Overview of physiological issues underlying an Autism Spectrum diagnosis

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Autism has conventionally been considered genetic and hardwired. However a growing body of physiological research and observations are not consistent with this generalization. These include 1) Increasing numbers, 2) Whole-brain involvement and changes after birth, 3) Involvement of the brain as a physical organ, 4) Whole-body involvement, 5) Remarkable brilliance among many people with autism, including some who can't talk; and 6) Both transient and persistent marked improvement and loss of diagnosis. All this suggests that the fundamental problem may be based in an interacting web of physiological problems that in combination lead to obstruction of function or obstruction of expression rather than deficient capability. This talk will review research supporting these points, and consider the medical, scientific and policy implications.

Autism: A *Behaviorally Defined* Syndrome

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

DSM-IV Criteria for Autistic Disorder (299.0)

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

Secondary Features of Autism

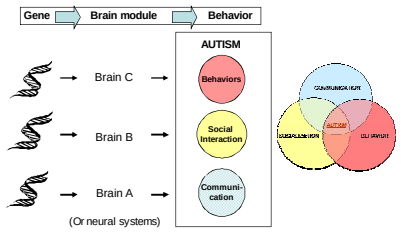
Seizures (~30%+), cognitive deficits, sensorimotor abnormalities, savant skills, immune impairments, GI distress(50-75%), food allergies (~50+%)

No biological markers exist to identify autism at this time

Autism is presumably *Heterogeneous* *biologically*

But autism is *biological*

From Definition to Model of Autism: Classic Modular Framework



Typical inference: autism is "hopeless and incurable"

Genes

↓

Prenatal

↓

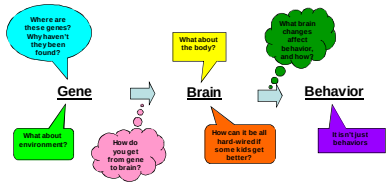
Hardwired

↓

Hopeless

Is this supported by science?

Missing links and open questions



Anomalies

- Not just genetic: Numbers going up
- Not just brain modules: whole brain involvement
- Not just prenatal: active processes throughout the lifetime
- Not just brain: Systemic features
- Not "hopeless": Resilience, creativity, improvement, recovery

Assumption: Autism is a "developmental disorder"

This seems obvious.

But it carries a lot of extra baggage.

Assumption: Autism is a "developmental disorder"

What are the IMPLICATIONS of this assumption?

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

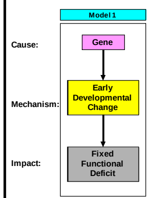
LET'S EXAMINE THE EVIDENCE

From Genetic to Gene x Environment and Epigenetics

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

Expanding the Spectrum of Autism Mechanisms:

1. Genetically caused static encephalopathy

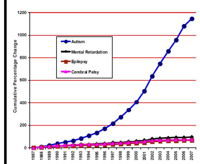


Herbert, Anderson 2008 in Zimmerman et al

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



Challenge to argument that this is all increased awareness and artifact:

- 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"

(*Epidemiology*, Hertz-Picciotto and Delwiche, 2009)

Is autism really "all" genetic?

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

:

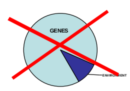
- More identical than fraternal twin pairs are *concordant* (share an autism diagnosis)
- But concordance is only 60% for full autism
- 90% concordance is for broad autistic spectrum (i.e., *milder*) in one of the twins

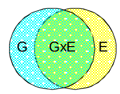
What accounts for the incomplete concordance?

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

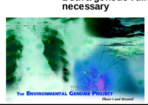
– Davis, Phelps, & Bracha, 1995

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





- G *and* E probably affect most cases; they don't have to add up to 100%
  - Population-attributable fraction – the number of cases that would not exist if a risk factor were absent
  - Both a genetic vulnerability and an environmental trigger could be necessary

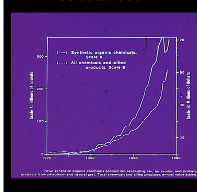


AUTISM AND ENVIRONMENTAL GENOMICS

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

Neurotoxicology, 2006

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



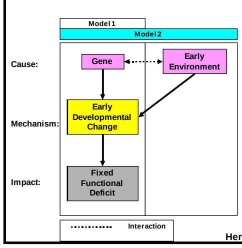
Of the 287 chemicals detected in umbilical cord blood:

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

www.bodyburden.org

Expanding the Spectrum of Autism Mechanisms:

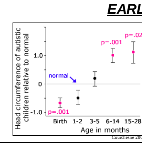
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy

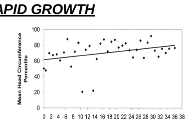


Herbert, Anderson 2008 in Zimmerman et al

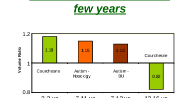
Not necessarily just prenatal

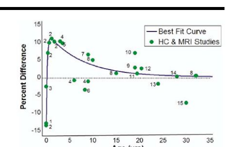
TIMING OF POSTNATAL ATYPICAL BRAIN GROWTH: *EARLY RAPID GROWTH*





Tapering off after the first few years

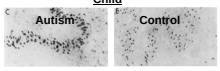




Ongoing postnatal cellular changes in the autistic brain

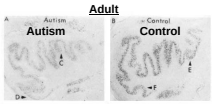
Neurons in autistic child:
- larger than control
- normal in appearance

Child



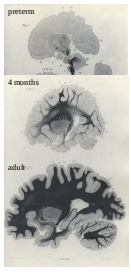
Neurons in autistic adult male:
- small in size
- adequate numbers

Adult



Kemper & Bauman 1992
Bauman and Kemper 2005

Myelination in the First Year



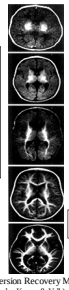
Flechsig, 1920

Here, myelin stains black.

Myelination proceeds in several gradients: deep to superficial, posterior to anterior.

The increased WM volume is in white matter areas that myelinate latest.

Radiate white matter myelinates late in 1st year and into 2nd year of life.



Here, myelin appears white.

Inversion Recovery MRI Image
(Van der Knaap & Valk)

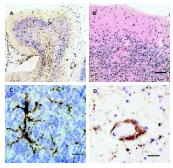
www.utm.utoronto.ca/~w3psy/courses01w/s318/brain1.ppt

Active Tissue pathophysiology in Brain

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

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

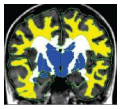
Oxidative stress in brain tissues from autistic patients increased concentration of isoprostanes
Vargas et al, 2005, Annals of Neurology



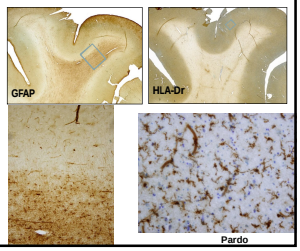
- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3-year old's brain

Pardo: Astrogliosis in Radiate White Matter

Microgliosis



Herbert:
Radiate White Matter Enlargement

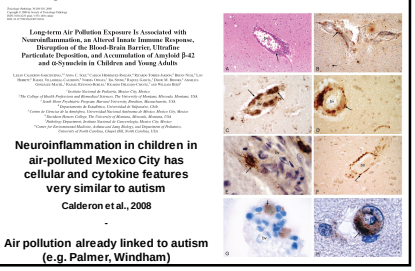


Pardo

Other evidence of pathophysiological alterations in brain tissue in ASD

- Elevated cerebellar 3-nitrotyrosine [Sajdel-Sulkowska 2008 (AJBB)]
- reduced neuronal density with increased glial density and lipofuscin in language-related cortex [Lopez-Hurtado 2008 (AJBB)],
- Immunocytochemical detection of three markers of oxidative injury and lipid peroxidation in ASD brain tissue [Evans et al 2008 (AJBB)]
- Elevated pro-inflammatory cytokines and chemokines [Li et al, 2009]
- Altered expression of immune-related genes in brain tissue [Garbett et al, 2008]

Air pollution and brain inflammation



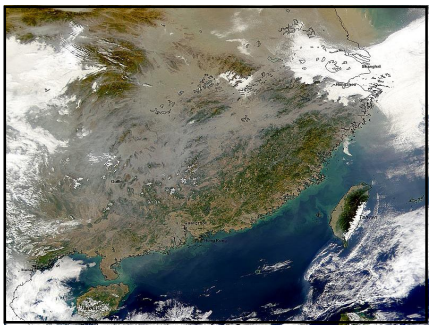
Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adults

Neuroinflammation in children in air-polluted Mexico City has cellular and cytokine features very similar to autism

Calderon et al., 2008

-

Air pollution already linked to autism (e.g. Palmer, Windham)



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 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, genetics, 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.

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

- What if brain abnormal function led to abnormal structure?
- Or maybe they reinforce each other?

Can we be sure that this is true?

- "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."

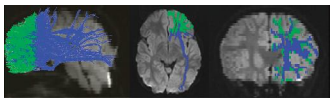
  – Researcher commenting on MET gene that is expressed in gut and brain

Common explanation of brain enlargement in ASD: Failure of "pruning"

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

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

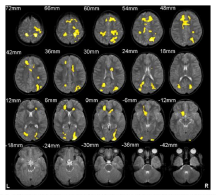
FA = Fractional Anisotropy: measure of white matter integrity. Lower is "worse".



- 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

Sundaram et al., 2008

REGIONS WITH INCREASED T2 RELAXATION TIME IN AUTISM



- Left parietal postcentral gyrus and underlying white matter extending through communicating white matter into ipsilateral left medial and superior frontal gyri and related white matter
- Right middle occipital gray matter and underlying white matter
- Right parietal postcentral gyrus and underlying white matter
- Left inferior and middle white matter extending through anterior corpus callosum into right inferior and middle white matter
- Left middle occipital gyrus and underlying white matter

Fig. 3. 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

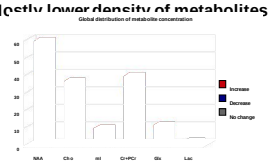
White matter abnormalities in autism detected through transverse relaxation time imaging. Hendry et al., Neuroimage, 2005.

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

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

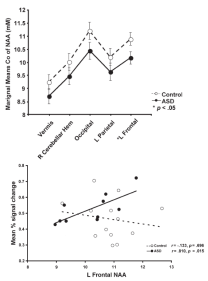
Cheung et al., 2009

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



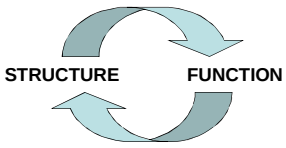
Metabolite level correlating with brain activation

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

Kleinhans et al, 2007

Structure → Function? Or Function → Structure

or



Rabbit or duck?

*Is autism a **BRAIN DISORDER***

or a

DISORDER THAT AFFECTS THE BRAIN?

Herbert, 2005

Autism is a Whole-Body, Whole-System Condition

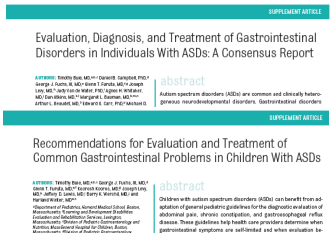
- Seizures (~30%+)
- Cognitive deficits
- Sensorimotor abnormalities
- Disordered sleep
- Immune impairments
- GI distress
- Food allergies
- Systemic metabolic disturbances

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

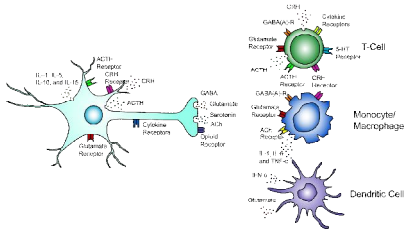
SUPPLEMENT ARTICLE

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

abstract

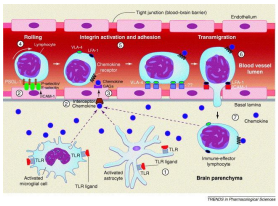
Children with autism spectrum disorders (ASDs) can benefit from adaptation of general pediatrics guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and gastroesophageal reflux disease. These guidelines help health care providers determine when gastrointestinal symptoms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

Immune system and CNS cross-talk



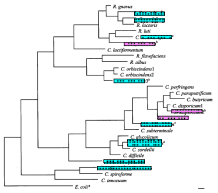
Ashwood

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



Not just human metabolism: Abnormal Clostridial bacteria species in autistic children's stool.

Finegold S, 2002



Abnormal gut flora *metabolism* can:
- **deplete vital nutrients**
- **alter metabolism of xenobiotics**
- **produce neurotrophic substances**
- **Alter immune function**

This can cause or worsen metabolic stress.

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

J Nicholson, Nature Review Microbiology, 2005

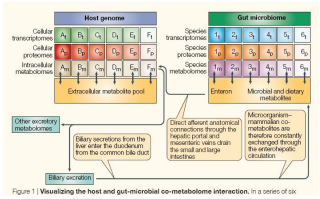


Figure 1 | **Visualizing the host and gut-microbial co-metabolome interaction.** In a series of six

The Every Day of Some Autisms

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

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

Ruhl, 2005

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

Glial cells in the gut

A. RÜHL

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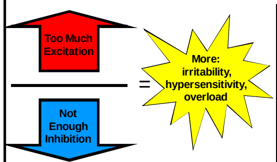
Abstract: The **enteric nervous system is composed of both neurons and glia**. Recent evidence indicates that enteric glia–which vastly outnumber enteric neurons–are actively involved in the control of gastrointestinal functions: they contain **neurotransmitter precursors**, have the machinery for **uptake 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**.

A FINAL COMMON PATHWAY?

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

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



Comments:

Increased excitation/inhibition ratio may explain many features of autism, e.g.:

a) Sensory sensitivities

b) Sleep disturbances

c) Seizures, epilepsy

Also, not just brain.

Inflammation and oxidative stress increase this E/I ratio systemically

Huge numbers of xenobiotics are excitotoxic

Treatments can modulate this ratio

Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders

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

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

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

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 et al., GLIA, 2007

A Different Model of Autism

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

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

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*

www.functionalmedicine.org

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

Functional problems in the brain

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

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

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

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

Not so hardwired

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**

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

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-

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]

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

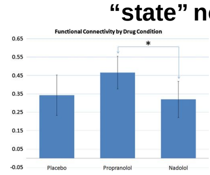
Journal of Neuroinflammation BioMed Central

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]

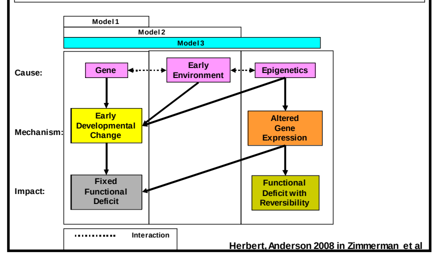
Rapid change in brain connectivity suggests "state" not "trait"



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

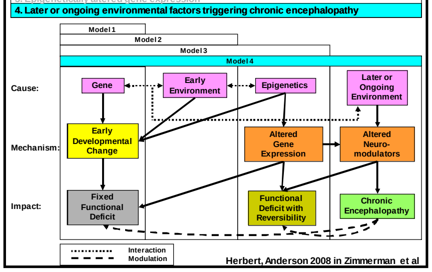
- **Functional connectivity, assumed to be a fixed trait, changed rapidly with drug that impacts brain stress level (propranolol)**

Expanding the Spectrum of Autism Mechanisms:
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. **Epigenetically altered gene expression**

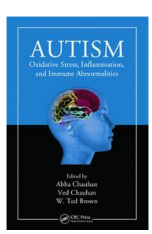


Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms:
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. Epigenetically altered gene expression
4. **Later or ongoing environmental factors triggering chronic encephalopathy**



Herbert, Anderson 2008 in Zimmerman et al



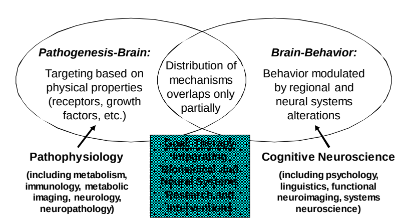
Article detailing much content for this talk:

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

By Martha R. Herbert, MD, PhD
2009

Autism: Oxidative stress, inflammation and immune abnormalities
Chauhan A, Chauhan V, Brown T, eds., in press, 2009, Taylor & Francis/CRC Press.

Linkage needed between Pathophysiology and Cognitive Neuroscience



Herbert & Ziegler, Neurotoxicology, 2005

TRANSCEND Research Program

Treatment
Research
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Neuro
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Evaluation of
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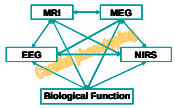
Disorders



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

www.transcendresearch.org
transcend@partners.org

A Multisystem Evaluation of Infants At Risk for Autism

Collaboration of TRANSCEND and LADDERS, DoD Funded
Martha Herbert: Initiating PI; Margaret Bauman: Partnering PI

The first prospective study to look at MEDICAL development with behavioral and brain development

- **Integrated systems biology measures, ages perinatal, 2 weeks, and 4, 9, 14, 20 and 30 months (and more intensive tracking if issues arise):**
  - *High density array EEG and ERP for signal processing analyses*
  - *Metabolic, Lipids, Immune, Toxics, Nutrition, biosample banking*
  - *Autonomic nervous system (stress measure)*
  - *Neuro and motor exams, neurocognitive, language*

Hypotheses / Questions:

- *Biological abnormalities may precede behavioral abnormalities and have developmental trajectories*
- *Environmentally sensitive immune & metabolic measures may predict risk*
- *For future studies: can early treatment of medical vulnerability reduce severity or prevent autism altogether?*

Treatment Research And NeuroSCIence Evaluation of Neurodevelopmental DIsorders

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

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