

Global and Regional Brain Morphology in Subjects with Huntington's Disease Prior to Diagnosis

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Introduction:

Huntington's Disease (HD) is an autosomal dominant degenerative brain disorder.

The discovery of the CAG repeat expansion in the huntingtin gene has allowed a unique opportunity to study subjects who undergo predictive testing for presence of the expansion.

The length of the CAG repeat expansion is highly correlated with age of diagnosis, making possible the prediction of the estimated diagnosis for persons with the expansion but no symptoms (referred to as preHD).

The PREDICT-HD study is an international 32-site study of preHD.

The aim of this study was to evaluate global and regional brain structures in preHD. By dividing participants into prognostic groups based on CAG repeat length and current age, we compared brain abnormalities across ranges disease according to estimated proximity to diagnosis.

Methods:

The sample consists of 652 participants: 146 gene-non-expanded and 506 gene-expanded participants.

Gene-expanded participants are divided into three prognostic group:

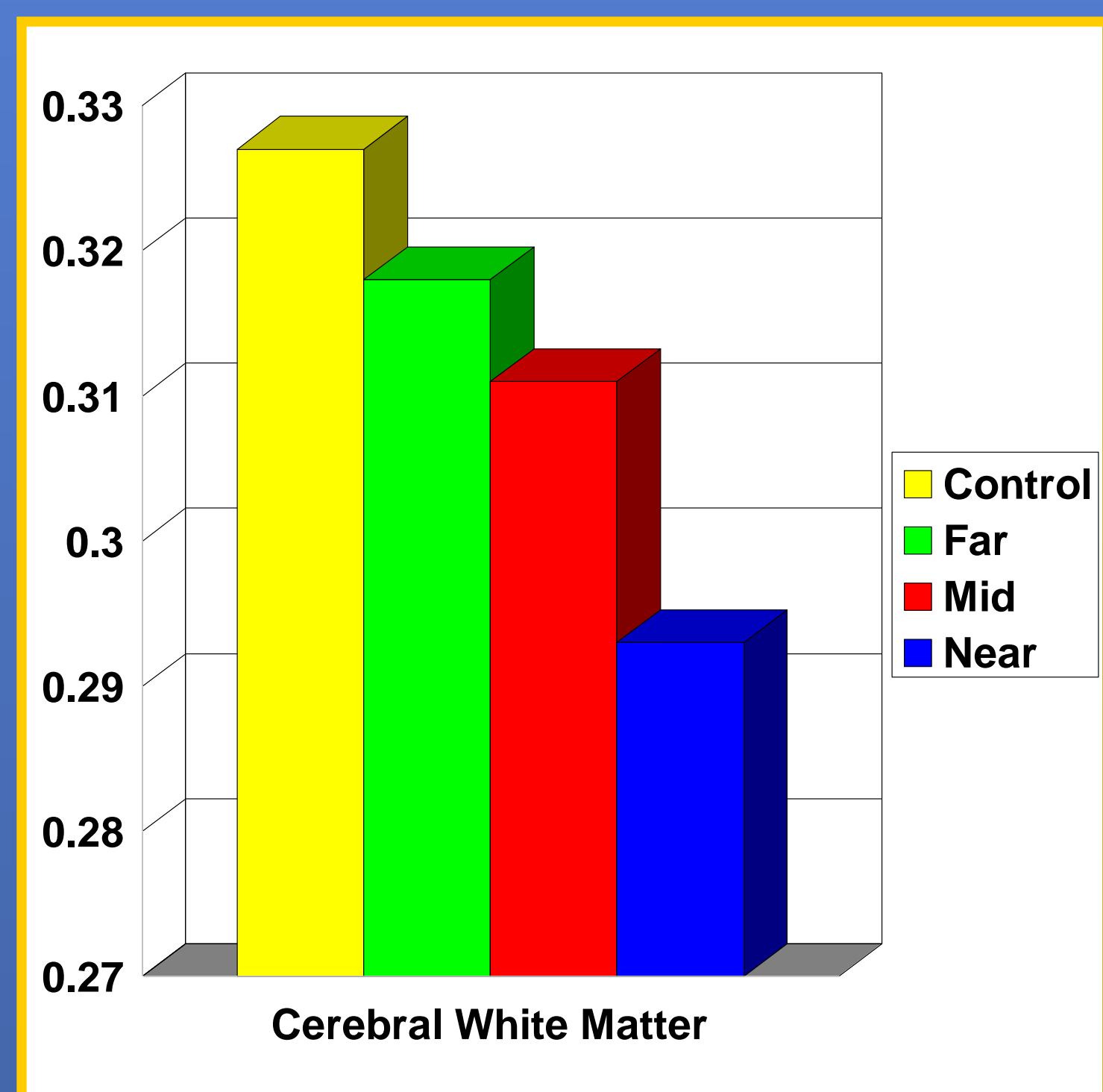
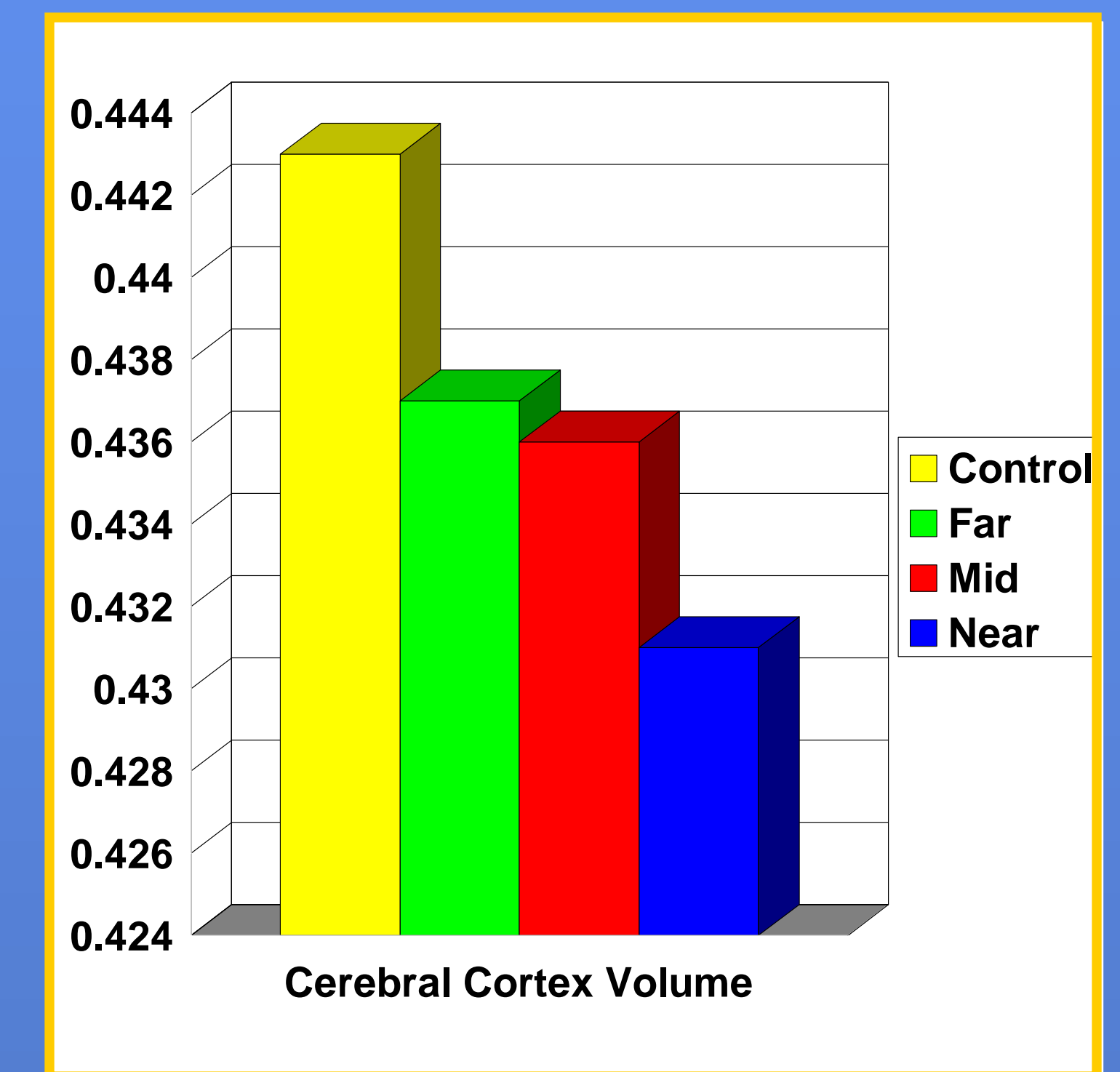
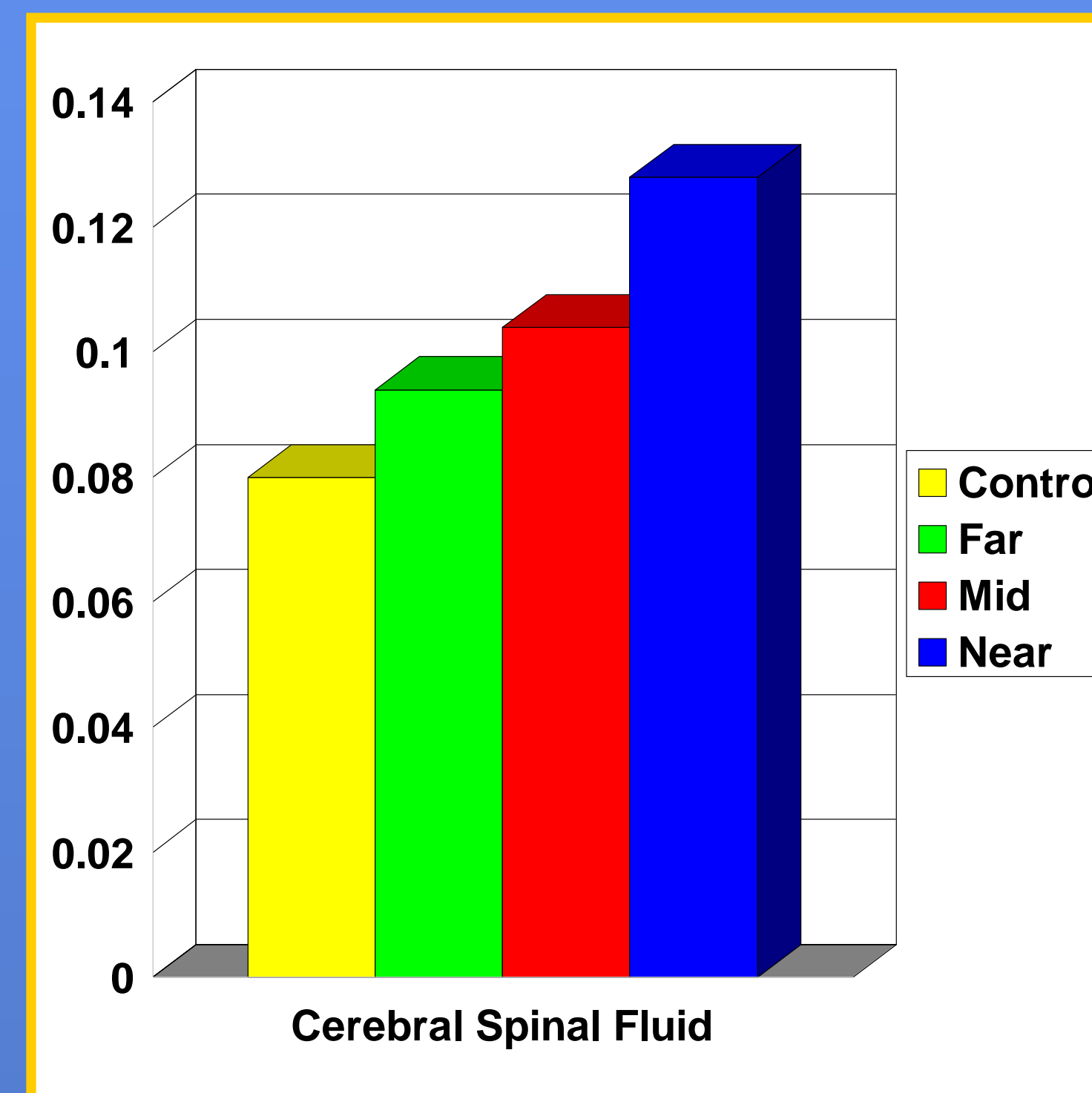
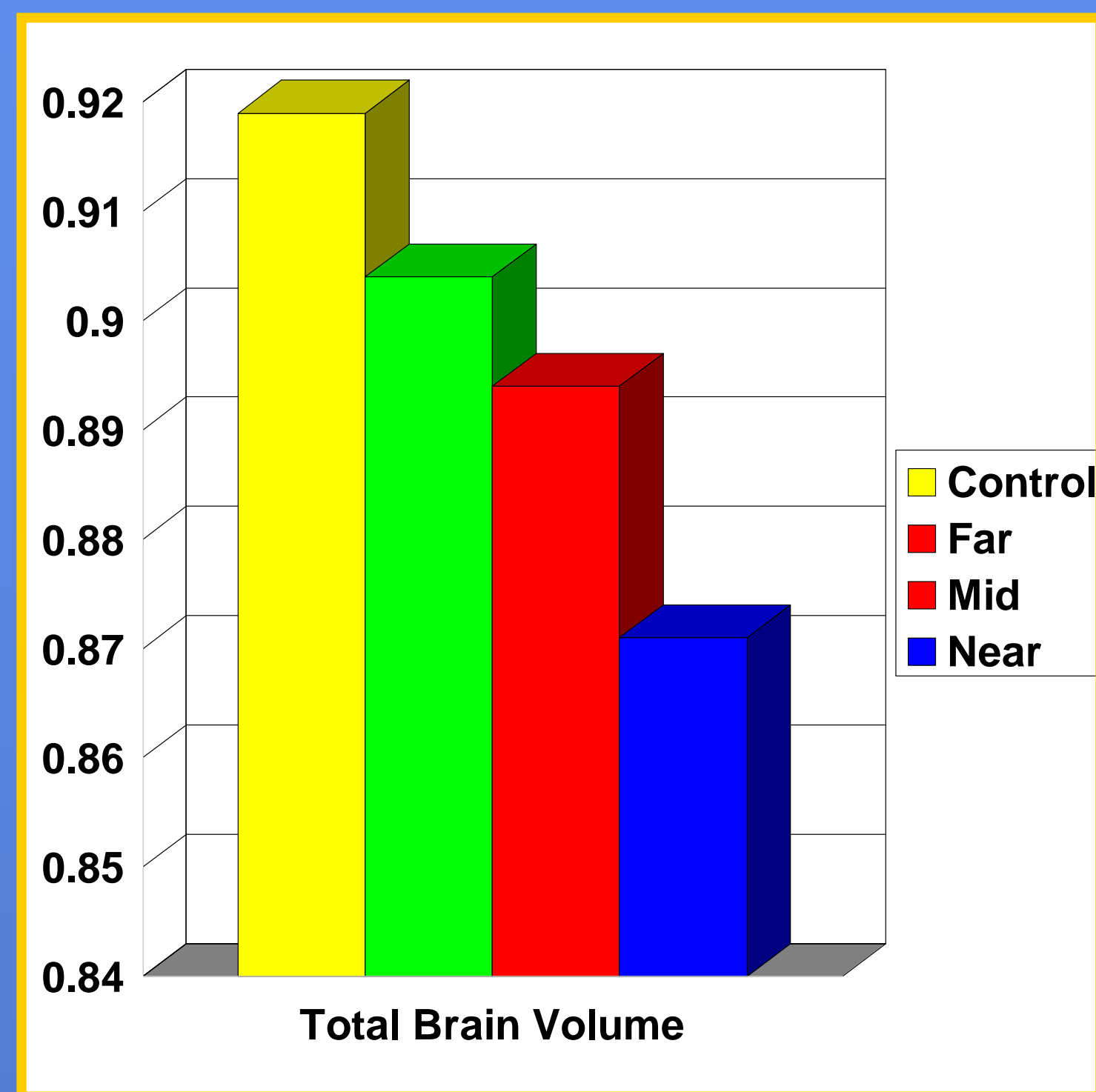
- 1) 'far- from-diagnosis' (> 15 years)
- 2) 'midway-to-diagnosis' (9 -15 years)
- 3) 'near-to-diagnosis' (<9 years)

Table 1 shows demographics

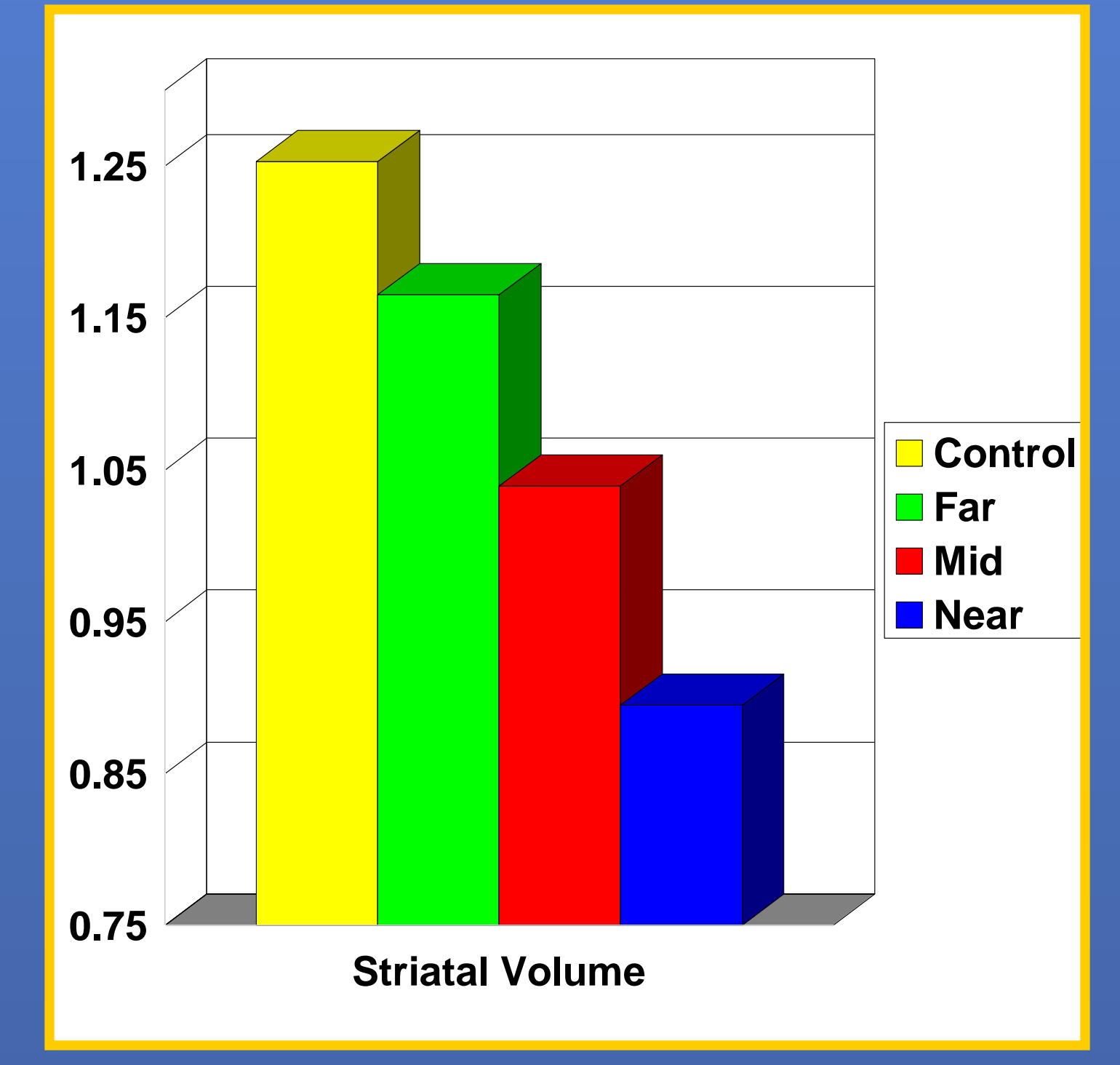
Scans were obtained using a standard multi-mode protocol with an axial 3D volumetric spoiled gradient echo series and a dual echo PDT2 series. All sites used a General Electric 1.5 Tesla scanner (with the exception of two sites using a 1.5 Tesla Siemens scanner).

Brain measures were obtained with a fully automated method using BRAINS2 software. Age, gender, and scanner-to-scanner variation were statistically controlled.

	Controls	Far from Diagnosis	Midway to Diagnosis	Near Diagnosis	Statistic P-value	Contrasts
N	166	180	184	127	--	--
Gender (% Female)	65	67	68	61	Chi-square = 2.30 (p = .5135)	
Age Mean (SD)	44.09 (11.67)	37.53 (8.45)	43.95 (10.11)	45.68 (9.98)	F=21.35 p <0.0001	Far<Controls=Mid=Near
CAG Mean (SD)	20.03 (3.36)	41.06 (1.56)	42.34 (2.14)	43.97 (2.85)	F=31.86 P<0.0001	Controls<Far<Mid<Near
UHDRS Motor Mean (SD)	2.91 (3.51)	3.69 (4.14)	4.65 (4.87)	8.13 (7.13)	F=30.29 P<0.0001	Controls, Far<Mid<Near



Charts
 Y axis = Brain Measure Volume / Intracranial volume (ICV)
 Y axis striatum = volume/ICV X100
 All measures in EVERY prognostic group (far, mid, near) significantly different that controls at p <0.0001
 Exception was the cerebellum which showed no structural differences in any prognostic group



Results:

All brain measures were found to be abnormal for every prognostic group meaning that as far back as we can look (>15 years to predicted diagnosis), the brain is substantially abnormal in structure (see results charts).

Effect sizes are moderate to very large (largest being striatum) suggesting these imaging measures provide robust separation from normal controls at baseline (see Figure 1).

White matter and striatum are powerful predictors of probability of diagnosis (see Figure 2).

Implications for clinical trials of neuroprotective agents:

- selection of participants should be 15 years from estimated diagnosis of motor disease

- Neuroimaging measures of cerebral white matter and/or striatum may offer the most predictive validity of diagnosis proximity

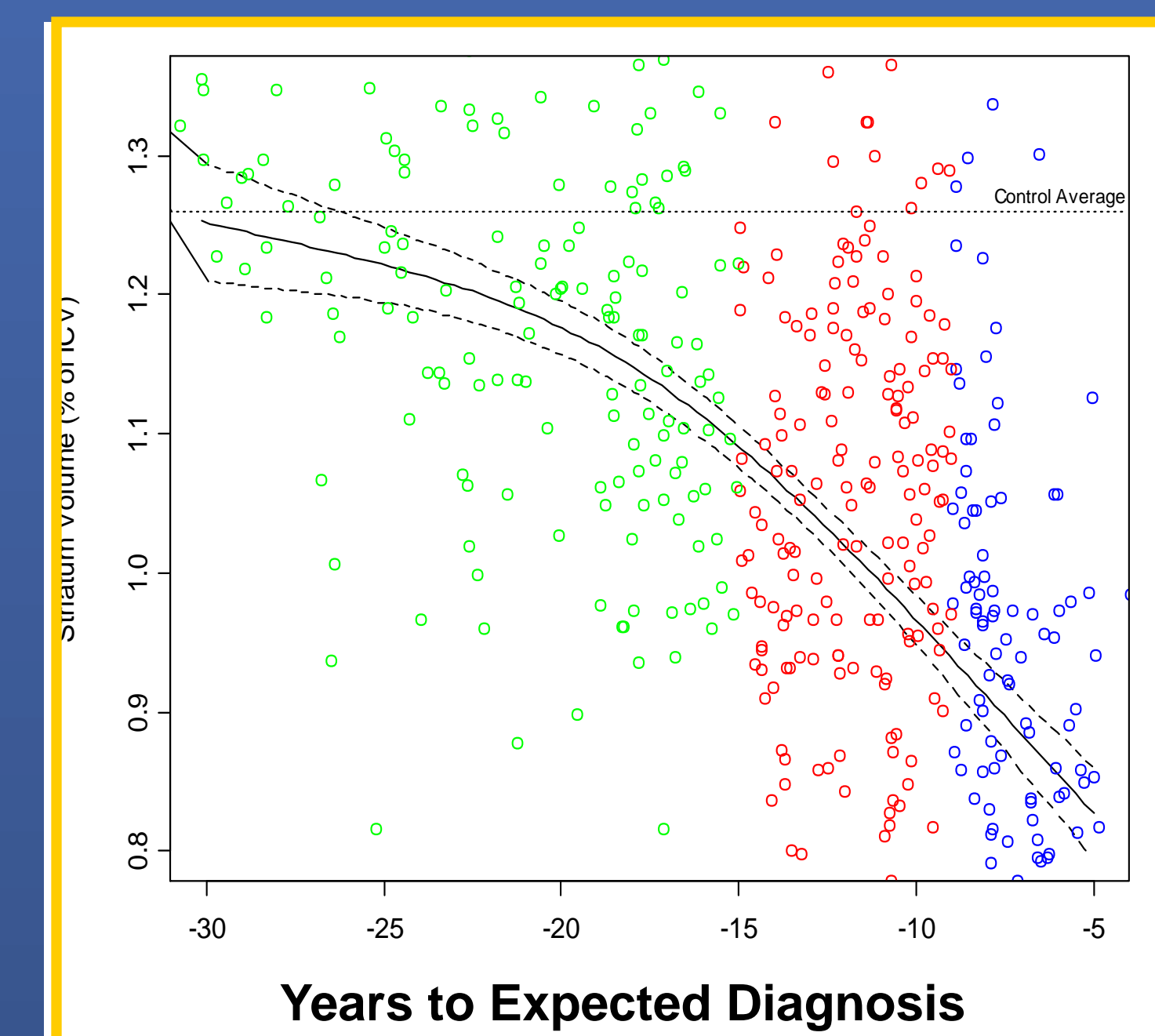
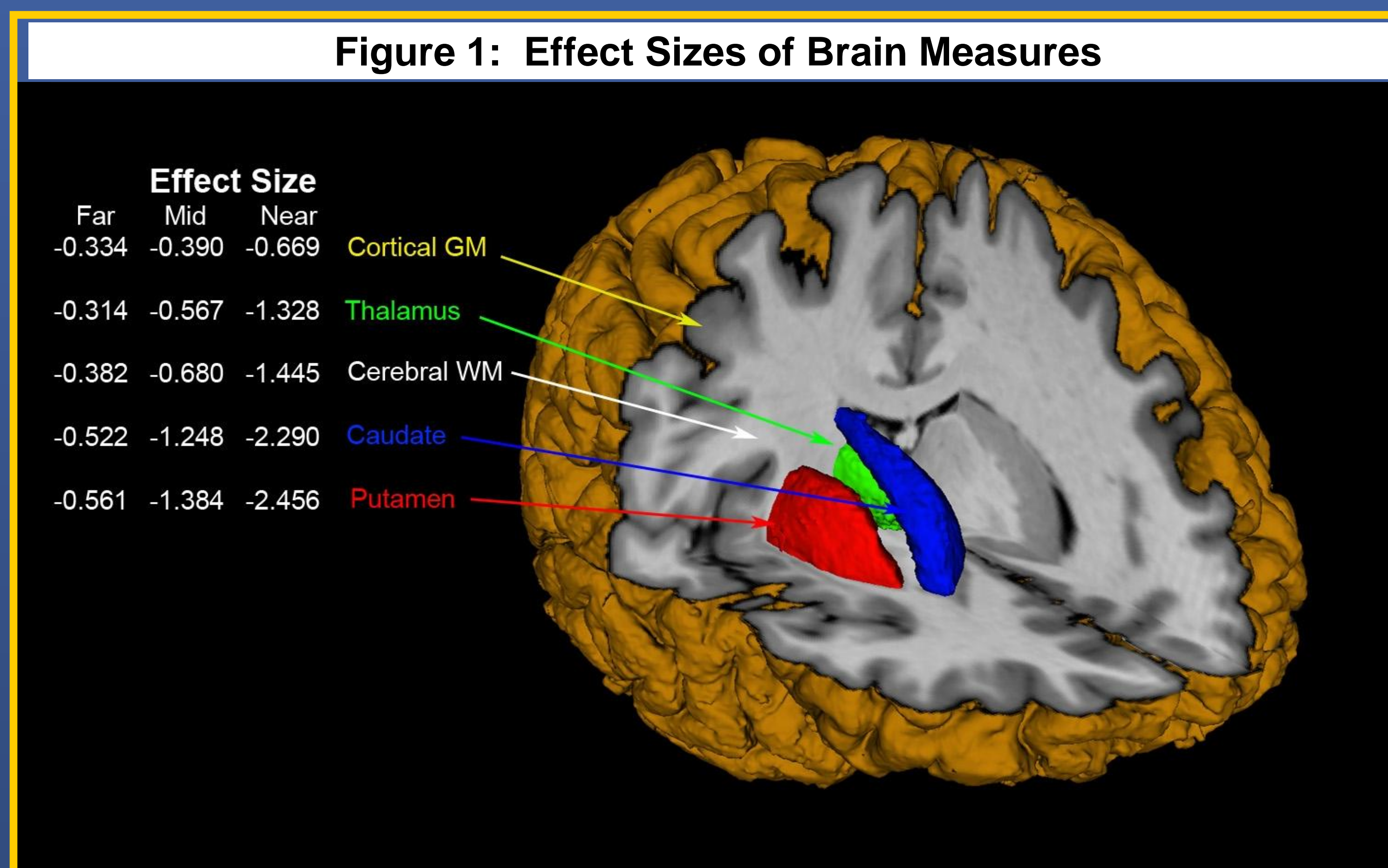


Figure 2: Relationship with Probability of diagnosis. Striatum (above) White matter (below)

Figure 2 Legend:

Far = ○
 Mid = ○
 Near = ○

