MULTIFACETED INFLUENCES ON NEUROAIDS: EFFECTS OF METHAMPHETAMINE, HCV AND AGE

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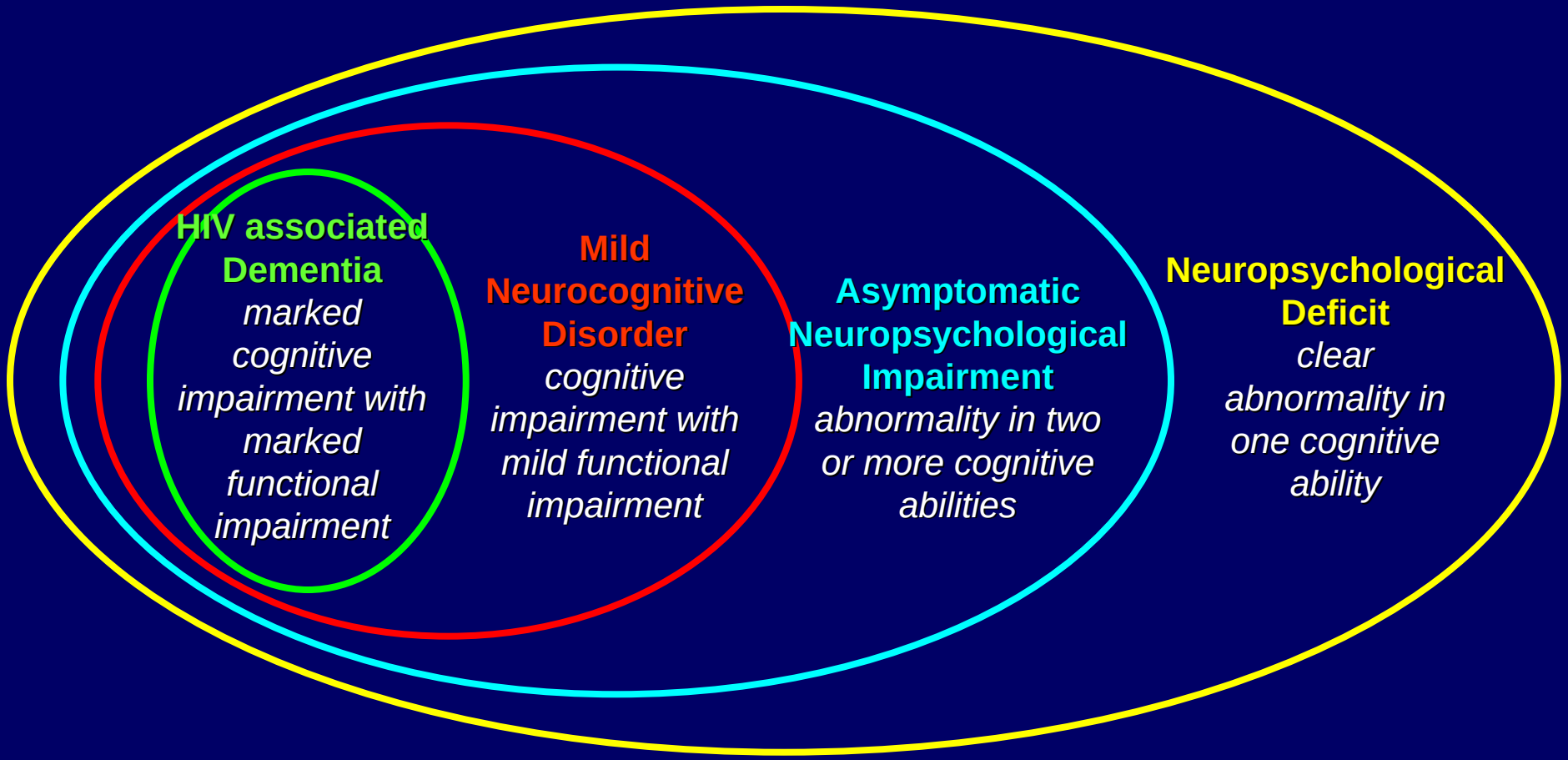
Range of HIV Associated Neurocognitive Disorders (HAND)



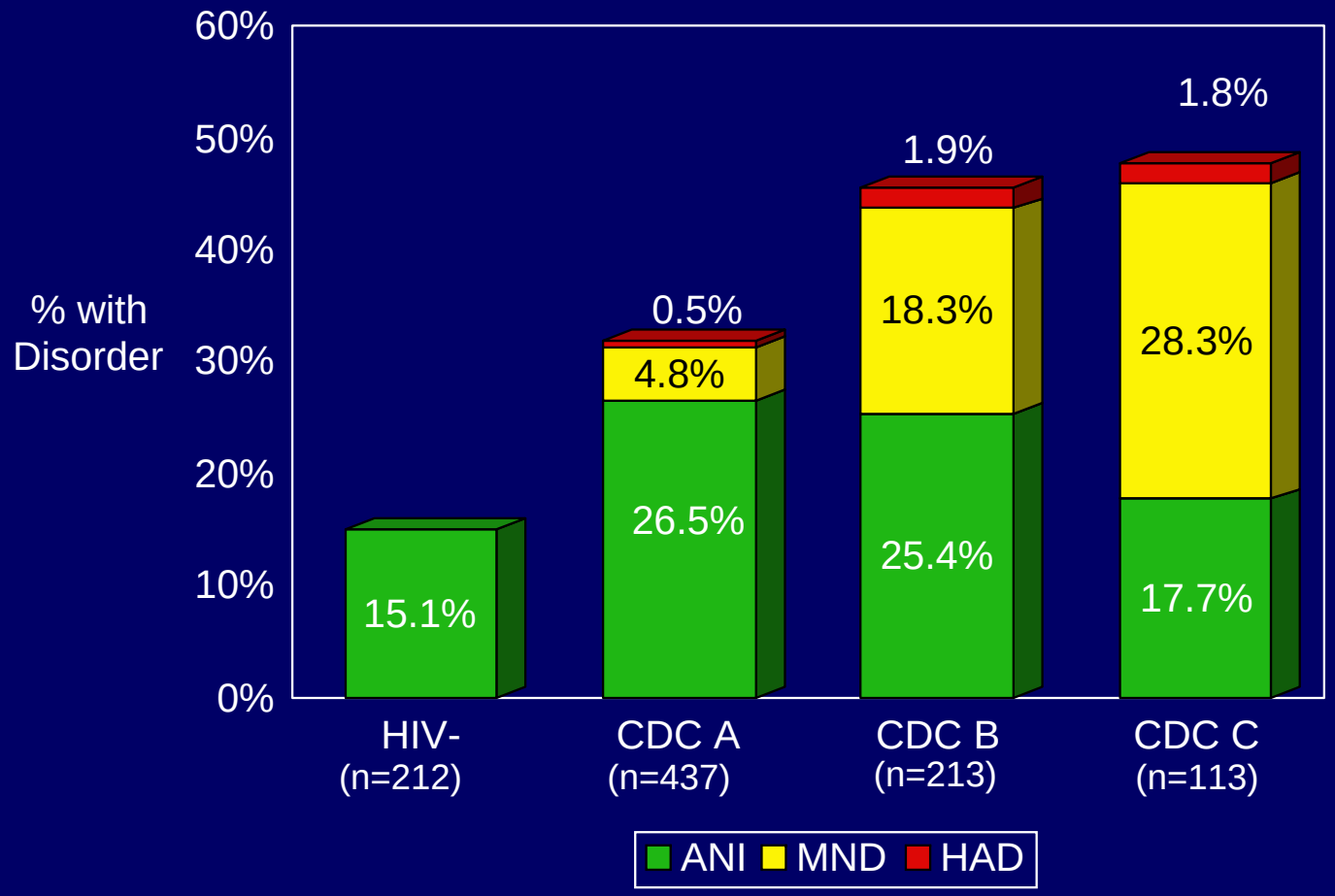
NEUROLOGY

Updated research nosology for HIV-associated neurocognitive disorders

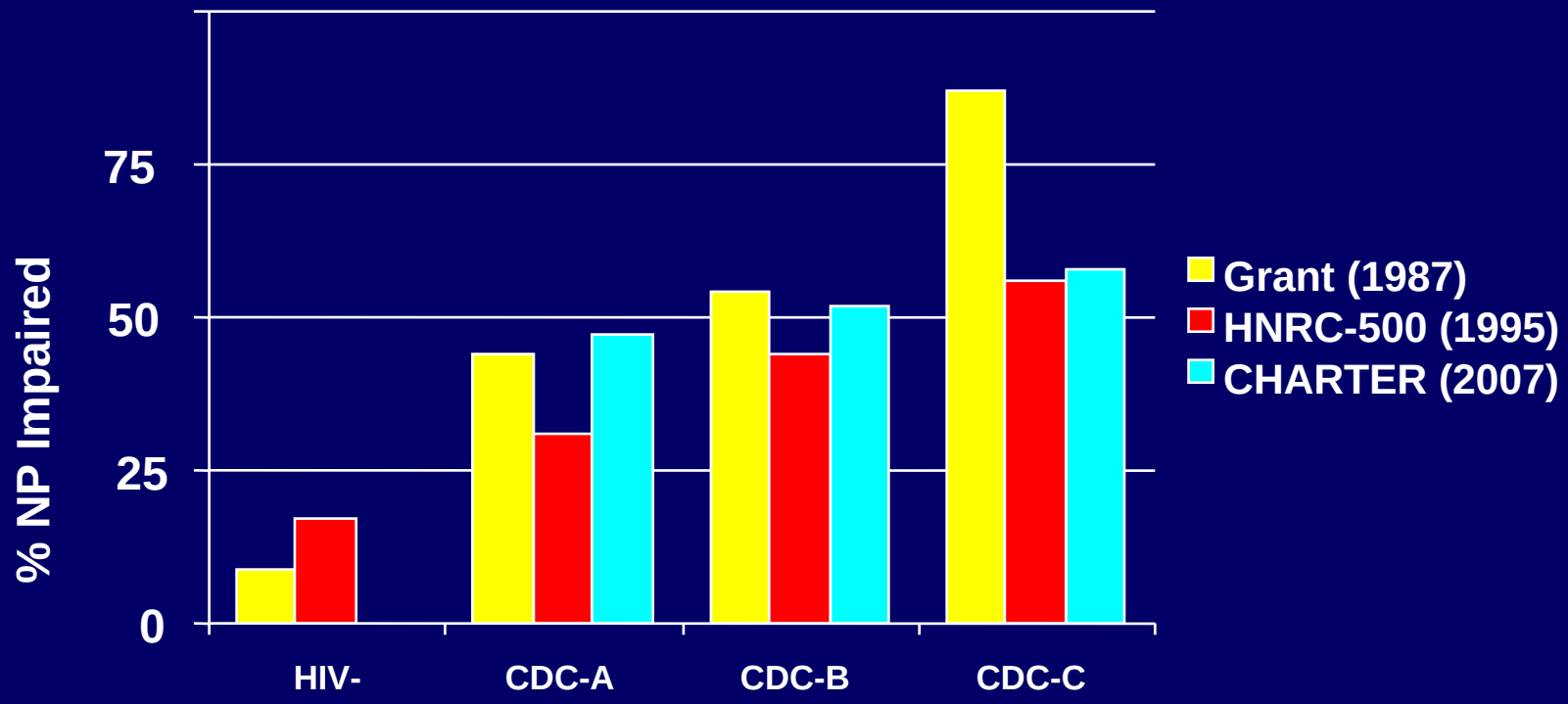
A. Antinori, G. Arendt, J. T. Becker, B. J. Brew, D. A. Byrd, M. Cherner, D. B. Clifford, P. Cinque, L. G. Epstein, K. Goodkin, M. Gisslen, I. Grant, R. K. Heaton, J. Joseph, K. Marder, C. M. Marra, J. C. McArthur, M. Nunn, R. W. Price, L. Pulliam, K. R. Robertson, N. Sacktor, V. Valcour and V. E. Wojna

Neurology 2007;69;1789-1799; originally published online Oct 3, 2007;
DOI: 10.1212/01.WNL.0000287431.88658.8b

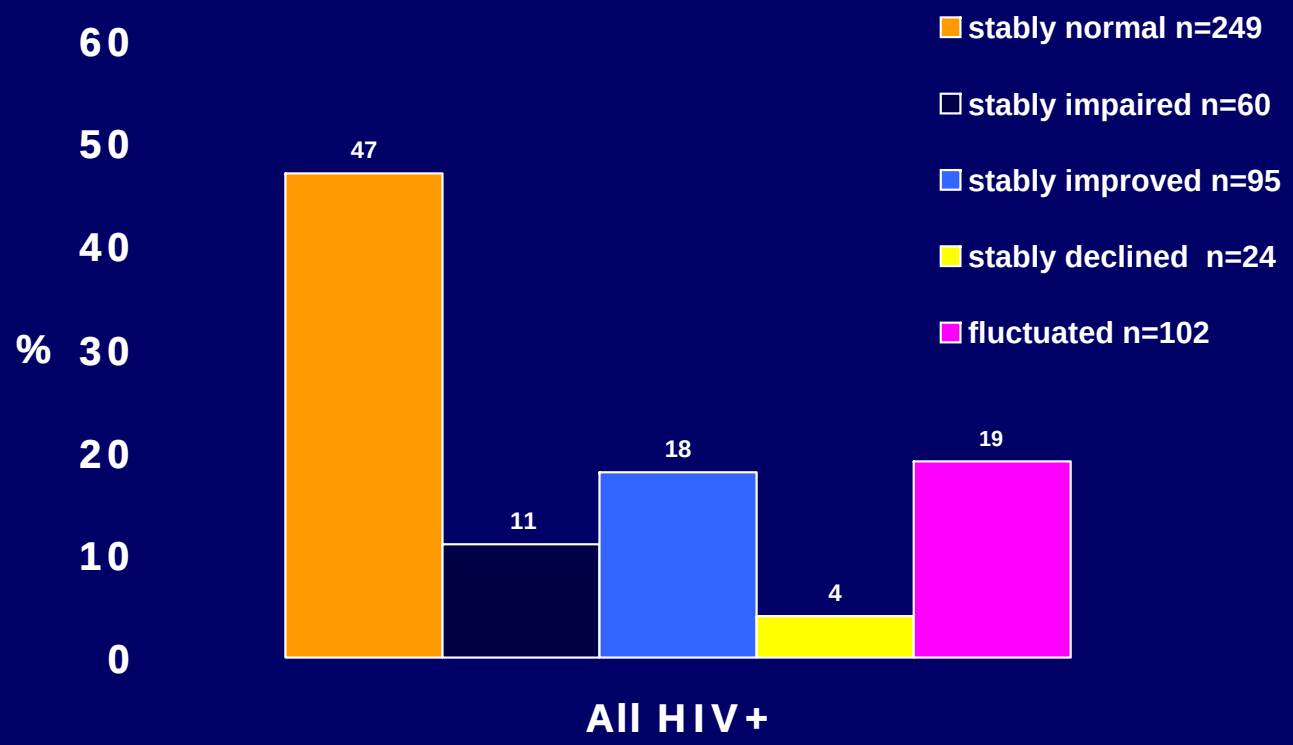
Prevalence of HAND by Stage of HIV Disease



Although combination antivirals improve health and prolong survival, NeuroAIDS remains prevalent

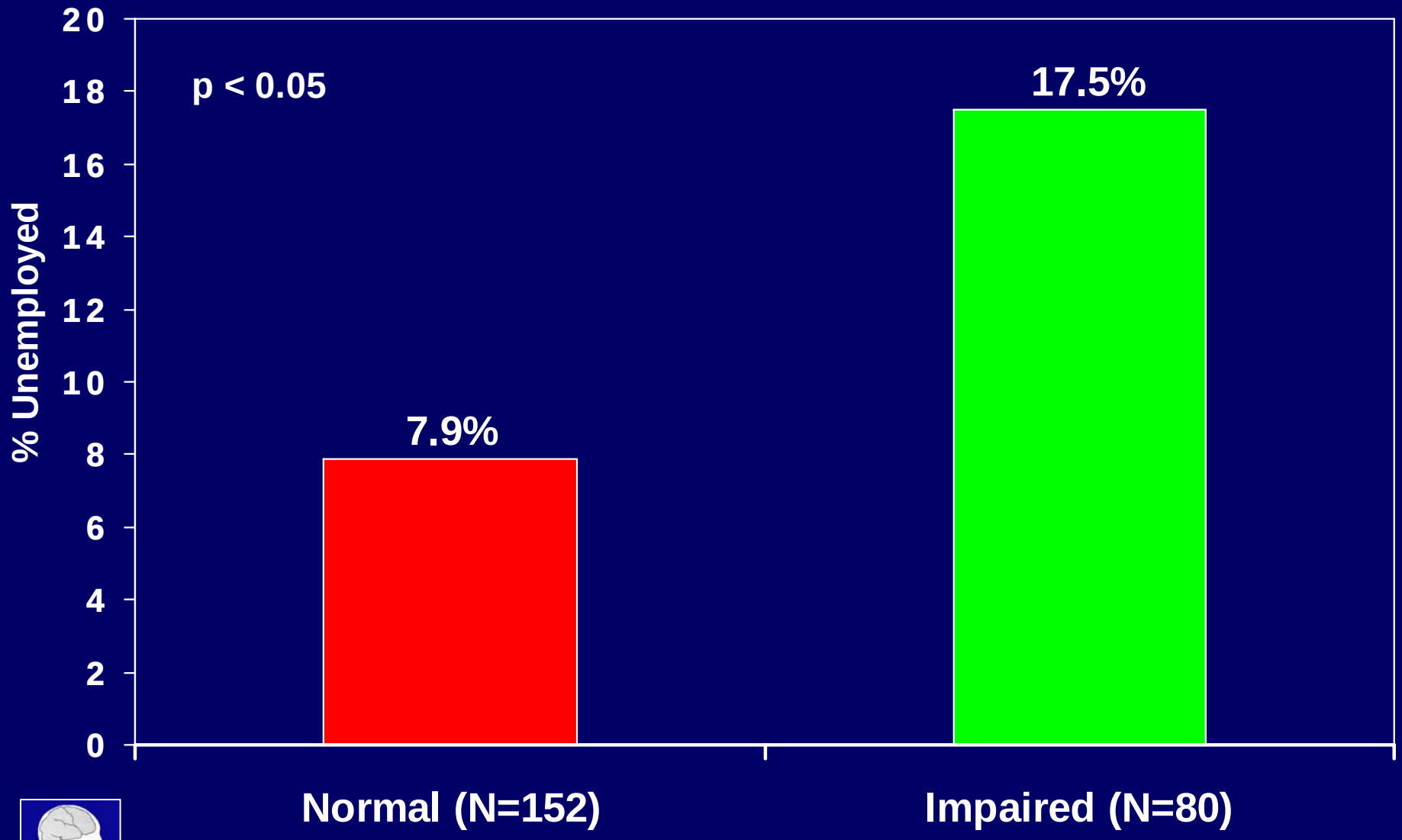


NP Course for HIV neurocognitive states N=534

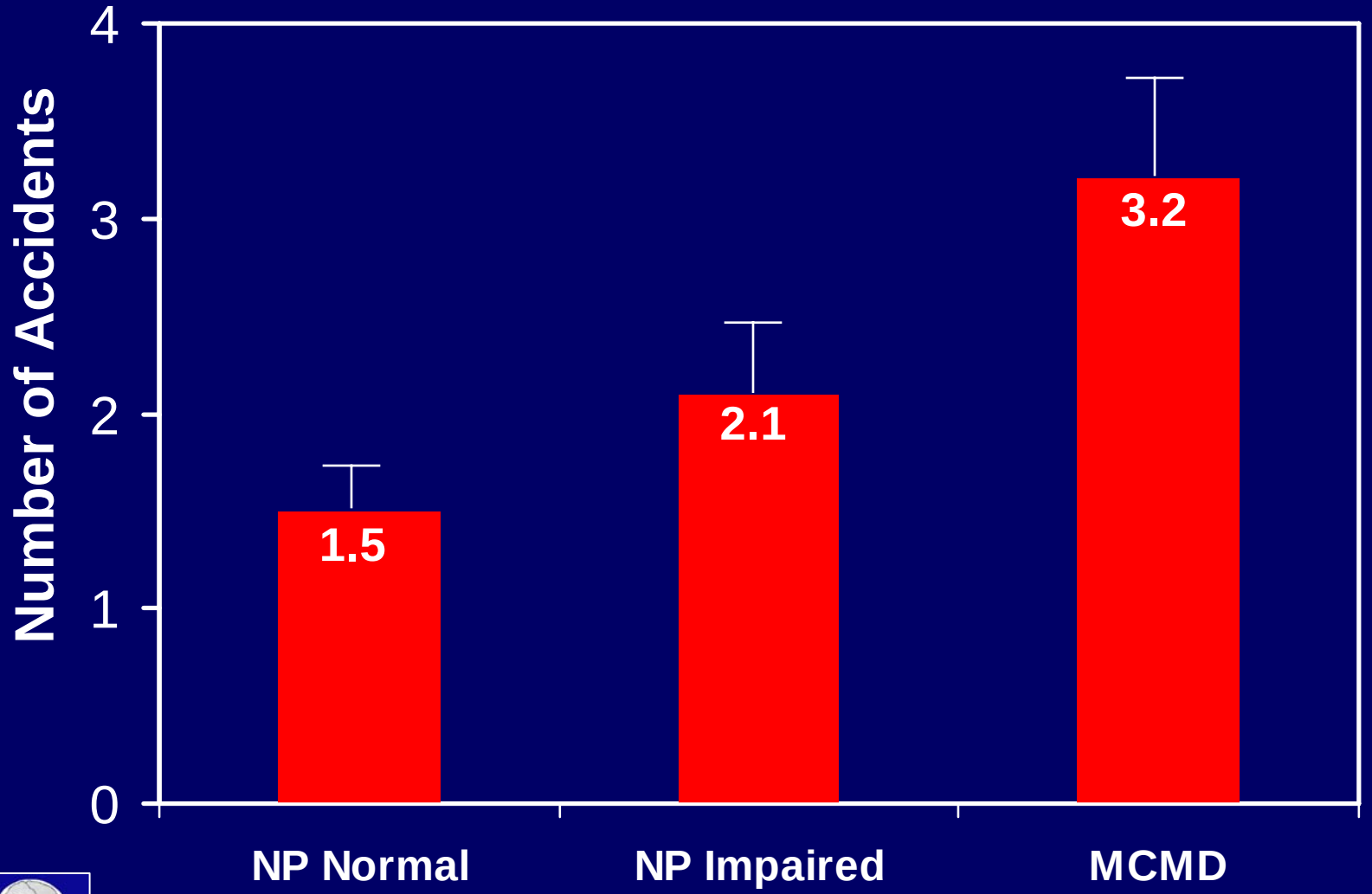


Definitional Criteria Work Group 1: Toward an updated nosology for HIV-associated neurocognitive disorders

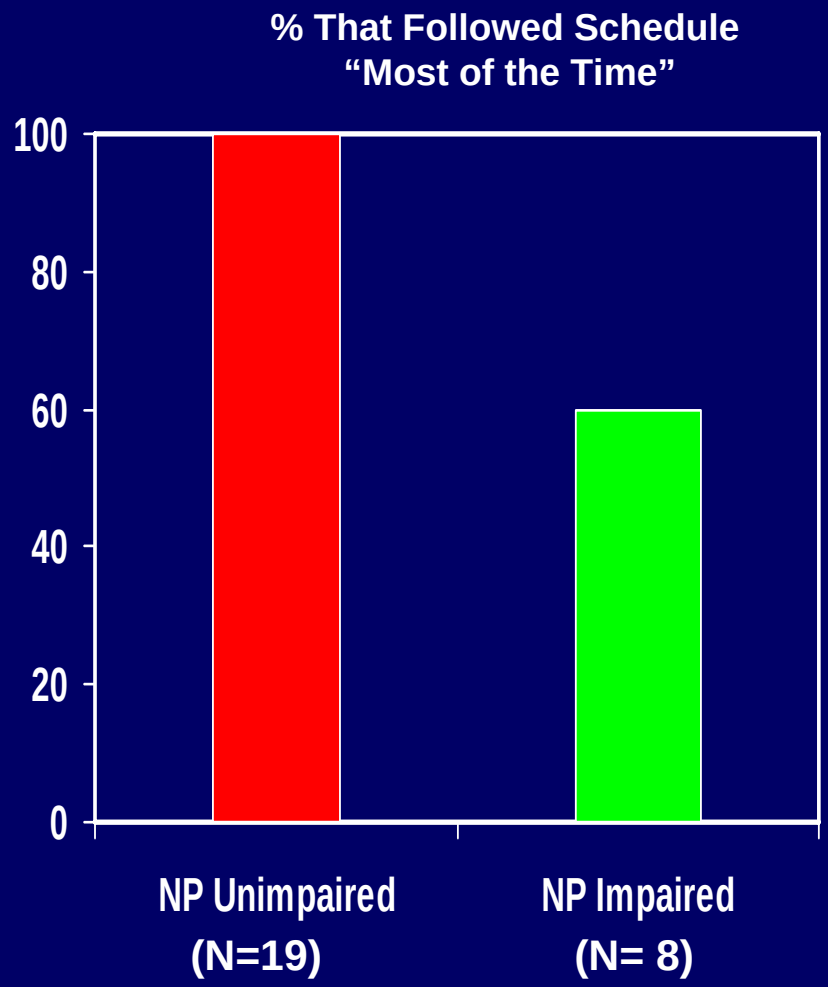
Meaning of NP Impairment: Employment

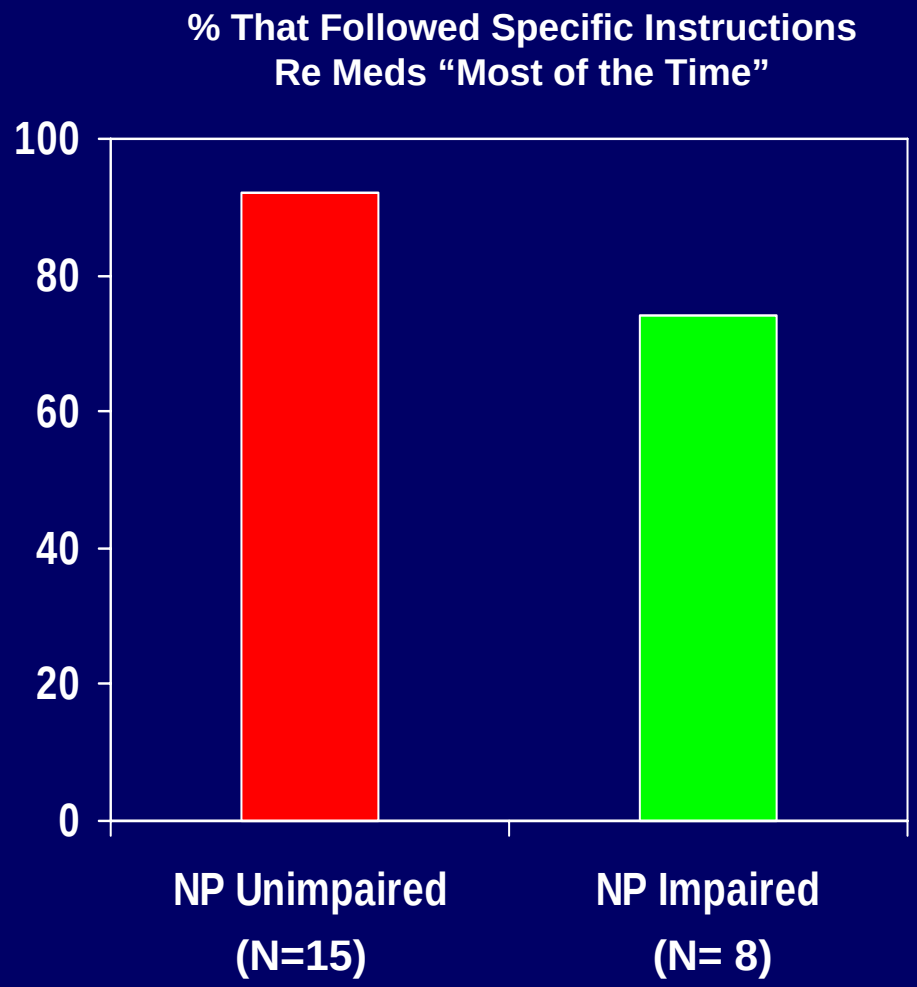


Mean Number of Accidents on City Driving Simulation

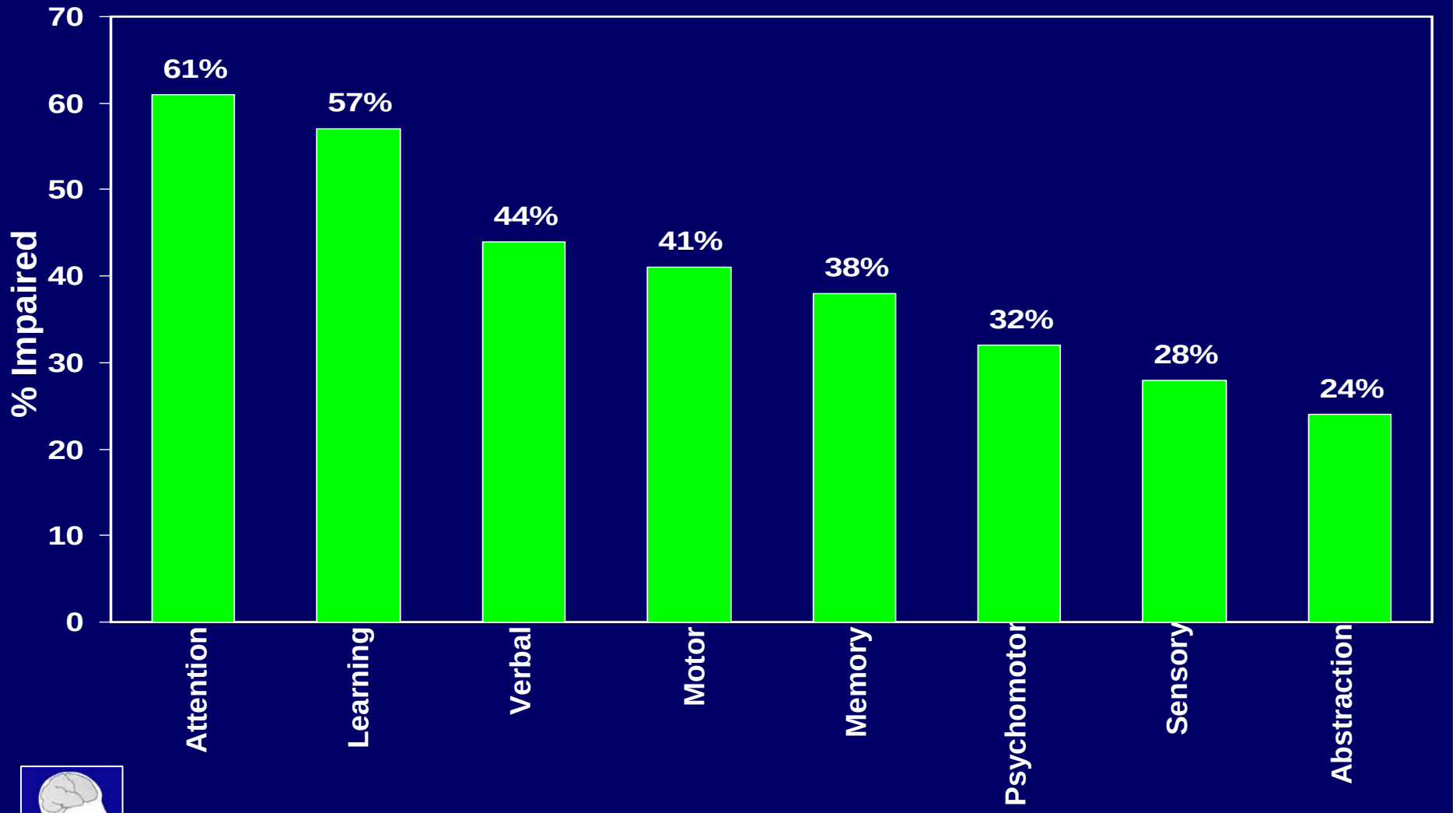


Adherence to Antiretrovirals Related to Neurocognitive Impairment

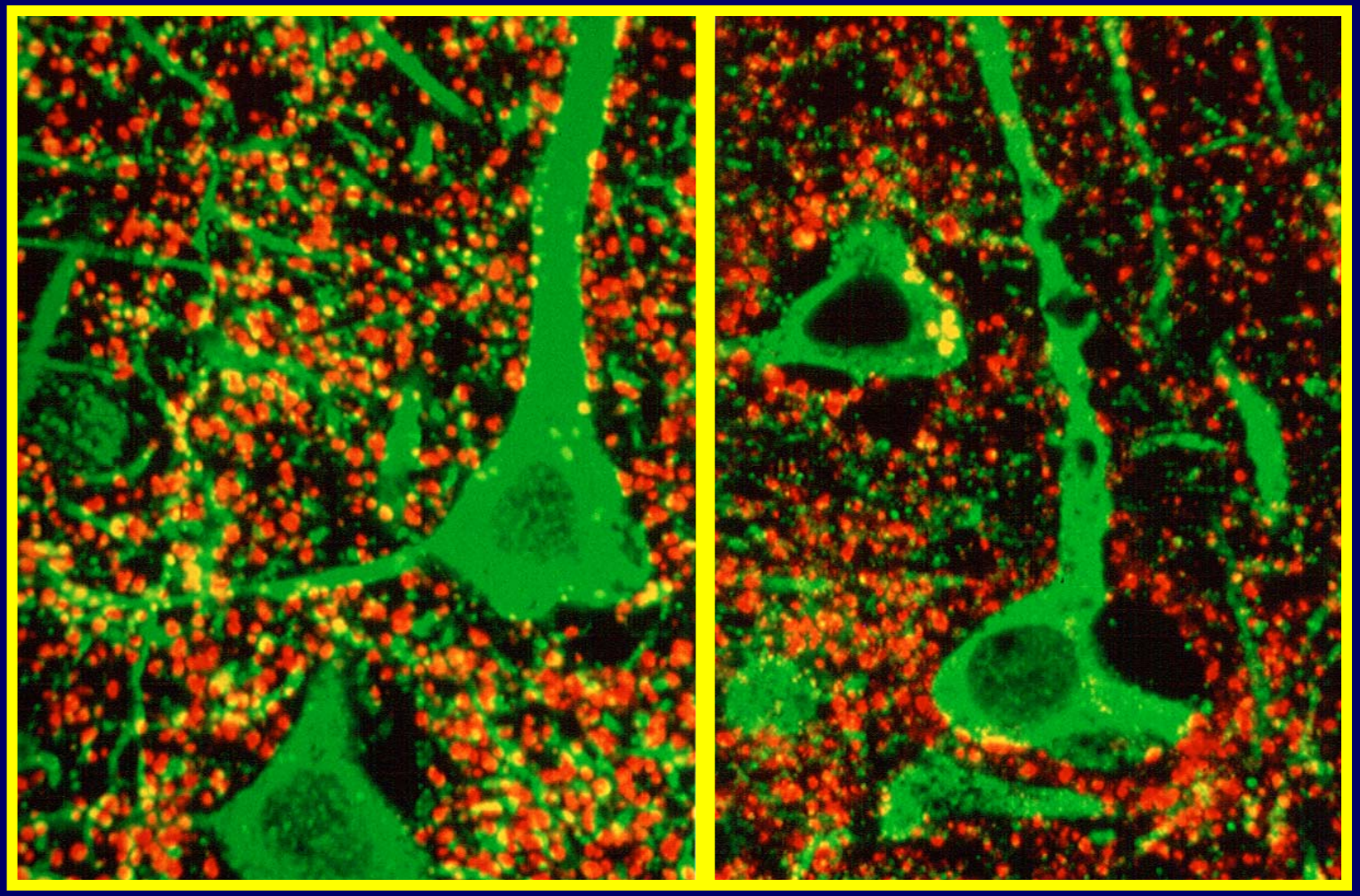




Proportions of Persons Judged to have Global NP Impairment that have Specific Ability Deficit



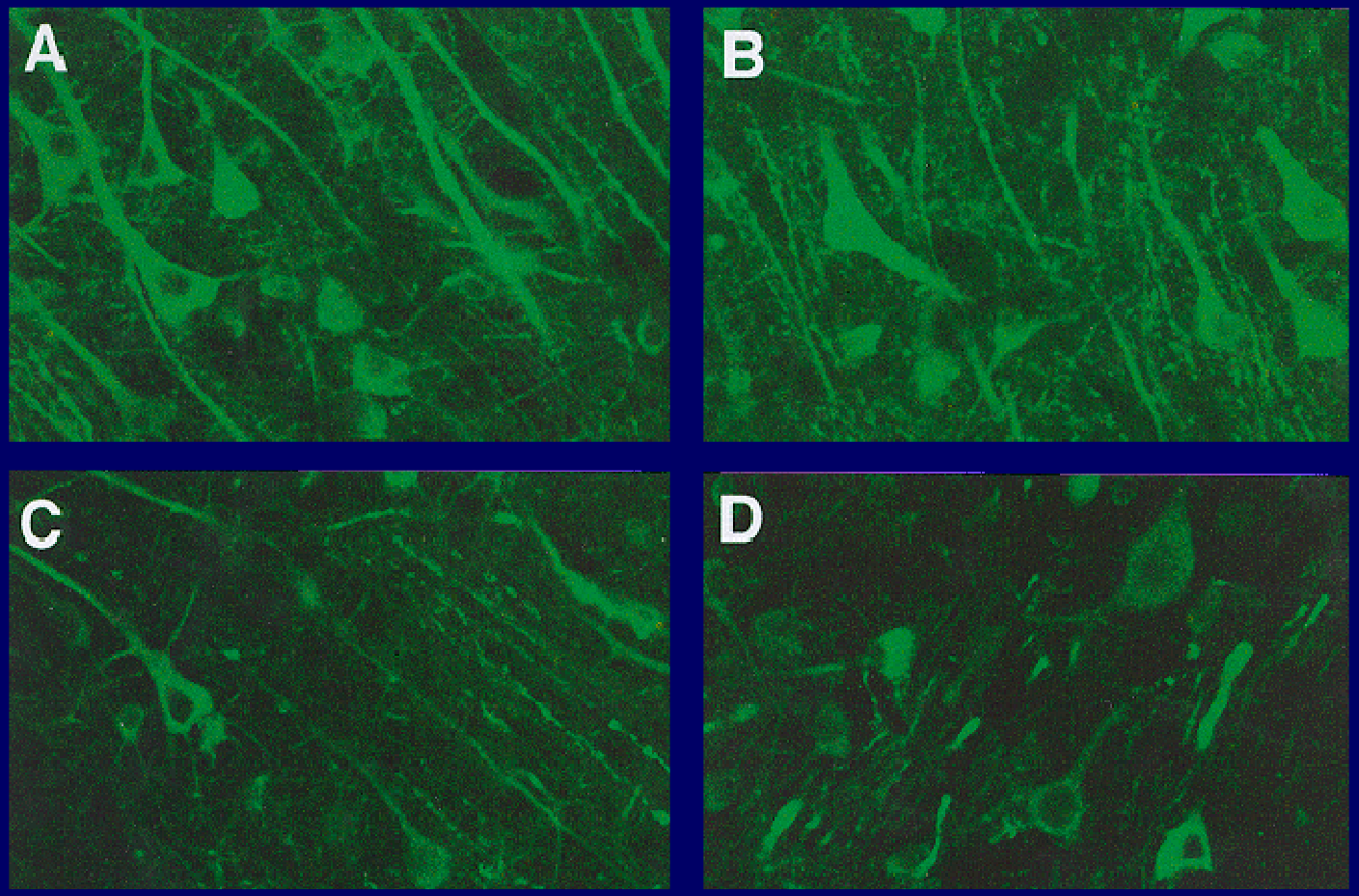
Synaptophysin & MAP-2 Immunostaining



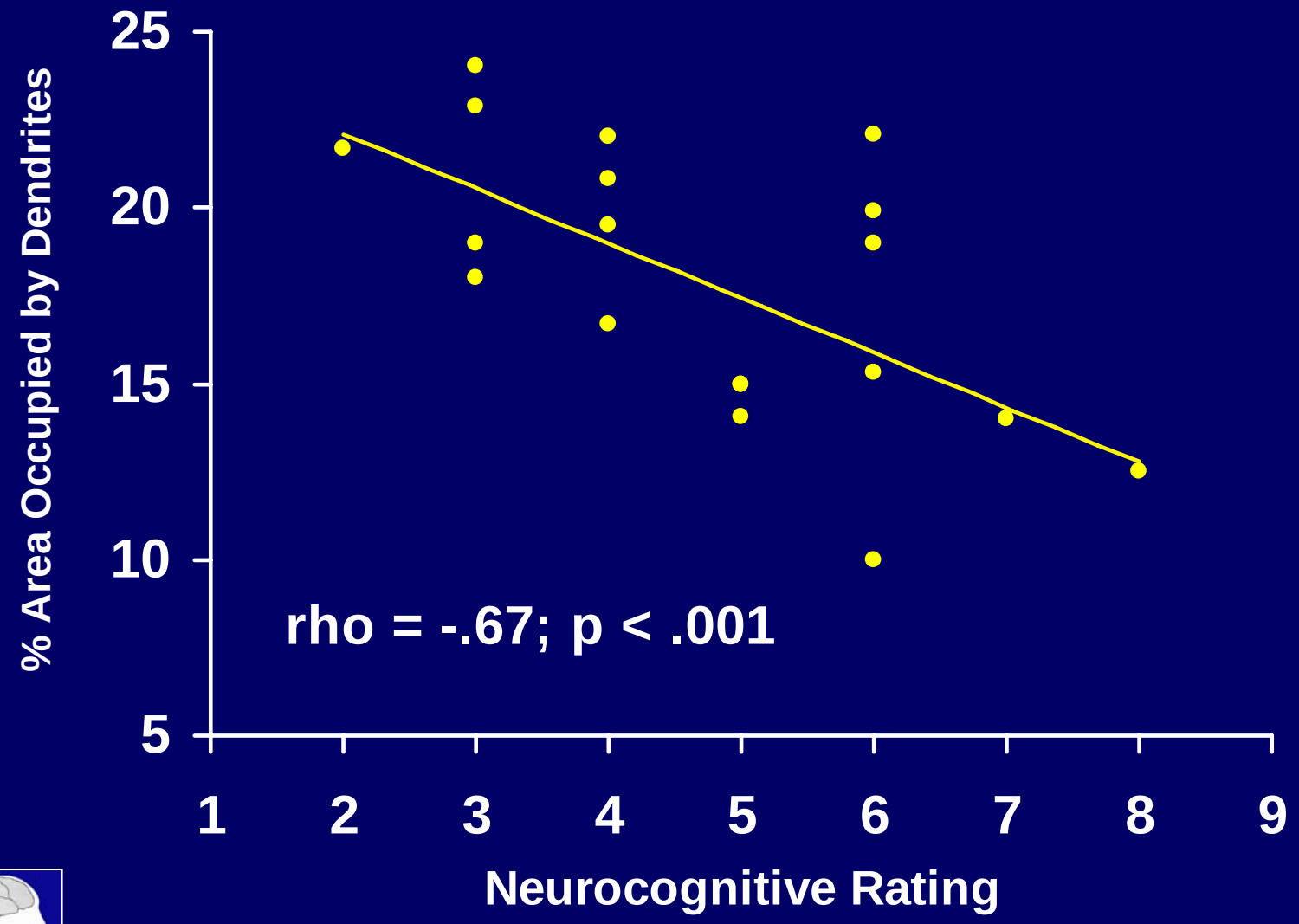
HIV-

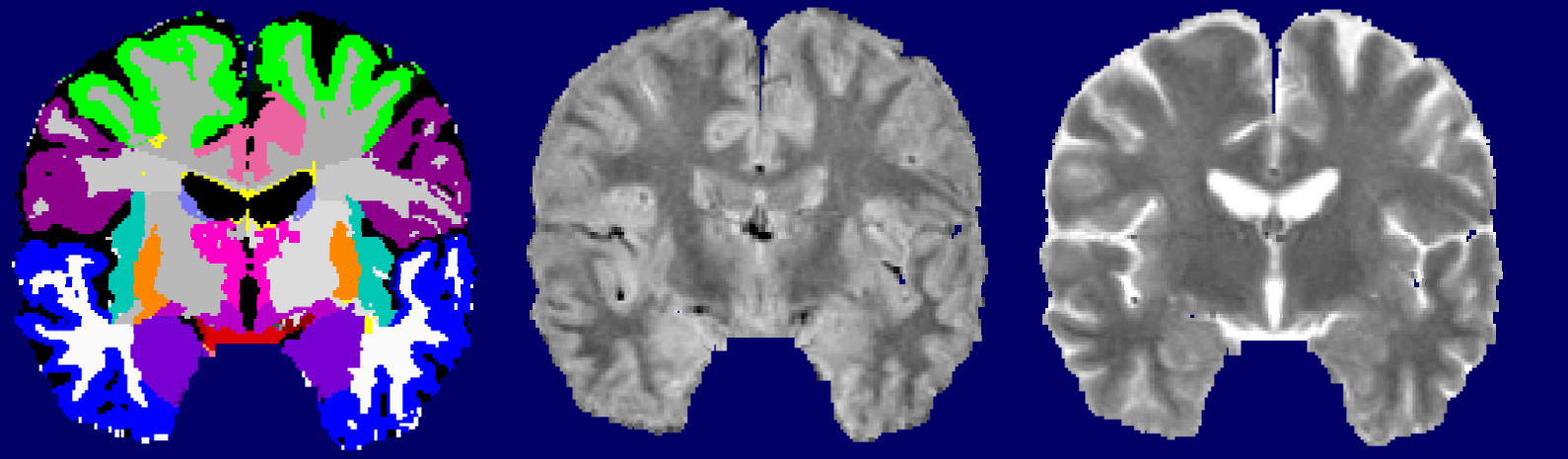
HIV+

Dendritic Complexity in Subjects with Varying Levels of Cognitive Impairment

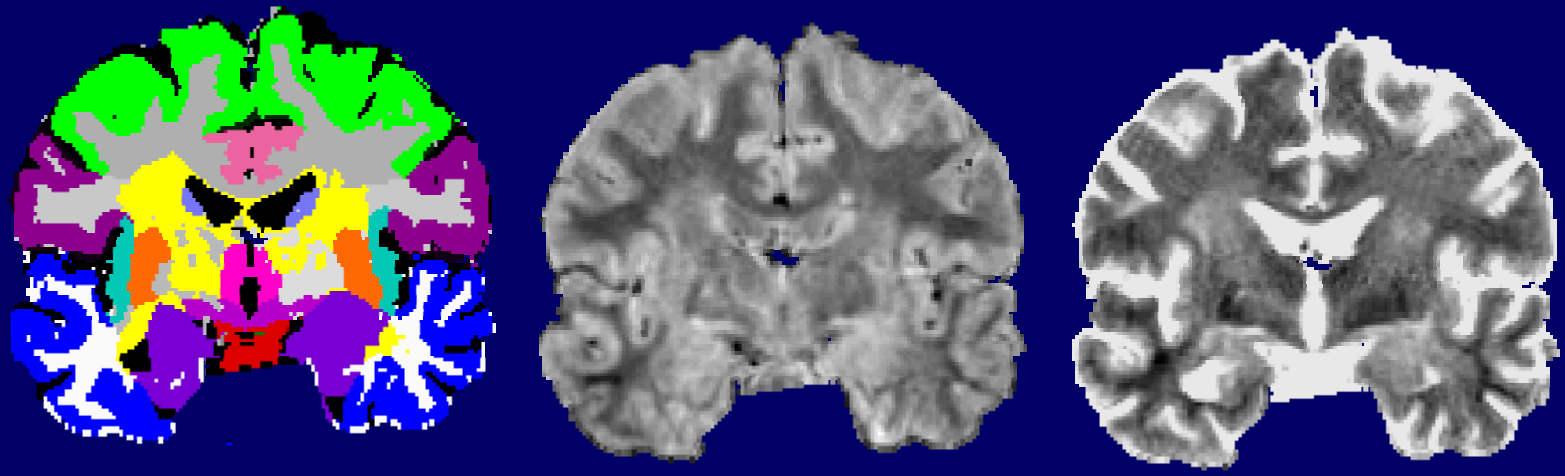


Relation of Dendritic Damage to Neurocognitive Impairment





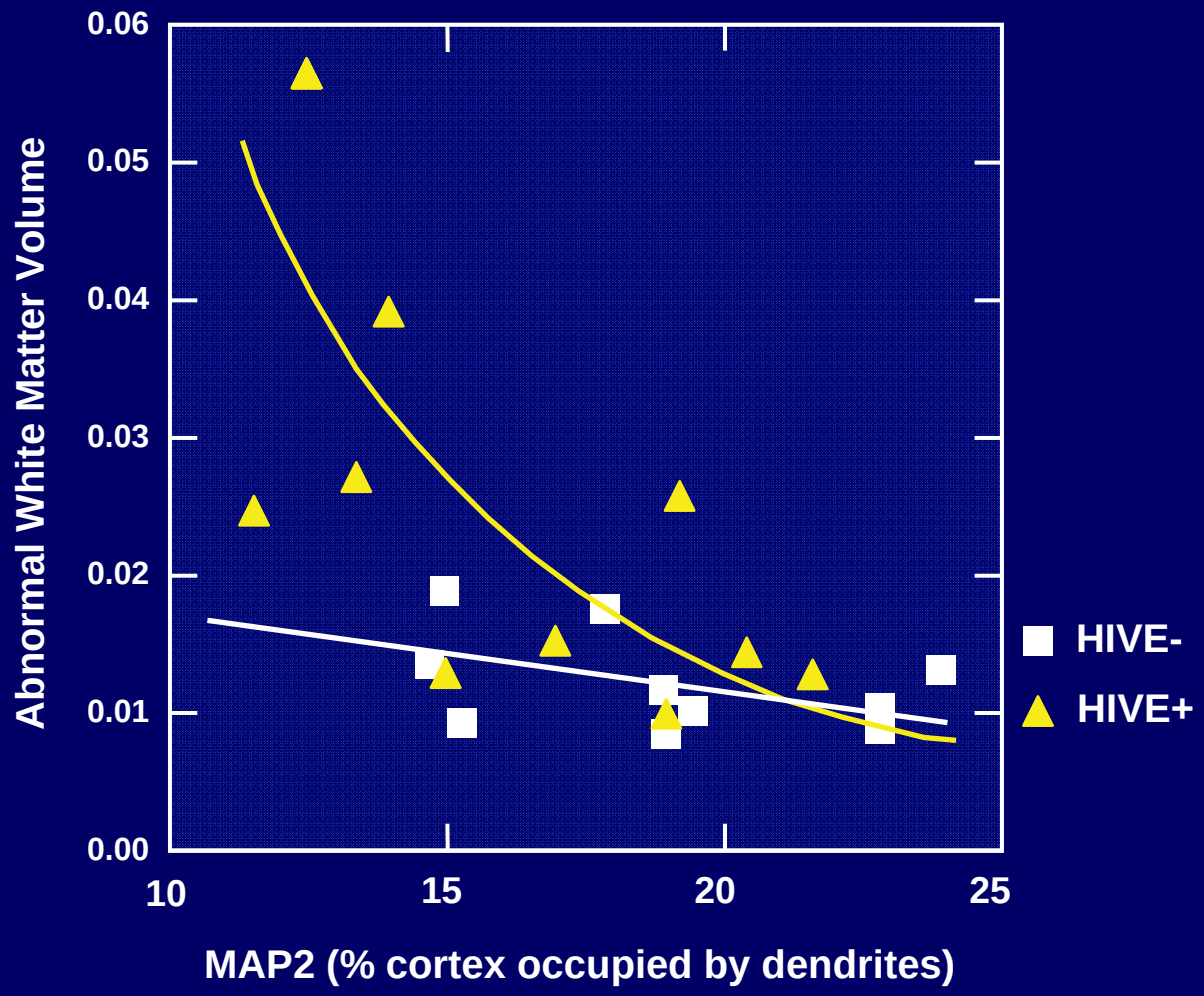
HIVE-



HIVE+

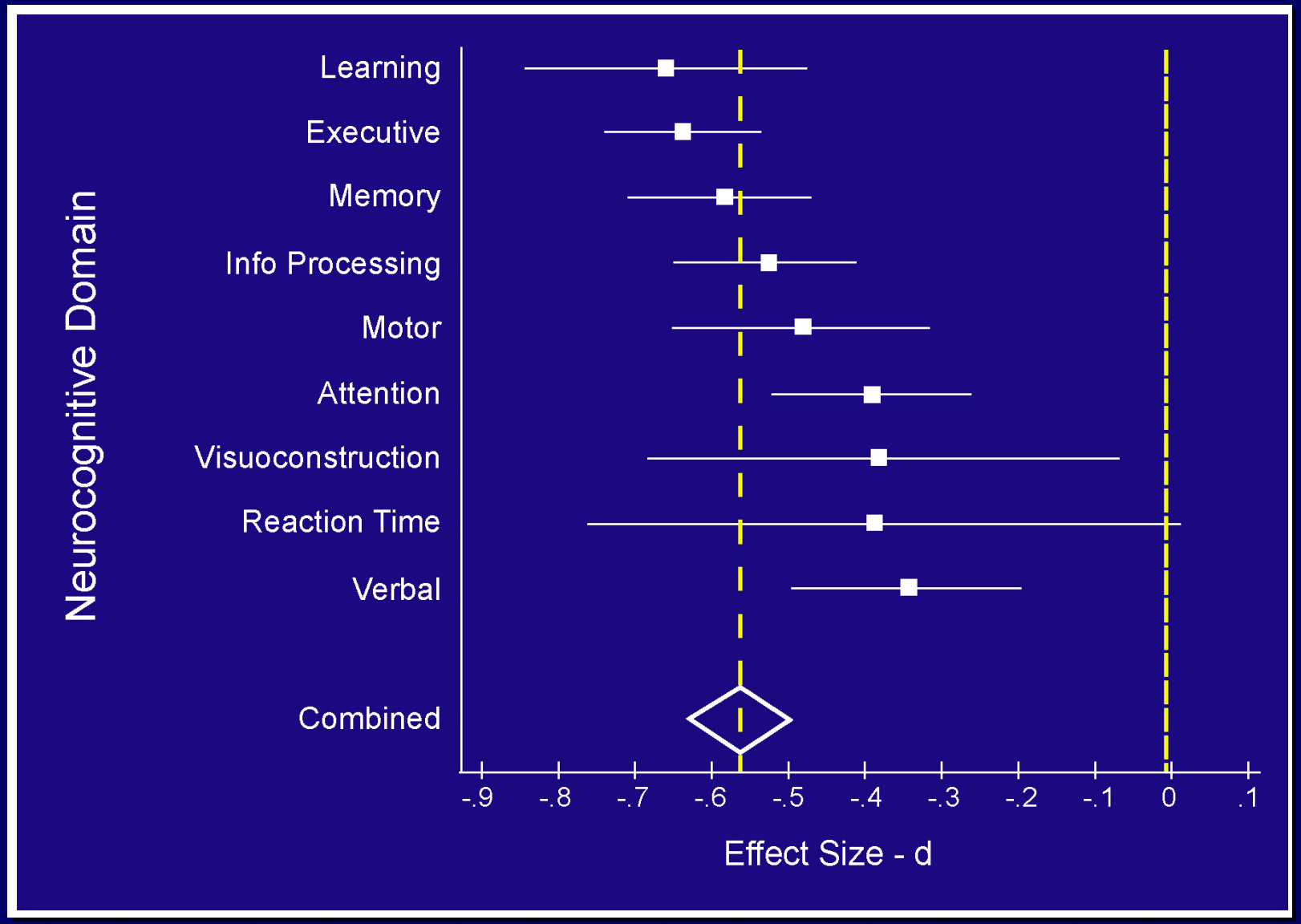
Abnormal White Matter

Increased abnormal white matter is related to dendritic loss at autopsy



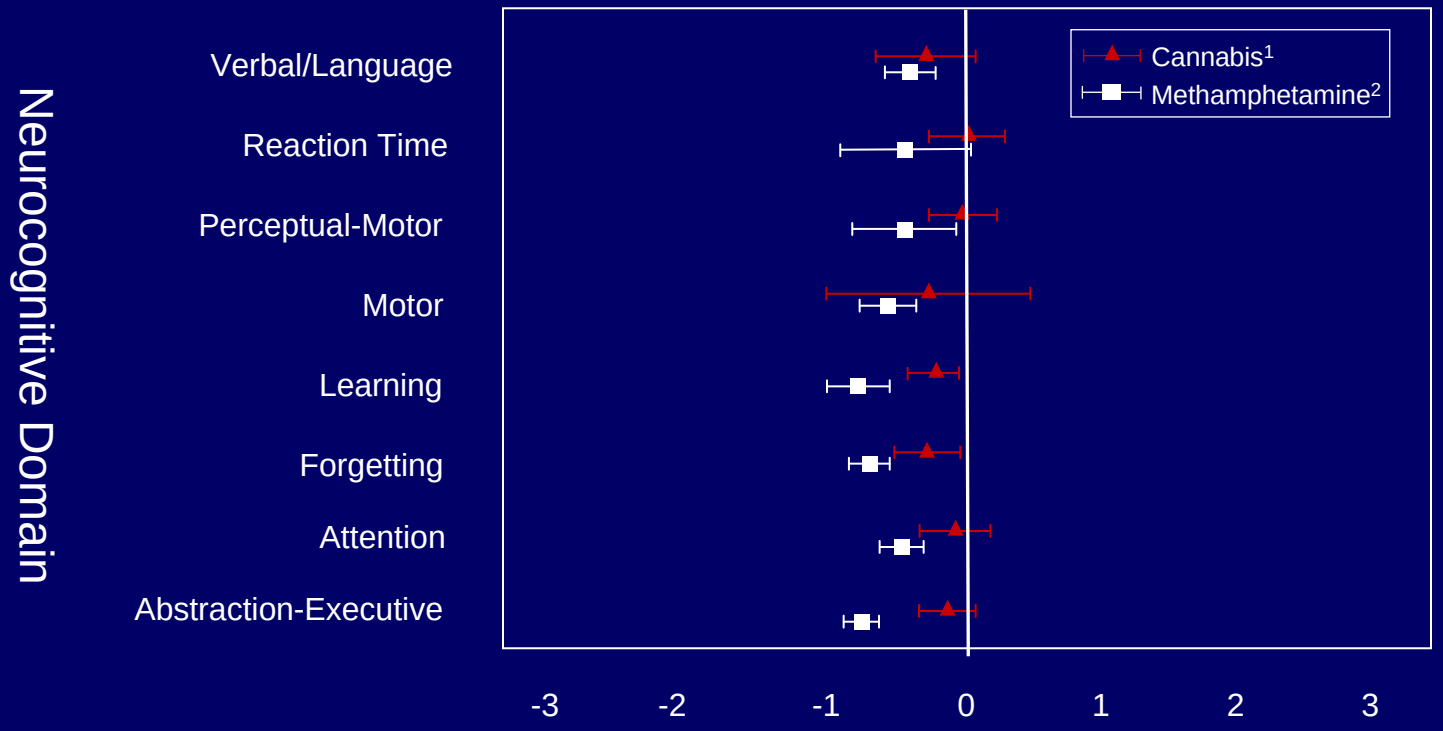
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments



Scott et al 2007 Neuropsych Rev

Long Term Neurocognitive Effects Methamphetamine vs. Cannabis

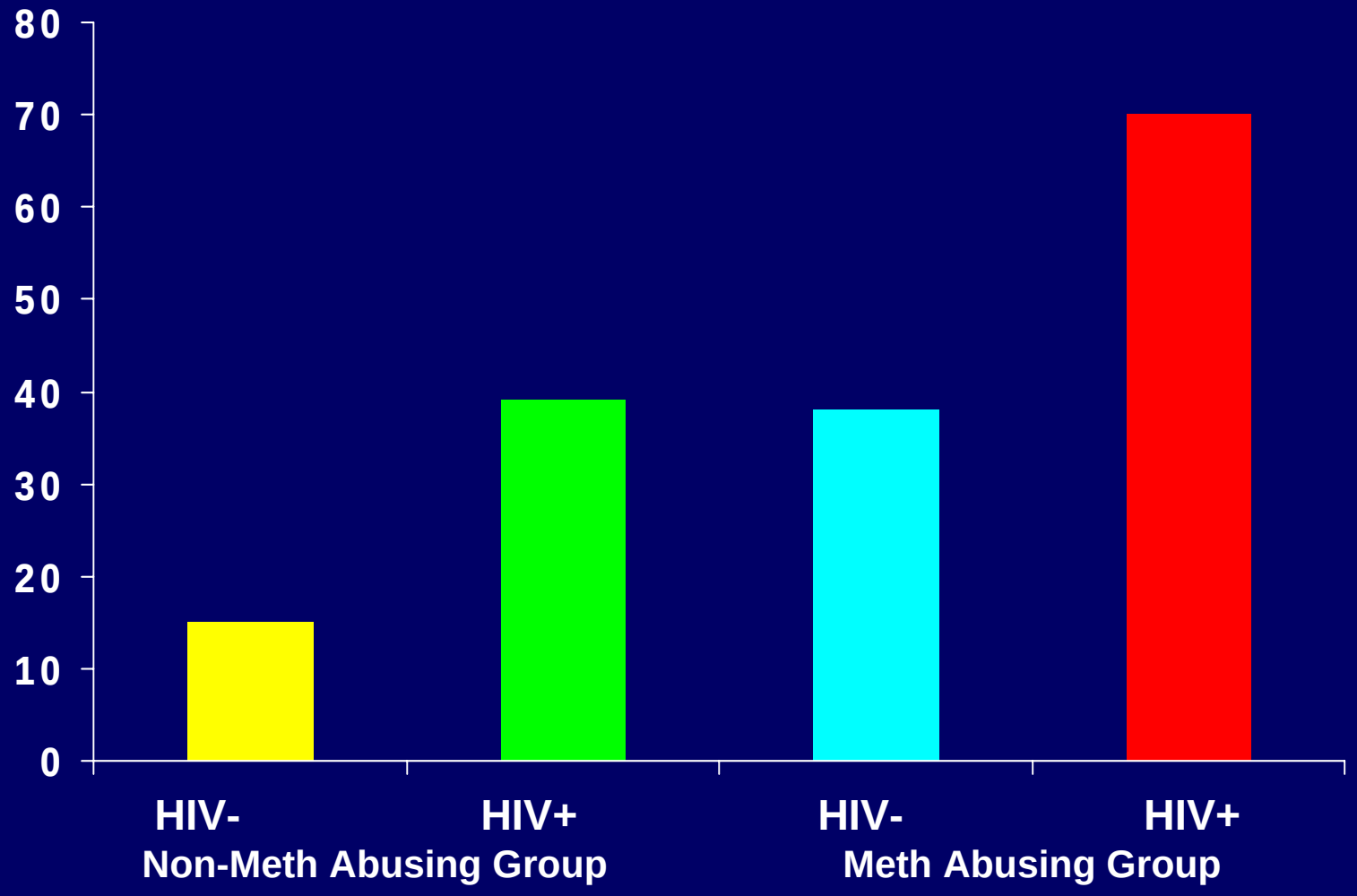


Scott et al 2007 Neuropsych Rev; Grant et al 2003 JINS

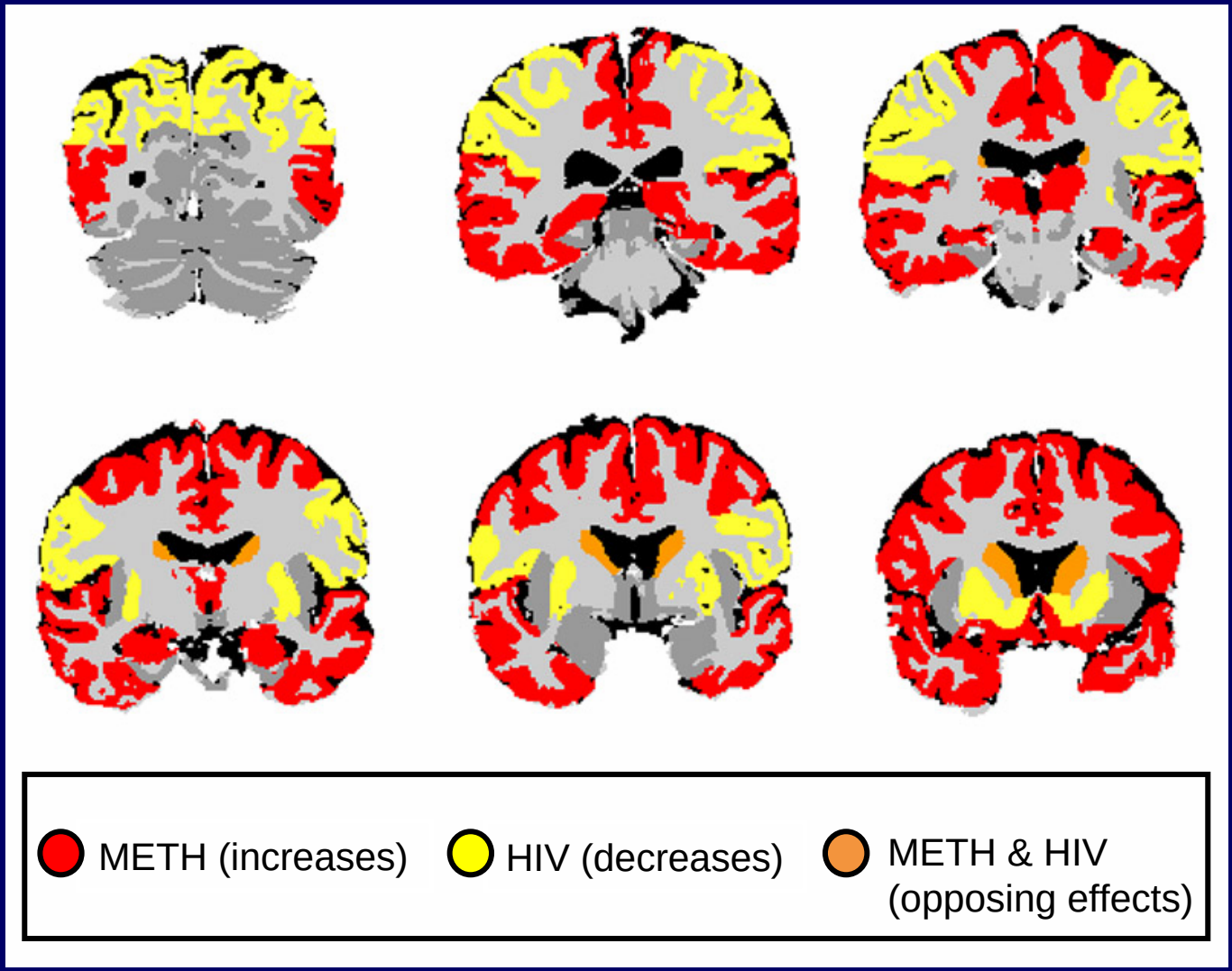
MA and HIV

- ~60% of persons seeking MA tx are HIV infected (Peck et al., 2005)
- MA use associated with
  - Loss of interneurons (Chana et al., 2007)
  - Additive NP effects (Rippeth et al., 2004)
    - - Immunocompromise (Carey et al., 2006)
  - HIV drug resistance (Colfax et al., 2007)
  - Problems in everyday functioning (Sadek et al., in press)
    - - Poor ARV adherence (Reback et al., 2003)

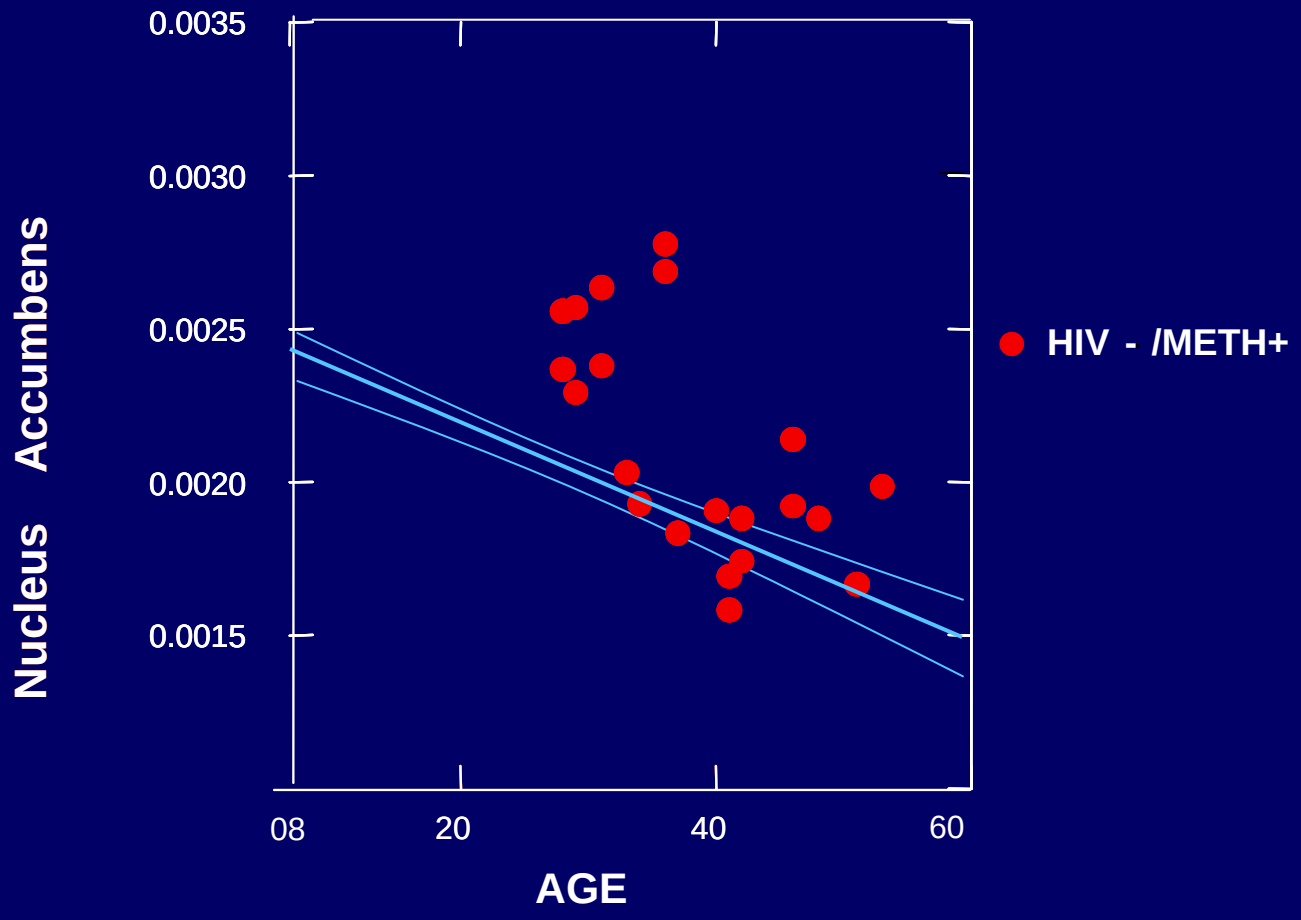
% Having Global NP Impairment by Methamphetamine Abuse and HIV Status



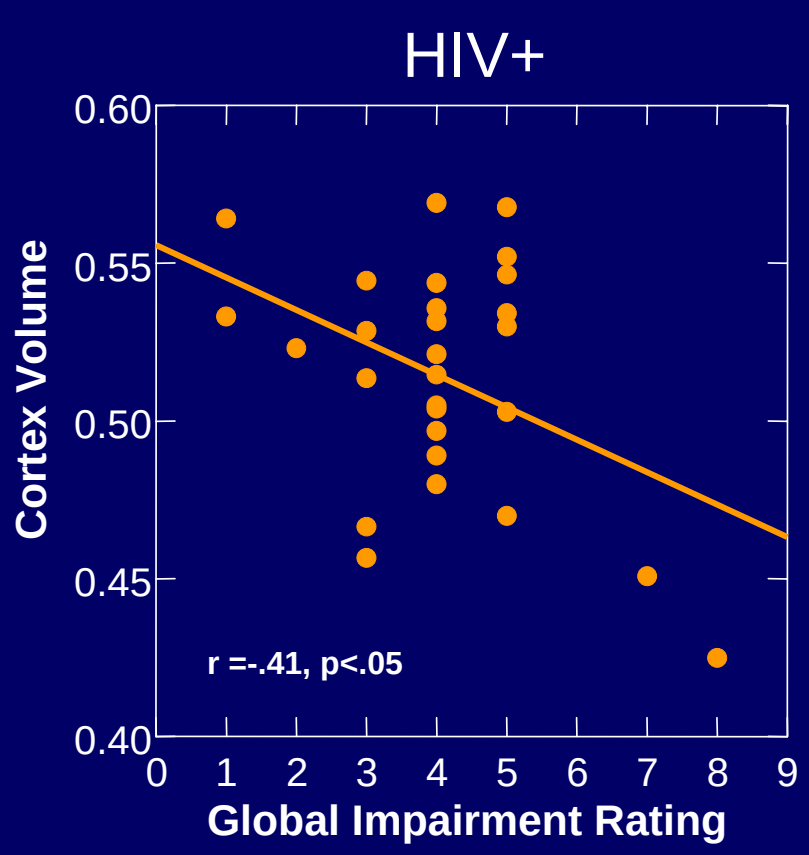
Significant regional volume alterations related to METH and/or HIV

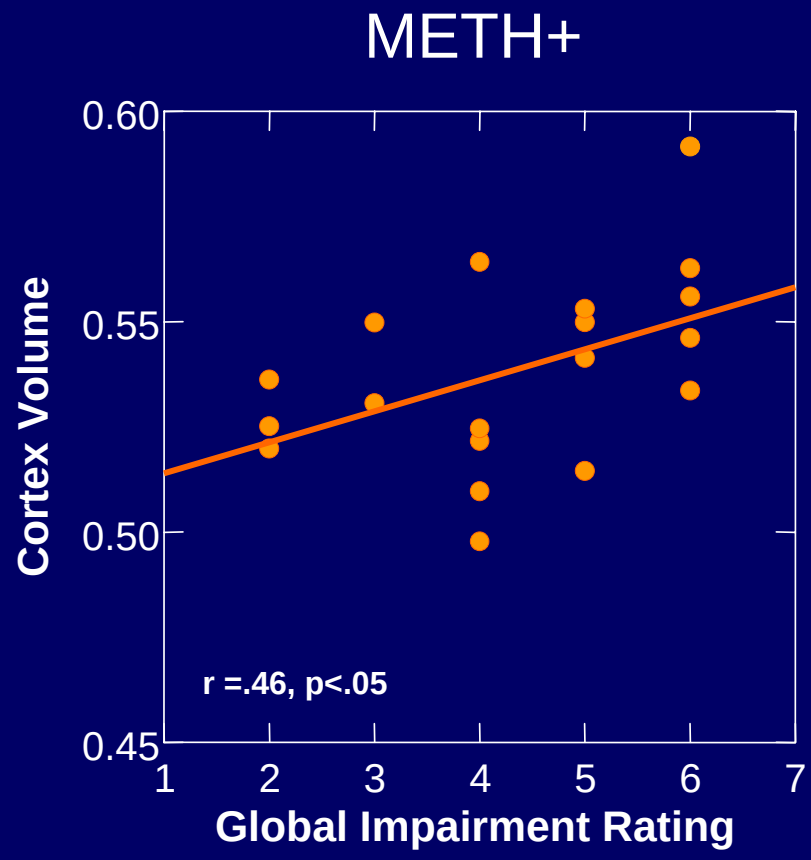


Meth have larger Accumbens volume for age relative to controls

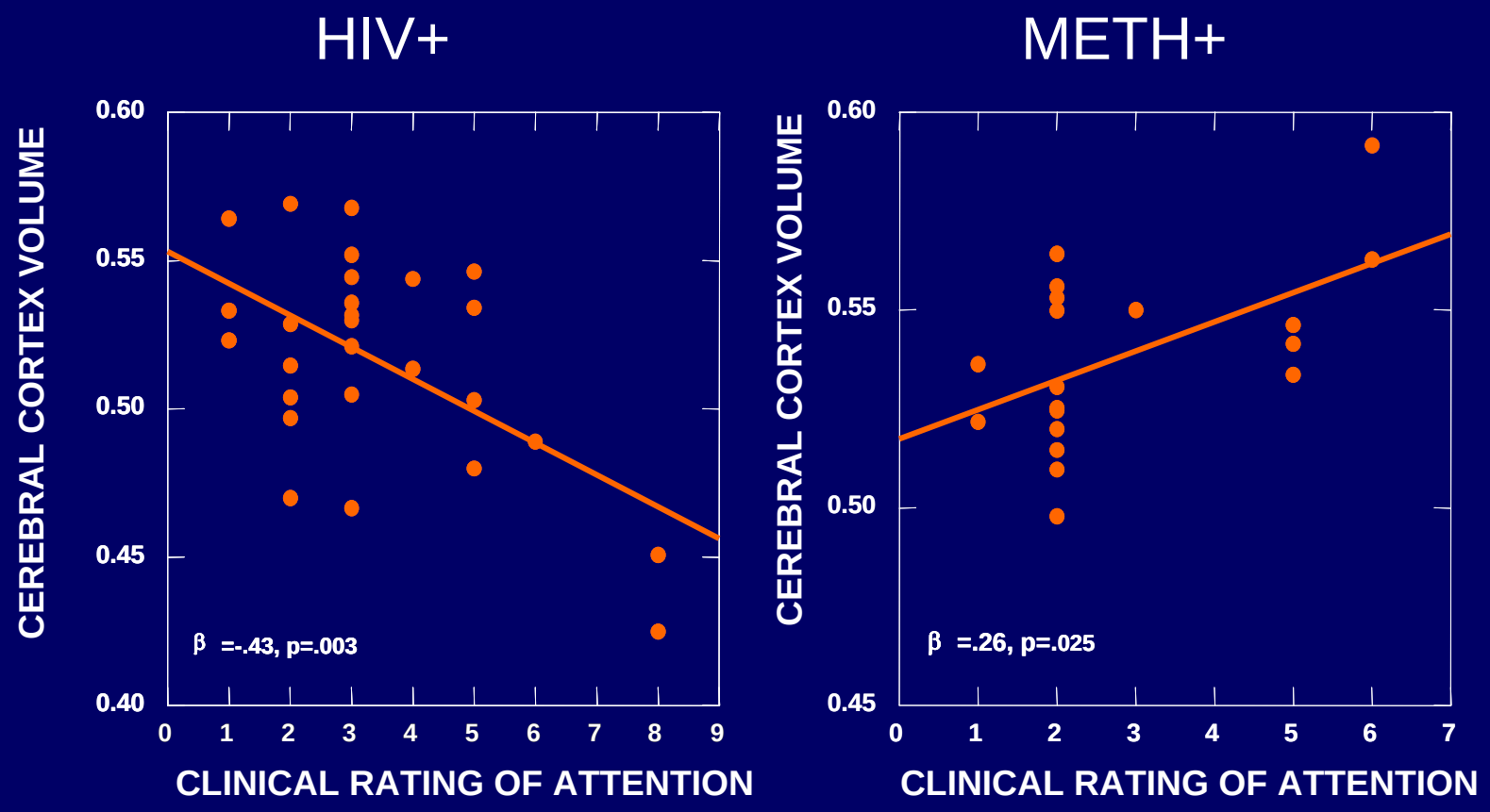


Association of Cortical Volumes with Impairment

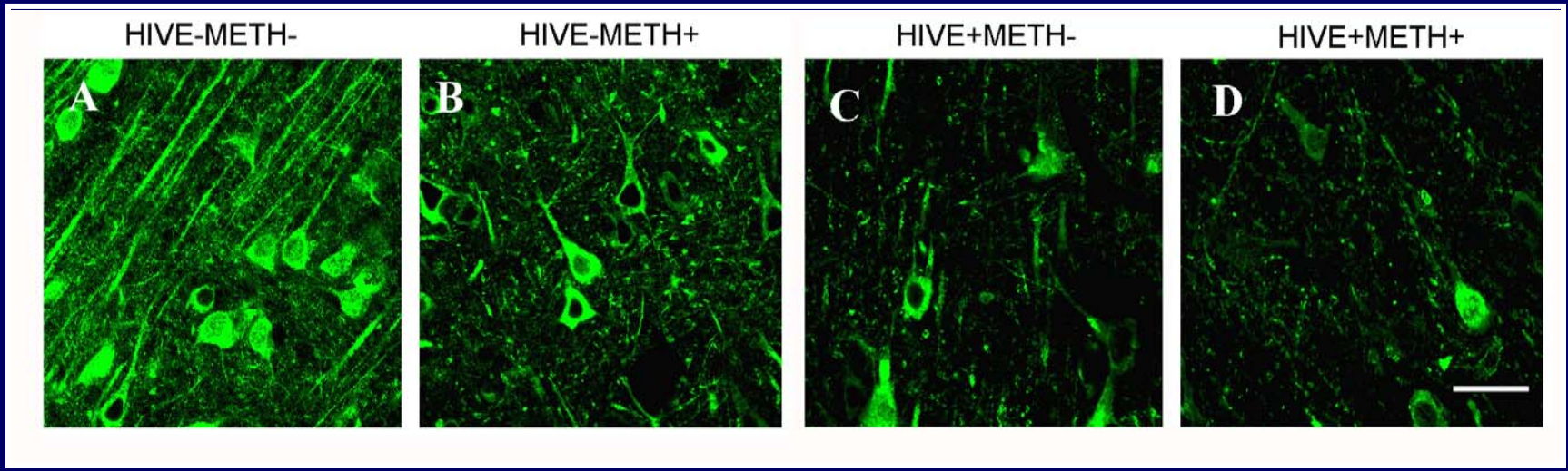




Association of Cortical Volumes with Attention Deficits

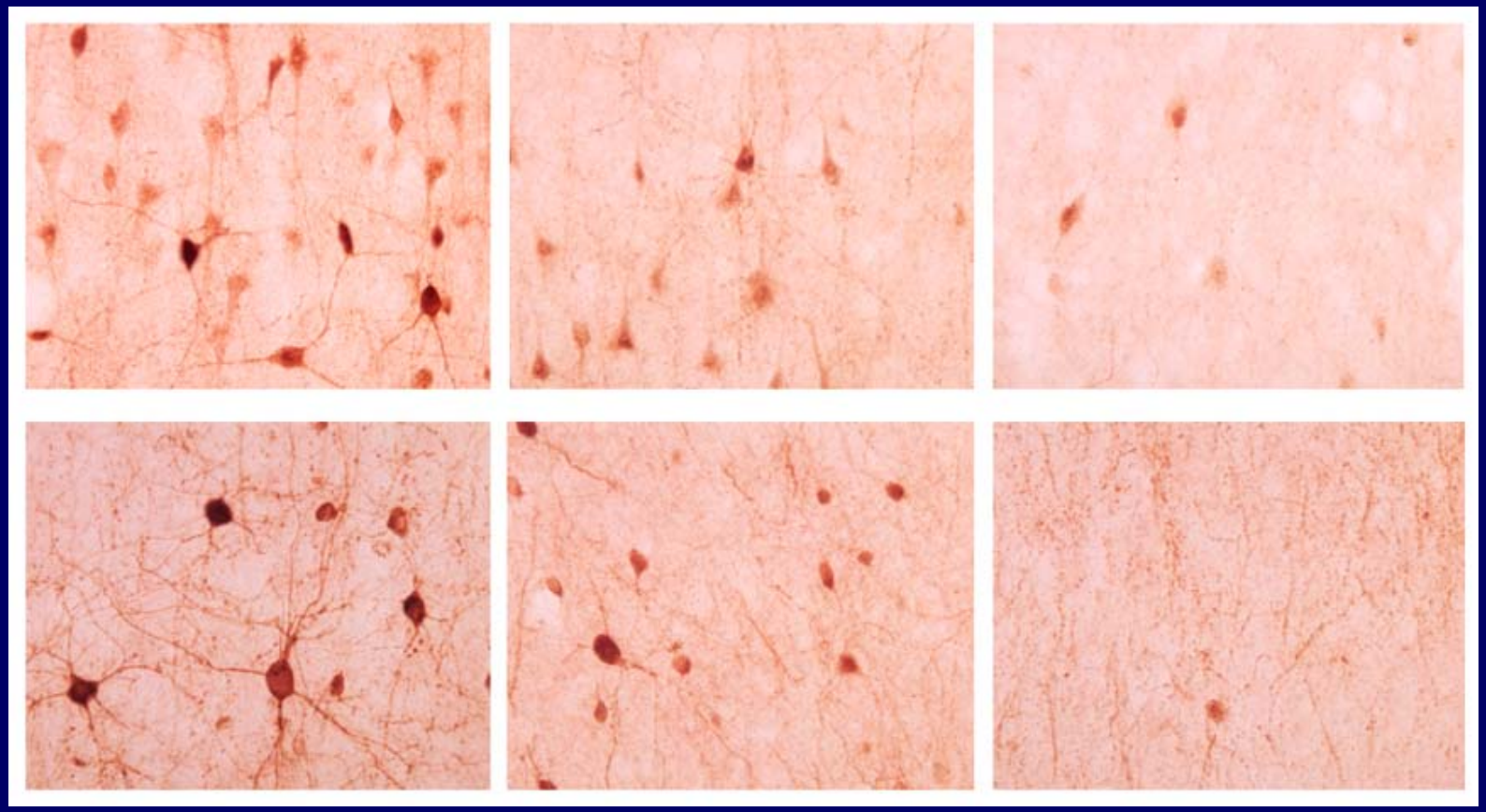


MAP-2 in midfrontal cortex of HIV+ cases with & without HIVE and with or without METH



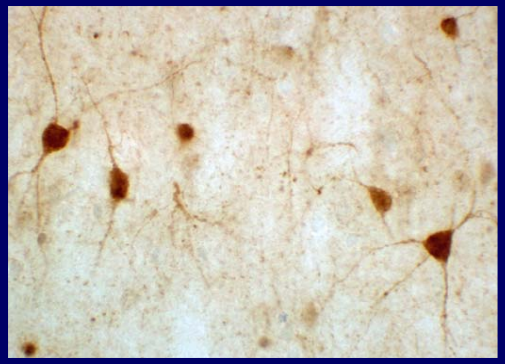
A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
Bar = 25 microns

Degeneration of Interneurons in HIVE+METH Users

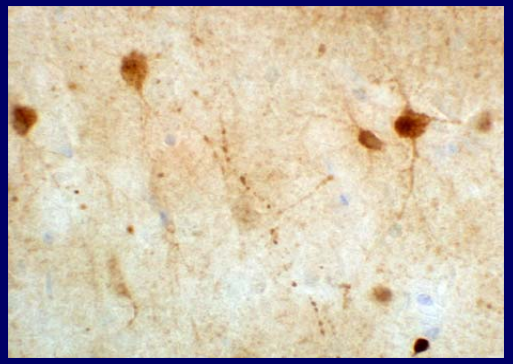


Loss of calbindin interneurons is associated with cognitive impairment and memory loss in METH users patients with HIVE patients

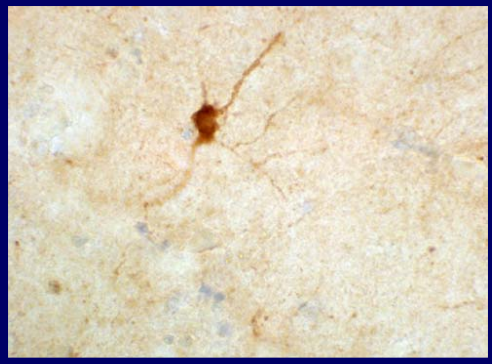
HIV+ (control)

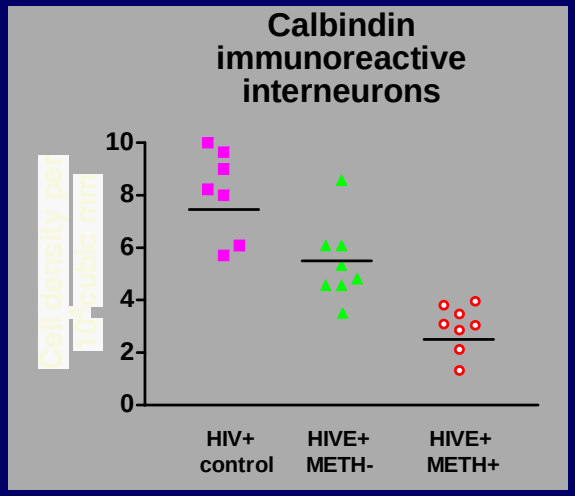


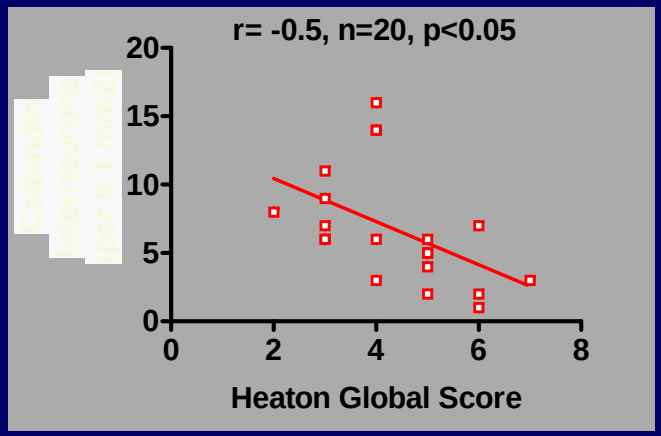
HIVE+ METH-

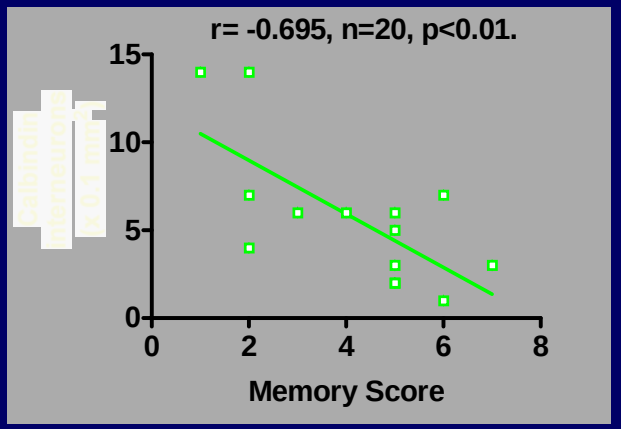


HIVE+ METH+







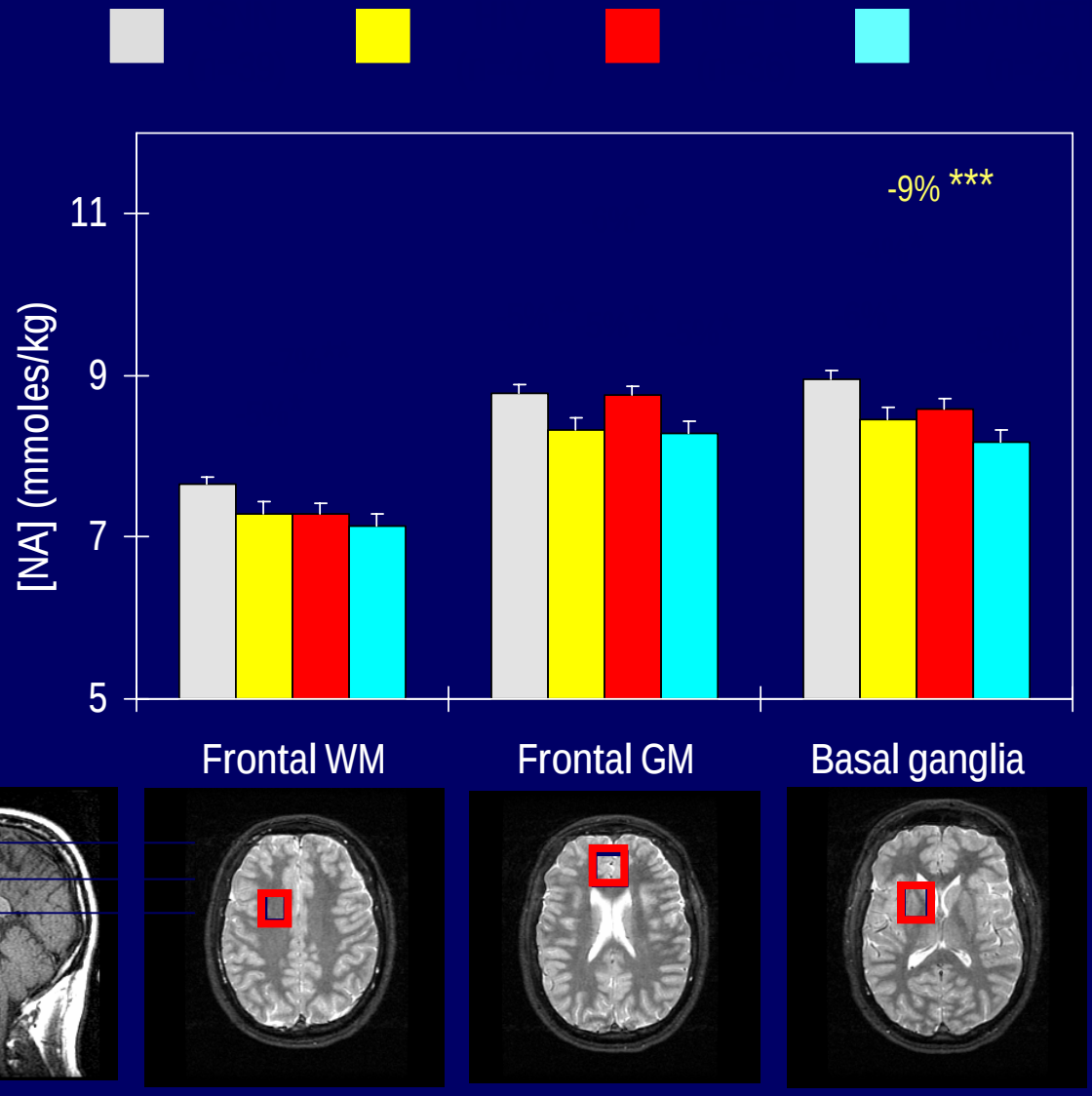


Mechanisms of neurodegeneration mediated by HIV and METH

1. Oxidative stress
2. Excitotoxicity
3. Mitochondrial dysfunction
4. Alterations in calcium metabolism
5. Interference with signaling pathways of trophic factors
6. Cytokines, chemokines and other neuro-inflammatory factors
7. Increased viral load, replication, trafficking, altered viral resistance

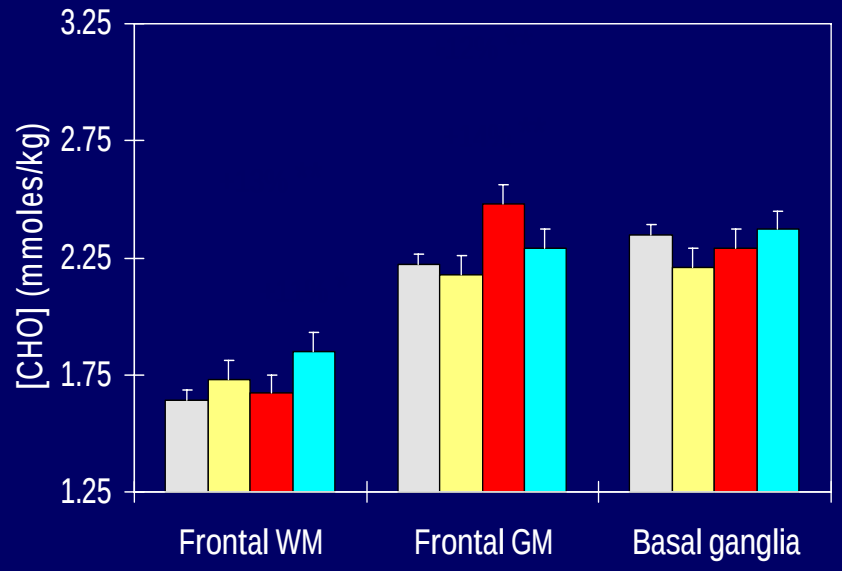
METH-Dependence Exacerbates HIV-Associated Neuronal Injury

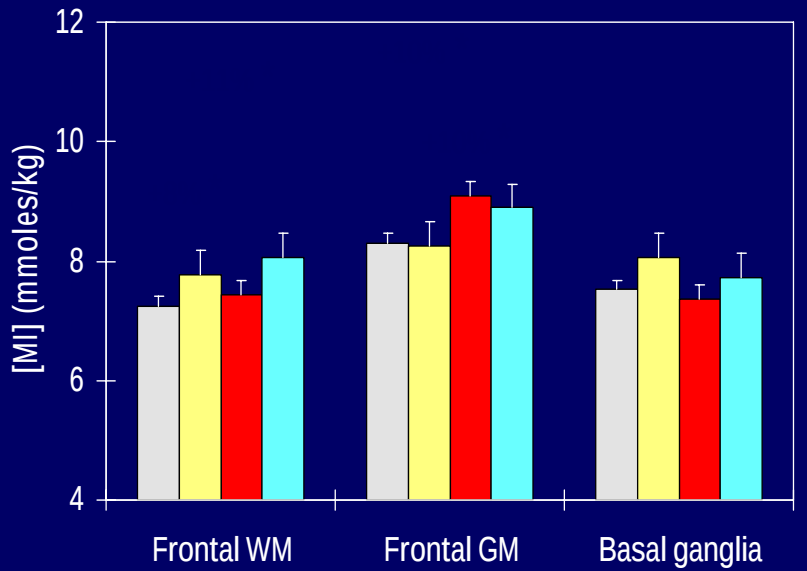
Chronic METH: Additional Neuronal Injury (especially in Striatum)

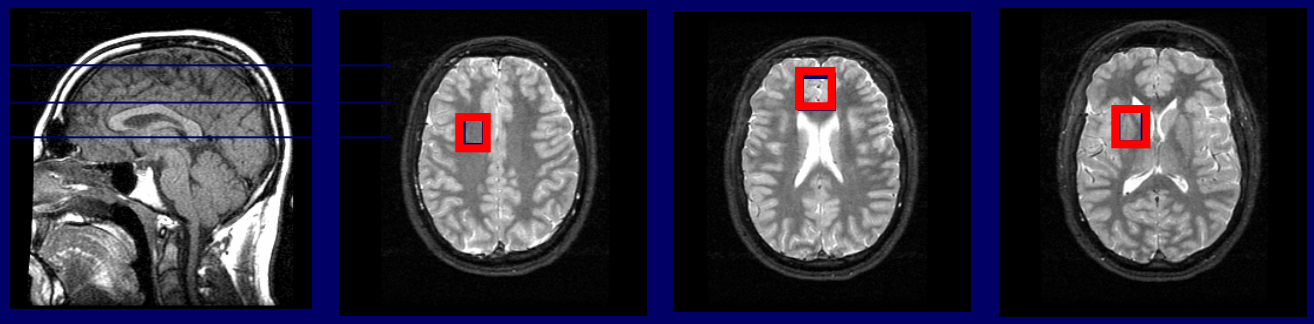


Chang et al, Am J Psychiatry 2005

METH-Dependence Exacerbates HIV-Associated Glial Response

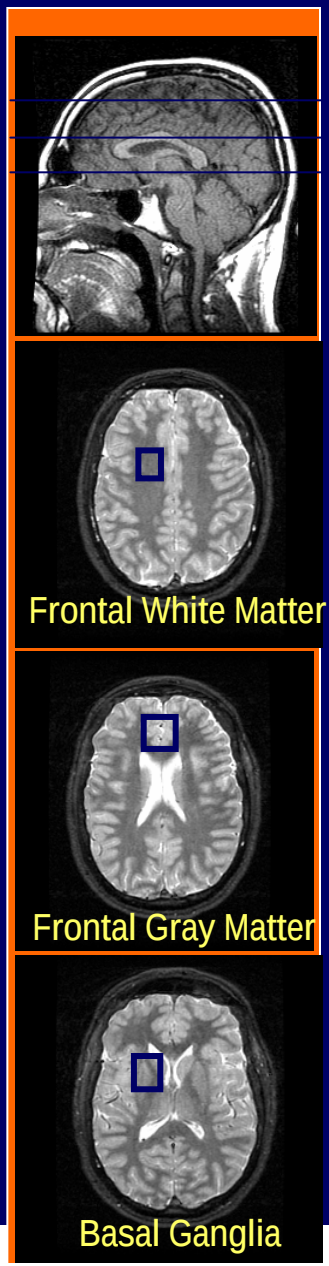


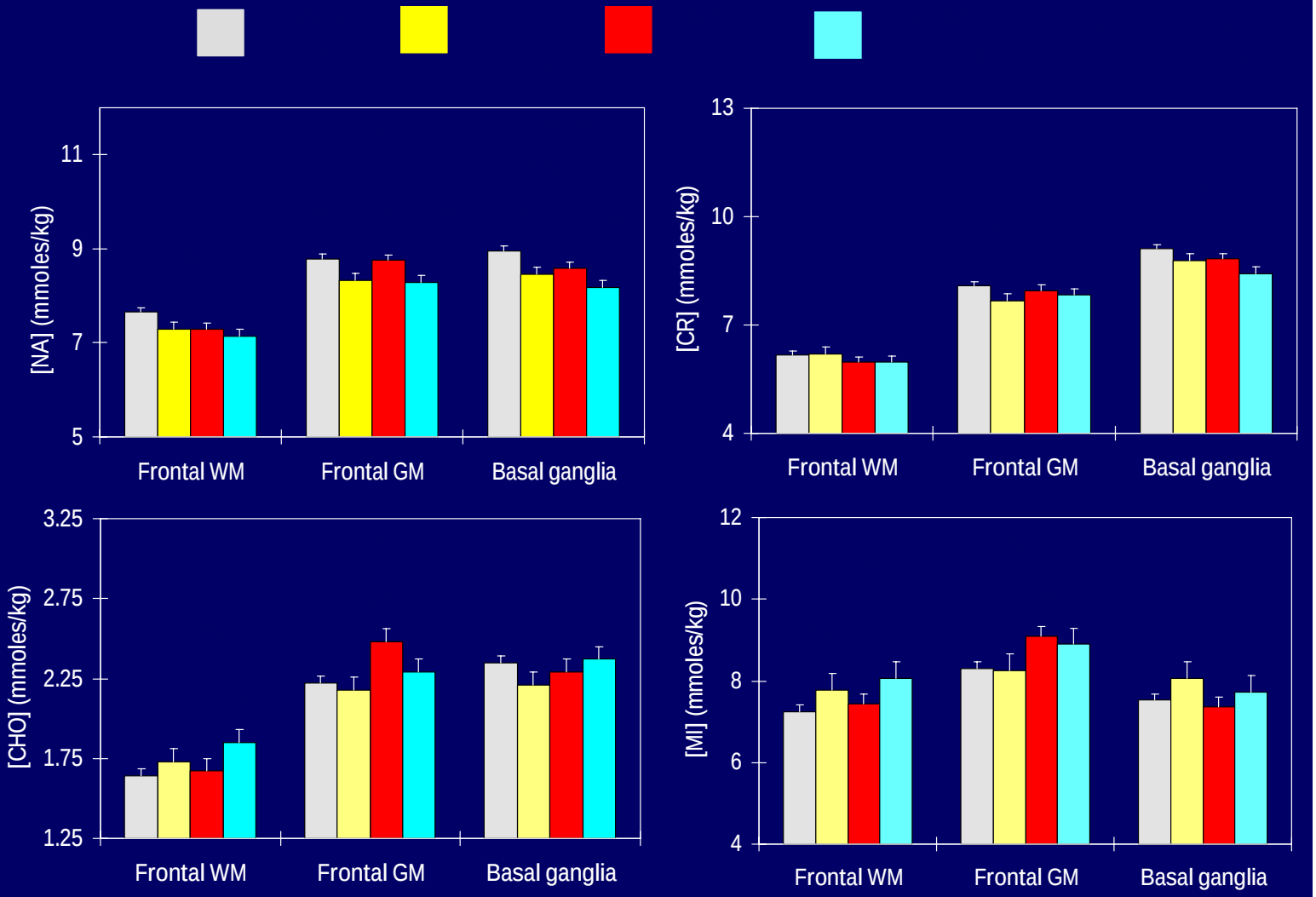




Chang et al Am J Psychiatry 2005

METH-Dependence Exacerbates HIV-Associated Brain Injury



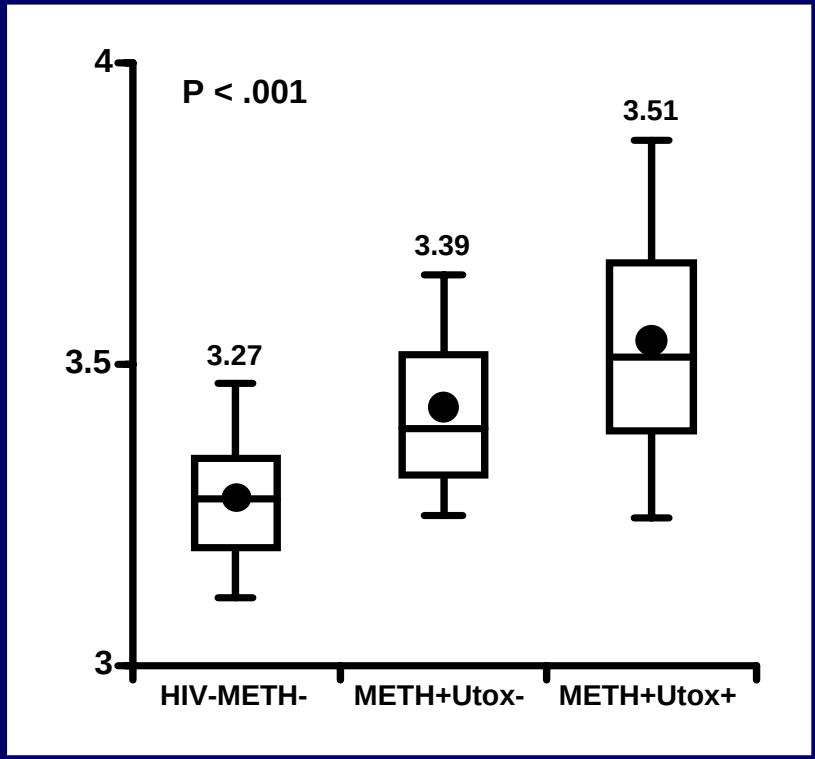


Chang et al Am J Psychiatry 2005

HIV NEUROBEHAVIORAL RESEARCH CENTER

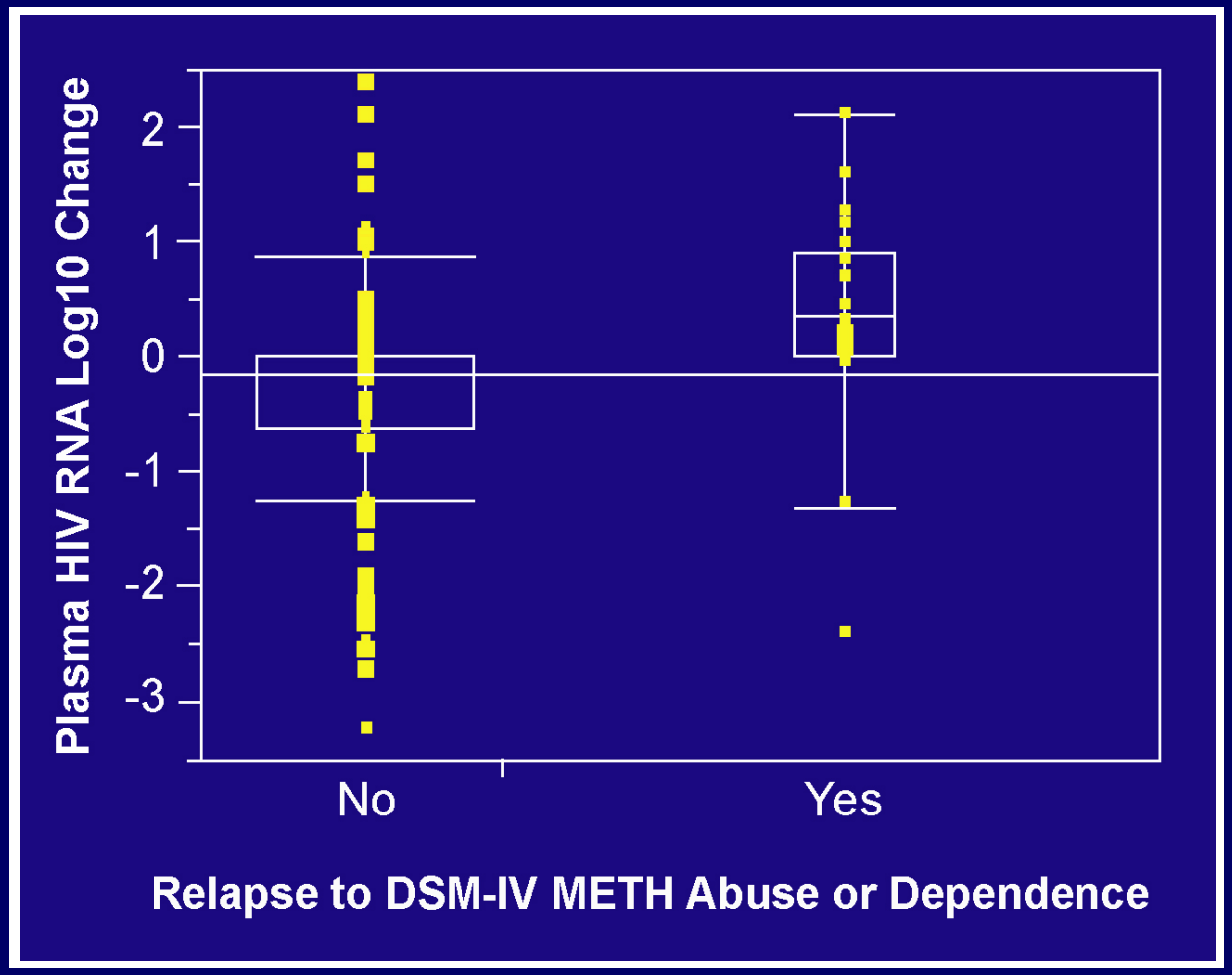
METH associated with elevated biomarkers of inflammation

- METH users had higher levels of 5 markers of macrophage activation* in plasma
  - 3 were also higher in CSF
- Similar to HIV RNA, levels varied with recency of METH use
  - HIV-METH- lowest
  - METH+Utox- intermediate
  - METH+Utox+ highest



**MCP-1, sCD14, sTNFR-II, TNF-alpha, and MIP-1 beta*

Relapse to METH Abuse or Dependence diagnosis during 12 month follow-up is associated with higher plasma HIV RNA (n=63)

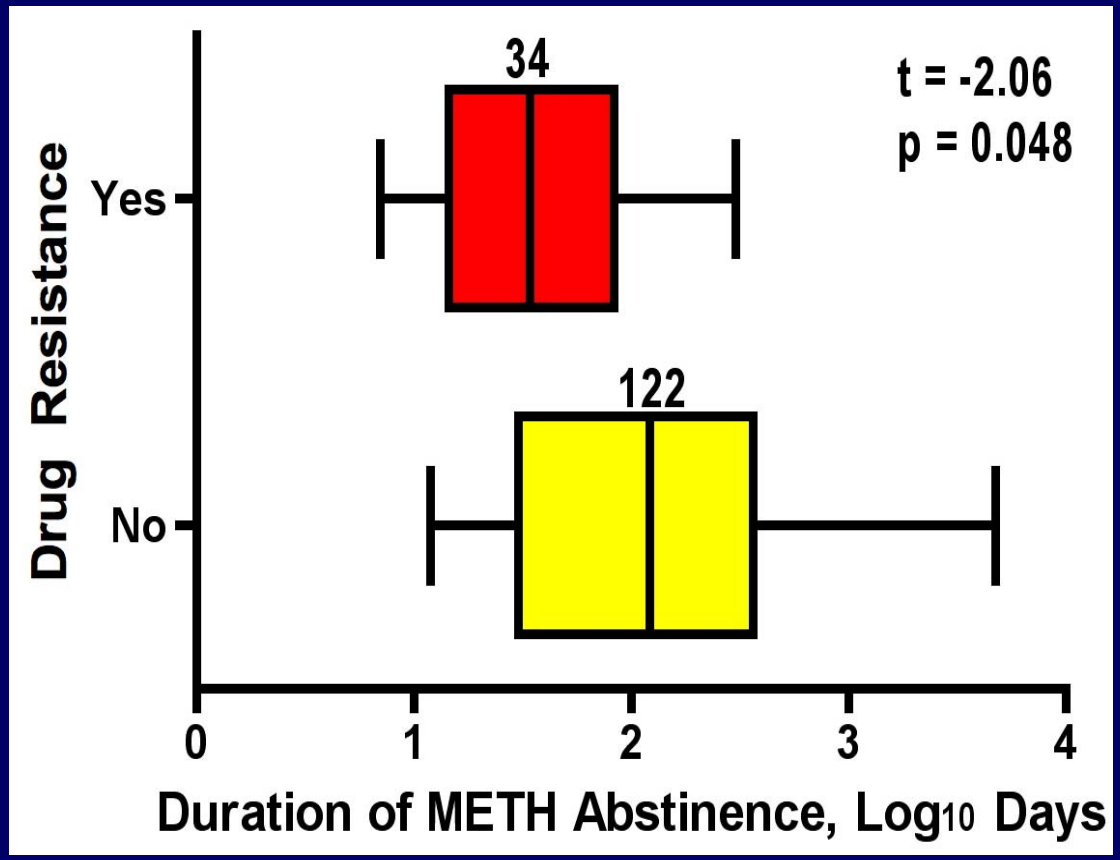


Wilcoxon Rank Sums Test **(2 = 11.45, p<.001)**

Antiretroviral Drug Resistance

Methamphetamine is Associated with DR

- Resistance mutations were determined in 63 subjects enrolled in NIDA-funded projects
- 45% had resistance mutations for at least one antiretroviral
- Among METH dependent individuals, DR was associated with shorter durations of METH abstinence



Hightower et al, XIV International HIV Drug Resistance Workshop

Cofactors in HIV Associated Neurocognitive Complications

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- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments

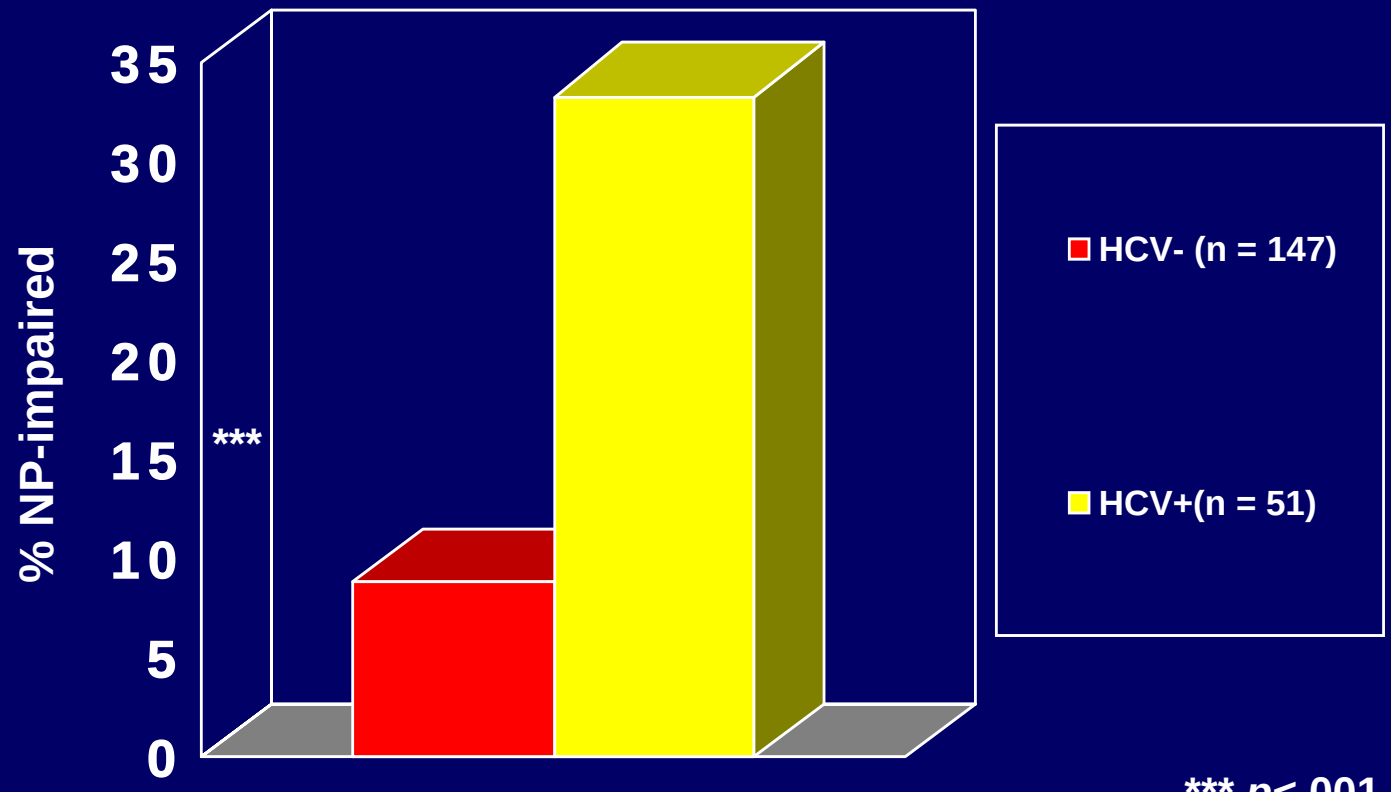
HCV and the Brain

Neurologic Syndromes

- Hepatic encephalopathy
- Anterior optic neuropathy
- CNS vasculitis with ischemic or hemorrhagic strokes
- Cranial neuropathy
- Demyelinating myelitis
- Restless leg syndrome
- Cognitive/mood changes with Rx

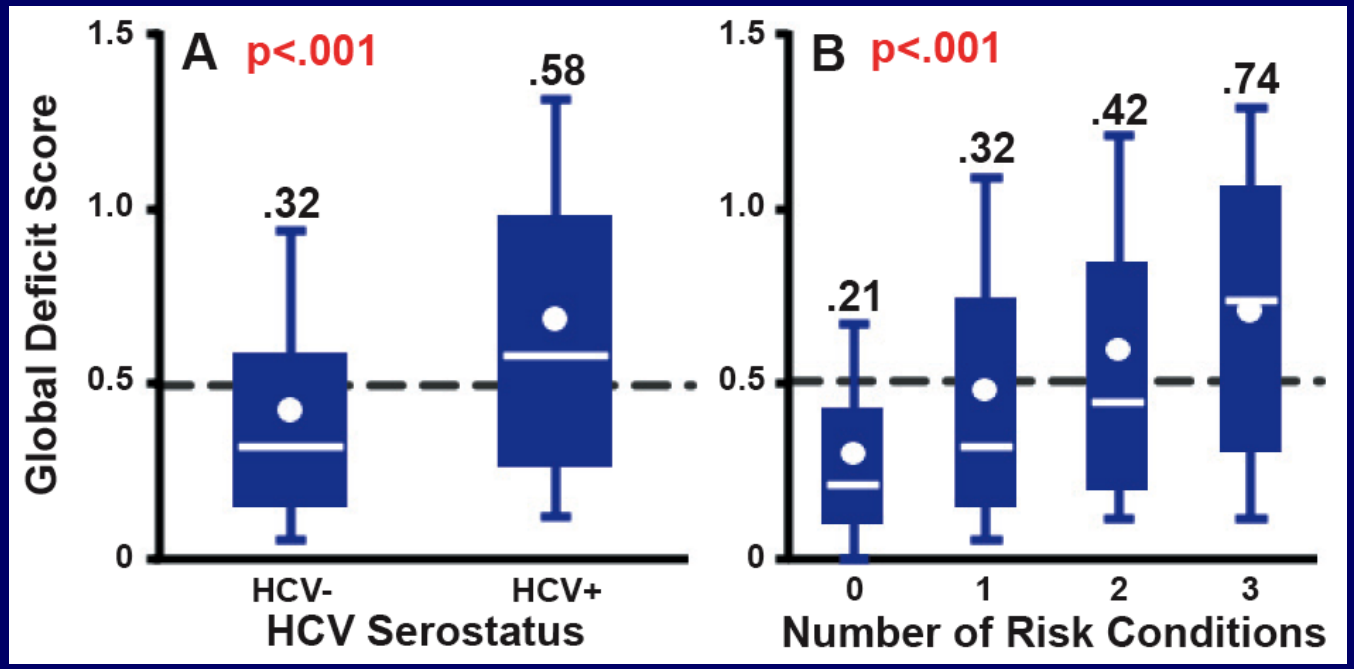
Tembl, Neurology, 1999; Marie, et al 2000; Grewal, J N Sci, 2004

Rate of Neurocognitive Impairment in HCV+ Persons in Anhui, China



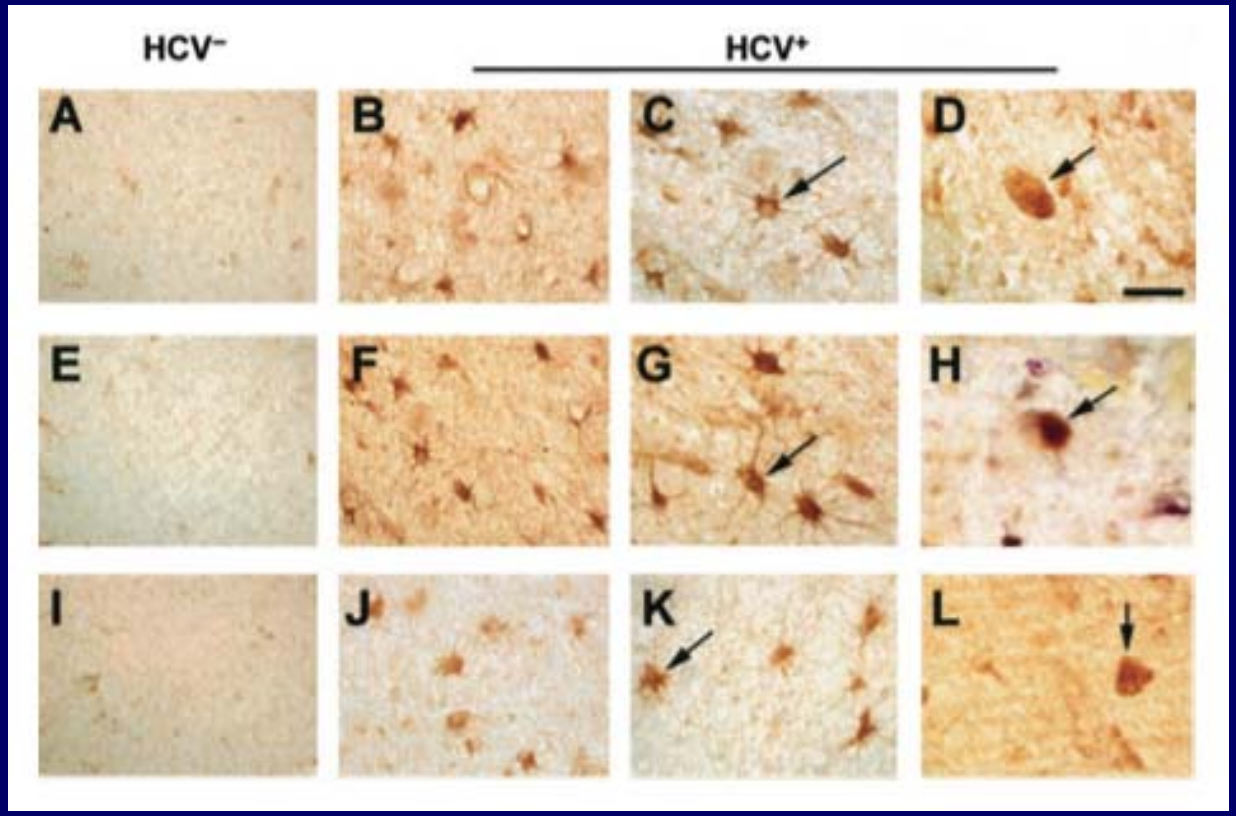
*** p<.001

HCV Confers Risk for Neurocognitive Impairment



Panel A shows worse neurocognitive score in HCV+ vs HCV-
Panel B shows as the number of comorbid conditions increases, neurocognitive performance worsens. The risks, in various combinations include HIV, HCV, and methamphetamine dependence

Cellular Localization of HCV in Brains of Persons Dying of HIV



A-D Polyclonal antibody to HCV NS5A structural protein; E-H monoclonal anitbody to NS5A; I-L monoclonal antibody to HCV core antigen. B,F,J, C,G,K consistent with astrocytic localization; D,H,L consistent with macrophage localization

Letendre et al 2007 JID 196, 361-370

Pattern of neuropsychological impairment according to risk factor

Deficit	Meth	HIV	HCV
Learning	+ + +	+ + +	+ + +
Retention	-	-	?
Attention / Working Memory	+	+ +	+
Speed of Information Processing	?	+	+ + +
Visuospatial Functioning	?	-	?
Motor			
Disinhibition	+ +	-	?
Slowing	+ + +	+ +	+ + +

= : effect - : no effect ? : uncertain

Pattern of neuropsychological impairment according to risk factor

Deficit	Meth	HIV	HCV
Executive Functioning			
Problem-Solving/Planning	**++**	**++**	**+**
Cognitive Disinhibition	**++**	**-**	**?**
Decision-making	**+++**	**+**	**?**
Frontal Systems Behavioral			
Disinhibition	**++**	**-**	**?**
Apathy	**-**	**++**	**?**
Executive	**+**	**++**	**?**

= : effect - : no effect ? : uncertain

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Effects of Aging on expression of HAND

- cART prolonging survival: 15% now age > 50
- Does chronic HIV interact with aging related changes in brain?
- Sacktor et al., report increased executive dysfunction in older HIV+ with HAND in Hawaii cohort

Sacktor, et al. 2007 J Neurovirol

Older (>50) have approximately 10% greater rate of NP Impairment relative to age appropriate norms

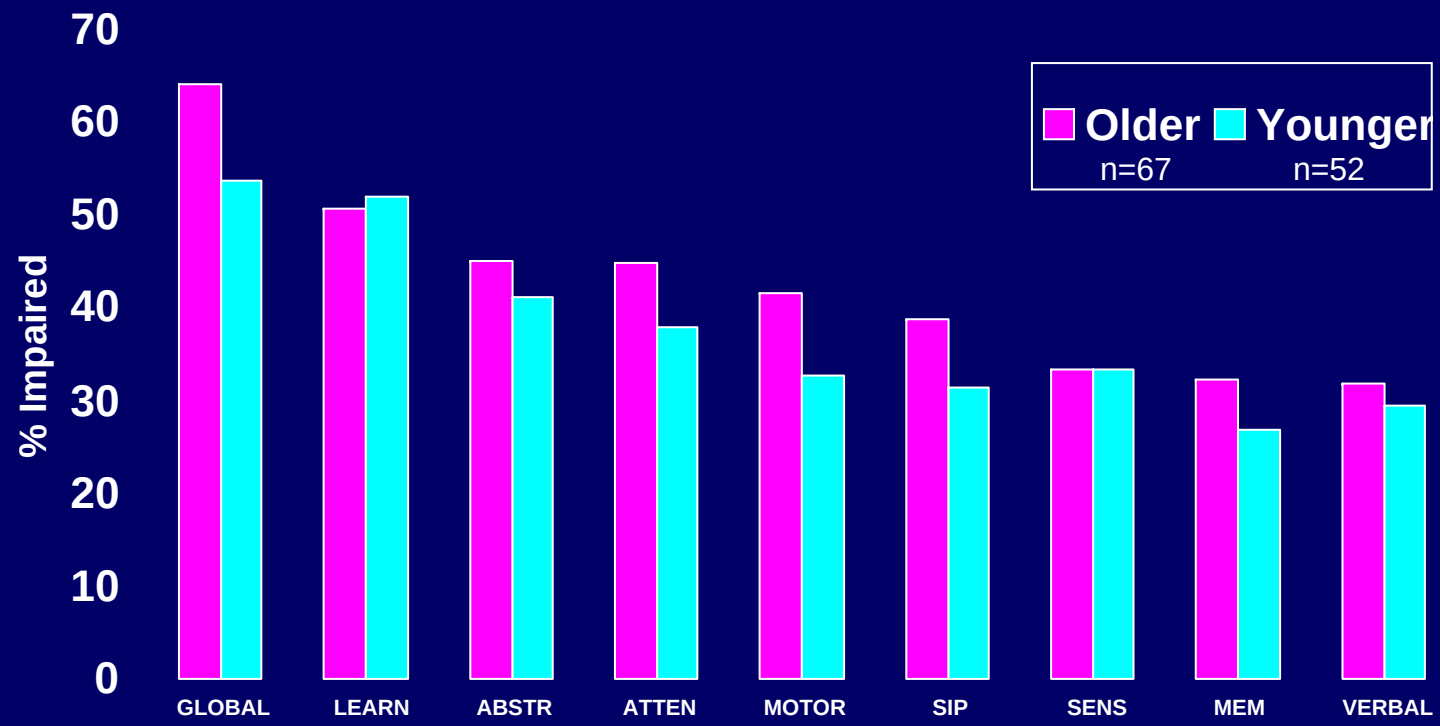
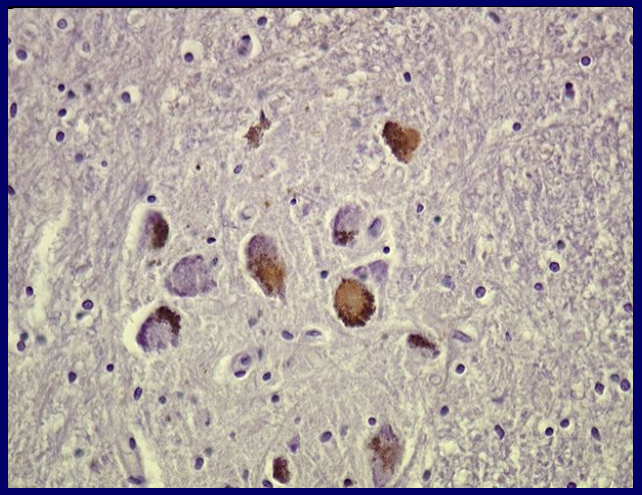
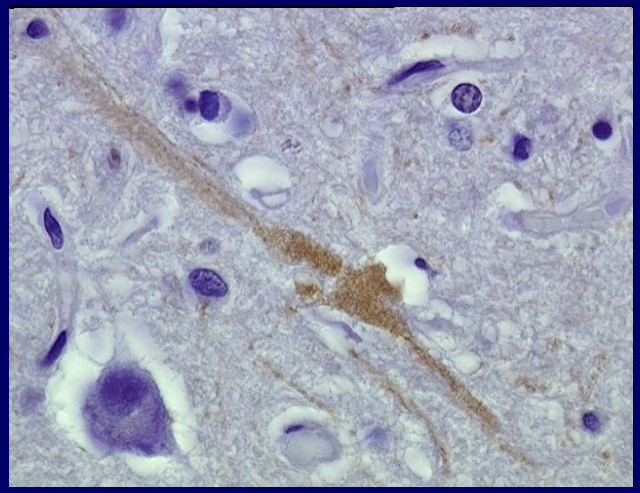


Figure 1. A photomicrograph (magnification x680) of intraneuronal staining of α-synuclein by immunocytochemistry, of neurons in the substantia nigra (A) and of neuritic staining in the temporal cortex (B). [courtesy I. Everall, et al., study of NNTC specimens]

A



B



Increased Frequency of α-Synuclein in HIV

- Study of 73 substantia nigra in HIV infected indviduals aged 55 years and more (also in temporal cortex in subset)
- 16% had α-synuclein staining, compared with 9% reported in the literature

Everall, et. al. from a study of NNTC brains

NeuroAIDS and Comorbidities Summary

- HAND is prevalent in cART era
- Synaptodendritic Injury is a substrate
- Even though most persons with HAND are not grossly demented, life functioning can be affected
- Comorbidities such as drug abuse [eg. Methamphetamine] and coinfection [eg. HCV] may contribute to persistence of HAND
- Joint effects of HIV, Meth, and HCV may involve common immunoneuropathogenesis
- Aging may increase hazard of HAND or HIV may advance other age related brain changes
- cART effects on CNS need to be examined in context of these comorbidities

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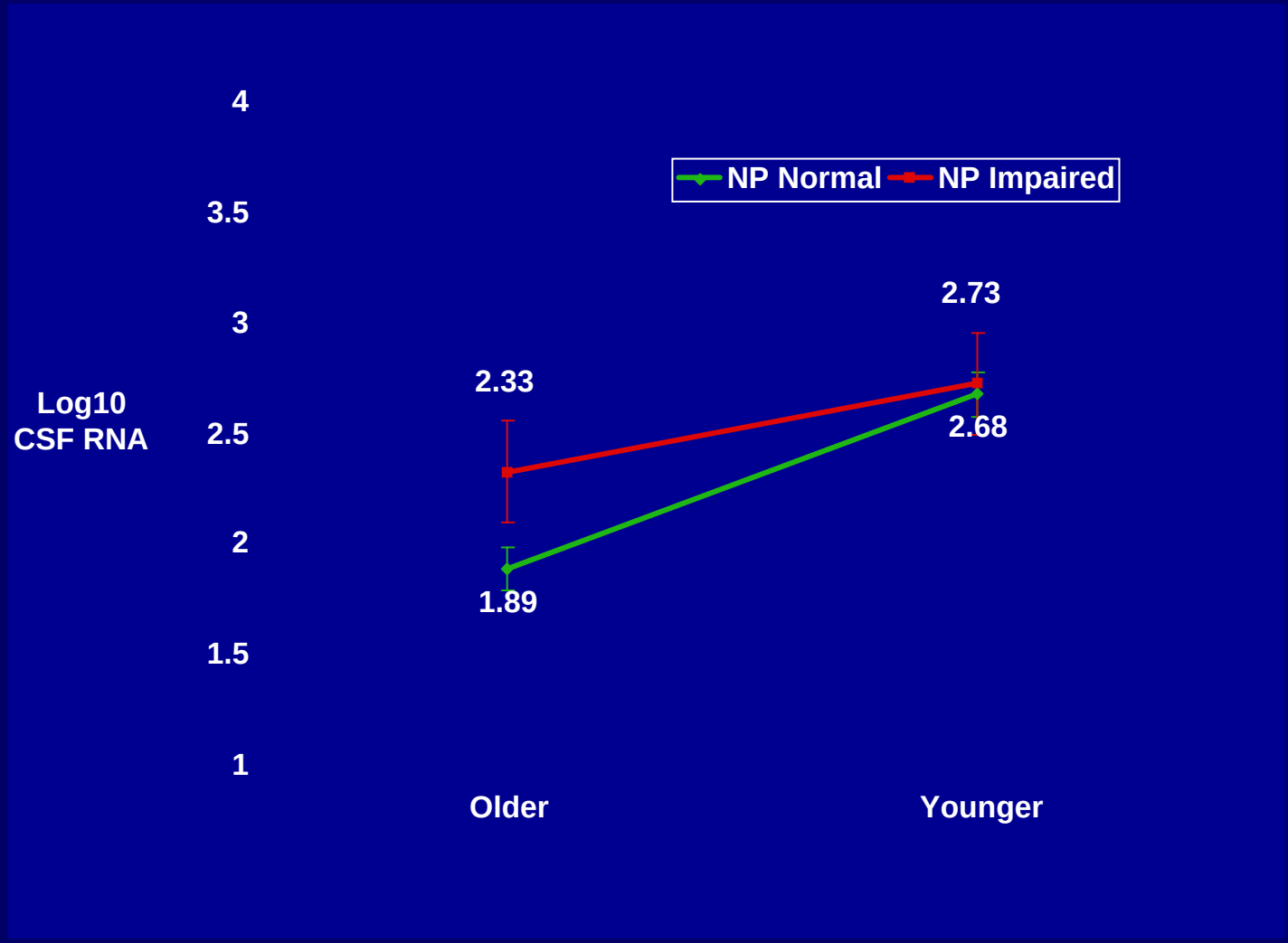
MULTIFACETED INFLUENCES ON NEUROAIDS: EFFECTS OF METHAMPHETAMINE, HCV AND AGE

Thank You!

Igor Grant, M.D.

HIV Neurobehavioral Research Center
University of California, San Diego
http://www.hnrc.ucsd.edu/

Interaction between age group and viral burden showing that levels of CSF HIV RNA differ according to NP impairment in older subjects but not in younger subjects.

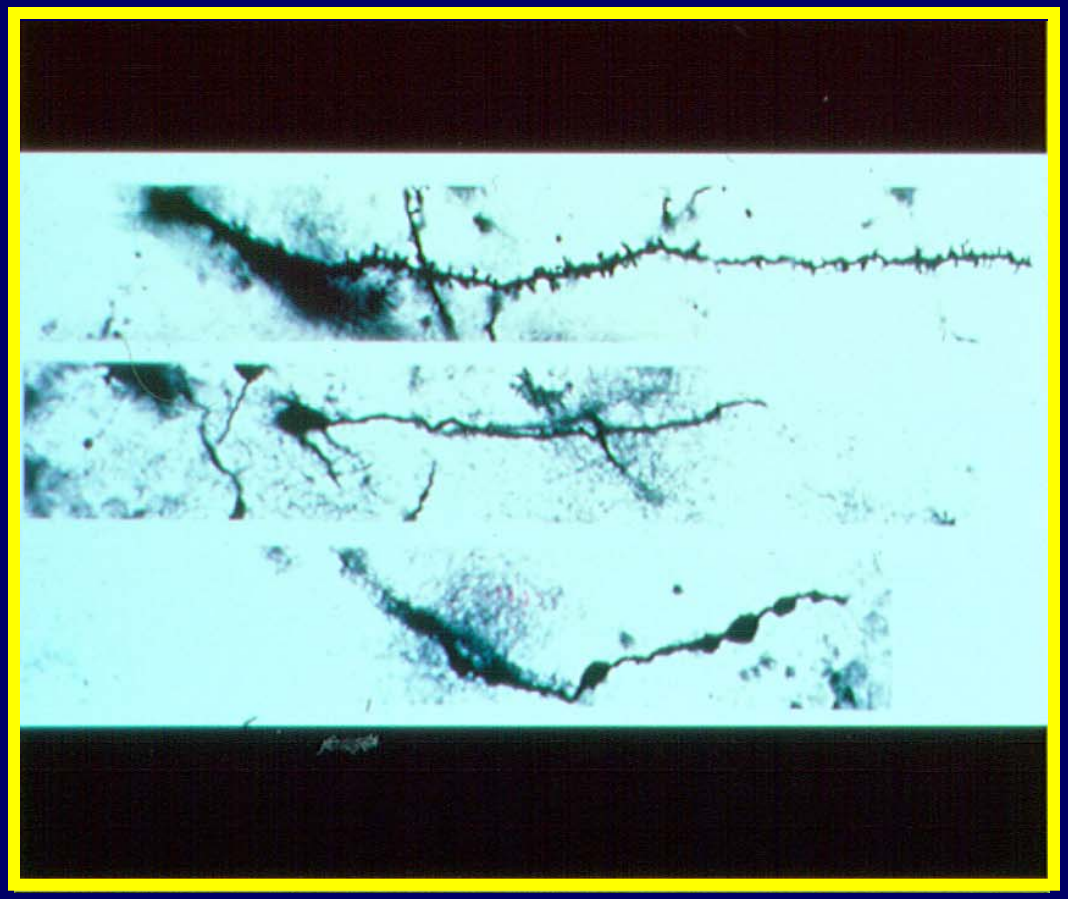


Percent of Various Cells at Autopsy Having HIV

	%
Microglia	80
Astroglia	?
Endothelial	10
Neurons	0

HIV-Associated Brain Damage Involves Neuronal Pathology

Synaptic Injury is Prominent



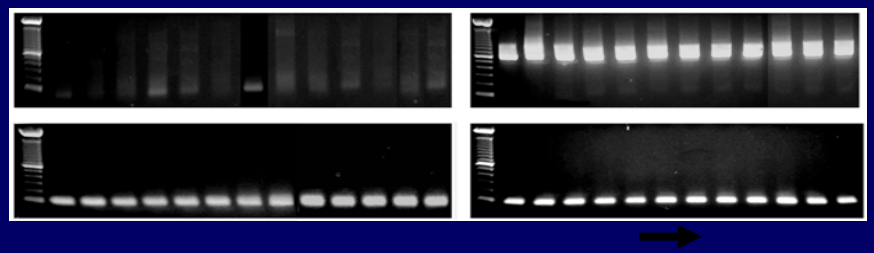
Cellular localization of HCV in macrophages and astrocytes in the brain

Nested PCR

HIV+ HCV- HIV+ HCV+

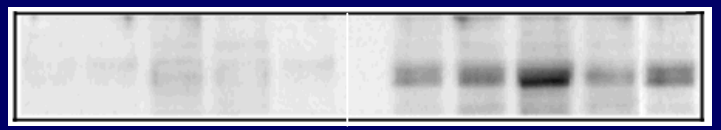
HCV mRNA

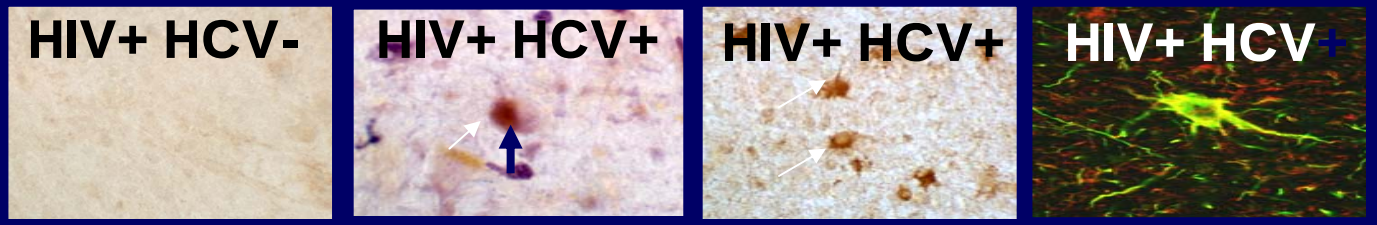
Actin mRNA



Western blot NS5a

HIV+ HCV- HIV+ HCV





Demonstration of HCV-Immunostaining in the brain METH cases with HIVE.

Chang, et al (2005)