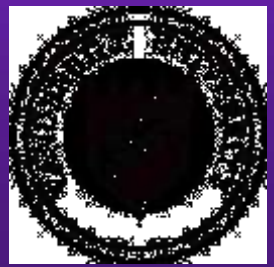
Alcoholism-Associated Brain Disorders: Psychiatric Nosology and Molecular Medicine

Peter R. Martin, M.D., F.R.C.P.(C)

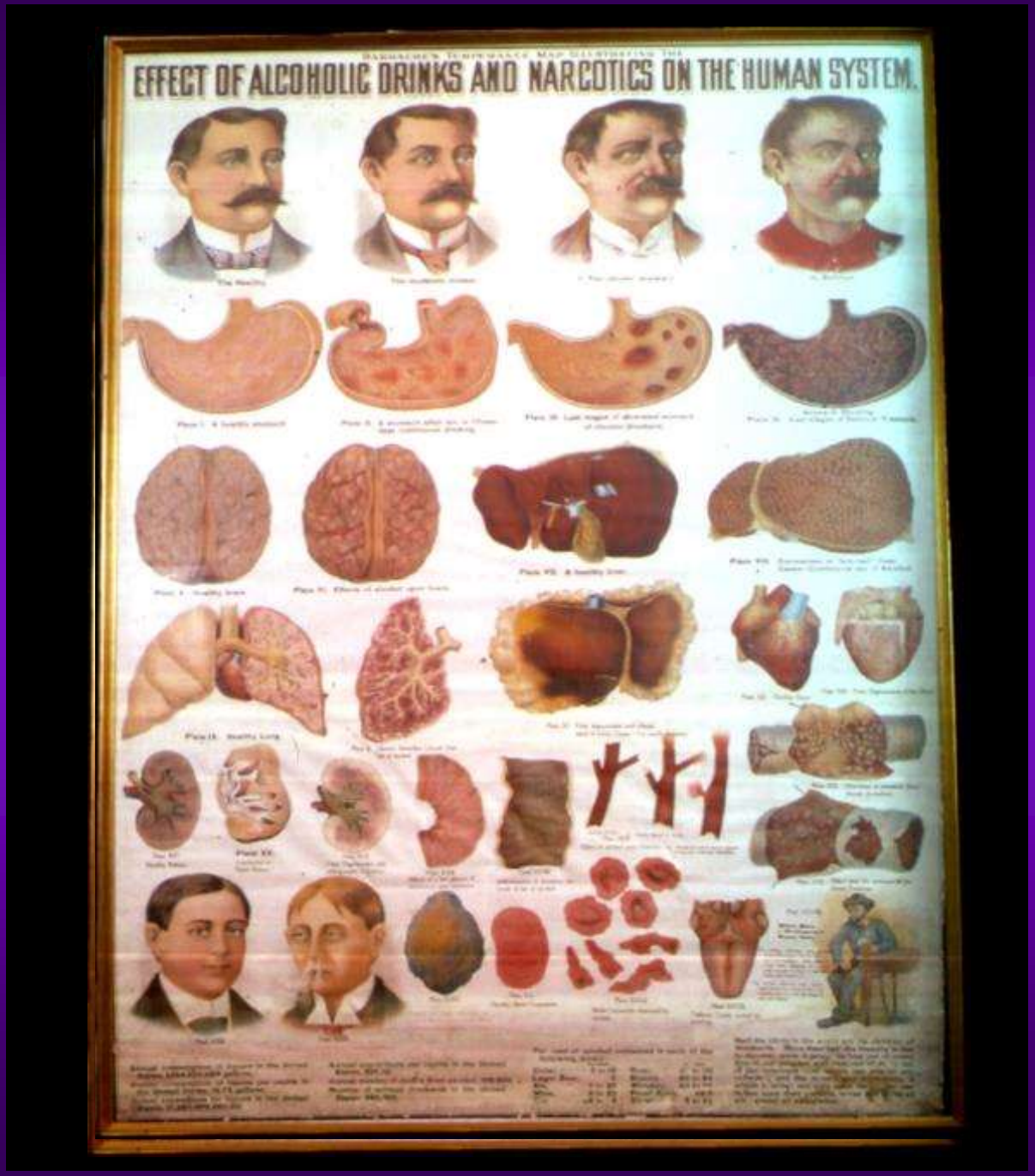
Professor of Psychiatry and Pharmacology

Vanderbilt University School of Medicine



Societal and Healthcare Costs of Substance Abuse

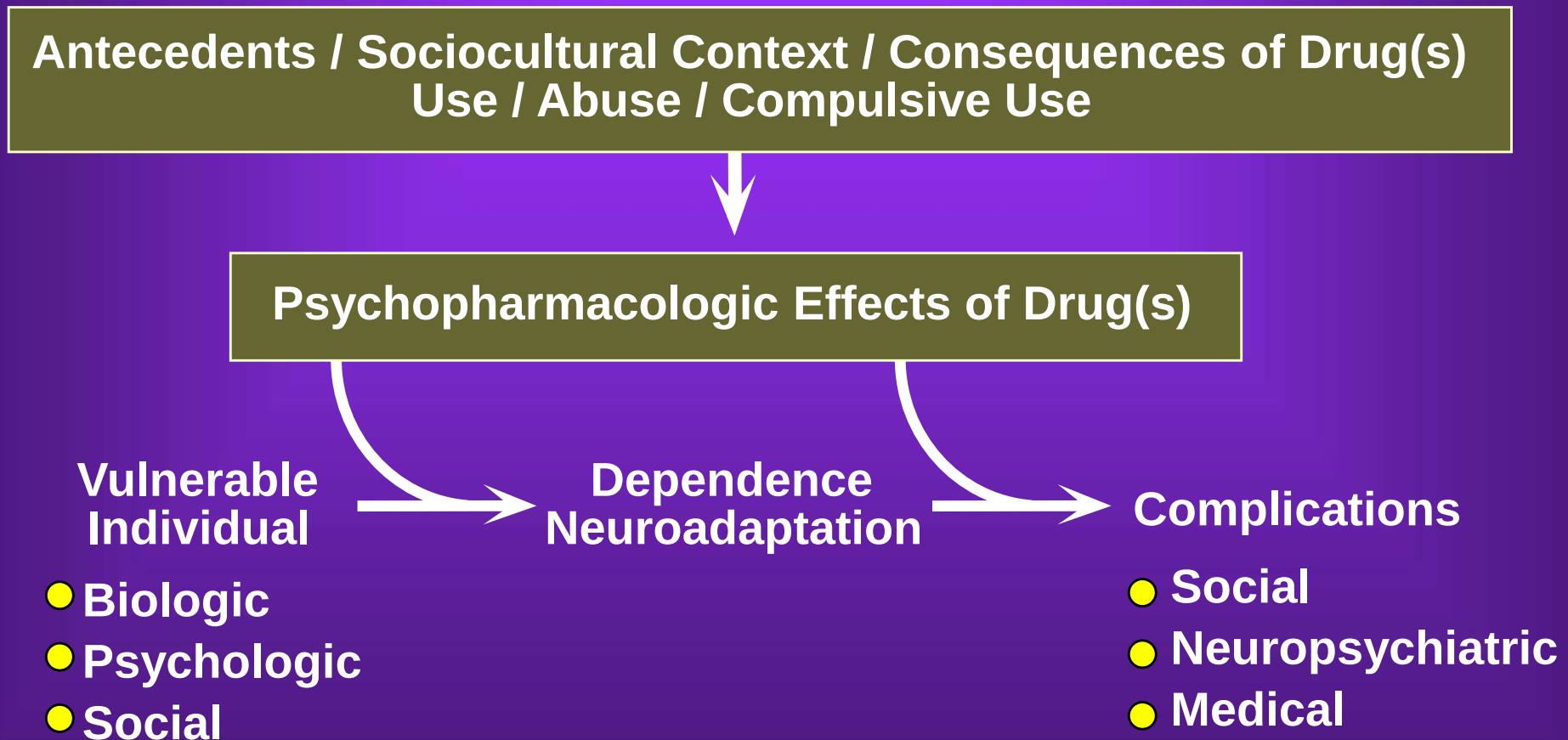
- Estimated US$300 (~NZ$7) billion/year for medical care and lost productivity
- Abuse of alcohol, tobacco, and drugs contribute to **each** of the ten leading causes of death in U.S.
- Large potential cost-savings in a capitated healthcare environment

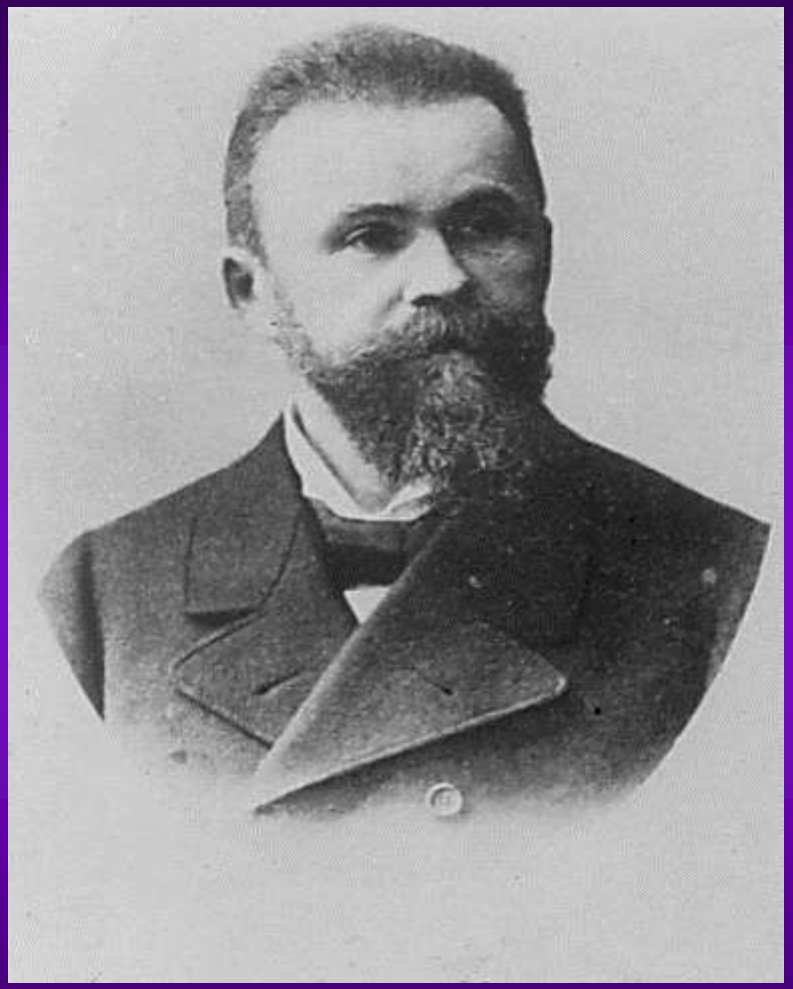

EFFECT OF ALCOHOLIC DRINKS AND NARCOTICS ON THE HUMAN SYSTEM.

Major Research Questions

- What are the ***molecular mechanisms*** that cause brain injury associated with chronic alcoholism?
- Are there ***genetic predisposing factor(s)*** to development of alcoholism-associated brain damage?
- Are these factors contributory to alcoholism *per se*?
- Can alcohol-induced ***brain injury*** be prevented and ***recovery with abstinence*** improved?

Longitudinal Progression of Substance Use Disorders





Carl Wernicke
1848-1905

S.S. Korsakoff
1853-1900

Syndromes of Impairment in Chronic Alcohol Dependent Patients

- 10% of alcoholics have ***severe*** brain dysfunction:
  - Alcohol amnestic disorder (Wernicke-Korsakoff syndrome)
  - Alcohol-induced persisting dementia

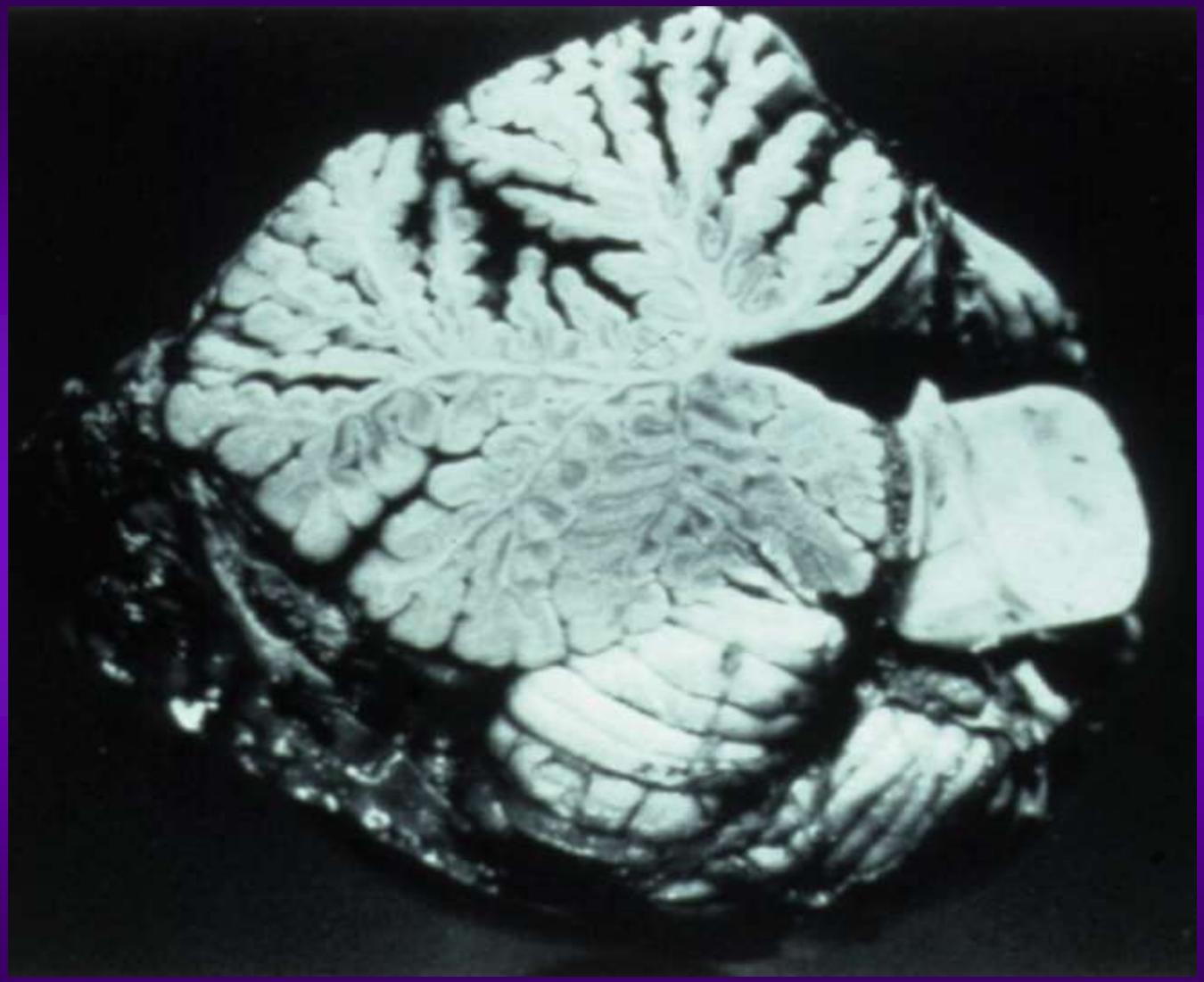
Syndromes of Impairment in Chronic Alcohol Dependent Patients

- 50-70% of alcoholics have ***mild to moderate*** verbal, abstracting/problem solving, learning/ memory, perceptual motor deficits
- ***Continuities*** of ***neuropsychological*** impairments and ***neuropathological*** findings among WKS, A-IPD, and less impaired alcoholics

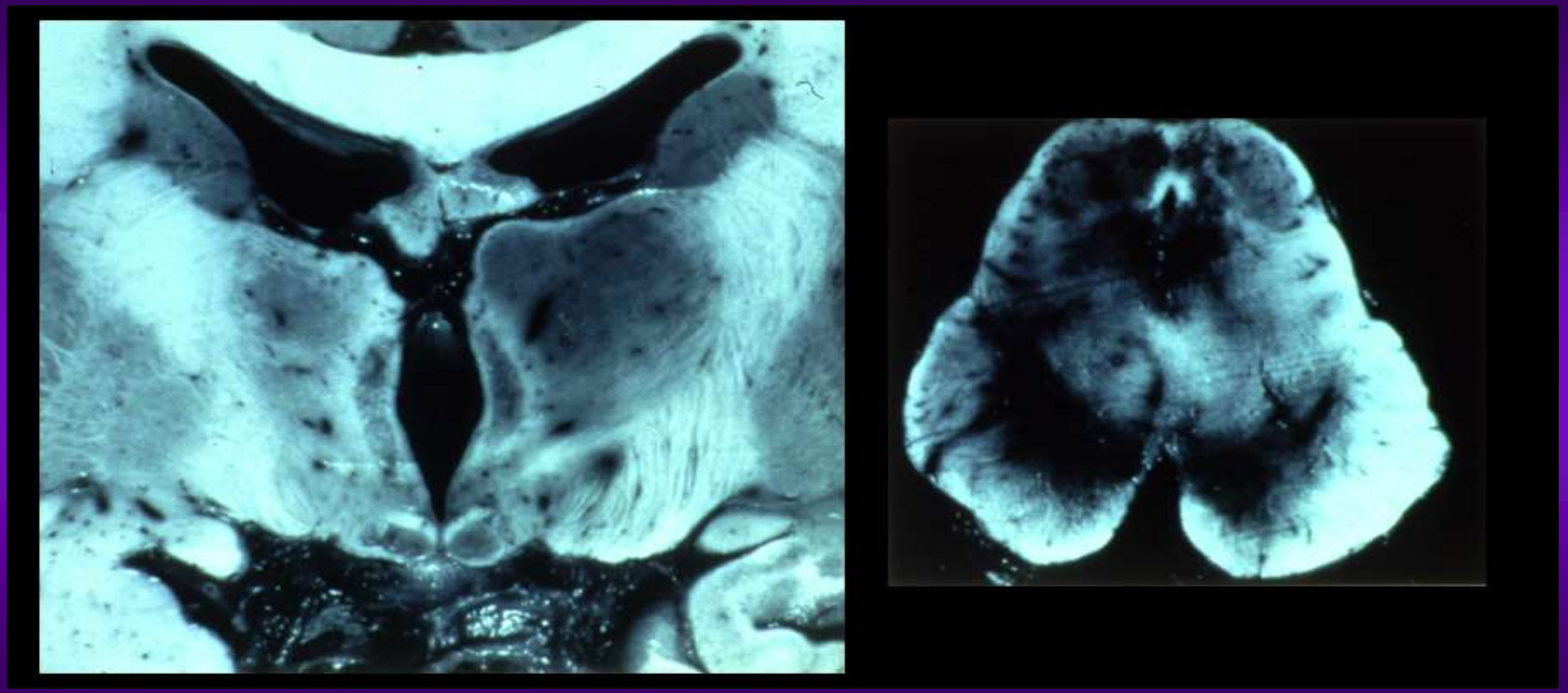
Neuropathological Abnormalities in Alcoholics

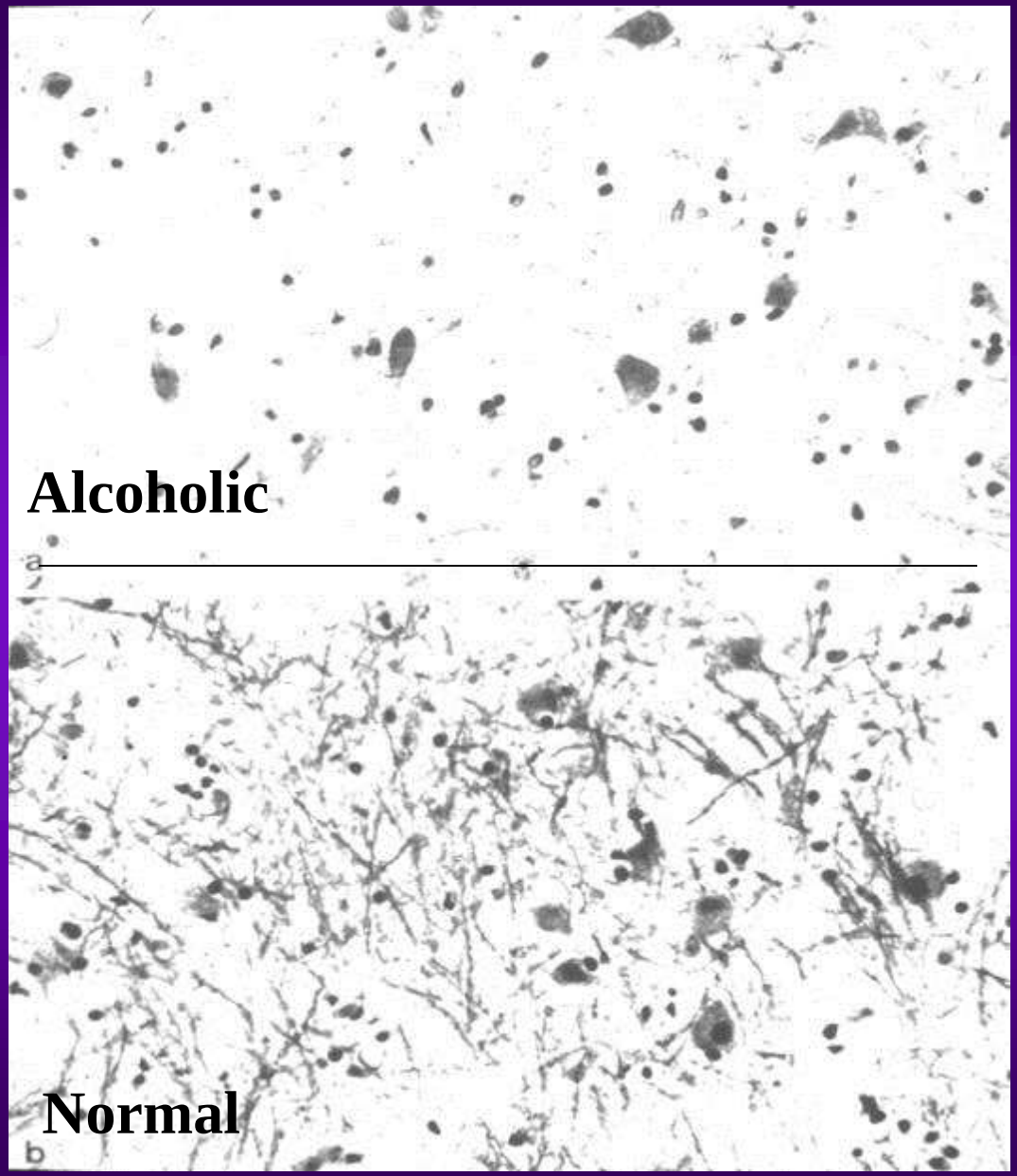
- ***Cerebellar*** degeneration (~40%) - *Torvik et al (1982)*
- Characteristic ***brainstem*** and ***diencephalic*** abnormalities of WKS (~13%) - *Torvik et al (1982);Harper and Kril (1993)*
- Reduced ***brain weight*** and/or ***volume*** (white matter predominantly) - *Harper and Kril (1985)*

Alcoholic Cerebellar Degeneration



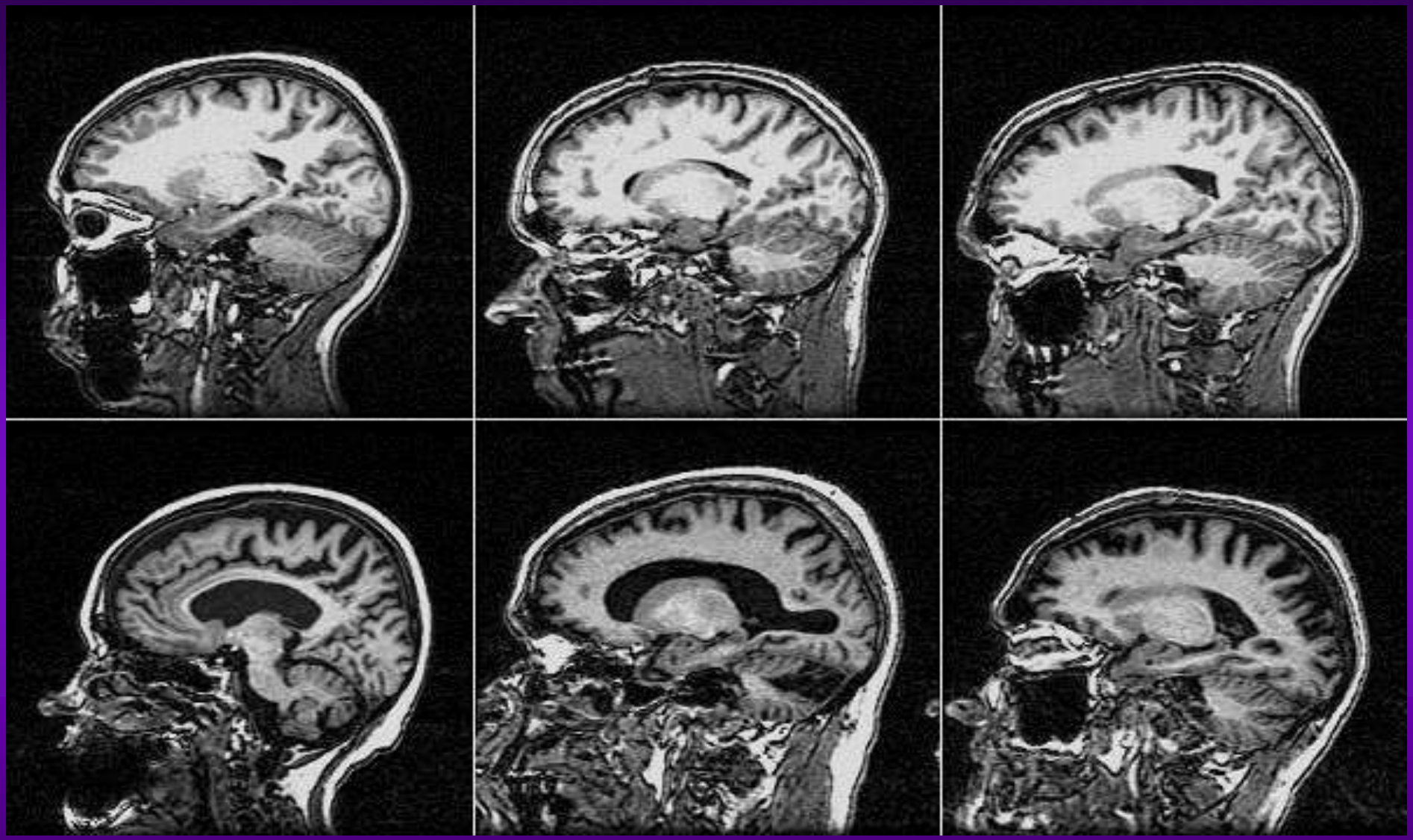
Wernicke-Korsakoff Syndrome





Demyelination of mammilary bodies in non-WKS alcoholics

Alling and Bostrom (1981)



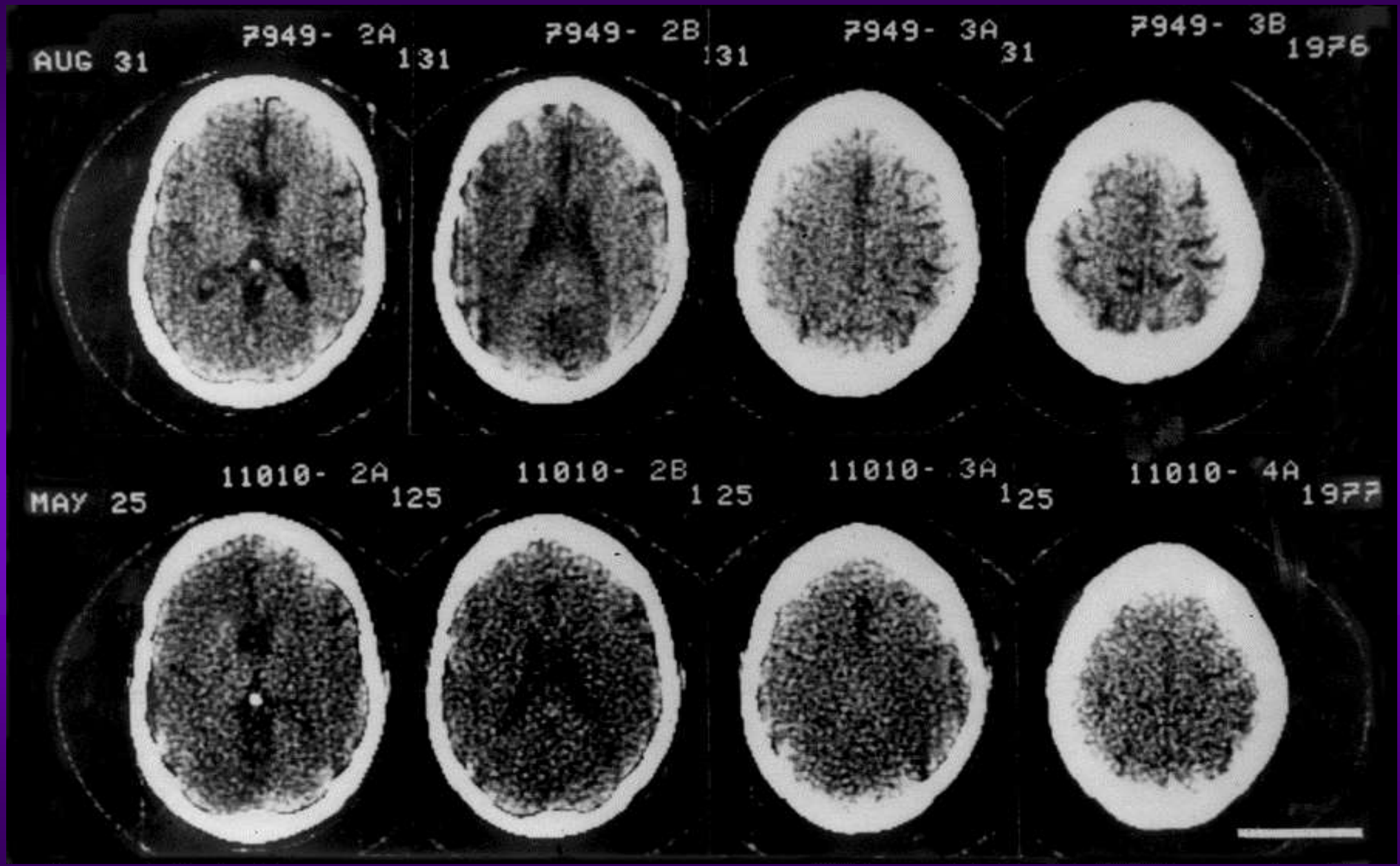
Top row, slice images from three normal subjects. Bottom row, slice images from three alcoholic subjects showing the large amount of ventricular enlargement and cortical and cerebellar atrophy.

Thiamine Deficiency and Alcohol-Induced Brain Injury

- TD is very common among alcoholics
- Thiamine rapidly reverses signs of TD (Wernicke's encephalopathy) leaving residual neuropsychiatric/neuropathologic deficits (Korsakoff's syndrome)

Thiamine Deficiency and Alcohol-Induced Brain Injury

- Brain morphometric abnormalities among alcoholics: WKS>cirrhosis>non-WKS (Harper)
- Findings of functional TD observed in brains of non-WKS alcoholics (Butterworth)
- Experimental TD can mimic and potentiate histological effects of alcohol in animal models (Langlais)

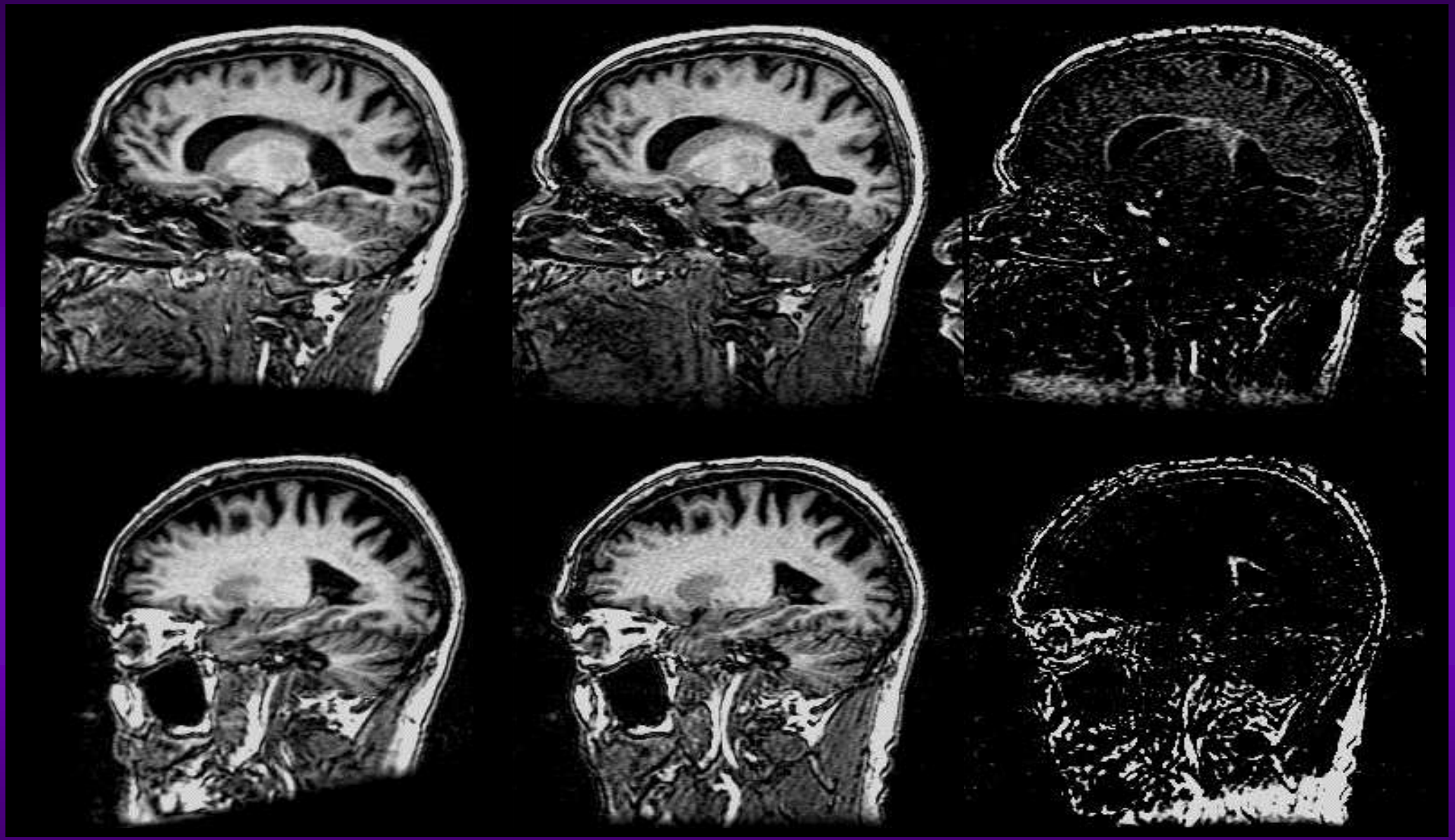

AUG 31
7949- 2A
131
7949- 2B
131
7949- 3A
31
7949- 3B
1976
MAY 25
11010- 2A
125
11010- 2B
1 25
11010- 3A
125
11010- 4A
1977

Recovery of Brain Structure/ Functions with Abstinence

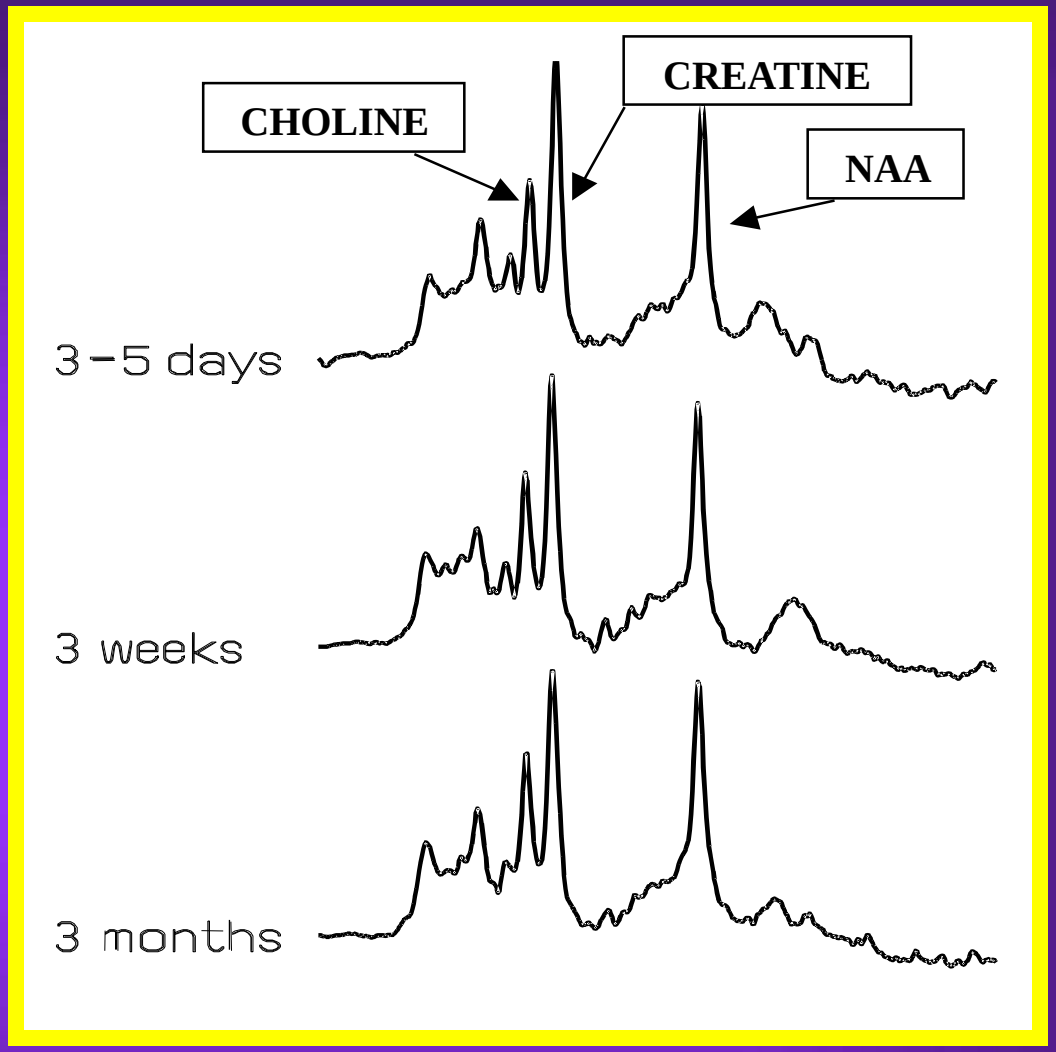
- Striking neurological/psychiatric/ neuropsychological improvements occur early in abstinence
- Improvements decrescendo for~3 weeks and may continue for years
- Some abnormalities may never improve (permanent *vs.* premorbid) and can significantly contribute to clinical course

Recovery of Brain Structure/ Functions with Abstinence

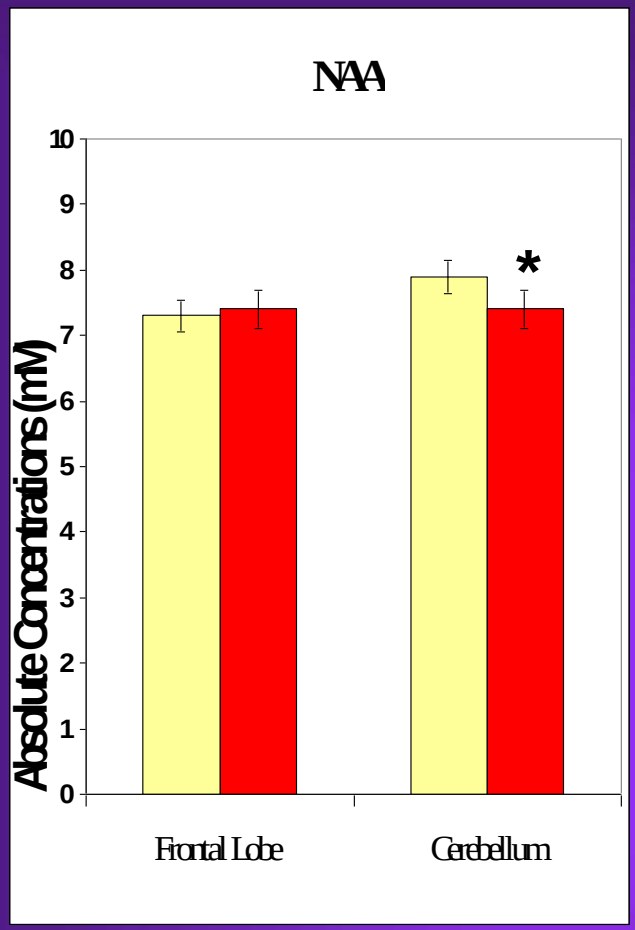
- Ventricular and sulcal enlargement on CT and MRI can reverse with abstinence
- Pathophysiology of brain recovery (especially role of thiamine) poorly understood
- Differential susceptibilities of brain areas (anterior superior cerebellar vermis, frontal white matter)

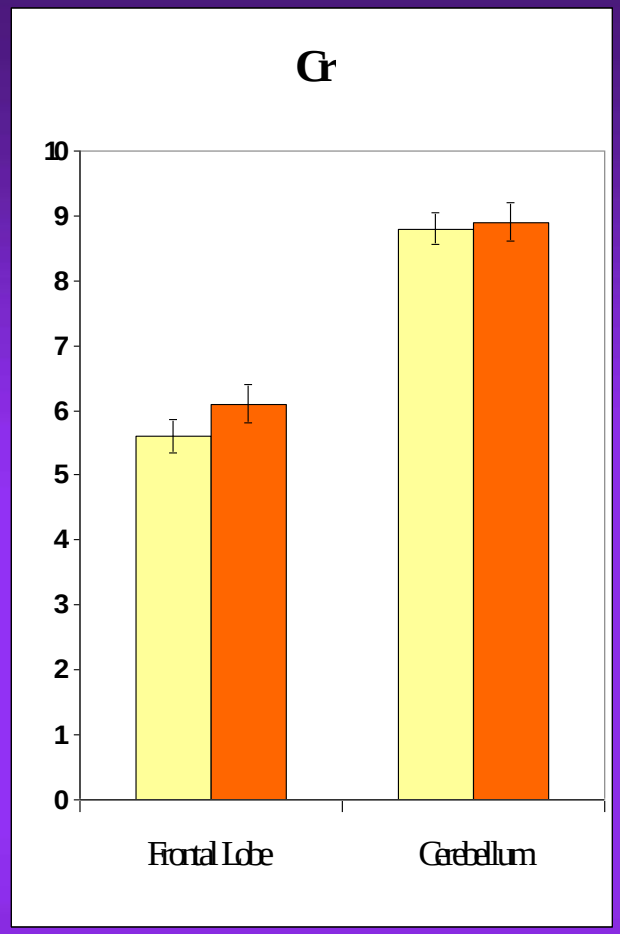


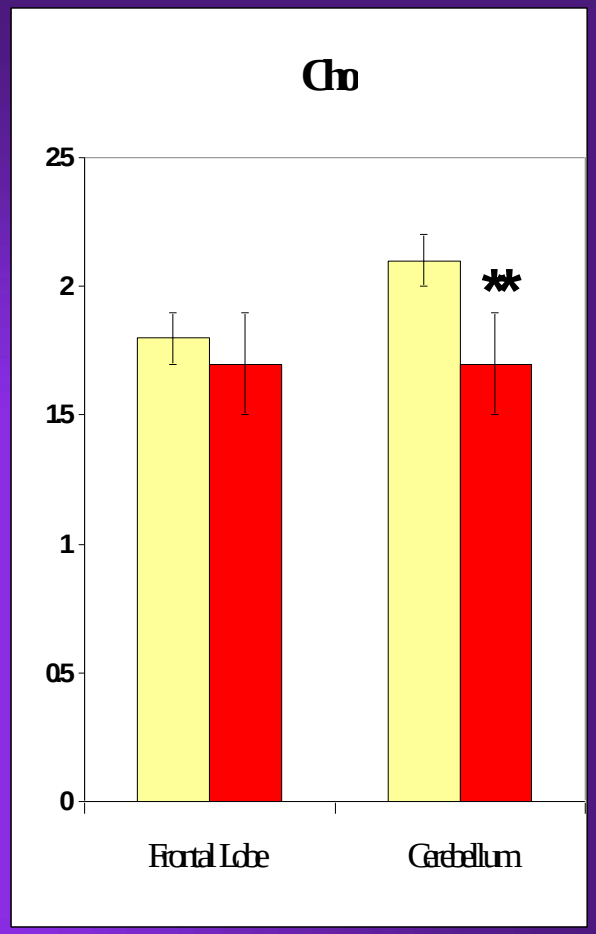
Volume changes measured between the first and third acquisitions in two different alcoholic subjects



Mid-sagittal MR image of the brain of a representative alcoholic subject (left). The white square in the image represents the scale ($8cm^3$) of the cerebellar VOI from which the proton MRS spectra (right) were repeatedly derived.







Mean (±SD) brain concentrations (mM) of N-acetylaspartate (NAA), Creatine (Cr), and Choline (Cho) in normal controls (n=12) and alcoholic subjects (n=31) within 3 to 5 days of last drink.

* P< 0.05 ** P< 0.001

Cerebellar Concentrations (mM) of MRS Metabolites and Clinical Course after 3-5 Days Abstinence

	Early Relapse N=8	Late Relapse N=12	No Relapse N= 11	Normal Control N=10	Bonferroni Adjusted
NAA	6.6 (0.5)	7.4 (1.1)	7.7 (2.0)	8.0 (1.0) *	ER<NC
Cr	8.2 (0.7)	9.2 (1.5)	9.0 (1.6)	9.0 (0.8)	NS
Cho	1.5 (0.1)	1.8 (0.5)	1.7 (0.4)	2.2 (0.3) **	ER, NR<NC

Distinguishing Clinical Features of ER, LR, and NR

- Age: ER<LR,NR
- Gender: NS but ER (all male)
- Family History Positive: NS but ER (100%)
- Age of alcoholism onset: ER, LR<NR

Distinguishing Clinical Features of ER, LR, and NR

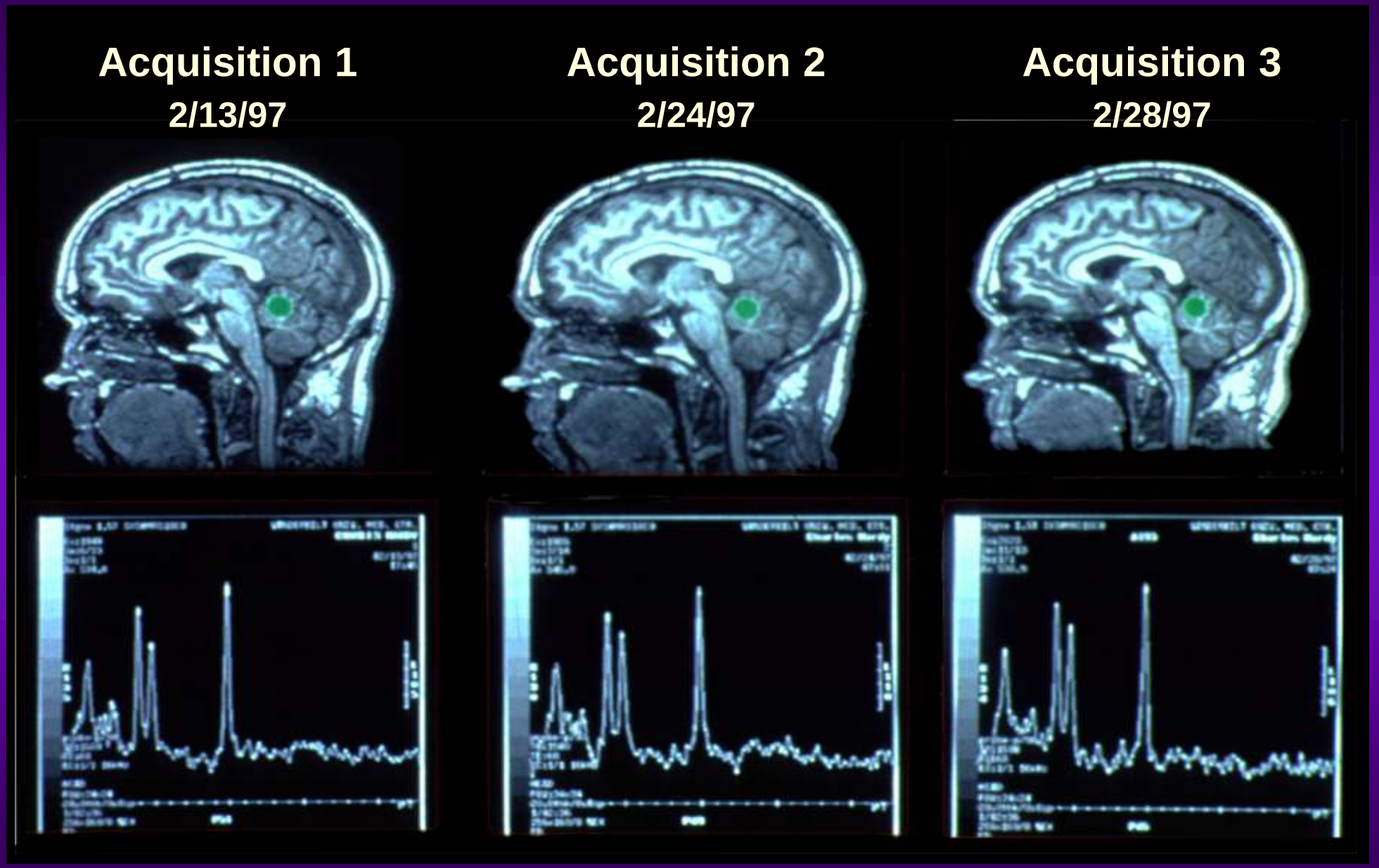
- Total years drinking: ER<LR,NR
- Lifetime alcohol intake, daily drinks, dependence severity: NS
- Neurocognitive screening battery (3-5 days): NS
- Neuropsychological battery (3 weeks): LR<NR

Characteristics of early onset alcoholism (Cloninger, 1987)

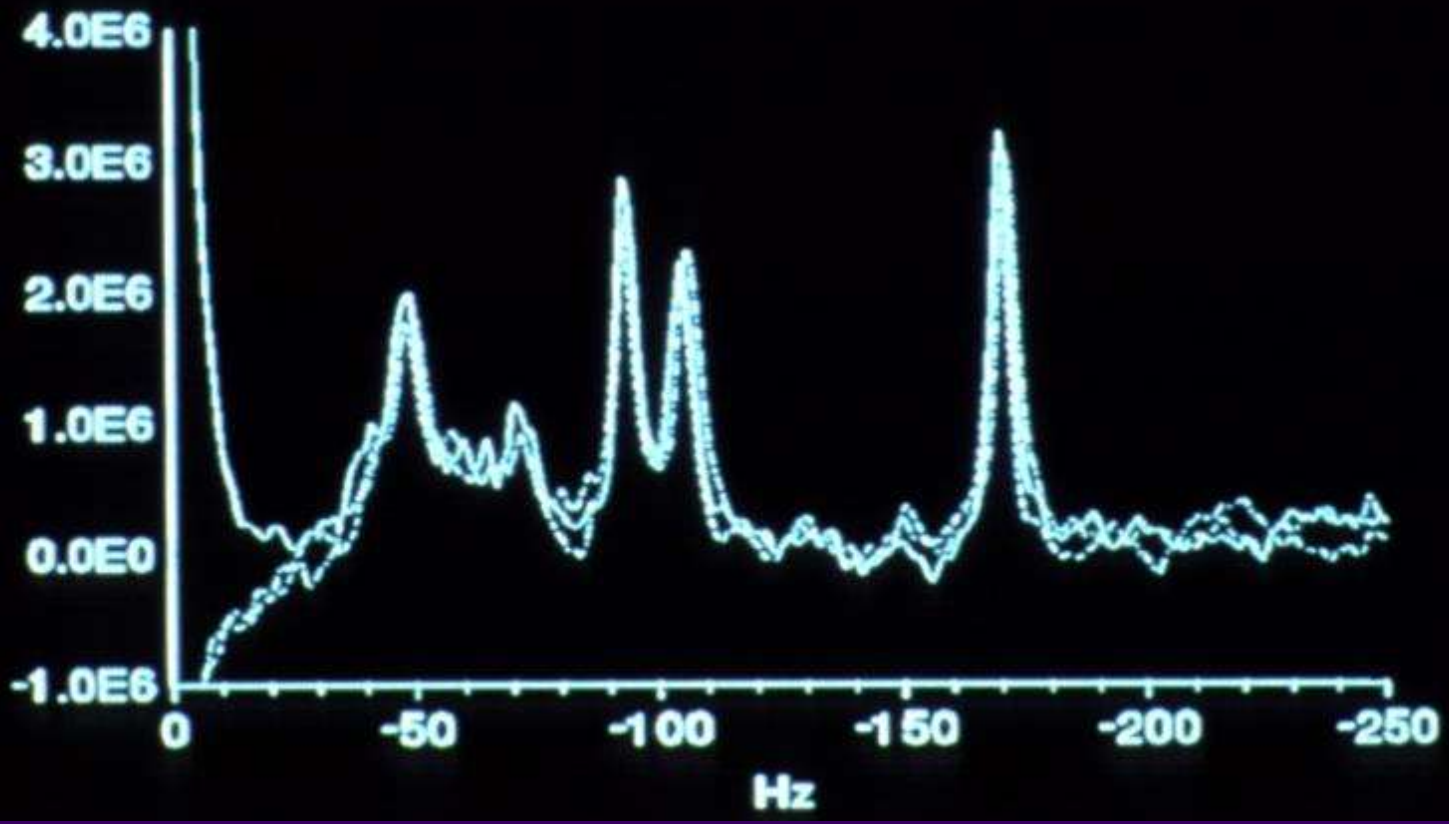
- High behavioral activation (impulsivity, novelty seeking) - dopamine
- Low behavioral inhibition (harm avoidance, aggression) - serotonin
- Behavioral maintenance (reward dependence) - norepinephrine

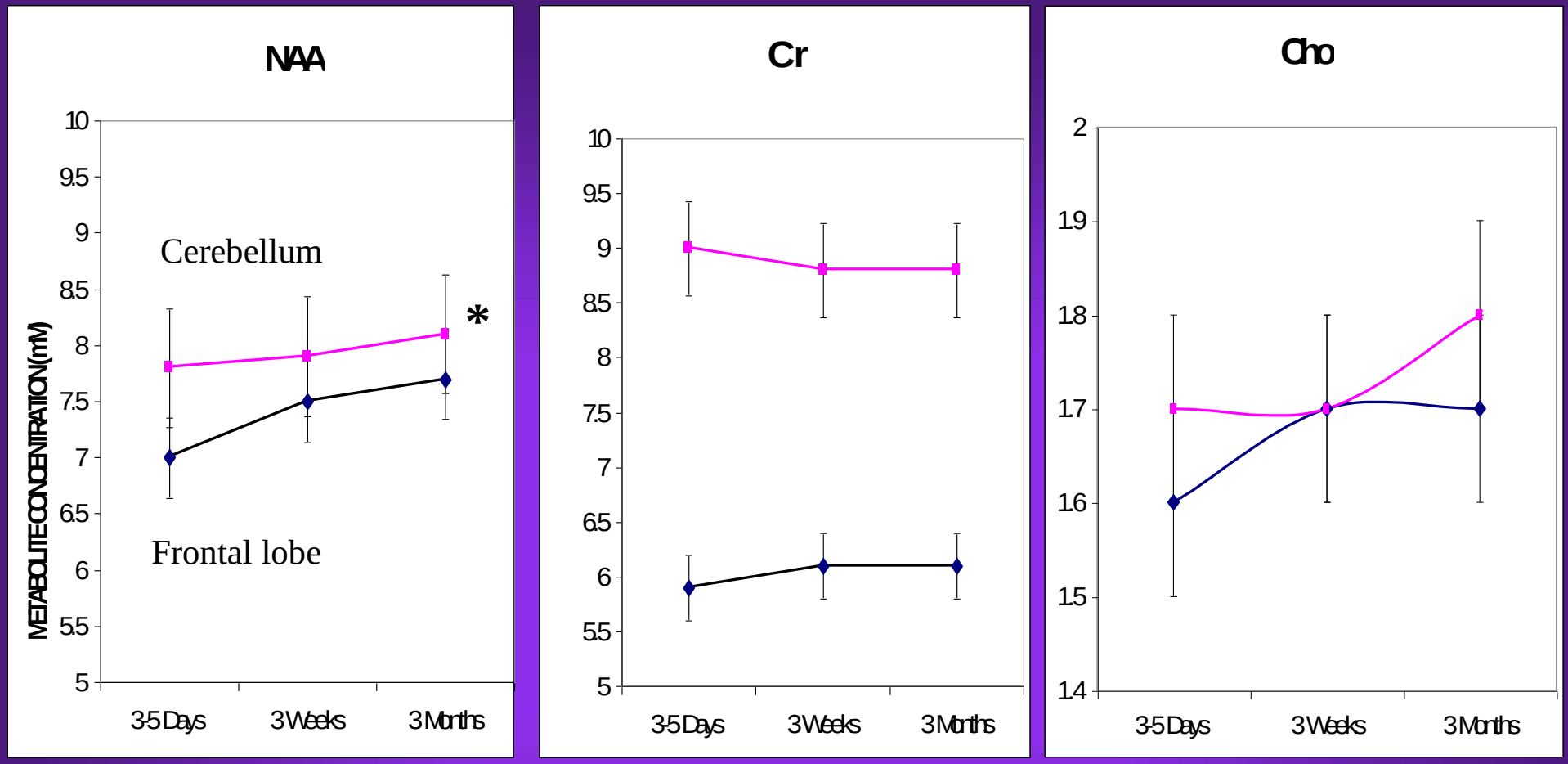
Additional characteristics of early onset alcoholism?

- Increased sensitivity to thiamine deficiency and alcohol-induced brain injury
- Premorbid affective symptoms and neurocognitive deficits
- Malignant clinical trajectory

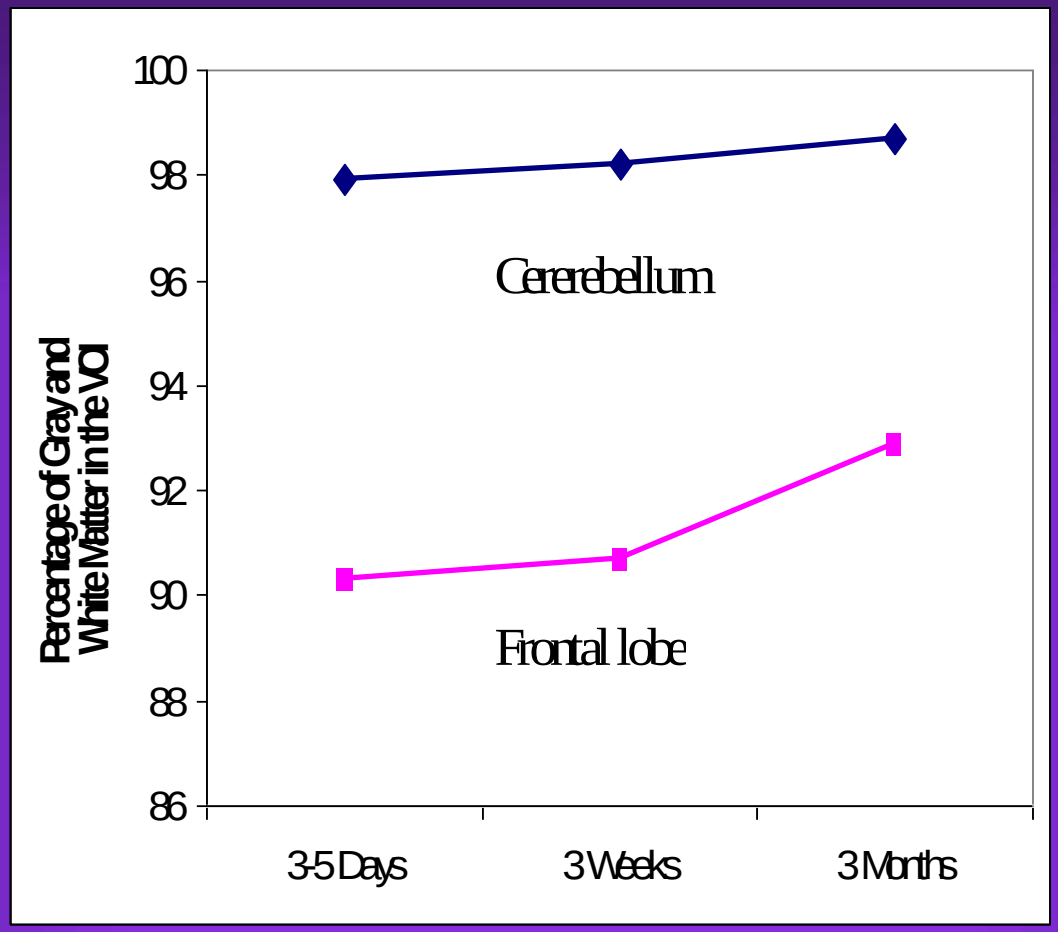

Acquisition 1
2/13/97
Acquisition 2
2/24/97
Acquisition 3
2/28/97

Feb 13, Feb 24, Feb 28



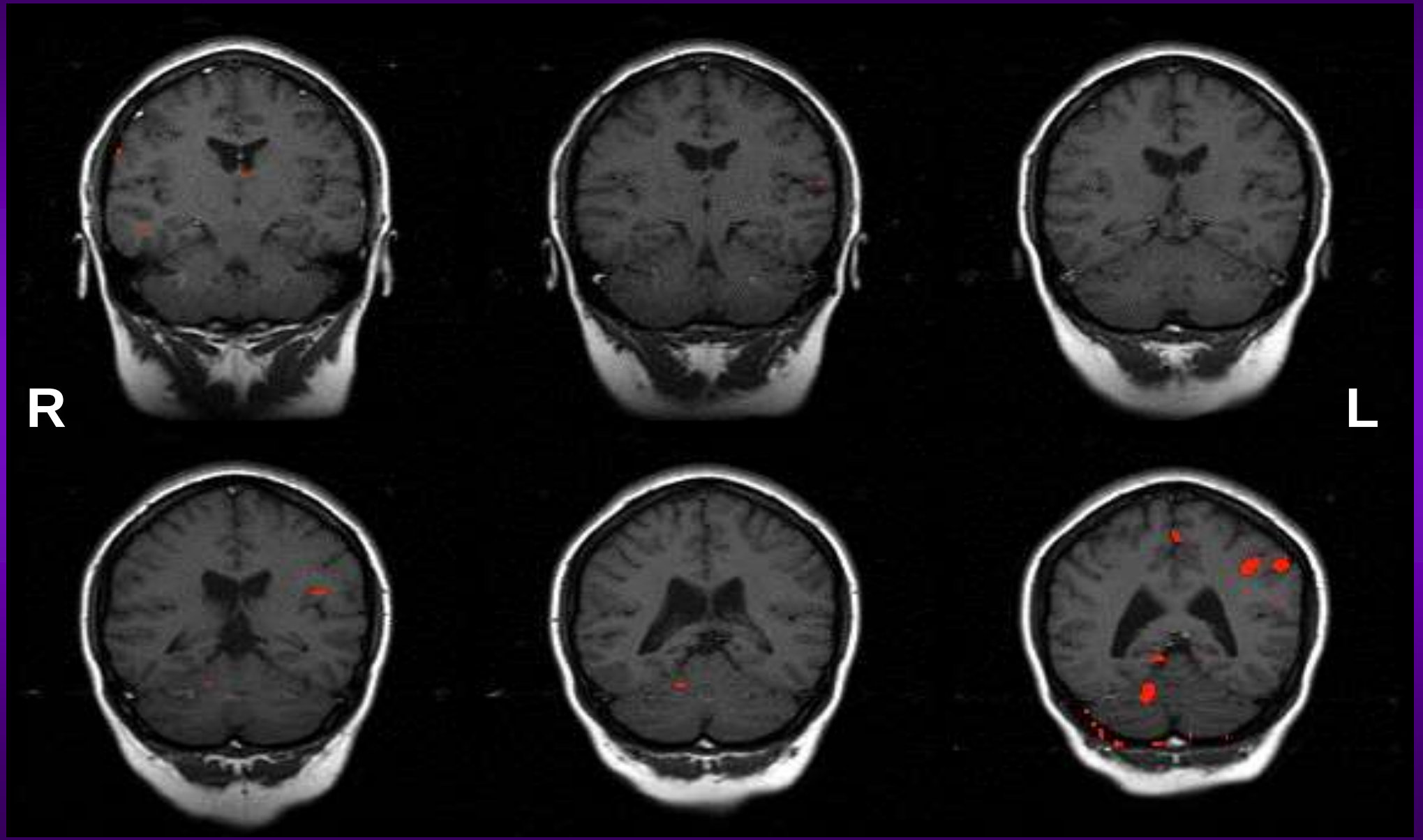


Longitudinal changes in brain NAA, Cr, and Cho concentrations (mM) in frontal lobe white matter and cerebellar vermis during 3 months in eleven NR patients. *P<0.05

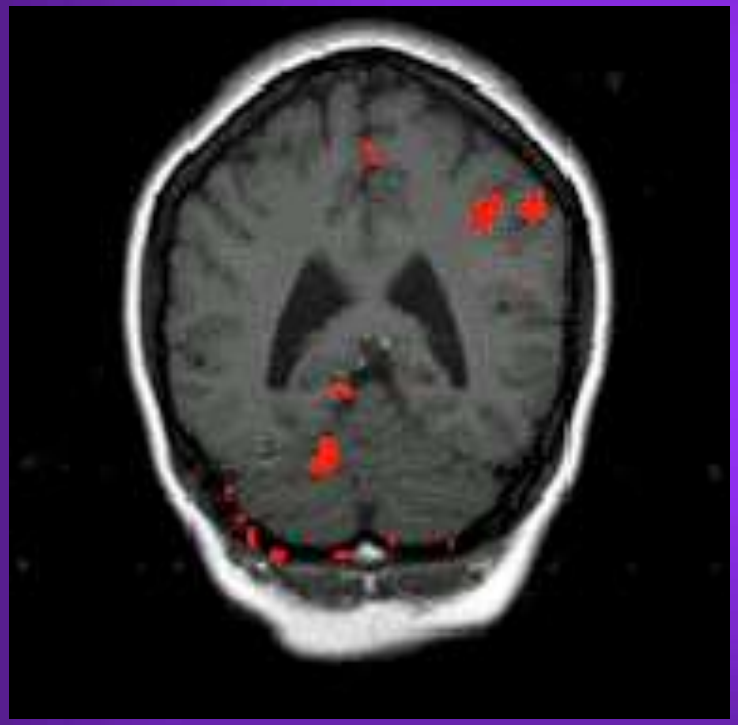


Brain tissue (Gray matter + white matter) in frontal and cerebellar VOIs in NR alcoholic patients over three months' abstinence.

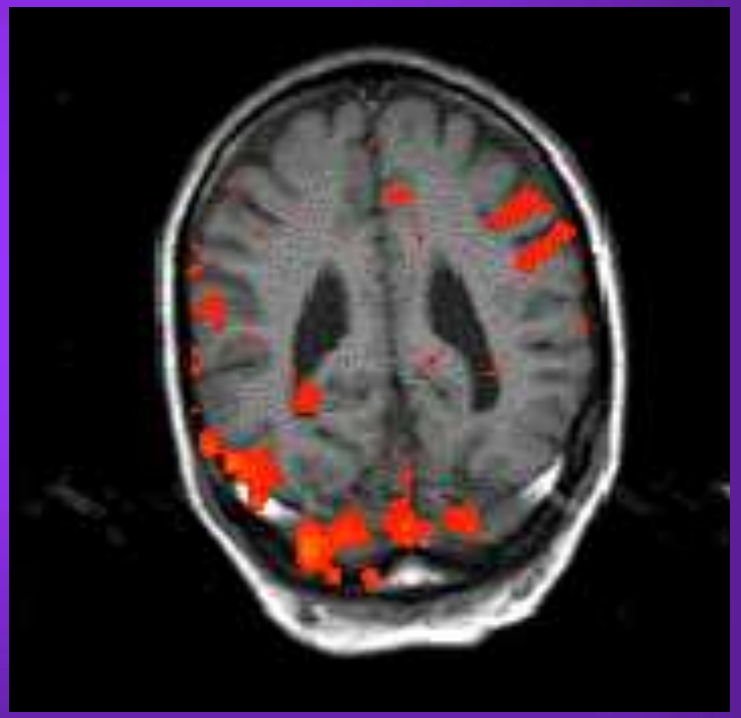
Dominant Hand Finger Tapping Normal Control



Brain Activation During Finger Tapping with Dominant Hand

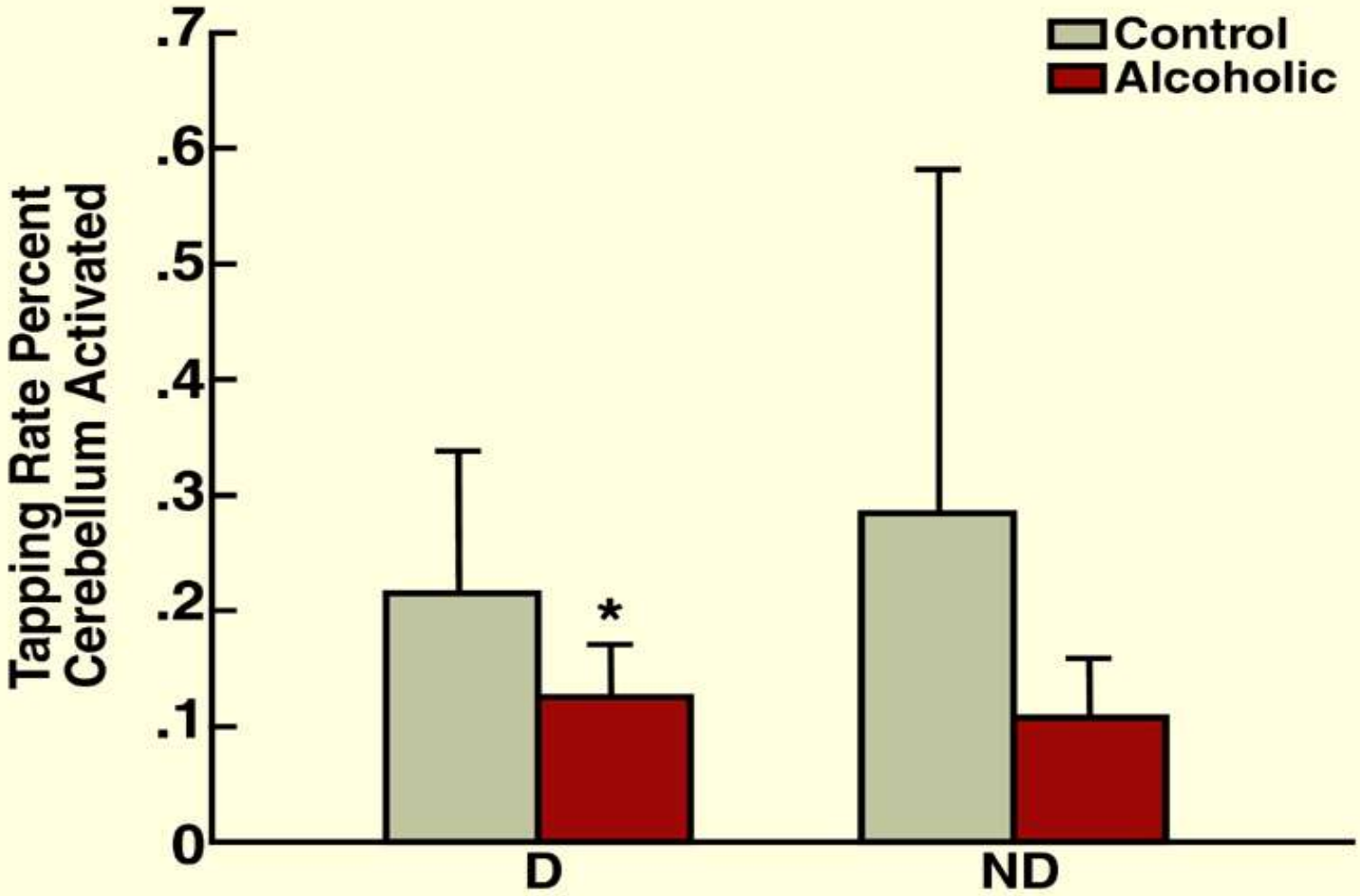


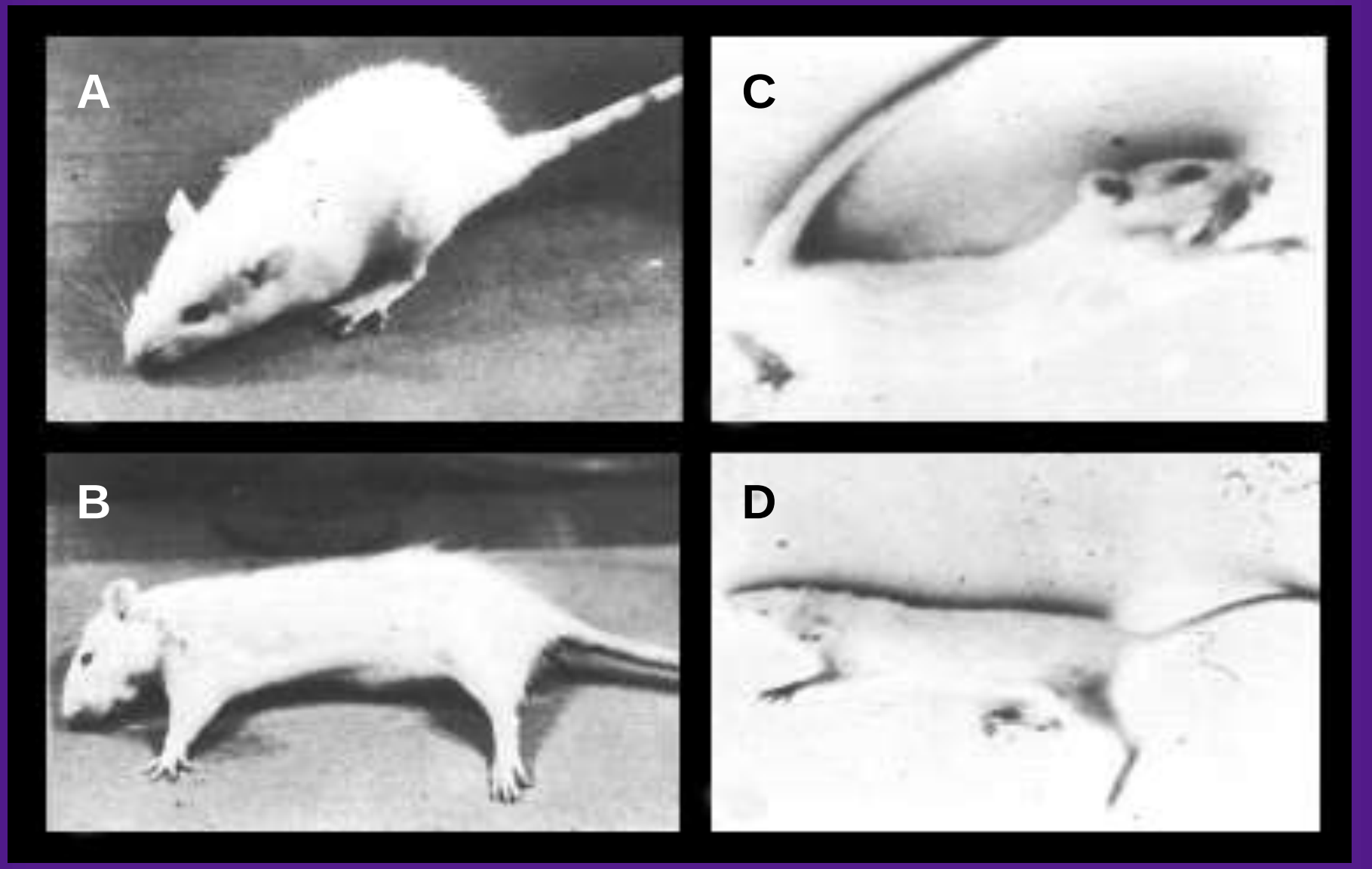
Normal Volunteer

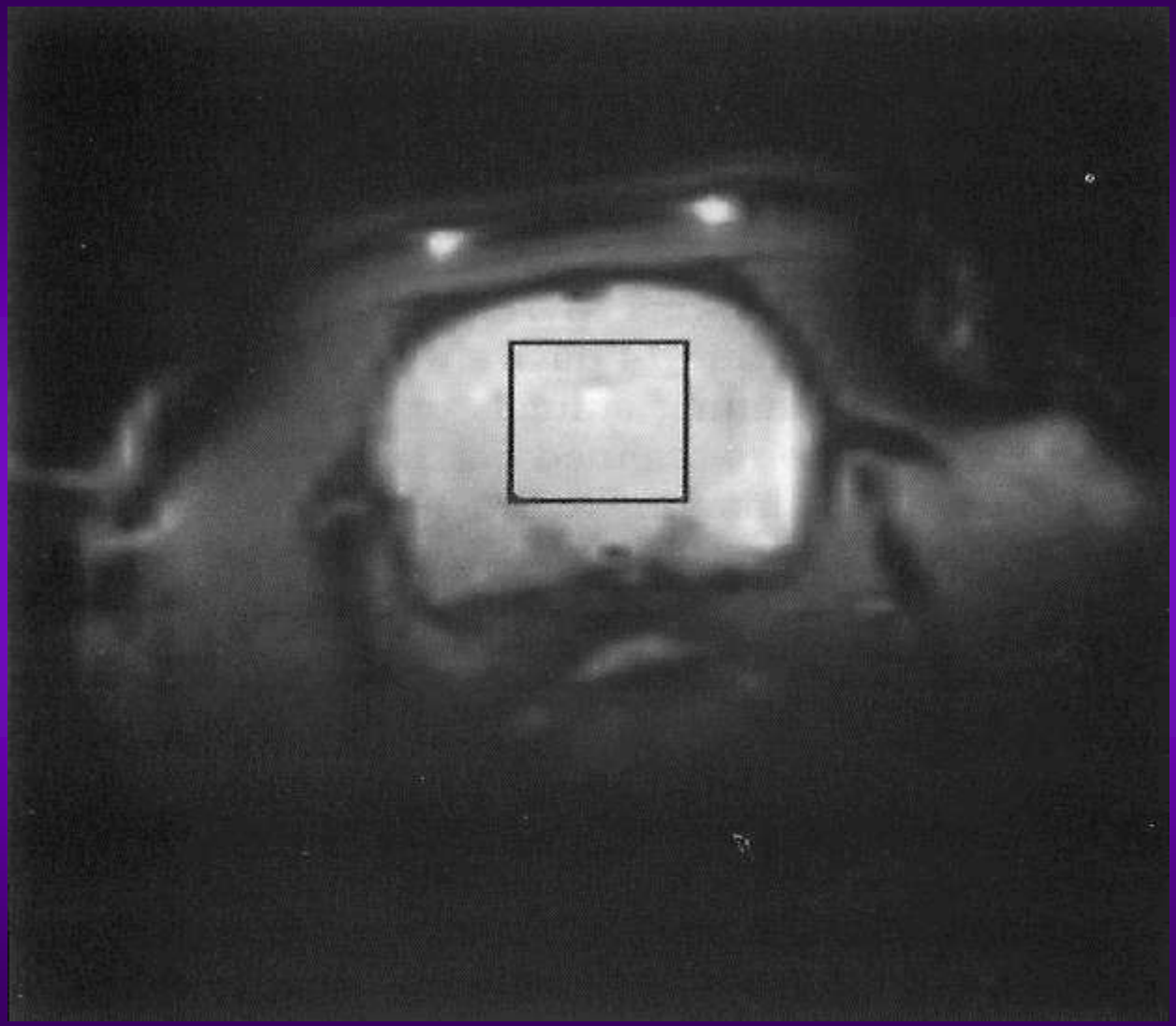


Alcoholic Patient

Finger Tapping Efficiency

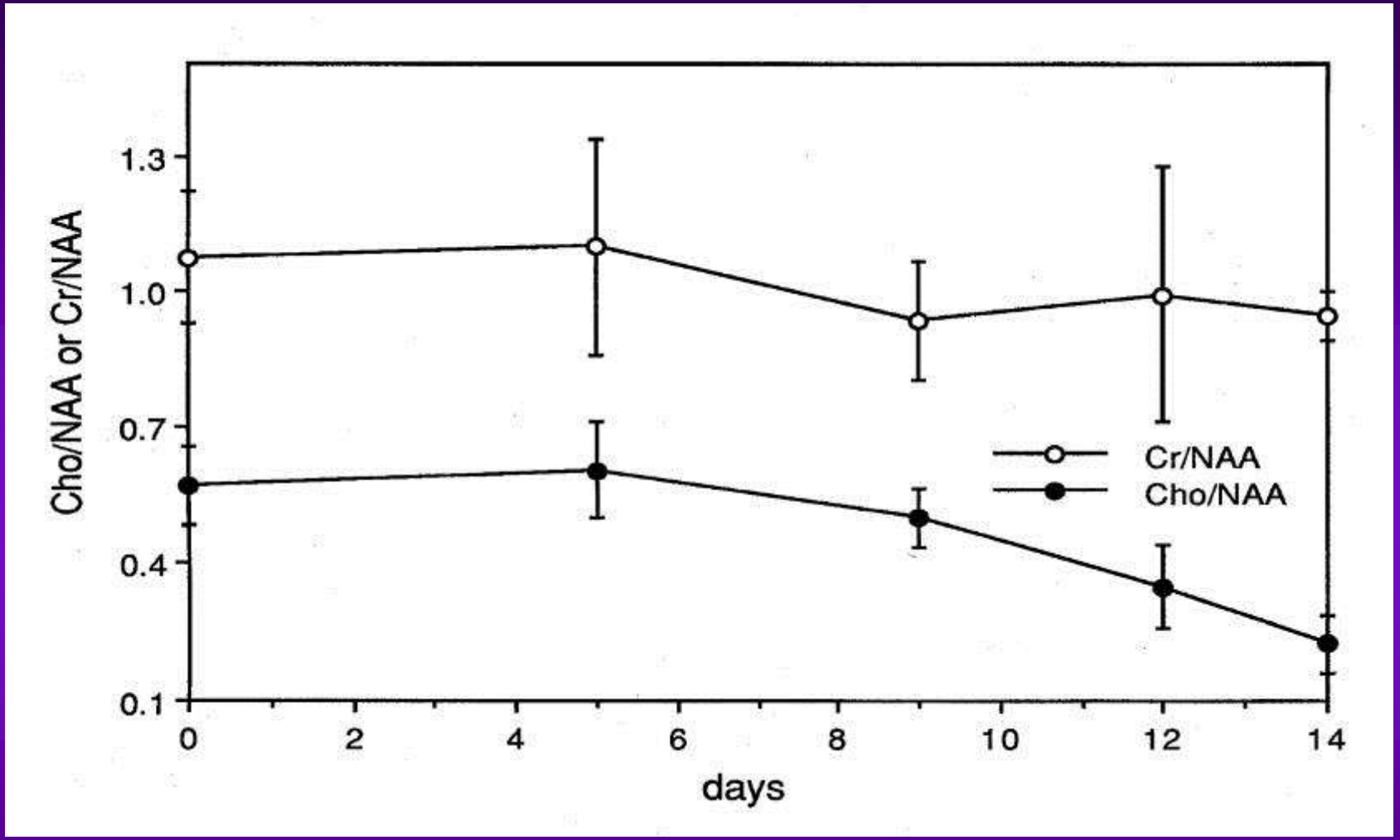



A
C
B
D



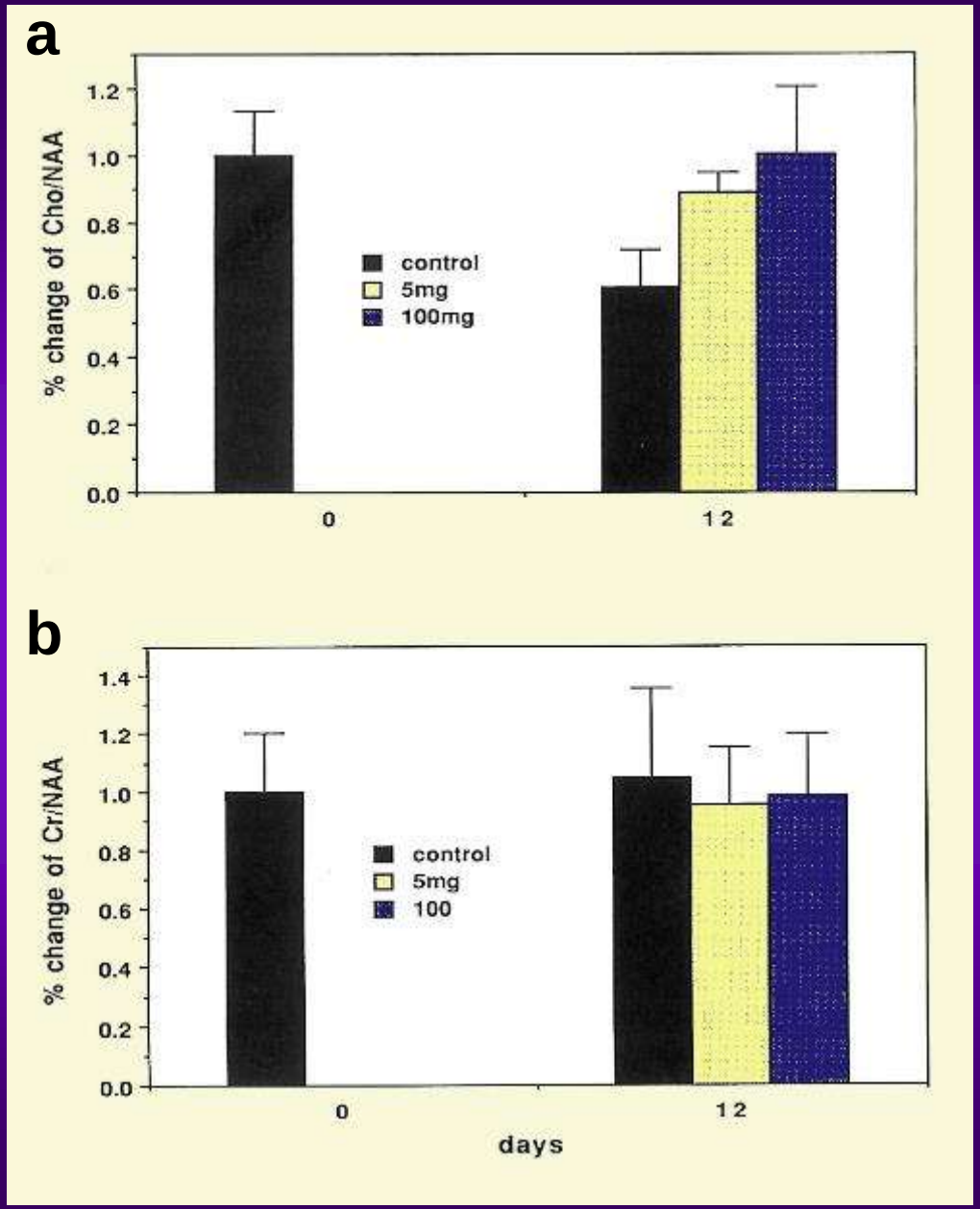
T ^{1}- weighted MR image of rat brain showing the location for volume (27 mm^{3}) selected for spectroscopy

MRM, 34:313-318 (1995)



Cho/NAA and Cr/NAA in rats administered thiamine deficient diet and pyrithiamine for 14 days.

MRM, 34:313-318 (1995)



(a) Cho/NAA

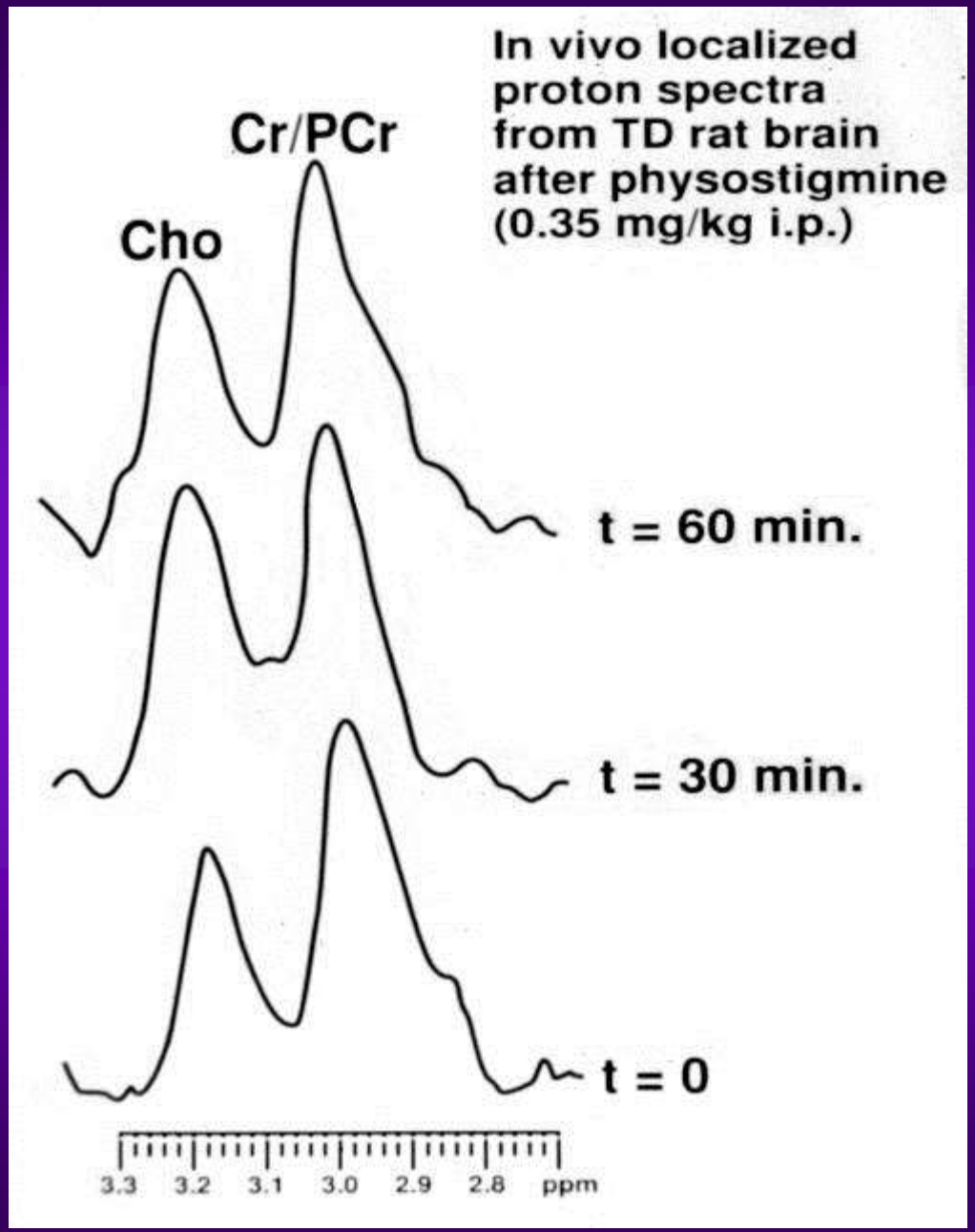
and

(b) Cr/NAA

2 hours after administration of thiamine hydrochloride (5 or 100 mg/kg, i.p.) in rats made TD by dietary deprivation and daily pyrithiamine (0.5 mg/kg) for 12 days

MRM,

34:313-318 (1995)


In vivo localized
proton spectra
from TD rat brain
after physostigmine
(0.35 mg/kg i.p.)
Cr/PCr
Cho
t = 60 min.
t = 30 min.
t = 0
3.3
3.2
3.1
3.0
2.9
2.8
ppm

Concentrations of metabolites in rat brain (mean±SD, μmol/wet g)

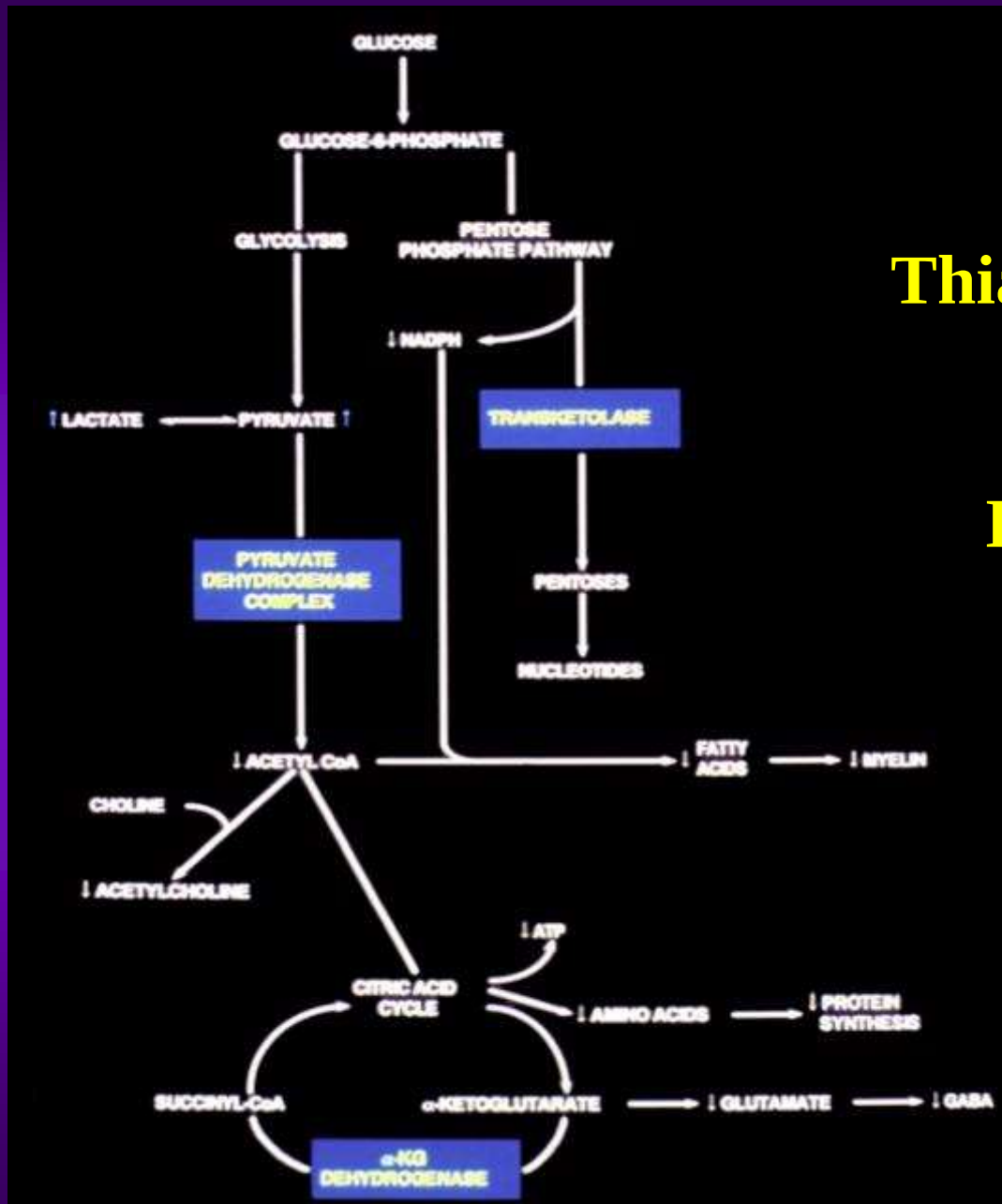
	*GPC	PC	Cho	PCr/Cr	NAA
Normal Control	0.46 ±0.06	0.23 ±0.04	0.05 ±0.02	8.00 ±0.91	5.90 ±0.77
Thiamine Deficiency	0.12 ±0.03	0.24 ±0.03	0.08 ±0.04	7.72 ±0.84	5.52 ±0.89
Thiamine Treatment	0.25 ±0.06	0.24 ±0.04	0.06 ±0.02	7.57 ±1.10	5.33 ±0.64

Molecular Explanations for Decreased Choline-containing Compounds?

- Changes in concentrations of membrane lipid constituents (myelin abnormalities)
- Changes in concentration of acetylcholine precursor choline (partial cholinergic deafferentation)
- Changes in production of glycerophosphocholine from degradation of phosphatidylcholine by phospholipase A_2

General Hypothesis

Genetic susceptibility to thiamine deficiency may determine why some, but not all individuals develop brain (or other end-organ) damage with equivalent lifetime exposure to alcohol when other risk factors (age, gender, family history, lifetime episodes of documented malnutrition or alcohol withdrawal) are covaried.



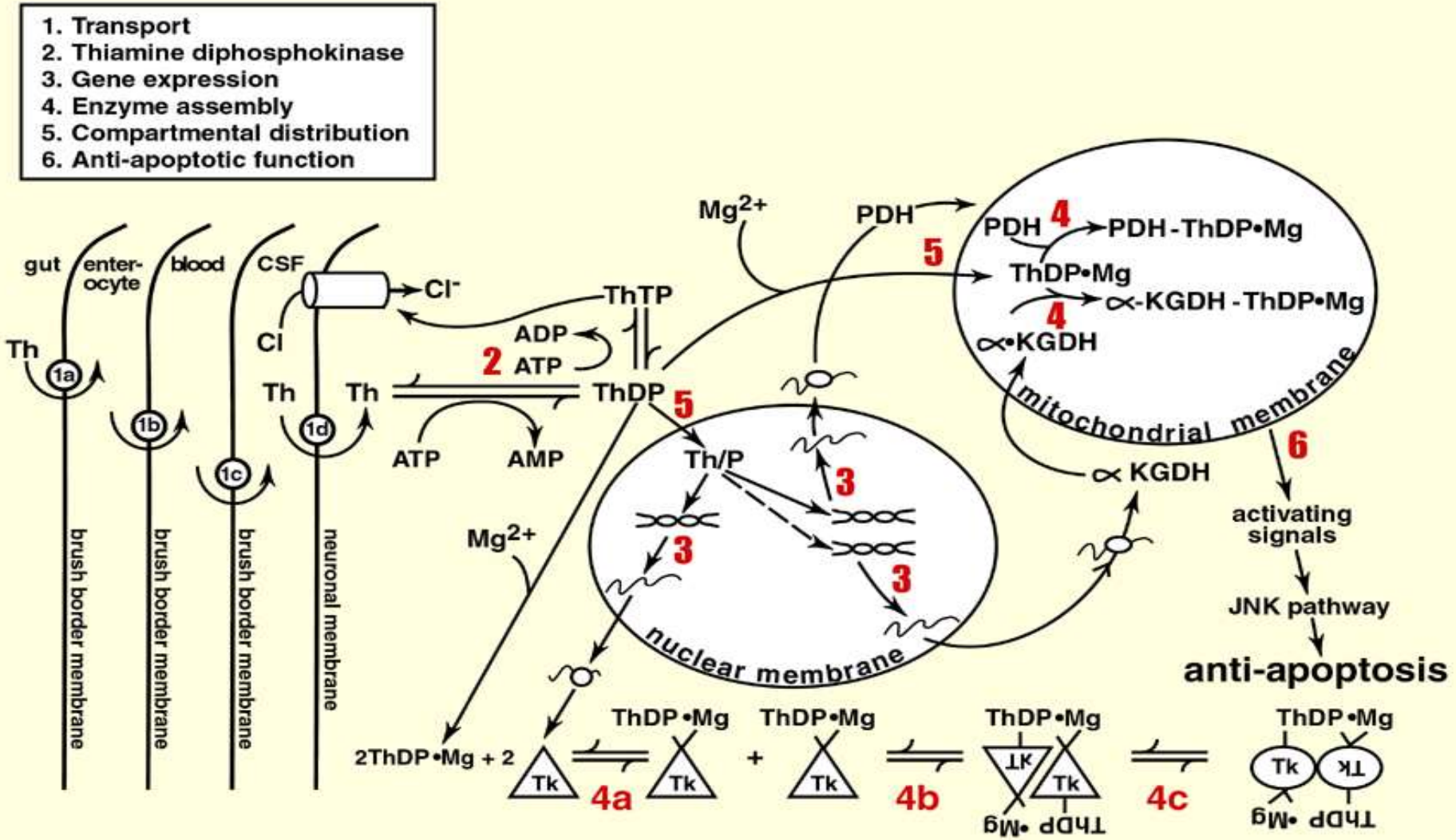
Effects of

Thiamine Deficiency

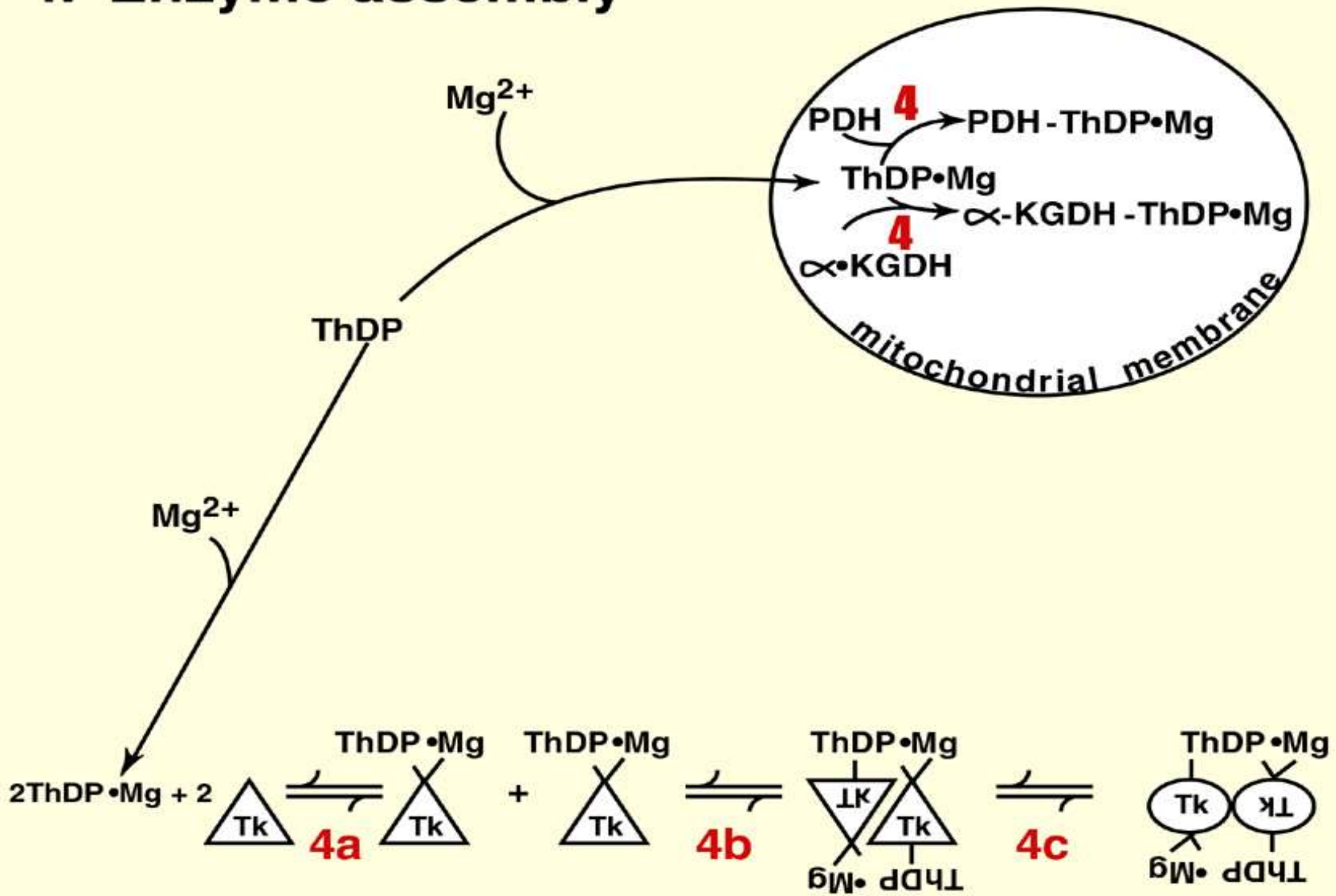
on

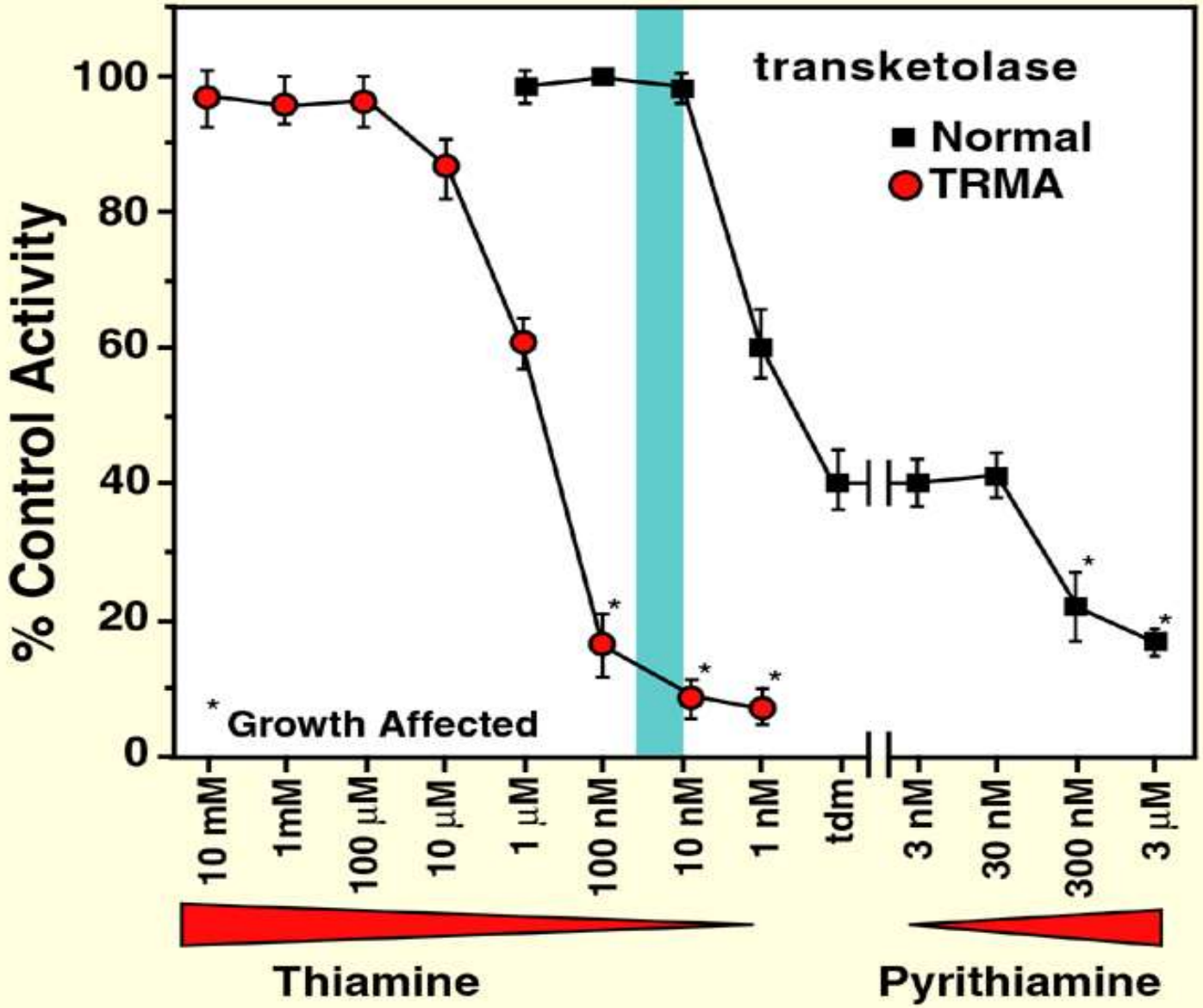
Brain Glucose Metabolism

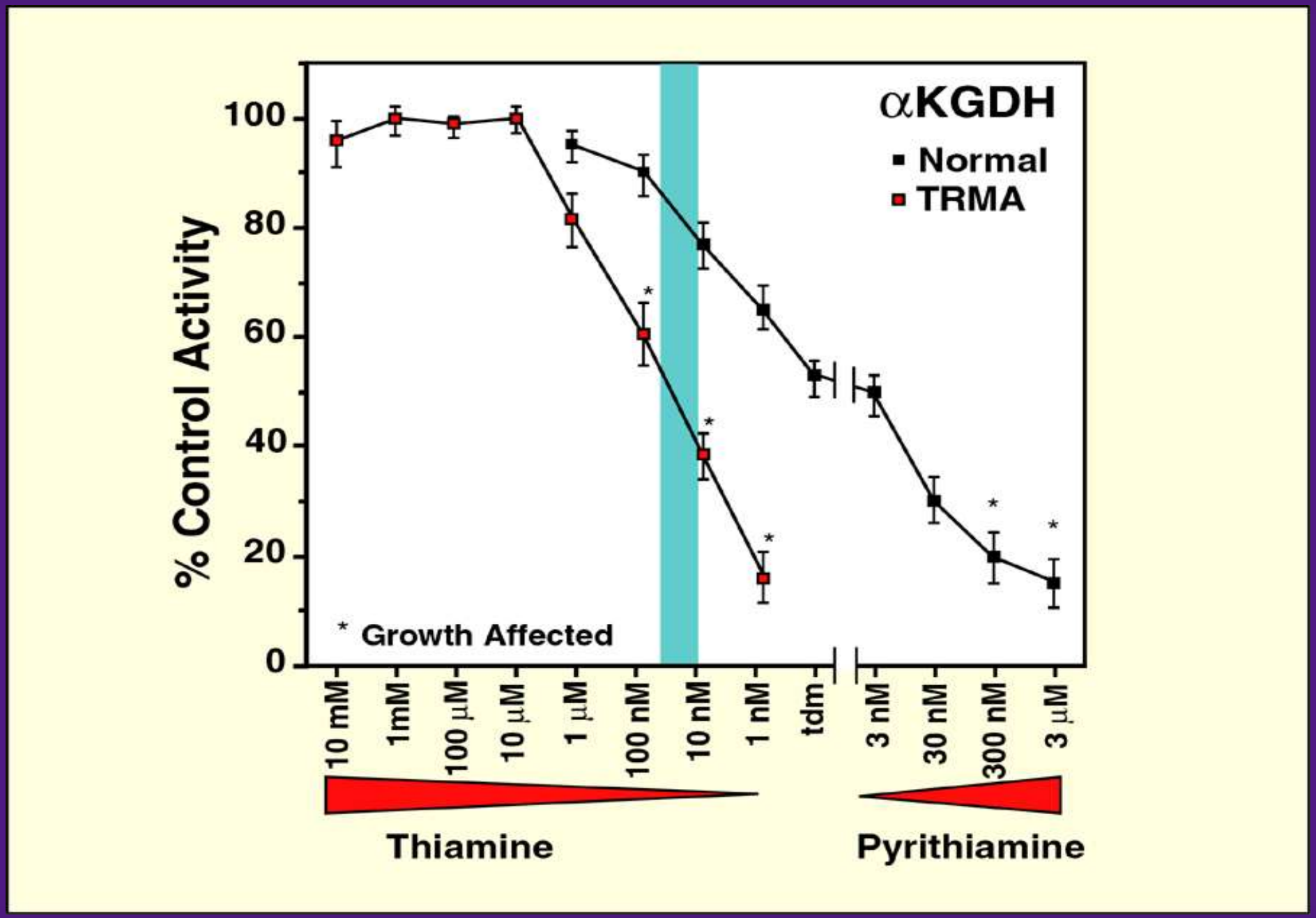
INTER-INDIVIDUAL DIFFERENCES IN THAMINE UTILIZATION



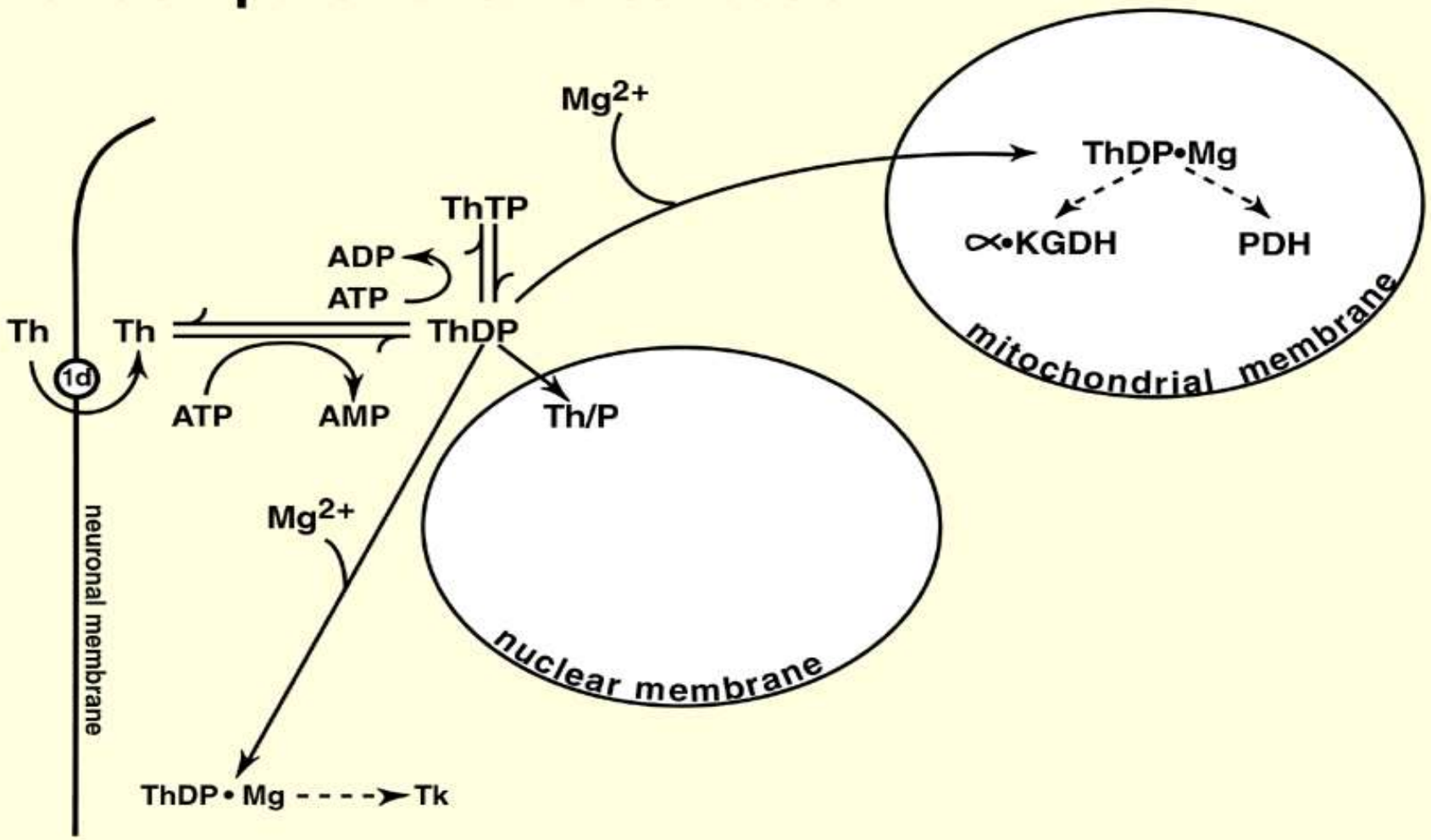
4. Enzyme assembly



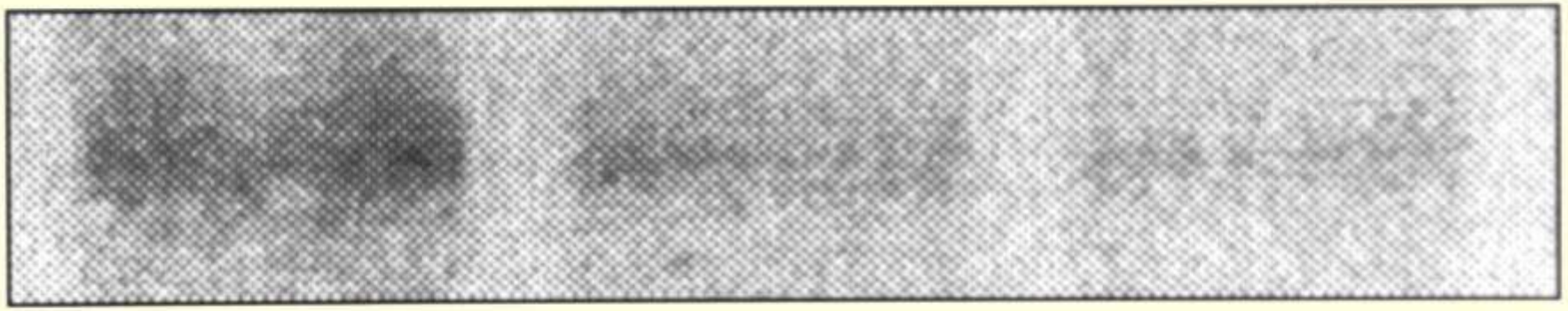

transketolase
Normal
TRMA
% Control Activity
100
80
60
40
20
0
* Growth Affected
10 mM
1mM
100 µM
10 µM
1 µM
100 nM
10 nM
1 nM
tdm
3 nM
30 nM
300 nM
3 µM
Thiamine
Pyrithiamine


αKGDH
Normal
TRMA
% Control Activity
100
80
60
40
20
0
* Growth Affected
10 mM
1mM
100 µM
10 µM
1 µM
100 nM
10 nM
1 nM
tdm
3 nM
30 nM
300 nM
3 µM
Thiamine
Pyrithiamine

5. Compartmental distribution



Transketolase mRNA during Thiamine Deficiency

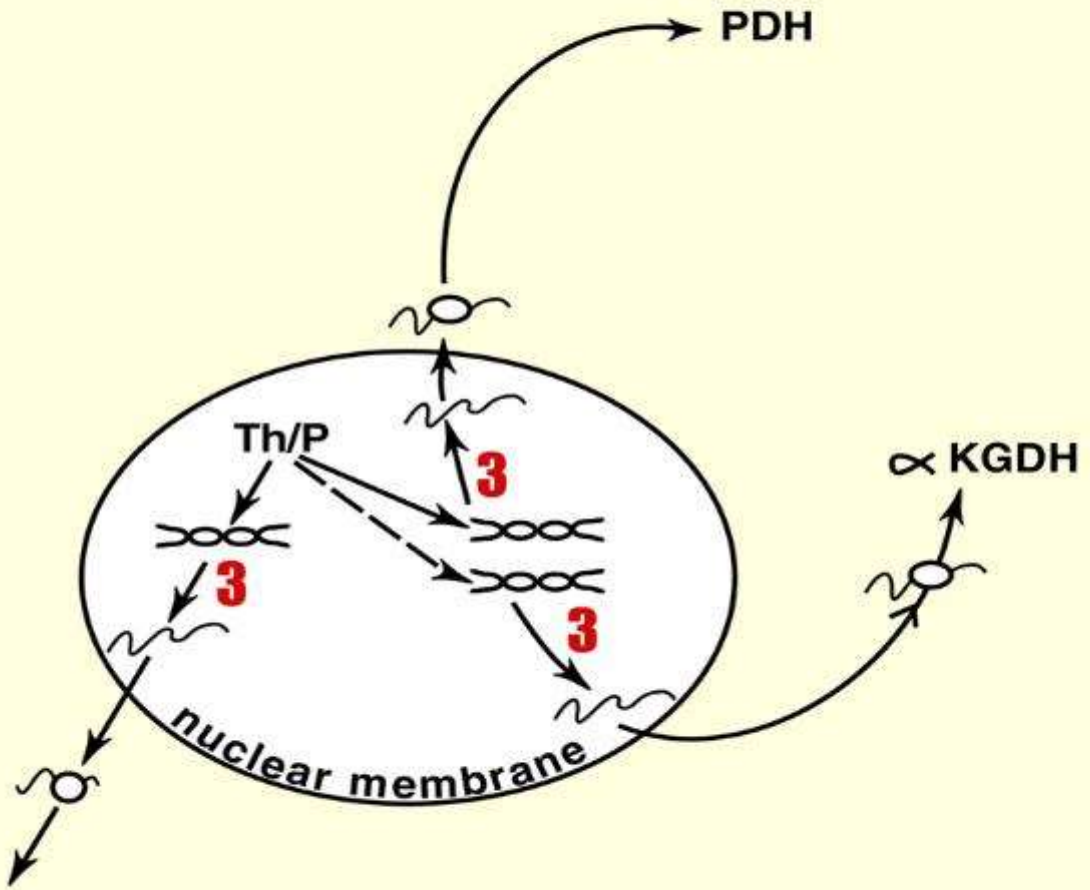


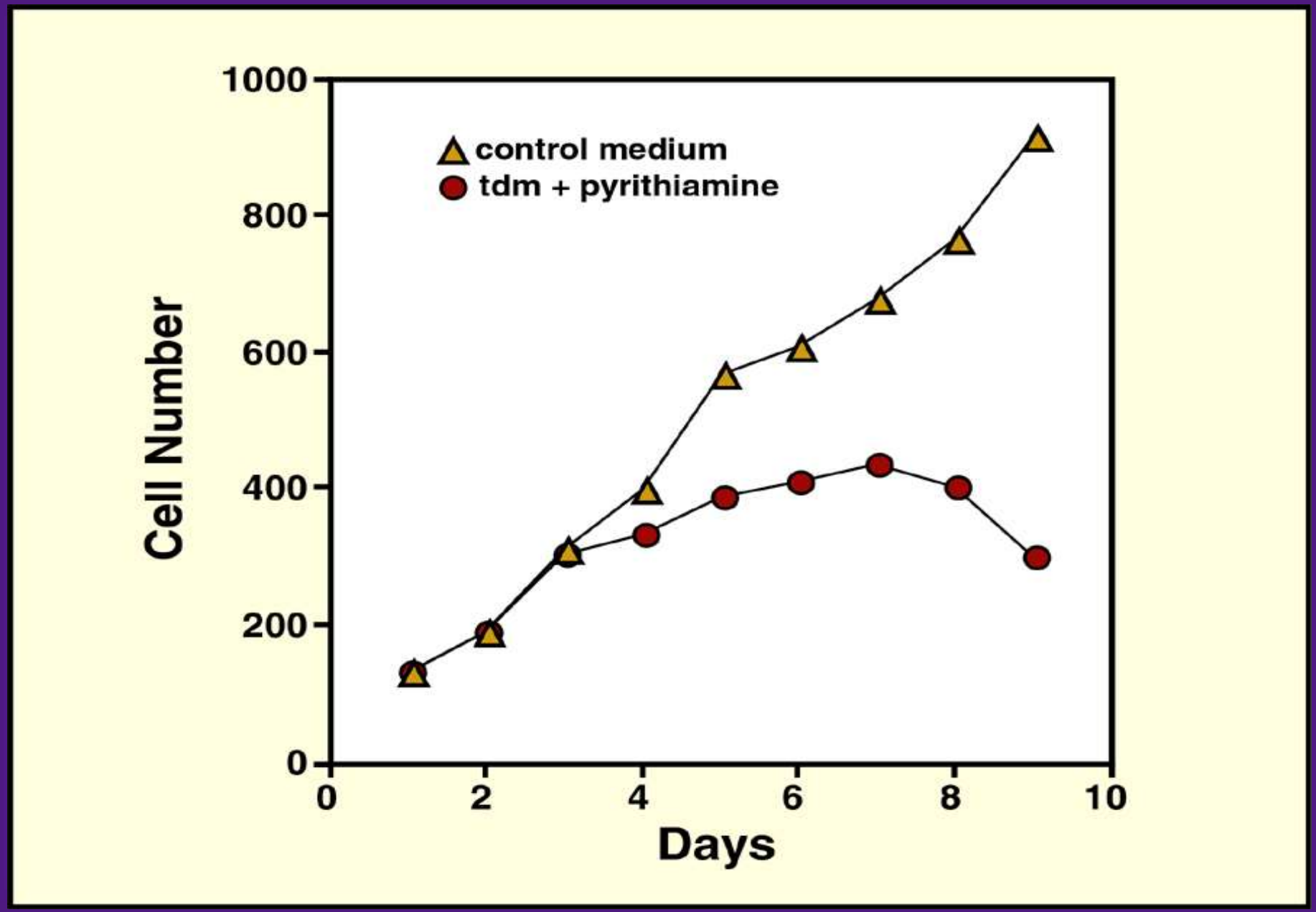
high thiamine

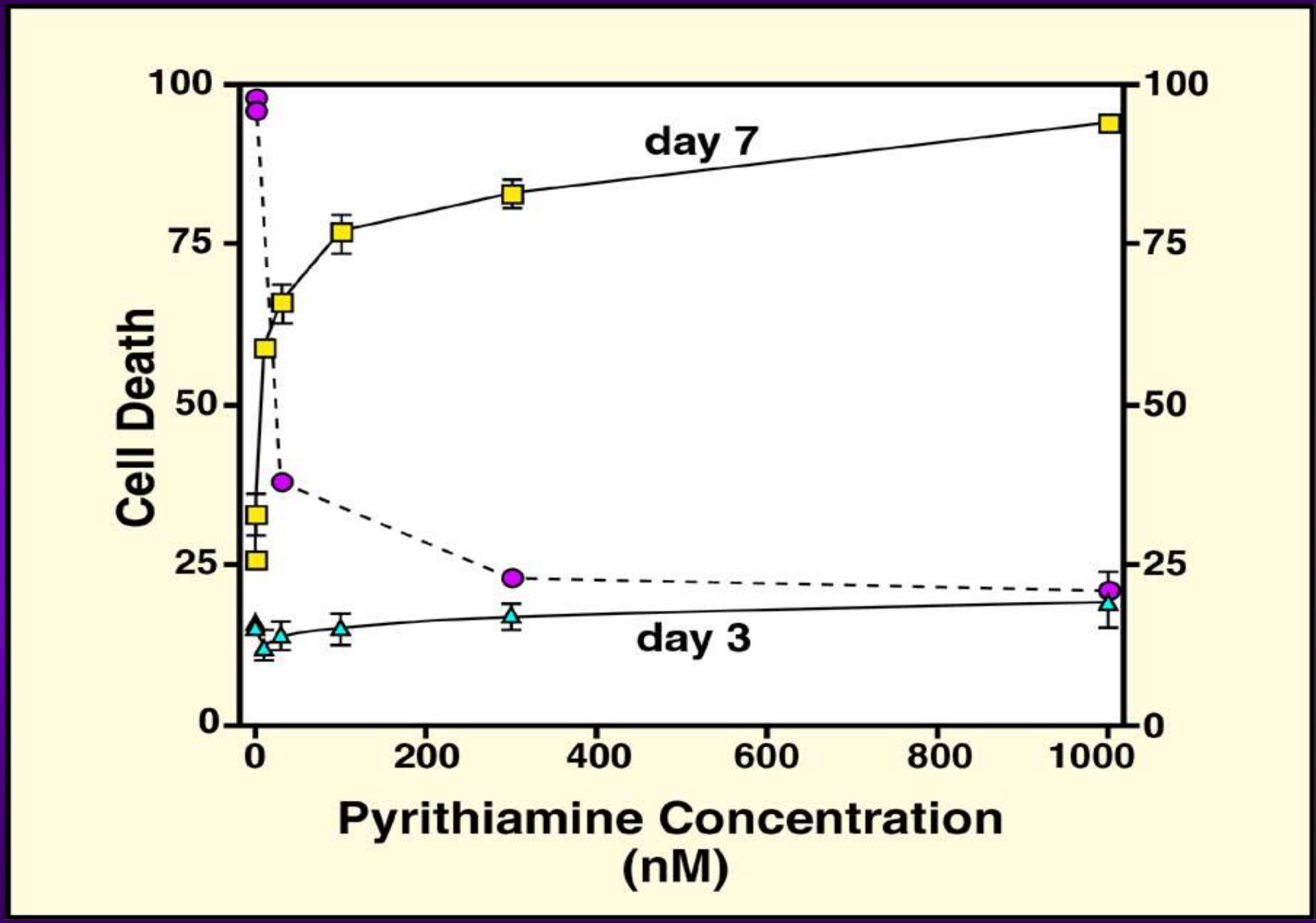
high thiamine + pyrithiamine

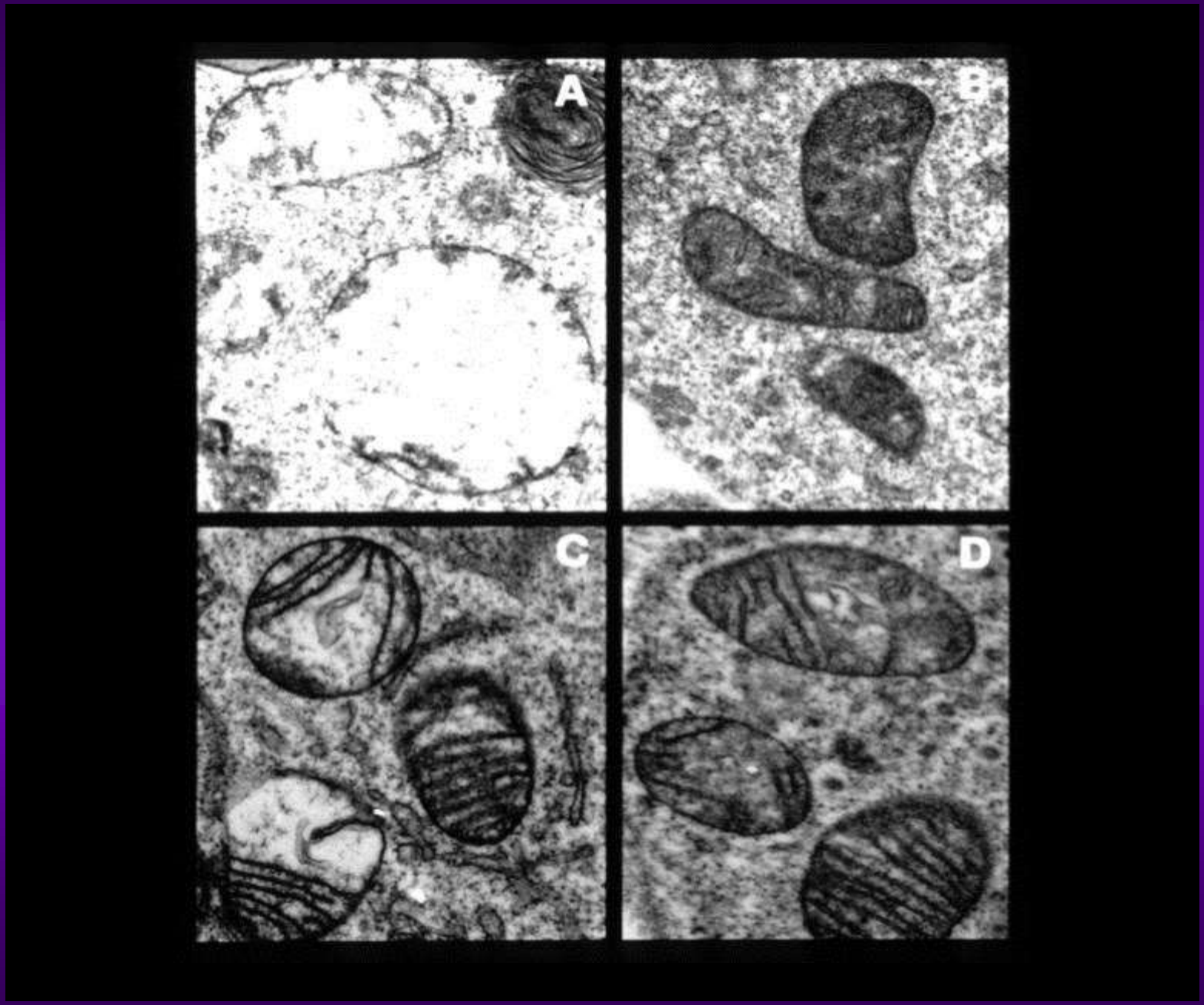
low thiamine

3. Gene expression

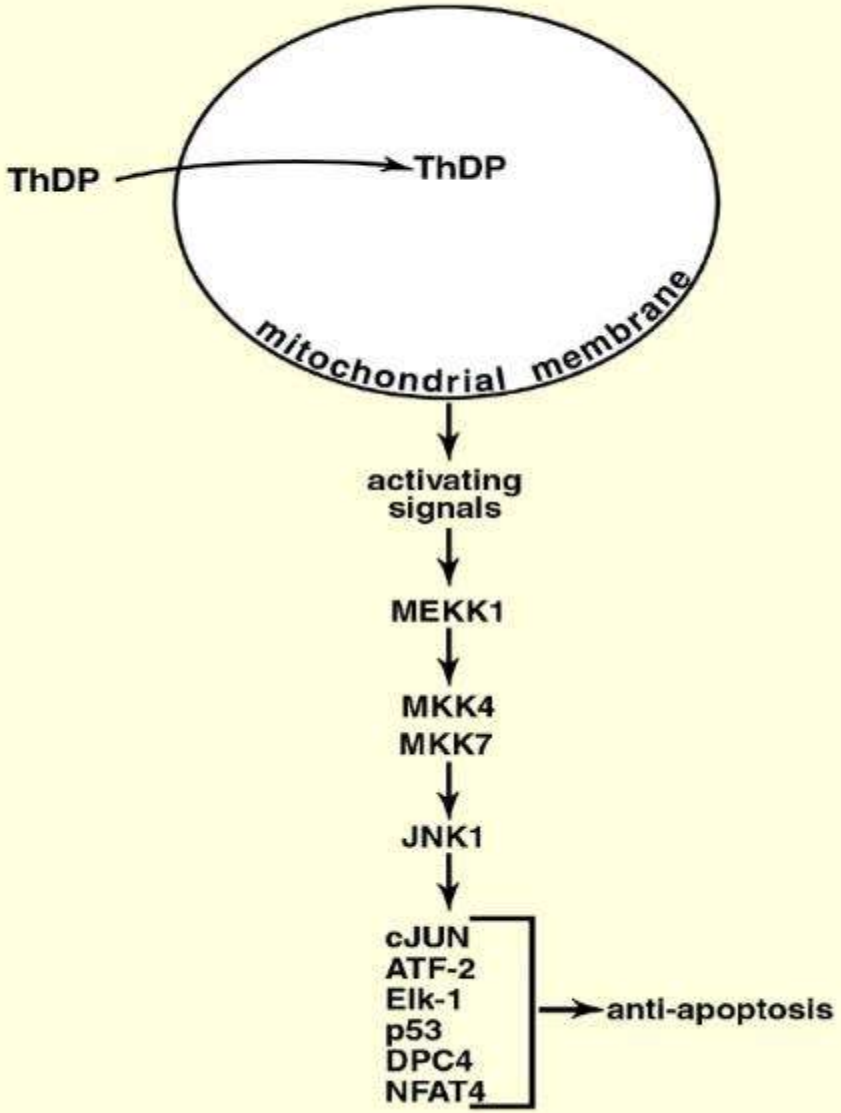



control medium
tdm + pyrithiamine
Cell Number
1000
800
600
400
200
0
0
2
4
6
8
10
Days


100
75
50
25
0
Cell Death
day 7
day 3
0
200
400
600
800
1000
Pyrithiamine Concentration
(nM)


A
B
C
D

6. Anti-apoptotic function



Conclusions

- Thiamine deficiency is the established cause of Wernicke-Korsakoff Syndrome
- Thiamine deficiency also contributes significantly to other forms of alcohol-induced brain injury

Conclusions

- Thiamine may initiate or facilitate recovery of brain functions with abstinence by modifying Cho-containing compounds (membrane turnover, acetylcholine, signal transduction)
- With repeated episodes of thiamine deficiency neuronal dropout may result (neuronal marker NAA)
- Genetic sensitivity to TD may predispose individuals to alcohol-induced brain injury, the pattern of brain damage, and ultimately a malignant, early-onset alcoholism

Collaborators

Vanderbilt University

Electrical/Computer Engineering

B.M. Dawant, Ph.D.
S.L. Hartmann

Molecular Biology

B.A. McCool, Ph.D.
S.R. Pekovich, Ph.D.
C.K. Singleton, Ph.D.
J-L. Wang, Ph.D.

Psychiatry

M.H. Parks, M.D.
D.D. Weinstein, M.D.
L.W. Welch, Ed.D.

Radiology/Radiological Sciences

S.J. Gibbs, Ph.D.
R. Kessler, M.D.
H. Lee, Ph.D.
V.L. Morgan, Ph.D.
D. Pickens, Ph.D.
R.R. Price, Ph.D.
W.R.Riddle, Ph.D.

National Institute on Alcohol Abuse and Alcoholism

B. Adinoff, M.D.
M.J. Eckardt, Ph.D.
D. Goldman, M.D.
M. Linnoila, M.D., Ph.D.
D.E. Rio, Ph.D.
R.R. Rawlings
J.W. Rohrbaugh, Ph.D.
H. Weingartner, Ph.D.

National Institute of Child Health and Human Development

A.B. Mukherjee, M.D., Ph.D.

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  - RO1: Molecular mechanisms of thiamine utilization
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