



## Researching the basic biology of autism

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## What is Autism?

- One of the 5 disorders under the umbrella of Pervasive Developmental Disorders
- Affects the developing brain
- Early signs seen at 12-18 months
- Most children now diagnosed at 3 years
- Impairment in 3 Core Domains:
  - Language
  - Social Communication
  - Repetitive Behaviors
- Comorbid epilepsy, GI, immune, metabolic, and sleep disturbances

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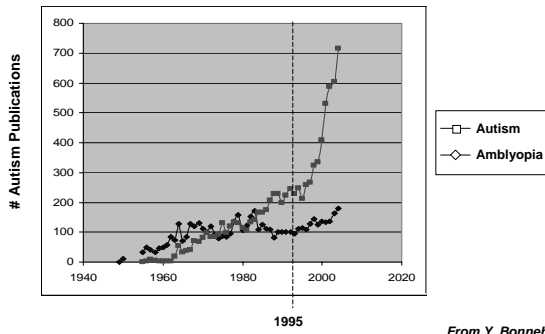
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## Building the base of biology



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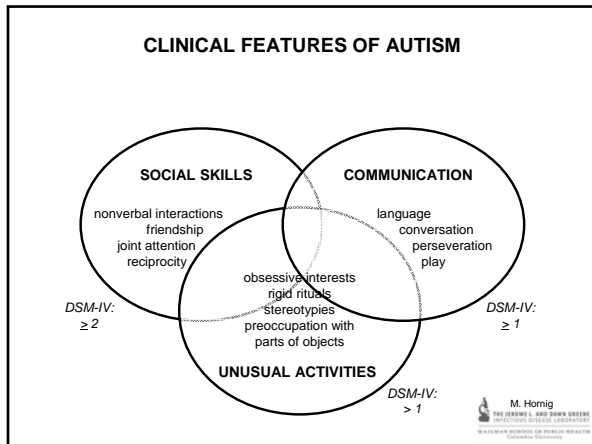
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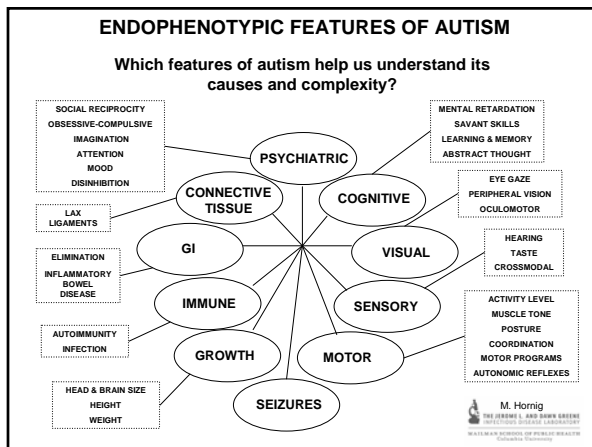
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- ### Today's Outline
- Three exciting published science stories from last two years
  - Framework for thinking about disease research and potential implications for autism biology research
  - Some treatment related-research and initiatives

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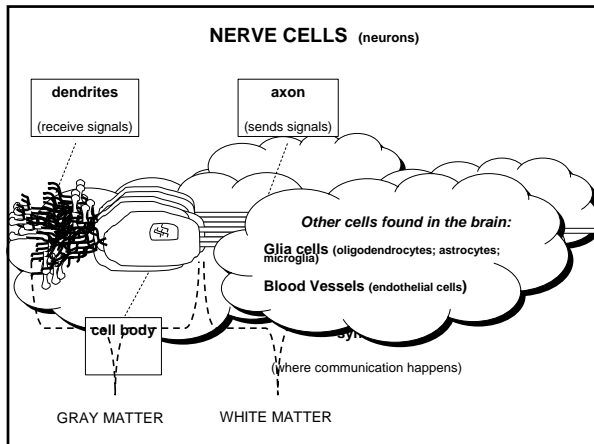
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
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### Some recent research breakthroughs

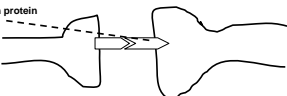
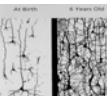
(Subtitle: These are SO cool)

**Anatomy**  
 Increase in superficial white matter; could lead to defective brain connectivity (anatomical and functional) Herbert et al., 2004



Bigger head → Bigger brain → Increased white matter → More "radiate" white matter



**Genetics**  
 Mutations in *neurexin* genes in some autistic individuals Van et al., 2004; Jamain et al., 2003

**Immune**  
 Evidence of on-going "neuroinflammation" in brains of some autistic patients Vargas et al., 2005


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### Some recent research breakthroughs

(Subtitle: CAN'S INVOLVEMENT HAS BEEN PIVOTAL)

**Anatomy**  
 Increase in superficial white matter

☆ CAN-funded studies. Dr. Herbert now recipient of CAN Innovator Award allowing her to continue work as rapidly as possible.

**Genetics**  
 Mutations in *neurexin* genes

☆ CAN investing in a follow-up grants to examine biological consequences of mutated Neuroxin proteins.

**Immune**  
 Evidence of on-going "neuroinflammation"

☆ CAN funded study, allowing Dr. Pardo to apply for an NIH grant. CAN facilitating follow-up experiments e.g., by providing AGRE samples.

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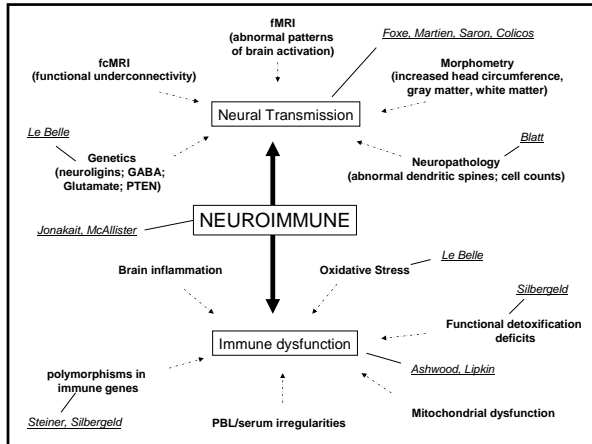
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The four questions of disease research...

<p><b>ETIOLOGY</b> What <u>causes</u> it?</p>	<p>► Why does someone develop autism?</p>
<p><b>PATHOLOGY</b> <u>What</u> is it?</p>	<p>► What are the problems associated with autism?</p>
<p><b>DIAGNOSIS</b> How do we <u>measure</u> it?</p>	<p>► How do we know if someone has autism?</p>
<p><b>TREATMENT</b> How do we <u>make it better</u>?</p>	<p>► How can we help autistic individuals?</p>

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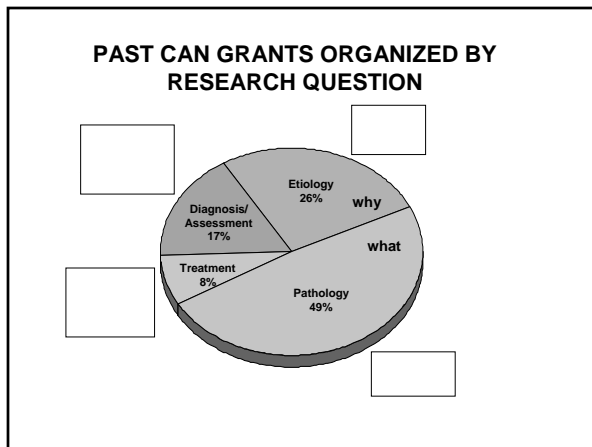
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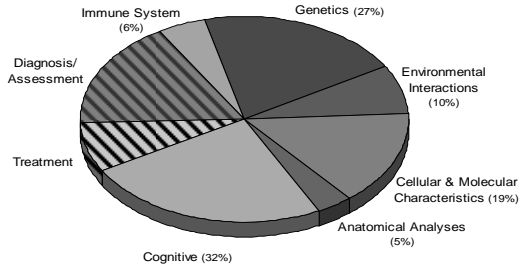
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**CAN ETIOLOGY AND PATHOLOGY GRANTS ORGANIZED BY RESEARCH SUBJECT**




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Another way of organizing research...

**An reductionist approach to understanding a problem**

- **SYSTEMS biology** – How complex networks function to determine behavior
- **CELLULAR biology** – How cells in the network are functioning
- **MOLECULAR biology** – How molecules drive the function of the cell

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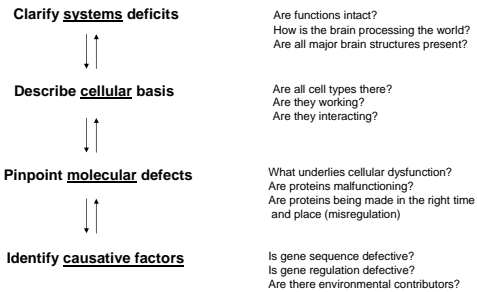
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Alternate classification scheme to understand our etiology and pathology autism research...




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ALS (Lou Gehrig's Disease) / Alzheimer's Disease		
<b>Systems Deficit</b>	loss of movement loss of movement	loss of memory
<b>Cellular Basis</b>	death of neuron that connects to muscle	formation of "debris" that clogs cells of neurons
<b>Molecular Basis</b>	oxidative stress + many others unknown	amyloid plaque production + many others unknown tau protein
<b>Cause</b>	SOD1 mutations + many unknown (environmental)	APP mutations, PS-1 mutations, PS-2 mutations, inheritance of ApoE4

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HYPOTHETICAL AUTISM EXAMPLE 1	
<b>Systems Deficit*</b>	sensory systems hypersensitive
<b>Cellular Basis</b>	too much neural transmission
<b>Molecular Basis</b>	glutamate (excitatory) transmission increased; GABA (inhibitory) transmission decreased
<b>Cause</b>	mutations in: NMDA receptors, AMPA receptors, Glutamate transporters, GABA receptors, Na <sup>+</sup> channels, Ca <sup>2+</sup> channels etc. etc.

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HYPOTHETICAL AUTISM EXAMPLE 2	
<b>Systems Deficit</b>	functional connectivity altered
<b>Cellular Basis</b>	1. axons can't find their targets 2. axons can't transmit information 3. synapses not functional 4. irregular patterning of brain regions
<b>Molecular Basis</b>	1. axon guidance or cell adhesion proteins are missing 2. myelin proteins are defective 3. synapse-forming proteins are absent 4. altered expression of cellular identity genes
<b>Cause*</b>	mutations in: <i>reelin; wnt2; neuroligin 1; neuroligin-2; neuroligin-3; neuroligin-4; neurexins; BDNF, NT3; dlx-1; dlx-2; dlx-5; eng-2; hox</i> genes; etc. etc. etc.  Exposure to toxins, inflammation during critical period of brain-wiring?

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HYPOTHETICAL AUTISM EXAMPLE 3	
Systems Deficit	Brain immune system chronically overstimulated
Cellular Basis*	Astrocytes/microglia activated ("reactive") and cell death
Molecular Basis	cytokines overproduced causing cellular inflammation
Cause	<p>exposure to foreign elements (viruses, toxins etc) stimulates immune reaction;</p> <p>genetic predisposition to a "susceptible" immune system (e.g., increased cytokine production)</p>

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*Why I went through this exercise...*

1. An integrative approach, examine same problem on multiple levels
2. Useful to find links between seemingly different pieces of research
3. It demonstrates there are many ways (causes) to explain the same problem
4. Given the incredible heterogeneity in the presentation of the disease, this is likely to be the case with autism....multiple causes...

 Negative take home message:  
 Roadmap of: "Find THE gene, replace with therapy" not particularly applicable

 Positive take home message:  
 Must be many ways at arriving at the same cellular and systems disruptions, i.e., THERE MUST BE FINAL COMMON PATHWAYS

**We need to know what those are!**

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	ALS	AD	PD	Cancer
Systems Deficit	loss of ability to move muscles	loss of memory	rigidity and tremor	tumors leading to body wasting
Cellular Basis	death of neuron that connects to muscle	formation of "debris" (plaques & tangles) leading to death of neurons	death of dopamine neurons	uncontrolled cell proliferation
Molecular Basis	oxidative stress ??	amyloid production and tangles of tau protein ?	ubiquitin proteasome ??	permanent turning on of cell proliferation pathways suppression of cell death pathways
Cause	SOD1 mutations ??	APP mutations, PS-1 mutations, PS-2 mutations, ApoE4 ??	parkin, alpha-synuclein, DJ-1 ???	mutations (tumor suppressors, kinases, growth factor signaling etc.) + environmental factors

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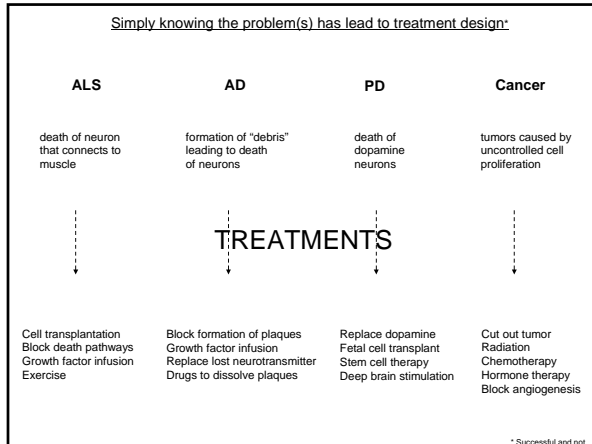
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Take home message from my analysis of autism field...

- People have been working hard to find causes (genetic and environmental)
- We are beginning to understand the systems disruptions
- Little is yet known about underlying cellular/molecular reasons
- This is important because the cellular/molecular basis is the most likely to lead to a direct idea for treatment and can simultaneously point to likely causative agents

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Sophia's resolution is to plug this hole...

Clarify functional deficits of autism and move to study their cellular basis!

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Two ways of giving out grant money...

1. **Sitting around and waiting for someone to approach you...**
2. **Deciding what needs to be done and finding someone to do it!**

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Deciding what needs to be done and doing it...

**TREATMENT**

- ▶ TAB, Neuroplasticity Initiative, ATN, ITA, CTN

**DIAGNOSIS**

- ▶ Lipomics; Psychometrics; ASDE (Clinical Consensus)

**PATHOLOGY**

- ▶ Brain Development Initiative; White Matter Think Tank; Neuroimaging Summit

**ETIOLOGY**

- ▶ AGRE; Environmental Initiative, Neuroimmune Summit

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## Treatment Research Grants

- Lovaas: Reading and writing intervention
- Rinehart: Transcranial Magnetic Stimulation to improve movement disabilities
- Schreibman: Early intervention & assessment for receptive language
- Woods: Cognitive Behavioral Therapy for anxiety

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## Treatment Initiatives

- Formation of autism Clinical Trials Network
- Organization of multi-site Memantine (“Namenda”) clinical trial
- Creation of Autism Treatment Network

*More info to come...*

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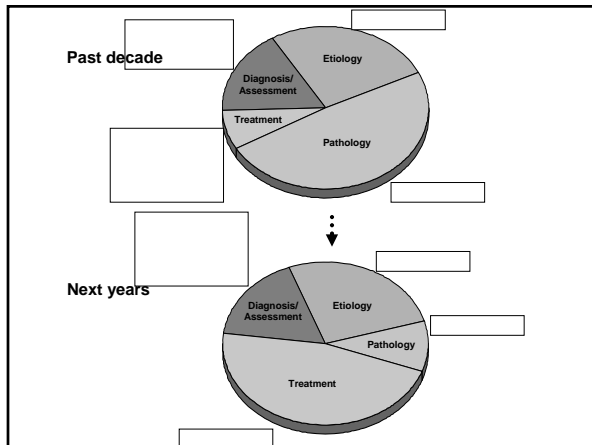
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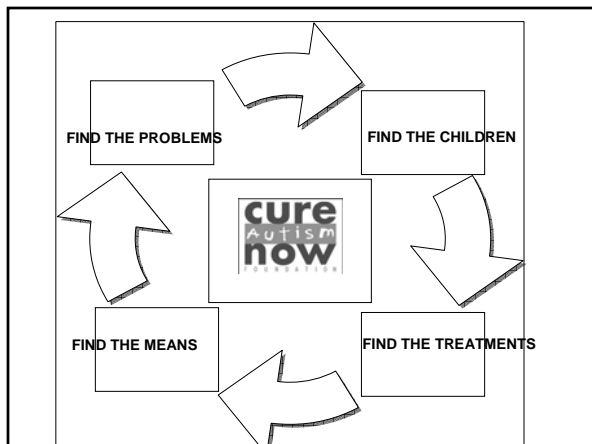
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How we will lead...

- Balance basic with clinical research
- Entice the right scientists
- Proactively fund
- Facilitate and feed

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- We have the people!
- We have the ideas!
- We have the drive!
- We need the money!  
(www.combatingautism.org)



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## “Neuroplasticity”

- The brain CAN learn and change, even as an adult
- Mike Merzenich (UCSF): Training causes re-wiring of neural circuitry i.e., your experiences shape your brain
- Example: Dyslexia is a disorder of temporal discrimination; ability to pick up “signal” is degraded. Fast ForWord Program exaggerates phonemes to teach brain to discriminate the sounds. Can improve reading level 2.5 years with only 25 hrs of training.
- Neuroplasticity Initiative – CAN Genius Award to Dr. Merzenich to have him work on understanding brain input issues in autism, and develop similar neural retraining “games” for autistic individuals

Kuhl et al. Developmental Science (2005) 8:1, pp F1-F12

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## Autism Treatment Network

ATN has been established by:

*MassGeneral Hospital for Children  
Baylor College of Medicine  
Cleveland Clinic  
Columbia University Medical School  
Oregon Health & Science University  
University of Washington*

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## Why was ATN created?

- Accelerate advances in autism treatment and make those advances broadly available
  - Research on treatment is underfunded, lacks scale and urgency
  - Promising practices exist in silos throughout the U.S.
  - Great controversy over health issues / effective treatment
  - Inconsistent / poor outcomes compared to potential
- Autism field lacks fundamental infrastructure for progress
  - Experience shows dramatic progress is possible
  - Cystic Fibrosis / Children's Cancer Network
- Needed: Vehicle, Framework, Support and Leadership

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## *Autism Treatment Network*

### *Mission:*

- To provide optimal diagnosis and comprehensive care for individuals with autism through evidence based practices with specific attention to associated medical conditions
- To disseminate this information to health care providers, educators, and parents
- To promote research aimed at improving treatment for autism

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### Formative Goals - 2005

- Agreements with six major centers for multidisciplinary collaboration
- Development of research database protocol

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### Key Activities and Outcomes 2005-2006

- *Clinical assessment protocol*
- *Standard protocols for GI, metabolic, and sleep conditions*
- *Determine prevalence of these three condition in ASD*
- *Conference: Emerging Practices*
- *Study: Association of GI symptoms with self-injurious behavior*

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### Clinical Assessment Protocol

- Following development of core research protocol, ATN clinical committee will:
  - Review and agree on common clinical assessment in all sites for all children
- Over time, expect all children in collaborating sites will have same initial assessment (i.e., all children in all sites will become part of ATN database)

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## Standard Protocols

- ATN will develop standard protocols for assessment for three key medical condition groups associated with ASD:
  - GI symptoms and conditions
  - Metabolic indicators
  - Sleep disorders

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## Prevalence of Medical Conditions in ASD

- Determine prevalence of GI conditions, metabolic indicators/conditions, and sleep conditions
- Will use initial ATN database to determine these – ie, based on the standard assessment protocols and the enrolled children and adolescents
- Do these conditions relate to cognitive/behavioral issues in autism
- Will treatment improve effects of behavioral and educational interventions for children with autism

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## Empact Conference

- Initial clinicians' conference to introduce ATN and share treatment information and experiences
- Emerging practices in the care of children and youth with autism
- Focus in 2005 on assessment of GI, metabolic, and sleep conditions in context of a multidisciplinary assessment and approach to ASD
- Publication of main papers from conference in *Pediatrics*

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## GI Symptoms and Self-Injurious Behavior

- Are GI symptoms associated with self-injurious behaviors?
  - Study will use the initial ATN database
    - Self-injurious behavior from ADI/ADOS
    - GI symptoms from the GI standard protocol
  - Relevance: would support more active search for GI conditions and next steps in identification

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## Summary...

- ATN: a collaboration of clinical leaders and institutions focused on improving treatment for individuals with autism
- ATN is a network of institutions which will:
  - **Establish multidisciplinary practice within established centers**
  - **Organize and record data from practice; epidemiology / efficacy**
  - **Pursue and deliver treatment based on network learning and research**
  - **Hold annual consensus conference for physician community**
  - **Publish and maintain treatment guidelines**
- [www.autismtreatmentnetwork.org](http://www.autismtreatmentnetwork.org)

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## Theory of cortical noise

1. **Catastrophic developmental events leads to "noisy" cortex**  
(genetic liabilities, environmental factors: pulsed noise, anoxia, poisons, immune?)
2. **Temporal/spatial fidelity of inputs destroyed**  
i.e., true signal is masked by background noise of brain (decreased signal:noise), causing information to arrive degraded and unpatterned
3. **Problems discriminating patterns of incoming information lead to disorganization of developing brain.**
4. **Brain remains undifferentiated, becomes unstable, hypersensitive and unable to attend appropriately.**

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