

Effects of HIV, HCV, and Stimulant Drug Dependence on the Central Nervous System

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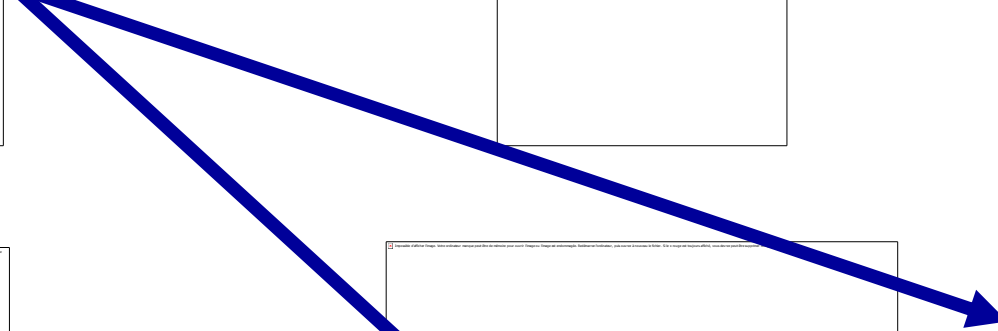
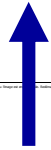
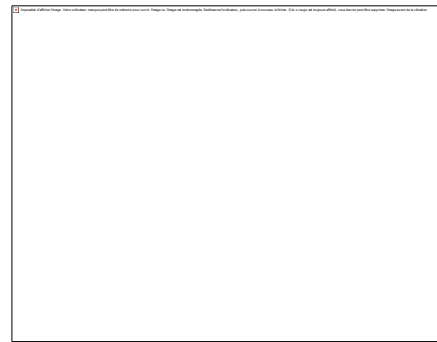
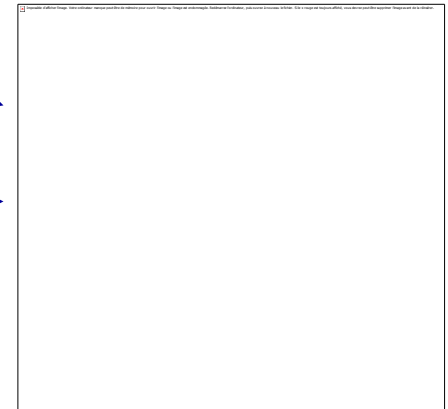
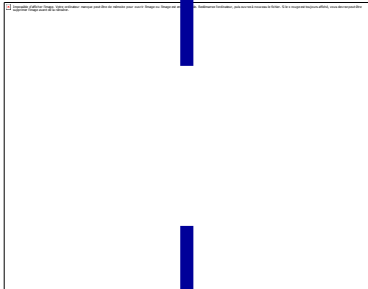
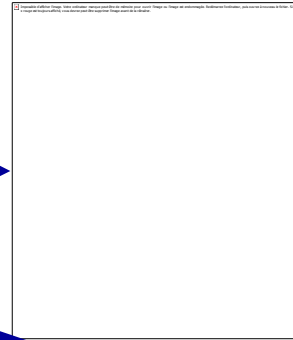
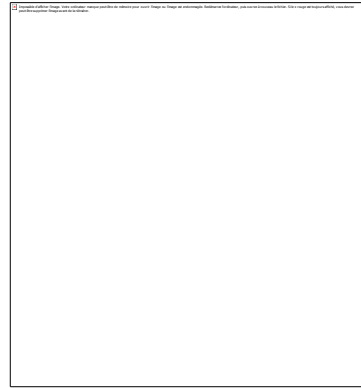
HIV NEUROBEHAVIORAL RESEARCH CENTER



HIV and HCV Co-infection

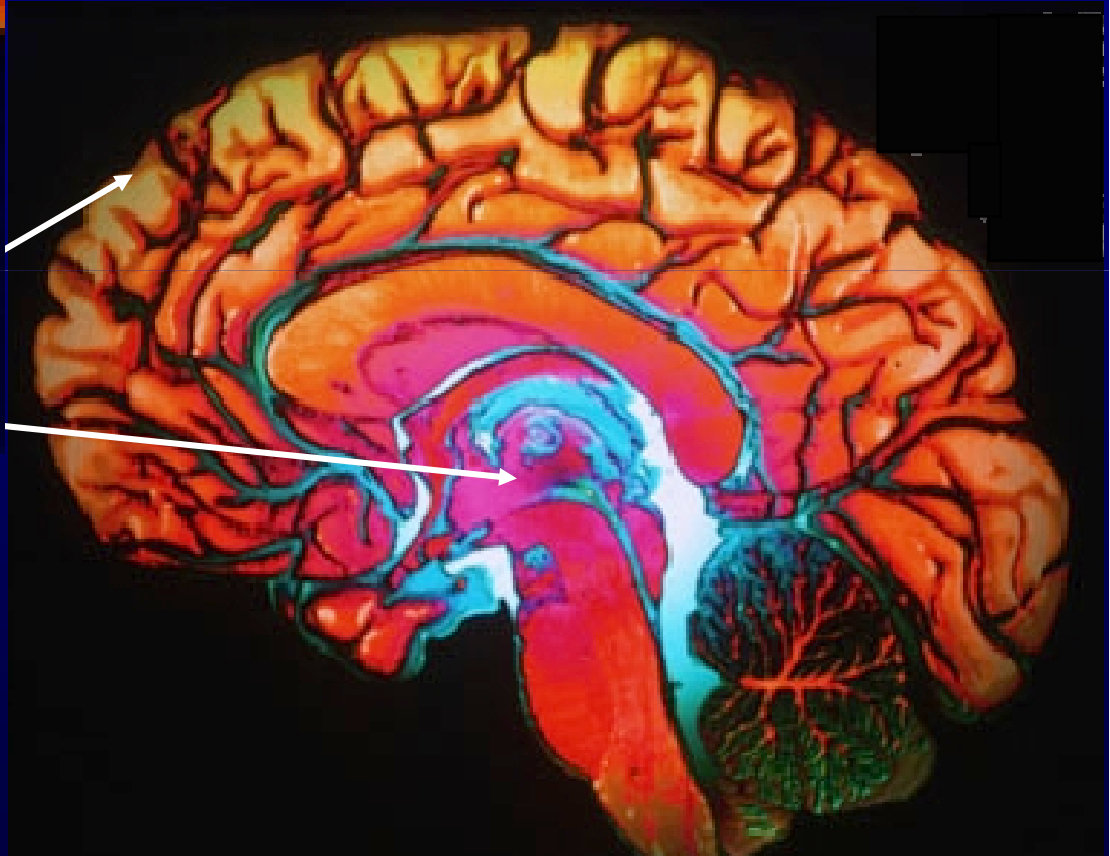
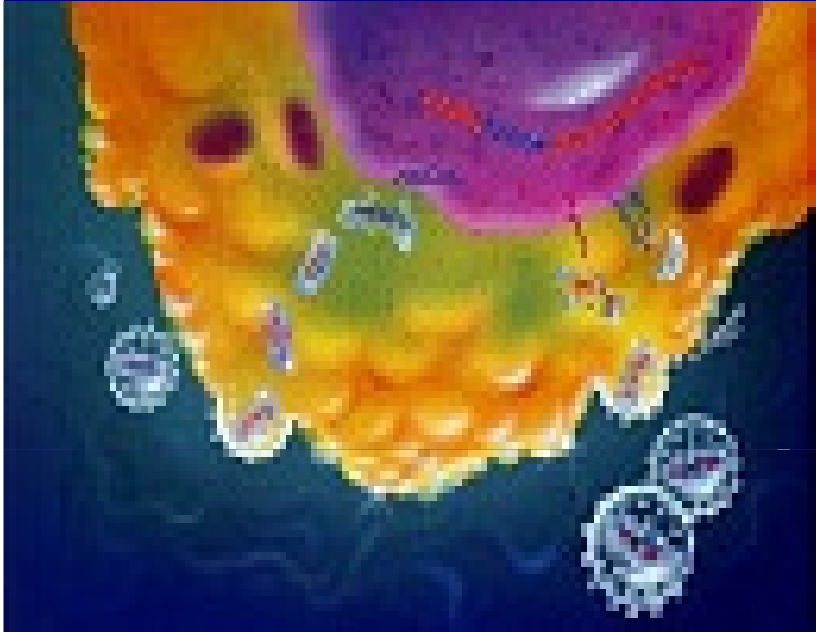
- ◆ **Since transmission routes are similar for HCV and HIV, co-infection is common**
 - **In EuroSIDA Study, 33% were co-infected**
 - **In the US, 240,000 are co-infected (~30% of all HIV-infected individuals)**





courtesy S. Letendre

HIV is a Neurotropic Virus



HIV Encephalitis

- ◆ Inflammation
- ◆ Oxidative Stress
- ◆ Apoptosis

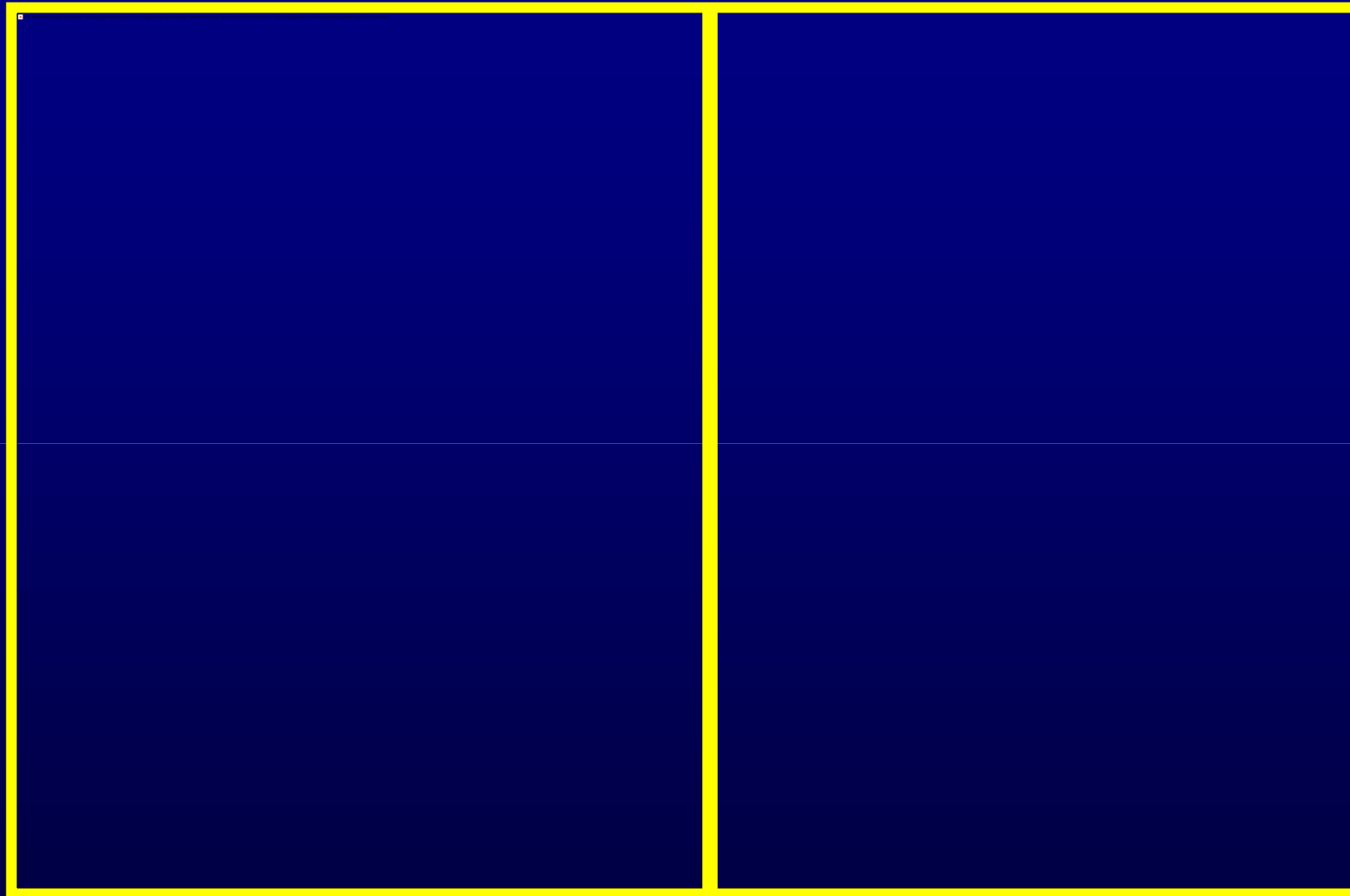
Multinucleated Giant Cells

Myelin Pallor

Microglial Nodule



Dendritic Simplification

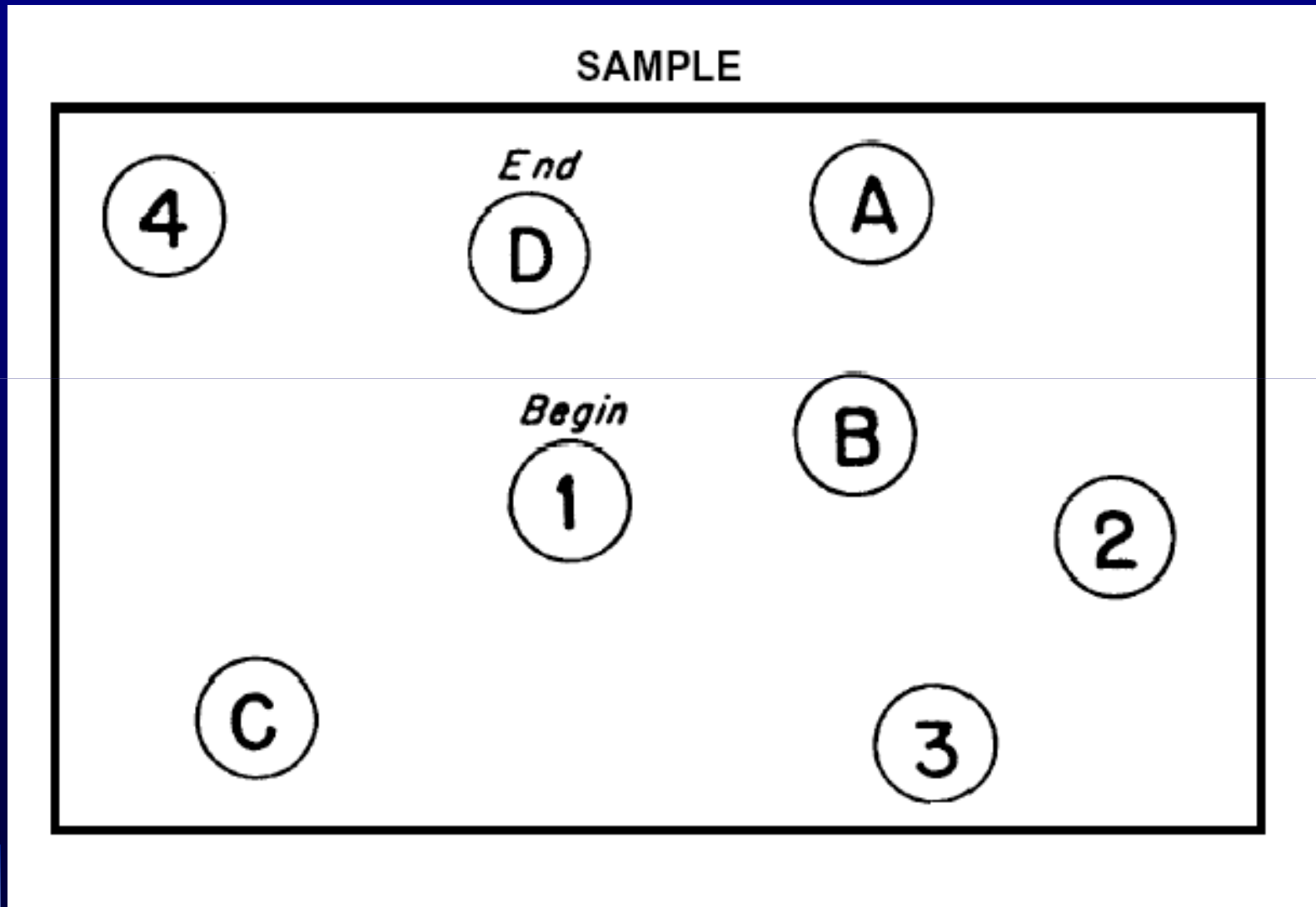


HIV-

HIV+



Trail Making Test B sample

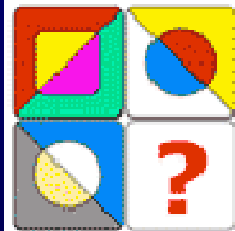


Concept Formation

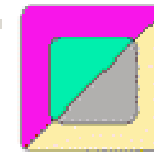
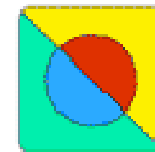
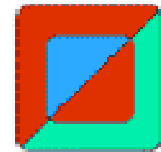
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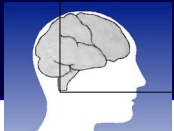


Find the picture that follows logically...



Prevalence of neurocognitive disorders before highly active antiretroviral treatment

n=975



Asymptomatic

Mild Sx

AIDS

Prevalence and Severity of NP Impairment in the HAART era (n = 380)



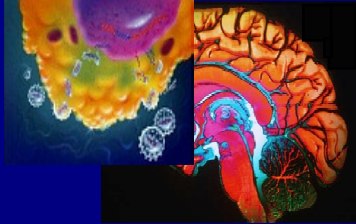
*Source: CHARTER Study,
presented with permission of
CHARTER Steering Committee*



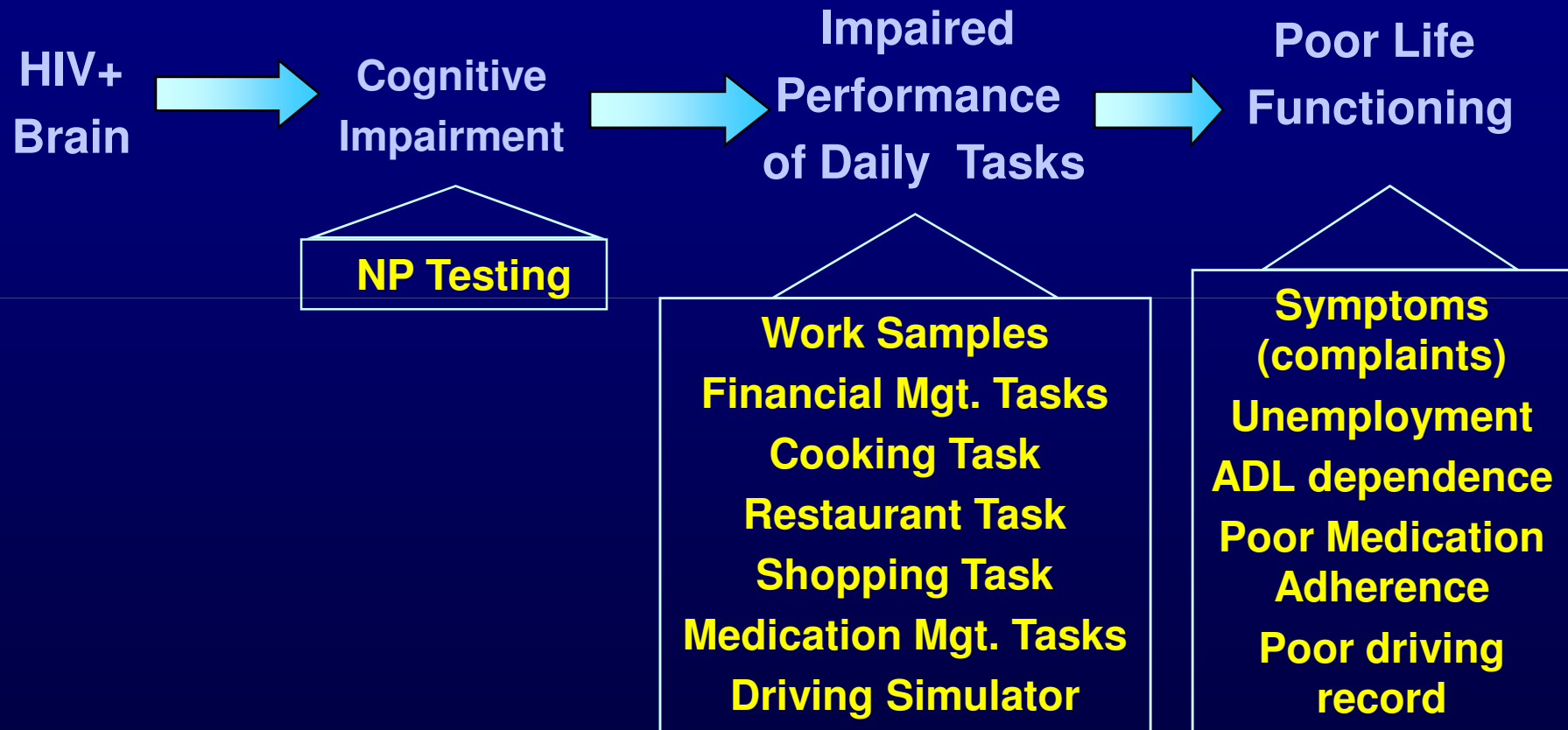
Relation of Dendritic Damage to Neurocognitive Impairment

% Area Occupied by Dendrites



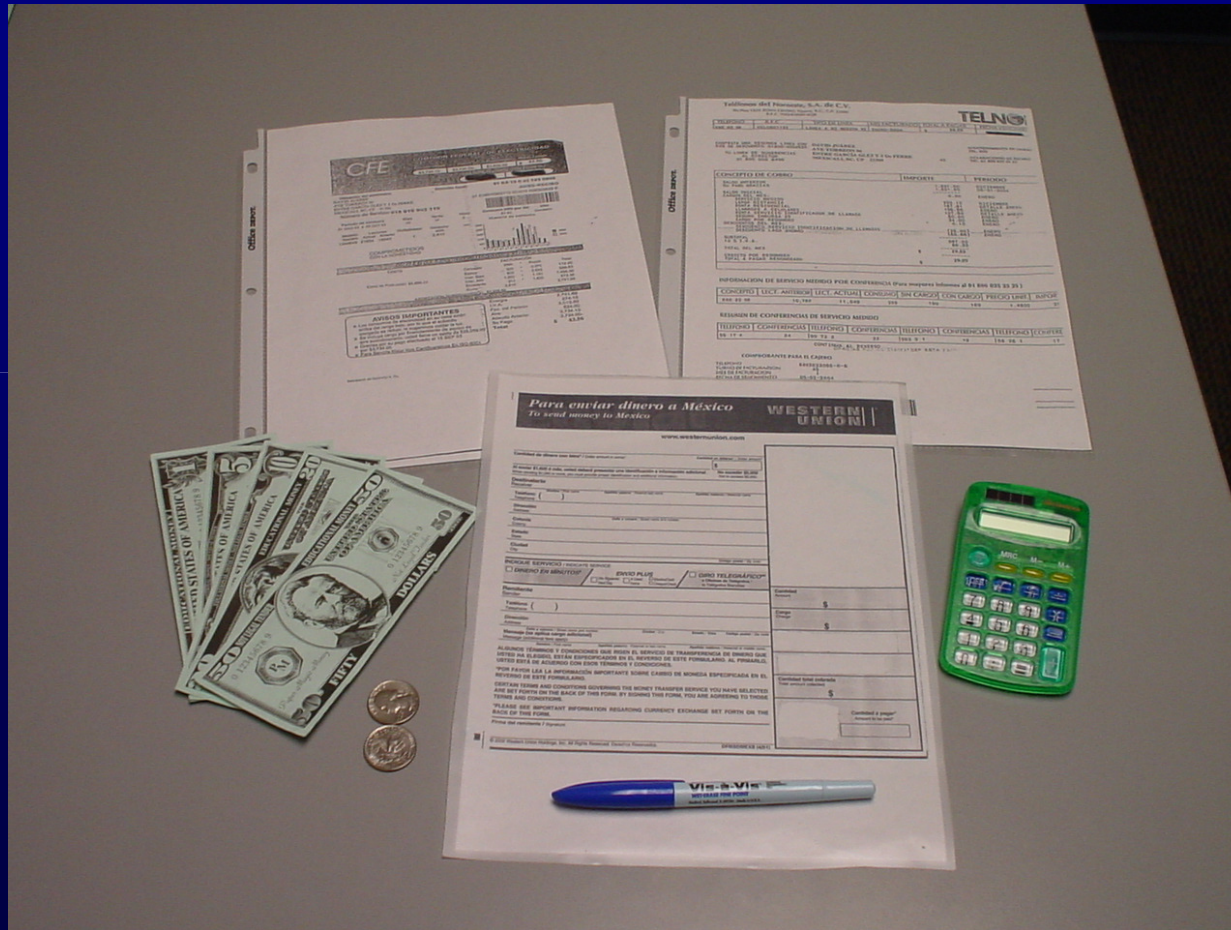


Effects of HIV-Related Brain Dysfunction on Everyday Functioning



(Heaton et al, 2004)

Daily Functioning: Money Management



Daily Functioning: Medication Management



Modified Columbia Medication Management task

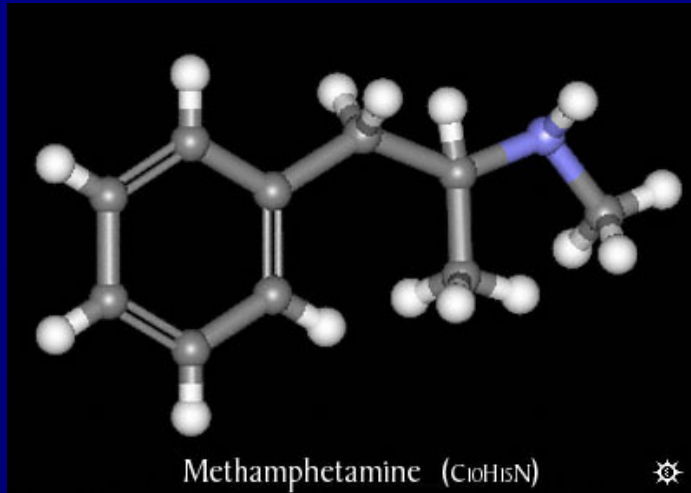


HIV+ NP impaired Ss have more difficulty on activities of daily living than NP normal Ss

* $p < .05$ ** $p < .01$ *** $p < .0001$



Methamphetamine



Carbon Hydrogen Nitrogen Oxygen Phosphorous Bromine Iodine Sulphur



Brain damage associated with heavy/chronic amphetamine use

NEUROVASCULAR

- ◆ **necrotizing angiitis**
- ◆ **arteritis**
- ◆ **vasculitis**
- ◆ **intracranial hemorrhage**
- ◆ **stroke, particularly in the subcortical white matter or basal ganglia**

NEUROPSYCHOLOGICAL

- ◆ **Learning/memory**
- ◆ **Attention**
- ◆ **Visuoconstructional abilities**
- ◆ **Abstraction**
 - **Concept formation**
 - **Decision-making**
- ◆ **Psychomotor Speed**
- ◆ **Motor Speed/dexterity**

Human Imaging Evidence of Meth-related Injury

- **Perfusion deficits in frontal and temporal brain regions ,**
- **Decreased concentrations of n-acetyl aspartate (NAA) in basal ganglia and frontal white and gray matter**
- **Hypometabolism in corticostriatal areas**
- **Hypermetabolism in the parietal lobe and cerebellum**
- **Decreased density of dopaminergic neurons in the caudate and putamen that was correlated with motor slowing and memory impairment**

Ernst *et al.*, 2000, Chang *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 1999, Iyo *et al.*, 1997; Volkow *et al.*, 2001

Proposed Mechanisms of Neurotoxicity

- ◆ Oxidative stress from dopamine metabolism
- ◆ Glutamatergic excitotoxic injury
- ◆ Increase in cytokine tumor necrosis factor (TNF- α) and expression of nuclear factor (NF)- $\kappa\beta$
- ◆ Glial activation

HCV infection of the brain

- ◆ HCV may enter the brain via infection of circulatory system cells (peripheral blood mononuclear cells [PBMCs] : monocytes) & macrophages^{1,2}
 - Proportion of infected circulating cells can vary from 8 to 83% between individuals³
 - Co-infected patients all had greater than 80%
 - HCV can be transmitted *in vitro* by infected macrophages⁴
 - HCV can persist in monocytes and macrophages even after seemingly effective therapy⁵
- ◆ HCV RNA present in cerebrospinal fluid⁶
- ◆ of RNA matches that PBMCs; evidence that they may carry HCV into the brain⁷

¹Zignego et al, *J Hepatol*, 1992; ²Bouffard et al, *JID*, 1992; ³Lerat et al, *Blood*, 1998; ; ⁴Revie et al, *Virology*, 2005; ⁵Radkowski, et al, *Hepatology*, 2005; ⁶Maggi et al, *J Neurovirology*, 1999; ⁷Laskus, et al, *J Virol*, 2002



HCV and the Brain

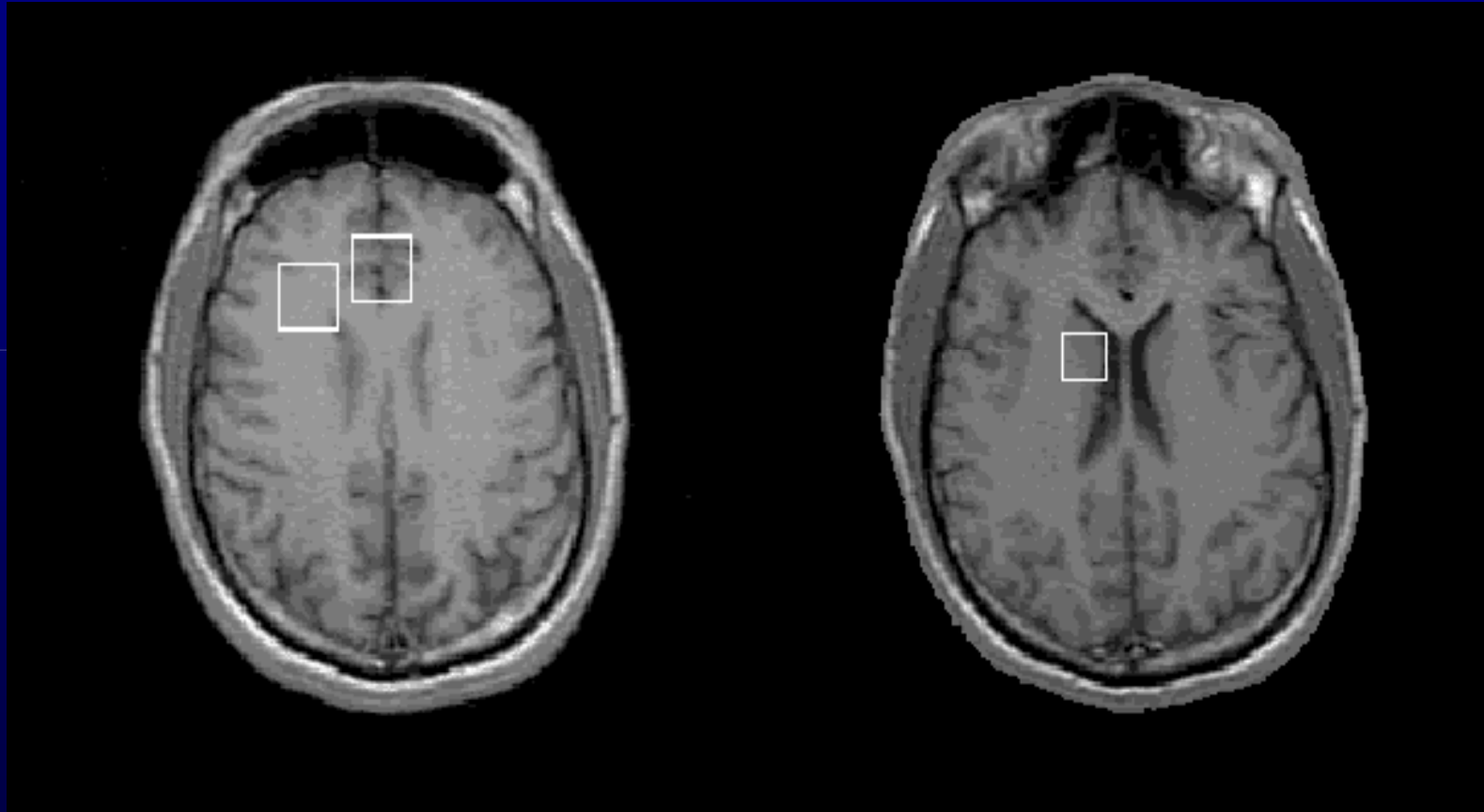
Neurologic Syndromes

- ◆ Hepatic encephalopathy
- ◆ Anterior optic neuropathy
- ◆ CNS vasculitis with ischemic or hemo-rrhagic strokes
- ◆ Cranial neuropathy
- ◆ Demyelinating myelitis
- ◆ Restless leg syndrome



Tembl, Neurology, 1999; Marie, et al 2000; Grewal, J N Sci,

Magnetic Resonance Spectroscopy (MRS) Regions of Interest



Sample MRS Spectrum

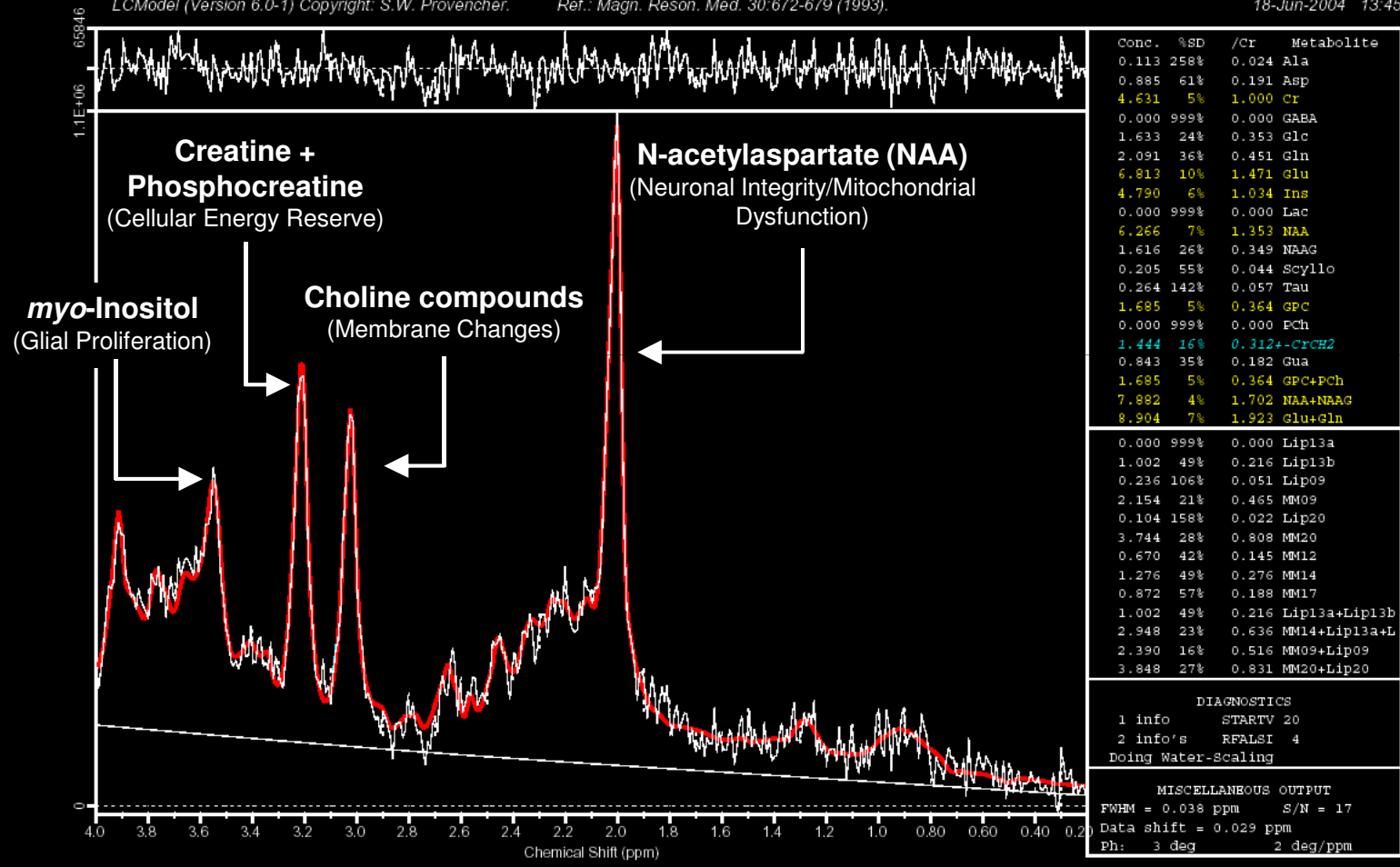
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SINAI MEDICAL CENT)

Data of: Psychiatry Department, San Diego VA Healthcare System

LCModel (Version 6.0-1) Copyright: S.W. Provencher.

Ref.: Magn. Reson. Med. 30:672-679 (1993).

18-Jun-2004 13:45



MR Spectroscopy: HCV associated with brain inflammation and neural injury

◆ HCV+

- Mild liver disease
- Elevated Cho/Cr levels compared with controls
- Healthy volunteers and HBV pts

◆ Unrelated to

- Hepatic encephalopathy
- IVDU

- Forton et al, Lancet, 2001

◆ HCV+METH+ had lower NAA levels in frontal white matter

◆ Both METH+ groups had lower NAA levels in frontal grey matter

- Taylor et al, JINS, 2003



HCV infection of the brain

- Negative strand RNA was found in brain tissue^{1, 2}
 - Evidence of active replication
- HCV infects astrocytes in vitro²

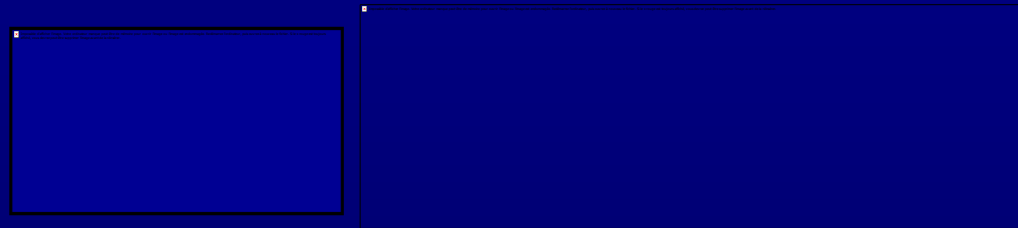


¹Forton, et al, *J Virol*, 2004; ²Letendre et al; 2007

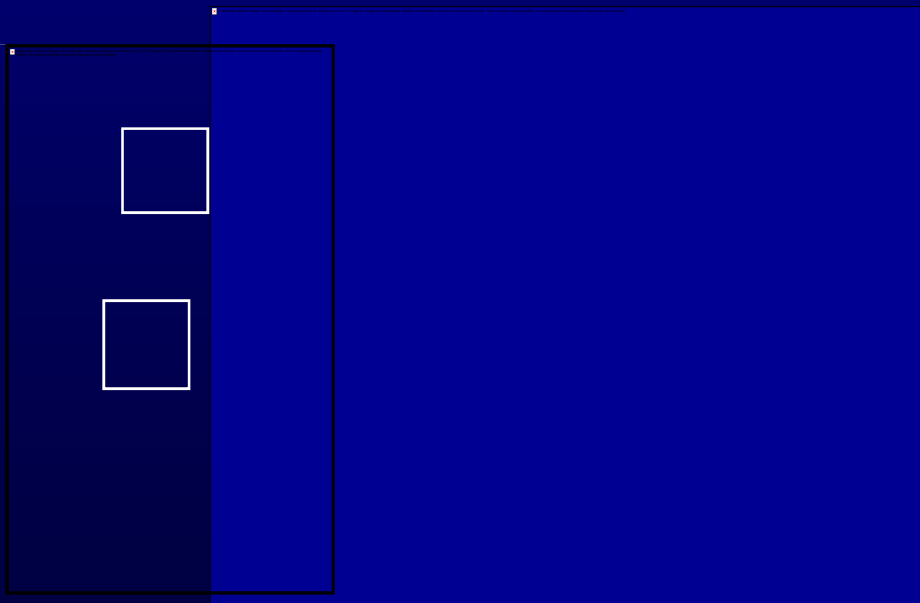
Hepatitis C

Infection of Astrocytes and Brain Macrophages

Detection of HCV mRNA in the brains of HIV HCV+ by nested PCR



Detection of HCV in astrocytes of HIV+ HCV+ cases



HCV infects primary astrocytes in vitro

	<i>Control</i>	<i>HCV</i>
<i>HCV-</i>		
<i>HCV+</i>		
<i>HCV+</i>		



Courtesy E. Masliah

HCV and the Brain

Summary of Published Data

- ◆ HCV is associated with worse performance on neuropsychological testing
 - Not limited to those with advanced liver disease
- ◆ HCV is associated with cerebral metabolite changes on magnetic resonance spectroscopy
- ◆ Evidence of HCV replication in the CNS
 - HCV RNA in CSF in some individuals
 - Negative strand RNA found in brain tissue
 - Distinct HCV genotypes in brain tissue



HIV and HCV Co-infection

- ◆ HIV and HCV influence each other's course
 - HIV is associated with higher HCV RNA levels, more rapid liver disease progression, and death
 - HCV is associated with more rapid progression to AIDS and death
- ◆ Antiretroviral treatment of HIV infection can result in lower HCV viral loads
- ◆ As survival of HIV-infected patients improves, morbidity and mortality due to HCV may increase



HIV - HCV coinfection and the Brain

- NP Testing -

- ◆ 220 women enrolled in the Women's Interagency HIV Study (WIHS)
- ◆ HCV+HIV+ ~twice as likely to be impaired as HCV-
 - ~5-fold increased odds when $CD4 \leq 200/\mu L$
 - ~7-fold increased odds when not taking ART
- ◆ Effect persisted independent of
 - Education, IQ, depression, sedating drug use, head injury, ethnicity, and history of substance use

• *Richardson et al, AIDS, 2005*



HIV - HCV coinfection and the Brain

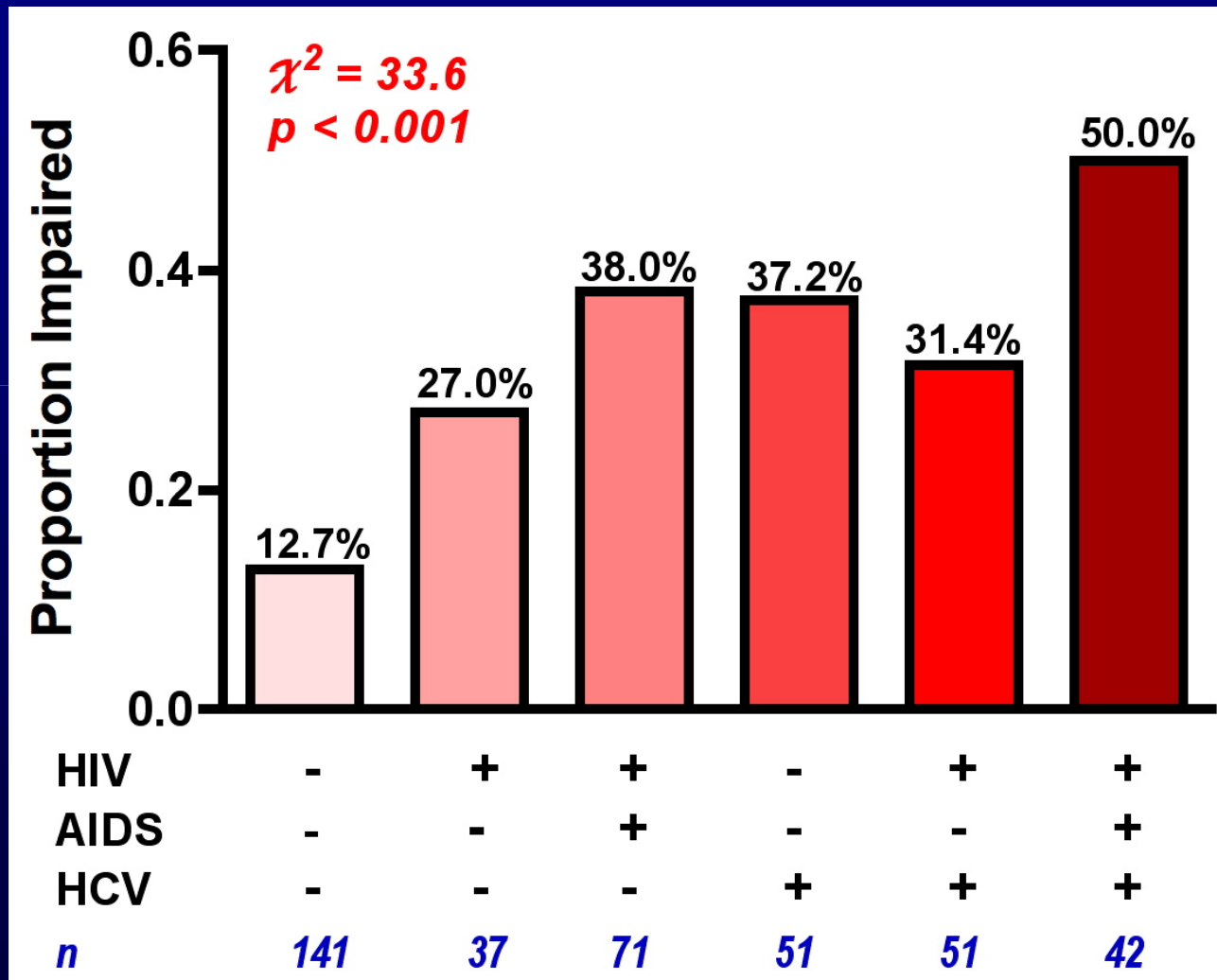
-NP Testing -

- ◆ 116 HIV+ individuals (67 HCV+, 49 HCV-) who had advanced HIV disease and enrolled in Manhattan HIV Brain Bank
 - HCV+HIV+ subjects were more likely to have past or current stimulant or opiate use
- ◆ HCV+HIV+ more likely to be
 - Impaired on tasks of executive function
 - Diagnosed with HIV-associated dementia
- ◆ Not associated with non-invasive indicators of liver disease

• *Ryan et al, Neurology, 2004*



Rates of NP impairment in Chinese former plasma donors with HIV and/or HCV (N=401)



courtesy
R. Heaton



Impaired Memory Performance is Associated with HCV RNA



Letendre et al, *AIDS*, 2005;

UCSD
Program Project on
NeuroAIDS Effects of
Methamphetamine
Igor Grant, MD, PI

funded by NIDA



Cognitive impairment in subjects with single or co-morbid HIV and Meth Risks (N=398)

Proportion HCV Infected



Rates of NP Impairment by Number of Risk Factors



Contribution of Each Risk Factor to NP Deficit Scores (β coefficients and 1-tailed p values)

DEFICIT SCORE	HCV		HIV		METH	
	β	p	β	p	β	p
Global	.15	.002	.15	.003	.07	.11
Learning	.14	.005	.12	.01	.11	.01
Recall	.11	.02	.08	.06	.05	.18
Motor	.15	.003	.12	.01	.16	.001
Abstraction	.13	.01	.11	.03	-.001	.49
Processing Speed	.10	.03	.11	.02	-.02	.38
Attention/Wk. Memory	.02	.34	.05	.18	.07	.10
Verbal	.07	.13	.05	.42	.07	.16

UCSD
Program Project on
NeuroAIDS Effects of
Methamphetamine and HCV

Igor Grant, MD, PI

funded by NIDA

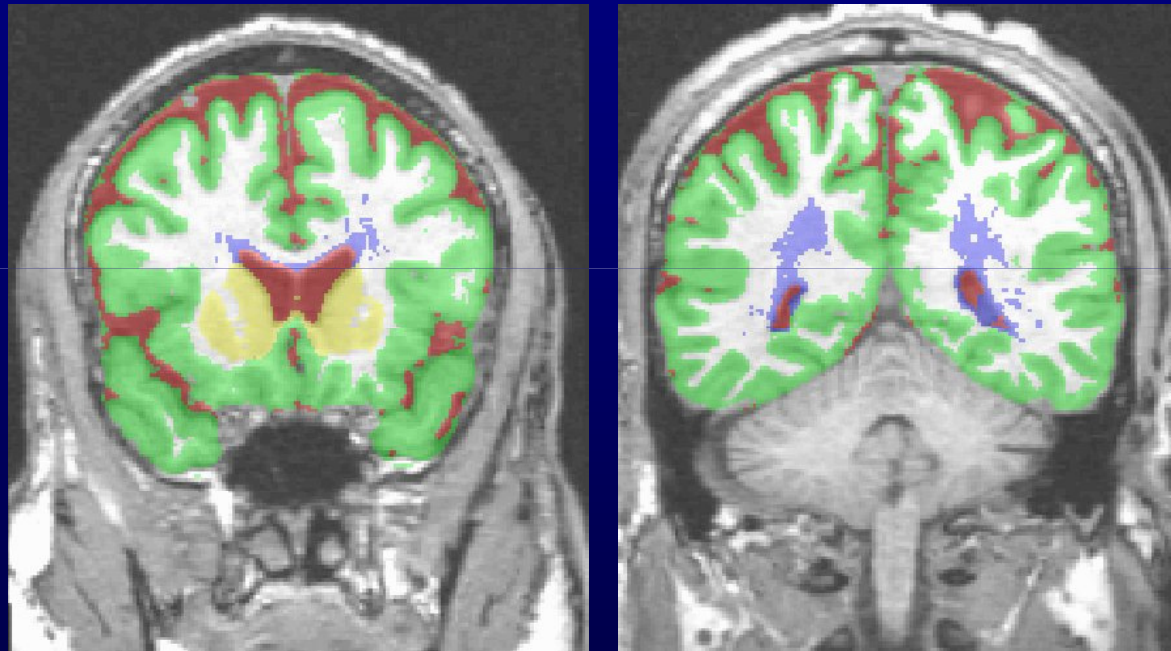


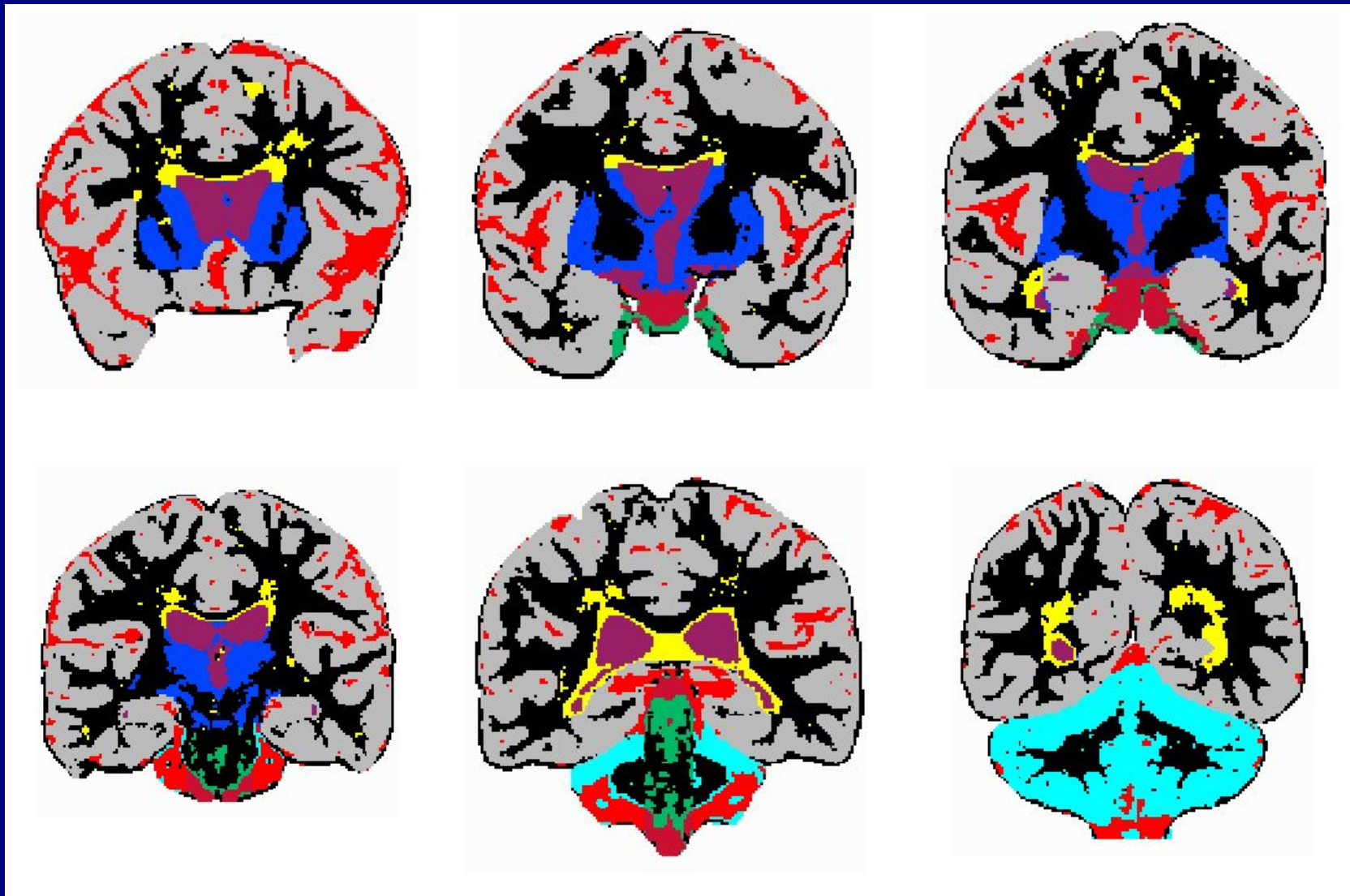


Neuroimaging of Evolving White Matter Damage:
Effects on Cognition in HIV and HCV

Terry L. Jernigan, Ph.D.

MRI: Morphometry Measures





CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Preliminary Observations from CHARTER Neuroimaging Studies

What disease factors relate to the
different forms of tissue damage?

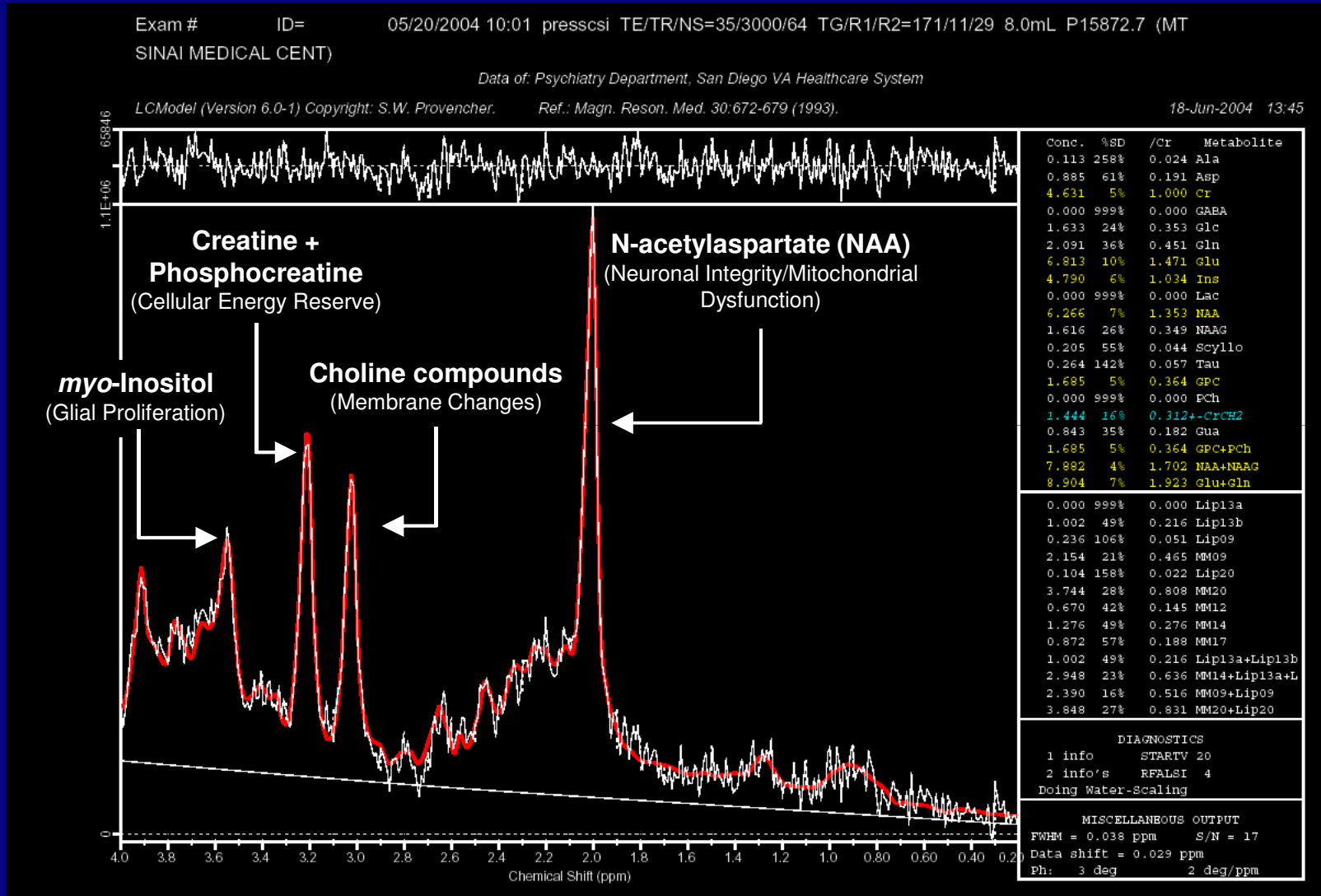
- Age
- Nadir CD4
- Current CD4
- HCV co-infection
- ARV regimen: naïve, HAART, ARVs discontinued



Factors Contributing to Cortical and White Matter Tissue Damage



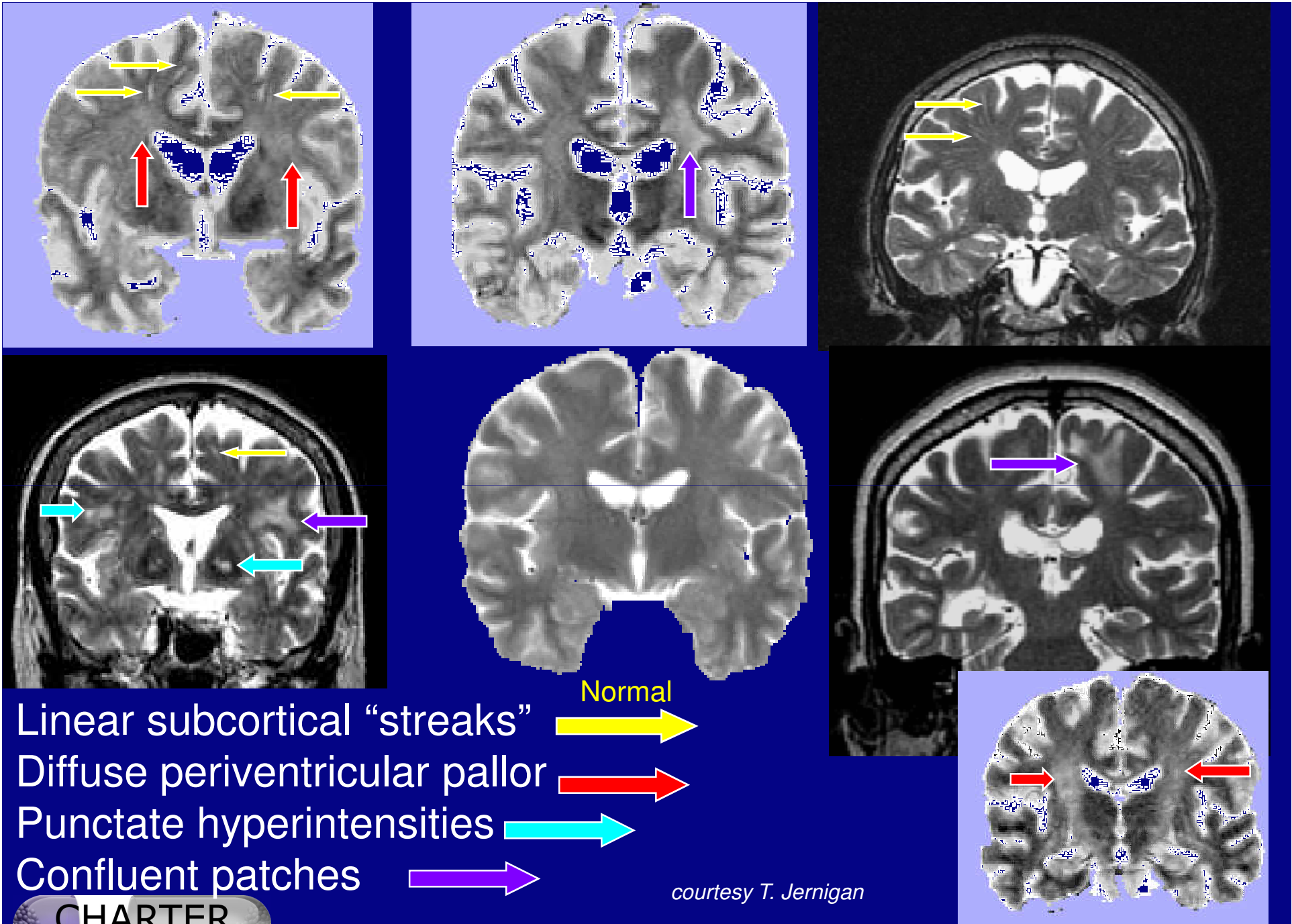
Sample MRS Spectrum



CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Follow-up Analyses of Factors Related to WM Damage

**WM Abnormalities in CHARTER
Participants Include Several
Lesion Types**



- Linear subcortical "streaks" ➡
- Diffuse periventricular pallor ➡
- Punctate hyperintensities ➡
- Confluent patches ➡

courtesy T. Jernigan



CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Factors Contributing to Different Types of White Matter Damage

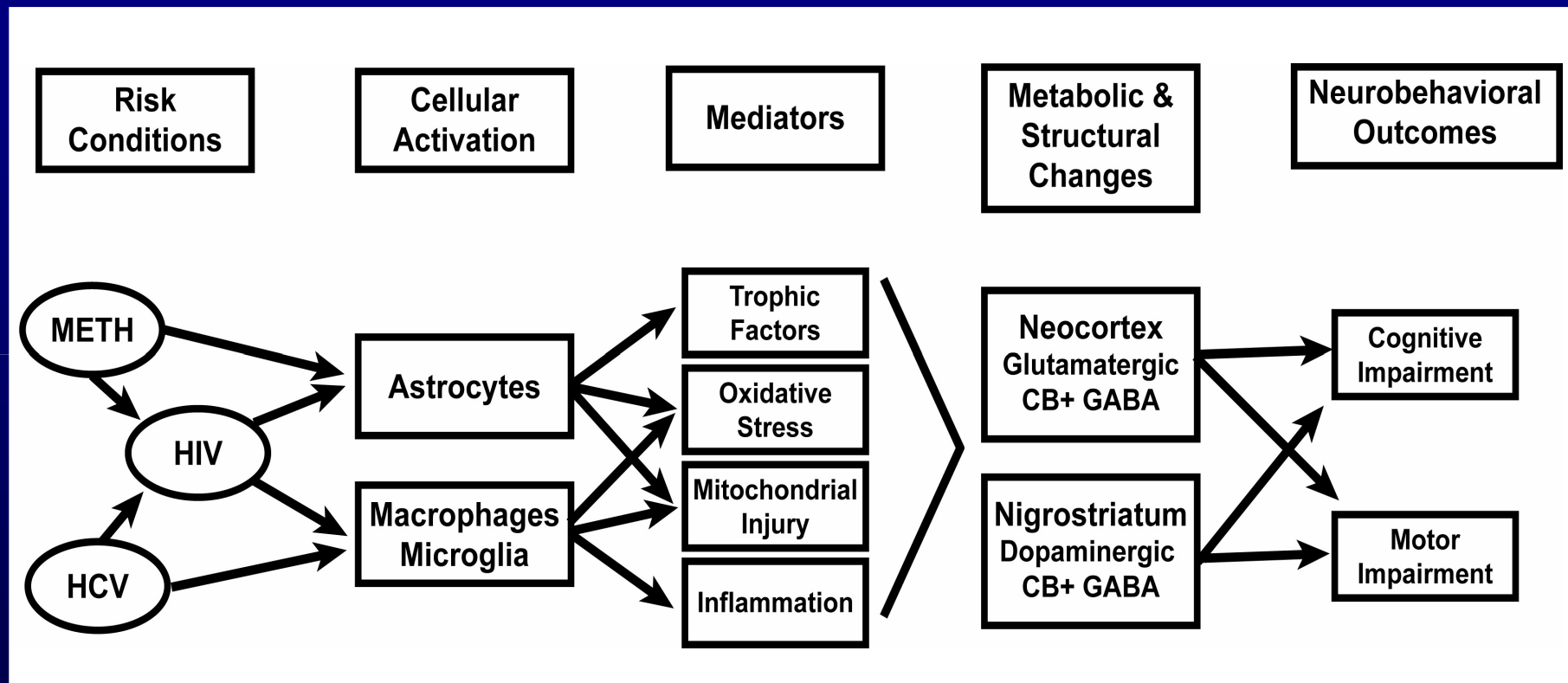


courtesy T. Jernigan



METH, HCV, and HIV

Multiple Levels of Interaction



courtesy S. Letendre

Acknowledgements

◆ Study Volunteers

- ◆ Symposium Organizers, Congress Organizers, and Translators
- ◆ National Institute on Drug Abuse
- ◆ National Institute of Mental Health

◆ HIV Neurobehavioral Research Center

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