Brain Issues in Autism: More Than Development

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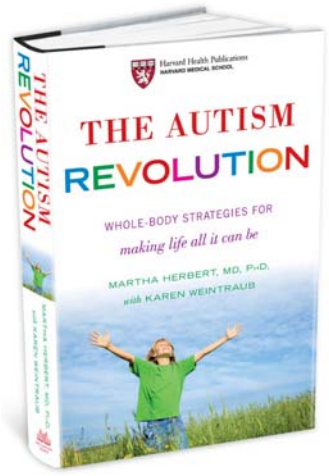
OVERVIEW

- THE BRAIN: AN INTRODUCTION
  - The brain: Why and How
  - What the brain is made of
  - How the brain works
  - Environmental influences on the brain
  - Things that can go wrong
- THE BRAIN IN AUTISM
  - The brain in autism – structure
  - The brain in autism – function
  - How we measure the brain
  - Therapies for brain problems in autism
  - HOW MUCH BETTER CAN THE BRAIN GET?
- FRONTIERS
  - Linking the fragments
  - Making a difference

I've written a book about autism –
But much in the book applies to all children, and everyone



Forthcoming book:

The Autism Revolution:
Whole Body Strategies for Making Life All It Can Be
Ballantine
Harvard Health Publications

March 27, 2012
available on Amazon for preorder

The brain, the inner world and the outer world

- The brain developed
  - To organize our inner world's activities
  - To organize how we find out what is going on around us
  - How we respond to the world
- Brain development has involved making these responses more sensitive and organized

Stages of brain evolution

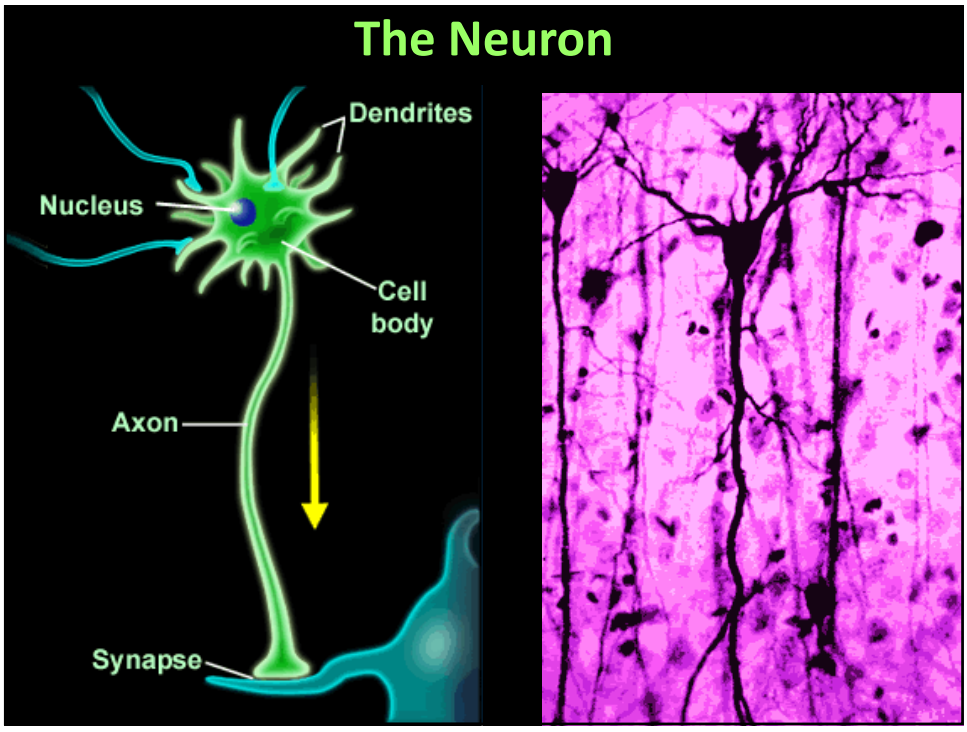
- Chemosensing
- Speeded up
  - With neurotransmission
  - Then with myelination

What the brain is made of: Structure

- More than neurons, for evolutionary reasons

Physical components of the brain

- Brain cells
  - Neurons
  - Glia
- Other basic physical parts of the brain
  - Blood vessels
  - Connective tissue
  - Cerebrospinal fluid



Neuron – Introduction

- Neurons are Core component of nervous system
- Electrically excitable:
  - process and transmit information by electrical and chemical signaling
- Types: Sensory Neuron; Motor neuron; Inter-neuron
- Do not generally undergo cell division or regenerate after injury.

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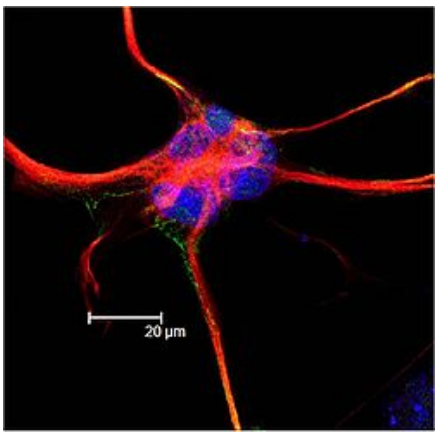
Astrocytes/Astroglial cells

- Star shaped glial cells in brain and spinal cord. ("Astro" = "star")
- Their processes envelope neuronal synapses and capillaries in brain.



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Astrocytes – Function

- Provide *Structural support* to brain.
- Form part of Blood-Brain Barrier
- Astrocyte activity is linked to blood flow to brain.
  - Contribute to neuronal regulation of blood flow.
  - Activated astrocytes get large and can compress capillaries, reducing blood flow
- Nervous system repair: ingest damaged neurons, and create scar tissue.
- Modulation of synaptic transmission and myelination
  –TRIPARTITE synapse (discussed later)

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Astrocyte modulation of neuronal metabolism

- Modulation of neuronal metabolism: *Neurons are very dependent upon astrocytes.* This kind of collaboration is efficient for the organism.
  - A form of "outsourcing" of vital functions
    - Energy
    - Ion regulation
    - Neurotransmitter regulation (especially glutamate)
    - Glutathione production

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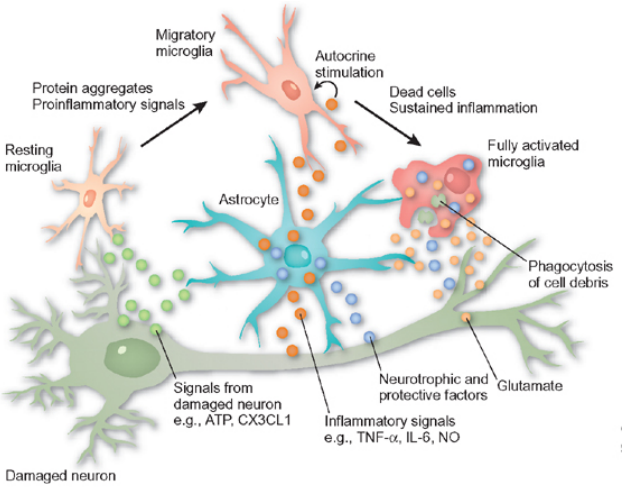
Microglial cells



Microglial cells in action – along with Astroglial cells.

Source: http://www.nature.com/nm/journal/v12/n8/fig_tab/nm0806-885_F1.html

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Microglia – Introduction

- First line of immune response in central nervous system.
- ORIGIN: originate in bone marrow from hematopoietic stem cells.
- Resident macrophages of brain and spinal cord.
- CNS is “immune privileged”, that is, blood brain barrier keep out most infections and antibodies
- Microglia are extremely sensitive to even small amount of pathological change – acting through their unique potassium channels.

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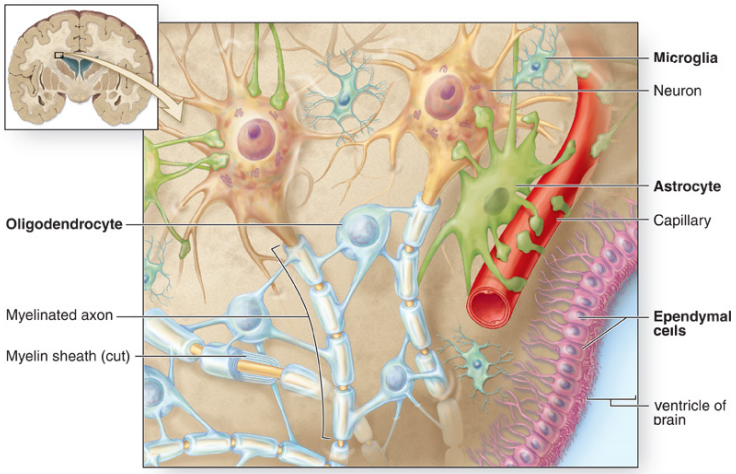
Oligodendrocytes – they make "white matter" white



Source: http://academic.kellogg.edu/herbrandsonc/bio201_mckinley/f14-6_cellular_organiza_c.jpg

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Oligodendrocyte Structure & Function

- Small round body with multiple processes.
- Main function is insulation of axons in CNS.
- Each cell can wrap its processes around 50 separate axons.
- Insulation strongly speeds signal transmission
- Oligodendrocytes contribute to regulation of signal coordination

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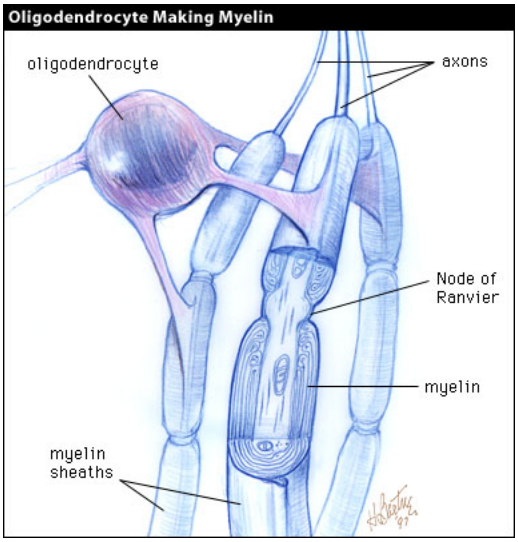
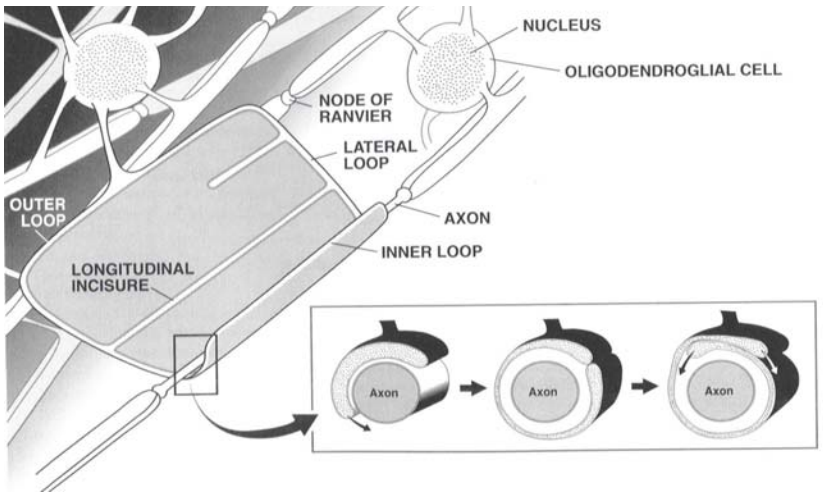
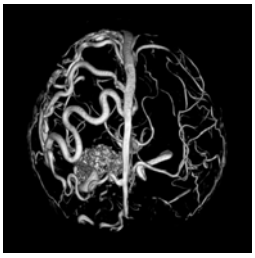
The White in White Matter: Myelin



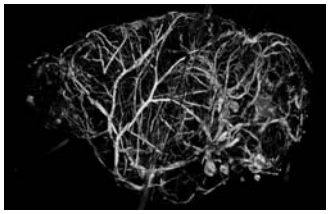
- Oligodendrocytes are glial cells in the brain that wrap around axons (the "wires" or cell processes that connect neurons with each other)
- The wrapping is "myelin," a fatty substance that is white—hence "white matter."
- Myelin insulates axons and speeds nerve conduction.
- Oligos help coordinate signals.

Myelination



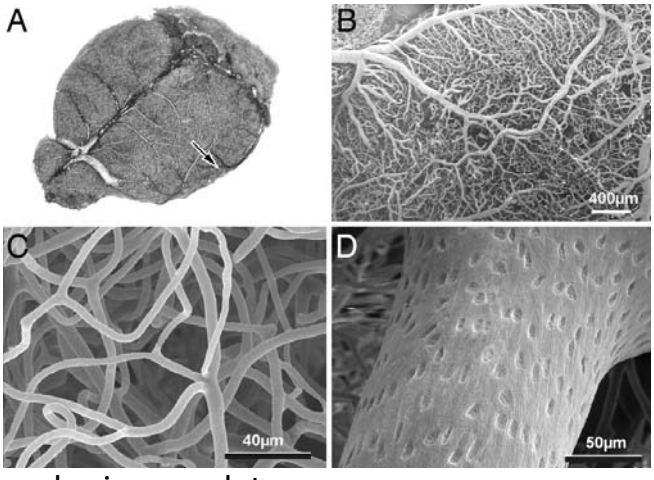


Brain blood vessels: large, medium and medium-small scales



- http://www.hitachi-medical-systems.eu/fileadmin/hitachi/onPage/at_work/ECHELON-Image2_bg.jpg
- www.jyi.org/research/re.php?id=1607
- research.cs.tamu.edu/bnl/galleryRecon.html

Brain blood vessels even smaller scales



A. Entire mouse brain vasculature.
B. Dense cortical blood vessel network.
C. Close-up of cortical capillaries.
D. Endothelial imprints on larger vessels.

www.pnas.org/content/105/9/3587/F1.expansion.html

Blood-Brain Barrier (BBB): What it is

- Barrier that separates blood from cerebrospinal fluid in the brain
- Protects the brain from things that don't belong there
- Helps maintain a stable environment for the brain
  - Stable fluid volume and electrolytes
  - Important for brain not to swell inside skull

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

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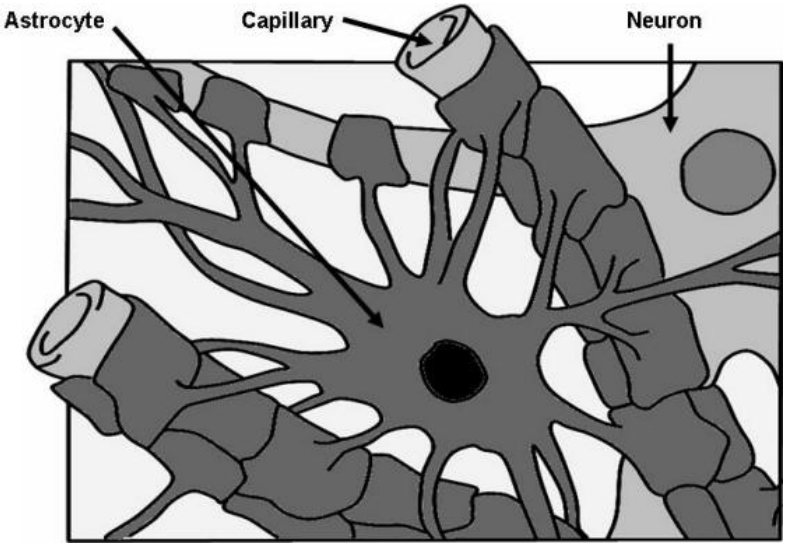
BBB Classic Image



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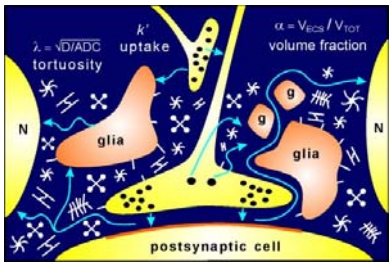
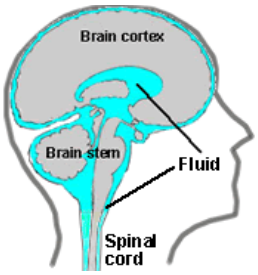
Brain "Connective tissue" – Extracellular matrix



- The "stuff" between cells
  - support structure
  - things diffuse through it and it filters (rich and complex activity)
- Previously not given much attention
- Recently getting lots of research attention
- This part of the brain plays critical roles in development and neurodegeneration
- It is also vulnerable with toxicity and with immune activation and inflammation

Cerebrospinal fluid (CSF)



- Fluid around the brain
- Bathes the brain, carries nutrients and other substances
- Carries out waste
- Interacts with the blood stream
- Its chemical composition is influenced by health and disease

What the brain does: Function

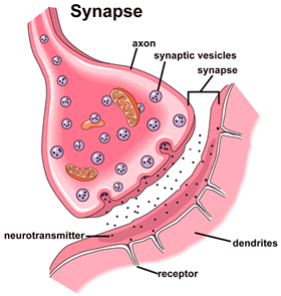
- Sensing
- Coordinating information to perceive and predict
- Responding
- Regulating

How the brain works:

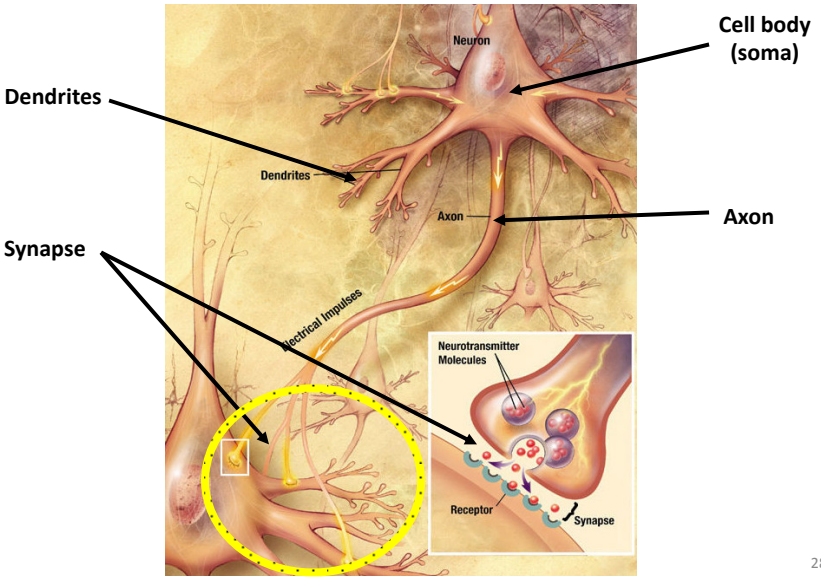
- The brain communicates and coordinates
  - Synapse – many say that autism is a “disorder at the synapse”
  - Gliotransmission
  - Oscillations
  - Networks
  - Synchronization
- Other aspects of brain regulation
  - Chemical (hormonal, metabolic, immune)
  - Electromagnetic

What is a synapse

- A **synapse** is a structure that permits a neuron to pass an electrical or chemical signal to another cell (neural or otherwise)



A NEURON connecting to another NEURON through SYNAPSE.



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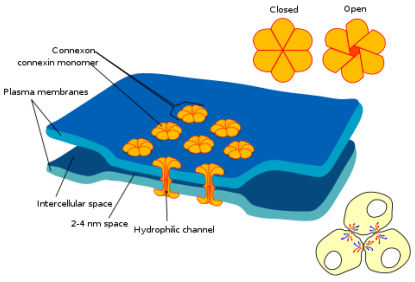
What is gliotransmission

- Glial cells play COMMUNICATION functions
- They do so in a few ways:
  - Gliotransmitters – like neurotransmitters only sent between cells by glial cells
  - Gap junctions – direct physical connections between cells that allow "calcium waves" to transmit rapidly across large areas of the brain

Gap Junctions

- 1-1.5 nm diameter
- Direct communication between cells
  - Electrical
  - Chemical
  - Small molecules
- Create a tight seal, preventing leaks
- Communicate when open, not when closed

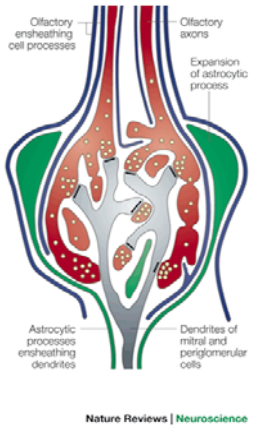


Gap junctions might become closed in association to medical problems in autism

Image Source: http://en.wikipedia.org/wiki/Gap_junction

The Tripartite Synapse: Neurons, Astrocytes and Blood Vessels working together

- Neurons and glial cells are intimately interrelated in the Tripartite Synapse
- Dysfunction in any aspect can cause alteration in function
- This abnormality can have local and widespread consequences
- *So it's not just neurons!*



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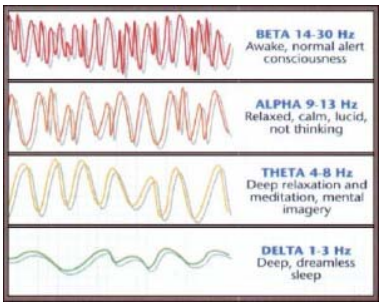
What are brain oscillations (or, "brain waves")

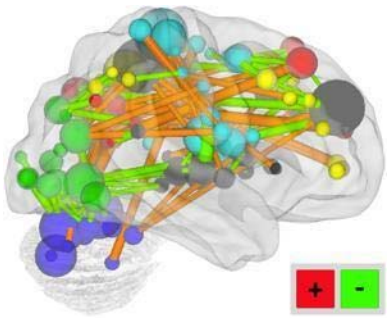
- Electrical activity in brain
- Occurs at different rates
- Different frequencies related to different levels of consciousness
- Rates relate to different kinds of neurons and other things that affect how neurons function



Delta, theta, alpha, beta
Gamma is even faster

What are brain networks

- Brain areas are linked together in networks
- These networks can be linked by pathways – bundles of nerve fibers



- *The brain regions that are important to assessing the maturity of the brain are shown as spheres, with the size of the sphere representing the region's relative importance.*
  - *Different sphere colors identify brain regions as members of different functional networks.*
- *The orange connections strengthen and the green connections weaken as the brain progresses toward adulthood.*

http://www.sciencedaily.com/releases/2010/09/100909141519.htm

What is synchronization and why is it important?

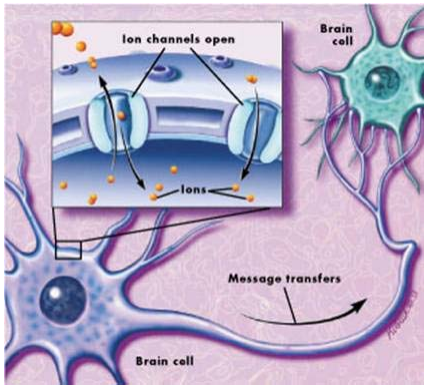
- When different parts of the brain oscillate together at the same frequencies, this gets information transferred
- Synchronization is not just a function of hardware (like neuronal cables) but also of waves that move rapidly across the brain

Environmental influences on the brain: From subcellular to larger scales

- Environment can influence the brain at many levels:
  - Ion channels
  - Receptors
  - Mitochondria
  - Membranes
  - Immune activation
  - Oxidative stress
  - Blood vessels/BBB
  - Coordination

Ion channels

- Ions (like sodium, potassium, chloride) pass in and out of cells through ion channels.
- Problems with CALCIUM CHANNELS are thought to be critical in autism



Defective/deficient GABAa Receptors in Autisms

+

Pesticides that antagonize GABAa Receptors

=

Gene *x* Environment Interaction

Increased Excitation/Inhibition Ratio

Non-Competitive GABA antagonists

Fipronil (4-alkyl-1-phenylpyrazole)

>800 tons applied in 2000

Regent®

Goliath®

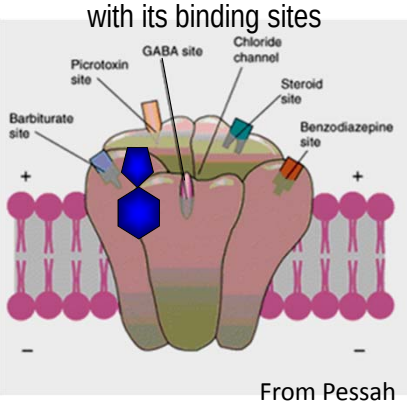
Nexa®

Adonis®

Chipco Choice®

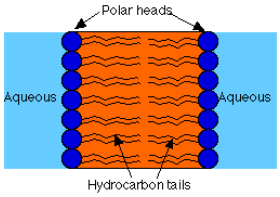
Frontline®

Schematic illustration of a $GABA_A$ receptor with its binding sites



From Pessah

Cell membranes



- All cells have membranes
- They are made of lipids
  - Inner and outer layers
- Also contain lots of proteins and carbohydrates
- They maintain cell structure and shape
- They allow different environments inside vs. outside of the cells
  - Different biochemical features
  - Different electrical charges
- Organelles inside cells also have membranes
- *Fatty acid deficiencies in diet are bad for membranes*
- *Membranes are damaged by toxicants, oxidative stress and inflammation*

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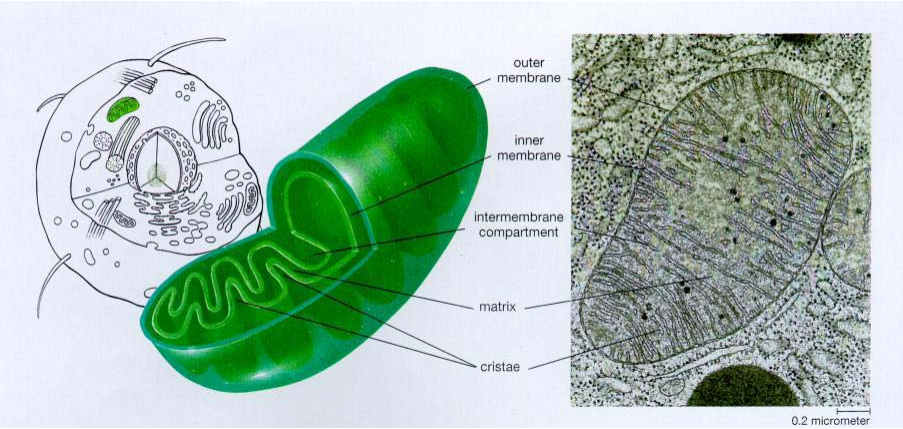
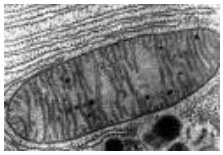
Energy and our cells: Mitochondria



MITOCHONDRIA are VERY VULNERABLE to ENVIRONMENTAL STRESSORS

Energy metabolism: Mitochondria and Brain



- Mitochondria handle energy metabolism

- NEURONS HAVE VERY HIGH ENERGY DEMANDS!
- Neurons with weaker energy metabolism will act differently
- Children with mitochondrial disorders frequently have autistic behaviors
  - Sometimes only intermittently, when they are “low-energy”

Mitochondrial vulnerability to environmental influences

- Mitochondria are highly vulnerable in:
  - Their biochemistry – toxicants and oxidative stress can interfere
  - Their membranes - membrane damage both causes and results from mitochondrial dysfunction
- Their exquisite structural and functional characteristics provide a number of primary targets for toxicant-induced bioenergetic failure

Wallace and Starkov, *Mitochondrial targets of Drug Toxicity,* Annu Rev Pharmacol Toxicol, 2000. 40:353-99

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Mitochondrial involvement in autism spectrum disorders

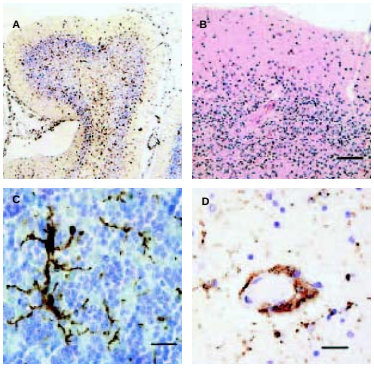
- 5-7% have diagnosable mitochondrial disease (compared with 1/10,000)
- 1 in 3 with ASD show some evidence of mitochondrial dysfunction
- Nearly 80% of those with diagnosable mitochondrial disease did not have indications of genetic abnormalities.

Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis, by Rossignol DA, Frye RE. Molecular Psychiatry, Jan 25, 2011. 42

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

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

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



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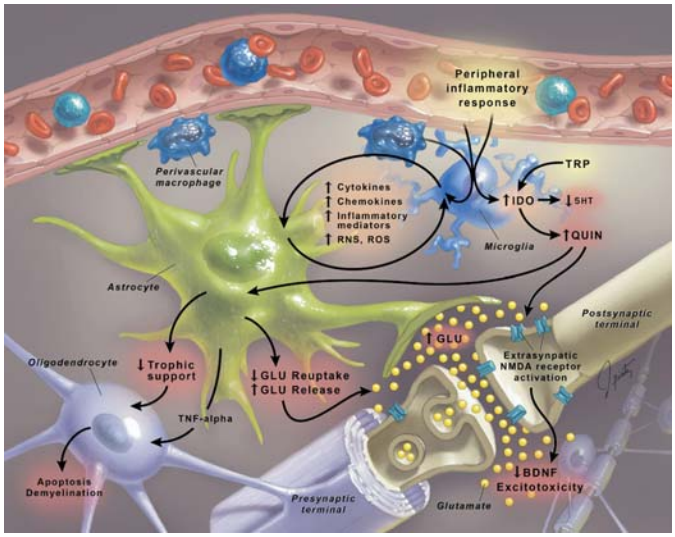
Brain cells in inflammation



Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression.
Miller et al., BIOL PSYCHIATRY 2009;65:732–741

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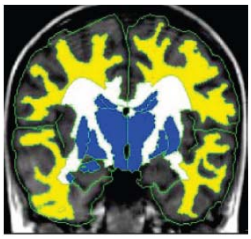
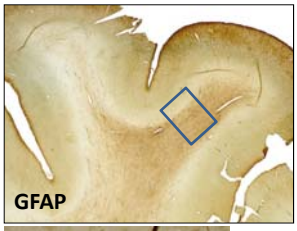
The white matter areas that are larger appear to have more inflammation.



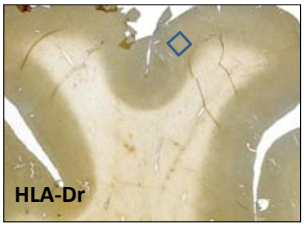
Herbert:

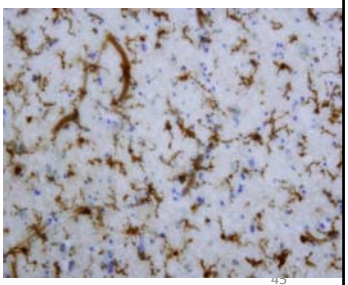
Large Brains from Radiate White Matter Enlargement

Astrogliosis



Microgliosis





Pardo

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Environment and Brain tissue vulnerability

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

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Air pollution and brain inflammation

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

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

Lilian Calderón-Garcidueñas,[1,2] Anna C. Solt,[3] Carlos Henríquez-Roldán,[4] Ricardo Torres-Jardón,[5] Bryan Nuse,[2] Lou Herritt,[2] Rafael Villarreal-Calderón,[6] Norma Osnaya,[7] Ida Stone,[2] Raquel García,[1] Diane M. Brooks,[2] Angelica González-Maciel,[1] Rafael Reynoso-Robles,[1] Ricardo Delgado-Chavez,[1] and William Reed[8]

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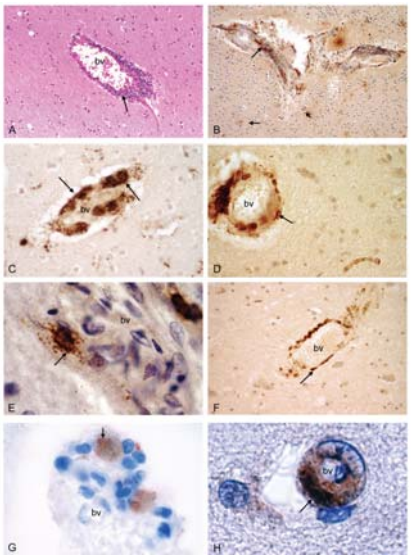
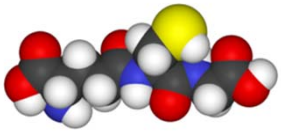
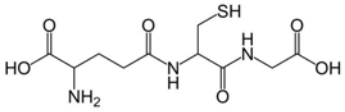


GLUTATHIONE is low in many with ASD and lots of other chronic conditions





Made of three amino acids
Glutamate
+
Cysteine
+
glycine

- **Important for protection of cells from damage**
- **Vital for detoxification**
- **The body's most potent anti-oxidant**
- ***The most abundant antioxidant in the brain***
- ***Depleted by oxidative stress, inflammation and nutrient-poor diet***

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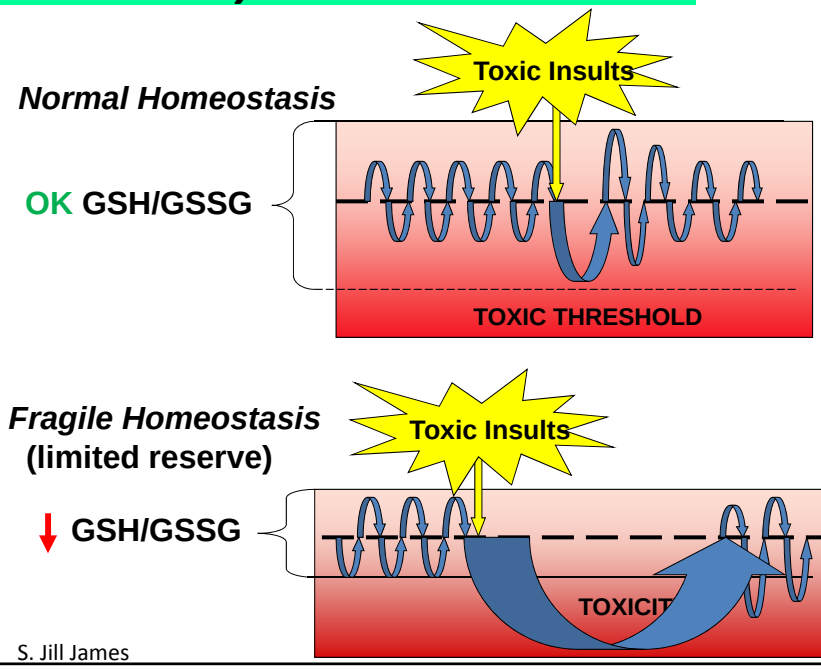
Vulnerability with low GSH



S. Jill James

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Things that can open the Blood-Brain Barrier

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

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

50

THE BRAIN IS WET!
and it's attached to the body!!!

It's not just a computer.

AND, the brain can GET PHYSICALLY ILL!

This physical illness can affect brain function.

And these brain health problems can potentially get better.

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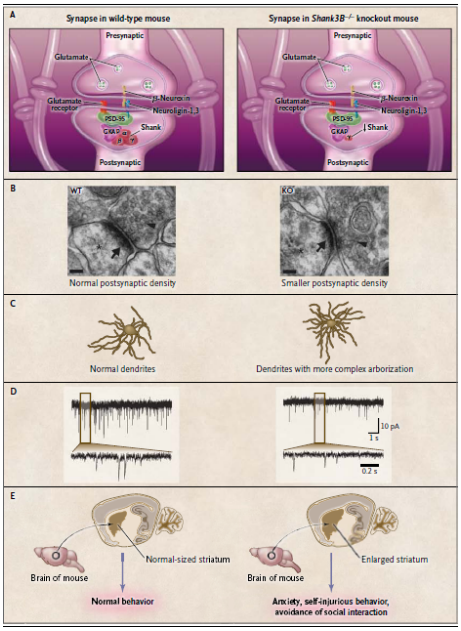
Things that go wrong
Physical problems

- Cellular mutations
- Developmental structural problems
- Diseases
- Cellular Dysfunction
  - Inflammation and oxidative stress
  - Mitochondrial dysfunction
- Infection
- Blood flow and tissue perfusion issues
- Tumors



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

Herbert *NEJM* 2011 commenting on Peça et al., *Nature* 2011

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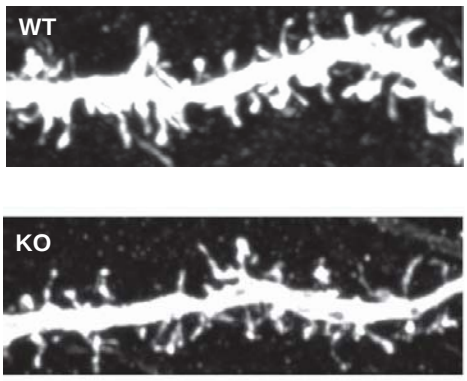
Lower dendritic spine density



- Spine density in striatal medium spiny neurons (MSNs) from *Shank3B*$^{-/-}$ mice is lower than that of wild-type MSNs

Peça et al., *Nature* 2011

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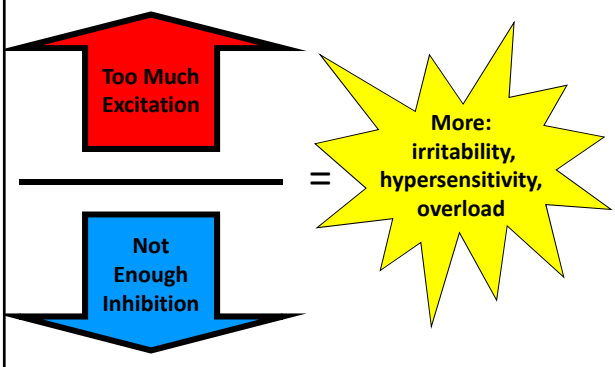
Things that can go wrong: Functional Problems

- Altered regulation of excitation/inhibition ratio
- Seizures
- Subclinical seizures
- Atypical frequencies and synchronization
  - Hypersynchronization
  - Hyposynchronization
- Altered sensory thresholds
- Disordered sleep
- Altered connectivity

Disturbed Neuronal excitation: 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

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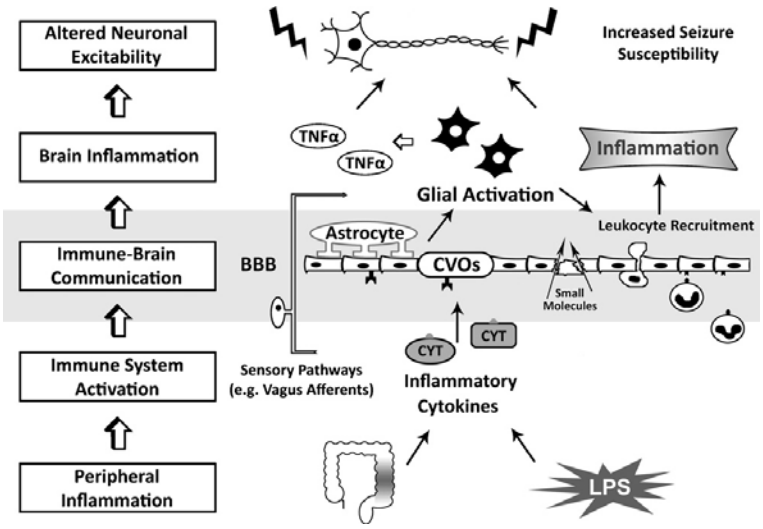
Seizures and Epilepsy

- Abnormal synchrony of brain waves
- Abnormal electrical discharges
- Many different types of seizures
- Present in 7-46% with autism
- Subclinical seizures may affect the majority with autism
- Seizures cause inflammation/oxidative stress/mitochondrial dysfunction AND VICE VERSA TOO.

Peripheral Inflammation and Neuronal Excitability



Riazi 2010, doi:10.1016/j.eplepsyres.2009.09.004

Disordered sleep

- Possible causes
  - Seizures
  - Abnormal brain waves
  - Pain
  - Gastroesophageal reflux
  - Constipation
  - Stress
  - Caffeine-containing foods and beverages
  - Lack of exercise
  - POOR SLEEP HYGIENE

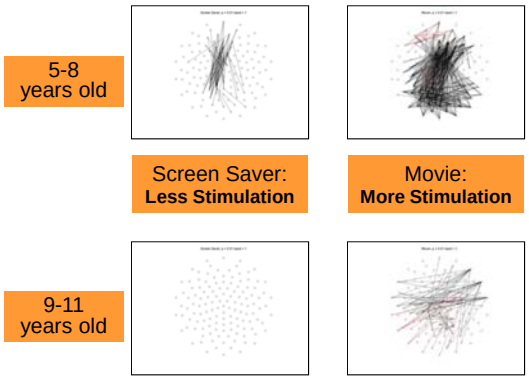
Altered brain connectivity

EEG of Sensory Responses

- Sensory stimulation can be overwhelming

➢ **Much more dysfunction when more stimulation**

➢ **Looks milder in older kids**



Martien et al. 2008

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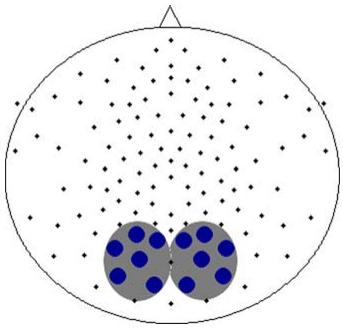
Reduced functional connectivity in visual evoked potentials in children with autism spectrum disorder

J.R. Isler, K.M. Martien, P.G. Grieve, R.I. Stark, M.R. Herbert

Clinical Neurophysiology 121 (2010) 2035–2043

EEG power and coherence within and between two 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.



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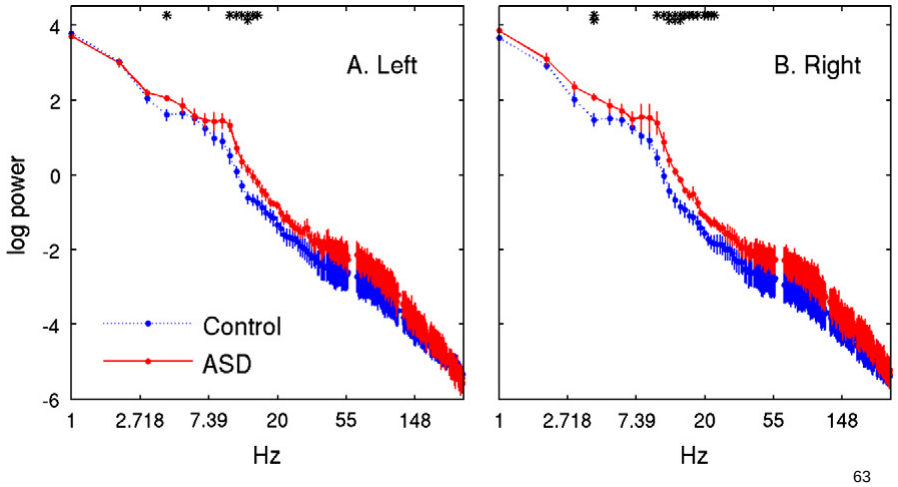
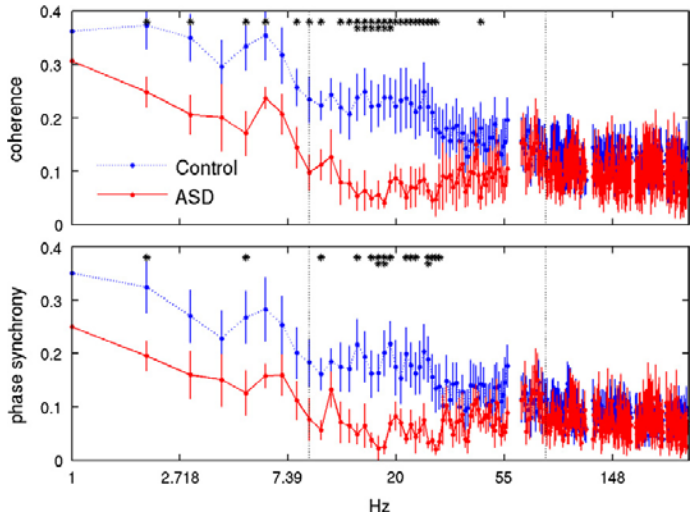
Group mean natural log power within the left (A) and right (B) ROI



63

Interhemispheric synchrony: coherence & phase synchrony



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Astrocyte neuroprotective role can change to damaging role

- Disturbed or impaired astrocyte metabolism can lead to poor support of neurons and increased excitatory input
- This can lead to
  - Excitotoxicity
  - If extreme and/or persistent, cell death

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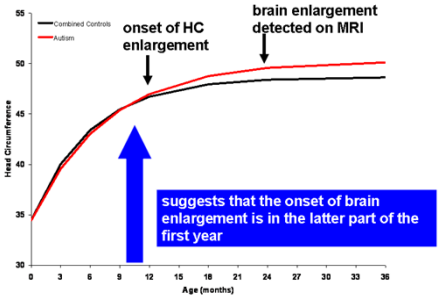
A systems challenge: Much documentation of large brains in autism

measures:
head circumference
brain weight
brain volume

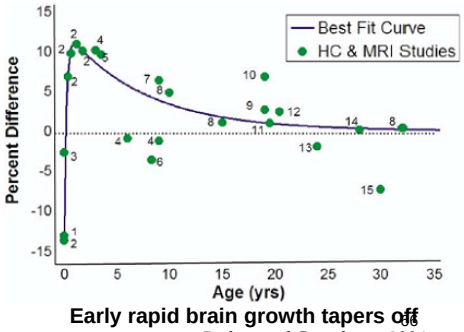


Hazlett 2005

- About 20% of young autistic heads are "macrocephalic" (>97th %ile)
- Most are above average in volume
- This is an *atypical* brain size ***distribution.***
- It occurs after birth.

Herbert, *The Neuroscientist,* October 2005

Redcay & Courchesne, 2005



Early rapid brain growth tapers off

Redcay and Courchesne 2004

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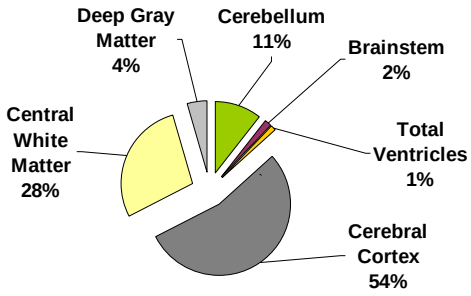
Disordered brain organization-Anatomy: Altered volumetric scaling

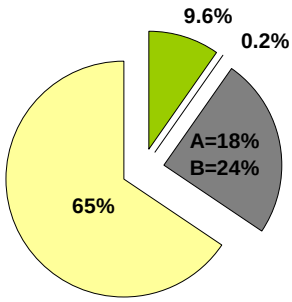
White matter accounts for the bulk of the volume increase in larger autistic brains

Key point: White matter is 28% of total brain volume, but contributes 65% of the overall volume increase.

Cerebral cortex, however, is 54% of total brain volume but contributes only 18% (group A) or 24% (group B) of the overall volume increase.



Regional proportions of total volume in control brains



Contributions to Autism Volume Increase

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Herbert et al., 2003

Larger brains and what might be their significance

- What parts of the brain get bigger?
- What is the "bigness" made of?
  - More neurons?
  - More white matter?
  - More extracellular matrix?
  - "Swelling"?
- What causes this?

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

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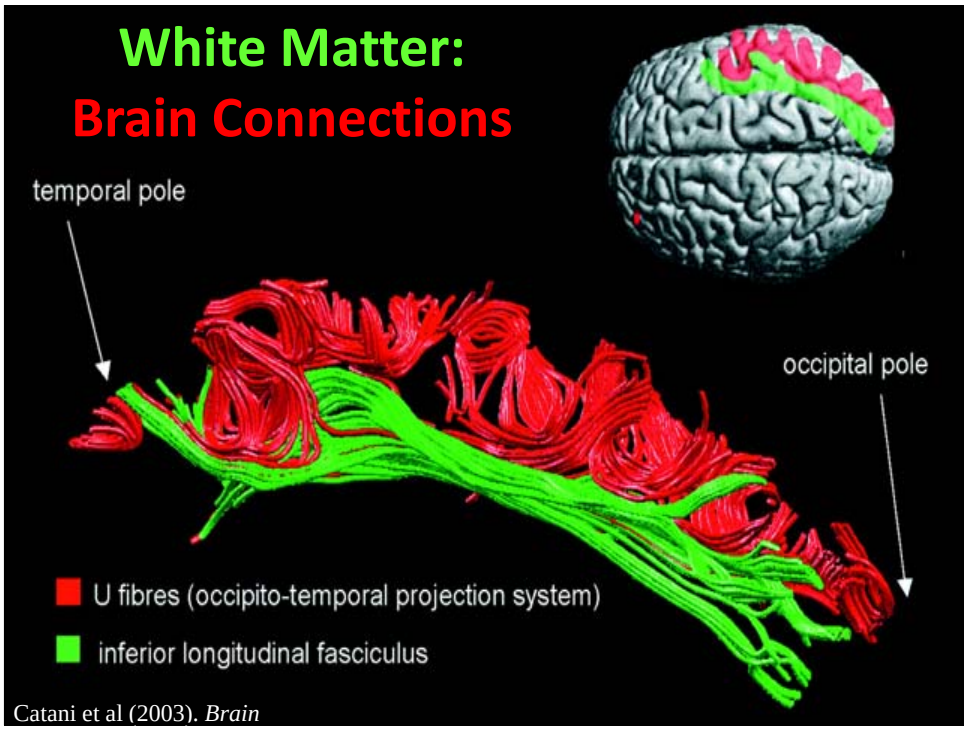
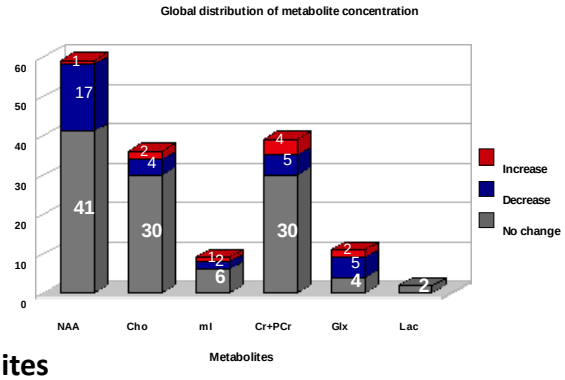


Catani et al (2003). *Brain*

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

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

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

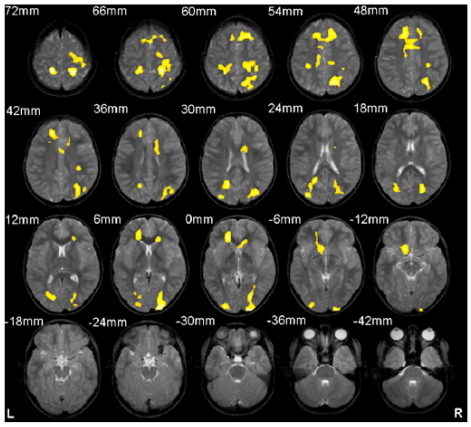


Fig. 2. Axial slices showing regions of increased T2 relaxation time in patients with autism compared to controls.

May be a reflection of altered tissue water properties

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

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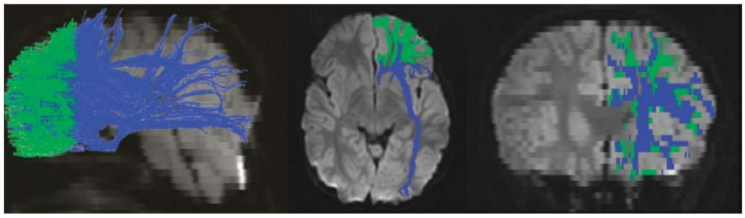
Reduced FA and Increased Diffusivity in Short-Range Fibers: Less fiber integrity, more disorganization

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



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

Sundaram et al., 2008

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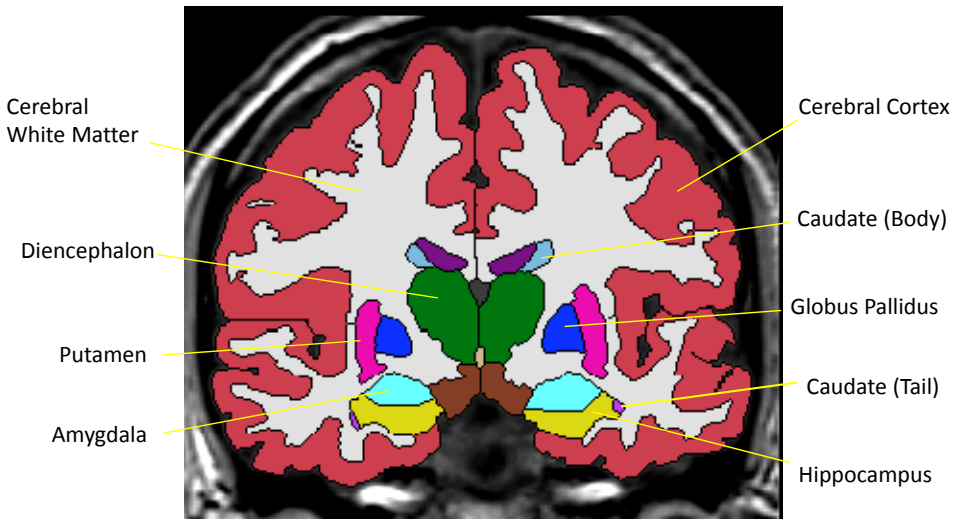
Specialized brain regions and how they may be implicated in autism

- Some examples:
  - Amygdala
  - Cerebellum
  - Fusiform face area
  - Anterior Cingulate
  - White matter

Major Brain Structures



Amygdala

- Associated with emotional processing, particularly fear
- Implicated in many studies
- Does not cause the full gamut of autism symptoms

Cerebellum

- Important for coordinating motor activities
- Also important for coordinating many other activities – like the pitch of your voice as you speak (prosody)
- Found abnormal in a variety of studies, not always in the same way

Anterior cingulate

- Important for judgment
- Connects to the autonomic nervous system which regulates bodily functions
- Implicated in many psychiatric conditions

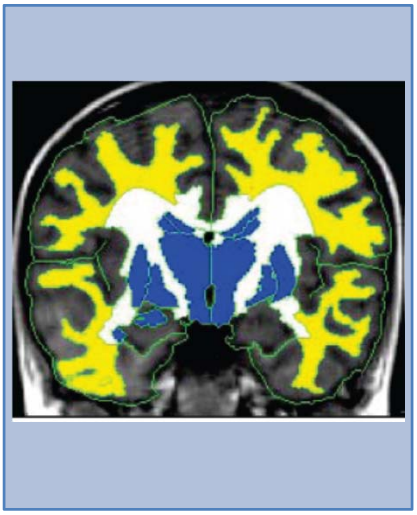
White matter

- Found to be larger in early to mid childhood in autism, smaller in teen and adult years
- Debate about what causes white matter enlargement
  - Genes (e.g. PTEN)
  - More cells and axons
  - Swelling - inflammation

Some characteristics of large brains in autism

Disproportionate increase of white matter

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



Herbert M. 2003, 2004, 2005

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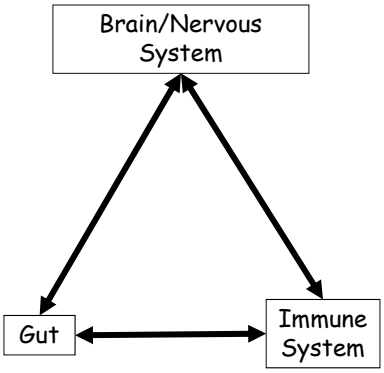
Distributed Mechanisms: Mechanisms Without Borders



GUT ⇒ BRAIN: Vagus afferents; Gut neuropeptides
BRAIN ⇒ GUT: Endorphins; Neuropeptides

IMMUNE ⇒ BRAIN: Cytokines; microglia activation
BRAIN ⇒ IMMUNE: Endorphins; Neuropeptides; Cortisol

IMMUNE ⇒ GUT: Cytokines; GALT
GUT ⇒ IMMUNE: Gut neuropeptides; microbial products

Kahler/James/Herbert

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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.

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Brain region differences: Downstream, causal or both?

- Are altered brain regions directly and primarily the cause of altered behavior?
- Or are they manifestations of other physical problems in the brain?
- Or both?

- What causes the alterations in these brain regions?
  - Some combination of
    - Genes
    - Environment and experience

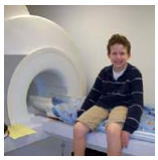
How we measure brain in living people

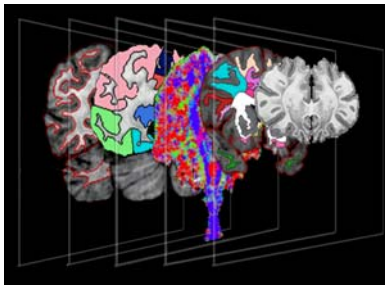
- Issues
  - Generally can't be invasive (no biopsy!)
  - Structural resolution
  - Temporal resolution
  - Sensitivity to materials

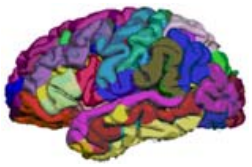
Brain imaging measures

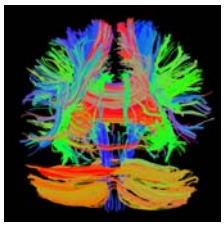
- MRI - structural
  - Volume – how big is it?
  - DTI –structure and "integrity" of white matter fibers
  - Contrast – leaky blood vessels? Are there too many vessels?
- MRI – measures of function
  - MRS – measures quantities of chemical metabolites
  - ASL (arterial spin labeling – measures blood flow)
  - fMRI (functional MRI – shows location of brain activation)
- EEG/MEG
  - Temporal sensitivity – measures things that happen in microseconds
- SPECT – measures activity
- PET – measures activity
- Multimodal: several approaches in same person

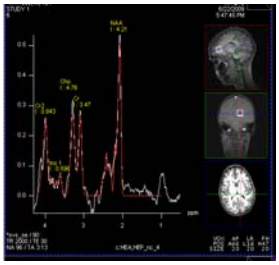
MRI: Brain Structure, Wiring and Chemistry



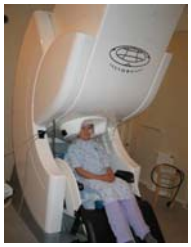


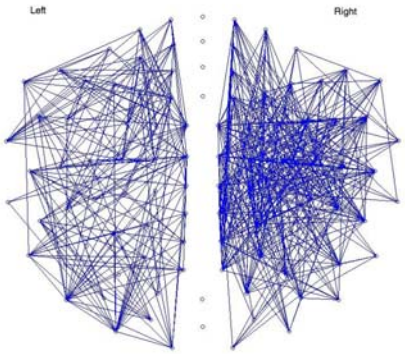






EEG and MEG: Brain Signaling Networks





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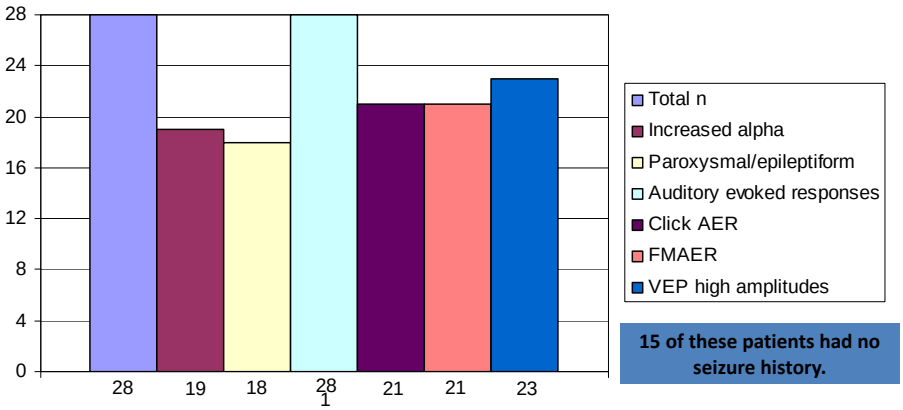
Autism Electrophysiological Abnormalities something in everyone, much in some

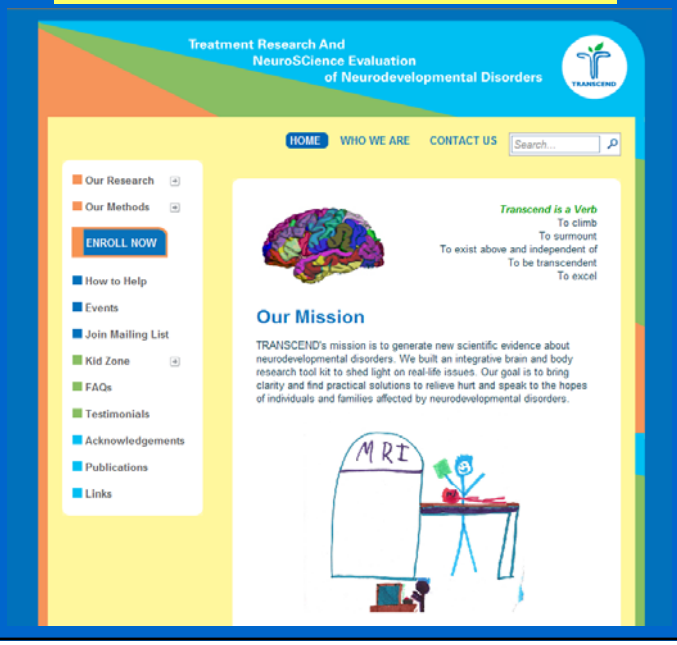


15 of these patients had no seizure history.

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

Martien & Duffy

www.transcendresearch.org



Therapies for the brain

- Medical
  - Anti-epileptic medications
  - Psychopharmacology
  - Nutrition and diet
    - Correction of metabolic deficits or excesses
- Functional
  - Behavioral interventions
  - Sensory integration
  - Neuromotor training
  - Neurofeedback
  - Stress Management
  - Exercise
  - More

Anti-epileptic medications

- Require strict medical supervision
- Alter seizure activity often by working with ion channels, receptors and/or neurotransmitters or glial cells
- Problems
  - Side effects common
  - May deplete certain nutrients such as carnitine or folic acid (depends on which drug)
  - Not possible to fully predict which will work or to test ahead of time

Psychopharmacology

- Aims to improve behaviors and decrease suffering through
  - Addressing neurotransmitter levels or synthesis
  - And/or addressing receptors and/or ion channels
  - Affecting neuronal cell function
- Problems:
  - Will not correct underlying metabolic or nutritional problems
  - Side effects fairly common
  - Not possible to fully predict which will work or to test ahead of time

Nutrition and Diet

- Aims to fortify
- Aims to correct metabolic and nutritional problems that may be interfering with biochemical function in the cells
- Problems
  - Testing is somewhat useful but inherently imprecise (people vary from day to day, while sick, etc)
  - Evidence strong physiologically, but weaker regarding clinical trials
    - Harder to test
      - Because controlling food is complicated
      - Because very expensive and hard to fund research –
      - Because can't be patented

Problems with food

- Nutrient-poor
  - Processing removes more than it puts back
  - Low-nutrient chemical fertilizers
  - Mineral-depleted soil
- Wrong stuff
  - Additives, pesticides
  - Imbalances, e.g. too much omega-6 and not enough omega-3

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High nutrient density is best

$$\text{Health} = \frac{\text{Nutrients}}{\text{Calories}}$$

(H=N/C)
That is, more nutrients per calorie

vs.
Junk food = low nutrients per calorie
= sickness

Fuhrman as well as others

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Environmental factors that may reduce risk

- Prenatal vitamins and One-Carbon Metabolism Gene Variants
  - Mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy (OR = 0.62 [95% confidence interval = 0.42-0.93]).
  - Significant interaction effects were observed for maternal MTHFR 677 TT, CBS rs234715 GT + TT, and child COMT 472 AA genotypes, with greater risk for autism when mothers did not report taking prenatal vitamins periconceptionally (4.5 [1.4-14.6]; 2.6 [1.2-5.4]; and 7.2 [2.3-22.4], respectively)

Schmidt et al., *Epidemiology,* 2011

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Brain change

- Regression
- Improvement
- Remission/recovery

Neuropsychol Rev
DOI 10.1007/s11065-008-9075-9

Can Children with Autism Recover? If So, How?

Molly Helt · Elizabeth Kelley · Marcel Kinsbourne · Juhi Pandey · Hilary Boorstein · Martha Herbert · Deborah Fein

Received: 2 September 2008 / Accepted: 11 September 2008

Abstract Although Autism Spectrum Disorders (ASD) are generally assumed to be lifelong, we review evidence that between 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills. Predictors of recovery include relatively high intelligence, receptive language, verbal and motor imitation, and motor development, but not overall symptom severity. Earlier age of diagnosis and treatment, and a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified are also favorable signs. The presence of seizures, mental retardation and genetic syndromes are unfavorable signs, whereas head growth does not predict outcome. Controlled studies that report the most recovery came about after the use of behavioral techniques. Residual vulnerabilities affect higher-order communication and attention. Tics, depression and phobias are frequent residual co-morbidities after recovery. Possible mechanisms of recovery include: normalizing input by forcing attention outward or enriching the environment; promoting the reinforcement value of social stimuli; preventing interfering behaviors; mass practice of weak skills; reducing stress and stabilizing arousal. Improving nutrition and sleep quality is non-specifically beneficial.

Keywords Autism spectrum disorders · Language development · Recovery · Stereotyped motor behavior

Introduction

Autism Spectrum Disorders (ASD) are a group of related developmental disorders that are characterized by impair-

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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

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Reversal in Mouse Models

PNAS

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

Mansuo L. Hayashi*†, B. S. Shankaranarayana Rao‡, Jin-Soo Seo§, Han-Saem Choi§, Bridget M. Dolan*, Se-Young Choi§, Sumantra Chattarji¶, and Susumu Tonegawa*||

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Contributed by Susumu Tonegawa, May 29, 2007 (sent for review May 21, 2007)

Fragile X syndrome (FXS), the most commonly inherited form of mental retardation and autism, is caused by transcriptional silencing of the *fragile X mental retardation 1 (FMR1)* gene and conse-

ticity at glutamatergic synapses, such as long-term potentiation (LTP) in the cortex and long-term depression in the hippocampus, is abnormal in *FMR1* KO mice (11–13).

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Jacky Guy,[1] Jian Gan,[2] Jim Selfridge,[1] Stuart Cobb,[2] Adrian Bird[1*]

Rett syndrome is an autism spectrum disorder caused by mosaic expression of mutant copies of the X-linked *MECP2* gene in neurons. However, neurons do not die, which suggests that this is

Reversal of learning deficits in a $Tsc2^{+/-}$ mouse model of tuberous sclerosis

Dan Ehninger[1], Sangyeul Han[2], Carrie Shilyansky[1], Yu Zhou[1], Weidong Li[1], David J Kwiatkowski[3], Vijaya Ramesh[2] & Alcino J Silva[1]

om/naturemedicine

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Short-term immune triggers cause long-term brain inflammation

- *TNF-α* increases are triggered by bacterial and other exposures.
  - In the bloodstream this increase lasts 9 hours
  - In the liver it lasts 1 week
  - ➢ IN THE BRAIN IT LASTS 10 MONTHS!!!

This means that someone who gets exposed to a trigger of TNF-α every now and then could look like they have a chronic and untreatable brain problem.

Qin, *GLIA, 2007*

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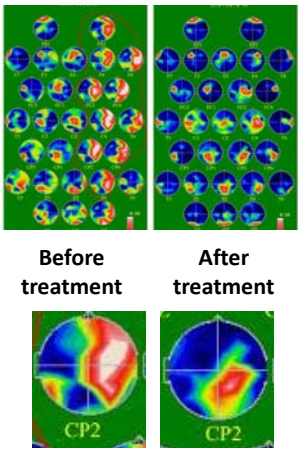
Improvement in brain function after treatment



Example:

- **Depakote was given for spike-waves during sleep that did not meet criteria for CSWS** (continuous spike-wave during sleep)
- **Substantial improvement resulted in speech and cognition**
- **Treatment of subclinical seizures is not standard practice**
- **Standard brain tests don't track change like this**

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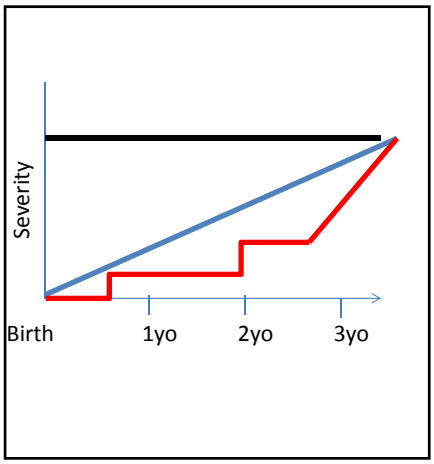
The BRAIN PLASTICITY Revolution

- ***The Brain that Changes Itself*** by Norman Doidge
- ***Kids Beyond Limits*** by Anat Baniel
- Michael Merzenich
- More and more others

Features of change we need to understand to help better

Regression



Improvement

- Do systems improve all together?
- Or some before others (e.g. gut before immune?)
- Is it different for some than others?
- How can we predict this and use it to figure out the best approach for each individual?

Hypothesis: Early correction or avoidance of abnormalities can be preventive.

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Testing the model: Studying brain change

- If autism develops over the first year or two of life rather than being present from birth this challenges the "it's all prenatal development" assumption
- If brain changes can be reversed through environmental/medical intervention this challenges the hard-wired assumption

HYPOTHESIS:

For at least many, "autism" involves "obstruction" of capacities rather than "impairment" or lack of capacities.

Frontiers

- Integrating the fragments
  - Connecting
    - Structure with function
    - Behavior with brain
    - Metabolic and immune dysfunction with with brain wave problems
  - Applying research in clinic
- Documenting brain change from interventions and improvement

Summary: Key Points

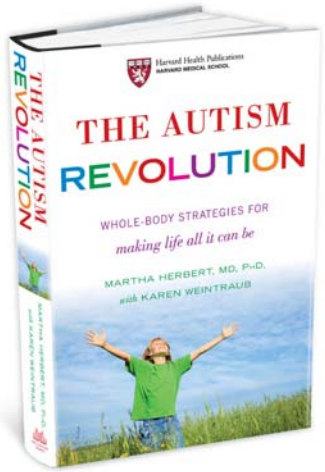
- The brain organizes how we learn about and respond to the environment
- All scales from molecules to cells to tissues to whole brain and body interact all the time
- Many brain problems have environmental contributors
- There is a lot you can do about the environmental contributors
- Remove interference and optimize learning to achieve resilience and maximal potential

Forthcoming book:

The Autism Revolution:

Whole Body Strategies for Making Life All It Can Be

Ballantine – Harvard Health Publications – March 27, 2012
Available on Amazon for preorder



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Forthcoming website
www.autismwhyandhow.org