**Longitudinal Change in Striatal Volume in Preclinical 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 (“preclinical”), 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 for 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 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:**