Brainstem Origins of ASD



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San Francisco

20 July 2015

Neurotoxic brainstem impairment as proposed threshold event in autistic regression.

McGinnis WR, Miller VM, Audya T, and Edelson S. Autism: Oxidative stress, inflammation and immune abnormalities. Eds Chauhan A, Chauhan V, Brown T. *CRC Press;* 2009:153-176.

Early hypothesis

1. Regression after 12 months is triggered by selective toxic effects on brainstem regions lacking BBB.
2. Earlier impairment of the same brainstem structures could predispose to regression, or result in early-onset autism.

Int J Environ Res Public Health. 2013 Dec 11;10(12):6955-7000. doi: 10.3390/ijerph10126955.

Proposed toxic and hypoxic impairment of a brainstem locus in autism.

McGinnis WR[1], Audhya T, Edelson SM.

Author information

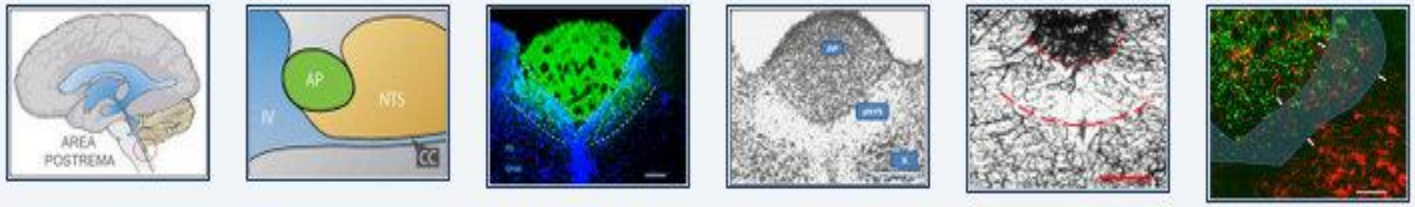
[1]Autism Research Institute, 4182 Adams Avenue, San Diego, CA 92116, USA. woody.mcginnis@gmail.com.

Abstract

Electrophysiological findings implicate site-specific impairment of the nucleus tractus solitarius (NTS) in autism. This invites hypothetical consideration of a large role for this small brainstem structure as the basis for seemingly disjointed behavioral and somatic features of autism. The NTS is the brain's point of entry for visceral afference, its relay for vagal reflexes, and its integration center for autonomic control of circulatory, immunological, gastrointestinal, and laryngeal function. The NTS facilitates normal cerebrovascular perfusion, and is the seminal point for an ascending noradrenergic system that modulates many complex behaviors. Microvascular configuration predisposes the NTS to focal hypoxia. A subregion--the "pNTS"--permits exposure to all blood-borne neurotoxins, including those that do not readily transit the blood-brain barrier. Impairment of acetylcholinesterase (mercury and cadmium cations, nitrates/nitrites, organophosphates, monosodium glutamate), competition for hemoglobin (carbon monoxide, nitrates/nitrites), and higher blood viscosity (net systemic oxidative stress) are suggested to potentiate microcirculatory insufficiency of the NTS, and thus autism.

PMID: 24336025 [PubMed - in process] PMCID: PMC3881151 Free PMC Article

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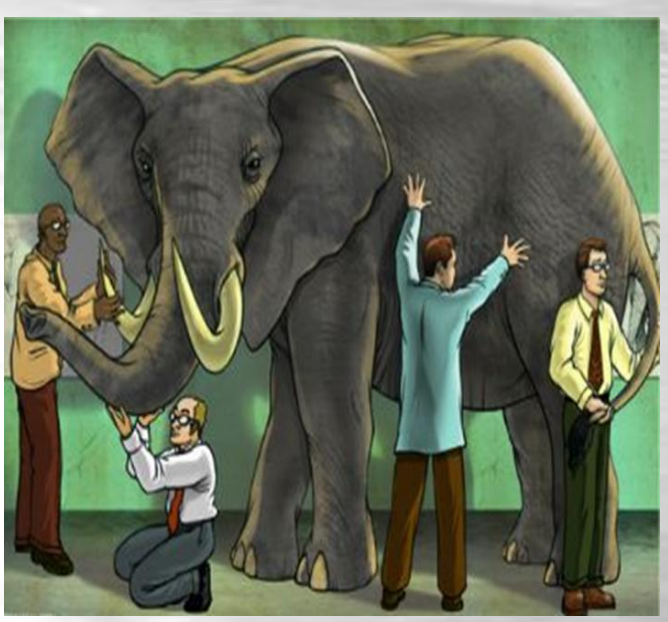


Hypothesis formation

Integrate data

No taboos

Cross disciplines



Assumptions

1. Widespread brain pathology in ASD does not preclude a primary site.

2. ASD is inherently a somatobehavioral syndrome.

Hypothesis statement

The autistic phenotype, both behavioral and visceral, largely results from primary injury to nucleus tractus solitarius, via the direct effect of:

A) Circulating toxin(s), OR
B) hypoxic/ ischemic insult.

Dual vulnerabilities

No BBB, so concentrates toxic cations.

Unique microvascular configuration, so prone to focal hypoxia/ischemia.

Lecture outline

I. Known BS abnormalities
II. NTS susceptibility to toxins
III. NTS susceptibility to ischemia
IV. Potentiation of hypoxia by toxins
V. Deafferentation and A2 impairment match ASD phenotype
VI. Therapeutic implications

Brainstem is suspect

Bernard Rimland 1964.

5-HT developmental flexibility 16283875

Lowest GSH and GR, high microglia
MacFabe D, AJBB 4(2) 146-166, 2008.

Affects development of higher brain.
18771507

Many consistent findings in autism.

Abnormal morphology

Small medulla / midbrain 8213050

Hypoplastic BS on MRI 9142760

Ectopic neurons, aberrant tracts, inferior olives ↑ then ↓ 8441369

Swollen axon terminals (“spheroids”) in medulla and hypothalamus in 5/6 1173276

Abnormal biochemistry

↓ Melatonin and lack normal circadian rhythm 11455326

↓ Oxytocin, predominantly non-amidated 11690596

Abnormal function

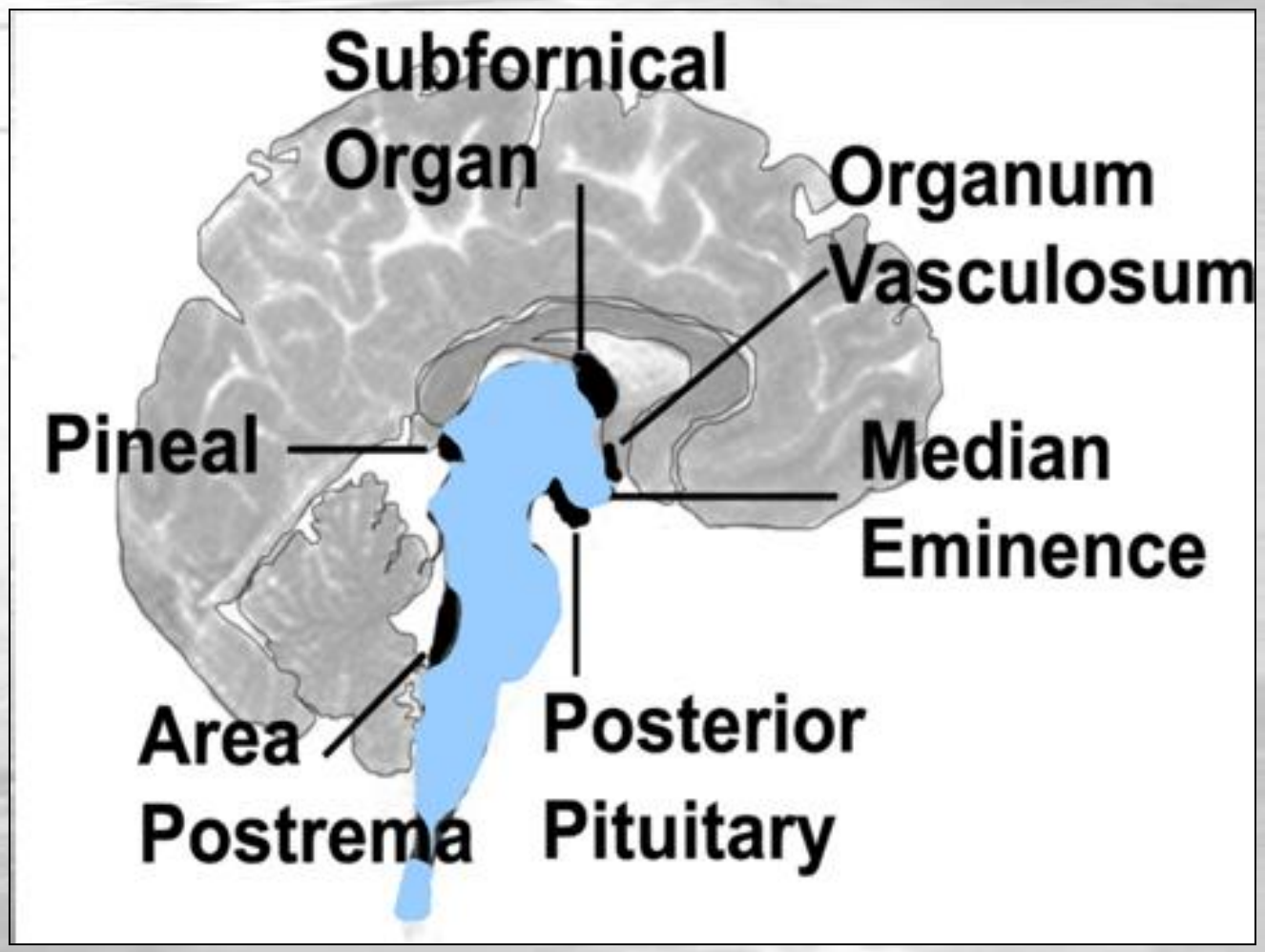
Post-rotatory response 6874265

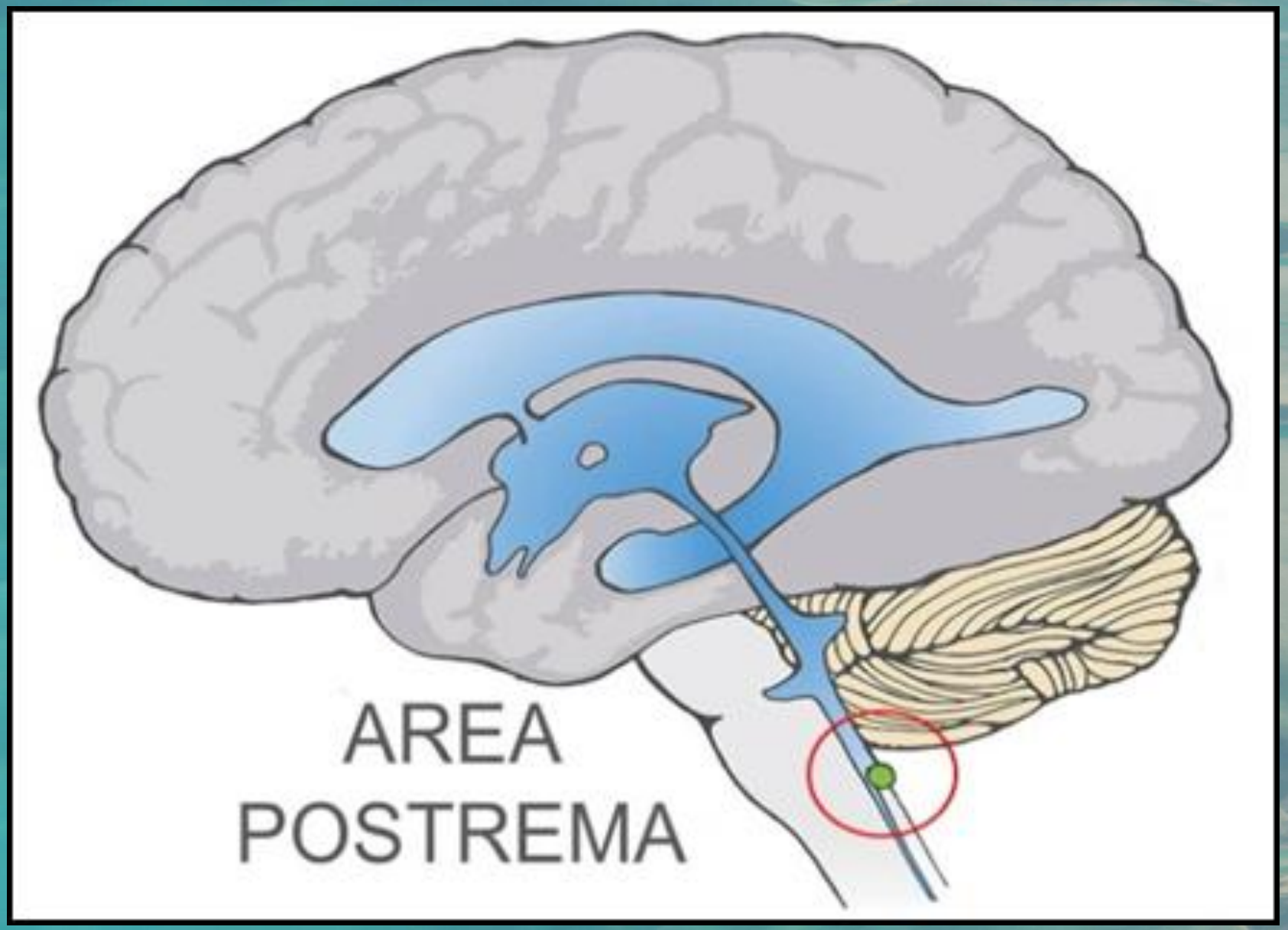
Auditory brainstem response, HR, respiratory and vascular.

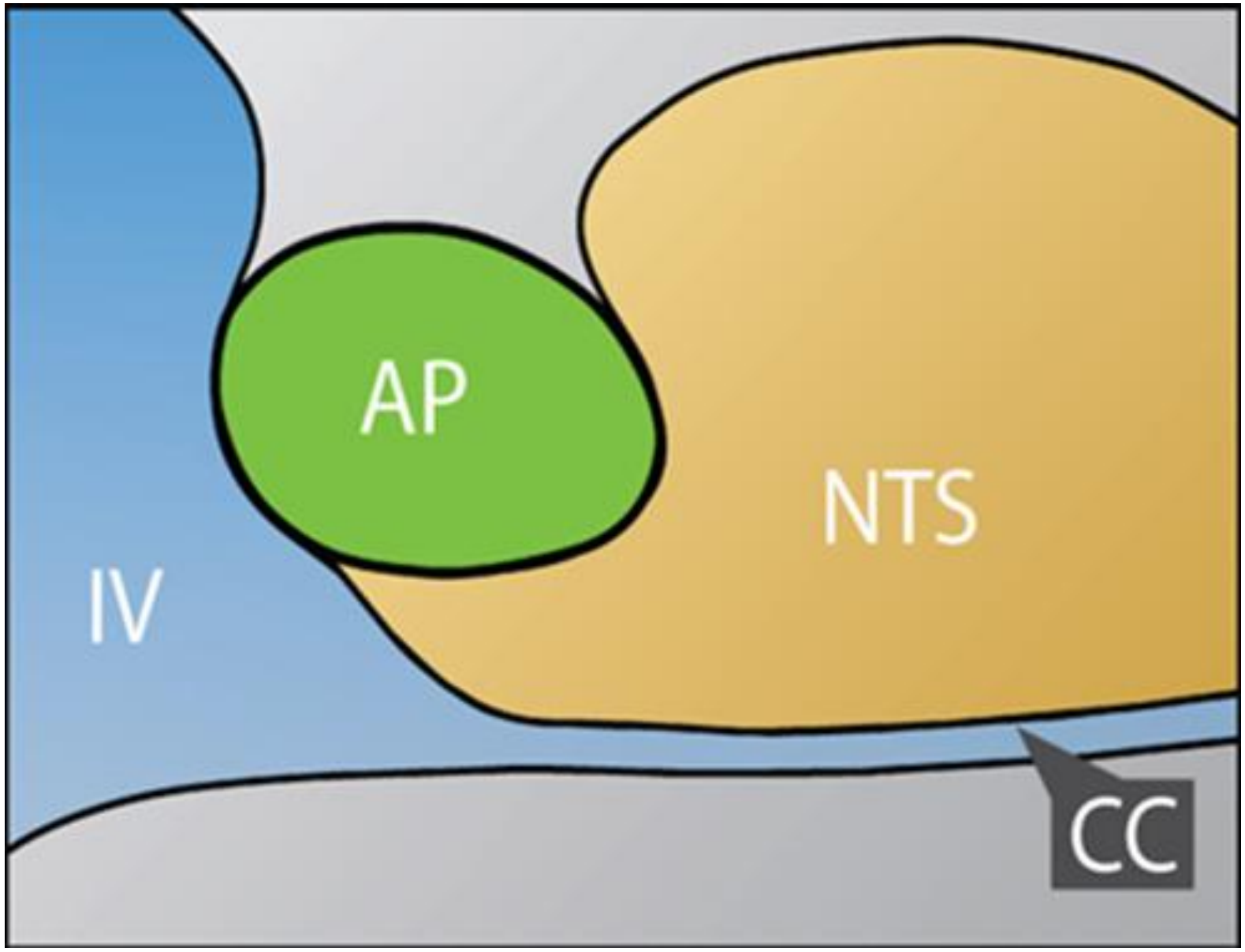
Abnormal BS transcription of speech 1935083

Site-specific NTS impairment 16198209

Portals for toxins




AREA
POSTREMA


AP
NTS
IV
CC

Early leads to NTS

Highest binding IV secretin 14715495

IVC secretin binds pNTS 6129683

Parental reports of potty-training after secretin consistent with NTS effect.

Early leads to NTS

Thalidomide: Days 20-24 critical period for ASD corresponds days 11.5-12.5 in rats. 9100317

NTS neuronal activity rats starts day 13. 9454844

NTS basics

1. First central synapse for visceral afference.
2. Modulates brain perfusion via baroreflex and autoregulation.
3. Seminal point for ascending noradrenergic system: social, arousal, mood, emotion, pain.

Regression as clue

Now widely recognized.

Subtle earlier problems in some cases.

An acute (days to weeks) loss of function, often extreme.

Brain findings in autism are consistent with toxicity

Oxidative stress

Inflammation

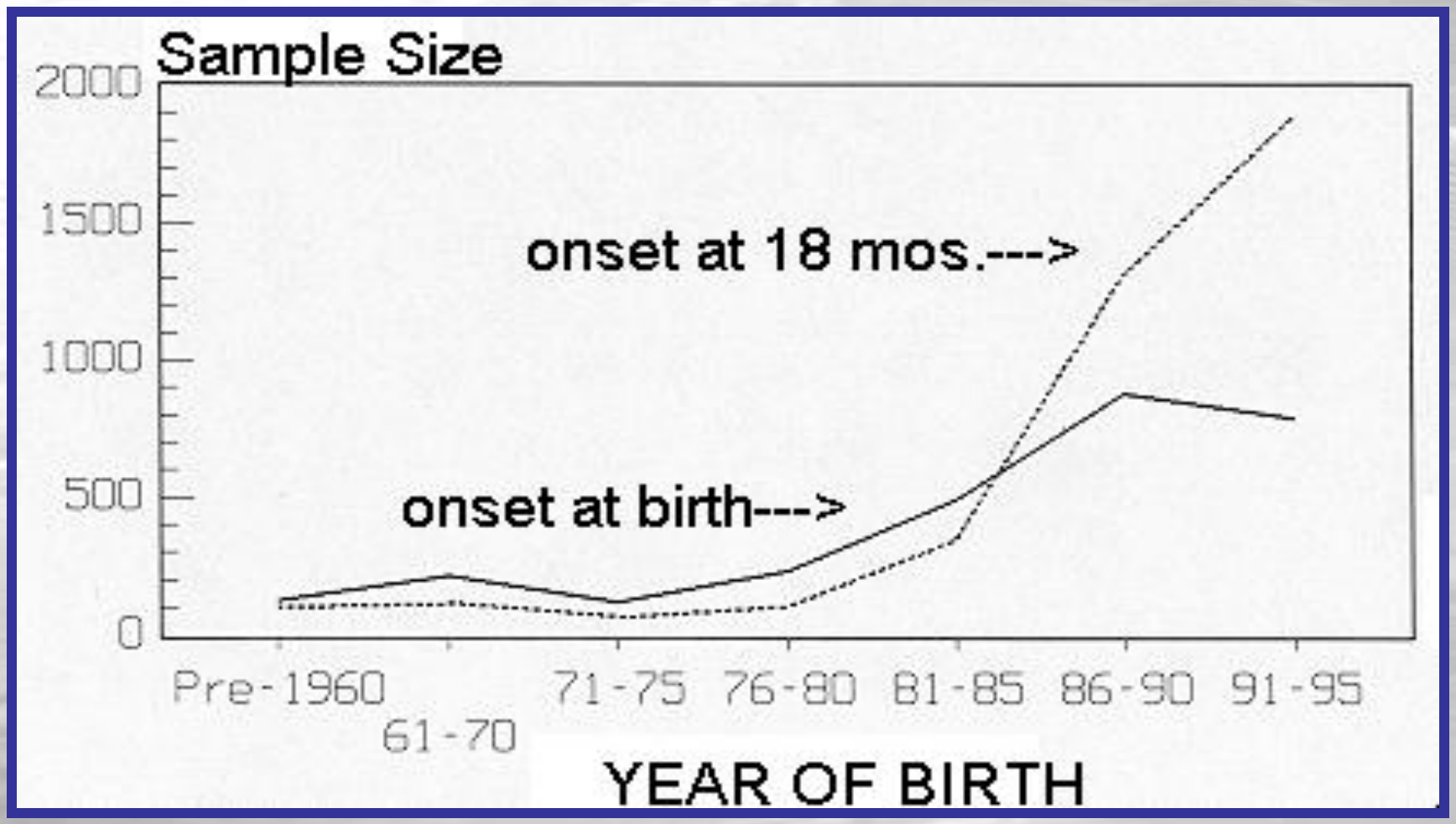
Gliosis

Neuronal loss

Is regression a poisoning?



ARI Database



Epidemiology

Parallel increase in autism and global toxins Lathe AJBB 2008

Autism rates correlate with:

- Landfills 21572830
- Estimated Cd and Hg 16966102
- Proximity to Hg 18353703
- Estimated Hg Nurses Health II 23816781

Inorganic mercury



Cadmium



MSG



Paraquat



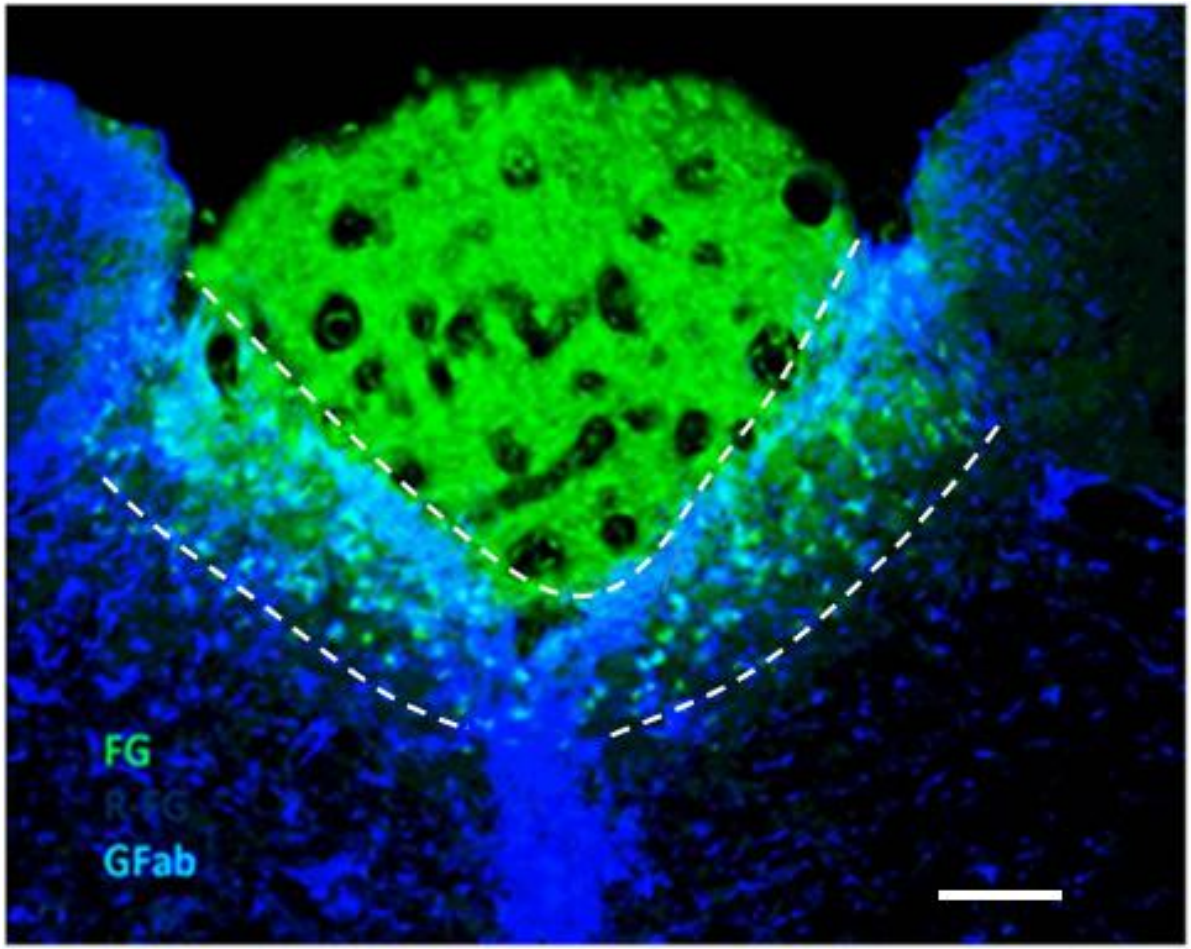
Endotoxin



Fluoride



permissiveNTS (pNTS)



Ionic mercury (Hg^{++})

Pink Disease 1890-1950

Of concern in food, air, water and soil. 19171026, 11569621

Accumulation in CVO associates with ↑ microglia, persists years. 8122267

Hallmarks are inflammation and autoimmunity. 17399758, 174554560

Daily organic mercury

In 6 brain areas, Hg^{++} averaged x30 at 6 months, x60 at 18 months.

By far, highest Hg^{++} at pituitary, only CVO examined.

Stop at 6 months, Hg^{++} in pituitary doubled at 12 months

8122267

Cadmium

Injections accumulate only in CVO (AP, pineal) 3822264

Strong oxidant, blocked by antioxidants 12927359, 18629305

Highly inflammatory (TNF-α) 15033544

Strongly inhibits NE uptake 6326468

Paraquat

Injections accumulate only in CVO, (AP, pineal) 7576891

Oxidative stress 8553365

↑TNF-α production, including LPS-stimulated monocyte TNF- α 18-fold

15890010, 1414690

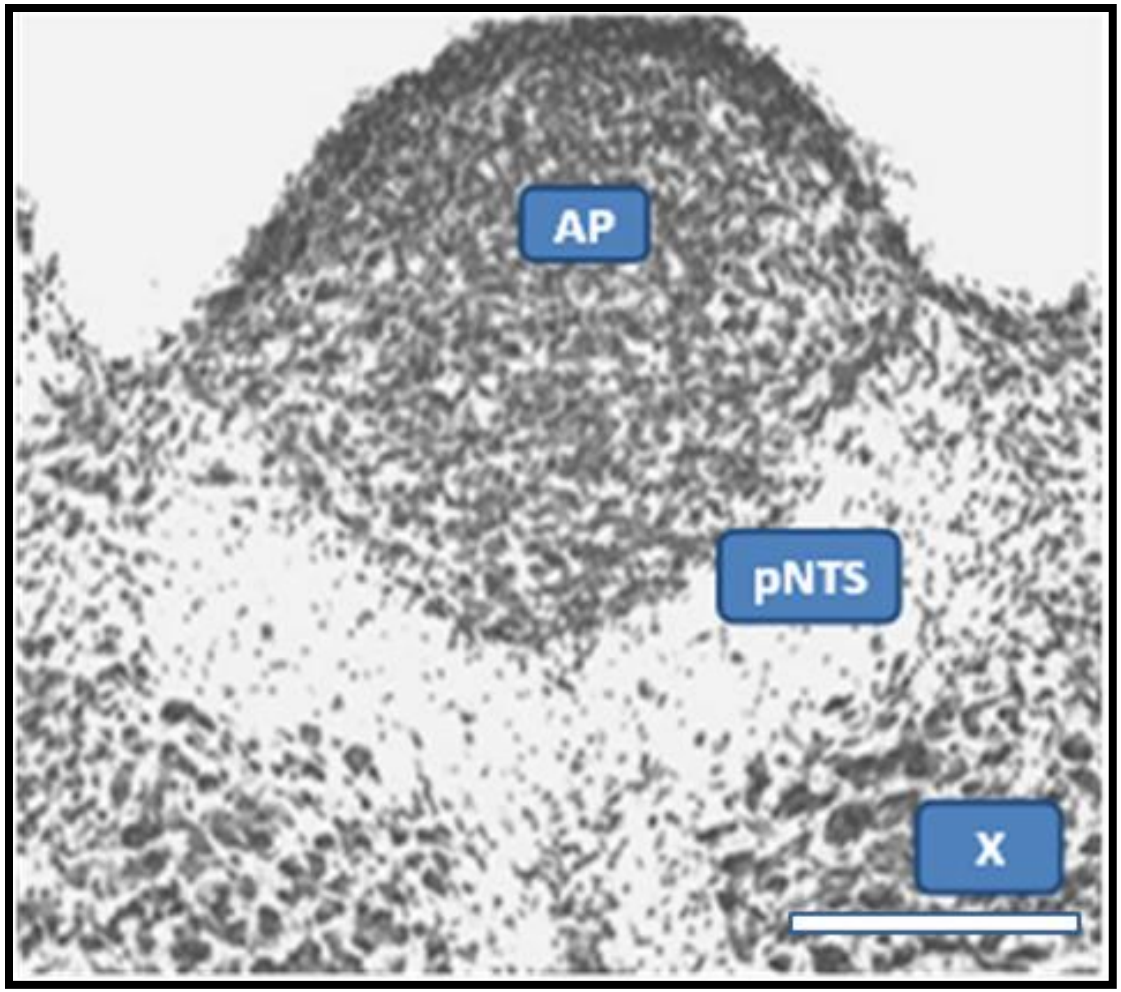
Monosodium Glutamate (MSG)

Injections accumulate only in CVO (AP / ME). 2415686, 2569986

Persistent oxidative effect. 12619899

TNF-α / neuronal death. 12419489

MSG effect on pNTS



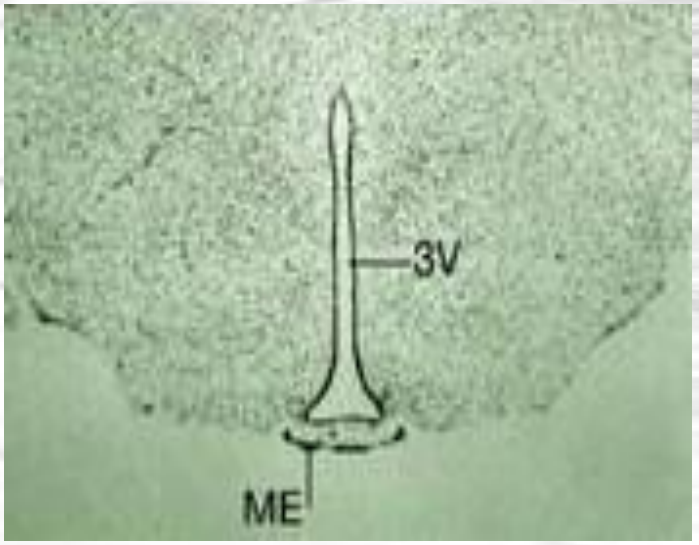
Endotoxin (LPS)

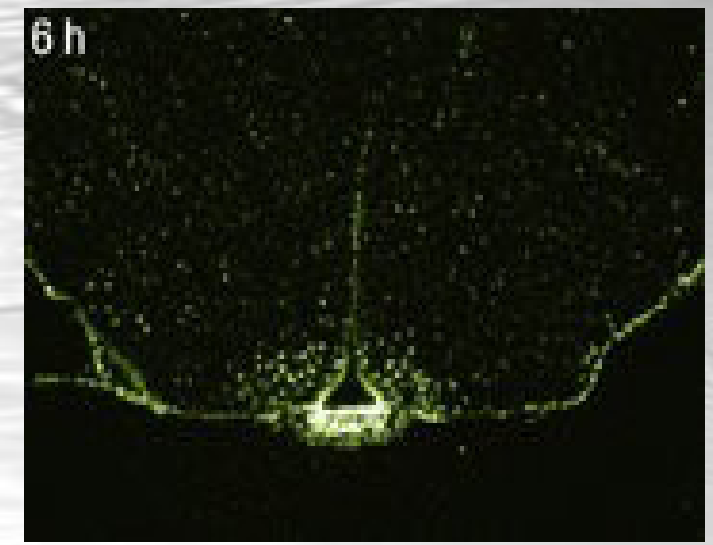
LPS induces immediate robust TNF-α only in CVO and adjacent structures, most intensely in AP and ME.

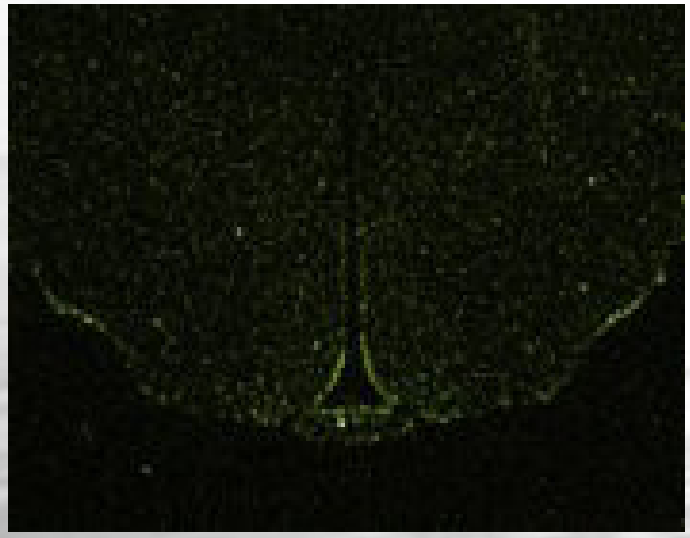
TNF-α expression in NTS at 1.5 hours, marked by 18 hours.

No TNF-α in DMV until 18 hours.

7972071

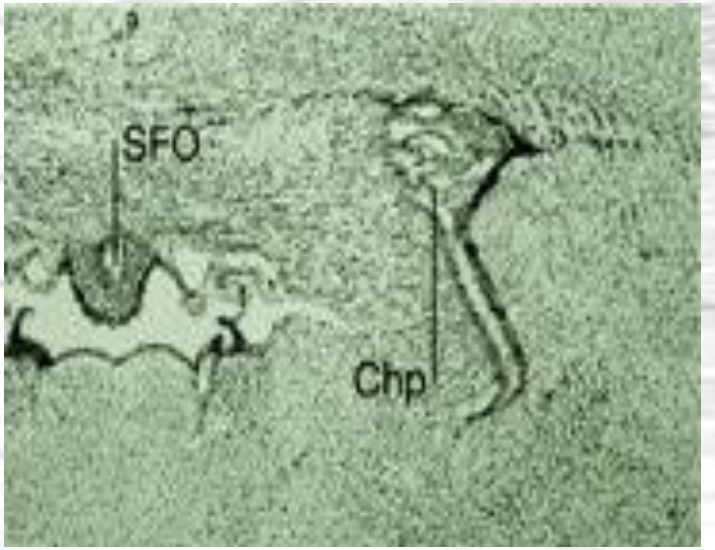


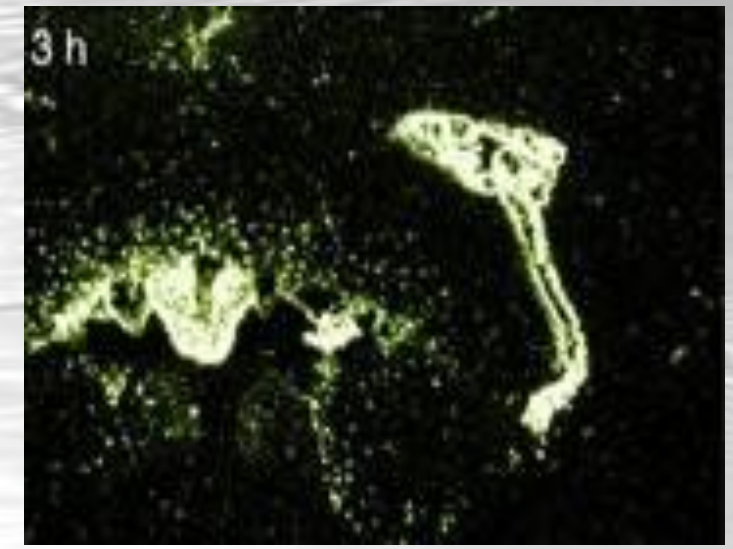


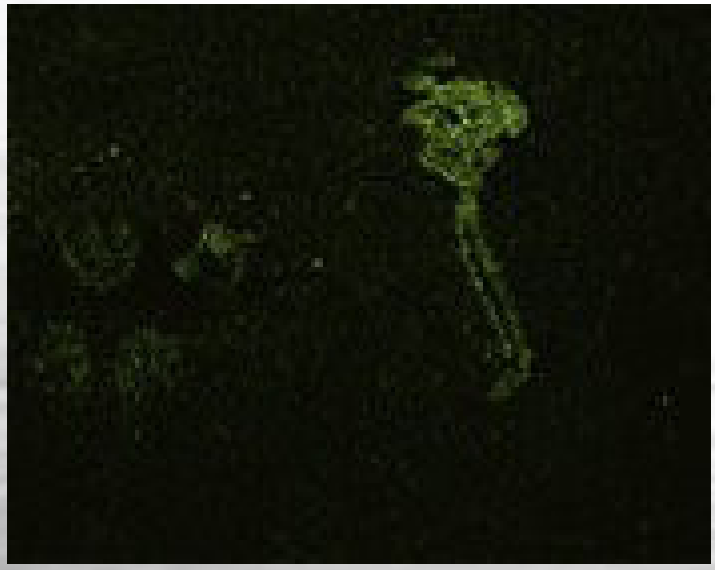


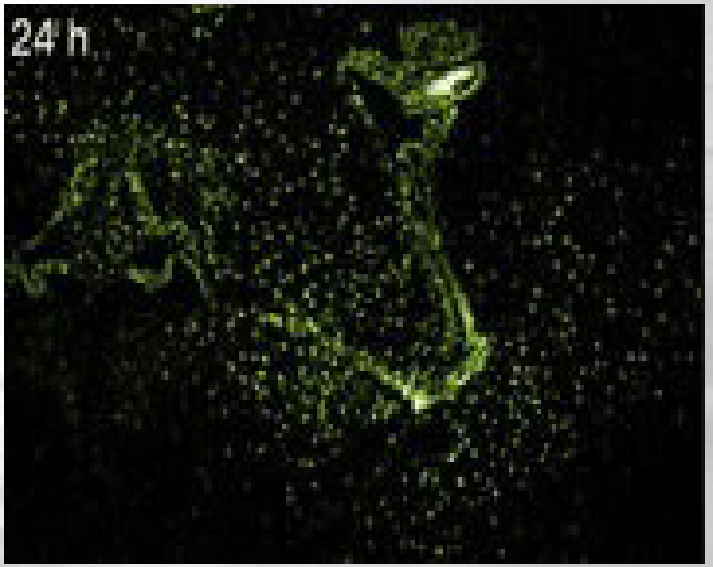


Nguyen MD, et al. Nature Reviews Neurosci 3, 216-27 (March 2002)


SFO
Chp


3 h




24 h

Chelation as clue

DMSA does not transit BBB.

Significant behavioral improvements in ASD after oral DMSA.

Pronounced effects on verbal communication and taste aversion.

19852790, 23400264



Case study: R.K.

Amalgam-associated regression consistent with laryngeal deafferentation.

- Age 4: Six amalgams
- Somnolent for 2 days
- Social and vocal decline; at 2 months whispered, “I am shouting,” then mute.

Case study: RK

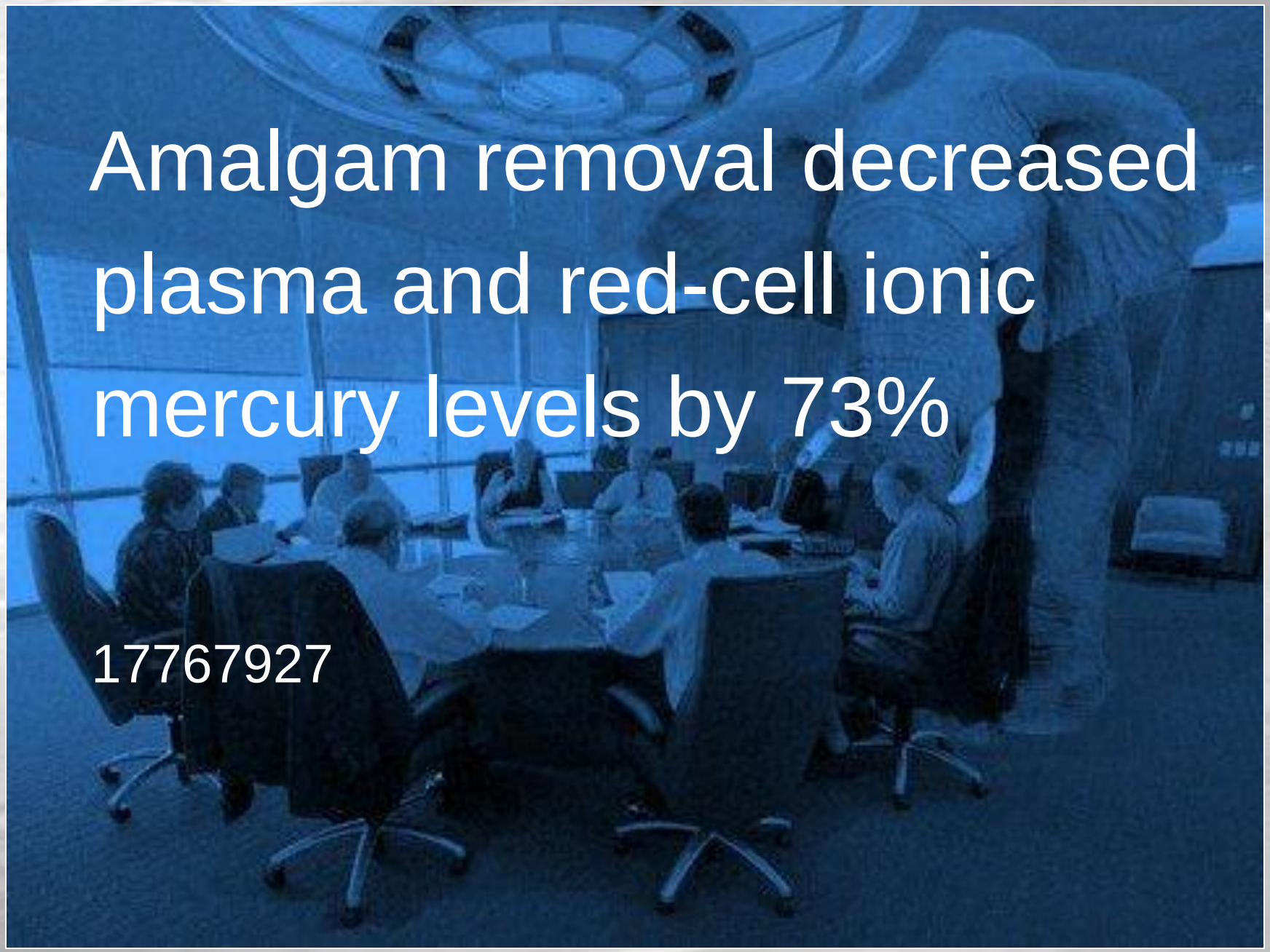
- 5 years: Dx LKS; few words, touch/sound sensitive, poor social.
- 6 years: More alert and talkative after secretin.
- 6 years 8 months: ~100 words; High Hg in serum, hair, urine. Lymphocytes very sensitive to Hg.

Case study: RK

- Age 7 amalgams removal without precautions
- “Band-aid” that night, mute in 48h
- Alert and cheerful on DMSA
- Low function age 16, surprising keyboard results

Case study: RK

- Consistent with amalgam-triggered regression
- Amalgam-Hg circulates as ionic
- Does whisper associate with regression?


Amalgam removal decreased plasma and red-cell ionic mercury levels by 73%
17767927

Whisper in regression

ARI data-base: whisper replaced baseline vocal X1 week in 4,029 ASD; of these 42% lost all vocal, 16% long-term whisper.

Surgical deafferentation→ severe vocal impairment; reduced GCF

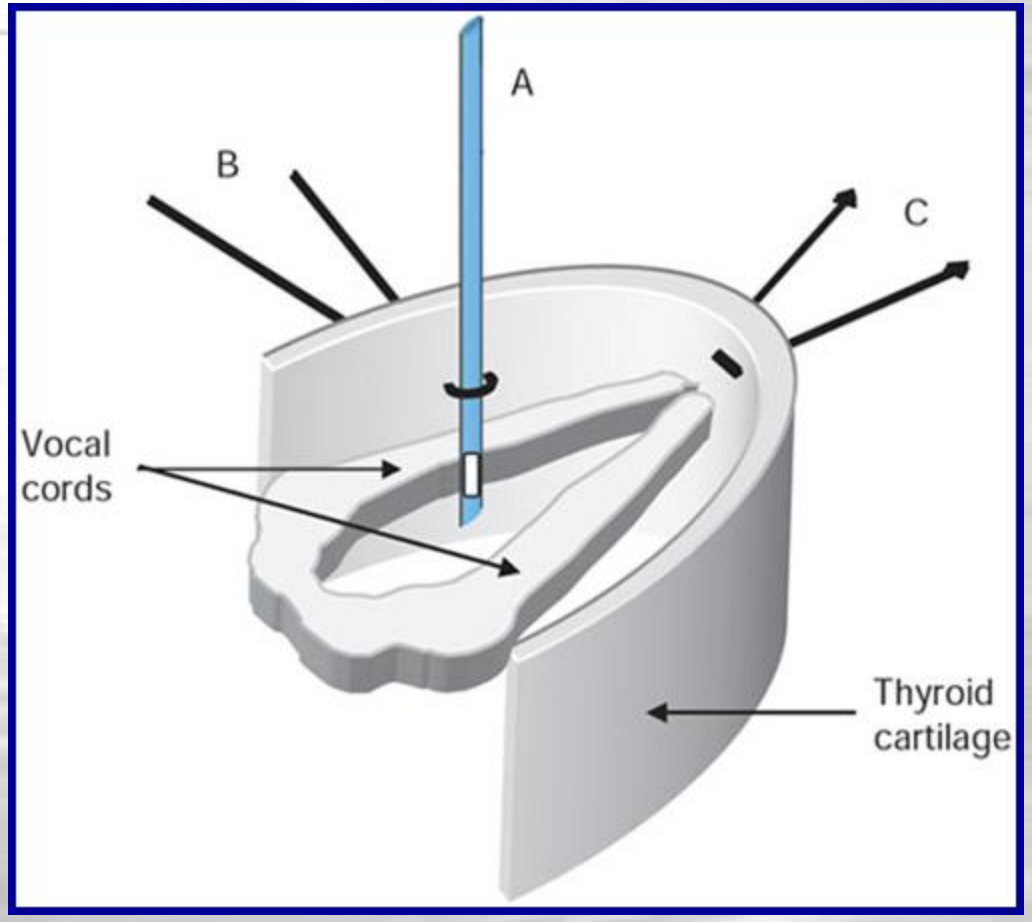
Laryngeal deafferentation

Unilateral division of SLN ↓ GCF 43% 15895781

Hyperthermia restored GCF 22097153

Temperature-sensitive vanilloid receptors in afferent terminals of NTS at level of AP 21734101

Reduced GCF → whisper



Parkinson's

Toxins suspected, inflammation is prominent.

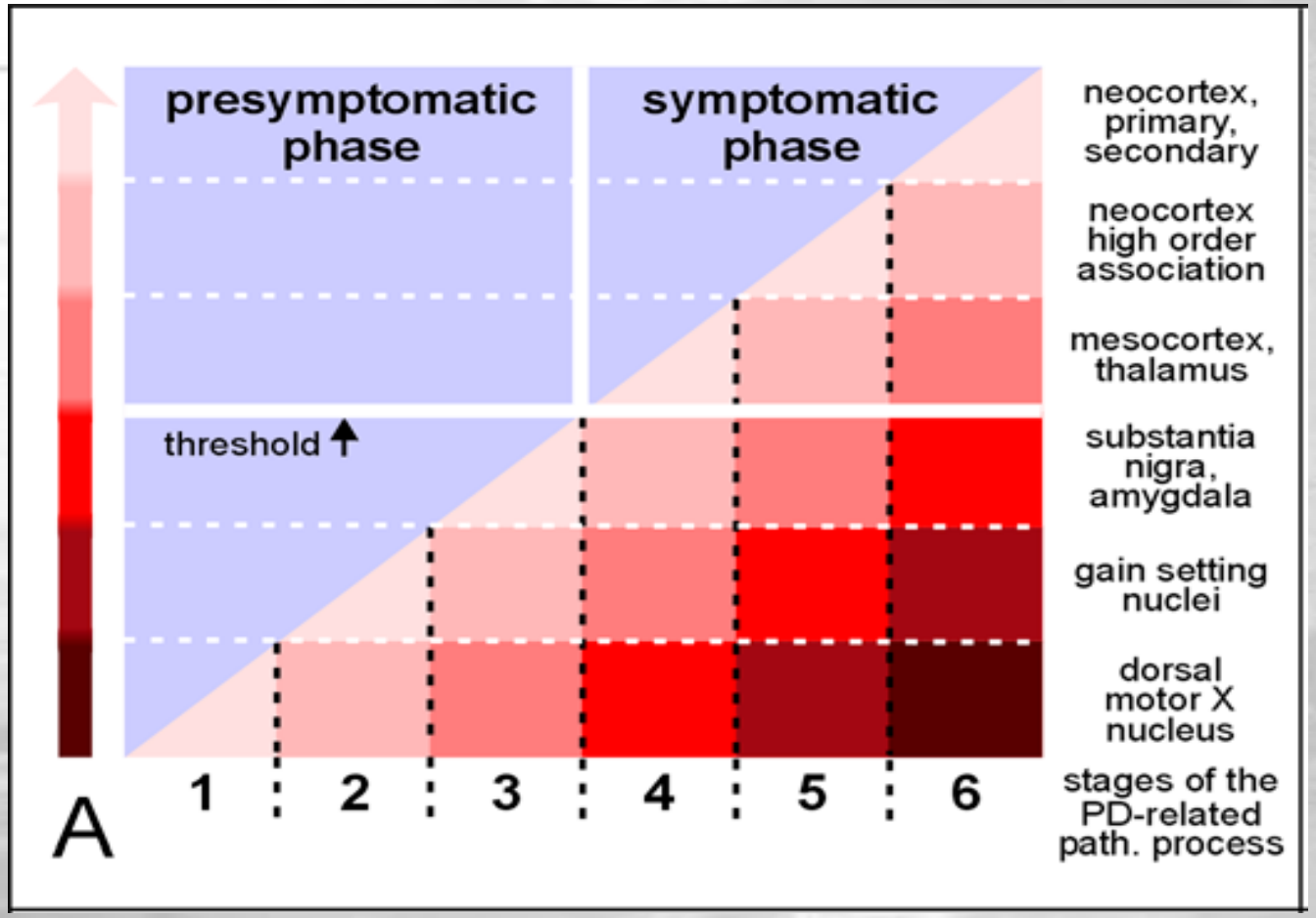
GI symptoms: ↓ motility, reflux 61%.

↓ GCF and associated whisper.

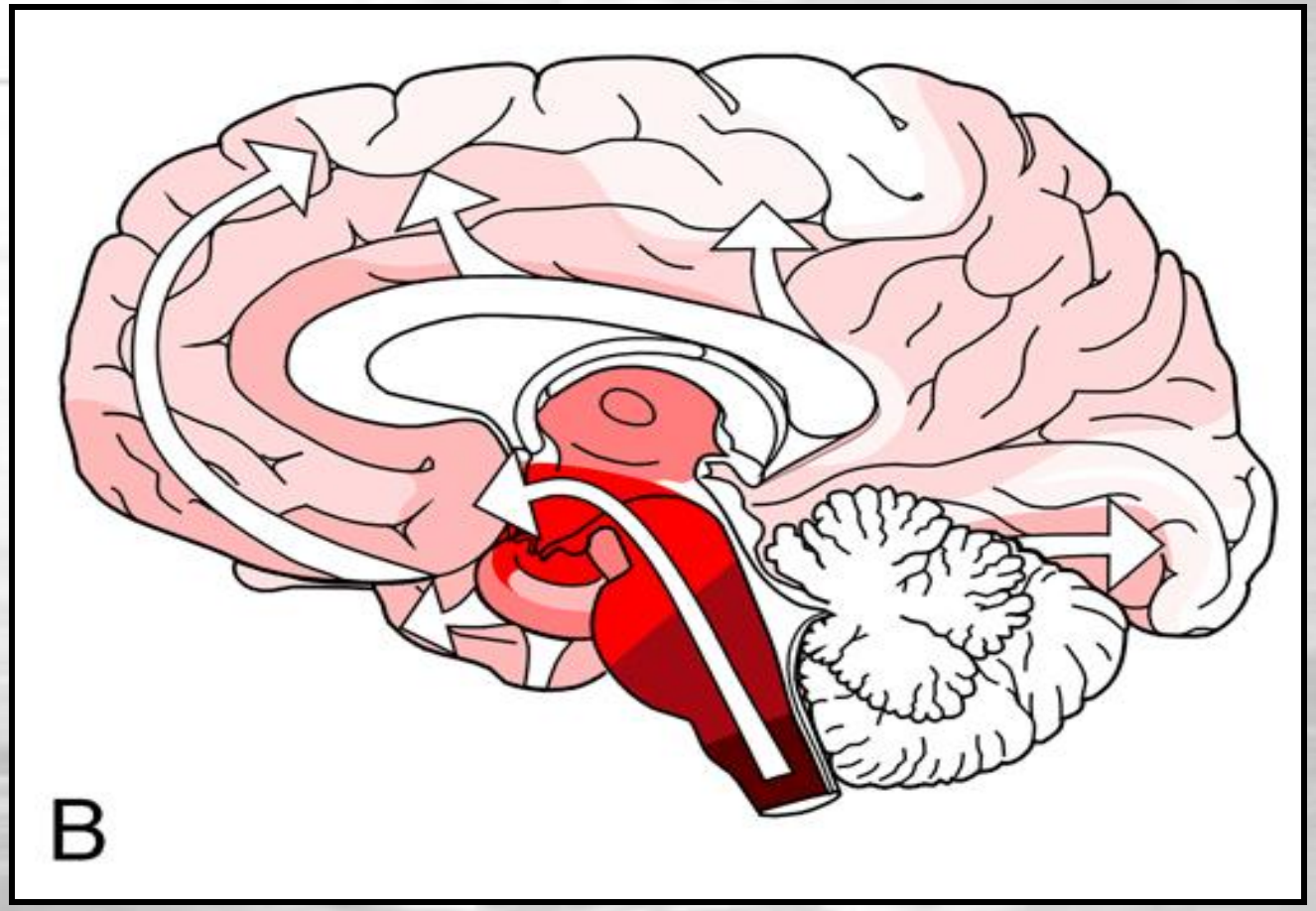
DMV proposed as first site of pathology

Ramifying pathology of PD

(Braak H., et al. *Cell Tissue Res* 2004;31:121-134)



Ramifying pathology of PD



Key realization

Afferent-block at NTS alters visceral function.

Gut deafferentation

Selective vagotomy→ ↓ gut secretory function 36992305

Opioid microinjection pNTS→ ↓ gastric motility 22796075

Splenic deafferentation

VNS studies of ACh knock-outs demonstrate that interruption of splenic afference shifts lymphocytes to proinflammatory, including increased TNFα.

21840939

pNTS and CBF

pNTS stimulation increases CBF. 11172744, 6727069

Lesions block baroreflex rapid adjustment of pulse to BP. 6697447, 10683503

Lesions block autoregulation of capillaries to local needs. 3090898

pNTS viscerotopy

- Baroreflex
- Autoregulation
- Stomach
- Intestine
- Larynx [Multiple refs in 24336025]

Experimental lesion increases salt and water intake, as in ASD

19448907, 10206527, McGinnis CRC 2010

NTS has borderline circulation

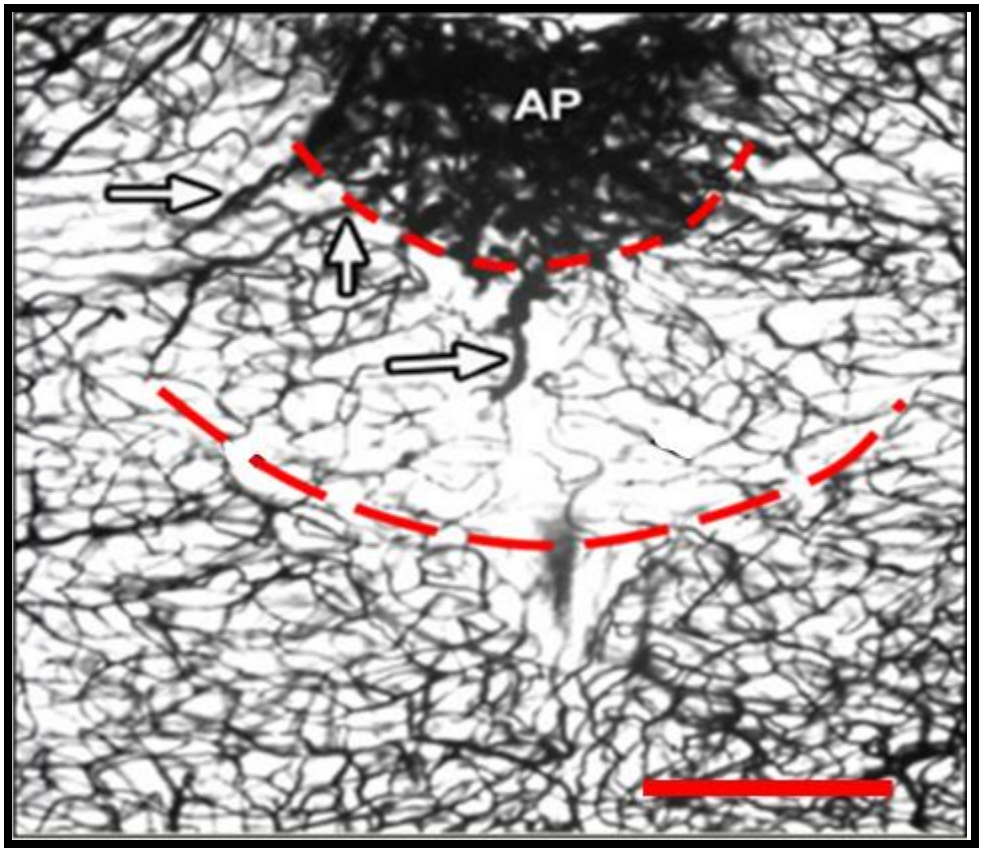
Localized NTS infarcts after hypoxic or hypotensive events 16167549, 10797184

High NMDA →hypoxic sensitive 10336064

Lower capillary density 2040734

Re-entrant blood from AP 17451045

Hypovascular pNTS



Hypoxic pNTS

AChE pro-dilatory and prominent

17451045

Ionic mercury, cadmium, MSG and nitrite reduce AChE

17355286, 17337106, 17451045, 20457208

Oxidative stress increases blood viscosity 10599593

Freeways and CO? 21156395

SHR: NTS inflammation

Ischemia/hypoxia → microvascular inflammation 18585782, 10203141

Marked inflammation, high pro-inflammatory JAM-1 in NTS microvasculature of SHR 17420334

Potent vasodilator CGRP ↑↑ in blood of SHR and neonates later diagnosed ASD 1742763, 11357950

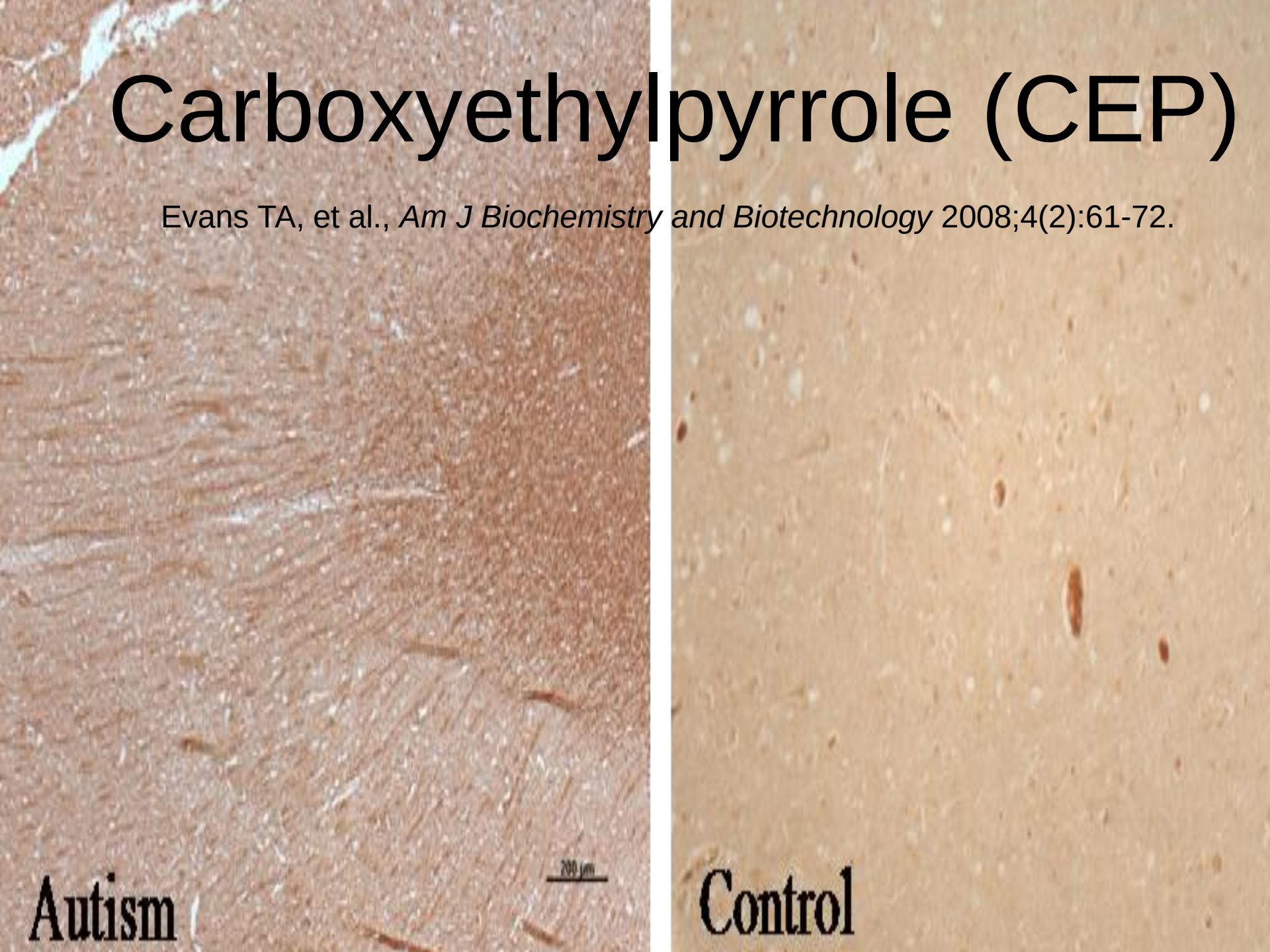
NTS as cytokine epicenter?

Proposed long-distance ascent of cytokines from CSF along nerve bundles 11126391

TNF-α known to diffuse via small channels outside myelinated axons 8596642

Carboxyethylpyrrole (CEP)

Evans TA, et al., *Am J Biochemistry and Biotechnology* 2008;4(2):61-72.



ASD and fetal hypoxia

Fetal distress, prolonged labor, cords, Apgars, C-section 19567888

Low fetal pH 20370976

Newborn encephalopathy X6 ASD 16417661

A_2 neurons

Ascending NA system: affect, social, learning, sickness behavior 20962208

NE compensatory in ischemia and excitoxicity 19279246

Clinical response to clonidine suggests central NE deficit 19059284

Clonidine acts at NTS to increase vagal tone 20553874

A_2 and hypoxia

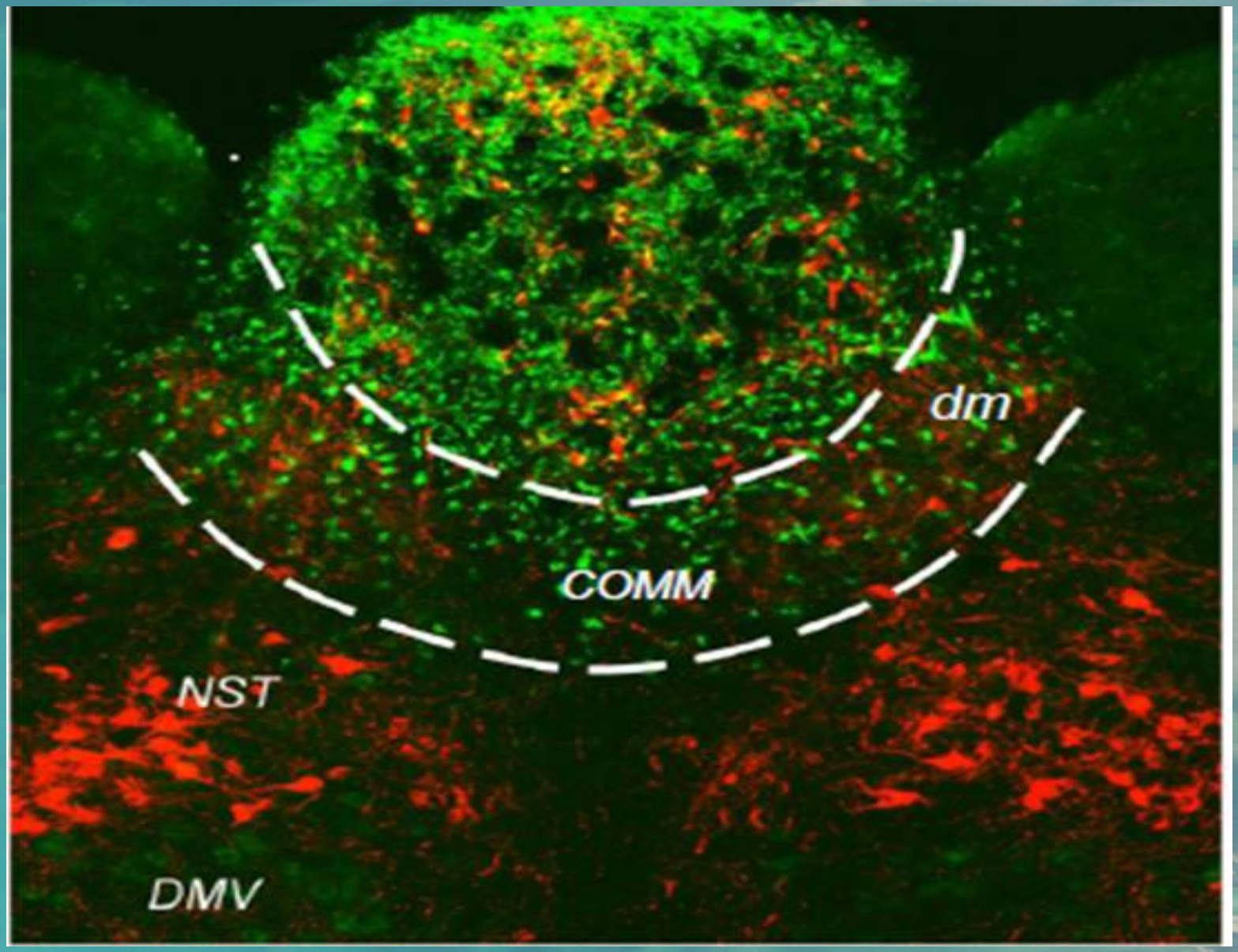
Hypoxic insult to A_2 may depress vasodilatory adenosine? 24336025

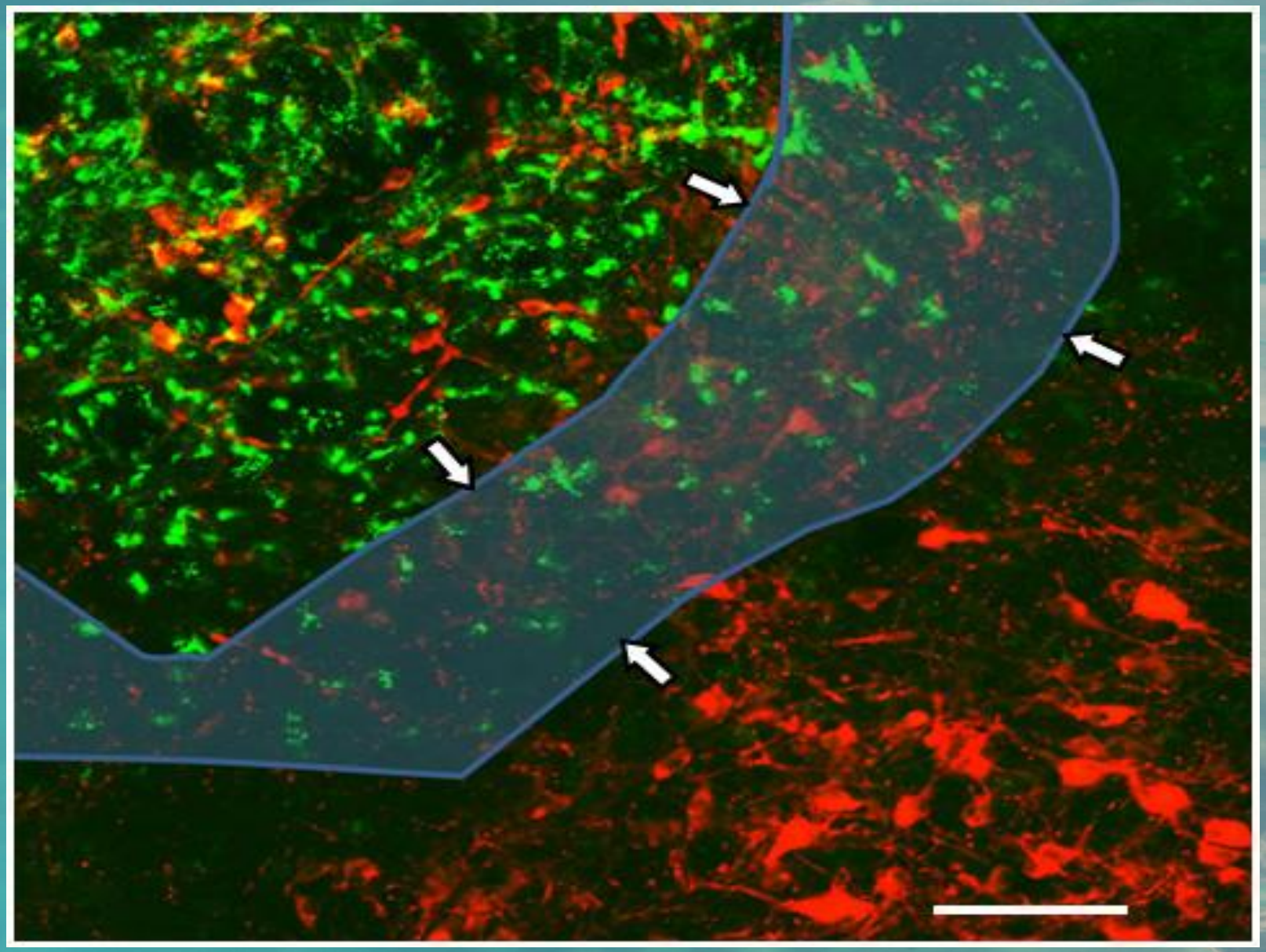
Hypoxic/ischemic pups: ↓ A_2 18356740

Neonatal asphyxia: persistent change in A_2 function 9443281,14577519

Perinatal MSG depressed NE from A2 long-term, no morphologic change.

14738902


dm
COMM
NST
DMV

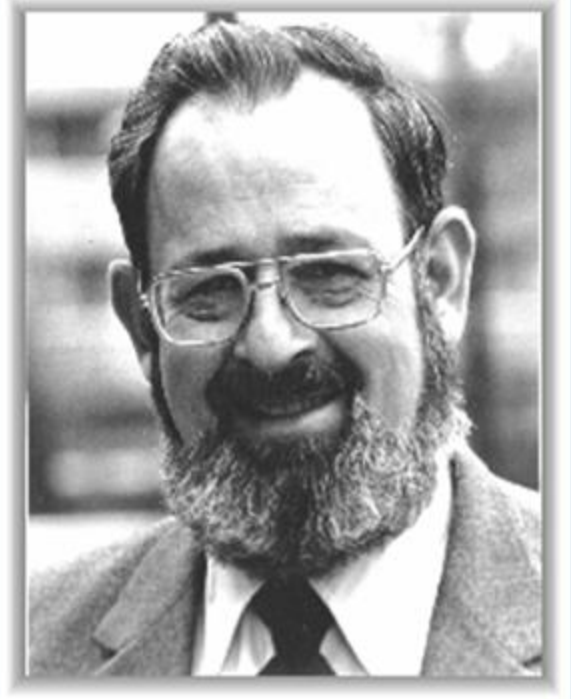


Vitamin B_6 and NTS

CBS is alternative pathway for H_2S

12213817

H_2S ↑ afferent Transmission in NTS 21734104



Potential treatments

Detoxification

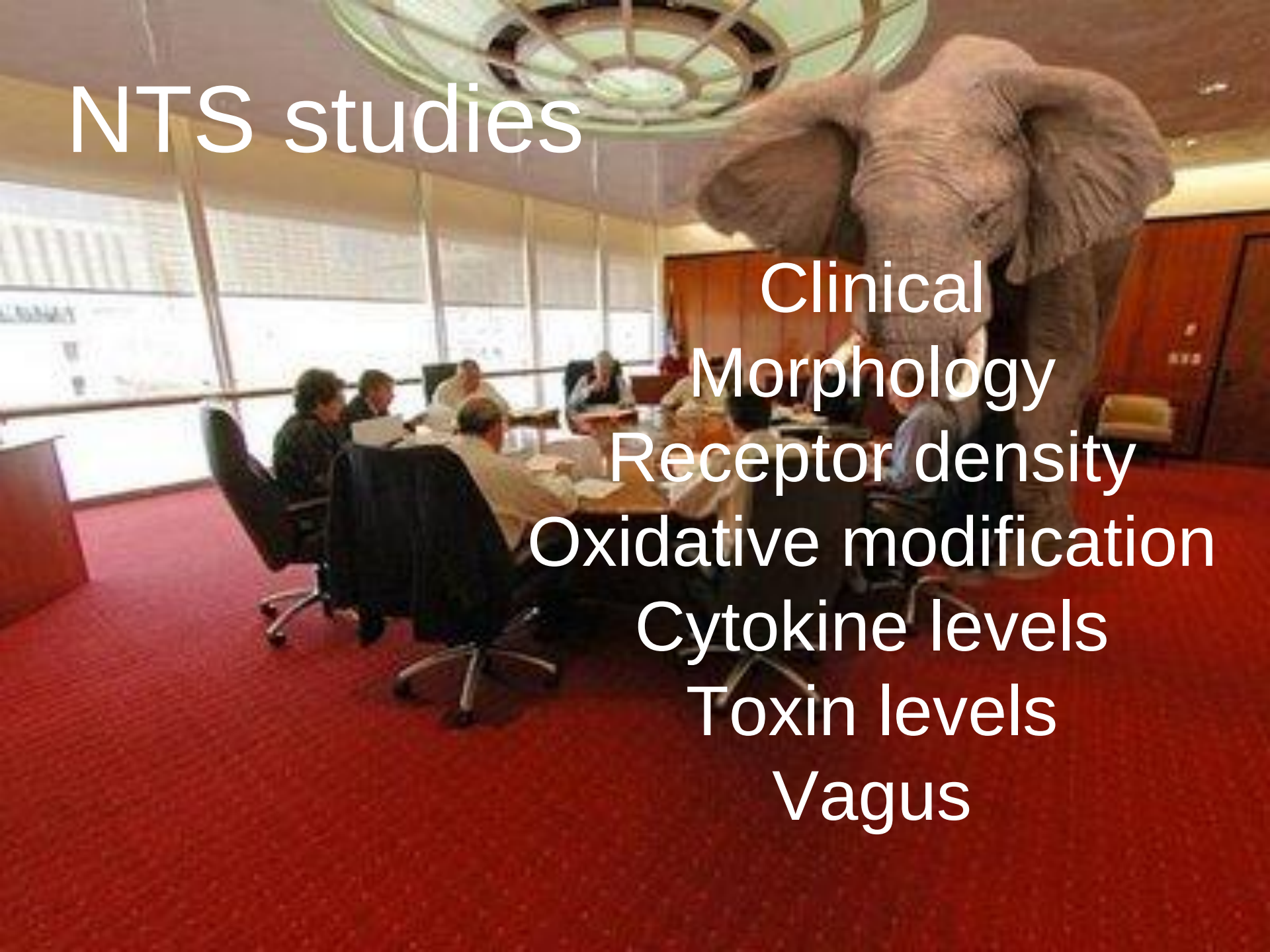
Immune modulation

Regenerative factors

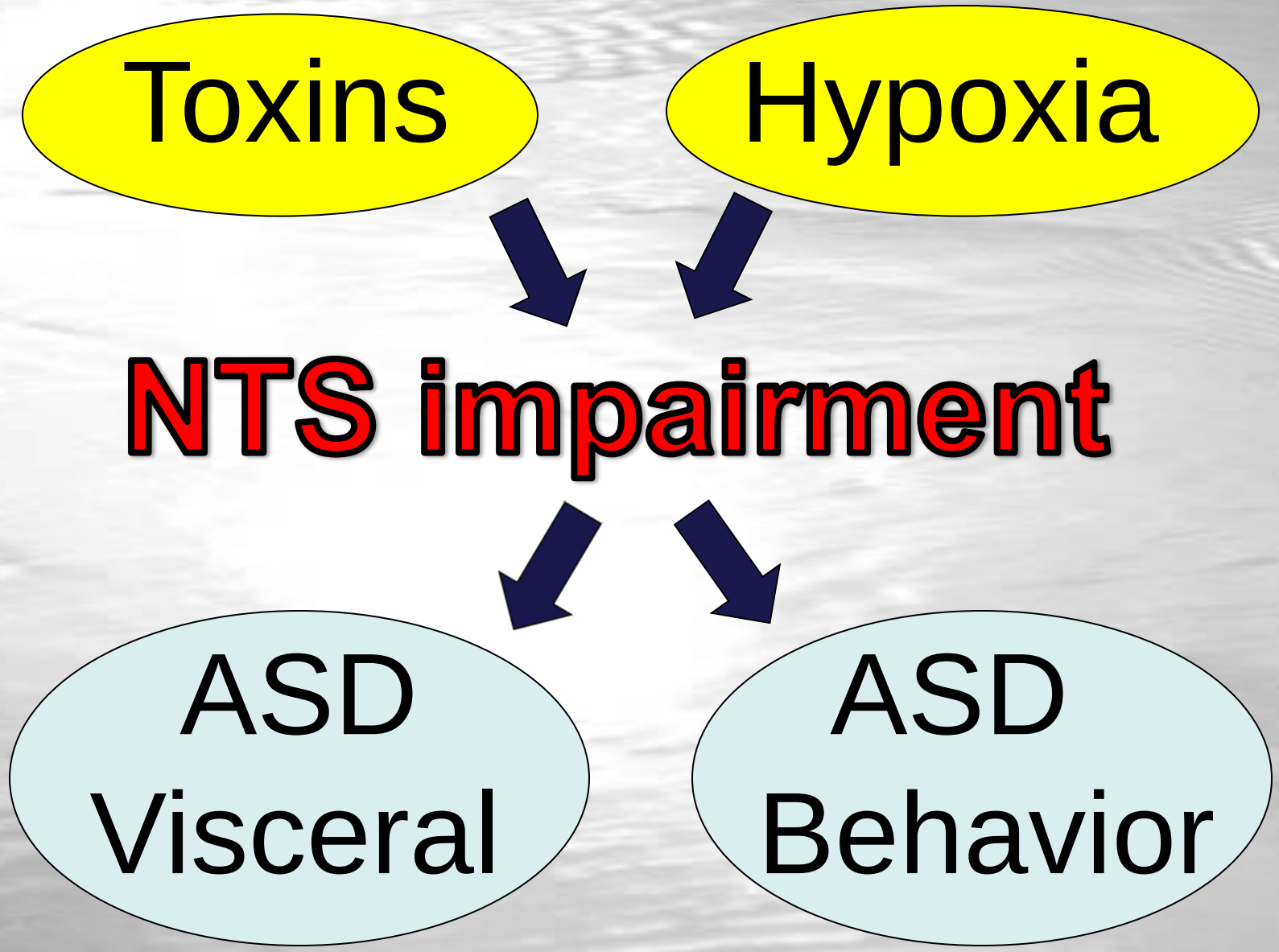
VNS, including auricular

Anmian point

NTS studies



Clinical
Morphology
Receptor density
Oxidative modification
Cytokine levels
Toxin levels
Vagus


Toxins
Hypoxia
NTS impairment
ASD
Visceral
ASD
Behavior

