Autism: Chronic Features and Dynamic Mechanisms

Learning Objectives
At the end of this presentation the participant will be able to:
1. Explain how the concept of “allostatic” or “total” load applies to the autism spectrum
2. List public health measures that could contribute to improving resilience on the autism spectrum and that could broaden access to appropriate medical care
3. Compare emerging systems biology models of what autism “is” with earlier models focusing mainly on the idea that autism is a lifelong static disorder stamped into the brain by genes
4. Explain how the concepts of neuroplasticity, bandwidth and signal-to-noise ratio may help identify actionable clinical targets in the autism spectrum
5. Describe health justice issues related to developing standards of care that emphasize the potential for plasticity and improvement by addressing actionable issues in autism.

Changing Concepts and Findings on Autism
Michael Rutter, JADD, 2012

• “New research findings provide major challenges regarding our understanding of the concept of autism. ….. It is concluded that, although there have been major research advances; there is a need for a reconceptualization and an avoidance of claims that go beyond the evidence.”
• In fact, many of the things we have believed about autism have gone beyond the evidence. We were doing the best we could. Now we have a great opportunity to regroup!

Many new observations in ASD: Where might they point?

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

From Definition to Model of Autism: Classic Modular Framework

Assumption: Autism is a “developmental disorder”

This seems obvious.

But it carries a lot of extra baggage.
Assumption: Autism is a “developmental disorder”

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

These assumptions are not supported by evidence.
Emerging science contradicts them.

Beyond Genes

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

Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome
Lintas et al., Neurobiol Dis, 2010

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

ALSO: genes most upregulated in autism in recent study were NEUROIMMUNE genes, not neurodevelopmental. --Kong/Kohane, 2012

Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting
C. Betancur, Brain Res 2011 42-77

- An exhaustive review of the clinical genetics and research genetics literature
- 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior.
- Commonalities with intellectual disability and epilepsy.

SHANK3, the Synapse and Autism

- Altered postsynaptic density (PSD) proteins
- Smaller PSD
- Fewer dendritic spines
- More dendritic arborization
- Weaker signaling
- Larger striatum
- Autistic-like behaviors

Lower dendritic spine density

- Spine density in striatal medium spiny neurons (MSNs) from Shank3B−/− mice is lower than that of wild-type MSNs

Peça et al., Nature 2011
Complications

- Well over 100 different genetic disorders involve an autistic phenotype (Betancur, Brain Res, 2011)
- These in turn comprise a small minority of cases with autism
- The synapse and PSD are highly complex
- Shank3 is expressed not just in brain but in gut and kidney, is involved in epithelial turnover and mucosal immune development, and is utilized by some gut pathogens in actin rearrangement. (Huett et al., Exp Cell Res, 2009)

Beyond the Brain

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

Problems that often precede the autism diagnosis (plenty of data on this)

- Parents with health problems
  - Health issues, particularly Metabolic Syndrome (diabesity, hypertension, etc)
  - Exposures (toxins, EMF/radiation, stress) leading to genotoxicity and metabolic dysfunction
- Pregnancy issues
  - Inadequate nutrition
  - Exposures (toxics, medications, EMF, stress, infections, allergens)
- Infancy issues
  - Infections, antibiotics that injure microbiome
  - Allergens, lack of microbiome support
  - Insufficiency of various nutrients for handling load of stressors

Beyond Neurons

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

- How much might the astrocytic dysfunction and swelling which impairs blood flow, and poor fluid flow in the extracellular matrix, be hindering synaptic function?
Beyond “Prenatally Programmed Deficit”

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

Circular thinking in autism data interpretation

- To do – we’ve proved that autism starts prenatally
- We believe autism starts prenatally
- We do a study
- We pick one of those mechanisms that fits best with our data

How to account for these phenomena?

- Patchy lesions were reported by Stoner et al. widely distributed in postmortem tissue samples of young people with ASD (top figures)
- We also observed widely distributed increases and decreases in Cortical Thickness (CT) in brains of children with autism as compared to the control mean volume

Just because cortical lamination develops prenatally, that does not mean that its disruption must emanate from primary neurodevelopmental processes.

Beyond Hopelessness

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

From Static to Dynamic Encephalopathy

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


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

Bilateral improvement in children with autism spectrum disorder

Rapid IMPROVEMENT in brain connectivity suggests “state” not “trait”

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

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

Inhibition of p21-activated kinase rescues symptoms of fragile X syndrome in mice

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Reversal of learning deficits in a Tg212 mouse model of tuberous sclerosis

The Center for Discovery: Whole Body SENSITIVE treatment of neurodevelopmental disabilities based on Biodynamic Farm

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

Derecki et al., Nature, 2012

- Rett features had been attributed to neuronal dysfunction related to MECP2 mutation
- Astroglial cells now known to contribute
- Now microglia shown to contribute as well: bone marrow transplant of wild type microglia
  - Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
  - Improvement even without direct change to neurons
  - Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited

Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment-Modulated Pathophysiology

Ch. 10 on Autism: By Martha Herbert
in Genetic Explanations: Sense and Nonsense Ed. Krimsy S and Gruber J

Contains detailed exposition, with extensive citations, of the argument that autism is a dynamic—not a static—encephalopathy

A Middle-Out Approach to Autism: Multi-Scale, (Patho)Physiology Centered

(see Denis Noble THE MUSIC OF LIFE)
**ENVIRONMENTALLY VULNERABLE PHYSIOLOGY**

Current Opinion in Neurology, April, 2010

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

*Martha R. Herbert*

Purpose of review: Environmental factors contribute to the environmental vulnerability to autism spectrum disorder (ASD). Risk factors for ASD include maternal smoking during pregnancy, low birth weight, maternal pre-pregnancy obesity, paternal obesity, maternal gestational contamination with heavy metals, talcum powder, and low milk ingestion, reduced maternal fish intake, and maternal and paternal smoking. These factors cause neuroplasticity changes, microglial activity, neuroinflammation, oxidative stress, and increased neurochemicals, which can lead to cognitive, behavioral, and social issues. A review of the literature is presented here.

Methods: A review of the literature to identify and summarize the environmental factors that may contribute to ASD.

Results: Environmental factors contribute to the environmental vulnerability to ASD. These factors include maternal smoking during pregnancy, low birth weight, maternal pre-pregnancy obesity, paternal obesity, maternal gestational contamination with heavy metals, talcum powder, and low milk ingestion, reduced maternal fish intake, and maternal and paternal smoking. These factors cause neuroplasticity changes, microglial activity, neuroinflammation, oxidative stress, and increased neurochemicals, which can lead to cognitive, behavioral, and social issues.

Conclusion: Environmental factors contribute to the environmental vulnerability to ASD. Further research is needed to understand the mechanisms by which these factors contribute to ASD.

Whole Body Systems Model:

**Symptoms** Emerge from Problems with **Underlying Functions**

**VISIBLE Social & Behavioral SYMPTOMS** are OUTPUT

**DISTURBANCE OF CORE UNDERLYING BODY FUNCTIONS** are GENERATORS


All the parts really influence each other

Body Cell Health Problems

Brain Cell Health Problems

Challenging Behaviors

Brain Function Glitches

Stress and Overwhelm

Slower to Learn Skills

Transduction: Critical Question in Multi-Scale Biology

- How do processes at one level get **TRANSDUCED** into changes at other levels?
- A classical model is sensory transduction
  - From light through eyes/brain to vision
  - From vibrations through ears/brain to sound
- For autism, from a middle-out perspective, the core question is:

  *How do we get from tissue pathophysiology to altered brain function?*

Location of white matter enlargement points to postnatal brain changes

What do we need to learn about the brain and about autism to understand this?

Inflammation and Oxidative Stress in Autism:

Chronic, ongoing postnatal medical problems, not confined to brain

- Neuroglial activation and neuroinflammation in the brain of patients with autism
  - Vargas et al. 2005, Annals of Neurology
- Oxidative stress in brain tissues from autistic patients
  - Increased concentration of isoprostanes
  - Vargas et al. 2005, Annals of Neurology
- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3-year old's brain
- Could increase in brain size relate to inflammation? Hard to test.
Could Connectivity Alterations in ASD be based in Tissue Issues?

- Water, not fiber changes in brain tissue
- Less white matter integrity
- Less restriction of water flow
- More diffusivity

• Lower perfusion in ASD brains (by many PET or SPECT studies) could impact brain function. How might this affect brain electrophysiology?

Local and long-range connectivity BOTH reduced in autism

- This does not map onto the anatomy
- It may not be primarily caused by damage to long-range axons (nerve fibers)
  - Khan/Kenet, PNAS 2013

Air Pollution and Brain Inflammation

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

Inflammation as a final common pathway

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

- GLUTATHIONE (GSH) is vital for detoxification
  - Mops up toxins and free radicals
  - The body’s most potent anti-oxidant
  - The most abundant anti-oxidant in the BRAIN
- Reduced Glutathione = GSH (active form)
- Oxidized Glutathione = GSSG (used-up form)
Glutathione and Oxidative Stress as “Final Common Pathways”

- GSH is depleted by thousands of toxins, oxidative stress, infection, inflammation, EMF and nutrient-poor diet
- Small exposures of any one thing can still add up to a substantial depletion of antioxidant resilience
- Oxidative stress present in the majority of DSM-IV psychiatric disorders including: autism, Rett’s, ADHD, schizophrenia, anxiety, and mood disorders
- “…all these psychiatric disorders might benefit from a change to a whole-food plant-based diet.” PMID 2330073

Brain cells in inflammation: What is the FUNCTIONAL IMPACT?

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

Could this be creating NOISE that crowds out the brain’s ability to process information?

Reduced functional connectivity in visual evoked potentials in children with autism spectrum disorder

J.R. Isler, K.M. Martien, P.O. Grive, R.I. Stark, M.R. Herbert
Clinical Neurophysiology 121 (2010) 2035–2043

EEG power and coherence within and between homologous regions of the occipital cortex were measured during long latency flash visual evoked potentials.

Measures were compared between two groups of children (5.5–8.5 years), one with autism spectrum disorders and the other with typical development.
“Inefficiency” in brain signaling in autism

Clinical Neurophysiology 121 (2010) 2035–2043

ASD has more power than controls… but less coherence

POOR SNR – Sound and Fury, signifying nothing

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EEG of Sensory Responses

- Sensory stimulation can be overwhelming
  - Autistic children fail to upregulate activity when stimulus increases
  - Looks milder in older kids

Prediction: Improved connectivity with effective treatment

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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

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

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Reversibility of reduced NAA after epilepsy surgery

- NAA (marker of neuronal density or function) reduced on the side opposite of a seizure focus
- After surgical resection of seizure focus, NAA on the other side returns to normal

Kleinhans et al., 2007

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IMPLICATION: The persistent aberrant electrical charges afflicting the opposite side appear to have taken those cells off line, but not "taken them out" since they came back online after the seizure electrical activity stopped.

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ALLOSTATIC LOAD MODEL: Genetic and Environmental Stressors are contributing to an ONGOING, CHRONIC DEGRADATION OF BRAIN AND BODY FUNCTION, and increase in ENTROPY

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

Pan, 2008

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

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Reduced informational complexity and organization
Increased signal to noise ratio
Reduced information to noise ratio
More instability, hypersensitivity, overload
Less Much oscillation
Not Enough Inhibition

Neurometabolism in Human Epilepsy

Pan, 2008

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Pan, 2008

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Pan, 2008
A must-read statement of a systems biology approach to complex illness:

From ‘omics’ to complex disease: a systems biology approach to gene-environment interactions in cancer
By Sarah S Knox: http://www.cancerci.com/content/10/1/11

Looks at cancer as accumulated ALLOSTATIC LOAD from diet and environment
Advocates a dynamic transdisciplinary systems biology approach aimed at reversing multiple levels of dysfunction.
JUST ABOUT EVERYTHING SHE SAYS APPLIES TO AUTISM

Metaphor: Tissue pathophysiology REDUCES BRAIN BANDWIDTH

Worse SNR, Less Bandwidth
Less SIGNAL
More NOISE

Better SNR, Better Bandwidth
More SIGNAL
Less NOISE

Better Reception Allows More Spontaneous Learning

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

- Rett features had been attributed to neuronal dysfunction related to MECP2 mutation
- Astroglial cells now known to contribute
- Now microglia shown to contribute as well: bone marrow transplant of wild type microglia
  - Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
  - Improvement even without direct change to neurons
  - Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited

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

Electron microscopy of therapeutically activated glia turning into “brain garbage collectors and transporters”

PROPOSITION / ASSERTION:
Everyday Epigenetics: From Molecular Intervention to Public Health and Lifestyle Medicine
By Martha R Herbert PhD MD
www.najms.net
July 25, 2013

Toward the Pathophysiology of Autistic Regression

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

Spelled out in more detail in Chapter 5 of THE AUTISM REVOLUTION (Herbert 2012)

BRAIN CHANGES IN INFANTS DEVELOPING AUTISM

- From higher to lower “FA”
- Decrease in fiber organization relative to controls
- This DEVELOPS over time
- It is probably DOWNSTREAM of the metabolic, cellular pileup of problems
- See blog critique of Wolff paper: Why aren’t we there yet? Valuable but incomplete brain imaging data in infants

What we CAN do, but don’t

The Diabetes Prevention Program (DPP) clinical trial and its 10-year outcomes study (DPPOS), both sponsored by the National Institutes of Health (NIH), showed that certain interventions could prevent or substantially delay the onset of type 2 diabetes both safely and cost-effectively.1,2 Yet diabetes prevention is not widely practiced in the United States, and the disease’s staggering human and financial costs continue to grow.

What are the consequences of poor lifestyle choices?

- Physiological dysfunction
  - Mitochondrial and metabolic dysfunction
  - Oxidative stress
  - Inflammation and immune dysfunction
- Chronic Illness
- Brain dysfunction
- Greater risk of life-threatening illness and early death

> ABUNDANTLY DOCUMENTED IN AUTISM

ABUNDANTLY DOCUMENTED IN AUTISM

> Autism IS a chronic illness
> Autism involves brain issues
> Evidence for this is starting to accumulate

Large scale systems failure in healthcare system

- Lifestyle intervention can prevent conversion into diabetes by 58% compared to the drug metformin (31%)
- CMS (Ctr for Medicare and Medicaid services) lacks statutory authority to reimburse nontraditional care providers, such as lifestyle coaches.
- Therefore we spend $750 BILLION dollars a year on diabetes treatment instead of prevention.

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

Initiating PI: Martha Herbert
Partnering PI: Margaret Bauman

- Longitudinal Multisystem assessment
  - Metabolism, Immune, Toxics, Endocrine
  - Brain (EEG), Autonomics
  - Medical Comorbidities
  - Developmental/Behavioral Phenotyping
- HYPOTHESIS: Autism emerges from a cascade of insults to physiological integrity culminating in a shift in the level of available brain function
Autism: **WHY and HOW?**

**WHAT IS AUTISM?**

**H ow IS AUTISM CAUSED?**

**H OW CAN WE HELP?**

www.autismWhyandHow.org

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

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**Sources detailing these arguments**

- **GENETIC EXPLANATIONS: Sense and Nonsense**

- **THE AUTISM REVOLUTION:**
  Whole-Body Strategies for Making Life All It Can Be
  Random House/Harvard Health Publications 2012 by Martha Herbert with Karen Weintraub

- For more technical detail on pathophysiology: “Autism and EMF? Plausibility of a Pathophysiological Link” in Pathophysiology, 2013, PMIDs 24095003 & 24113318

- “Everyday Epigenetics: From Molecular Intervention to Public Health and Lifestyle Medicine”, 2013, [http://najms.net/v06i03p167a](http://najms.net/v06i03p167a) or [www.marthaberbert.org/publications](http://www.marthaberbert.org/publications)

- Further papers: [www.marthaberbert.org](http://www.marthaberbert.org) or [http://connects.catalyst.harvard.edu/Profiles/display/Person/47629](http://connects.catalyst.harvard.edu/Profiles/display/Person/47629)

- Overview of multiple synergistic viewpoints on autism: [www.autismWHYandHOW.org](http://www.autismWHYandHOW.org)

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

[www.transcendresearch.org](http://www.transcendresearch.org)

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