

HEPATIC ENCEPHALOPATHY: CLINICAL AND LABORATORY ADVANCES

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Hepatic Encephalopathy in Chronic Liver Disease

- Neuropsychiatric Syndrome
- Personality changes, sleep disorders
- Attention deficit, motor incoordination
- Asterixis
- Stupor
- Coma

Hepatic Encephalopathy in Chronic Liver Disease

- Impact on quality of life
- Precipitating factors
 - Protein load
 - Gastrointestinal bleed
 - Sedatives
 - Hypoglycemia
 - Infection

Hepatic Encephalopathy Post-TIPS

- New or worsening encephalopathy in ~50% of cases
- Predictors
 - Prior encephalopathy
 - Non-alcoholic etiology
 - Hypoalbuminemia
 - Patient age

Recent Progress in the Pathophysiology of Hepatic Encephalopathy

1. Neuropathology
2. Neuroimaging
 - Positron Emission Tomography (PET)
 - Magnetic Resonance Imaging (MRI)
3. Spectroscopy
4. Molecular Biology
5. Implications for New Therapeutic Strategies
 - GABA modulation (neurosteroids)

Images of the Brain in Liver Failure

1. Neuropathology

2. Neuroimaging

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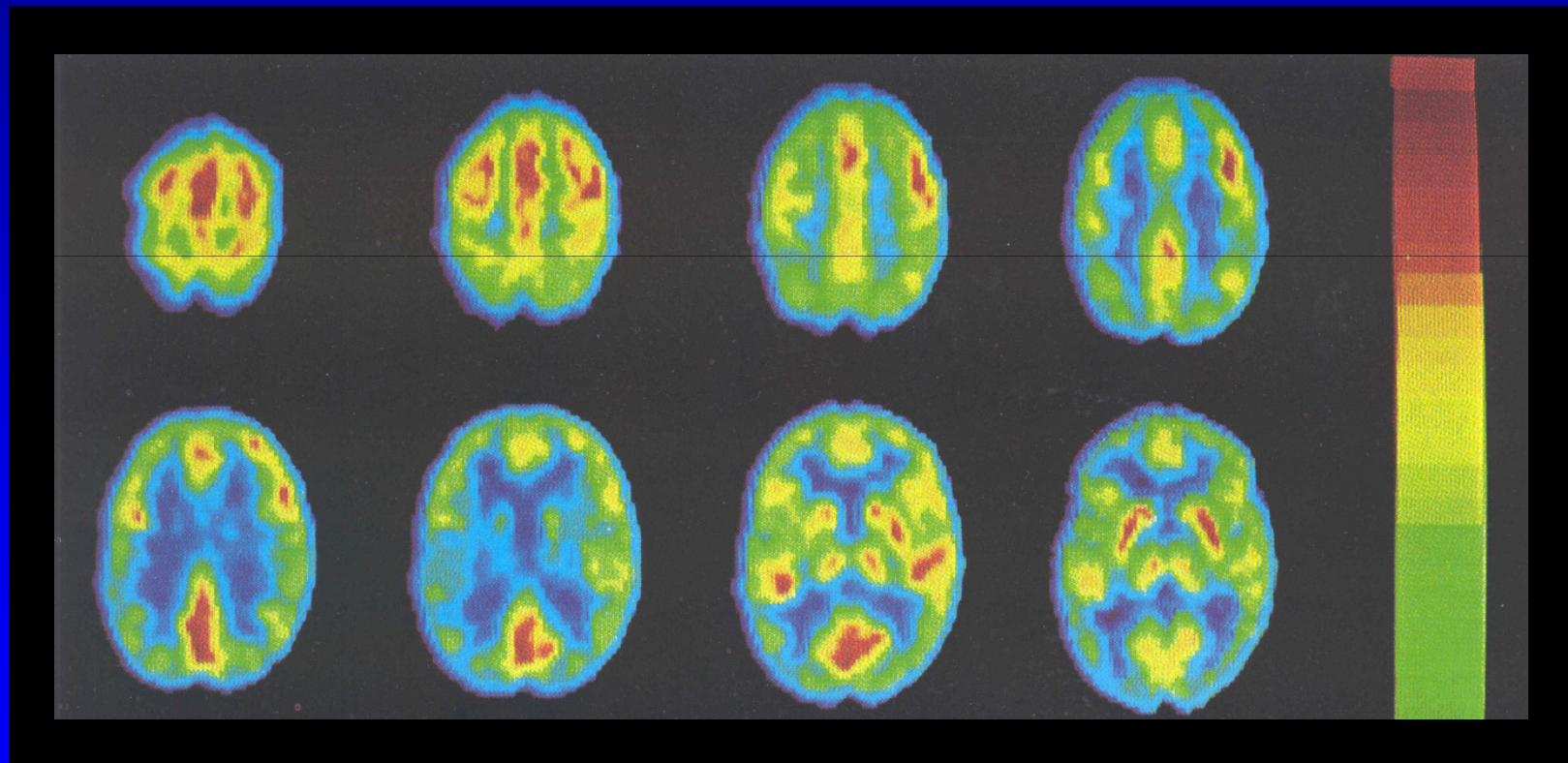
Neuroimaging in Liver Failure

➤ POSITRON EMISSION TOMOGRAPHY (PET)

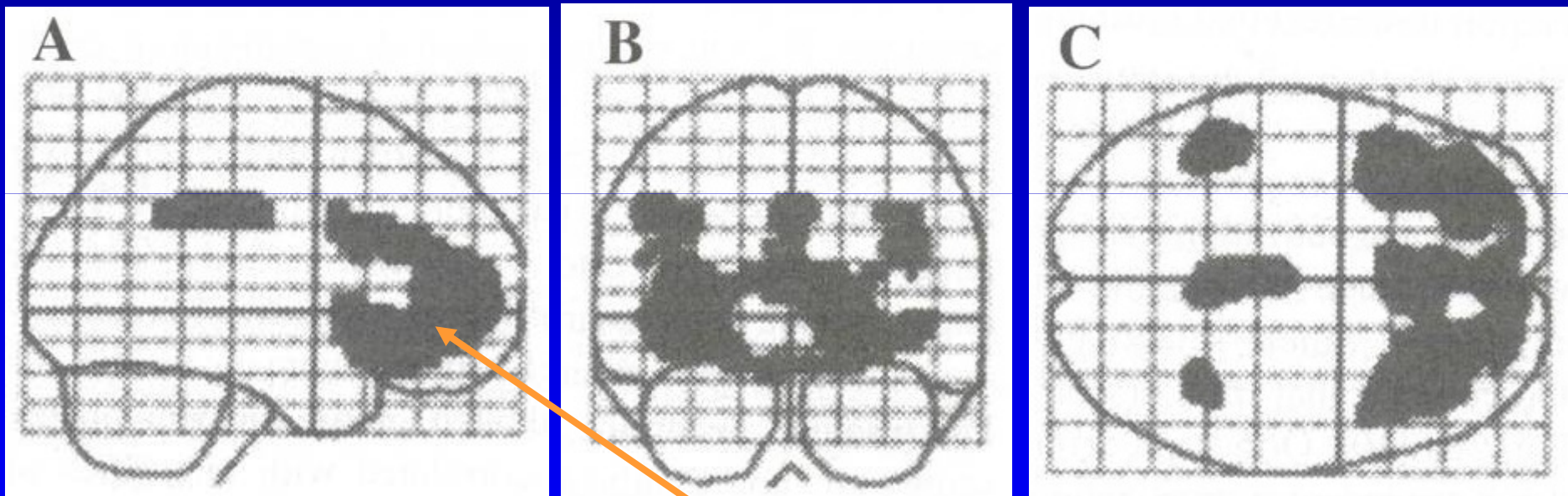
- ^{18}F -DEOXYGLUCOSE

- ^{13}N - NH_3

Local Cerebral Glucose Utilization (LCGU) using ^{18}F -Deoxyglucose (PET)



Correlation Between Decreased LCGU and Impaired Psychometric Test Performance in Cirrhotic Patients with Mild HE



Anterior cingulate
cortex

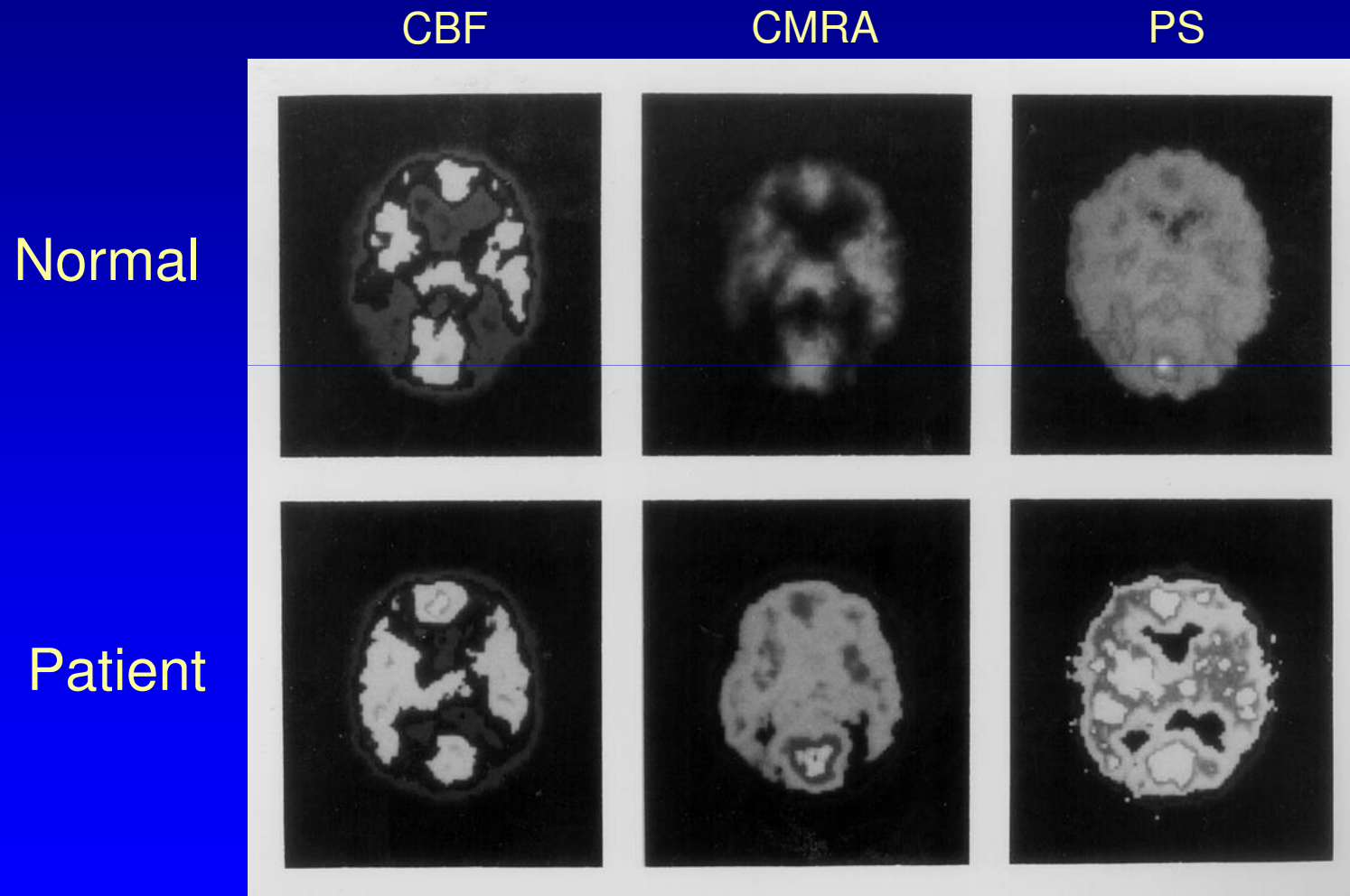
Neuroimaging in Liver Failure

➤ POSITRON EMISSION TOMOGRAPHY (PET)

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PET Images of Brain using $^{13}\text{NH}_3$ in a Patient With Mild HE



[*JCBFM*, 11: 337-341, 1991]

PET Imaging Studies: Data

	Controls (5)	Patients (5)
Arterial NH ₃ (mM)	0.03±0.007	0.062±0.02*
CMR/NH ₃	0.35±0.15	0.91±0.36*
BBB transfer (NH ₃) (ml/g/min)	0.13±0.03	0.22±0.07*

*p<0.01

[*JCBFM*, 11: 337-341, 1991]

Neuroimaging in Liver Failure

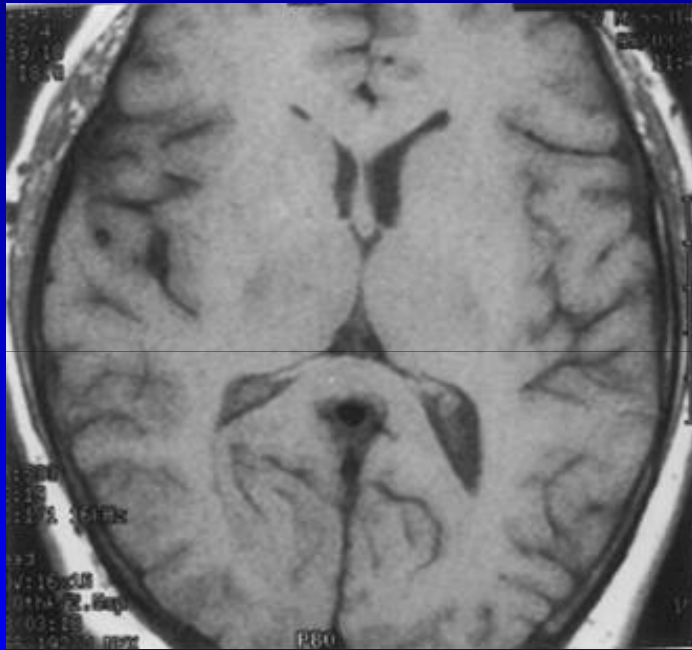
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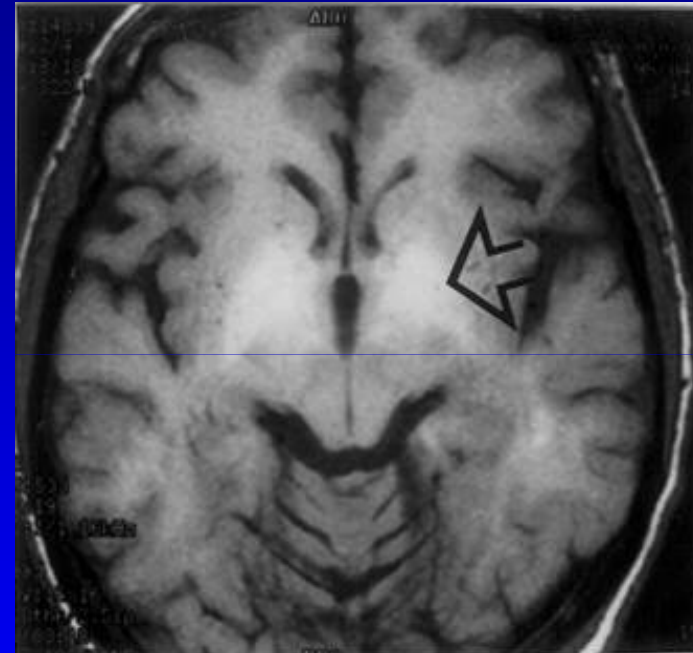
- MAGNETIC RESONANCE IMAGING (MRI)

Magnetic Resonance Imaging in Chronic Liver Failure

C



P

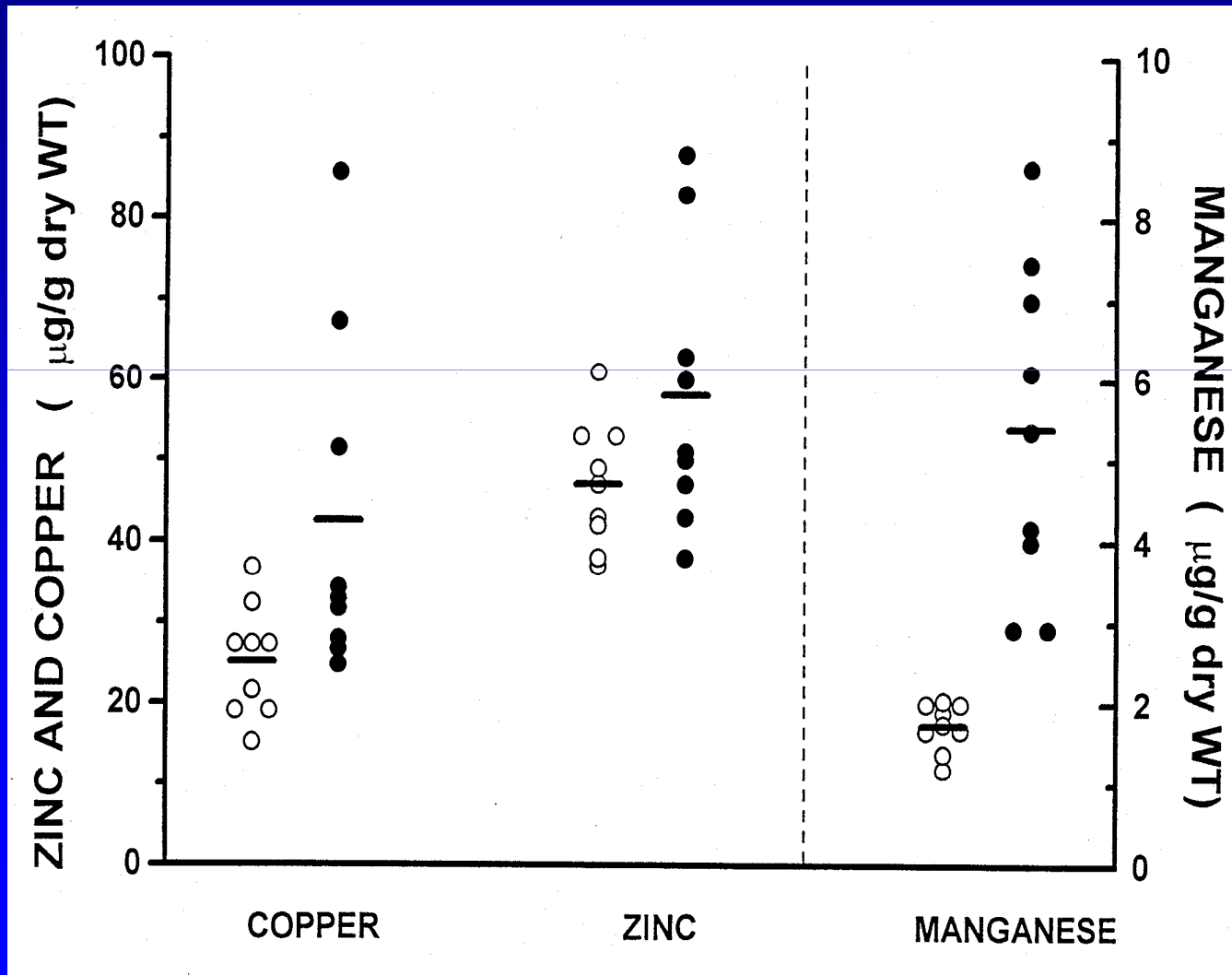


Note: Bilateral T_1 -weighted signal hyperintensities in globus pallidus of patient (P) compared to control (C)

Manganese

- 98% cleared by liver, excreted in the bile
- Accumulates in globus pallidus following chronic intoxication
- Causes Alzheimer type II astrocytosis

Selective Increase of Brain Manganese in Globus Pallidus of HE Patients

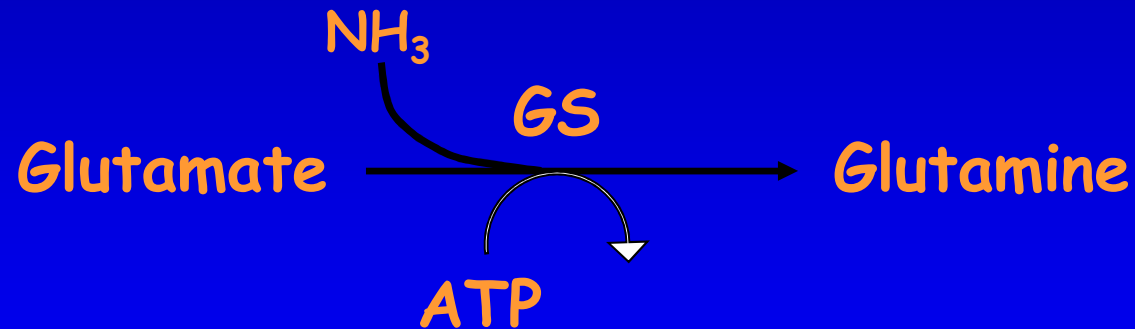


Toxins Normally Removed by Hepatobiliary System Which Accumulate in Brain in Chronic Liver Failure

- Ammonia
- Manganese

Ammonia removal by brain

- . No urea cycle
- . Glutamine synthetase major system involved



- . GS uniquely ASTROCYTIC

IMAGES OF THE BRAIN IN LIVER FAILURE

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2. Neuroimaging

- Positron Emission Tomography (PET)
- Magnetic Resonance Imaging (MRI)

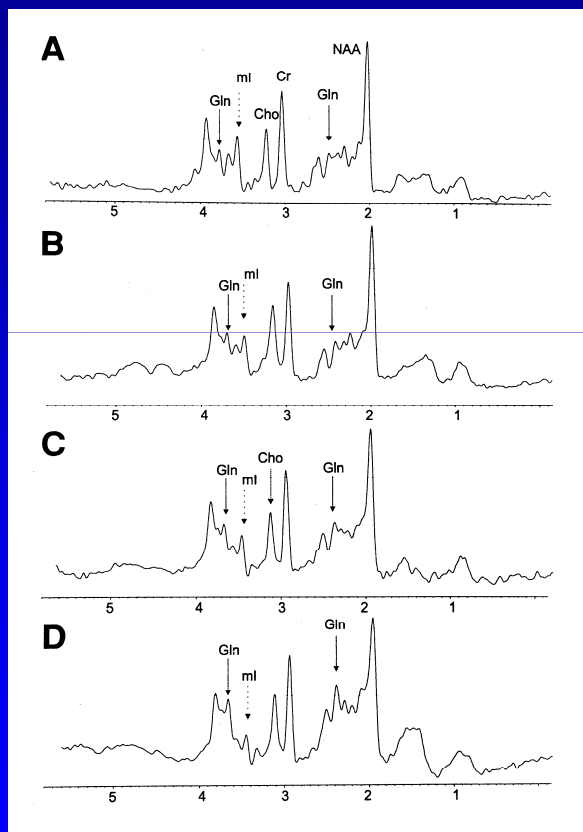
3. Spectroscopy

4. Molecular Biology

5. Implications for New Therapeutic Strategies

- GABA modulation (neurosteroids)
- Hypothermia

Increased brain glutamine correlates with severity of encephalopathy in chronic liver failure: results of ^1H -MRS studies



Normal

Mild HE

Moderate HE

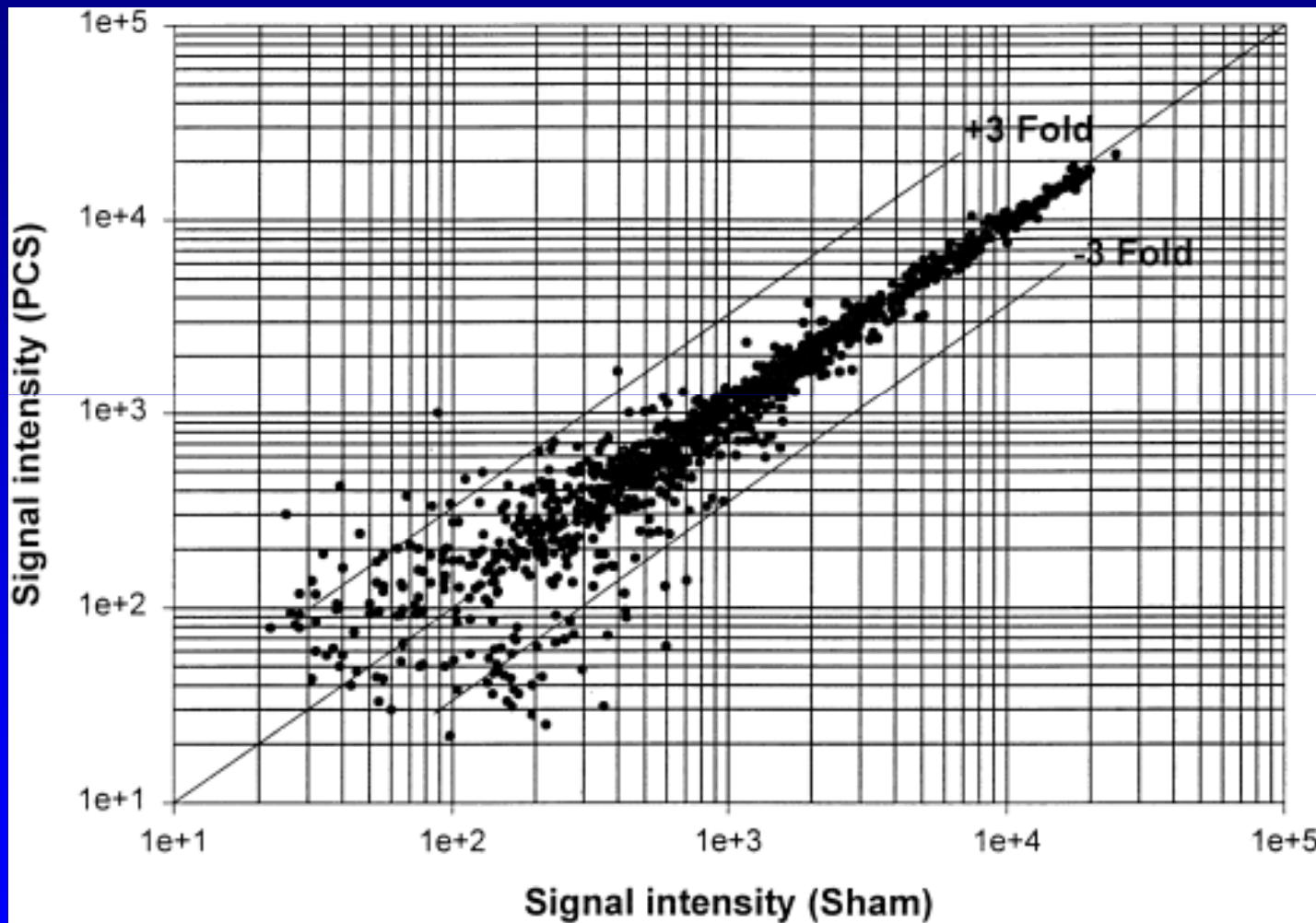
Severe HE

[*Gastroenterology*, 112: 1610-1616, 1997]

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Altered Transcripts following Portacaval Anastomosis in Rat Cerebral Cortex

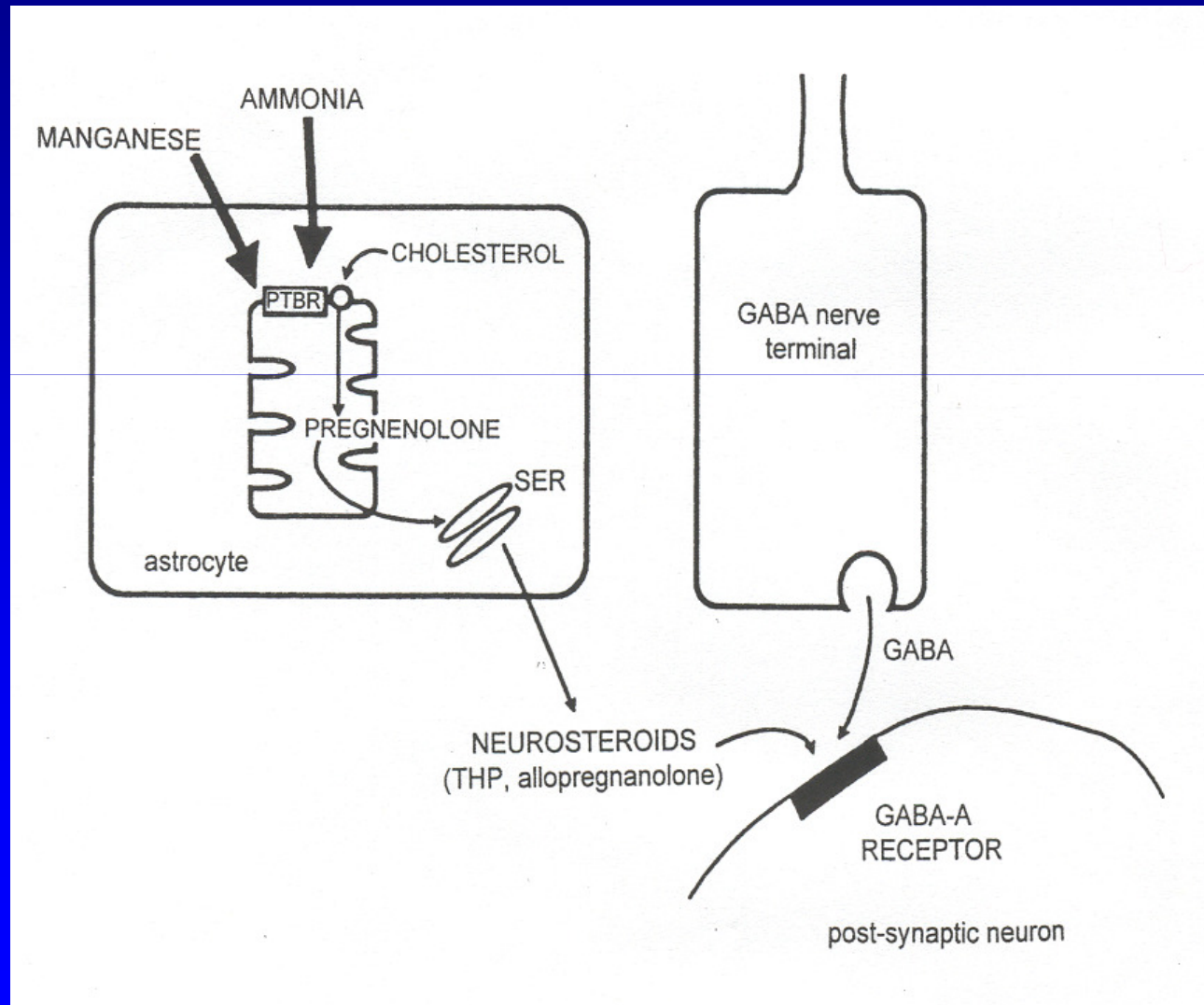


[J Neurosci Res 68(6), 2002]

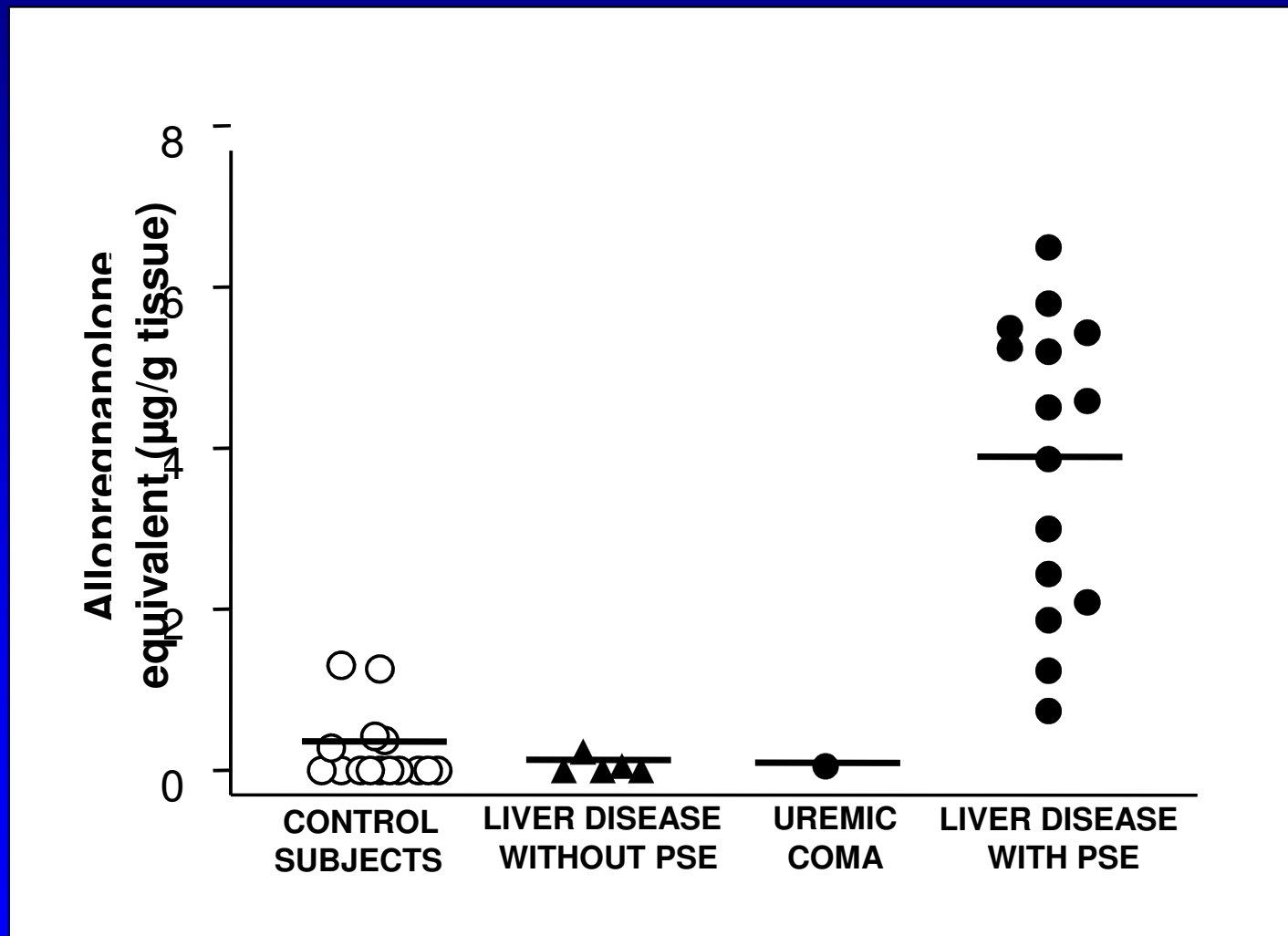
Chronic Liver Failure Results in Increased Gene Expression in Brain

- Peripheral-type benzodiazepine receptor (PTBR)
- Nitric oxide synthase (nNOS isoform)
- Monoamine oxidase (MAO-A isoform)

Allopregnanolone is a Potent Inhibitory Neurosteroid with GABA-Agonist Properties



Increased Brain Concentrations of Allopregnanolone in Patients With HE



Treatment of Hepatic Encephalopathy in Chronic Liver Disease

1. Treatment of precipitating factor
2. No protein restriction (maintain 1-2g/kg/day)
3. Ammonia-lowering strategies
 - Aimed at residual liver (L-ornithine L-aspartate)
 - Aimed at the gut (Lactulose, antibiotics)
 - Aimed at the muscle (L-ornithine L-aspartate)
 - Aimed at the brain (none yet)

Treatment of Hepatic Encephalopathy in Chronic Liver Disease

4. Neuropharmacology

- Benzodiazepine Receptor Antagonists (Flumazenil) effective in Bz-induced encephalopathy, otherwise only in small subgroup
- Dopamine agonists (L-DOPA, Bromocriptine). No clear effects in controlled clinical trials; may improve motor dysfunction.
- Use of opioid receptor antagonists, serotonin reuptake inhibitors, non-sedative antihistaminics suggested from animal studies but no translational research in this area.

Pathogenesis of Hepatic Encephalopathy: Take Home Message

- Neuropsychiatric Disorder
- High Impact on Quality of Life
- Precipitating Factor in >80% of cases
- Occurs in ~50% of TIPS cases
- Results from altered function of brain ASTROCYTES
- Brain regional selectivity (anterior cingulate cortex)
- Neurotoxins
 - Ammonia (throughout brain)
 - Manganese (globus pallidus)
- Altered expression of GENES coding for key brain proteins

Treatment of Hepatic Encephalopathy: Take Home Message

- Treat precipitating Factor
- Maintain protein at 1-2g/kg/day
- Lower circulating ammonia
 - Lactulose, antibiotics (gut)
 - L-ornithine L-aspartate (muscle, liver)
- Neuropharmacology
 - Flumazenil (if Bz precipitation component of encephalopathy)
 - Limited translational research in this area

AGRADECIMENTOS

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