

Longitudinal Change in Striatal Volume in Pre-Clinical Huntington's Disease

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Introduction: Because individuals who carry the gene expansion for Huntington's disease (HD) demonstrate significant atrophy in the striatum long before motor symptoms are observed, it will be important to treat this disorder before the onset of diagnostic symptoms, and it will be necessary to conduct clinical trials using reliable and valid biomarkers. Previous studies have suggested the potential utility of MRI measures of striatal volume change as an outcome measure in clinical trials for Huntington's Disease.

Methods: PREDICT-HD is a large multi-site study of individuals with the HD gene expansion who have not yet been diagnosed with the disorder ("pre-HD"), as well as a smaller group of gene-negative controls. Participants have been followed yearly with extensive neuropsychological testing, clinical evaluation, and psychiatric assessment, and every two years with MRI. The sample used for the current analysis included 211 pre-HD participants, and 60 age- and gender-matched controls. Two scans, obtained with an interscan interval of 2 years, were analyzed for each participant. Measurements included volumes of caudate, putamen, thalamus, and total striatum. Pre-HD participants were divided into groups, based on their estimated proximity to onset (far: > 15 years; mid: 9-15 years; and near: <9 years). Sample sizes were estimated for clinical trials using striatal volume change as an outcome measure for each group.

Results: All groups, including Controls, showed significant reduction over time in the volumes of each measured structure. Pre-HD participants in the Mid and Near groups showed significantly greater 2-year volume reduction than Controls for all structures. Pre-HD participants in the Far group showed significantly greater 2-year volume change than Controls for total striatum only. Degree of 2-year change did not differ on any structure for the Mid and Near groups, suggesting that rate of atrophy, once it begins, remains fairly constant in the preclinical stage. Effect sizes were greater for total striatum than for any other measured structure.

Conclusions: Disease-related longitudinal change in striatal volume is observable over a two year period in individuals who are within 15 years of estimated disease onset, and rate of change is fairly consistent over time once it begins. MRI measures of caudate and putamen can be used as reliable and valid outcome measures for future clinical trials in pre-HD. Volume change in striatum has the highest effect size, suggesting that it will be the best outcome measure for future clinical trials.

References:

Aylward, EH (2004), 'Onset and rate of striatal atrophy in preclinical Huntington disease', *Neurology*, vol. 63, no. 1, pp. 66-72.
Aylward, EH (2007), 'Change in MRI striatal volumes as a biomarker in presymptomatic Huntington's disease', *Brain Res Bull*, vol. 72, no. 2-3, pp. 152-158.

Demographic Information, Based on Group Assignment at Time 1

	Control	Preclinical Groups—Proximity to Estimated Onset			p*
		Far (> 15 years)	Mid (9 to 15 years)	Near (< 9 years)	
N at Time 1	60	82	73	56	
Mean Age at Time 1** (s.d.)	44.68 (10.72)	37.83 (8.42)	44.55 (10.57)	47.34 (8.26)	<.0001
Gender (% female)	71.7	64.6	63.0	69.6	0.68
Mean CAG Repeat Length*** (s.d.)	NA	41.10 (1.62)	42.25 (2.09)	43.55 (3.03)	<.0001
Mean Inter-scan Interval (months) (s.d.)	24.1 (1.1)	24.4 (1.6)	24.4 (1.4)	24.6 (1.9)	.40

* Based on ANOVA for Age and CAG repeats; Chi-Square for Gender

** Far from onset group significantly younger than other groups; no significant differences among Controls, Mid, and Near groups

*** Every group differed from every other group in CAG repeat length

Effect Sizes for 2-Year Volume Change

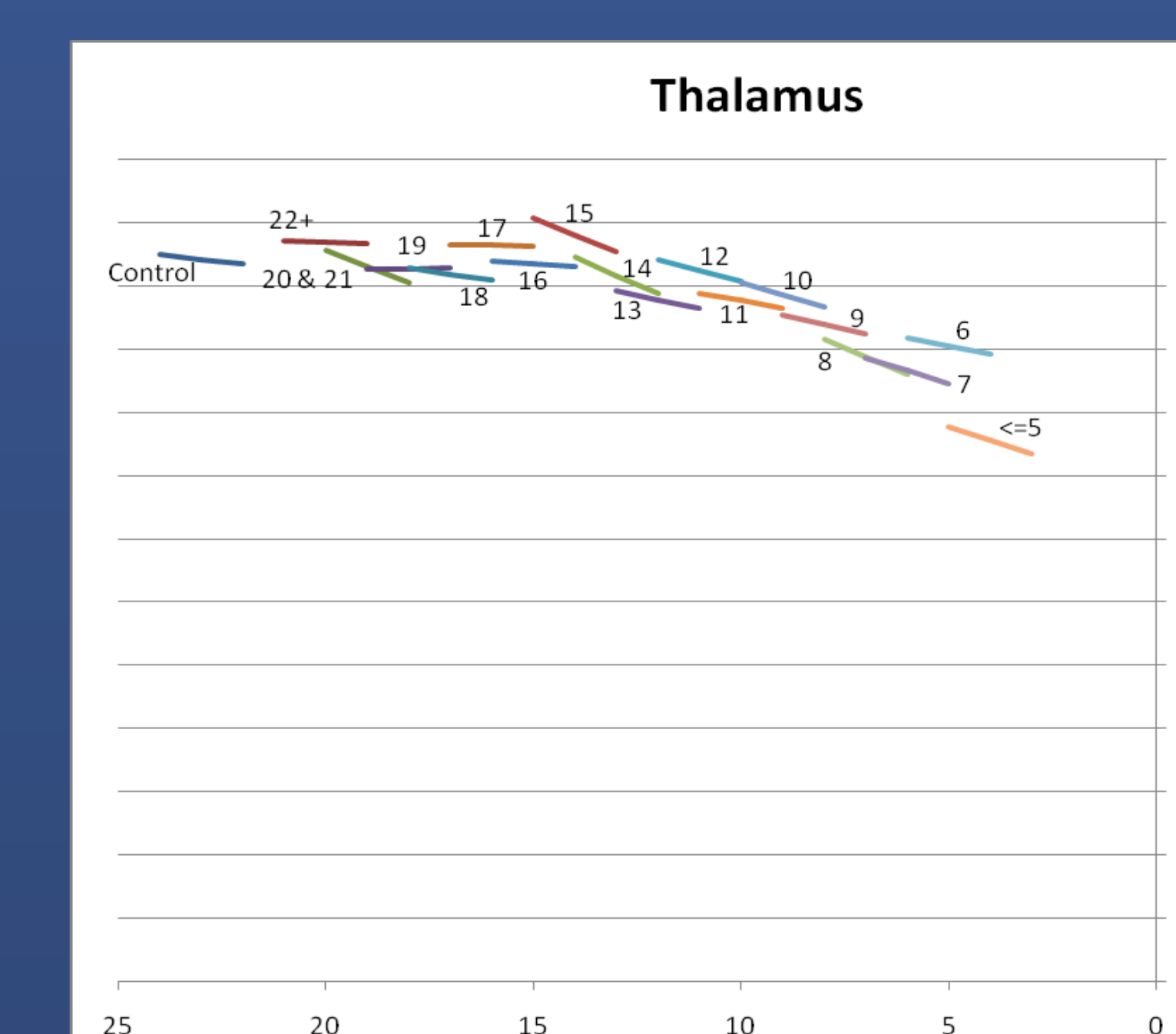
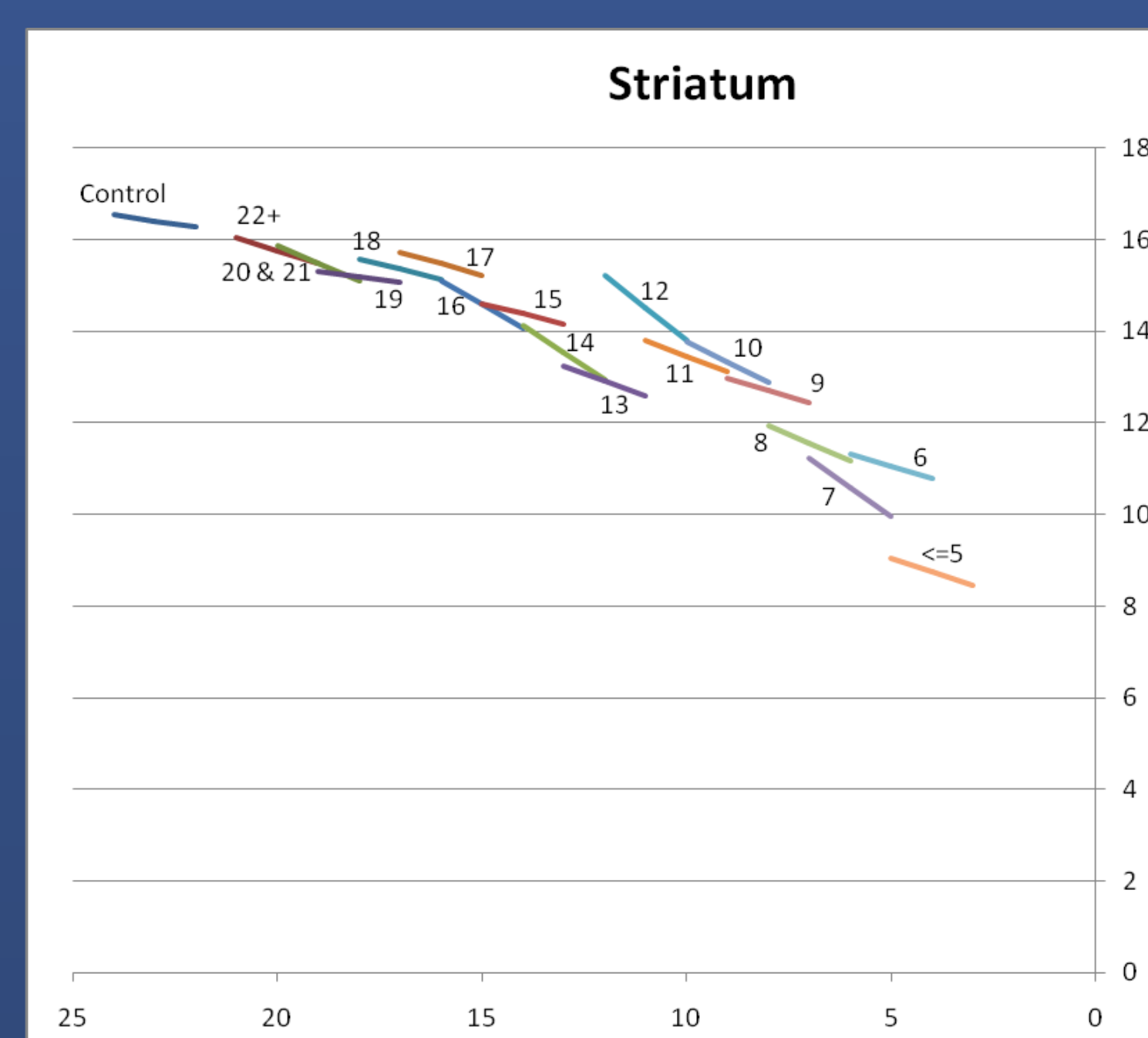
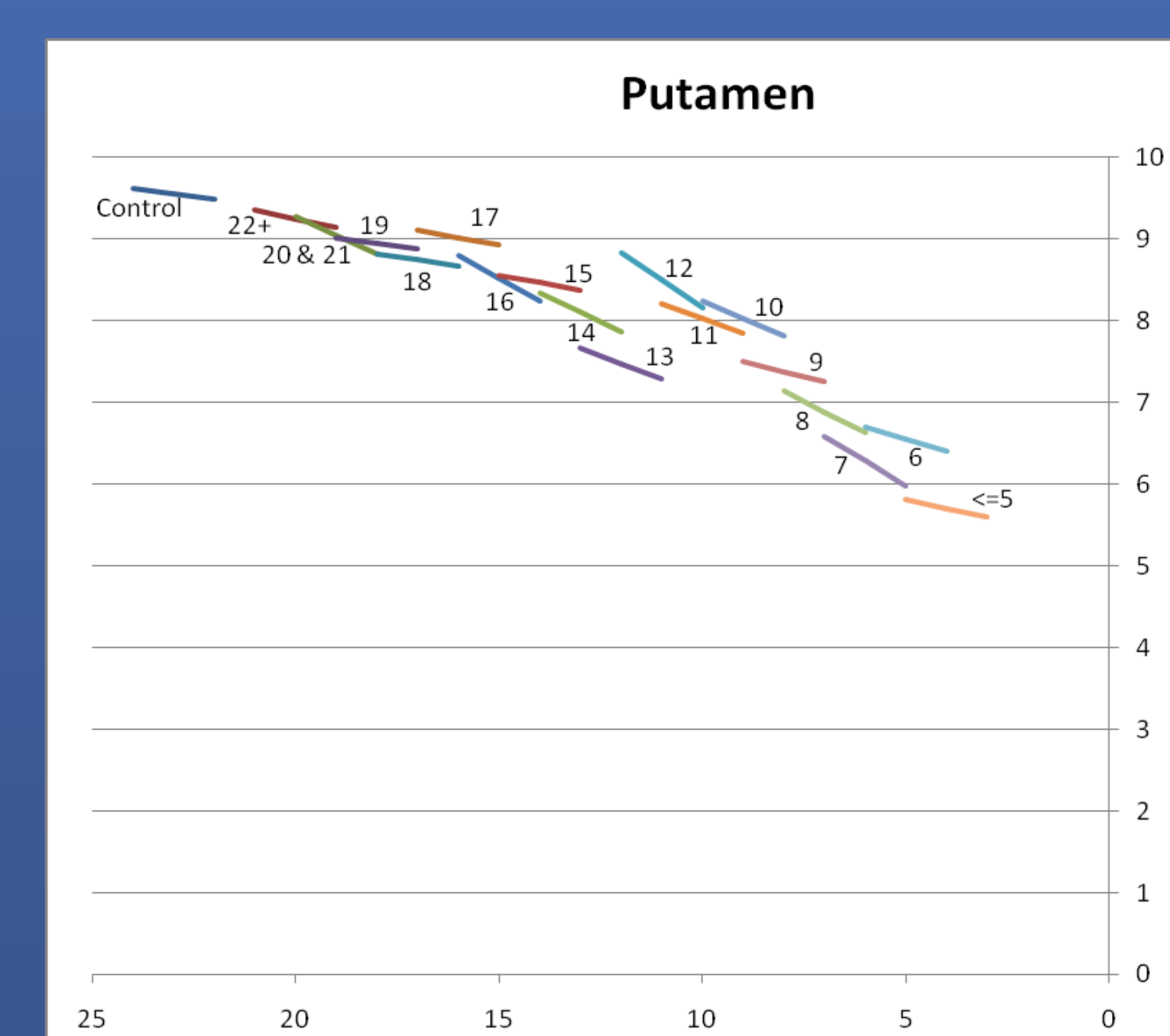
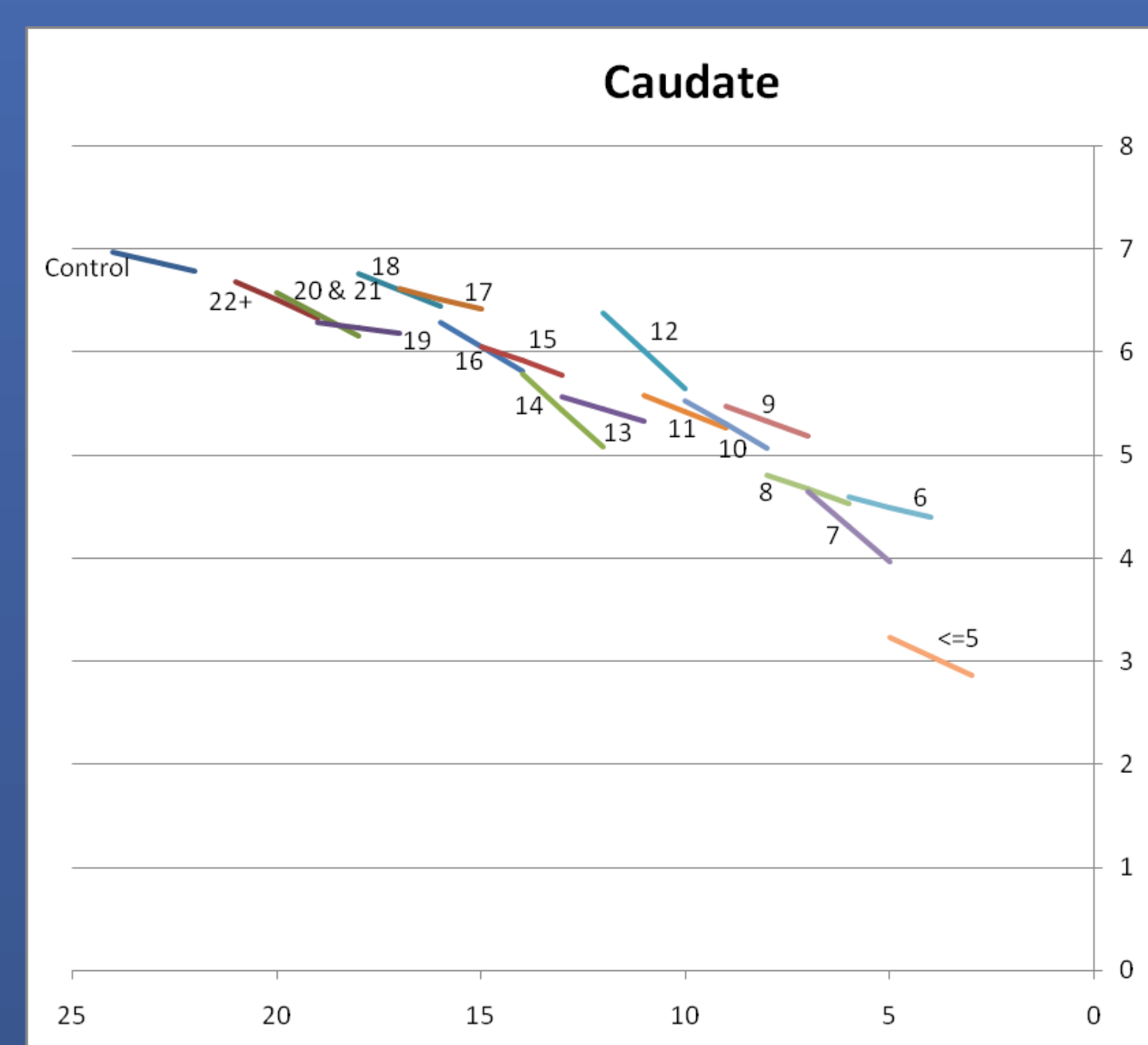
Group	Caudate	Putamen	Total Striatum	Thalamus
Control	-0.33	-0.30	-0.29	-0.26
Far	-0.68	-0.55	-0.69	-0.32
Mid	-1.16	-0.90	-1.17	-0.63
Near	-0.95	-0.94	-1.06	-0.74

Longitudinal Change in MRI Volumes of Caudate, Putamen, Total Striatum, and Thalamus (s.d.)

	Controls	Preclinical Groups—Proximity to Onset			F (p) for Longitudinal Change	
		Far	Mid	Near	Unadjusted	Adjusted*
Caudate—Time 1 (cc)	6.97 (1.19)	6.56 (1.21)	5.78 (1.14)	4.61 (1.37)		
Caudate—Time 2 (cc)	6.79 (1.02)	6.24 (1.16)	5.31 (1.07)	4.25 (1.39)		
Caudate 2-Year Change (cc)**	0.11 (0.40)	0.32 (0.41)	0.48 (0.48)	0.36 (0.41)	7.68 (<0.0001)	8.06 (<0.0001)
Percent Caudate Change per year***	0.78%	2.40%	4.08%	3.81%		
Putamen—Time 1 (cc)	9.61 (1.20)	9.10 (1.21)	8.26 (1.22)	6.81 (1.24)		
Putamen—Time 2 (cc)	9.48 (1.26)	8.85 (1.20)	7.84 (1.24)	6.41 (1.15)		
Putamen 2-Year Change (cc)**	0.13 (0.56)	0.25 (0.43)	0.42 (0.43)	0.40 (0.45)	5.51 (0.001)	7.08 (.0001)
Percent Putamen Change per year***	0.67%	1.35%	2.50%	2.86%		
Striatum—Time 1 (cc)	16.54 (2.18)	15.67 (2.29)	14.04 (2.21)	11.43 (2.50)		
Striatum—Time 2 (cc)	16.27 (2.10)	15.10 (2.21)	13.16 (2.18)	10.66 (2.45)		
Striatum 2-Year Change (cc)**	0.20 (0.82)	0.57 (0.70)	.91 (.80)	0.76 (0.75)	9.87 (<0.0001)	11.28 (<0.0001)
Percent Striatum Change per year***	0.60%	1.79%	3.19%	3.24%		
Thalamus—Time 1 (cc)	11.49 (1.25)	11.56 (1.36)	11.16 (1.41)	9.89 (1.53)		
Thalamus—Time 2 (cc)	11.35 (1.32)	11.42 (1.34)	10.80 (1.46)	9.46 (1.49)		
Thalamus 2-Year Change (cc)**	0.14 (.61)	0.13 (0.53)	0.36 (0.56)	0.43 (0.55)	4.83 (0.003)	3.21 (0.02)
Percent Thalamus Change per year***	0.61%	0.55%	1.59%	2.12%		

Mean volumes at Time 1 and Time 2 for pre-HD participants with different estimated years to onset (YTO).

Colored lines represent data from groups of participants with the same estimated proximity to diagnosis. Each line represents the structural volume change over 2 years.



Estimated Years to Onset

