Glial Cells – "The Other Brain" that the Neurons can't live without

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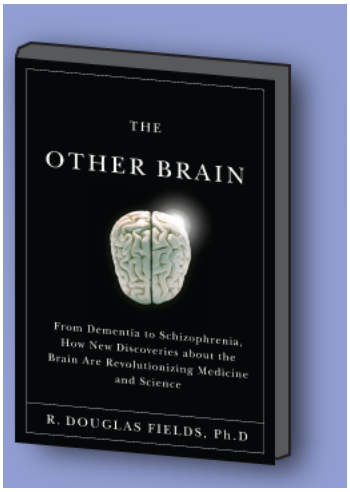
It's not just neurons up there

In order to understand the impact of biomedical approaches on autism, we need to understand the physical and physiological aspects of the brain

– and in particular, the roles of glial cells in the brain (and gut too!)

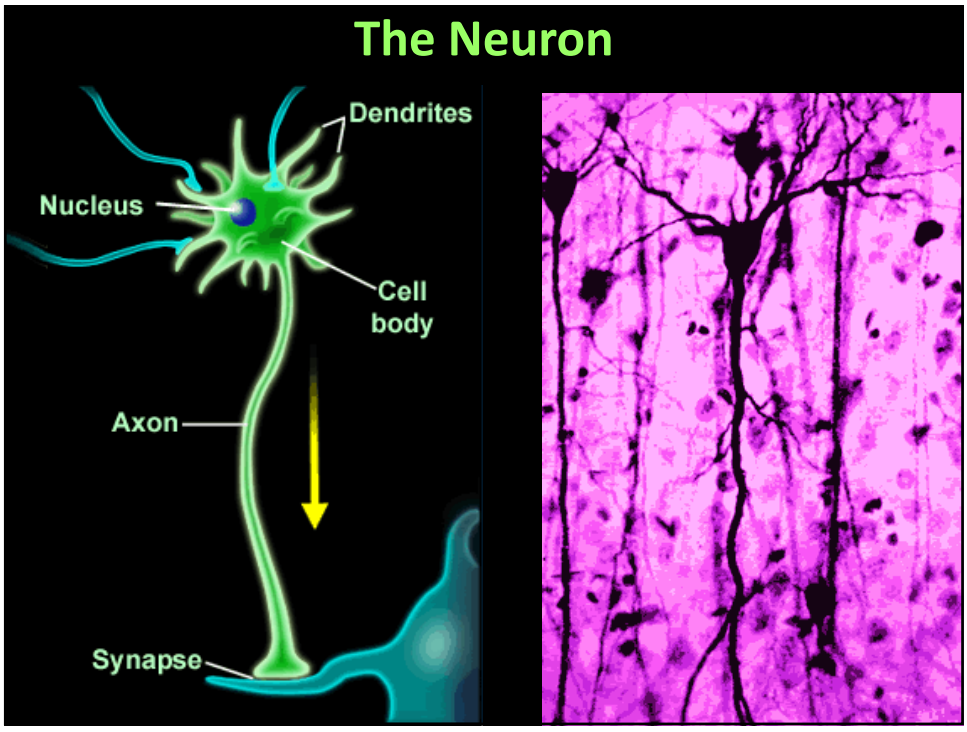
THE OTHER BRAIN
by Douglas Fields, PhD, NIH scientist



ABOUT GLIAL CELLS WHICH GREATLY OUTNUMBER NEURONS IN THE BRAIN AND GUT

A readable book about the non-neuron cells in the brain and how they are revolutionizing medicine

www.theotherbrainbook.com



Neuron – Introduction

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

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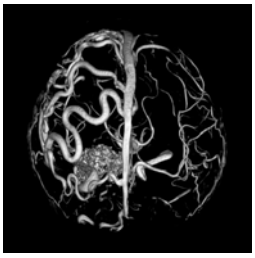
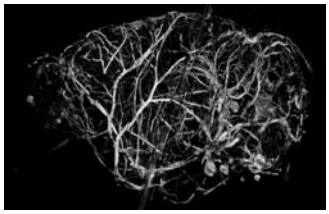
OTHER PARTS OF THE BRAIN THE NEURONS CAN'T LIVE WITHOUT

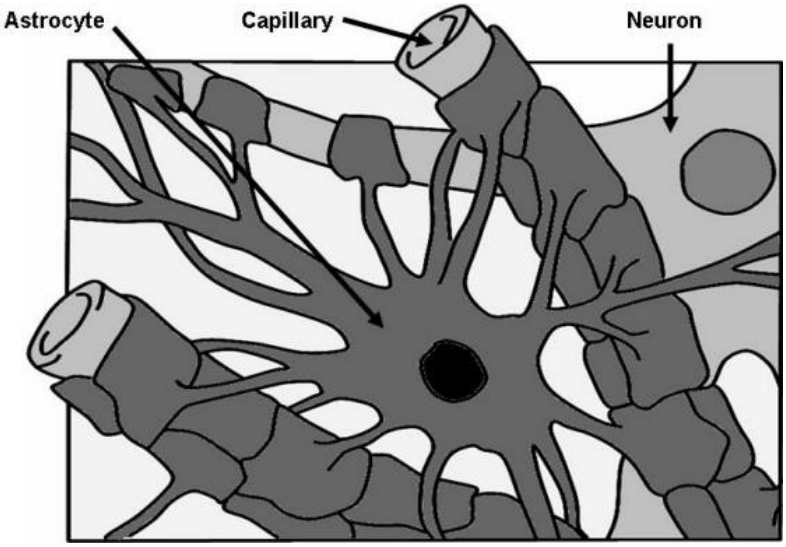


Brain blood vessels: large, medium and medium-small scales



- 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

BBB Classic Image



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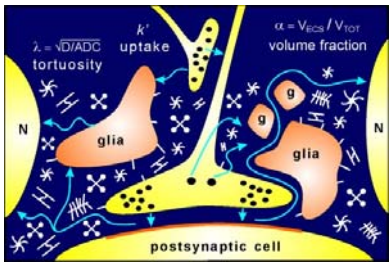
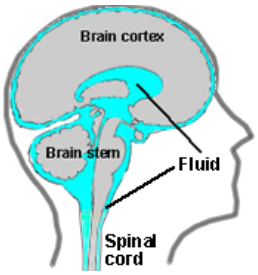
Brain "Connective tissue" – Extracellular matrix



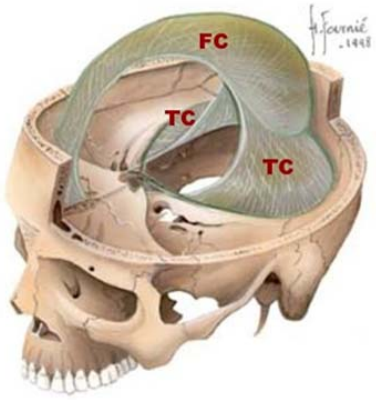
- The "stuff" between cells
  - support structure
  - things diffuse through it and it filters (rich and complex activity)
- Previously not given much attention
- Recently getting lots of research attention
- This part of the brain plays critical roles in development and neurodegeneration
- It is also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

Cerebrospinal fluid (CSF)

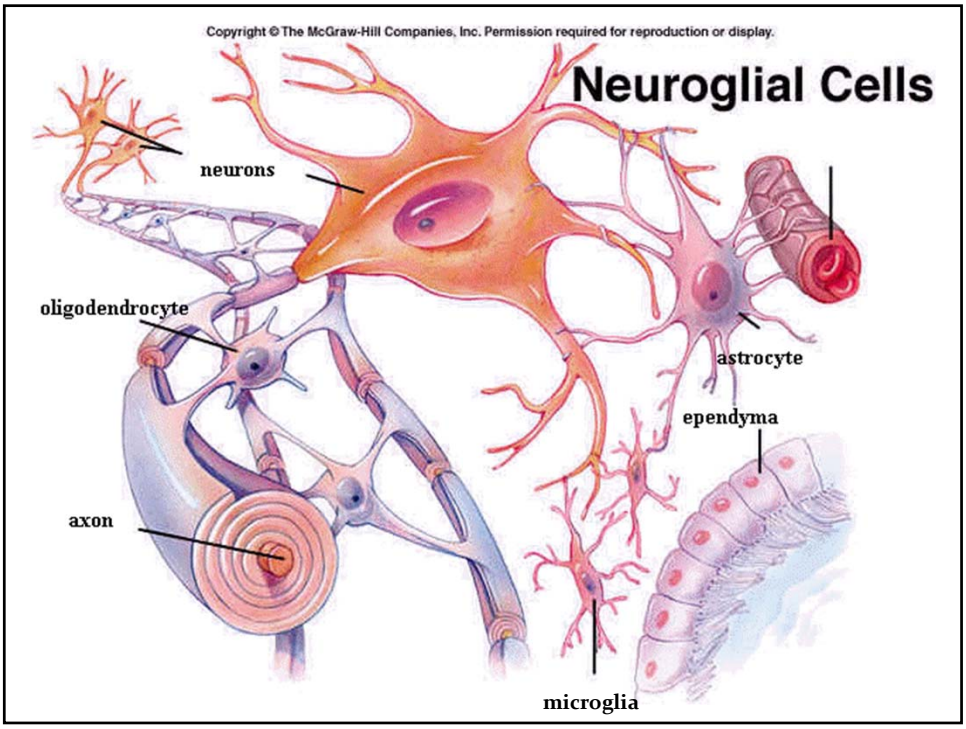


- Fluid around the brain
- Bathes the brain, carries nutrients and other substances
- Carries out waste
- Interacts with the blood stream
- Its chemical composition is influenced by health and disease

Skull and membranes



- The external structures of the brain are vulnerable to strains and torques, especially in childbirth
- Cranial osteopathy has contributed greatly in understanding this

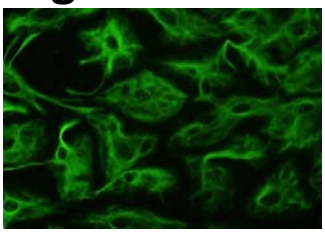


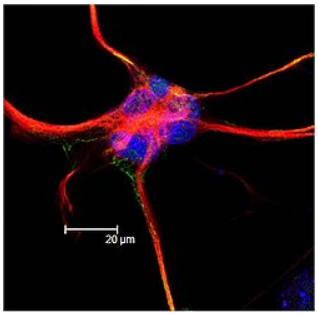
Types of Glial Cells

- Astrocytes
- Oligodendrocytes
- Ependymal Cells
- Radial Glia
- Schwann Cells
- Satellite Cells
- Enteric Glial Cells

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 conspire with neurons during progression of neurological disease

James C McGann, Daniel T Lioy and Gail Mandel, Current Opinion in Neurobiology 2012, 22:1–9

As astrocytes are becoming recognized as important mediators of normal brain function, studies into their roles in neurological disease have gained significance. Across mouse models for neurodevelopmental and neurodegenerative diseases, astrocytes are considered key regulators of disease progression. In Rett syndrome and Parkinson's disease, astrocytes can even initiate certain disease phenotypes. Numerous potential mechanisms have been offered to explain these results, but research into the functions of astrocytes in disease is just beginning. Crucially, in vivo verification of in vitro data is still necessary, as well as a deeper understanding of the complex and relatively unexplored interactions between astrocytes, oligodendrocytes, microglia, and neurons.

Types of astrocytes/astroglial cells

- Fibrous
  - Within white matter,
    - Few organelles, long un-branched cellular processes
  - Vascular feet connecting to outside of capillary walls
- Protoplasmic
  - Most prevalent, found in gray matter
    - Many organelles
    - Short and highly branched tertiary processes
- Radial
  - Perpendicular to cortex and ventricles
    - Guide-wires for migration of neurons during development
    - Persist in cerebellum

Astrocytes – Structural Contributions

- STRUCTURE
  - Provide *Structural support* to brain.
  - Closely associated with neuronal synapses
  - Cover surfaces of dendrites, cell bodies
  - Contribute to *glia limitans* in outer surface of brain and spinal cord
  - Nervous system repair: ingest damaged neurons, and create scar tissue.
  - Support myelination of oligodendrocytes

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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.
- Modulation of synaptic transmission and myelination
  - TRIPARTITE synapse (discussed later)
  - A form of "outsourcing" of vital functions
    - Energy
    - Ion regulation
    - Neurotransmitter regulation (especially glutamate)
    - Glutathione production

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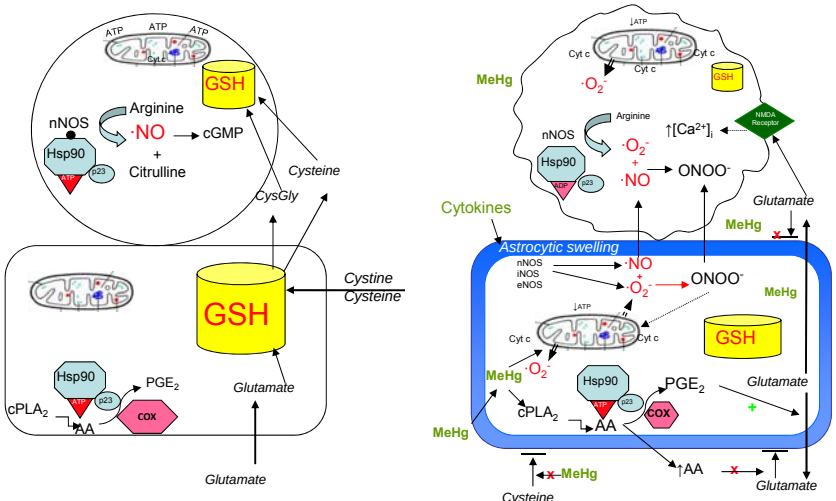
Cartoon Illustrating the Alterations in Cell Signaling that Mediate MeHg-induced Neurotoxicity

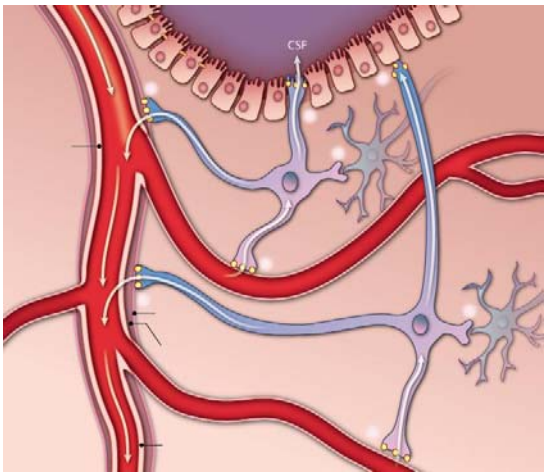


M. Aschner (see Aschner 1999)

Astrocytes as trash collectors

- Toxicants accumulate in astrocytes until they can't take any more which contributes to astrocyte dysfunction
- Example: Manganese: - inhibits ability of astrocytes to promote neuronal differentiation
  - Giordano, G., D. Pizzurro, et al. (2009).
- They also dump garbage into the circulation
  - See next slide

Astrocytes facilitate CSF flow and help clear solutes



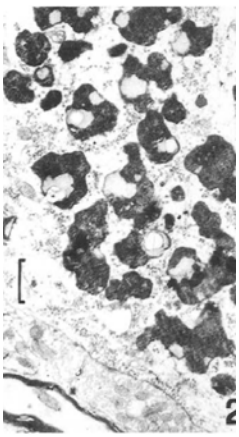
In the brain microcirculation, both astrocytes and tanycytes have long processes that run through the brain tissue and connect the cells with other structures. The tanycytes and astrocytes form endfeet (a) that are applied closely to the microvasculature that forms the BBB and express AQP4 adjacent to the endothelial basement membrane (basal lamina). The cells also bear processes that connect the cells with other brain structures. These processes may either interdigitate with the ependymal cells (c) that line the brain ventricles and directly contact the CSF (b) or may abut the ependymal cells and extend to the pial surface of the brain, which faces the subarachnoid CSF space (d). Other processes also terminate at neuronal cell bodies (e). The ependymal epithelium that covers the choroid plexuses across which CSF is secreted has tight junctions between the cells (f), as do the endothelial cells that form the BBB. Possible directions for water fl ow though the cells are indicated by the arrows.

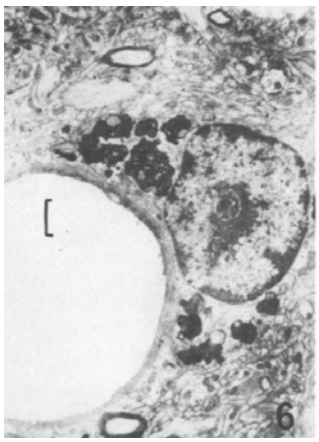
Begley, DG, Brain Superhighways, Science translational Medicine 4:147

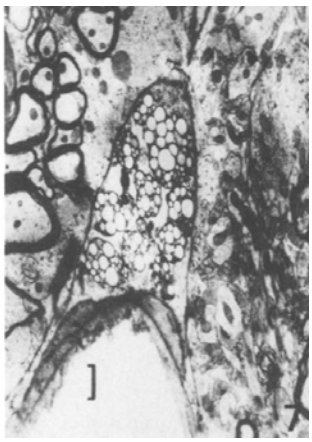
J. J. Iliff et al., A paravascular pathway facilitates CSF fl ow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci. Transl. Med. **4**, 147ra111 (2012).

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

RIGA, S. et al., *Ann. N.Y. Acad. Sci.* 1067: 383–387 (2006)
RIGA, S. et al., *Arch. Gerontol. Geriatr.* suppl. 4 (1994) 227-234







Astrocytes: Blood flow and Barrier functions

- 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
  - Contribute to Blood-Brain Barrier

Astrocytes – Energy Metabolism

- METABOLISM
  - Glycogen fuel reserve
  - Provide neurons with nutrients
    - Lactate, Glutathione
  - Help regulate extracellular ion concentrations

Astrocytes and the Extra-Cellular Matrix

- Astrocytes play key role in organizing the extracellular matrix
  - Particularly the “perineuronal nets”, which help regulate the sprouting and pruning of synapses
    - These are important in brain plasticity after early brain development

Astrocytes and Neurotransmission

- NEUROTRANSMISSION
  - Membranes contain neurotransmitter receptors
    - Glutamate receptors on astrocytes and oligodendrocytes inform these cells about rates of firing of glutamate neurons
  - Modulation of synaptic transmission
  - Glial cells can speed up or slow the rate of synaptic transmission in different areas at different rates, contributing to brain integration

Astrocytes and Modulation of Excitation/Inhibition

- MODULATION OF EXCITATION – GLUTAMATE
  - Astrocyte filopodia absorb synaptic glutamate and end neurotransmission
    - glutamate-induced filopodia motility is mediated by mGluRs 3 and 5
    - Under stress these filopodia are withdrawn and excess excitatory firing ensues
    - Reichenbach, A., A. Derouiche, et al. (2010). "Morphology and dynamics of perisynaptic glia." Brain Res Rev **63**(1-2): 11-25
- MODULATION OF INHIBITION – GABA
  - Astrocytes can take up GABA, increasing neuronal firing rate
  - Astrocytes can release D-serine, causing GABA release and decrease of neuronal firing rate

Astrocytes and Analogic Communication

- Chemical as well as electrical transmission is important in the brain
  - "Extrasynaptic transmission: extracellular diffusion of transmitters and modulators – short distance form of Volume Transmission Fuxe, K. et al. (2012)
- Waves of Calcium
- Waves of ATP
- Gap junctions
- Autocrine and/or paracrine signalling can occur from glio- or neuro-transmitters in extracellular space
  Verkhratsky, A. et al. (2012)

Astrocytes, Integration, Information

- http://scienceblogs.com/neurophilosophy/2008/06/20/astrocytes-starring-role-in-the-brain/

More on Astrocytes and communication through gap junctions

- Large numbers of astrocytes are physically linked to one another through gap junctions,
  - This creates an electrically coupled "syncytium."
- Increase in intra-cellular calcium levels propagate through this syncytium (gap junctions), using a combination of IP3 and ATP signaling.
- This increase of intra-cellular calcium is a primary mechanism of astrocyte activation.

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Gap Junctions

- 1-1.5 nm diameter
- Direct communication between cells
  - Electrical
  - Chemical
  - Small molecules
- Create a tight seal, preventing leaks

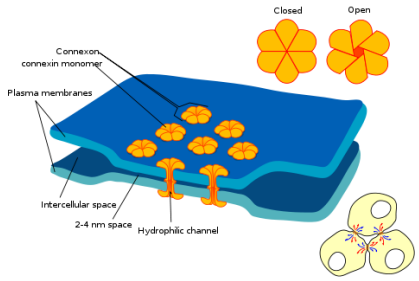

Image Source: http://en.wikipedia.org/wiki/Gap_junction

Factors that can open or close gap junctions

- Prolonged increased H+ ions concentration (acidity)
- Prolonged increased exposure to Ca2+ ions
- Closed gap junctions may greatly impede optimal brain connectivity

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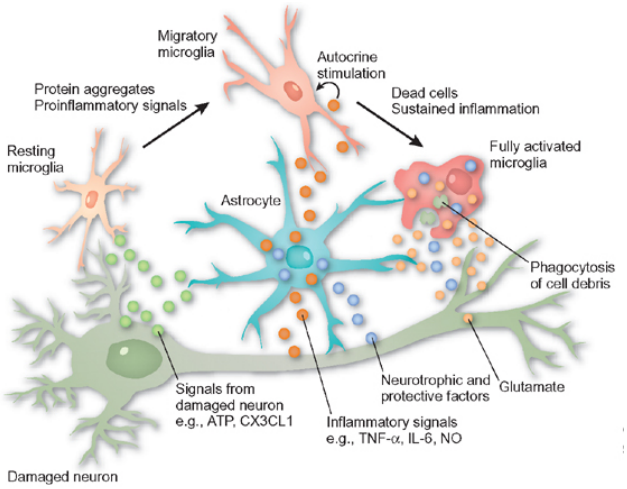
Astrocytes: Their Plasticity

- Astrocytes in the brain are highly mobile
- They also display structural plasticity
  - Then can undergo morphological changes *IN A MATTER OF MINUTES* (Theodosis et al., 2008)
  - This alters the extracellular space as well as relations with neurons
- Whey they are mobile, astrocytic-neuronal interactions *BECOME HIGHLY DYNAMIC*
  - This modifies extracellular homeostasis, neurotransmission, glitransmission and neuronal function at cellular and system levels

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

Microglia – Introduction

- Resident Macrophages of Brain and Spinal Cord
  - First line of immune response in central nervous system.
- 20% of total glial cell population
- ORIGIN: originate in bone marrow from hematopoietic stem cells.

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Microglia and immune role

- CNS is “immune privileged”, that is, blood brain barrier and endothelial cells keep out most infections and antibodies
- Microglia are extremely sensitive to even small amount of pathological change – acting through their unique potassium channels.

Types of forms/roles Microglia take 1. Non-activated

- **Ameboid**
  - Allows rapid movement through neural tissue
  - Can phagocytose debris but don't play antigen-presenting and inflammatory roles
- **Ramified**
  - Found in strategic locations; "resting form" with long branching processes and small cellular body
  - Remains fairly motionless but branches constantly surveying surrounding area
  - Do not phagocytose or play immune roles
  - They are available to detect and fight infection

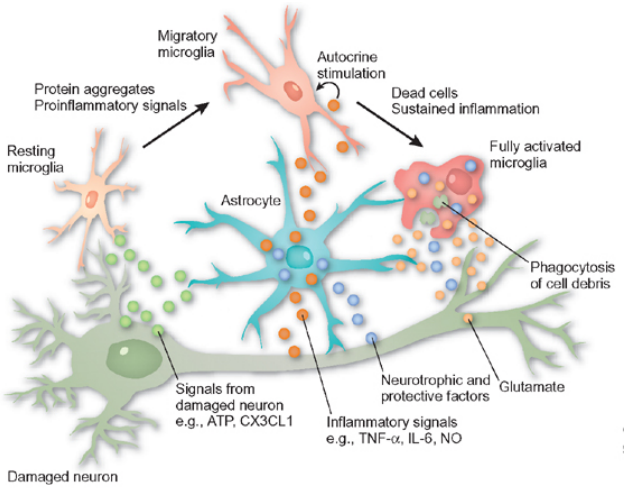
Types of forms/roles Microglia take 2. Activated

- **Non-phagocytic**
  - Starting to activate
  - Bushy, rod-like or small ameboid
  - Rapidly proliferating to prepare for battle
- **Phagocytic**
  - Maximally immune responsive
  - Large ameboid
  - Antigen presenting, cytotoxic, inflammatory
  - Interact with astrocytes
- **Gitter cells**
  - Stuffed – canpt engulf more – grainy – can show past infection

Types of forms/roles Microglia take 3. Perivascular, Juxtavascular

- **Perivascular**
  - Mainly within walls of basal lamina
  - Perform normal microglial functions, but replaced by bone marrow derived precursor cells
  - React strongly to macrophage differentiation antigens
  - Essential for repair of vascular walls
- **Juxtavascular**
  - Contact basal lamina of blood vessels but are not within the walls
  - No rapid turnover and not replaced by bone marrow cells

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

Microglial Functions

- **Antigen presentation**
  - Can develop this from MHC class I/II proteins or from IFN-gamma
- **Synaptic stripping from nerves near damaged tissue**
  - Helps promote growth and remapping of damaged circuitry
- **Promotion of repair**
  - Stripping, antiinflammatory cytoknes, recruitment of neurons and astrocytes to damaged area, and gitter cells
- **Extracellular signaling**
  - Maintaining homeostasis through comlex xignaling

Microglia in chronic inflammation

- Activate proinflammatory cytokines
- Contribute inflammatory chemokines
- Secrete proteolytic enzymes
  - Degrade extracellular matrix, nearby neurons
- Amyloid precursor protein in response to excitotoxic injury

Microglia and infection

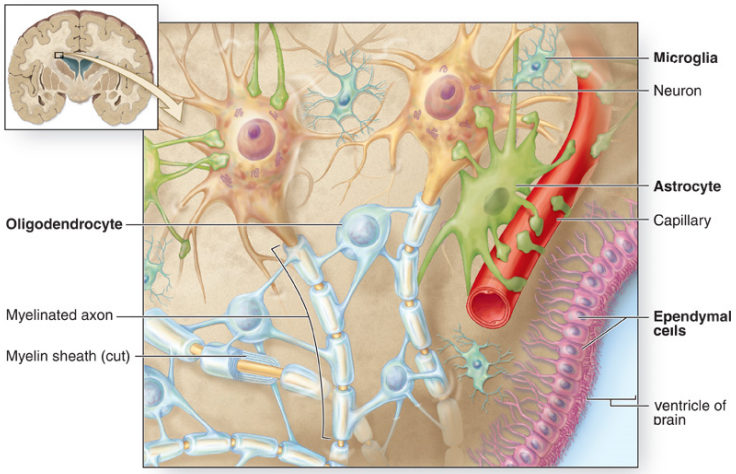
- Microglia fight infection but also release neurotoxic mediators that contribute to disease progression
- Chronic bacterial exposure can produce different microglial changes than acute exposure

"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
- 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

Oligodendrocytes – they make "white matter" white



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

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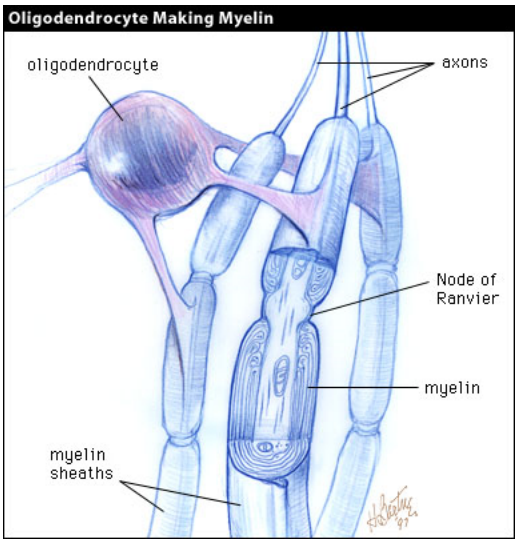
The White in White Matter: Myelin



- 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.

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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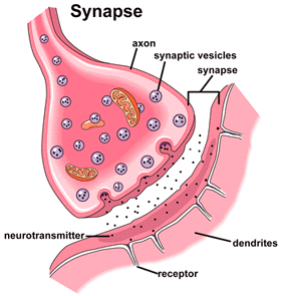
Fibrous Astrocytes and Myelination

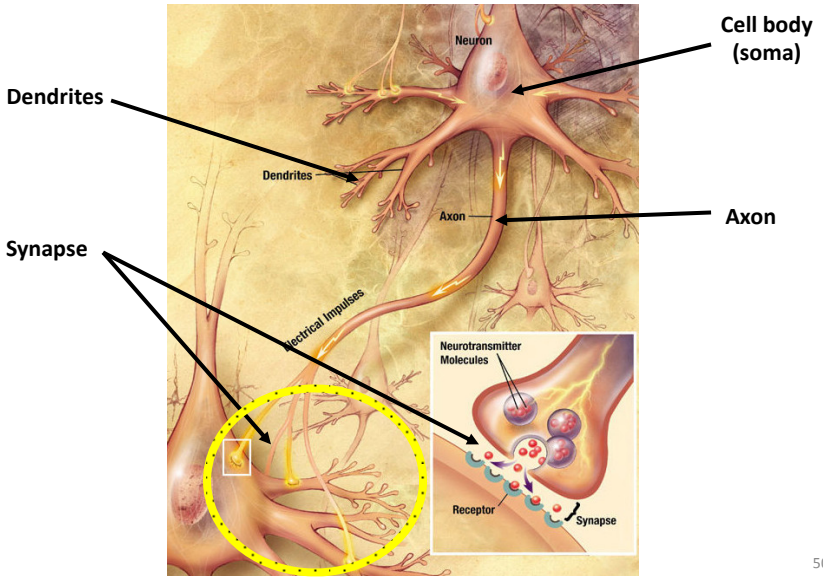
- Fibrous astrocytes in the layers of myelin wrapping axons detect information about the firing rate of the axon
- This modulates the amount of myelination, which in turn impacts the speed of neurotransmission

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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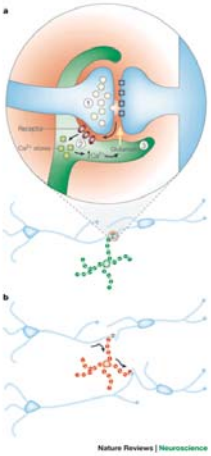
The Tripartite Synapse: Neurons and Astrocytes working together

- 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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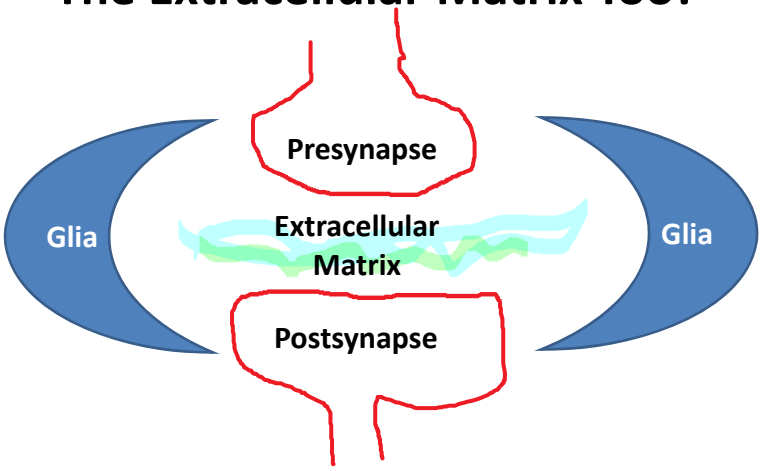
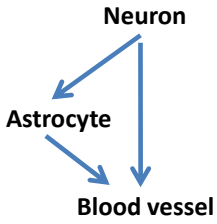
Tetra-partite Synapse: The Extracellular Matrix Too!



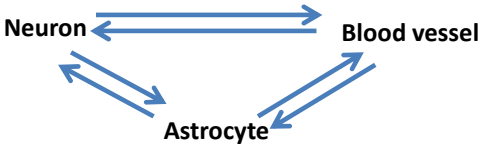
Alexander Dityatev[1,2] and Dmitri A Rusakov[3]
Molecular signals of plasticity at the tetrapartite synapse
Curr Opin Neurobiol. 2011 April; 21(2): 353–359.

Neurometabolic regulation: Neuro-glio-vascular Unit

The old model: Neuron as top-dog



The new model: teamwork, and A web with two-way streets



Housekeeping and Higher Function are Profoundly Intertwined

- See my blog about this, on
  - www.autismWHYandHOW.org/blog

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
- All of these can impact the composition and function of
  - Neurons
  - Glial Cells
  - Blood & Blood Vessels
  - Extracellular Matrix
- Which in turn can impact
  - Neuro- and glio-transmission
  - Brain networks and connectivity

NEUROINFLAMMATION

What is neuroinflammation

- Acute neuroinflammation
  - Response to an injury
- Chronic inflammation
  - Failure of acute inflammation to resolve
  - Toxic mediators exert destructive effects, worsening the illness
- Activated glial cells play a critical role

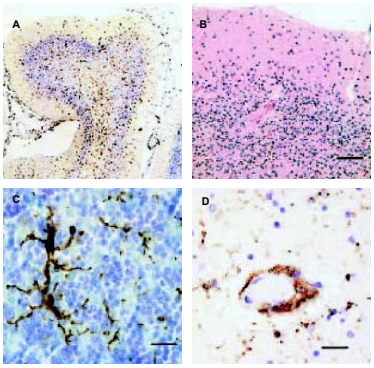
Neuropathological evidence of neuroinflammation in ASD

- Vargas
- Morgan
- Upregulated genes
- GFAP
- Lipofuscin
- Fiber tract abnormalities
- Proinflammatory cytokines

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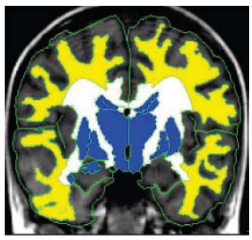
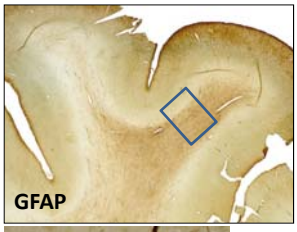
The white matter areas that are larger appear to have more inflammation.



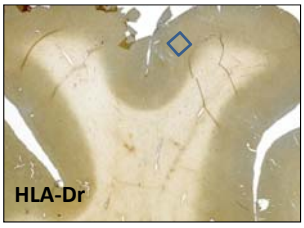
Herbert:

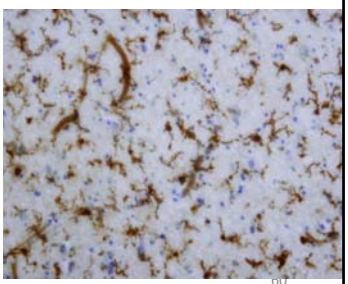
Large Brains from Radiate White Matter Enlargement

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
- These include
  - Poor nutrition, toxics, radiation, trauma, noise, stress

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Air pollution and brain inflammation

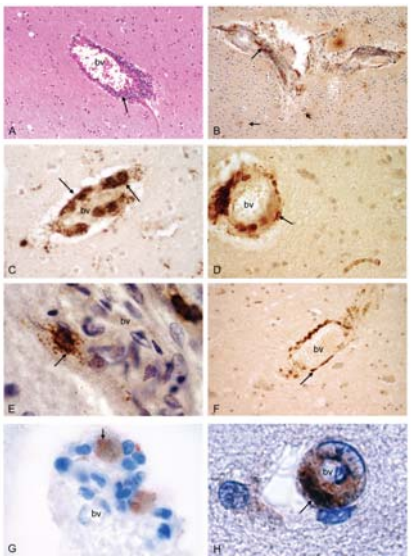
Air pollution leads to brain inflammation much like what we see in autism.

Toxicologic Pathology, 36:289–310, 2008
Copyright © 2008 by Society of Toxicologic Pathology
ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623307313011

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

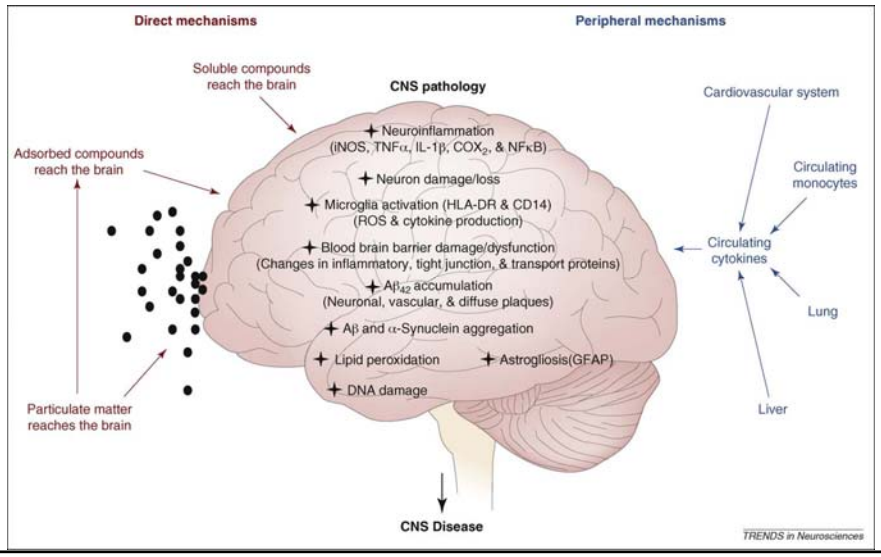
LILIAN CALDERÓN-GARCIDUEÑAS,[1,2] ANNA C. SOLT,[3] CARLOS HENRIQUEZ-ROLDAN,[4] RICARDO TORRES-JARDÓN,[5] BRYAN NUSE,[2] LOU HERRITT,[2] RAFAEL VILLARREAL-CALDERÓN,[6] NORMA OSNAYA,[7] IDA STONE,[2] RAQUEL GARCIA,[2] DIANE M. BROOKS,[2] ANGELICA GONZALEZ-MACIEL,[7] RAFAEL REYNOSO-ROBLES,[8] RICARDO DELGADO-CHAVEZ,[5] AND WILLIAM REED[9]

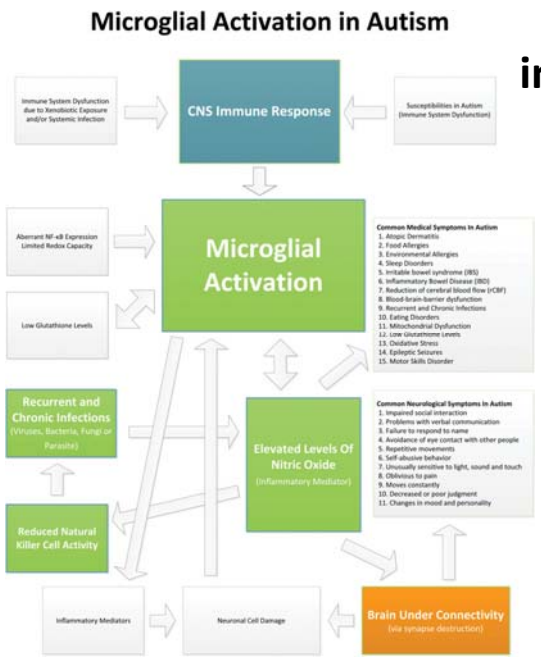
[1] *Instituto Nacional de Pediatría, Mexico City, Mexico*
[2] *The College of Health Professions and Biomedical Sciences, The University of Montana, Missoula, Montana, USA*
[3] *South Shore Psychiatric Program, Harvard University, Brockton, Massachusetts, USA*
[4] *Departamento de Estadística, Universidad de Valparaíso, Chile*
[5] *Centro de Ciencias de la Atmósfera, Universidad Nacional Autónoma de México, Mexico City, Mexico*
[6] *Davidson Honors College, The University of Montana, Missoula, Montana, USA*
[7] *Pathology Department, Instituto Nacional de Cancerología, Mexico City, Mexico*
[8] *Center for Environmental Medicine, Asthma and Lung Biology, and Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina, USA*



Air Pollution and Brain Inflammation

Block and Calderon-Gardicuenas, TNS, 2009



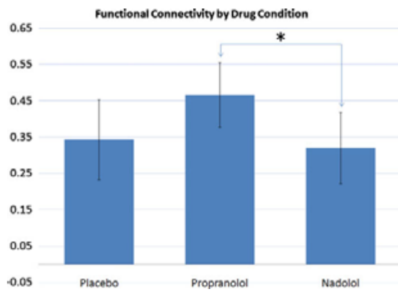


One model of inflammation in ASD

- Complex etiology
- This model focuses on synapse destruction as cause of underconnectivity
- There are other possible mechanisms prior to/along with physical loss of connections.

Rodriguez & Kern, 2012

Rapid IMPROVEMENT in brain connectivity suggests autism may be "state," not "trait"



- Functional connectivity changed rapidly with drug that impacts brain stress level (propranolol)
- Most research assumes it is a fixed trait
- *Could other interventions reducing total load also decrease stress and improve brain function*?

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

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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*||

*The Picower Institute for Learning and Memory, Howard Hughes Medical Institute, RIKEN–Massachusetts Institute of Technology Neuroscience Research Center, and Departments of Biology and Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; ‡Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bangalore 560029, India; §Department of Physiology, College of Dentistry, Seoul National University, Seoul 110-749 Korea; and ¶National Center for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560065, India

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

Fragile X syndrome (FXS), the most commonly inherited form of mental retardation and autism, is caused by transcriptional silencing of the *fragile X mental retardation 1 (FMR1)* gene and conse- ticity at glutamatergic synapses, such as long-term potentiation (LTP) in the cortex and long-term depression in the hippocampus, is abnormal in *FMR1* KO mice (11–13).

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

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

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

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

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

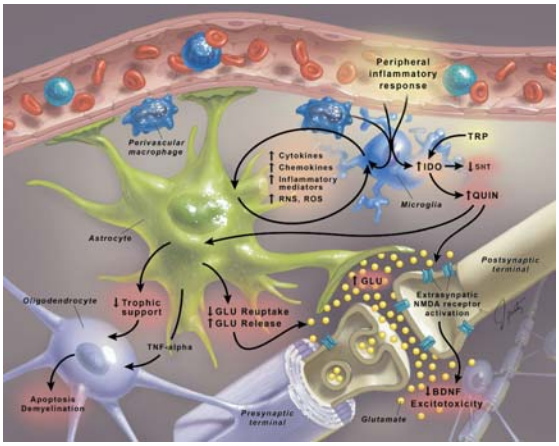
om/naturemedicine

"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
- 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

Brain cells in inflammation



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

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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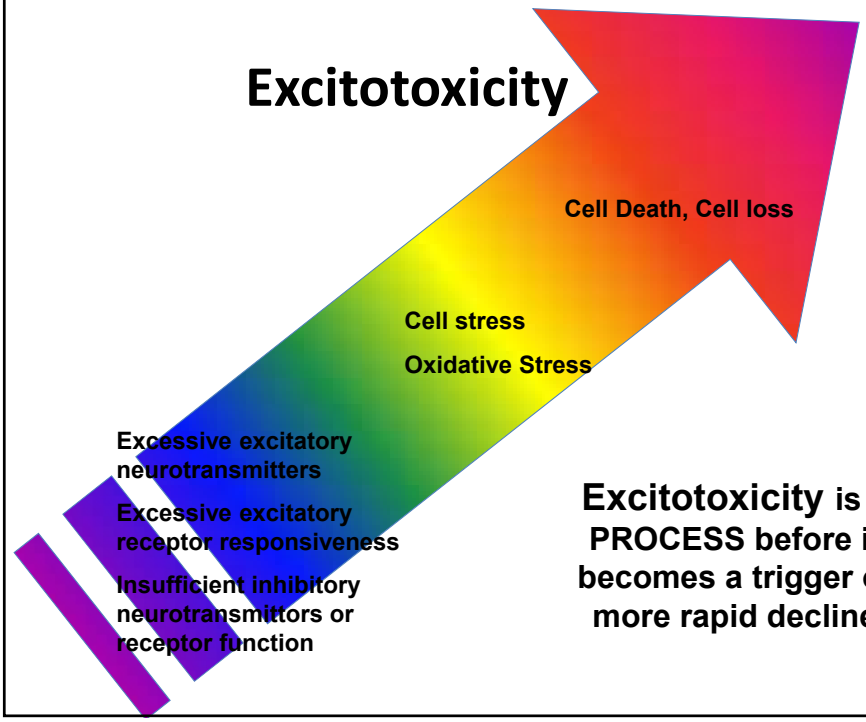
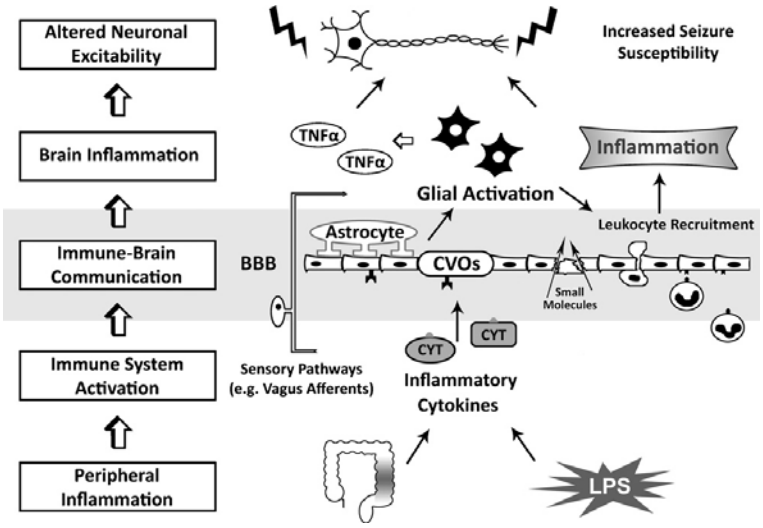


Consequences: Functional and Anatomical

- Functional consequences
  - Alteration of cell health
  - Alteration of regulation and communication
  - Altered blood flow and supply of cells
- Anatomical/Structural
  - Altered cell size
  - Altered cell number
- IMPORTANT NOT TO BLUR THESE TOGETHER

Major example of functional impact: Peripheral Inflammation and Neuronal Excitability



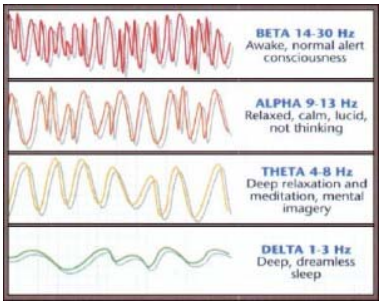
Riazi 2010, doi:10.1016/j.eplepsyres.2009.09.004

Lower perfusion in ASD brains could impact brain function. It could be maintained by active pathophysiology.

- 17 of 19 PET and SPECT studies showed low perfusion
- Those that showed areas of high perfusion still showed lower perfsuion more than higher
- Possible pathophysiology
  - Vasoconstriction
    - Oxidative stress acting on endovasculature
    - Astroglia swell when activated constricting capillary lumen
  - Blood viscosity
    - RBC lipid peroxidation (stiffer membranes → poor RBC deformability)
    - platelet activation (increased thromboxane)
    - increased nitric oxide (oxidative stress marker),
    - depressed glutathione peroxidase
    - depressed SOD
    - depressed catalase

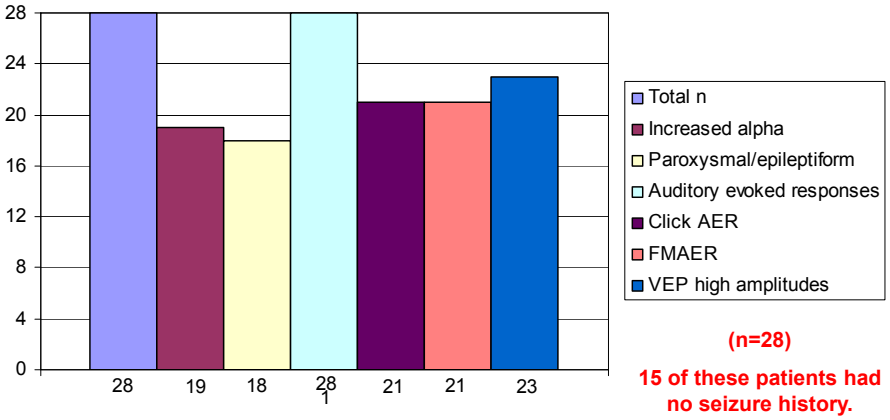
What are brain oscillations (or, "brain waves")

- 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

Autism Electrophysiological Abnormalities: Seizures and much more



(n=28)

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

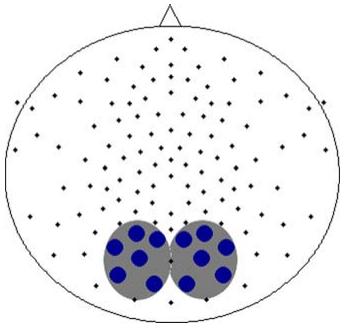
Reduced functional connectivity in visual evoked potentials in children with autism spectrum disorder

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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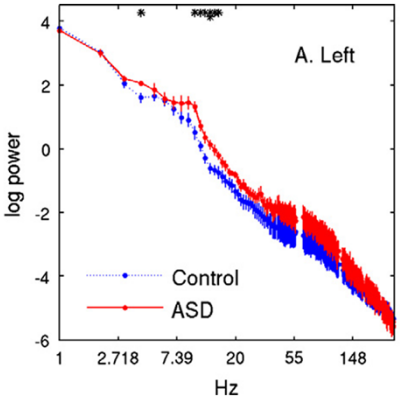
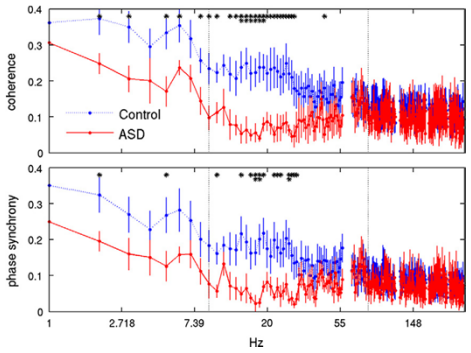
"Inefficiency" in brain signaling in autism

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

Clinical Neurophysiology 121 (2010) 2035–2043

ASD has <u>more power</u> than controls… but <u>*less coherence*</u>





Too much noise, not enough signal
BETTER BANDWIDTH SHOULD IMPROVE THIS

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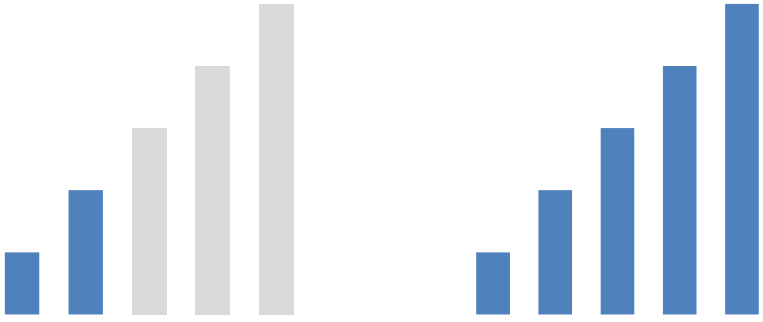
Are seizures on a continuum with sensory hypersensitivity?

- Does excitotoxicity drive sensory intolerance?
- This is poorly understood at present from a neurobiological point of view.
- But biomedical treatment anecdotally appears to reduce sensory issues in at least some cases.

Healthier Brains have more "Bandwidth"

Poor Bandwidth: Limited Reception

Lots of Bandwidth: Good Reception



Good Reception Allows Learning

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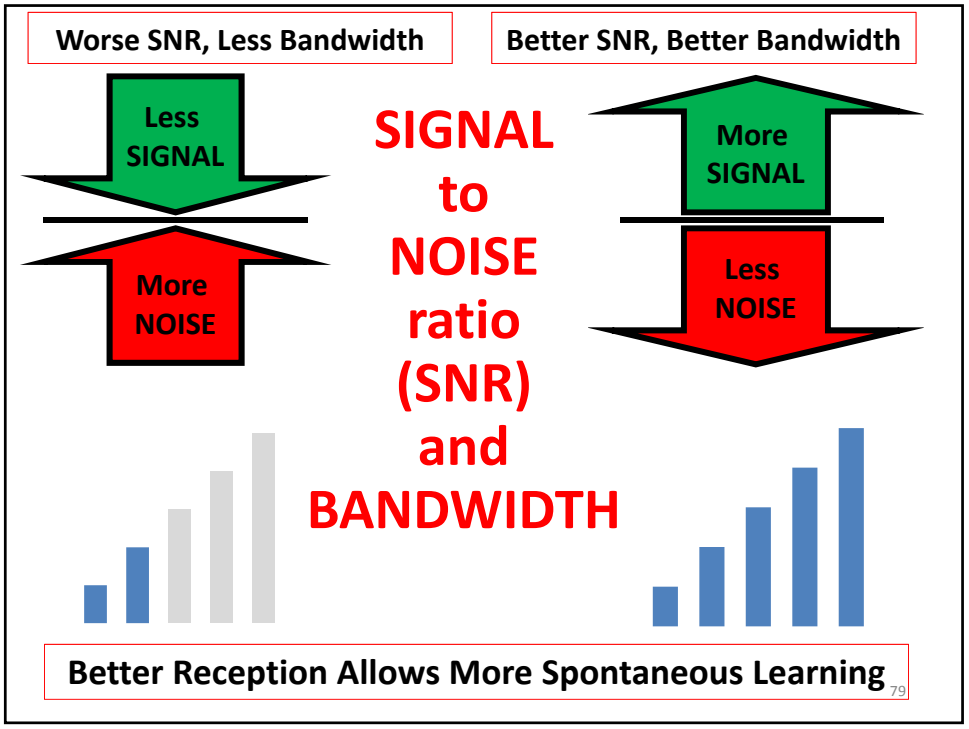


Functional problems in the brain

- Connectivity
- Sensory processing

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

➢ Or are they caused by cell metabolism problems?

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

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

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

Example of structural + functional impact Lower FA in key regions Linked to higher (worse) diagnostic scores

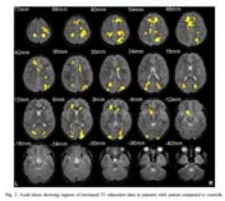
- White matter FA was significantly lower in key regions of prefrontal lobe and right ventral temporal lobe.
- Lower FA linked to higher (worse) diagnostic symptom scores
- Author interpretation:
  In light of spectroscopy showing lower NAA ➔ less neuronal integrity or number, lower structural integrity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

Cheung et al., 2009

The "Fluid Theory" of Connectivity Alterations in ASD

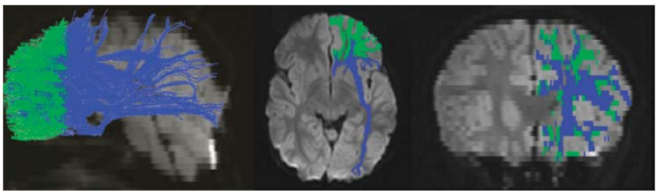
- **Water, not fiber changes in brain tissue**

Hendry 2005



The idea that brain connectivity abnormalities arise from metabolic, immune and vascular disturbances that affect synaptic function.

- **Less white matter integrity**
- **Less restriction of water flow**
- **More diffusivity**

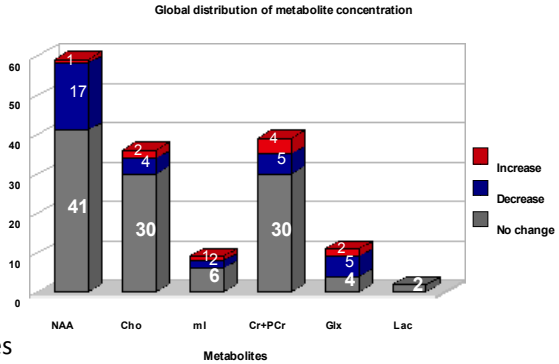


Sundaram 2008

- **Lower perfusion in ASD brains (by many PET or SPECT studies) could impact brain function.**

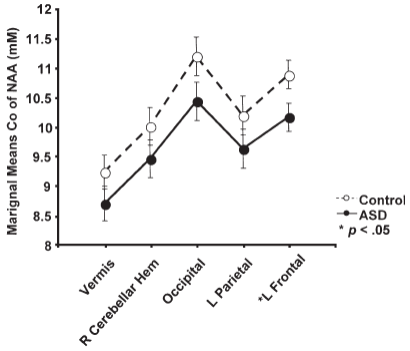
How might this affect brain electrophysiology? 83

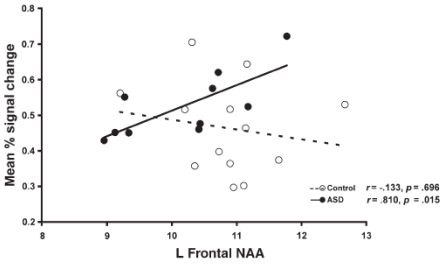
Brain magnetic resonance spectroscopy summary of findings in literature to date: Mostly lower density of metabolites



- 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
Dager review chapter 2008 and many papers





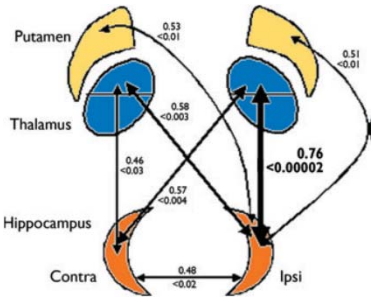
Metabolite level correlating with brain activation

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

- NAA = N-acetylaspartate

Kleinhans et al, 2007

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

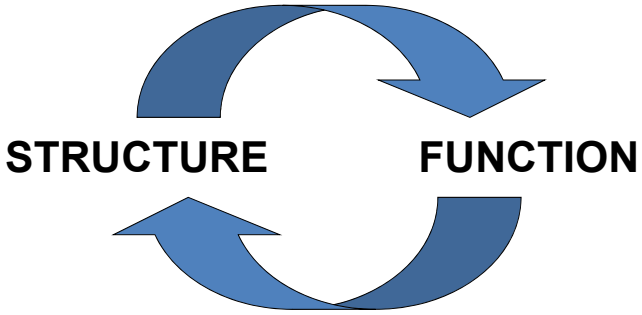
Pan, 2008
Neurometabolism in Human Epilepsy

NAA = n-acetylaspartate

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

Structure ➔ Function?
Or Function ➔ Structure

or



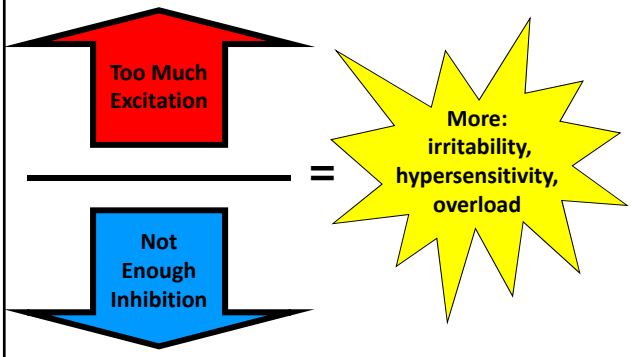
Active tissue pathophysiology undermines the idea that brain structure changes cause abnormal function

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

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

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



Reduced informational complexity and organization

Reduced signal to noise ratio

Increased chaos and confusion

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

A model of possible role of glial cells in autistic regression

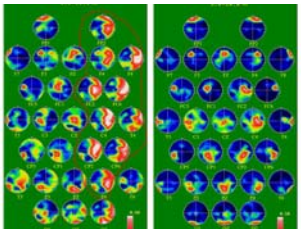
- Degradation of metabolic supports for healthy glial function through chronically poor food, toxins, allergens and stress
- Degradation of blood supply- narrow small vessel lumen, stickier blood
- Reaching a tipping point possibly through acute stressors
- Change of system "attractor state" into autism
- Lots of coordinated work needs to be done to change "attractor state" back to better connectivity and greater options

- See chapter 5 of THE AUTISM REVOLUTION for more details
- Also see Herbert chapter in Chauhan 2009 book AUTISM: OXIDATIVE STRESS, INFLAMMATION AND IMMUNE ABNORMALITIES

Environment can also improve brain tissue health

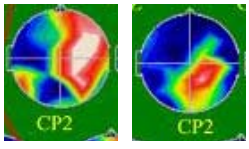
- Nutrition
- Sleep
- Exercise
- Potentially careful detox

Improvement in brain function after treatment



Before treatment

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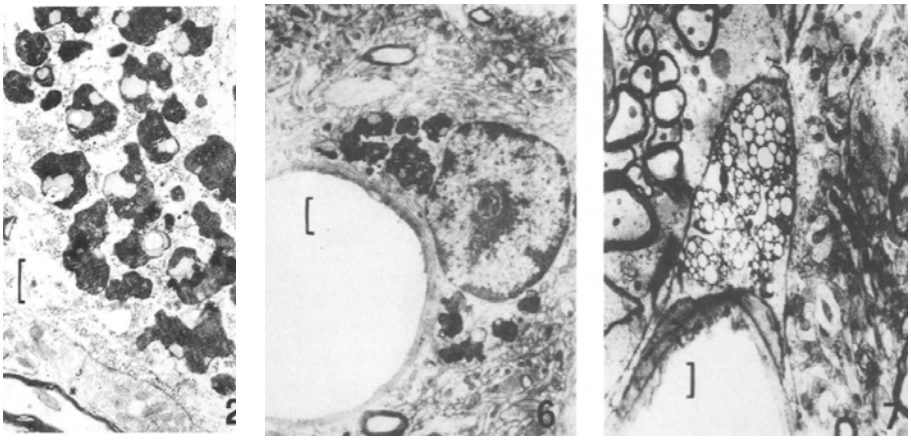
Electron microscopy of therapeutically activated glia turning into "brain garbage collectors and transporters"

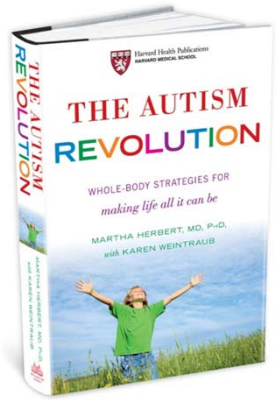
RIGA, S. et al., *Ann. N.Y. Acad. Sci.* 1067: 383–387 (2006)
RIGA, S. et al., *Arch. Gerontol. Geriatr.* suppl. 4 (1994) 227-234



Possible implications of the ability of glial cells to clear out "brain trash"

- Neurodegeneration might be at least somewhat reversed
- The limits to this reparative process may be pushed back substantially by biologically informed interventions

Chapter 5 of The Autism Revolution lays out what is in this talk



www.AutismRevolution.org
See also: www.autismWHYandHOW.org and references listed on www.marthaherbert.org
Particularly Herbert chapter entitled: "Autism: Autism: The centrality of active pathophysiology and the shift from static to chronic dynamic encephalopathy in Chauhan book , CRC press, 2009