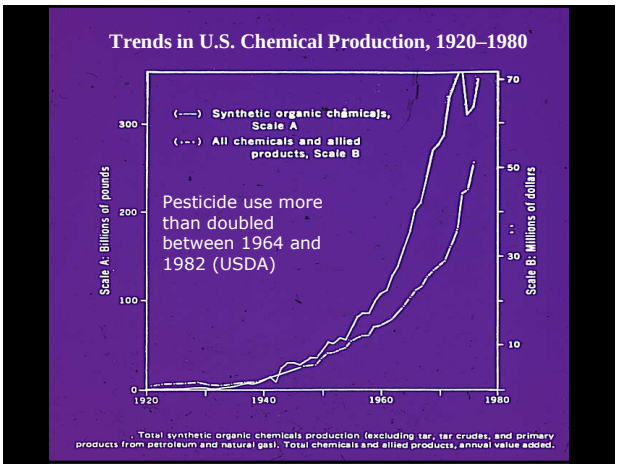

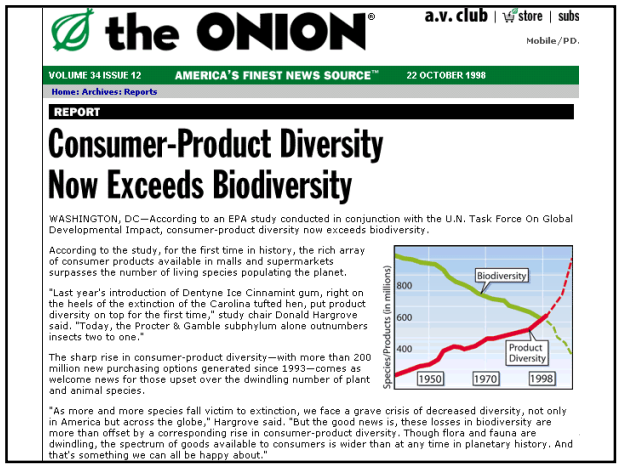

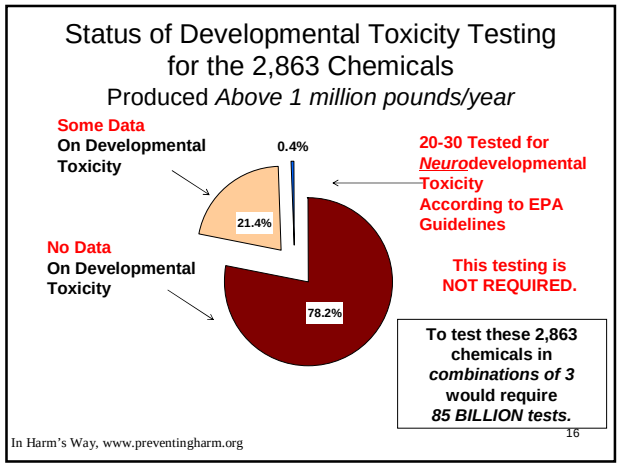

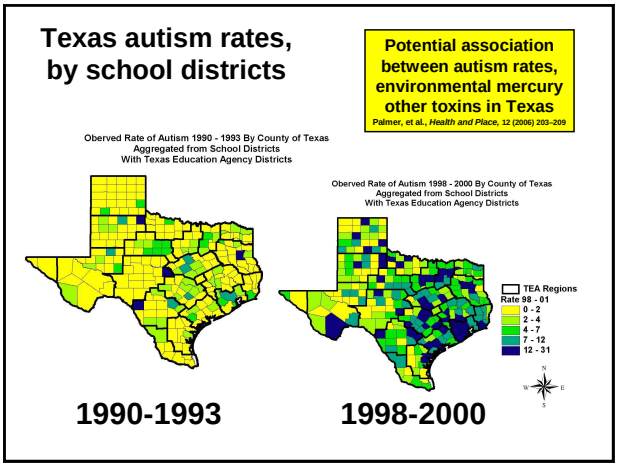

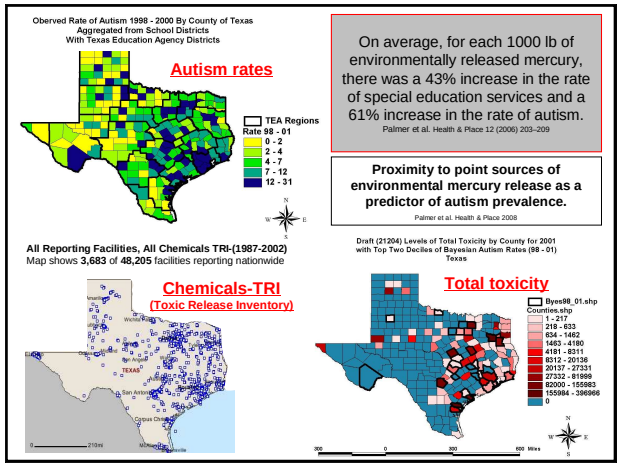

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EHP Vol 6, 2006: Online 21 June 2006

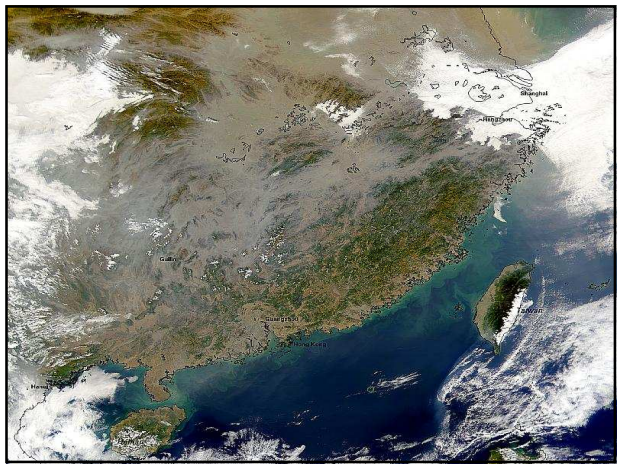
ehp Environmental Health PERSPECTIVES

ehponline.org

Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area (Windham et al., 2006)

Results: The adjusted odds ratios (AOR) were elevated by 50% in the top quartile of chlorinated solvents and heavy metals (95% Confidence Intervals (CIs) = 1.1-2.1), but not for aromatic solvents. Adjusting for these three groups simultaneously led to decreased risks for the solvents and increased risk for metals (AORs for metals: fourth quartile 1.7, 95% CI 1.0-3.0; third quartile 1.95, 95% CI 1.2-3.1). The individual compounds that contributed most to these associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride.

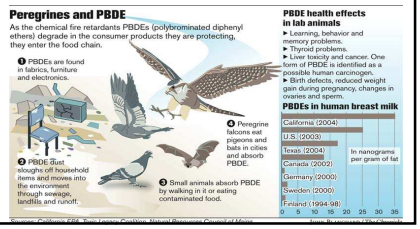
Conclusions: Our results suggest a potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence, requiring confirmation and more refined exposure assessment in future studies.

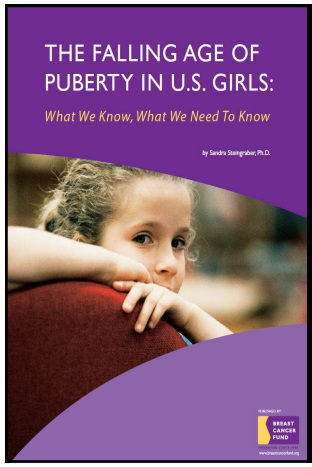


Flame retardant found in peregrine falcon eggs

Jane Kay, Thursday, May 8, 2008 San Francisco Chronicle

The eggs of peregrine falcons living in California's big cities **contain some of the highest levels ever found in wildlife** of a flame retardant used in consumer products, a new study has found. **Urban wildlife are the sentinel species that can tell us about chemicals of emerging concern** from city exposures. Information from these species can be useful to us in protecting the sensitive members of our population like infants, children and pregnant women.



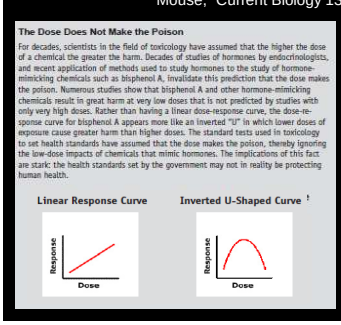


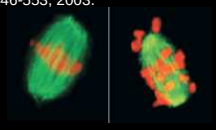
Several studies suggest that girls whose *mothers were exposed to high levels of pesticides*, particularly the banned pesticide DDT, show signs of accelerated puberty.

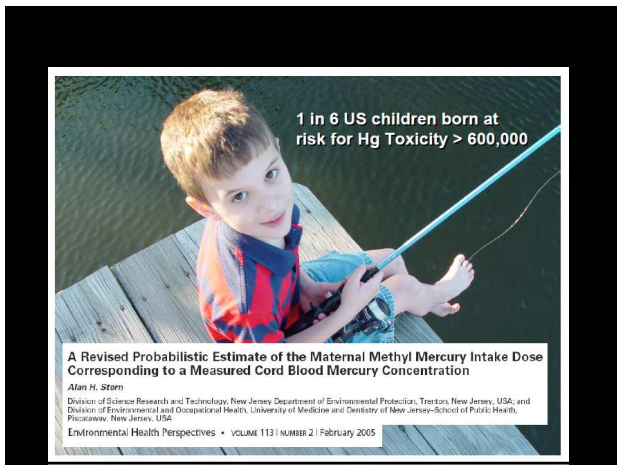
Recent research shows early puberty associated with increased risk for breast cancer

Bisphenol A Causes Chromosomes to Sort Incorrectly During the Development of Egg Cells

P.A. Hunt et al, "Bisphenol A Exposure Causes Meiotic Aneuploidy in the Female Mouse," Current Biology 13:546-553, 2003.







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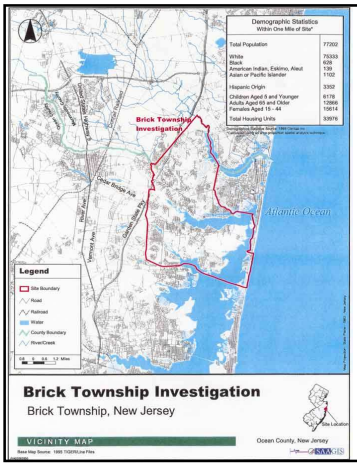

PUBLIC HEALTH ASSESSMENT: BRICK TOWNSHIP AUTISM INVESTIGATION

OCEAN COUNTY, NJ
EPA FACILITY ID: NJXCRA455000
November 29, 2000
Superfund Site Assessment Branch
Division of Health Assessment and Consultation
Agency for Toxic Substances and Disease Registry

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Appendix A: Contaminants of Concern in Brick Township Screening exposures for risk

Acetone	1,000ppb	Dioxin (2,3,7,8 TCDD)	.00001ppb
Anthracene	3,000ppb	Endosulfan	20ppb
Arsenic	3ppb	Ethyl benzene	700ppb
Benzene	1ppb	Flouranthene PAH)	400ppb
Benzo(b)flouranthene (PAH)	0.2ppb	Heptachlor	0.008ppb
Benzo(a)pyrene (PAH)	0.005ppb	Heptachlor epoxide	0.004ppb
Benz(a)anthracene (PAH	)2,800ppb	Hexachlorocyclohexane	0.02ppb alpha
Bis-phthalate	6,000,00 ppb	0.006ppb	beta0.02ppb
Bromoform	**4ppb**		gamma0.4ppb
Butyl benzyl phthalate	2,000ppb	Lead	0ppb
Cadmium	5ppb	Mercury	2ppb
Carbon tetrachloride	0.3ppb	MCLMethylenechloride	5ppb
Chlordane	0.6ppb	Naphthalene	20ppb
Chlorobenzenes	100ppb	Nickel	100ppb
Chloroform	**6ppb**	PCB's	0.02ppb
Chromium	100ppb	Pyrene(PAH)	300ppb
Copper	100ppb	Silver	50ppb
DDT	5ppb	**Tetrachloroethylene(PCE)0.7ppb**	
Di-n-butyl phthalate	1,000ppb	Toluene	200ppb
Dibenzo(a,h)anthracene	0.3ppb	1,1,1-Trichloroethane	200ppb
1,2-Dichlorobenzene	600ppb	1,1,2-Trichloroethane	0.6ppb
1,4-Dichlorobenzene	75ppb	Trichloroethylene	20ppb
Dichloroethanes	0ppb	Vinyl Chloride	0.2ppb
1,1-Dichloroethene	0.06ppb	Xylene	2,000ppb
Diethylstilbestrol		Zinc	3,000ppb

The CDC looked at these one at a time, and used adult toxicity levels to evaluate impacts on infants

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Pyrethrin Pet Shampoos and Autism

Anti-flea Pet Shampoos with Pyrethrin May Play a Role in Autism

mothers of children with autism spectrum disorders were twice as likely to report that they had shampooed their pets with pyrethrin-containing antiflea/antitick shampoos around the time of their pregnancy

Hertz-Picciotto, UC Davis MIND Institute; presented at 7th Annual International Meeting for Autism Research May 15-17, 2008.

Medscape Medical News

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Research | Children's Health

Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley

Risk of exposed mother having child develop autism increased with the poundage of organochlorine applied and decreased with distance from field sites.

(Odds ratio 6.1)

ns2

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the ONION
America's Finest News Source

McDonald's Stock Slides As More Consumers Turn To Food

January 15, 2003 | Issue 39•01

OAK BROOK, IL—The McDonald's Corporation announced Tuesday that it will close 175 restaurants and cut nearly 600 corporate jobs, responding to a plunge in stock prices blamed on a depressed economy and rising consumer interest in actual food.

McDonald's Stock Graph

"Though still America's number-one hamburger retailer," McDonald's CEO Jim Cantalupo said, "we have entered a brief period of restructuring due to the steady growth of other convenience eateries and, more significantly, growing competition from producers and distributors of demonstrably

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Some of the possible environmental contributors to autism being studied

- **Pesticides**
  - **Organophosphates**
  - **Others**
- **Heavy metals**
  - **Lead**
  - **Mercury**
  - **Cadmium**
- **Solvents**
  - **Triethylbenzene**
  - **Xylene**
  - **Trimethylbenzene**
  - **Others**
- **PCBs (polychlorinated biphenyls)**
- **Vaccines**
- **Flame retardants**
- **Antimicrobial ingredient in hand soaps**
- **Vitamin D deficiency**
- **Antibiotic overexposure and injury to intestinal "good bacteria"**
- **Essential fatty acid deficiency**
- **Greater genetic need combined with relative dietary deficiency of certain nutrients**
  - **Folic acid**
  - **Vitamin B12**
  - **Magnesium**
- **Valproic acid (depakote)**
- **Thalidomide**
- **Rubella and other infections during pregnancy**
- **In vitro fertilization**

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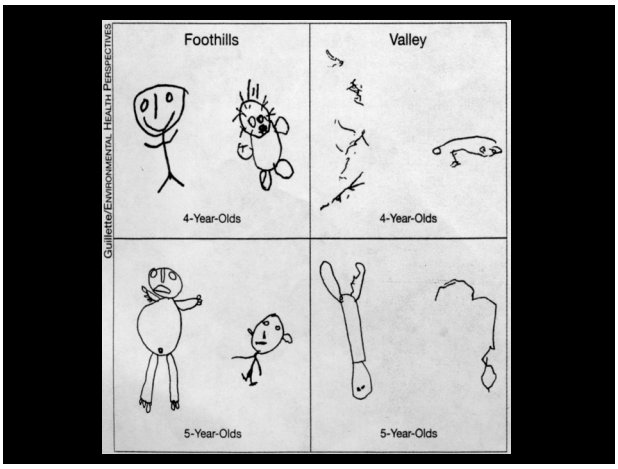
Slide 28

ns2 norm, 30/10/2007



The planet is not stable.

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

Brains are on average unusually large in autism, and they grow larger than average after birth, not before

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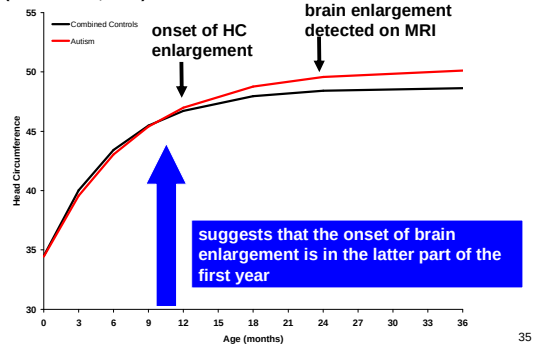
The Timing of Brain Enlargement: Clues from Head Circumference
(Hazlett et al., 2005)



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Brain enlargement is due more to white matter getting bigger than to gray matter getting bigger

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Some characteristics of large brains in autism

Disproportionate increase of white matter

White matter increase localizes to outer ("radiate") white matter

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Herbert M. 2003, 2004, 2005

To understand the impact of brain enlargement, we need to learn what cellular changes are causing the size increase

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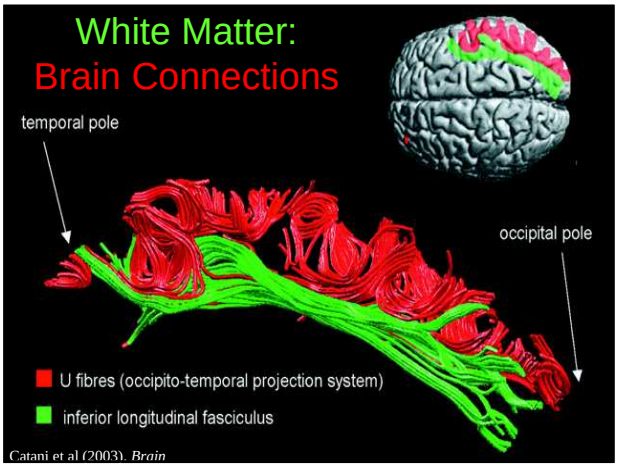
White Matter: Brain Connections



Catani et al (2003). *Brain*

But it does *not* look like the brain enlargement is due to an increase in axon density.

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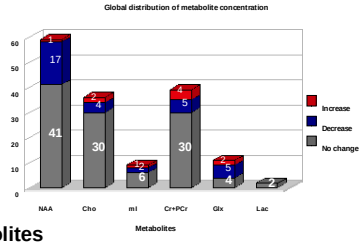
Brain magnetic resonance spectroscopy summary of findings in literature to date: Mostly lower density of metabolites



- **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

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Brain imaging suggests that areas that are larger might have more water, not more axons

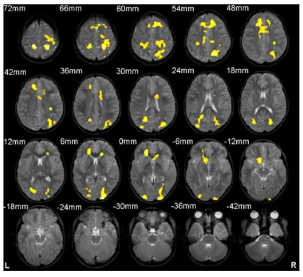

Fig. 2. Axial slices showing regions of increased T2 relaxation time in patients with autism compared to controls.

May be a reflection of altered tissue water properties

White matter abnormalities in autism detected through transverse relaxation time imaging. Hendry et al., *Neuroimage*, 2005.

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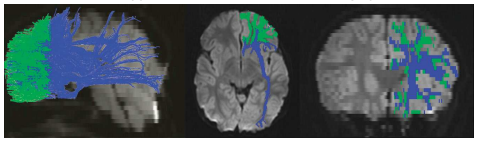
Reduced FA and Increased Diffusivity in Short-Range Fibers: Less fiber integrity, more disorganization

FA = Fractional Anisotropy: measure of white matter integrity. Lower is "worse".



- Short-range and long-range association fibers of frontal lobe – separated without arbitrary demarcation
- Fractional Anisotropy (FA):
  - Short-range fibers: Autism less (less white matter integrity) bilat
  - Long-range fibers: no difference
- Apparent Diffusion Coefficient (ADC):
  - Long range greater (more white matter disorganization) bilat, $p < 0.001$
  - Short range fibers: autism more disorganized bilaterally

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Sundaram et al., 2008

More than Brain Circuits: Brain tissue

- Could brain enlargement come from inflammation?

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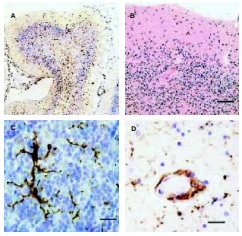
Brain tissue shows signs of immune activation or "neuroinflammation."

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
Vargas et al, 2005, Annals of Neurology



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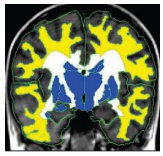
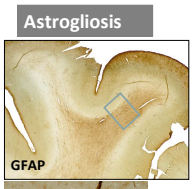
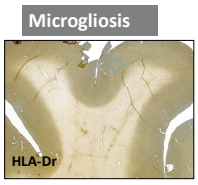
The white matter areas that are larger appear to have more inflammation.

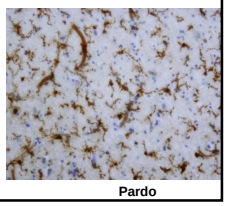


Herbert:

Large Brains from Radiate White Matter Enlargement







Pardo

Environment and Brain tissue vulnerability

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

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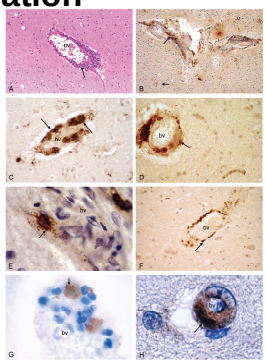
Air pollution and brain inflammation

Air pollution leads to brain inflammation much like what we see in autism.

Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adults



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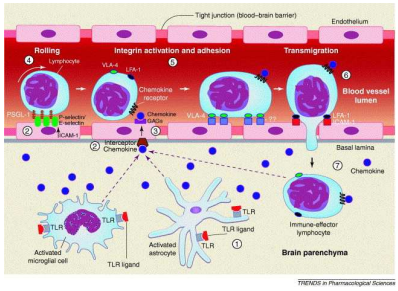
Factors documented in autism increasing blood viscosity and reducing perfusion

- decreased red-cell membrane fluidity
- increased urinary marker for thromboxane which activates and aggregates platelets,
- increased signs of oxidative stress in red blood cells in ASD, including increased NO
- increased xanthine oxidase
- depressed glutathione peroxidase (GSHPX)
- depressed SOD
- depressed catalase
- increased lipid peroxides

W. McGinnis

The "Blood-Brain Barrier" is not an absolute barrier



Things that can open the BBB

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

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

Astrocyte activation can impair perfusion by constricting small vessels

- **Astroglia are part of the blood-brain barrier and the swelling they undergo with activation can reduce capillary lumen by as much as 50%, reducing perfusion**

Lower perfusion in ASD brains has been abundantly documented but remains marginal to most brain research. The surface has barely been scratched in researching the physical reasons for this.

- **17 of 19 PET and SPECT autism studies showed low perfusion**
- **Those that showed areas of high perfusion still showed lower perfusion more than higher**
- **Almost all studies analyzed this *psychologically,* not *medically:***
  - **discussed only implications of location of low perfusion in brain**
  - **Did not ask what physically what might be causing this**
  - **Seemed to assume that this low perfusion was permanent**

What's wrong with this statement?

"Nevertheless, cerebral hypoperfusion remains out of the mainstream of scientific thought on the source of autism, which is now focused on variant genes and environmental factors that combine to impair development in early childhood."

— From news report

More than Brain: Body Problems

Autism is a Whole-Body, Whole-System Condition

- **Seizures (~30%+)**
- **Cognitive deficits**
- **Sensorimotor abnormalities**
- **Disordered sleep**
- **Immune impairments**
- **GI distress**
- **Food allergies**
- **Systemic metabolic disturbances**

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**

AAP Autism GI Consensus Reports January 2010

SUPPLEMENT ARTICLE

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

abstract

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

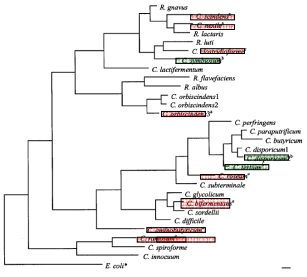
SUPPLEMENT ARTICLE

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

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-

GI problems including Abnormal gut bacteria



Finegold S, 2002

Microbiome problems may underlie many health issues.
Beyond the Human Genome to the Extended Genome:
Host and gut-microbial co-metabolome interaction
J Nicholson, Nature Review Microbiology, 2005

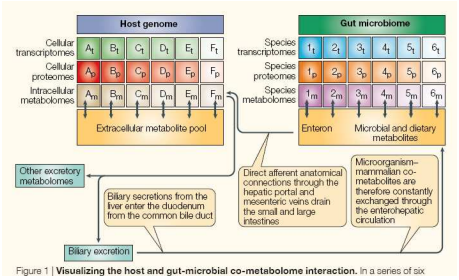


Figure 1 | **Visualizing the host and gut-microbial co-metabolome interaction.** In a series of six

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Diet and Nutrition for Gut Health

- Fermented foods were part of traditional diets
  - Include them again – can buy or make at home
- Probiotics
  - Finally an active area of research
- Avoid foods that make gut problems worse
  - Especially avoid simple sugars

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Elimination diets and gut health

- Many benefit from elimination diets
  - Gluten free, casein free
  - Specific carbohydrate diet: eliminates all grains and more
- Some of these diets are almost opposite of self-imposed restriction to gluten and casein
- Possible mechanisms
  - Reduction of immune challenges
  - Improvement of gut flora
  - Elimination of psychoactive byproducts of inadequate gluten and casein digestion

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Gluten and casein problems

- Evidence for gluten problems in schizophrenia
- Early evidence in ADHD
- Recent strong study in autism:
  - Whitely et al., Nutr Neurosci. 2010 Apr;13(2):87-100.
- Strong anecdotal support for casein elimination in some cases of autism, asthma, ADHD
- More research is needed

63

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

Ruhl, 2005

Neurogastroenterol Motil (2004) 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**.

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Immune signs and symptoms and measures in autism

- **Recurrent infections**
- **Autoantibodies**
- **Family history of autoimmune disease**
- **Autoimmune features**
- **Food allergies and sensitivities**
- **Atypical cytokine and chemokine levels**
- **Abnormal immunoglobulin levels**

Eczema

Onychomycosis

Allergic Facies

Energy metabolism: Mitochondria

- Mitochondria handle energy metabolism

- Children with mitochondrial disorders frequently have autistic behaviors
  - Sometimes only intermittently, when they are “low-energy”

- Neurons with weaker energy metabolism will act differently

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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*
Protection and defense	• *Autoimmune problems*
Elimination of waste	• *Impaired intestinal function* • *Impaired detoxification*

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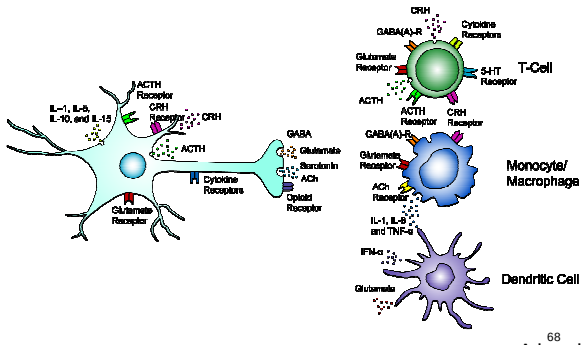
www.functionalmedicine.org

Systems are Deeply Interconnected: Immune and Nervous system cross-talk



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Ashwood

TEXTBOOK OF FUNCTIONAL MEDICINE

"Principles of a science-based, systems-biology approach to chronic, environmentally modulated illness"

www.functionalmedicine.org

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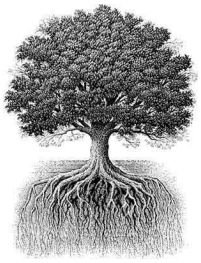
Going for the ROOTS

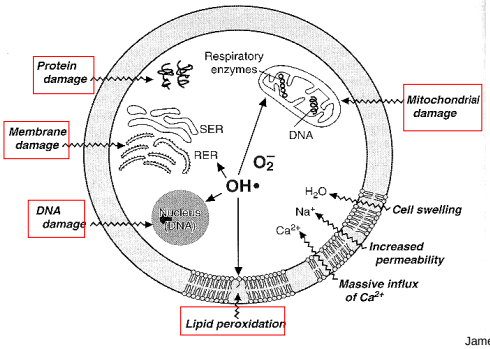


- **Go to and treat the roots of the problems**
- **Identify and treat problems early before they become catastrophic**

Oakbranchestoroots.jpg

70

Injury at the cellular level throughout the body



71

James

Influencing Vulnerability

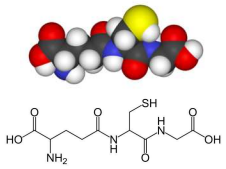
- Things can increase vulnerability

Or

- Decrease vulnerability

72

GLUTATHIONE is low in many with ASD



- Important for protection of cells from damage
- Vital for detoxification
- The body's most potent anti-oxidant

73

Pentagon designs nutrient-glutathione patch for "high-stress conflict" (e.g. chemical & biological warfare)


UNITED STATES DEPARTMENT OF DEFENSE

SEARCH

Dec. 12, 2005 | War on Terror | Transformation | News Products | Press Resources | Images | Websites | Contact Us

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Updated: 14 Jan 2003

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Patch May Deliver Nutrients to Future Warfighters

By Jim Garamone
American Forces Press Service

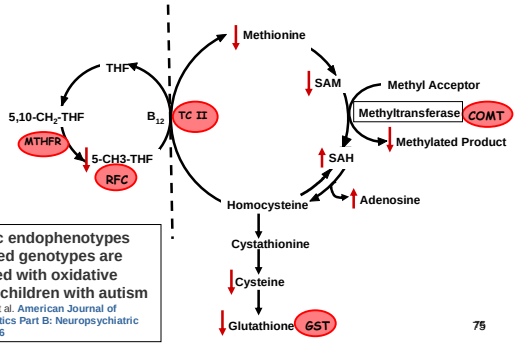
WASHINGTON, Feb. 28, 2000 -- U.S. combat troops may get part of their daily diet through their arms if a new concept works out.

Army Soldier Center researchers in Natick, Mass., are working on a transdermal nutrient delivery system -- a skin patch similar in concept to nicotine and motion sickness patches. The new system could be a part of every combat service member's kit by 2025.

Gerald Darsch, joint project director for the DoD Combat Feeding Program at Natick, said the current developmental version is about the size of a conventional adhesive bandage and three to four times thicker. The final version will be encased in some polymer to be very flexible, he speculated.

http://www.defenselink.mil/news/Feb2000/n02282000_20002282.html

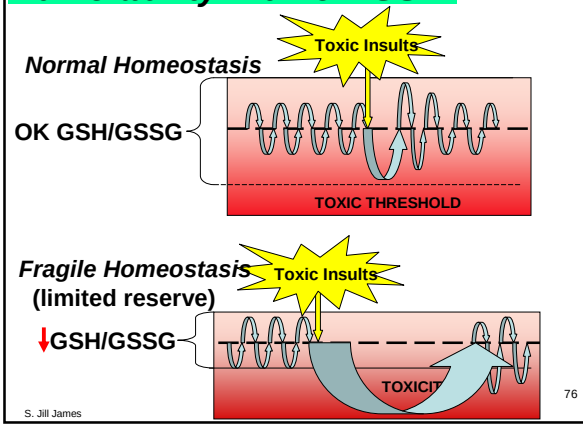
Abnormal metabolic-chemical processes create many vulnerabilities



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

75

Vulnerability with low GSH



S. Jill James

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Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders

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

- The cause of autism remains largely unknown because it is likely **multifactorial, arising from the interaction of biologic, genetic, and environmental factors**.
- Current research may provide insight into the **pathophysiologic underpinnings of autism, at least in some patients**.
- **Some known neurometabolic disorders** have an autistic phenotype.
- **Possible involvement of mitochondrial disorders and dysfunction.**
- **Increased vulnerability to oxidative stress may be the route by which various environmental toxins produce metabolic alterations that impair normal cellular function**.
- **Emergence of a broader understanding of underlying metabolic disturbance even in the absence of known disease.**

77

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

Impact on Brain function

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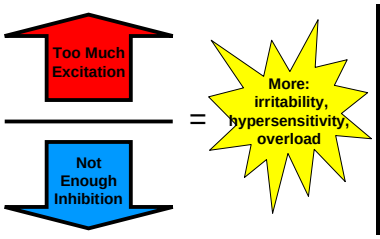
Rubenstein & Merzenich,
Genes, Brain and Behavior (2003) 2: 255-267

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



Comments:

Increased excitation/inhibition ratio may explain many features of autism, such as:

a) Sensory sensitivities

b) Sleep disturbances

c) Seizures, epilepsy

AND – inflammation and oxidative stress increase this E/I ratio!

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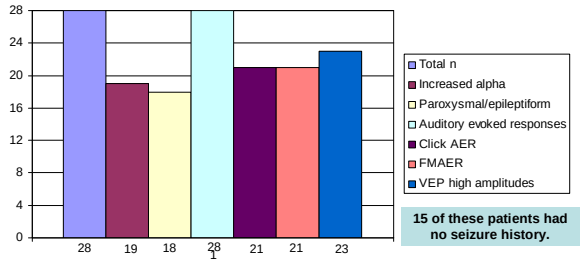
Autism Electrophysiological Abnormalities something in everyone, much in some



15 of these patients had no seizure history.

Increased VEP amplitude standard deviation was 2.42-8.92 SD (average 5.4 SD)

Martien & Duffy

80

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

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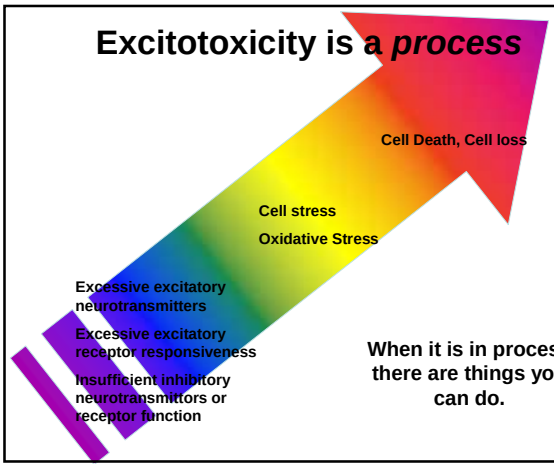
Excitotoxicity is a *process*



When it is in process there are things you can do.

82

Autism Nervous System Electrical Abnormalities: Sensitive Brains

Stress

Sensory

Sleep

Seizures

83

What's wrong with this statement?

- "You can treat the gut if you want, but that won't affect the autism because the autism is caused by structural changes in the brain."

– Researcher with finding about a gene that affects multiple systems beyond brain

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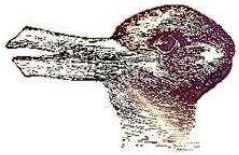
VICIOUS CIRCLES:
Each thing makes the next thing worse

85

Rabbit or duck?



Is autism a BRAIN DISORDER

or a

DISORDER THAT AFFECTS THE BRAIN?

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**Autism:
A Brain Disorder?
*Or a Disorder that Affects the Brain?***
Herbert, 2005

A Different Model of Autism

- **Autism could be a 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**
- ***Many cellular problems can be treated***

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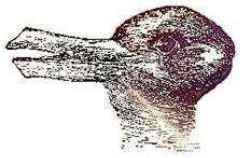
Rabbit or duck?



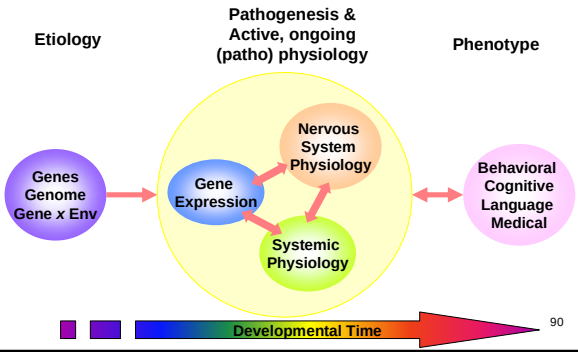
Is autism a BRAIN DISORDER

or a

DISORDER THAT AFFECTS THE BRAIN?

89

Functional, Dynamic Dimensions of Autism:
Active Pathophysiology – A 'Middle-Out' Approach



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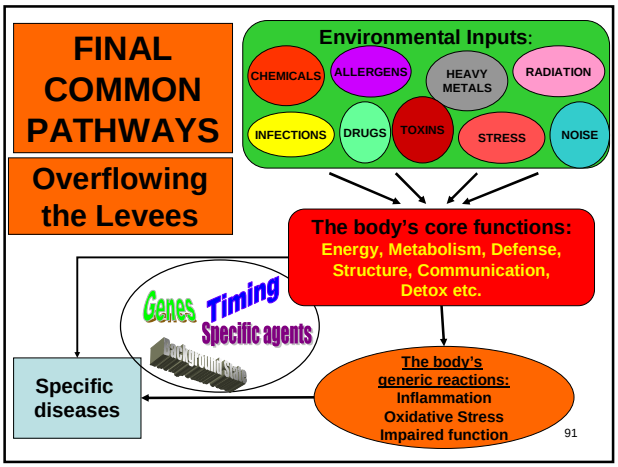
Autism & Environmental Vulnerability

Martha Herbert, MD, PhD



Current Opinion in Neurology, April, 2010

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

Martha R. Herbert

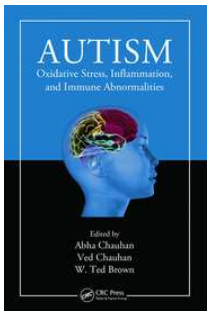
TRANSCEND Research Program, Pediatric Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, USA

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

Current Opinion in Neurology 2010, 23:000–000

Purpose of review
To present a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs).
Recent findings
Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150 only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation.
Summary
Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

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
In Press

Autism:
Oxidative stress, inflammation
and immune abnormalities

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

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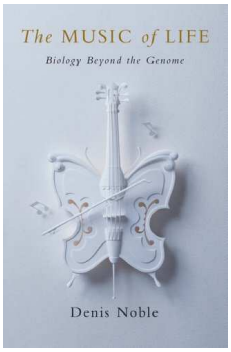
The Music of Life: Biology Beyond the Genome



Beautiful readable book

Discusses physiology and the "middle→out" approach

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

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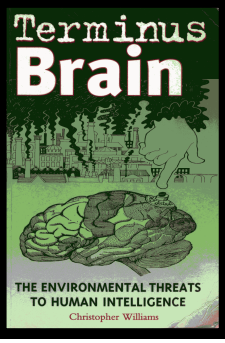
Terminus Brain:
Environmental Threats to Human Intelligence
and the Physical Capacity for Integrative Brain Functions



More than Autism

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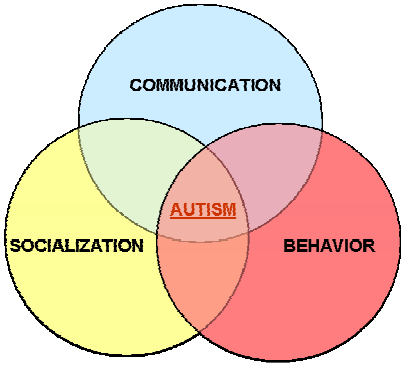
Autism & Environmental Vulnerability

Martha Herbert, MD, PhD

From a unique behavioral syndrome



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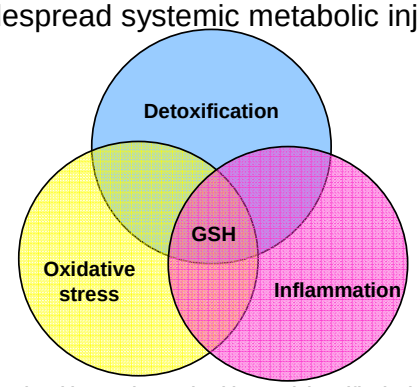
To a developmental outcome of a widespread systemic metabolic injury



GSH = Glutathione, prime anti-oxidant and detoxifier in the body

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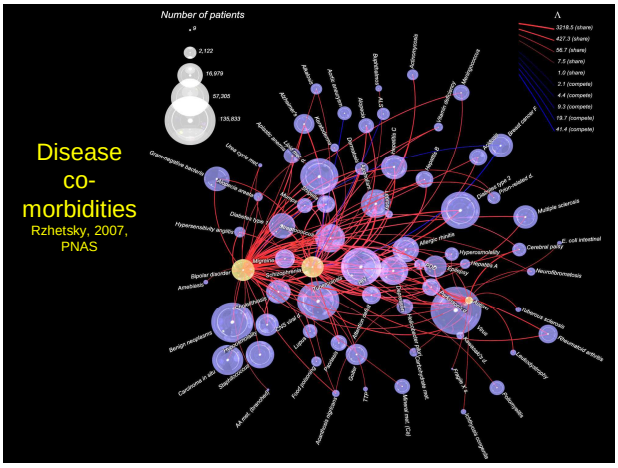
S Baker

Disease co-morbidities

Rzhetsky, 2007, PNAS



Autism comorbidities

Rzhetsky, 2007, PNAS

Pervasive Developmental Disorders
- PDD, Fragile X

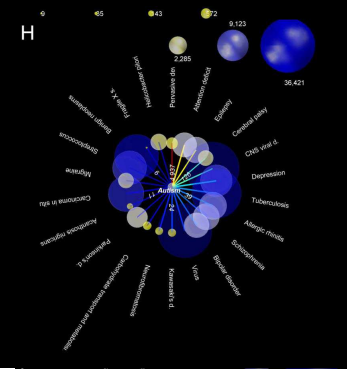
Neurological disorders
- Attention deficit, epilepsy, cerebral palsy, schizophrenia, bipolar disorder, neurofibromatosis, Parkinson's Disease, Migraine

Bacterial, viral, protozoan
- Viral infections of CNS, tuberculosis, viral infections of other systems, staphylococcal and *Helicobacter pylori* infections

Allergies, Autoimmune disorders
- Allergic rhinitis, eczema, psoriasis

Benign and Malignant Neoplasms

Other
- Kawasaki's disease, acanthosis nigricans, aberrations of carbohydrate metabolism



Genes that had biggest impact and/or occurred most commonly across 9 comorbid conditions largely had *immune function*

ADHD
cerebral palsy
depression
schizophrenia
tuberculosis
allergic rhinitis
bipolar disorder
Parkinson's

NR4A2	DRD2
TNF	CD14
IL6	SLC11A1
IL4	GAD1
SLC6A4	HLA-DRB1
DRD4	NOS2A
SLC6A3	IL1B
ACE	IL18
IFNA1	CYP2D6
COMT	MAOA
IL10	LTA
MBL2	TPH1
ADRB2	PTGS2
BDNF	TLR4
APOE	IFNG
HTR2A	HLA-DQB1
IL13	VDR
NOS3	

- **Substantial overlap in genes implicated in multiple co-morbid conditions**
- **Many of the genes highly ranked in multiple conditions have immune relevance**

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Method: GeneSelectAssist service in CDC's HuGE website

Genetic overlaps between multiple conditions

- Genes affecting synapses
- Genes affecting immune functions
- Genes affecting environmental responses
- CNVs (copy number variants)
  - Often predispose to more than one condition
    - e.g. Guilmatre, Archives Gen Psychiatry 2008
- Genes affecting core cellular functions

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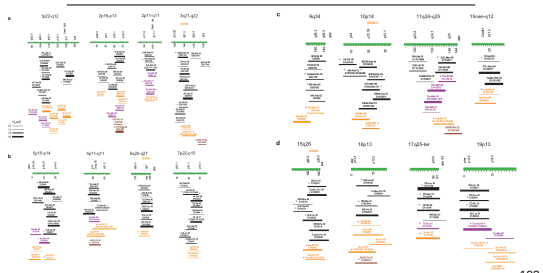
Disorders without Borders

CTLA4	Rheumatoid arthritis, Grave's Disease, MS, Hashmoto's thyroditis, Diabetes mellitus type 1
PPARc	Diabetes mellitus 2, higher body mass index, increased serum leptin, plasma total cholesterol, LDL, HDL, obesity, many others
CD14	Atopy, IgE, expired myocardial infarction, alcoholic liver disease, atopy, Crohn's disease
TNFa	Asthma, primary biliary cirrhosis, sepsis, psoriasis, leprosy, GVHD, silicosis, SLE, Celiac, chronic bronchitis, Grave's disease

Becker, 2004 *Common Variants, Multiple Diseases*



Autism, asthma, inflammation, and the hygiene hypothesis
Kevin G. Becker, 2007

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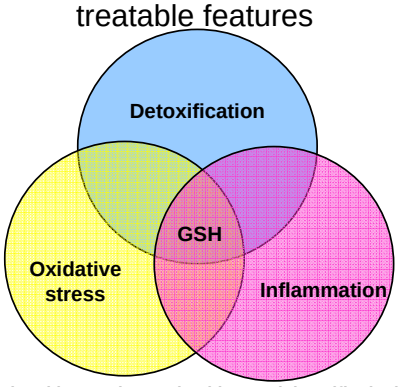
All the components of this injury have treatable features



GSH = Glutathione, prime anti-oxidant and detoxifier in the body

104
S Baker

More than Prenatal

105

Brain changes do not just happen before birth but also after birth and into the lifespan.

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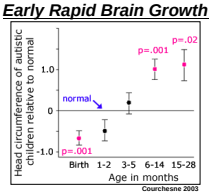
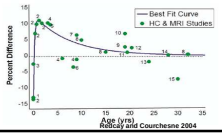
BRAIN CHANGES AFTER BIRTH

Early Rapid Brain Growth

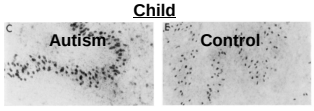


Tapering off after the first few years

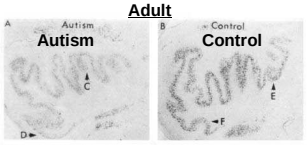


Ongoing cellular changes into the lifespan

Child



Adult



Kemper & Bauman 1992
Bauman and Kemper 2005

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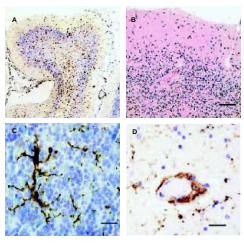
Neuroinflammation continues far into the lifespan

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**

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Not static but dynamic: Plasticity

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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

Challenges posed by this study:

- **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**

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

Other improvement in autism

- Short-term, transient
  - Improvement in core features
    - During antibiotic treatment
    - During "clear fluids only" prep for colonoscopy
    - Postoperatively after anesthesia
    - Treatment of allergies
    - During times of emotional intensity
- Longer term
  - Improvement in some core features with anti-epileptic meds in some
  - Loss of diagnosis
    - After intensive therapy
    - Goes away by itself in some?

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How can autism be purely a hard-wired brain structure disorder, a "static" encephalopathy, if things change?

If core features can improve even transiently, could it be a "dynamic" encephalopathy?

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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

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-

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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]

om/naturemedicine

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Rapid reversal of Alzheimer's symptoms by drug that *inhibits TNF-α* and therefore *inhibits inflammation*

Journal of Neuroinflammation BioMed Central

Case report Open Access

Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration

Edward L Tobinick*[1,2] and Hyman Gross[1,2]

BMC Neurology BioMed Central

Research article Open Access

Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease

Edward L Tobinick*[1] and Hyman Gross[2]

Short-term immune triggers cause long-term brain inflammation

- *TNF-α* increases are triggered by bacterial and other exposures.
  - In the bloodstream this 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*

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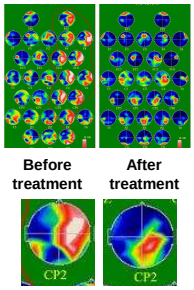
Improvement in brain function after treatment



Example:

- **Depakote was given for spike-waves during sleep that did not meet criteria for CSWS** (continuous spike-wave during sleep)
- **Substantial improvement resulted in speech and cognition**
- **This was measurable in brain by techniques not in standard use**
- **Where does this leave us?**

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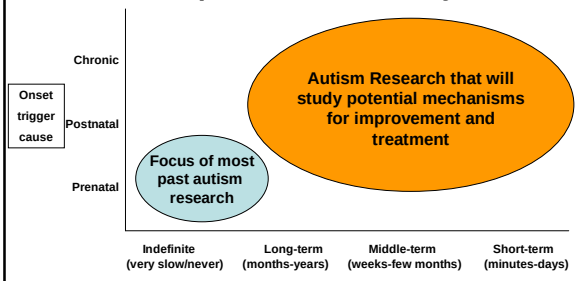
Implications of clinical observations of good days/bad days and improvement/recovery



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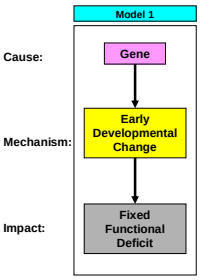
Expanding the Spectrum of Autism Mechanisms :

1. Genetically caused static encephalopathy



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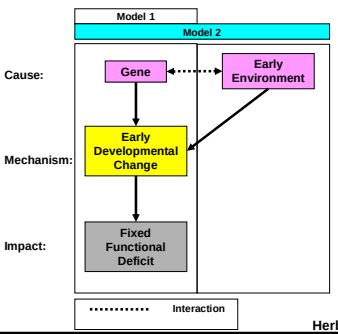
Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms :

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



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Herbert, Anderson 2008 in Zimmerman et al

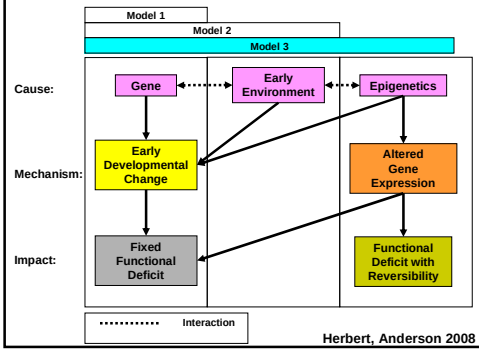
Mindd Foundation
Healthy Cells for Life

Autism & Environmental Vulnerability

Martha Herbert, MD, PhD

Expanding the Spectrum of Autism Mechanisms :

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



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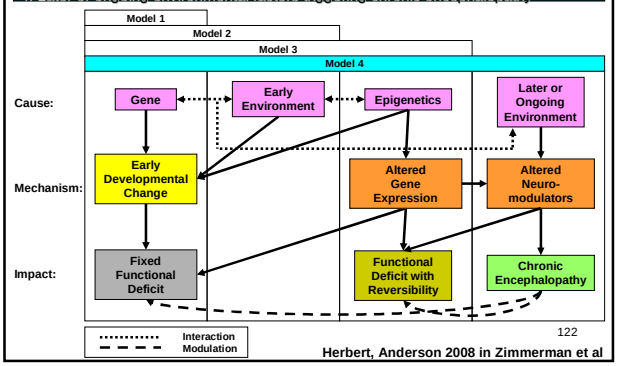
Herbert, Anderson 2008 in Zimmerman et al

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



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Herbert, Anderson 2008 in Zimmerman et al

Realize that practical day-to-day things may be of some help

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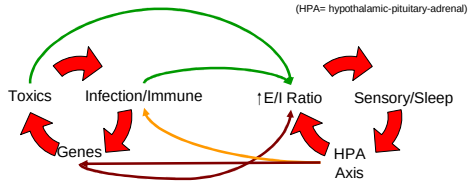
Self-reinforcing or "vicious" circles

- Genes modulate vulnerability to toxic, immune and infectious stress
- Toxics impair immunity
- Infection and immune stress alter gene expression
- Increased excitation/inhibition contributes to sensory overload and sleep disruption
- These contribute to stress
- Stress worsens the HPA axis contribution to biological factors increasing the I/E ratio

(HPA= hypothalamic-pituitary-adrenal)



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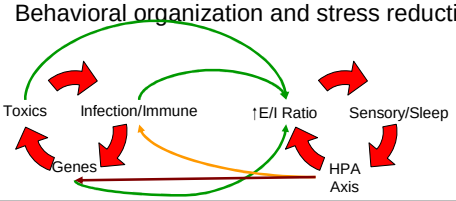
Chilling out "vicious" circles and allowing adaptive self-re-regulation

- Less toxic exposure
- Better ability to detoxify
- Improved nutritional status
- Immune support
- Reduce/avoid infection
- Behavioral organization and stress reduction



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Autism research has been focused on describing a "broken brain" and looking for genes that broke it

But new science is suggesting the brain in autism and other neurodevelopmental disorders may not be "broken" so much as *heavily challenged*.

We need a fresh approach to brain research that focuses on avoiding harm and optimizing potential.

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Healthy Cells for Life

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

If recovery is possible, then we need to *take a fresh look.*

Received: 2 September 2008 / Accepted: 11 September 2008

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

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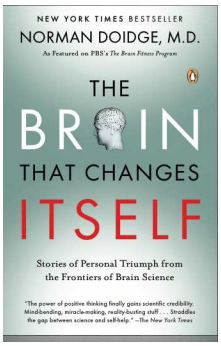
Brain "plasticity" is in the air



If Brain Change is Possible, We need careful documentation and study

- **Rigorous tracking of change**
- **Sophisticated measures of change**

Learning from the autism catastrophe: key leverage points
By Martha R. Herbert
Altern Ther Health Med. 2008 Nov-2008 Dec 31; 14(6)28-30

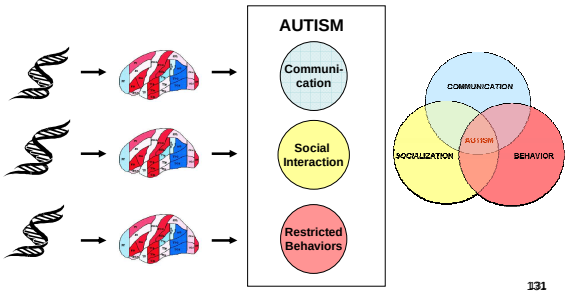
Treatment
Research
And
Neuro
SCience
Evaluation of
Neurodevelopmental
Disorders

TRANSCEND

A Whole-Body Approach to Brain Research

Standard Model:

Gene → Brain module → Behavior

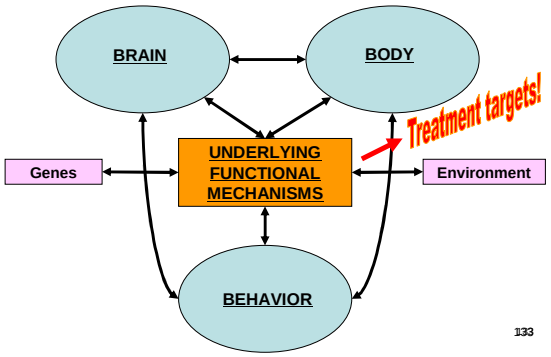


Findings that inspired TRANSCEND to go beyond (to transcend) Gene → Brain → Behavior

- **Widespread brain enlargement *after birth***
- **Inflammation in the brain**
- **Many with autism spectrum have medical problems (gut, immune, etc.)**
- **EEG is abnormal even without seizures**
- **More and more children with autism spectrum**
- **Documented improvements in core autism features**

Mindd Foundation
Healthy Cells for Life

TRANSCEND Middle➔Out approach: Mechanism-based disease model



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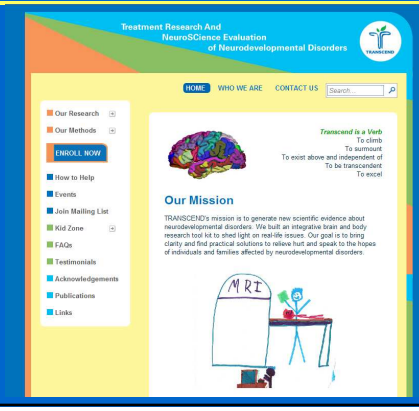
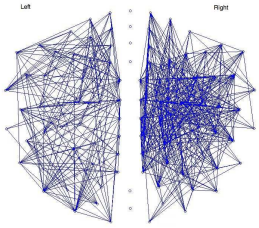
www.transcendresearch.org



EEG and MEG: Brain Signaling Networks



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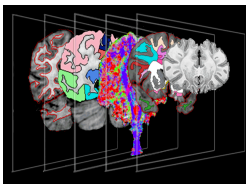
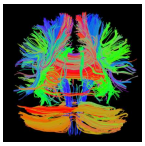
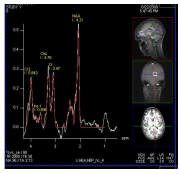
MRI: Brain Structure, Wiring and Chemistry

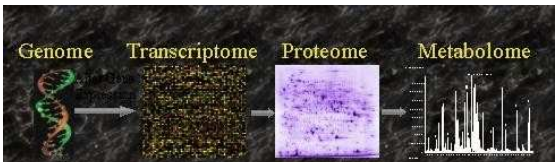






Biomarkers

- **Connecting brain and body through molecular and physiological science**



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TRANSCEND is a Verb

trānscendere
trāns- + -scendere,

To climb
To surmount
To exist above and independent of
To be transcendent
To excel

www.transcendresearch.org

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Example of TRANSCEND Work
Infants at Risk

- **Baby Sibs ➔ *it's the whole body!***

A Multisystem Evaluation of Infants At Risk for Autism

- ***The first study to look at MEDICAL development alongside behavioral and brain development***
- **New functional measures:**
  - ***EEG***
  - ***Metabolic, Immune, Toxics, Nutrition***
  - ***Autonomic nervous system (stress measure)***

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Example of TRANSCEND Work
Infants at Risk -- Continued

QUESTIONS:

- ***Do biological abnormalities precede behavioral abnormalities?***
- ***Are there biological predictors?***
- ***Are there things we could treat very early that might reduce severity or prevent autism altogether?***

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Discussion of Whole Baby Sibs and TRANSCEND intellectual framework is in press

Chapter 25

A Whole Body Approach to ASD

By Martha R. Herbert

In

The Neuropsychology of Autism

Edited by Deborah A. Fein, PhD

Oxford University Press, 2011

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Infant EEG

Photos used with permission

Crisis means
Danger + Opportunity

- **DANGER:**
  - **Suffering and damage to more and more**
    - **Children**
    - **People of all ages**
    - **All life and our planet**
- **OPPORTUNITY:**
  - **Get a grip**
  - **Create better, healthier lives for everyone**

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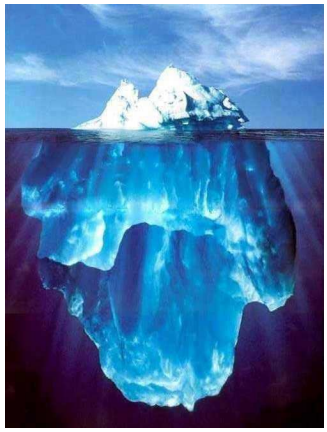
A Perspective on the Autism Spectrum:

Tip of the Iceberg, Canary in the Coal Mine



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

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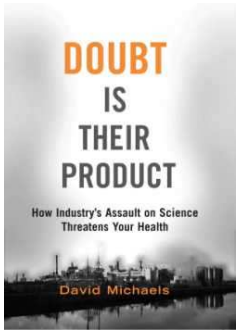
"And so, while the end-of-the-world scenario will be rife with unimaginable horrors, we believe that the pre-end period will be filled with unprecedented opportunities for profit."

For further details: THE SHOCK DOCTRINE by Naomi Klein 146

Manufacturing Uncertainty



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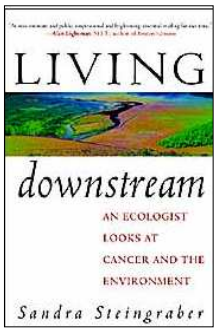
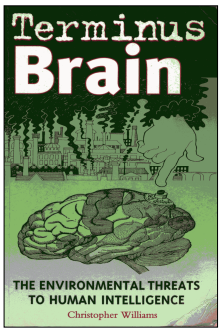
We all live downstream
Everyone, Everywhere





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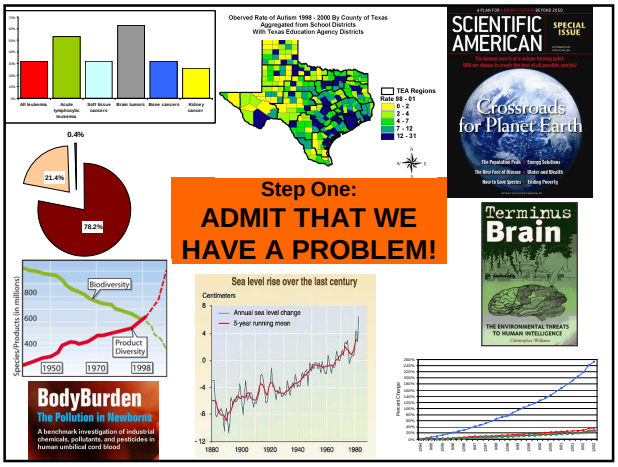

Autism:
Thinking the unthinkable

To cling to a purely genetic explanation of autism is a desperate attempt to maintain the illusion that one lives in a comfortable and rational world where new chemicals and technologies always mean progress, experts are always objective and thorough, corporations are honest, and authorities can be trusted. That human actions, rather than genetics, might be responsible for compromising the health of a significant proportion of a whole generation is so painful as to be, for many unthinkable.

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Will Women Lead the Environmental Health Movement?

How can we imagine that ordinary people might be able successfully to challenge the overwhelming internal logic of the global economic system because of concern over environmental health?

There is an Ethiopian proverb that when spider webs unite they can tie up a lion. The lion of the globally destructive patterns of production and consumption may one day be ensnared and ultimately domesticated by the gossamer webs of human consciousness and community action. What will happen when ordinary people, whose lives are often mortally wounded by the destruction of the biosphere, come to understand that their wounds are so often intimately related to the wounds of the earth?

What will happen when a working woman comes to a realization that her own breast cancer, her husband's lymphoma, her brother's melanoma, her son's learning disability, his best's friend's attention deficit disorder, her daughter's endometriosis, her niece's cleft palate, her cousin's chronic anxiety and panic disorder, her best friend's severe chemical sensitivity, her best friend's daughter's asthma, her uncle's infertility, her neighbor's son's testicular cancer, and her sister's daughter's childhood leukemia, *may* form a pattern?

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What will happen when this working woman begins to understand that these new human pandemics, that affect her family and her community directly, *may be* profoundly connected to what is happening to the fish in the sea, the birds in the sky, and the animals of the earth?

I believe this working woman will understand that the cancers and infertility of the fish, the disappearance of the frogs, the cleft palates of the mice, the shifts in gender orientation of the birds, the susceptibility to viruses and infections of the seals, the disappearance of the songbirds, -- that all this and much, much more *may be* telling us a story that is also our story.

The story that the birds and the fish and the mice are telling us is the story of InterBeing -- the story that all life on earth is truly, breathtakingly, concretely connected *right now*, and that what we do to the mice of the field and the birds of the forest, we also ultimately do also to ourselves and our families *right now*.

I do not believe that we can hide from this story much longer. It is among the great stories of our time.

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Making our own hope

continued from Lerner, Age of Extinctions

This very human protest against a massive entrenched and toxic global system of production and consumption may seem unrealistic economically and politically. But is it any less realistic than the Quaker protests in Europe and the United States that played such a key role in ending the 350-year-old slave trade? I do not invoke the parallel to ending the slave trade lightly. For we are as enchained by toxic chemicals and ozone depletion and climate change and the destruction of nature as we were once enchained by slavery. I believe environmental health may be one of the greatest human rights issues of the millennium. That is our best hope.

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Chief Seattle

**We are part of the earth
and it is part of us.
We do not weave the web of life,
we are merely a strand in it.
Whatever we do to the web,
we do to ourselves.**

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Canary in a Coal Mine

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**To climb
To surmount
To exist above and
independent of
To be transcendent
To excel**

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