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The Brain Concerns in ASD are More than the Gut – Brain Connection: Neurotransmitters and Neuroimmune Issues in Autism Spectrum Disorders

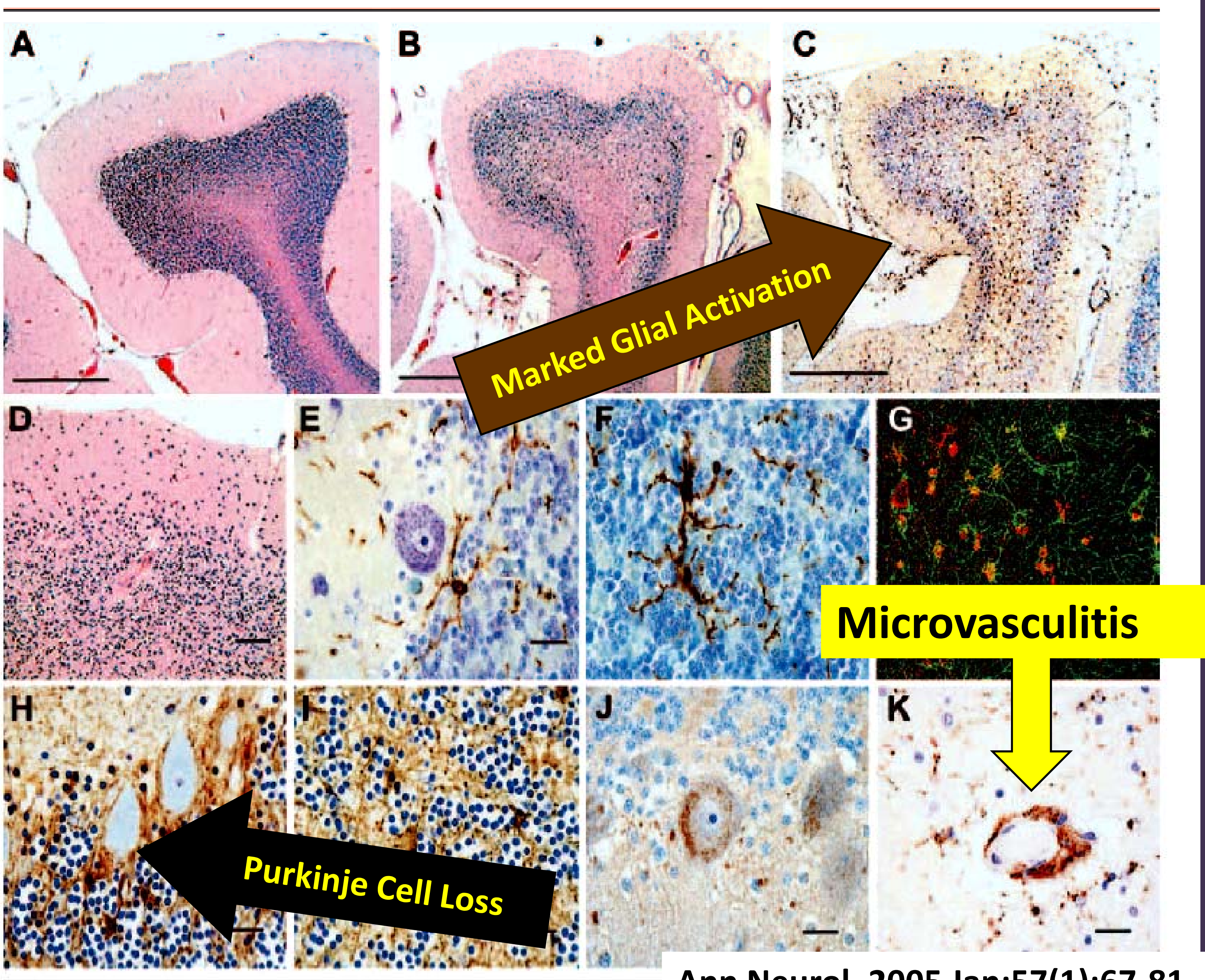
James Jeffrey Bradstreet MD, MD(H) FAAFP
Director, ICDRC, Florida, Arizona & California
Adjunct Professor: Southwest College of Naturopathic Medicine
321-259-7111
www.icdrc.org

Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,[1,2] Caterina Nascimbene, MD,[1–3] Chitra Krishnan, MHS[1]
Andrew W. Zimmerman, MD,[1,4] and Carlos A. Pardo, MD[1,2,5]

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)–1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Ann Neurol. 2005 Jan;57(1):67-81



Ann Neurol. 2005 Jan;57(1):67-81

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Neurobiology of Disease 30 (2008) 303 – 311

Immune transcriptome alterations in the temporal cortex of subjects with autism

Krassimira Garbett,[a] Philip J. Ebert,[a] Amanda Mitchell,[a] Carla Lintas,[b,c] Barbara Manzi,[d] Károly Mirnics,[a,e,*] and Antonio M. Persico[b,c,*]

[a] *Department of Psychiatry, Vanderbilt University, Nashville, USA*
[b] *Laboratory of Molecular Psychiatry and Neurogenetics, University "Campus Bio-Medico", Rome, Italy*
[c] *Laboratory of Molecular Psychiatry and Psychiatric Genetics, Department of Experimental Neurosciences, I.R.C.C.S. "Fondazione Santa Lucia", Rome, Italy*
[d] *Department of Child Neuropsychiatry, University "Tor Vergata", Rome, Italy*
[e] *Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, USA*

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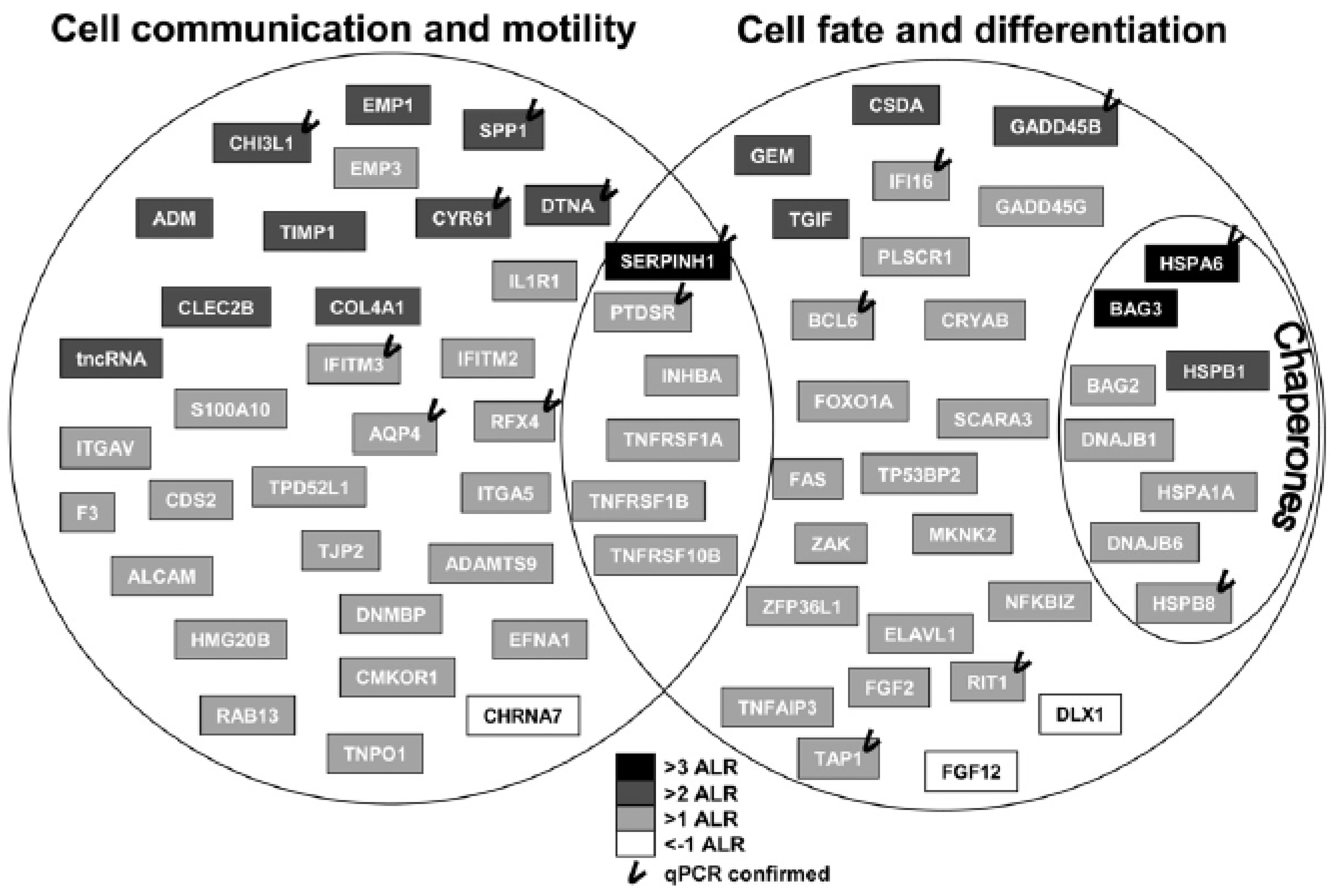
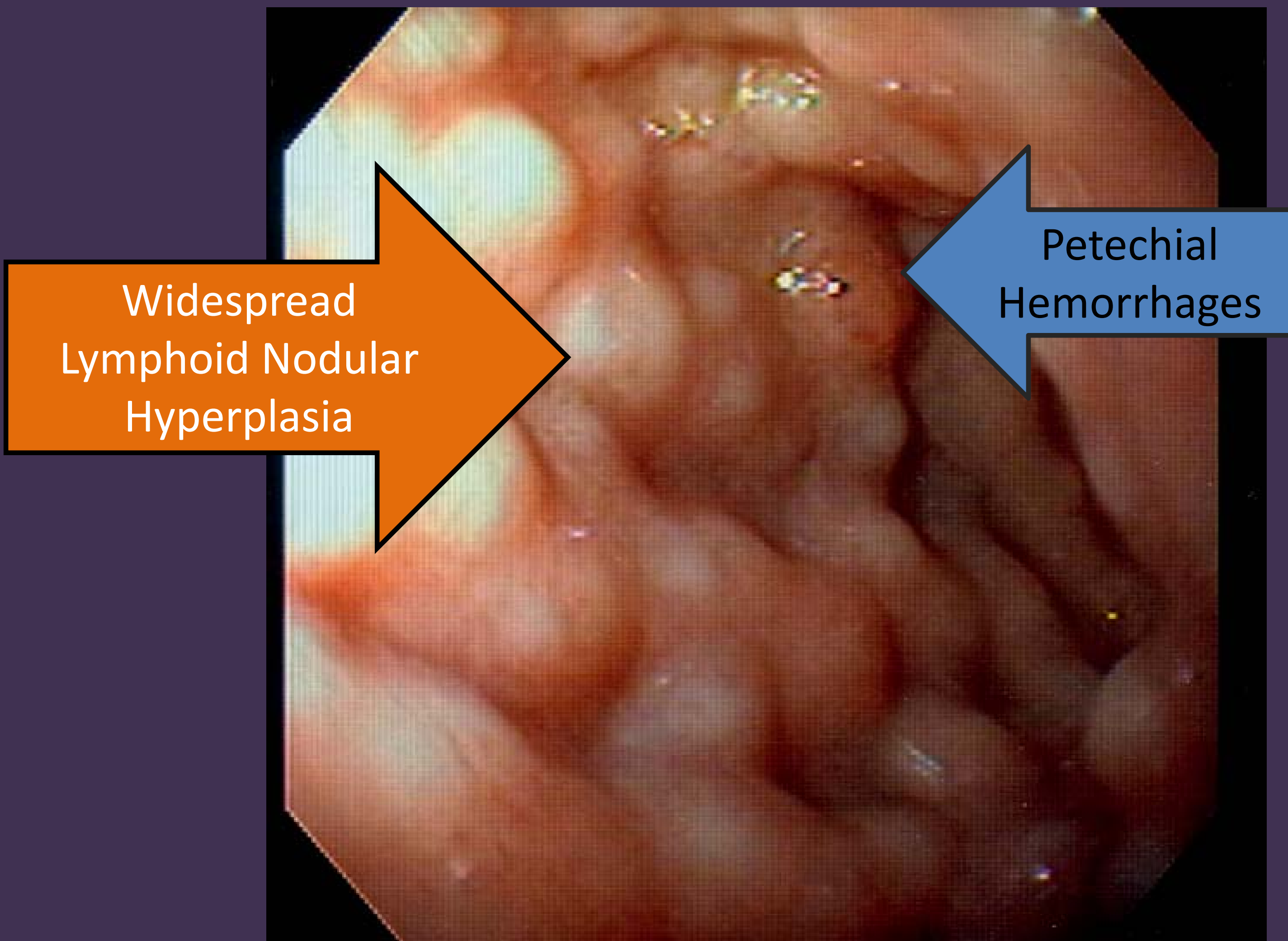
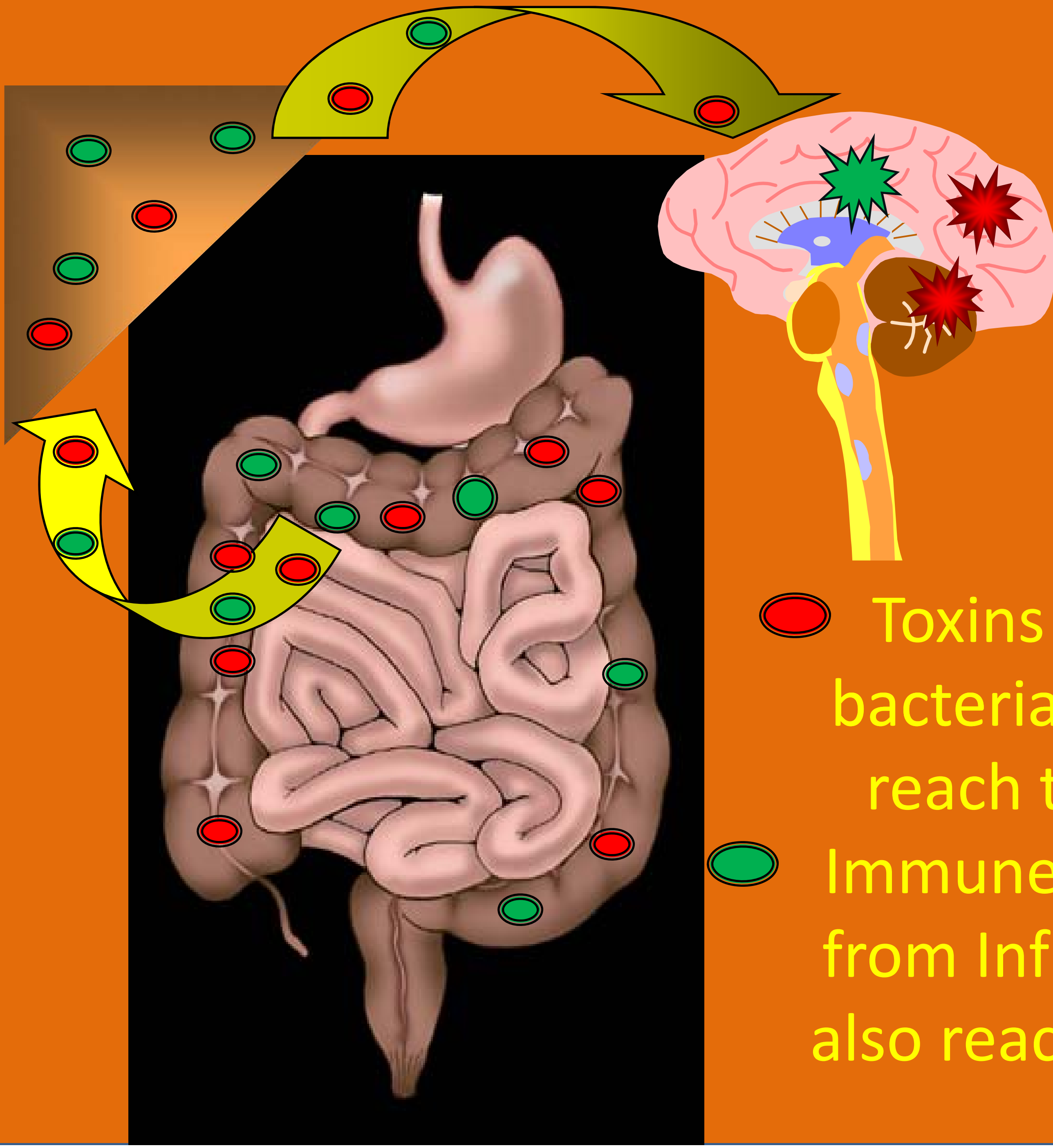


Fig. 3. Autistic samples show altered expression of transcripts involved in cell communication and differentiation. Differentially expressed genes were functionally classified based on literature search (for references, see Supplemental material 2). We observed a strong overrepresentation of differentially expressed transcripts mediating cell communication and motility, cell fate and differentiation, and chaperones. The magnitude of the gene expression change is coded by cell shading, and checkmarks denote successful qPCR validation of differential expression. Note that the transcript inductions (grey boxes) greatly outnumbered transcript repressions (white boxes).

Inflammation is present in the gut of ASD children





Toxins from gut bacteria and yeast reach the brain.

Immune chemicals from Inflammation also reach the brain

Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders

Anne M. Connolly, MD, Michael G. Chez, MD, Alan Pestronk, MD, Susan T. Arnold, MD, Shobhna Mehta, BSc, and Ruthmary K. Deuel, MD

(J Pediatr 1999;134:607-13)

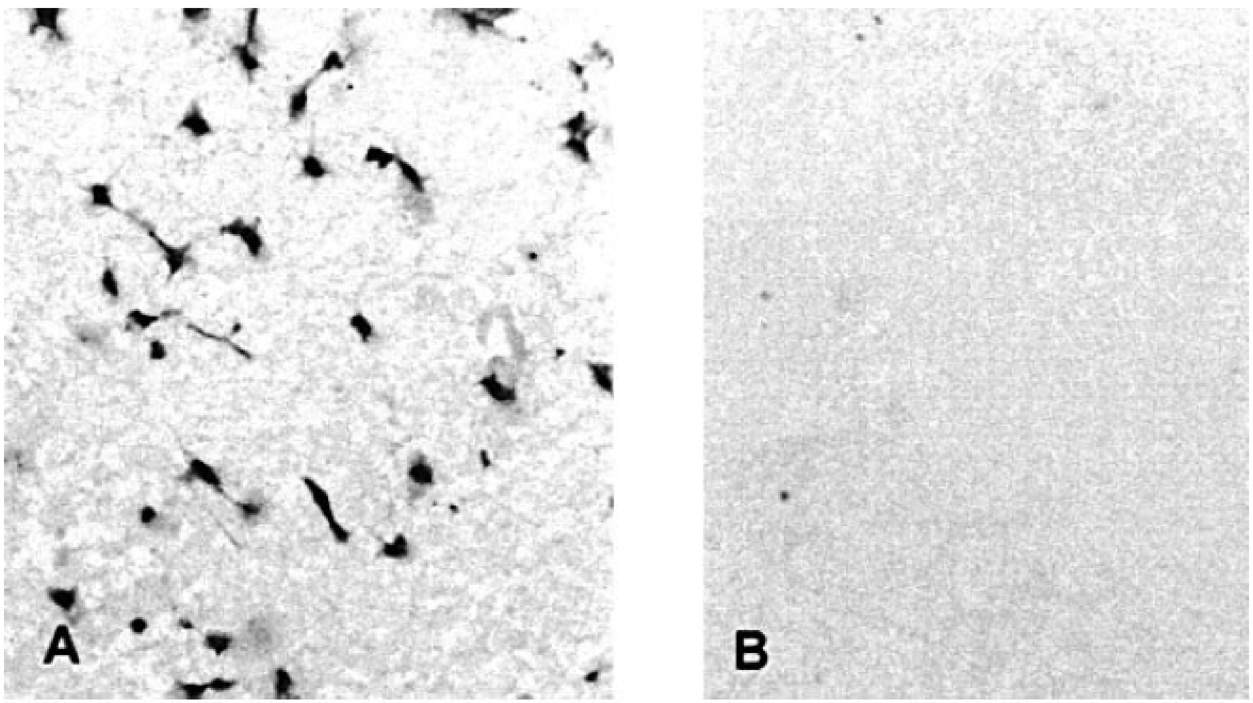
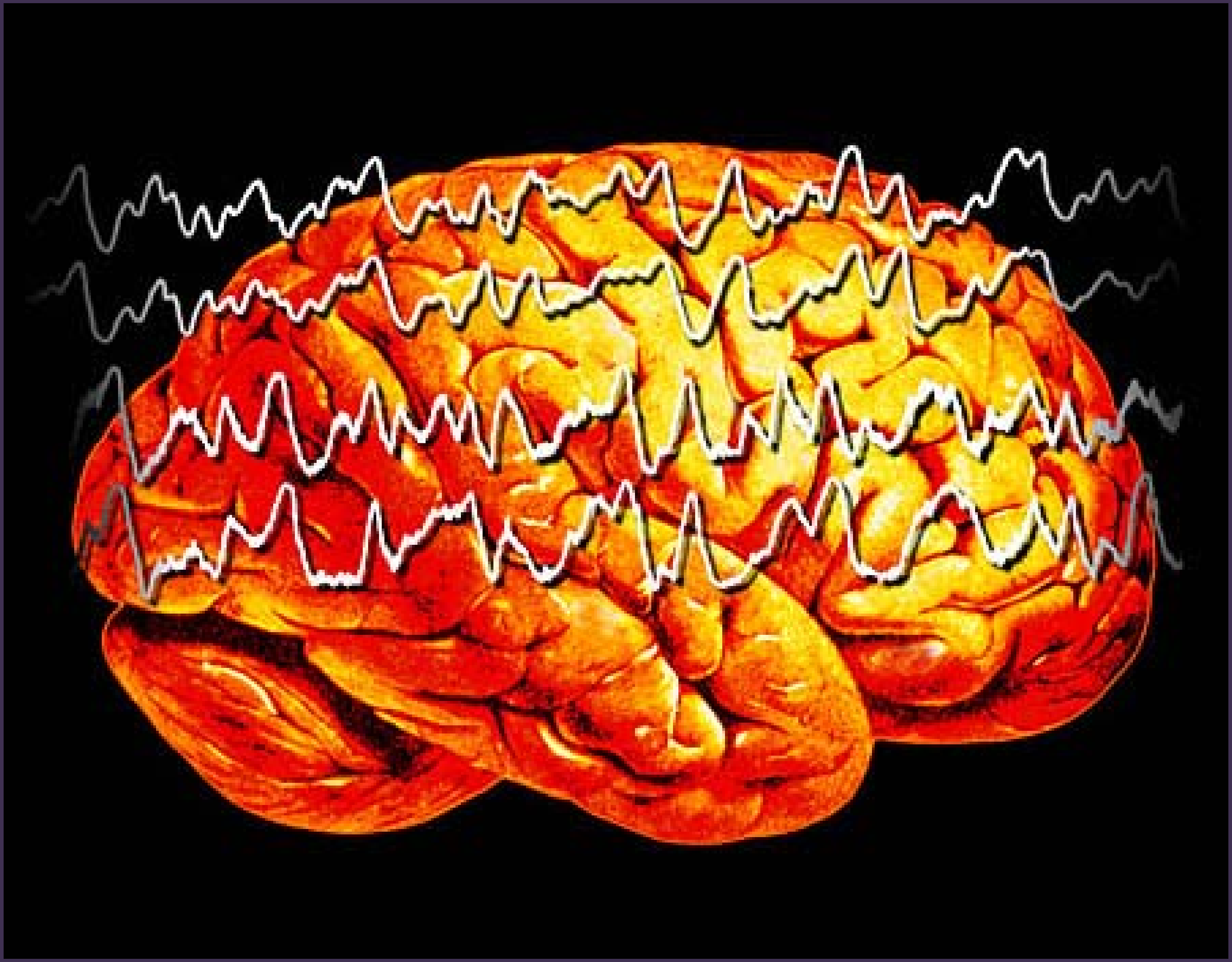
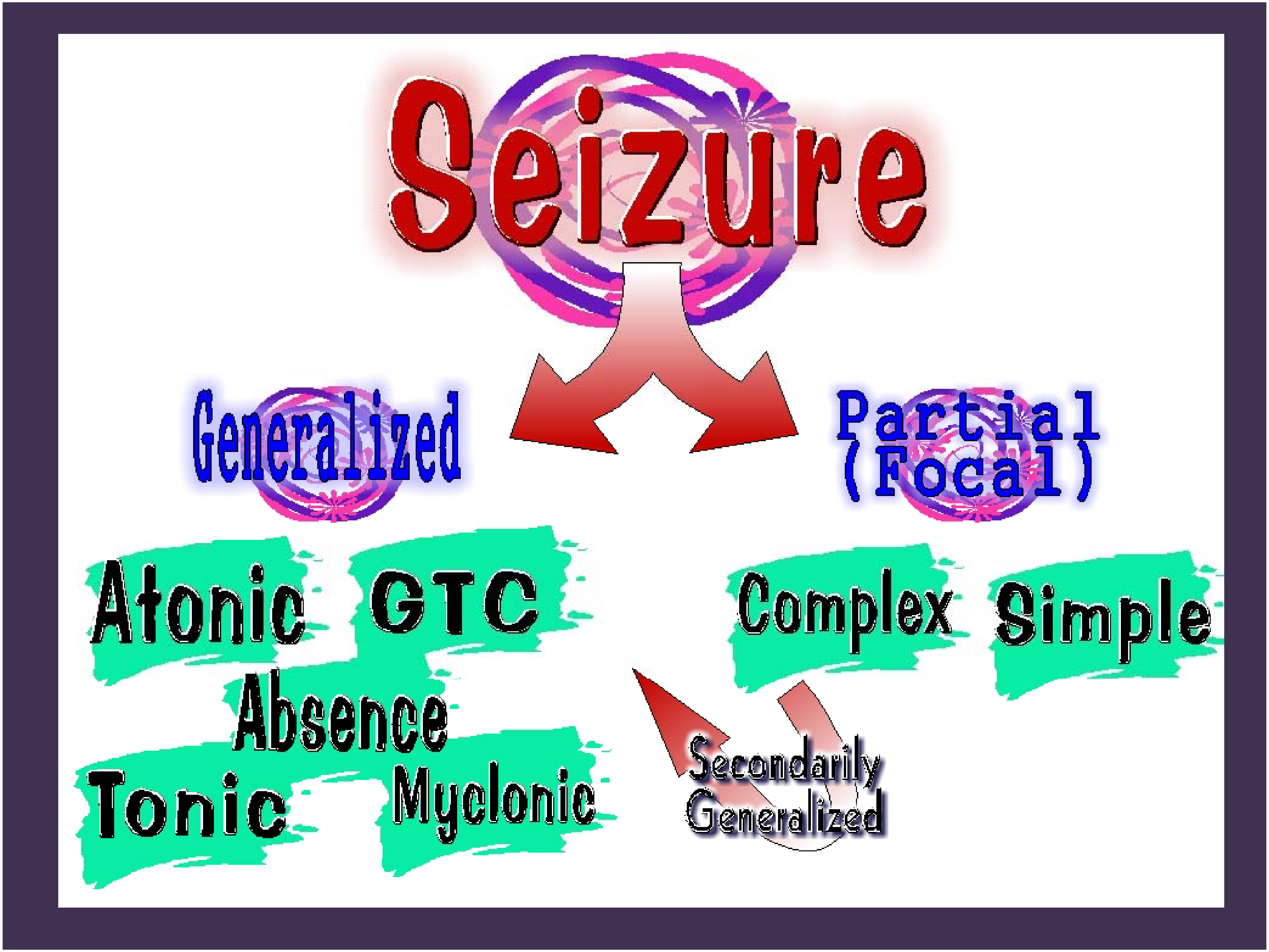


Fig 1. **A,** IgG antibodies from a child with LKSV binding to small blood vessels in human temporal lobe cortex (original magnification ×80). Immunostaining (1:100) demonstrates distinct capillary staining. **B,** Control serum shows no specific labeling.

Epilepsy and ASD




Seizure
Generalized
Partial
(Focal)
Atonic
GTC
Absence
Tonic
Myclonic
Complex
Simple
Secondarily
Generalized

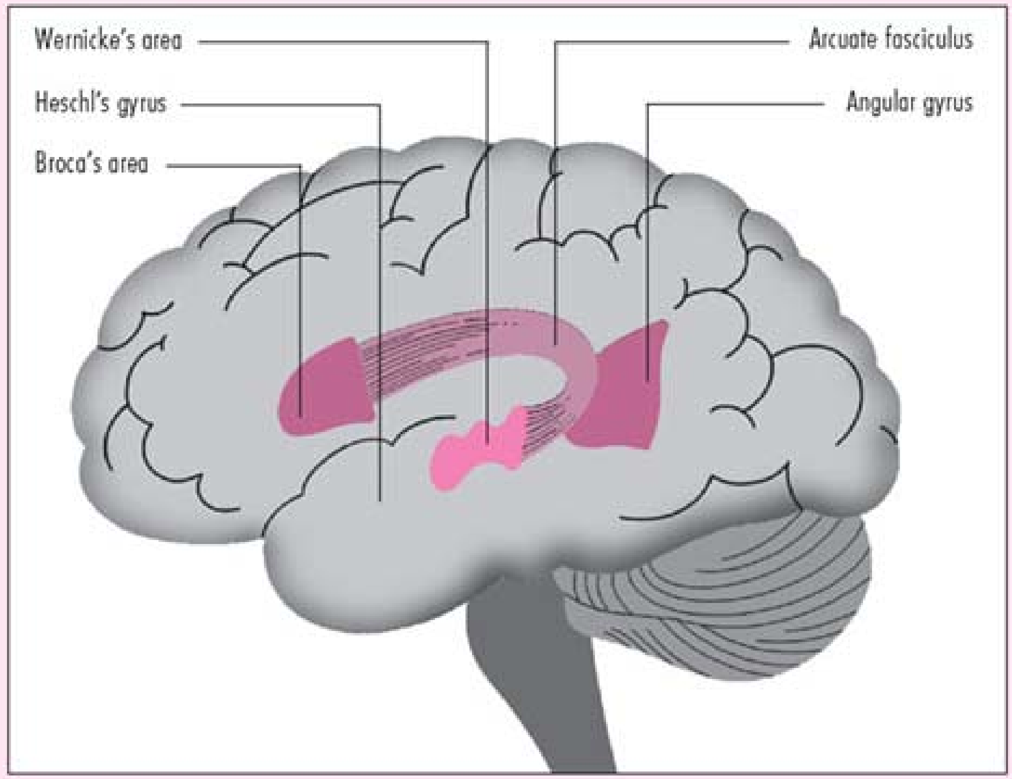
Landau Kleffner Syndrome

When seizures occur in sleep in the region of the expressive language cortex. Autoantibodies to endovasculature occur more commonly in autism and LKS.

(Connolly et al. *J Pediatr. 1999 May;134(5):607-13.)*

Where language originates

Aphasia reflects damage to one or more of the brain's primary language centers, which, in most persons, are located in the left hemisphere. *Broca's area* lies next to the region of the motor cortex that controls the muscles necessary for speech. *Wernicke's area* is the center of auditory, visual, and language comprehension. It lies between *Heschl's gyrus*, the primary receiver of auditory stimuli, and the *angular gyrus*, a "way station" between the brain's auditory and visual regions. Connecting Wernicke's and Broca's areas is a large nerve bundle, the *arcuate fasciculus*, which enables the repetition of speech.



Landau Kleffner Syndrome EEG

LKS: Sources of MEG-spikes

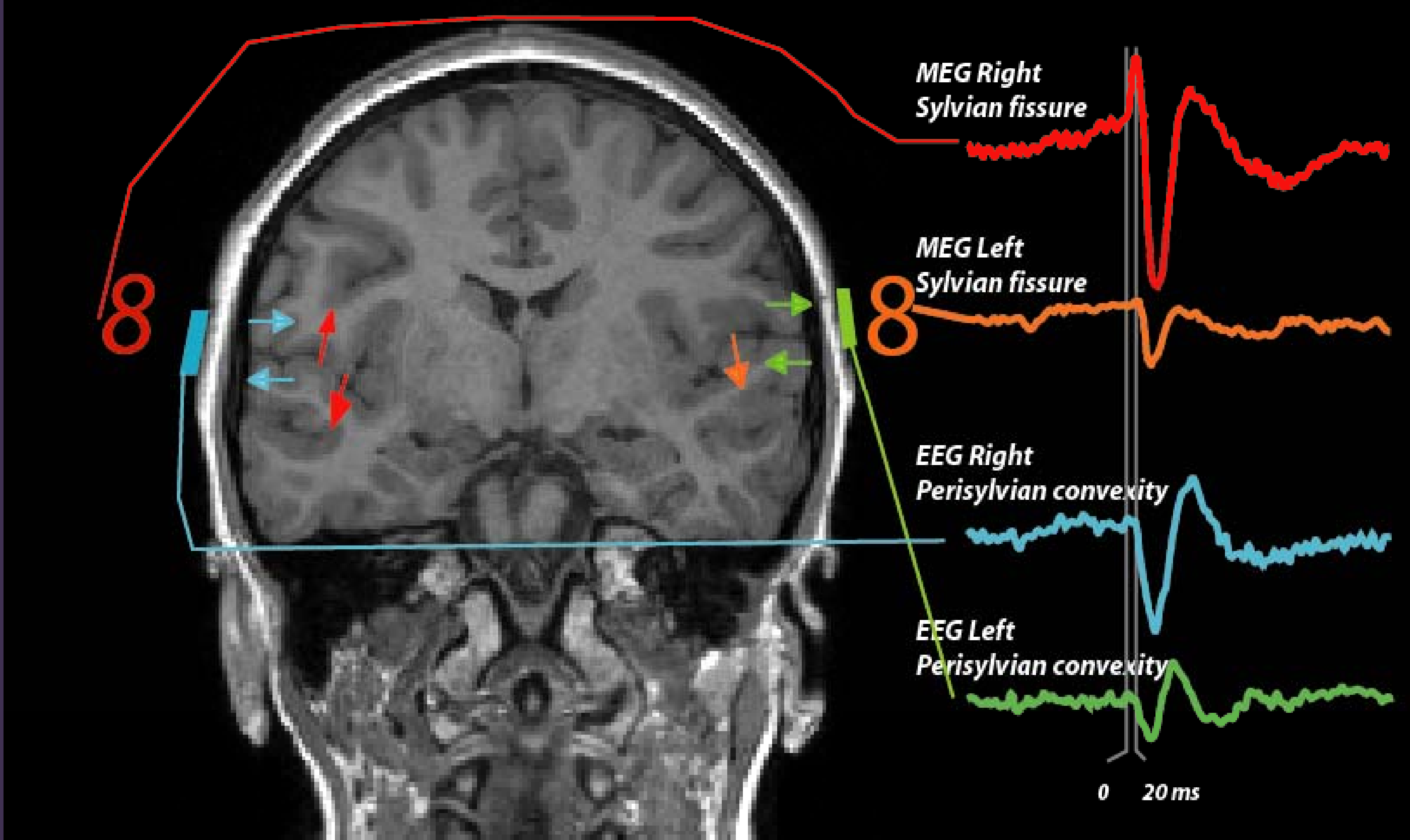
(Lewine 2000)

- *Classical LKS* — *N=6*
  - *Sylvian unilateral* — *2/6 (33%)*
  - *Sylvian bilateral, dependent* — *3/6 (50%)*
  - *Sylvian, bilateral interpendent* — *1/6 (17%)*

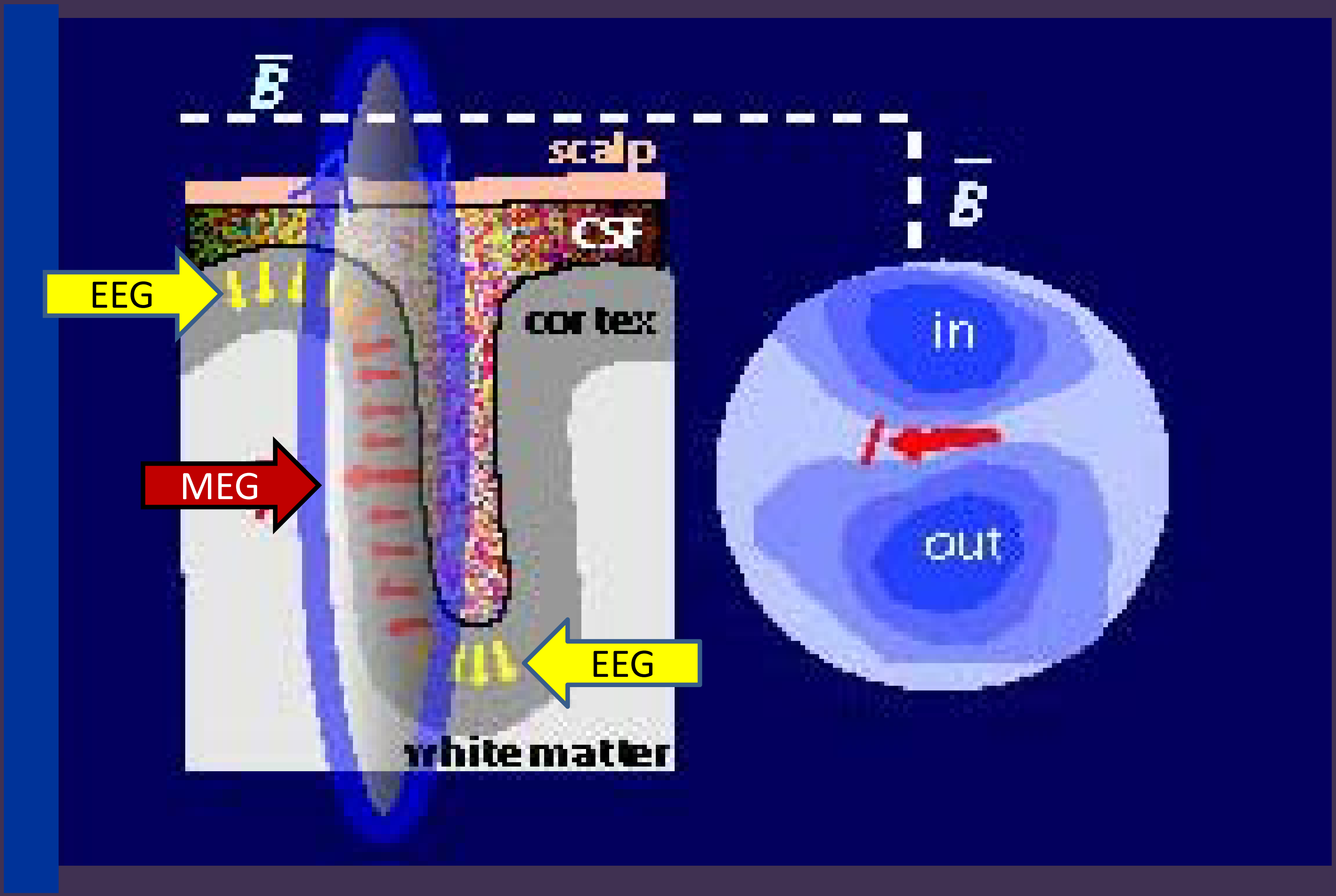
- *Variant LKS* — *N=9*
  - *Sylvian & frontal spikes* — *9/9 (100%)*

- *Autistic Epileptic Regression* — *N=100*
  - *Sylvian & multifocal* — *70/100*

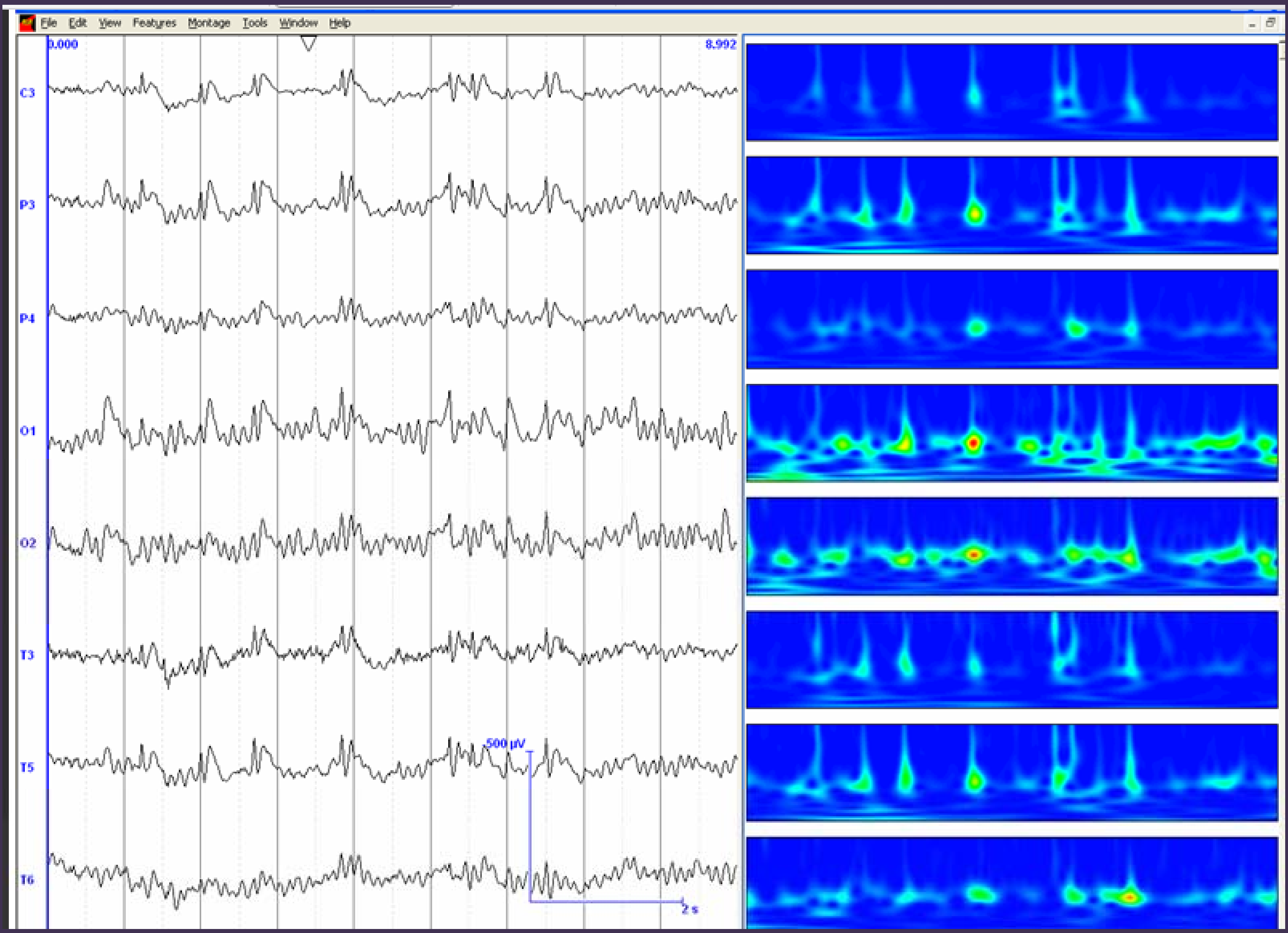
MEG and EEG signals reflect different neuron populations



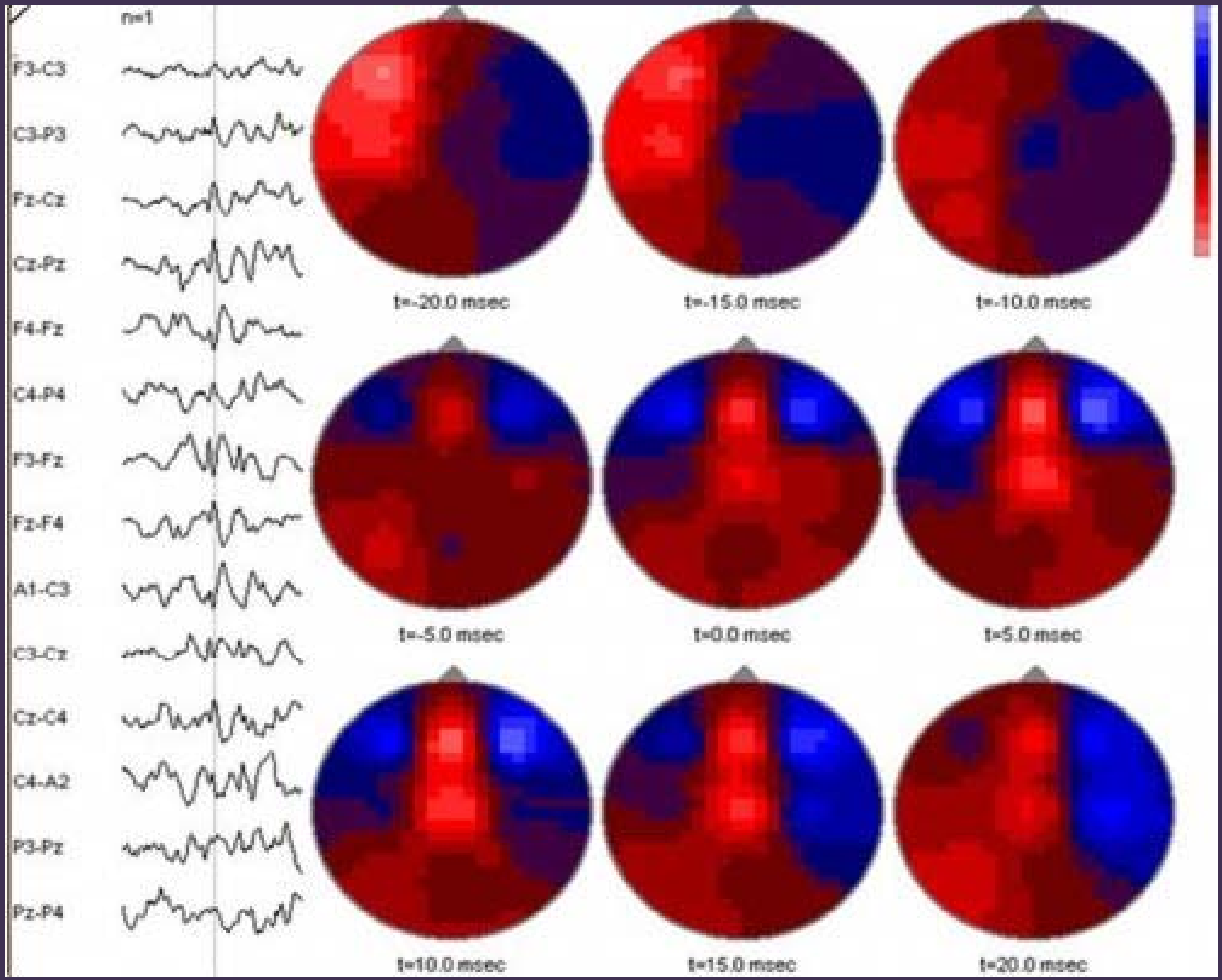
MEG reflects fissural cortex activity, EEG is dominated by gyral crown activity



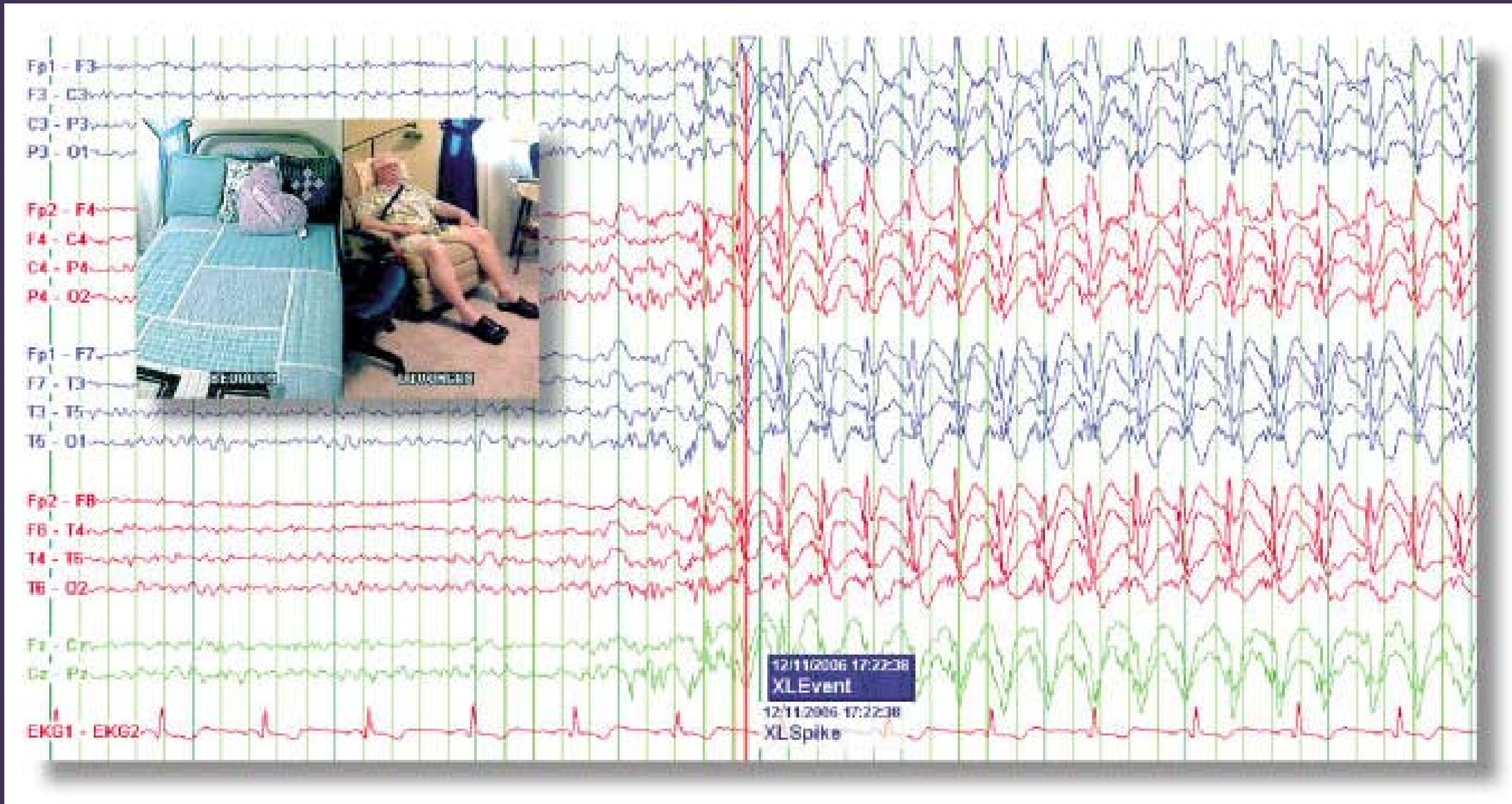
Wavelet Analysis of EEG Spiking



QEEG Localization of Spiking

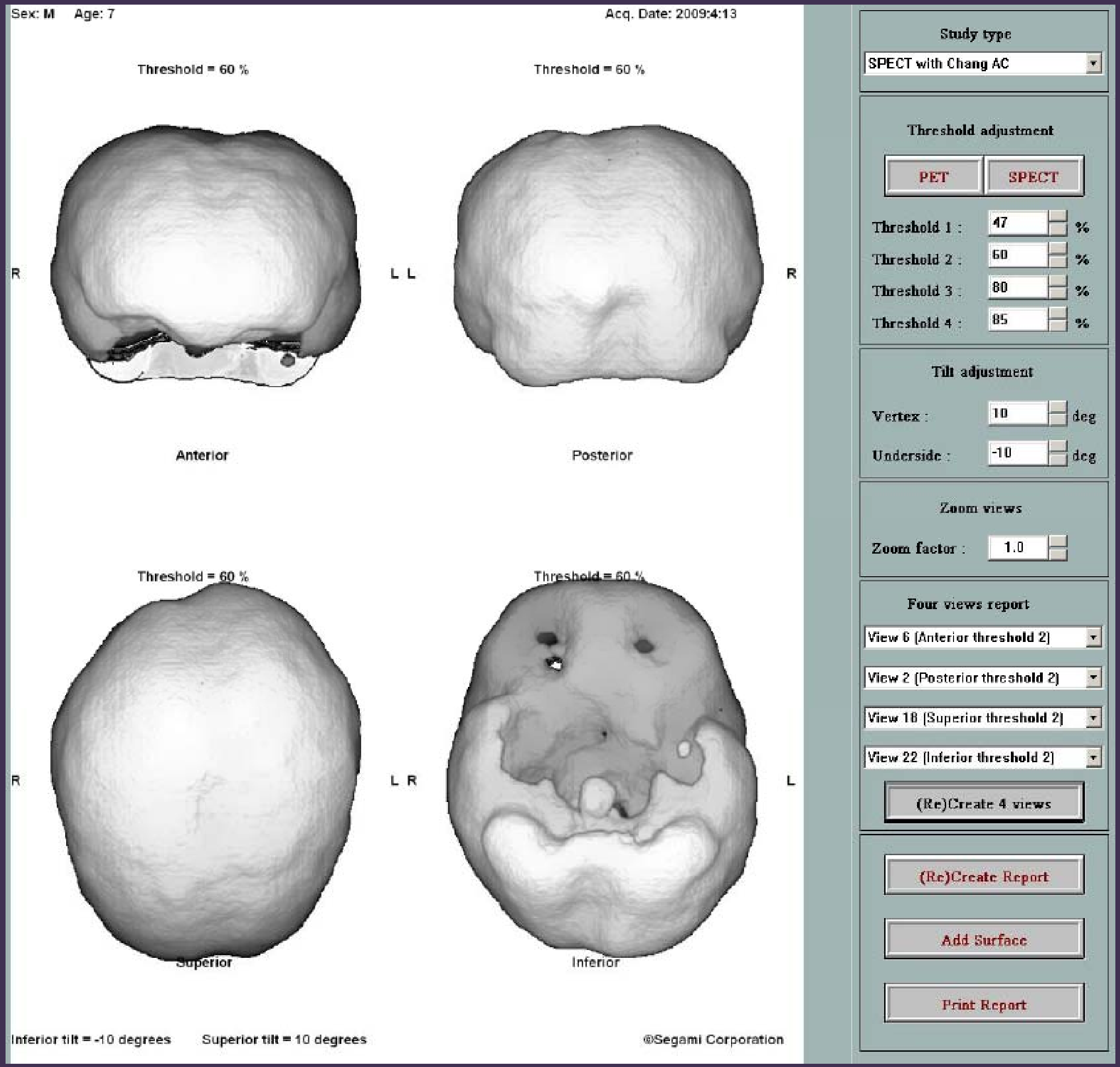


Video EEG

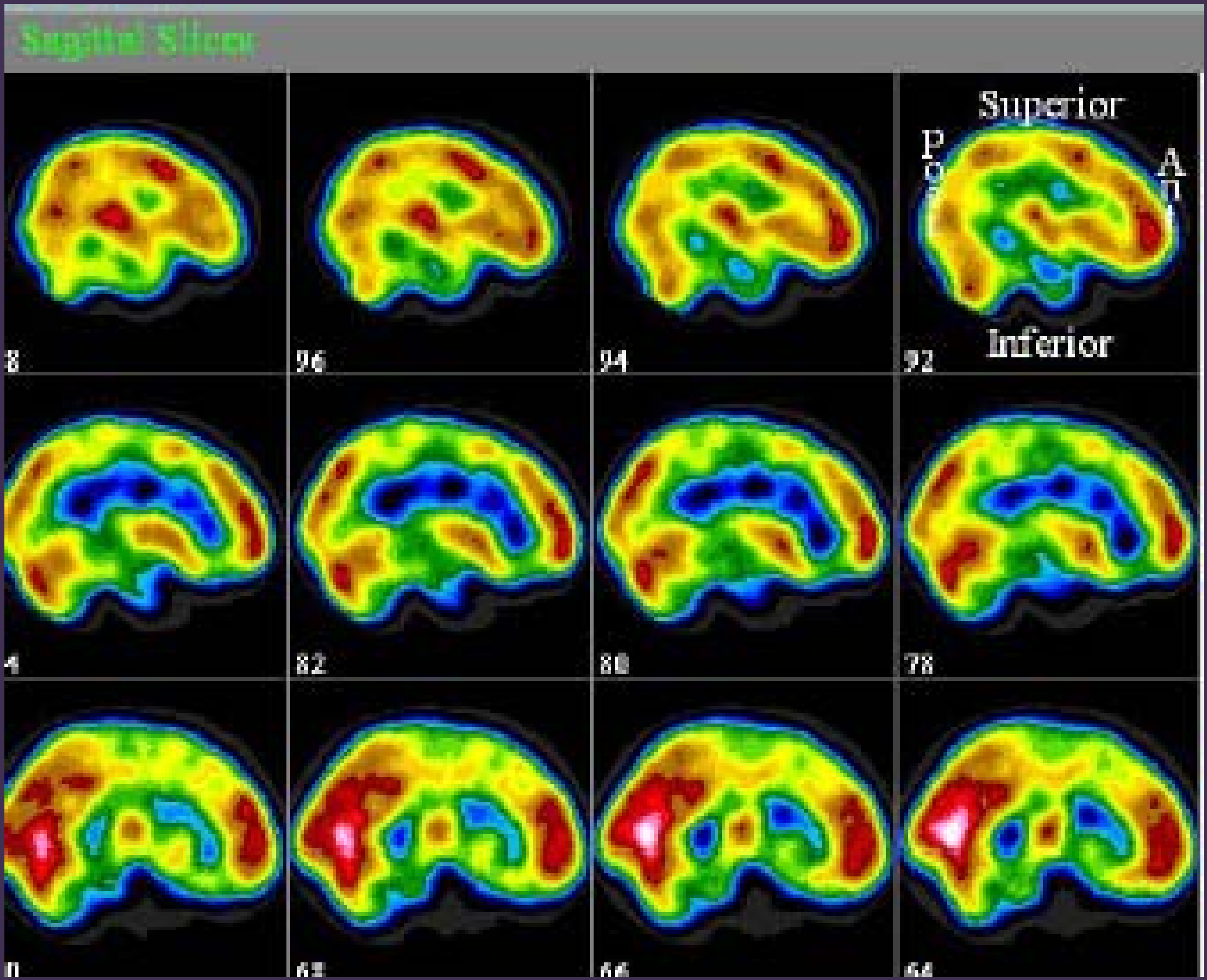


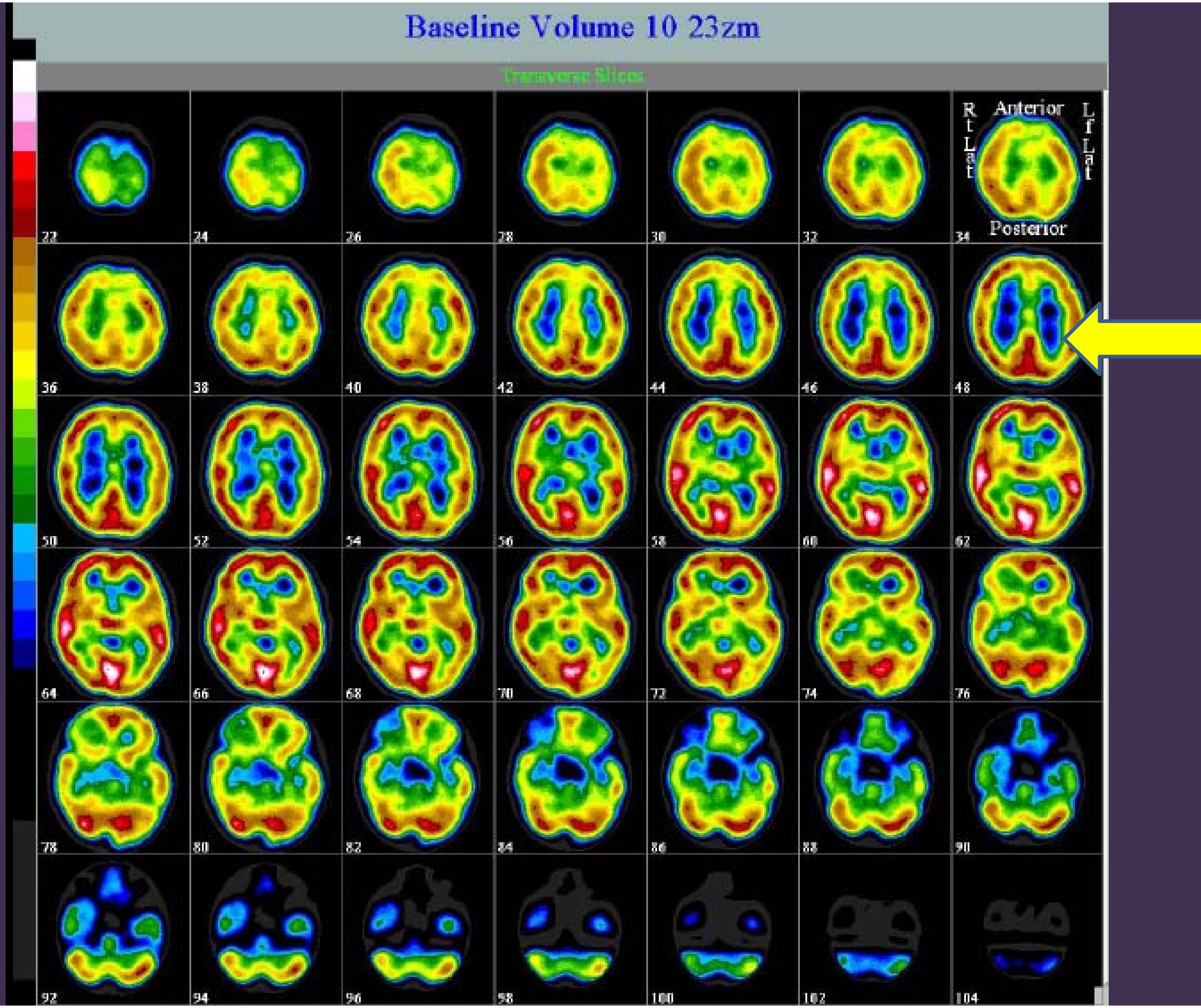
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
Fz - Cz
Cz - Pz
EKG1 - EKG2
12/11/2006 17:22:38
XLEvent
12/11/2006 17:22:38
XLSpike

SPECT Neuroimaging



When Autism Isn't Typical




Baseline Volume 10 23zm
Transverse Slices
Rt Lat
Anterior
Lf Lat
Posterior
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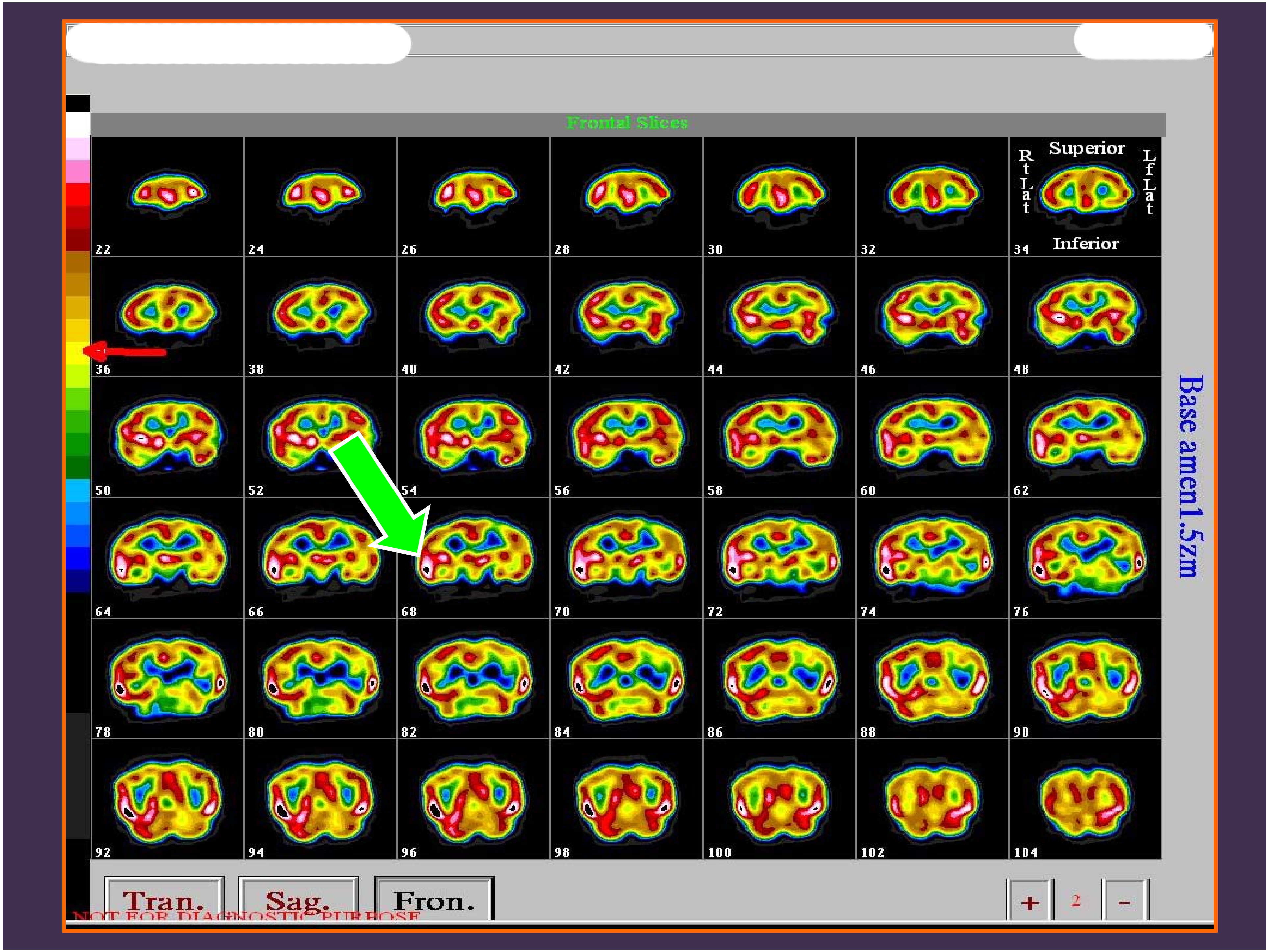

Frontal Slices
Superior
Inferior
Rt Lat
Lf Lat
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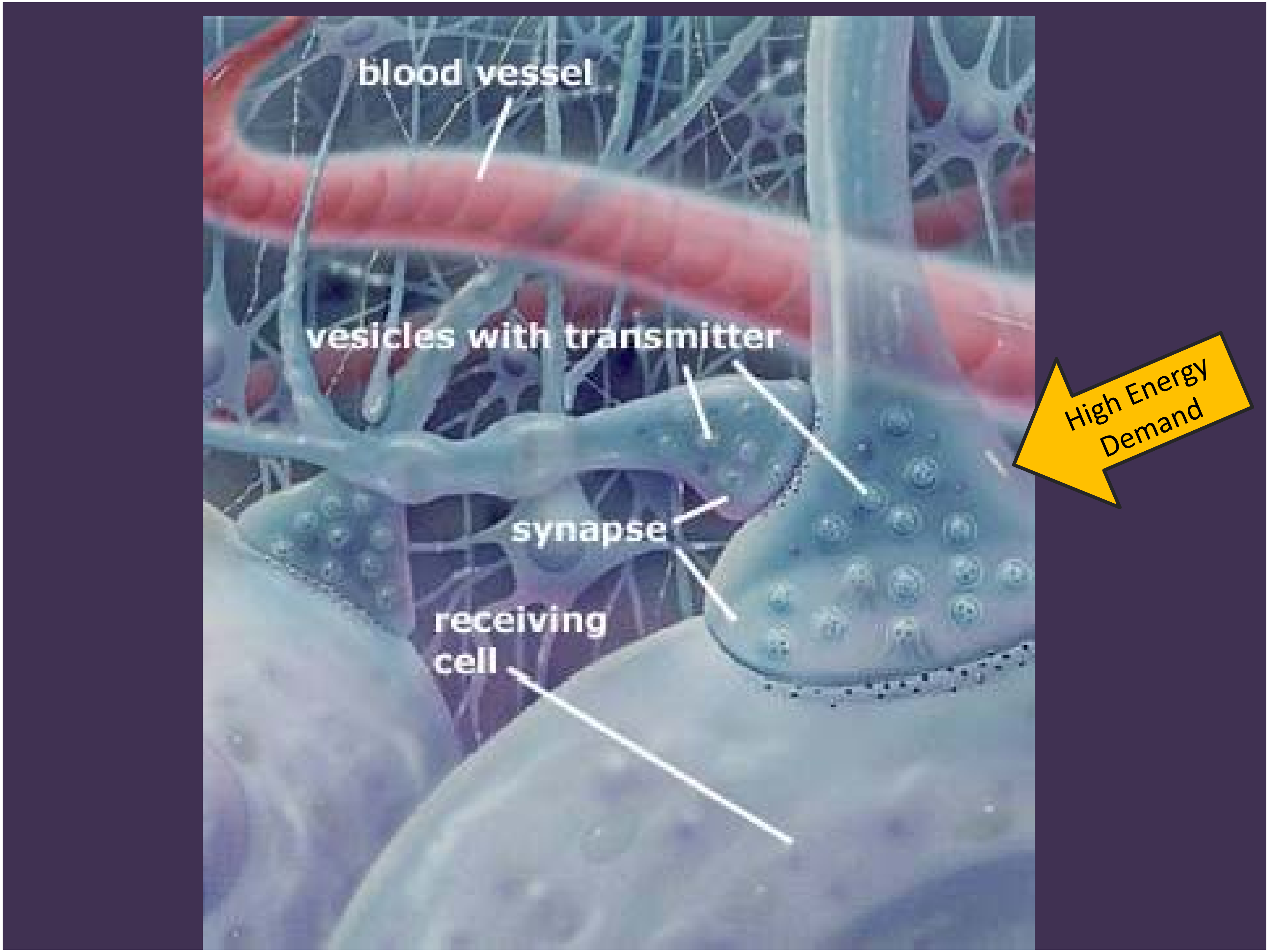
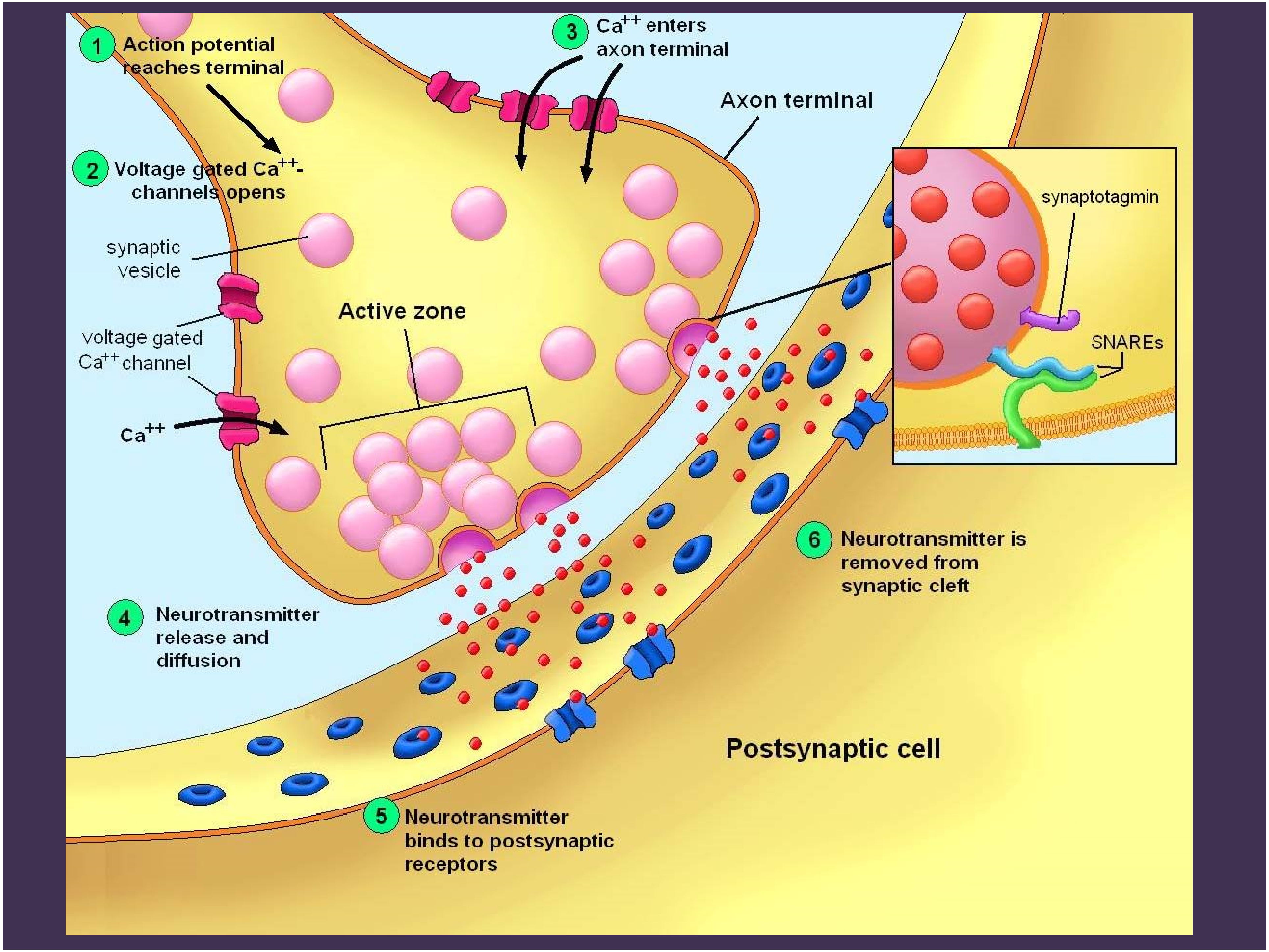
Tran.
Sag.
Fron.
NOT FOR DIAGNOSTIC PURPOSE
+
2
-


blood vessel
vesicles with transmitter
synapse
receiving
cell
High Energy
Demand

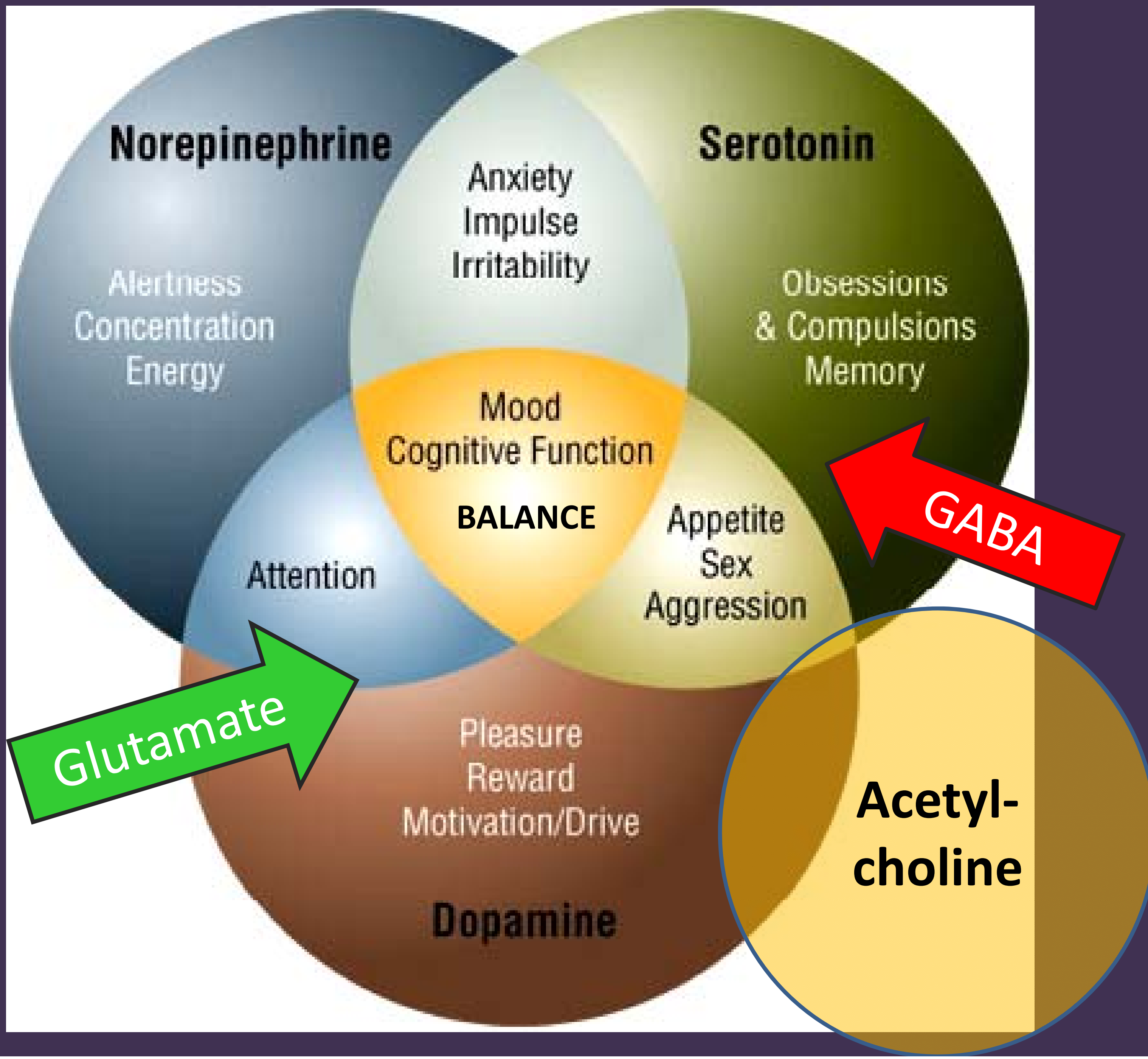
Synaptic Events

- Electrical Signal reaches axon terminal
- Chemical substance released by vesicles into the synapse
  - **Neurotransmitter (NT)**
- Diffuses across synapse where they
- Bind to **receptor** proteins
- This opens ion channels and the post-synaptic nerve depolarizes when enough **channels open = signal**
- **NT released and is recycled or degraded**

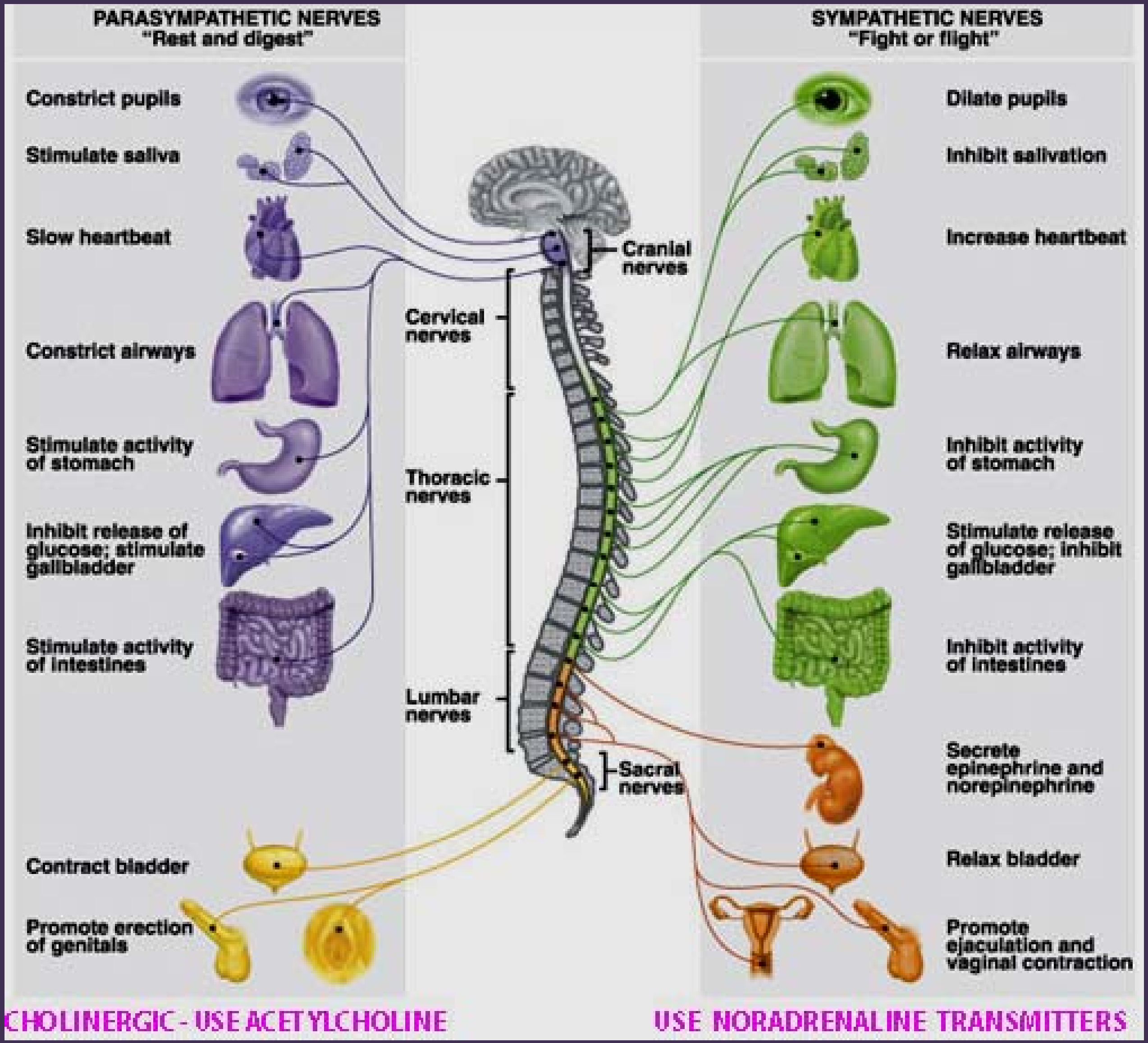


1 Action potential reaches terminal
2 Voltage gated Ca++- channels opens
3 Ca++ enters axon terminal
Axon terminal
synaptic vesicle
voltage gated Ca++ channel
Ca++
Active zone
synaptotagmin
SNAREs
4 Neurotransmitter release and diffusion
5 Neurotransmitter binds to postsynaptic receptors
6 Neurotransmitter is removed from synaptic cleft
Postsynaptic cell

Neurotransmitter	Function	Effect of Deficit	Effect of Surplus
Acetylcholine (ACh)	Excitatory: It produces muscle contractions and is found in the motor neurons; in the hippocampus, it is involved in memory formation, learning and general intellectual function.	Paralysis; A factor associated with Alzheimer's disease: levels of acetylcholine are severely reduced associated with memory impairment.	Violent muscle contractions
Dopamine	Excitatory: involved in voluntary muscle movements, attention, learning, memory, and emotional arousal and rewarding sensations	Muscle rigidity; A factor associated with Parkinson's disease: degeneration of neurons in the substantia nigra that produce dopamine.	One factor associated with schizophrenia-like symptoms such as hallucinations and perceptual disorders, addiction
Serotonin	Inhibitory or excitatory: involved in mood, sexual behavior, pain perception, sleep, eating behavior, maintaining a normal body temperature and hormonal state	Anxiety, mood disorders, insomnia; One factor associated with obsessive-compulsive disorder and depression	Autism
Endorphins	Inhibitory: regulates pain perception and involved in sexuality, pregnancy, labor, and positive emotions associated with aerobic exercise—the brains natural opiates.	Body experiences pain	Body may not give adequate warning about pain
Norepinephrine	Excitatory and inhibitory: involved in increasing heartbeat, arousal, learning, memory, and eating	One factor associated with depression.	Anxiety
GABA (gamma aminobutyric acid)	Inhibitory: communicates messages to other neurons, helping to balance and offset excitatory messages. It is also involved in allergies	Destruction of GABA-producing neurons in Huntington's disease produces tremors and loss of motor control, as well as personality changes.	Sleep and eating disorders


Norepinephrine
Alertness
Concentration
Energy
Anxiety
Impulse
Irritability
Serotonin
Obsessions
& Compulsions
Memory
Mood
Cognitive Function
BALANCE
Attention
Appetite
Sex
Aggression
GABA
Glutamate
Pleasure
Reward
Motivation/Drive
Dopamine
Acetyl-
choline

Autonomic Nervous System



Acetyl Choline Nicotine effect

Noradrenaline effect

Reduced cardiac parasympathetic activity in children with autism.

Brain Dev. 2005 Oct;27(7):509-16
Ming X, et al

Department of Neuroscience, New Jersey Medical School, UMDNJ, Newark, 90 Bergen Street, DOC 8100, NJ 07103, USA. mingxu@umdnj.edu

Many of the clinical symptoms of autism suggest autonomic dysfunction. **results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism whether or not they have symptoms or signs of autonomic abnormalities.**

Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children.

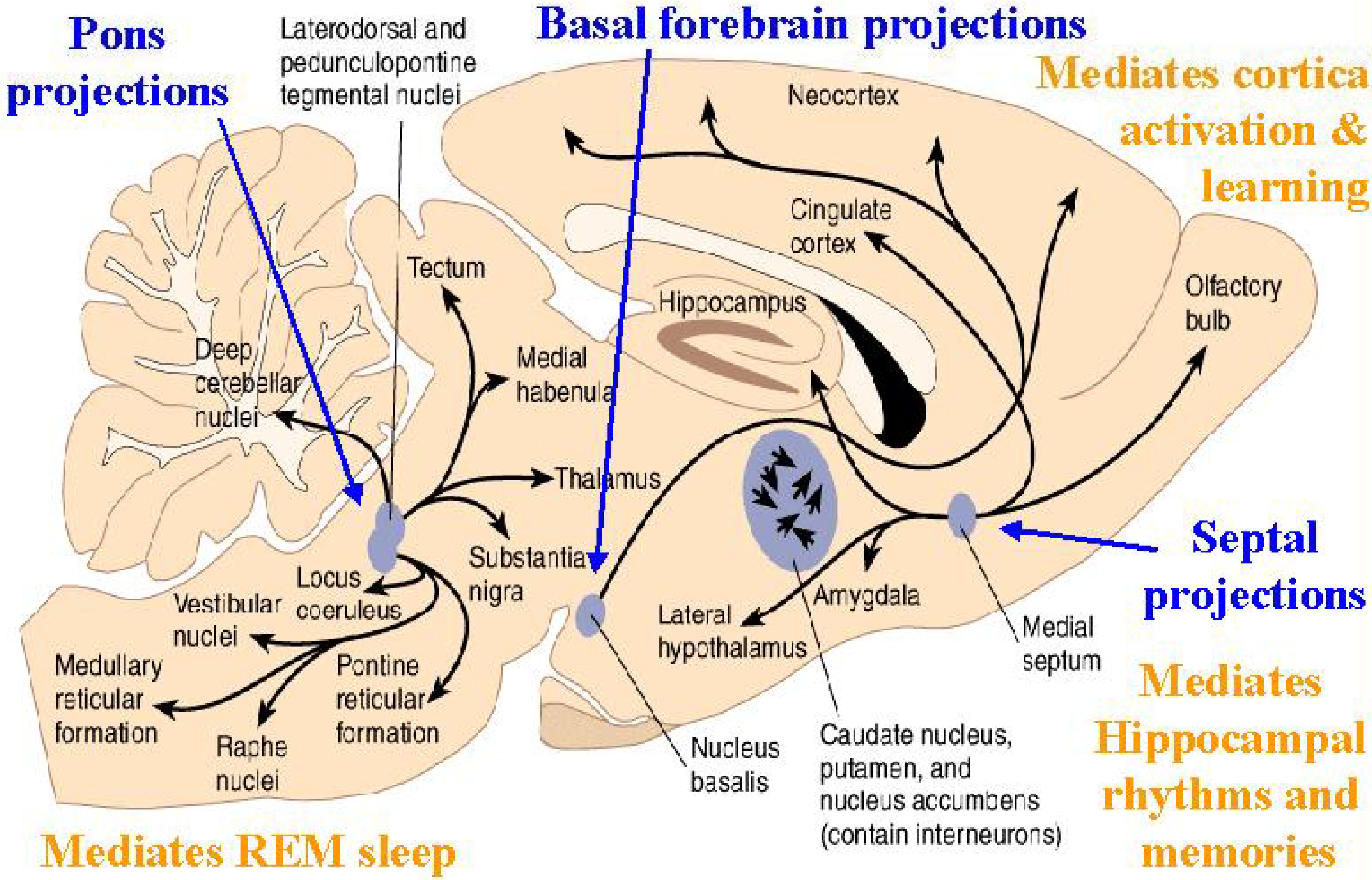
Int Arch Occup Environ Health. 2006 May;79(5):379-86. Epub 2005 Dec 20.

Murata K, Sakamoto M, Nakai K, Dakeishi M, Iwata T, Liu XJ, Satoh H

Department of Environmental Health Sciences, Akita University School of Medicine, 010-8543, Akita, Japan, winestem@med.akita-u.ac.jp.

Conclusions: Despite the potential limitations involved in the retrospective study, **these findings suggest that prenatal methylmercury exposure (median of estimated maternal hair mercury at parturition, 2.24 mug/g) may be associated with reduced parasympathetic activity and/or sympathovagal shift**.

Cholinergic Brain Regions



The Cholinergic Anti-inflammatory Pathway: A Missing Link in Neuroimmunomodulation

Valentin A Pavlov,[1] Hong Wang,[1] Christopher J Czura,[1] Steven G Friedman,[1,2] and Kevin J Tracey[1]

This review outlines the mechanisms underlying the interaction between the nervous and immune systems of the host in response to an immune challenge. The main focus is the cholinergic anti-inflammatory pathway, which we recently described as a novel function of the efferent vagus nerve. This pathway plays a critical role in controlling the inflammatory response through interaction with peripheral α7 subunit–containing nicotinic acetylcholine receptors expressed on macrophages. We describe the modulation of systemic and local inflammation by the cholinergic anti-inflammatory pathway and its function as an interface between the brain and the immune system. The clinical implications of this novel mechanism also are discussed.

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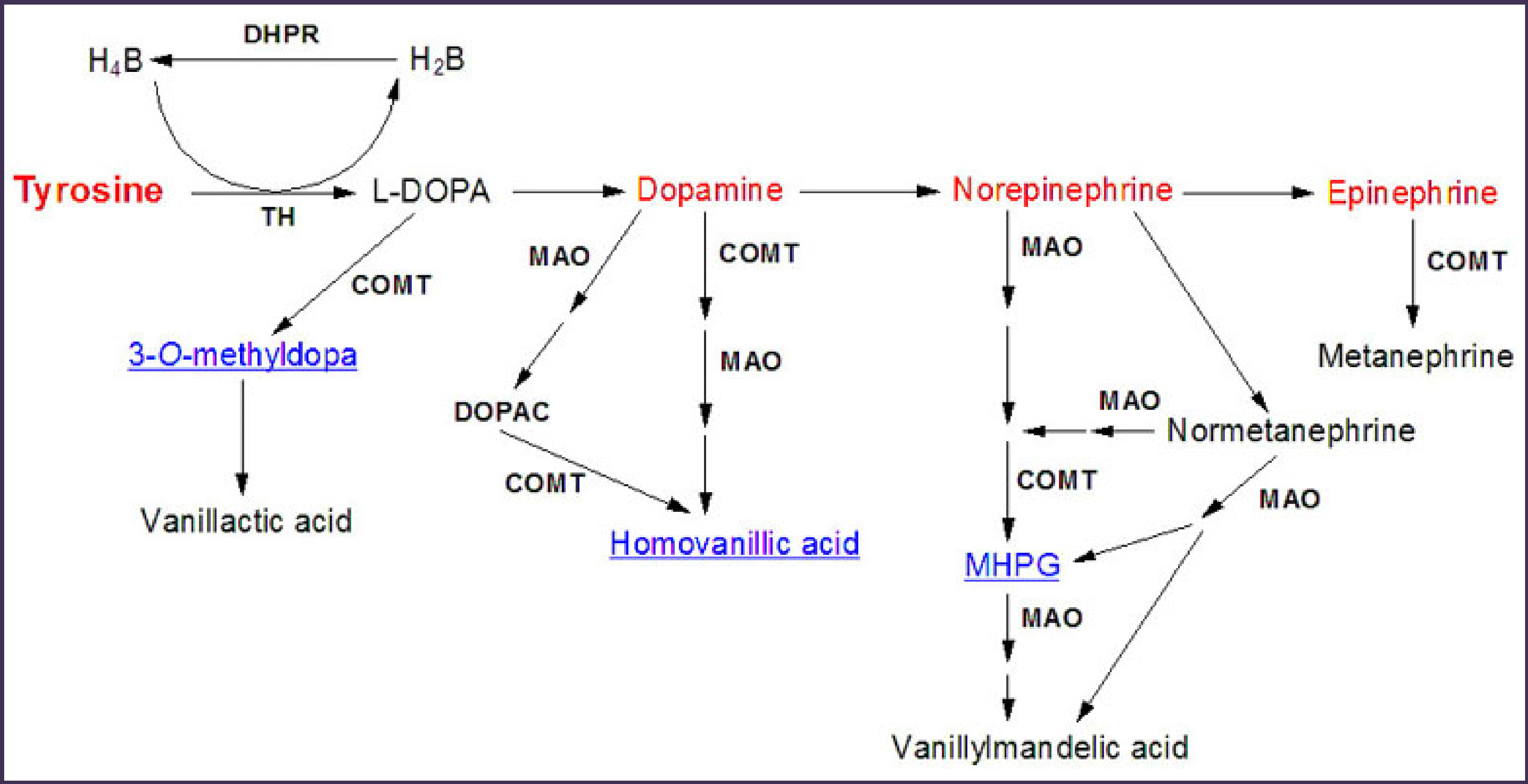
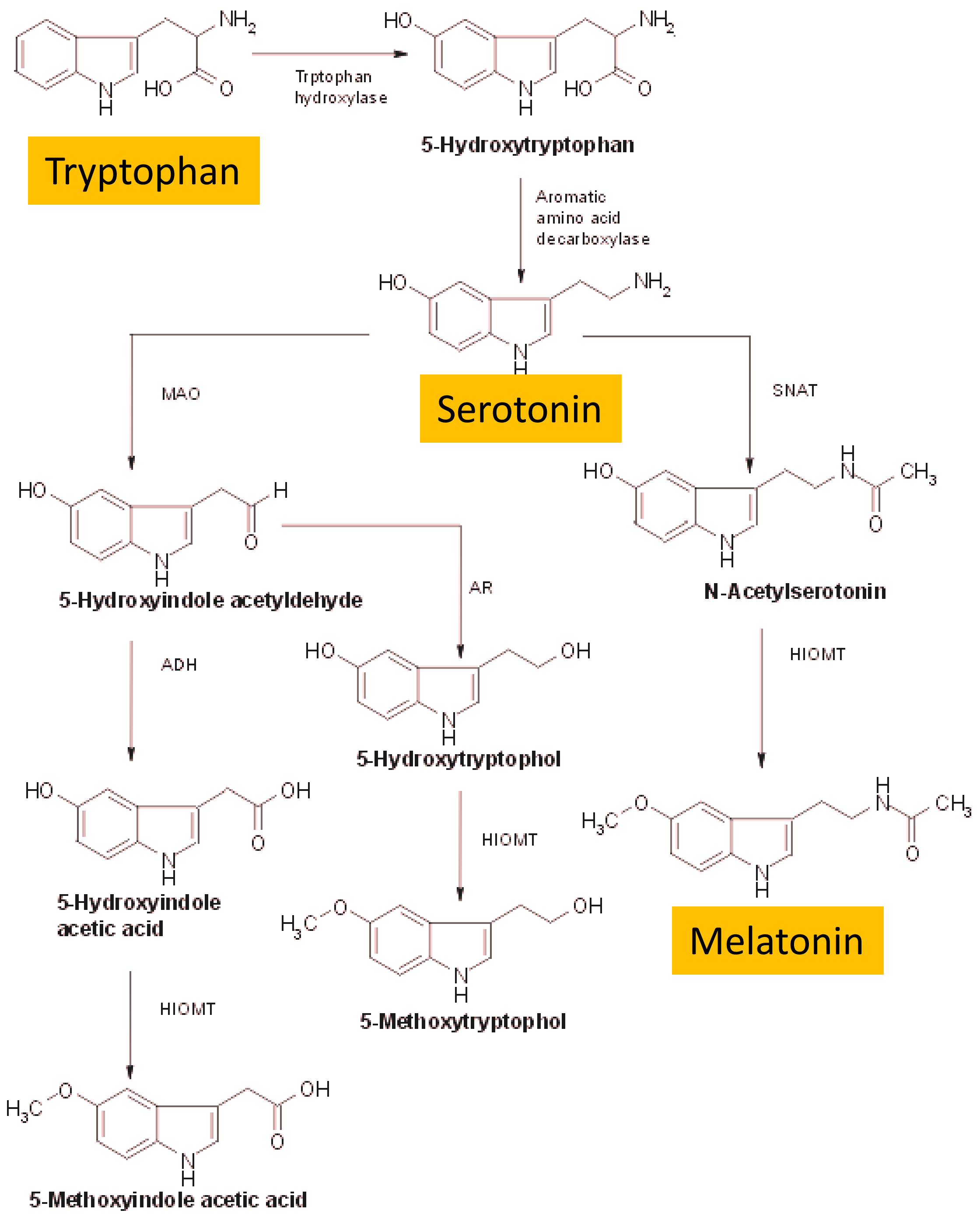
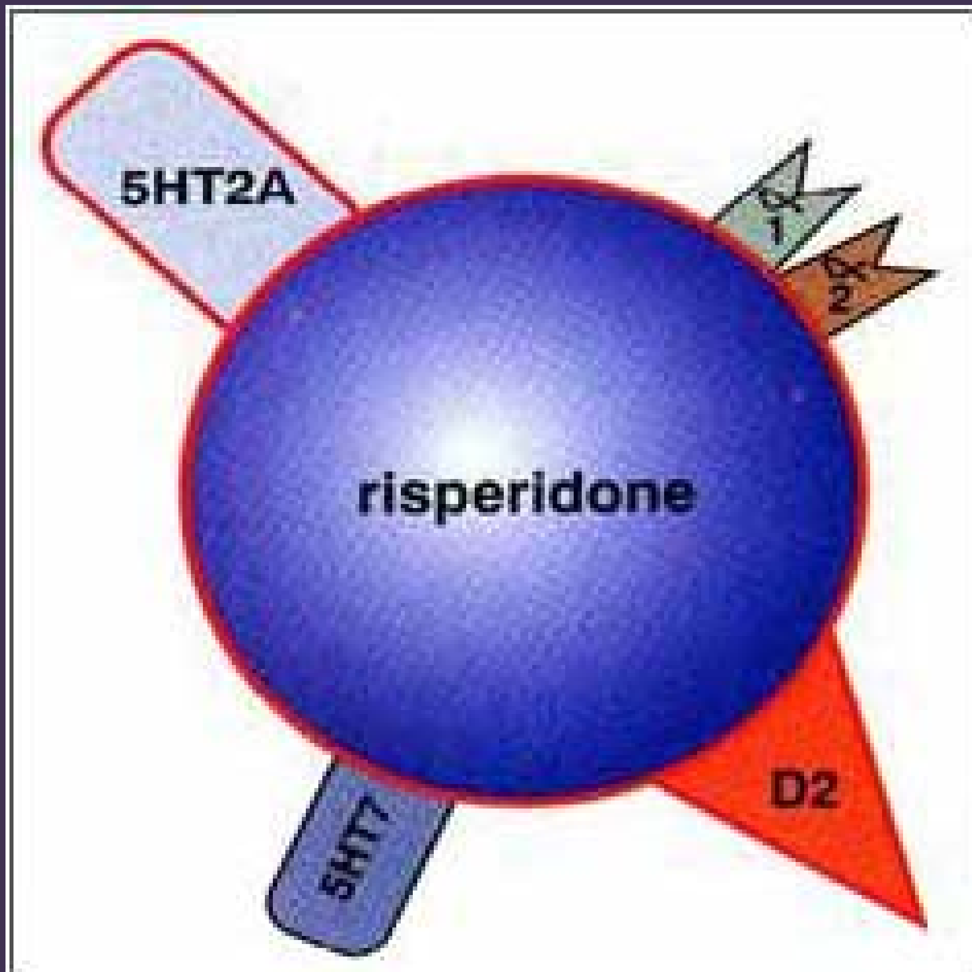
Monoamine NT Biochemistry



Serotonin and Melatonin Biochemical Pathways



Risperidone: Multiple Sites of Action



Cognitive effects of risperidone in children with autism and irritable behavior

- J Child Adolesc Psychopharmacol. 2008 Jun;18(3):227-36.
- 38 children, ages 5-17 (n=38) years with severe autism
- Risperidone (0.5 to 3.5 mg/day) or placebo for 8 weeks.
- A double-blind placebo-controlled parallel groups design was used. Dependent measures included tests of sustained attention, verbal learning, hand-eye coordination, and spatial memory .
- CONCLUSION: Performance on a cancellation task and a verbal learning task was better on risperidone than on placebo (without correction for multiplicity). Risperidone given to children with autism at doses up to 3.5 mg for up to 8 weeks appears to have no detrimental effect on cognitive performance.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 16, Number 5, 2006
Mary Ann Liebert, Inc.
Pp. 621–629

A Prospective, Open-Label Trial of Galantamine in Autistic Disorder

Rob Nicolson, M.D., Beth Craven-Thuss, M.A., and Judy Smith

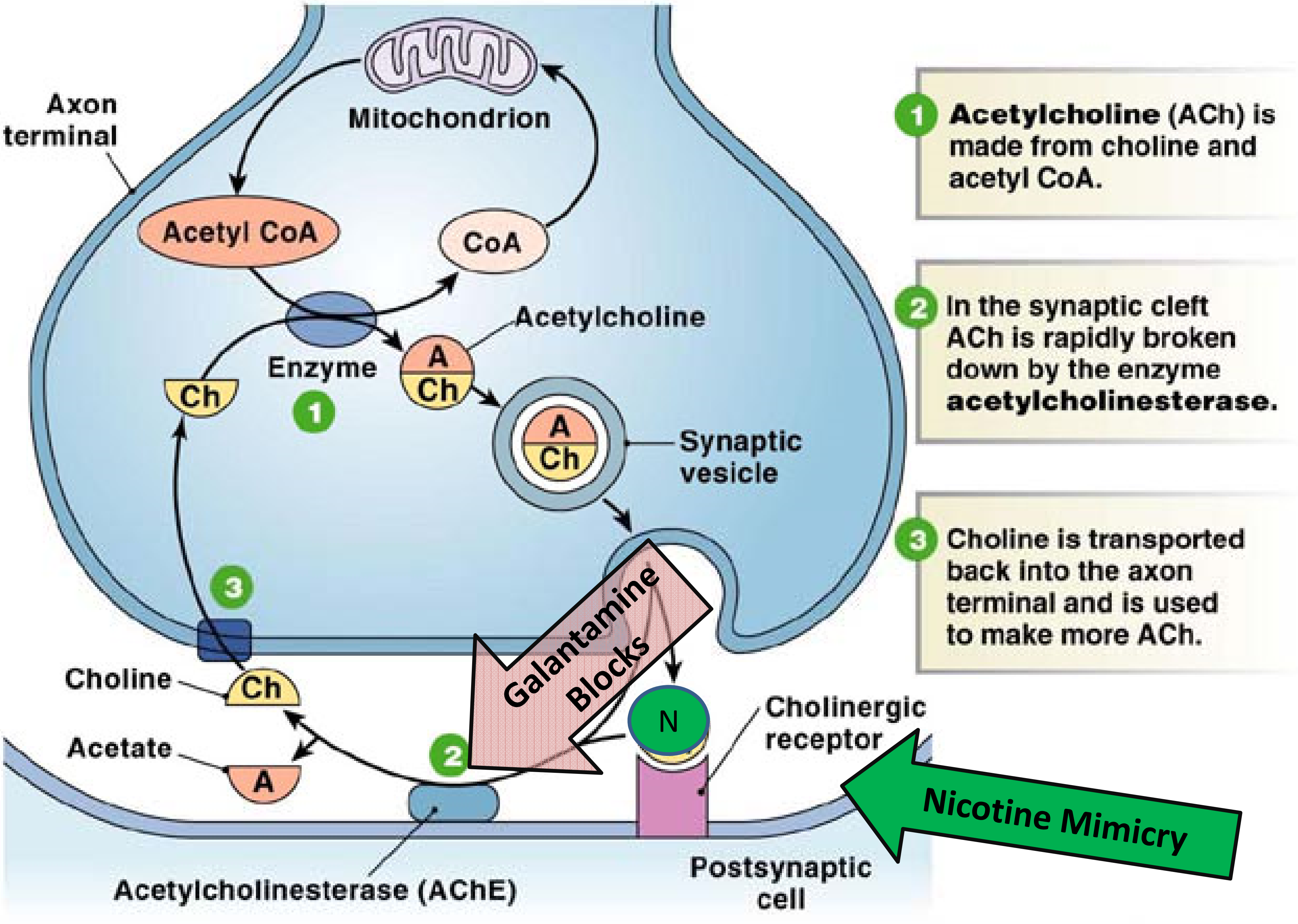
ABSTRACT

Objective: Post-mortem studies have reported abnormalities of the cholinergic system in autism. The purpose of this study was to assess the use of galantamine, an acetylcholinesterase inhibitor and nicotinic receptor modulator, in the treatment of interfering behaviors in children with autism.

Methods: Thirteen medication-free children with autism (mean age, 8.8 ± 3.5 years) participated in a 12-week, open-label trial of galantamine. Patients were rated monthly by parents on the Aberrant Behavior Checklist (ABC) and the Conners' Parent Rating Scale—Revised, and by a physician using the Children's Psychiatric Rating Scale and the Clinical Global Impressions scale.

Results: Patients showed a significant reduction in parent-rated irritability and social withdrawal on the ABC as well as significant improvements in emotional lability and inattention on the Conners' Parent Rating Scale—Revised. Similarly, clinician ratings showed reductions in the anger subscale of the Children's Psychiatric Rating Scale. Eight of 13 participants were rated as responders on the basis of their improvement scores on the Clinical Global Impressions scale. Overall, galantamine was well-tolerated, with no significant adverse effects apart from headaches in one patient.

Conclusion: In this open trial, galantamine was well-tolerated and appeared to be beneficial for the treatment of interfering behaviors in children with autism, particularly aggression, behavioral dyscontrol, and inattention. Further controlled trials are warranted.


Axon terminal
Mitochondrion
Acetyl CoA
CoA
Acetylcholine
Enzyme
A
Ch
Ch
1
Synaptic vesicle
3
Choline
Acetate
2
Galantamine Blocks
N
Cholinergic receptor
Nicotine Mimicry
Acetylcholinesterase (AChE)
Postsynaptic cell
1 Acetylcholine (ACh) is made from choline and acetyl CoA.
2 In the synaptic cleft ACh is rapidly broken down by the enzyme acetylcholinesterase.
3 Choline is transported back into the axon terminal and is used to make more ACh.

Galantamine and nicotine have a synergistic effect on inhibition of microglial activation induced by HIV-1 gp120.

Brain Res Bull. 2004 Aug 30;64(2):165-70.

Giunta B, et al Neuroimmunology Laboratory, College of Medicine, University of South Florida, 3515 E. Fletcher Avenue, Tampa, FL 33613, USA.

Chronic brain inflammation is the common final pathway in the majority of neurodegenerative diseases and central to this phenomenon is the immunological activation of brain mononuclear phagocyte cells, called microglia. This inflammatory mechanism is a central component of HIV-associated dementia (HAD). Recent data from our laboratory indicates that cultured microglial cells also express this same receptor and that microglial anti-inflammatory properties are mediated through it and the p44/42 mitogen-activated protein kinase (MAPK) system. Here we report for the first time the creation of an in vitro model of HAD composed of cultured microglial cells synergistically activated by the addition of IFN-gamma and the HIV-1 coat glycoprotein, gp120. **Furthermore, this activation, as measured by TNF-alpha and nitric oxide (NO) release, is synergistically attenuated through the alpha7 nAChR and p44/42 MAPK system by pretreatment with nicotine, and the cholinesterase inhibitor, galantamine. Our findings suggest a novel therapeutic combination to treat or prevent the onset of HAD through this modulation of the microglia inflammatory mechanism.**

Original Article

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Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

Michael G. Chez, MD, Quinn Burton, MS, Timothy Dowling, Mina Chang, MS, Pavan Khanna, MS, and Christopher Kramer, MS

Autism and Pervasive Developmental Disorder Not Otherwise Specified are common developmental problems often seen by child neurologists. There are currently no cures for these lifelong and socially impairing conditions that affect core domains of human behavior such as language, social interaction, and social awareness. The etiology may be multifactorial and may include autoimmune, genetic, neuroanatomic, and possibly excessive glutaminergic mechanisms. Because memantine is a moderate affinity antagonist of the *N*-methyl-D-aspartic acid (NMDA) glutamate receptor, this drug was hypothesized to potentially modulate learning, block excessive glutamate effects that can include neuroinflammatory activity, and influence neuroglial activity in autism and Pervasive Developmental Disorder Not Otherwise Specified. Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. To generate a clinician-derived Clinical Global Impression Improvement score for language, behavior, and self-stimulatory behaviors, the primary author observed the subjects and questioned their caretakers within 4 to 8 weeks of the initiation of therapy. Chronic maintenance therapy with the drug was continued if there were no negative side effects. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects.

Keywords: autism treatment; pervasive developmental disorders; memantine

Available online at www.sciencedirect.com

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Pharmacology, Biochemistry and Behavior 88 (2008) 407–417

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder

Alexandra S. Potter *, Paul A. Newhouse

Clinical Neuroscience Research Unit, Department of Psychiatry, College of Medicine, University of Vermont, Burlington, VT 05401, United States

Received 25 May 2007; received in revised form 8 September 2007; accepted 19 September 2007
Available online 26 September 2007

Abstract

Objective: The strong association between ADHD and cigarette smoking and the known effects of nicotine on cognition has lead to interest in the role of cholinergic function in ADHD cognitive deficits. We have previously demonstrated that acute nicotine improves behavioral inhibition in adolescents with ADHD. This study examined acute nicotine in young adults with ADHD-Combined type on cognitive domains including behavioral inhibition, delay aversion, and recognition memory.

Methods: 15 non-smoking young adults (20±1.7 years) diagnosed with ADHD-C received acute nicotine (7 mg patch for 45 min) and placebo on separate days. Cognitive tasks included the Stop Signal Task, Choice Delay task, and the High–Low Imagery Task (a verbal recognition memory task). Three subjects experienced side effects and their data was excluded from analysis of cognitive measures.

Results: There was a significant ($p<.05$) positive effect of nicotine on the Stop Signal Reaction Time measure of the Stop Signal Task. The SSRT was improved without changes in GO reaction time or accuracy. There was a trend ($p=.09$) for nicotine to increase tolerance for delay and a strong trend ($p=.06$) for nicotine to improve recognition memory.

Conclusions: Non-smoking young adults with ADHD-C showed improvements in cognitive performance following nicotine administration in several domains that are central to ADHD. The results from this study support the hypothesis that cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target.

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

S

ARTICLE

Transdermal Nicotine for Mildly to Moderately Active Ulcerative Colitis

A Randomized, Double-Blind, Placebo-Controlled Trial

William J. Sandborn, MD; William J. Tremaine, MD; Kenneth P. Offord, MS; George M. Lawson, PhD; Bret T. Petersen, MD; Kenneth P. Batts, MD; Ivana T. Croghan, PhD; Lowell C. Dale, MD; Darrell R. Schroeder, MS; and Richard D. Hurt, MD

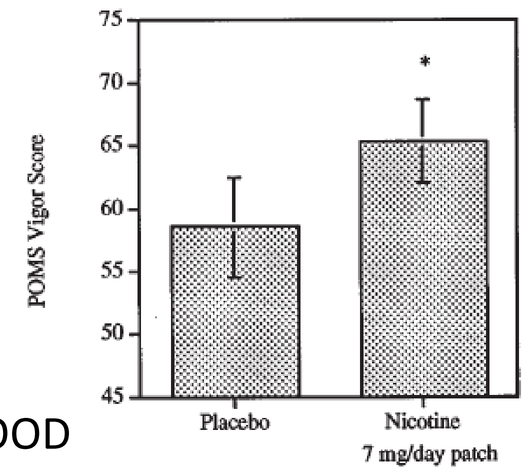
1 March 1997 | Volume 126 Issue 5 | Pages 364-371

Psychopharmacology (1998) 140 : 135–141

ORIGINAL INVESTIGATION

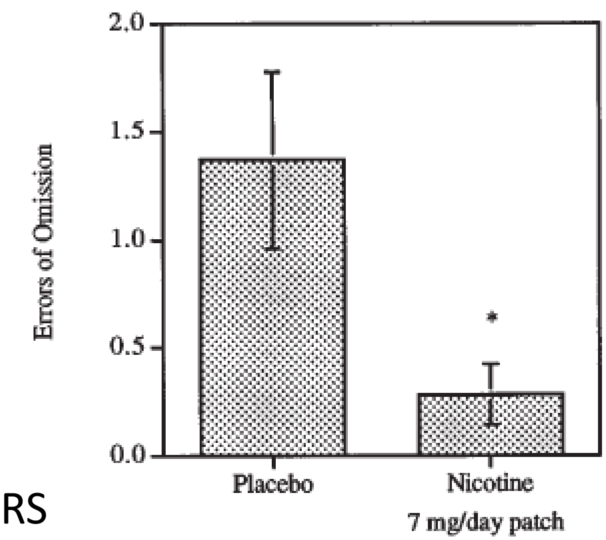
Edward D. Levin · C. Keith Conners · Donna Silva
Sean C. Hinton · Warren H. Meck · John March
Jed E. Rose

Transdermal nicotine effects on attention



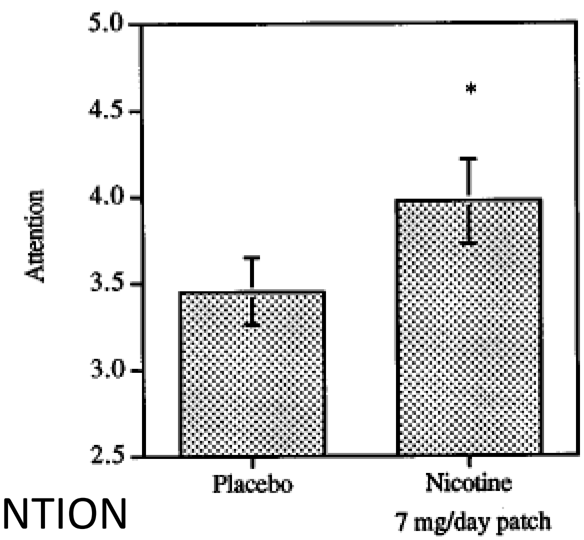
MOOD

Fig. 1 Profile of mood states (*POMS*) vigor score (mean ± SEM). There was a significant nicotine-induced increase in vigor (*$P < 0.05$)



ERRORS

Fig. 2 Conners continuous performance task (*CPT*) errors of omission (mean ± SEM). There was a significant nicotine-induced decrease in errors of omission (*$P < 0.05$)



ATTENTION

Fig. 4 Conners continuous performance task (*CPT*) composite attention score (mean ± SEM). There was a significant nicotine-induced increase in the attention score (*$P < 0.05$)

TDN Superior to Methylphenidate

K.-H. Krause et al. / Neuroscience and Biobehavioral Reviews 27 (2003) 605–613 609

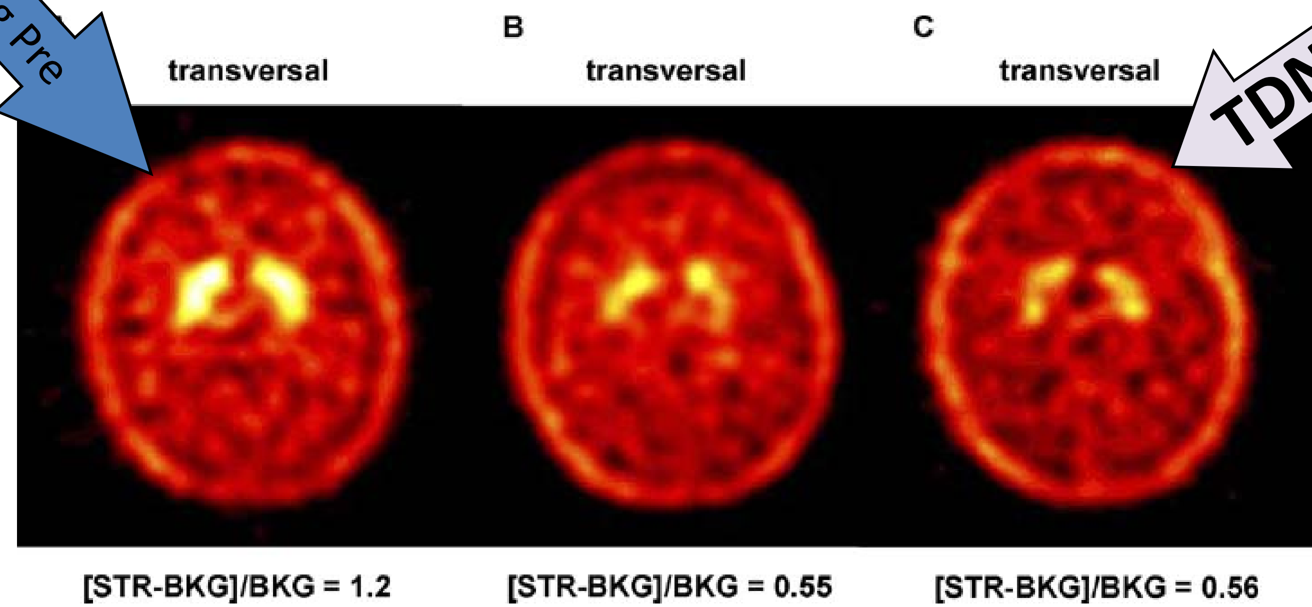


Fig. 2. Dopamine transporter binding in the striatum of a 53 years old non-smoker before (A), after 5 h of intake of 20 mg methylphenidate (Ritalin SR®) (B), and 3 months later after 5 h of wearing a 17.5 mg/24 h nicotine skin patch (C), shown by specific accumulation of [Tc-99m]TRODAT-1 in SPECT scans.

Therapeutic Effect of Ritalin SR 20

Psychopharmacology (2004) 176: 182–194
DOI 10.1007/s00213-004-1874-y

ORIGINAL INVESTIGATION

Alexandra S. Potter · Paul A. Newhouse

Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder

Table 2 Observer visual analog scale adjusted mean±SE significance represents main effect of drug treatment. *PLC* placebo; *MET* methylphenidate (usual dose); *NIC* nicotine (7 mg).

	PLC	MET	NIC	Significance
Drowsy	27.23±10.84	0.00±0.00	20.60±9.70	NS
Motoric restlessness	6.76±4.60	10.40±3.88	22.40±14.01	NS
Disoriented	0.00±0.00	0.00±0.00	0.00±0.00	NS
Impaired speech	0.00±0.00	0.00±0.00	0.00±0.00	NS
Euphoria	5.50±5.38	13.40±8.21	16.80±13.37	NS
Irritability	8.45±6.18	2.60±2.60	4.40±2.86	NS
Sweating	3.45±8.39	0.00±0.00	12.20±7.51	NS
GI distress	0.00±0.00	0.00±0.00	17.8±7.55	NS
Motor incoordination	0.00±0.00	0.00±0.00	0.00±0.00	NS
Fatigue	22.75±21.31	2.00±2.00	16.20±10.28	NS
Depression	4.75±2.48	0.00±0.00	0.00±0.00	NS
Anxiety	17.20±6.63	22.40±3.23	15.00±6.63	*P*=0.05
Alertness	65.57±11.12	99.40±.60	68.40±14.02	*P*<0.01

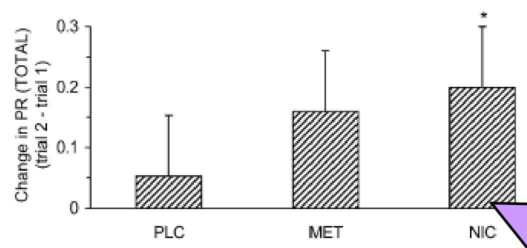


Fig. 4 Hi–low imagery task: learning score (trial 2–trial 1), placebo; *NIC* nicotine (7 mg); *MET* methylphenidate (usual dos
*$P<0.05$ difference PLC versus NIC

TDN Superior to MET

Adverse Reactions to 7 mg/24hr Nicotine patch in young adults with ADHD

Reaction	Nicotine Group (n = 31)	Placebo Group (n = 33)	P Value*
	%		
Skin irritation, erythema, or contact dermatitis	58	12	<0.001
Lightheadedness or dizziness	29	3	0.005
Nausea	29	0	<0.001
Vomiting	6	0	>0.05
Headaches	10	0	>0.05
Sleep disturbance or violent or sexual dreams	6	3	>0.05
Stimulation of central nervous system	3	3	>0.05
Diaphoresis or sweating	3	0	>0.05
Shakiness or tremor	3	0	>0.05
Tachycardia	3	0	>0.05
Miscellaneous	23	15	>0.05
Any adverse reaction	77	30	<0.001

* By the Fisher exact test.

NS ???

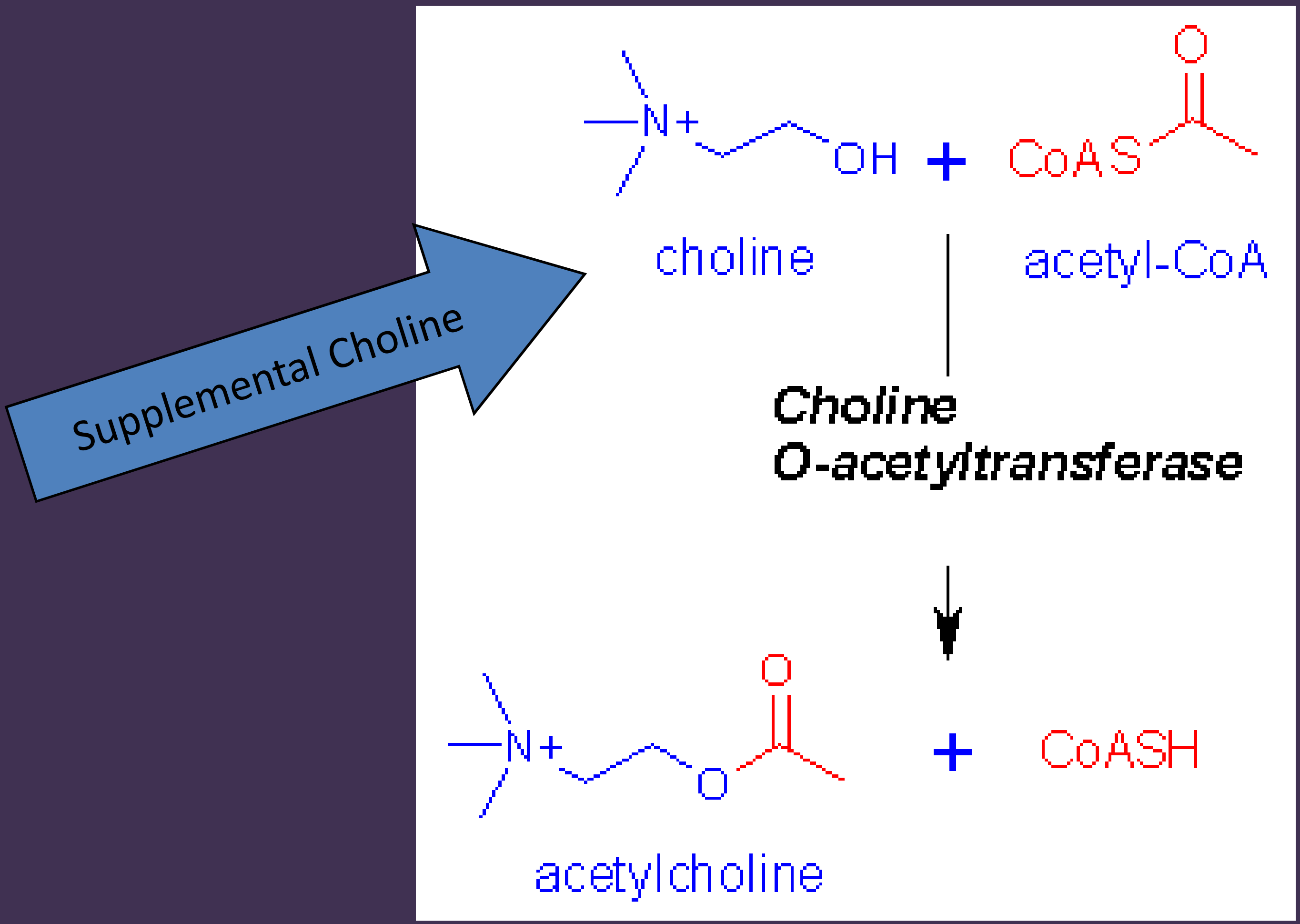
Data from ABC scoring
9 yo female after 2 months

- Teacher Pre total ABC score = 42
- Teacher Post total ABC score = 9
- Change = 33
- Mother Pre total ABC score = 57
- Mother Post total ABC score = 18
- Change = 39
- All domains dramatically reduced

TDN

- Step 1 = 21 mg/per 24 hrs
- Step 2 = 14 mg/24 hrs
- Step 3 = 7 mg/24 hrs
- Usual dose we are using is ¼ to ½ of 7mg patch which is under 0.15 mg per hour
- Manufacturer warns NOT to cut the patch, but in practice thus far it has worked extremely well.
- Skin reactions #1 issue: less with generic
- Nausea and dizziness next
- Cigarettes deliver 2-3 mg per cigarette or 40 to 120 mg per 24 hours for typical smokers

Acetylcholine is made from Choline and Acetyl-CoA



Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly

This version first published online: 20 April 2005 in Issue 2, 2005
Cochrane Database of Systematic Reviews 2005, Issue 2.

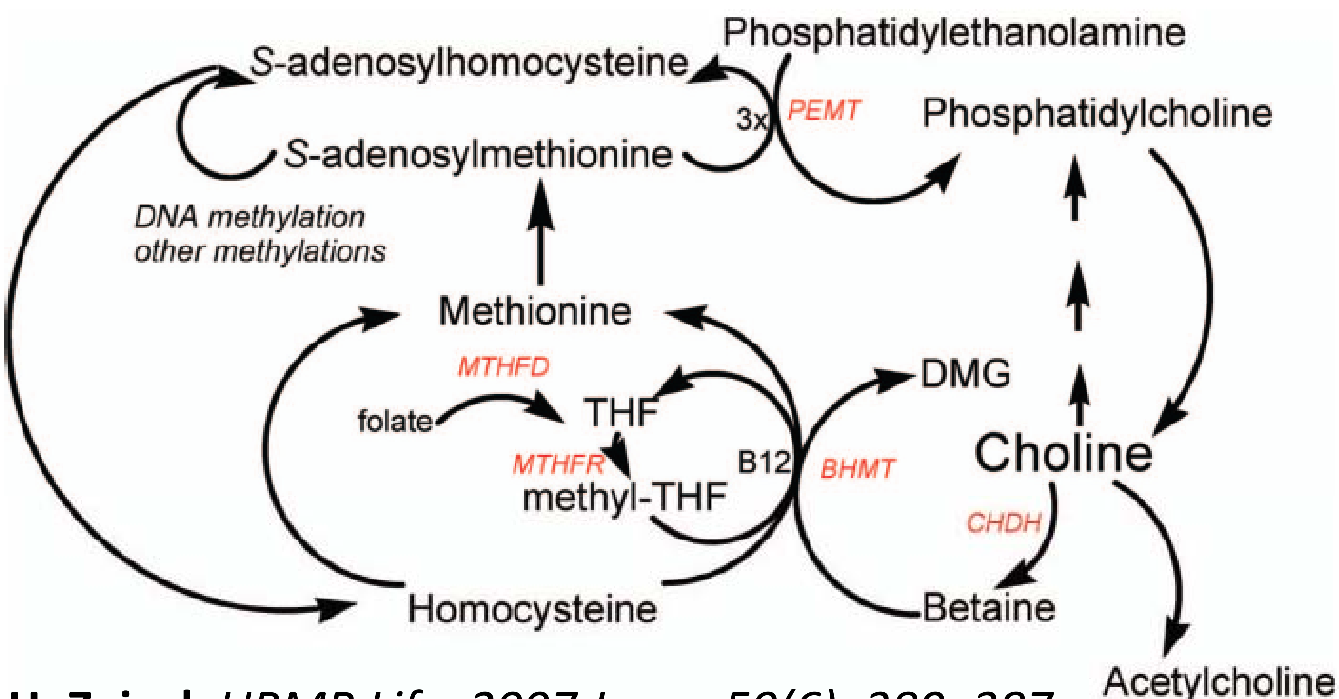
CDP-choline (cytidine 5'-diphosphocholine) is a precursor essential for the synthesis of phosphatidylcholine, one of the cell membrane components that is degraded during cerebral ischaemia to free fatty acids and free radicals. Animal studies suggest that CDP-choline may protect cell membranes by accelerating resynthesis of phospholipids. CDP-choline may also attenuate the progression of ischaemic cell damage by suppressing the release of free fatty acids. CDP-choline is the endogenous compound normally produced by the organism. When the same substance is introduced as a drug it can be called citicoline.

Due to its effects on the adrenergic and dopaminergic activity of the CNS, CDP-choline has also been used as an adjuvant in the treatment of Parkinson's disease.

Plain language summary
Some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short/medium term in elderly people with cognitive deficits associated with chronic cerebral disorders of the brain.

Accepted evidence the orthomolecular approach can be effective therapy in certain cases.

Interaction of Choline with Methylation and Transsulfation



Steven H. Zeisel *UBMB Life. 2007 June ; 59(6): 380–387*

Figure 1.
Choline metabolism and links to methionine and folate metabolism. The pathways described are all present in the liver, with other tissues having one or more of these pathways. PEMT, phosphatidylethanolamine-N-methyltransferase; CHDH, choline dehydrogenase; BHMT, betaine homocysteine methyltransferase; MTHFR, methylene tetrahydrofolate reductase; MTHFD, methylene tetrahydrofolate dehydrogenase.

NT Orthomolecular Options

- Vitamins: B6 and Magnesium in ASD and Schizophrenia. Thiamine and other vitamins
- Lithium in near nutritional doses
- Precursor Molecules:
  - Tryptophan (5HTP?) > Serotonin and Melatonin
  - Tyrosine > Monoamines (Dopamine, etc)
  - DMAE (Dimethylaminoethanol) > Acetylcholine
  - CDP Choline > Acetylcholine

CNS Anti-inflammatories

- Things active in the gut may not cross into the brain, ie: 5-ASA (sulfasalazine) type meds.
- Nonsteroidals may work but at the risk of further worsening esophagitis and gastritis.
- Steroids may be effective but long term problems limit use.
- IVIG often effective but expensive and insurance coverage limited.
- Novel Agents; Pioglitazone (Actos), Spironolactone, Minocycline and others.

Urinary levels of neopterin and biopterin in autism

S. Messahel[a,b], A.E. Pheasant[a,*], H. Pall[b], J. Ahmed-Choudhury[a], R.S. Sungum-Paliwal[c], P. Vostanis[c]

[a]School of Biochemistry, University of Birmingham, Edgbaston Park Road, Birmingham B15 2TT, UK
[b]Department of Neurology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[c]Department of Child Psychiatry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Neuroscience Letters 241 (1998) 17–20

Table 1

Urinary neopterin and biopterin levels in autistic children, their siblings and control children

	Neopterin (μmol/mol creatinine)	Biopterin (μmol/mol creatinine)
Autistic children ($n = 14$)	3116 ± 686*	3691 ± 882**
Siblings ($n = 21$)	1490 ± 346	2923 ± 626**
Control children ($n = 16$)	908 ± 201	359 ± 80

Data are the mean ± SEM. Significantly different from controls: *$P < 0.01$; **$P < 0.001$.

"The observed increase in urinary native **neopterin** in autism agrees with our previous observations and indicates activation of cellular immunity in these children thus supporting the possible involvement of **autoimmunity** in the pathogenesis* of autism."

Messahel et al, Neuroscience Letters 241 (1998) 17–20

*Pathogenesis = the cause of disease

FEBRUARY 2008 VOL 4 NO 2 NATURE CLINICAL PRACTICE NEUROLOGY

Drug Insight: steroids in CNS infectious diseases—new indications for an old therapy

Michael T Fitch and Diederik van de Beek*

SUMMARY

Infectious diseases of the CNS lead to overwhelming inflammatory processes within the brain and spinal cord that contribute substantially to patient morbidity and mortality. Pharmacological strategies to modulate inflammation have been investigated, although the resulting guidelines have sometimes been contradictory. Steroids have been proposed as adjunctive treatments for bacterial meningitis, tuberculous meningitis and herpes simplex virus encephalitis. Well-designed randomized controlled trials have established dexamethasone as an adjunctive therapy for adult patients receiving antibiotics for bacterial meningitis, and physicians prescribing the initial antibiotics need to be aware of current guidelines. Morbidity and mortality in patients with tuberculous meningitis exceeds 50%. Steroid treatments reduce mortality through an as yet unknown mechanism, although their effects on morbidity are less clear. Herpes simplex virus encephalitis is also associated with considerable morbidity and mortality. Despite a lack of randomized trials, there is some evidence that steroids used alongside antiviral therapy might be beneficial in this condition. As we discuss in this Review, systemic steroid treatment is an important aspect of treatment regimens for CNS infectious diseases, and the recent literature provides guidelines for the use of steroids in combination with appropriate antimicrobial therapy.

Journal of Autism and Developmental Disorders, Vol. 26, No. 4, 1996

Brief Reports

Brief Report: Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics[1]

Sudhir Gupta,[2] Sudeepta Aggarwal, and Cathy Heads
Division of Basic and Clinical Immunology, University of California, Irvine

Journal of Nutritional & Environmental Medicine
December 2005; 15(4): 169–176

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Improvement in children with autism treated with intravenous gamma globulin

MARVIN BORIS, MD[1], ALLAN GOLDBLATT, PA-C[2] & STEPHEN M. EDELSON, PhD[3]

[1]*New York University School of Medicine, New York, USA,* [2]*Truro College, New York, USA, and* [3]*Autism Research Institute, 4182 Adams Ave, San Diego, CA 92116, USA*

Medical Hypotheses (2007) 68, 979–987

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http://intl.elsevierhealth.com/journals/mehy

Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

James Jeffrey Bradstreet [a,*], Scott Smith [a], Doreen Granpeesheh [b], Jane M. El-Dahr [c], Daniel Rossignol [d]

[a] *International Child Development Resource Center, Melbourne and Florida Hospital, Celebration, 1688 West Hibiscus Boulevard, Melbourne, FL 32901, United States*
[b] *Center for Autism Related Disorders, Tarzana, CA, United States*
[c] *Tulane University Health Sciences Center, Departments of Pediatrics and Medicine, Section of Pediatric Allergy, Immunology and Rheumatology, New Orleans, LA, United States*
[d] *University of Virginia, Department of Family Medicine, P.O. Box 800729, Charlottesville, VA, United States*

Table 2 Summary of the proposed effects of spironolactone on autism findings

Clinical finding	Autism finding	Effect of spironolactone
Interferon gamma	↑ [19]	↓ [55]
TNF-α	↑ [24,25]	↓ [54,55]
MCP-1	↑ [34]	↓ [54,56]
Inflammation	↑ [27,34]	↓ [53,55]
Oxidative stress	↑ [57]	↓ [62]
Testosterone effects	↑[a] [5–7]	↓ [59]

[a] Elevated in a subset of autistic individuals.

Mitochondria, Oxidative Stress and Neurodegeneration

Developmental Neuroscience

Dev Neurosci 2000;22:384–392

Received: September 13, 1999
Accepted: November 25, 1999

Microglial Cells in Culture Express a Prominent Glutathione System for the Defense against Reactive Oxygen Species

Johannes Hirrlinger Jan Mirko Gutterer Lothar Kussmaul
Bernd Hamprecht Ralf Dringen

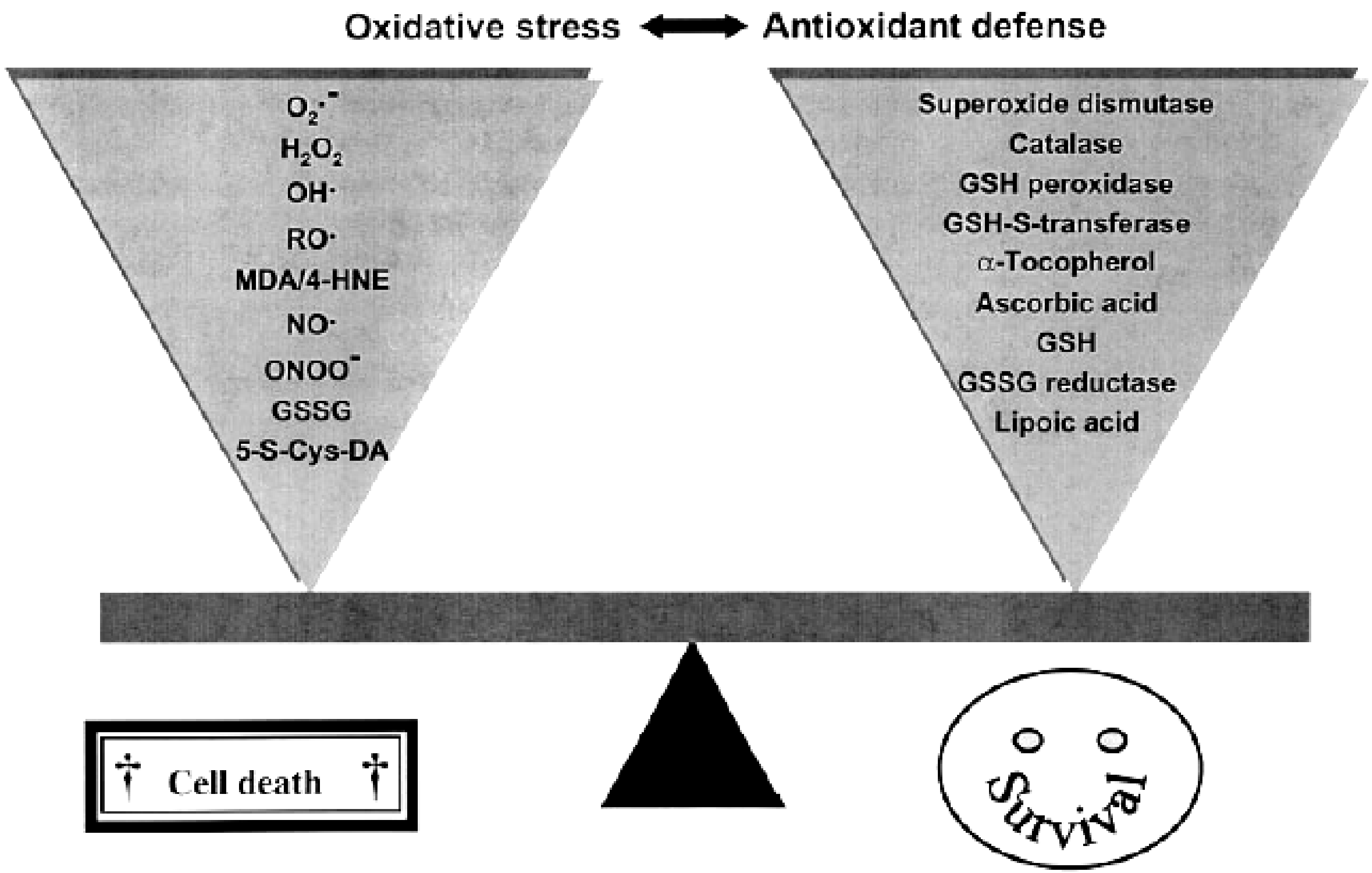
Physiologisch-Chemisches Institut der Universität, Tübingen, Germany

MINIREVIEW Eur. J. Biochem. 267, 4904–4911 (2000) © FEBS 2000

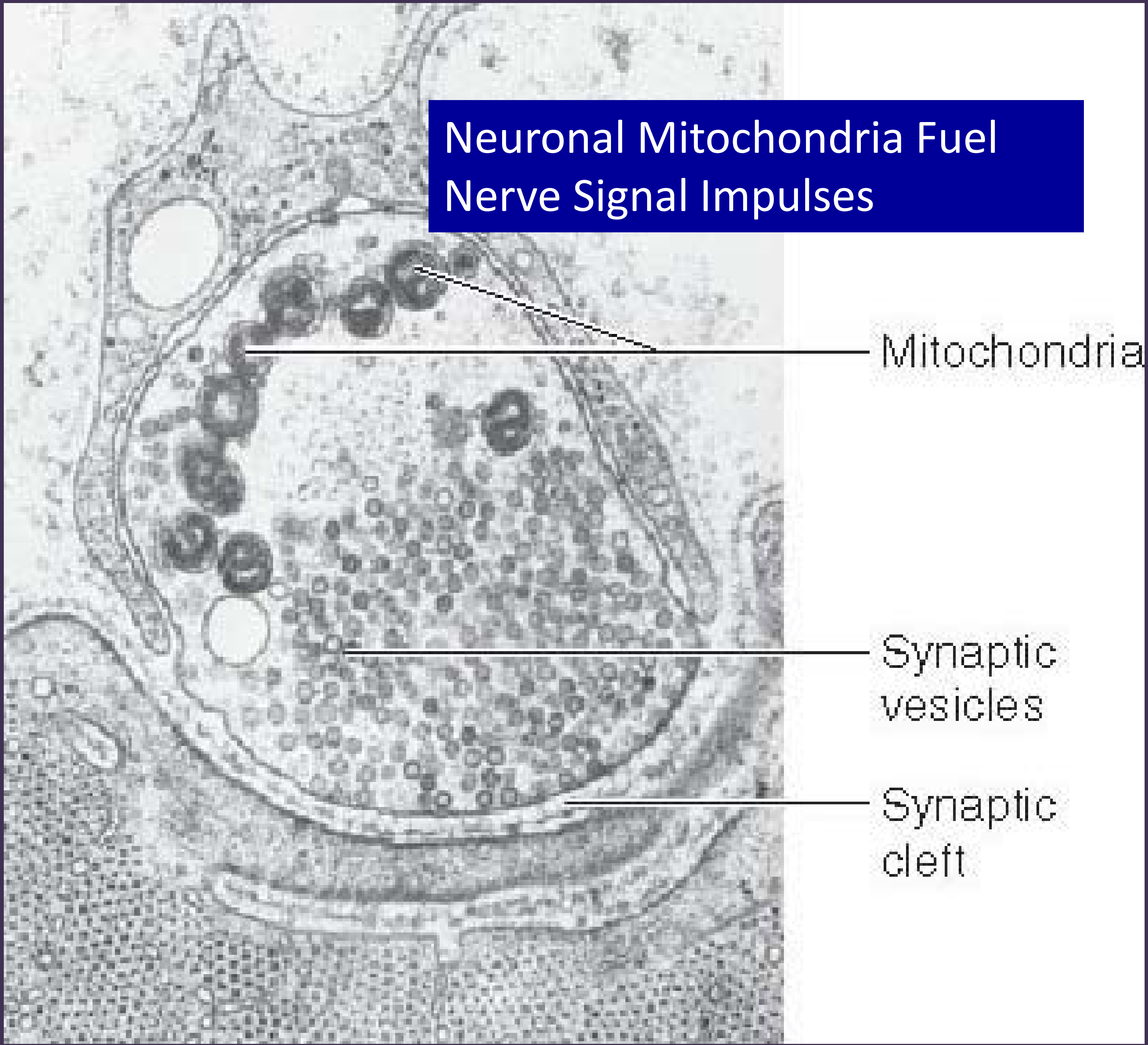
Glutathione, oxidative stress and neurodegeneration

Jörg B. Schulz, Jörg Lindenau, Jan Seyfried and Johannes Dichgans

Neurodegeneration Laboratory, Department of Neurology, University of Tübingen, Germany



Neuronal Mitochondria Fuel Nerve Signal Impulses



American Journal of Biochemistry and Biotechnology 4 (2): 208-217, 2008
ISSN 1553-3468

Evidence of Mitochondrial Dysfunction in Autism and Implications for Treatment

Daniel A. Rossignol, J. Jeffrey Bradstreet
International Child Development Resource Center, 3800 W. Eau Gallie Blvd., Suite 105, Melbourne, FL 32934

Abstract: Classical mitochondrial diseases occur in a subset of individuals with autism and are usually caused by genetic anomalies or mitochondrial respiratory pathway deficits. However, in many cases of autism, there is evidence of mitochondrial dysfunction (MtD) without the classic features associated with mitochondrial disease. MtD appears to be more common in autism and presents with less severe signs and symptoms. It is not associated with discernable mitochondrial pathology in muscle biopsy specimens despite objective evidence of lowered mitochondrial functioning. Exposure to environmental toxins is the likely etiology for MtD in autism. This dysfunction then contributes to a number of diagnostic symptoms and comorbidities observed in autism including: cognitive impairment, language deficits, abnormal energy metabolism, chronic gastrointestinal problems, abnormalities in fatty acid oxidation, and increased oxidative stress. MtD and oxidative stress may also explain the high male to female ratio found in autism due to increased male vulnerability to these dysfunctions. Biomarkers for mitochondrial dysfunction have been identified, but seem widely under-utilized despite available therapeutic interventions. Nutritional supplementation to decrease oxidative stress along with factors to improve reduced glutathione, as well as hyperbaric oxygen therapy (HBOT) represent supported and rationale approaches. The underlying pathophysiology and autistic symptoms of affected individuals would be expected to either improve or cease worsening once effective treatment for MtD is implemented.

Mitochondrial Dysfunction May Play a Role in Autism Spectrum Disorders Etiology

Caroline Cassels

April 15, 2008 (Chicago, IL) — New research suggests mitochondrial dysfunction may play a role in the etiology of autism spectrum disorders (ASD) in a subset of this patient population.

Here at the American Academy of Neurology 60th Annual Meeting, a retrospective analysis of 41 children with ASD who were being evaluated for suspected mitochondrial disease showed that 32 (78%) had defects in skeletal muscle oxidative phosphorylation (OXPHOS) enzyme function and 29 of 39 (74%) harbored abnormalities in the OXPHOS proteins.

"We're very excited by these findings, and, based on these results, we will continue to pursue this [mitochondrial dysfunction] as a potential cause in a segment of the autistic population," principal investigator John Shoffner, MD, owner of Medical Neurogenetics, in Atlanta, Georgia, told *Medscape Neurology & Neurosurgery*.

Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Jacqueline R. Weissman[1], Richard I. Kelley[2], Margaret L. Bauman[3], Bruce H. Cohen[4], Katherine F. Murray[3], Rebecca L. Mitchell[5], Rebecca L. Kern[2], Marvin R. Natowicz[1,4,5,6]*

1 Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, United States of America, **2** Department of Pediatrics, Johns Hopkins University Medical Center and Division of Metabolism, Kennedy Krieger Institute, Baltimore, Maryland, United States of America, **3** Department of Pediatrics and Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS), Massachusetts General Hospital, Boston, Massachusetts, United States of America, **4** Neurological Institute and Pediatrics Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, **5** Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, **6** Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America

Abstract

Background: Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

Methodology/Principal Findings: We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex III (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

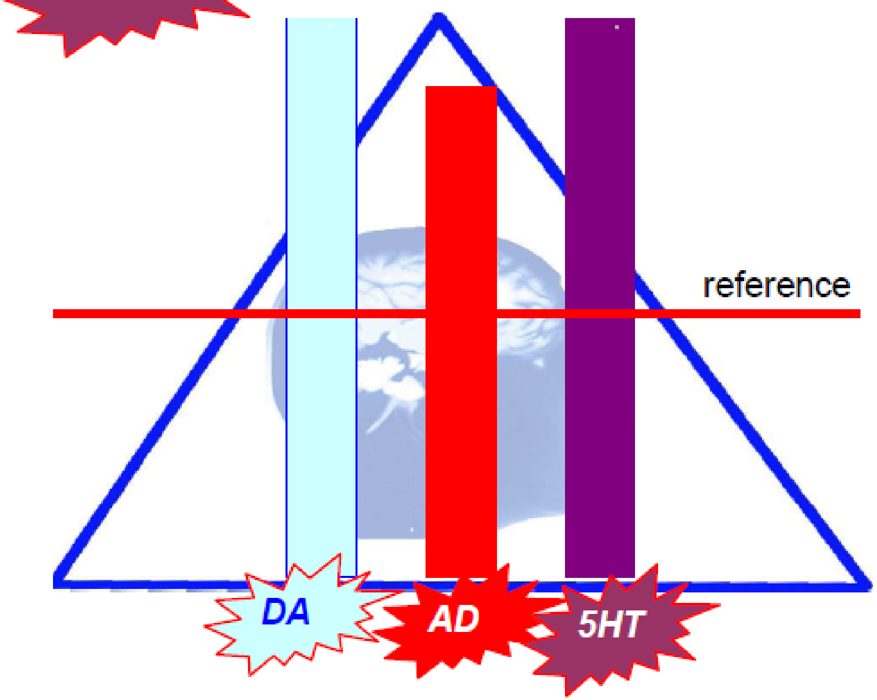
Conclusions/Significance: Although all patients' initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These and prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.

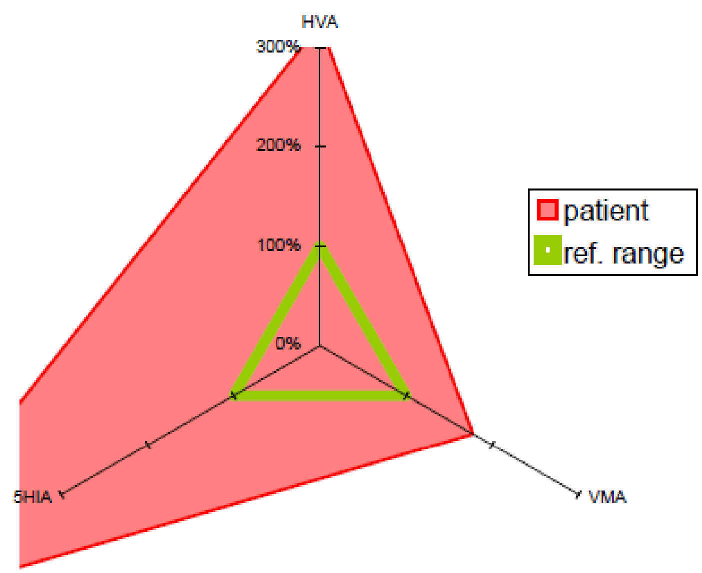
Maladaptive Neurotransmitter Compensation for Mitochondrial Dysfunction

06/10/2008

Neurotransmitter metabolism

	catabolites	patient	reference	Intrepretation
DA	hva	9,68	2,5-3,5	Sharply increased Dopaminergic activity
AD	vma	5,3	2,5-3,5	Sharply increased Adrenergic activity
5HIA	5hia	20,5	3,0-4,5	Sharply increased Serotoninergic activity





Relative Carnitine Deficiency in Autism

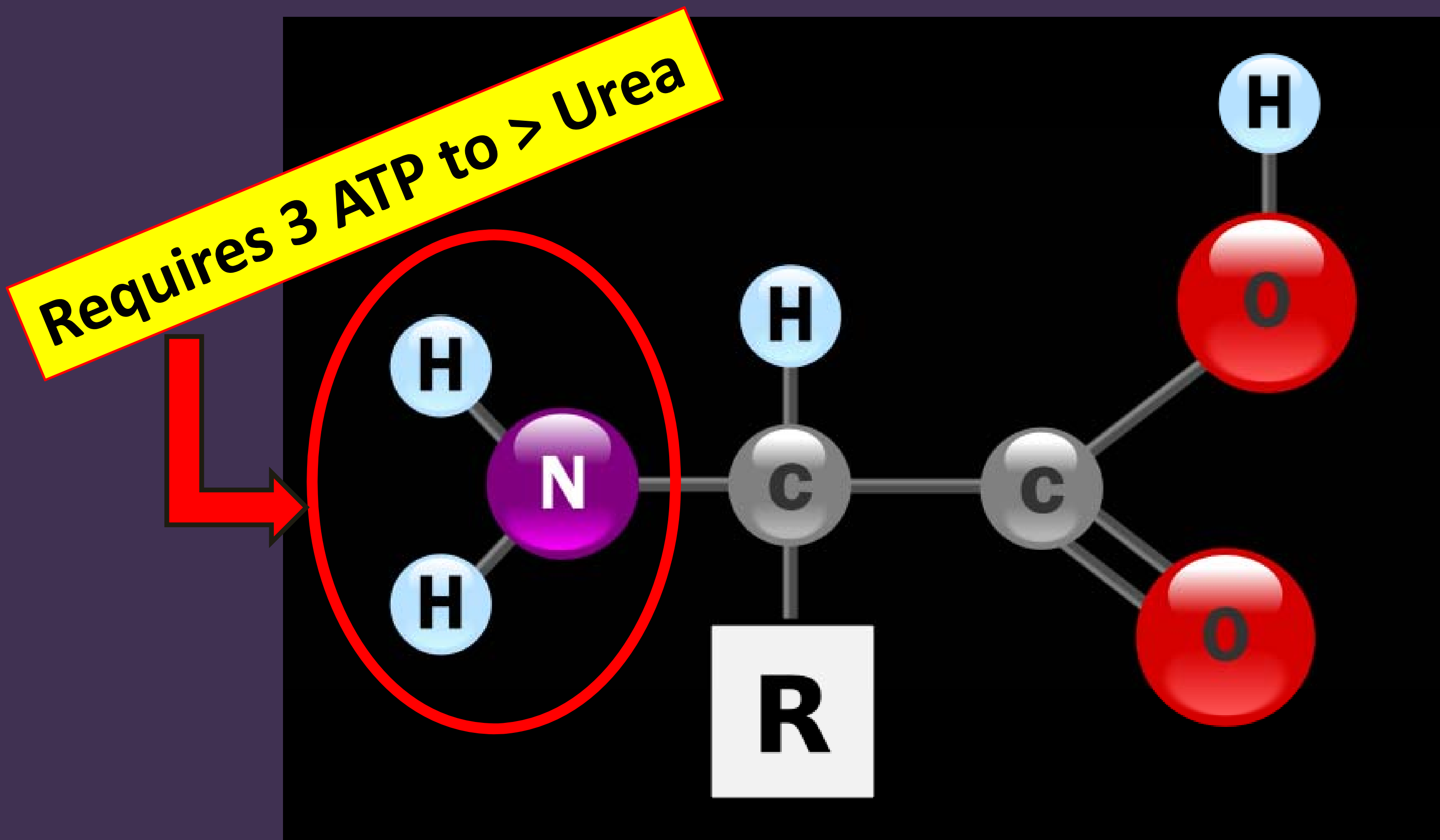
Journal of Autism and Developmental Disorders, Vol. 34, No. 6, December 2004 (© 2004)

Pauline A. Filipek,[1,2] Jenifer Juranek,[1] Minh T. Nguyen,[1] Christa Cummings,[1] and J. Jay Gargus[1,3,4]

A random retrospective chart review was conducted to document serum carnitine levels on 100 children with autism. Concurrently drawn serum pyruvate, lactate, ammonia, and alanine levels were also available in many of these children. Values of free and total carnitine ($p < 0.001$), and pyruvate ($p = 0.006$) were significantly reduced while ammonia and alanine levels were considerably elevated ($p < 0.001$) in our autistic subjects. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, is suggestive of mild mitochondrial dysfunction. It is hypothesized that a mitochondrial defect may be the origin of the carnitine deficiency in these autistic children.

Significantly increased NH3 and Alanine with mild increase in Lactate = Mitochondrial Dysfunction

Amino acids = Source of Ammonia



Amine + Carbohydrate ⟷ Amino Acid

Mitochondrial Cocktail

- D-Ribose: generates ATP via a bypass of the pentose phosphate shunt pathway. ATP = energy storage.
- Acetyl L Carnitine: Fuels CNS mitochondria better than plain carnitine.
- UBQH: more active form of CoQ10, a facilitator of mitochondrial activity.
- Antioxidants: protect mitochondrial OXPHOS
- Multiple small feedings per day – no large meals – constant supply of energy
- Moderation of protein intake – expensive for cells to get rid of extra ammonia.

Antioxidant Effect per 1 gram of whole food

Muscadine Grape Seed**	559
Acai*	387
Goji Berry*	253
Noni*	151
Pomegranates*	105
Raspberries*	82
Blueberries*	77
Red Grapes*	74
Prunes*	57
Cherries*	67
Strawberries*	36

*Antioxidant Capacities of Foods. J. Agric. Food Chem., Vol. 52, No. 12, 2004 4027

*Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL, J Agric Food Chem. "Lipophilic and hydrophilic antioxidant capacities of common foods in the United States." 2004 Jun 16;52(12):4026-37

Pediatric
Obsessive
Compulsive
Disorder
Research

Pediatrics & Developmental Neuropsychiatry Branch

PDN

Pediatrics & Developmental Neuropsychiatry Branch

NIMH National Institute of Mental Health

Reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavior

PANDAS

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

7 yo boy with persistent severe OCD and ASD issues and NO signs of Strep Infection

ANTI-STREPTOLYSIN O	1502	H	<150 IU/mL
IMMUNOGLOBULIN A	163		41-368 mg/dL
IMMUNOGLOBULIN M	85		47-311 mg/dL
DNASE-B ANTIBODY	>1360		titer

Reference range:

Pre-school:	=< 60 titer
School:	=< 170 titer
Adult:	=< 85 titer

Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders

Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, and Susan E. Swedo

Background: *The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) describes a subgroup of children with obsessive-compulsive disorder and/or tic disorder that experience symptom exacerbations following streptococcal infections. We hypothesized that the prevention of streptococcal infections among children in the PANDAS subgroup would decrease neuropsychiatric symptom exacerbations.*

Methods: *Twenty-three subjects with PANDAS were enrolled in a double blind, randomized controlled trial. Antibiotic prophylaxis with penicillin or azithromycin was administered for 12 months. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year prior to entry.*

Results: *Significant decreases in streptococcal infections during the study year were found with a mean of .1 (.3 SD) per subject, compared to the baseline year with 1.9 (1.2 SD) in the penicillin group and 2.4 (1.1 SD) in the azithromycin group [$p < .01$]. Significant decreases in neuropsychiatric exacerbations during the study year were also found with a mean of .5 (.5 SD) per subject in the penicillin group and .8 (.6 SD) in the azithromycin group, compared to the baseline year with 2.0 (.9 SD) in the penicillin group and 1.8 (.6 SD) in the azithromycin group [$p < .01$].*

Conclusions: *Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.*

BIOL PSYCHIATRY 2005;57:788–792

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B:1–10 (2006)

Letter to the Editor

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

S. Jill James,[1]* Stepan Melnyk,[1] Stefanie Jernigan,[1] Mario A. Cleves,[1] Charles H. Halsted,[2] Donna H. Wong,[2] Paul Cutler,[3] Kenneth Bock,[4] Marvin Boris,[5] J. Jeffrey Bradstreet[Q1],[5,6] Sidney M. Baker,[7] and David W. Gaylor[8]

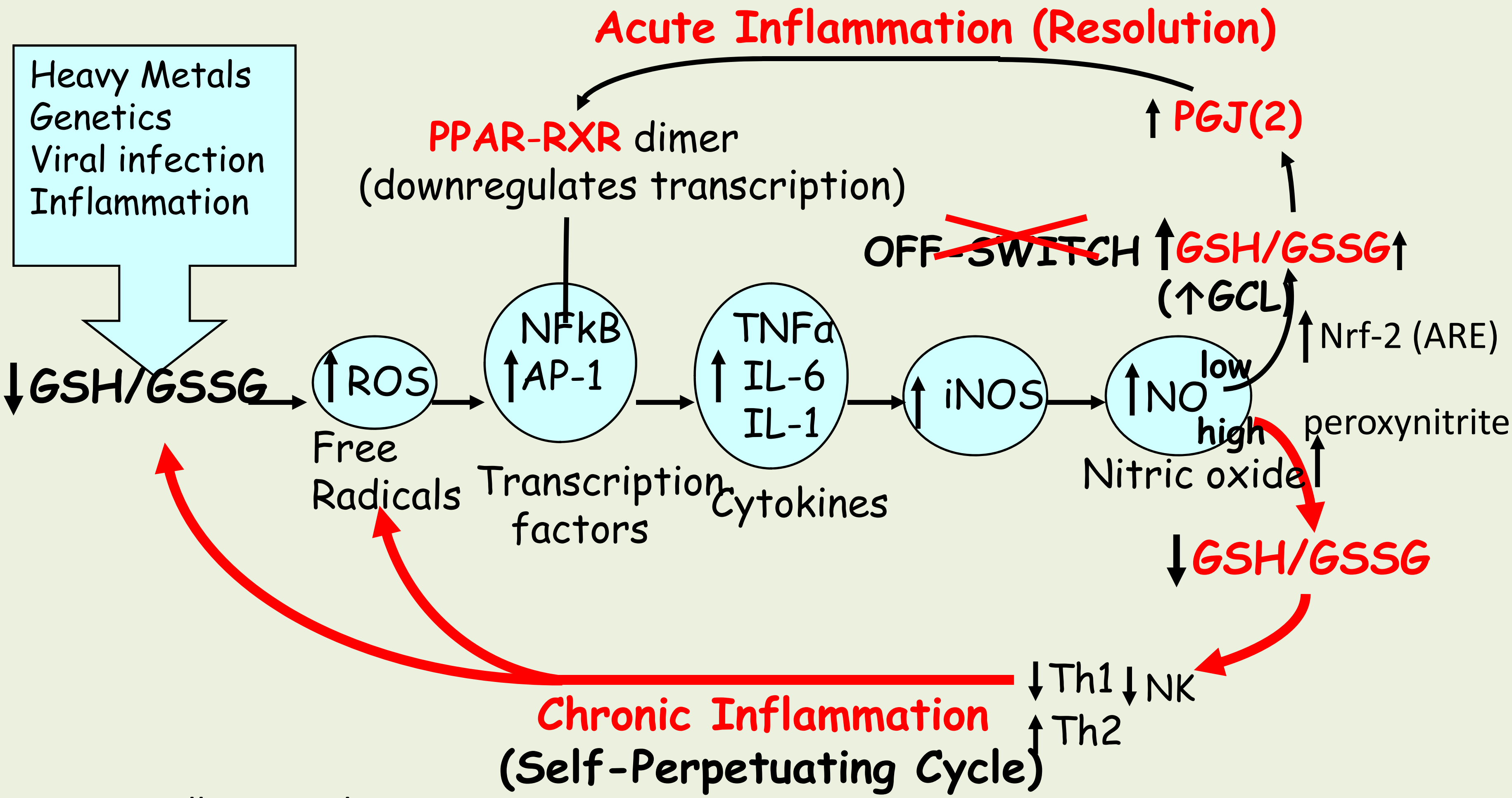
[1]*Department[Q2] of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas*
[2]*Genome and Biomedical Sciences Facility, West Health Science Drive, University of California Davis, Davis California*
[3]*Elmwood Ave., Niagara Falls, New York, New York*
[4]*Rhinebeck Health Center, Rhinebeck, New York, New York*
[5]*Froelich Farm Blvd., Woodbury, New York, New York*
[6]*International Child Development Resource Center, Hibiscus Blvd, Melbourne, Florida*
[7]*Sag Harbor, New York, New York*
[8]*Department of Biostatistics, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas*

TABLE II. Transmethylation and Transsulfuration Metabolites in Autistic Cases and Controls

	Control[a] (n = 73)	Autistic[a] (n = 80)	*P*-value
Methionine (µmol/L)	28.0 ± 6.5	20.6 ± 5.2	<0.0001
SAM (nmol/L)	93.8 ± 18	84.3 ± 11	<0.0001
SAH (nmol/L)	18.8 ± 4.5	23.3 ± 7.9	<0.0001
SAM/SAH ratio	5.5 ± 2.8	4.0 ± 1.7	<0.0001
Adenosine (µmol/L)	0.19 ± 0.13	0.28 ± .13	0.001
Homocysteine (µmol/L)	6.0 ± 1.3	5.7 ± 1.2	0.03v
Cystathionine (µmol/L)	0.19 ± 0.1	0.24 ± 0.1	<0.0001
Cysteine (µmol/L)	207 ± 22	165 ± 14	<0.0001
Cysteinylglycine (µmol/L)	39.4 ± 7.3	38.9 ± 11	0.78
Total GSH (µmol/L)	7.53 ± 1.7	5.1 ± 1.2	<0.0001
Free GSH (µmol/L)	2.2 ± 0.9	1.4 ± 0.5	<0.0001
GSSG (µmol/L)	0.24 ± 0.1	0.40 ± 0.2	<0.0001
Total GSH/GSSG ratio	28.2 ± 7.0	14.7 ± 6.2	<0.0001
Free GSH/GSSG ratio	7.9 ± 3.5	4.9 ± 2.2	<0.0001

SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; GSH, glutathione; GSSG, glutathione disulfide.
[a]Means ± SD.

The failure to maintain GSH/GSSG redox balance and to resolve acute inflammatory stress promotes a self-perpetuating cycle of chronic inflammation



Courtesy Jill James PhD

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Research

Succimer Chelation Improves Learning, Attention, and Arousal Regulation in Lead-Exposed Rats but Produces Lasting Cognitive Impairment in the Absence of Lead Exposure

Diane E. Stangle,[1] Donald R. Smith,[2] Stephane A. Beaudin,[3] Myla S. Strawderman,[3] David A. Levitsky,[1,3] and Barbara J. Strupp[1,3]

[1]Department of Psychology, Cornell University, Ithaca, New York, USA; [2]Department of Environmental Toxicology, University of California, Santa Cruz, California, USA; [3]Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA

BACKGROUND: There is growing pressure for clinicians to prescribe chelation therapy at only slightly elevated blood lead levels. However, very few studies have evaluated whether chelation improves cognitive outcomes in Pb-exposed children, or whether these agents have adverse effects that may affect brain development in the absence of Pb exposure.

OBJECTIVES: The present study was designed to answer these questions, using a rodent model of early childhood Pb exposure and treatment with succimer, a widely used chelating agent for the treatment of Pb poisoning.

RESULTS: Pb exposure produced lasting impairments in learning, attention, inhibitory control, and arousal regulation, paralleling the areas of dysfunction seen in Pb-exposed children. Succimer treatment of the Pb-exposed rats significantly improved learning, attention, and arousal regulation, although the efficacy of the treatment varied as a function of the Pb exposure level and the specific functional deficit. In contrast, succimer treatment of rats not previously exposed to Pb produced lasting and pervasive cognitive and affective dysfunction comparable in magnitude to that produced by the higher Pb exposure regimen.

CONCLUSIONS: These are the first data, to our knowledge, to show that treatment with any chelating agent can alleviate cognitive deficits due to Pb exposure. These findings suggest that it may be possible to identify a succimer treatment protocol that improves cognitive outcomes in Pb-exposed children. However, they also suggest that succimer treatment should be strongly discouraged for children who do not have elevated tissue levels of Pb or other heavy metals.

Cysteine Deficiency : male age 3

Deficit in Cysteine

0,0-

Cystéine	**59**	130-310

Oxidative Biomarkers and Treatment

- Isoprostane = oxidized fatty acid membranes
- 8 OHG = oxidized RNA
- Biopterin = oxidation due to inflammation
- Neopterin = immune activation which will lead to oxidation
- Build up Cysteine and Glutathione (Methionine)
- Porphyrins = coproporphyrin may rise from oxidation not just metal related events.
- Ammonia & lactic acid link to mito dysfunction
- Dysbiosis markers may reflect on these issues

Increased excretion of a lipid peroxidation biomarker in autism.

Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC.
Department of Neurosciences, UMDNJ-New Jersey Medical School, Newark, 07103, USA.

Prostaglandins Leukot Essent Fatty Acids. 2005 Nov;73(5):379-84.

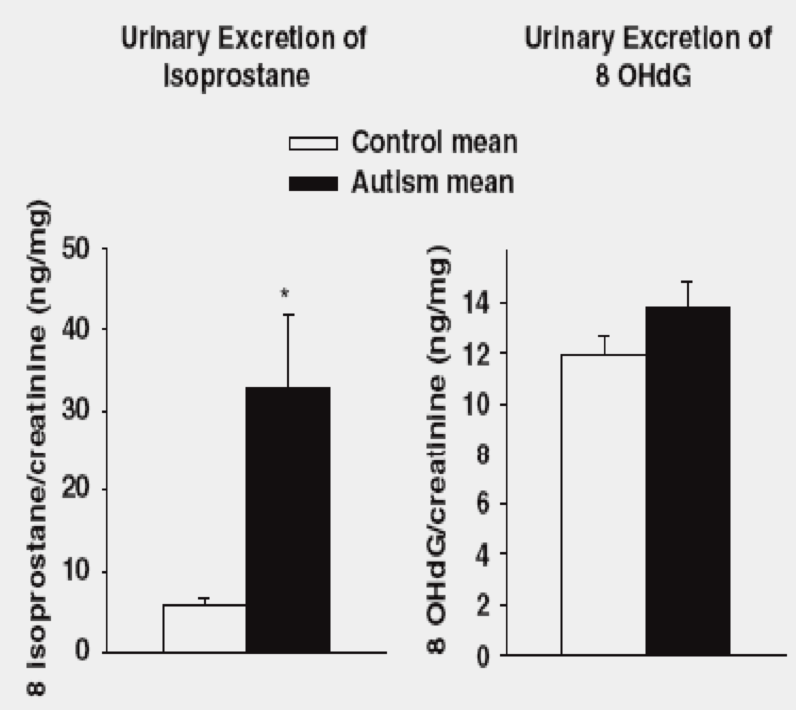


Fig. 1. Urinary excretion of isoprostane and 8-OHdG in children with autism and controls. *$P < 0.05$, Student's *t*-test.

Immune/Gut Case male age 3

Membrane Oxidative Damage

Urinary IsoprostaneF2-alpha

LC/MS-MS-immunoaffinity cartrige extraction -deuterated standard

8-iso-PGF2 alpa	**618** ng/gCr	80-160

Increased oxidative stress damage

Immune/Gut Case male age 3

02/01/2008

DNA Oxidative Stress

			reference range
8OHdG	**26**	nmole/gCr	12-25

urinary 8-hydroxy deoxyguanosine

Moderate elevated urinary 8OHdG, reflecting mildly increased DNA oxidative damage

In Children 3-9 years old, urinary 8OHdG is 25% higher than in adults (Bogdanov et al, Free Radical Biol. Med 27, 647-686, 1999)

RNA Oxidative Stress

8 OHG	**123**	nmole/gCr	20-40

urinary 8-hydroxy guanosine

strongly increased urinary 8OG, reflecting high RNA oxidative damage

RNA/DNA

8OHG/8OHdG	**4,7**	<2

urinary creatinin **955** mg/l

Immune/Gut Case male age 3

Immune system Methode : HPLC

	patient µmole / mole Cr	reference	result
urinary Neopterine (NEO)	1147	110-180	increased cellular immunity activation
Urinary Biopterin	434		
Biopeterin / Neopterin	0,4	>1,5	very low ratio

Gut Immunology

Analyte	Result	Reference Range
3. Eosinophil Protein X	4.0	<= 7.0 mcg/g
4. Calprotectin	122	<= 50 mcg/g

Gastrointestinal Microflora Studies in Late-Onset Autism

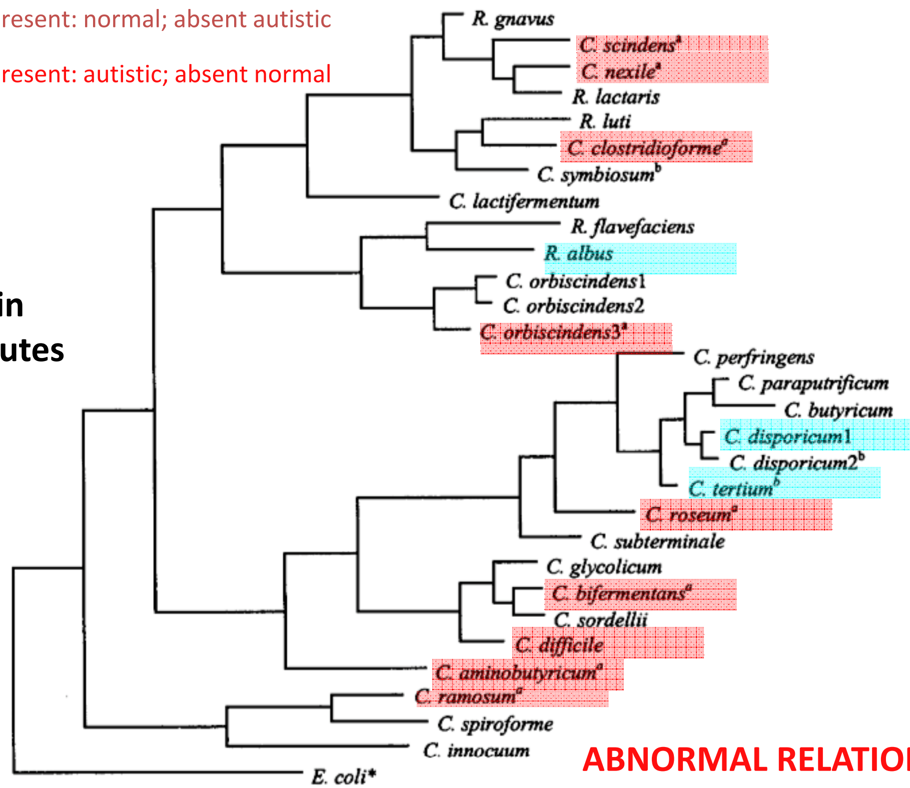
Clinical Infectious Diseases 2002;35(Suppl 1):S6–16

Sydney M. Finegold,[1,4,5] Denise Molitoris,[2] Yuli Song,[2] Chengxu Liu,[2] Marja-Liisa Vaisanen,[2] Ellen Bolte,[6] Maureen McTeague,[3] Richard Sandler,[6] Hannah Wexler,[2,5] Elizabeth M. Marlowe,[2,5] Matthew D. Collins,[10] Paul A. Lawson,[10] Paula Summanen,[2] Mehmet Baysallar,[2] Thomas J. Tomzynski,[2] Erik Read,[2] Eric Johnson,[7] Rial Rolfe,[8] Palwasha Nasir,[11] Haroun Shah,[11] David A. Haake,[1,5] Patricia Manning,[9] and Ajay Kaul[9]

Present: normal; absent autistic

Present: autistic; absent normal

Phylogenetic Relationships in the Gut Firmicutes

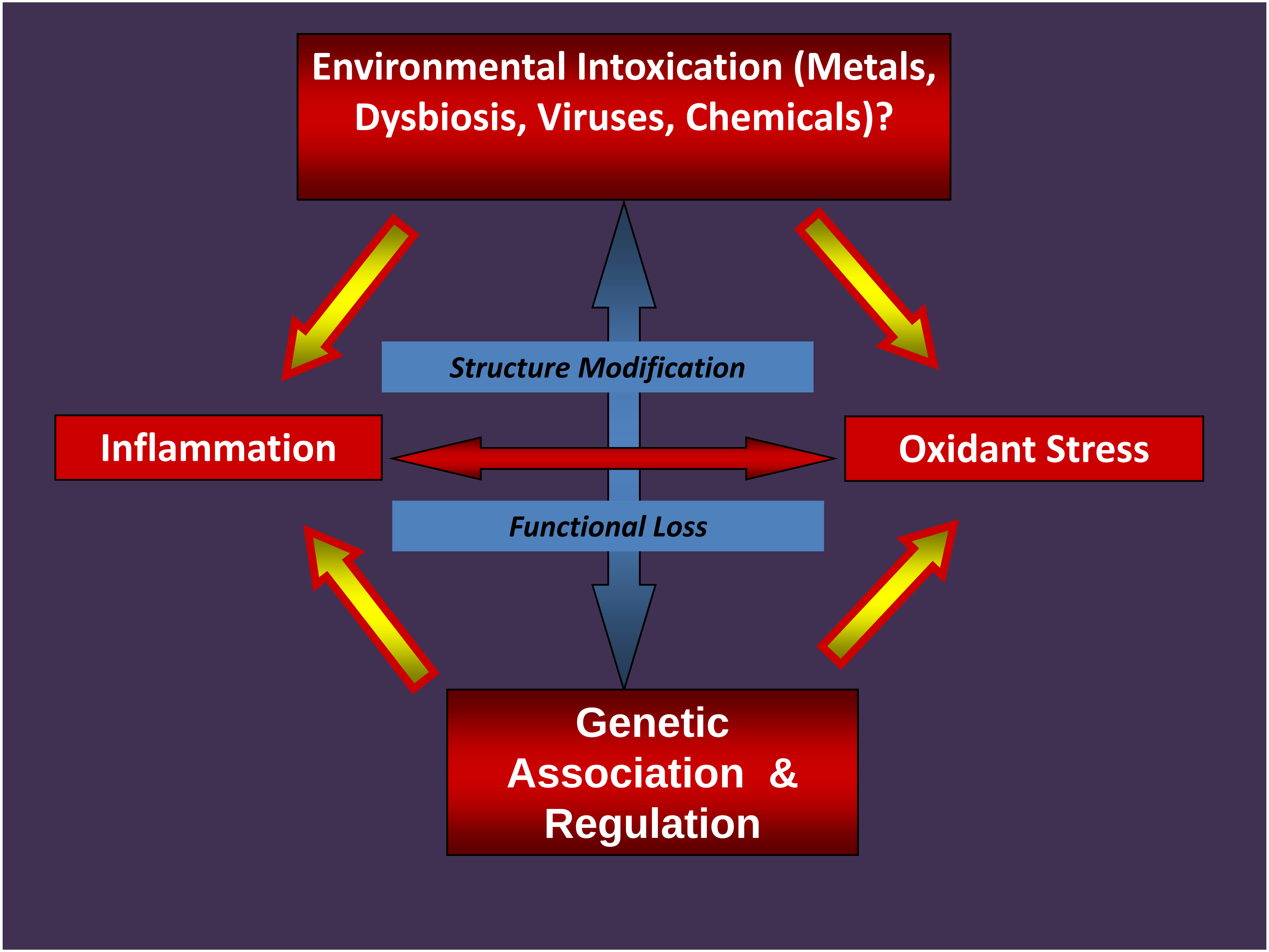


ABNORMAL RELATIONSHIPS IN FIRMICUTES IN AUTISM!

Figure 1. Dendrogram showing the interrelationships within the *Clostridium* and *Ruminococcus* species isolated from autistic and control children's stool specimens. The bar denotes 1% sequence divergence. The asterisk (*) denotes the outgroup standard. [a]*Clostridium* species isolated only from the stool specimens of children with autism. *Clostridium cocleatum* is not shown in this figure because the sequence data are not available. [b]*Clostridium* species isolated only from the stool specimens of control children.

Possible pathways for bacteria-related autism.

- Immune-mediated
- Toxin
- Toxic metabolic product(s)
  - p-cresol and phenols
  - Casomorphin, gliadomorphin, and endorphins
  - Products required for sulfation (e.g., glycosaminoglycans and sulfotransferases) or interfering with sulfation (sulfatase and sulfate-reductase)
  - Indole derivatives, including serotonin and indolylacryloyl glycine
  - Naphthalene derivatives
  - Naphtha derivatives
  - Mercury (especially methyl mercury) or other metallic ions
  - Interferons and cytokines


Environmental Intoxication (Metals, Dysbiosis, Viruses, Chemicals)?
Structure Modification
Inflammation
Oxidant Stress
Functional Loss
Genetic Association & Regulation