



HIV NEUROBEHAVIORAL RESEARCH PROGRAMS

HAND is Common and Important in Patients on ART

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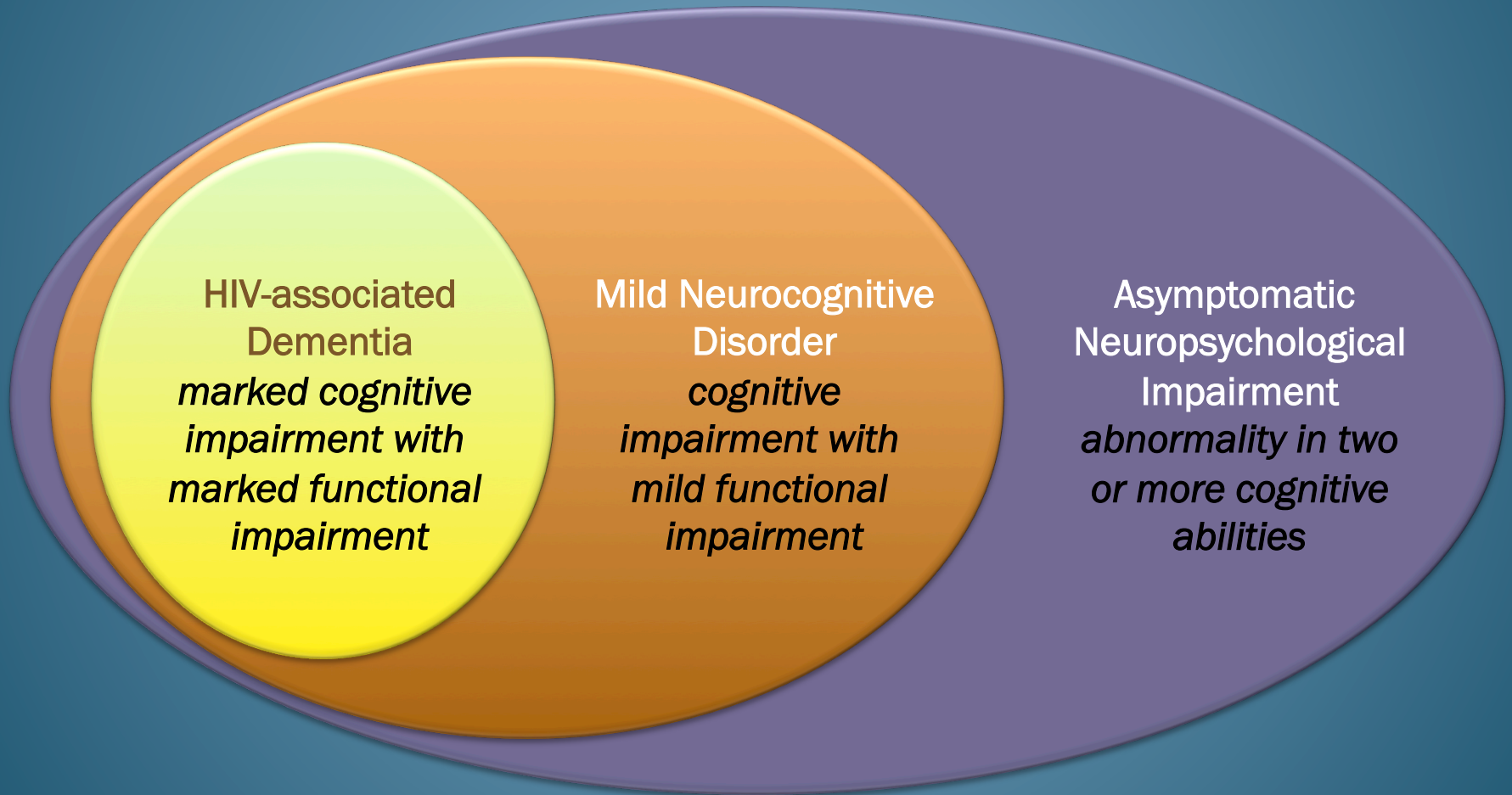
University of California, San Diego

Points to be covered

- How is HAND diagnosed?
- How prevalent is it?
- What are the effects of ARV:
- Significance of HAND: biological and functional correlates
- What about ANI? If it is asymptomatic, does it matter?
- Is the whole thing a statistical artifact?

Grant I, et al., In Preparation

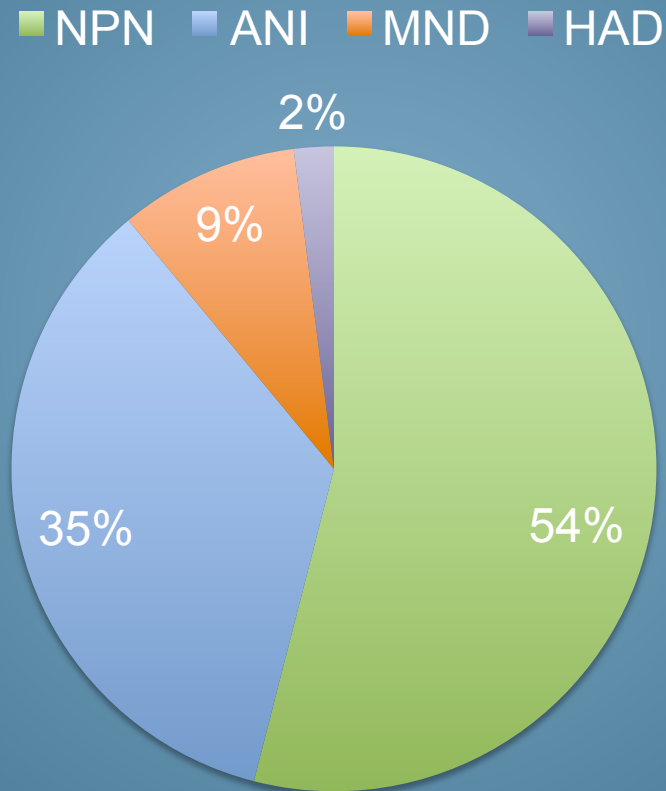
HIV Associated Neurocognitive Disorders (HAND): Frascati Criteria



Antinori, et al., Neurology 2007, 69 (18):1789-99

Prevalence of HAND

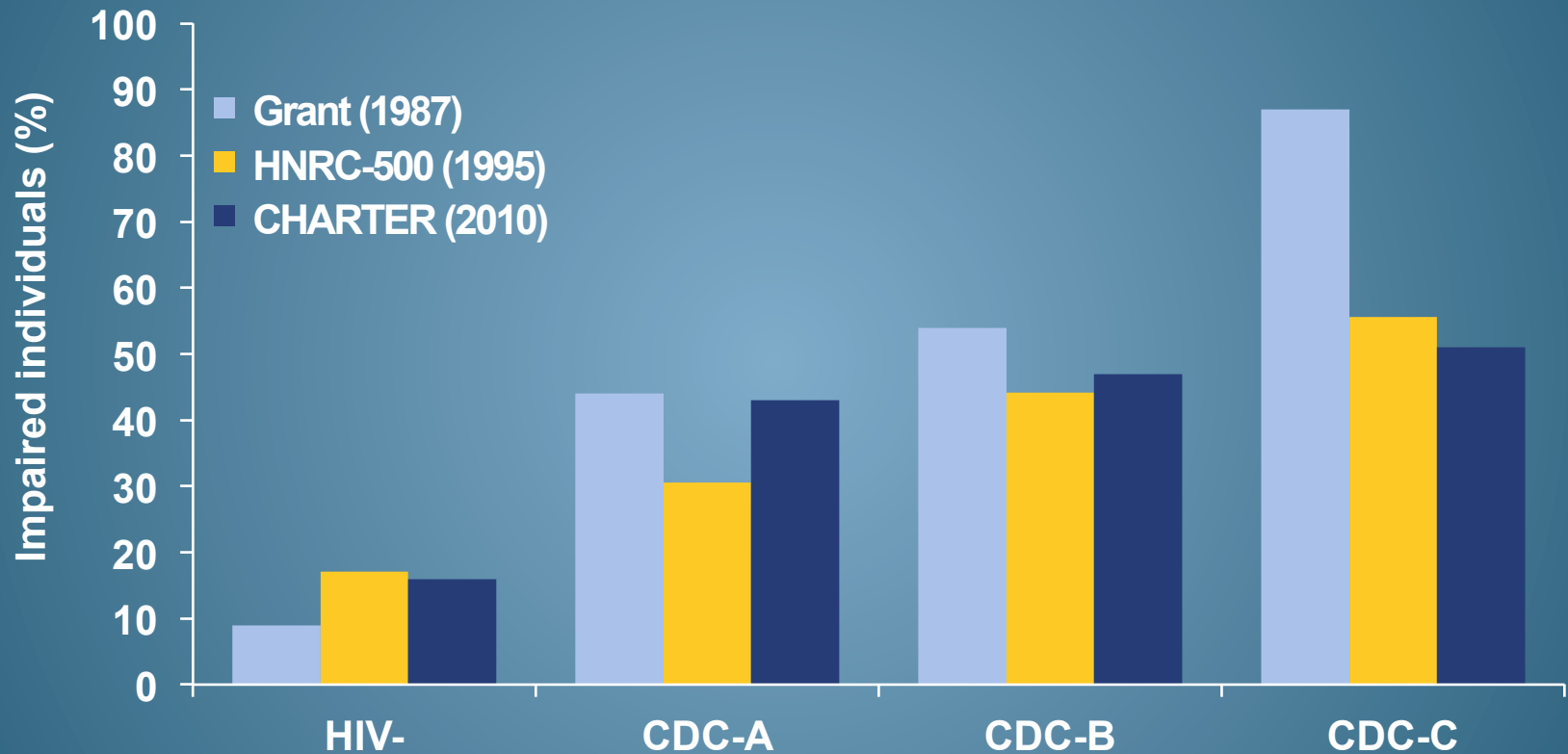
Prevalence of Specific HAND Diagnoses in CHARTER (N=1555 HIV+):



Heaton et al., Neurology 2010, 75(23): 2087-96

How have modern ARV regimens affected HAND?

Despite ARV benefits on morbidity and mortality HAND remains prevalent



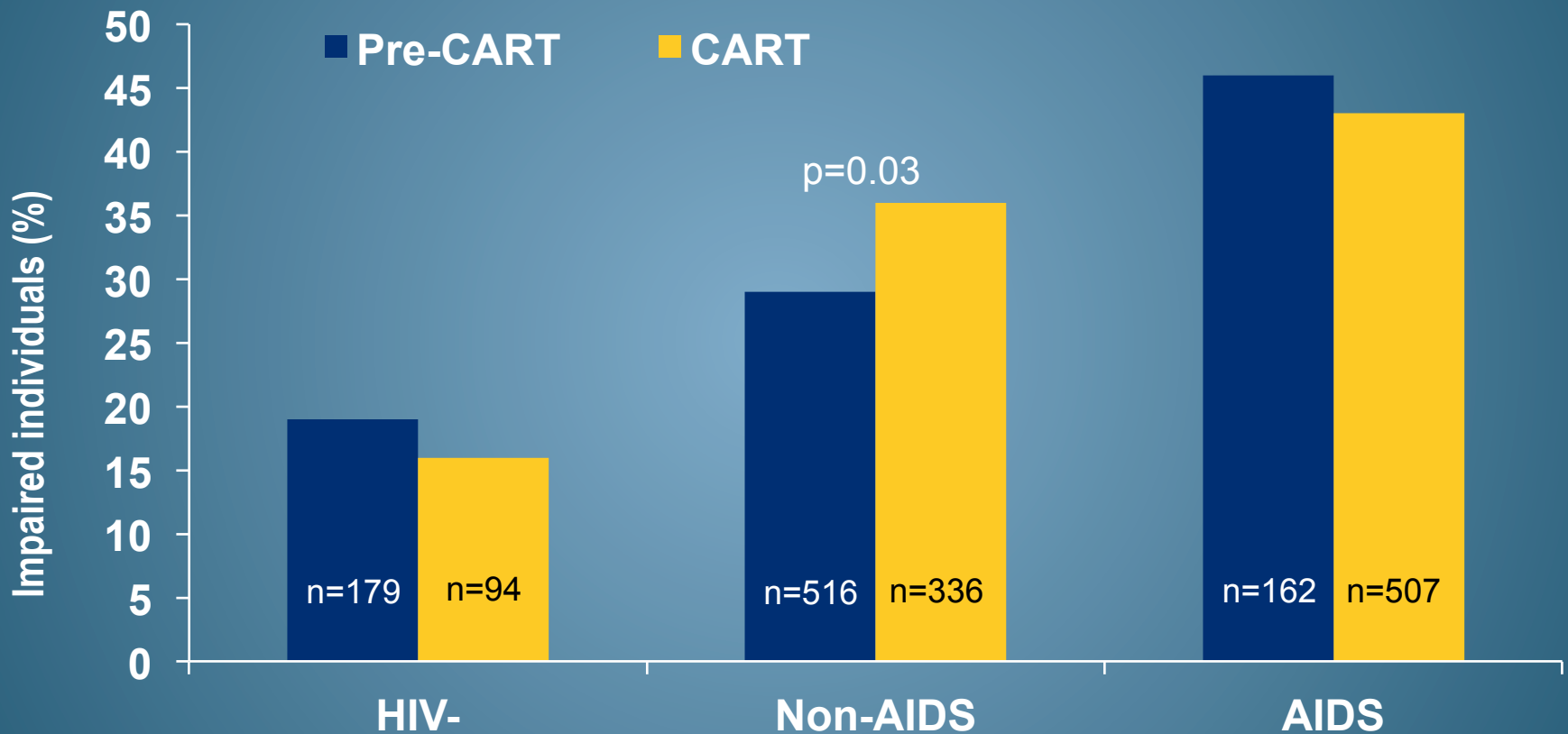
ARV, antiretroviral; CDC, Centers for Disease Control; HAND, HIV-associated neurocognitive disorders

Grant I, et al., Ann Intern Med 1987;107:828–36.

Heaton RK., et al. J Int Neuropsychol Soc 1995;1:231–51.

Heaton RK, et al., Neurology 2010;75:2087–2096.

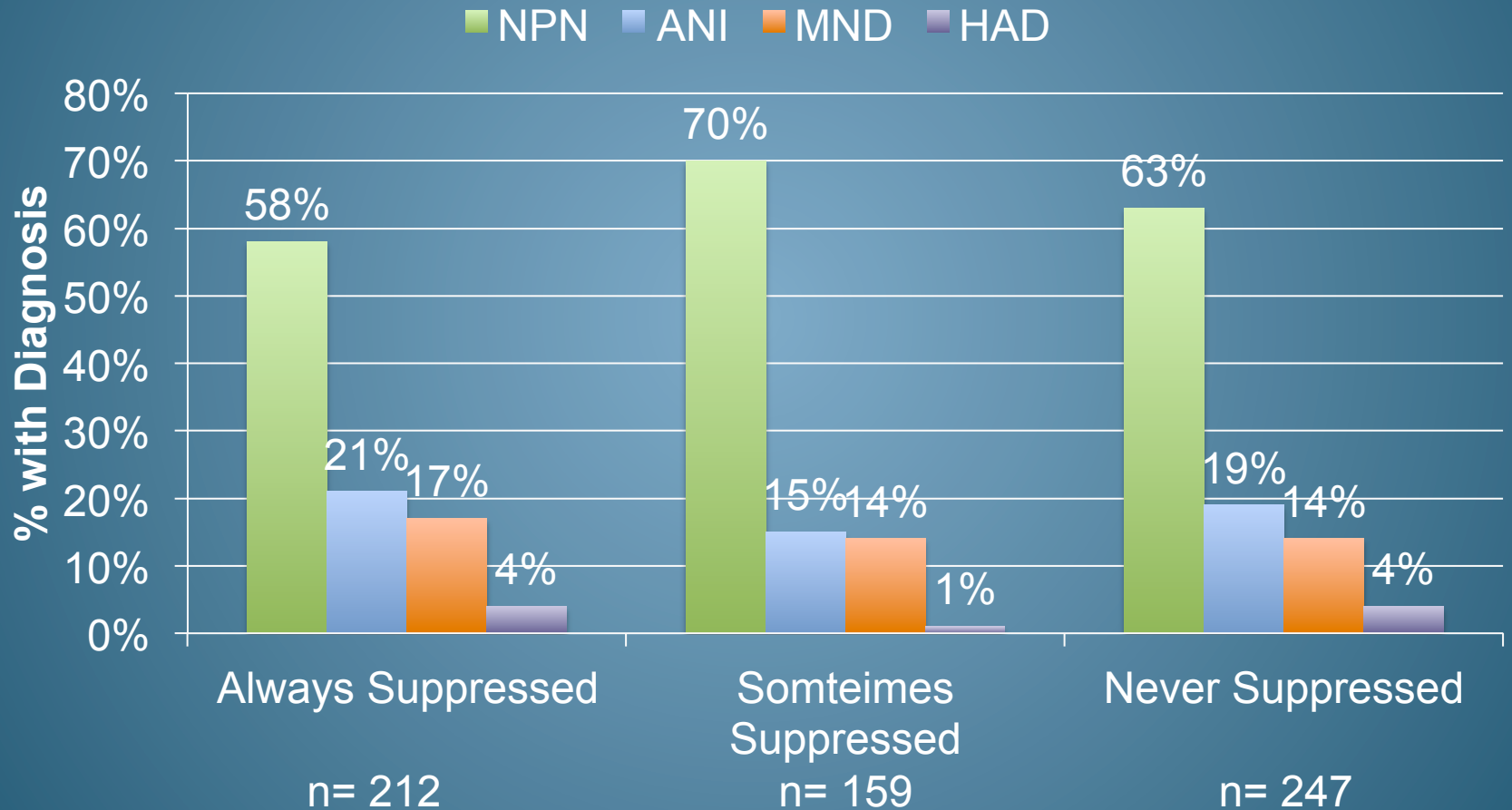
The prevalence of HAND increases as persons with HIV remain medically asymptomatic for longer



CART = combined antiretroviral therapy

Heaton RK, et al., *J Neurovirol* 2011;17:3-16.

HAND Diagnoses by Viral Suppression Across 2 Visits (n=618)



CHARTER Data

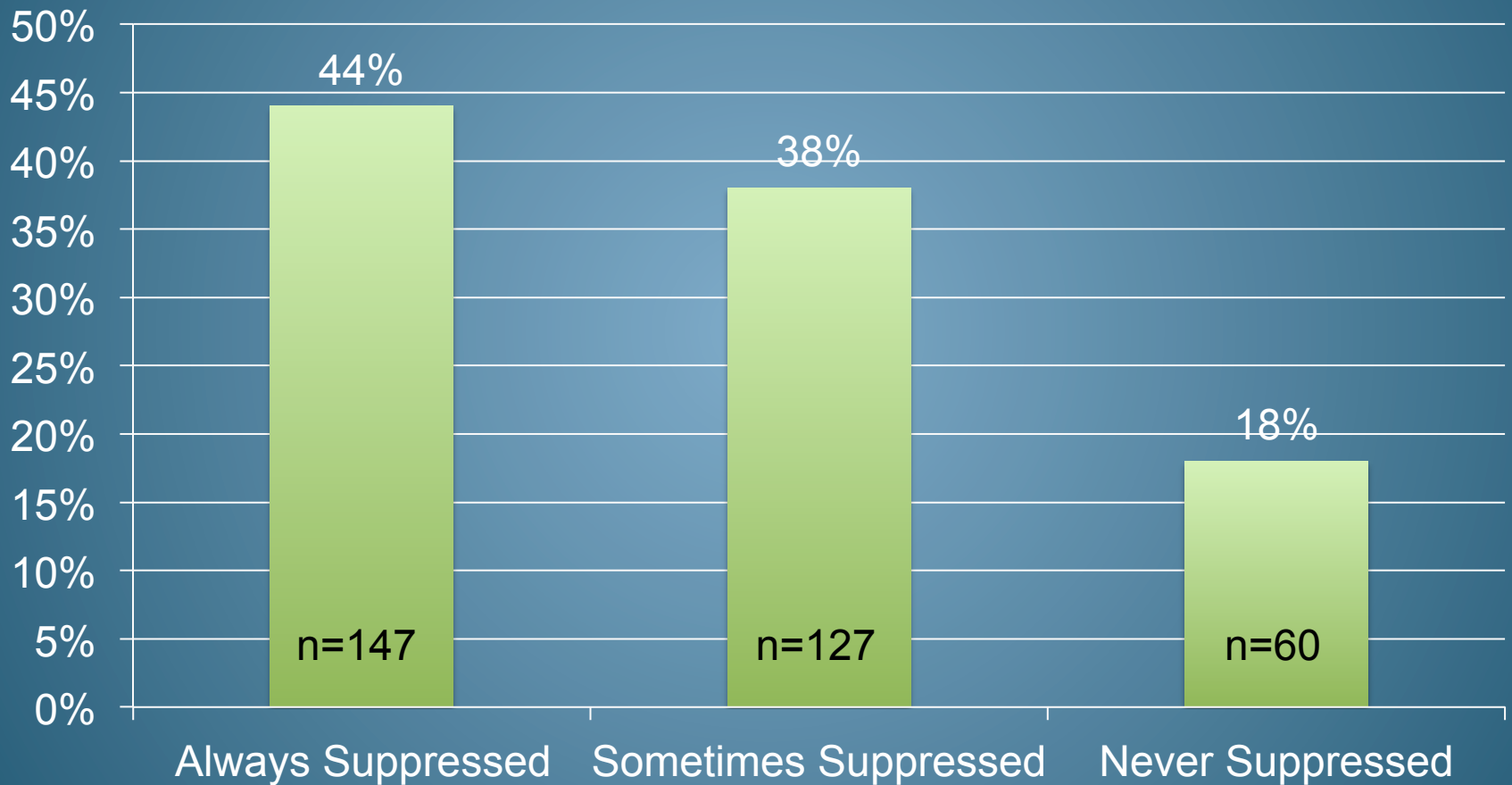
Viral Suppression Across to Visits: Demographic Characteristics

| | Always Suppressed | Sometimes Suppressed | Never Suppressed | p-value |
|------------|-------------------|----------------------|------------------|---------|
| n | 212 | 156 | 247 | |
| Age | 45.9 (8.0) | 42.8 (9.1) | 42.5 (8.6) | <.0001 |
| Education | 12.9 (2.5) | 13.1 (2.4) | 12.8 (2.6) | |
| Gender | | | | |
| %Male | 77% | 82% | 79% | |
| %Female | 23% | 18% | 21% | |
| Ethnicity | | | | |
| % Afr. Am. | 37% | 45% | 44% | |
| % Cauc. | 51% | 42% | 41% | |
| % Hisp. | 11% | 9% | 12% | |
| % Othr. | 1% | 4% | 3% | |

Viral Suppression Across to Visits: Disease Characteristics

| | Always Suppressed | Sometimes Suppressed | Never Suppressed | p-value |
|----------------------------|-------------------|----------------------|------------------|---------|
| n | 212 | 156 | 247 | |
| % AIDS | 72% | 63% | 51% | <.0001 |
| Current CD4 | 518 [367-697] | 451 [280-608] | 405 [264-565] | <.0001 |
| Nadir CD4 | 131 [22-242] | 168 [37-300] | 213 [86-362] | <.0001 |
| Est. Duration HIV+ (years) | 12.1 [6.5-16.0] | 10.9 [2.4-16.0] | 8.8 [3.6-14.8] | 0.0013 |
| ART Status | | | | |
| HAART | 98% | 86% | 48% | <.0001 |
| No ARVs | 1% | 9% | 22% | |
| ARV Naive | 0% | 5% | 30% | |

Stability of Viral Suppression Over 3 Visits (n=334*)



* All participants were stably on ART; limit of detection = 50 copies/mL

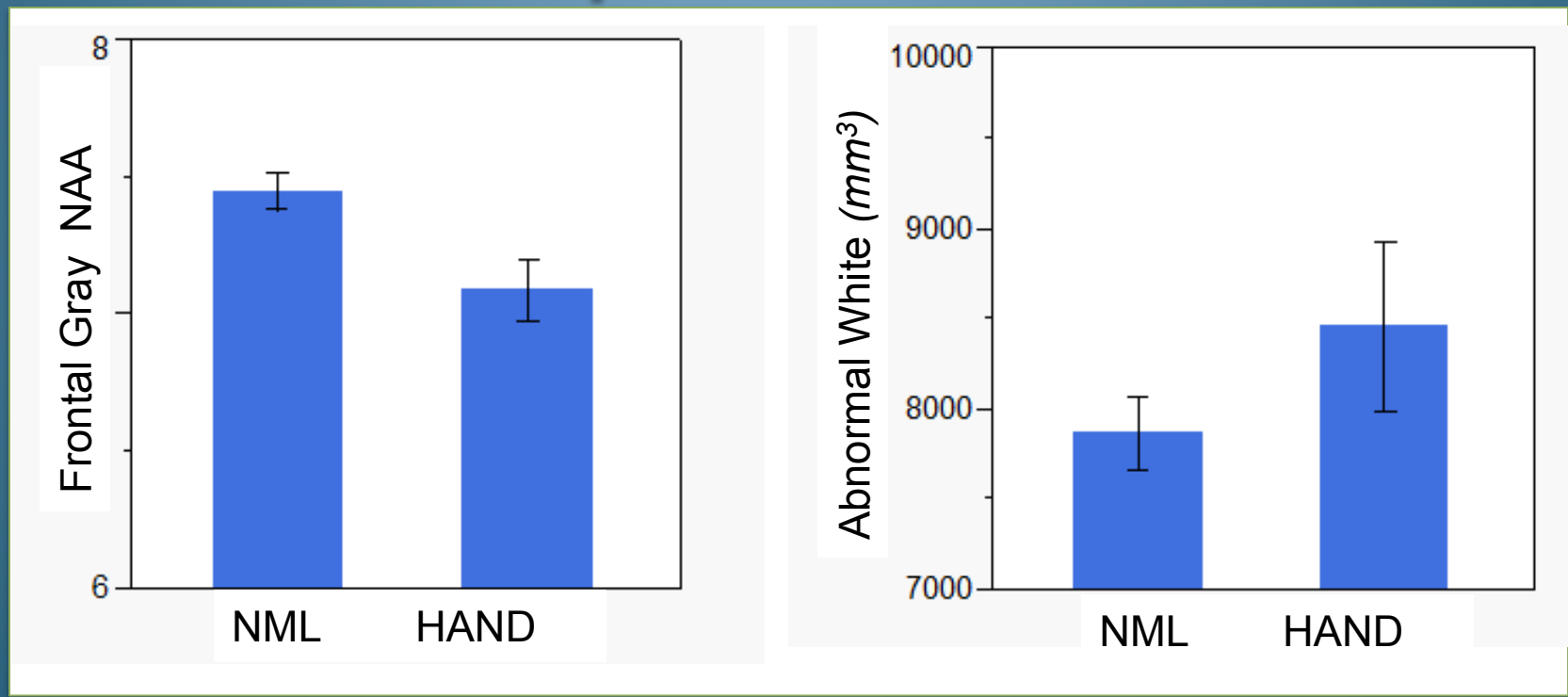
CHARTER Data

Does HAND matter?

HAND associated with reduced neuronal integrity and more white matter abnormalities

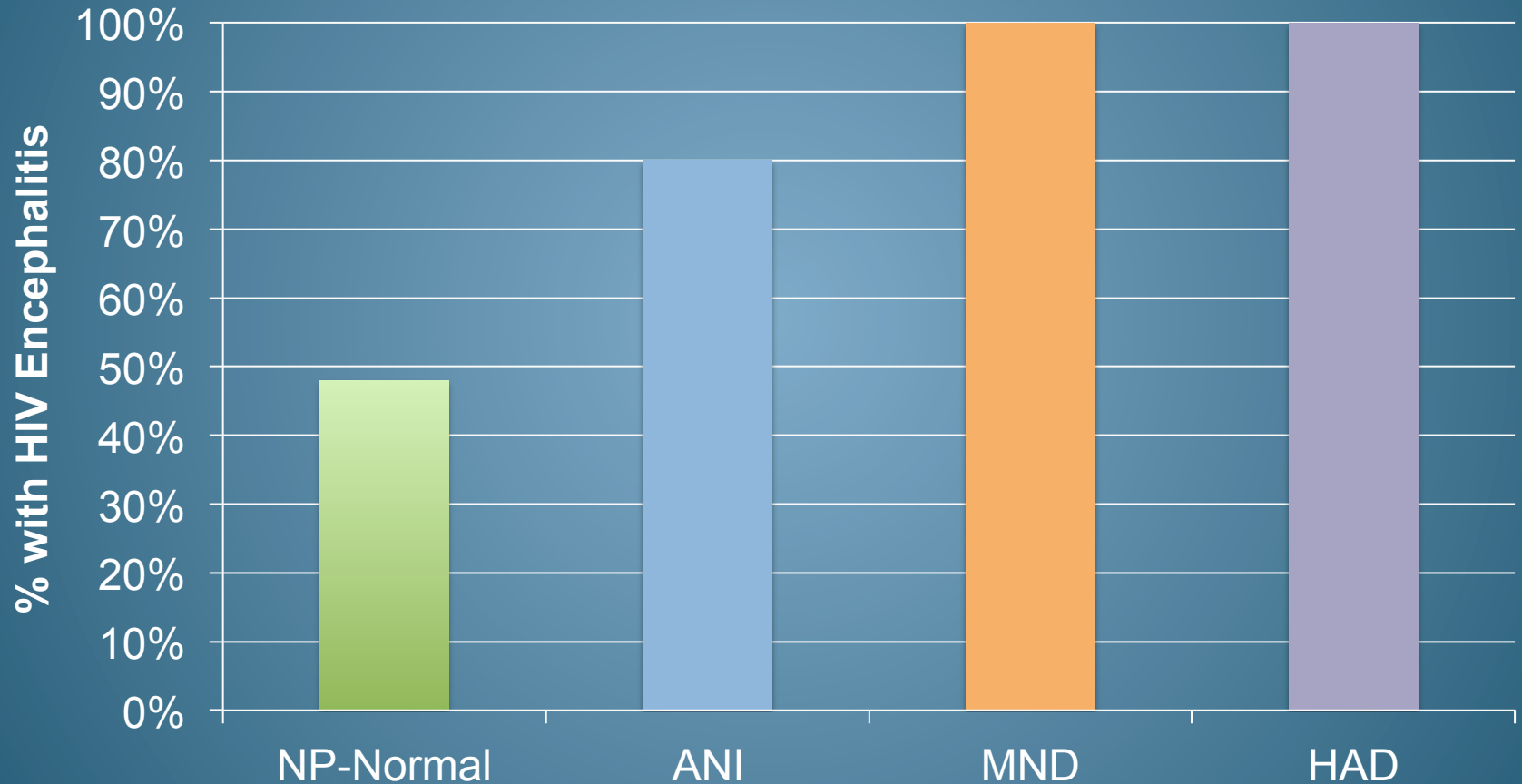
HAND classification (Normal vs. HAND) best predicted by

↓ FGM NAA and ↑ abnormal white matter



Fennema-Notestine et al. CROI 2013

Likelihood of HIVE according to Antemortem NP Status

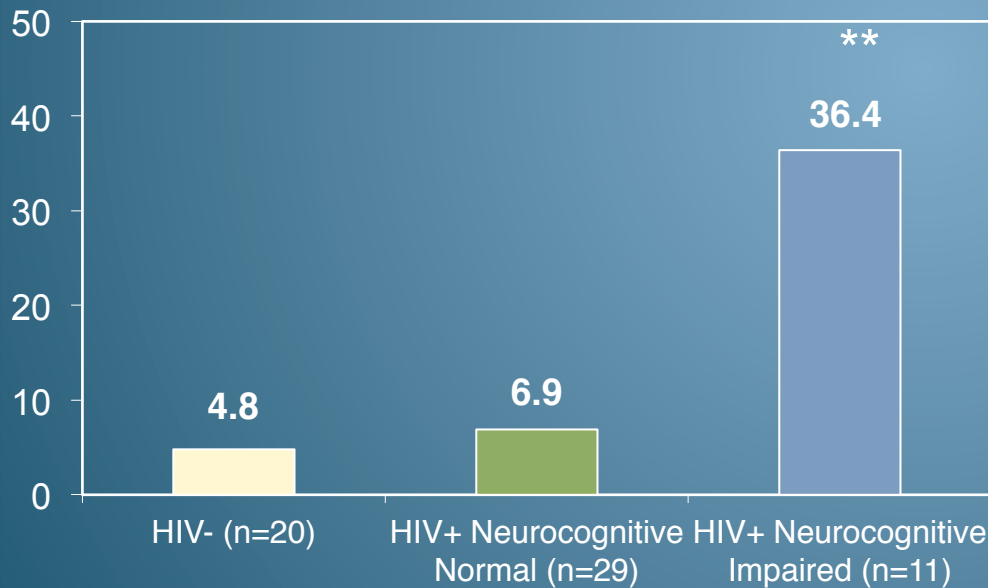


Cherner M, et al., Neurology; 2002;59(10),1563-7

Neurocognitive Impairment Matters

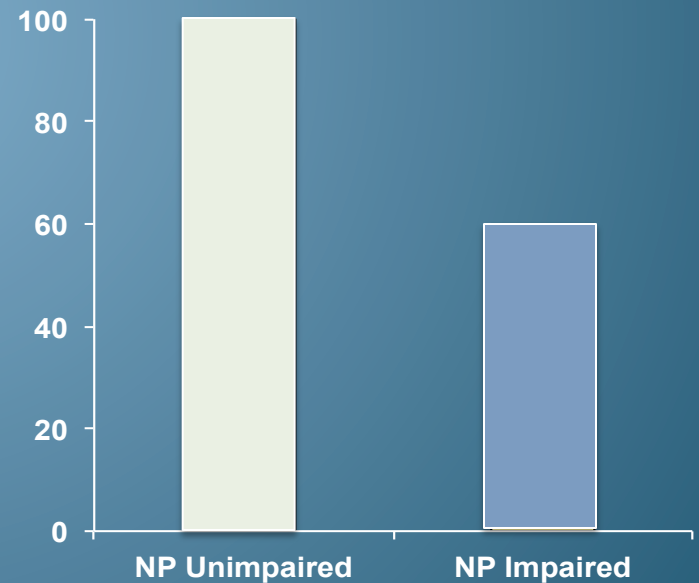
It can lead to problems in everyday functioning such as work inefficiency, driving impairment, and worse adherence to treatment

% Failing an On-road Driving Assessment



Marcotte et al., *Neurology* 2004, 63 (8): 1417-22

% That Followed Schedule "Most of the Time"

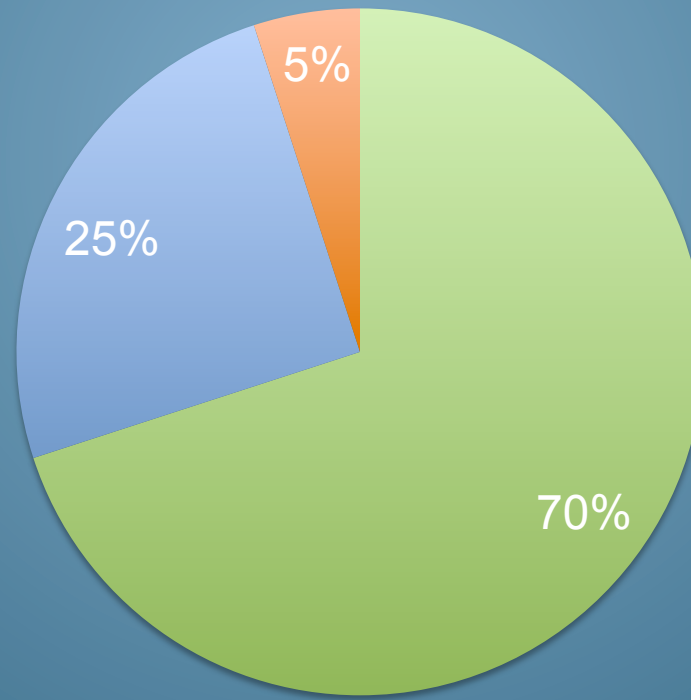


HNRC Data

ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT (ANI): Does it Matter?

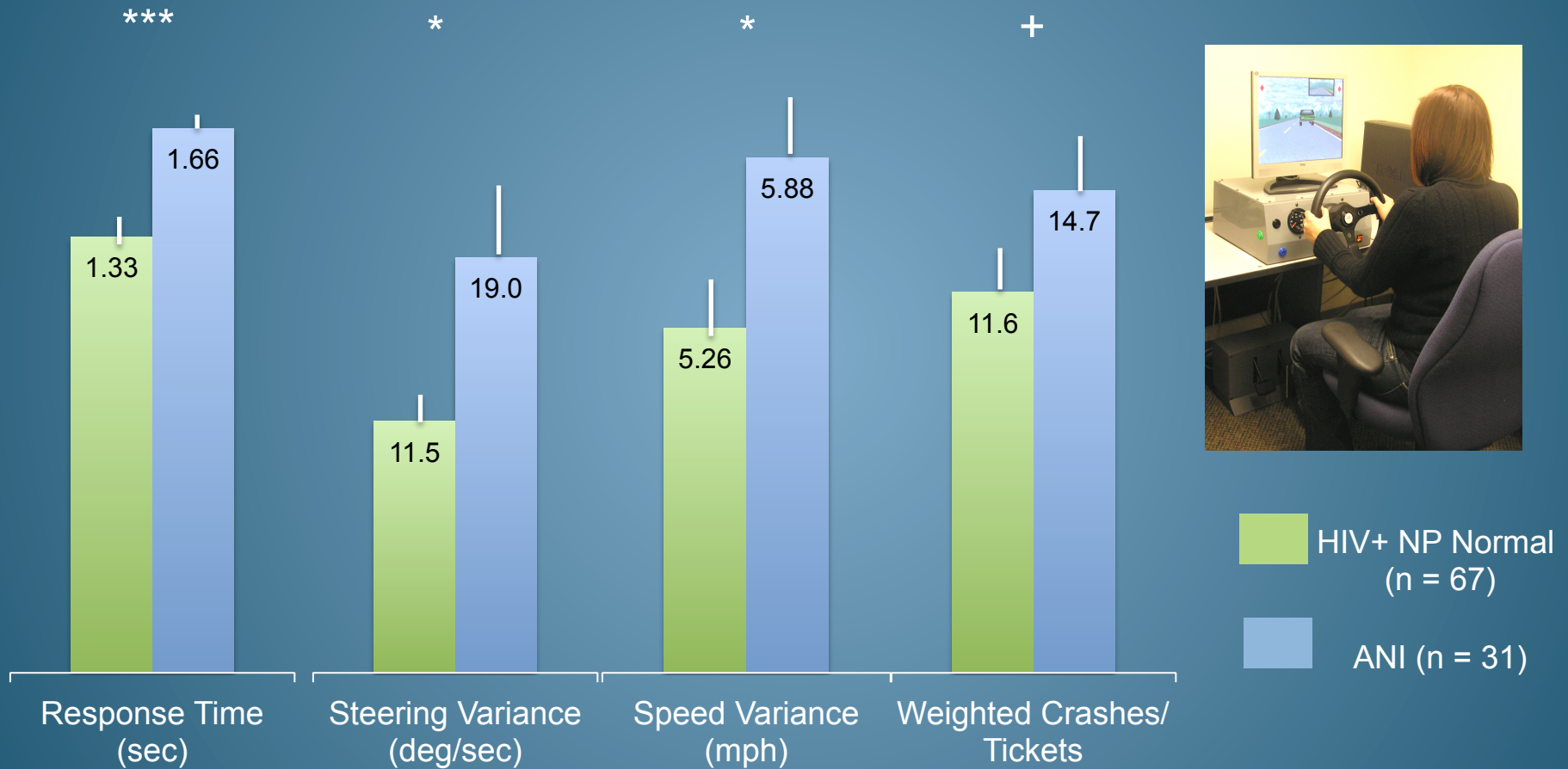
Prevalence of Specific HAND Diagnoses in CHARTER: (NCI Only)

■ ANI ■ MND ■ HAD



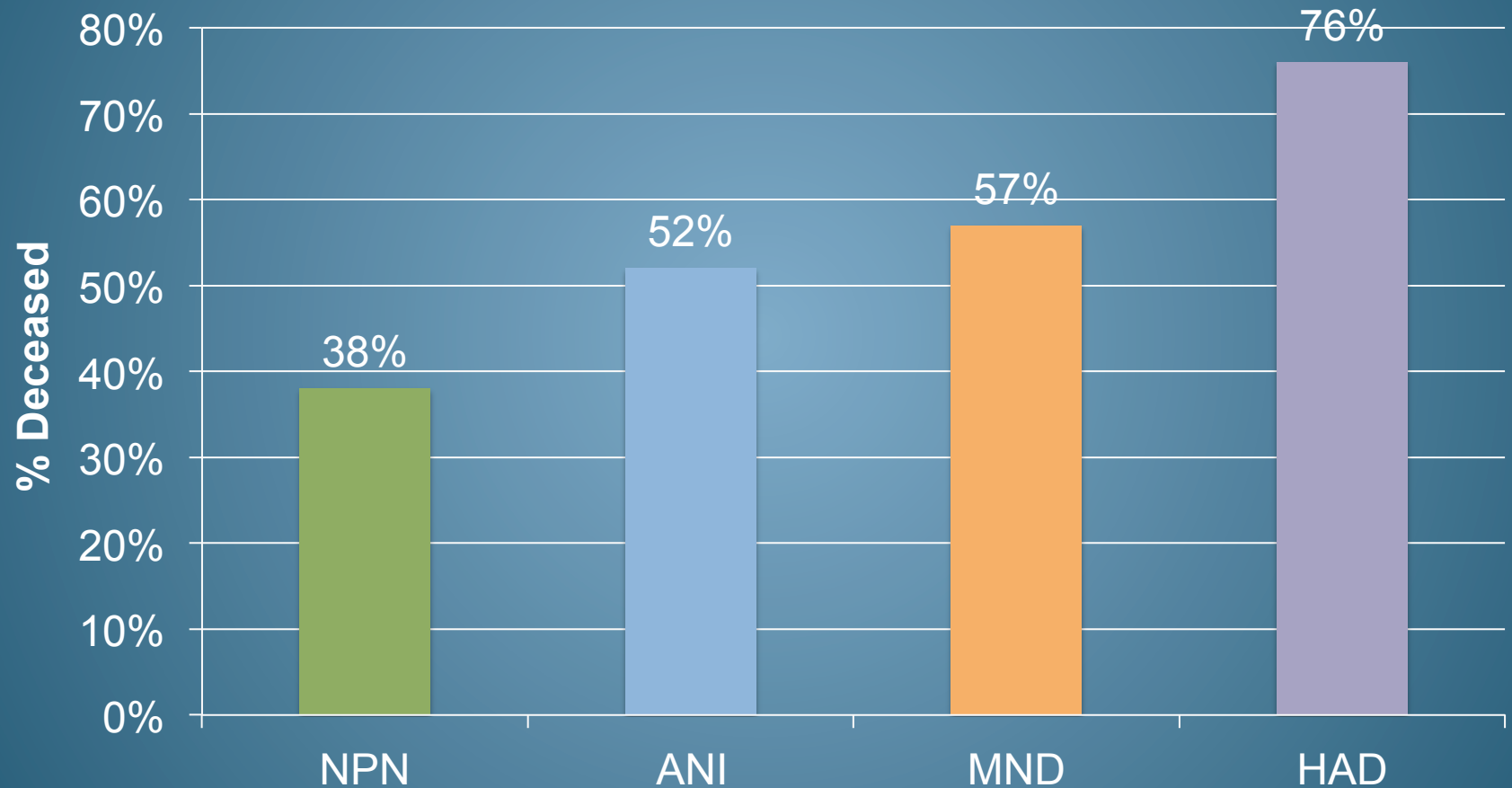
Heaton et al., Neurology 2010, 75(23): 2087-96

ANI is associated with worse simulated driving performance



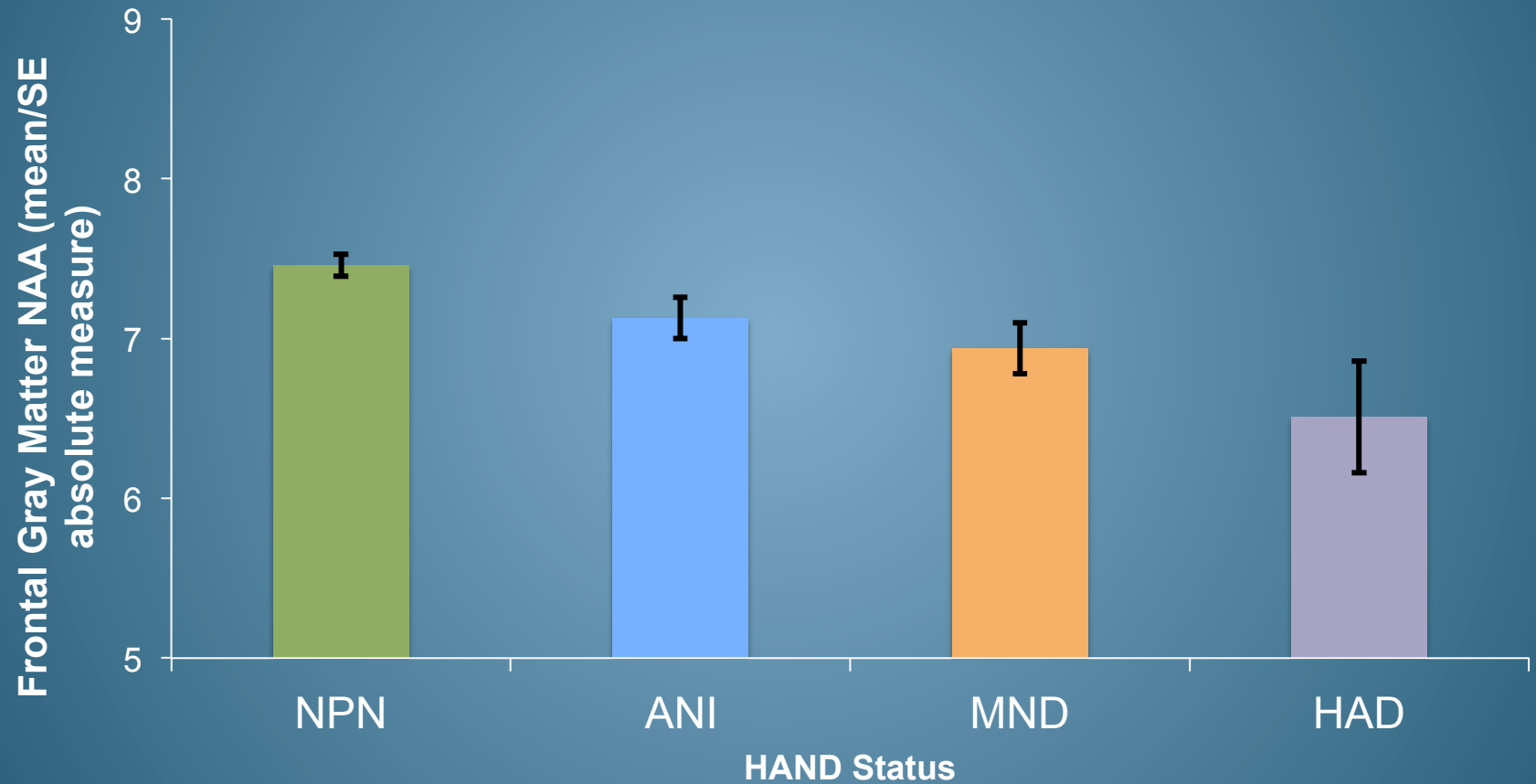
Marcotte et al., in preparation

Mortality by HAND Diagnosis: 543 cases from the National NeuroAIDS Tissue Consortium



Rooney A, et al. In Submission

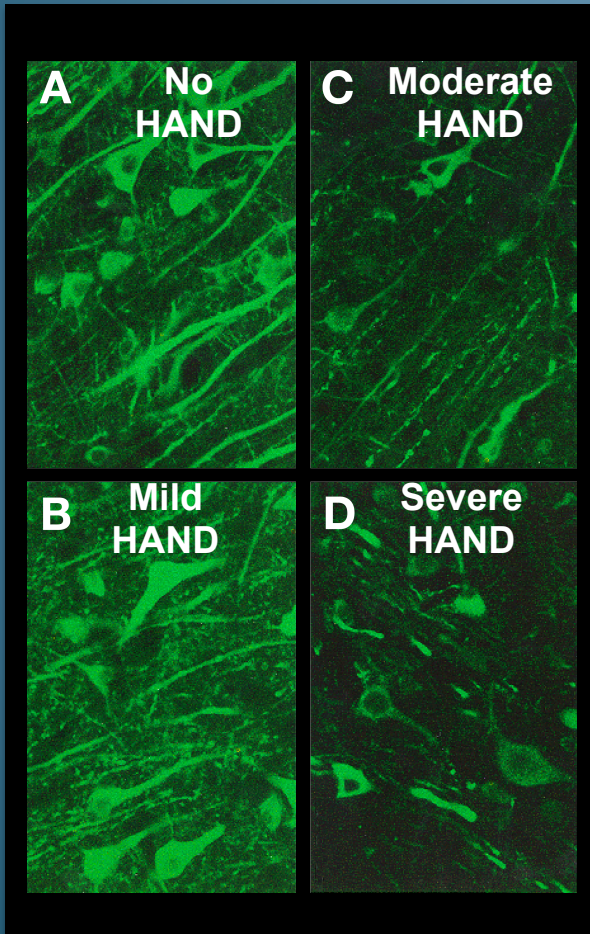
Frontal Gray Matter NAA by HAND Status



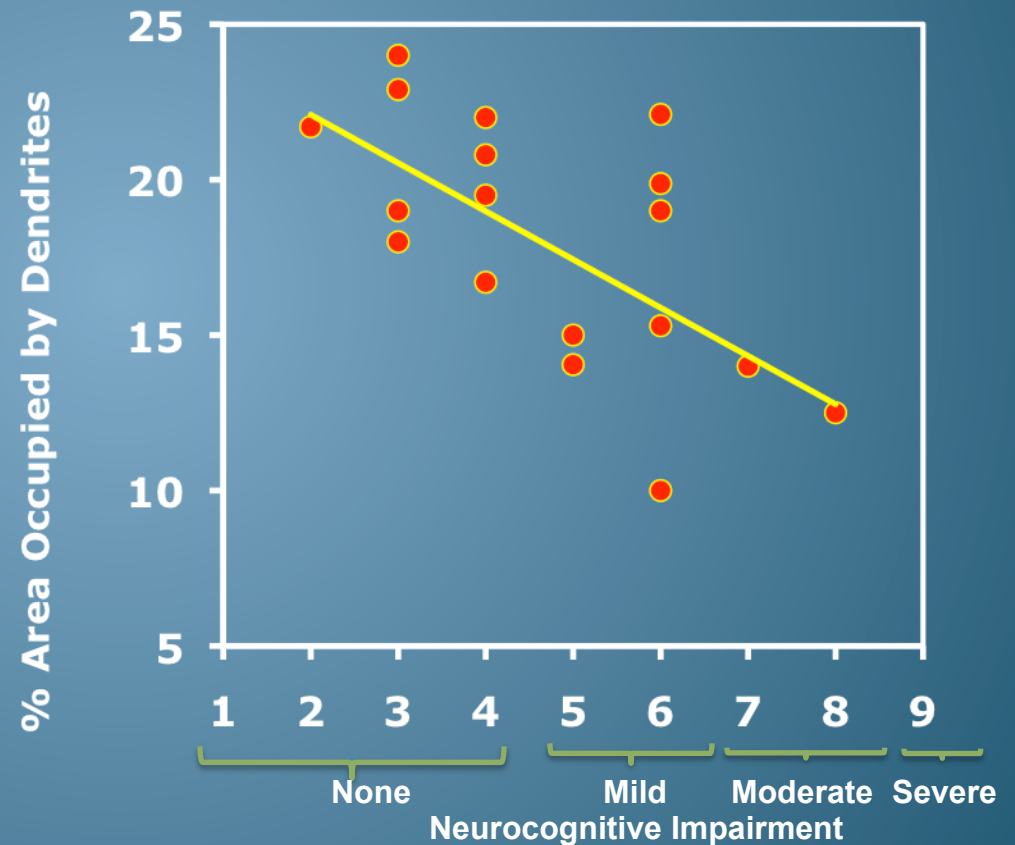
CHARTER Data

Injury to synapses and dendrites may form a basis of HIV neurocognitive impairment

Progressive Dendritic Loss from No HAND (A) to Severe HAND (D)



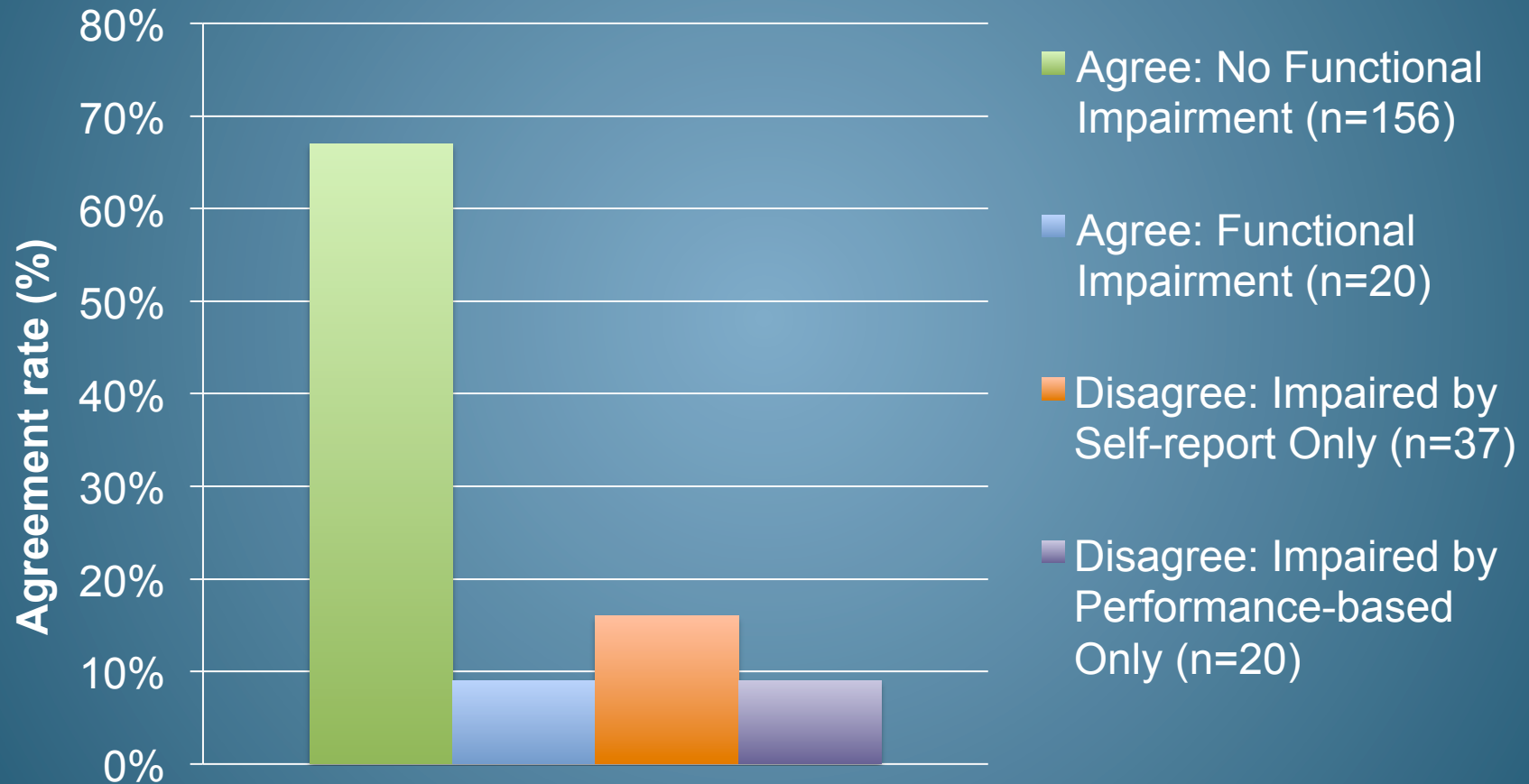
Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



Masliah, et al. *Ann Neurol.* 1997, 42(6): 963-72

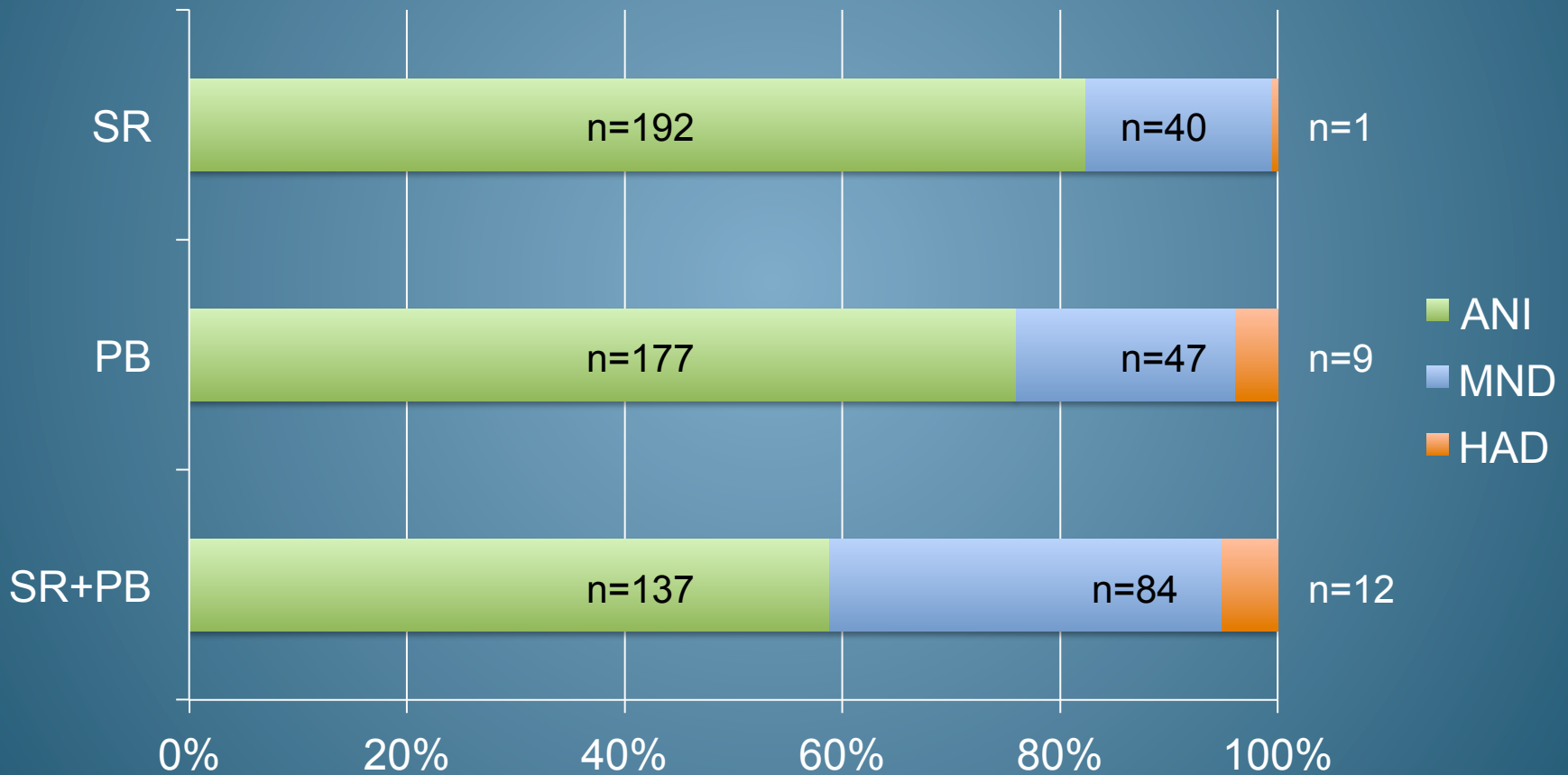
Many clinicians agree that MND, which requires both neurocognitive impairment and decline in everyday functioning, has clinical significance (eg., see EACS guidelines). But the ascertainment of functional impairment can be challenging

Agreement between self report (SR) and performance based (PB) functional measures



Blackstone, et al., JINS, 2012, 18: 79-88

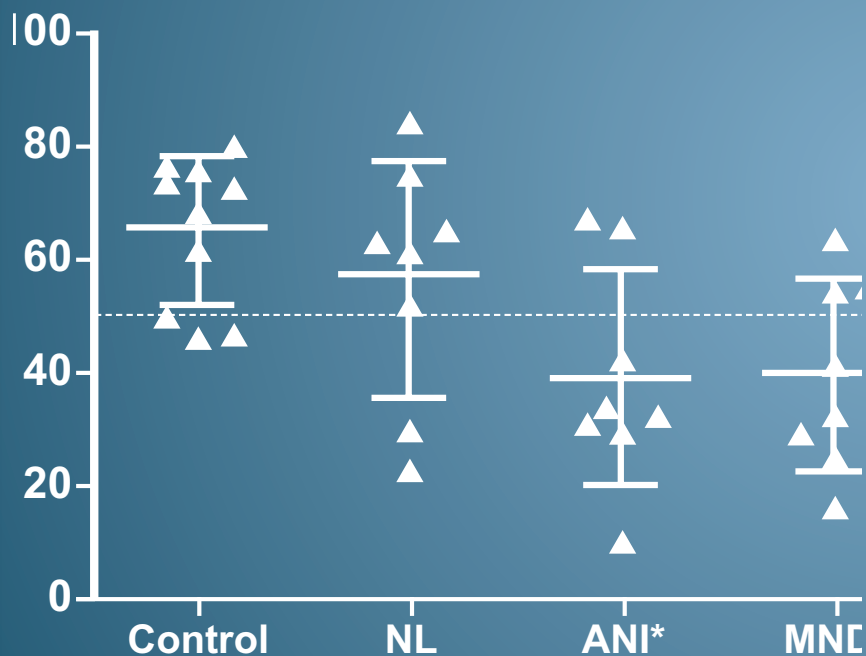
Assessment of function: HAND diagnoses based on self report (SR) and performance based (PB) data



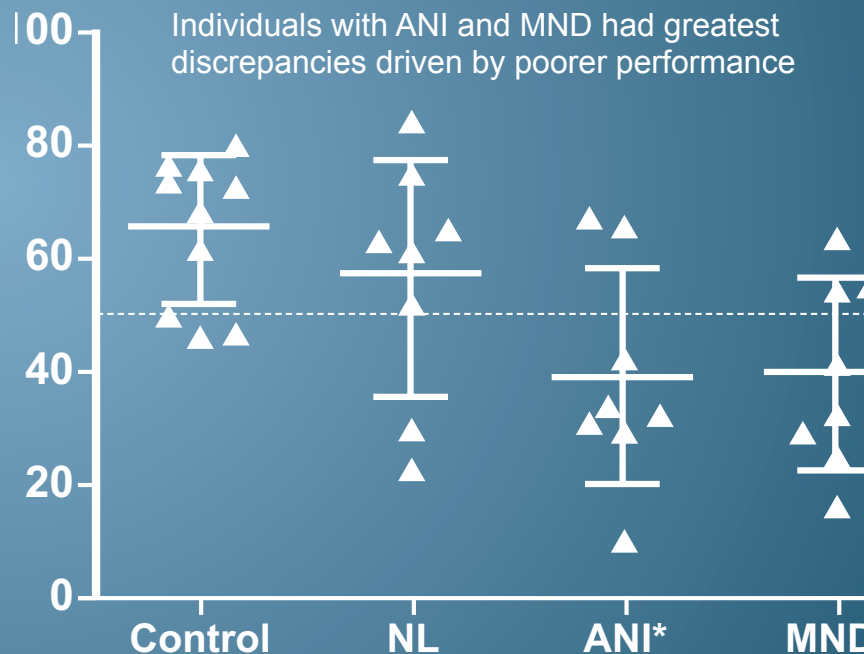
Blackstone, et al., JINS, 2012, 18: 79-88

ANI is associated with reduction in self-awareness of impairment

Performance on the NAB across diagnostic groups

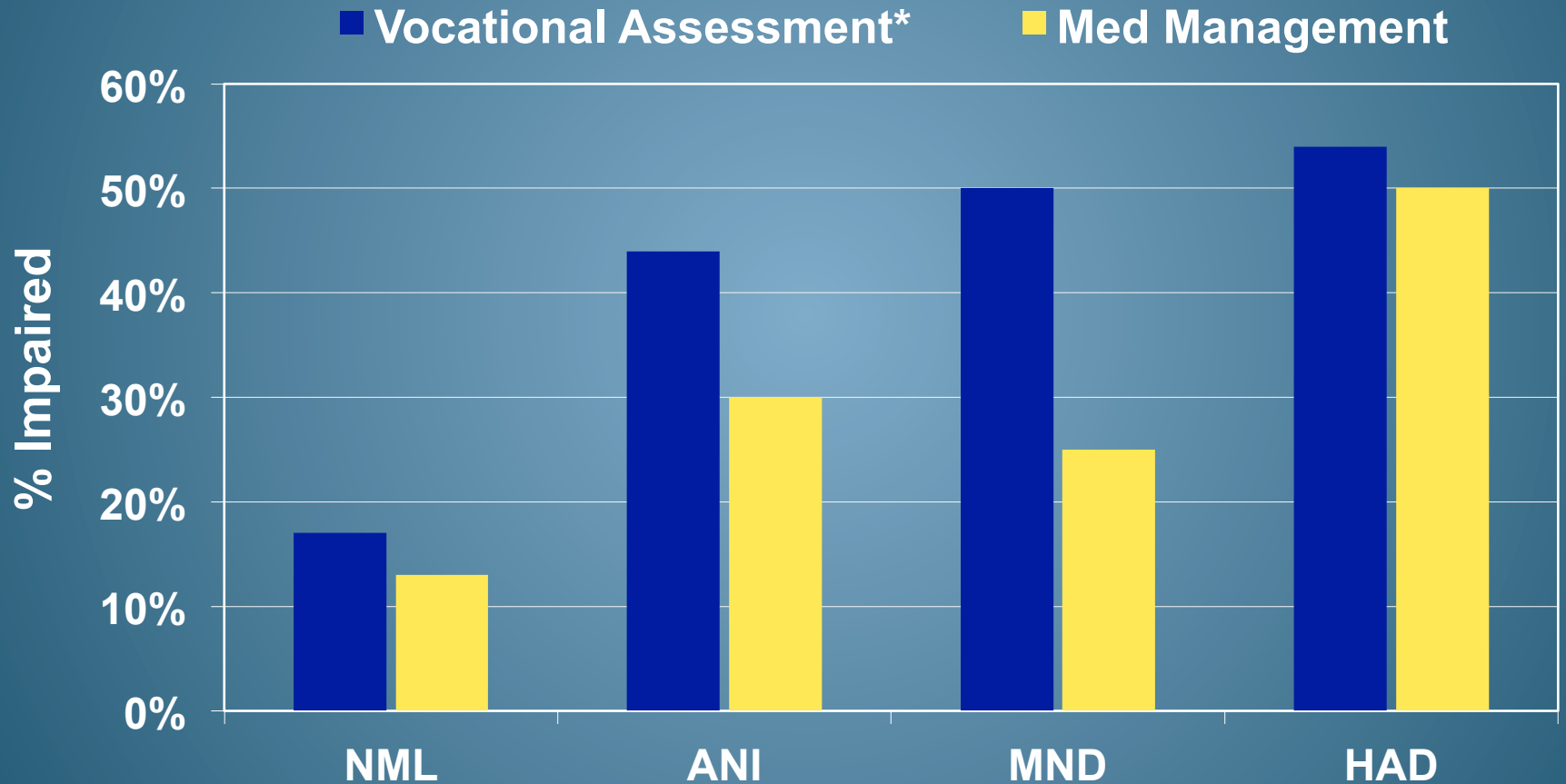


Discrepancy between performance and self-assessment of performance measured post-testing



Chiao, S, et al. (2013). *AIDS Res Hum Retroviruses*, Mar 20

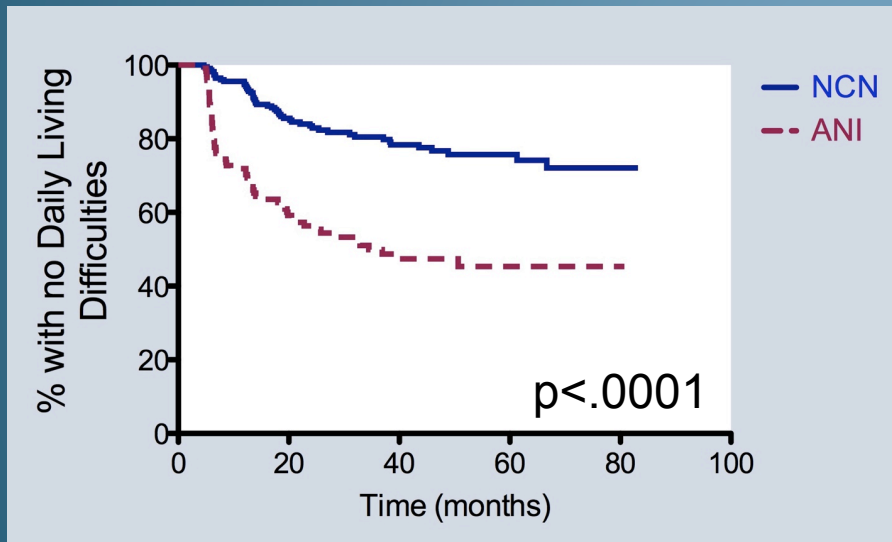
Performance-based Functional Impairment by HAND Diagnosis



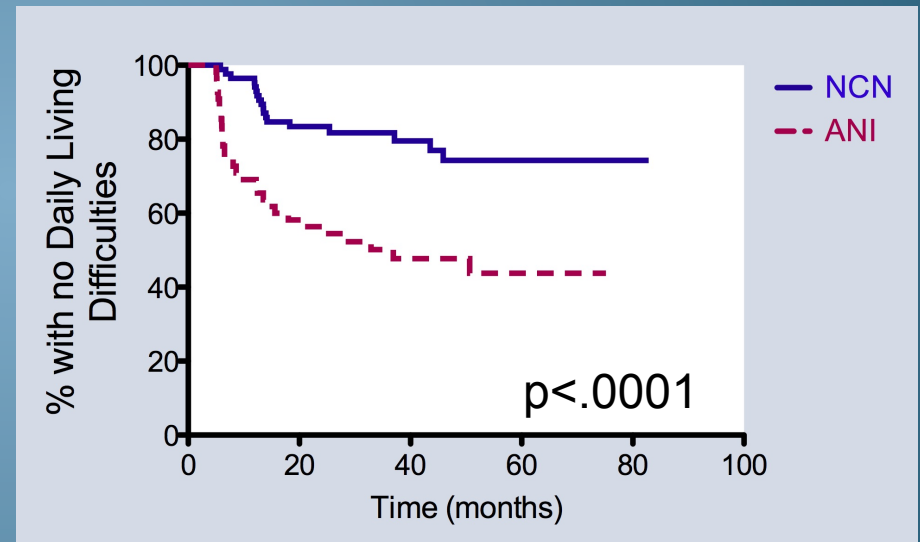
*Valpar Work Sample; CHARTER Data

ANI Increases Risk for Symptomatic HAND: Self-report or Performance-based

Total Sample



Virologically Suppressed



NML: n=226 Relative Risk: 3.02
 ANI: n=121 CI: 2.08, 4.42

NML: n=85 Relative Risk: 3.1
 ANI: n=55 CI: 1.7, 5.7

Grant I, et al., In Preparation

If we cannot treat HAND why bother diagnosing it? Why worry people?

- In general this seems somewhat nihilistic. Historically there were few conditions that Medicine diagnosed that had good treatments initially. Indeed, effective treatments are predicated on accurate diagnosis and systematic assembly of clinical data
- In our experience, discussing with patients that they may have cognitive challenges actually helps them understand why they may not have been “up to par” and opens avenues for dealing with cognitive compromise; and does not cause undue anxiety
- While it is true that ARV and non ARV pharmacological treatments have shown only modest benefit at best, even modest improvements may be very meaningful to patients
- Some preliminary evidence suggests cognitive training approaches may be helpful

ANI improves after 3 months of cognitive rehabilitation

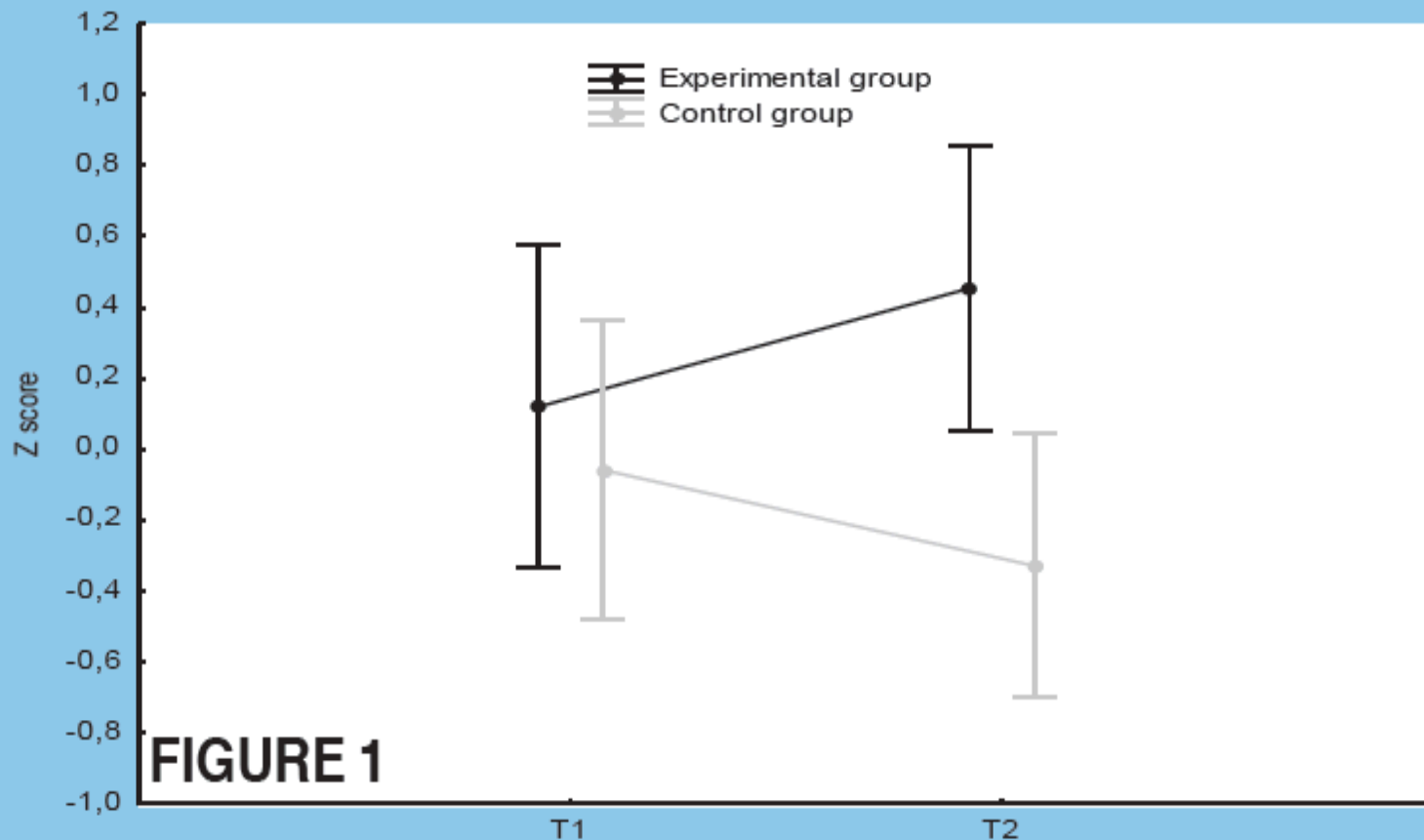
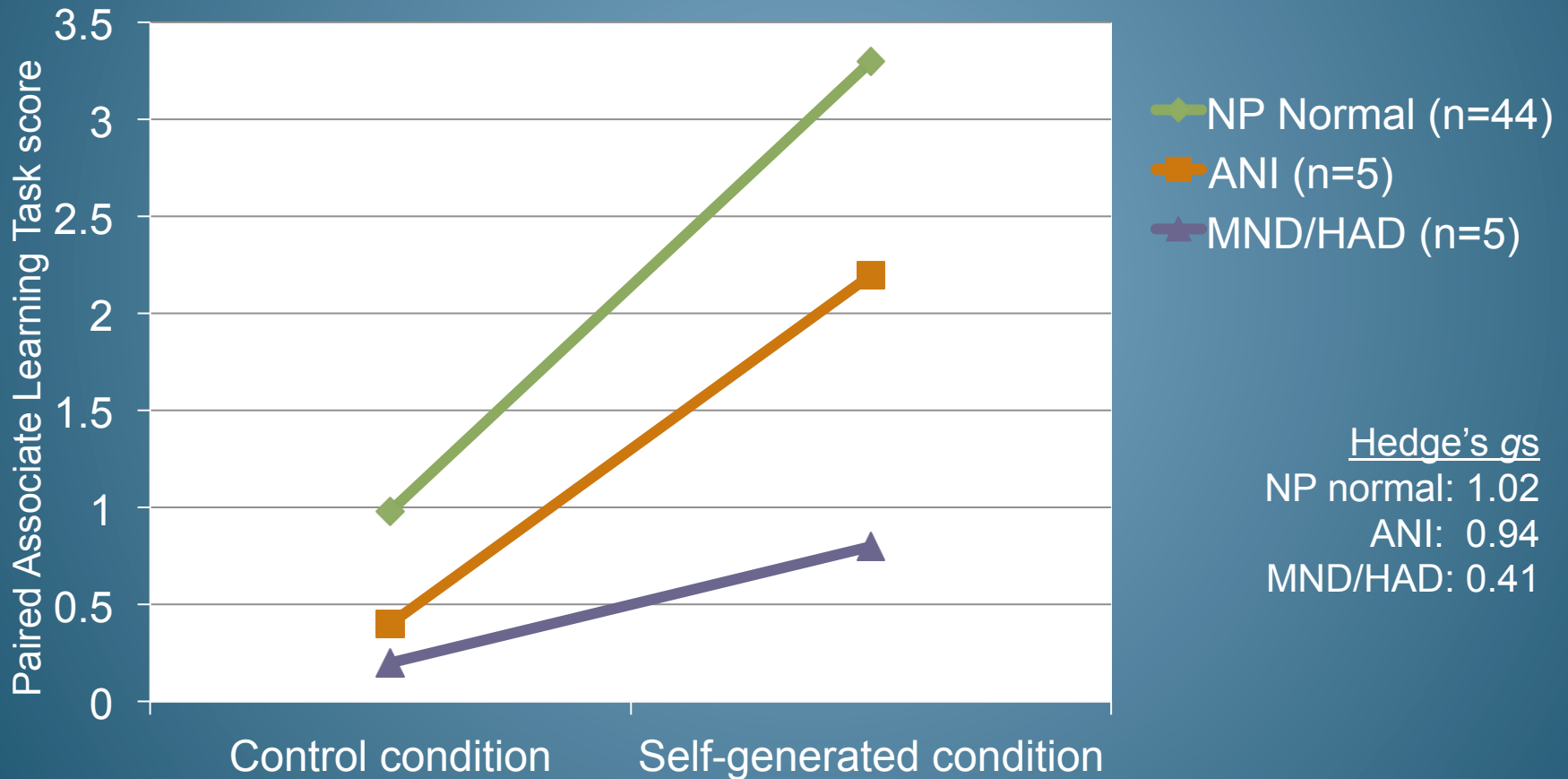


FIGURE 1

LEGEND: clinical evolution discordant between the two groups: the experimental group showed an improvement differential at T1, this improvement does not occur in the control group, which instead show a worsening of neurocognitive performance compared from T0 to T1.

Livelli, et al., CROI 2013

ANI more amenable to memory rehabilitation strategies than MND/HAD

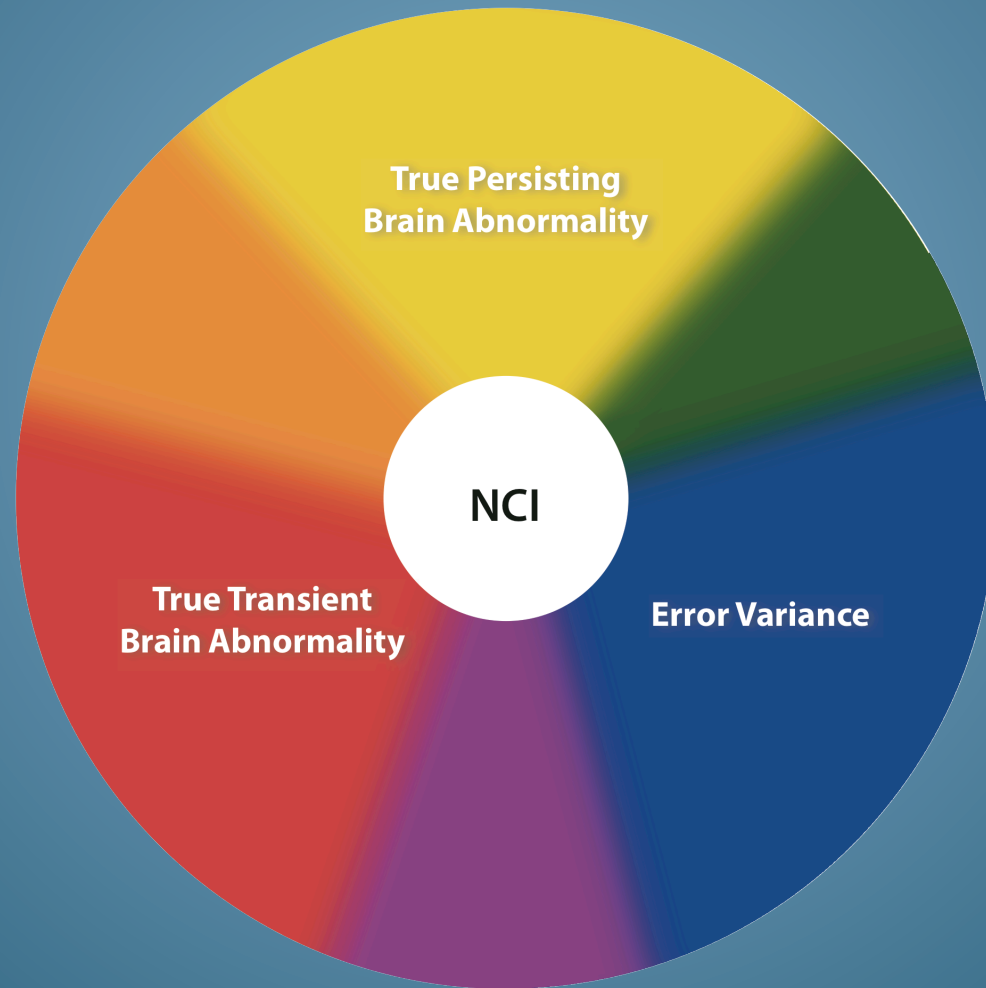


Woods SP : R01 MH73419

**If 15-20% of HIV uninfected persons
score mildly “impaired” on
Neurocognitive Testing, does it not mean
it is all a statistical artifact?**

Not necessarily!

Why might someone score in the neurocognitively impaired range?



Neurocognitive Impairment Reliability on Retesting

- We examined the test-retest reliability of neurocognitive impairment (NCI) among HIV- controls tested twice approximately one year apart
- If NCI diagnostic is random, then cross-classification of the diagnostic in test-retests should be consistent with random assignment (i.e., the 15-20 % impaired at time 2 should be a random sample and not typically be the same people as were impaired at time 1)
- Instead, we find very strong evidence that NCI diagnostic as used in HAND is informative and with substantial test-retest reliability

Stability of Impairment: HNRC Study HIV-Controls

| | Time 2 | | |
|--------------|----------|--------------|-------|
| Time 1 | Impaired | Not impaired | Total |
| Impaired | 13 | 8 | 21 |
| Not Impaired | 5 | 91 | 96 |
| Total | 18 | 99 | 117 |

- 117 HIV- controls
- Odds of impairment at time 2
 - If impaired at time 1: $13/8 = 1.625$
 - If not impaired at time 1: $5/91 = 0.055$
- OR = 29.6, 95% CI (8.94, 114.4), p-value < 0.001
- Cohen's kappa = 0.603 (substantial)

HNRC Data

Conclusions

- HAND can be reliably diagnosed. To avoid misclassifications, repeat assessment of initially impaired cases is advisable
- HAND is associated with worse everyday functioning, therefore has significance to the patient
- Converging evidence indicates HAND has neurobiological underpinnings, and may influence mortality
- Diagnosing MND based on self report only may underestimate its occurrence
- There are no reliable ARV or non ARV medications for HAND; however, if we assess for HAND systematically, particularly in clinical trials, new therapeutic insights may emerge
- The apparently high rate (15 – 20%) of NCI in HIV- controls does not mean it is a statistical artifact; for most HIV- people the NCI is a reliable finding, perhaps reflecting mild TBIs, developmental issues, etc.
- In HIV+ the rate of NCI is typically double that of HIV-. This indicates that there is an HIV effect, over and above background events

Acknowledgment

- We would like to thank all of the volunteers and investigators who participated in the studies listed below:

| Grant | Agency |
|------------------------------|------------|
| MH62512 | NIMH |
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| MH83506 | NIMH |
| MH73419 | NIMH |
| MH78748 | NIMH |
| Hansa 2013 meeting | Abvie |

**Thank you
for your attention**

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