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Longitudinal change in regional brain volumes in prodromal Huntington disease

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Abstract

Objective—As therapeutics are being developed to target the underlying neuropathology of Huntington disease (HD), interest is increasing in methodologies for conducting clinical trials in the prodromal phase. This study was designed to examine the potential utility of structural MRI measures as outcome measures for such trials.

Methods—Data are presented from 211 prodromal individuals and 60 controls, scanned both at baseline and two-year follow-up. Prodromal participants were divided into groups based on proximity to estimated onset of diagnosable clinical disease: Far (>15 years from estimated onset); Mid (9–15 years); and Near (<9 years). Volumetric measurements of caudate, putamen, total striatum, globus pallidus, thalamus, total gray and white matter, and CSF were performed.

Results—All prodromal groups showed a faster rate of atrophy than Controls in striatum, total brain, and cerebral white matter (especially in the frontal lobe). Neither prodromal participants nor Controls showed significant longitudinal change in cortex (either total cortical gray or within individual lobes). When normal age-related atrophy (i.e., change observed in the Control group) was taken into account, there was more statistically significant disease-related atrophy in white matter than in striatum.

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Statistical analysis: Douglas Langbehn, MD, PhD, at The University of Iowa takes responsibility for the integrity and accuracy of the data analysis.

Conclusion—Measures of volume change in striatum and white matter volume, particularly in the frontal lobe, may serve as excellent outcome measures for future clinical trials in prodromal HD. Clinical trials using white matter or striatal volume change as an outcome measure will be most efficient if the sample is restricted to individuals who are within 15 years of estimated onset of diagnosable disease.

Keywords

Huntington disease; striatum; white matter; longitudinal; MRI

Clinical trials are underway to test the effectiveness of potential treatments for HD. Because previous research has indicated that neurodegeneration begins many years before the onset of diagnosable motor impairment,[1–3] treatment efforts are beginning to focus on the prodromal stage of HD. PREDICT-HD is an international multi-site study following a large sample of prodromal participants (individuals who have tested positive for the HD mutation, but do not yet have motor features indicating onset of diagnosable HD) as well as gene-negative controls. As part of this study, we aim to identify which measures from structural MRI scans show significant longitudinal change over a two-year period, and to identify when in the course of prodromal HD such longitudinal change becomes significant. This will allow us to establish potential outcome measures that can be used in prodromal HD individuals for whom traditional measures of disease progression (namely, increases in symptom severity) are not useful and to identify the prodromal stages during which participants will be most appropriate for future clinical trials.

Many cross-sectional studies have been published regarding volume differences in cortex, white matter, and subcortical regions in presymptomatic individuals, with results suggesting at least some atrophy in all of these regions prior to diagnosis.[1, 4–6] Few longitudinal studies have been reported, however, and these studies have included much smaller samples than the current study.[3, 7–10] Here we present data from a large, multi-site longitudinal study of prodromal HD that compares rates of atrophy in regions throughout the brain. These data allow us to determine which structural MRI change measures are the strongest indicators of disease progression in prodromal HD.

METHODS

Sample

The analyses presented here are based on a subsample of 211 prodromal participants (individuals who have tested positive for the HD mutation, but did not at the time of enrollment have motor features indicating onset of diagnosable HD) and 60 Controls (individuals who are offspring of an HD-diagnosed parent, but who have themselves tested negative for the HD gene mutation). All PREDICT-HD participants were included for whom baseline and two-year follow-up MRI scans were available and image analysis was completed. Participants were seen yearly by clinicians experienced in the evaluation of movement disorders and specifically trained on administration of the UHDRS for PREDICT-HD. In accordance with clinical practice,[11] diagnosis is made on the basis of “an otherwise unexplained characteristic movement disorder,” operationally defined as a score of 4 on the HD Diagnostic Rating Scale of the UHDRS,[12] which indicates that the clinician had ≥99% certainty that the participant showed “unequivocal presence of an otherwise unexplained extrapyramidal movement disorder.” Participants were excluded from the current study if they received a rating of 4 at either baseline or at the follow-up visit during which the second MRI scan was performed. All aspects of the study were approved by the Institutional Review Board at each participating institution, and all participants gave written informed consent.

Prodromal participants were categorized according to estimated proximity to diagnosis, based on their CAG repeat length and age.[13–14] (See Supplemental Material for details.) Consistent with previous reports involving this cohort,[15] cases were considered "Far" from onset if their estimated onset was >15 years, "Mid" to onset if estimated onset was 9–15 years, and "Near" to onset if estimated onset was <9 years. Table 1 provides demographic information for Controls and the prodromal groups.

MRI Measures

All scans were obtained using a standard multi-modal protocol that included an axial 3D volumetric spoiled gradient echo series and a dual echo proton density/T2 series. Scans were processed at The University of Iowa using AutoWorkup, an automated procedure implemented in BRAINS[16] and artificial neural networks.[17] Volume measures were determined for caudate, putamen, total striatum (caudate + putamen), globus pallidus, thalamus, total cortical gray matter, cerebral white matter, total brain, ventricular CSF, surface CSF, and total CSF. In addition, gray and white matter volumes within each of the four lobes, as well as subcortical white matter, were calculated. After completion of AutoWorkup, all scans were individually inspected for correct realignment and coregistration, tissue classification, and accuracy of brain and subcortical structures. (See Supplemental Material for details on scan acquisition and analysis.)

Statistical Analysis

For each structure region, volume change (in cc) between Time 1 and Time 2 was analyzed directly as the outcome variable in a mixed linear model. The main predictor of interest was group membership (Control, Far, Mid, Near). We controlled for gender, age at Time 1, and inter-scan interval as a priori-defined covariates. Effect sizes for two-year change in each group were calculated for each brain region, allowing us to estimate the number of participants per treatment arm that would be needed for clinical trials. For each regional measure, partial correlations were performed between CAG repeat length and volume change, controlling for initial structure volume. (See Supplemental Materials for further details on statistical analyses.)

RESULTS

Longitudinal Change

Table 2 presents volume change for each region for the Control, Far, Mid, Near groups, as well as both unadjusted and adjusted group comparisons. Unadjusted volumes from Time 1 and Time 2 are presented in Supplemental Table 1. Volumes for caudate, putamen, and thalamus were significantly smaller at Time 2 than Time 1 for all groups, including Controls, with the reverse being true for all CSF measures (ventricular, surface, total). For the striatum (caudate, putamen, and total striatum) volume change from Time 1 to Time 2 was highly significant ($p < 0.0001$) for all three prodromal groups, while changes over time for the Control group were more modest (*p*s ranging from 0.02 to 0.05). The globus pallidus was significantly smaller at Time 2 than Time 1 for the Far and Near groups only. Volumes of cortical gray matter (total and within individual lobes) did not change significantly over time for any group. For cerebral white matter and total brain volume, all prodromal groups showed significantly smaller volumes at follow-up than at baseline, but the Control group did not. Longitudinal white matter changes for the prodromal groups were fairly evenly distributed across frontal, parietal, and temporal lobes, and were not significant in either occipital lobe or subcortical areas (Supplemental Table 2).

Group Differences in Rate of Change

Results below are based on group differences in *amount of volume change over time*, not total structure volumes, and all analyses were performed controlling for gender, age, and inter-scan interval. Analyses were repeated with adjustment for intracranial volume (ICV), yielding results that were essentially the same as those reported, but with significance levels slightly decreased.

(a) Subcortical structures—For striatum, caudate, putamen, and thalamus, Controls had slower rates of change than Mid and Near groups, with no difference between the Mid and Near groups on rate of change. Only striatum showed a significant difference between Controls and the Far group, with group differences approaching significance ($p = 0.06$) for caudate. For globus pallidus, the Far and Near groups showed significantly greater change than the Controls but did not differ from each other; the Mid group had significantly less change than the Near group. Other post-hoc analyses are presented in Table 2 and described more fully in Supplemental Table 3.

(b) Gray/White/CSF—There was no difference in rate of change between any of the groups on any of the cortical measures (total or within each lobe). Rates of white matter atrophy were greater for all prodromal groups than for Controls in all regions except subcortical white matter, with the greatest difference in frontal lobes (see Supplemental Materials for fuller description of white matter regions). Controls showed a slower rate of change than the Near group for white matter, total brain, and all CSF measures, and slower rate of change than the Mid group for white matter, total brain, and all CSF measures except extracerebral CSF. Rate of change differed between Controls and the Far group for cerebral white matter and total brain volume, with a trend toward significance for ventricular CSF. All post-hoc analyses are presented in Table 2 and described more fully in the Supplemental Material.

CAG repeat length

Over 95% of prodromal participants had CAG repeat lengths in the 39–52 range. (We do not list more detailed extremes in order to protect participant privacy.) To address the question of whether increased CAG repeat length was associated with faster rate of atrophy, analyses were performed correlating these two variables, controlling for the region volume at Time 1. CAG repeat length was significantly associated with rate of change for caudate ($r = -0.18$; $p = 0.009$) and total striatum ($r = -0.16$, $p = 0.02$); there was a trend toward a significant association for putamen ($r = -0.12$, $p = 0.07$), with a faster rate of atrophy occurring in individuals with higher CAG repeat lengths. No significant associations were observed for any other regions, with p values ranging from 0.13 to 0.85.

Effect Sizes/Sample Size Calculations

Table 3 presents effect sizes for two-year change for each region for each group. (In addition to the major regions we analyzed, effect sizes are presented for frontal white volume, as this was the specific region of white matter that showed the greatest group differences in amount of change.) Further analyses were completed to estimate the sample sizes that would be needed for clinical trials using volume change in these regions as outcome measures in clinical trials. Because significant atrophy is associated with normal aging, sample size calculations are based on the rate of atrophy in each group that is over and above the atrophy that would be expected based on age alone (i.e., disease-related change). Table 4 presents the estimated number of participants that would be required per treatment arm for a two-year clinical trial, based on the assumption of 30%, 40%, or 50% reduction in rate of case-control atrophy difference. Because of the exceptional sparing of white matter over two years

among Controls, sample size calculations suggest that fewer participants might be needed for clinical trials if white matter volume change was used as the outcome measure than if any of the other regional measures were used, especially for the Far and Mid groups. More specifically, using frontal lobe white matter volume change as an outcome measure may require the smallest sample sizes, especially for individuals more than 15 years from estimated onset. Although effect sizes are greater for striatum than for cerebral or frontal white matter for the Far and Mid groups, the amount of change observed for Control participants in the striatum was also relatively high, resulting in greater sample size estimates for striatum than for the white matter measures, especially in the Far and Near groups.

DISCUSSION

This is the largest longitudinal study to date comparing rates of atrophy in striatum with rates in other brain regions in prodromal HD. Results indicate that the annual percent volume change for prodromal participants in striatum and globus pallidus (1.8 to 4.01% per year for Far to Near groups) is greater than in cerebral white matter (0.6 to 2.2% per year), with no significant volume change in cortex for any of the prodromal groups. However, when normal age-related atrophy (i.e., change observed in the Control group) is taken into account, there appears to be more disease-related atrophy in white matter than in striatum. Significant rates of striatal atrophy have been demonstrated previously in much smaller studies using manual tracing of structures, with results indicating somewhat faster annual rates of atrophy (4.3% for caudate and 3.1% for putamen) than the current study. Our finding of a significant rate of white matter atrophy in prodromal HD is consistent with previous cross-sectional studies indicating white matter abnormalities prior to diagnosis of HD, either using DTI[18–20] or structural imaging,[5, 21] and with one small longitudinal study.[5] White matter volume reductions were not observed, however, by Rosas et al.[19] in a small cross-sectional study (N = 15 prodromal participants) or in two small longitudinal studies (17 prodromal participants each) [8, 10] using voxel-based morphometry approaches. Kipps et al. [10] suggest that cortical and white matter atrophy may be more variable in location compared with the relatively concentrated striatal loss, making it more difficult to detect using voxel-based measurement techniques. Rate of globus pallidus atrophy was also significantly greater in the Far and Near groups than in the Controls, consistent with cross-sectional reports of prodromal volume reduction in this area.[22–23]

We did not find evidence of faster rate of atrophy in cortical gray for any of the prodromal groups in comparison to controls. This is somewhat surprising, considering widespread cortical involvement in later stages of manifest HD.[24–26] Our results are consistent with two much smaller longitudinal studies[8, 10] using voxel-based morphometry that showed no difference between prodromal and control participants in rate of cortical atrophy. Cross-sectional studies,[27–28] however, have generally shown prodromalwidespread cortical thinning, although one small study using voxel-based morphometry [6] found only regionally specific cortical loss. Examination of our own cross-sectional data from a larger prodromal sample, which included the current longitudinal sample,[21] found significant differences in cortical volume between control and prodromal participants (even participants in the Far group), although these group differences were much smaller than for white matter and striatal volume. Our current longitudinal finding of no group differences in *rate of change* suggests that any cortical volume reduction observed in prodromal HD is either the result of very prolonged and/or very slow volume decrease or failure to reach normal cortical volume early in life.

One major goal of this study was to determine which measures of regional brain volume would make the strongest outcome measures for future clinical trials at various prodromal

stages. For individuals >15 years from estimated onset, sample sizes using any region would be large. Although rate of change was significantly greater for all prodromal groups in striatum than in other brain regions, our findings suggest that change in cerebral white matter (and specifically, in frontal white matter) compares quite favorably to change in striatum as a potential outcome measure. For the Mid group (9–15 years from estimated onset), frontal white matter, total cerebral white matter, or striatal volume change would require approximately equal numbers of participants; and for the Near group frontal white matter, total cerebral white matter and ventricular CSF volume change would require approximately equal numbers of participants. Our results are consistent with previous findings from much smaller studies indicating significant longitudinal change for striatal volume, even in individuals who are decades away from diagnosis. The current study, for the first time, includes data from control participants and suggests that selection of the most effective MRI outcome measures must take into account normal age-related atrophy. Because white matter shows much slower change related to normal aging than striatum, it may allow better assessment of actual therapeutic effects than measures of striatum, even though striatal volume shows a greater annual percent decline.

Another goal of this study was to determine which prodromal participants would be the best ones to include in clinical trials, based on the degree of longitudinal change at various points in the prodromal phase. Our results suggest that only total striatum, globus pallidus, cerebral white matter, and total brain volume showed significantly greater rate of change for the Far group than Controls, with a trend for caudate and ventricular CSF. However, the difference from Controls was much stronger for the Mid and Near groups than for the Far group (except for globus pallidus), suggesting that clinical trials can be conducted with much smaller samples if they include only individuals who are within 15 years of estimated clinical onset. (This, of course, assumes that the therapy is also appropriate for targeting pathogenetic processes at this stage of disease development.)

In addition to relatively quick change over time, another desirable feature for potential outcome measures is low variability in rate of change among study participants.[29] For striatal measures and white matter (total cerebral and frontal white matter), there were no significant differences between the Mid and Near groups in amount of longitudinal change, although both total cerebral white matter and frontal white matter showed trends toward faster rate of atrophy in the Near group than in the Mid group (*p*s = 0.10 and 0.11, respectively; see post-hoc group analysis in Supplemental Table 3). Measures with the least amount of difference in rate of change between Mid and Near groups were total striatum and putamen, suggesting a fairly stable rate of atrophy across participants who are within 15 years of estimated onset, regardless of their exact proximity to onset. Although globus pallidus showed a rapid rate of change for the Near group (4.01% per year), this differed significantly from rate of change for the Mid group. Thus, in clinical trials that include prodromal participants with a fairly wide range of estimated years to onset (within 15 years), striatum and putamen measures may provide a more consistent method of assessing change than other measures.

CAG Repeat Length

Although it is clearly established that CAG repeat length has an effect on age at onset of HD,[30–31] few studies have examined the effect of CAG repeat length on rate of brain atrophy. In longitudinal studies of symptomatic participants, Ruocco et al.[32] found that higher repeat length (>45) was associated with faster rate of atrophy in frontal, occipital, parietal, and cerebellar regions, and in a sample including both symptomatic and prodromal individuals, Henley et al.[7] found that an increase of CAG repeat length by one was associated with an increase in whole-brain atrophy rate of 0.12% per year (after adjusting for age and gender). Our analyses demonstrated that increased CAG repeat length is associated

with faster progression of atrophy in prodromal HD for caudate and total striatum (with a trend toward faster progression for putamen), but not in cortical, CSF, or white matter volumes. Thus, for individuals who are at the same stage of striatal atrophy, those with longer CAG repeat lengths exhibit a faster rate of striatal volume loss. This may suggest that HD has a more direct effect on striatum than on other brain regions. Our lack of finding a significant correlation between CAG repeat length and rate of atrophy in overall brain measures is inconsistent with findings of Ruocco et al.[32] in a sample of symptomatic HD and Henley et al.[7] in a sample combining symptomatic and prodromal participants. These studies did not, however, control for initial structure volume. Controlling for baseline volume was done through partial correlation in the current study to eliminate effects of faster rate of atrophy among participants who were closer to estimated onset, who were already known to have longer CAG repeat lengths.

Limitations

Although participants in this study had not received a diagnosis of HD, some individuals, especially those close to predicted onset were not totally free of HD signs and symptoms. Clinicians were instructed to make a diagnosis based on ≥99% certainty that participants had unequivocal presence of an otherwise unexplained extrapyramidal movement disorder. Although study clinicians were trained on the UHDRS specifically for PREDICT-HD and met reliability criteria, it is unlikely that they all used precisely the same criteria for making this judgment. One goal of PREDICT-HD is to identify measures that can be used more reliably than clinicians' ratings of symptom onset as outcome measures in clinical trials with prodromal participants.

Another limitation of the study involves its reliance on estimated proximity to onset rather than retrospectively established known time to HD diagnosis. As participants continue to be followed, we will be able to determine the accuracy of our method for estimating proximity to onset and to determine whether the formula for estimating onset can be improved by including additional relevant variables, such as MRI structure volumes.

Lack of consistency among neuroimaging studies in HD (and other disorders) is often attributed to differences in scan acquisition and analysis. Although our segmentation methods have been validated,[33] it is possible that tissue changes that accompany progression toward HD onset may affect segmentation results. For example, if white matter neurodegeneration results in decreased MRI tissue intensity, it is possible that white matter might be misclassified as gray matter, and that this misclassification will increase as neurodegeneration increases. It is clear that tissue loss is occurring with disease progression in prodromal HD, as evidenced by reductions in total brain volume, so true cortical atrophy would only be missed if disease progression results in both continuous cortical volume reduction and continuous misclassification of white matter as gray matter. Studies implementing alternative segmentation methods are underway, which will allow further validation of our results. Regardless, our current measurement of white matter change is an excellent indicator of disease progression, even if the underlying neuropathology being assessed is more complicated than simple white matter volume reduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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Table 1

Demographic Information, Based on Group Assignment at Time 1

		Prodromal Groups—Proximity to Estimated Diagnosis			Statistic *p*-value	Contrasts
	Control	Far (>15 years)	Mid (9 to 15 years)	Near (<9 years)		
N at Time 1	60	82	73	56	_	_
Gender (% Female)	71.7	64.6	63.0	69.6	Chi-sq = 1.5 $p = 0.68$	
Mean Inter-scan Interval (months) (SD)	24.1 (1.1)	24.4 (1.6)	24.4 (1.4)	24.6 (1.9)	F = 1.0 $p = 0.39$	
Mean Age at Time 1 (SD)	44.7 (10.7)	37.8 (8.4)	44.5 (10.6)	47.3 (8.3)	F = 13.1 $p < 0.0001$	F < C, M, N
Mean CAG Repeat Length (SD)	19.8 (2.7)	41.1 (1.6)	42.2 (2.1)	43.5 (3.0)	F = 1399.7 $p < 0.0001$	C < F < M < N
Mean UHDRS Motor Score (SD)	2.4 (2.6)	4.8 (4.3)	4.5 (4.9)	9.7 (7.9)	F = 20.8 $p < 0.0001$	C < F, M < N

Table 2

Longitudinal change in MRI regional volumes (means and standard deviations)

		Prodromal groups -- proximity to onset			*F*(*p*) for longitudinal change		Post-Hoc Analyses (adjusted)*
	Controls	Far	Mid	Near	Unadjusted	Adjusted*	
Caudate 2-year change (cc)**	− 0.12 (0.40)	− 0.32 (0.41)	− 0.48 (0.49)	− 0.36 (0.41)	7.68 (<0.0001)	7.78 (<0.0001)	C < M = N F < M = N C < F (trend)
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)	6.94 (0.0002)	C = F < M = N
Striatum 2-year change (cc)**	− 0.20 (0.82)	− 0.57 (0.70)	− 0.91 (0.80)	− 0.77 (0.75)	9.87 (<0.0001)	11.00 (<0.0001)	C < F < M = N
Globus Pallidus 2-year change (cc)**	0.05 (0.27)	− 0.05 (0.29)	− 0.03 (0.29)	− 0.14 (0.24)	4.79 (0.003)	4.69 (0.003)	C < F=N C = M F = M M < N
Thalamus 2-year change (cc)**	− 0.14 (0.61)	− 0.13 (0.53)	− 0.36 (0.56)	− 0.43 (0.56)	4.83 (0.003)	3.04 (0.03)	C < M = N C = F < N F < M (trend)
Cortical gray 2-year change (cc)**	− 3.04 (15.37)	− 0.80 (12.88)	− 0.44 (14.6)	− 2.17 (12.8)	0.50 (0.68)	0.60 (0.61)	NA
Cerebral white 2-year change (cc)**	0.99 (13.51)	− 5.15 (15.13)	− 12.71 (18.12)	− 17.42 (15.15)	16.38 (<0.0001)	15.91 (<0.0001)	C < F < M = N
Total brain 2-year change (cc)**	− 2.52 (17.39)	− 6.62 (17.53)	− 14.68 (20.76)	− 21.37 (16.24)	13.01 (<0.0001)	12.26 (<0.0001)	C < F < M < N
Ventricular CSF 2-year change (cc)**	0.61 (1.73)	1.02 (1.62)	1.86 (2.02)	2.92 (2.11)	18.02 (<0.0001)	14.90 (<0.0001)	C < M < N F < M < N C < F (trend)
Surface CSF 2-year change (cc)**	1.12 (3.22)	0.68 (3.12)	1.79 (3.19)	2.85 (3.25)	5.60 (0.001)	4.92 (0.002)	C < N C = F C = M F < M = N

		Prodromal groups -- proximity to onset			*F*(*p*) for longitudinal change		Post-Hoc Analyses (adjusted)*
	Controls	Far	Mid	Near	Unadjusted	Adjusted*	
Total CSF 2-year change (cc)**	6.85 (16.33)	6.63 (16.34)	12.08 (18.37)	18.12 (19.06)	5.96 (0.0006)	5.95 (0.0006)	C < M < N C = F < N F < M (trend)

*Adjusted *F* and *p* values are based on analyses controlling for age, gender, and inter-scan interval as fixed effects and MRI scanner as a random effect.

**Change measures reflect the average two-year change in volume (i.e., Time 2 volume - Time 1 volume, not controlling for minor group differences in inter-scan interval). Negative numbers reflect atrophy; positive numbers reflect volume increase over time.

Table 3

Effect sizes for two-year volume change, based on adjusted volume change

	Control	Far	Mid	Near
Caudate	− 0.35	− 0.68	− 1.16	− 0.95
Putamen	− 0.30	− 0.55	− 0.90	− 0.93
Total striatum	− 0.30	− 0.69	− 1.17	− 1.05
Thalamus	− 0.27	− 0.33	− 0.63	− 0.73
Globus Pallidus	0.15	− 0.28	− 0.12	− 0.52
Cortical gray	− 0.21	− 0.04	0.01	− 0.10
Cerebral white	0.09	− 0.40	− 0.80	− 1.08
Total brain	− 0.11	− 0.44	− 0.73	− 1.09
Ventricular CSF	0.31	0.62	0.98	1.51
Surface CSF	0.39	0.28	0.64	0.91
Total CSF	0.40	0.45	0.75	1.09
Frontal white	− 0.09	− 0.63	− 0.95	− 1.24

Table 4

Estimated sample sizes* for clinical trials using change in regional volumes as an outcome measure

	Far				Mid				Near			
	Effect size difference from controls	**Expected therapeutic effect****			**Effect size difference from controls**	**Expected therapeutic effect****			**Effect size difference from controls**	**Expected therapeutic effect****		
		50%	40%	30%		50%	40%	30%		50%	40%	30%
Caudate	− 0.33	749	1171	2082	− 0.81	126	197	350	− 0.60	235	366	652
Putamen	− 0.25	1366	2134	3794	− 0.60	233	363	646	− 0.63	211	329	585
Total striatum	− 0.39	535	835	1485	− 0.87	111	173	307	− 0.75	147	230	409
Thalamus	− 0.06	27783	43411	77176	− 0.36	661	1032	1835	− 0.46	397	620	1103
Globus Pallidus	− 0.43	454	710	1262	− 0.27	1154	1803	3205	− 0.67	188	294	523
Cortical gray	+ 0.17	3094	4834	8594	+ 0.22	1739	2717	4829	+ 0.11	7799	12185	21663
Cerebral white	− 0.49	343	535	951	− 0.89	106	166	295	− 1.17	61	96	171
Total brain	− 0.33	748	1169	2078	− 0.62	216	338	601	− 0.98	87	136	242
Ventricular CSF	+ 0.31	879	1374	2443	+ 0.67	188	294	524	+ 1.20	59	92	163
Surface CSF	− 0.11	7697	12027	21381	+ 0.25	1309	2045	3636	+ 0.52	303	474	842
Total CSF	+ 0.05	36241	56627	100671	+ 0.35	691	1080	1920	+ 0.69	179	280	497
Frontal white	− 0.54	286	447	795	− 0.86	112	175	311	− 1.15	63	98	174

* N per treatment arm for a two-year clinical trial, assuming two-sided alpha = 0.05; 90% power

** % reduction in rate of case-control atrophy difference.