Neurological disorders and environmental toxicants: insights and observations

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Jerusalem, Israel

Possible associations between autism spectrum disorders and environmental exposures to hazardous air pollutants:

Concentrations of Metals Potentially Relevant to Autism

Windham et al, *Environ Health Perspect* 114:1438–44 (2006)

				Mean ± SD (mcg/m^3)	
Metal	**Suspected neurologic toxicant**	Recognized developmental toxicant	Suspected endocrine toxicant	Cases	Controls
Lead	**X**	X	X	0.009 ± 0.011	0.008 ± 0.009
Manganese	**X**			0.003 ± 0.001	0.003 ± 0.001
Mercury	**X**	X	X	0.0008 ± 0.0019	0.0006 ± 0.001

Possible associations between Neurological disorders and environmental toxicants:

Strategies for addressing this question:

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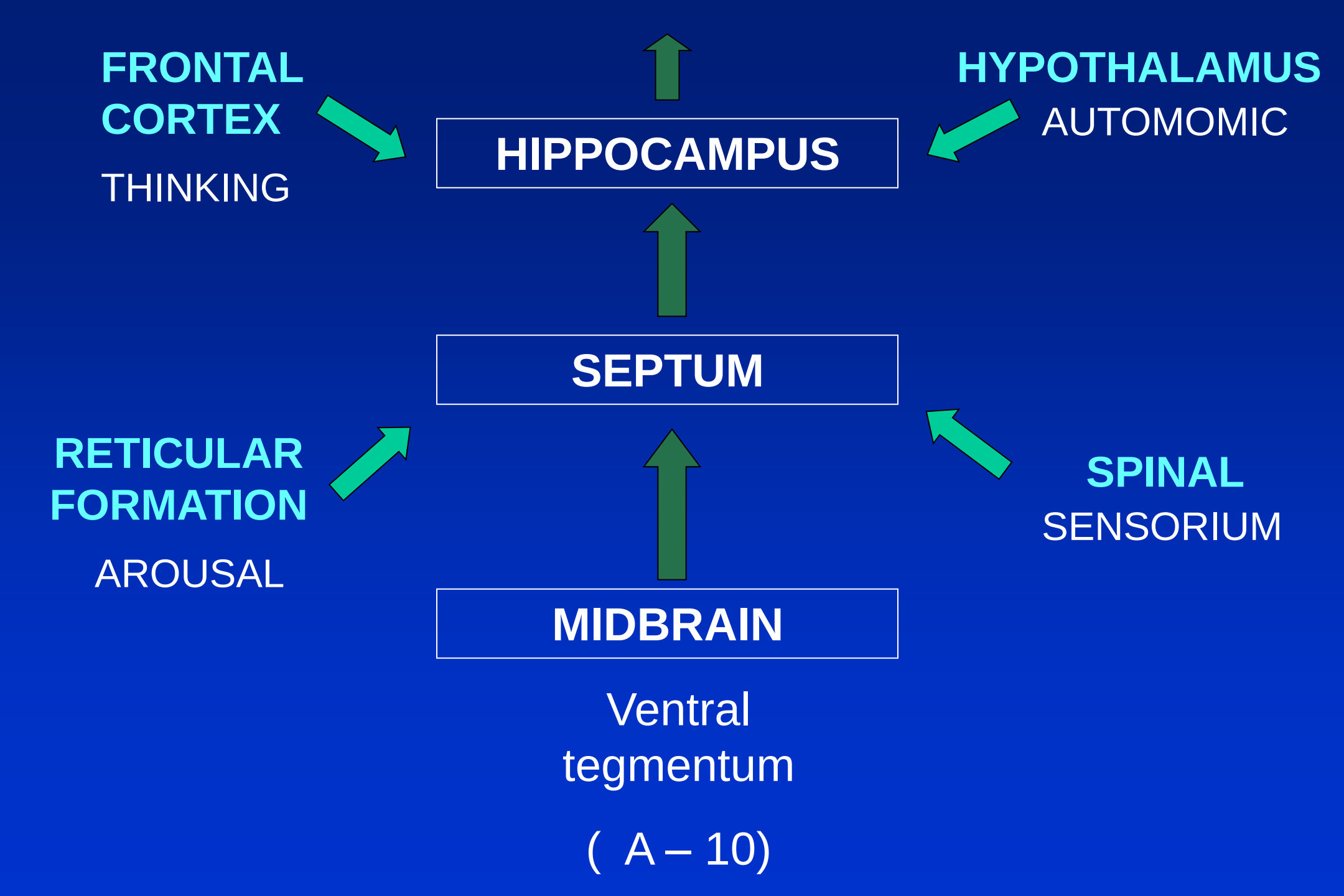
d. Interdisciplinary Studies on Association between Atmospheric Levels of Toxicant and Biological Markers

ERETHISM

Hg^0 Neurotoxicity


FRONTAL CORTEX
THINKING
HIPPOCAMPUS
HYPOTHALAMUS
AUTOMOMIC
SEPTUM
RETICULAR FORMATION
AROUSAL
SPINAL
SENSORIUM
MIDBRAIN
Ventral tegmentum
(A – 10)

NeuroToxicology 17:291-5 (1996)

The enigma of parkinsonism in chronic borderline mercury intoxication, resolved by challenge with penicillamine

Y. Finkelstein, J. Vardi, M. M. Kesten, I. Hod

Unit and Service of Neurology and Toxicology, Shaare Zedek Medical Center

Jerusalem, Israel

A 47 year old female dentist suffered from Parkinsonism

A baseline quantitative urinary mercury excretion was 46 micrograms/day

The patient was treated with chelating agent d-penicillamine for a week. Chelation therapy resulted in clinical improvement of Parkinsonism and in dynamic changes in daily urinary mercury excretion

This case may be evidence, therefore, of a rare clinical variant of elemental mercury intoxication associated with Parkinsonism, in the absence of most classical neuropsychiatric signs of chronic mercurialism

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NeuroToxicology 28 (2007) 1003–1014

Modulation of cholinergic systems by manganese

Yoram Finkelstein [a,b,*], Dejan Milatovic [b], Michael Aschner [b]

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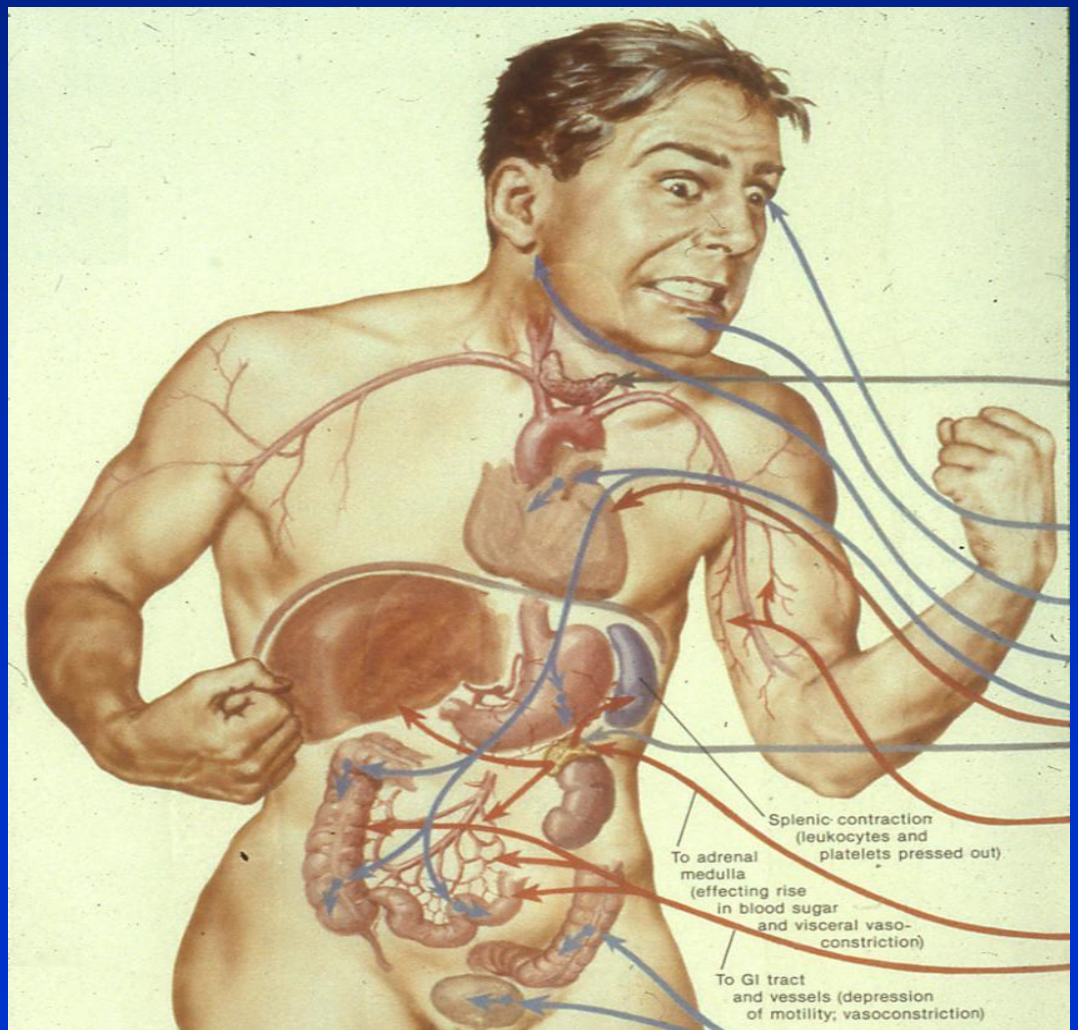
[b] Department of Pediatrics and the Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, TN, USA

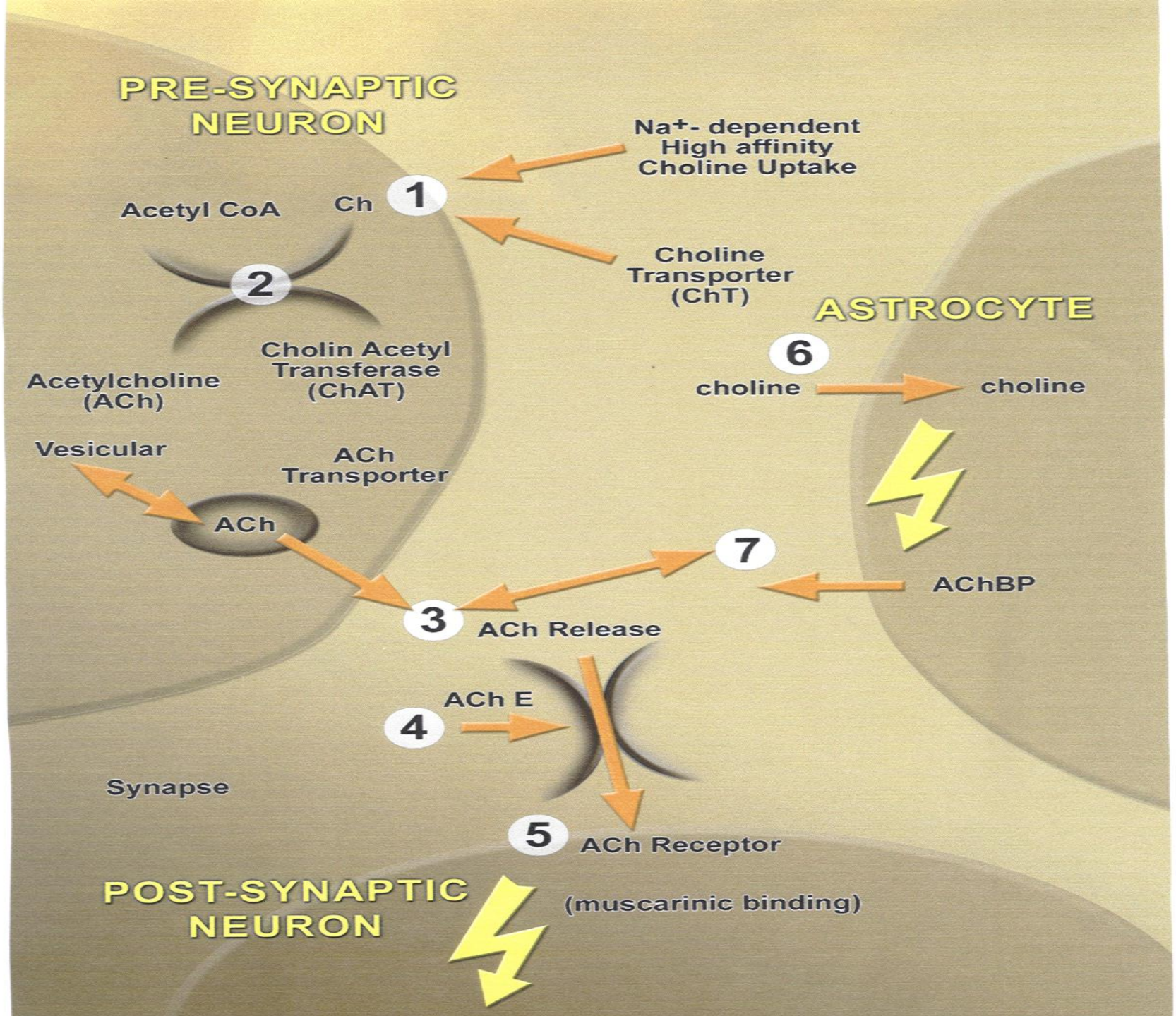
Locura Manganica



Manganism - Extrapyramidal stage

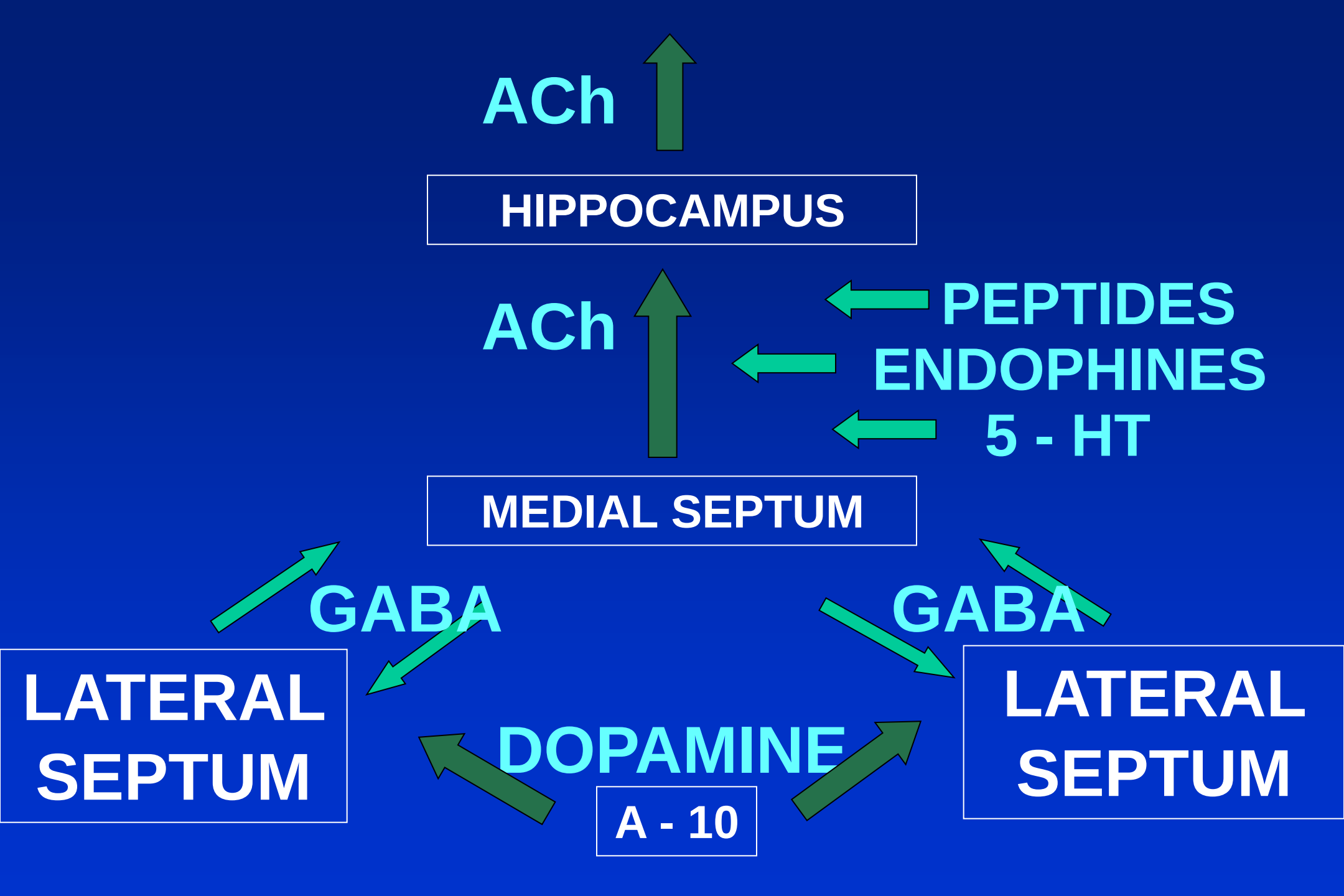
The organic mental syndrome is usually followed by disturbances of gait and excessive salivation, as the first manifestations of a movement disorder:

an extrapyramidal syndrome
clinically resembling Parkinson's Disease


PRE-SYNAPTIC NEURON
Na+- dependent High affinity Choline Uptake
1
Ch
Acetyl CoA
Choline Transporter (ChT)
2
ASTROCYTE
Cholin Acetyl Transferase (ChAT)
6
Acetylcholine (ACh)
choline
choline
Vesicular
ACh Transporter
ACh
7
AChBP
3
ACh Release
ACh E
4
Synapse
5
ACh Receptor
POST-SYNAPTIC NEURON
(muscarinic binding)

Glial targets for manganese activity:

Manganese exerts its effect
on the highly dynamic reciprocal relationship
between
astrocytes and cholinergic neurons.


ACh
HIPPOCAMPUS
ACh
PEPTIDES
ENDOPHINES
5 - HT
MEDIAL SEPTUM
GABA
GABA
LATERAL SEPTUM
LATERAL SEPTUM
DOPAMINE
A - 10

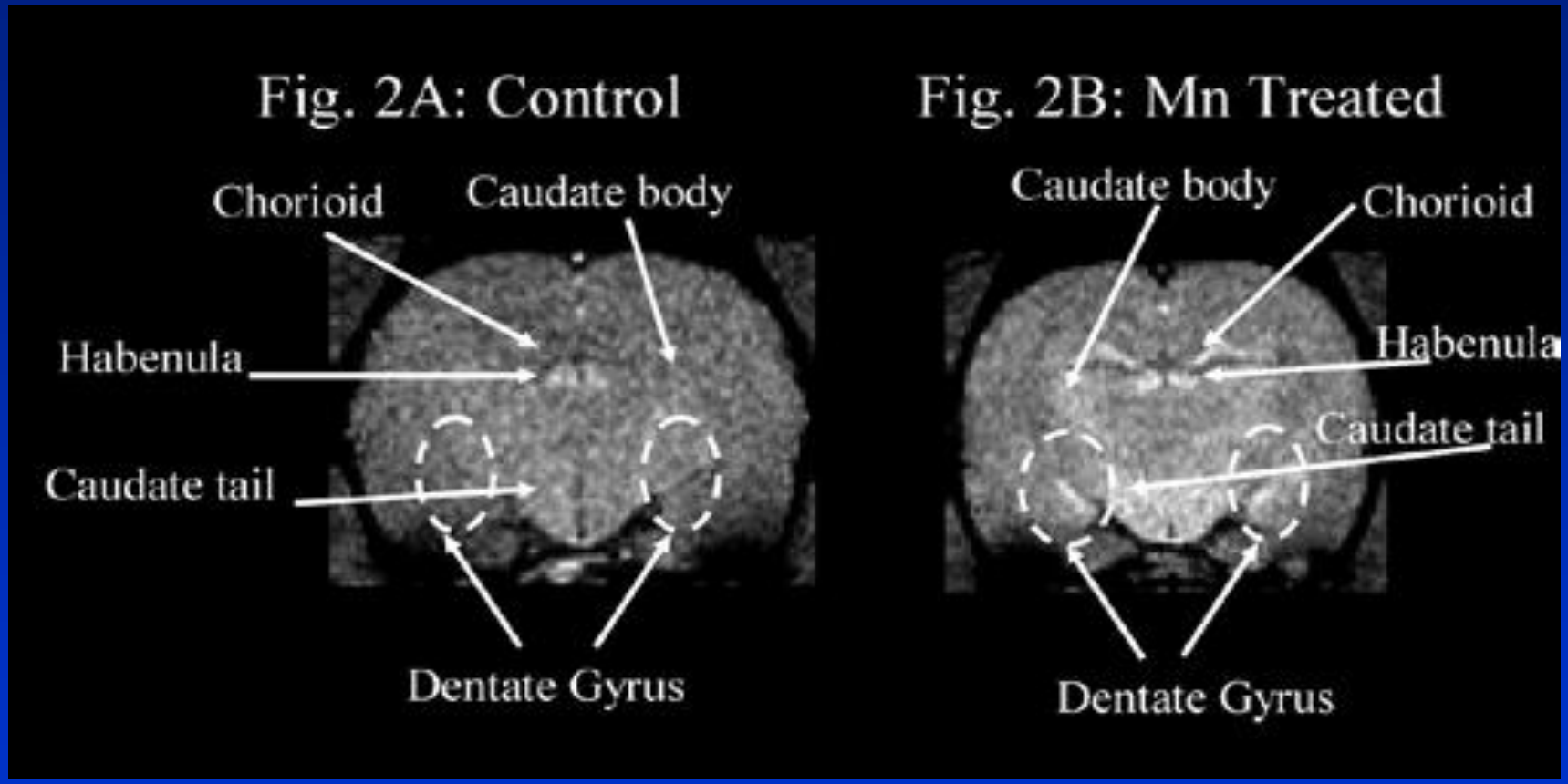
Israel Medical Association Journal 2008;10:793–798

Differential Deposition of Manganese in the Rat Brain Following Subchronic Exposure to Manganese: a T1-Weighted Magnetic Resonance Imaging Study

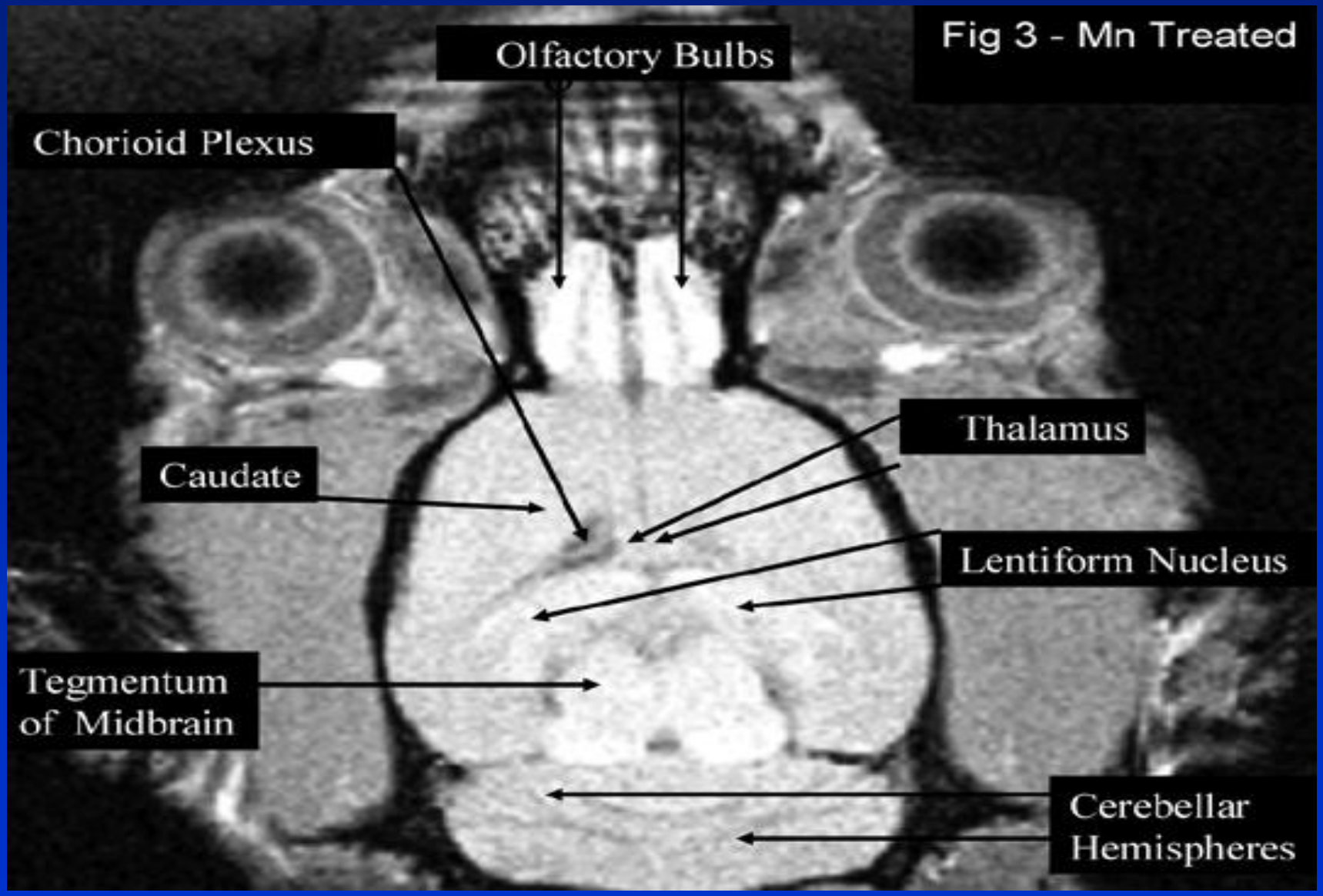
Yoram Finkelstein[1], Na Zhang[3,9], Vanessa A. Fitsanakis[2], Malcolm J. Avison[4-6,9], John C. Gore[3,4,6,7,9] and Michael Aschner[5,8,10,11]

[1]Neurology and Toxicology Unit and Service, Shaare Zedek Medical Center, Jerusalem, Israel
[2]Department of Biology, King College, Bristol; and Departments of [3]Physics & Astronomy, [4]Radiology & Radiological Sciences,
[5]Pharmacology, [6]Neurology, [7]Biomedical Engineering, [8]Molecular Physiology & Biophysics and [9]Pediatrics, [10]Institute of Imaging
Science, [11]Center for Molecular Neuroscience and [12]Center of Molecular Toxicology, Vanderbilt University, Nashville, TN, USA

Differential Deposition of Manganese in the Rat Brain



Differential Deposition of Manganese in the Rat Brain



Anatomical selectivity of manganese-induced cholinergic effects

is compatible with the clinical correlates of manganism, involving :

impairment of emotional response, decline in higher cortical functions and movement disorder

Brain Research Reviews 27: 168–176, 1998

Full-length review

Low-level lead-induced neurotoxicity in children: an update on central nervous system effects

Yoram Finkelstein [a], Morri E. Markowitz [b], John F. Rosen [b]

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[b] *Division of Environmental Sciences, Department of Pediatrics, Albert Einstein College of Medicine, Montifiore Medical Center, Bronx, NY, USA*

READING AND MATH

N=4853; 6-16 Year old; Mean Blood Lead=1.9 mcg/DL

For every 1 mcg/dL increase in Blood Lead Level:

- **- 1 POINT IN READING**
- **-.7 POINT IN MATH**
- **-.1 POINT IN REASONING**
- **-.5 POINT IN SHORT TERM MEMORY**

DEFICITS OBSERVED AT LOW BLOOD LEAD LEVELS <5 mcg/dL

Lanphear, Pub Health Reports 2000

Lead and Behavior

Yule 1983: n=166, 6-12 y, Lead Blood Level: 7-32 mcg/dL

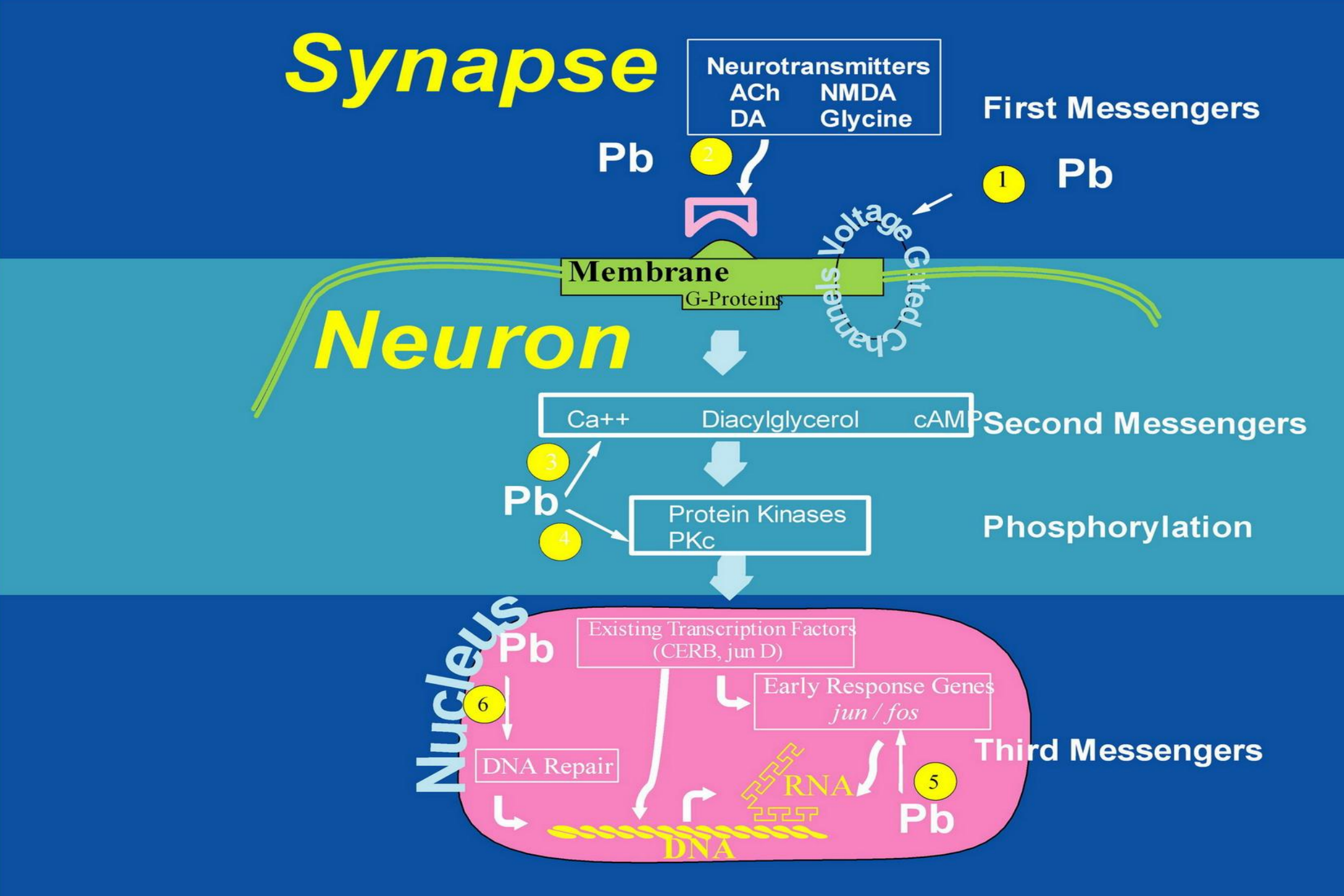
Teacher's Rating Scale (Rutter):
Squirming, fights, thumb sucking
Conners' Scale:
conduct problem, inattention

Winnecke 1994: n=367, 6 y, Lead Blood Level: 1-19 mcg/dL

Tapping: max. # taps of index finger/10 sec
Pattern recognition
Jigsaw pattern identification

LEAD NEUROTOXICITY:

INTRACELLULAR MECHANISMS


Synapse
Neurotransmitters
ACh NMDA
DA Glycine
First Messengers
Pb
2
1
Pb
Voltage Gated Channels
Membrane
G-Proteins
Neuron
Ca++ Diacylglycerol cAMP
Second Messengers
3
Pb
4
Protein Kinases
PKc
Phosphorylation
Nucleus
Pb
Existing Transcription Factors
(CERB, jun D)
Early Response Genes
jun / fos
6
DNA Repair
Third Messengers
RNA
5
Pb
DNA

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Long-Term Community Exposure to Drift-Containing Organophosphate Pesticides – Are there Neurobehavioral Effects in Children?

[1]Yoram Finkelstein MD, PhD, [1] Amit Ophir, MSc, [3] Michael Aschner, PhD and [2] Elihu D. Richter, MD, MPH

[1]Service and Unit of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel

[2] Dept of Occupational and Environmental Medicine, the Hebrew University School of Medicine, Jerusalem , and

[3]Department of Pediatrics, the Vanderbilt University Medical Center, Nashville, TN, USA

Examine the neurobehavioral status, cognition skills and task performance in schoolchildren in a rural area

A control group:

Schoolchildren in kibbutzim in another area who, in all likelihood, are not exposed to pesticide drifts


Map
Satellite
2 mi
2 km
Google
Imagery ©2009 TerraMetrics, Map data ©2009 ORI

Interview Questionnaires - preliminary observation:

24 out of the 60 (40%) respondents in the study group reported that at least one of their children had been diagnosed with Attention Deficit/Hyperactivity Disorder (ADD/ADHD)

ADD/ADHD Prevalence in Children in Israel and Elsewhere:

- No data exist in the Israel Central Bureau of Statistics
- A few have suggested that ADD/ADHD affects 5%-7% of the children in Israel

- Elsewhere: ADD/ADHD affects 5%-9% of the children

ADD/ADHD in Children

	VALLEY	MOUNTAIN	CONTROL	TOTAL
ADD/ADHD	13 (40%)	4 (19%)	3 (15%)	20
TOTAL	32	21	19	72

Interview Questionnaires preliminary observation

This finding raises concern, as current theory suggests that a genetic factor is primarily responsible for the pathogenesis of ADHD

Low Level Long Term Exposure to OP Pesticides

Adding novel parameters, including

PON-1 (paraoxonase-1)

– a genetic parameter of polymorphism

Adults: blood test

Children: buccal smear

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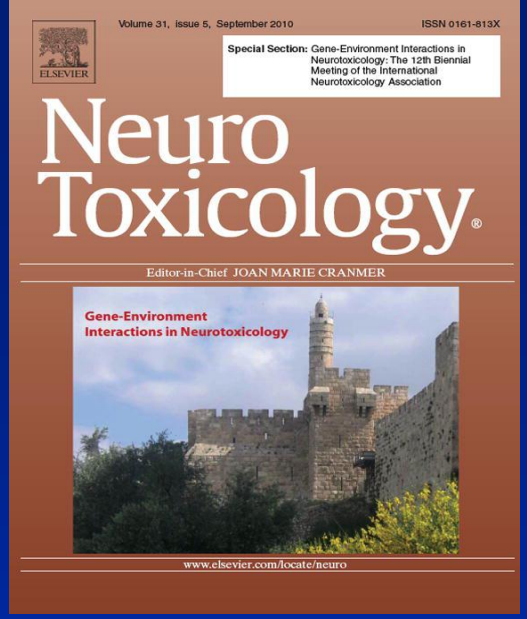
Neurological changes in children induced by sprayed organophosphorous pesticides and the atmospheric variables contributing to it

Yoram Finkelstein, Yael Dubowski,
Amit Ophir, Ohad Zivan, Michael Aschner,
Michal Segal-Rosenhaimer, Igal Bar-Ilan,
Elyakim Doitsch and Elihu D. Richter

Precautionary Measures:

- Education
- Prevention



NeuroToxicology 31: 621–626 (2010)

Impact of integrated pest management (IPM) training on reducing pesticide exposure in Illinois childcare centers

Debby F. Mir[a], Yoram Finkelstein[b], Gayle D. Tulipano[c]

[a] Tel Hai Academic College – Department of Environmental Sciences, Israel

[b] Shaare Zedek Medical Center – Unit and Service of Neurology and Toxicology, Jerusalem, Israel

[c] Northeastern Illinois University (NEIU) – Department of Geography and Environmental Studies, Chicago, USA

New Actions Taken at Childcare Centers following IPM Training

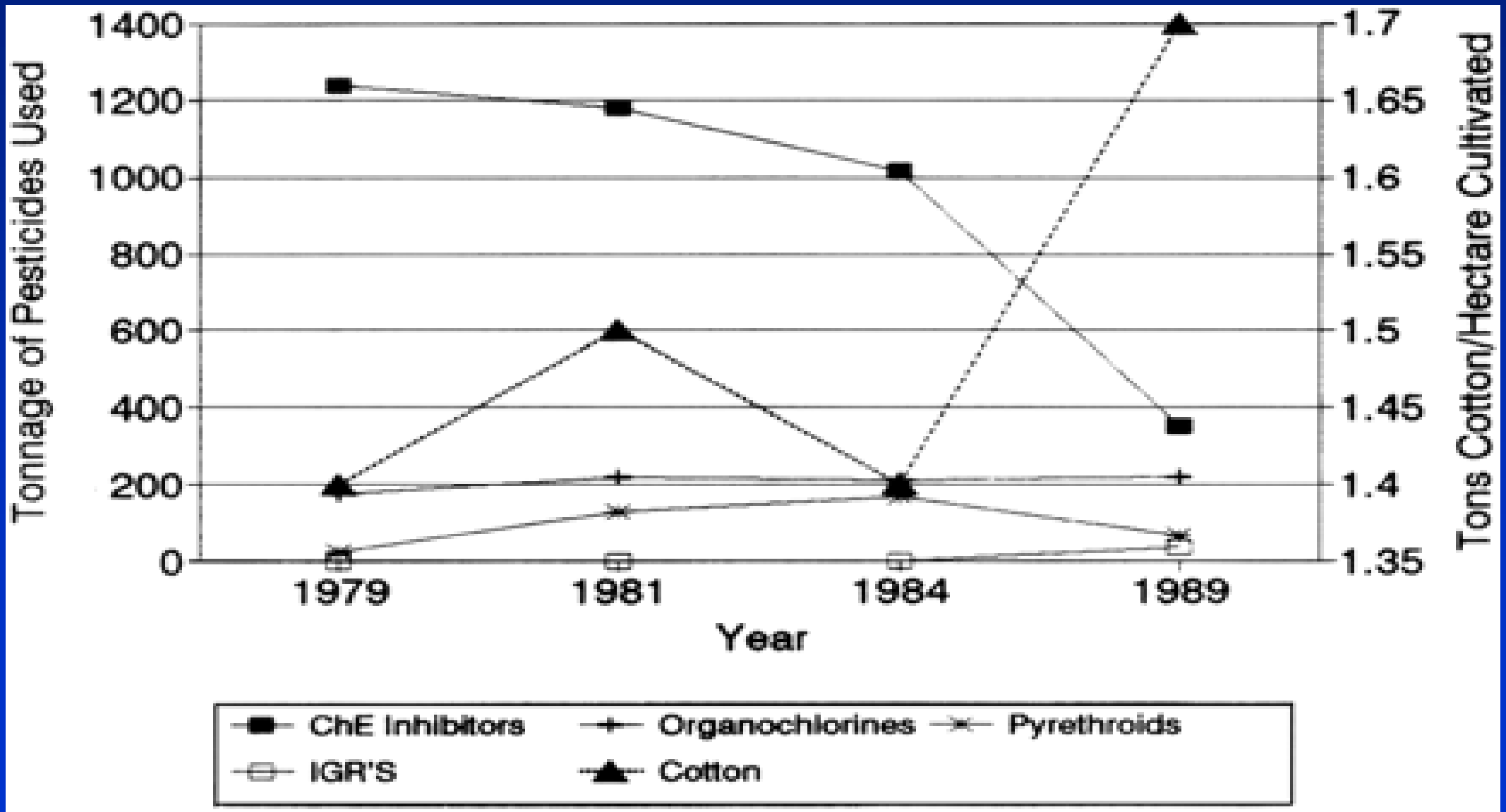
New Pest Control Practices Adapted Post Training					
Program Management	% Uptake	**Pesticide Practices**	(%) Uptake	**Preventative Measures**	**(%) Uptake**
Assigned an IPM Coordinator	32	**Stopped spraying**	27	**Clean behind appliances**	**56**
Use pest sighting logs	32	**Stopped using all pesticides**	13	**Install door sweeps**	**30**
Use monitor traps	29	**Use baits instead of sprays**	41	**Patch holes around pipes**	**60**
Create notification procedures	28	**Notify parents before spraying**	31	**Control clutter**	**60**
No change	**19**	**No change**	**23**	**No change**	**14**

Precautionary Measures:

- Education
- Prevention

Cotton yield Vs pesticide use in Israel

Richter et al, 1998



A fence at the top of the cliff
is better
than an ambulance at the bottom

“……If not now, when…”

We are indebted to:

Environmental Health Fund

The Chief Scientist, Israel Ministry of Environmental Protection

The Chief Scientist, Israel Ministry of Industry,

Trade and Labor Committee for Preventive Activity and Research

in Health and Safety at Work