ON THE EMERGING ROLE OF NEUROPSYCHOLOGY IN UNDERSTANDING BRAIN EFFECTS OF MEDICAL ILLNESSES: EXAMPLE OF HIV

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http://www.hnrc.ucsd.edu/

PART 1

- A brief history of how a physician got hooked on neuropsychology

  – Once upon a time there was a psychiatry resident who wondered: Is there really


ADULTS ONLY!
The Sweet "PILL" that MAKES LIFE BITTER!
WOMEN CRY FOR IT— MEN DIE FOR IT!
"REEFER MADNESS"
SEE
YOUTHFUL MARIHUANA VICTIMS
WHAT ACTUALLY HAPPENS!
DRUG-CRAZED ABANDON


MARIJUANA
WEED FROM THE DEVIL'S GARDEN!
One MOMENT of BLISS — A LIFETIME of REGRET!
HUNTING A THRILL, THEY INHALED A DRAG OF CONCENTRATED SIN!
"Reefer MADNESS"
A 35th CLASS C
With DAVE O'BRIEN · LILLIAN MILES · DOROTHY SHORT CARLETON YOUNG
WAKE UP AMERICA! HERE'S A ROADSIDE WEED THAT'S FAST BECOMING A NATIONAL HIGH-WAY!

THE JOURNAL OF NERVOUS AND MENTAL DISEASE

Vol. 156, No. 4
Printed in U.S.A.

A NEUROPSYCHOLOGICAL ASSESSMENT OF THE EFFECTS OF MODERATE MARIHUANA USE

IGOR GRANT, M.D.,[1] JOSEPH ROCHFORD, M.D., TIM FLEMING, M.D.[2]
AND ALBERT STUNKARD, M.D.[3]

There is very little information on the effects of long term usage of marihuana on man, and even less on moderate long term usage, such as that of the majority of youthful users. Twenty-nine male medical students who had smoked marihuana moderately and regularly for at least 3 years were compared on a large battery of sensitive neuropsychological tests with 29 students who had never used marihuana or other drugs. Essentially no difference between the two groups was found. Moderate social usage of marihuana in this stable group does not result in sufficient impairment of function that it can be detected by the most sensitive neuropsychological instruments now available.

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A NEUROPSYCHOLOGICAL ASSESSMENT OF THE EFFECTS OF MODERATE MARIHUANA USE

TABLE 1
Mean Scores and Standard Deviations on Neuropsychological Tests

Test	Controls, (N = 29)		Experimental Subjects (N = 29)		t test*
	Mean	S.D.	Mean	S.D.	
Raven's matrices	26.55	4.08	26.07	3.96	.457
Halstead Category test	26.14	16.06	21.93	11.27	1.145
Reitan Trail-Making, part A: time (sec)	19.34	4.79	18.52	3.99	.718
Reitan Trail-Making, part B: time (sec)	43.10	11.82	40.07	11.87	.968
Tactual Performance test: time (sec)	479.69	139.35	512.59	159.99	−.902
Tactual Performance test: memory	8.45	1.41	8.12	.91	.744
Tactual Performance test: localization	6.83	2.59	5.41	2.09	2.272†
Goal-directed Serial Alternation	190.93	105.89	158.21	63.53	1.415

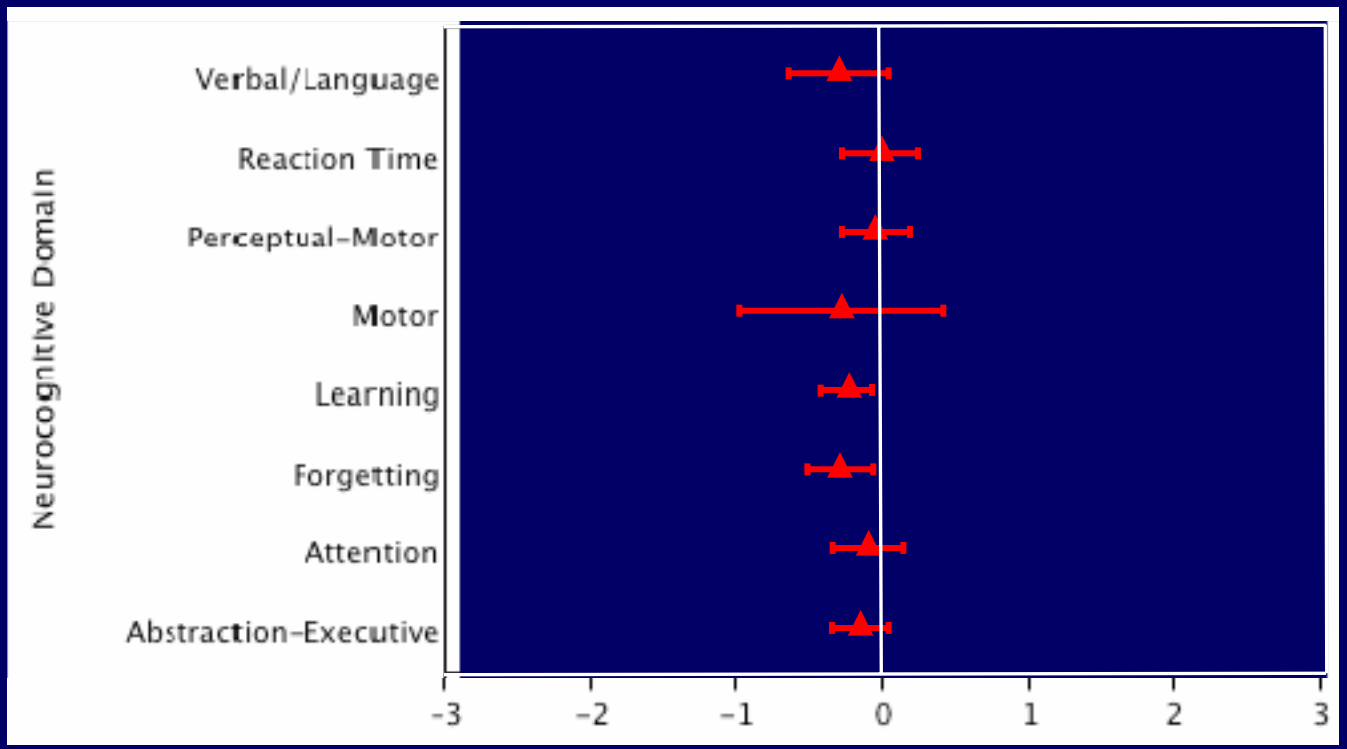
* Two-tailed, $df = 56$.
† $p < .05$.

LESSON 1

- Sometimes there is no fire behind the smoke
- Neuropsychology can be the light that replaces the heat

Long Term Neurocognitive Effects of Marijuana

Results of Meta-analysis of 15 NP studies



Reprinted from the Archives of General Psychiatry
August 1976, Volume 33

A Neuropsychological Study of Polydrug Users

Igor Grant, MD; Lynn Mohns, MA; Michael Miller, MD; Ralph M. Reitan, PhD

• **The long-term neuropsychological effects of persistent nonmedical drug use are still unknown. In this study, 22 young men, all extensive "polydrug" users, were examined while free from drugs for an average of 60 days by means of the Halstead-Reitan Neuropsychological Test Battery. Their performance was compared to that of age-education-sex-matched neurologically intact medical patients and a similarly matched group of neurologically impaired patients.**

Blind independent ratings of test protocols by two experienced clinicians judged 41% to 64% of the drug users, 11% to 26% of the medical patients, and 84% to 89% of the neurologic patients to be impaired. Interpretation of these results suggests that in some individuals, heavy "polydrug" use may be associated with neuropsychological dysfunction, which persists at least an average of two months beyond cessation of drug use.
(*Arch Gen Psychiatry* 33:973-978, 1976)

A Neuropsychological Study of Polydrug Users

Igor Grant, MD; Lynn Mohns, MA; Michael Miller, MD; Ralph M. Reitan, PhD

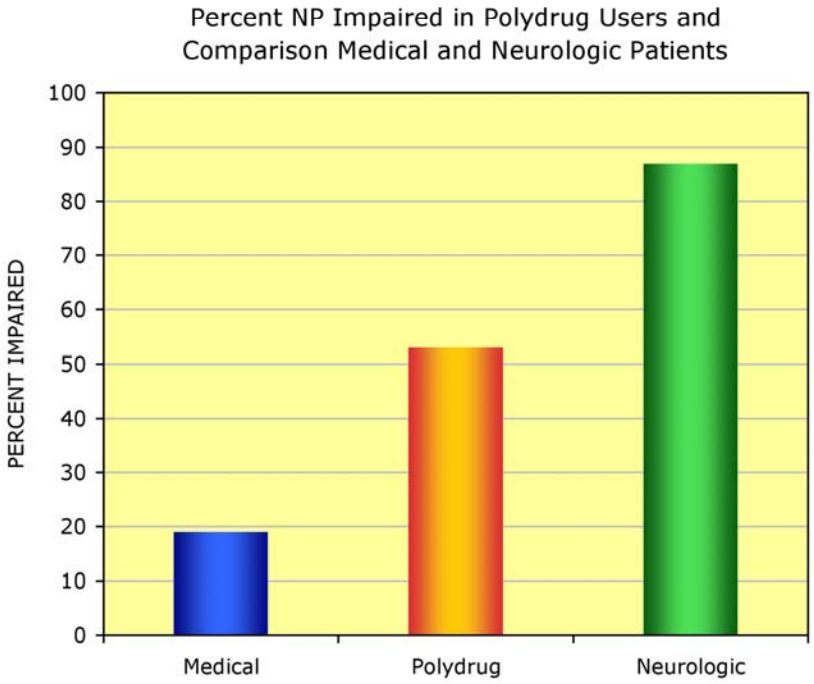
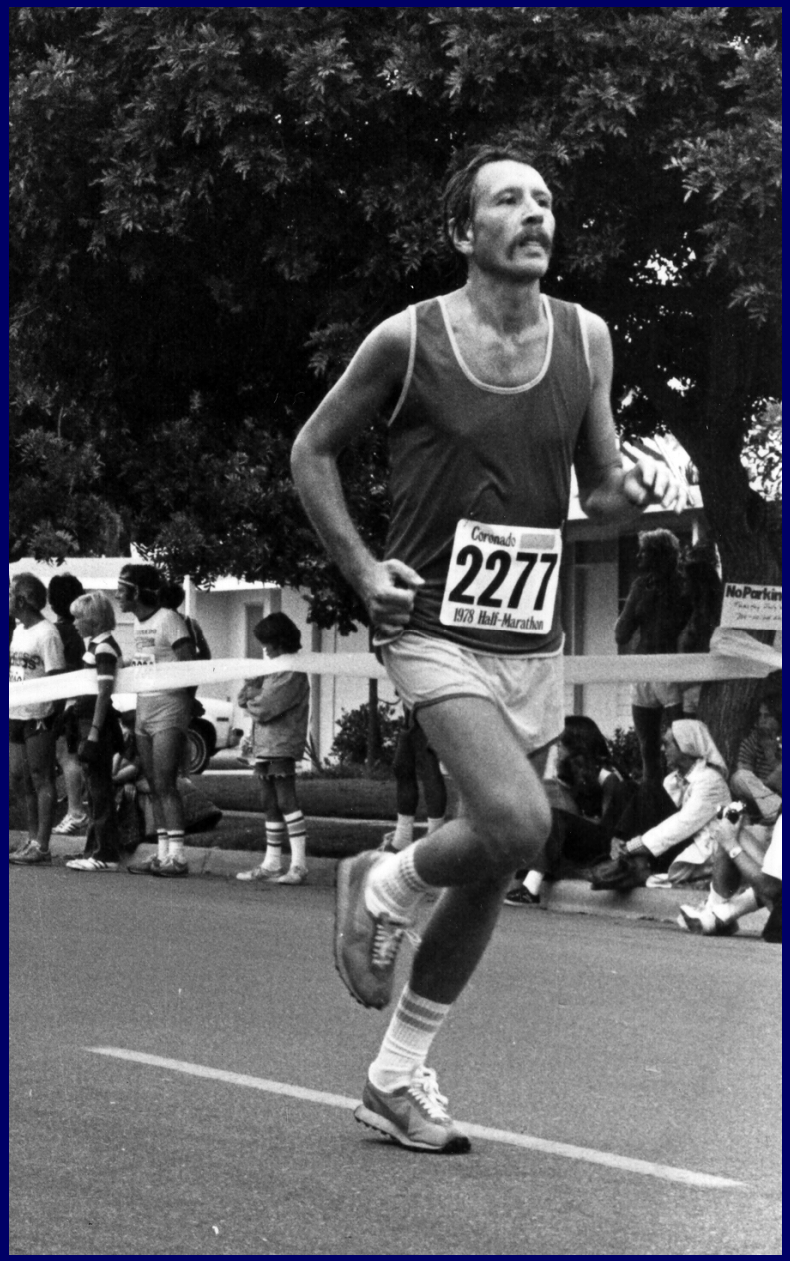


Table 2.—Results of Clinical Assessments of Neuropsychological Protocols by Two Raters

Group	Raters Agree		Raters Disagree		% Agreement
	Impaired	Not Impaired	I.G. Not Impaired* R.M.R. Impaired†	I.G. Impaired* R.M.R. Not Impaired†	
Neurologic (N=19)	16	2	0	1	95
Medical (N=19)	1	13	4	1	74
Drug (N=22)	9	8	5	0	77

*Rating by Igor Grant.
†Rating by Ralph M. Reitan.

"Where's that payline, anyway?"



Reprinted from the Archives of General Psychiatry
September 1978, Volume 35

The Collaborative Neuropsychological Study of Polydrug Users

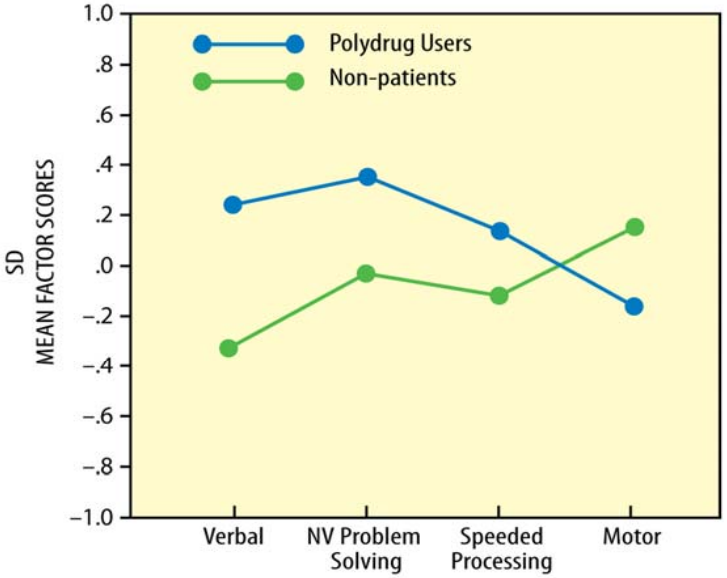
Igor Grant, MD; Kenneth M. Adams, PhD; Albert S. Carlin, PhD; Phillip M. Rennick, PhD†; Lewis L. Judd, MD; Kenneth Schooff, MD

• **A controlled three-month prospective collaborative investigation involving eight National Institute on Drug Abuse-supported polydrug units was carried out. Clinical review of test protocols assessed 37% of polydrug users, 26% of psychiatric patients, and 8% of nonpatients as impaired on the Halstead-Reitan Battery. Impairment in test performance was related to increasing age, educational deprivation, and premorbid medical factors in all groups, extensive use of CNS depressants and opiates among polydrug users, and extensive use of antipsychotic drugs in psychiatric patients. Both language-related and perceptuomotor neuropsychological test deficits were found in polydrug users, but only the latter in psychiatric patients. At three-month follow-up 34% of polydrug users, 27% of psychiatric patients, and 4% of nonpatients were impaired in these test performances. Recent drug-taking (polydrug group) and schizophrenia diagnosis (psychiatric patients) were additional correlates of test impairment. Persistence of performance deficit in polydrug users raises the possibility that CNS depressants and opiates may have longer-term, slowly reversible, or even permanent effects on neuropsychological tests. The same possibility exists for antipsychotic drugs. The link of these test deficits to other specific neuropsychological functions, to performance in life situations generally, or to specific brain dysfunction, as well as the basis for a lack of test impairments in the majority of polydrug subjects remain to be determined.**
(*Arch Gen Psychiatry* 35:1063-1074, 1978)

Reprinted from the Archives of General Psychiatry
September 1978, Volume 35

The Collaborative Neuropsychological Study of Polydrug Users

Igor Grant, MD; Kenneth M. Adams, PhD; Albert S. Carlin, PhD; Phillip M. Rennick, PhD†; Lewis L. Judd, MD; Kenneth Schooff, MD



Mean NP Factor Scores for Polydrug Users and Controls

Table 5.—Neuropsychological Performance Change Over Three Months

Group	Initial Rating	Follow-up Status: Substantial Improvement No.	%	Un-changed No.	%	Substantial Worsening No.	%
Polydrug users	Unimpaired	5	9	48	85	3	5
	Impaired	9	25	25	69	2	6
Psychiatric	Unimpaired	6	15	25	64	8	21
	Impaired	5	39	7	54	1	8
Nonpatients	Unimpaired	5	10	43	88	1	2
	Impaired	0	0	2	100	0	0

ALCOHOL AND THE BRAIN:

Igor Grant, MD

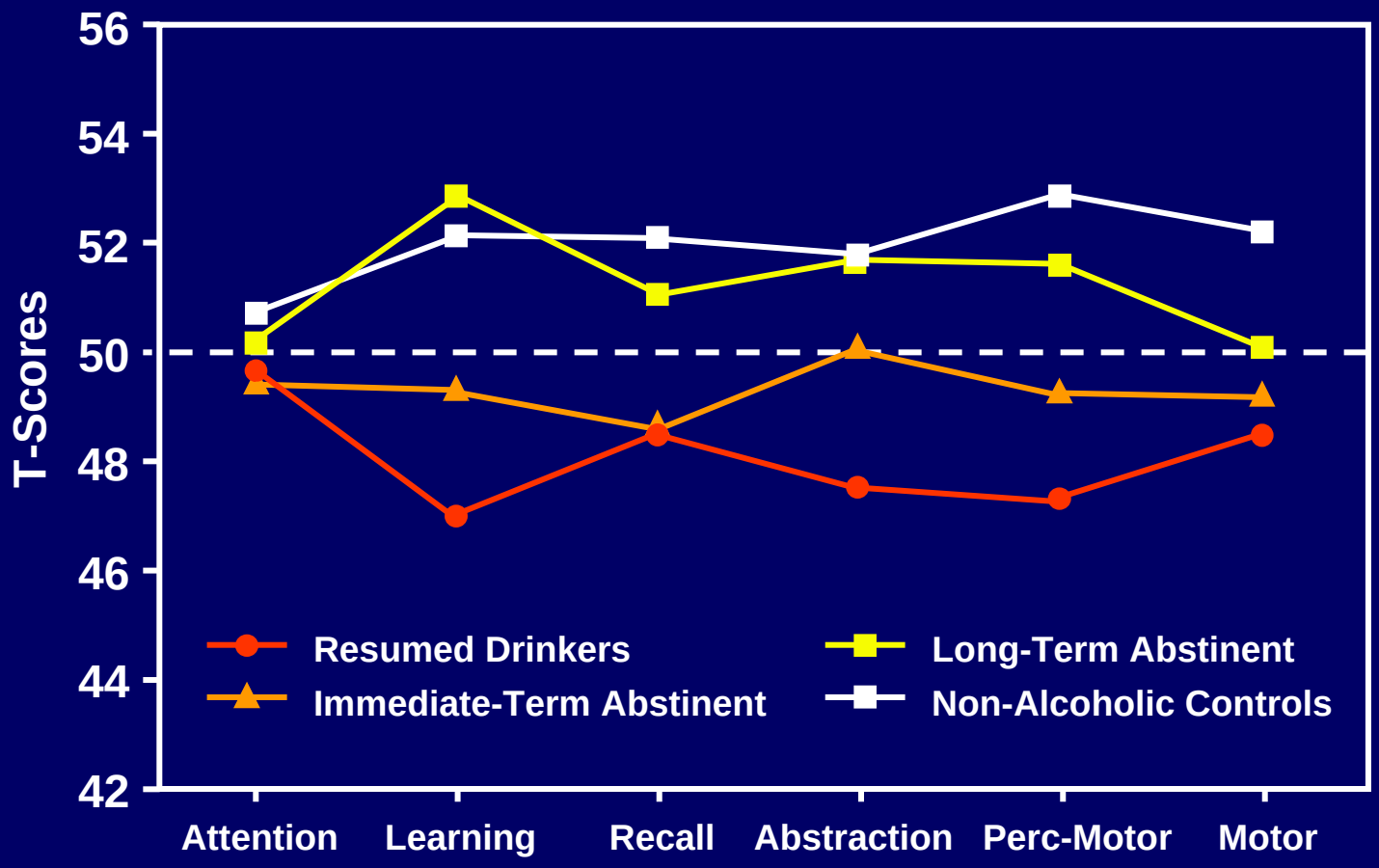
Aging, Abstinence, and Medical Risk Factors in the Prediction of Neuropsychologic Deficit Among Long-term Alcoholics

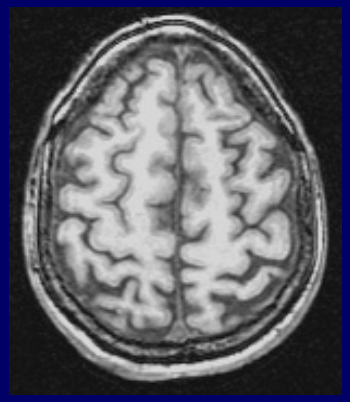
Igor Grant, MD; Kenneth M. Adams, PhD; Robert Reed, MS

• **Halstead-Reitan assessments were conducted with 71 male alcoholics sober for four weeks, 65 alcoholics sober for four years, and 68 nonalcoholics. Recently detoxified alcoholics showed learning and problem-solving difficulties, as did older persons in all groups. Aging, not alcoholism, was related to psychomotor slowing. There were no age-alcohol interactions for any neuropsychologic test. Time since last drink predicted neuropsychologic performance modestly, as did head injury, age, and education. Long-term sober alcoholics were indistinguishable from controls. Our results suggest that alcoholics abstinent one month suffer a subacute alcohol-related organic mental disorder that might resolve with prolonged abstinence, that the neuropsychologic findings in such alcoholics are more consistent with an "independent decrements" rather than "premature aging" hypothesis, and that neuromedical and other risk factors must be considered before permanent neuropsychologic deficit among alcoholics can be attributed solely to neurotoxic effects of alcohol. (*Arch Gen Psychiatry* 1984;41:710-718)**

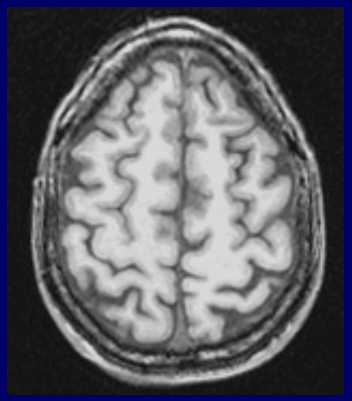
Reprinted from the Archives of General Psychiatry
July 1984, Volume 120

NP Performance in Alcoholics Related to Length of Abstinence





During Treatment



1 ½ Years Later

VA San Diego Alcohol Study

Rourke & Grant, 1996

LESSON 2

- If you can't get the grant you want, get the grant you can get
- You will learn something important anyway, and eventually you might get the grant you want

NP AND COMPLEX MEDICAL CONDITIONS: EXAMPLE OF COPD

- NHLBI sponsored trials of oxygen and Intermittent Positive Pressure Breathing were examining various medical outcomes
- By the way, might hypoxemia affect their mental functioning?
- Can we have a 5-10 min assessment of the brain?

COPD STUDIES Battery (1)

- **Verbal**
  - WAIS-R Information
  - WAIS-R Vocabulary
  - WAIS-R Comprehension
  - WAIS-R Similarities
  - Aphasia Screening Exam
  - Boston Naming Test
  - Thurstone Word Fluency
  - BDAE Complex Ideation
  - Letter Fluency
  - Animal Fluency
- **Abstraction**
  - Category Test
  - Trails B
- **Perceptual-Motor**
  - TPT Time/Block
  - WAIS-R Picture Completion
  - WAIS-R Picture Arrangement
  - WAIS-R Block Design
  - WAIS-R Object Assembly
  - WAIS-R Digit Symbol
  - Trails A
  - Spatial Relations

COPD STUDIES Battery (2)

- **Learning**
  - Tactual Performance Test
  - Story Learning
  - Figure Learning
- **Memory**
  - Story Loss
  - Figure Loss
- **Sensory**
  - Tactile Form Recognition
  - Sensory Exam
- **Motor**
  - Finger Tapping
  - Grip Strength
  - Grooved Pegboard
- **Attention**
  - WAIS-R Digit Span
  - WAIS-R Arithmetic
  - Seashore Rhythm
  - Speech Sounds Perception
  - Digit Vigilance
  - Paced Auditory Serial Addition

Reprinted from the Archives of Internal Medicine
August 1982, Volume 142

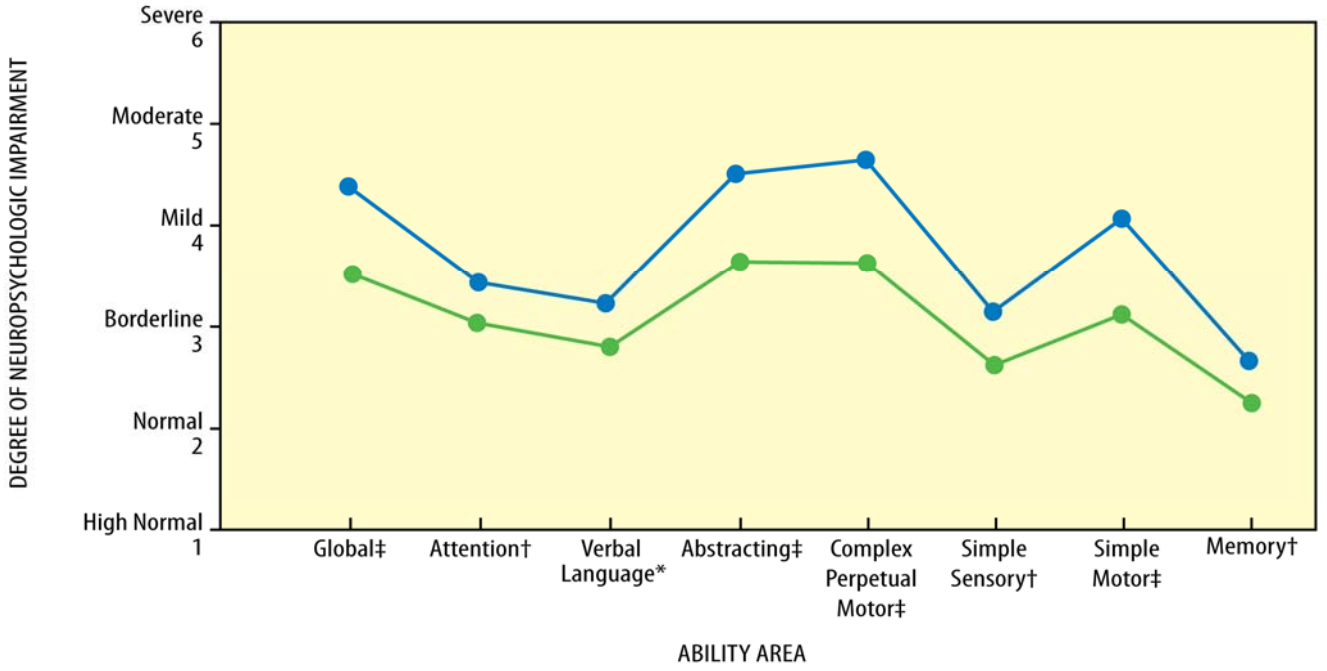
Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease

Igor Grant, MD; Robert K. Heaton, PhD; A. John McSweeny, PhD; Kenneth M. Adams, PhD; Richard M. Timms, MD

● **As part of a six-center clinical trial of the effectiveness of continuous *v* nocturnal oxygen in the management of hypoxemic chronic obstructive pulmonary disease (COPD), we performed detailed neuropsychologic assessments of these patients prior to their beginning treatment. The 203 patients (age, 65 years; Pao_2, 51 mm Hg; forced expiratory volume in 1 s, 0.74 L) performed significantly worse than controls on virtually all neuropsychologic tests. Moderate to severe test impairment suggestive of cerebral dysfunction was found in 42% of the patients, as compared with 14% of controls. Higher cognitive functions (abstracting ability, complex perceptual-motor integration) were most severely affected, although half the patients also showed decrements in motor speed, strength, and coordination. Low-order significant inverse correlations were found between neuropsychologic impairment and Pao_2, resting arterial oxygen saturation and hemoglobin levels and maximum work. It is concluded that cerebral disturbance is common in hypoxemic COPD and may be related in part to decreased availability of oxygen to the brain.**

(*Arch Intern Med* 1982;142:1470-1476)

Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease



Group mean scores for patients with chronic obstructive pulmonary disease (blue) and neighborhood controls (green) based on clinicians' ratings of neuropsychologic ability areas. Significance of differences between groups, based on Mann-Whitney *U* test is as follows: asterisk, $P < .05$; dagger, $P < .01$; and double dagger, $P < .001$.

Arch Intern Med—Vol 142, Aug 1982

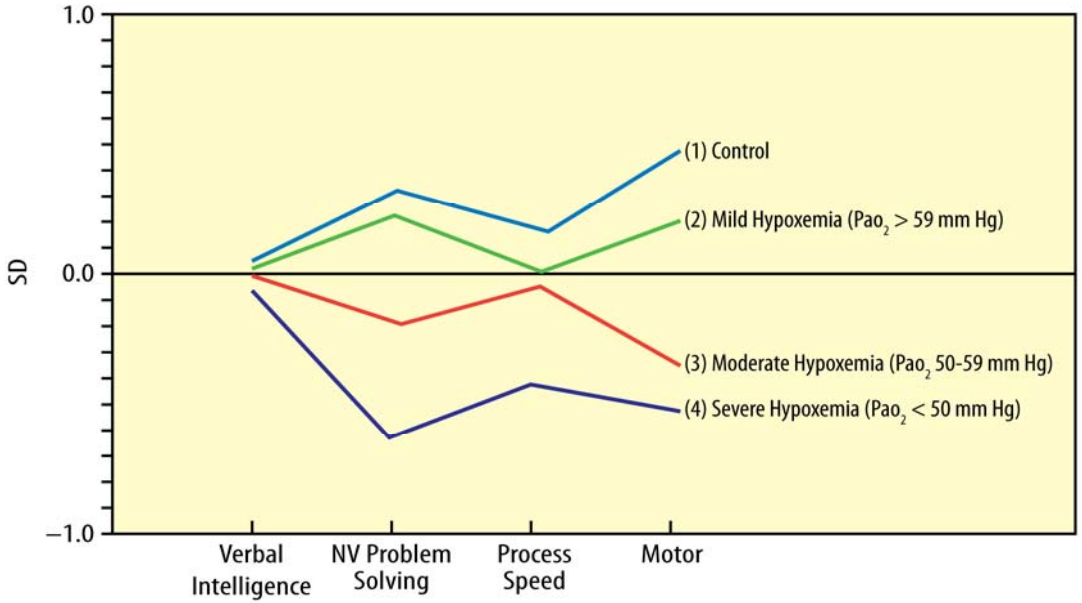
Progressive Neuropsychologic Impairment and Hypoxemia

Relationship in Chronic Obstructive Pulmonary Disease

Igor Grant, MD; George P. Prigatano, PhD; Robert K. Heaton, PhD; A. John McSweeny, PhD; Elizabeth C. Wright, MPH; Kenneth M. Adams, PhD

• In previous work we showed that patients with chronic obstructive pulmonary disease (COPD) suffered decrements in neuropsychologic functioning suggestive of organic mental disturbance. This study combined data from two multicenter clinical trials to explore the nature and possible determinants of such neuropsychologic change. Three groups of patients with COPD whose hypoxemia was mild (N=86), moderate (N=155), or severe (N=61) were compared with age- and education-matched nonpatients (N=99). The rate of neuropsychologic deficit rose from 27% in mild hypoxemia to 61% in severe hypoxemia. Various neuropsychologic abilities declined at different rates, suggesting differential vulnerability of neuropsychologic functions to progress of COPD. Multivariate analyses revealed a consistent significant relationship between degree of hypoxemia and neuropsychologic impairment, but the amount of shared variance was small (7%). Increasing age and lower education were also associated with impairment.
(*Arch Gen Psychiatry* 1987;44:999-1006)

Progressive Neuropsychologic Impairment and Hypoxemia



Factor-analytically derived ability scores for patients with chronic obstructive pulmonary disease at three levels of hypoxemia and controls. Pao_2 indicates arterial oxygen pressure.

Arch Gen Psychiatry—Vol 44, Nov 1987

Neuropsychologic Impairment—Grant et al

LESSON 3

- Pulmonary specialists do not diagnose COPD just with their stethoscope. They use extensive PFTs and imaging
- The brain is at least as complicated as the lung. Neuropsychologists should not sell themselves short if they want to make serious contributions to understanding the effects of complex medical disorders on brain and behavior. Quick and dirty won't cut it!

Reprinted from ANNALS OF INTERNAL MEDICINE Vol. 107; No. 6 December 1987
Printed in U.S.A.

Evidence for Early Central Nervous System Involvement in the Acquired Immunodeficiency Syndrome (AIDS) and Other Human Immunodeficiency Virus (HIV) Infections

Studies with Neuropsychologic Testing and Magnetic Resonance Imaging

IGOR GRANT, M.D.; J. HAMPTON ATKINSON, M.D.; JOHN R. HESSELINK, M.D.; CAROLINE J. KENNEDY, M.D.; DOUGLAS D. RICHMAN, M.D.; STEPHEN A. SPECTOR, M.D.; and J. ALLEN McCUTCHAN, M.D.; La Jolla, California

Although a high prevalence of central nervous system disease is seen in persons with the acquired immunodeficiency syndrome (AIDS), the natural history of brain involvement with human immunodeficiency virus (HIV) remains poorly understood. Neuropsychologic evaluations of 55 ambulatory homosexual men revealed abnormalities in 13 of 15 with AIDS, 7 of 16 with AIDS-related complex, 7 of 13 with HIV-seropositivity only, and 1 of 11 with HIV-seronegativity. Common neuropsychologic problems included impaired abstracting ability, learning difficulties, and slowed speed of information processing. Magnetic resonance imaging had abnormal findings in 9 of 13 patients with AIDS and 5 of 10 patients with AIDS-related complex who were available for scans. The commonest abnormalities were sulcal and ventricular enlargement and bilateral patchy areas of high signal intensity in the white matter. We postulate that central nervous system involvement by HIV may begin early in the course of AIDS and cause mild cognitive deficits in otherwise asymptomatic persons.

▶ From the Departments of Psychiatry, Radiology, Medicine, Pathology, and Pediatrics, the University of California at San Diego; and the Psychiatry, Laboratory, and Medicine Services, San Diego Veterans Administration Medical Center, La Jolla, California.

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Evidence for Early Central Nervous System Involvement in the Acquired Immunodeficiency Syndrome (AIDS) and Other Human Immunodeficiency Virus (HIV) Infections

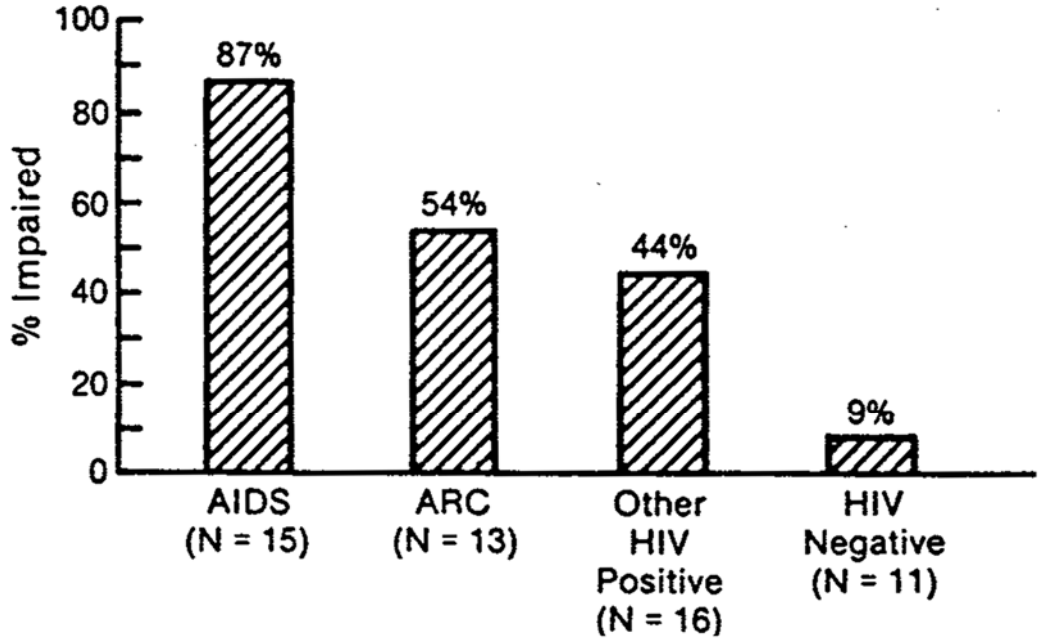
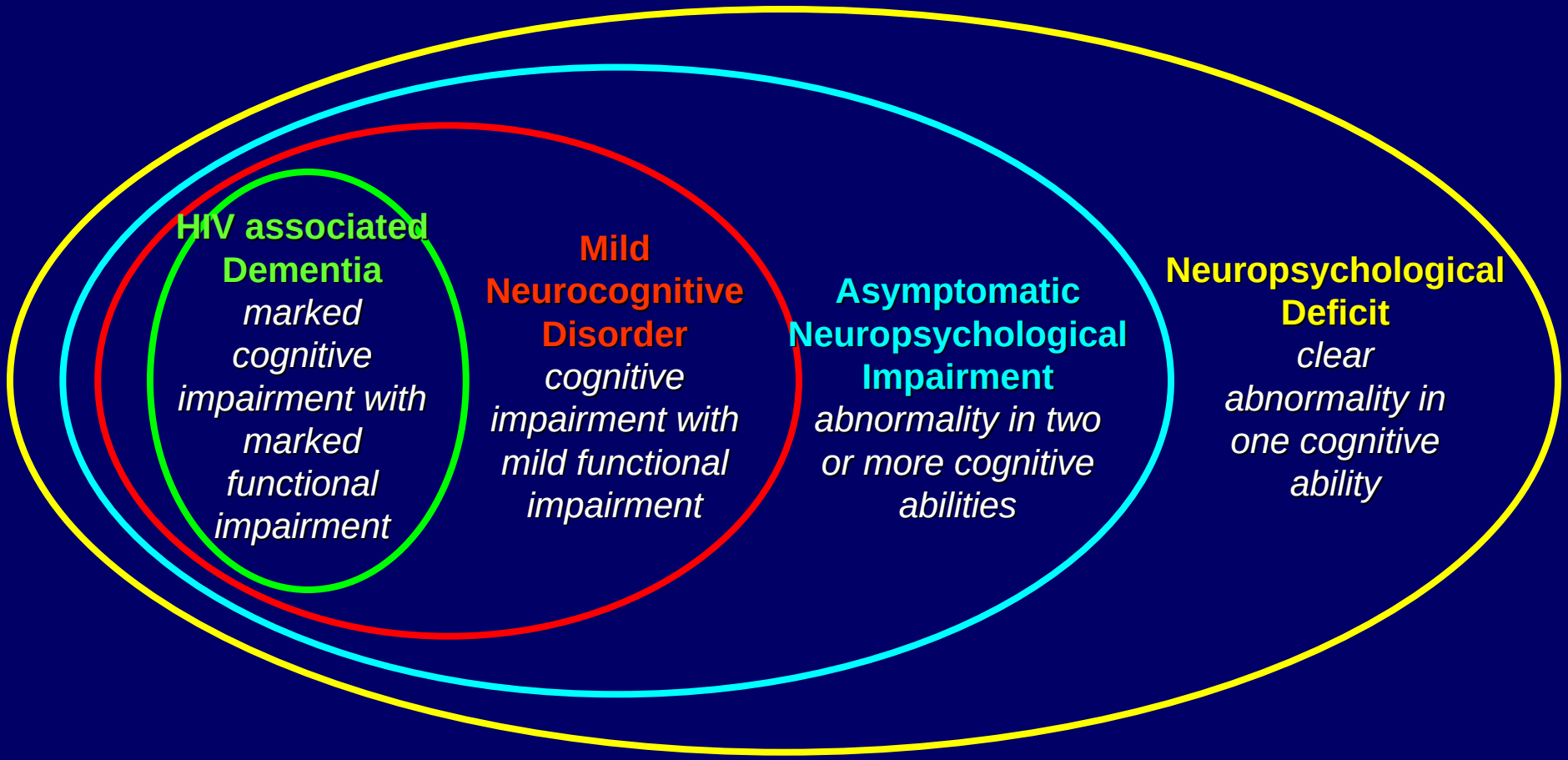


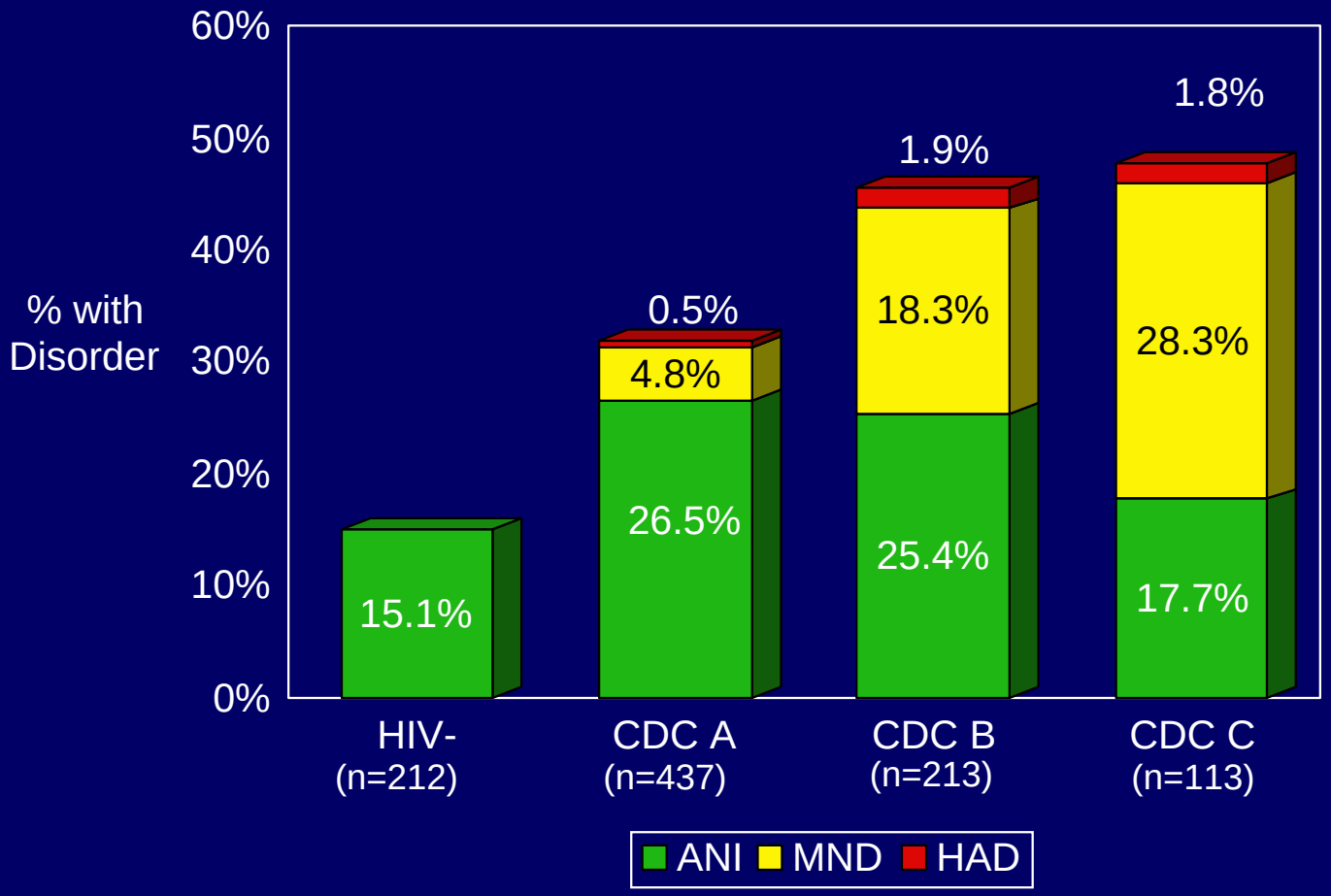
Figure 2. Proportion of subjects manifesting atypical and impaired neuropsychologic performances. AIDS = patients with acquired immunodeficiency syndrome; ARC = patients with AIDS-related complex; HIV-positive = persons positive for human immunodeficiency virus (HIV) antibodies; HIV-negative = persons negative for HIV antibodies.

Annals of Internal Medicine. 1987;107:828-836.

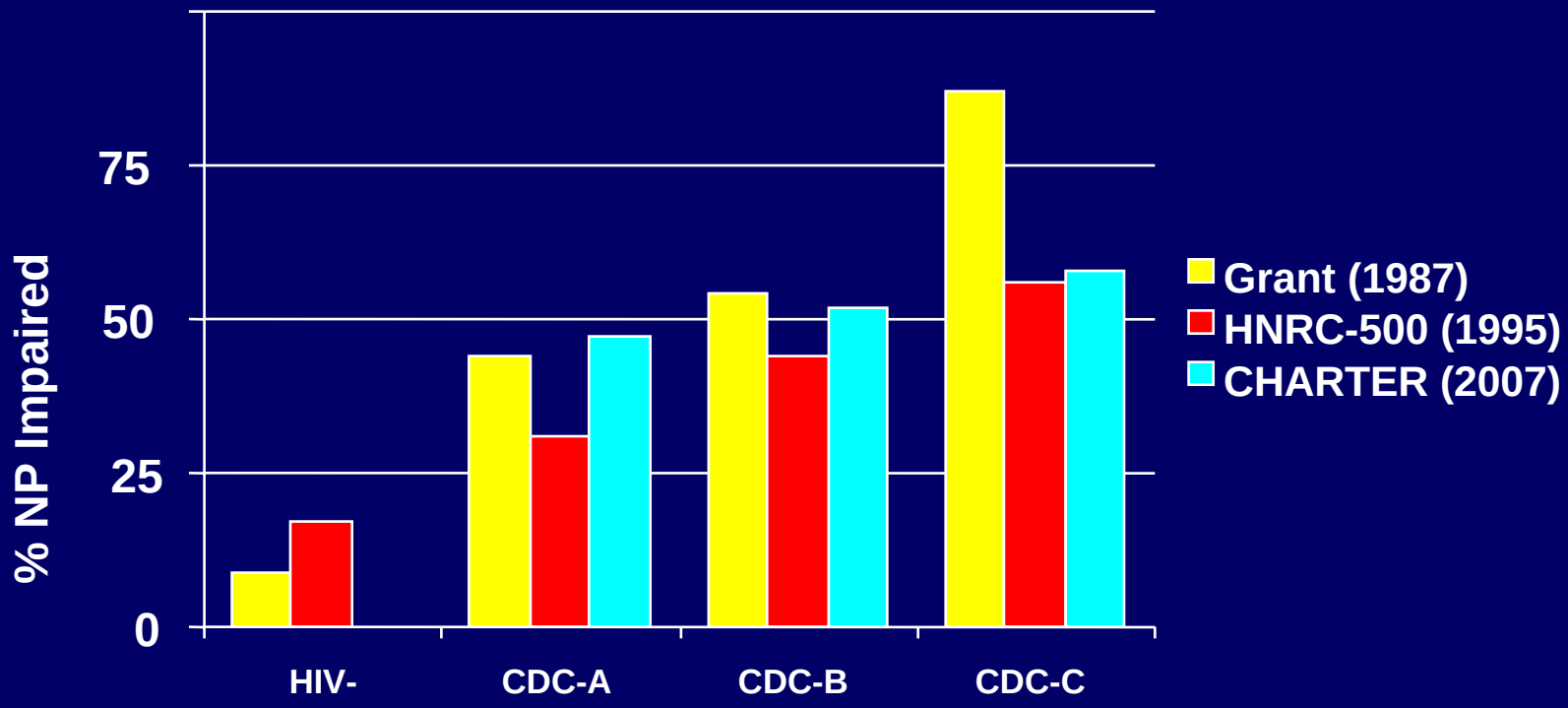
Range of HIV Associated Neurocognitive Disorders (HAND)



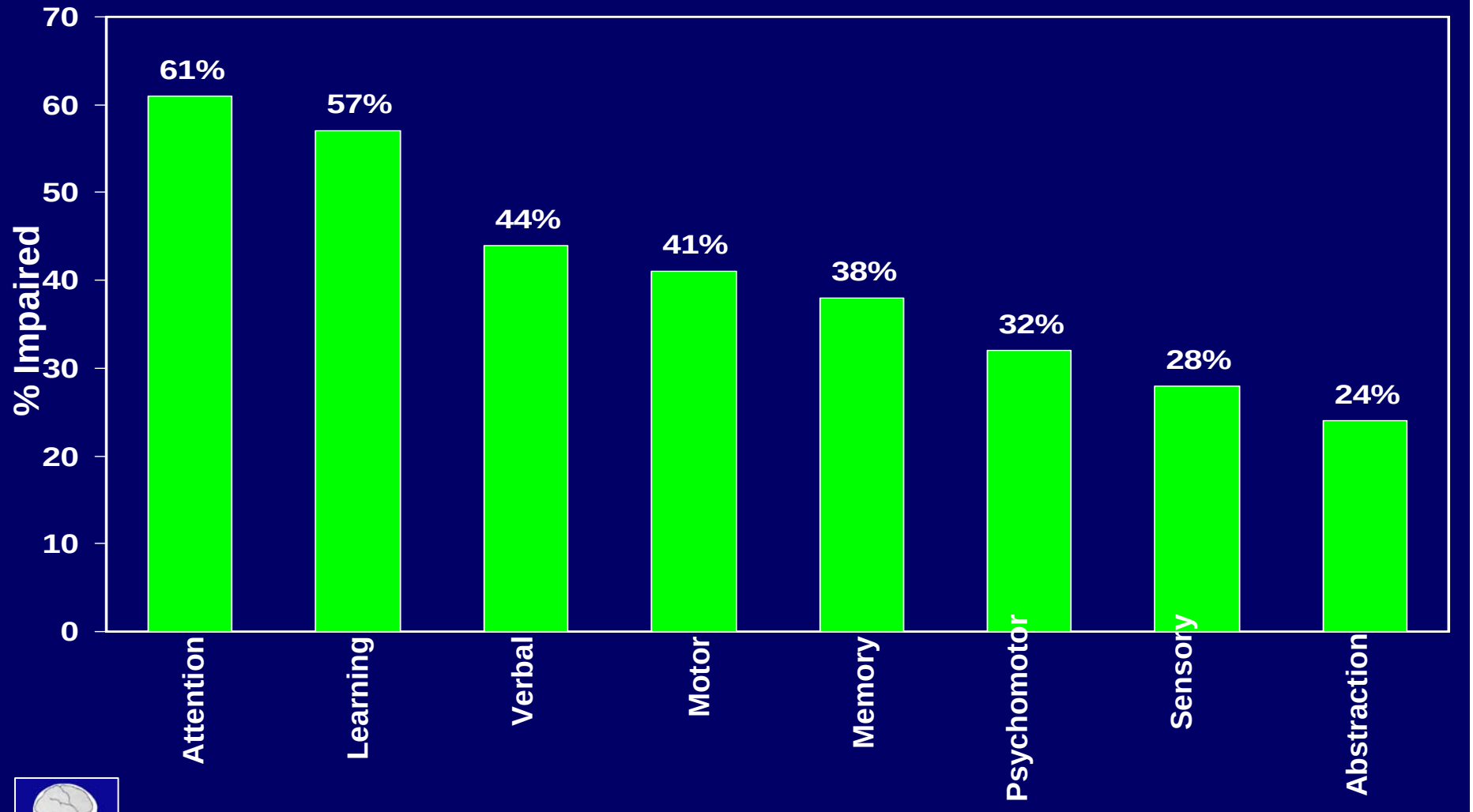
Prevalence of HAND by Stage of HIV Disease



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



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



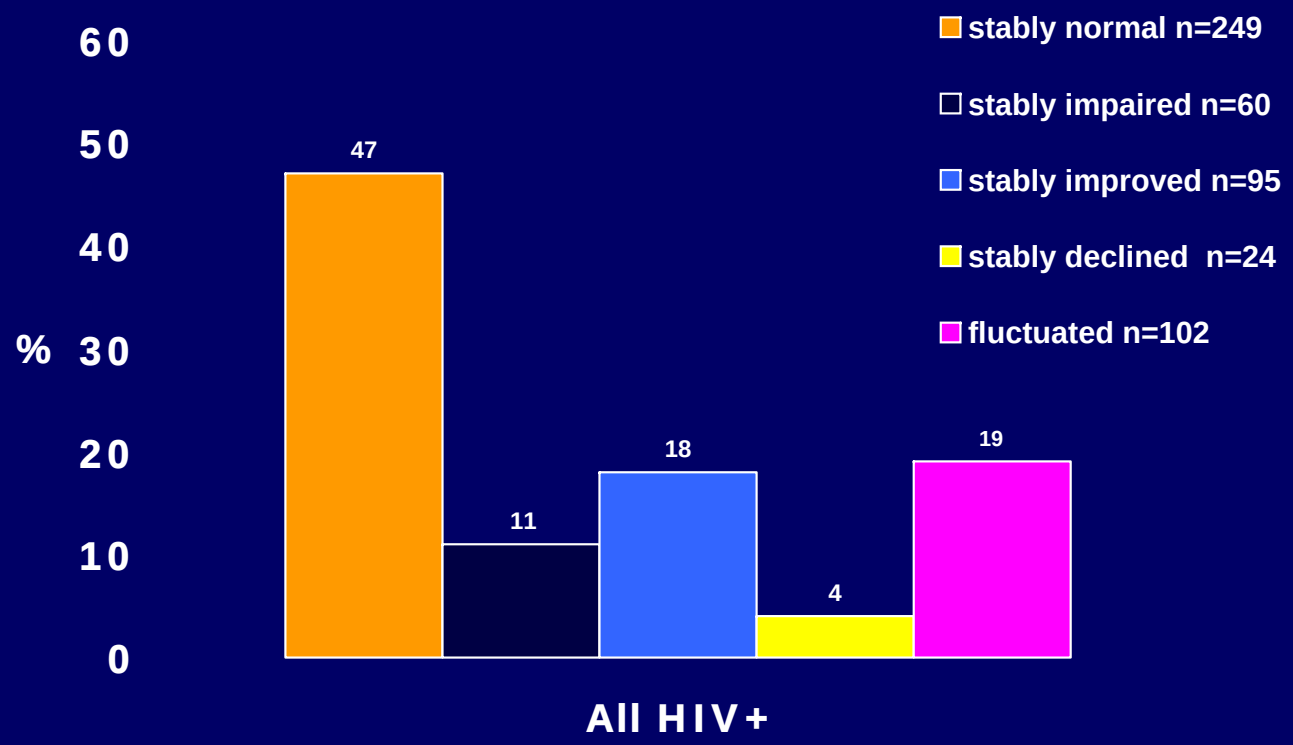
NEUROLOGY

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

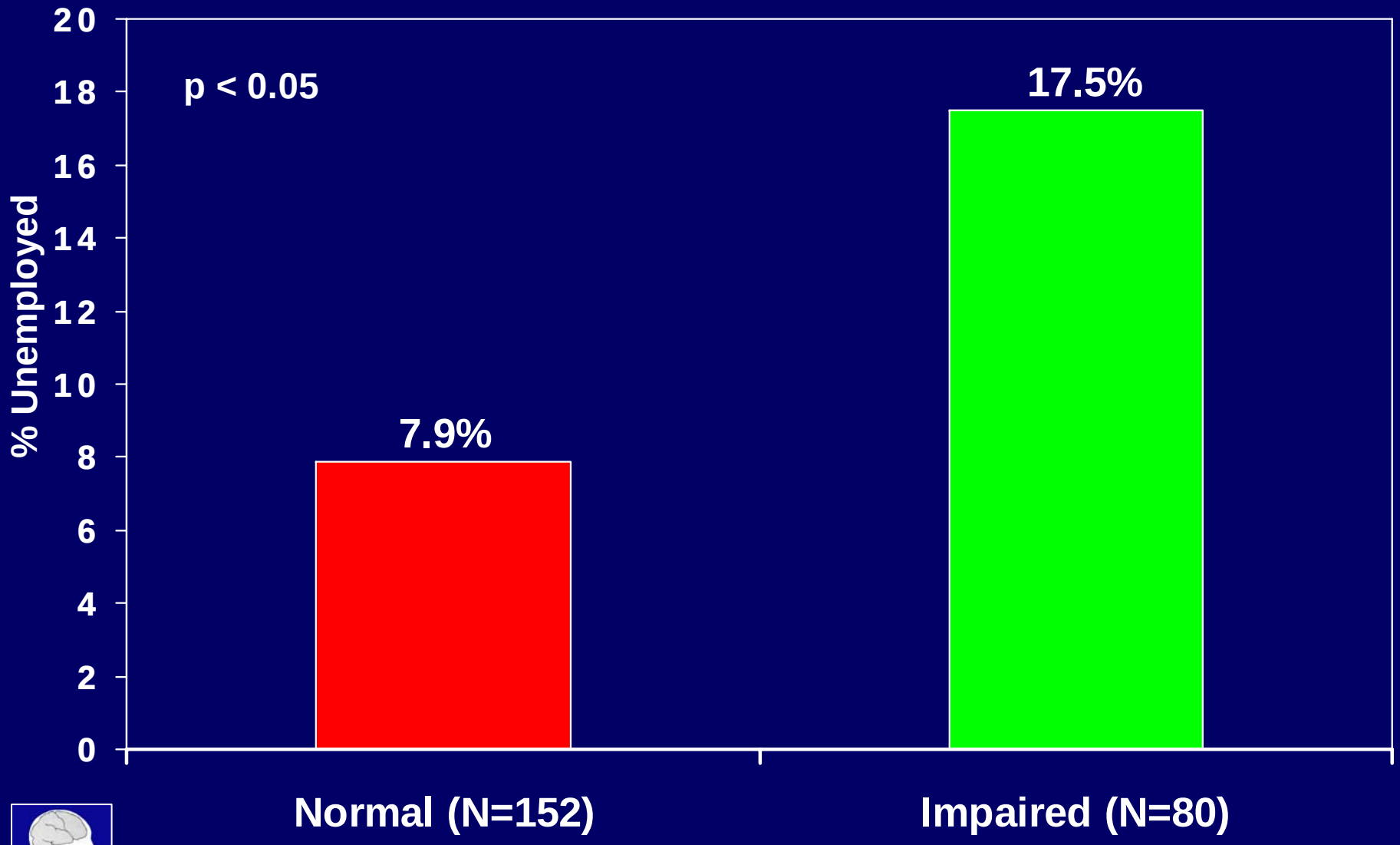
Neurology 2007;69;1789-1799; originally published online Oct 3, 2007;
DOI: 10.1212/01.WNL.0000287431.88658.8b

NP Course for HIV neurocognitive states N=534

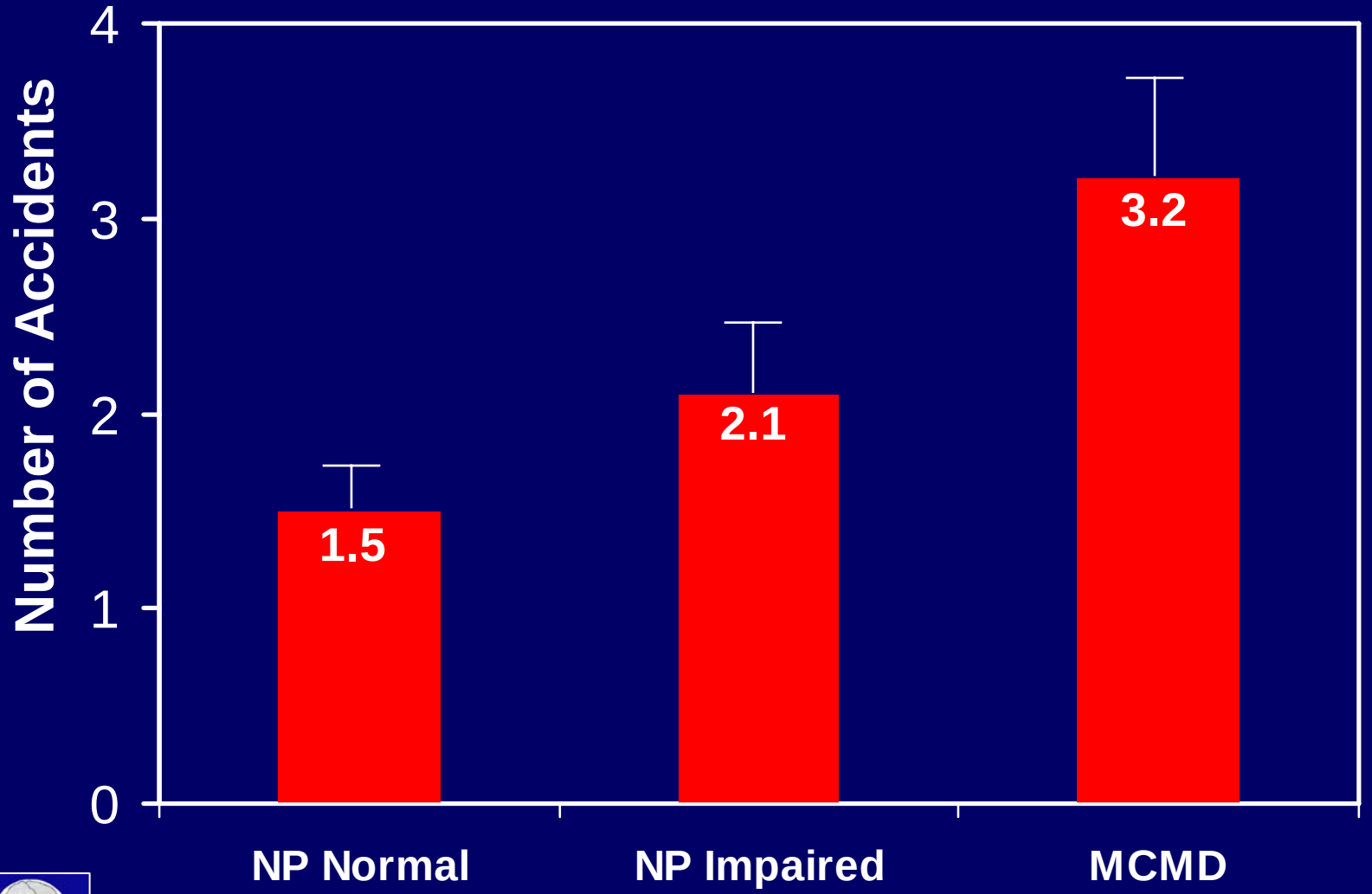


Definitional Criteria Work Group 1: Toward an updated nosology for HIV-associated neurocognitive disorders

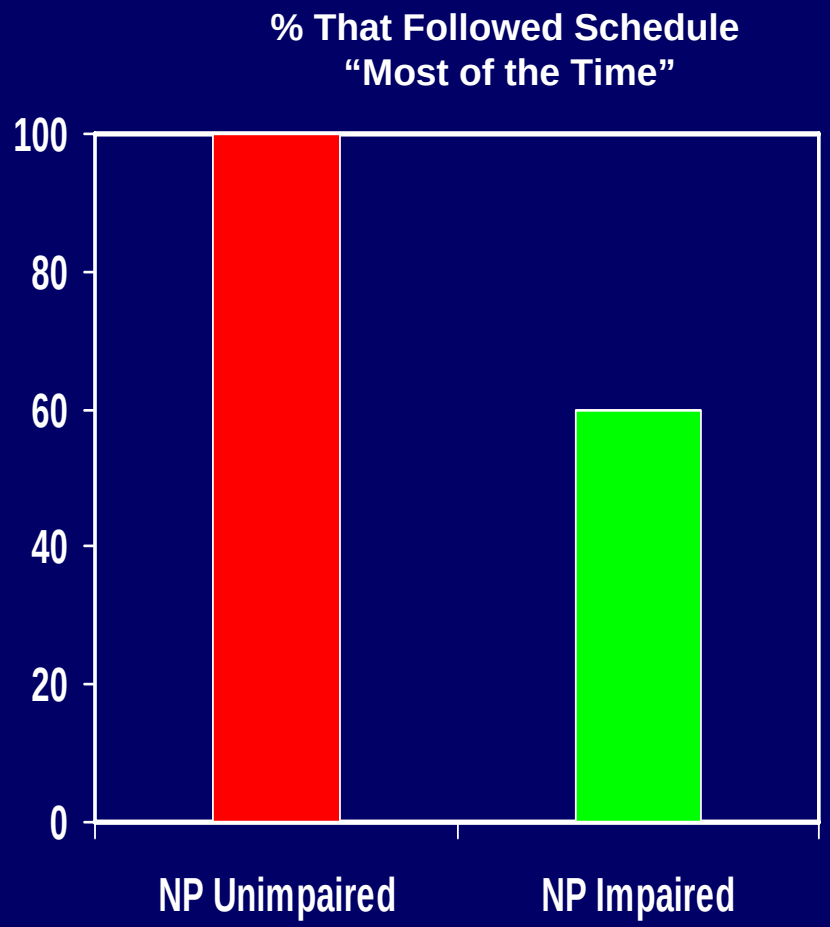
Meaning of NP Impairment: Employment

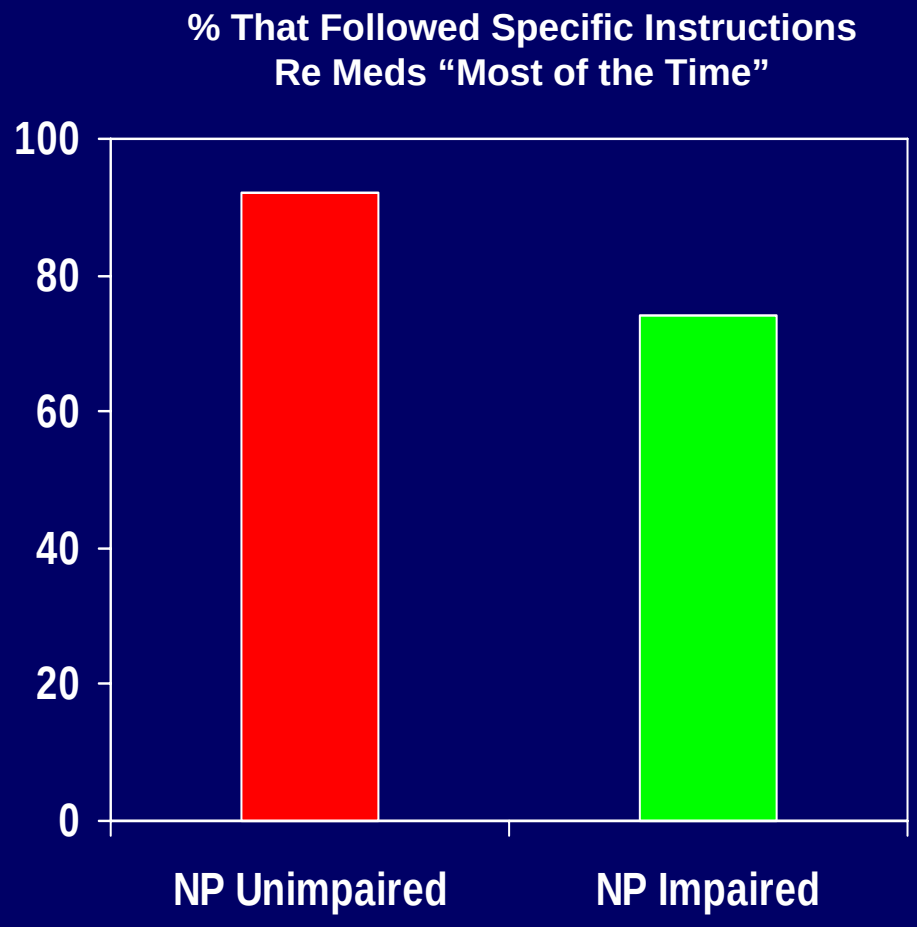


Mean Number of Accidents on City Driving Simulation

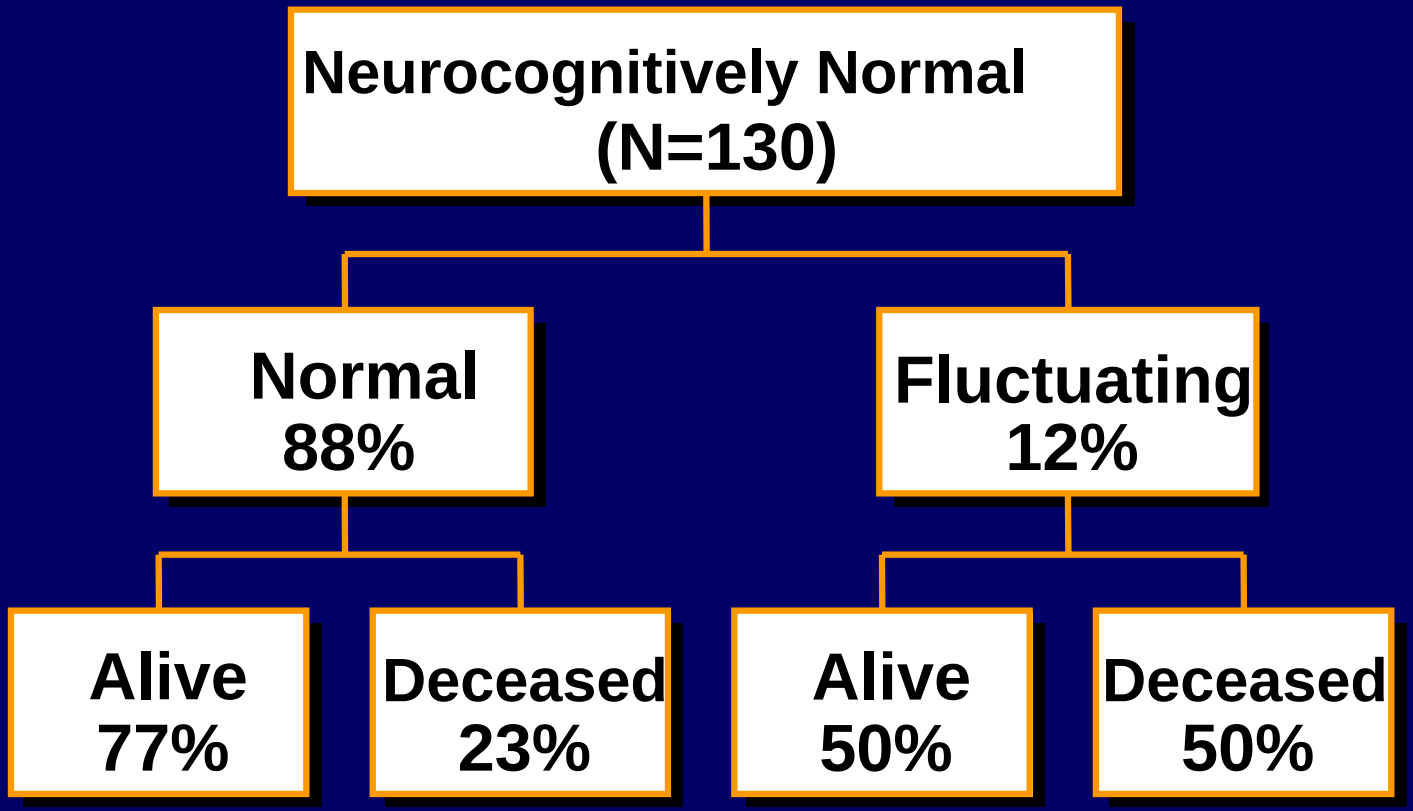


Adherence to Antiretrovirals Related to Neurocognitive Impairment



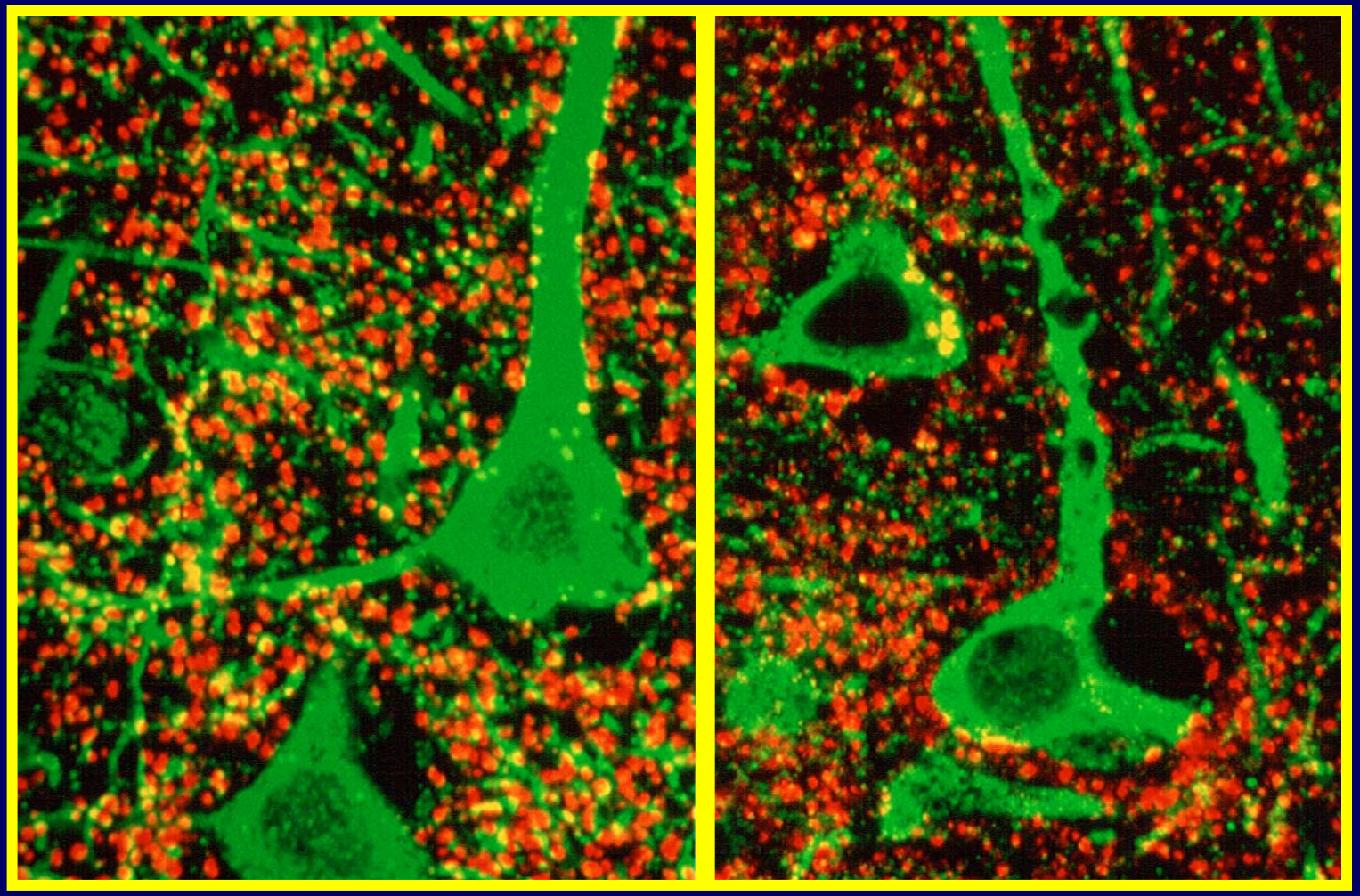


Longitudinal Course of Participants who were Neurocognitively Normal at Baseline



Participants with annual and/or semiannual assessments over a minimum of 2 and up to 8 years

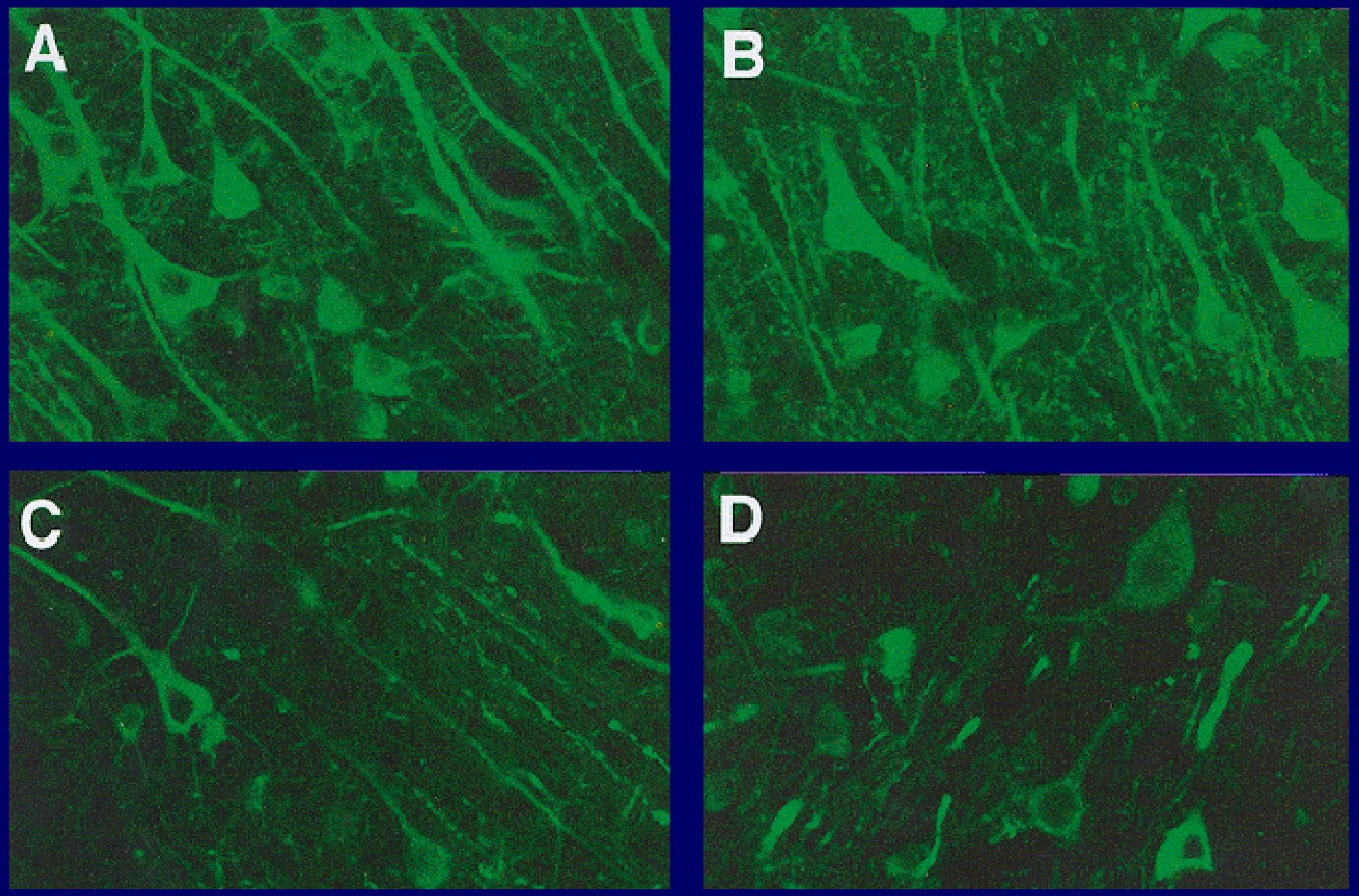
Synaptophysin & MAP-2 Immunostaining



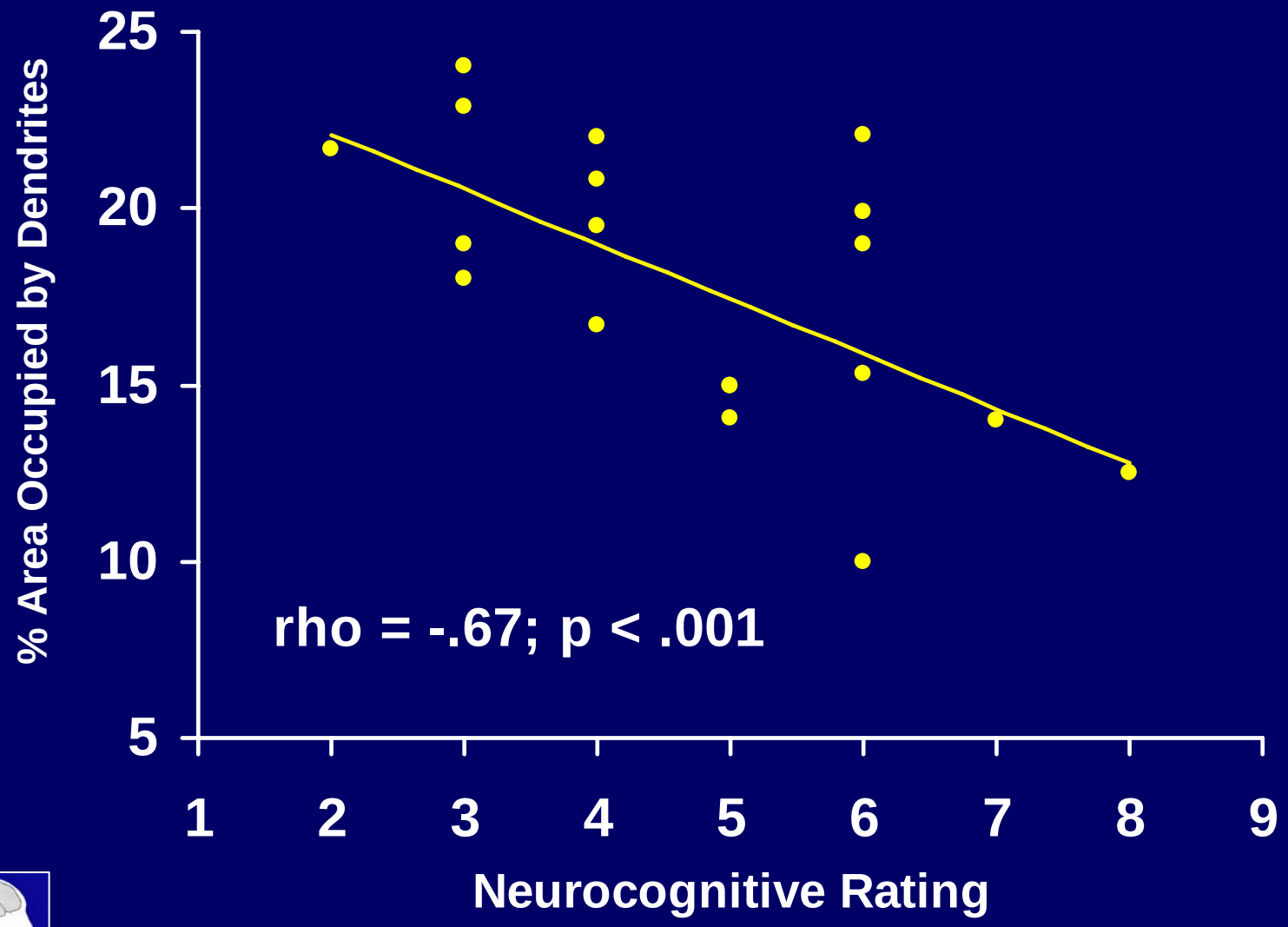
HIV-

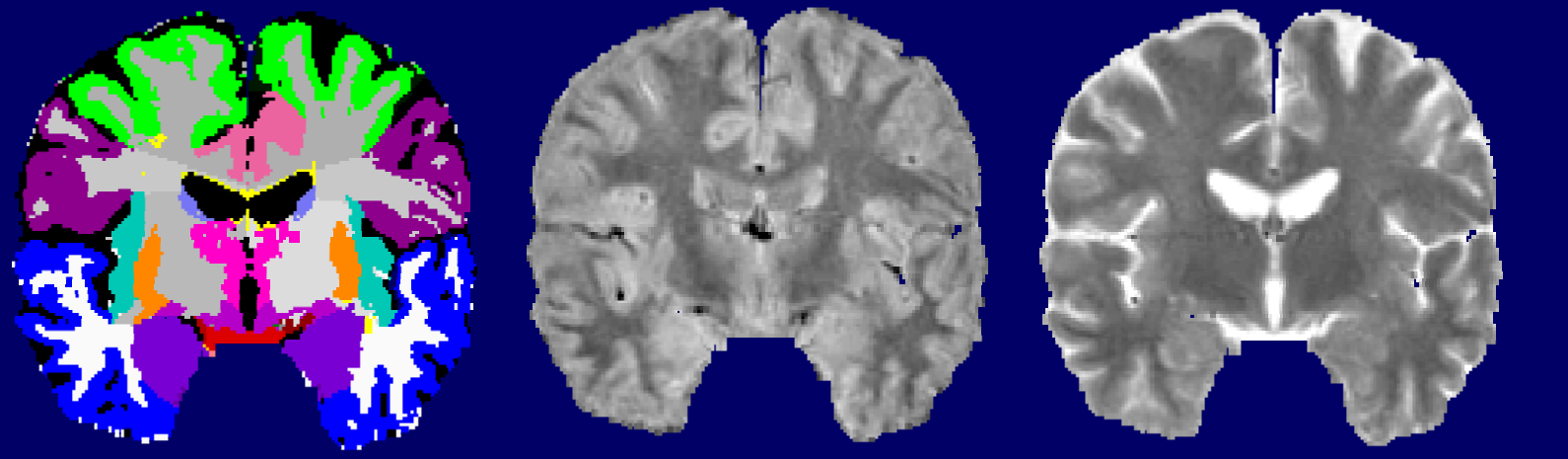
HIV+

Dendritic Complexity in Subjects with Varying Levels of Cognitive Impairment

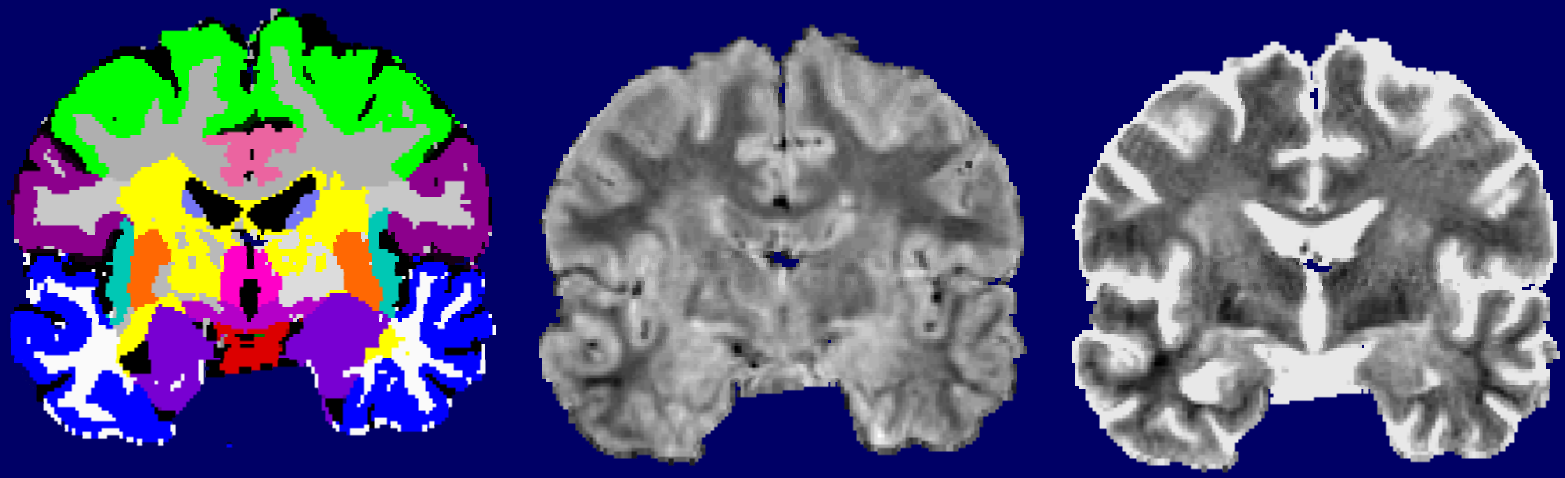


Relation of Dendritic Damage to Neurocognitive Impairment





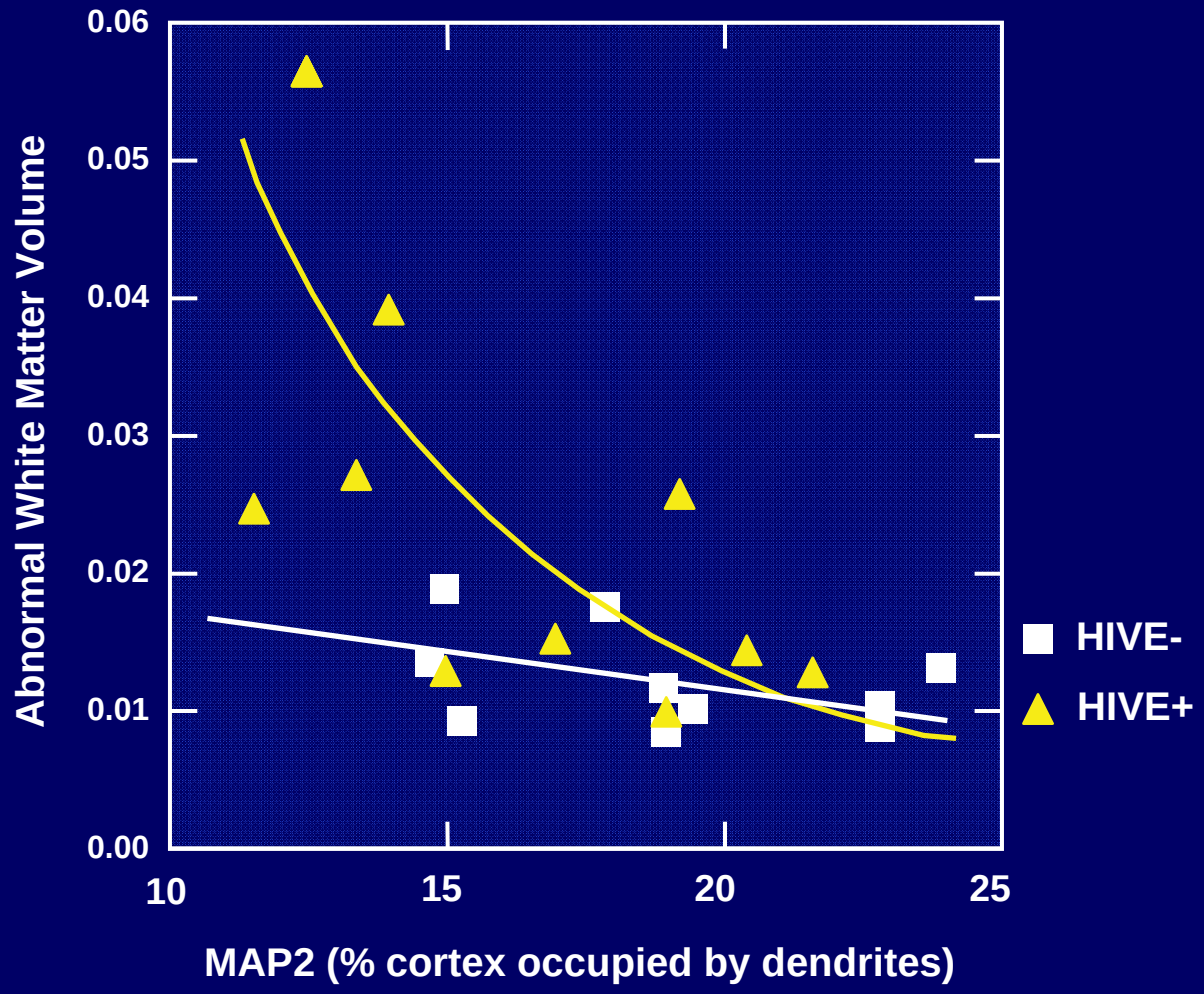
HIVE-



HIVE+

Abnormal White Matter

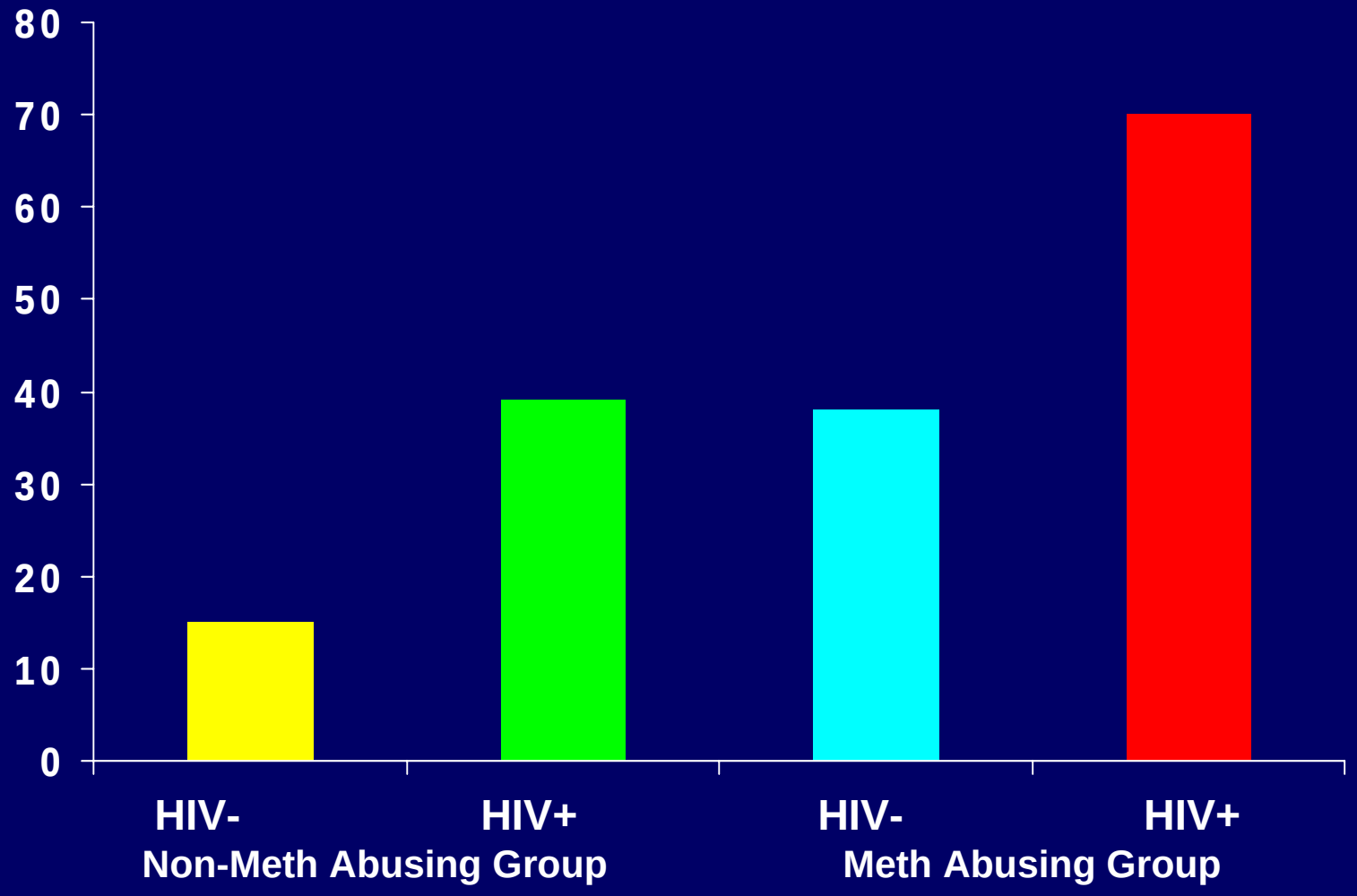
Increased abnormal white matter is related to dendritic loss at autopsy



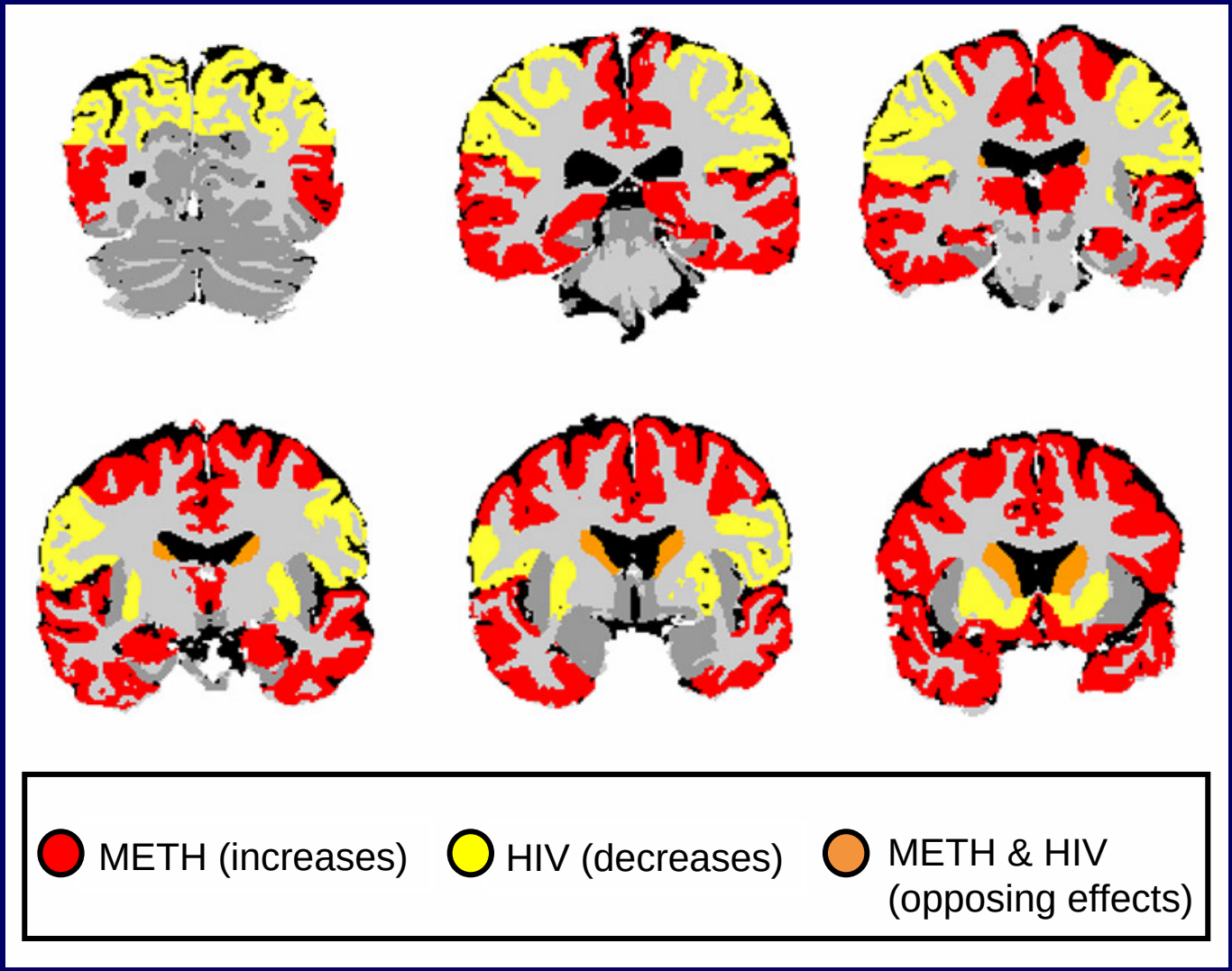
Cofactors in HIV Associated Neurocognitive Complications

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

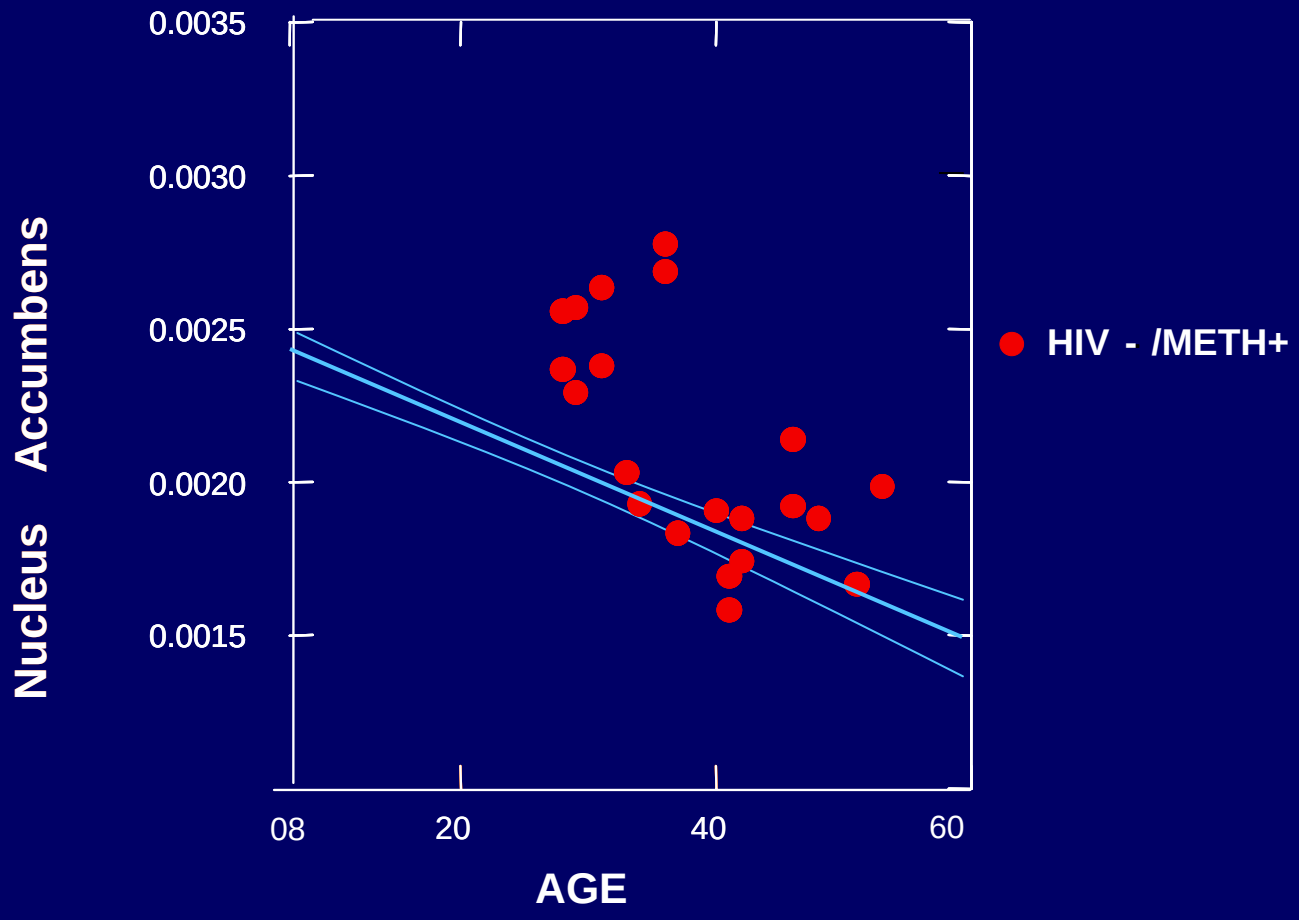
% Having Global NP Impairment by Methamphetamine Abuse and HIV Status



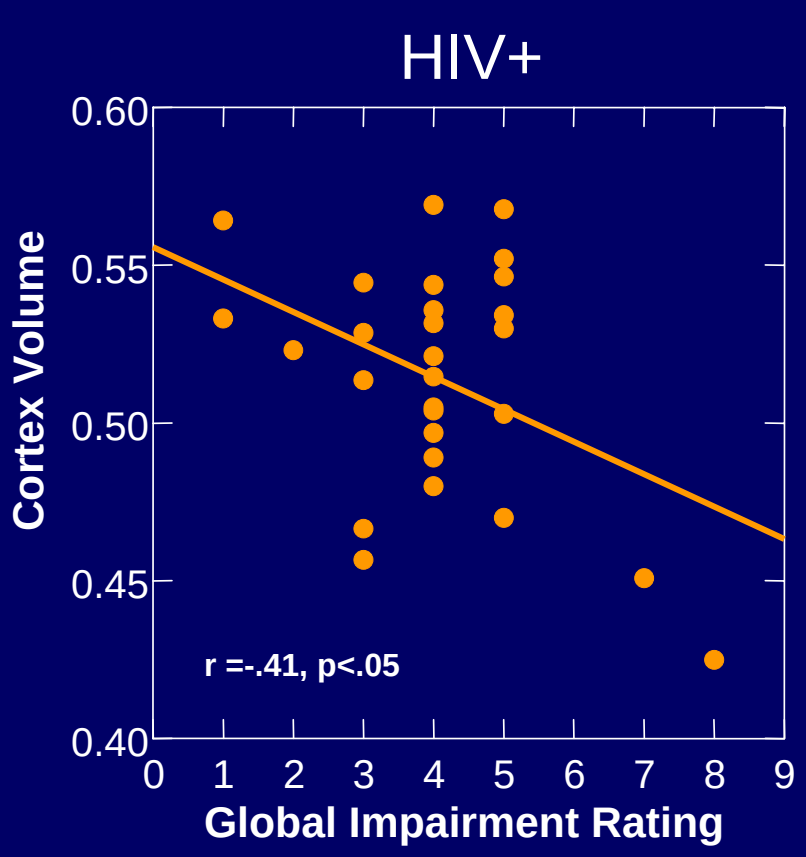
Significant regional volume alterations related to METH and/or HIV

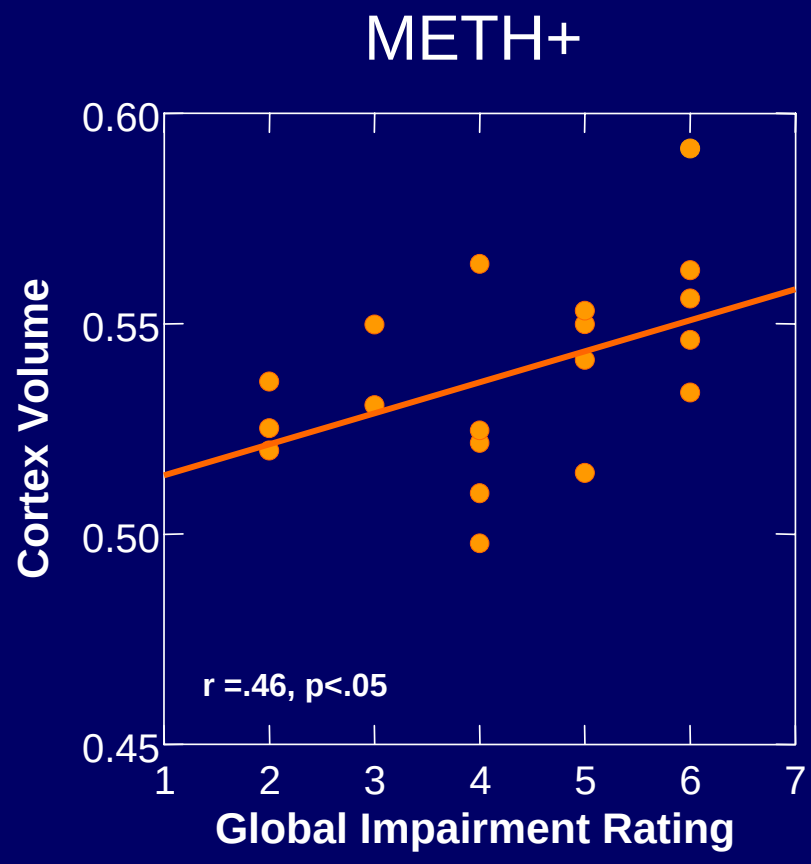


Meth have larger Accumbens volume for age relative to controls

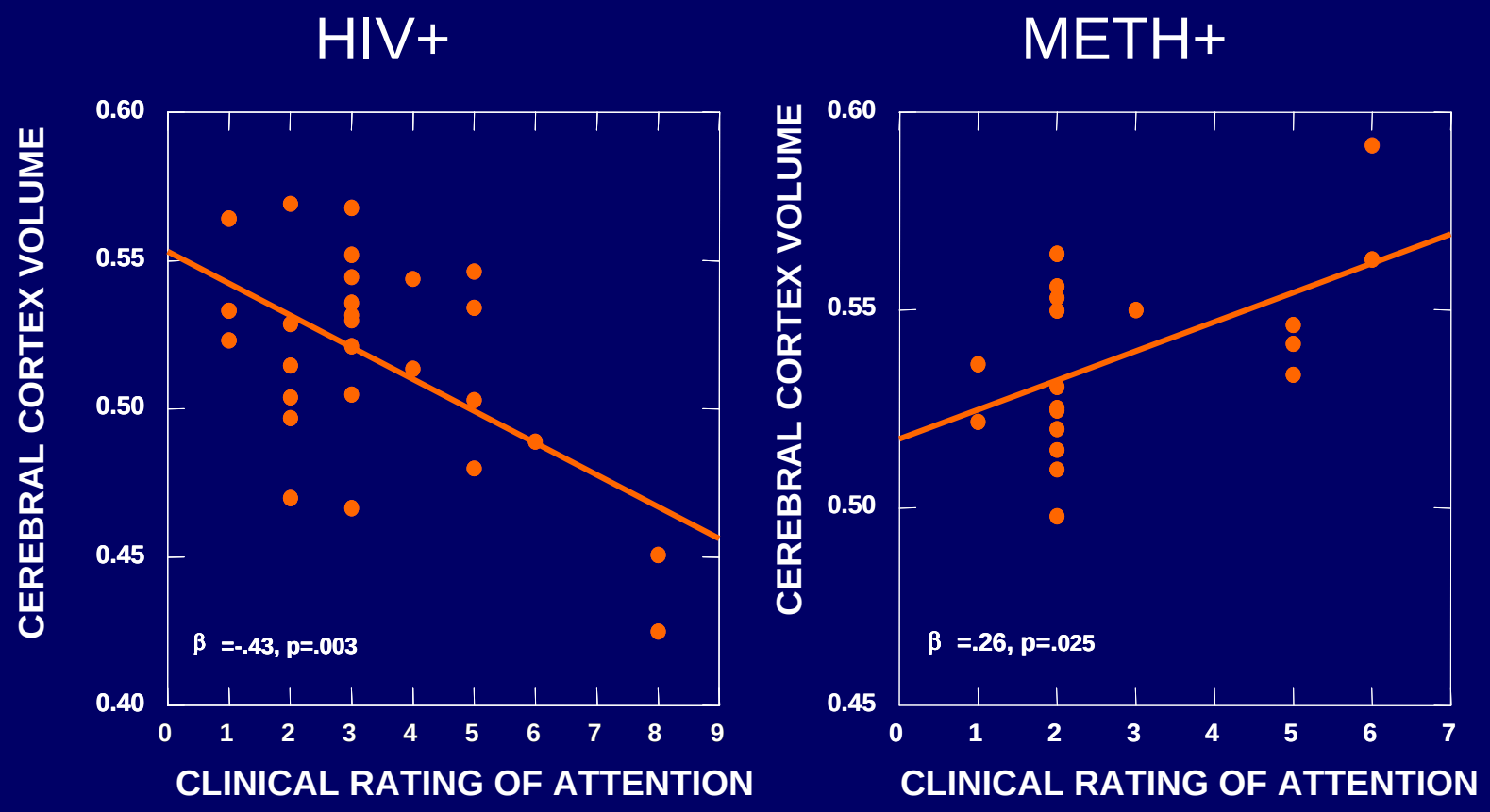


Association of Cortical Volumes with Impairment

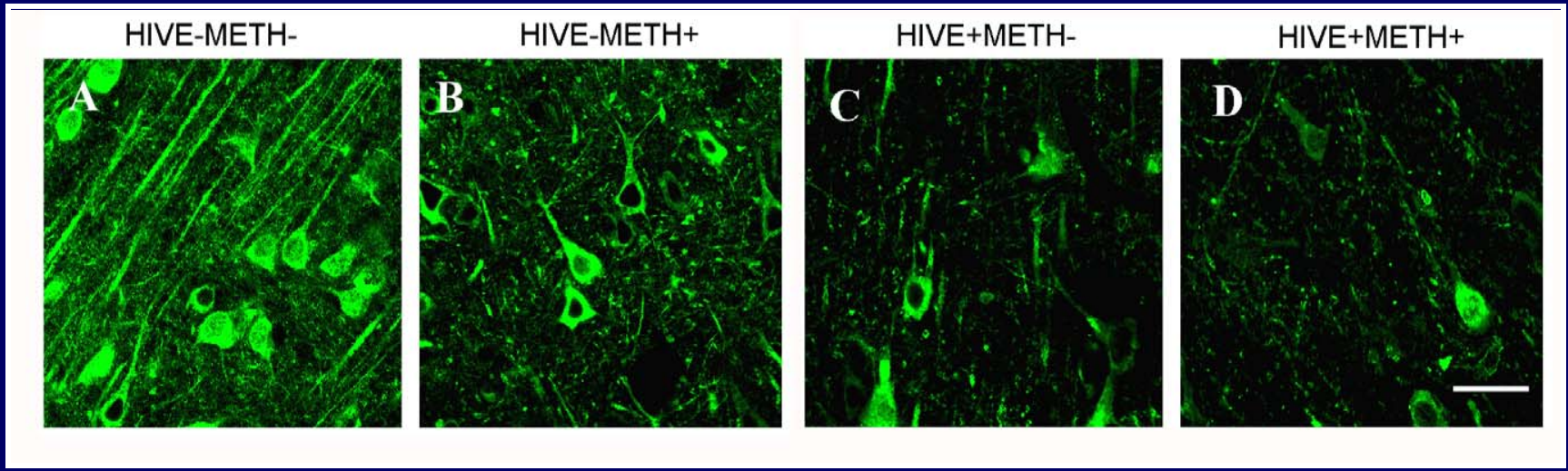




Association of Cortical Volumes with Attention Deficits

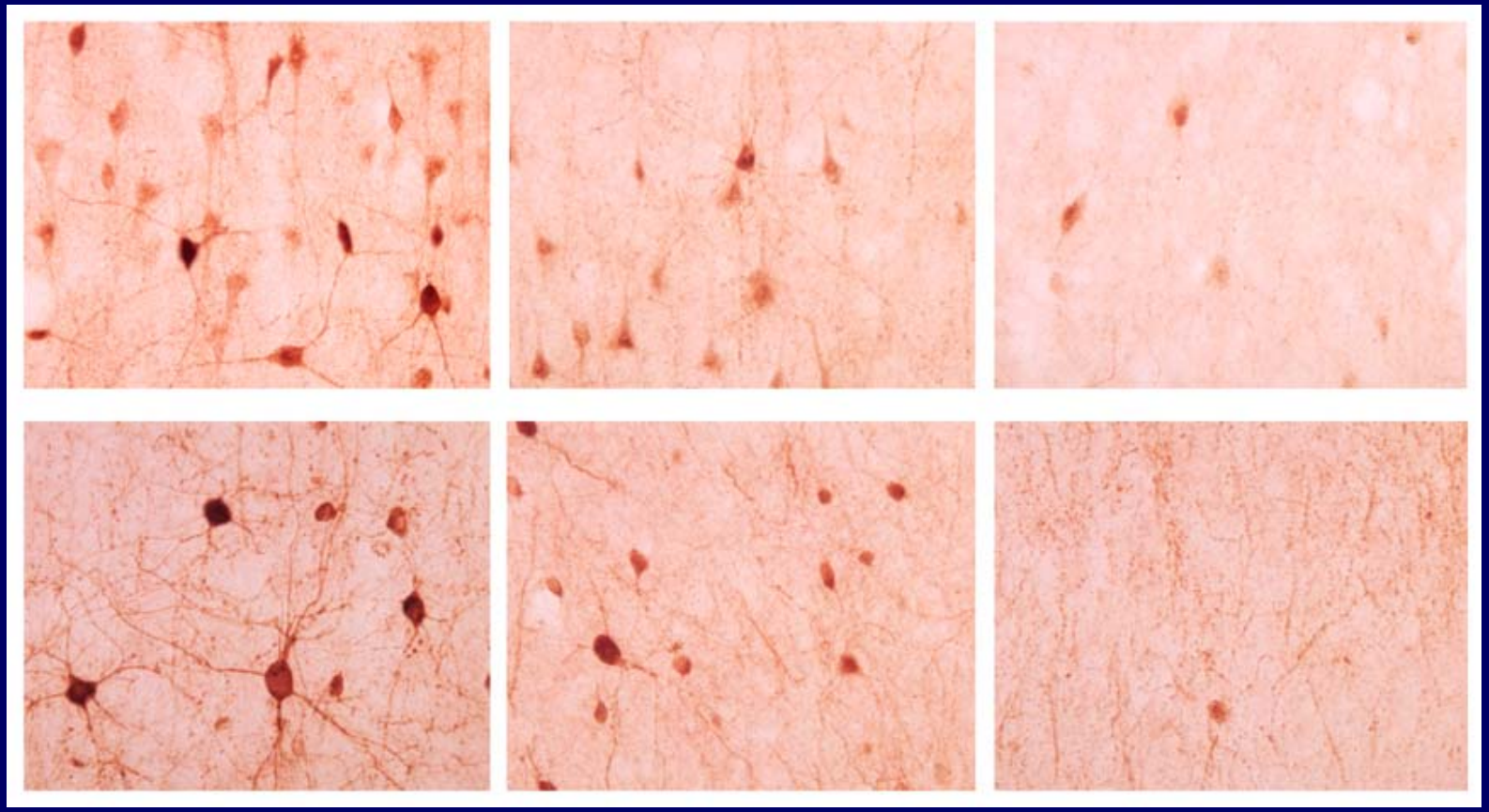


MAP-2 in midfrontal cortex of HIV+ cases with & without HIVE and with or without METH



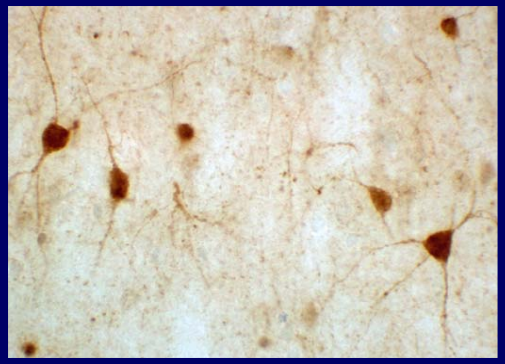
A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
Bar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

Degeneration of Interneurons in HIVE+METH Users

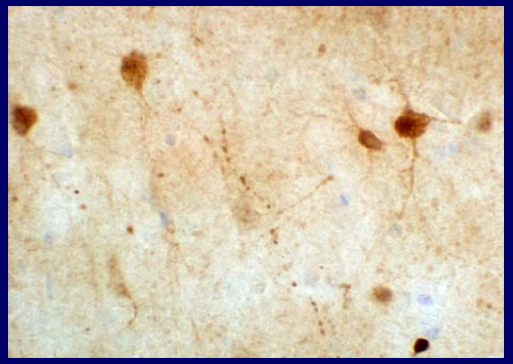


Loss of calbindin interneurons is associated with cognitive impairment and memory loss in METH users patients with HIVE patients

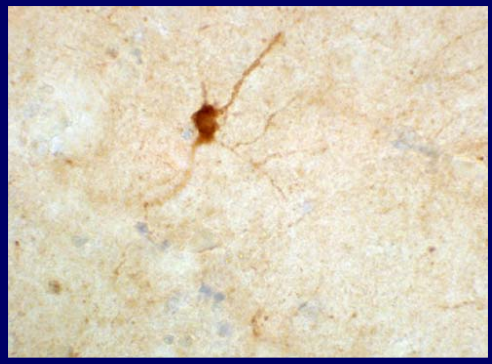
HIV+ (control)

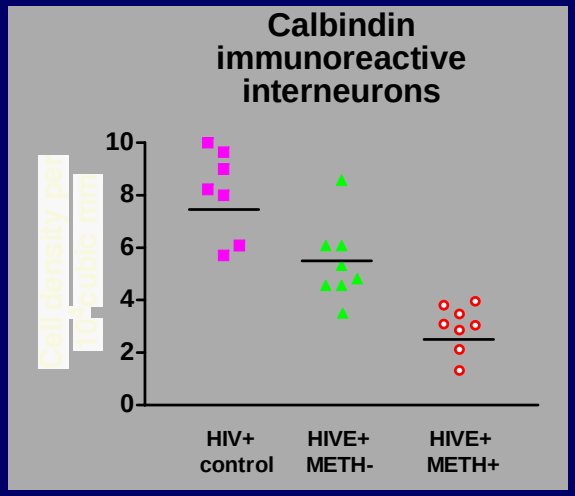


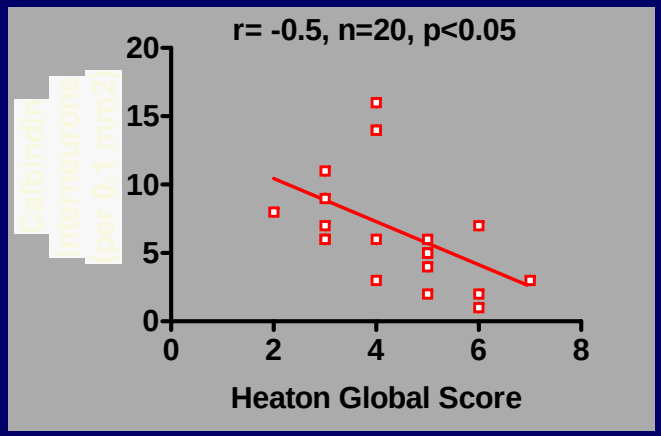
HIVE+ METH-

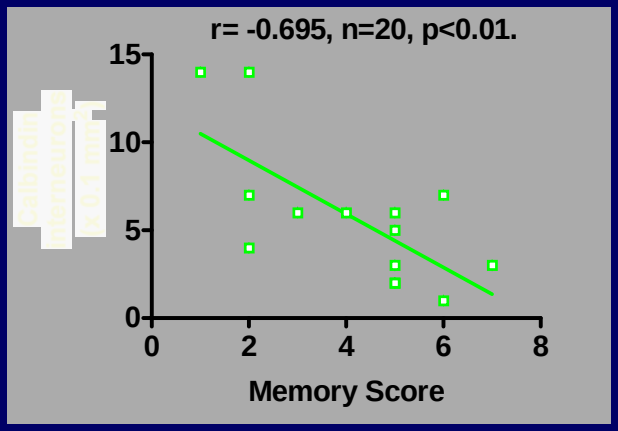


HIVE+ METH+









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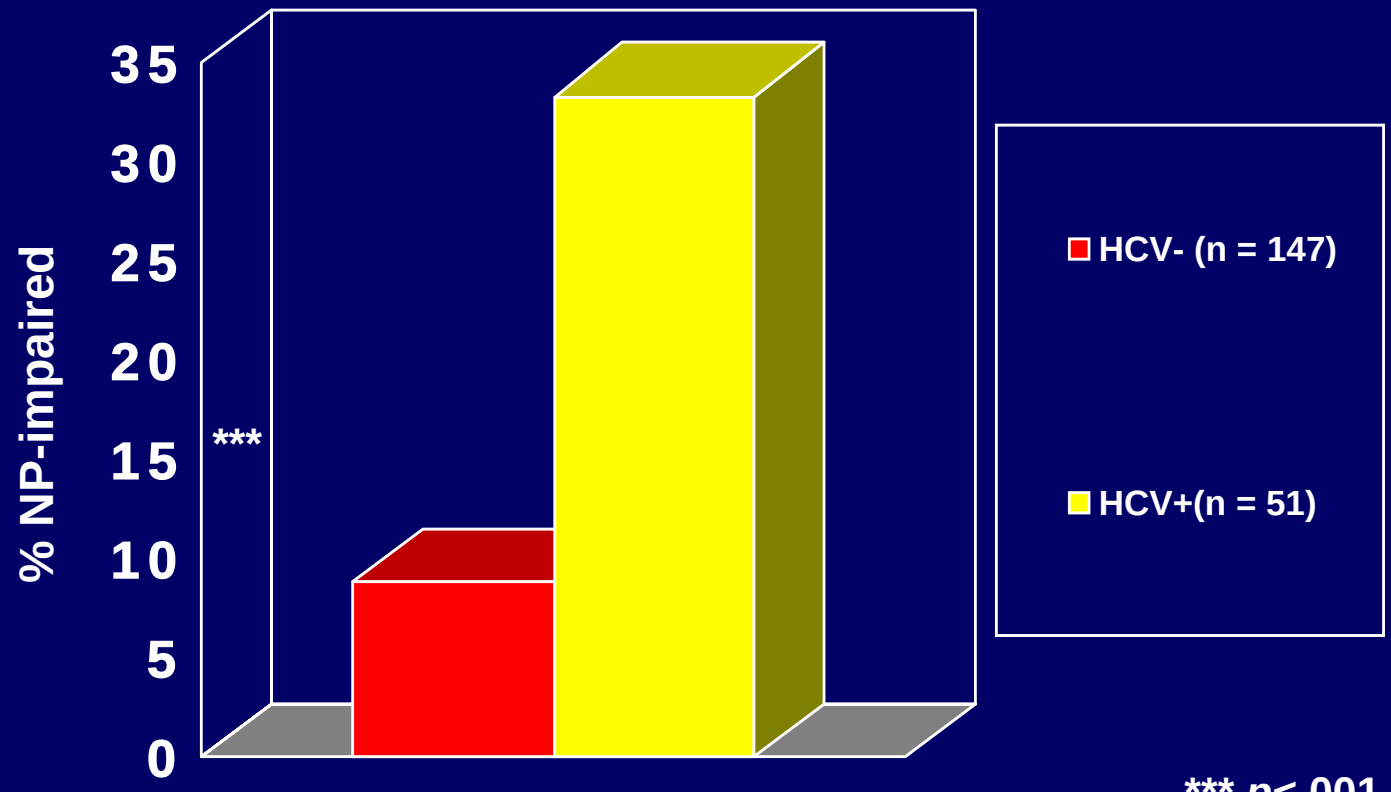
HCV and the Brain

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

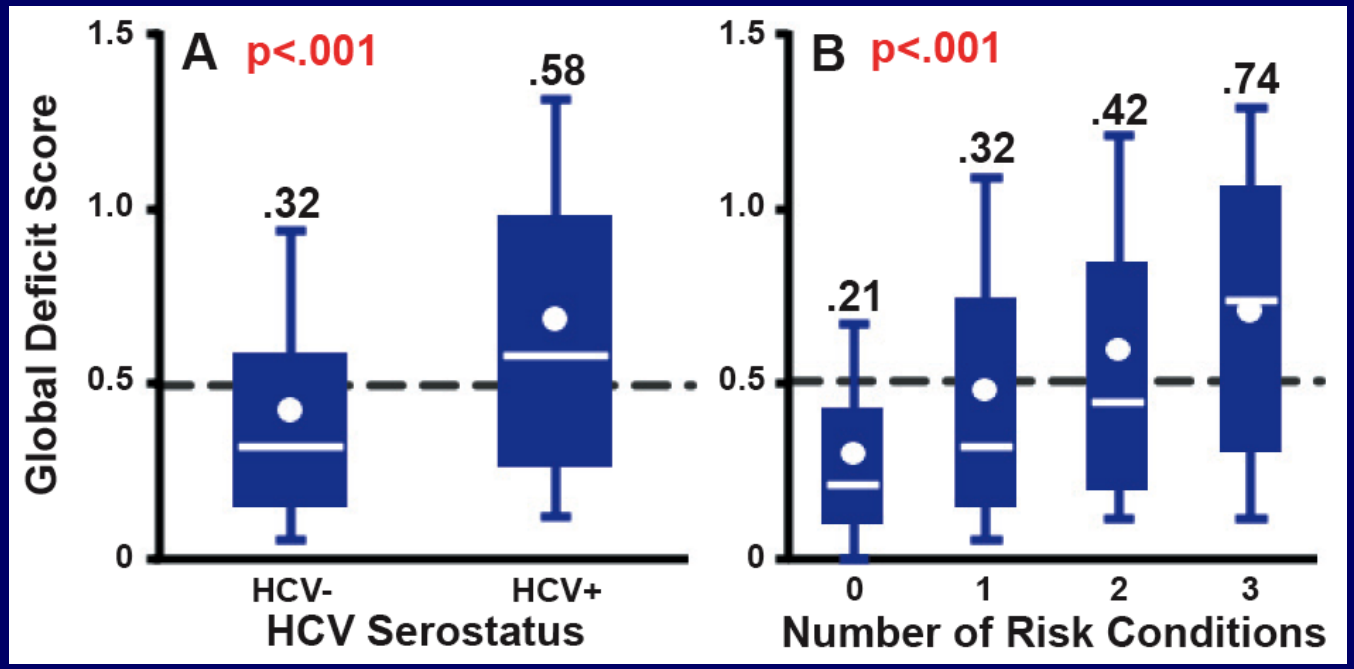
Tembl, Neurology, 1999; Marie, et al 2000; Grewal, J N Sci, 2004

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



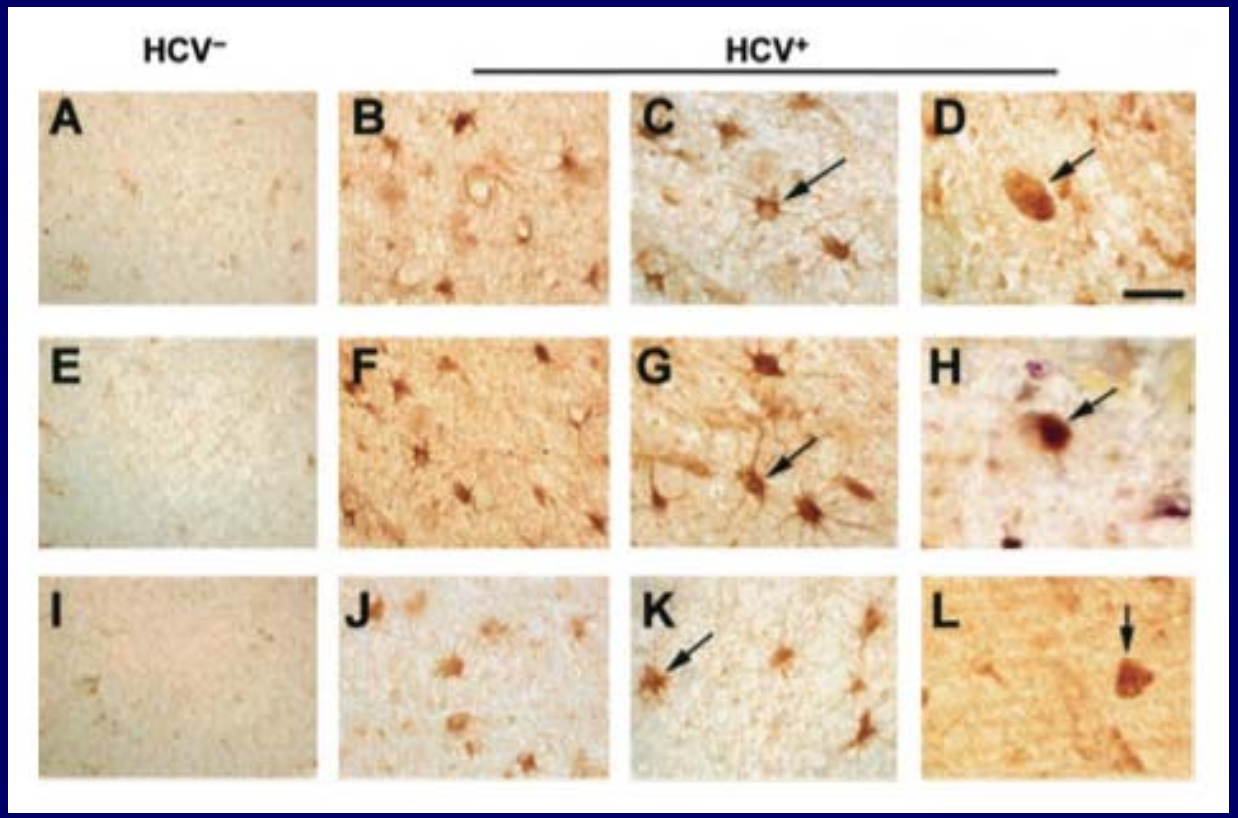
*** $p<.001$

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

Special Thanks to our Trainees

Catherine Carey
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Lauren Kwon Dawson
Jennifer Iudicello
Jennifer Manly
Lauralynn Miles
David Moore
Erin Morgan
Carolina Posada
Julie Rippeth
Joseph Sadek
James Cobb Scott
Brian Schweinsburg
Paola Suarez
Michael J. Taylor
Steven P. Woods

Thank you for honoring me and indulging me in the ongoing saga!