Eye on Autism



Woody McGinnis MD

Autism primer

Autism Spectrum (ASD)

Early or Regressive

Behavioral Diagnosis

Evolving concepts

Psychological v Biological

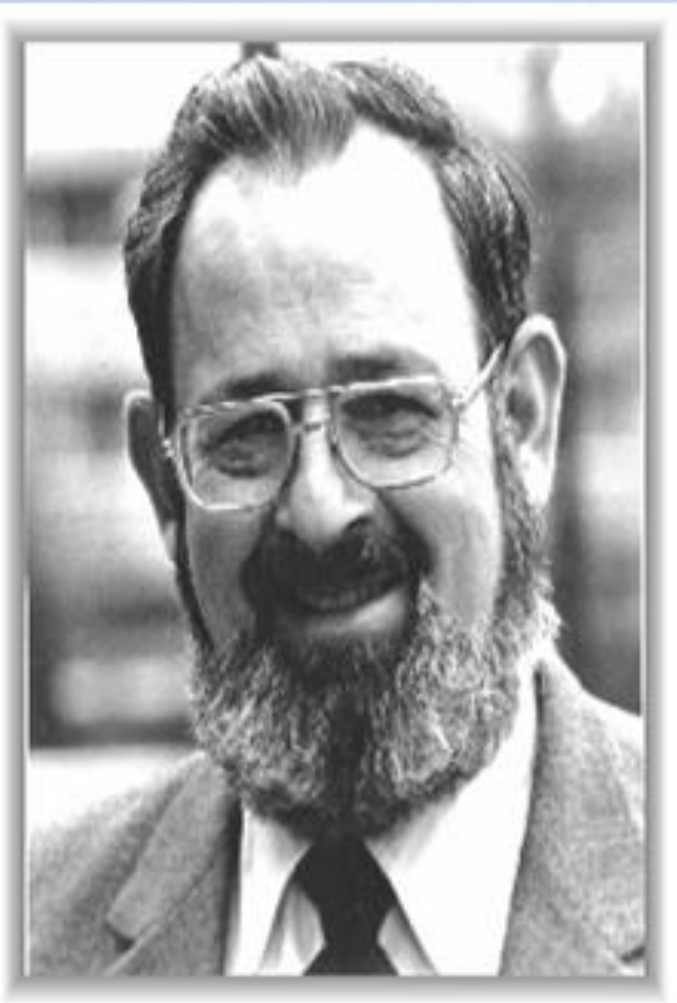
Static v Dynamic 16151044

Genetic v Environmental

Somatobehavioral 24336025

Bernard Rimland

1928-2006



Brain in ASD

Larger in young ASD

↑ White-matter

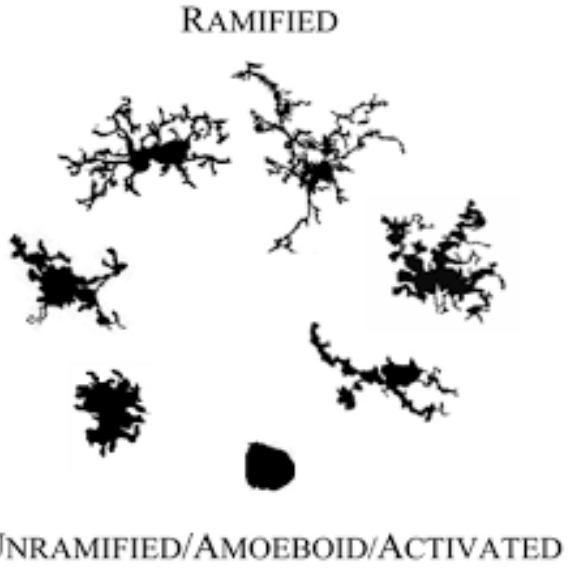
↓ Connectivity

Neuroinflammation

16151044

Neuroinflammation

↑ Microglia / activity cortex
9/13, including 2/3 < 5 y.
Density ↑ gray matter,
Volume ↑ white 20674603



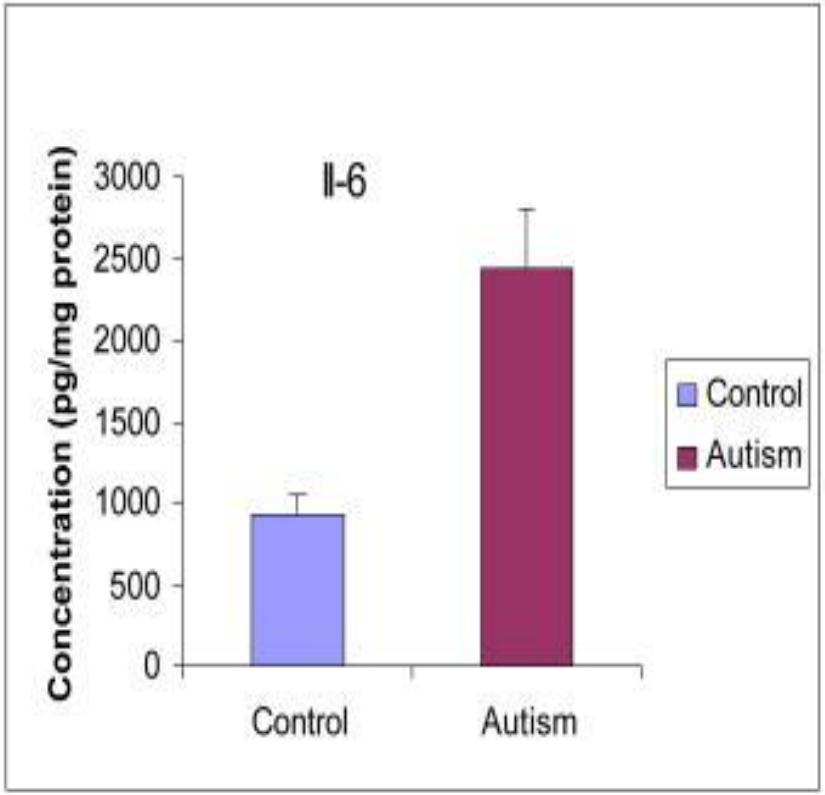
↑ Microglial activity on PET scans of
ASD aged 18-31 in midbrain, pons,
fusiform, cerebellum, cortex 23404112

Cytokines in brain

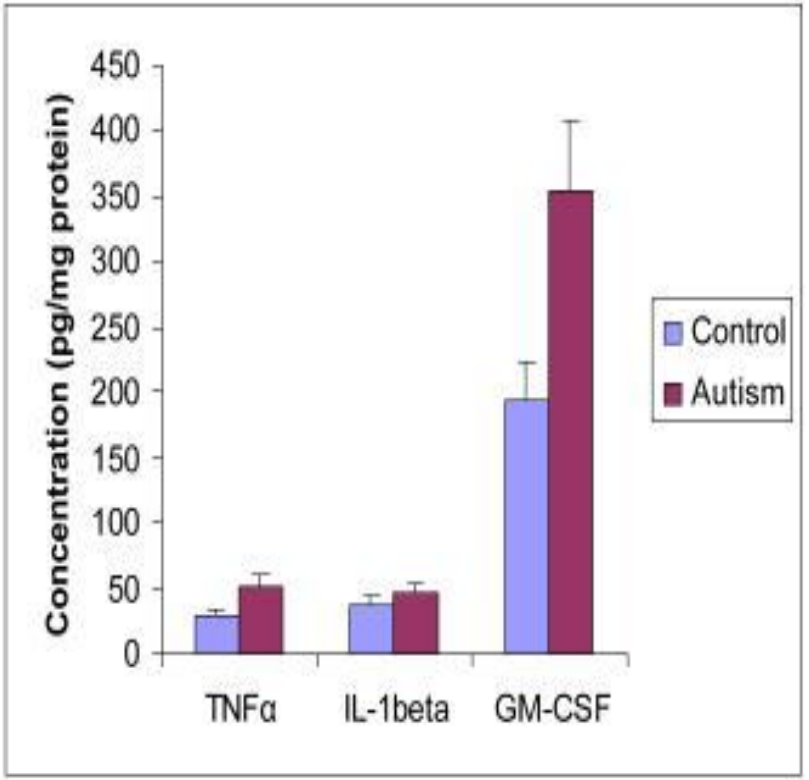
↑ MCP-1, TGF-β1 cortex, white matter, cerebellum 15546155

↑↑ TNF-α, IL-6, INF-ϒ, IL-8, and shift to Th-1 age 4-37 19157572

Cytokines in brain



A



B

Peripheral cytokines

↑ plasma TNF-α and IL-6 in 2-5 y.o. ASD, mostly in regressed; behavioral associations 20705131

↑ PBMC Th-1 (IL-2, IL-1)

↑ ↑ Th-2 (IL-4, IL-5), but no compensatory shift IL-10 16360218

Peripheral phenotype

More oxidants

↑$NO^{\cdot}$ (x2)* and XO (x3)

Less protection

↓GSH, GSHPx*, catalase

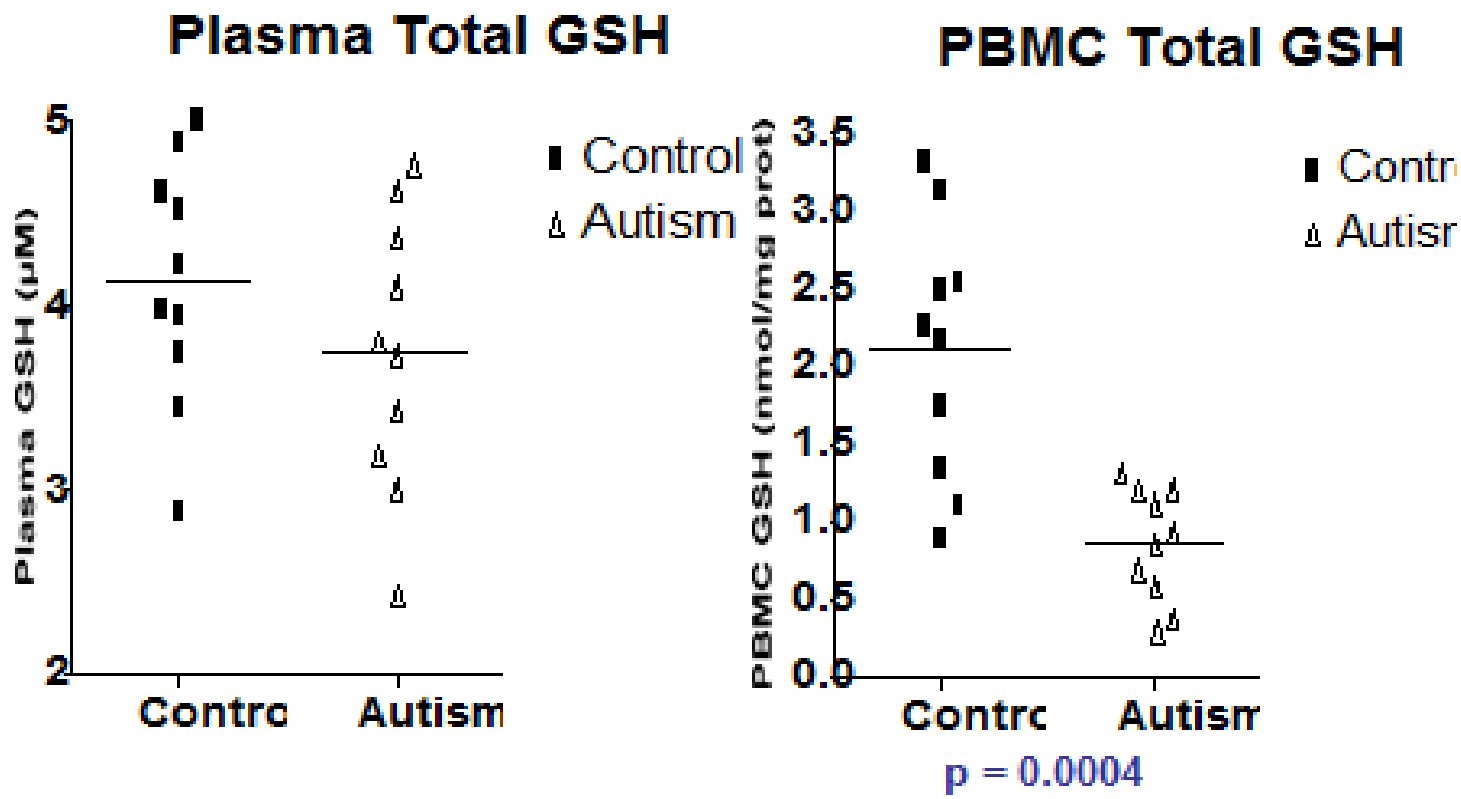
ceruloplasmin, transferrin

More oxidized biomolecules

↑LPO (x2)* and isoprostanes



GSH in autism



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Brain is sensitive

High oxygen consumption

Oxidizable catecholamines

Fragile blood-brain barrier

Modest catalase and GSH

High glutamate, Fe and fat

Oxidized brain

↑ Lipofuscin, associated with neuronal loss

↑ Axonal CEP, isolevuglandin and hemoxygenase

↑ Nitrotyrosine, correlates with mercury level



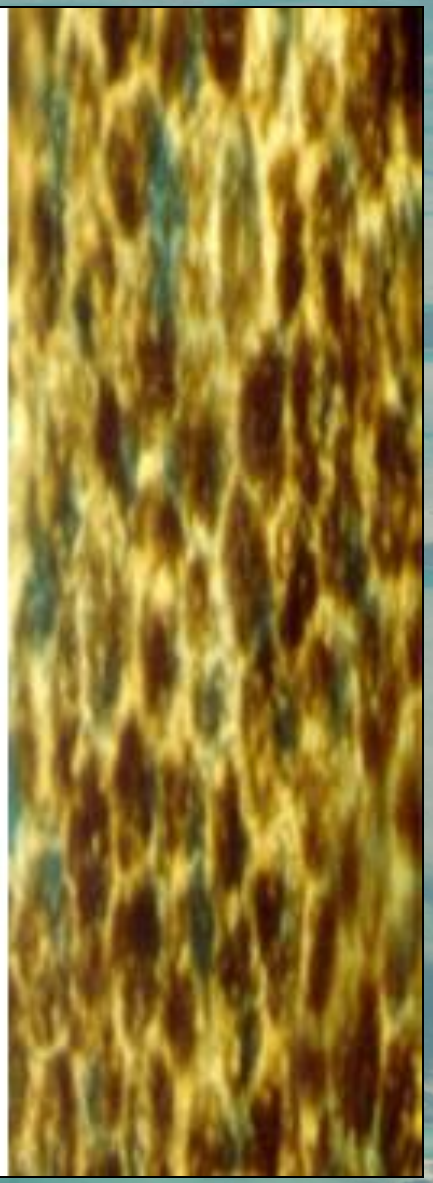
Lipofuscin facts

Oxidized lipid and cross-linked protein.

Depot for heavy metals.

Classically associated with neurodegeneration.

Inverse to brain activity and slowed by vitamin E.



Univ. M. Hernandez

Areas 22 (speech), 39 (reading), 44 (language production).

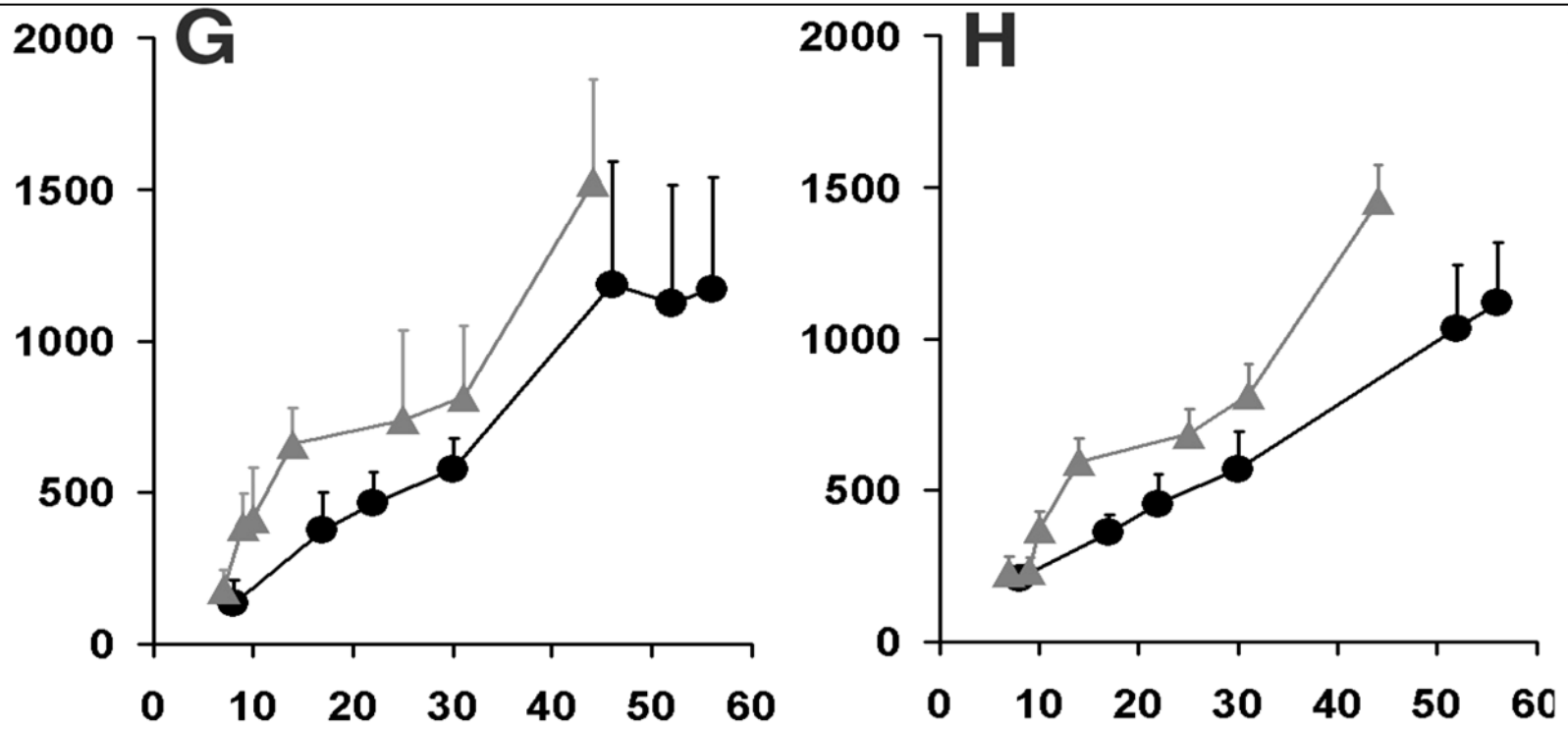
Age 7- 44 years.

Progressive ↓ neurons and ↑ glial cells in specific layers.

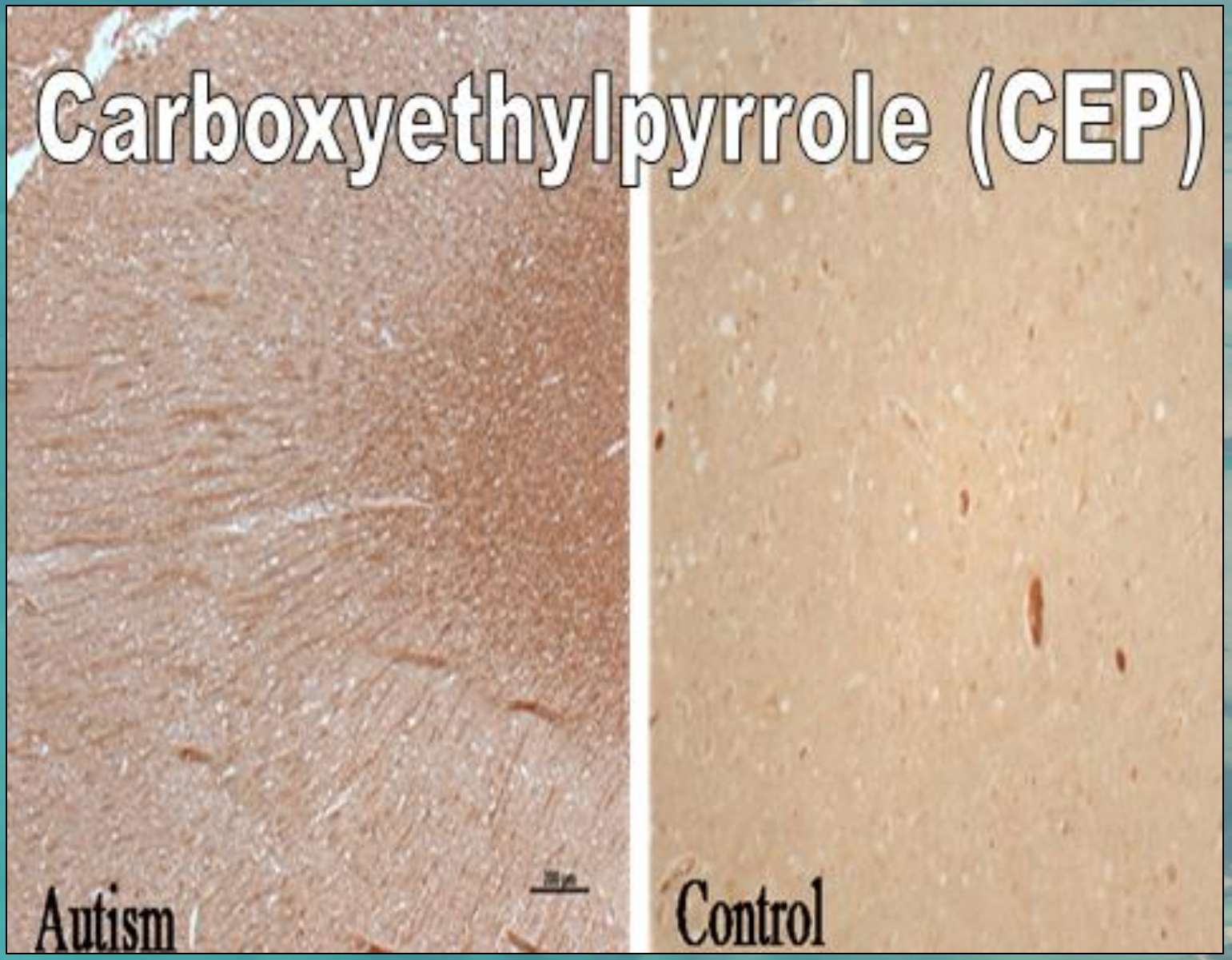
Progressively ↑ lipofuscin throughout.



Cortical Lipofusin



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Carboxyethylpyrrole (CEP)
Autism
Control

Harvard study

Increased cerebellar nitrotyrosine (3-NT)

Cerebellar 3-NT and mercury correlated

p = 0.0001



Neurodegenerative?

Neuronal loss

Activated microglia

Inflammatory cytokines

Oxidative modification

Loss of function (regression)

23925007

Excitotoxic?

↓ GAD by 50% ASD cortex

↓ GAD mRNA by 40% Purkinje

↑ Glutamate in plasma

↓ ATP cortex of ASD on MRI

15624347

Systemic Autoimmunity?

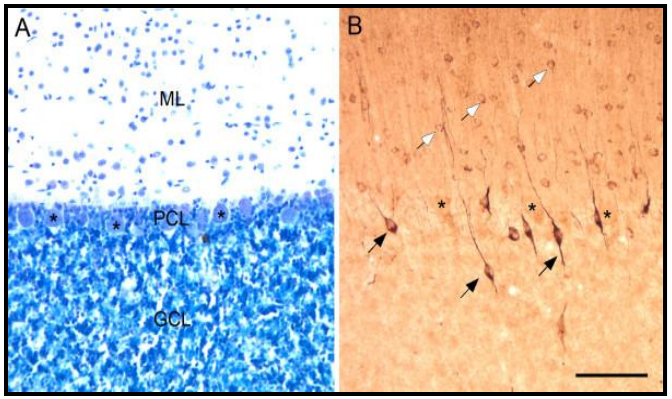
↑ IgG4 in plasma	19136055
ANA seropositive (20 v 2%)	19135624
Ab to nucleosomes 48%ASD	24708718
↑ Ab to endothelium	26087852

Brain-Binding Abs

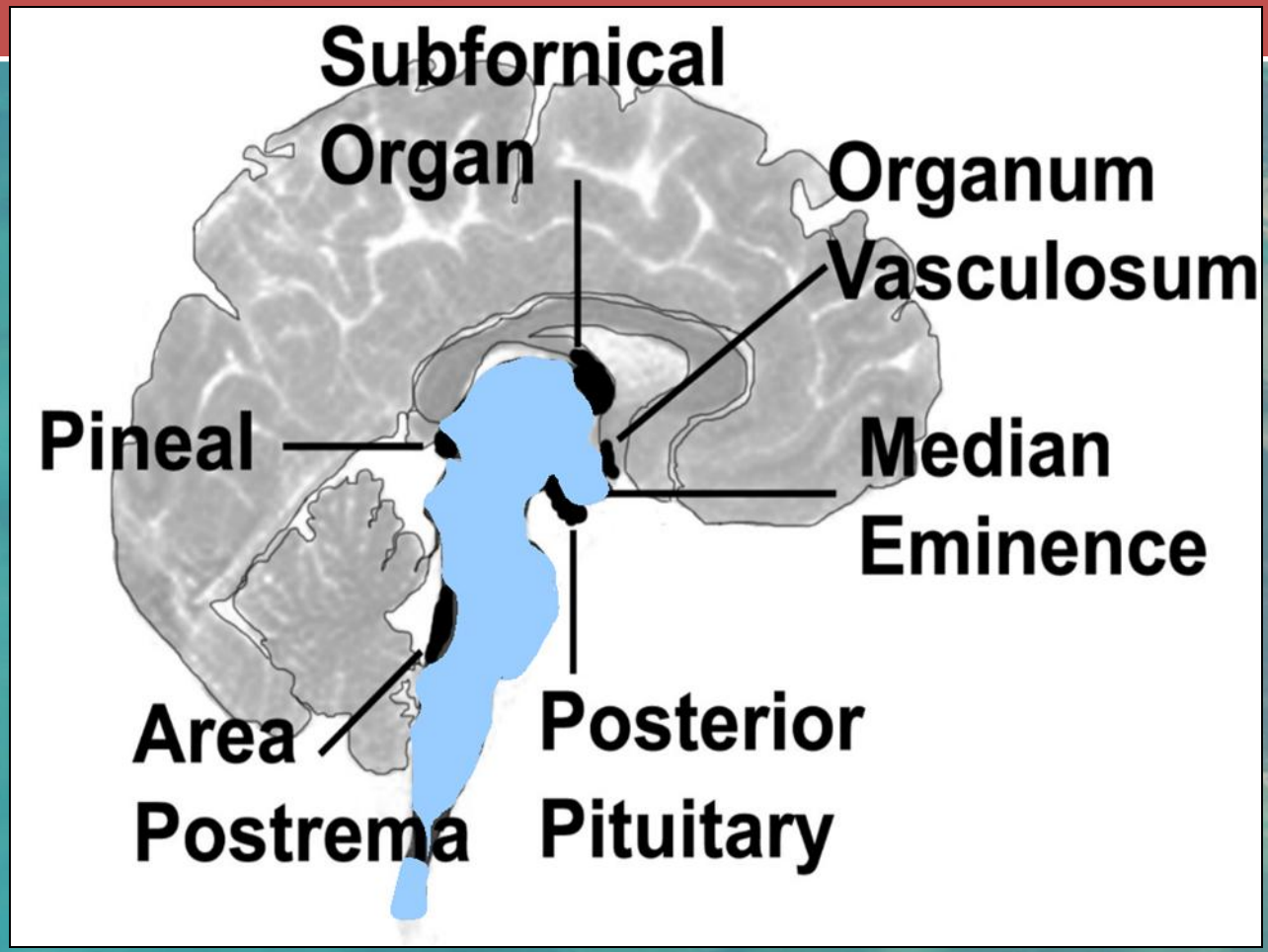
↑ Ab to MBP 75% ASD 25773150

Ab binds brain nuclei 27% ASD, 45% LKS, 2% controls 10228297

Ab binds (only) GABAergic Golgi 21% ASD 21521495



IgG from ASD binds control brain extracts (37 v 13% controls), especially hypothalamus 17804536



Microglial and Toxins

Release of inflammatory cytokines and oxidants

Associated neuronal loss

Certain toxins are known or expected to be highly stimulatory

Visceral Dysfunction

- ✓ Immunological
- Gastrointestinal
- Cardiovascular
- Laryngeal

24336025

Gastrointestinal

Esophageal reflux 67% ASD

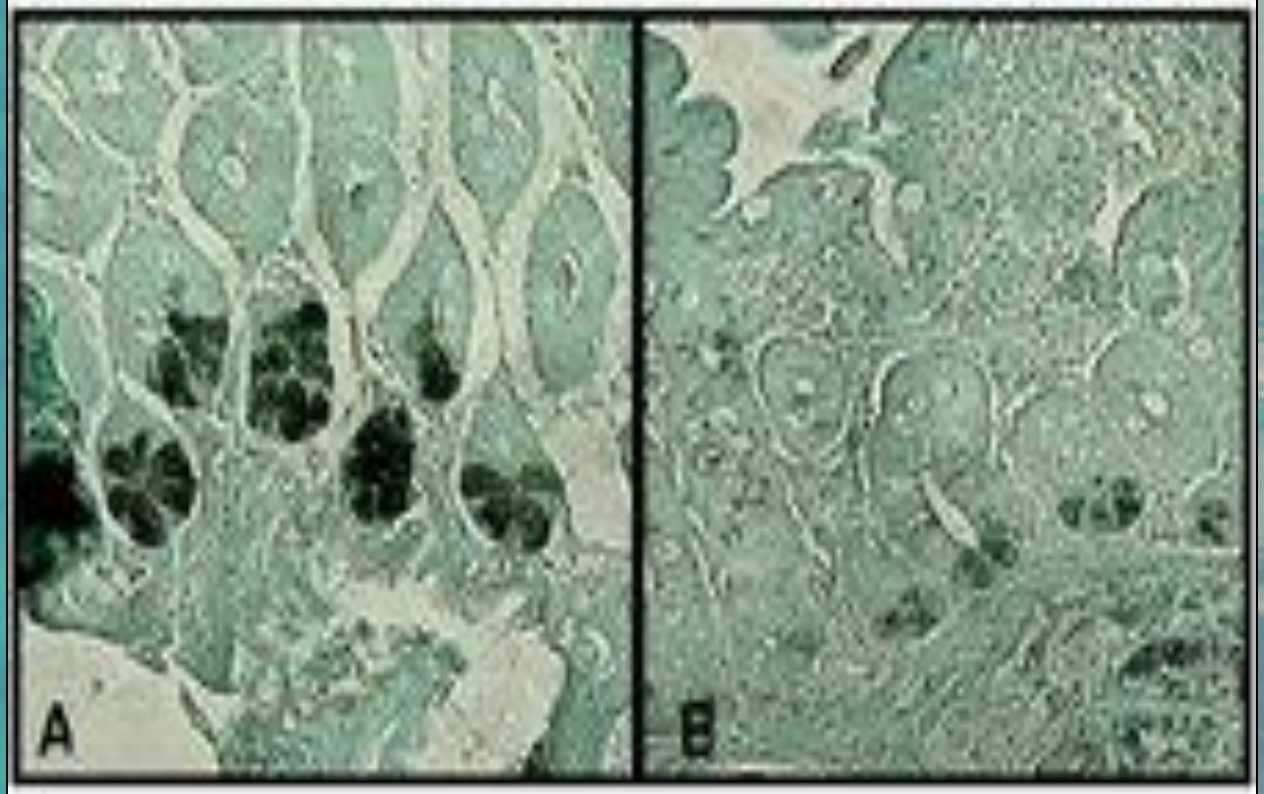
Paneth retention 10547242

Constipation with fecal-loading

100% regressed cohort 11986981

Simultaneous with regression

15366972, 15075959


A
B

Cardiovascular

↑ pulse and blood pressure

↓↓ Cardiac vagal tone and baroreflex 16198209

CVT a marker for social and language 22212893

Cardiovascular

↓↓ Temporal and frontal perfusion 11097965, 1096004

"Global Dysregulation" and asymmetric CBF 21740749

Possible neurovascular couple inversion 1457624

Laryngeal

Abnormal tone / prosody 15909407

Communication device 23372546, 17516231

Whisper with vocal regression in 17% ASD; 42% of whom lost all vocalization, 16% long-term whisper 24336025

