### Title

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# Regional Atrophy Associated with Cognitive and Motor Function in Prodromal Huntington Disease

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## Abstract

**Background—**Neuroimaging studies suggest that volumetric MRI measures of specific brain structures may serve as excellent biomarkers in future clinical trials of Huntington disease (HD).

**Objective—**Demonstration of the clinical significance of these measures is an important step in determining their appropriateness as potential outcome measures.

**Methods—**Measures of gray- and white-matter lobular volumes and subcortical volumes (caudate, putamen, globus pallidus, thalamus, nucleus accumbens, hippocampus) were obtained from MRI scans of 516 individuals who tested positive for the HD gene expansion, but were not yet exhibiting signs or symptoms severe enough to warrant diagnosis ("pre-HD"). MRI volumes (corrected for intracranial volume) were correlated with cognitive, motor, psychiatric, and functional measures known to be sensitive to subtle changes in pre-HD.

**Results—**Caudate, putamen, and globus pallidus volumes consistently correlated with cognitive and motor, but not psychiatric or functional measures in pre-HD. Volumes of white matter,



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nucleus accumbens, and thalamus, but not cortical gray matter, also correlated with some of the motor and cognitive measures.

**Conclusions—**Results of regression analyses suggest that volumes of basal ganglia structures contributed more highly to the prediction of most motor and cognitive variables than volumes of other brain regions. These results support the use of volumetric measures, especially of the basal ganglia, as outcome measures in future clinical trials in pre-HD. Results may also assist investigators in selecting the most appropriate measures for treatment trials that target specific clinical features or regions of neuropathology.

### Keywords

Huntington disease; magnetic resonance imaging; cognitive; psychiatric; motor

## Introduction

Cognitive and motor measures are associated with brain atrophy in individuals with a Huntington disease (HD) diagnosis [1–3] and in individuals in the prodromal stages (pre-HD) who carry the HD gene mutation, but do not yet show signs or symptoms severe enough to warrant diagnosis [4–10]. Although these findings support a link between brain atrophy and some clinical variables, the relationships have not been well characterized. With the development of treatment interventions that would ideally be administered before the manifestation of diagnosable signs and symptoms, it is vital to understand the relationship of regional atrophy measures with clinical measures if they are to be used as outcomes in clinical trials. An understanding of the neuropathological correlates of early clinical signs of disease progression may also aid in identifying the best MRI measures for clinical trials aimed at preventing or delaying the progression of specific cognitive, motor, psychiatric, or functional impairments. Furthermore, understanding the association between specific regional brain volumes and behavioral measures will broaden our understanding of the role of these brain regions in normal neurocognitive function and in other neurodegenerative diseases.

To date, little is understood about the neuropathological correlates of subtle changes in pre-HD on a spectrum of clinical measures. In larger studies of pre-HD participants (those with more than 50 participants), investigations of brain-behavior relationships have been restricted to only a few brain regions, notably the striatum and/or cerebral white matter volume [8, 11] or to a few specific motor and functional measures [3]. Other studies combined large samples of pre-HD and early diagnosed HD participants, such that the results are not specific to the pre-HD period [1, 12, 13]. For example, a large, multi-site study of combined pre-and-early stage HD, TRACK-HD, reported strong correlations between many gray- and white-matter regions and measures of tongue force, metronome tapping precision, antisaccade error rate, and recognition of negative emotions [13]. In the prodromal period, the PREDICT-HD study has demonstrated that atrophy and cortical thinning in specific brain regions increase [8, 14, 15] and performance on measures of cognitive and motor functioning worsens as individuals approach diagnosis [8, 11, 16]. However, the relationships between brain morphometry and a broad range of clinical variables that are known to exhibit subtle changes in the prodromal period have not been

comprehensively studied in pre-HD. The main objective of the present study was to better characterize *relationships* between regional brain volumes in pre-HD and functioning on a battery of key clinical variables from the PREDICT-HD study [17]. In the most comprehensive analyses to date of pre-HD individuals, we correlated regional MRI volumes with measures of cognitive performance in different domains, motor impairments, psychiatric manifestations, and functional capacity. We were particularly interested in determining whether subtle behavioral changes in pre-HD are simply a reflection of striatal atrophy, which is known to begin many years before diagnosis, or depend partially on atrophy in regions outside of the striatum. A secondary aim was to determine the relative importance of specific brain areas in explaining performance variability on cognitive, motor, psychiatric, and functional measures. Based on early literature in HD [18] and pre-HD [5], we hypothesized that cognitive measures would be more highly correlated with caudate volume than with other structure volumes, while motor measures would be more highly correlated with putamen volume than with other structure volumes. This hypothesis is supported by the anatomy of basal ganglia-thalamocortical circuits [19], wherein the caudate is a component of the dorsolateral prefrontal cortex circuit, which modulates cognitive-control processes, and the putamen is a component of the motor circuit, which governs motor control functions. Interestingly, more recent literature in small samples of pre-HD suggests that globus pallidus volume is more strongly correlated than striatal volume with motor functioning [6] and cerebral white-matter volume is more strongly correlated than striatal volume with cognitive functioning [20]. Our analyses were able to better evaluate these findings in a much larger sample of pre-HD participants.

## Materials and Methods

### Participants

Study participants included 516 pre-HD cases enrolled in the PREDICT-HD study [17], an international multi-site observational study following a large sample of pre-HD participants and gene-negative control participants who are offspring of parents with HD. Demographic and clinical/behavioral data are presented in Table 1. Control participants (N = 164) were not included in the correlational analyses, but their data are included in Table 1 for comparison with the pre-HD participants. All pre-HD participants were considered at the time of enrollment to be free of signs and symptoms that were severe enough to warrant a diagnosis of HD. This judgment was based on examination by clinicians experienced in the evaluation of movement disorders and specifically trained on administration of the Unified Huntington's Disease Rating Scale [21] for PREDICT-HD. Using this standardized scale that includes a series of specific assessments of HD-related motor movements, the clinician assigns a motor score, ranging from 0 to 124, and then assigns a score from 0 to 4 on the HD Diagnostic Confidence Level (DCL) scale, which indicates the rater's level of confidence that the motor abnormalities reflect the presence of HD. In accordance with clinical practice [22], HD diagnosis is operationally defined as a score of 4, indicating that the rater has ≥99% certainty that the participant shows “unequivocal presence of an otherwise unexplained extrapyramidal movement disorder.” Participants were excluded from the current study if they received a rating of 4 at baseline. Pre-HD participants were also assigned a “CAP” score, based on age and CAG repeat length, a proxy for their time to HD

diagnosis [23]. All aspects of the study were approved by the Institutional Review Board at each participating institution, and all participants gave written informed consent.

## Cognitive, motor, psychiatric, and functional measures

PREDICT-HD participants are seen yearly for evaluation that includes a comprehensive assessment battery [8, 17]. All data presented here are from the baseline assessment. The cognitive, motor, psychiatric, and functional capacity measures that were chosen for our analyses cover a wide range of the behavioral manifestations observed in symptomatic HD. The selection of specific cognitive and motor measures was guided by past reports showing they discriminate between pre-HD participants and age-matched gene-negative controls, and are correlated with estimates of participants' proximity to onset of diagnosable signs and symptoms [11, 24].

### Cognition

The correlation of brain atrophy with cognitive functioning might depend on the role of specific region(s) in mediating a particular cognitive function. As such, we selected five tests that represent different domains of cognition. These tests discriminate between pre-HD participants and age-matched gene-negative controls [16, 24]. They also correlate with estimates of proximity to diagnosis [11, 24]. The Symbol Digit Modalities Test (SDMT; total correct in 90 seconds) is a measure of attention and processing speed [25, 26]. The Hopkins Verbal Learning Test-Revised (HVLT-R; Immediate Recall (total learning; total number correct)) measures verbal learning and memory [27, 28]. The emotional recognition test (number correct; negative emotions only) is sensitive to negative emotion processing impairments in pre-HD [29]. The Wechsler Adult Intelligence Scale-III Letter-Number Sequencing (total correct) is a measure of working memory [30]. The self-paced timing task (550 ms pace; reciprocal of the standard deviation of the within-subject inter-tap interval when participants tap during the continuation phase without an external pacing cue) is a measure of timing proficiency [31, 32].

### Motor

Measures in this domain included the speeded tapping task, which measures maximum tapping speed of the non-dominant index finger (mean inter-tap interval for five 10-sec trials [16, 33]), the UHDRS total motor score [11, 21], and four of its five subscales (based on a factor analysis of the total UHDRS in patients with manifest HD): Oculomotor, Bradykinesia, Dystonia, and Chorea [34] (the UHDRS Rigidity subscale was not included because it did not discriminate the pre-HD subjects from the controls.)

### Psychiatric

Analyses included scores from two instruments, each of which was administered separately to the participant and to a companion familiar with the participant's behavior: the Frontal System Behavior Scale (FrSBe) [35, 36] and the Symptoms Checklist–90 Revised (SCL-90-R) [37, 38]. The FrSBe total scores were created by summing scores (from 1 to 5) on measures of frequency and distress for 18 individual behaviors, with total scores ranging from 36 to 180, and higher scores representing more impairment. For the SCL-90-R, the

Global Severity Index (GSI) T-scores were used for both the companion and self-report versions.

### Functional

Changes in functional capacity were assessed using two self-report instruments designed primarily for assessment of functional decline in patients with manifest HD, previously described by Beglinger and colleagues in greater detail [39]. Scores on the Total Functional Capacity (TFC) scale [40] and the Functional Assessment Scale (FAS) were based on participant interview, administered as part of the UHDRS [41].

### MRI acquisition and analysis

All MRI scans were obtained at the same visit as the clinical measures, using a standard protocol that included an axial 3D volumetric spoiled gradient echo series, obtained on 1.5T scanners. Scans were processed at The University of Iowa using AutoWorkup [42], an automated procedure implemented in BRAINS [43] and artificial neural networks [44]. This segmentation method is reliable [45] and sensitive to changes in brain volumes in cross-sectional and longitudinal studies of pre-HD [8, 15]. Volume measures were computed for gray- and white-matter in each lobe and for subcortical structures including the caudate, putamen, globus pallidus, thalamus, nucleus accumbens, and hippocampus.

Previous analyses of volumetric data from these brain regions have demonstrated significant age-adjusted volume reduction, even in pre-HD individuals who are far from estimated onset of diagnosable impairments, for caudate, putamen, thalamus, total cortical gray matter and total white matter, as well as significant correlations with estimated proximity to onset of diagnosable signs and symptoms for these same structures [8]. Significant longitudinal change has also been documented in caudate, putamen, thalamus, and total white matter for pre-HD individuals who are within 15 years of estimated onset [15]. Other regions included in this analysis (nucleus accumbens, hippocampus, and globus pallidus) have been found to be reduced in some studies of pre-HD [3, 6, 7, 10, 46, 47] and correlate with motor scores in pre-HD and HD [3].

After completion of AutoWorkup, all scans were individually inspected for correct realignment and coregistration, tissue classification, and accuracy of brain and subcortical structures. Participants were included in this study only if they had scans that passed inspection for all measures. All analyses here are based on regional measures divided by intracranial volume.

### Statistical analysis

Table 1 presents means and standard deviations (SD) for each of the measures used in the correlational analyses. Our correlational analyses were performed on the entire group of pre-HD subjects, because this provides the strongest test of the anatomical correlates of clinical symptoms, owing to the wide range of MRI volumes and performances on the clinical measures. Supplemental Table 1 presents means and standard deviations for pre-HD subjects divided into groups based on their CAP scores (as well as controls), to demonstrate the severity of impairment and atrophy at the various prodromal stages. First, we conducted

partial correlation analyses to examine the relationship between the regional volume measures and the cognitive, motor, psychiatric, and functional capacity measures, controlling for age, education (number of years), and sex. A false discovery rate (FDR) method was used to correct for multiple comparisons [48]. For measures that were significantly correlated with regional volumes, stepwise linear multiple regression analyses were performed to identify the best unique neuroimaging predictors (of those that were significantly correlated in the first step) of clinical variables, after controlling for age, years of education, and sex. For UHDRS motor subscales only, the dependent measure was binary (normal vs. abnormal), and logistic regression was used to examine the association of the imaging variables and these motor subscales. Imaging predictors were entered into the regression models one by one if they were significant at a $p = 0.05$ level and stayed in the model if they were significant at a $p = 0.01$ level.

## Results

As demonstrated in previous reports [8, 11, 16], all of the cognitive and motor measures used for the correlational analysis showed significant cross-sectional group differences between pre-HD participants and controls (Table 1), and most showed group differences between pre-HD subjects with low, medium, and high CAP scores (Supplemental Table 1). Table 2 presents significant partial correlations between the neuroimaging measures and the cognitive and motor measures, controlling for age, education, and sex. In general, the caudate, putamen, and globus pallidus were the regions whose volumes most strongly correlated with cognitive and motor measures. For correlations with motor and cognitive measures, volumes of three basal ganglia structures (caudate, putamen, and globus pallidus) generally yielded quite similar correlation values, and no single structure consistently demonstrated higher correlations with cognitive or motor measures than the others. All significant correlations were in the expected direction, with greater atrophy predicting greater impairment. Measures of cortical gray matter volume and hippocampus volume did not correlate with any of the cognitive and motor measures. None of the correlations between neuroimaging measures and the Frontal System Behavior Scale (companion or self-report), the Symptoms Checklist–90 Revised (companion or self-report), the dystonia subscale of the UHDRS, or the two measures of functional capacity were significant after FDR correction, so these correlations are not presented in Table 2. Also omitted are all of the partial correlations between regional measures of cortical gray matter volumes or hippocampus with all of the cognitive, motor, psychiatric, or functional measures, as they also failed to reach significance. (See Supplemental Table 2 for all correlations.)

Table 3 presents results of the multiple regressions conducted to identify the imaging measures summarized in Table 2 that best accounted for the variability in each of the motor and cognitive measures, after controlling for age, sex, and education. As would be expected from the results of the partial correlations, the regression analyses showed that one or both of the structures that had the highest partial correlations with a particular clinical measure were also the strongest predictors, in combination, for that measure, suggesting that each structure provided some unique explanation of the variance. The only exception was for oculomotor functioning, where the nucleus accumbens and frontal white matter contributed most strongly, with no additional significant contribution from the other basal ganglia

structures. For all five cognitive measures, either caudate or putamen volume best accounted for the variability, with globus pallidus accounting for additional variance in four of the five measures. Putamen volumes were more associated with cognitive measures that contained a significant motor output component, whereas caudate volumes correlated with cognitive measures that minimized motor output and emphasized executive control. In contrast, the subcortical volumes that best correlated with the motor functioning differed depending on the specific measure. Specifically, the putamen (speeded tapping), the caudate (UHDRS total motor score), the globus pallidus (chorea and bradykinesia), and the nucleus accumbens (oculomotor) best accounted for the variability in the different motor measures.

## Discussion

Our results demonstrate atrophy of the basal ganglia and white matter are associated with many motor and cognitive measures that are known to be sensitive to early subtle changes in pre-HD. All of the cognitive and motor measures (except dystonia) correlated strongly with caudate, putamen, and globus pallidus volumes. This is not entirely unexpected, since significant atrophy is present in these regions even in pre-HD individuals who are far from onset (defined in previous studies as less than 15 years from estimated onset of diagnosable signs and symptoms) [8], and all of the motor and cognitive variables assessed in this study show significant decline in individuals who are 9–15 years from estimated onset of diagnosable signs and symptoms. Impairments on the emotion recognition task and UHDRS total motor score are found in individuals even farther from estimated diagnosis (greater than 15 years) [24].

The absence of correlations between striatal volumes and psychiatric measures is somewhat surprising, as significant group differences have been reported between control participants and pre-HD participants on SCL-90 Global Severity Index and FrSBe [35, 38]. The severity of subtle motor impairment also correlates with the SCL-90 GSI (participant ratings) and FrSBe (companion and participant ratings) [38]. In addition, companion ratings of FrSBe, but not participant ratings, correlated with probability of diagnosis within five years [35]. Thus, we expected psychiatric impairment would be associated with striatal volumes, yet this was not found. This finding is likely the result of the high degree of variability in the psychiatric measures across the range of genetic exposure[1], including the absence of any psychiatric manifestations in many pre-HD individuals, as well as the transient nature of some impairments. It is also possible that psychiatric impairments are associated with brain regions not measured (e.g., amygdala) or that our brain measurements were not sufficiently sensitive to detect atrophy in smaller, functionally specific cortical regions (e.g., anterior cingulate gyrus) that might be associated with psychiatric measures. There may also be variability across participants in the brain regions that underlie subtle psychiatric impairment. The association between psychiatric measures and specific brain regions may also be obscured by effective treatment of psychiatric symptoms in some individuals. Thus, while it is likely that psychiatric impairment is, at least in part, related to underlying HD-

[1]The term “genetic exposure” is being used to reflect the individual's progression through the disease process, from presymptomatic through manifest HD, based on CAG and age. It is meant to encompass terms such as “disease burden,” and “genetic burden” that have been used in previous literature.

associated neuropathology, it does not appear that atrophy, as measured in the present study, relates to psychiatric dysfunction. Our finding is consistent with results from Scahill et al. [13], where no association was found between MRI measures and any of their psychiatric measures. Unlike our statistical approach, however, the analyses of Scahill and colleagues controlled for genetic exposure, included both symptomatic and pre-HD participants, and used a different method of correction for multiple comparisons. In the present study, the absence of an association between the functional measures and brain volumes may be due to the ceiling effect on measures of functional capacity, as most participants had little or no functional impairment.

The present study also did not find any relationship between cortical gray matter volumes and the cognitive, motor, psychiatric, or functional variables. This is somewhat surprising, as other studies using imaging methodologies similar to ours have demonstrated such relationships, especially for cognitive impairments, in other disorders. For example, Batista et al. showed that neocortex and basal ganglia volumes correlated with measures of executive function in individuals with multiple sclerosis [49]. Similarly, Fein et al. reported correlations between gray matter volumes and spatial processing in alcoholics [50]. Recently, cognitive tests of executive functioning, memory, visuospatial functioning and visuoconstruction were also associated with distinct patterns of regionally-specific cortical volume changes in Parkinson's patients without dementia [51]. In addition, studies of cortical thickness in smaller numbers of participants, using voxel-based morphometry (VBM) or VBM-like techniques, have demonstrated correlations between both cognitive and motor measures and specific areas of cortex in pre-HD [9] and in combined samples of pre-HD and symptomatic HD [1]. VBM-type measures of cortical thickness may be more sensitive than our measures of lobular cortical volumes, although there are concerns about the reliability and validity of these types of measures [52, 53]. In addition, there is some disagreement in the literature regarding the onset and longitudinal change within cortex in pre-HD, which may be relevant to the absence of correlations between clinical measures and cortical volume in this study. Tabrizi et al. found that pre-HD participants do not show significantly greater cortical atrophy than control participants in any areas except the occipital lobe, and this does not occur until participants are within 10 years of estimated onset [54]. In contrast, data from our previous studies suggest that cortical volumes throughout the brain are reduced in pre-HD, even in those participants who are very far from estimated onset [8]. Cortical gray matter volume and thickness also are significantly reduced throughout much of the cortex in pre-HD individuals who are estimated to be nine to 15 years from diagnosis [14]. However, our longitudinal analyses demonstrated the rate of atrophy over a two-year period is not significantly different from controls in any cortical regions studied [15] or in any subgroup of pre-HD (categorized according to estimated proximity to onset). Lack of longitudinal change in cortical volume during pre-HD would suggest that the subtle cognitive and motor changes that are occurring during this time may be the result of atrophy in other brain regions. One possibility is that these subtle declines are more related to a weakening in cortical-striatal and cortical-cortical interactions due to white matter changes. Interestingly, worse performances on most cognitive measures were associated with white matter volume reductions in the parietal, but not the frontal lobe (the primary target area for striatal neuron projections). In contrast, worse performances on

motor measures were associated with reduced frontal, but also parietal and sometimes temporal and occipital white matter volume. Despite findings of early atrophy in the occipital lobes [14], occipital white matter was not associated with most cognitive and motor measures. This is in contrast to results from Hobbs et al. [55], which suggested that occipital gray- and white-matter volumes (in addition to internal capsule and thalamus) had the highest correlations with the UHDRS total motor score in early HD.

Because of the high correlation between caudate and putamen volumes ($r = 0.76$; $p < 0.0001$), our multiple regression analyses typically demonstrated that only one of the two striatal volumes (caudate or putamen) accounted for the variance in motor and cognitive measures, although both are likely biologically important. Nonetheless, the multiple regression analyses examined whether non-striatal structure volumes explained additional variability in behavioral outcomes, beyond striatal volumes. Multiple regression analyses found that caudate volume was the region that accounted for the greatest amount of variability in most tests of cognitive functioning in pre-HD. The exceptions were symbol digit modalities and paced timing, both tests with a large motor component, for which caudate volume did not explain additional variance after putamen and globus pallidus volumes were included in the model. After controlling for caudate or putamen volume, globus pallidus volume also contributed significantly to most of the cognitive measures. However, as caudate, putamen, and globus pallidus volumes were all highly and similarly correlated with cognitive and motor measures, and are highly correlated with one another, it would not be valid to over-interpret small differences in the correlations to conclude that cognitive function is more dependent on caudate atrophy than on atrophy in other basal ganglia structures. No regions outside the basal ganglia contributed significantly to the prediction of any of the cognitive measures after controlling for volume of at least one basal ganglia structure. While cognitive function in normal individuals depends on multiple brain regions, in pre-HD the variance in most of these measures is accounted for primarily by basal ganglia volume reduction.

Similar to predictors for the cognitive measures, the strongest predictors for motor measures were primarily caudate, putamen, and globus pallidus volumes, but also included nucleus accumbens, frontal white matter, and temporal white matter volumes for oculomotor and bradykinesia scores. Caudate volume contributed strongly to the prediction of UHDRS total motor score, which is in agreement with the Van den Bogaard et al. finding for pre-HD (but not for symptomatic HD, where it surprisingly did not have a significant correlation) [3]. Our results do not support the hypothesis that putamen volume is superior to caudate volume in predicting motor impairment in pre-HD, as suggested by several smaller studies of early HD [18, 56] and other basal ganglia disorders [57].

Like Jurgens et al. [6], we also found strong involvement of globus pallidus in UHDRS total motor score, as well as in other cognitive and motor scores. Based on imaging and neuropathological studies, Majid et al. [7] concluded that changes in the globus pallidus are likely to be due to the loss of striatopallidal fibers projecting from striatal medium spiny neurons, such that both striatal and pallidal atrophy in pre-HD may result from the same pathological process of medium spiny neuron loss (and are unlikely due to cell loss within

the pallidum). The observed correlations between both cognitive and motor measures and globus pallidus volume, as well as striatal volume, would be consistent with this view.

It can be argued that the neurobehavioral relationships observed in the present study do not necessarily reflect a direct role of the striatum or white matter volume in cognitive or motor functioning. As Scahill et al. [13] note, specificity of the association between regional volume loss and clinical impairment can be improved by controlling for measures of disease severity or genetic exposure in the case of pre-HD. When controlling for genetic exposure (as well as age, sex, study site, education, total intracranial volume, and CAG repeat length), Scahill et al. [13] found no significant association between any cognitive measures and striatal volume. Presumably, genetic exposure is so highly correlated with striatal volume that controlling for this variable eliminates the contribution made by striatum. An exception was their finding that striatal volumes still correlated with a task similar to our self-paced timing task, consistent with our results. Likewise, their finding that striatal volumes correlate with measures of tongue force and antisaccade error rate, even after controlling for genetic exposure, may reflect the contribution of the striatum to motor impairment outside of the HD-related neuropathological process. Choosing to include genetic exposure (and/or the combination of age and CAG repeat) as a covariate depends on the question one is trying to answer.

Studies assessing correlations between longitudinal change in neuroimaging measures and longitudinal change in clinical measures may provide more evidence for direct causal linkages between specific regional atrophy and specific behavioral changes than was possible with our cross-sectional data. In a study of early-stage HD, 24-month change in volumes of whole brain, total gray matter, and total white matter correlated with decline on the UHDRS total functional capacity and the total motor score [54], suggesting some overlap between cross-sectional and longitudinal studies of neurocognitive relationships. However, this needs to be examined more carefully, since most longitudinal studies in which MRI and clinical variables are both tracked, have been conducted across relatively short periods of time (e.g., 12 to 36 months), rendering it more challenging to uncover potential neurocognitive relationships.

In summary, our results demonstrate that regional volumes, especially in the striatum and globus pallidus, are associated with subtle cognitive and motor impairments in pre-HD. One criterion for selecting outcome measures for clinical trials is that they relate to clinical signs and symptoms, and our results suggest that volumetric MRI measures meet this criterion. The choice of MRI volumetric measures as outcome measures in pre-clinical HD is further strengthened by demonstrations that these measures distinguish pre-HD individuals from healthy controls, are associated with proximity to onset of diagnosable signs and symptoms, and show longitudinal changes within short periods (one to two years) with relatively low variability in the rate of change across participants [15, 54]. Selection of cognitive, motor, and neuroimaging measures as outcomes in future clinical trials in pre-HD may depend on the specific clinical feature(s) being targeted. Speeded tapping had the highest correlations with striatal volumes, with significant unique contributions from both putamen and caudate, suggesting that it may be the best clinical measure for reflecting underlying striatal pathology in pre-HD, and thus might be the most appropriate clinical measure for evaluation

of treatments expected to target striatal neurons. On the other hand, if treatments are expected to target maintenance of white matter, inclusion of cognitive or motor measures with strong correlations to white matter volumes (e.g., symbol digit modalities test) might also be considered as appropriate outcome measures. Of course, behavioral measures other than those tested in the current study might also prove to be strong outcome measures. In conclusion, the neurocognitive and motor associations revealed in this study demonstrate the clinical relevance of neuroimaging measures and can assist investigators in the selection of appropriate outcome measures for future clinical trials, including indices of cognitive function, motor impairment, and regional brain atrophy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1
## Demographic, clinical, and structural volume data

| | Pre-HD mean (SD) | Control mean (SD) | Test statistic (*p*-value) |
|---|---|---|---|
| *N* | 516 | 164 | |
| Sex | 65.7% female | 64.6% female | $X^2$ = 0.0622 (0.8030) |
| CAG repeat length | 42.47 (2.54) | NA | |
| Age (years) | 40.50 (9.75) | 43.78 (11.17) | *t* = −3.37 (0.0009) |
| CAP* | 344.11 (83.60) | NA | |
| Education (years) | 14.41 (2.64) | 14.88 (2.69) | *t* = −1.98 (0.0481) |
| *Motor* | *N*= 504 | *N*= 164 | |
| Speeded tapping | 251.77 (55.05) | 228.23 (27.07) | *t* = 7.25 (<.0001) |
| UHDRS total motor | 4.81 (4.94) | 2.59 (3.35) | *t* = 6.51 (<.0001) |
| UHDRS oculomotor | 1.46 (2.11) | 0.67 (1.30) | *t* = 5.71 (<.0001) |
| UHDRS bradykinesia | 1.98 (2.27) | 1.30 (1.96) | *t* = 3.74 (0.0002) |
| UHDRS dystonia | 0.093 (0.44) | 0.03 (0.21) | *t* = 2.48 (0.0134) |
| UHDRS chorea | 0.93 (1.62) | 0.29 (0.77) | *t* = 6.96 (<.0001) |
| *Cognitive* | | | |
| Symbol-digit modalities | 50.72 (11.04) | 54.58 (9.05) | *t* = −4.50 (<.0001) |
| Hopkins verbal learning | 26.54 (4.97) | 28.31 (4.52) | *t* = −4.06 (<.0001) |
| Emotional recognition | 25.43 (5.89) | 28.57 (5.15) | *t* = −6.51 (<.0001) |
| Self-paced timing | 0.023 (0.0086) | 0.029 (0.0087) | *t* = −6.95 (<.0001) |
| Letter-number sequencing | 11.47 (2.78) | 12.64 (3.25) | *t* = −4.04 (<.0001) |
| *Psychiatric* | | | |
| Frontal system behavior scale (participant) | 59.40 (19.30) | 53.90 (12.67) | *t* = 4.21 (<.0001) |
| Frontal system behavior scale (companion) | 53.68 (17.49) | 49.04 (11.31) | *t* = 3.83 (0.0002) |
| Symptoms checklist–90 revised global severity index (participant) | 52.94 (13.84) | 48.93 (9.01) | *t* = 4.30 (<.0001) |
| Symptoms checklist–90 revised global severity index (companion) | 51.92 (13.00) | 50.16 (12.83) | *t* = 1.47 (0.1410) |
| *Functional* | | | |
| Total functional capacity | 12.80 (0.71) | 12.98 (0.15) | *t* = −5.27 (<.0001) |
| Functional assessment scale | 24.84 (0.72) | 24.95 (0.27) | *t* = −2.97 (0.0031) |
| *Structural MRI*** | | | |
| Putamen | 0.56 (0.10) | 0.65 (0.077) | *t* = −12.02 (<.0001) |
| Caudate | 0.40 (0.08) | 0.46 (0.057) | *t* = −10.79 (<.0001) |
| Globus pallidus | 0.16 (0.032) | 0.18 (0.023) | *t* = −10.10 (<.0001) |
| Thalamus | 0.96 (0.088) | 0.97 (0.083) | *t* = −1.50 (0.1353) |
| Nucleus accumbens | 0.045 (0.0078) | 0.048 (0.0081) | *t* = −4.91 (<.0001) |
| Hippocampus | 0.37 (0.034) | 0.37 (0.035) | *t*= 0.79 (0.4287) |
| Frontal gray | 17.77 (1.13) | 18.02 (1.16) | *t* = −2.46 (0.0141) |
| Parietal gray | 9.90 (0.71) | 9.93 (0.71) | *t* = −0.51 (0.6124) |
| Occipital gray | 5.21 (0.54) | 5.08 (0.45) | *t*= 3.15 (0.0018) |
| Temporal gray | 11.03 (0.79) | 10.90 (0.65) | *t*= 2.20 (0.0283) |
| Frontal white | 12.88 (1.38) | 13.51 (1.28) | *t* = −5.19 (<.0001) |

| | Pre-HD mean (SD) | Control mean (SD) | Test statistic (*p*-value) |
|---|---|---|---|
| Parietal white | 7.39 (0.79) | 7.59 (0.69) | $t = -3.09$ (0.0022) |
| Occipital white | 3.05 (0.47) | 3.15 (0.37) | $t = -2.92$ (0.0037) |
| Temporal white | 5.18 (0.62) | 5.36 (0.55) | $t = -3.35$ (0.0009) |

* CAP= CAG Age Product =(age at entry) ×(CAG – 33.66) (Zhang et al., 2011).

** Corrected volumes =(structure volume/intracranial volume)×100.

**Table 2**

**Significant partial correlations between neuroimaging measures and motor and cognitive measures**

| | Putamen | Caudate | Globus pallidus | Thalamus | Nucleus accumbens | Frontal white | Parietal white | Occipital white | Temporal white |
|---|---|---|---|---|---|---|---|---|---|
| *Motor* (*N*= 504) | | | | | | | | | |
| Speeded tapping | −0.42 | −0.42 | −0.36 | −0.14 | −0.20 | −0.15 | −0.21 | | |
| UHDRS total motor | −0.27 | −0.29 | −0.30 | | −0.14 | −0.15 | −0.12 | | −0.13 |
| UHDRS oculomotor | −0.18 | −0.20 | −0.20 | | −0.13 | −0.12 | | | |
| UHDRS bradykinesia | −0.22 | −0.25 | −0.24 | | | −0.16 | −0.17 | −0.13 | −0.17 |
| UHDRS chorea | −0.22 | −0.21 | −0.27 | | | | | | |
| *Cognitive* (*N* = 486) | | | | | | | | | |
| Symbol-digit modalities | 0.33 | 0.31 | 0.35 | 0.12 | 0.13 | | 0.23 | 0.19 | 0.12 |
| Hopkins verbal learning | 0.23 | 0.33 | 0.29 | | | | | | |
| Emotion recognition | 0.31 | 0.33 | 0.33 | | 0.15 | | 0.16 | 0.13 | |
| Self-paced timing | 0.32 | 0.32 | 0.34 | | | | 0.18 | | |
| Letter-number sequencing | 0.15 | 0.20 | 0.18 | | | | 0.13 | | |

Only significant correlations that survived FDR correction are presented. All neuroimaging volume measures are corrected for intracranial volume. Correlations are corrected for age, sex, and years of education. For all motor measures, lower scores reflect better performance, while the opposite is true for all cognitive measures (thus explaining negative correlations with regional brain volumes for motor measures and positive correlations for cognitive measures). Correlations were not significant (FDR corrected) for any cortical gray matter or hippocampal volume measures, for any psychiatric or functional measures, or for the UHDRS Dystonia subscales. See Supplemental Table 2 for a list of all correlations, including those that were non-significant.

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**Table 3**

**Linear multiple regressions for motor and cognitive measures**

| | F or chi-square for model | *p* for model | Structural MRI measures contributing to the model after controlling for age, sex, and education | | | | |
|---|---|---|---|---|---|---|---|
| | | | **Structure** | **Parameter estimate** | **SE** | ***t* or $\chi^2$** | ***p*** |
| *Motor* | | | | | | | |
| Speeded tapping | $F$= 37.29 | <0.0001 | putamen | −133.50 | 31.59 | $t$= −4.23 | <0.0001 |
| | | | caudate | −169.54 | 40.21 | $t$= −4.22 | <0.0001 |
| UHDRS Total Motor | $F$= 15.84 | <0.0001 | caudate | −11.44 | 3.51 | $t$= −3.26 | 0.0012 |
| | | | globus pallidus | −31.69 | 9.11 | $t$= −3.48 | 0.0005 |
| UHDRS oculomotor | $\chi^2$ = 23.55 | 0.0003 | nucleus accumbens | −34.26 | 12.17 | $\chi^2$ = 7.93 | 0.0049 |
| | | | frontal white | −0.20 | 0.07 | $\chi^2$ = 7.56 | 0.0060 |
| UHDRS bradykinesia | $\chi^2$ = 38.85 | <0.0001 | globus pallidus | −12.38 | 3.38 | $\chi^2$ = 13.38 | 0.0003 |
| | | | temporal white | −0.59 | 0.17 | $\chi^2$ = 12.60 | 0.0004 |
| UHDRS chorea | $\chi^2$ = 33.20 | <0.0001 | globus pallidus | −18.20 | 3.39 | $\chi^2$ = 28.83 | <0.0001 |
| *Cognitive* | | | | | | | |
| Symbol-digit modalities | $F$= 33.24 | <0.0001 | putamen | 22.16 | 5.71 | $t$= 3.88 | 0.0001 |
| | | | globus pallidus | 77.76 | 18.83 | $t$= 4.13 | <0.0001 |
| Hopkins verbal learning | $F$= 23.34 | <0.0001 | caudate | 14.48 | 3.42 | $t$= 4.23 | <0.0001 |
| | | | globus pallidus | 23.38 | 8.83 | $t$= 2.65 | 0.0084 |
| Emotion recognition | $F$= 32.71 | <0.0001 | caudate | 14.46 | 3.93 | $t$= 3.68 | 0.0003 |
| | | | globus pallidus | 40.55 | 10.15 | $t$= 4.00 | <0.0001 |
| Self-paced timing | $F$= 24.14 | <0.0001 | putamen | 0.01 | 0.00 | $t$= 2.98 | 0.0030 |
| | | | globus pallidus | 0.06 | 0.02 | $t$= 4.22 | <0.0001 |
| Letter-number sequencing | $F$= 22.04 | <0.0001 | caudate | 6.51 | 1.50 | $t$= 4.33 | <0.0001 |

Regressions were performed only for clinical measures that were significantly correlated with neuroimaging measures (Table 2). For all motor measures, lower scores reflect better performance, while the opposite is true for all cognitive measures. All neuroimaging volume measures are corrected for intracranial volume. For UHDRS oculomotor, bradykinesia, and chorea, scores were converted to a binary measure (normal vs. abnormal), and chi-square was used to test significance of the model.