Overview of physiological issues underlying an Autism Spectrum diagnosis

Autism has conventionally been considered genetic and hardwired. However, a growing body of physiological research and observations is 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

*Psychology 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
4. Secondary features of Autism

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

Gene — Brain module — Behavior

Typical inference: autism is “hopeless and incurable”

Is this supported by science?

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

### 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 for broad autistic spectrum (i.e., milder)

**What accounts for the incomplete concordance?**
- Swedish study of schizophrenic identical twins
  - Probable same placenta: 60% concordance
  - Different Placentas: 11% concordance

**Twin studies of other conditions:**
- Scz: 65% concordance
- AD: 35% concordance
- PD: 25% concordance

### 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%
- Both a genetic vulnerability and an environmental trigger could be necessary

### “Environment” is not a constant: Unprecedented production of new substances

- 100 chemicals detected in umbilical cord blood
- 257 cause cancer in humans or animals
- 217 are toxic to the brain and nervous system
- Nearly 200 have been banned from the market for years

### Not necessarily just prenatal

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

**AUTISM UP 1200%**
- 600% increase in reported cases 1990-2001
- 200% can be explained by non-environmental factors
- 30% age at diagnosis
- 50% inclusion of milder cases
- 80% inclusion of milder cases (Zimmerman et al., 2008 & CA DMH, 2006)
- The rest of the increase (400%) may have been from environmental contributors

### Expansion of the Spectrum of Autism Mechanisms

**Model 1**
- Genetically caused static encephalopathy
  - Cause:
  - Mechanism:
  - Impact:

**Model 2**
- Gene 
  - Early Developmental Change
  - Fixed Functional Deficit

### Not necessarily just prenatal

**Timing of Postnatal Atypical Brain Growth:**

- Early Rapid Growth
- Tapering off after the first 3 years
Ongoing postnatal cellular changes in the autistic brain

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

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

Kemper & Bauman 1992
Bauman and Kemper 2005

Inversion Recovery MRI Image (Van der Knaap & Valk)

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 stains black.
Here, myelin appears white.

Active Tissue pathophysiology in Brain

Pardo: Astrogliosis in Radiate White Matter

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

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

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

- 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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Current Opinion in Neurology, April, 2010

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

Folstein, S., 2005

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Current Opinion in Neurology, April, 2010

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

Folstein, S., 2005
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

- Fractional Anisotropy (FA): 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

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

May be a reflection of altered tissue water properties

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

- Reduced 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

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

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

Structure  Function? Or Function  Structure
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: “Disorders and fever following smallpox vaccination ... healthy except for large tonsils and adenoids.
Case 4: “Not a very healthy child ... still taking any kind of nourishment at those elevents ... also had the habit of crying a great deal ... his skin and eye indications and rapidity in developing no verbal complaints.”
Case 5: “Conditions of food intolerance through the birth marks ...”
Case 6: “Tonsils were removed ...”
Case 7: “Vs. were removed ...”
Case 8: “Large and ragged tonsils ...”
Case 9: “None of the usual children's diseases.” [? Overactive immune system?]
Case 10: “Frequent hospitalizations because the feeding problem ...”
Case 11: “Gastrointestinal symptoms.” [? Overactive immune system?]

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

Immune system and CNS cross-talk

The “Blood-Brain Barrier” is not an absolute barrier

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

Kongerud, 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

Johansson, Mora, and other in January, 2016

The Every Day of Some Autisms

What we need: Clinical labs that will detect and report pertinent gut pathogens
A FINAL COMMON PATHWAY?
Model of autism: Increased ratio of excitation / inhibition in key neural systems

**FUNCTION**
- Energy Production
- NMDA plasticity
- Lipid Membranes
- Transmitter Specificity
- Glial Support

**Comments:** Increased excitation/inhibition ratio may explain many features of autism, e.g.
- Sensory sensitivity
- Sleep disturbance
- Seizure, epilepsy
- Anxiety, agitation

Inflammation and oxidative stress increase this E/I ratio systemically

**Huge numbers of xenobiotics are excitotoxic**

**Treatments can modulate this ratio**

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**

CLASSES OF CORE FUNCTIONS

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

- Brain energetics
- Mitochondrial dysfunction
- Bioenergetics
- Metabolic dysfunction
- Transport, circulation
- Cerebral hypoperfusion
- Communication, inside and outside the cell
- Immune dysregulation
- Neurotransmitters, hormones
- Structural integrity
- Hypoxia
- Protection and defense
- Autoimmune problems
- Elimination of waste
- Impaired intestinal function
- Impaired detoxification

CHRONIC MECHANISMS CAN IMPACT BRAIN FUNCTION

- Free Radicals
- Calcium Dysregulation
- Peroxidation
- Toxic Mediators
- Chronic Inflammation

**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

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

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

Effect of Propranolol on Functional Connectivity in Autism Spectrum Disorder—A Pilot Study

Rapid change in brain connectivity suggests state’ not “trait”

Rapid reversal in Mouse Models

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Reversal of learning deficits in a Tac2<sup>−/−</sup> mouse model of tuberous sclerosis

Rapid improvement in verbal fluency and aphasia following peripheral vagus nerve stimulation in Alzheimer’s disease

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

Article detailing much content for this talk:

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

Herbert, Anderson 2008 in Zimmerman et al

Pathogenesis-Brain:
Targeting based on physical properties (receptors, growth factors, etc.)

Pathophysiology (including inflammation, immunology, synaptic plasticity, neurogenetics, neuromodulation, neurochemistry)

Brain-Behavior:
Behavior modulated by regional and neural systems alterations

Cognitive Neuroscience
Linkage needed between Pathophysiology and Cognitive Neuroscience

Herbert, Anderson 2010 in Zimmerman et al
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 behavior 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, Toxins, Nutrition, biosample banking
  - Autonomic nervous system (stress measures)
  - Neuro and motor exams, neurocognitive, language
Hypothesis / 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?

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

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