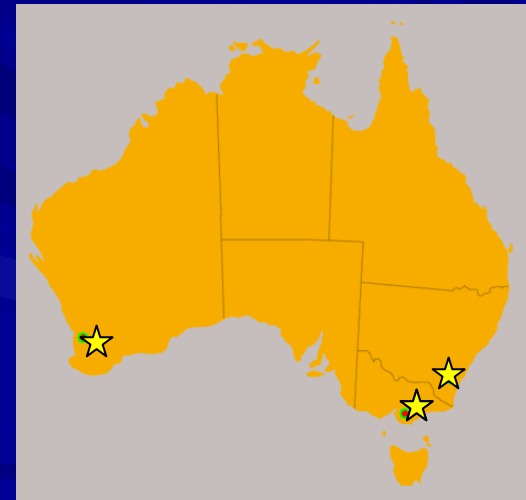
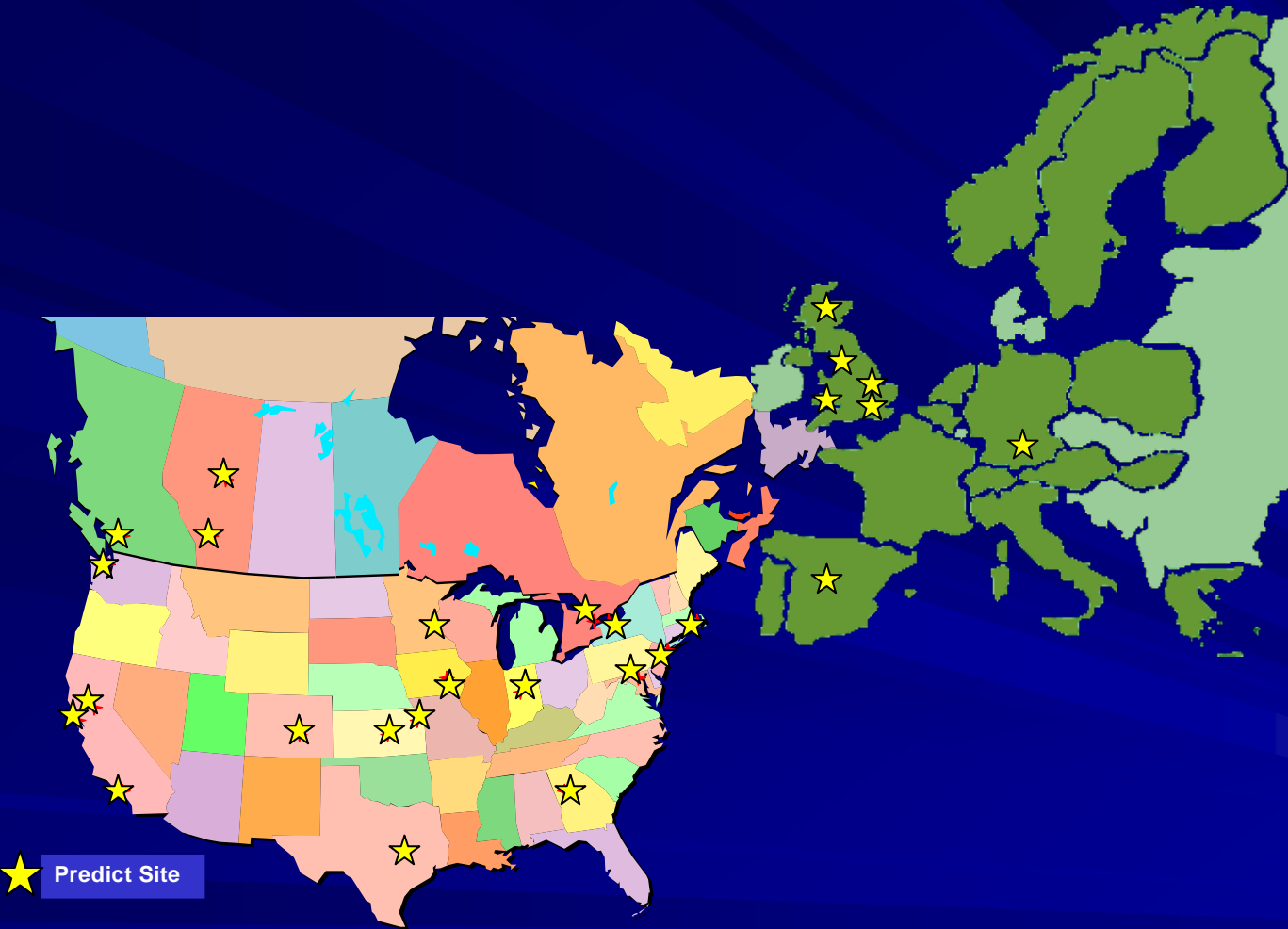


Prediagnostic Stages of HD: Recent Findings



Jane S. Paulsen
The University of Iowa
EHDN Meeting
September 16, 2006

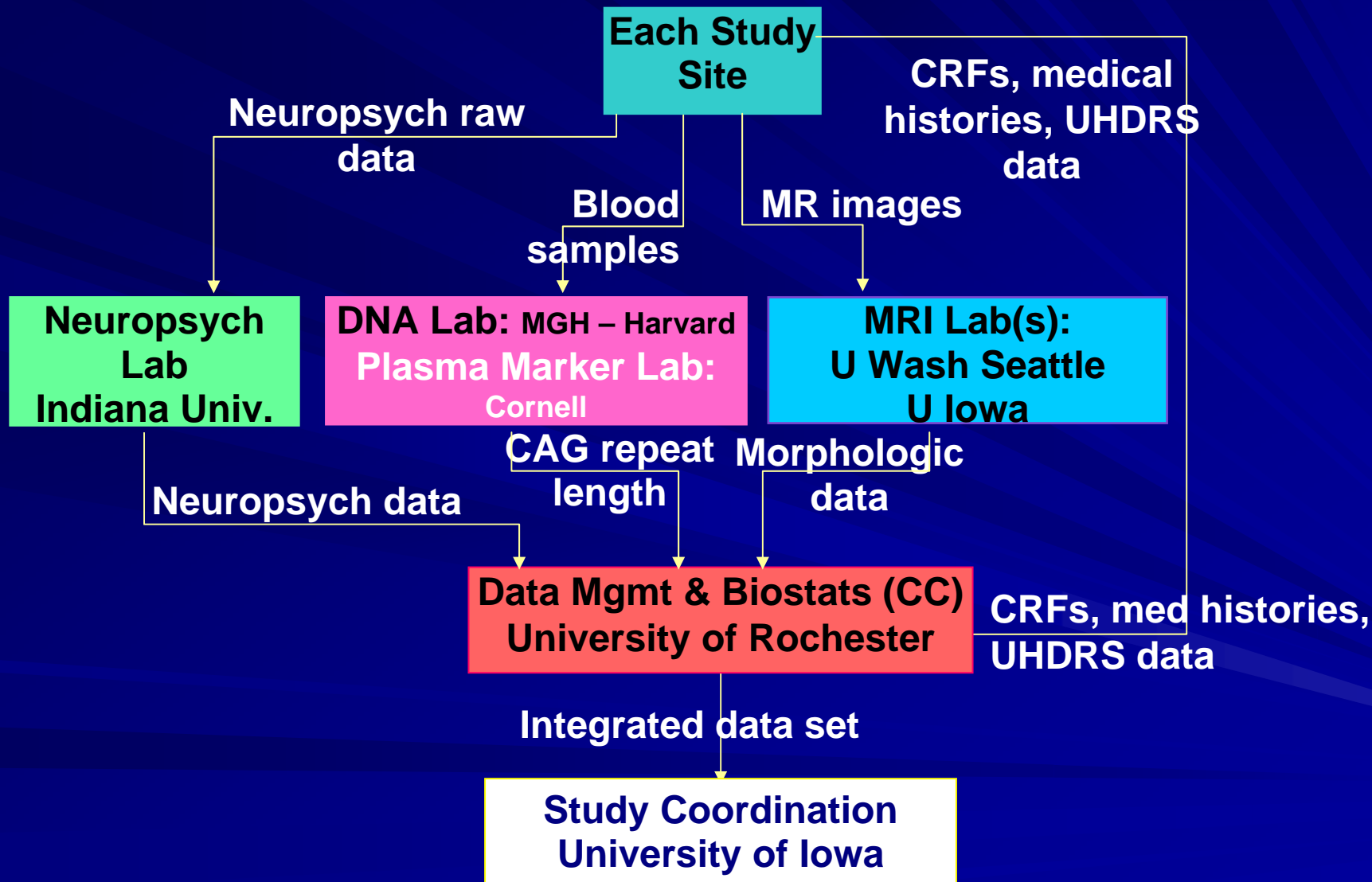
PREDICT-HD SITES



PREDICT-HD Visits

- One visit every year; longitudinal prospective study
 - Motor exam
 - Cognitive evaluation
 - Psychiatric ratings
 - Functional evaluation
- History
- UHDRS
- Psychiatric and Psychosocial Ratings
 - Speed
- Cognitive tests
 - Timing and Sequencing
 - Learning and memory
 - Executive Skills
 - Visual and Emotional Identification
- Blood draw for DNA/marker analyses
- Brain scan

Predict HD Data flow



Predict-HD Recent Findings

- “Estimated Onset” formula which/how to use?
- Phenoconversion what is it and why use it?
- Cognitive markers can we shorten that (*!?) battery?
- Psychiatric Associations why bother with behavior?
- Imaging
 - Striatal Imaging
 - Extrastriatal Imaging
 - fMRI
 - DTI
 - Automated Morphometry

“Langbehn et al” Formula

N = 2,913 with HD mutation
2,298 affected
615 presymptomatic

Fit by nonlinear parametric survival equation.

$$\frac{1}{1 + e^{\frac{\pi (-b_0 - e^{b_1 - b_2 x + t})}{\sqrt{3} \sqrt{e^{s_1 - s_2 x + s_0}}}}}$$

x = CAG length, t = Age, {b₀, b₁, b₂, s₀, s₁, s₂} = constants

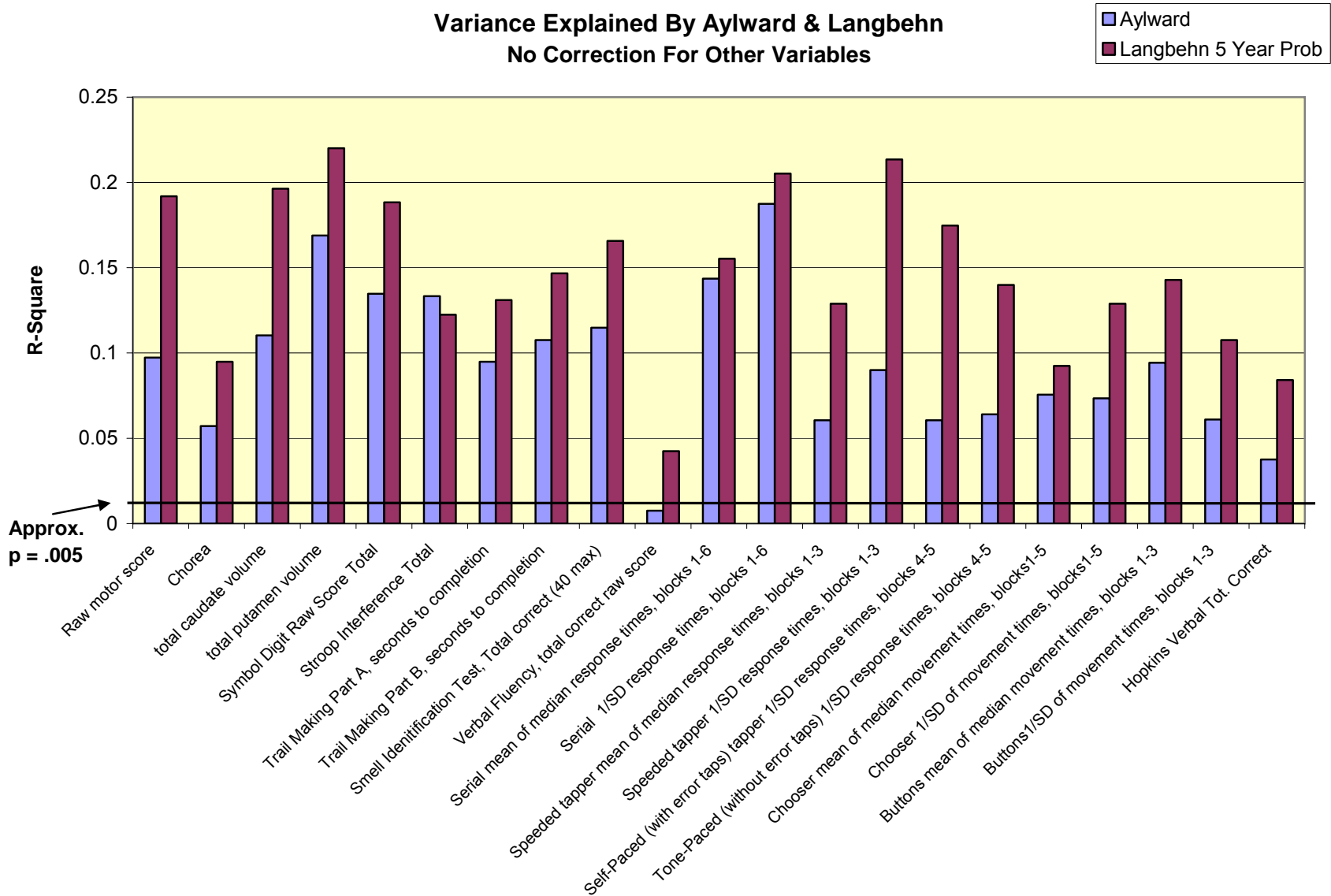
- Langbehn, D., Brinkman, R., Falush, D., Paulsen, J. S., Hayden, M. ***Clinical Genetics***, 65, 267-277, 2004.

Aylward et al Formula

- Estimated Age of Onset =
 $-0.81 * \text{CAG} + 0.51 * (\text{parent's onset age}) + 54.87$
- Estimated Years to onset =
Estimated Age of Onset – Current Age
 - Based on **50** symptomatic patients
 - Linear Regression; simple to compute
- Aylward EH, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt, J. *Arch Neurol*, 53: 1293-1296, 1996

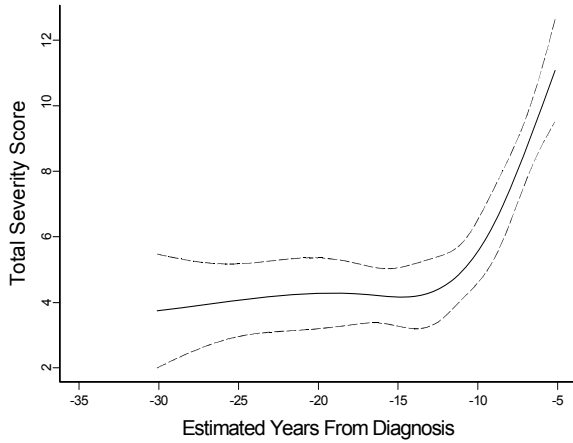
Linear Correlations With Baseline Data

Variance Explained By Aylward & Langbehn
No Correction For Other Variables

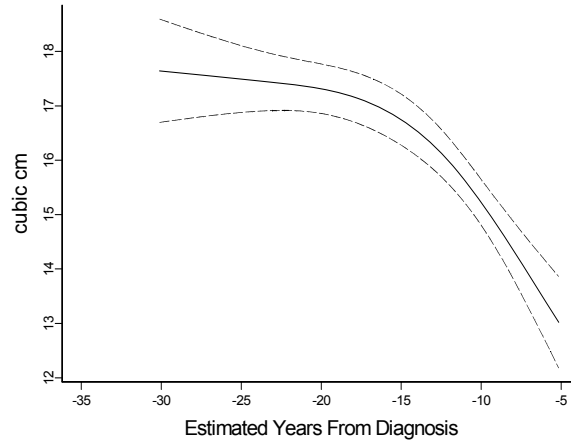


Baseline Curves

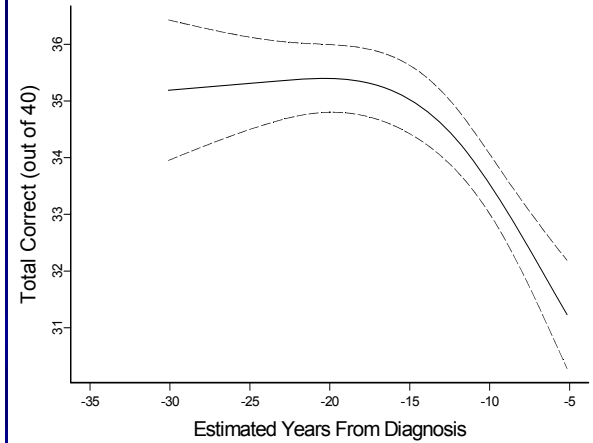
Motor Exam Score



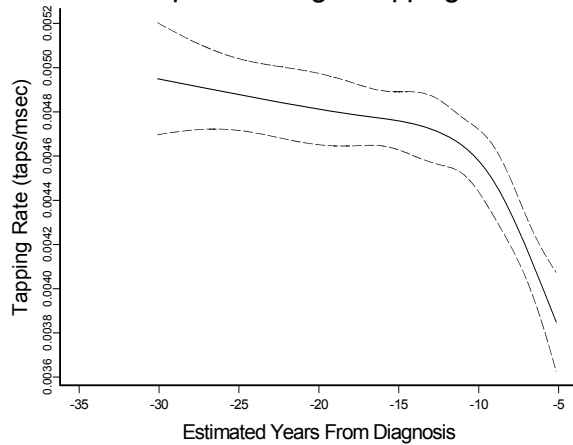
Striatal Volume



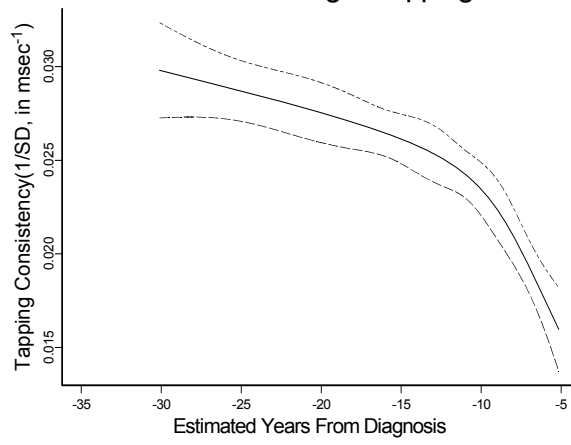
Odor Identification



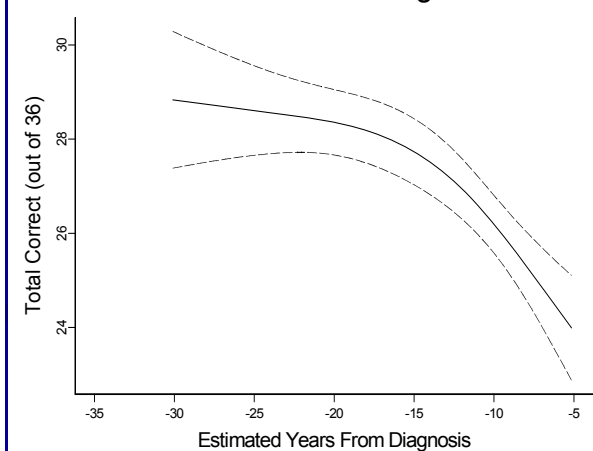
Speeded Finger Tapping



Self-Timed Finger Tapping



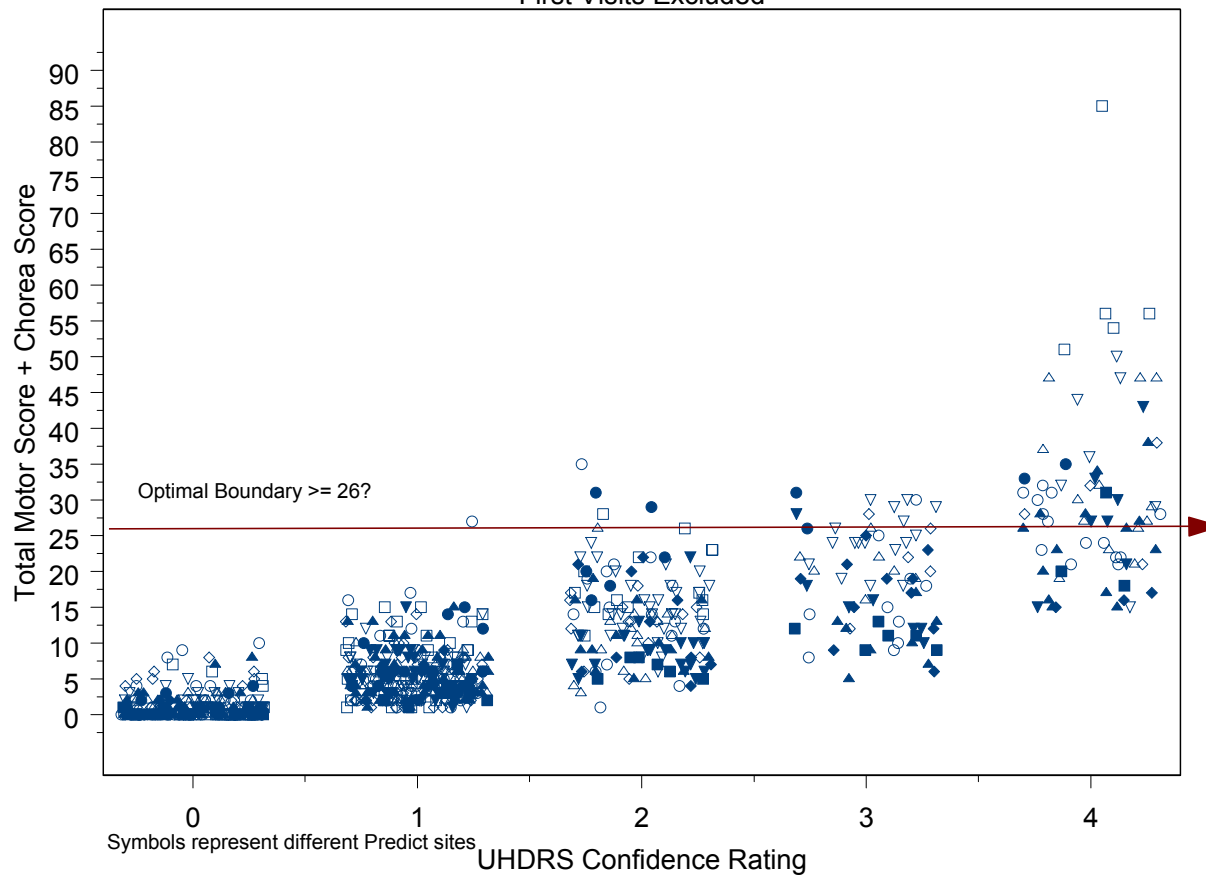
Word List Learning



Average Rater Call HD "4" at Total Motor + Chorea = 26

Motor + Chorea Scores Versus UHDRS Confidence In 4 06 Data Cut

First Visits Excluded



TMS 26 vs UHDRS 17 New Diagnoses

	TMS 26 No Dx	TMS 26 Dx	Total
UHDRS 17 No Dx	397	11	408
UHDRS 17 Dx	20	21	41
Total	417	32	449

Note: Excludes cases without return visits

UHDRS Item 80

	UHDRS 80 No Dx	UHDRS 80 Dx	Total
UHDRS 17 No Dx	628	19	647
UHDRS 17 Dx	2	52	54
Total	630	71	701

Is UHDRS 80 More Valid?

- Logistic Regression, Prob5yr adds to prediction of UHDRS 80 dx from UHDRS 17 dx.

	Effect	Estimate	Error	DF	t Value	Pr > t
	Intercept	-5.2396	0.5231	752	-10.02	<.0001
UHDRS17	four	6.9333	0.7814	752	8.87	<.0001
	prob5yr	5.7682	1.2067	752	4.78	<.0001

- Prob5yr does not add to prediction of UHDRS 17 from UHDRS 80

	Effect	Estimate	Error	DF	t Value	Pr > t
	Intercept	-6.1216	0.8144	304.9	-7.52	<.0001
	uhdrs80	7.0969	0.8317	752	8.53	<.0001
	prob5yr	0.1830	1.6625	187.9	0.11	0.9125

Association with Validators

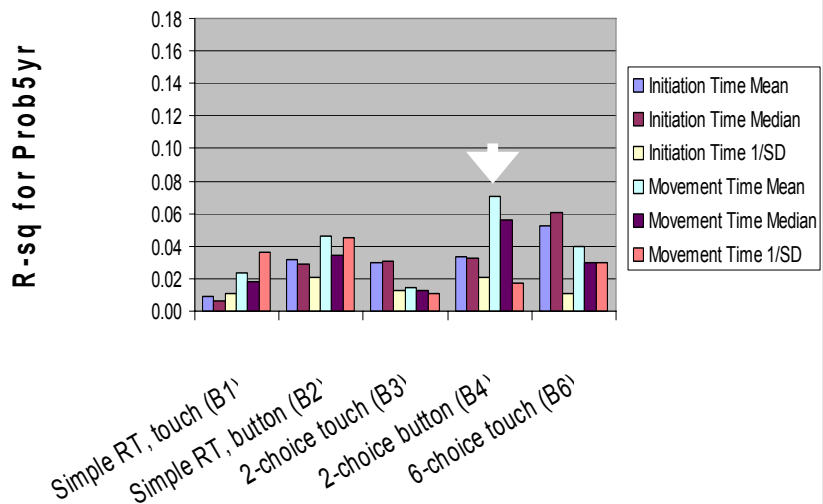
t-scores

Diagnosis	prob5yr	baseline striatum	baseline symbol digit
Motor score + chorea > 26	6.41	3.55	4.82
Uhdrs 17	6.01	2.91	6.20
Uhdrs 80	7.64	3.80	6.26

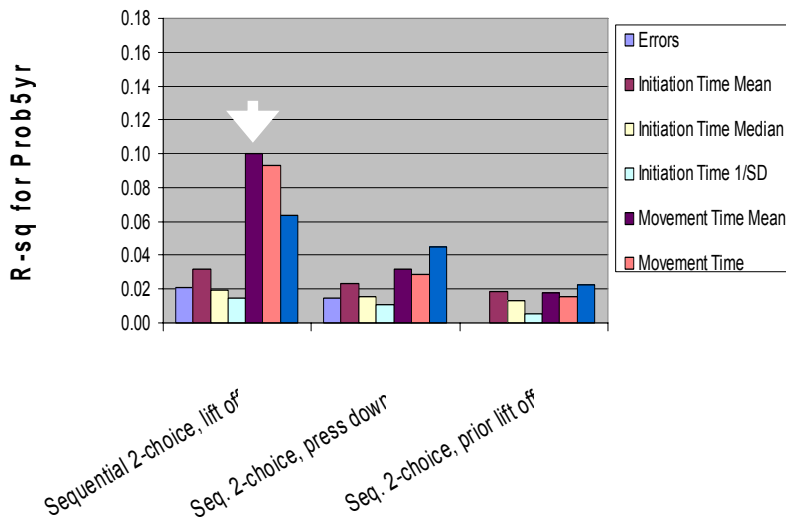
446 subjects at follow up visits at 789 follow-up visits
(177 subjects at 390 visits for striatum)

Interpretation complicated a bit by different frequencies of diagnosis

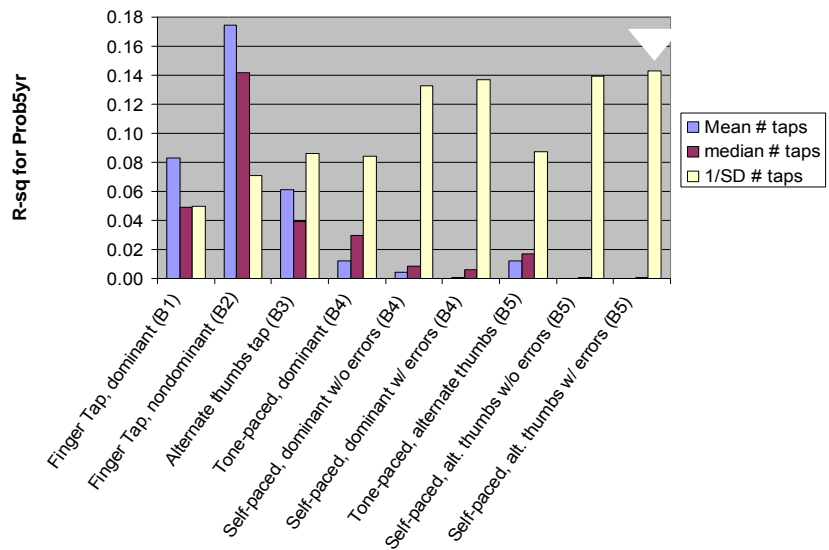
Chooser v. Prob5yr



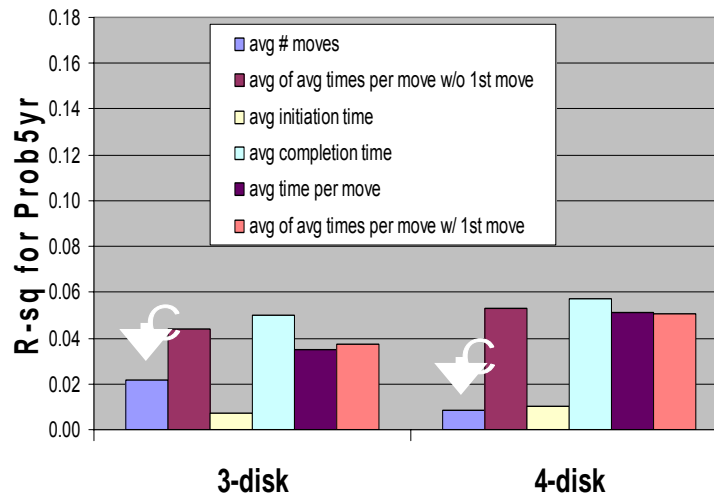
Buttons v. Prob5yr



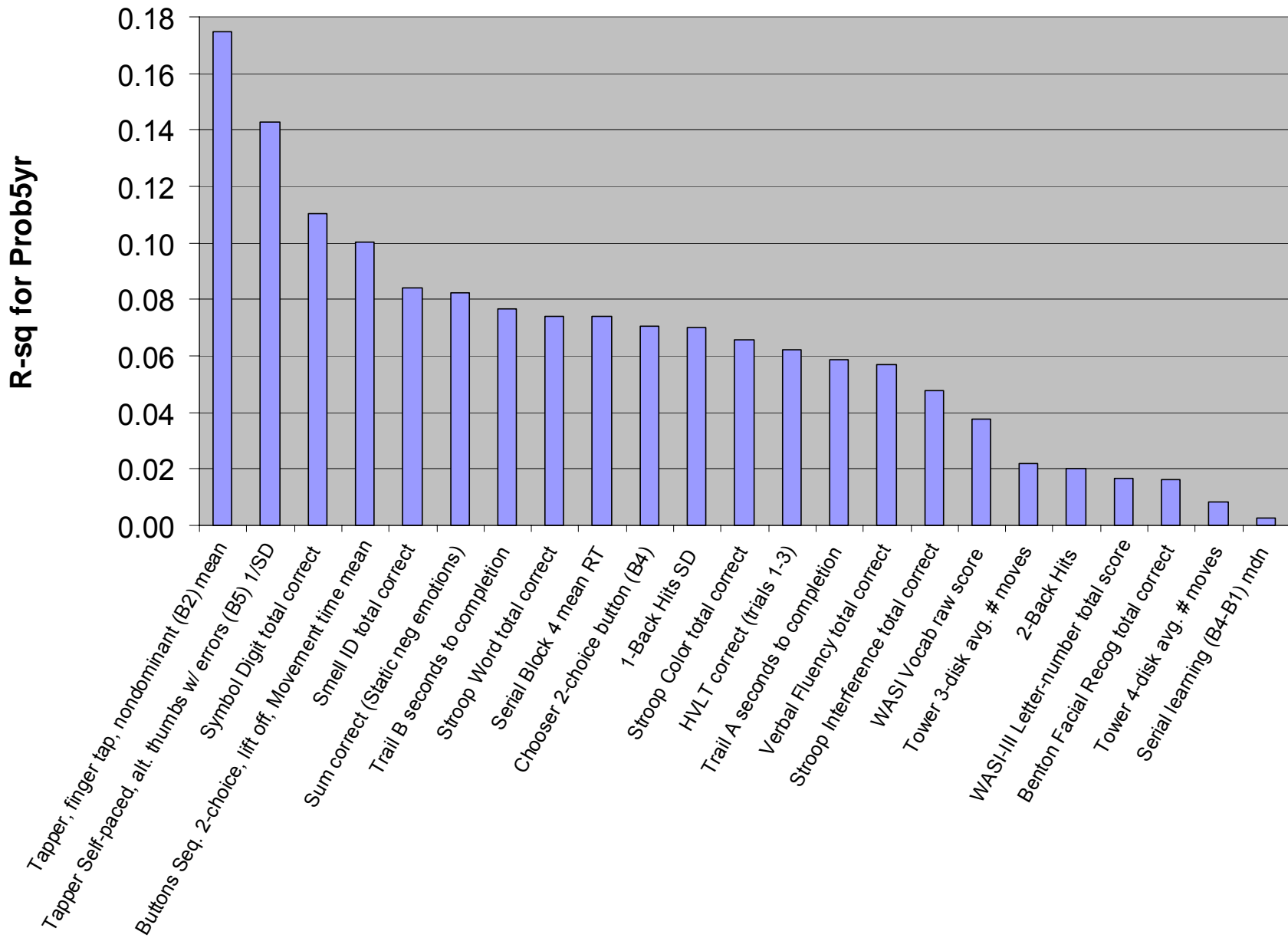
Tapper Inter-tap Intervals



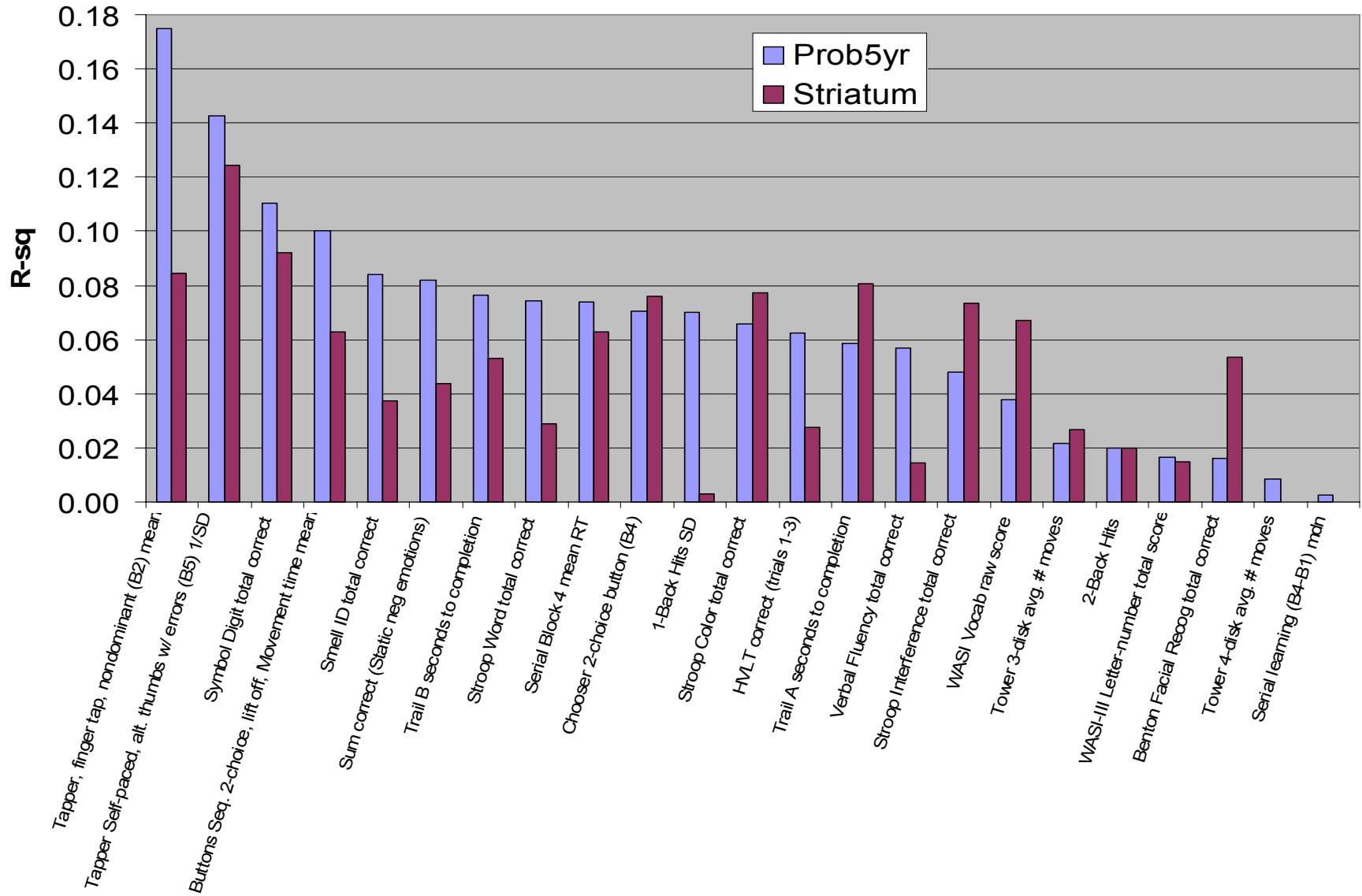
Tower v. Prob5yr



Prob5yr R-sq Ranks



Prob5yr & Striatum R-sq Ranks



Relationships of psychiatric measures with motor scores

- SCL-90 PSDI related to change in Total Motor score ($p=.03$)
- Total score on LES related to change in Total Motor score ($p=.03$)
- UHDRS total behavioral score **comp** related to baseline and change in Total Motor score ($p=.03$)
- FrSBe part and **comp** related to baseline Total Motor score and FrSB3 **comp** related to change in Total Motor score ($p=.01$)

Relationships of psychiatric measures with cognitive scores

- Cognition (p-values, controlling for age, gender, educ, anart)

	FrSBe p	FrSBe c	BDI-II	GSI p	UHDRS	LES	PSS
Stroop Color	.001						
Stroop Word	.003						
Stroop Interf		.001			.02		
Symbol Digit		.002		.05	.05		
Verb Fluency		.02	.02				
TMTA			.001	.05		.03	
TMTB			.001				.002

Relationships of psychiatric measures with genetic and brain measures

■ Probability of onset

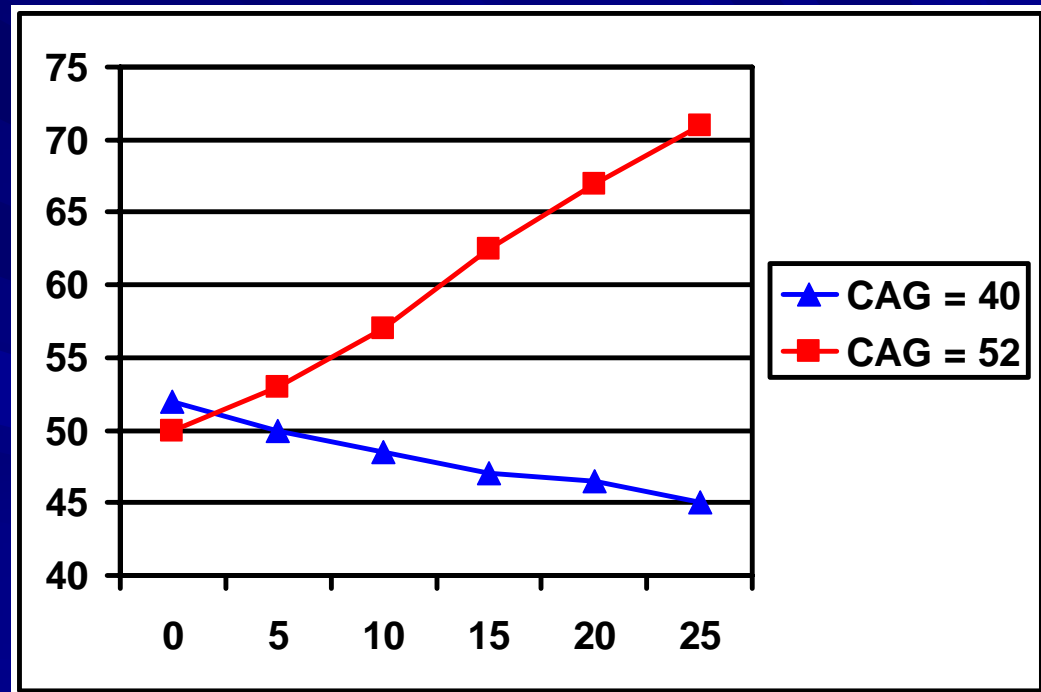
- FrSBe **companion** related to prob of onset ($p=.008$)
- BDI-II related to prob of onset ($p=.004$)
- LES related to prob of onset ($p=.02$)

■ Striatal volumes

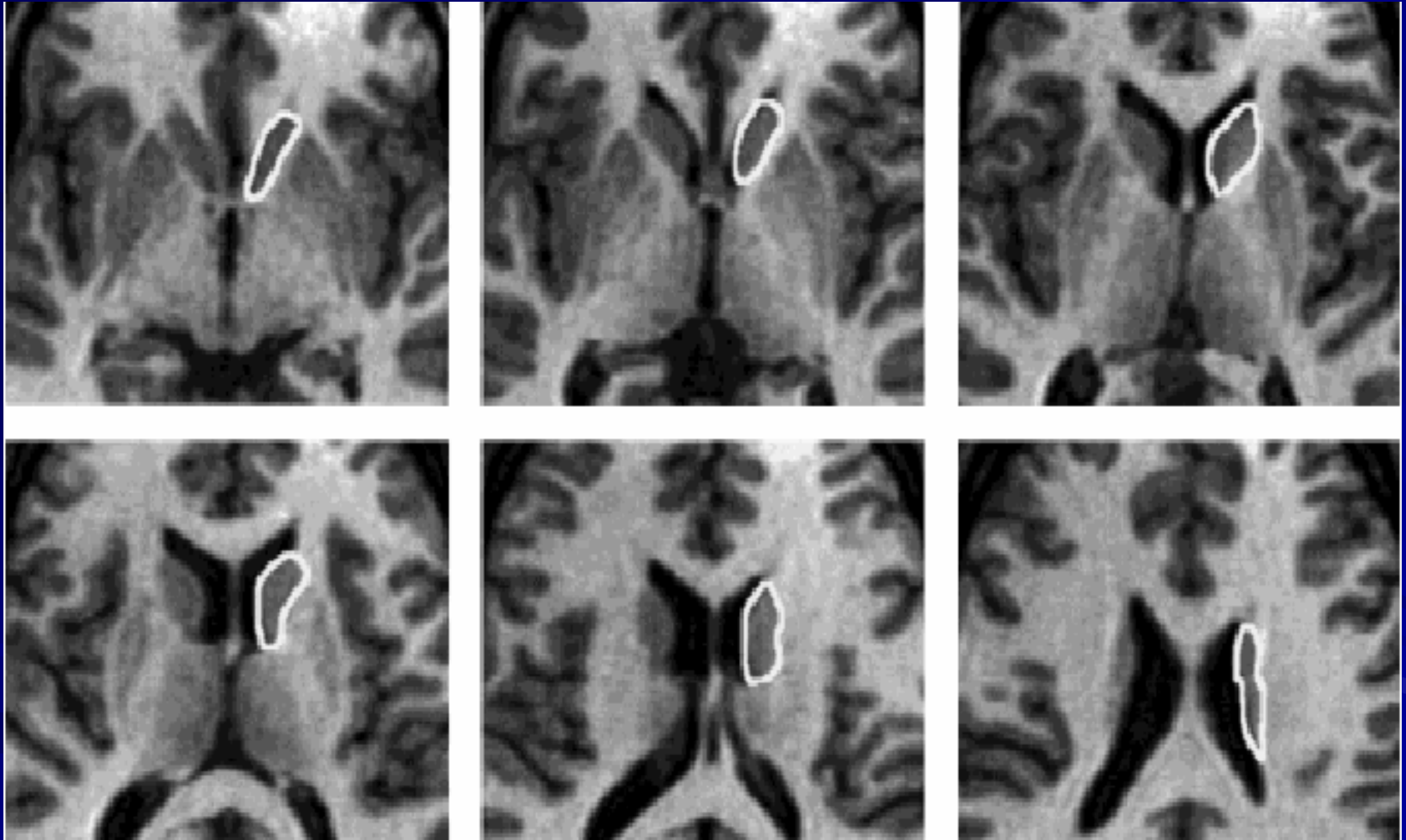
- PSS related to striatum ($p=.02$)
- SCOPI part related to striatum ($p=.01$)
- SCOPI **comp** related to striatum ($p=.03$)

Relationships with other markers of disease ...

- Time since predictive testing
 - If gene expanded, then psychiatric scores decrease with time since genetic testing
 - But longer CAG lengths (e.g., ≥ 52) moderate this effect
 - BDI-II, FrSBe, PSDI of SCL90R, LES, UHDRS

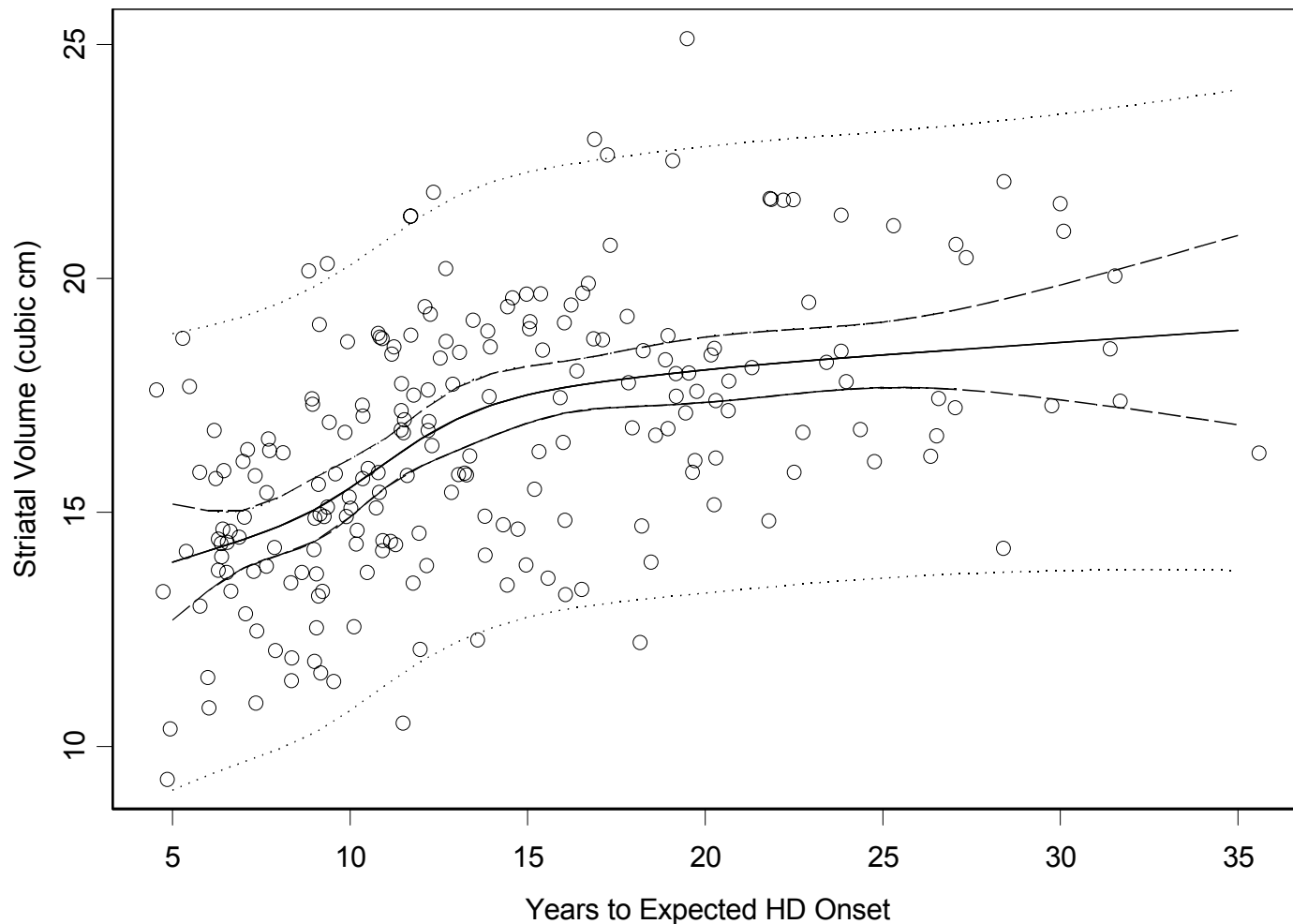


Quantification of Caudate Volumes: Regions of Interest



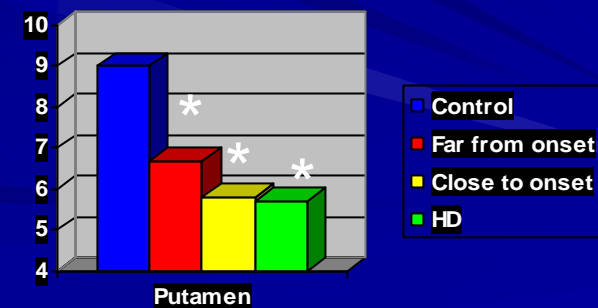
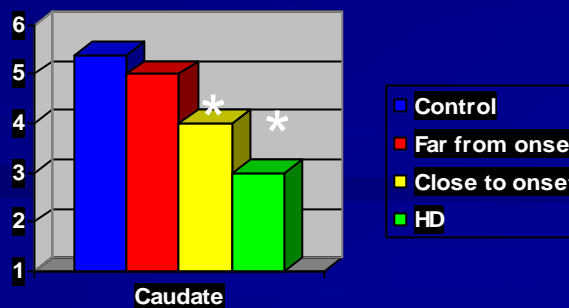
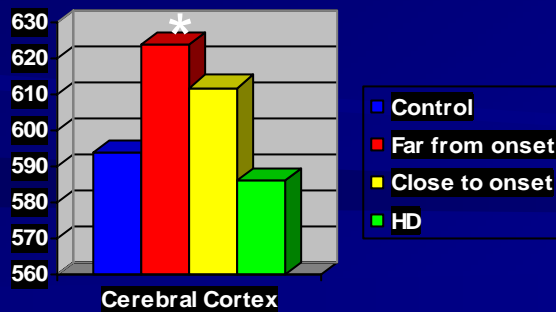
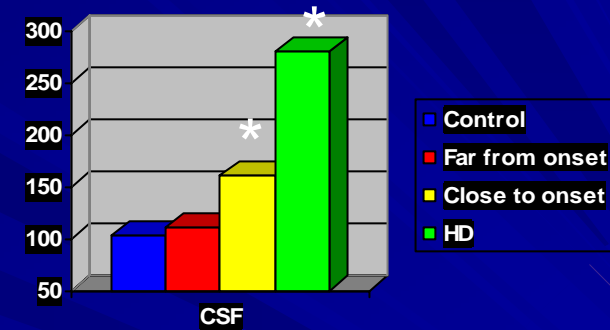
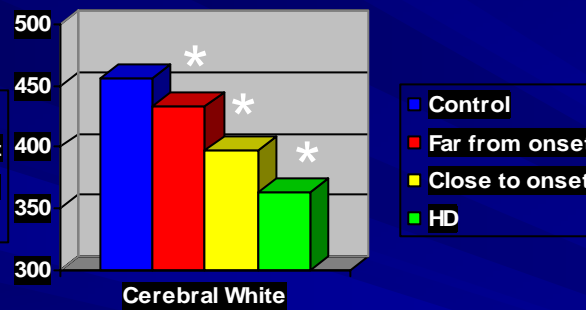
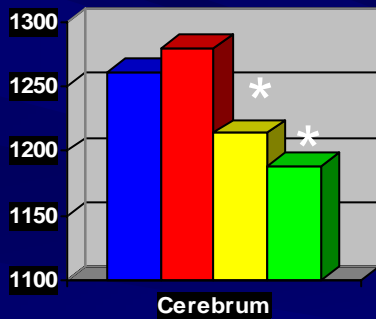
--Aylward et al Neurology 2004

Estimated Onset and Striatal Volumes from Predict-HD

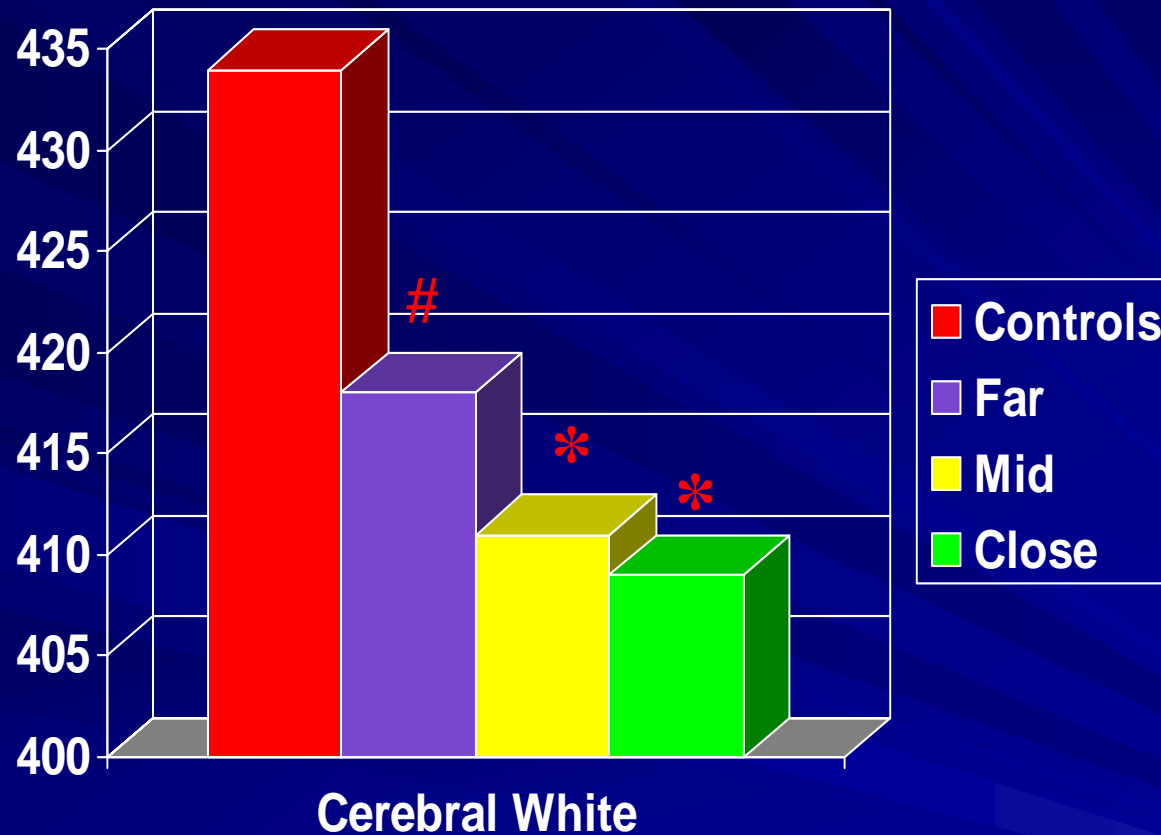


Abnormal Brain Morphology in PreHD

Using MANCOVA, controlling for age, sex and total brain tissue volume.



* Different than controls, $p < 0.05$



*MANCOVA $F = 7.13$ $p = 0.0002$

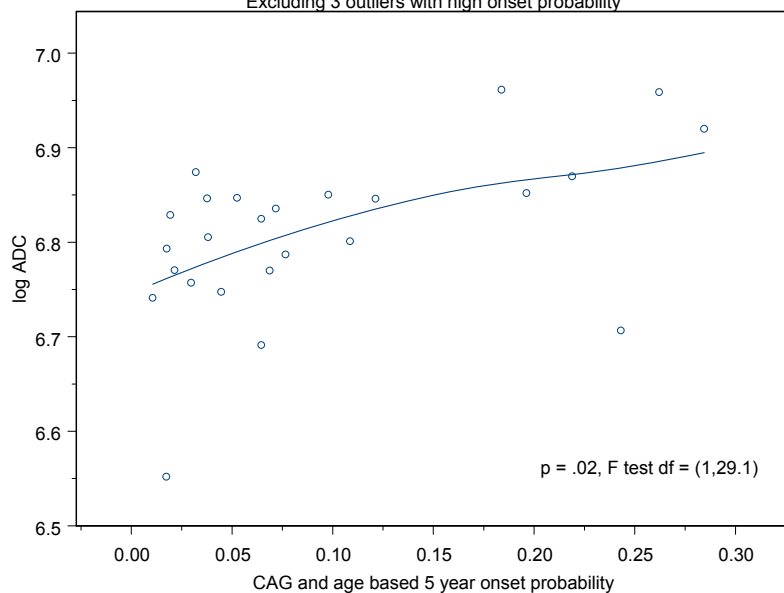
*Results of least square means analysis, $p < 0.05$

#Results of least square means analysis, $p = 0.08$

ADC Plots in Gene Expanded Predict HD Participants

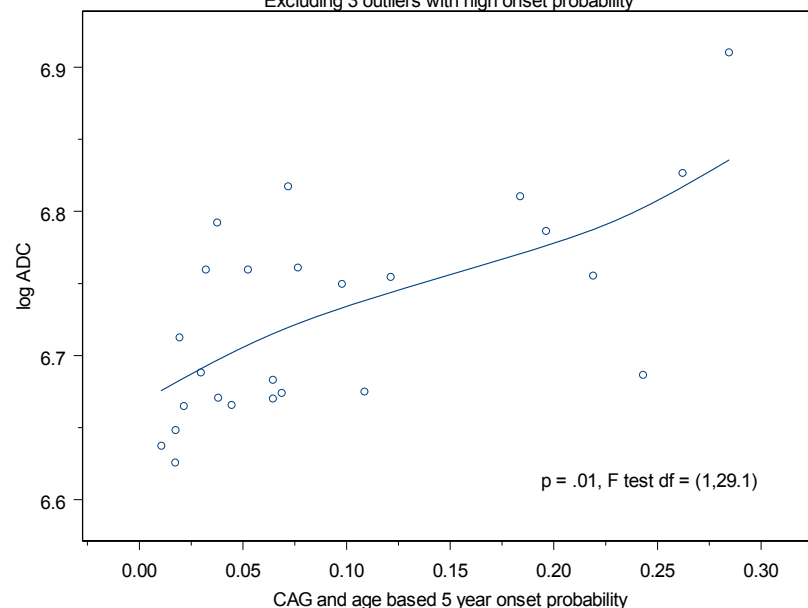
Parietal Log ADC by 5 year onset probability

Excluding 3 outliers with high onset probability



Temporal Log ADC by 5 year onset probability

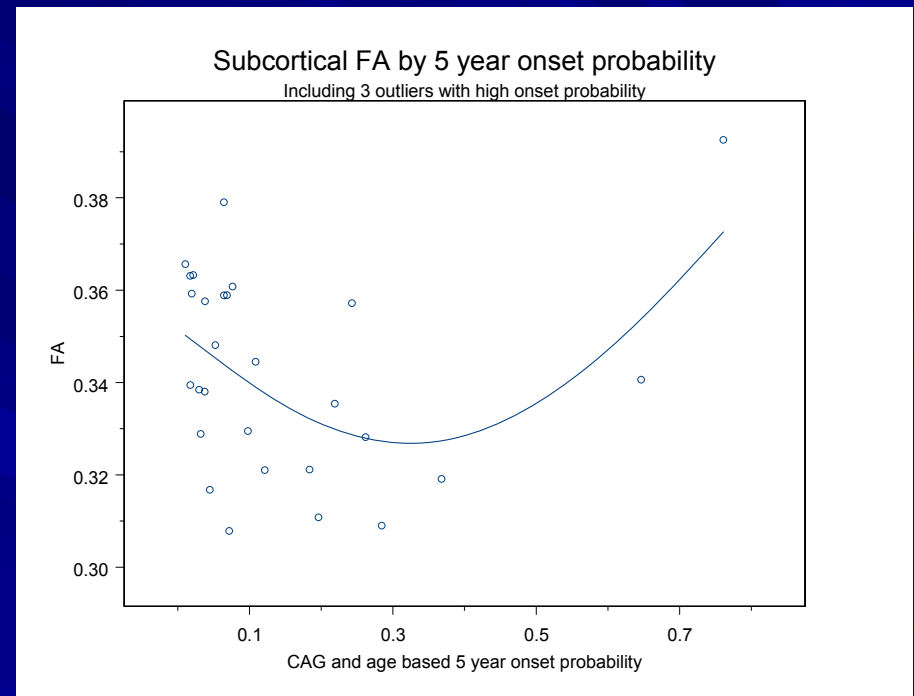
Excluding 3 outliers with high onset probability



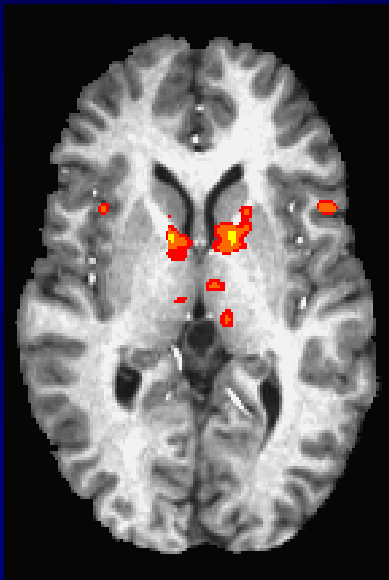
Apparent diffusion coefficient

FA Results

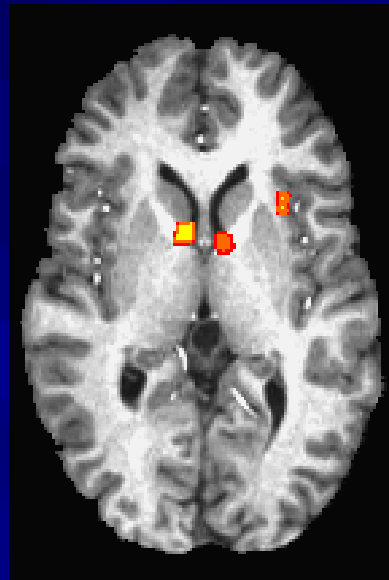
- Overall trend is reduced FA and increased ADC for subjects with less than a 30% likelihood of developing symptomatic HD within 5 years
- More subjects needed to better understand changes in those more likely to develop into symptomatic subjects



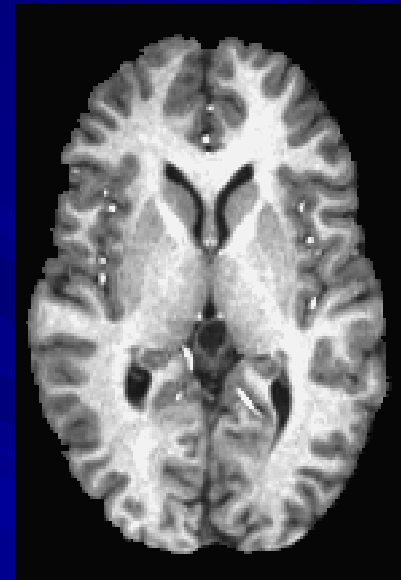
fMRI Studies in Presymptomatic HD



Control



Far HD



Close HD

Paulsen et al. 2005
Journal of Neuroradiology

Acknowledgements

- NINDS
- High Q Foundation
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