

# **fMRI and MRS in Psychiatry**

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**Constance Moore**

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**Perry Renshaw**

**Deborah Yurgelun-Todd**

**Ron Cowan**

**Jon Levin**

**Ika Rogowska**

**Claudia Diaz**

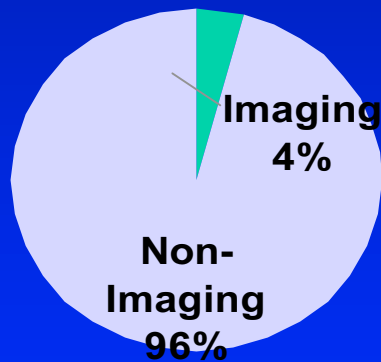
**Russ Loeber**

**Mike Rohan**



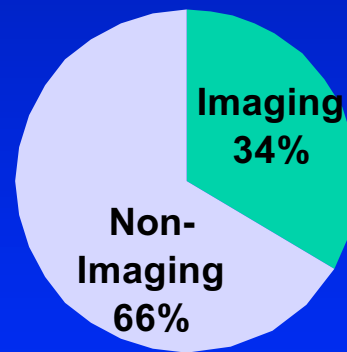
# Neuroimaging is widely used in Psychiatric Research

CPDD 2002



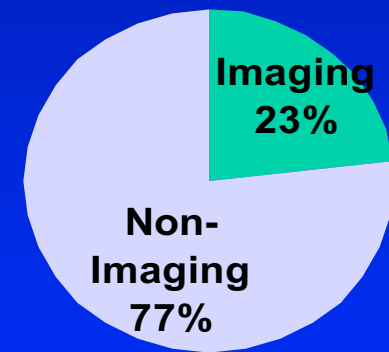
Drug Abuse

Biological Psychiatry 2002



Psychiatric Disease

Neurology 2002



Neurological Disease

THE WALL STREET JOURNAL.

FRIDAY, OCTOBER 11, 2002

# Survival of the Busiest

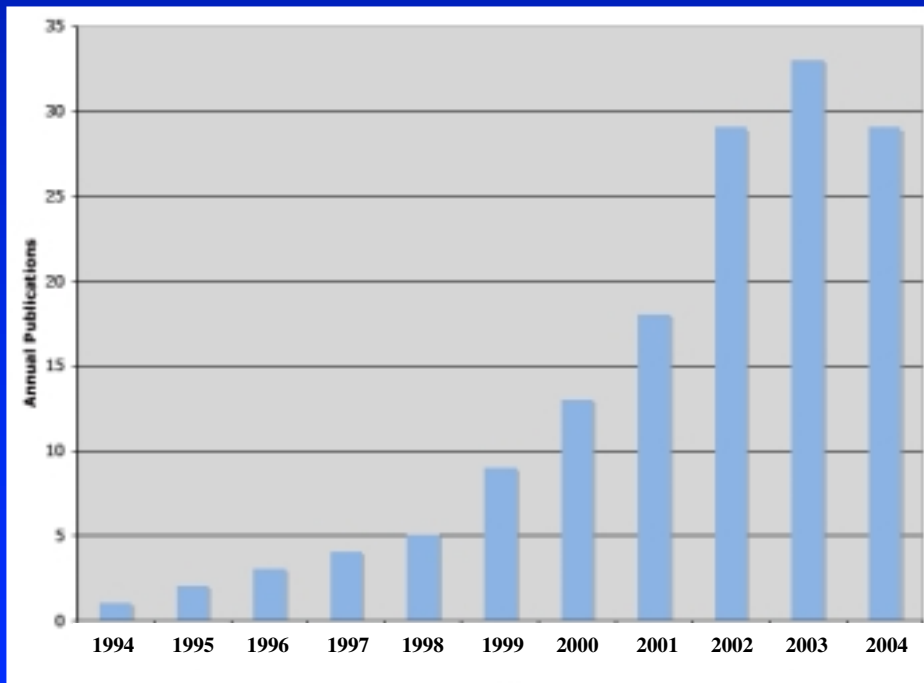


**A Comprehensive Review is  
Beyond the Scope of a 25  
Minute Talk**

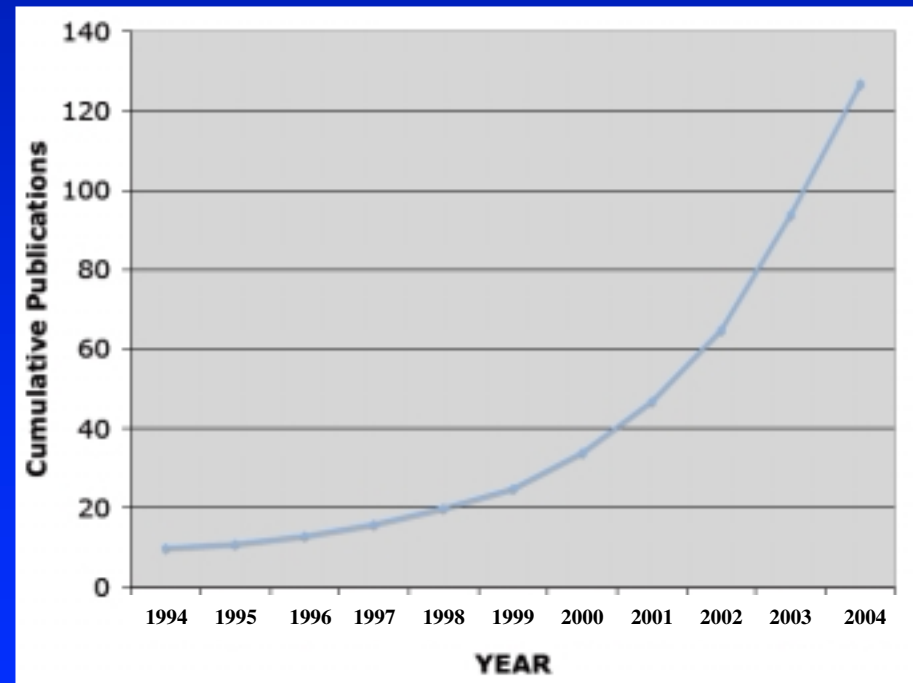
**Interest in functional  
MRI is very high.**

# fMRI and Schizophrenia: Annual and Cumulative Publications

## Annual



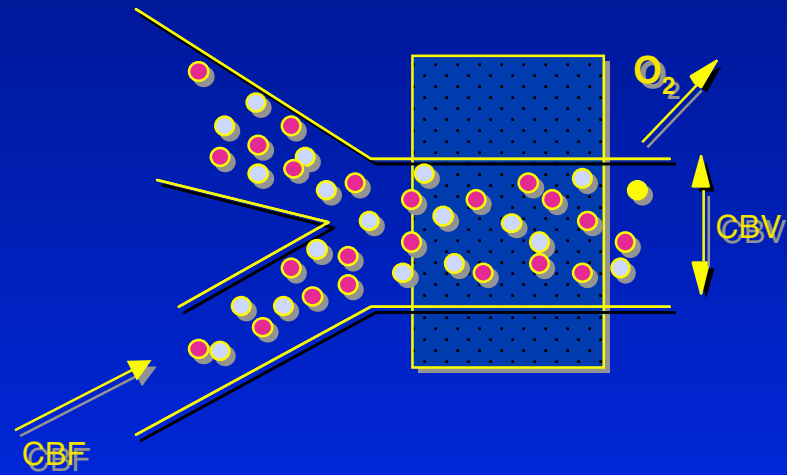
## Cumulative



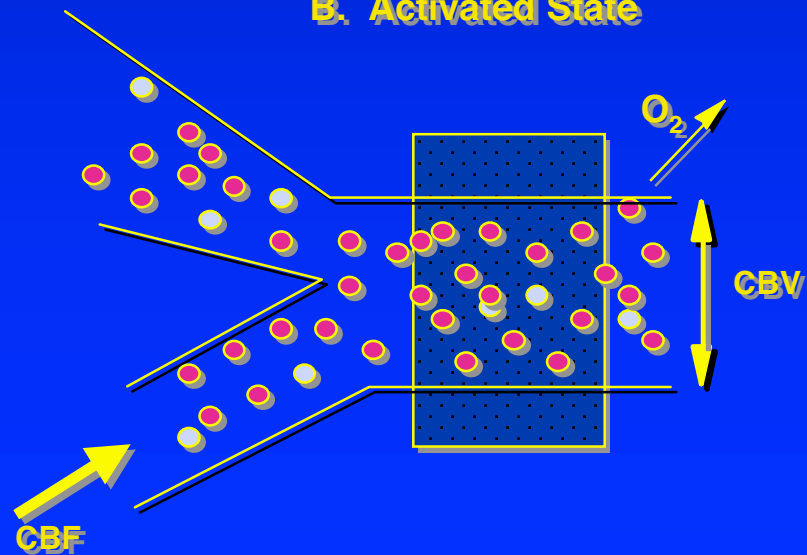
**Clinical factors tend to be  
ignored in attempts to  
“model” physical  
phenomena.**

# Physiologic Basis of BOLD

## A. Resting State



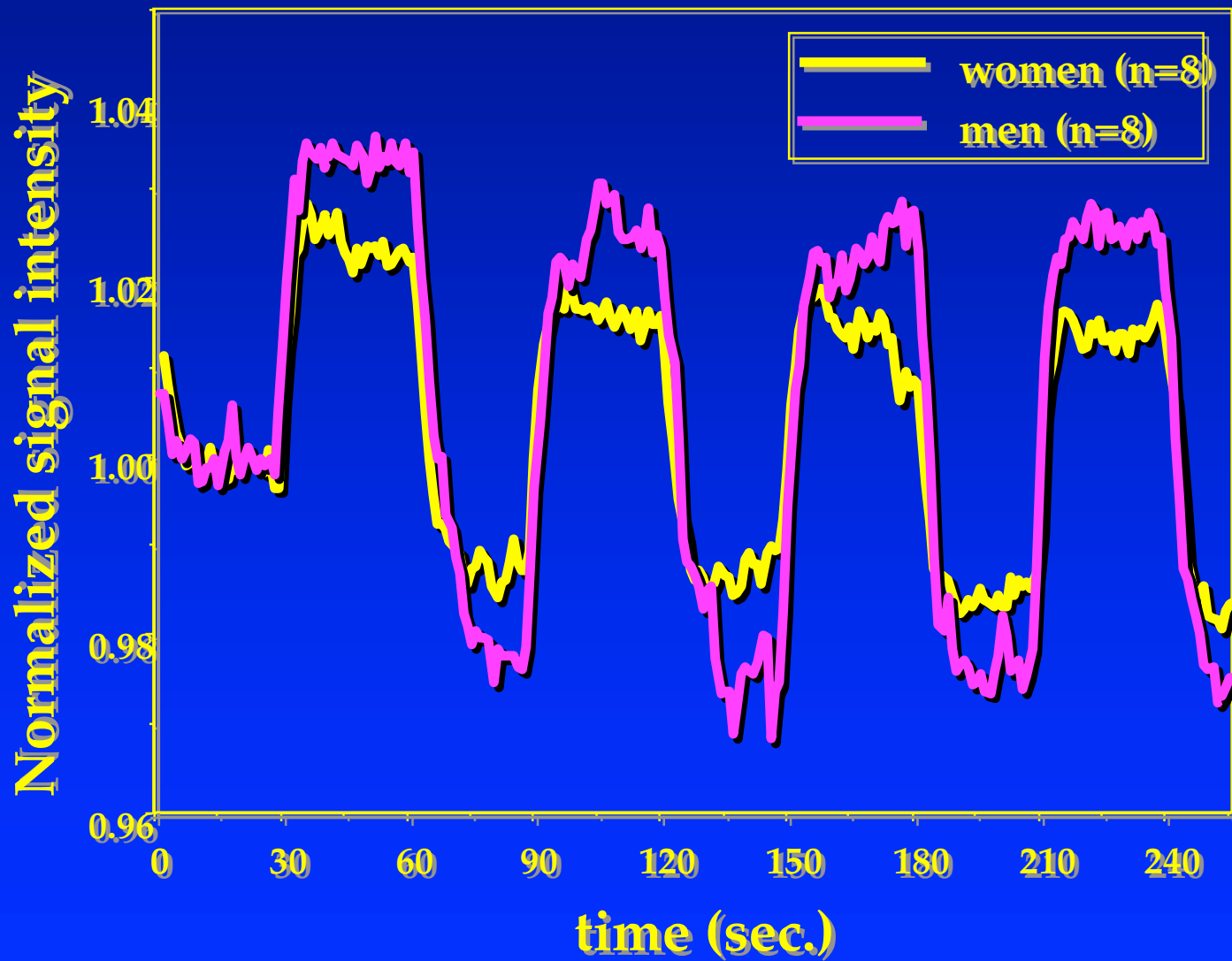
## B. Activated State



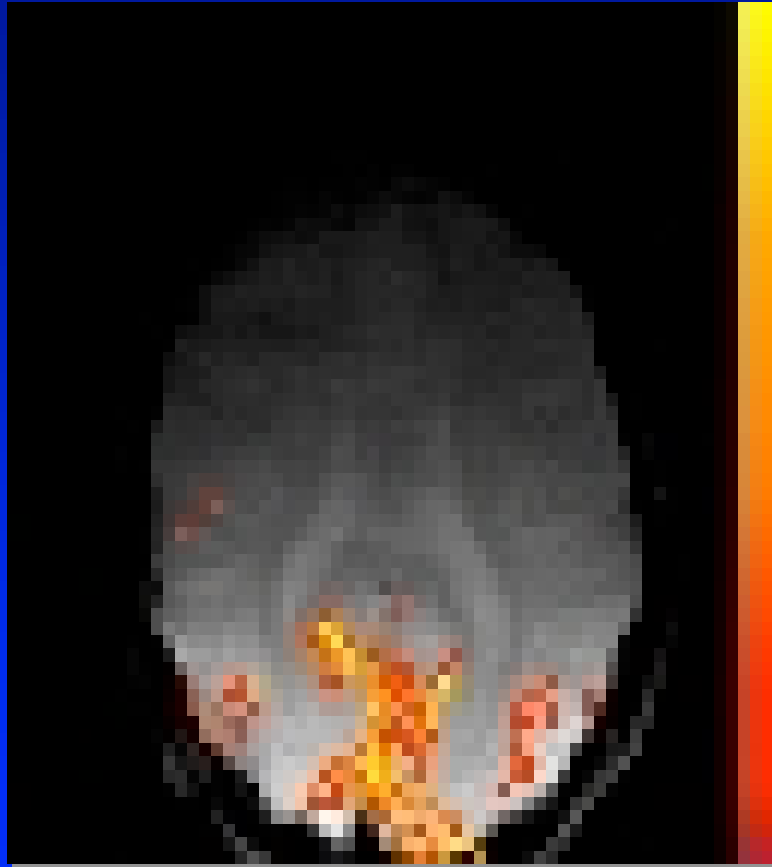
● Oxyhemoglobin

● Deoxyhemoglobin

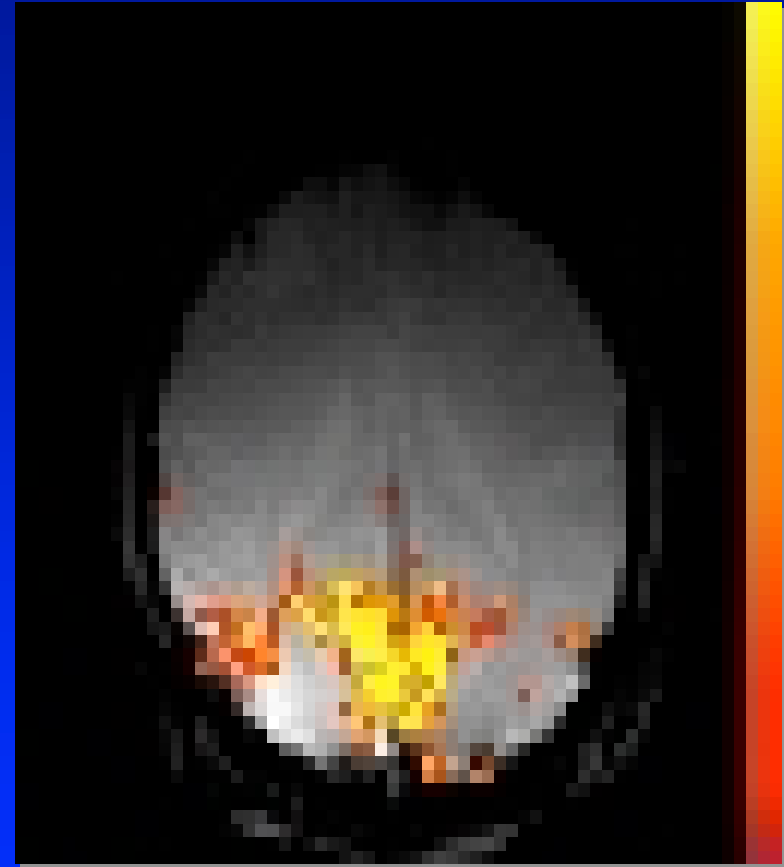
# BOLD photic response - composite



# BOLD fMRI with photic stimulation

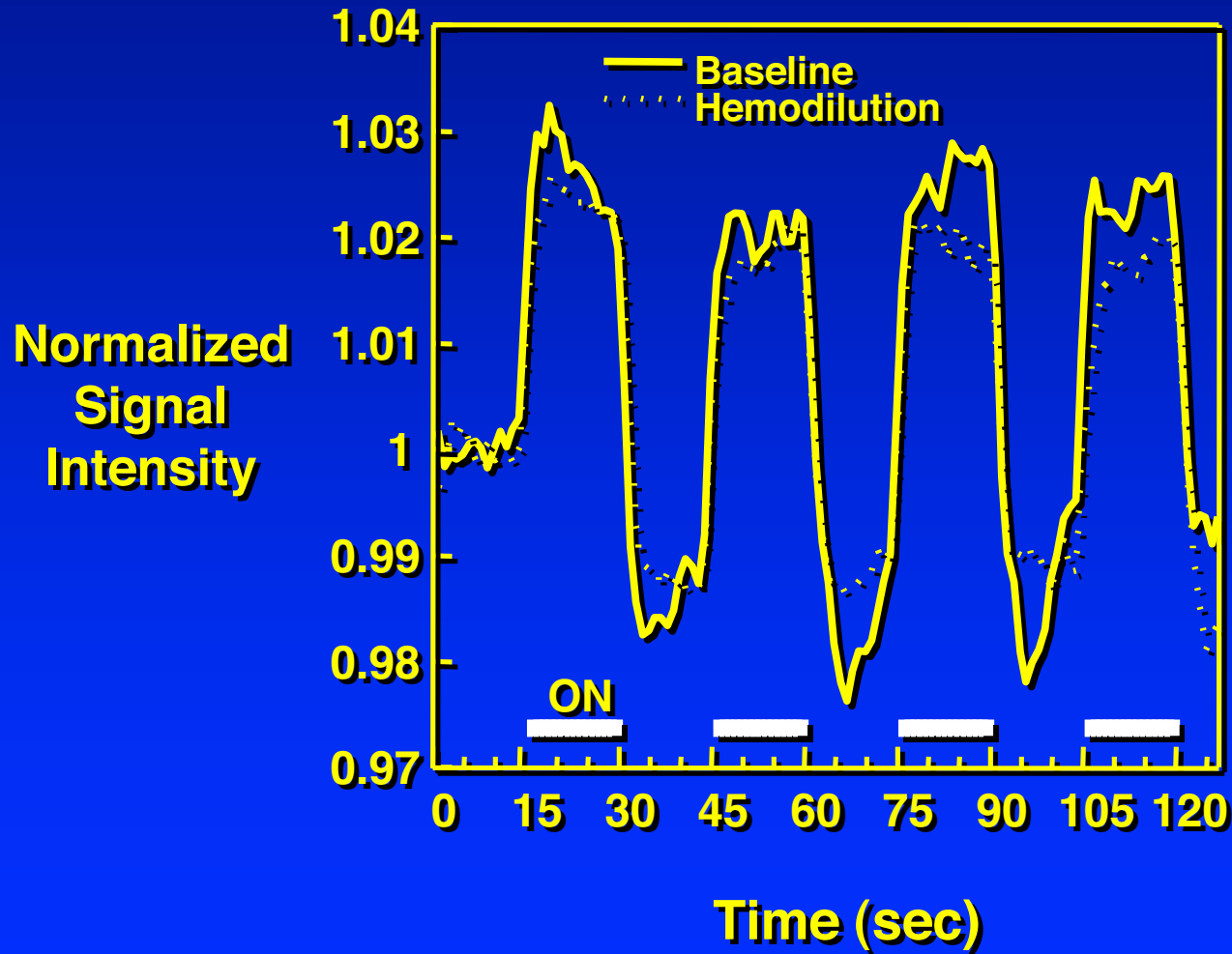


**23 year old woman**



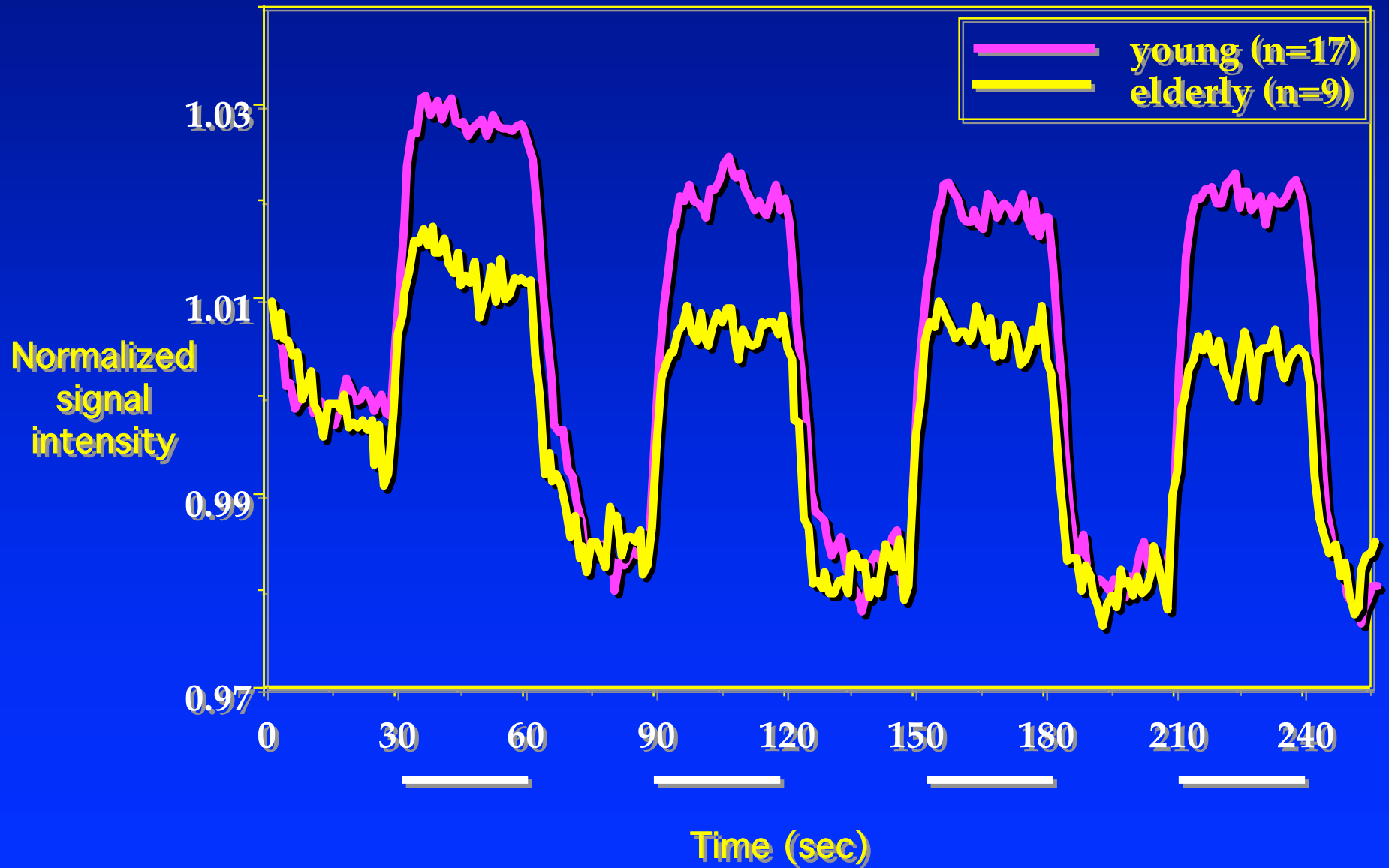
**28 year old man**

# Effect of Hemodilution on BOLD Photic Activation



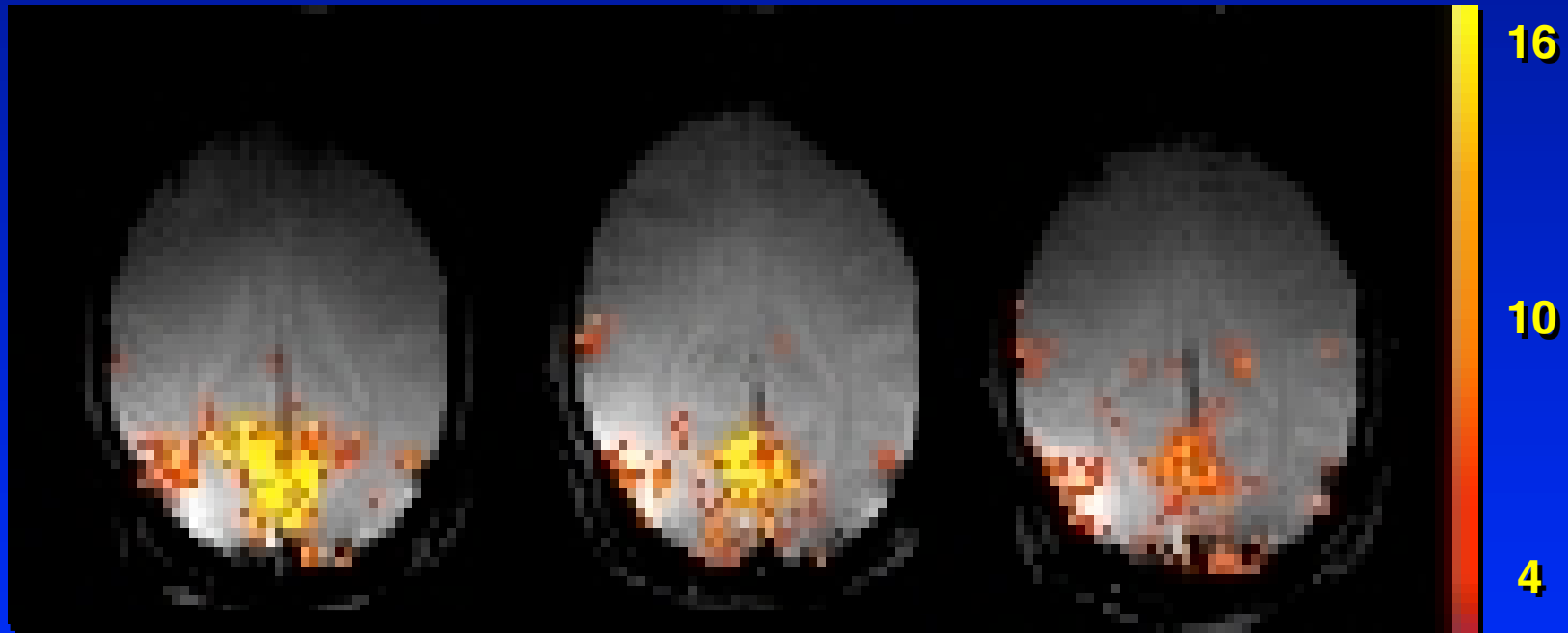
J.M. Levin, M.D.

# Effect of aging on BOLD signal



# Photic Stimulation: Effects of Alcohol

J.M. Levin et al., *Psychiatry Res.* 82:135, 1998



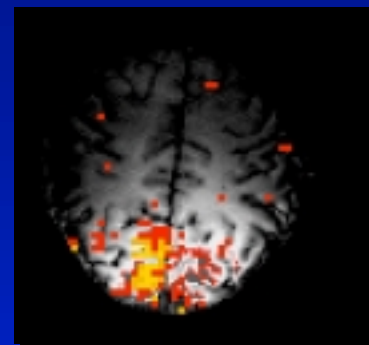
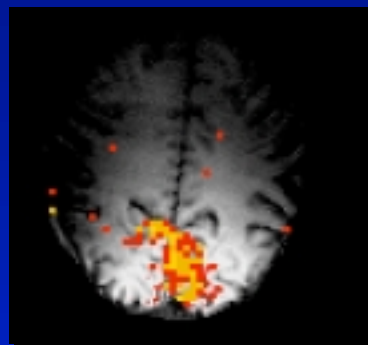
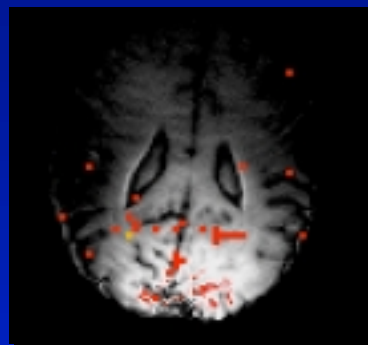
**Baseline**

**+25 Minutes**

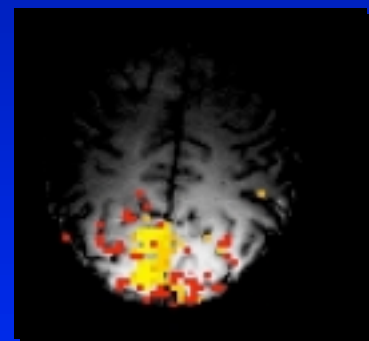
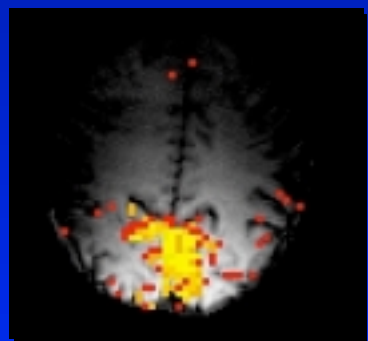
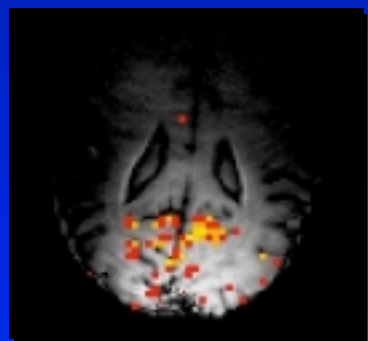
**+50 Minutes**

# Cocaine: Effect on BOLD Photic Activation

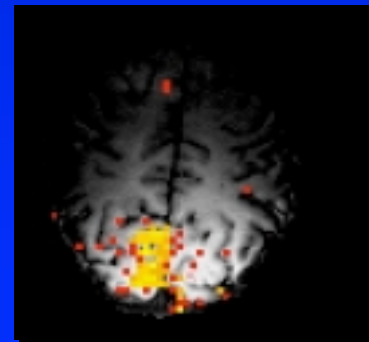
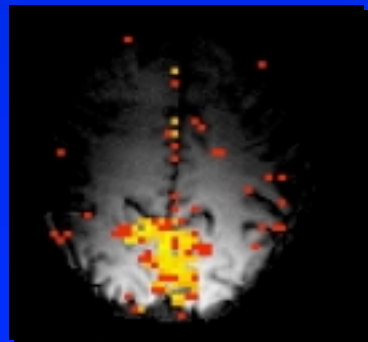
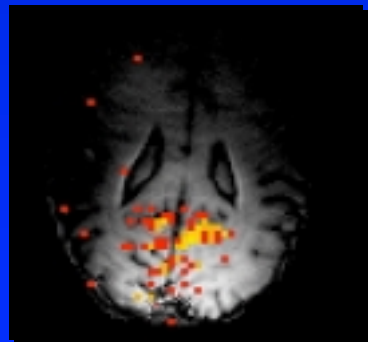
Baseline



5 min.  
post

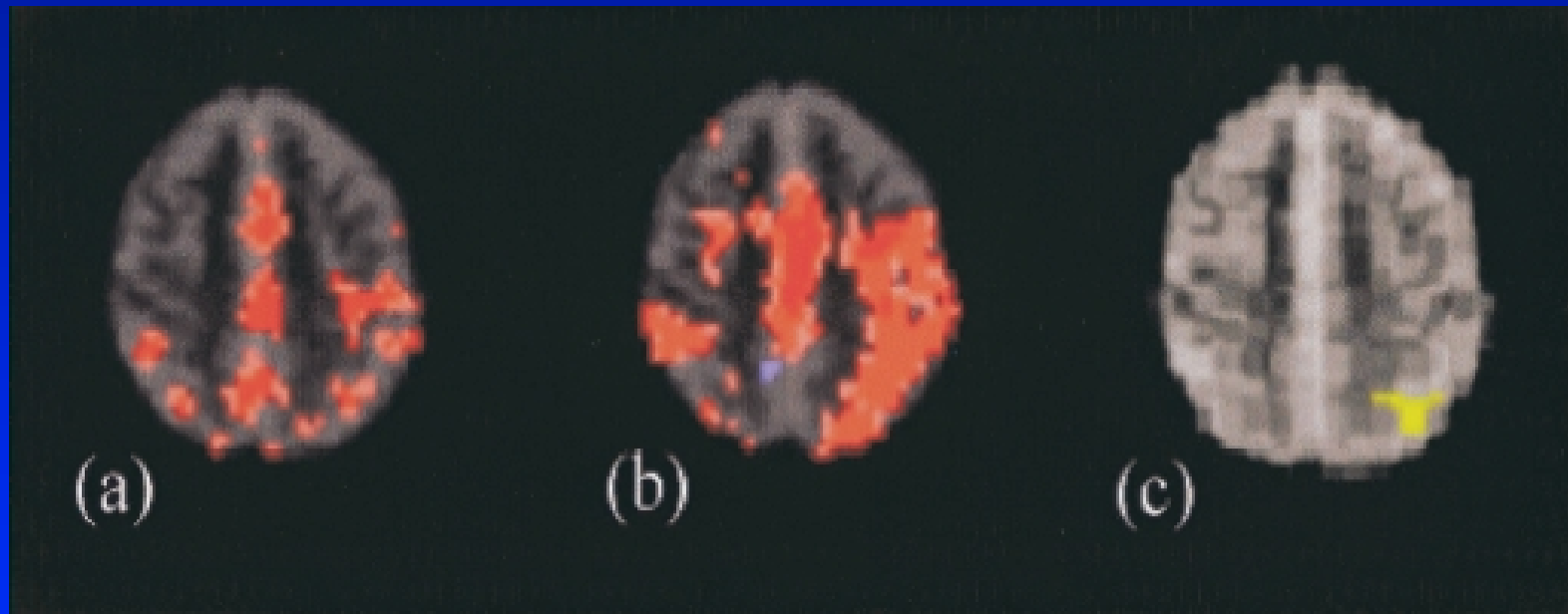


20 min.  
post



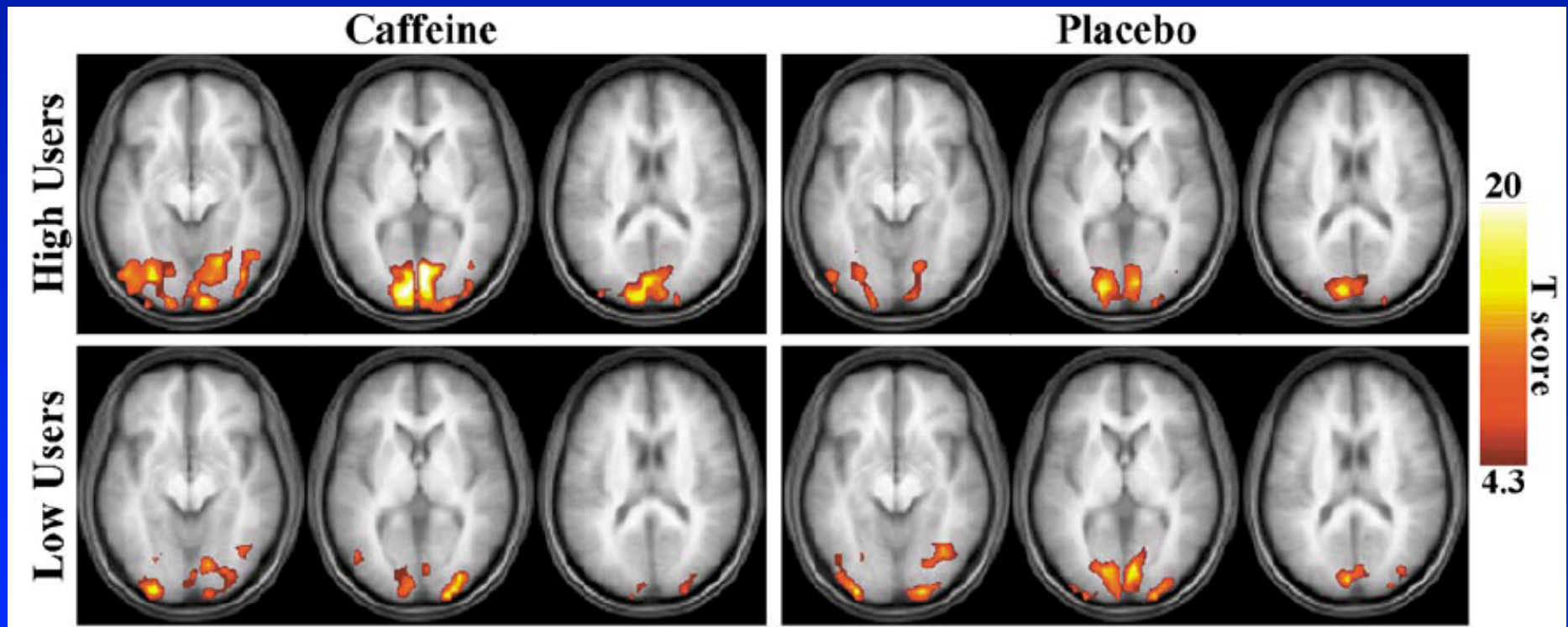
J.M. Levin, MD.

# Brain Activation Maps from Cognitive Tests During (a) Euglycemia, (b) Hypoglycemia, and (c) a Comparison of the Two

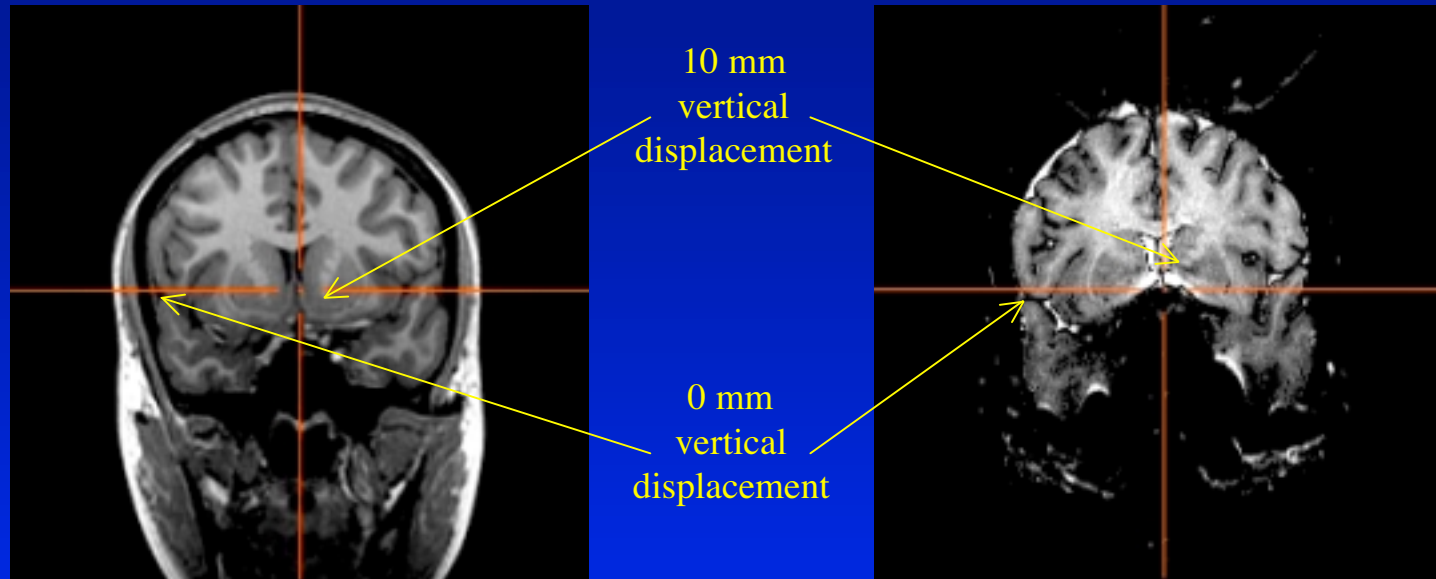


The red areas show regions of increased BOLD signal. The small blue area in (b) is an area activated out of phase with the test. The yellow areas (c) show regions where BOLD signal increased significantly ( $P > 0/005$ ) when differences between the first and second data sets from study 1 were compared with the differences between the two data collections in study 2, and they show the effect of hypoglycemia.

# Caffeine: Effect of Visual Stimulation on BOLD Activation in the Visual Cortex



# Geometric distortion in EPI



- EPI images undergo non-rigid-body deformation due to magnetic field inhomogeneity which high resolution anatomic images (left) do not.
- Structures in the basal forebrain, such as the nucleus accumbens, can be displaced by as much as 10 mm relative to peripheral brain structures.
- It is possible to acquire high resolution images with distortions identical to EPI images (right); structures can easily be registered using these images.
- Anatomical referencing to undistorted images will lead to misidentification of activated structures.

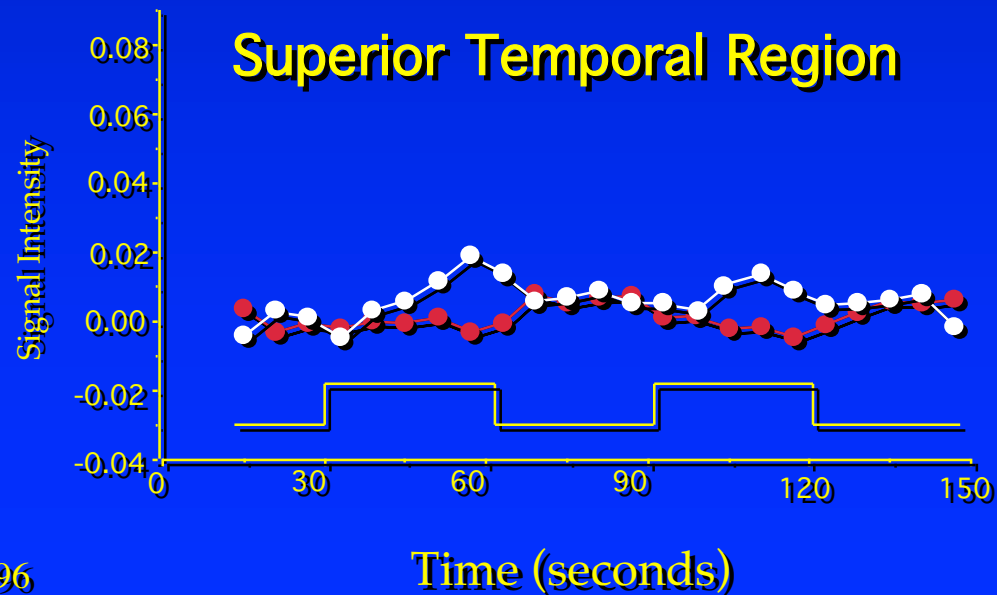
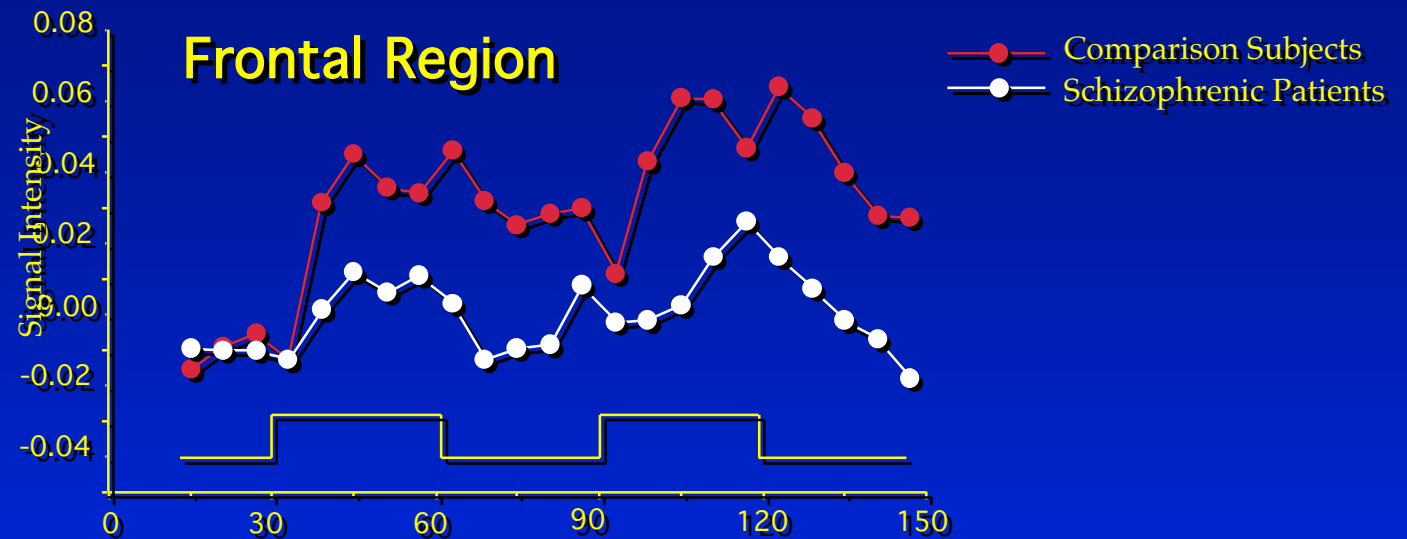
**Clinical Relevance of Most Work to  
Date is Limited:**

**What Does it Mean When Signal  
Goes Up, Down, or Stays the Same?**

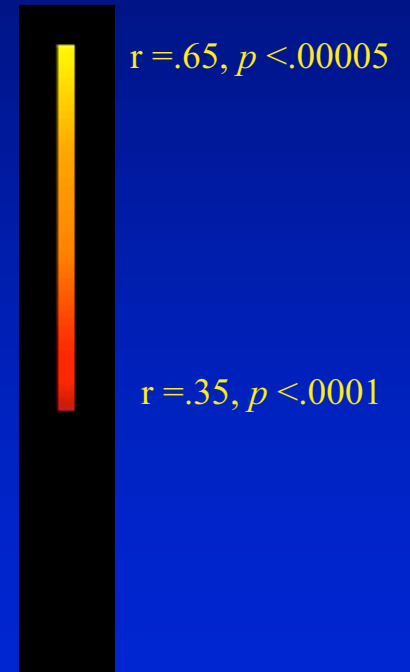
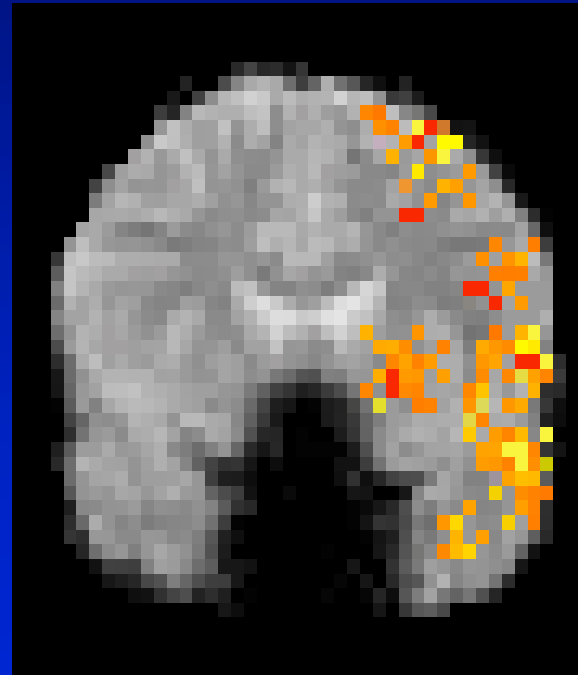
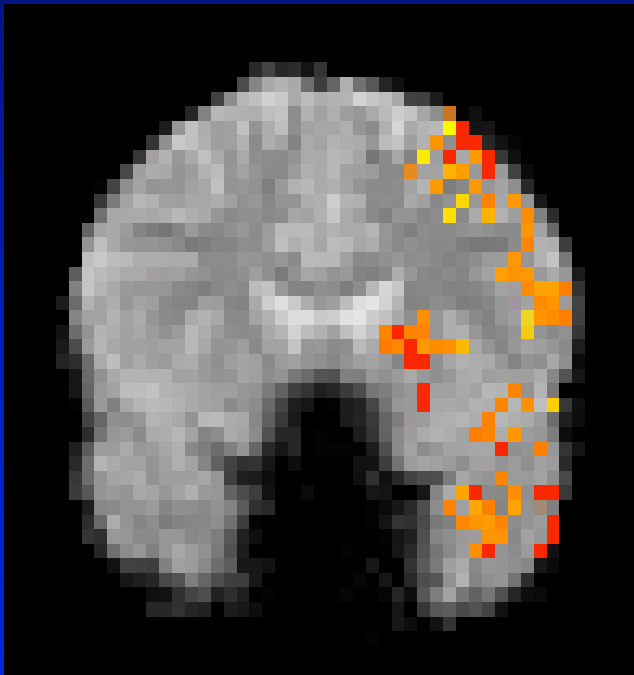


**Disease-Related, Abnormal  
“Wiring” Offers the Most  
Promise for Clinical Utility**

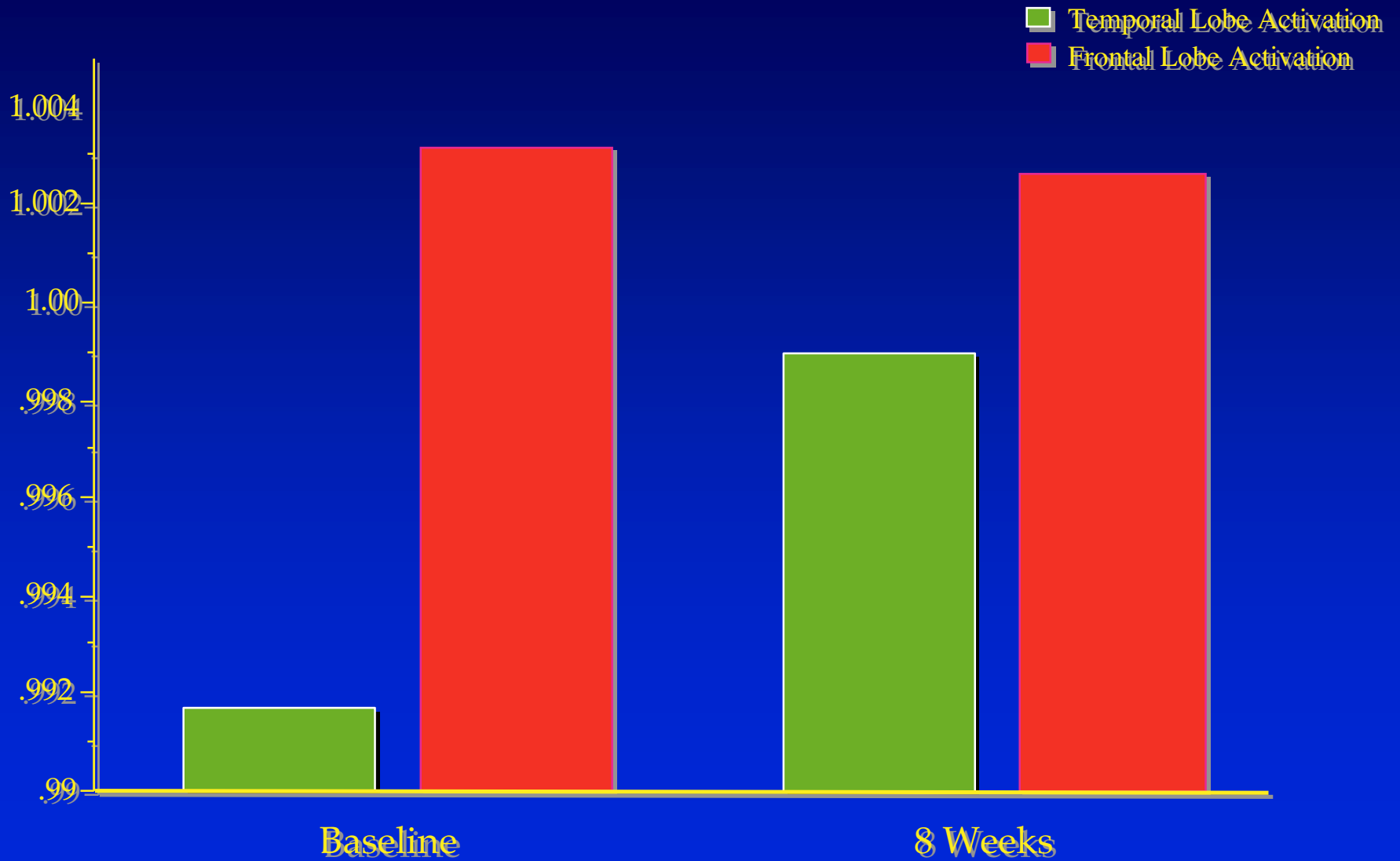
# Regional Activation (Verbal Fluency - Counting)



Change in Signal Intensities During Verbal Fluency:  
Baseline (left) and 8 Weeks of Treatment with  
D-Cycloserine(right)

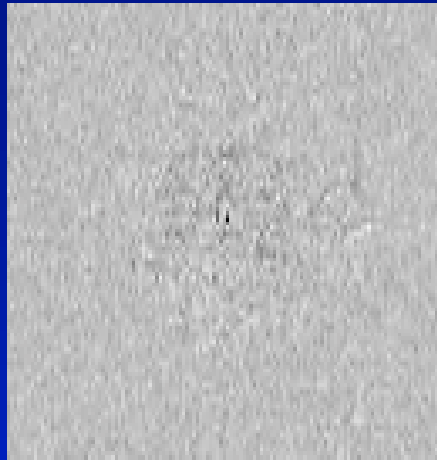


## Activation During Verbal Fluency



*Yurgelun-Todd et al.*

# **Dynamic Susceptibility Contrast**



**6**



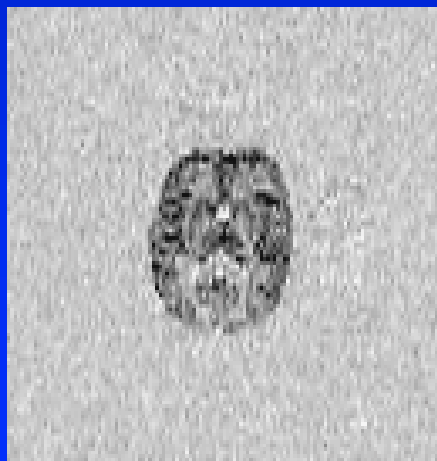
**7**



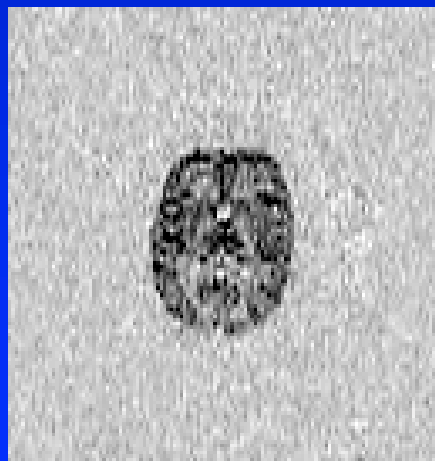
**8**



**9**



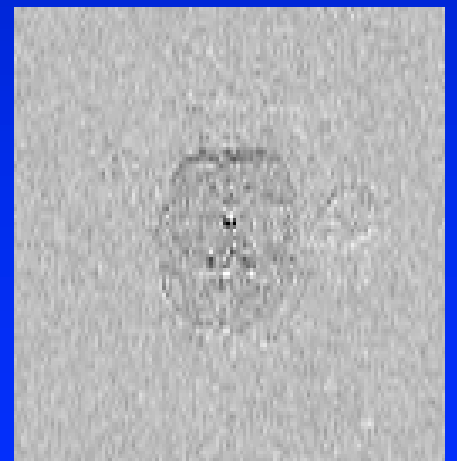
**10**



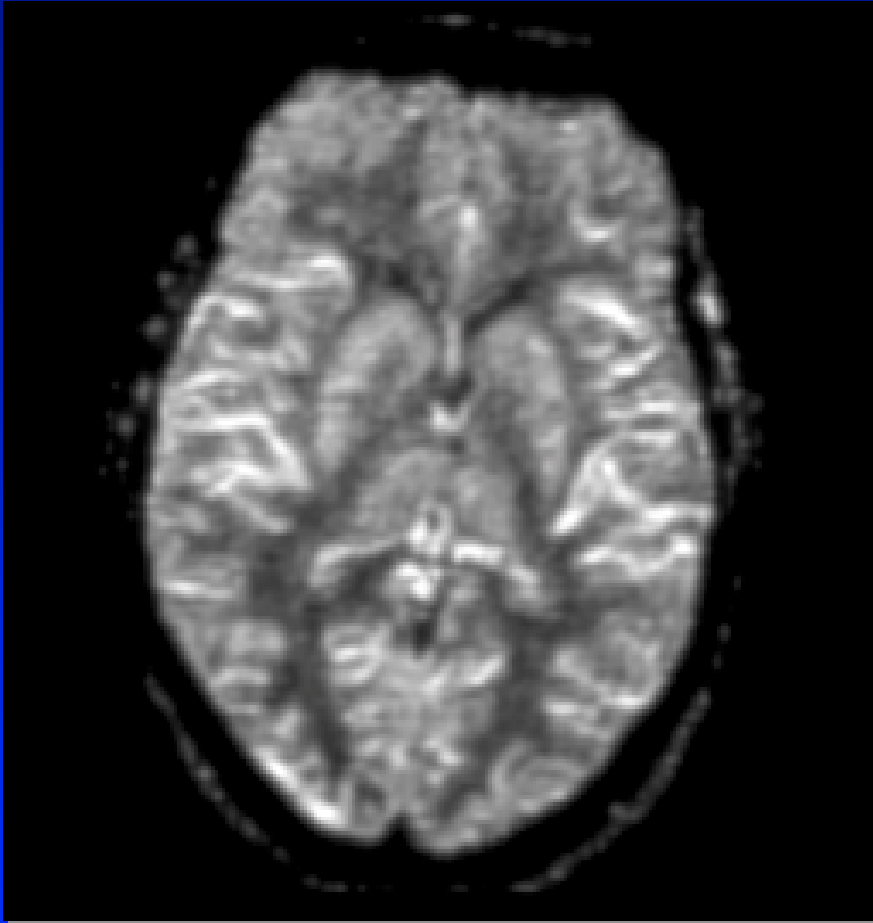
**11**



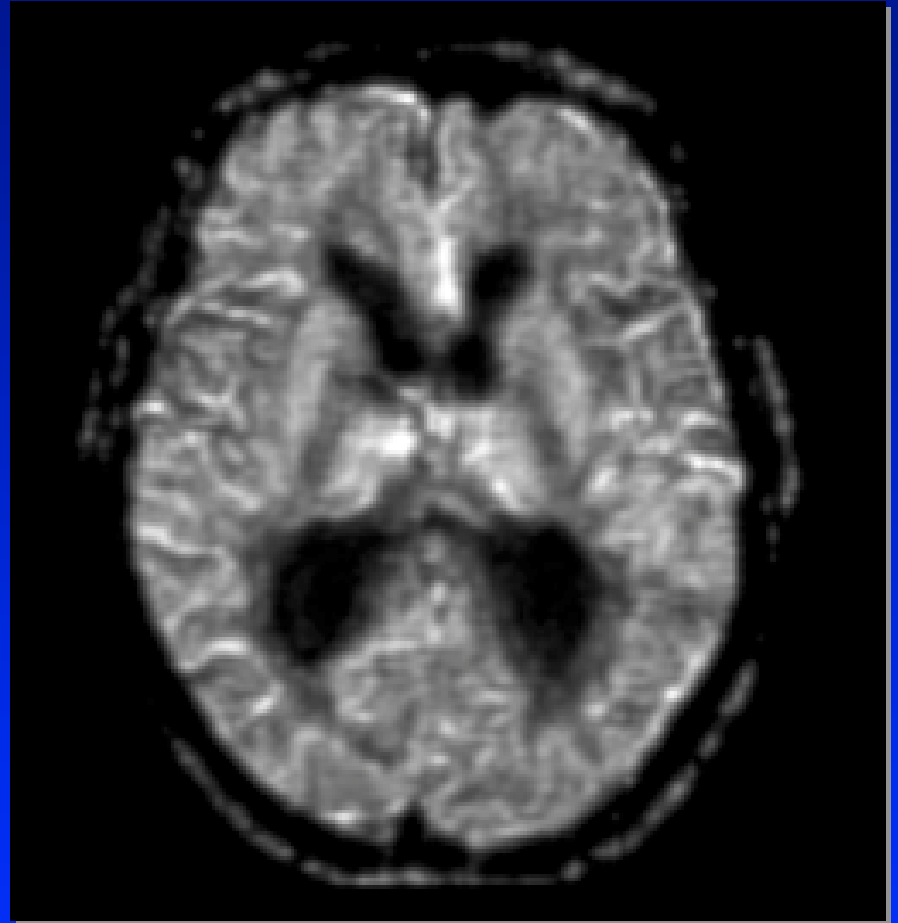
**12**



**17**

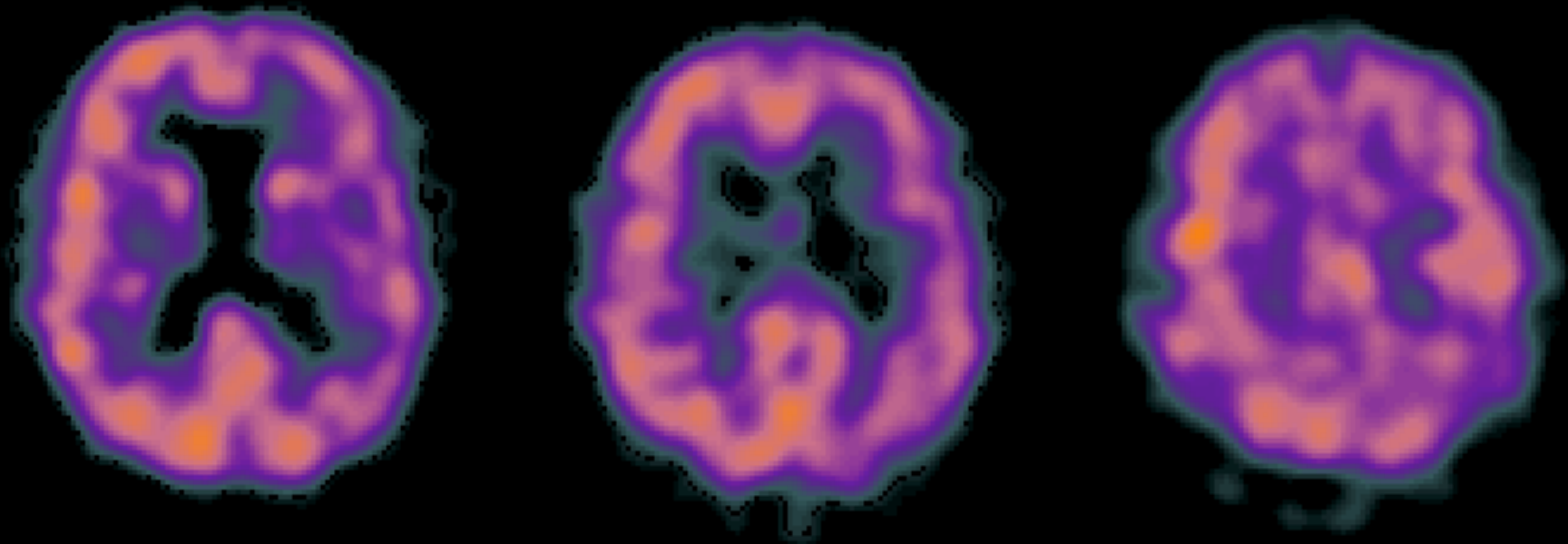


Normal



Alzheimer's

# Probable Alzheimer's Disease



$^{99m}\text{Tc}$ -HMPAO SPECT

# Sensitivity and Specificity of Temporoparietal Hypoperfusion in Alzheimer's Disease

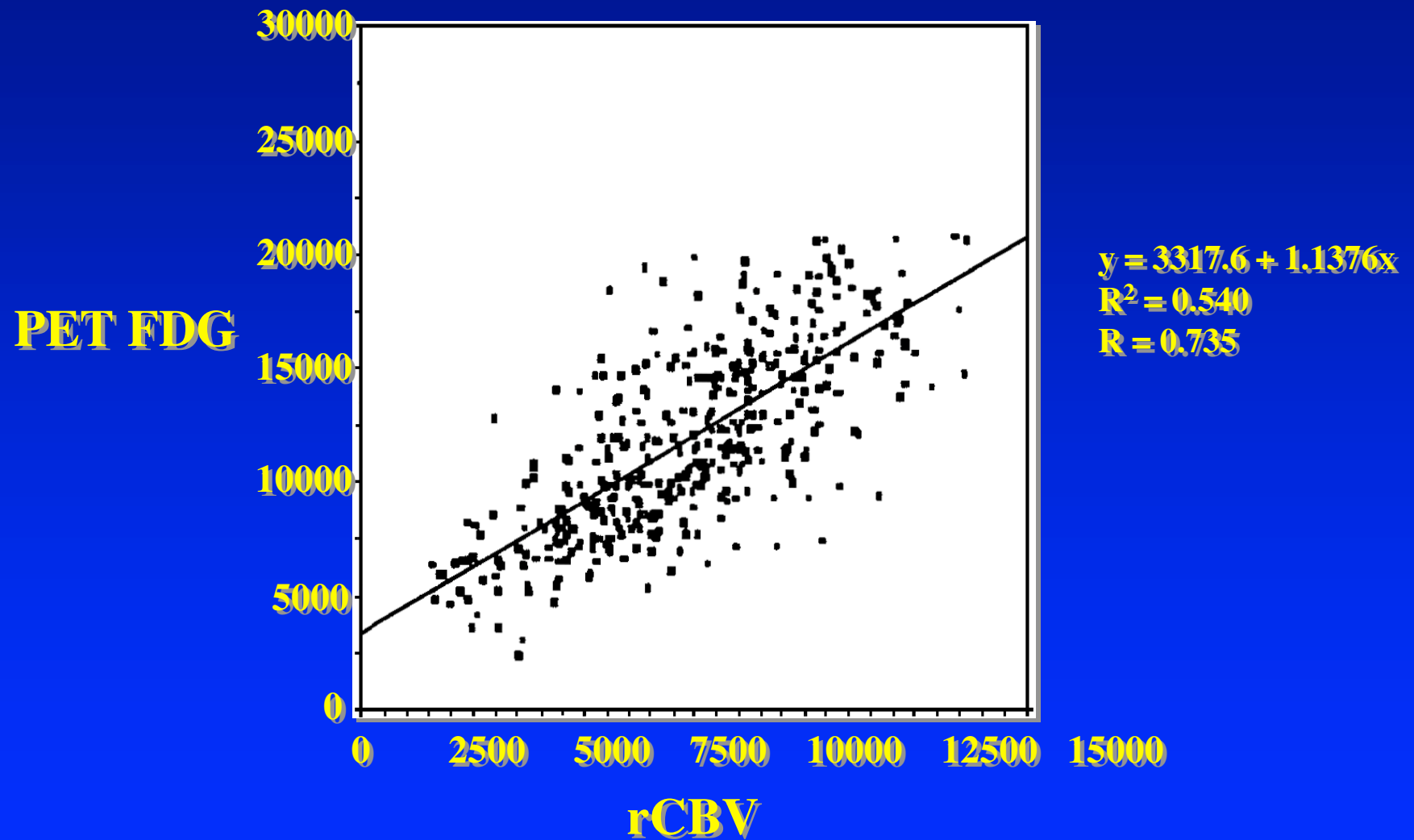
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		<u>Sensitivity</u>	<u>Specificity</u>
<u>AD vs. Normal</u>	<b>15 Studies</b> <b>414 AD Subjects</b> <b>275 Controls</b>	<b>83%</b>	<b>93%</b>
<u>AD vs. Other</u>	<b>21 Studies</b> <b>575 AD Subjects</b> <b>508 Other Diagnoses</b>	<b>77%</b>	<b>84%</b>

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**From: Masterman et al., J Geriatric Psychiatry and Neurology**

# Probable AD: fMRI vs. PET



From: González et al, 1995  
AJNR, 1763.

## HMPAO Tc-99m Brain Spect in Patients with Alzheimer's Disease

Region	Alzheimer's N=20	Control N=8	% Diff	t	P
<b>Temporo-Parietal</b>					
Left	89 ± 9	106 ± 7	16%	4.78	<0.0005
Right	86 ± 10	108 ± 8	20%	5.33	<0.001
<b>Sensory-Motor</b>					
Left	94 ± 9	100 ± 5	6%	1.77	0.09
Right	92 ± 11	103 ± 6	11%	2.17	0.05

# Dynamic Susceptibility Contrast MRI in Patients with Alzheimer's Disease

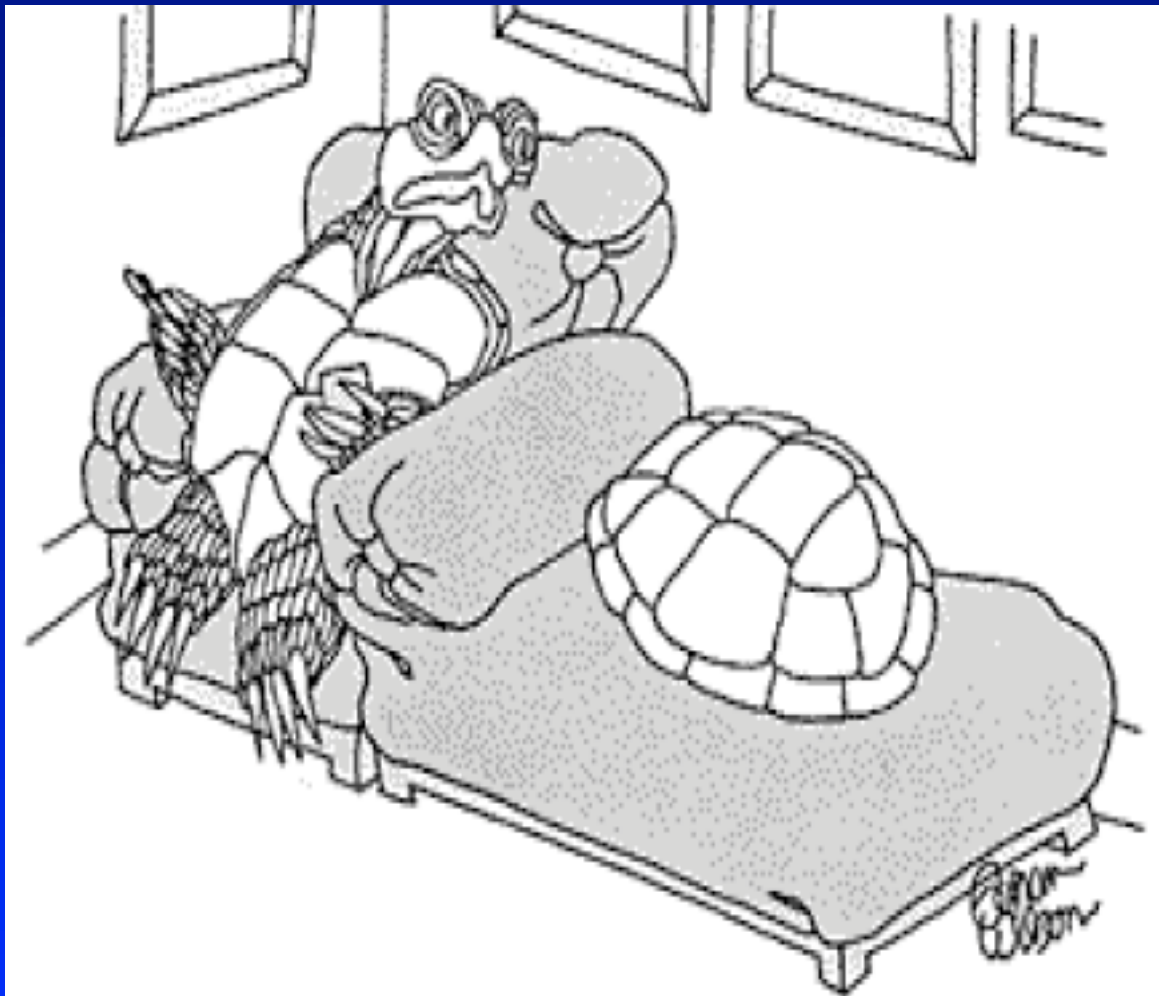
Region	Alzheimer's N=13	Control N=13	% Diff	t	P
<b>Temporo-Parietal</b>					
Left	93 ± 11	112 ± 7	17%	5.25	<0.0001
Right	94 ± 17	113 ± 7	17%	3.76	<0.001
<b>Sensory-Motor</b>					
Left	98 ± 13	106 ± 11	8%	1.88	0.07
Right	98 ± 18	108 ± 14	10%	1.61	0.12

## **fMRI – DSC MRI Limitations**

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**Data are similar to SPECT and PET measures. However, DSC MRI avoids use of radiotracers and is well tolerated as a five minute examination.**

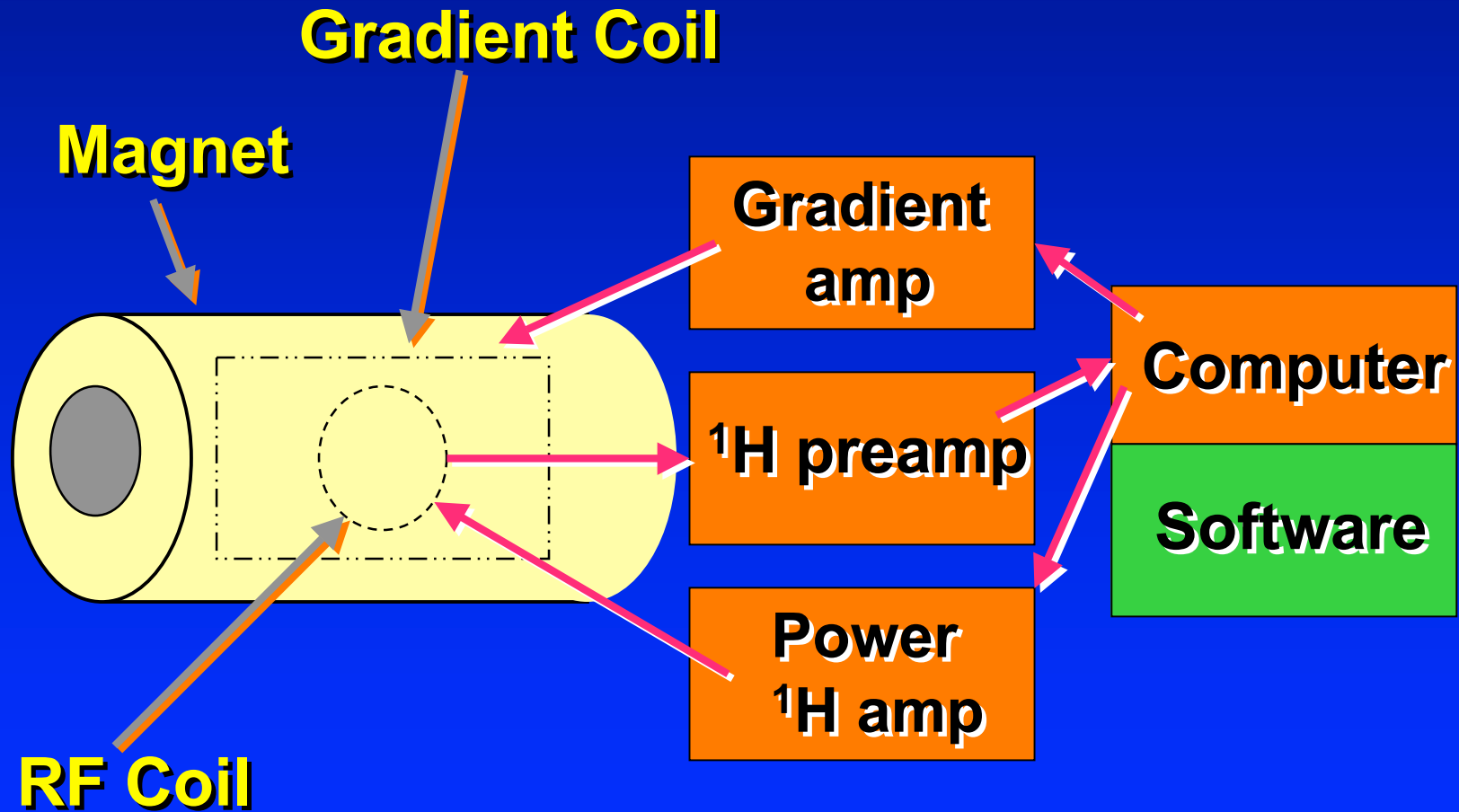
**Only limited longitudinal results are available at the present time.**



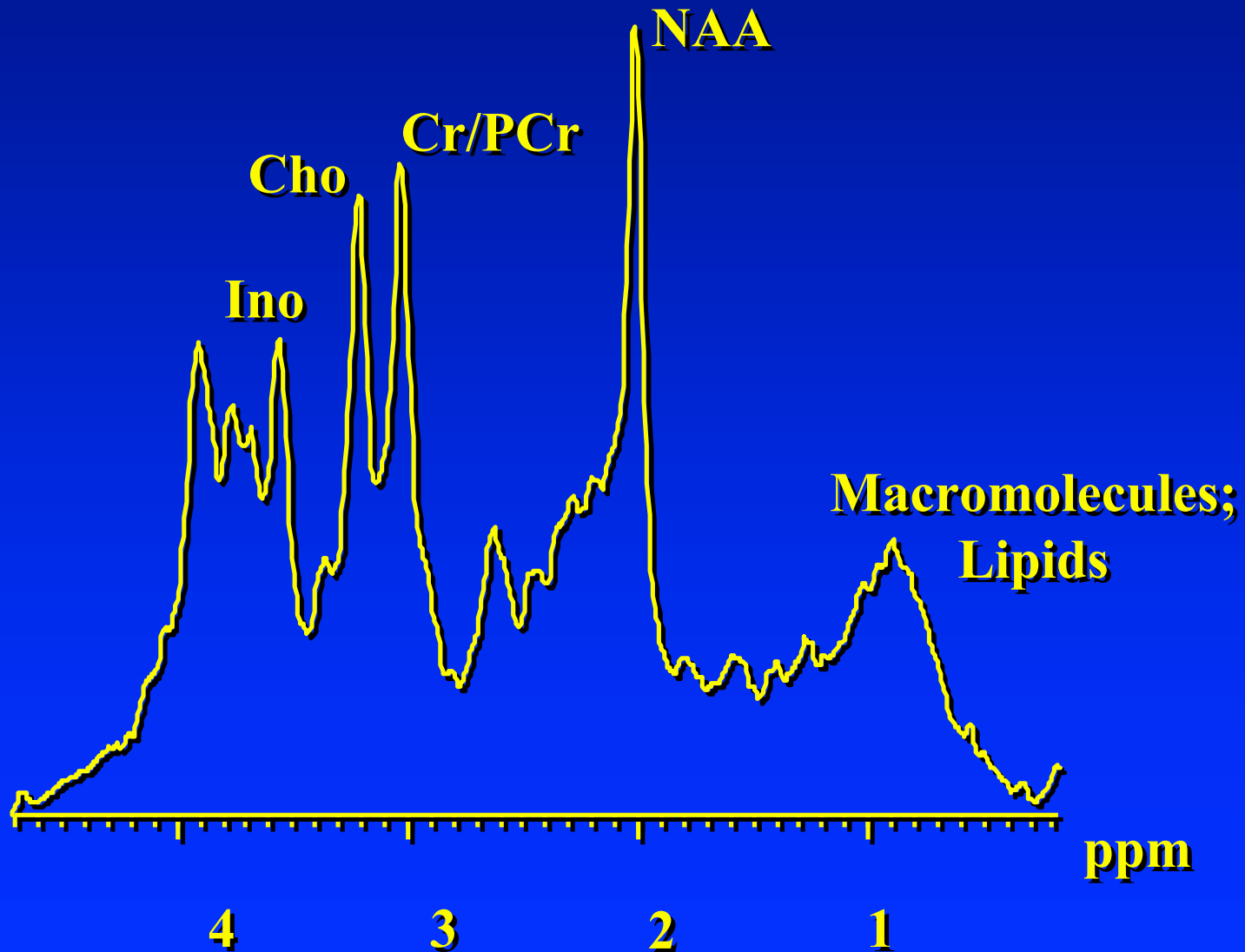
*"This is getting us nowhere!"*

**MRS Tends to Get Short Shrift**

# MR Scanner - $^1\text{H}$ MRS vs. MRI



**30 ms STEAM spectrum from an 8 cm<sup>3</sup> voxel in the left dorsolateral frontal lobe of a 35 year old male subject.**



# Schizophrenia

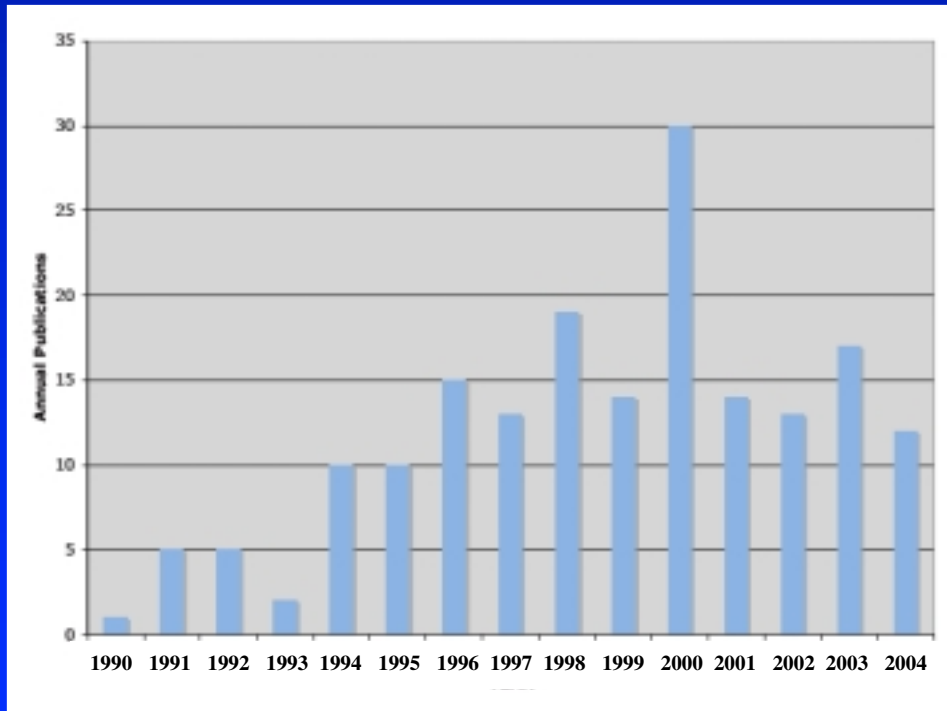
- 2.2 Million American Adults have SCZ
- SCZ affect men and women with equal frequency
- SCZ often appears earlier in men than women
- 10% commit suicide



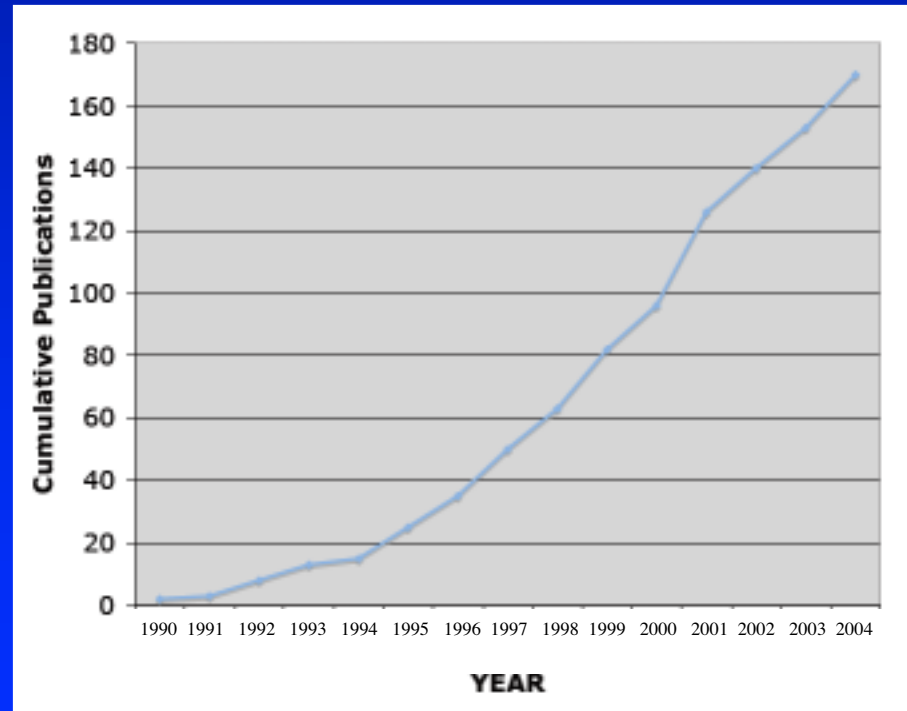
Reproduced from NIMH factsheet  
'When Someone Has Schizophrenia'

# MRS and Schizophrenia: Annual and Cumulative Publications

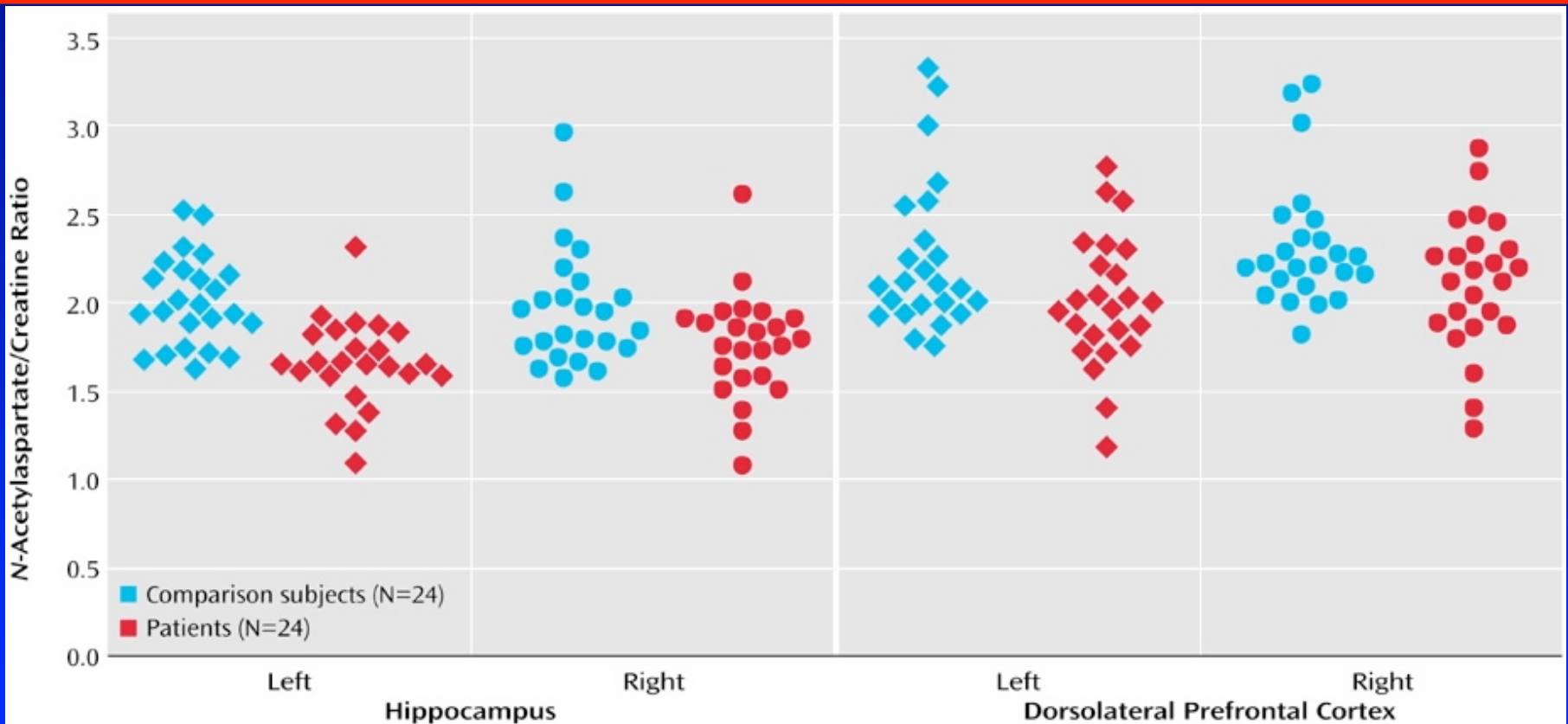
**Annual Publications**



**Cumulative Publications**



# N-Acetylaspartate in Patients With Schizophreniform Disorder



**N-Acetylaspartate/Creatine Ratios in the Hippocampus and Dorsolateral Prefrontal Cortex in Schizophreniform Disorder**

*Bertolino et al., Am J Psychiatry 2003*

# Quantitative MR Spectroscopy

$$I = c_1 \cdot N \cdot [M] \cdot V \cdot B_1(r) \cdot L \cdot \sin(\theta) \cdot \exp(-t_D/T_2^*) \cdot (1 - \exp(-TR/T_1))$$

$I$  = signal intensity

$c_1$  = constant

$N$  = number of fluorine atoms per drug molecule  
(three for DF and dNF)

$[M]$  = metabolite concentration

$V$  = volume

$B_1(r)$  = reception field distribution

$L$  = function of RF coiling loading

$\theta$  = RF excitation tip angle

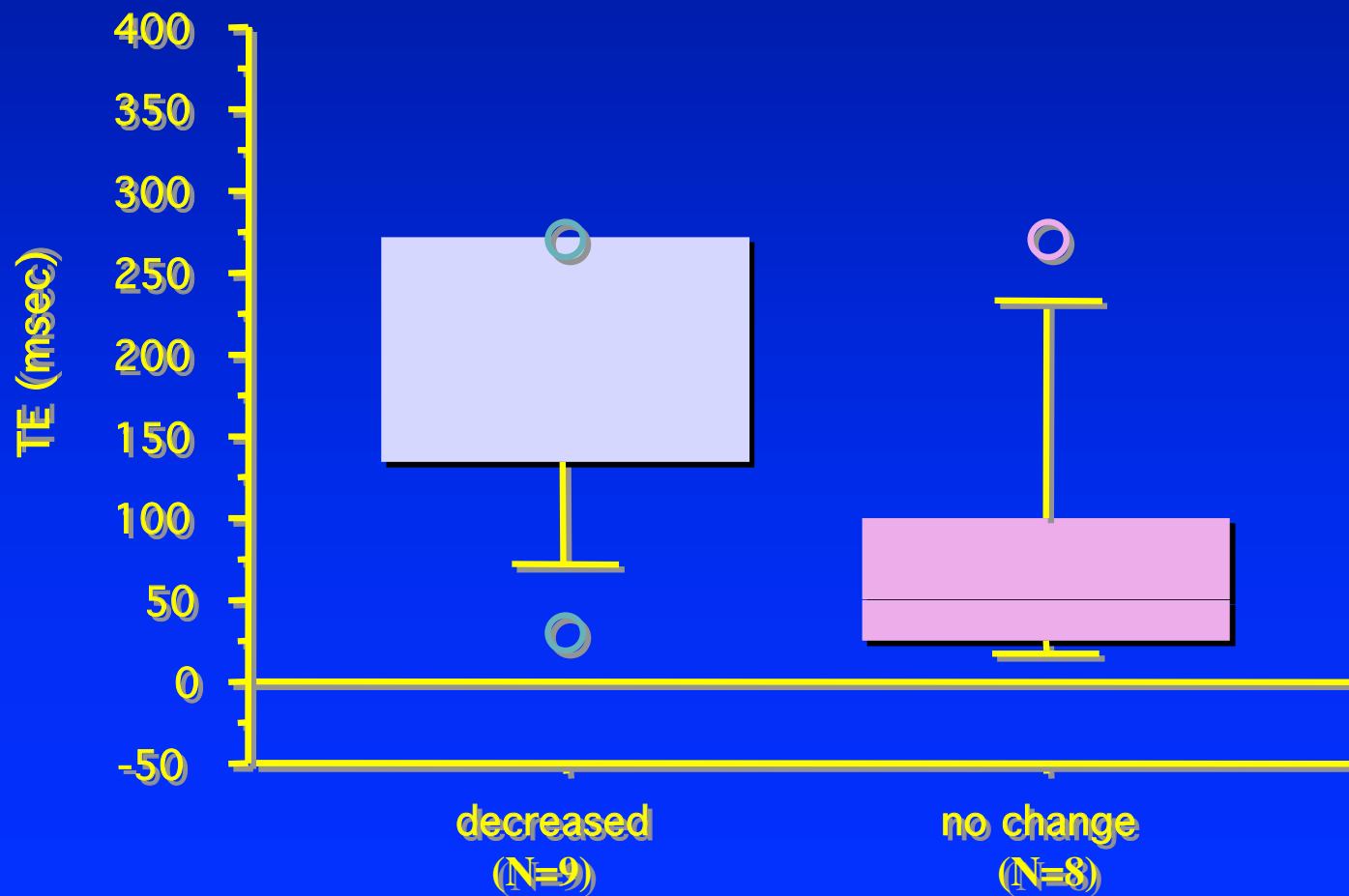
$t_D$  = acquisition delay

$T_2^*$  = spin-spin relaxation time including static field effects

$TR$  = pulse repetition time

$T_1$  = spin-lattice relaxation time

# Frontal and temporal lobe changes in NAA in schizophrenics vs. controls



**Intermittently Reported NAA Deficits in  
Schizophrenia May Reflect Changes in  
Relaxation Times**

*Ke, et al., ISMRM, 2002*

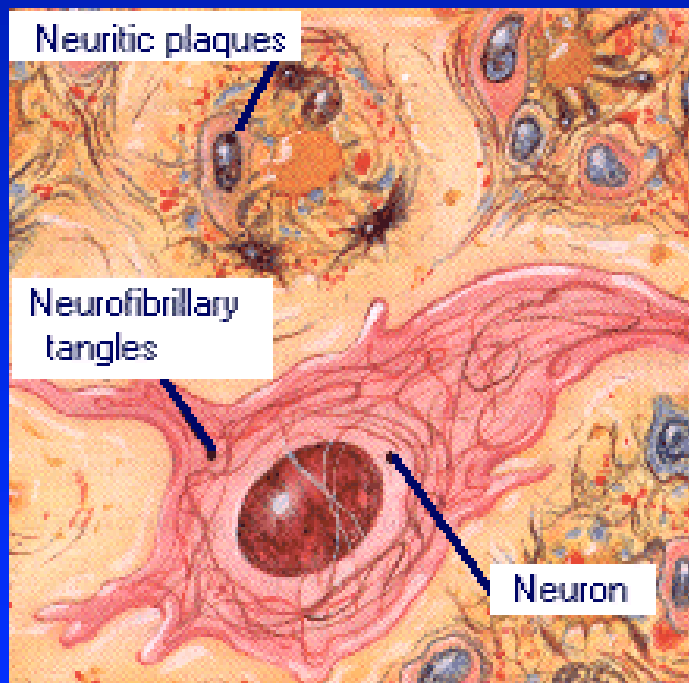
# MRS Studies following typical and atypical antipsychotics

Study	N	Method	Alterations
Braus et al 2001	SPR-typical (12) SPR-atypical (11)	<sup>1</sup> H MRS of the anterior cingulate gyrus	SPR-atypical: greater NAA levels
Braus et al 2002	SPR-typical SPR-atypical	<sup>1</sup> H MRS of the anterior cingulate gyrus Wisconsin Card Sorting Test	Duration on atypical antipsychotics is positively correlated with NAA levels and the performance in Wisconsin Card Sorting test
Goff et al 2002	SPR (10)	Medication changed from haloperidol to olanzapine <sup>1</sup> H-MRS of cingulate cortex	Subjects with improvement in negative symptom showed an increase in glutamate concentrations
Rieheman et al 2002	SPR(72) NC (32)	Retrospective evaluation of 3 studies of <sup>31</sup> P-MRS	Modified pH value was found only in SPR treated with the atypical neuroleptic clozapine

SPR-typical: Schizophrenia subjects who are taking typical antipsychotics, SPR-atypical: Schizophrenia subjects who are taking atypical antipsychotics, NC: normal control

# Alzheimer's Disease

- 4 Million Americans are affected

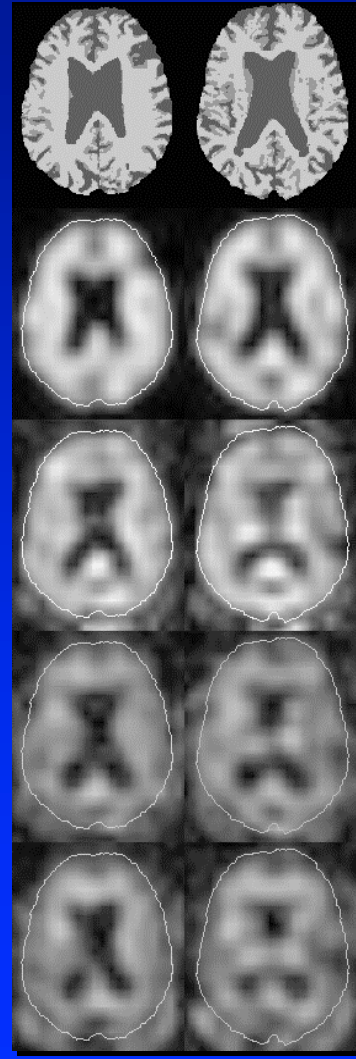
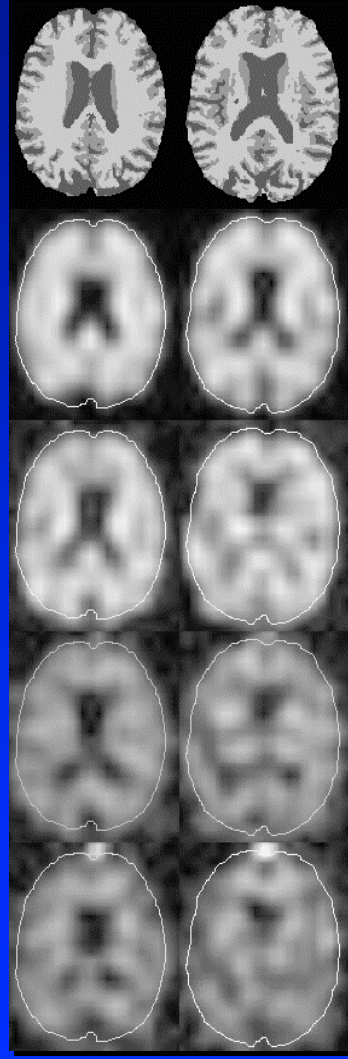
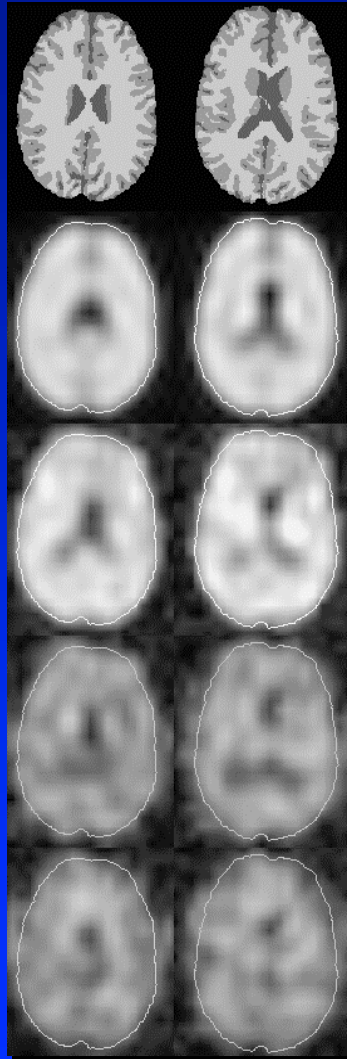


- Progressive and Neurodegenerative Brain Disorder
- Effects memory, reason, judgment, language, and the ability to carry out tasks

# Young Control

# Elderly Control

# Alzheimer's Disease



Segmented image

Low-pass tissue image

NAA image

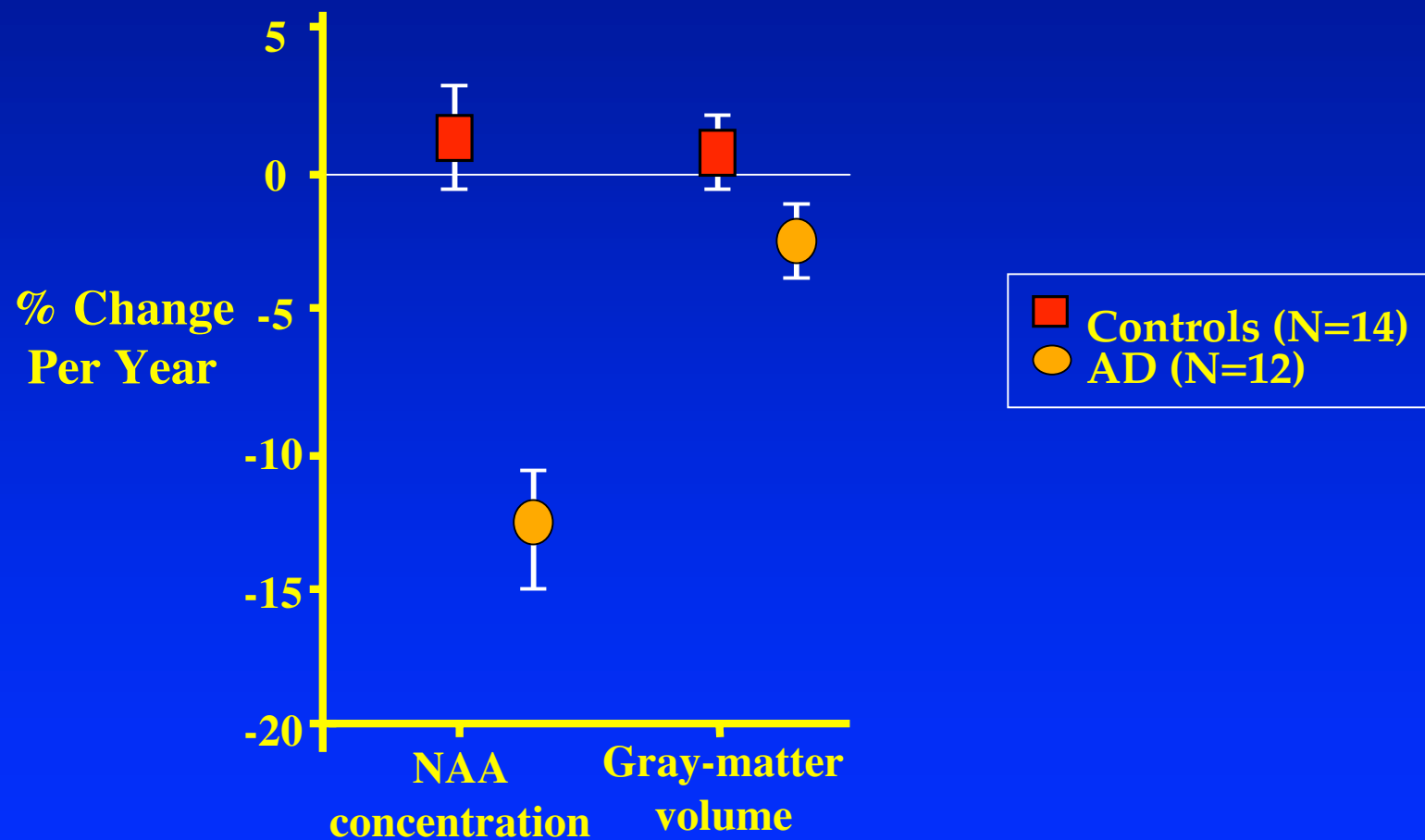
Creatine image

Choline image



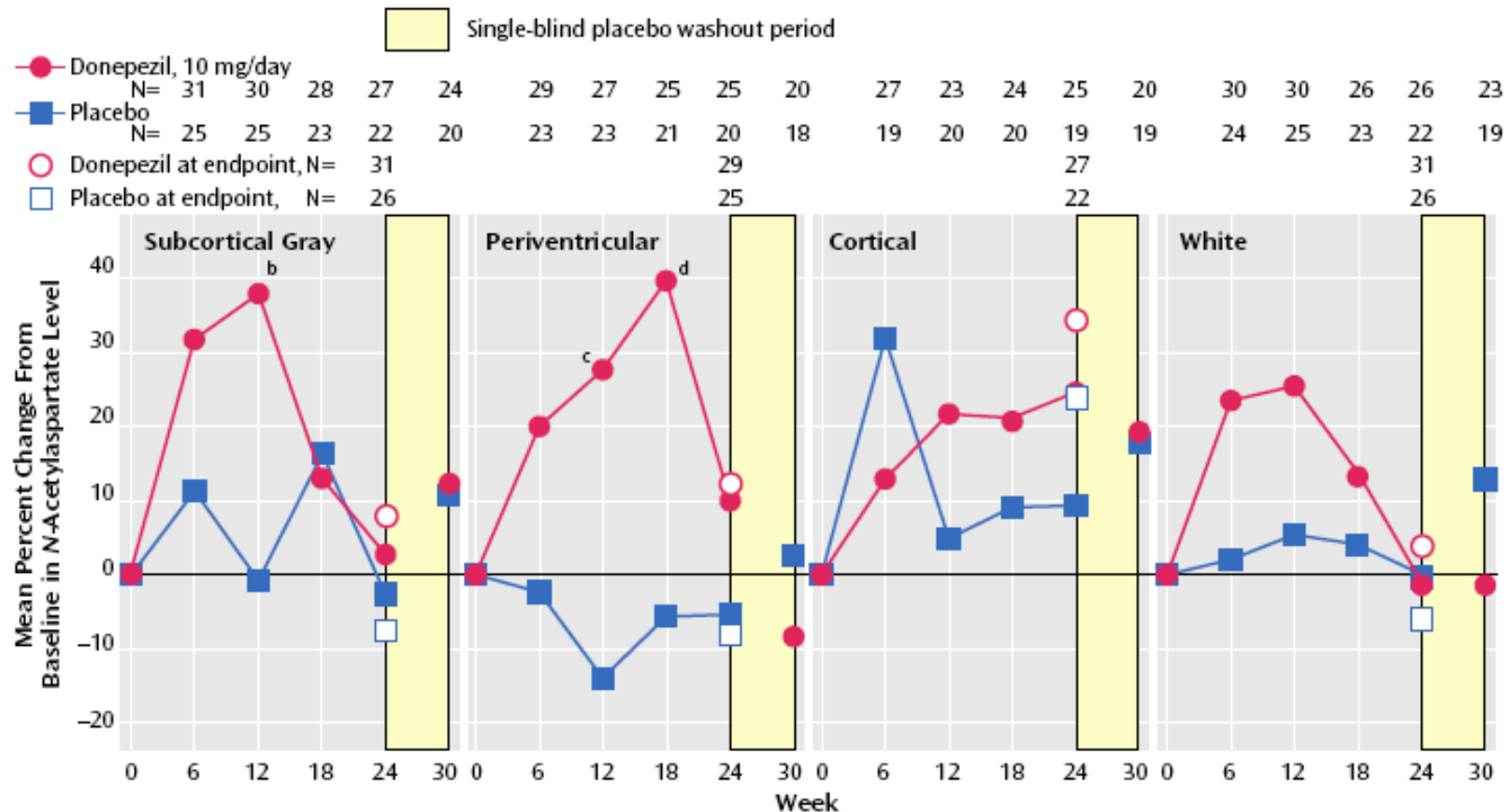
A. Pfefferbaum

# Gray-Matter NAA and Volume Change



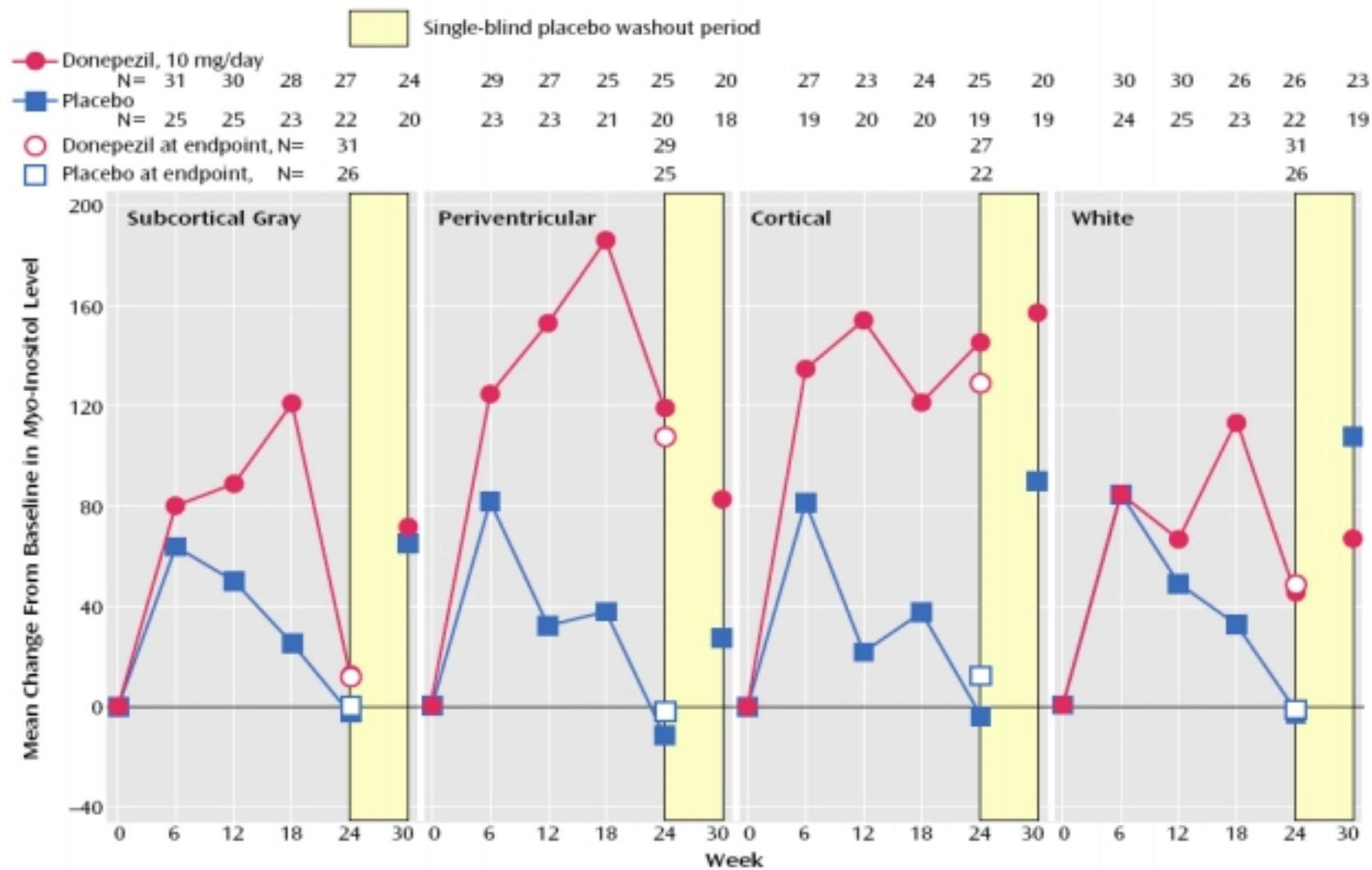
Reproduced - Adalsteinsson E. et al., 2000

# Change from Baseline in N-Acetylaspartate Concentrations in the Subcortical Gray, Periventricular, Cortical, and White Matter Areas of the Brain of Patients with Alzheimer's Disease Randomly Assigned to 24 Weeks of Double-Blind Treatment with Donepezil<sup>a</sup> or Placebo



<sup>a</sup> Dose=5 mg/day for the first 28 days and 10 mg/day thereafter.  
<sup>b</sup> Significant difference between groups (p<0.03, unpaired t test).  
<sup>c</sup> Significant difference between groups (p<0.02, unpaired t test).  
<sup>d</sup> Significant difference between groups (p<0.03, unpaired t test).

# Change From Baseline in Myo-Inositol Concentrations in the Subcortical Gray, Periventricular, Cortical, and White Matter Areas of the Brain of Patients with Alzheimer's Disease Randomly Assigned to 24 Weeks of Double-Blind Treatment Donepezil or Placebo



<sup>a</sup> Dose=5 mg/day for the first 28 days and 10 mg/day thereafter.

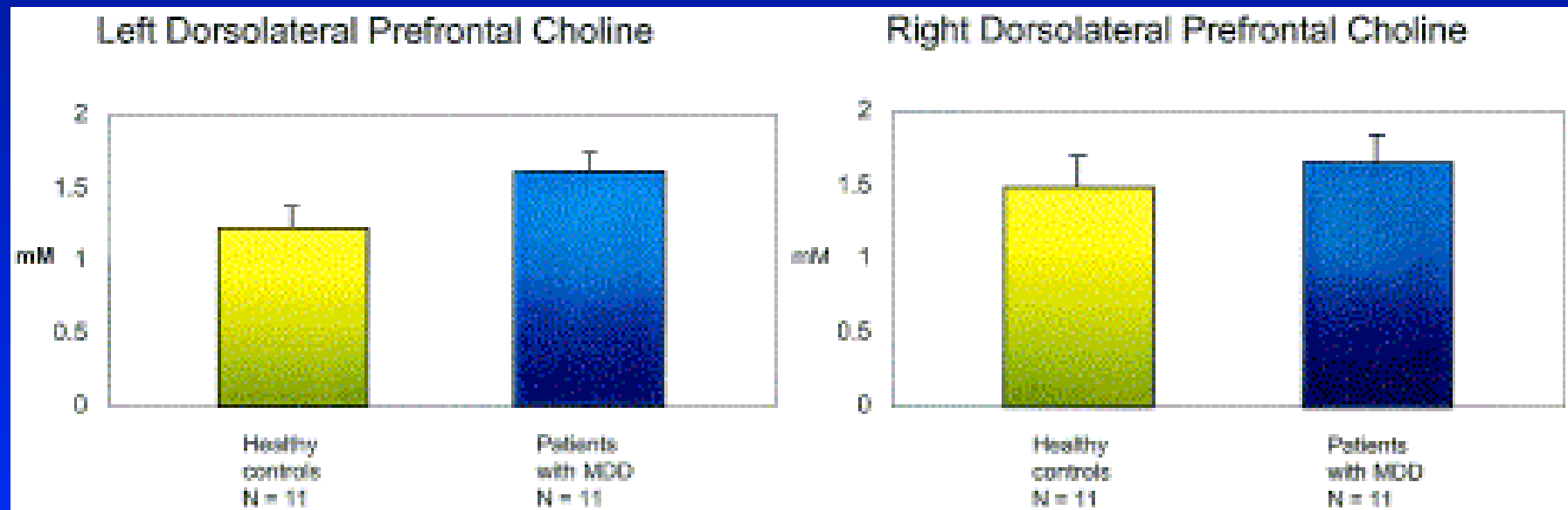
*Krishnan et al., 2003*

# Major Depression

- Second most morbid condition worldwide
- Prevalence 5-20% (F >> M)
- Affects mood, sleep, interest, guilt, energy, concentration, appetite, activity
- Rx generally effective, limited by side effects



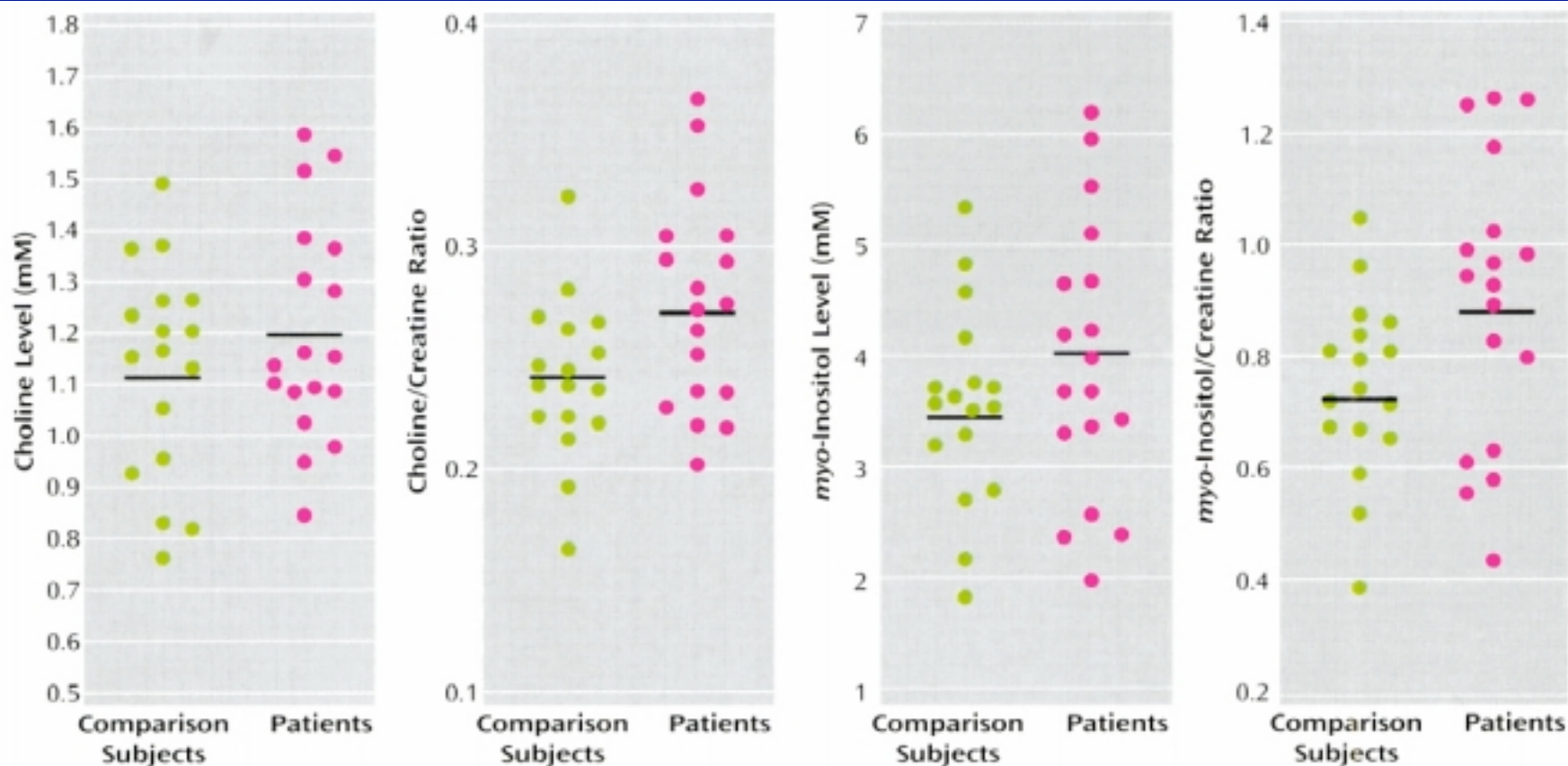
# Dorsolateral prefrontal cortex choline in pediatric major depressive disorder



**Left but not right dorsolateral prefrontal cortex choline concentrations are significantly elevated in pediatric MDD patients versus control subjects.**

*Farchione et al., Biol Psychiatry 2002*

## Frontal White Matter Biochemical Abnormalities in Late-Life Major Depression Detected With $^1\text{H}$ -MRS

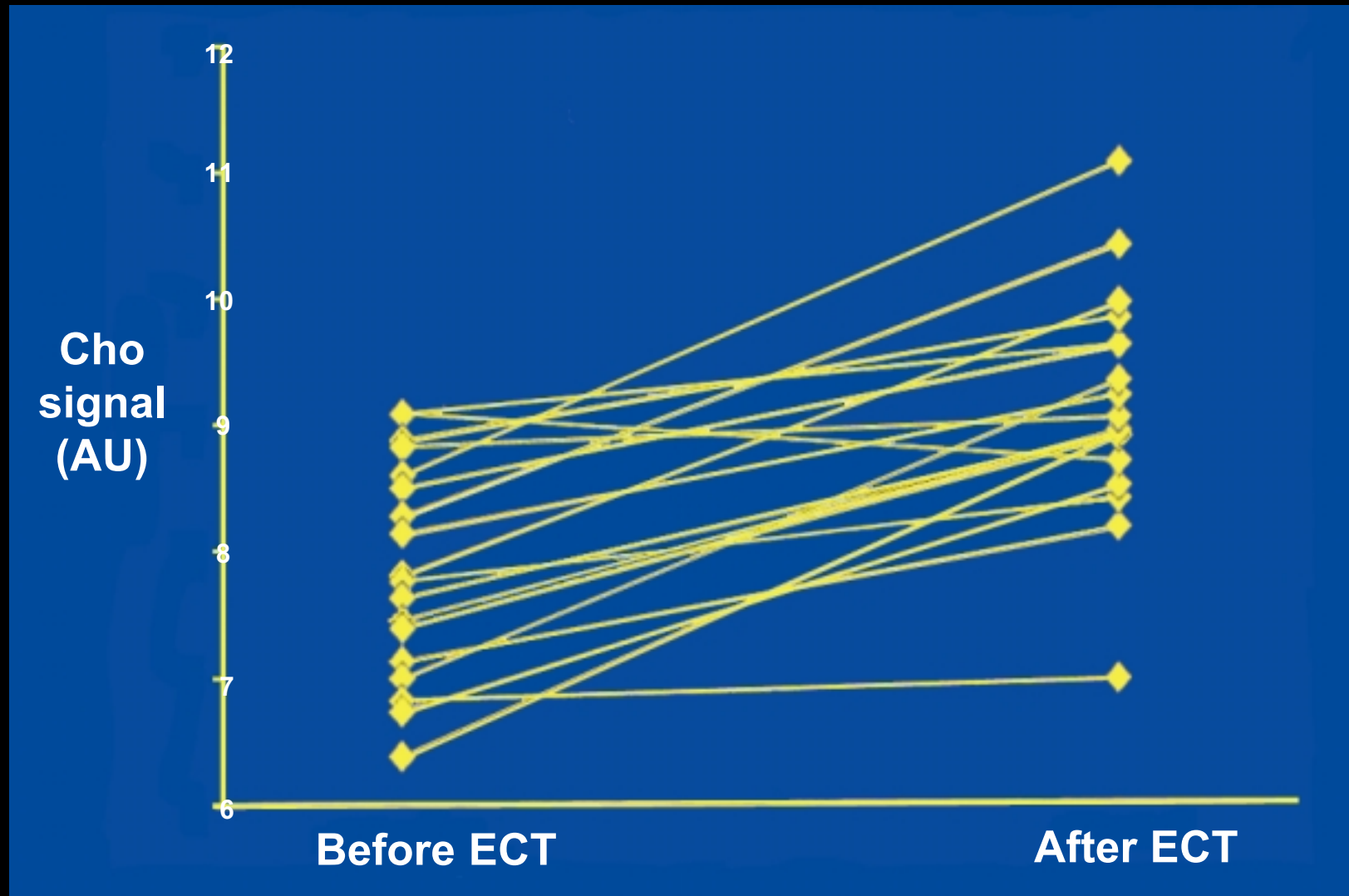


<sup>a</sup> Scatterplots represent data from only those subjects with high-quality spectra for the region of interest.

*myo*-Inositol/creatine and choline/creatine ratios were significantly higher in the frontal white matter in the major depression group

*Kumar et al.,  
Am J Psychiatry 2002*

# Individual Choline-containing Compound (Ch) Signals (N=18)

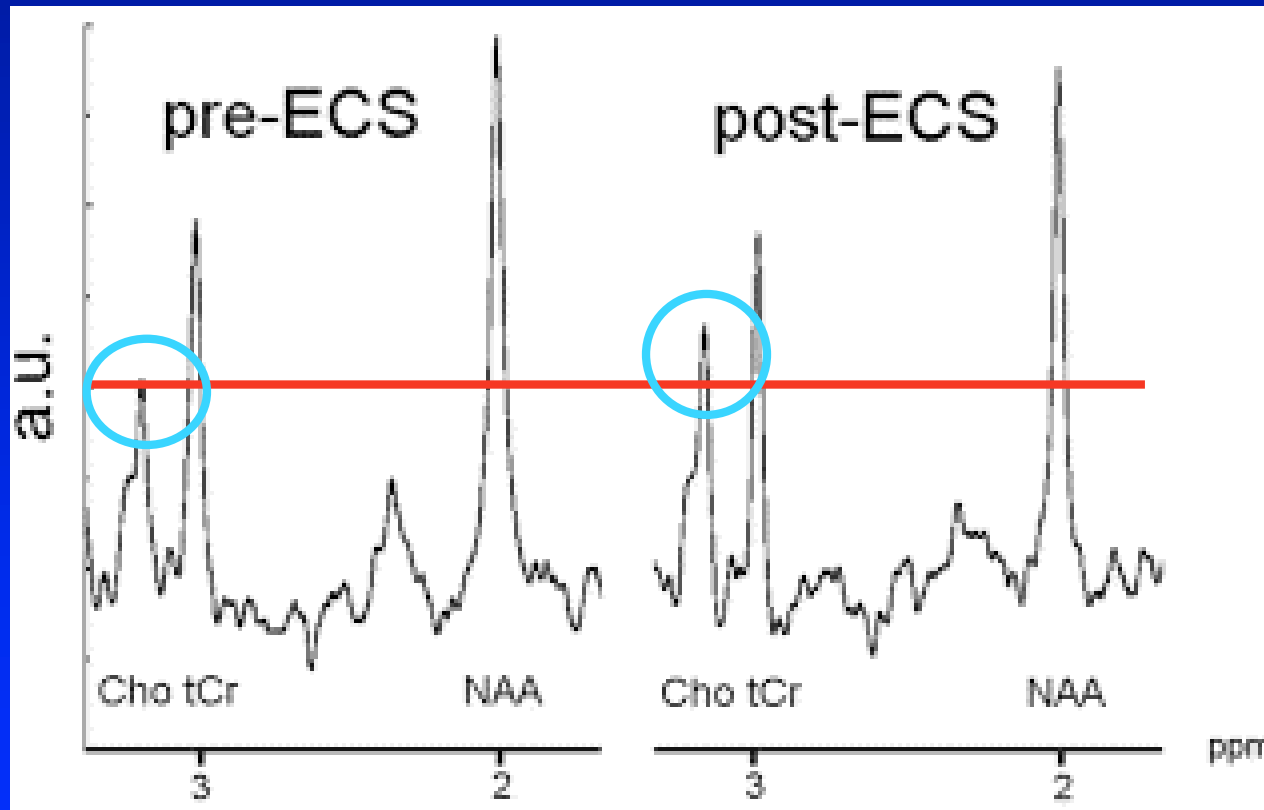


AU = arbitrary units

2 data pairs were acquired during 2 successive courses of ECT in one patient.

*Ende G, et al., 2000*

# Choline rise in the rat hippocampus induced by electroconvulsive shock treatment



Typical hippocampal  $^1\text{H}$ -MRS with marked choline (Cho), total creatine (tCr), and N-acetylaspartate (NAA) peaks pre- and post- ECS.

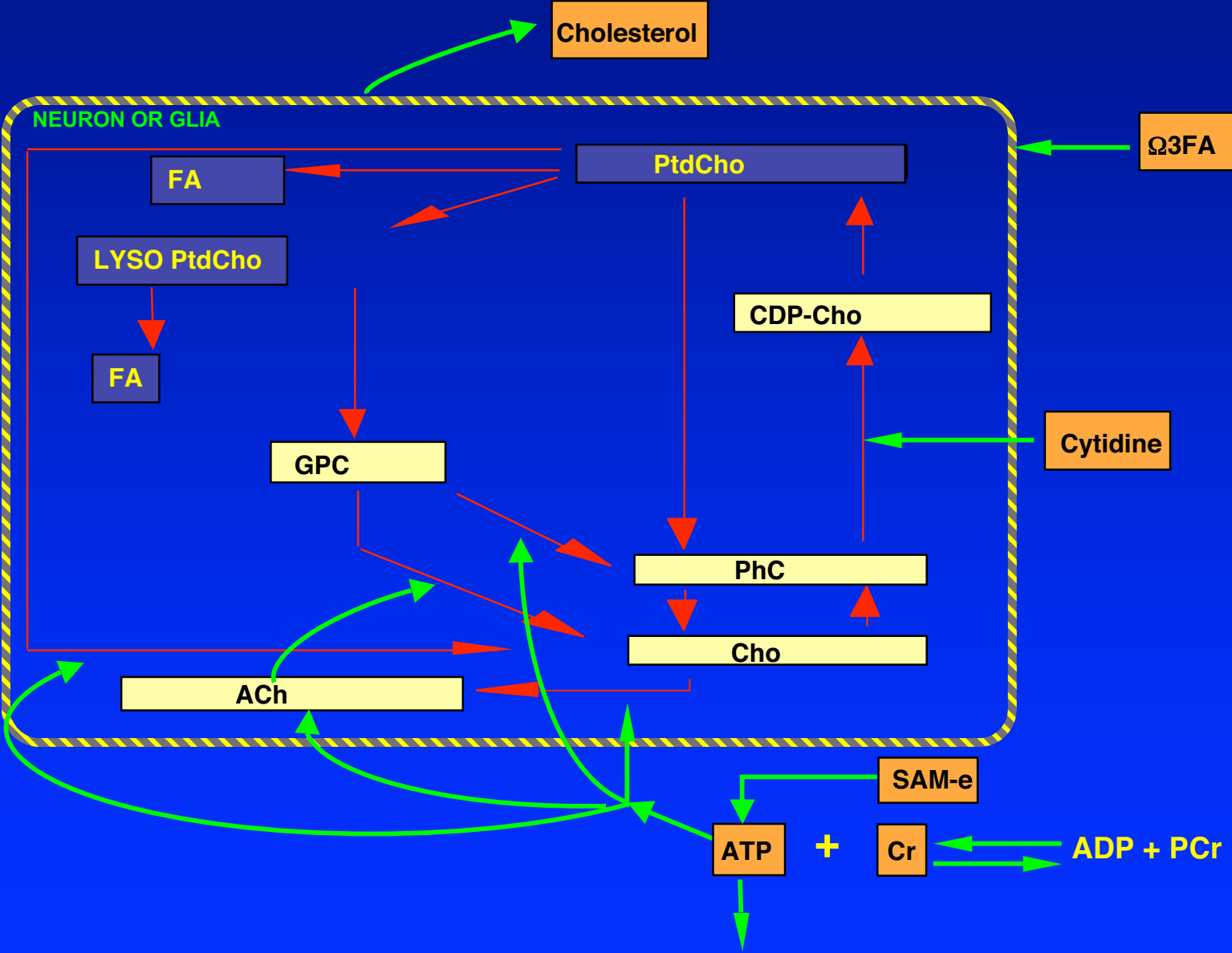
# MRS Studies of Mood Disorders

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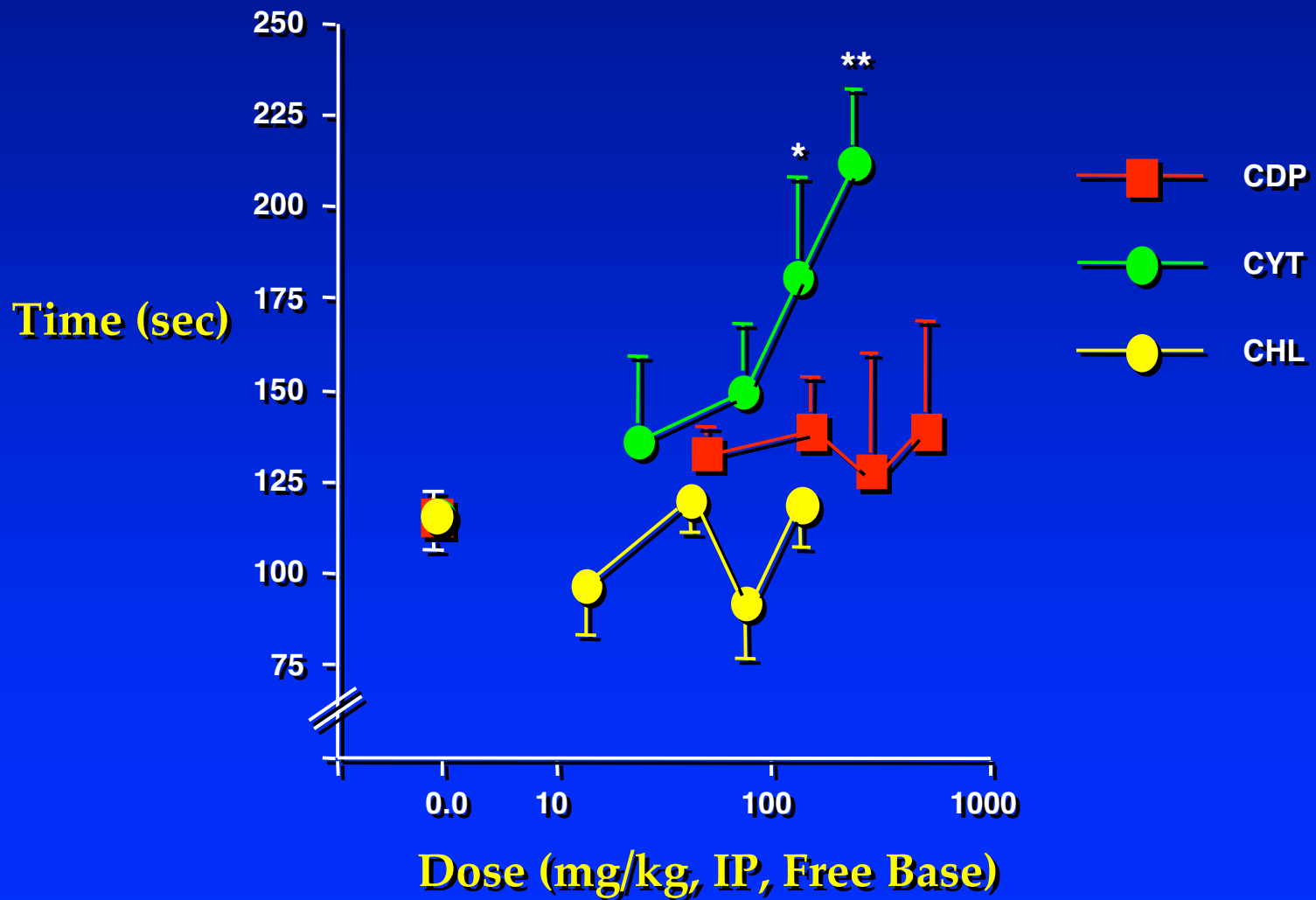
Factors which may alter Cho/PME:

1. Cell signaling (PtdCho hydrolysis)
2. Glucose metabolism
3. Thyroid hormone
4. Cortisol
5. Medications

# Novel Treatment Strategies for Mood Disorders



# Latency to Immobility



Carlezon et al., 2001.

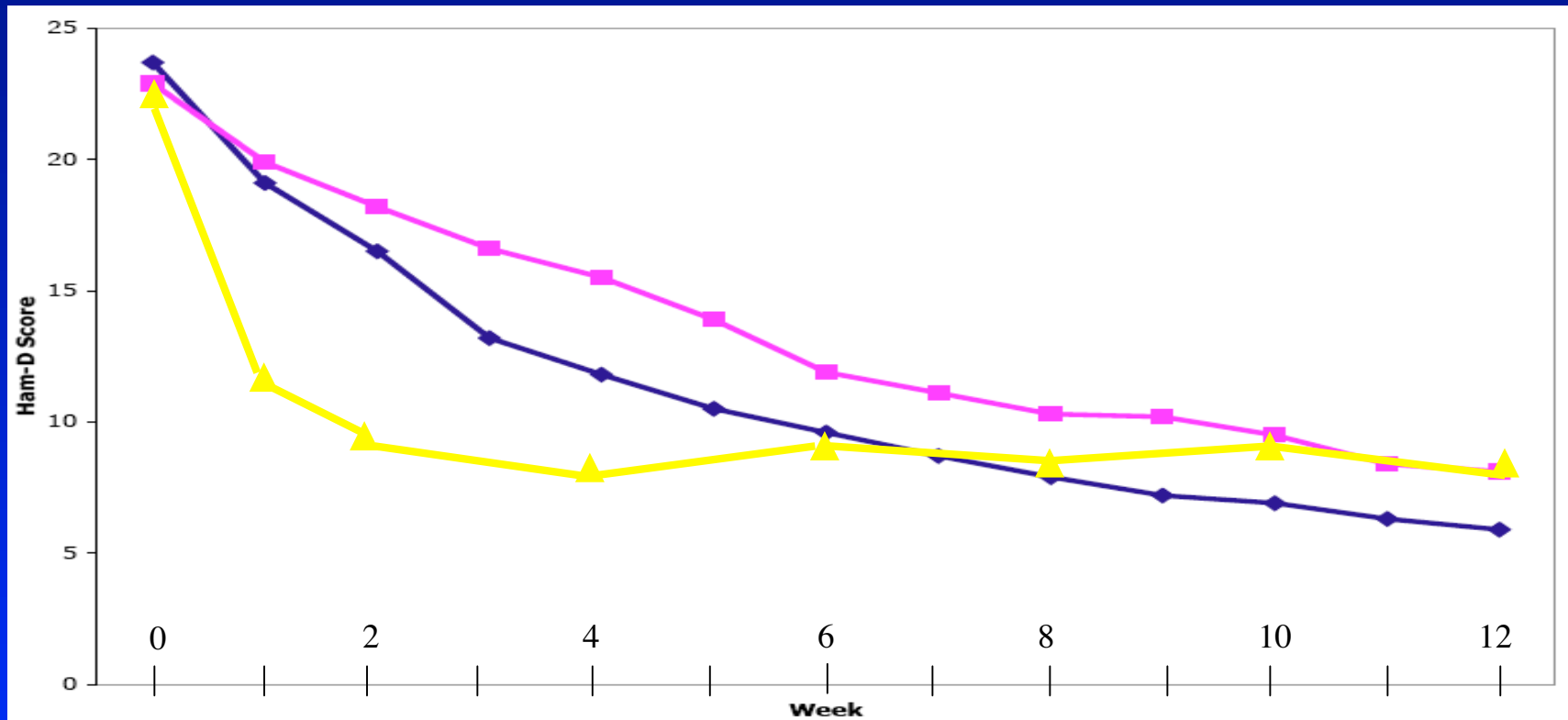
# **Cytidine Trial**

## **McLean- Seoul National University**

---

- 65 depressed subjects with bipolar disorder studied
- Treatment A: 33 subjects receiving cytidine;  
Treatment B: 32 subjects receiving placebo
- 12-week study
- Magnetic resonance scans at baseline, 2, 4, and 12 weeks.

## Comparison of HAM-D score changes with treatment: Lyoo et al., in progress; Winsberg et al., 2001)



▲ --> Divalproex sodium treatment (Winsberg et al., 2001)

◆ --> Treatment A (Lyoo et al., in progress): Cytidine and Divalproex combination

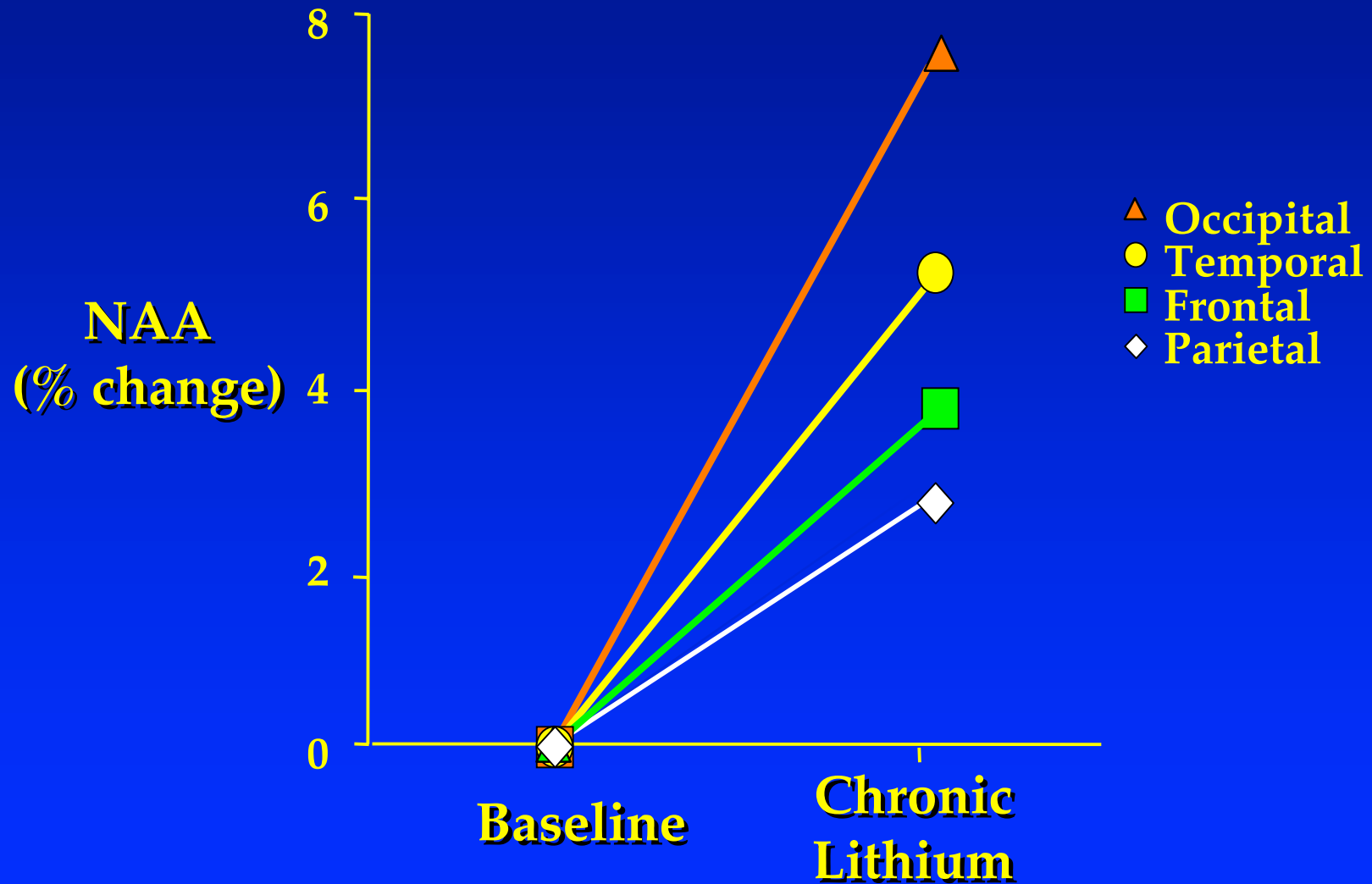
■ --> Treatment B (Lyoo et al., in progress): Divalproex only

# Bipolar Disorder

- Affects 2.3 Million adult Americans
- Severe depressions and manias
- Associated with increased IQ, creativity
- Suicide occurs in 10-15% of patients
- Rx of lithium and anticonvulsants

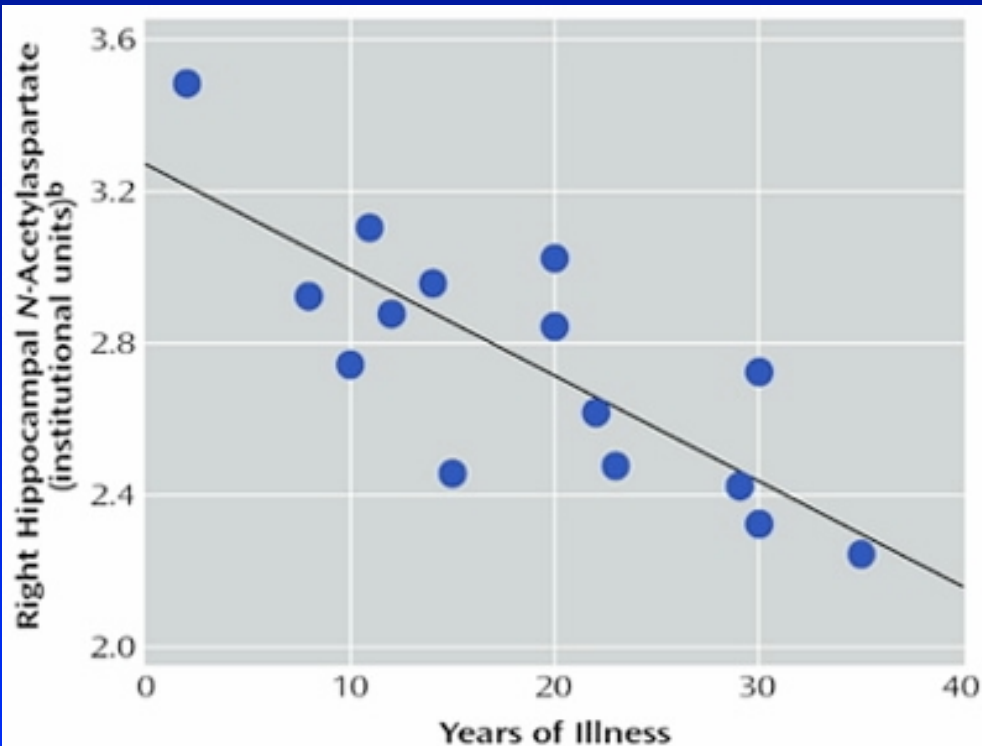


# NAA Increases On A Regional Basis



*Reproduced - Moore GJ et al., 2000*

# Lower Concentration of Hippocampal *N*-Acetylaspartate in Familial Bipolar I Disorder



<sup>a</sup>  $r = -0.66$ ,  $N = 15$ ,  $p = 0.003$ , adjusted for the effect of age.

<sup>b</sup> Institutional units = metabolite intensity per tissue volume. Metabolite intensity is the area under the metabolite resonance curve, including corrections for instrumental variables (such as receiver gain and differential head coil loading). Tissue volume is the amount of brain tissue enclosed in an MRS voxel.

**Correlation Between Right Hippocampal *N*-Acetylaspartate Concentration and Years of Illness in Euthymic Male Outpatients With Bipolar I Disorder**

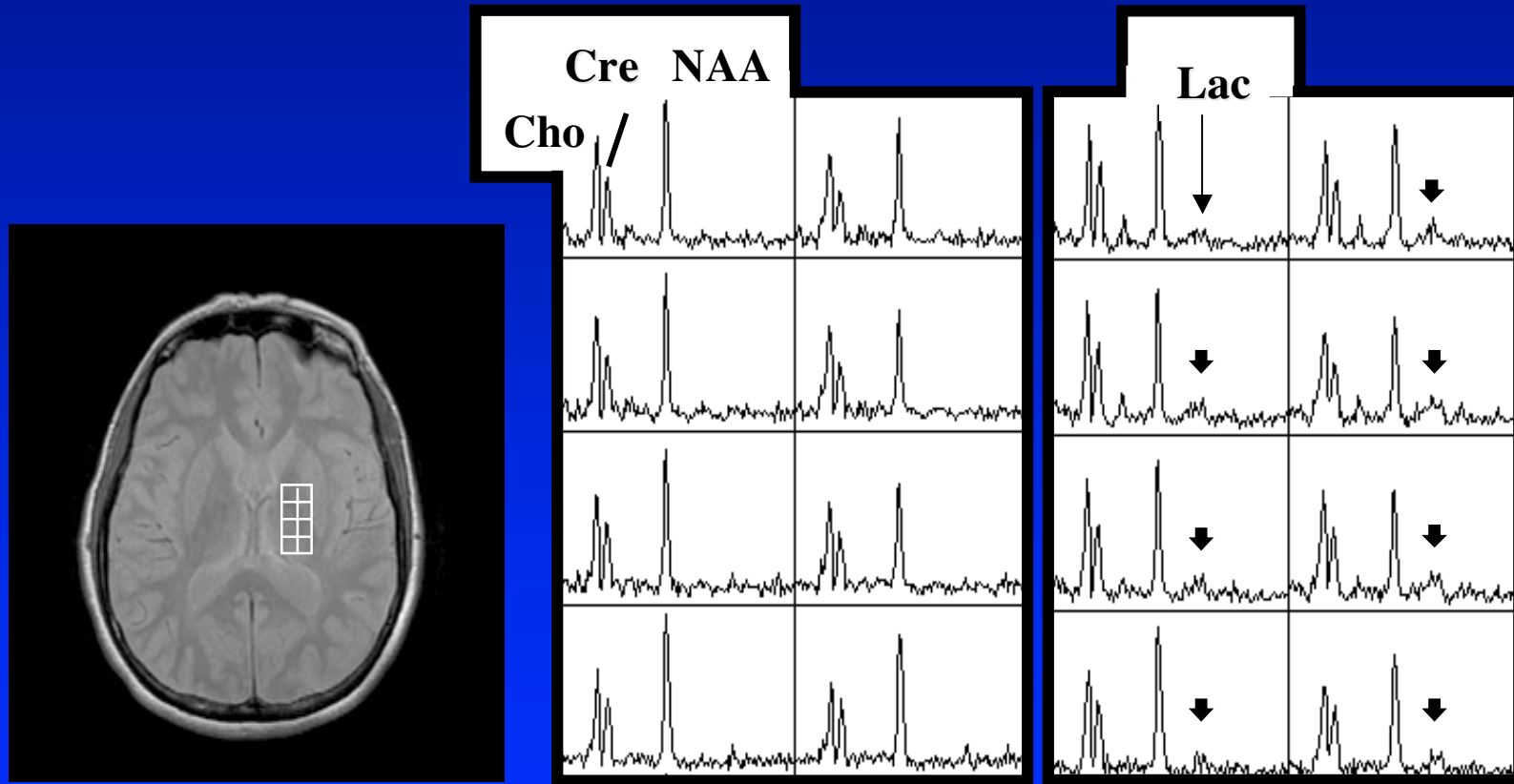
*Deicken et al., Am J Psychiatry 2003*

# Panic Disorder

- Unexpected and repeated episodes of intense fear accompanied by physical symptoms
- 2.4 Million Americans have panic disorder
- Women are twice as likely as men to develop panic disorder
- Typically strikes in young adulthood



# Lactate Response to Infusion

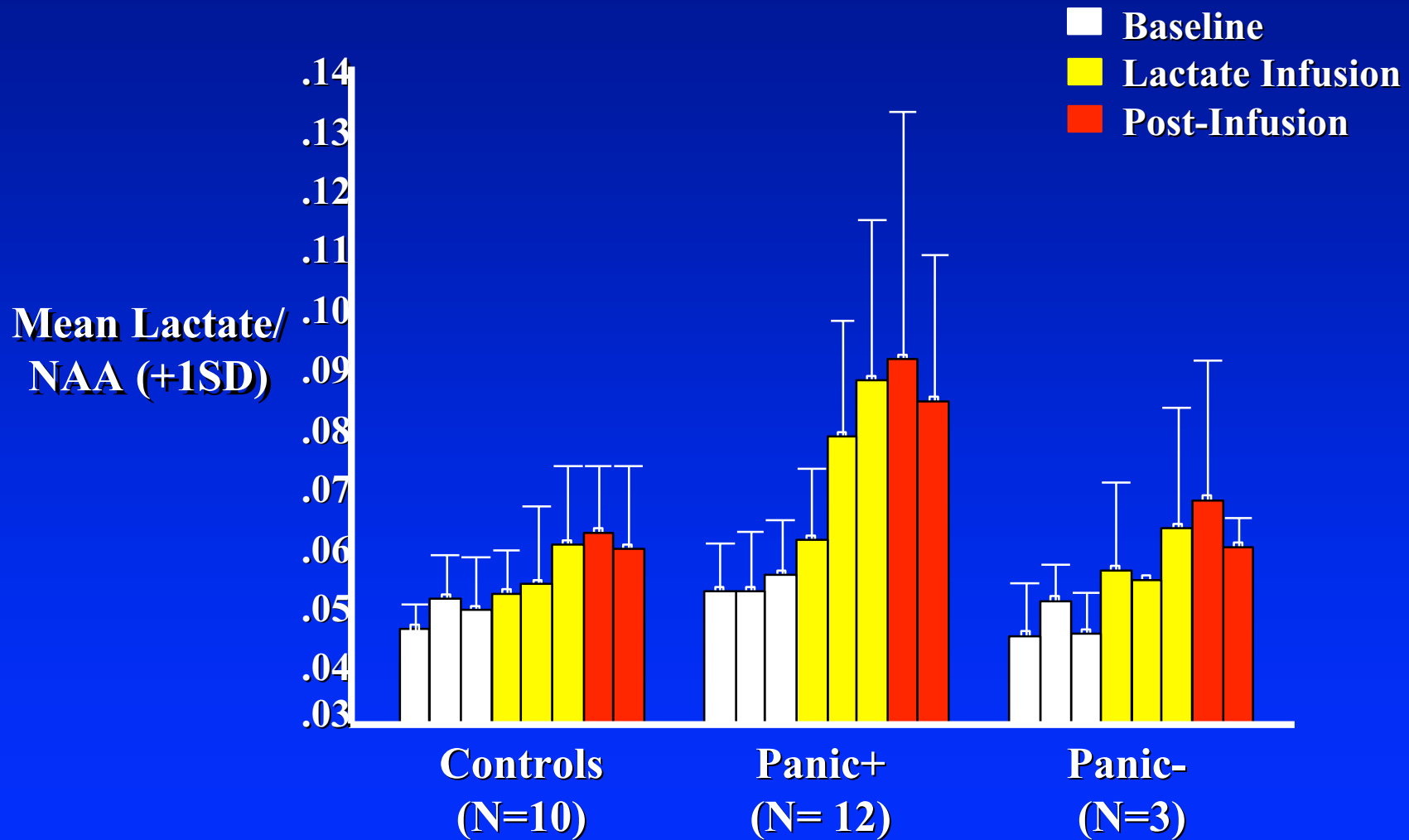


Baseline  
(Scan 3)

Post-Infusion  
(Scan 7)

Dager et al. Arch Gen Psych 1999

# Global Brain Lactate/NAA Response



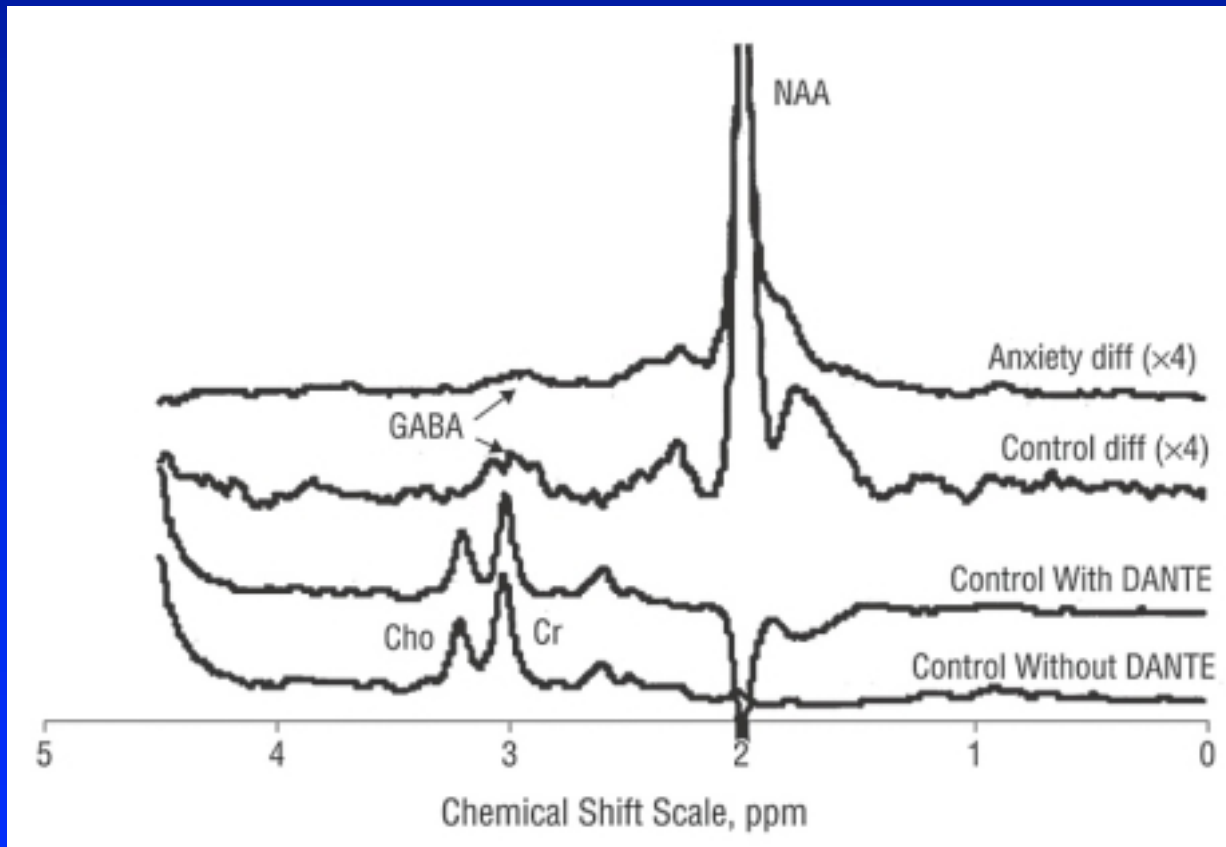
Dager et al. Arch Gen Psych 1999

# Reductions in Occipital Cortex GABA Levels in Panic Disorder detected with $^1\text{H}$ -MRS

GABA spectra from a control subject and a patient with panic disorder.

Top 2 traces, Subtraction spectra (control and patient) highlighting the GABA peaks.

Bottom 2 traces, Control spectra with and without application of the DANTE (Delays-Alternating with Nutations-for Tailored Excitation) pulse.



*Cho indicates choline; Cr, creatine; NAA, N-acetylaspartate; and diff, difference.*

*Goddard et al., Arch Gen Psychiatry 2002*

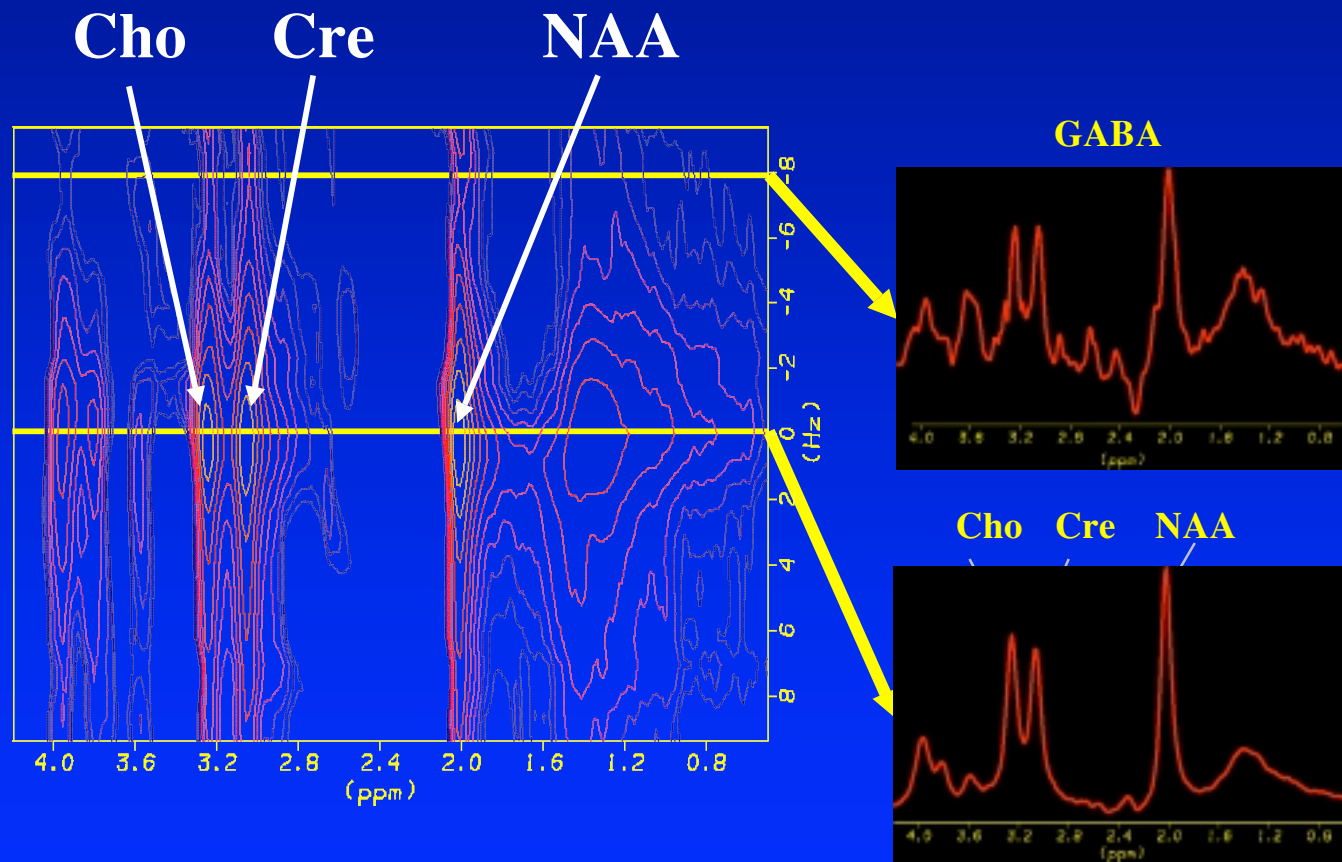
# **$^1\text{H}$ MRS**

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## ***Key Findings - GABA***

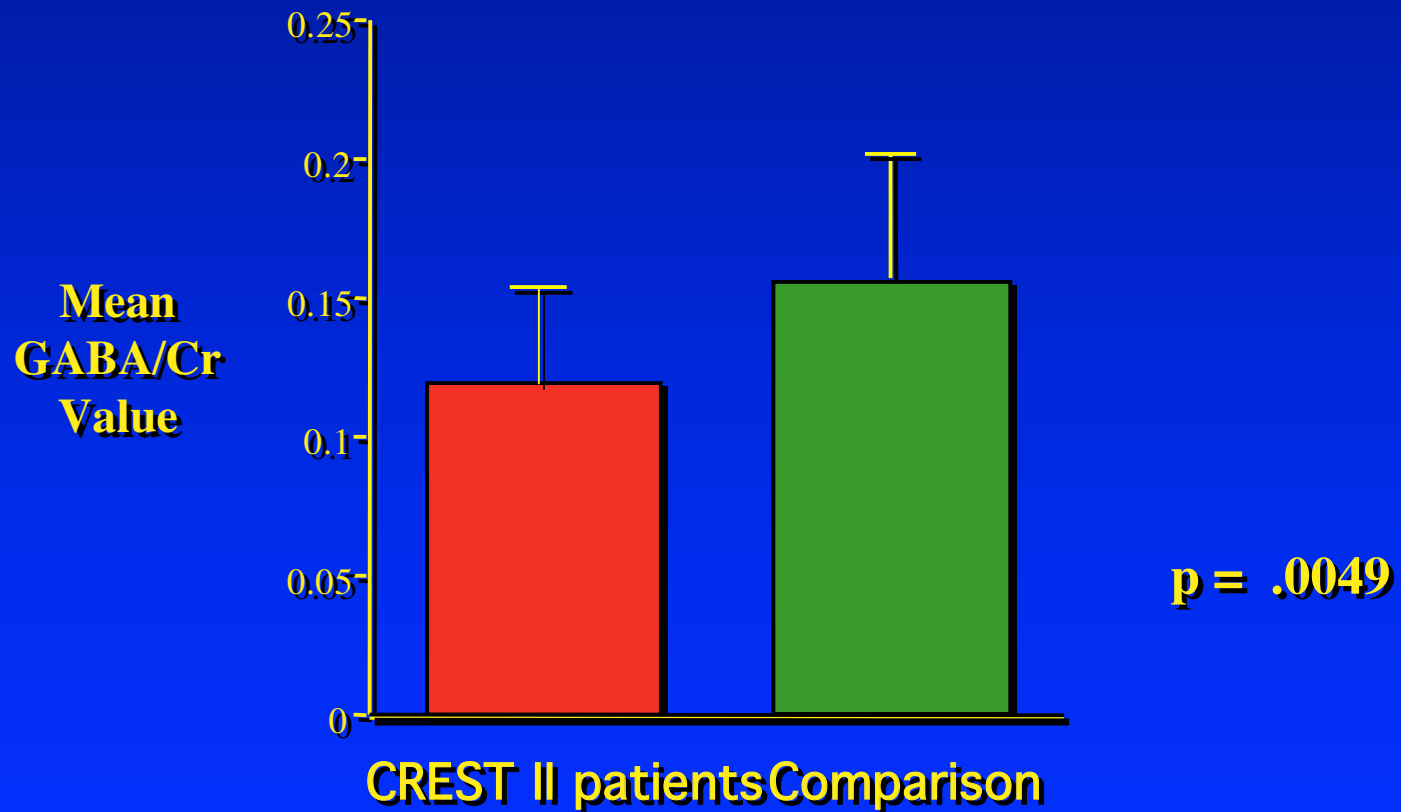
- **Pioneered by Yale investigators**
- **Much easier at higher field strength**
- **Levels are decreased in depression, anxiety disorders, alcoholism, cocaine dependence**
- **Pharmacotherapy alters levels**

# J-resolved 2D MRS of Prefrontal Lobe of a Cocaine Dependent Subject

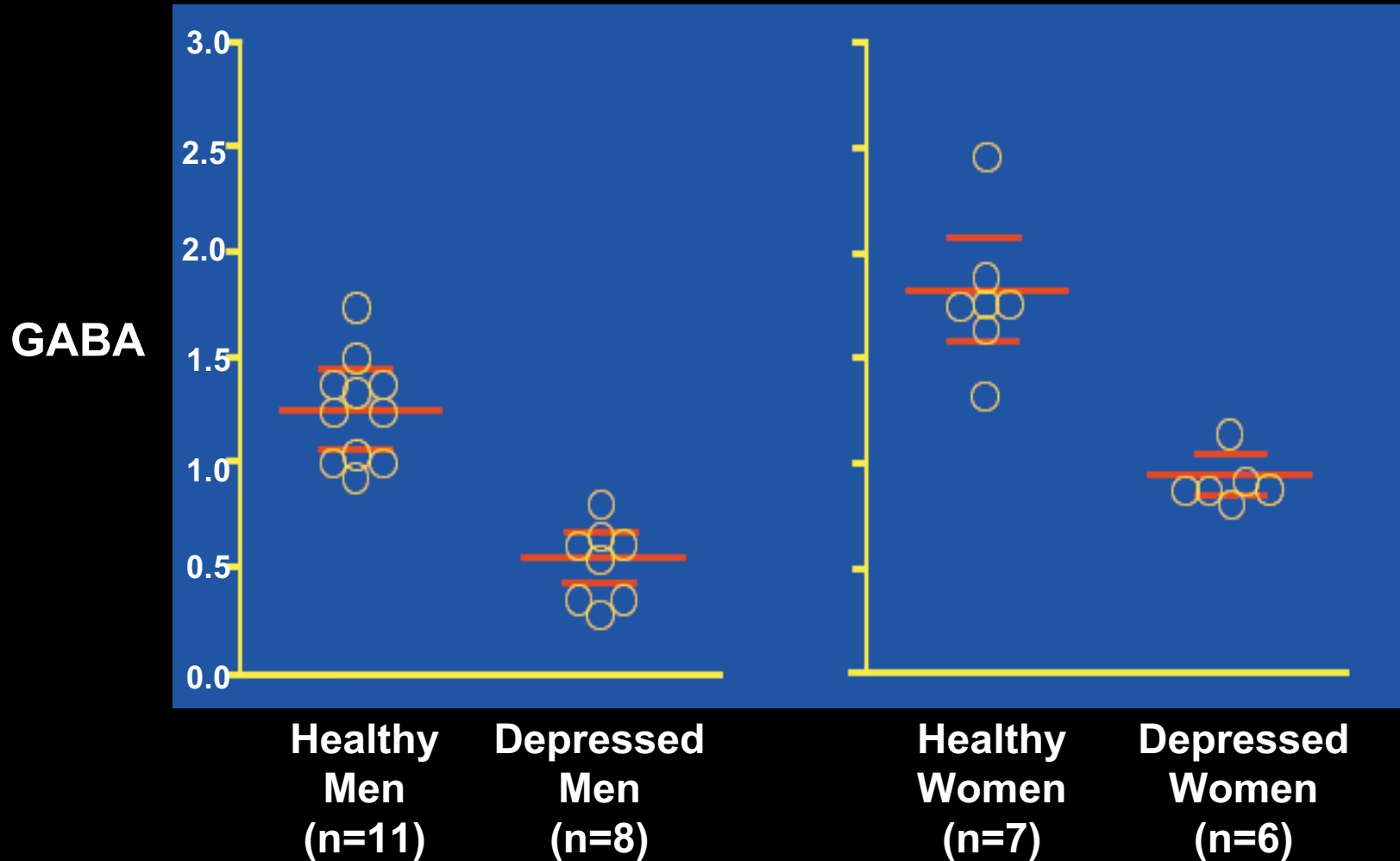


# Mean GABA/Cr Values of CREST II Patients and Comparison Subjects at Baseline

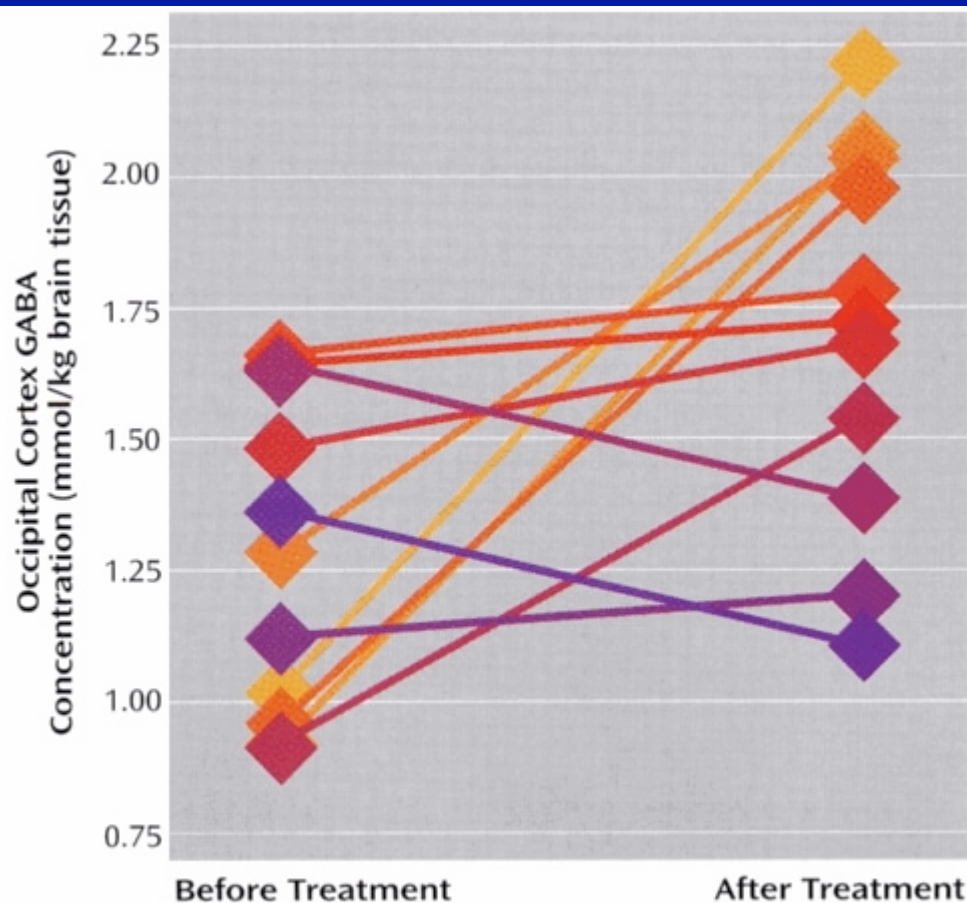
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**Individual subjects' proton MRS determined cortical GABA levels in brain tissue with means and 95% confidence intervals displayed.**



# Human Occipital Lobe GABA Concentration Increases With SSRI Treatment of Major Depression



<sup>a</sup> Each patient was treated for at least 5 weeks. Eight patients received fluoxetine, and three received citalopram.

**Change in Occipital Cortex GABA Concentrations After SSRI Treatment of Major Depression in 11 Patients**

*Sanacora G et al.,  
Am J Psychiatry 2002*



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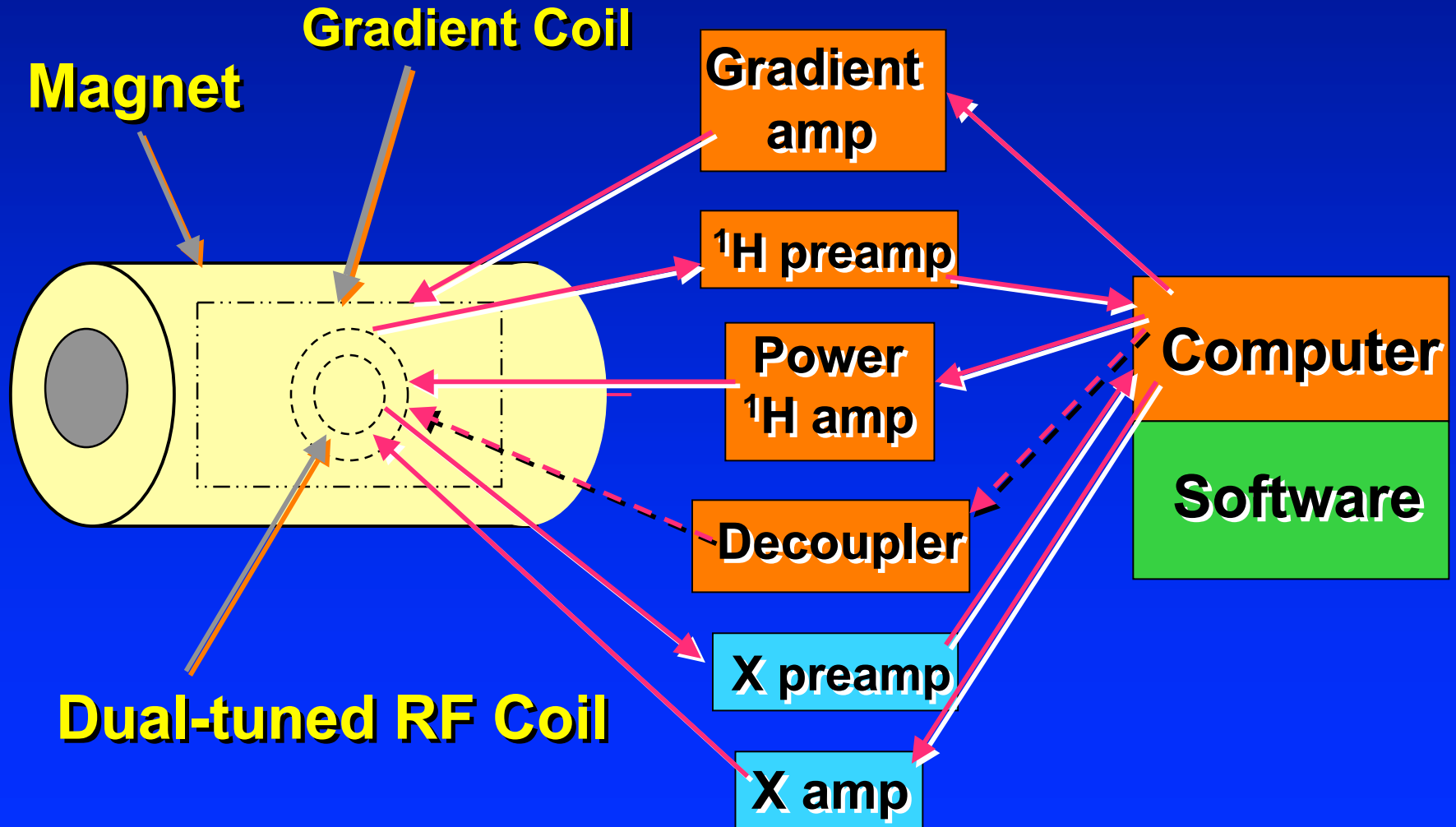
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# **X-Nuclear MRS in Psychiatry**

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- **Lithium-7 MRS**
- **Fluorine-19 MRS**
- **Phosphorus-31 MRS**
- **Carbon-13 MRS**

# MR Scanner - X MRS vs. MRI

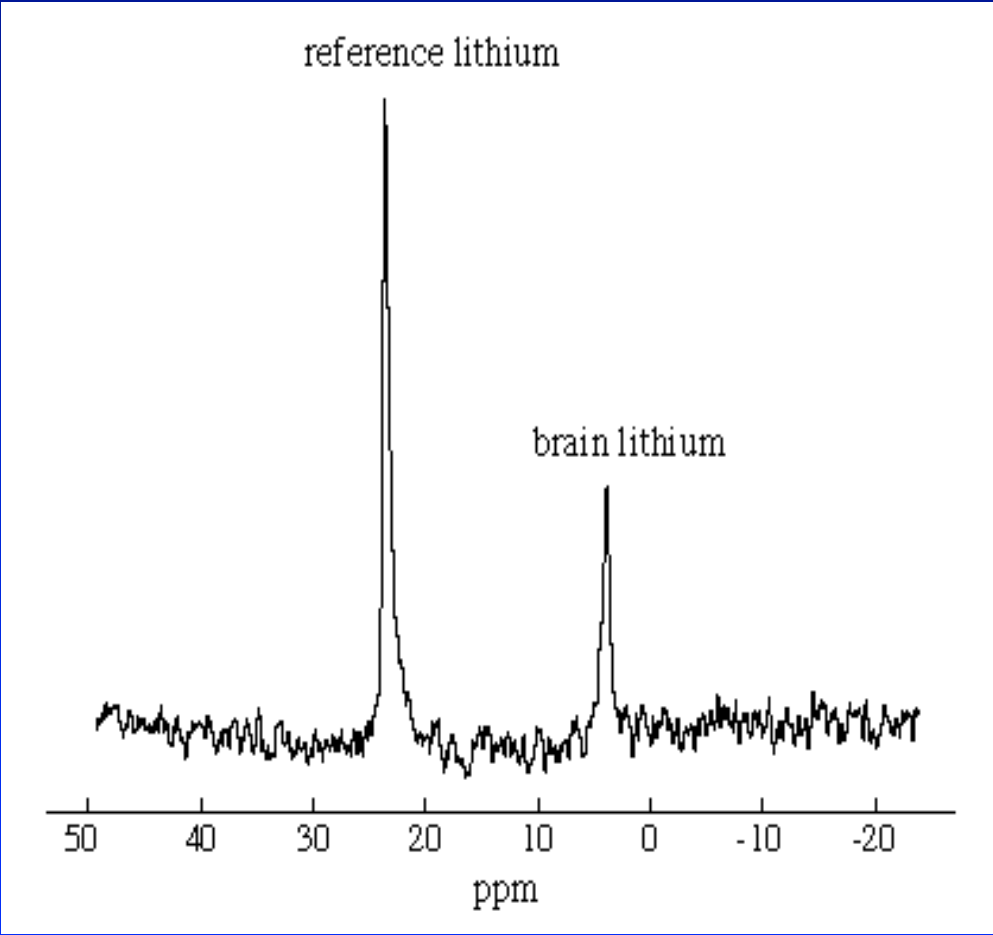


# Relative NMR Sensitivities

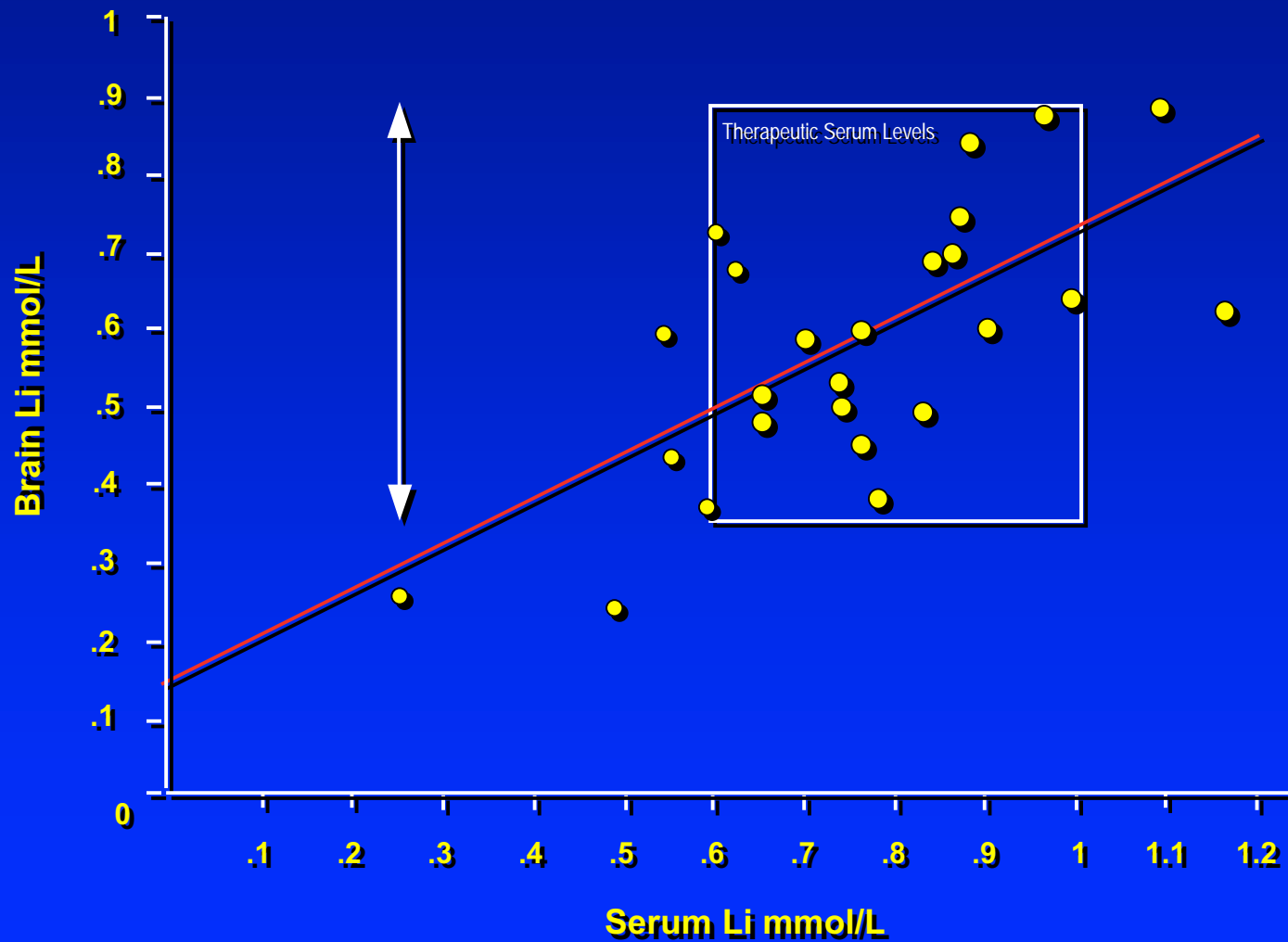
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Nucleus	Spin Quantum Number	NMR Frequency at 10 kG (MHz)	Relative Sensitivity at Constant Field	% Natural Abundance
$^1\text{H}$	1/2	42.58	1	99.8
$^{19}\text{F}$	1/2	40.05	0.83	100
$^7\text{Li}$	3/2	16.55	0.29	92.58
$^{23}\text{Na}$	3/2	11.26	0.09	100
$^{31}\text{P}$	1/2	17.25	0.06	100
$^{13}\text{C}$	1/2	10.71	0.02	1.1
$^{39}\text{K}$	3/2	1.99	0.0005	93.2

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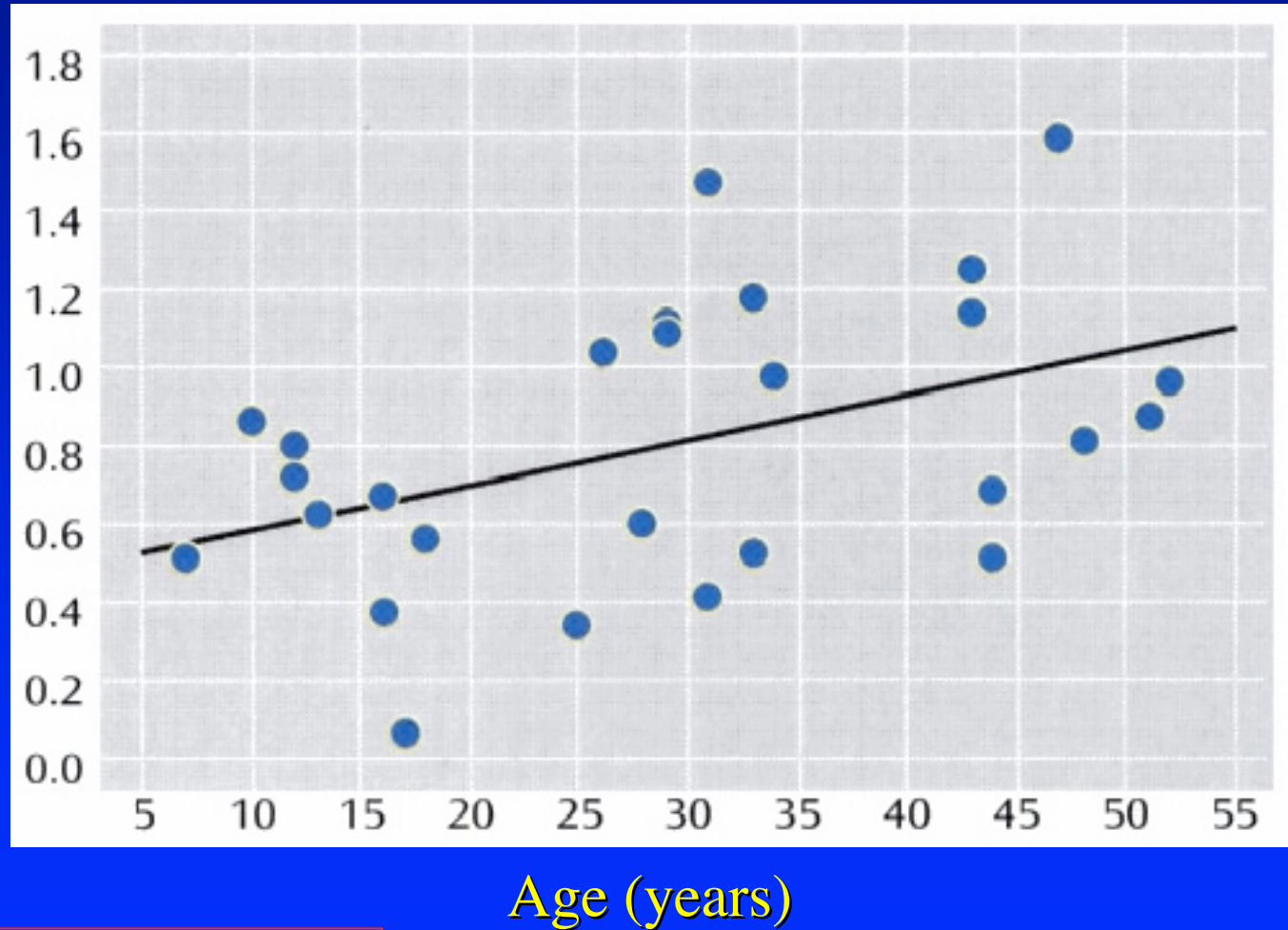
# Correlation between serum and brain lithium levels



Sachs et al., 1995

# Lithium Brain to Serum Ratios versus Age

Average  
Brain/Serum  
Lithium  
Ratio



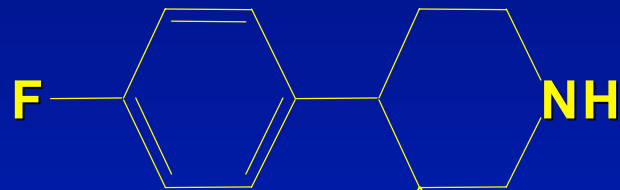
$r = 0.44, N = 27, p < 0.02$

# Fluorine-19 MRS

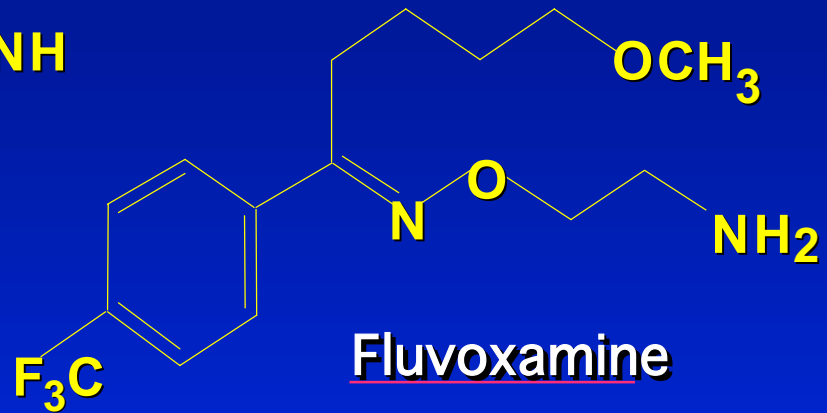
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- **Many psychotropic drugs contain fluorine-19**
- **Brain drug concentrations and brain:plasma drug ratios vary across species**
- **Dose selection for early human studies in complicated for illnesses without defined pathology**
- **Safety issues are important in the FDA approval process**

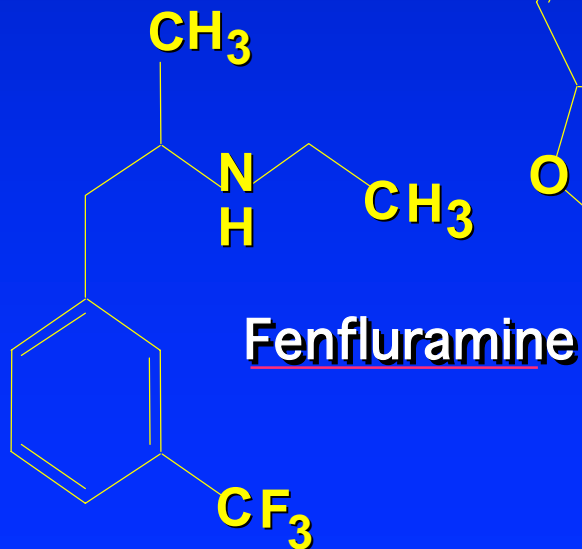
# Drugs Studied by $^{19}\text{F}$ Fluorine MRS



Paroxetine



Fluvoxamine



Fenfluramine



Fluoxetine

# **$^{19}\text{F}$ MR Spectroscopy**

$$\mathbf{I} = c_1 \cdot N \cdot [D] \cdot V \cdot B_1(\mathbf{r}) \cdot L \cdot \sin(\theta) \cdot \exp(-t_D/T_2^*) \cdot (1 - \exp(-TR/T_1))$$

$I$  = signal intensity

$c_1$  = constant

$N$  = number of fluorine atoms per drug molecule  
(three for DF and dNF)

$[D]$  = drug concentration

$V$  = volume

$B_1(\mathbf{r})$  = reception field distribution

$L$  = function of RF coiling loading

$\theta$  = RF excitation tip angle

$t_D$  = acquisition delay

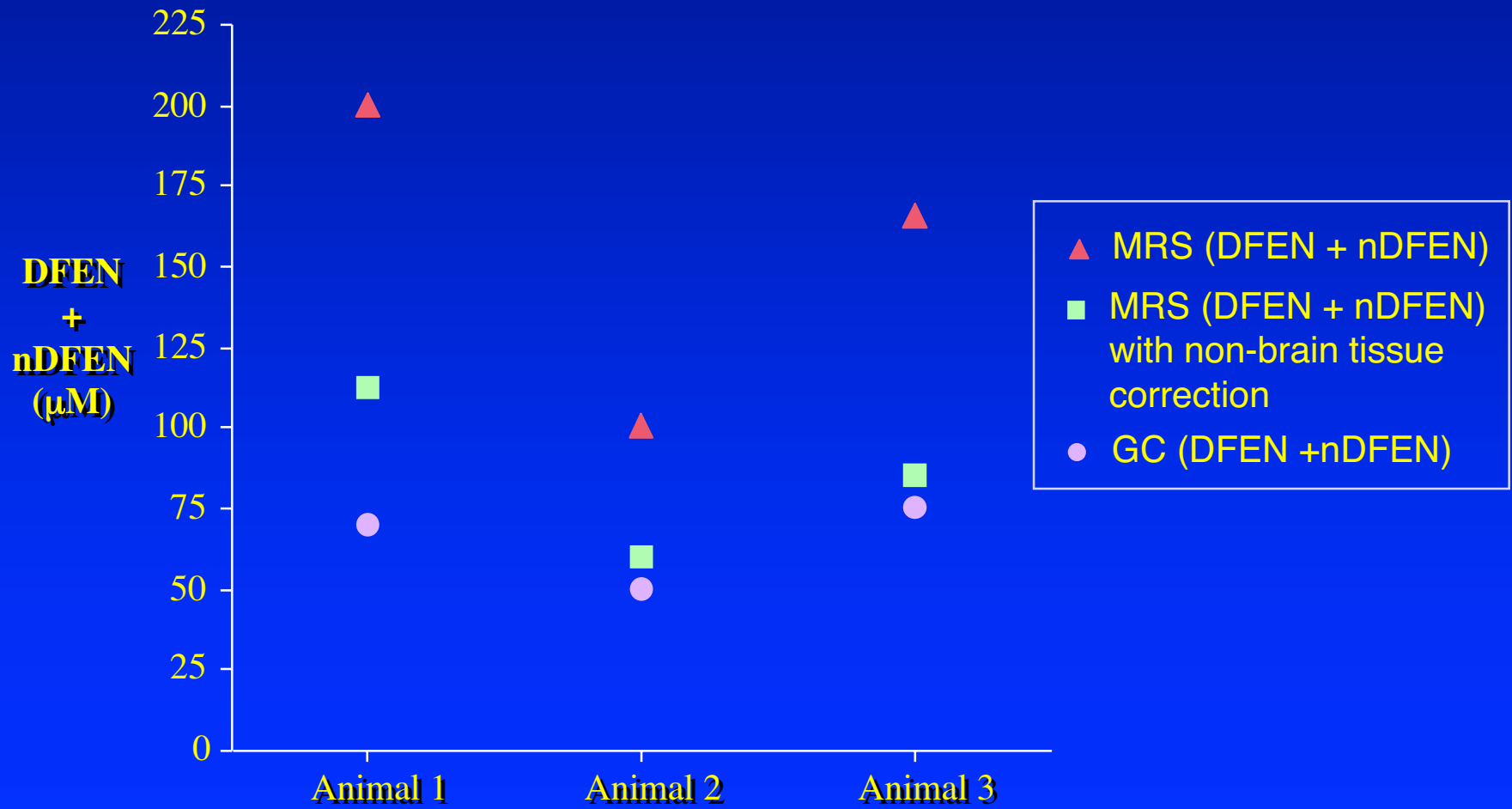
$T_2^*$  = spin-spin relaxation time including static field effects

$TR$  = pulse repetition time

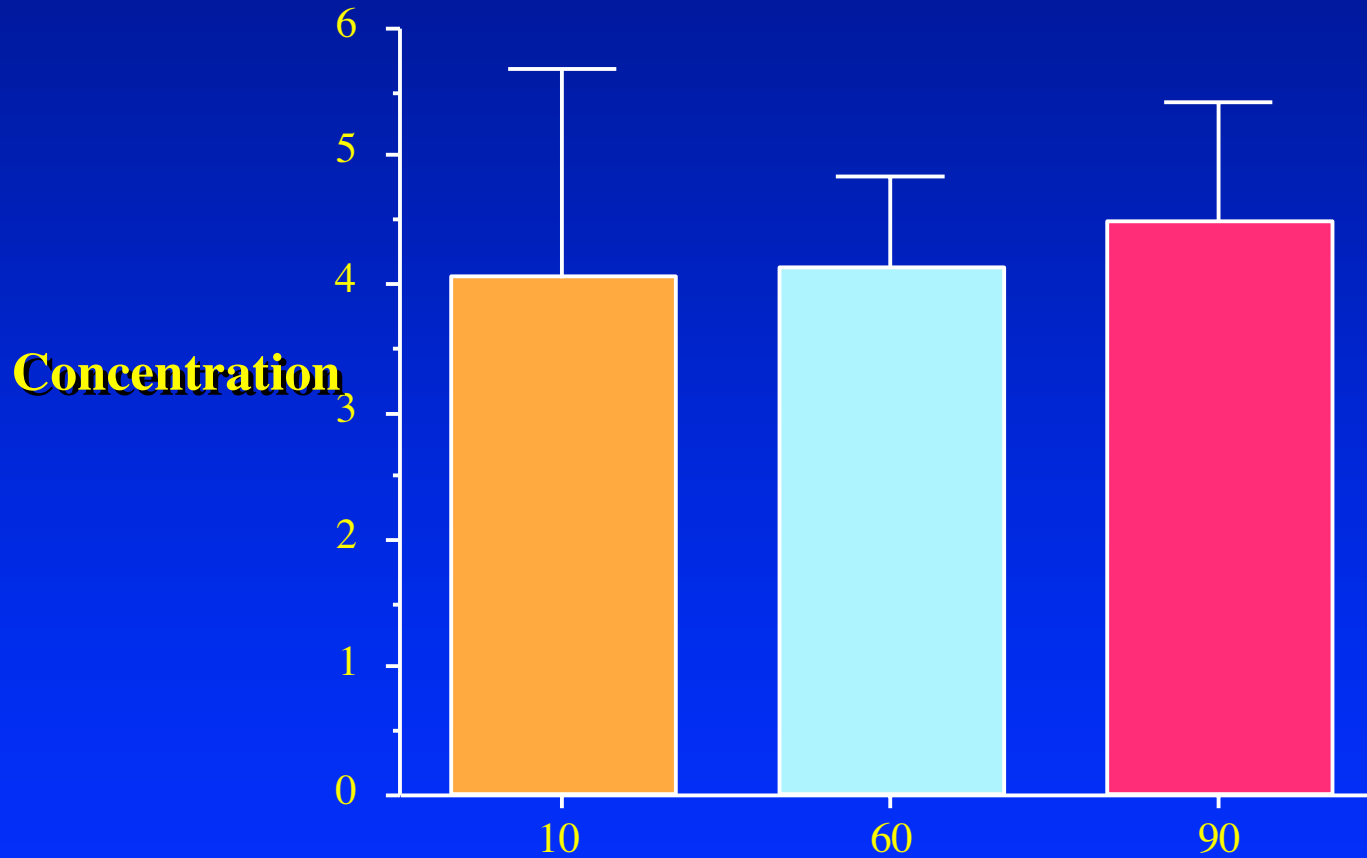
$T_1$  = spin-lattice relaxation time



# Rhesus Brain DFEN + nDFEN Concentrations Measured by $^{19}\text{F}$ -MRS and Gas Chromatograph (GC) Demonstrate that DFEN is Fully Detected by $^{19}\text{F}$ -MRS



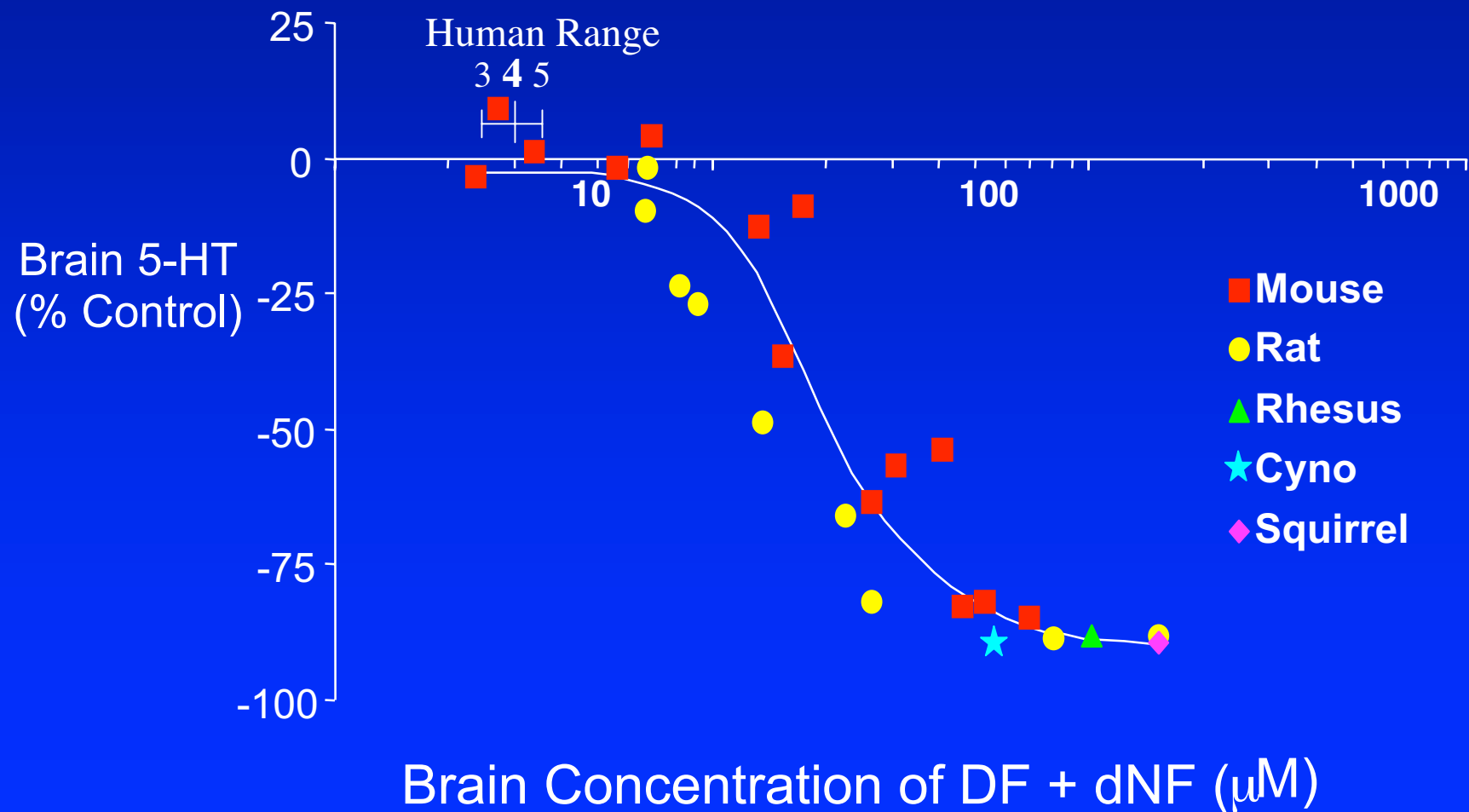
# Dexfenfluramine plus nor-Dexfenfluramine Concentrations in Human Brain as measured by <sup>19</sup>F- MRS



**Day of Dexfenfluramine Treatment**

Average of  
11 subjects

# Serotonin Brain Levels in Various Species



# Phosphorus-31 MRS

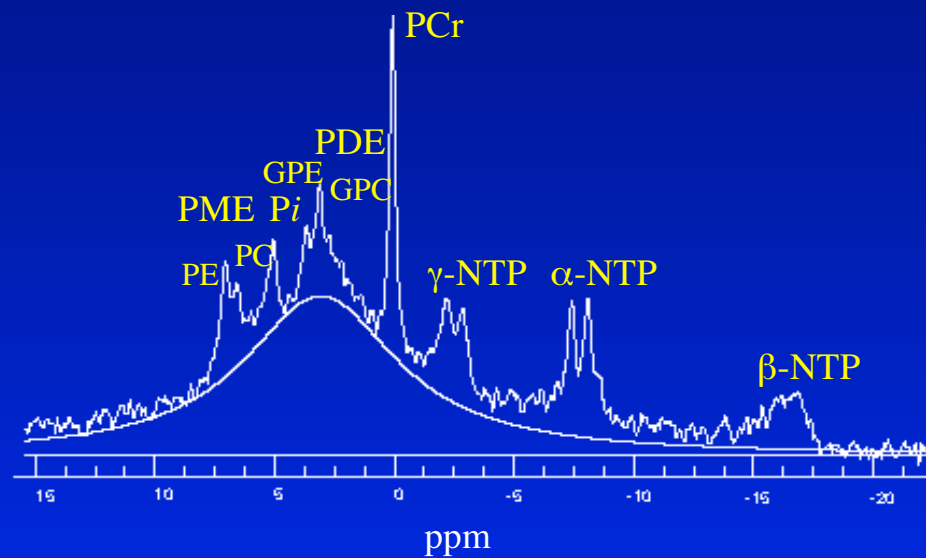
- First in vivo X-nucleus studied (1973 )
- Assessment of high energy phosphates and phospholipid metabolites
- Complex resonances (multiple components)
  - Phosphodiester (PDE)
    - phospholipids (1.5T but not 4T)
    - glycerophosphocholine
    - glycerophosphoethanolamine

# Phosphorus-31 MRS

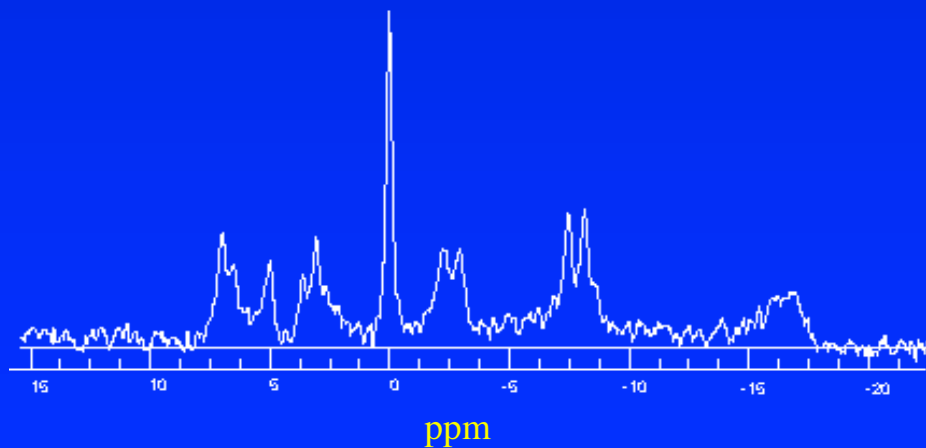
(continued)

- **Complex resonances (multiple components)**
  - **Phosphomonoesters (PME)**
    - **phosphoethanolamine**
    - **phosphocholine**
    - **sugar phosphates**
- **Decoupling is valuable, especially at 1.5T**
- **Typical voxel volumes 25 cm<sup>3</sup> - 1000cm<sup>3</sup> at 1.5T**
- **Studies are significantly improved at higher field strength**

# Typical Decoupled $^{31}\text{P}$ MR Spectrum from 5mm Axial Slice



## $^{31}\text{P}$ MR Spectrum After Subtraction of the Broad Phospholipid Resonance



# Metabolite Levels in the Dorsal Prefrontal Cortex of Drug-Naïve, First-Episode Schizophrenics and Controls

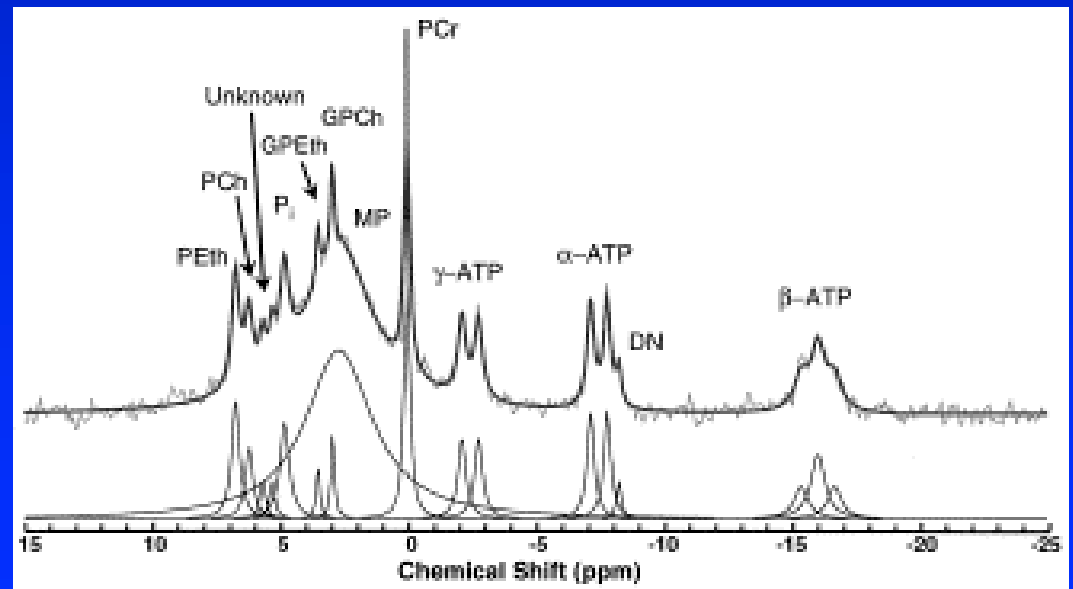
## Mole % of Total Observable Phosphorus in the Dorsal Prefrontal Cortex

Metabolite	Schizophrenics Controls		P
	(n=11)	(n=10)	
Phosphomonoester	15.5 (0.9)	20.3 (0.9)	.002
Inorganic			
orthophosphate	7.9 (0.9)	9.9 (0.5)	.01
Phosphodiester	36.4 (1.5)	32.2 (0.6)	.02
Phosphocreatine	11.3 (0.4)	11.9 (0.5)	NS
Ionized ends	7.4 (0.3)	7.2 (0.3)	NS
Esterified ends	12.3 (0.7)	10.8 (0.9)	NS
Middles	9.0 (0.5)	7.4 (0.4)	.02

*Pettegrew JW, et al., 1991*

# Schizophrenia P-31 Controversy

- Potwarka et al. believe differences arise from the phospholipid peak (MP)
- Bluml et al. believe differences arise from the mobile phospholipids (GPCo, GPEth) and PCr
- Estilaei et al. have shown that alcohol consumption lowers the MP peak.



# Carbon-13 MRS

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- Low natural abundance (1%) facilitates labeling studies (very expensive substrate)
- Large brain volumes studied (e.g. whole brain)
- Glutamine turnover may correlate with glutamatergic activity
- Methodologically complex

# **MRS in Psychiatry - Summary**

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- Many positive observations at research level**
- Relatively strong rationale for X-nuclear studies**
- Direct interpretations of metabolite signal changes**
- No clear clinical utility at present**

