HIV, METH AND THE BRAIN: IMPLICATIONS FOR HIV RISK

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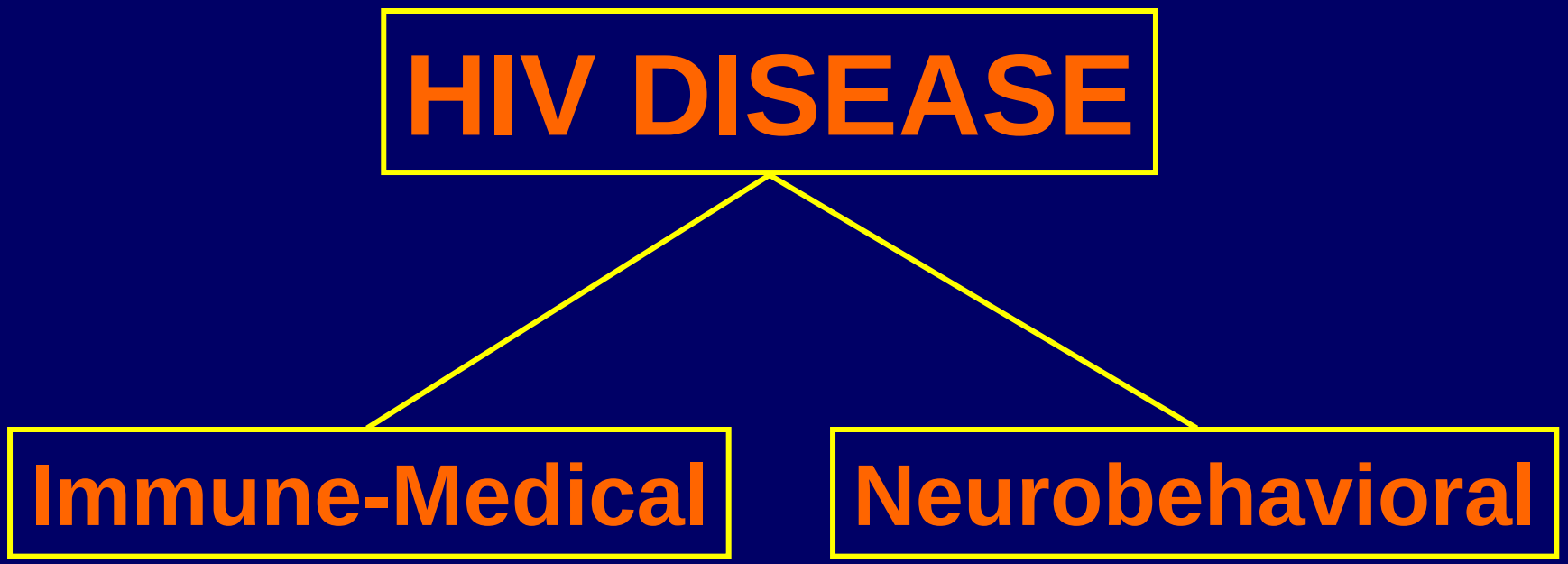

HIV DISEASE
Immune-Medical
Neurobehavioral

HIV NEUROBEHAVIORAL DISTURBANCES

NEUROCOGNITIVE

Primary

- Asymptomatic Neurocognitive Impairment
- Mild Neurocognitive Disorder
- Dementia

Secondary

- Infection
- Neoplasia
- Cerebrovascular
- Nutritional
- Treatment Related

EMOTIONAL & OTHER BEHAVIORAL

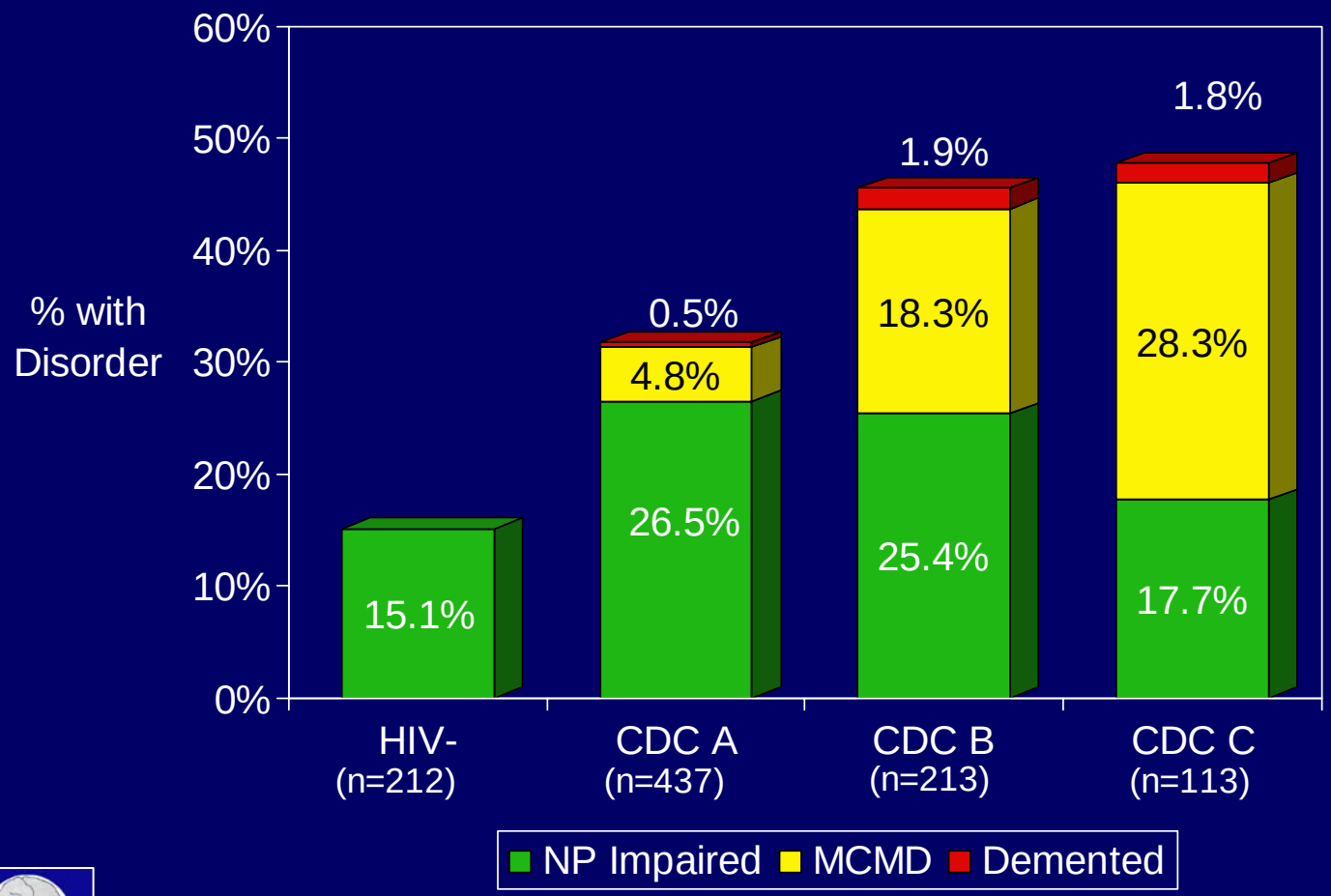
New Onset

- Depression
- Anxiety
- Adjustment Disorders
- HIV Mania
- HIV Psychosis

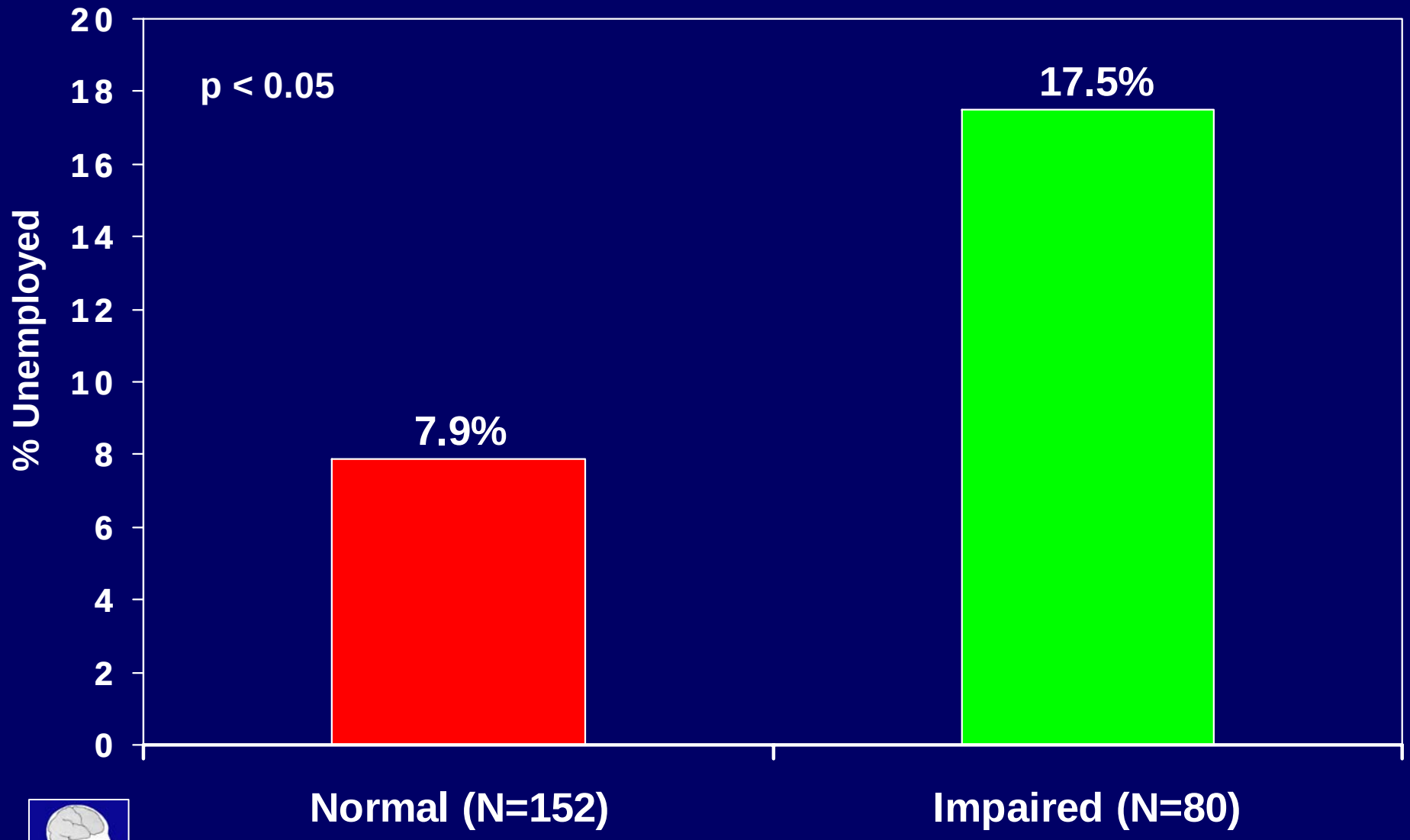
Recurrent/Comorbid

- Mood Disorders
- Substance Use Disorders
- Other Mental Disorders

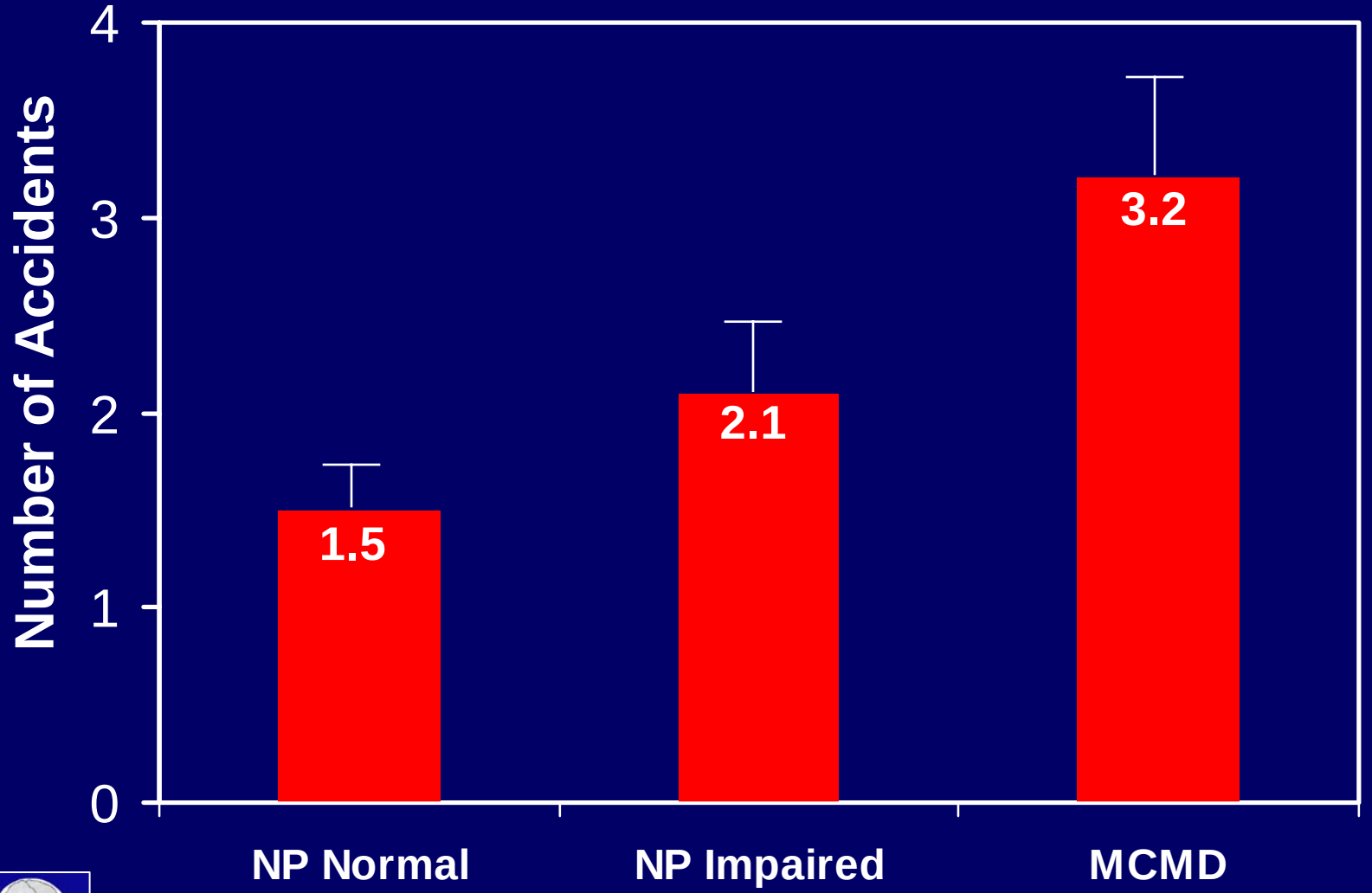
Prevalence of Neurocognitive Disorders by Stage of HIV Disease



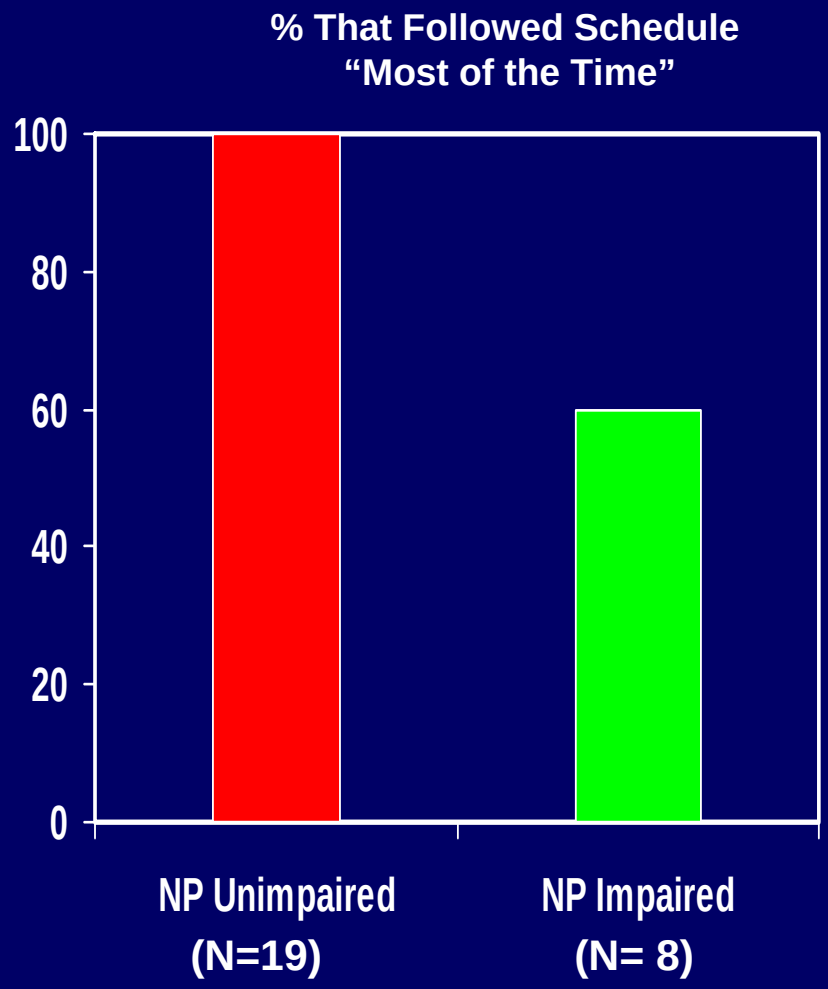
Meaning of NP Impairment: Employment

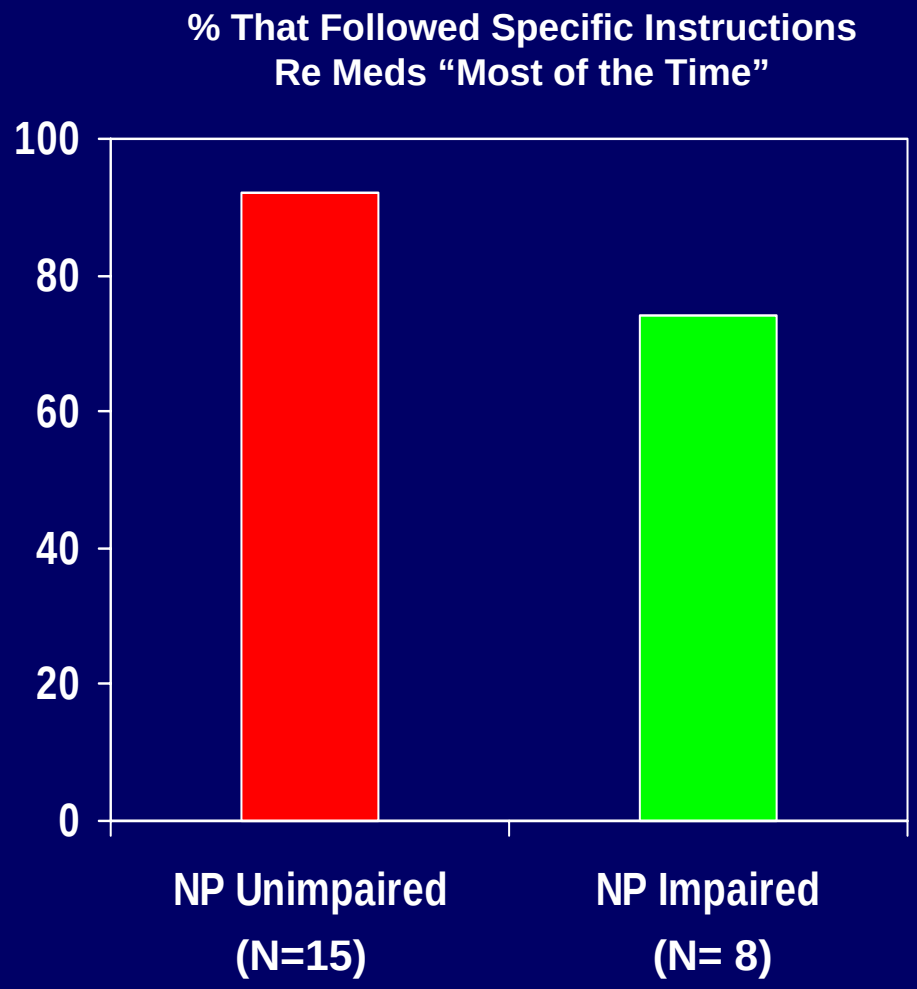


Mean Number of Accidents on City Driving Simulation

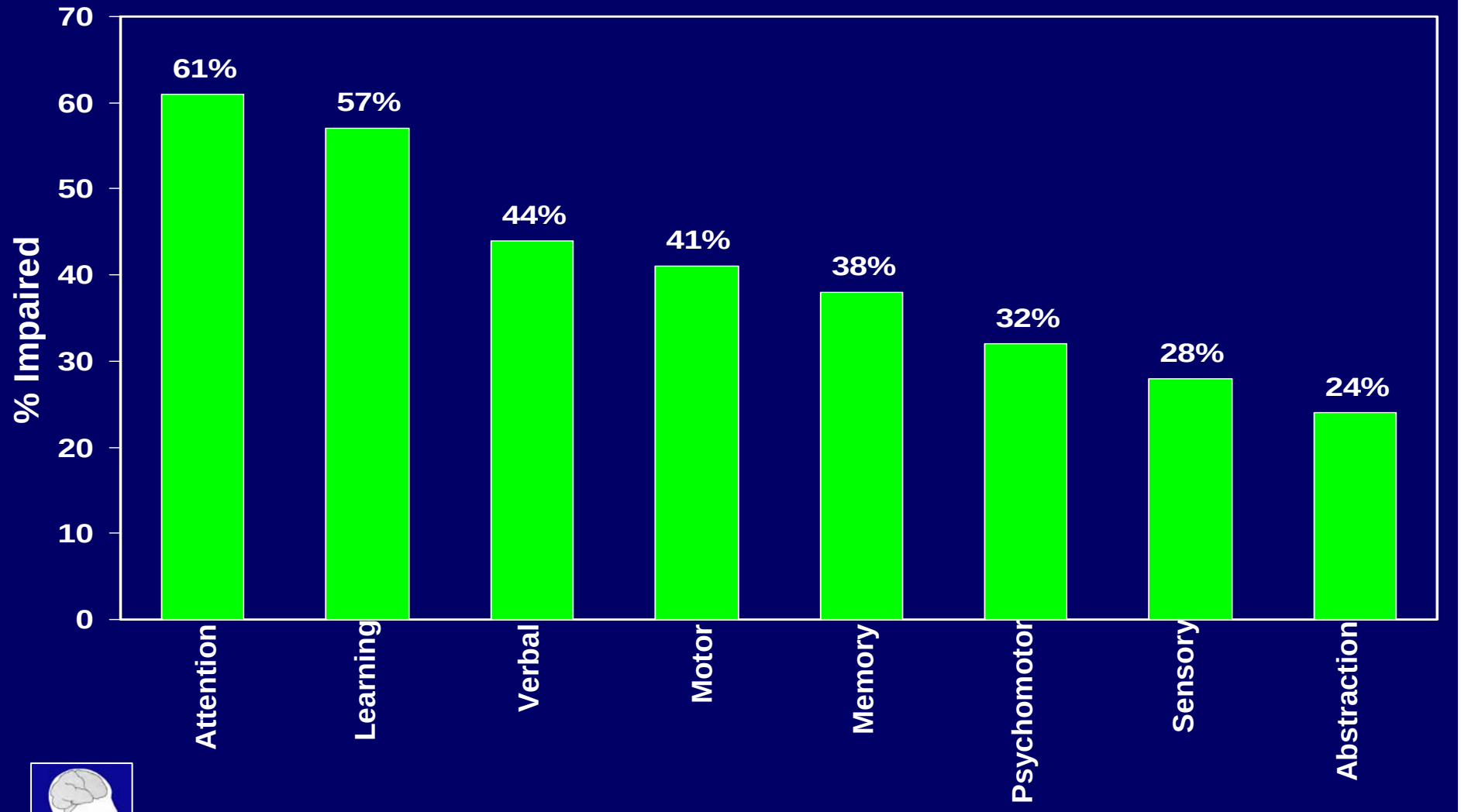


Adherence to Antiretrovirals Related to Neurocognitive Impairment





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

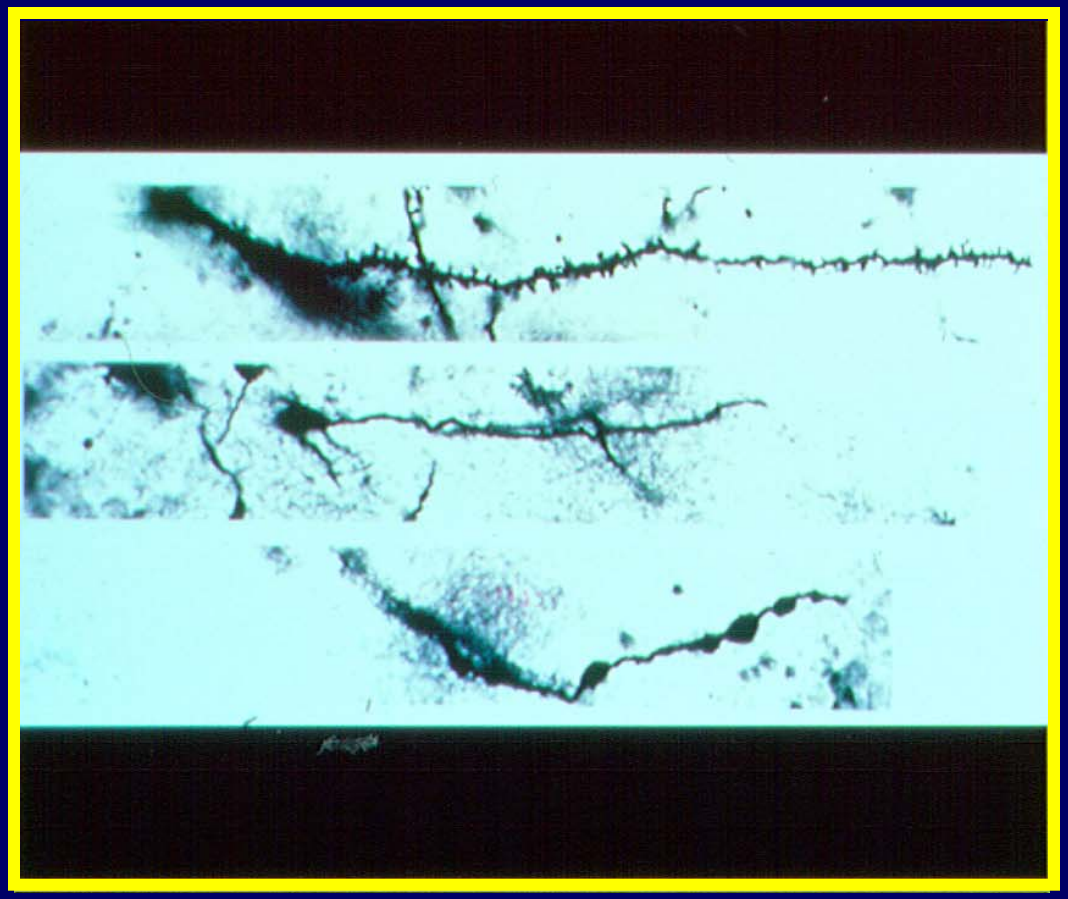


Percent of Various Cells at Autopsy Having HIV

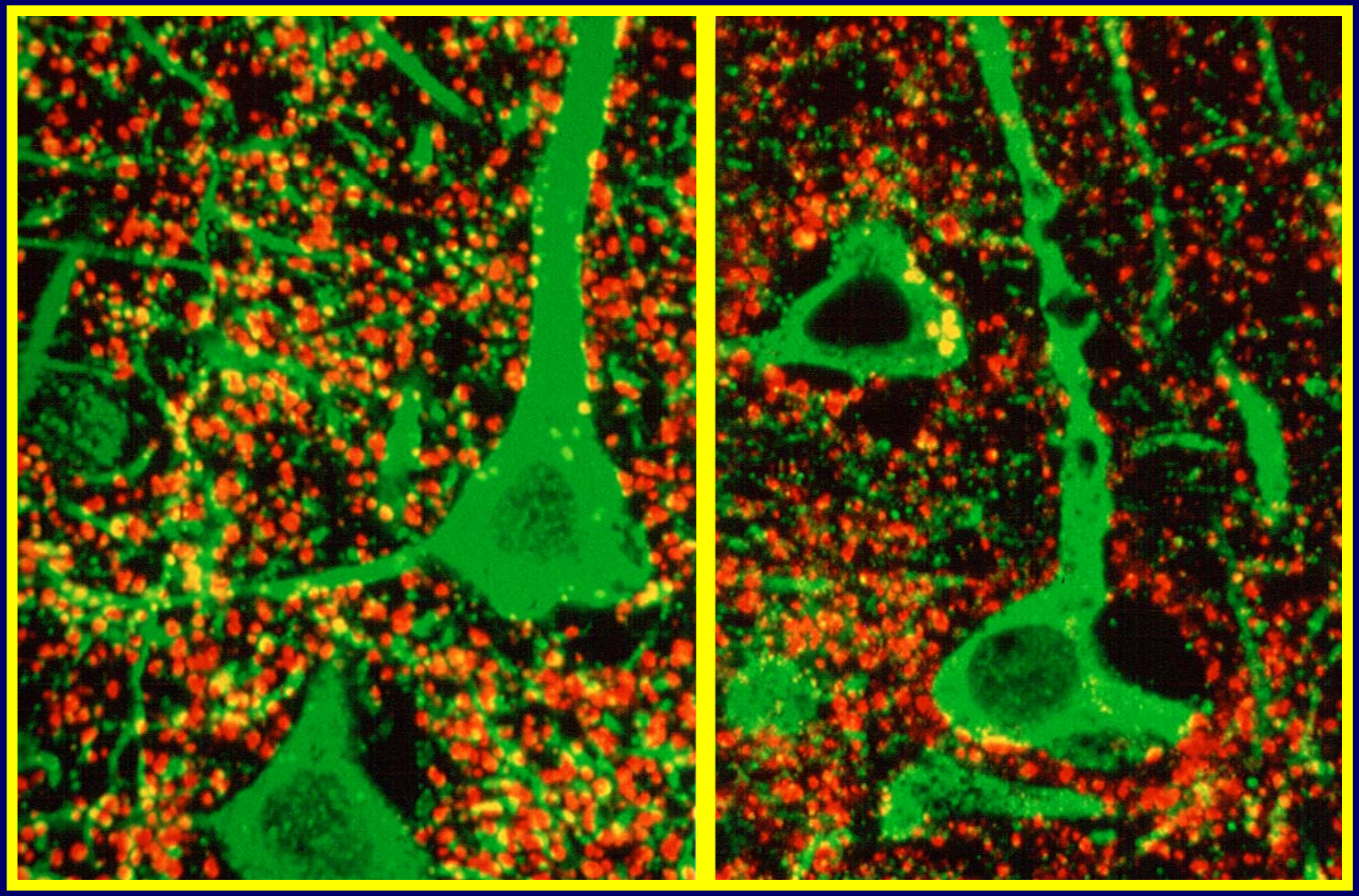
	%
Microglia	80
Astroglia	?
Endothelial	10
Neurons	0

HIV-Associated Brain Damage Involves Neuronal Pathology

Post-synaptic Injury is Prominent



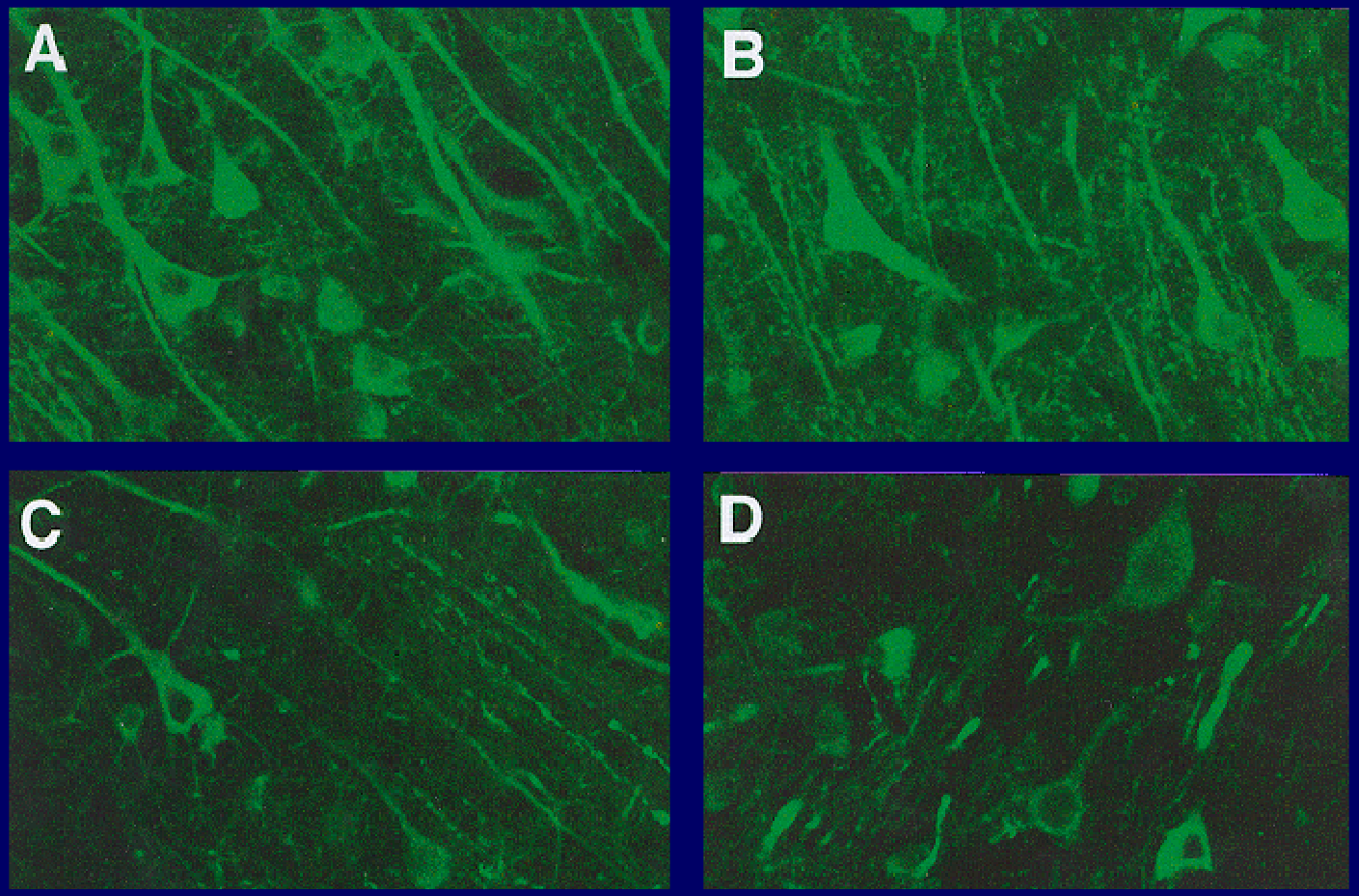
Synaptophysin & MAP-2 Immunostaining



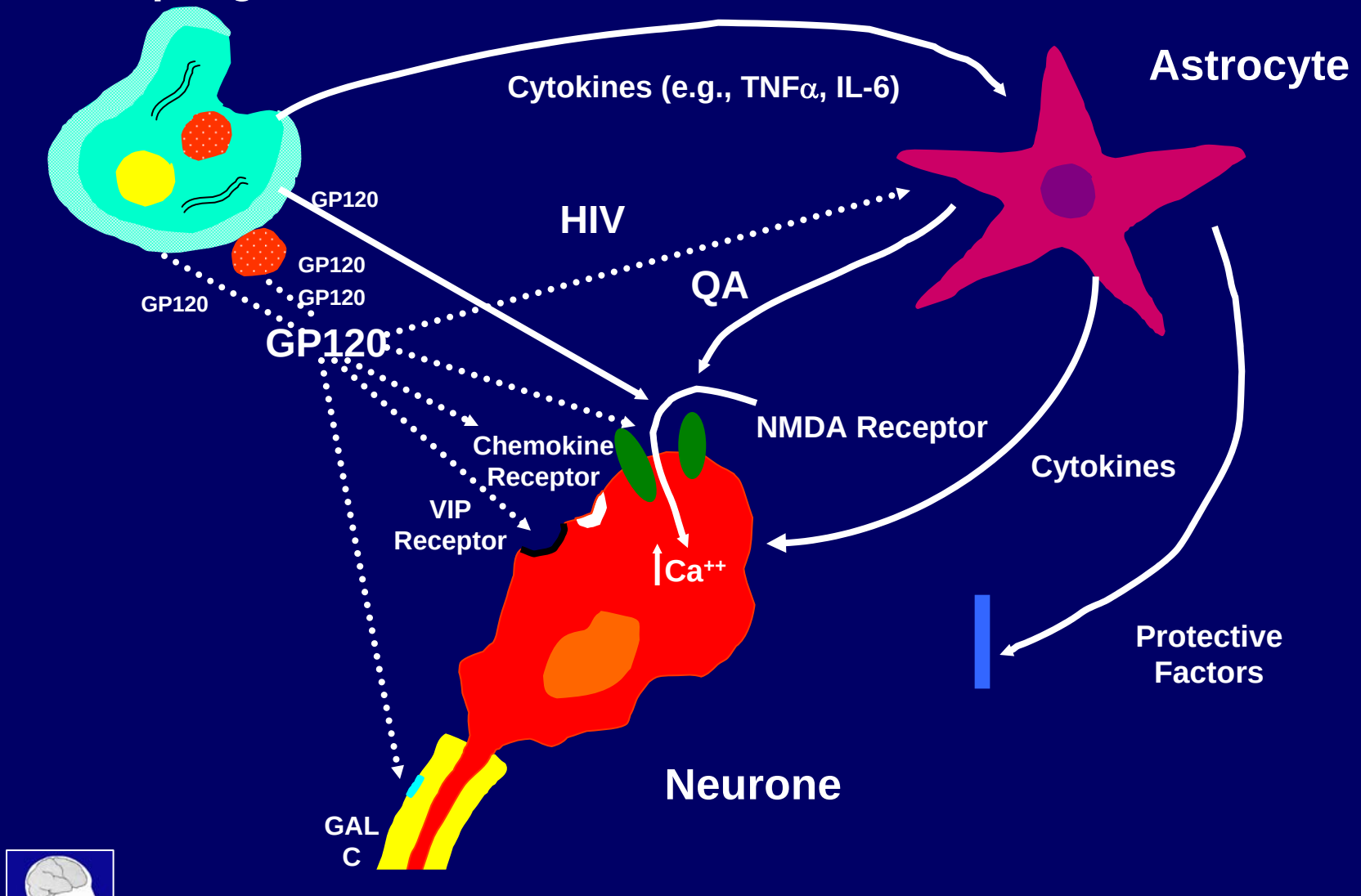
HIV-

HIV+

Dendritic Complexity in Subjects with Varying Levels of Cognitive Impairment



Possible Mechanisms of Neurotoxicity in HIV-1 Infection

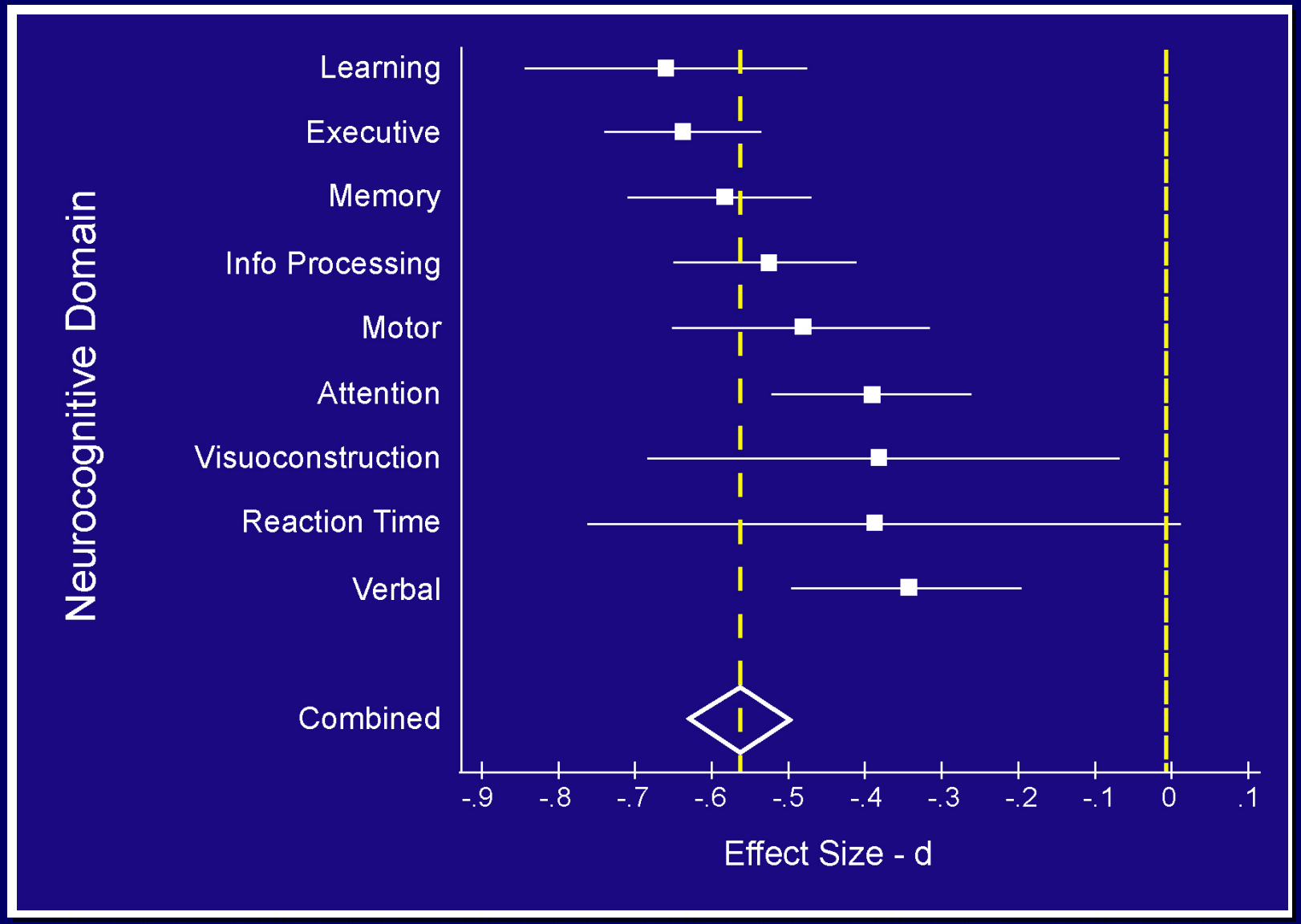


Cofactors in HIV Associated Neurocognitive Complications

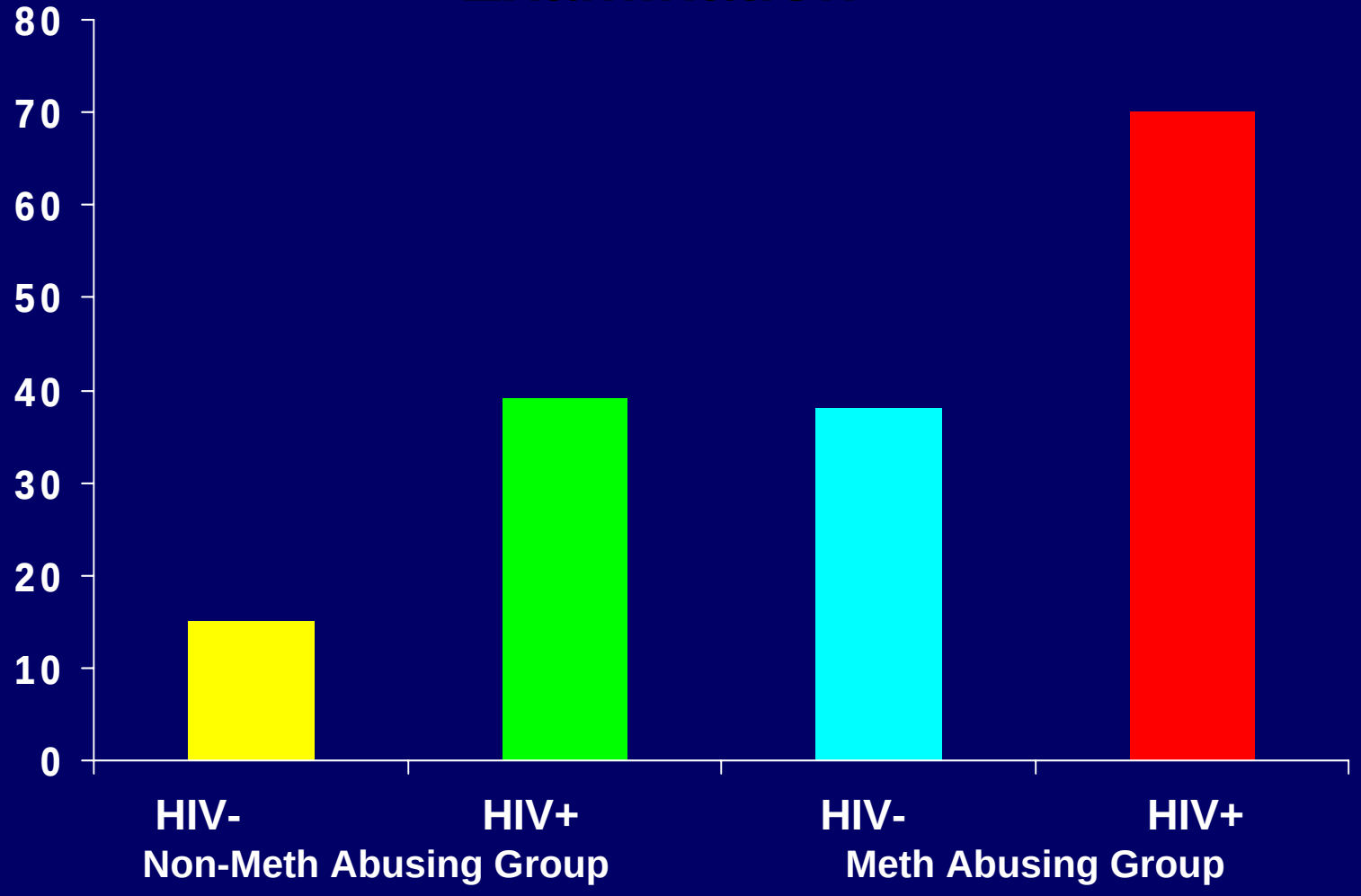
- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Neurotoxic Treatments

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)


Neurocognitive Domain
Learning
Executive
Memory
Info Processing
Motor
Attention
Visuoconstruction
Reaction Time
Verbal
Combined
-.9
-.8
-.7
-.6
-.5
-.4
-.3
-.2
-.1
0
.1
Effect Size - d

% Having Global NP Impairment by Methamphetamine Abuse and HIV Status Accounting for Acute Intoxication on Day of NP Examination



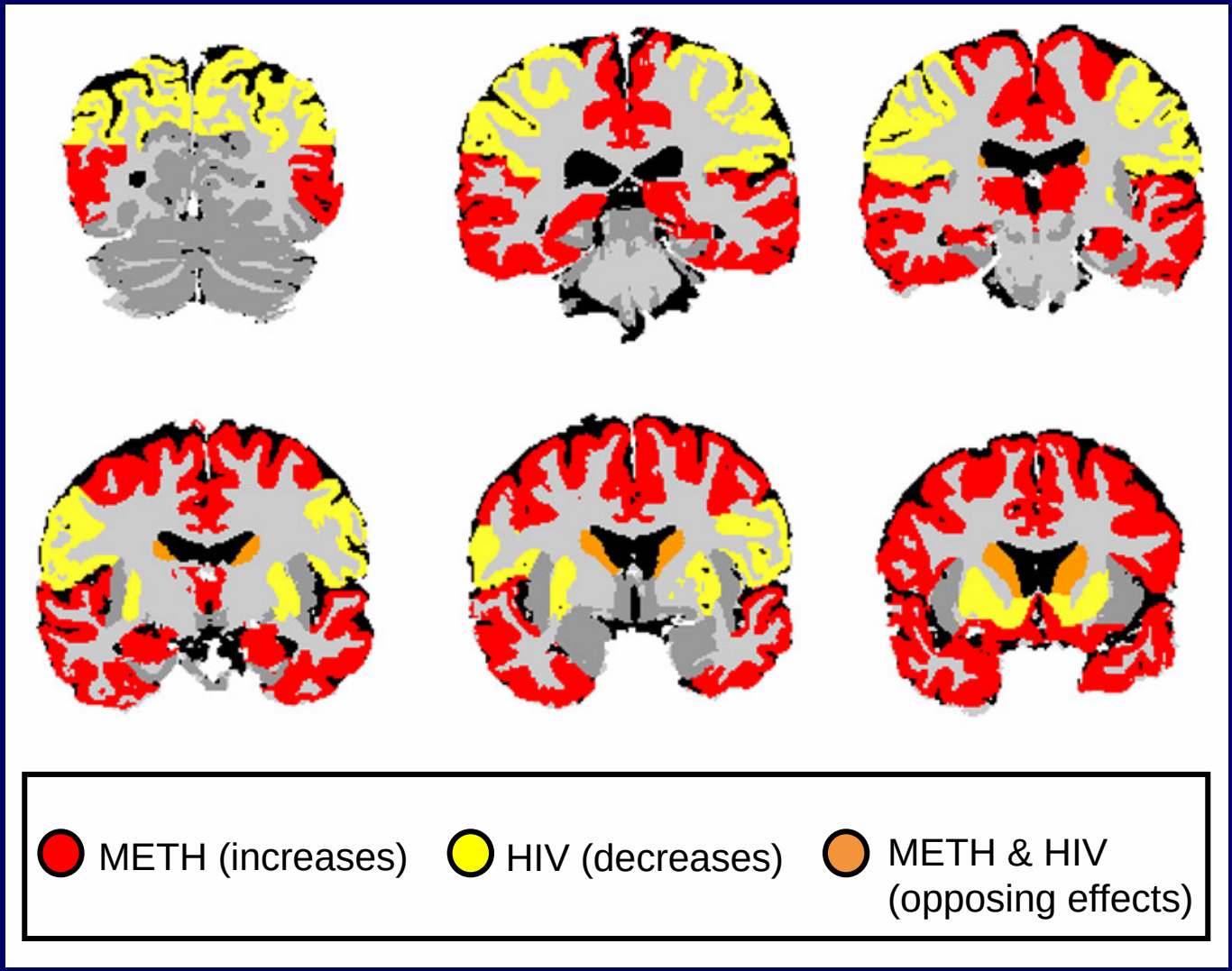
Pattern of neuropsychological impairment according to risk factor

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

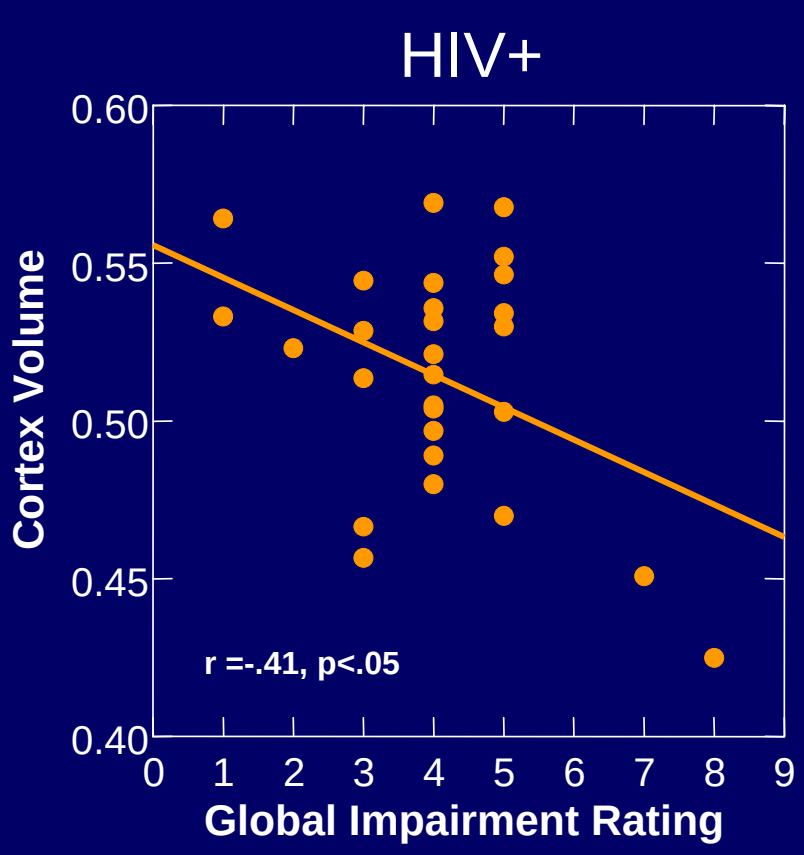
Pattern of neuropsychological impairment according to risk factor

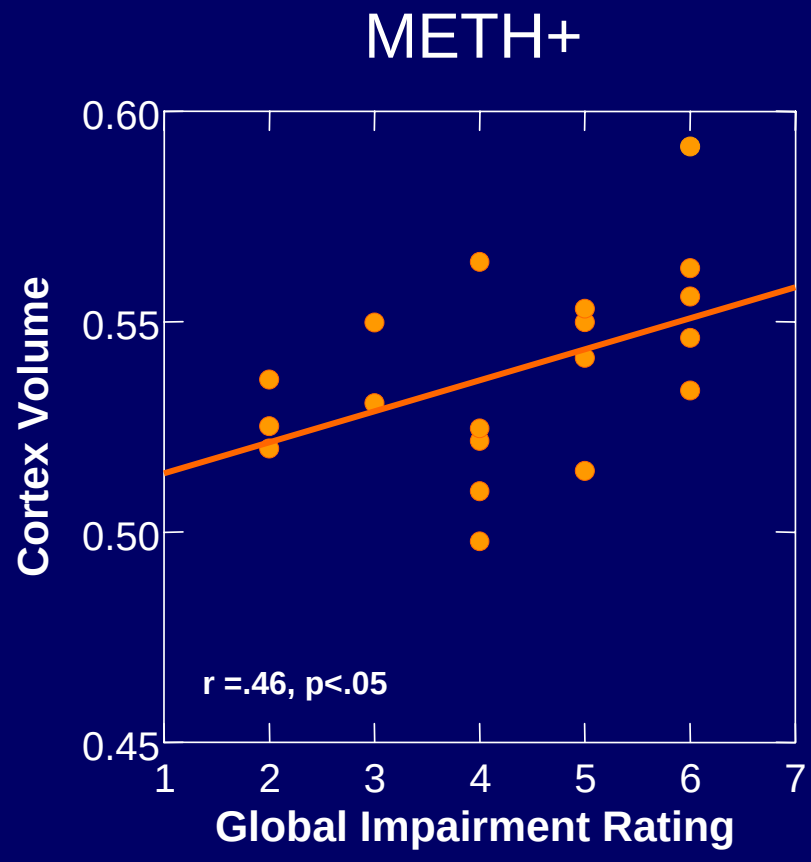
Deficit	Meth	HIV	HCV
Executive Functioning			
Problem-Solving/Planning	**++**	**++**	**+**
Cognitive Disinhibition	**++**	**-**	**?**
Decision-making	**+++**	**+**	**?**
Frontal Systems Behavioral			
Disinhibition	**++**	**-**	**?**
Apathy	**-**	**++**	**?**
Executive	**+**	**++**	**?**

Significant regional volume alterations related to METH and/or HIV

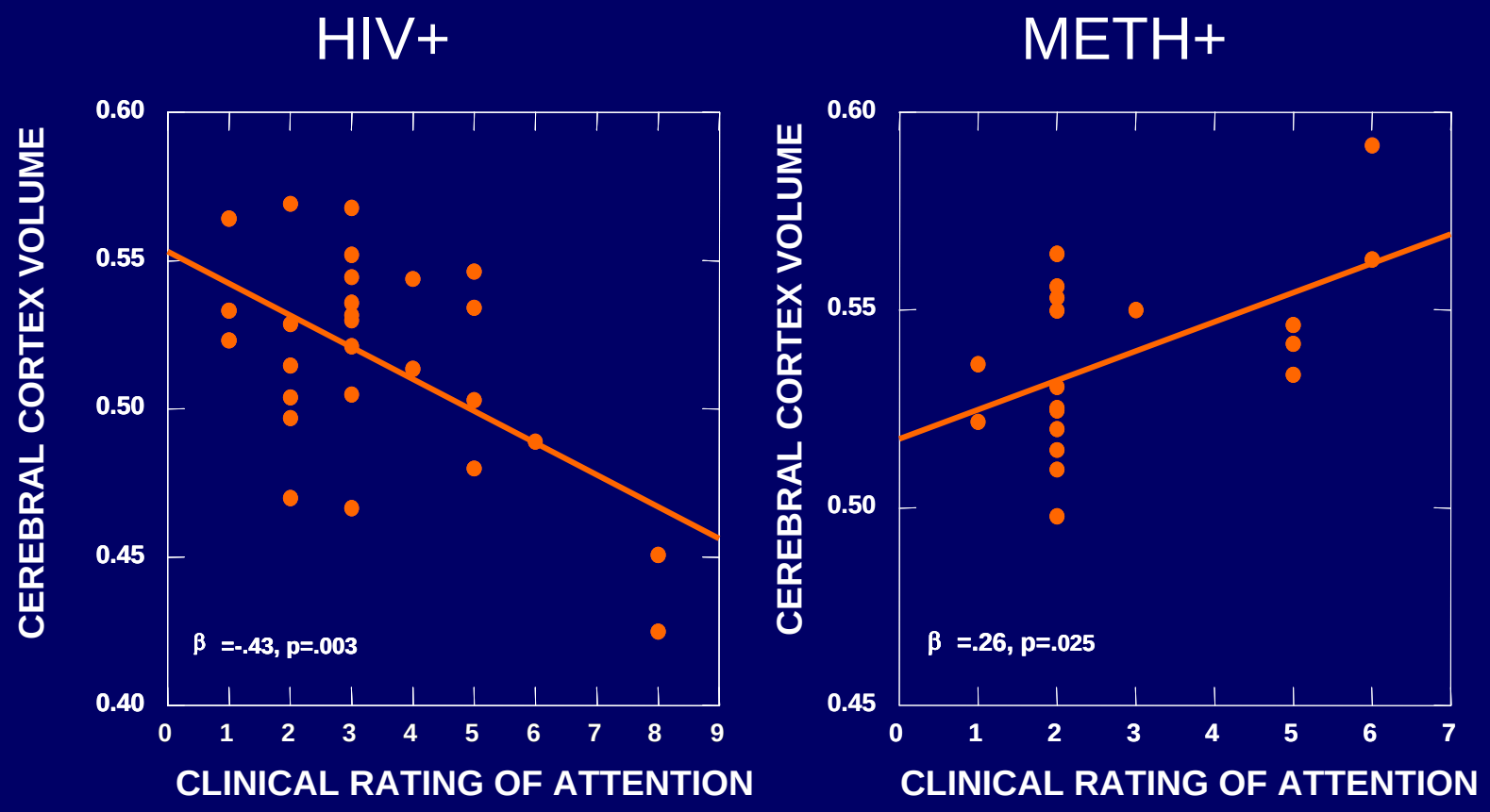


Association of Cortical Volumes with Impairment

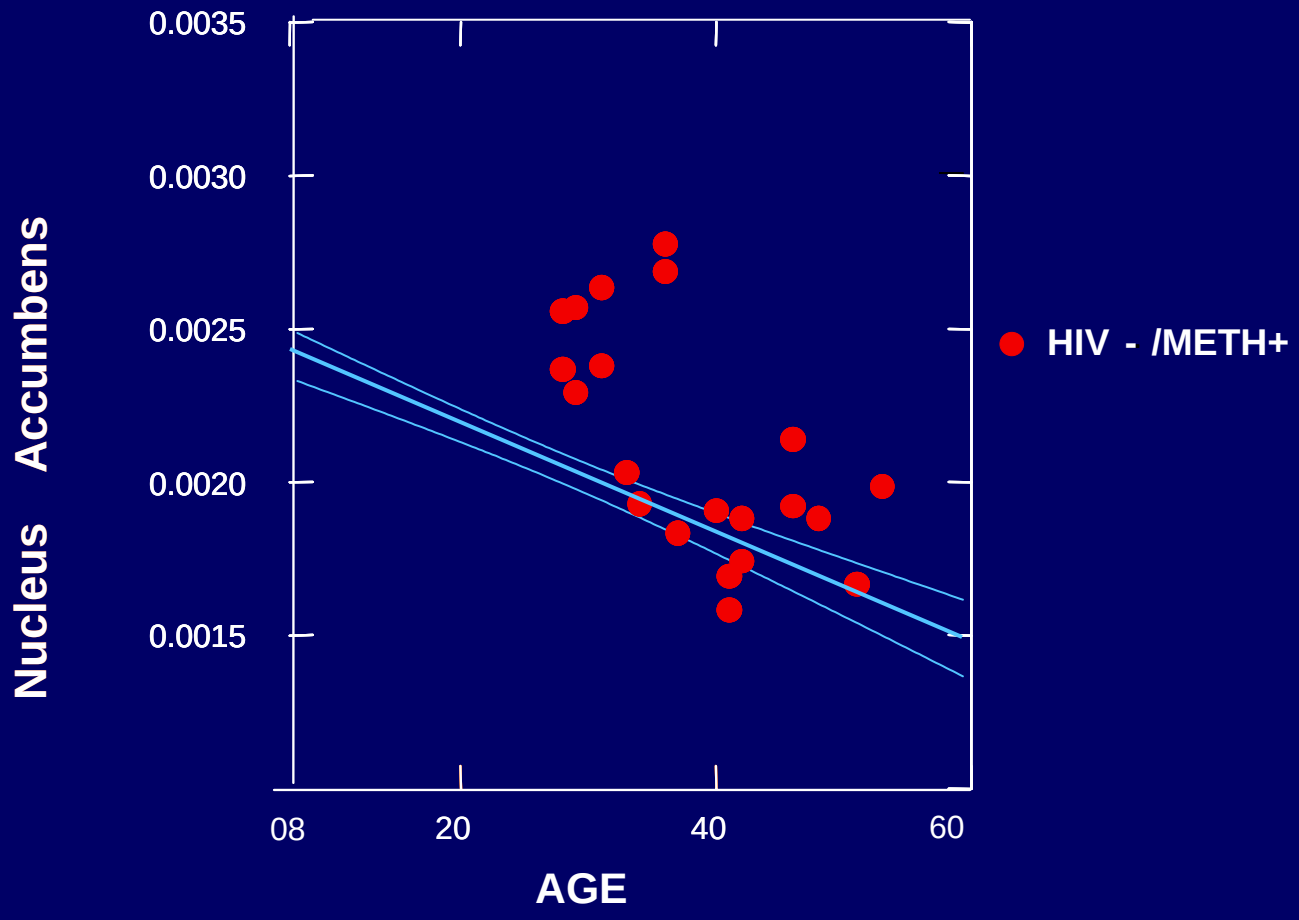




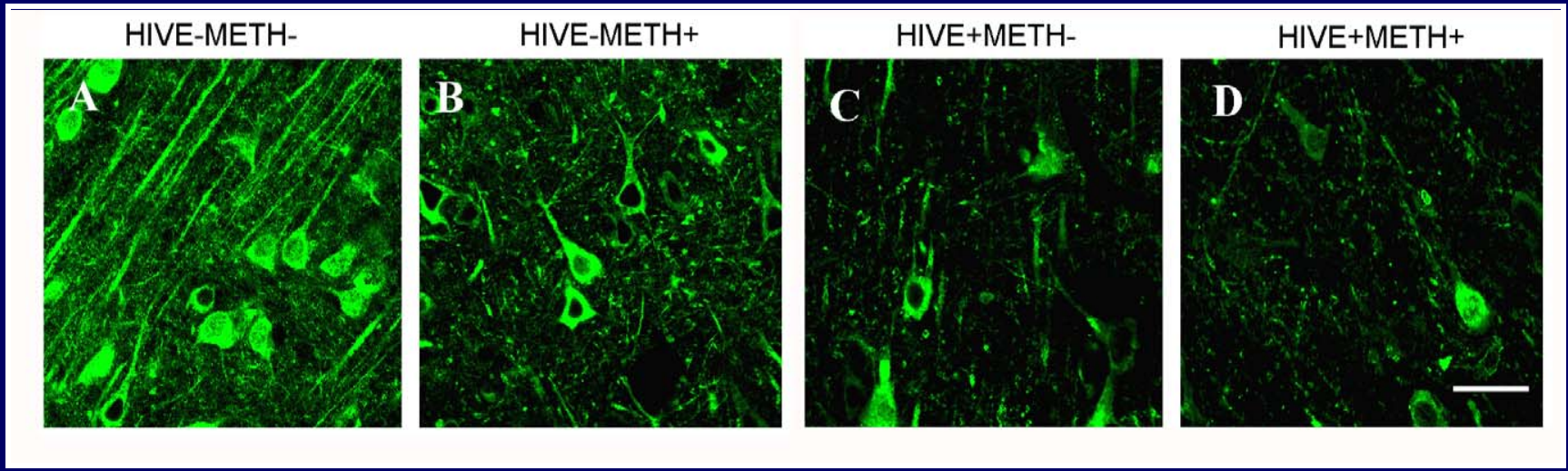
Association of Cortical Volumes with Attention Deficits



Meth have larger Accumbens volume for age relative to controls

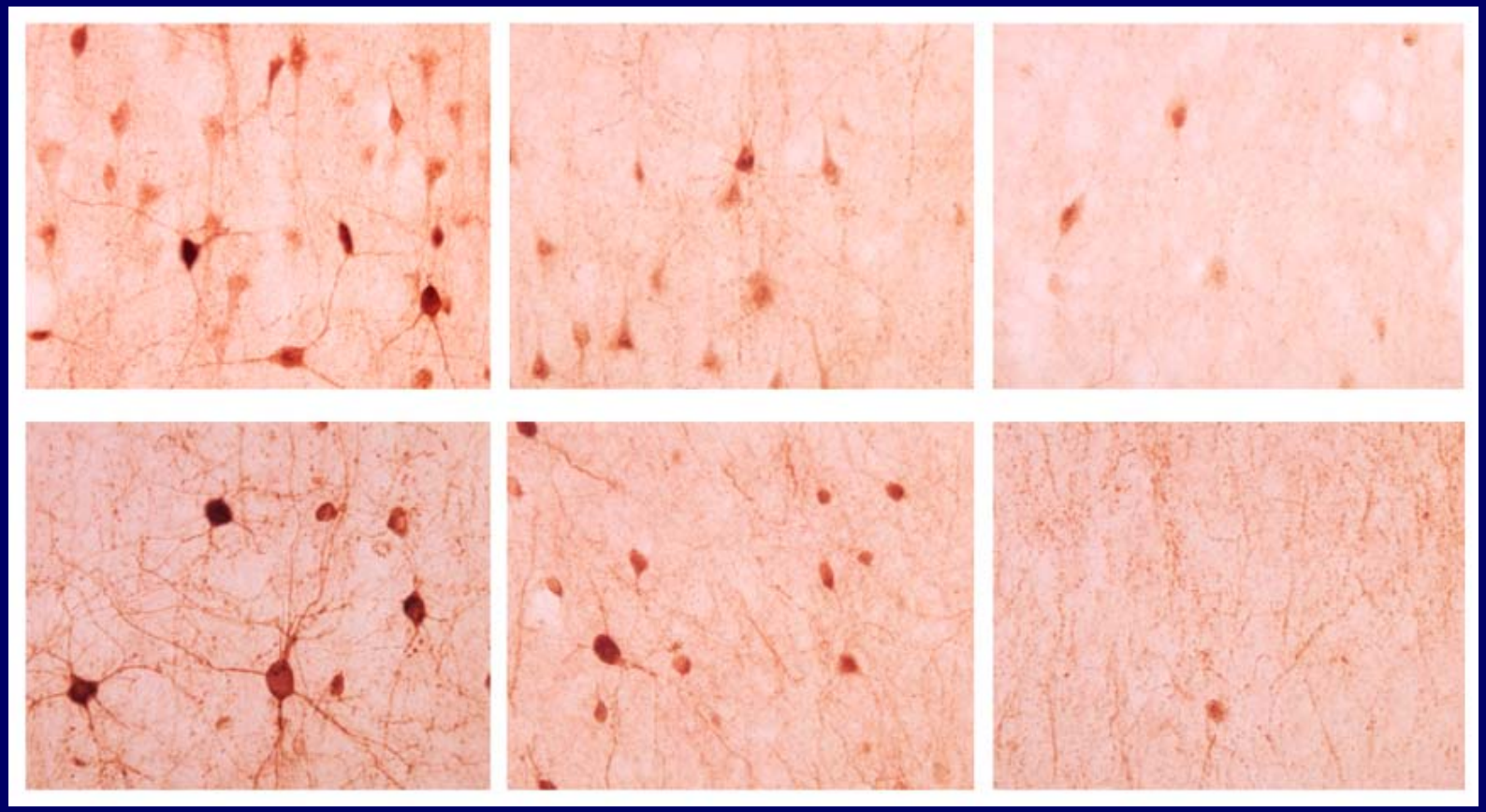


MAP-2 in midfrontal cortex of HIV+ cases with & without HIVE and with or without METH



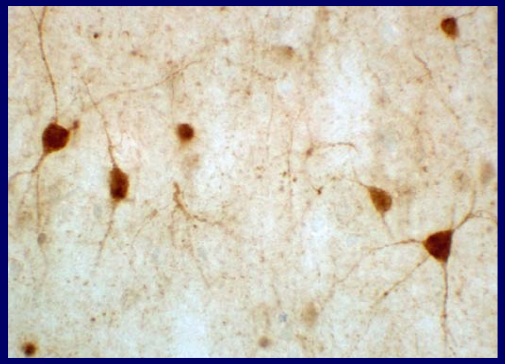
A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
Bar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

Degeneration of Interneurons in HIVE+METH Users

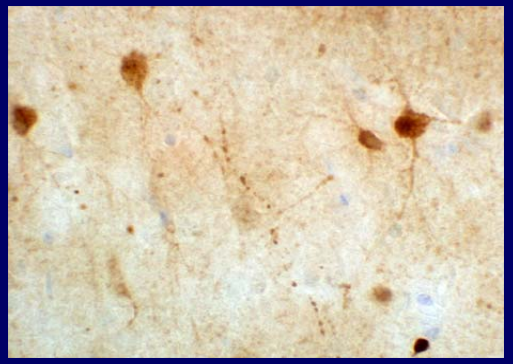


Loss of calbindin interneurons is associated with cognitive impairment and memory loss

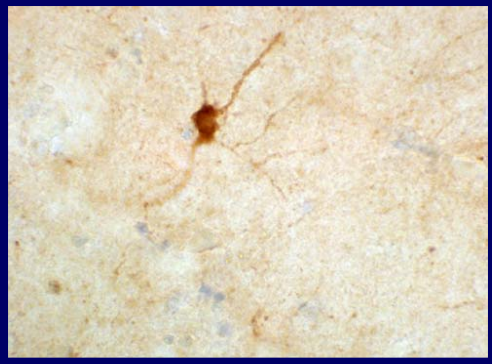
HIV+ (control)

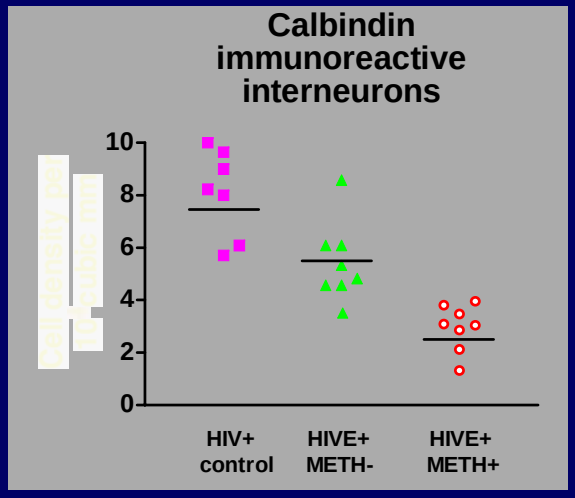


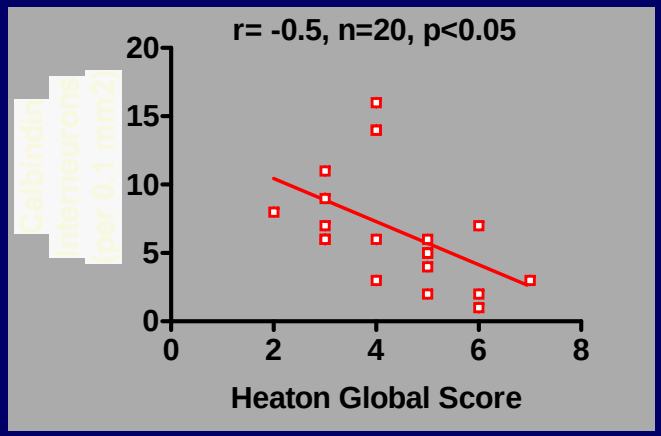
HIVE+ METH-

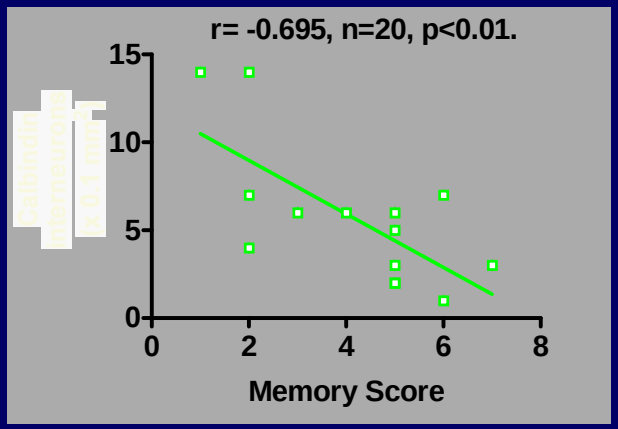


HIVE+ METH+





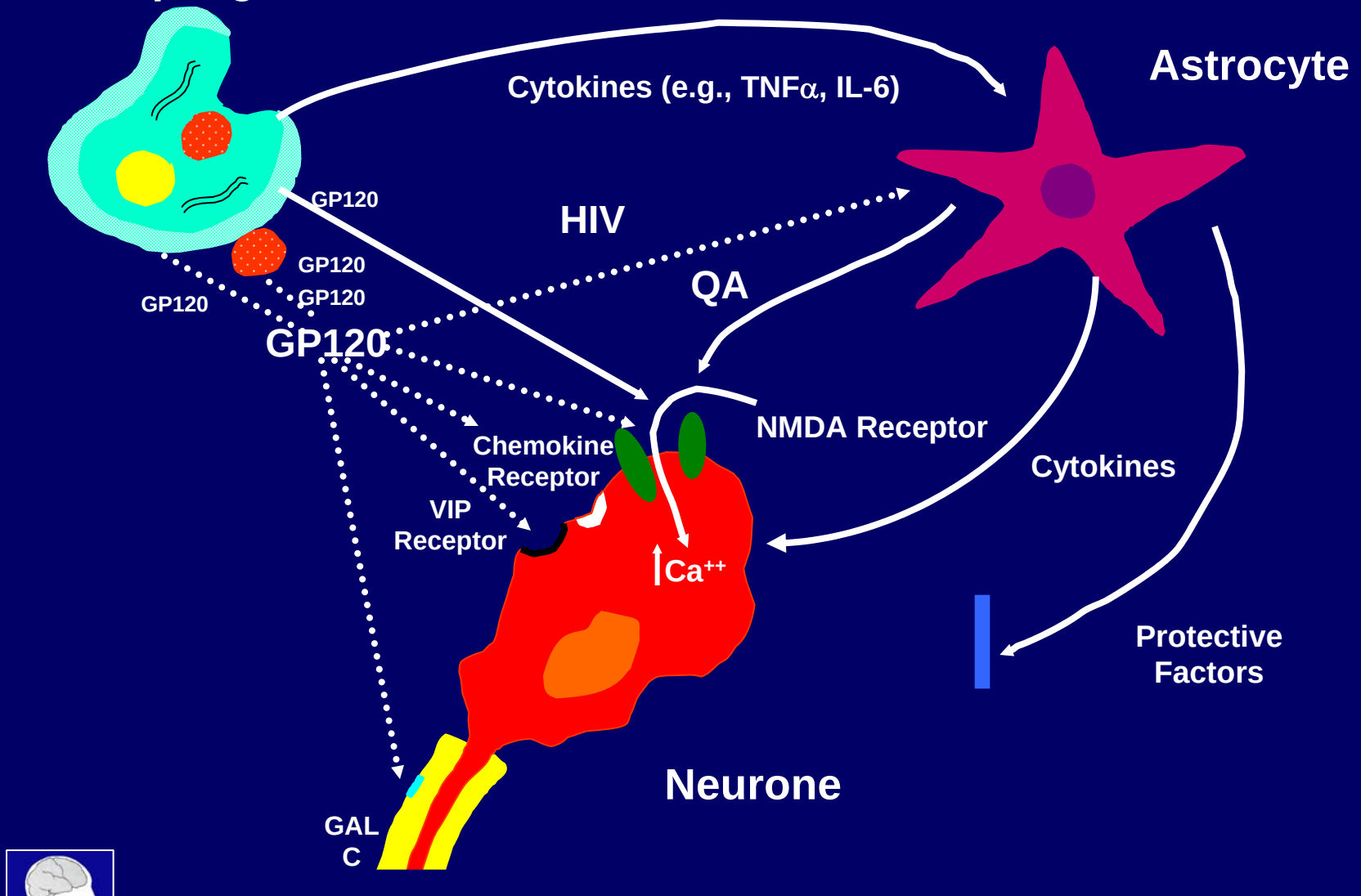




Mechanisms of neurodegeneration mediated by HIV and METH

1. Oxidative stress
2. Excitotoxicity
3. Mitochondrial dysfunction
4. Alterations in calcium metabolism
5. Interference with signaling pathways of trophic factors
6. Caspase mediated apoptosis
7. Cytokines, chemokines and other neuro-inflammatory factors

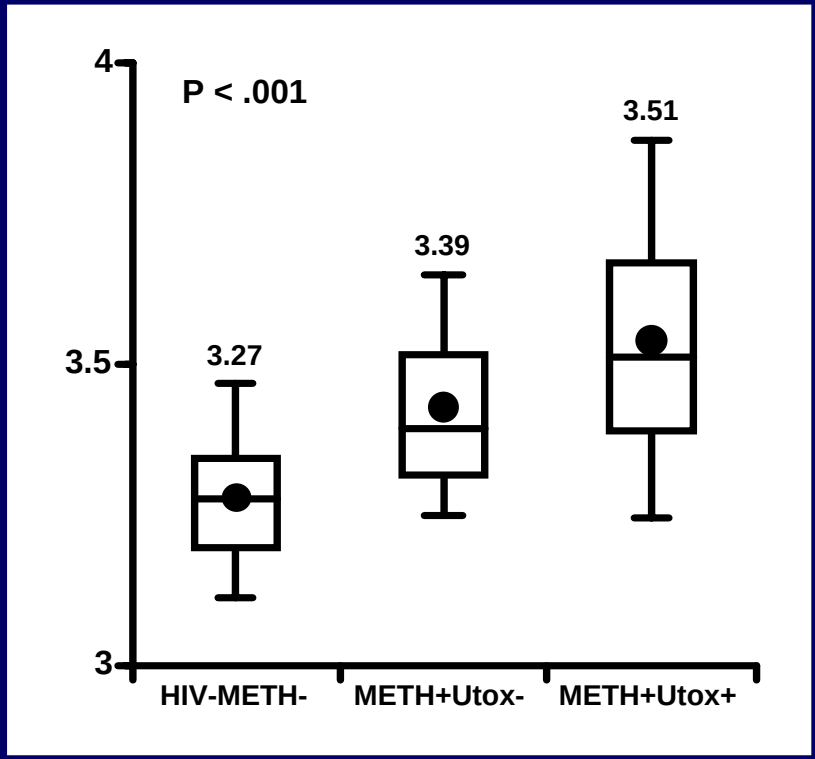
Possible Mechanisms of Neurotoxicity in HIV-1 Infection



METH and Inflammation

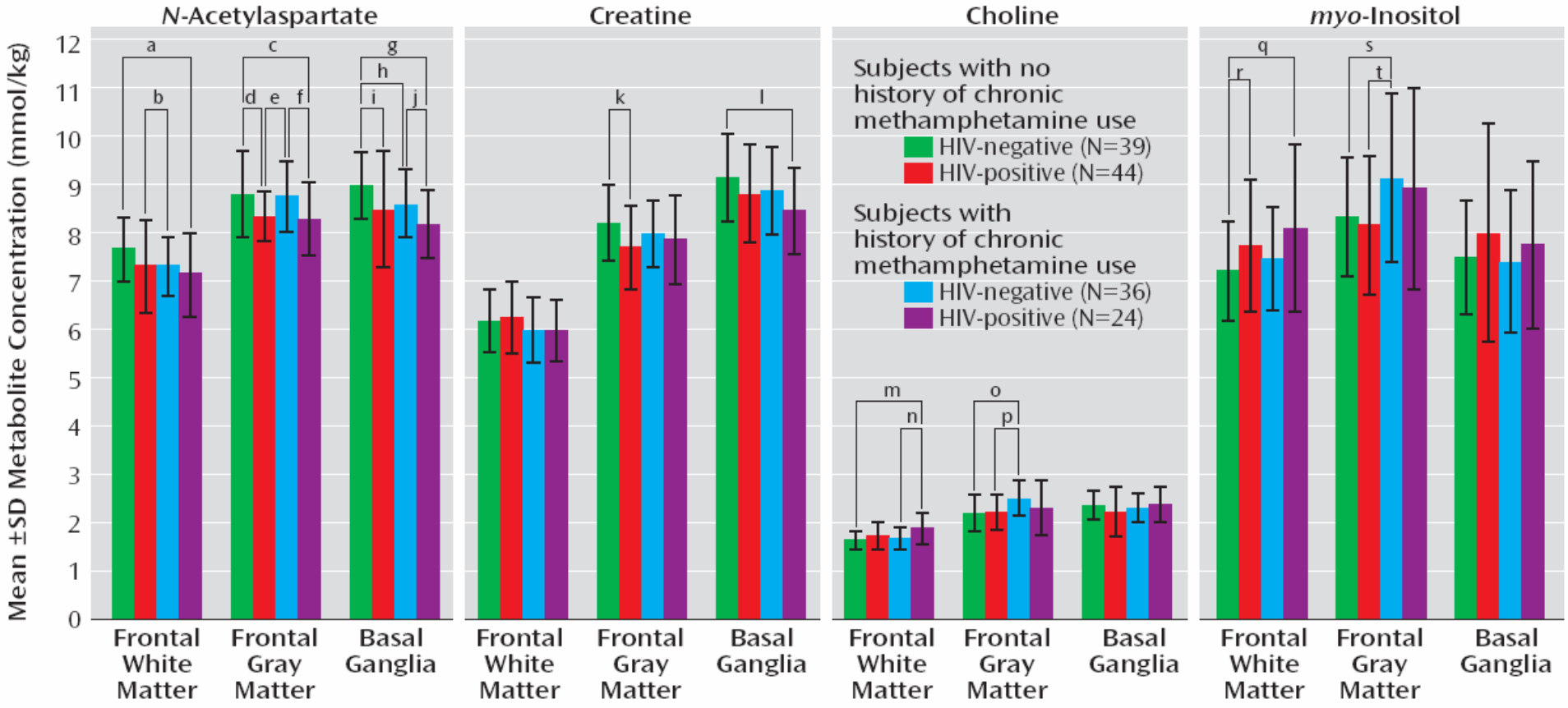
More Inflammation in METH Users

- 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*

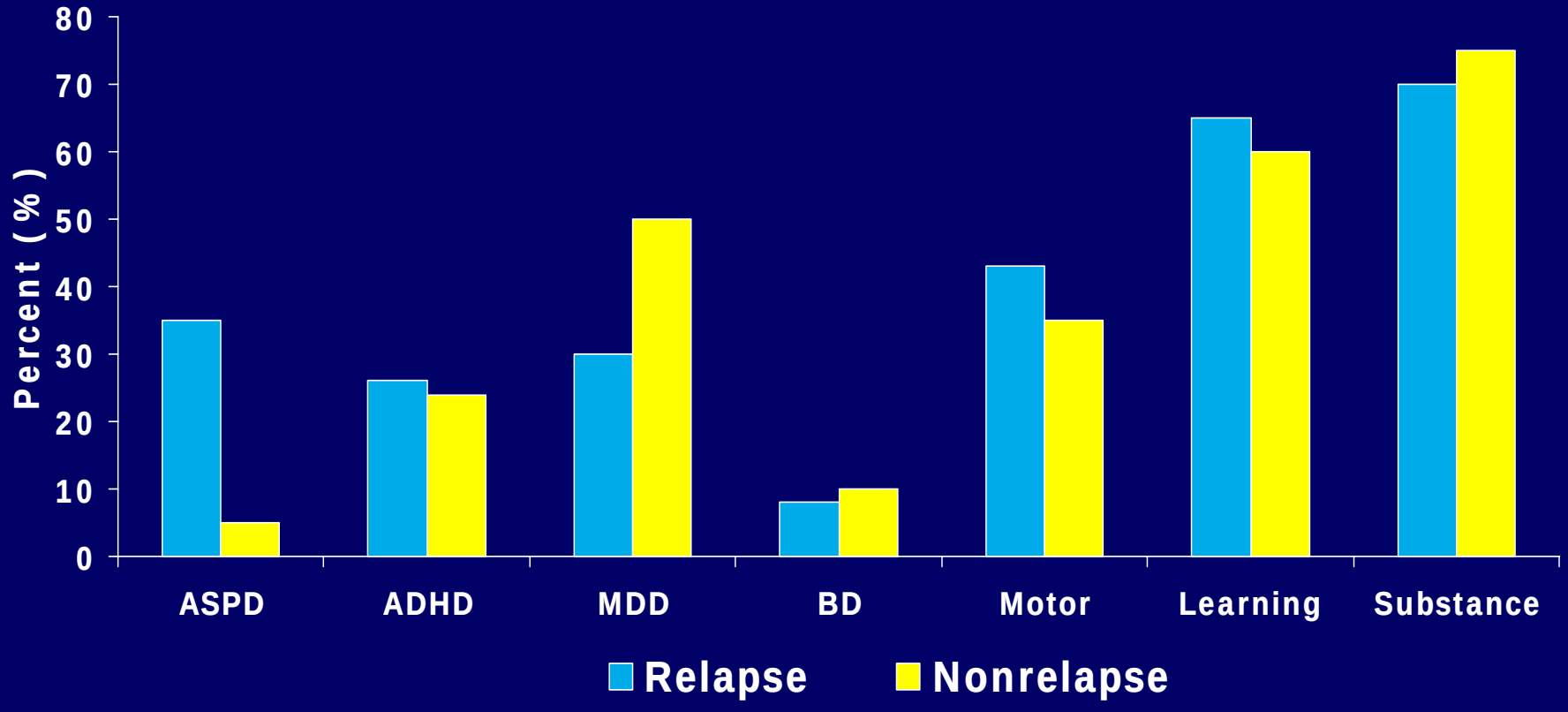
Chang, et al (2005)



Predictors of Meth Relapse after 2 yrs

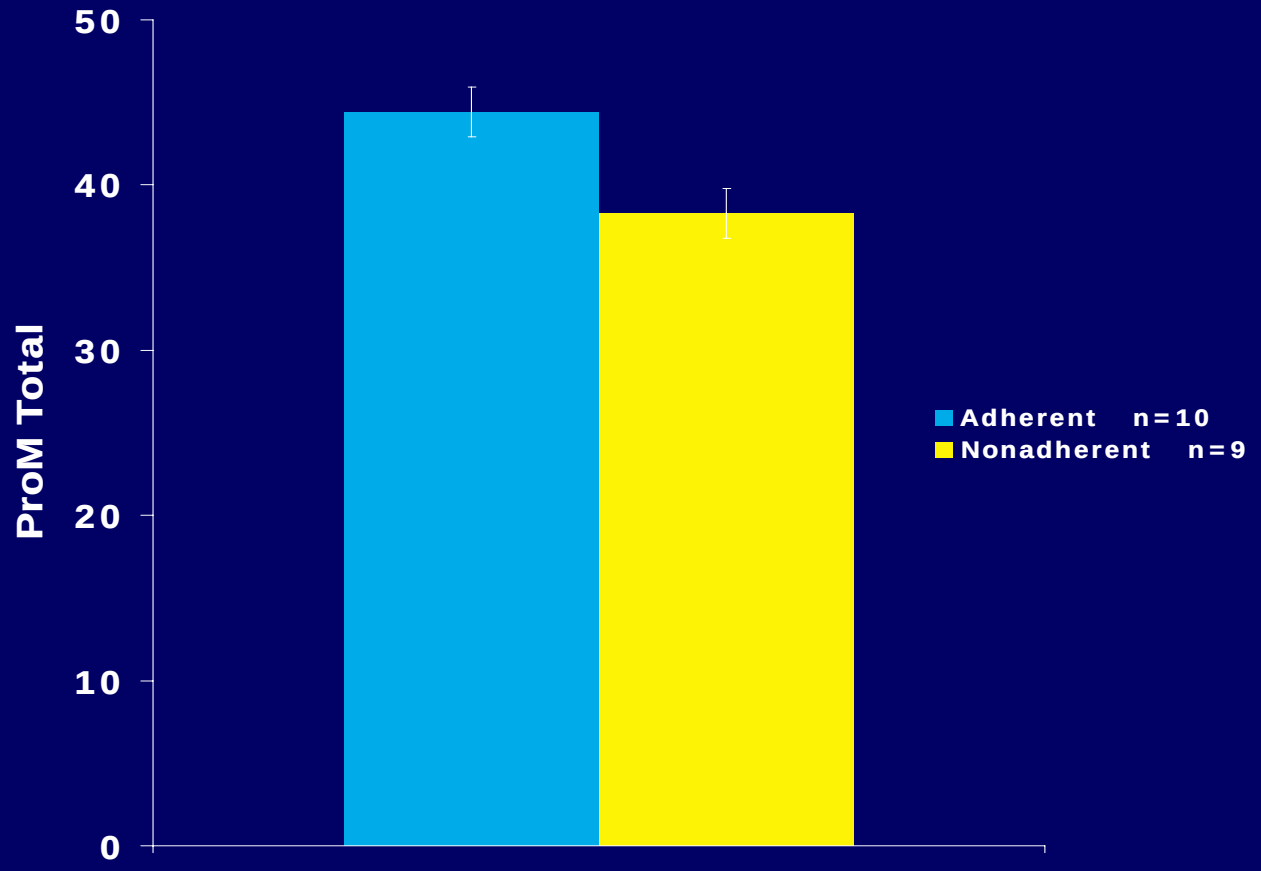
- 53% of a sample of HIV+ MA abusers relapsed over a 2-year follow-up period
- Predictors of relapse in HIV included:
  - Younger age
  - Fewer years of education
  - Earlier age at MA use onset
  - Greater amounts of MA use
  - Higher baseline HIV RNA in plasma
  - No AIDS diagnosis
  - ASPD, absence of depression
  - Cognitive impairment

Cognitive & Psychiatric Status Correlates of Meth Relapse

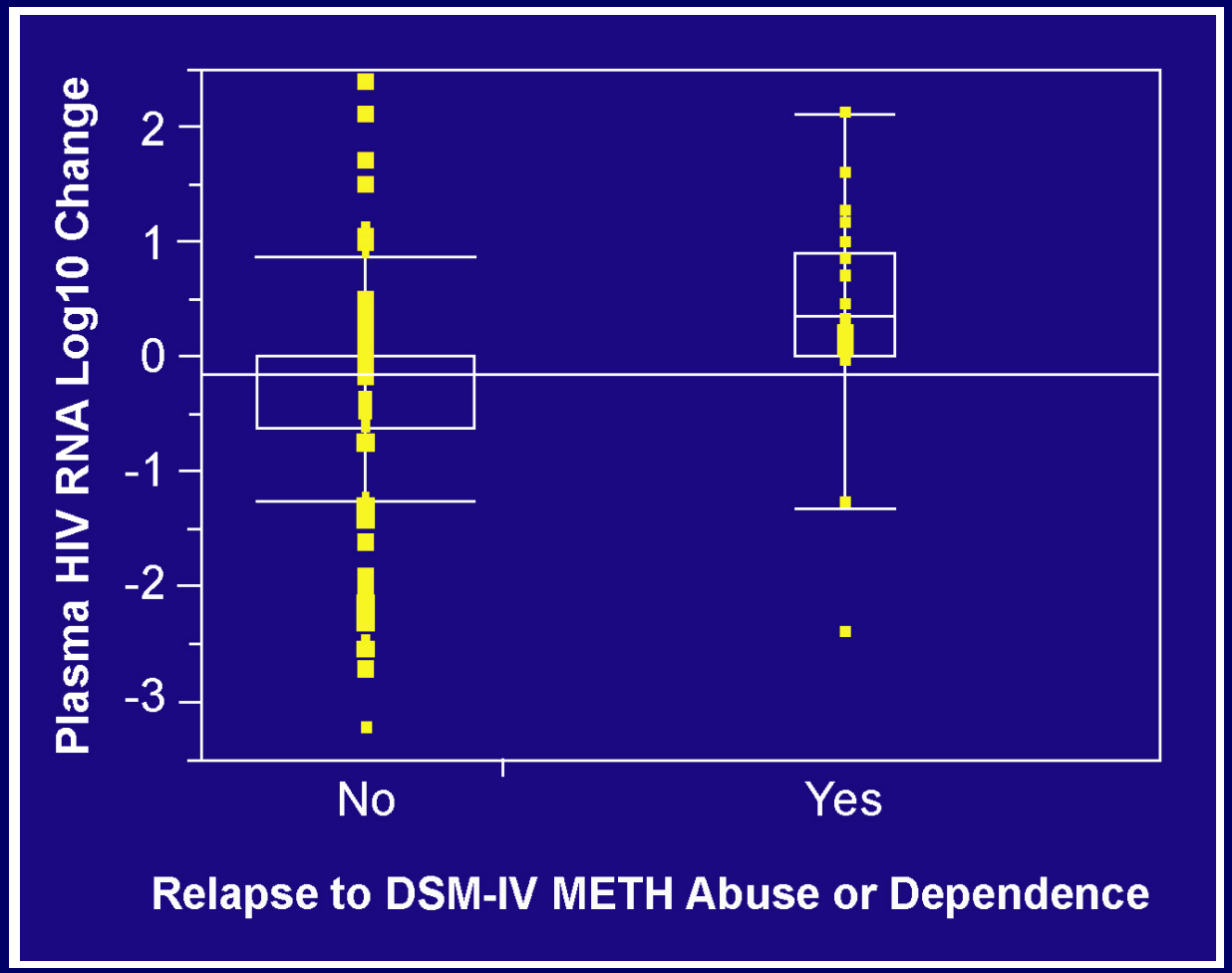


Medication Adherence

- Prospective memory impairment predicts ARV nonadherence at 5 weeks in HIV+ substance abusers (*d* = -1.1)



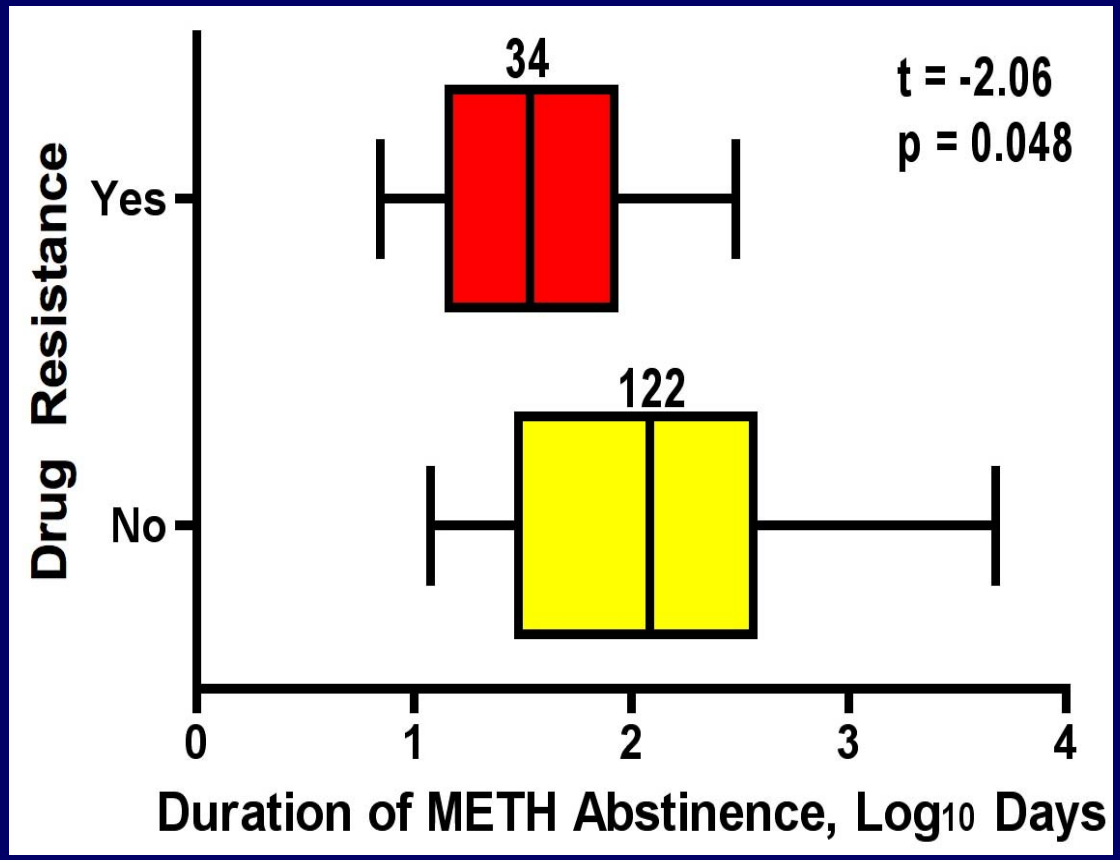
Relapse to METH Abuse or Dependence diagnosis during 12 month follow-up is associated with higher plasma HIV RNA (n=63)



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, Submitted

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Developmental Core: I Everall MD PhD, SA Lipton MD PhD

International Core: JA McCutchan MD

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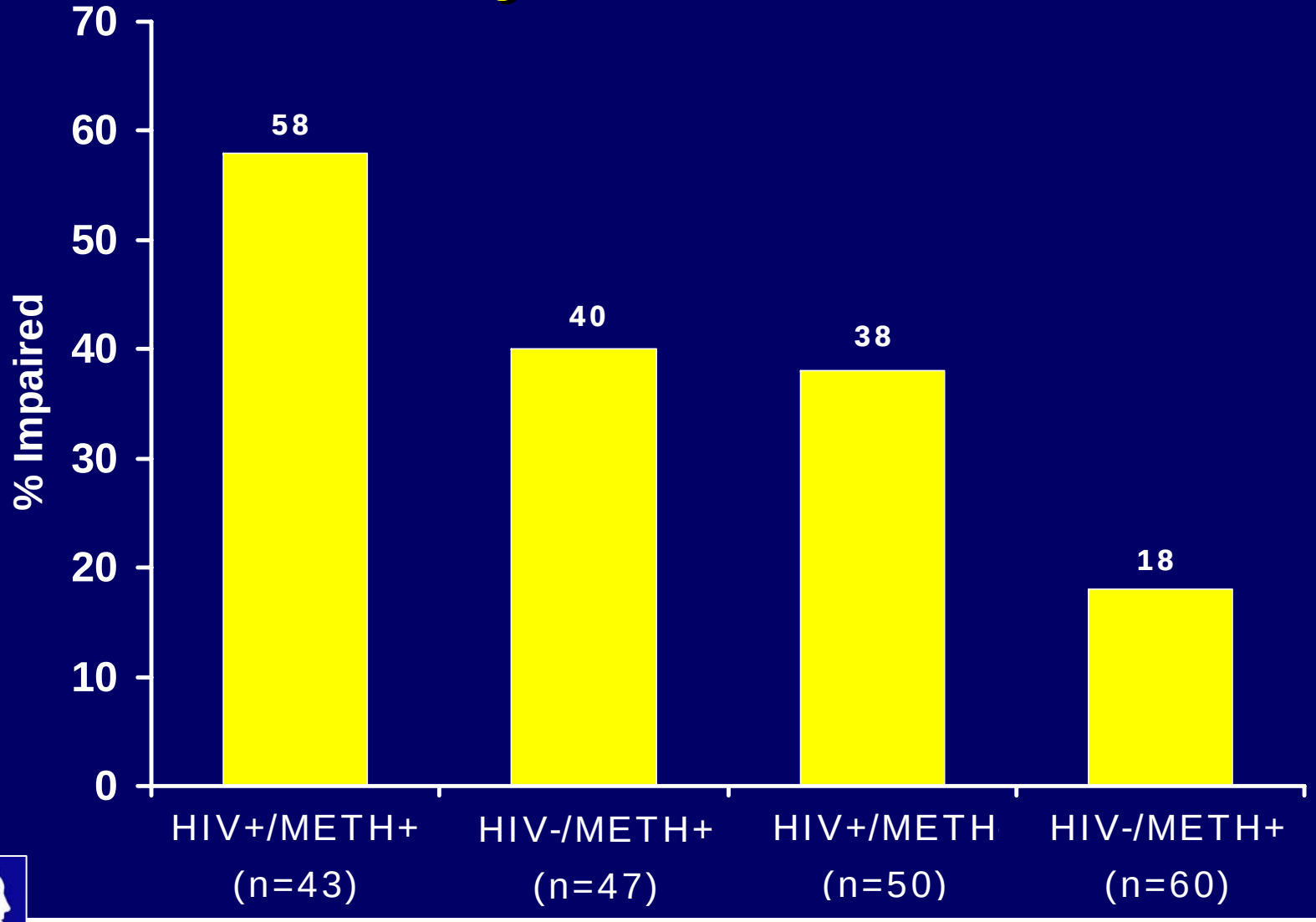
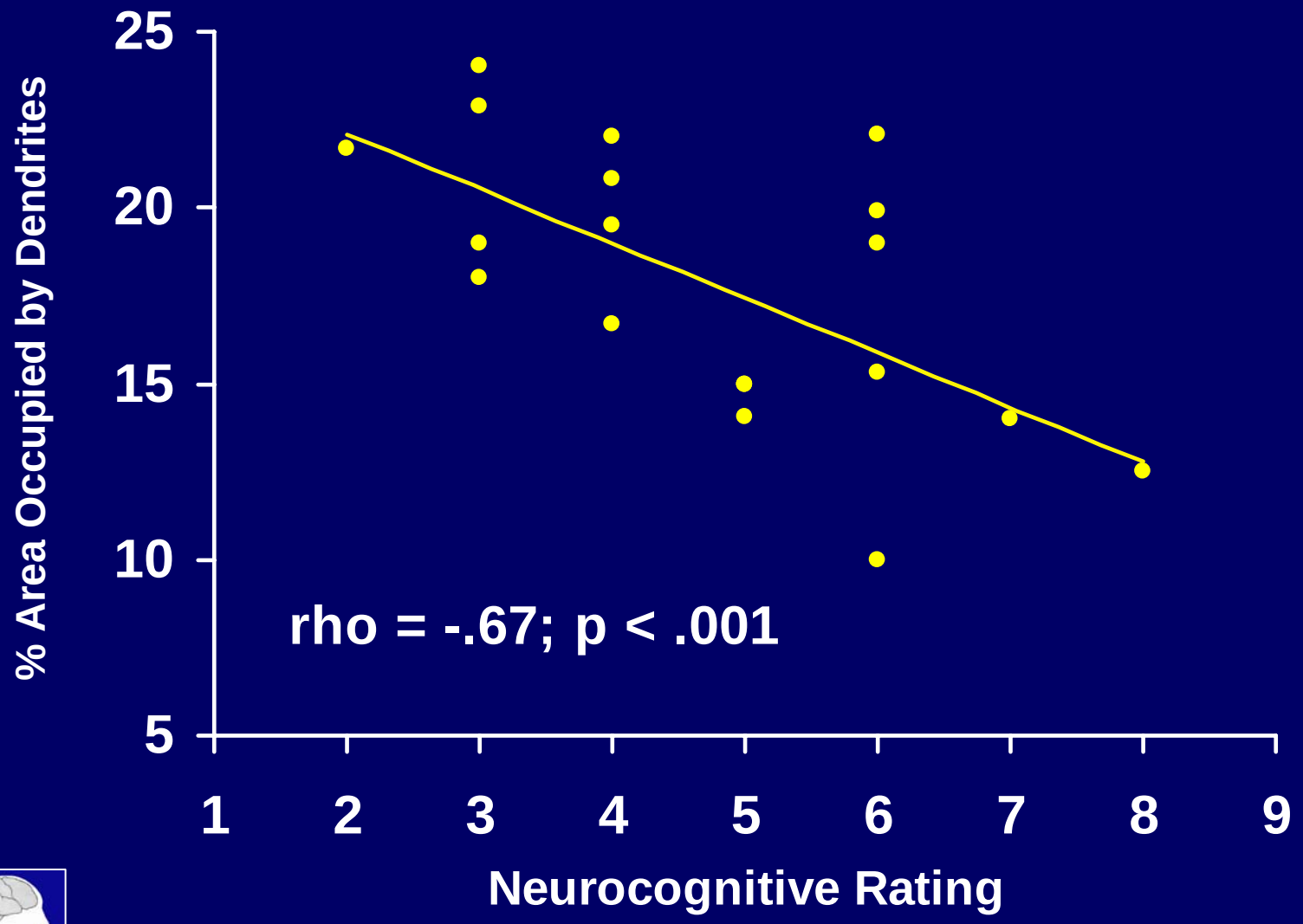
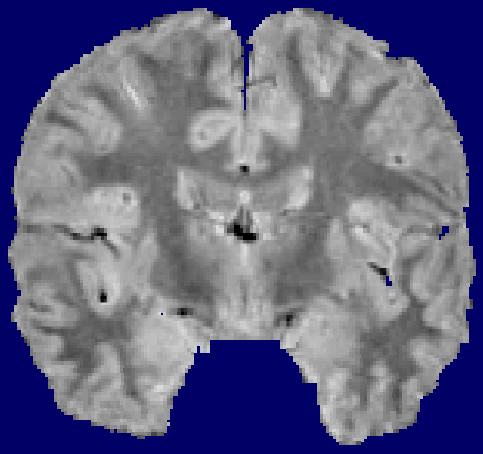
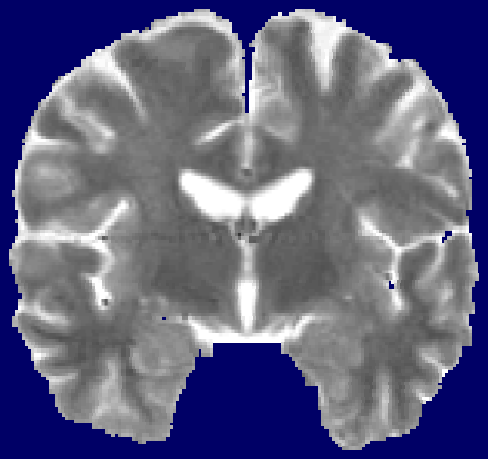
Rates of Global NP Impairment as determined by GDS cut-off scores



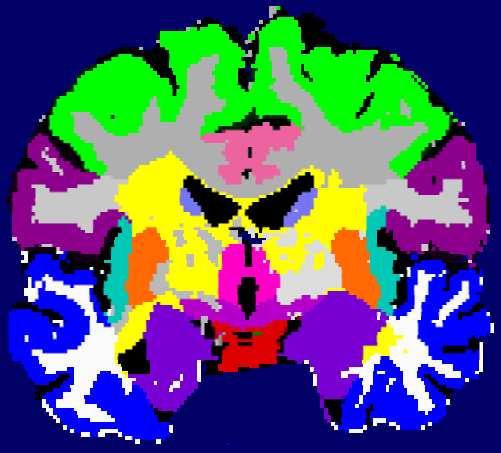
Relation of Dendritic Damage to Neurocognitive Impairment

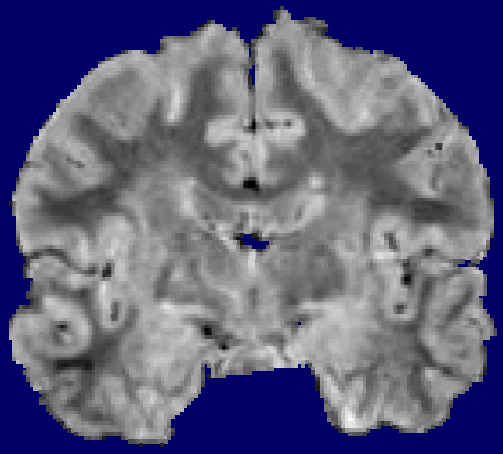


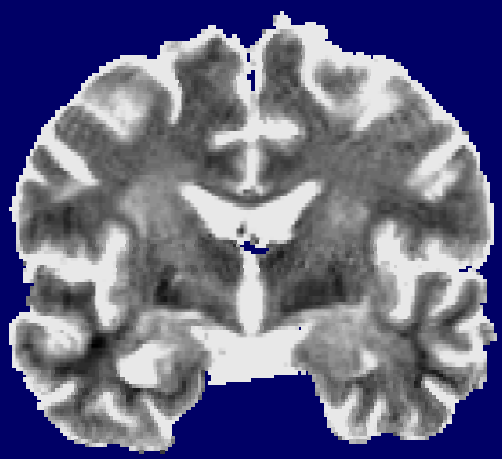




HIVE-



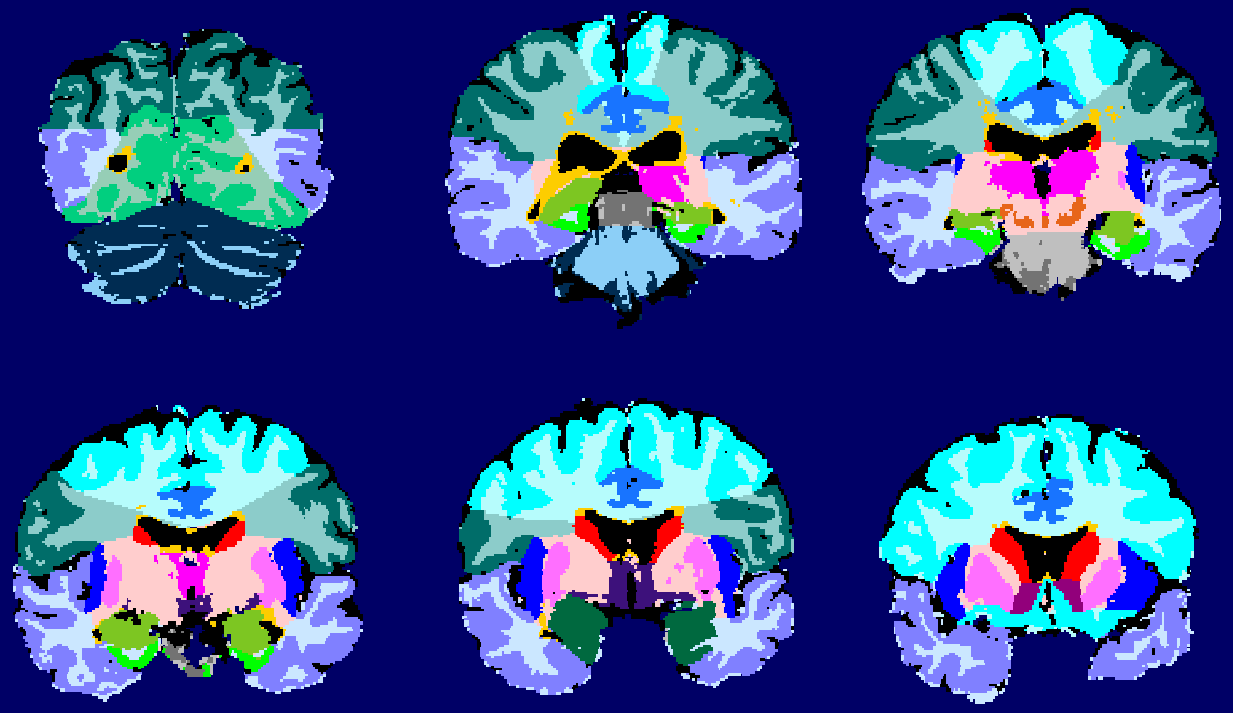




HIVE+

Abnormal White Matter

Example sections from morphometric analysis



Cerebral Lobes

- Frontal Cortex/White
- Temporal Cortex/White
- Parietal Cortex/White
- Occipital Cortex/White

Cerebellum

- Cortex/White

Subcortical Regions

- White Matter
- Basomesial Diencephalon
- Caudate Nucleus
- Lenticular Nucleus
- Nucleus Accumbens
- Thalamus
- Substantia Nigra

Other Structures

- Insular Cortex
- Cingulate Cortex
- Hippocampus
- Amygdala
- Parahippocampal Gyrus
- White Matter w/ Elevated Signal

Abnormal white matter volume predicts HIV encephalitis and dendritic loss at autopsy