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# 1 Genetic load determines atrophy in hand cortico-striatal 2 pathways in presymptomatic Huntington's disease

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15

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17

## 18 Abstract

19 Huntington's disease (HD) is an inherited neurodegenerative disorder that causes progressive breakdown  
20 of striatal neurons. Standard white matter integrity measures like fractional anisotropy and mean  
21 diffusivity derived from diffusion tensor imaging were analyzed in prodromal-HD subjects; however, they  
22 studied either a whole brain or specific subcortical white matter structures with connections to cortical  
23 motor areas. In this work, we propose a novel analysis of a longitudinal cohort of 243 prodromal-HD  
24 individuals and 88 healthy controls who underwent two or more diffusion MRI scans as part of the  
25 PREDICT-HD study. We separately trace specific white matter fiber tracts connecting the striatum  
26 (caudate and putamen) with four cortical regions corresponding to the hand, face, trunk, and leg motor  
27 areas. A multi-tensor tractography algorithm with an isotropic volume fraction compartment allows

28 estimating diffusion of fast-moving extra-cellular water in regions containing crossing fibers and provides  
29 quantification of a microstructural property related to tissue atrophy. The tissue atrophy rate is separately  
30 analyzed in eight cortico-striatal pathways as a function of CAG-repeats (genetic load) by statistically  
31 regressing out age effect from our cohort. The results demonstrate a statistically significant increase in  
32 isotropic volume fraction (atrophy) bilaterally in hand fiber connections to the putamen with increasing  
33 CAG-repeats, which connects the genetic abnormality (CAG-repeats) to an imaging-based microstructural  
34 marker of tissue integrity in specific white matter pathways in HD. Isotropic volume fraction measures in  
35 eight cortico-striatal pathways are also correlated significantly with total motor scores and diagnostic  
36 confidence levels, providing evidence of their relevance to HD clinical presentation.

37

38 **Keywords:** Prodromal-HD, diffusion MRI, isotropic volume fraction, CAG-repeats, cortico-striatal pathways

39

## 40 **1. Introduction**

41 Huntington's disease (HD) is a genetic brain disorder that causes physical and mental decline, including  
42 uncontrollable movements, emotional problems, and loss of thinking abilities. Huntington's disease is caused by  
43 expansion of CAG (cytosine-adenine-guanine) repeats in the Huntington (HTT) gene, with a threshold of 36 or more  
44 repeats (Vonsattel and DiFiglia, 1998). During the presymptomatic (prodromal-HD) phase, individuals do not  
45 manifest the characteristic motor symptoms necessary for a diagnosis, but they have been shown to exhibit mild sub-  
46 clinical cognitive, psychiatric and motor deficits. Symptoms of Huntington's disease vary between individuals and  
47 its progression may evolve over years before formal diagnosis. Studies show that brain atrophy occurs gradually and  
48 typically starts years before symptom onset. Although this inherited disease currently has no cure, identification of  
49 reliable markers might be useful for future Huntington's disease clinical trials to monitor disease progression and  
50 evaluate therapeutic efficacy (Ross et al., 2014).

51 Neuroimaging provides a powerful tool for detecting, understanding, and monitoring disease progression. Early  
52 works proposed to use Magnetic Resonance Imaging (MRI) to elucidate structural abnormalities in Huntington's  
53 disease (Bohanna et al., 2008; Georgiou-Karistianis et al., 2013). In the PREDICT-HD and TRACK-HD studies,  
54 MRI measures, e.g., the whole-brain volume, caudate and putamen volumes, were examined to understand  
55 Huntington's disease progression (Paulsen et al., 2008; Tabrizi et al., 2013; Paulsen et al., 2014). Several studies

56 have shown that volume reductions in the striatum, particularly within the caudate, can be observed as early as 10  
57 years before diagnosis in prodromal-HD individuals (Harris et al., 1999; Thieben et al., 2002; Paulsen et al., 2008).  
58 Volume reductions in the globus pallidus (Harris et al., 1999; Thieben et al., 2002) and thalamus (Harris et al., 1999;  
59 Paulsen et al., 2006) have also been observed. The literature on cortical thinning has however been controversial.  
60 While some studies have found decreased cortical thickness in prodromal-HD (Rosas et al., 2005; Nopoulos et al.,  
61 2007; Bohanna et al., 2008), others have found increased grey matter volume (Aylward et al., 1996; Aylward et al.,  
62 1998; Paulsen et al., 2006). The relatively large longitudinal TRACK-HD study failed to find differences in cortical  
63 volumes at baseline and 12 months (Tabrizi et al., 2009; Tabrizi et al., 2011) in prodromal-HD, but did find reduced  
64 cortical thickness in occipital areas in prodromal-HD individuals who were closest to diagnosis at 24 months  
65 (Tabrizi et al., 2012), suggesting that cortical thickness changes may not be tied to motor symptom onset or that they  
66 occur only as secondary collateral damage measurable late in the prodromal-HD stage of the illness.

67 In addition to volumetric measures, studies of tissue microstructure have shown changes in Huntington's disease.  
68 Mean diffusivity derived from diffusion weighted magnetic resonance imaging (dMRI) was found to have increased  
69 in the prefrontal cortex of prodromal-HD subjects (Rosas et al., 2006; Phillips et al., 2013; Matsui et al., 2014). In  
70 addition, the IMAGE-HD study (Poudel et al., 2015) showed evidence of longitudinal decline in white matter  
71 integrity in symptomatic Huntington's disease using diffusion tensor imaging (DTI, a special case of dMRI which  
72 assumes a Gaussian diffusion profile at each voxel) data. DTI studies have also provided evidence of white matter  
73 degeneration in terms of reduced fractional anisotropy and increased radial diffusivity. It was suggested that these  
74 measures may provide unique information about the time-course and diagnosis of neurodegeneration in prodromal-  
75 HD (Liu et al., 2016). Other studies have reported reduced fractional anisotropy in several regions including the  
76 corpus callosum (Stoffers et al., 2010; Phillips et al., 2013), frontal tracts (Poudel et al., 2014; Phillips et al., 2014),  
77 thalamic tracts (Stoffers et al., 2010; Phillips et al., 2014), and white matter surrounding the striatum (Stoffers et al.,  
78 2010). These DTI findings have been thought to reflect degeneration at the cellular level and a reduction in white  
79 matter tract integrity (due to reduction in fractional anisotropy). Another recent work (Shaffer et al., 2016) used a  
80 multi-tensor tractography framework to analyze changes in the motor pathways in three groups clustered using the  
81 CAP score (product of CAG-repeats and age). The results showed significant differences in fractional anisotropy in  
82 the three groups in the motor pathways.

83 However, as has been shown in several recent works in diseases such as schizophrenia and Parkinson's (Pasternak  
84 et al., 2015; Rotenberg et al., 2015; Planetta et al., 2016), the DTI model is simplistic and may not be appropriate to  
85 draw inferences about the neurobiological abnormalities in tissue. Adding an isotropic volume fraction compartment  
86 (Pasternak et al., 2009) to the standard DTI model provides more specificity and allows to quantify the volume  
87 fraction of fast moving extra-cellular water. The existence of the isotropic volume fraction has been validated in  
88 mouse models of demyelination and tissue loss (Wang et al., 2011). Similarly, it has been used in popular models  
89 like neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012). In their work on comparing  
90 different diffusion models, Panagiotaki et al. show that adding an isotropic compartment better explains the dMRI  
91 signal (Panagiotaki et al., 2012).

92 In the study of schizophrenia and Parkinson's (Pasternak et al., 2015; Rotenberg et al., 2015; Planetta et al.,  
93 2016), the authors have shown that including this isotropic volume fraction compartment provides better  
94 neurobiological clarity about the underlying tissue abnormality. For example, an increase in the isotropic volume  
95 fraction component could indicate loss of neurons or tissue atrophy. In schizophrenia, a simple DTI model pointed  
96 to decreased fractional anisotropy in several brain regions implying decreased white matter integrity. However,  
97 incorporating the isotropic volume fraction model pointed to widespread neuro-inflammation as a possible  
98 mechanism and very little change in white matter integrity (Pasternak et al., 2009; Pasternak et al., 2015). Thus, we  
99 hypothesize that the inferences drawn from the DTI model about reduced white matter integrity in Huntington's  
100 disease may not be entirely accurate and need to be further tested using more advanced models of diffusion as is  
101 done in this work.

102 Recent studies on mouse models of Huntington's disease have reported the existence of widespread brain atrophy  
103 in several brain regions (Steventon et al., 2016). Consequently, in this paper, we propose to use the isotropic volume  
104 fraction (a measure of tissue atrophy) estimated in an unscented Kalman filter based multi-tensor tractography  
105 framework (Malcolm et al., 2010; Baumgartner et al., 2012) to characterize white matter atrophy in prodromal-HD  
106 subjects. This framework allows to trace fiber tracts through crossing fiber regions while simultaneously estimating  
107 the isotropic volume fraction along the tracts. We hypothesize that we see a higher isotropic volume fraction in  
108 prodromal-HD subjects compared to normal controls, indicating increased brain atrophy. Note that, most earlier  
109 works have not investigated this aspect of Huntington's disease pathophysiology due to the limitations of the DTI  
110 model.

111 Another novel aspect of our work is the design of a methodology to extract specific cortico-striatal tracts  
112 corresponding to the hand, face, trunk, and leg motor regions, as shown in **Fig. 1**. Previous studies have shown that  
113 the cortico-striatal pathway in the brain is key to early Huntington's disease symptomatology and that Huntington's  
114 disease affects the white matter causing dysfunction due to neuronal loss in the striatal circuits and cortical neurons  
115 that make up the cortico-striatal pathways (Macdonal et al., 2002; Cepeda et al., 2003; Cepeda et al., 2007;  
116 Vonsattel et al., 2008). However, for the first time in this study, we trace and differentially analyze these specific  
117 tracts connecting the hand, face, trunk, and leg areas in the cortex to the caudate and putamen (Haber and Calzavara  
118 2009) and estimate the isotropic volume fraction in these tracts in a large longitudinal data set. This allows us to  
119 evaluate the sensitivity of isotropic volume fraction to detect tissue atrophy in different motor areas and its  
120 specificity to different anatomical parts of the cortico-striatal pathway.

121 To investigate if specific cortico-striatal pathways exhibit differential rates of atrophy in prodromal-HD subjects,  
122 we analyze the PREDICT-HD data, which is a longitudinal dataset collected from gene expansion negative controls  
123 and subjects with prodromal-HD. Specifically, we investigate the longitudinal isotropic volume fraction from three  
124 perspectives: 1) its sensitivity to brain atrophy in prodromal-HD subjects in comparison to healthy controls; 2) its  
125 correlation to genetic load, the CAG repeats; 3) its correlation to behavioral and clinical tests, such as total motor  
126 scores and diagnostic confidence level. We performed these tests using linear mixed-effects models for the  
127 population of healthy controls and prodromal-HD, respectively. The experimental results (after multiple hypothesis  
128 correction) indicate that the isotropic volume fraction, specifically in the bilateral hand motor tracts could be used as  
129 an imaging marker of genetic load and symptom severity in prodromal-HD.

130

## 131 **2. Materials and methods**

132 In this work, we analyzed the longitudinal diffusion MRI data set of prodromal-HD subjects acquired as part of the  
133 PREDICT-HD project (Paulsen et al., 2014). Under the guidance of an expert neuroanatomist (Dr. Makris) we  
134 manually created a modification of the Desikan-Killiany cortical atlas (Desikan et al., 2006) typically used with  
135 FreeSurfer (Fischl et al., 2004), to produce a new atlas that includes delineations of the hand, face, trunk, and leg  
136 sub-regions of the motor cortex. These new expert-defined atlas regions were spatially mapped to the T1-weighted  
137 image of each individual subject. Whole brain multi-tensor tractography was performed on the dMRI data and white  
138 matter tracts connecting the striatum (caudate and putamen) with each of the four cortical motor regions were

139 extracted, as shown in **Fig. 1**. The isotropic volume fraction was estimated in each of the fiber bundles (a total of  
 140 sixteen fiber bundles; four cortico-caudal and four cortico-putamen in each hemisphere) and mixed-effects models  
 141 (Pinherio and Bates, 2004) were used to analyze the data as described in the subsequent section.

## 142 2.1. Linear mixed-effects model

143 Typically, regression models are selected to estimate the correlation between variables, for example, the correlation  
 144 of the isotropic volume fraction with age, CAG, or total motor scores. Mixed-effects models are an extension of  
 145 standard regression models and are more suitable for longitudinal data because they can account for the dependency  
 146 due to repeated measures or data in groups. A mixed-effects model has both fixed and random effects while a  
 147 standard regression model has only fixed effects. Specifically, the fixed-effects terms in a mixed-effects model  
 148 correspond to the conventional regression part, and the random-effects terms are associated with individual  
 149 experimental units drawn at random from a population. In this paper, we use a linear mixed-effects model to study a  
 150 population of longitudinal data, i.e., the population of healthy controls and the population of prodromal-HD subjects.  
 151 Assume in a population there are  $N$  subjects and the dMRI measures for subject  $i$  ( $i = 1, \dots, N$ ) are collected at  $n_i$   
 152 time points. For such longitudinal data, the mixed-effects model estimates the relationship between a dMRI measure  
 153 and associated subject attributes through multilevel regression. The model can be expressed as:

$$154 \quad y_{ij} = \underbrace{\beta_0 + \beta_1 x_{ij}}_{\text{fixed effects}} + \underbrace{\gamma_{0i} + \gamma_{1i} u_{ij}}_{\text{random effects}} + \epsilon_{ij}, \quad i = 1, 2, \dots, N, \quad j = 1, 2, \dots, n_i. \quad (1)$$

155 Here,  $y_{ij}$  corresponds to the response, e.g., the isotropic volume fraction, for the  $i$ -th individual measured at the  $j$ -th  
 156 time point;  $x_{ij}$  is the independent variable and depends on the task, e.g., the age of the subject or the CAG repeats if  
 157 we regress out the age effect later;  $u_{ij}$  is the independent variable in the random effect term analogous to  $x_{ij}$ . The  
 158 parameters  $\beta_0$  and  $\beta_1$  are the average intercept and slope shared among the population, while  $\gamma_{0i}$  and  $\gamma_{1i}$  are the  
 159 random effects intercept and slope, the specific parameters for subject  $i$ . The random variable  $\epsilon_{ij} \sim N(0, \sigma^2)$  is the  
 160 independent error, which follows a normal distribution with zero mean and a standard deviation of  $\sigma$ . The random  
 161 effects are designed to account for the dependency of the data in several variables. For example, the dependency  
 162 could exist in the data collected from the same subject, the same gender (Zielonka et al. 2013), the same scanner, or  
 163 subjects with the same CAG repeats. Hence, our linear mixed-effects model has the following formulation:

$$164 \quad y_{ij} = \underbrace{\beta_0 + \beta_1 x_{ij}}_{\text{fixed effects}} + \underbrace{\gamma_{0i}^{sub} + \gamma_{1i}^{sub} u_{ij}}_{\text{random effects subject-specific}} + \underbrace{\gamma_{0k}^{gen} + \gamma_{1k}^{gen} v_{ij}}_{\text{random effects gender-specific}} + \underbrace{\gamma_{0r}^{CAG} + \gamma_{1r}^{CAG} w_{ij}}_{\text{random effects CAG-specific}} + \underbrace{\gamma_{0s}^{scan} + \gamma_{1s}^{scan} s_{ij}}_{\text{random effects scanner-specific}} + \epsilon_{ij}, \quad (2)$$

165 where  $k$  represents male or female,  $r$  is the number of CAG repeats,  $s$  represents the scanner site; while  $u_{ij}$ ,  $v_{ij}$ ,  $w_{ij}$ ,  
 166 and  $s_{ij}$  are random effect variables analogous to  $x_{ij}$ . Note that our data was collected at several different sites, and  
 167 hence we use the scanner site as a co-variate to account for scanner related differences. This linear mixed-effects  
 168 model can be used to detect the caudate and putamen volume loss over age, to measure the change in the isotropic  
 169 volume fraction with age in a population, and to estimate the correlation of the isotropic volume fraction with total  
 170 motor scores and diagnostic confidence levels.

171 Meanwhile, we are also interested in exploring the correlation between the isotropic volume fraction and CAG  
 172 repeats for Huntington’s disease subjects. As is known from literature, dMRI measures such as fractional anisotropy  
 173 and the isotropic volume fraction change with age. To compute correlation between the isotropic volume fraction  
 174 and CAG repeats, we should first remove the effect of age on the estimated the isotropic volume fraction. Therefore,  
 175 we estimated the change in the isotropic volume fraction with age in the normal control population and regressed it  
 176 out from the HD group. In particular, we used the above linear mixed-effects model (Eq. 2) to estimate the normal  
 177 control group trend, represented by the fixed effects parameters ( $\beta_0^{normal}$  and  $\beta_1^{normal}$ ). With respect to the  
 178 estimated normal control group trend, we compute the residuals of the isotropic volume fraction for prodromal-HD  
 179 subjects  $\delta y_{ij}^{HD}$  as follows:

$$180 \quad \delta y_{ij}^{HD} = y_{ij}^{HD} - (\beta_0^{normal} + \beta_1^{normal} x_{ij}^{HD}), \quad (3)$$

181 where  $x_{ij}^{HD}$  represents the age of the HD subject and  $y_{ij}^{HD}$  represents its measured the isotropic volume fraction. This  
 182 is further used to compute the correlations between the residuals and CAG repeats using the linear mixed-effects  
 183 model. In this task, since the age effect has been regressed out,  $x_{ij}$  in Eq. 2 corresponds to CAG repeats,  
 184  $y_{ij}$  corresponds to the isotropic volume fraction residuals for prodromal-HD subjects, and the random effects involve  
 185 the subject-, gender-, and scanner-specific dependency.

186

## 187 2.2. PREDICT-HD data

188 We use data collected by the PREDICT-HD project (Paulsen et al., 2014), an observational study of the earliest  
 189 signs of Huntington’s disease. This study involved more than 600 participants, but we used the data from only those  
 190 individuals who have at least two MRI scans. This yielded 331 subjects with 830 scans collected at 2 to 5 time

191 points. Specifically, 202 subjects have 2 scans, 94 subjects have 3 scans, 31 subjects have 4 scans, and 4 subjects  
192 have 5 scans. Additionally, the PREDICT-HD study provides genetic load for each subject, i.e., the CAG repeats,  
193 and clinical scores, e.g., total motor scores and diagnostic confidence levels after each visit. The demographic and  
194 clinical information of the data used in this study is shown in **Table 1**.

195 **Participants.** This study included 243 individuals with prodromal-HD and 88 normal controls. All participants were  
196 right handed and underwent at least two longitudinal imaging sessions, resulting in a total of 611 prodromal-HD and  
197 219 healthy control imaging sessions. Additional demographic characteristics for this sample are shown in **Table 1**.  
198 The groups did not differ in terms of number of imaging sessions performed per participant, overall duration of time  
199 between imaging sessions, or education. PREDICT-HD exclusion criteria included (a) sufficient motor signs for a  
200 motor diagnosis at study entry; (b) history of traumatic brain injury or other central nervous system injury or  
201 diseases; (c) pacemakers or metallic implants; (d) prescribed antipsychotic or phenothiazine-derivative antiemetic  
202 medication in the past six months; and (e) clinical evidence of unstable medical or psychiatric illness.

203  
204 **Imaging Parameters.** A total of 830 T1 and T2-weighted anatomical and diffusion-weighted images were acquired  
205 on 3T scanners at 15 sites, representing 3 scanner manufacturers (GE, Phillips, and Siemens). Due to varying  
206 scanning site capabilities and support resources, a minimum set of criteria were specified for merging the diffusion-  
207 weighted imaging (DWI) data sets from different sites: 1) Only DWI data sets with more than 28 quality approved  
208 gradient directions, 2) voxel volume was required to be less than 9.6 cubic mm with a maximum voxel length of  
209 2.4mm, 3) All directional gradients needed to be within 2% of 1000 for their b-value, and 4) anatomical coverage  
210 needed to completely include all the tracts of interest. The most frequently used MRI acquisition parameters are  
211 given in **Table 2**. After visual inspection of all images, we excluded 13 T2-weighted MRI scans, resulting in 636  
212 multimodal and 13 single modal inputs for structural MRI processing. Processed T2-weighted images were then  
213 used along with DWI data in the diffusion analysis pipeline and the T1-weighted images were used for the 13  
214 sessions where the T2- weighted images were not available.

215

### 216 2.3. Image Processing

217 Structural and diffusion-weighted MR images were processed using the BRAINSTools suite  
218 (<https://github.com/BRAINSia/BRAINSTools.git>) and ANTs packages (Avants et al., 2009). An extensible

219 processing pipeline was developed in Nipype (Gorgolewski et al., 2011) that utilizes high performance computing  
220 resources to achieve time-efficient data processing and tractography analysis on large-scale multi-center diffusion-  
221 weighted images.

222

223 **Structural MRI Processing.** Structural MR Images (T2-weighted (T2-w) and/or T1-weighted (T1-w) images) were  
224 utilized to fix susceptibility-induced anatomical distortions in diffusion-weighted imaging data and provide precise  
225 anatomical labeling for dMRI processing and analysis. All available structural modalities, T1- and when available  
226 T2-weighted images, of each dataset were processed jointly to improve the robustness of the processing using  
227 complimentary information provided by multiple modalities. In the 13 cases where the T2 image was not available,  
228 a T1-only data processing was performed to identify anatomical brain regions. The T1-only morphometric  
229 processing was accurate enough for the subsequent tracts of interest extraction method. First, structural MR data  
230 were spatially normalized to a common reference orientation defined by anterior commissure-posterior commissure  
231 (AC-PC) line and inter-hemispheric fissure (Lu and Johnson, 2010; Ghayoor et al., 2017). The images were then  
232 processed through an Expectation Maximization (EM) and a fuzzy k-Nearest Neighbor (KNN) tissue classification  
233 that incorporates bias-field correction, image registration, and tissue classification (Kim and Johnson, 2013;  
234 Ghayoor et al., 2016). Whole brain segmentation (i.e. labeling) was performed first by applying the standard  
235 FreeSurfer pipeline (Fischl et al., 2004), and then by augmenting the resulting Desikan-Killany segmentation of the  
236 cortex (Desikan et al., 2006) with a custom-made parcellation of the motor cortex into four functional sub-regions,  
237 as described in further detail in a section below.

238 **Diffusion MRI Processing.** The dMRI processing first employed the quality-control procedures described in our  
239 previous works (Matsui et al., 2014; Oguz et al., 2014) to prepare dMRI scans by removing slice-wise and interlace  
240 artifacts as well as correcting for eddy-current and motion artifacts. The quality-controlled dMRI scans were further  
241 processed to integrate susceptibility artifact correction using a non-linear constrained registration in the phase-  
242 encoding direction available from the ANTs packages (Avants et al., 2009). The constrained registration only allows  
243 warping within the plane (i.e. within image slice) for the phase encoding direction, and is primarily used to improve  
244 anatomical alignment of the diffusion images to the morphometric scans. To enhance the quality of our data and to  
245 allow for detection of multiple fibers from the sparse set of gradient directions acquired, we used our compressed

246 sensing algorithm (Michailovich et al., 2011; Rathi et al., 2014) to reconstruct the signal into a canonical set of 81  
247 gradient orientations.

248 **Multi-tensor tractography.** Whole brain tractography was performed using our multi-fiber (multi-tensor) model to  
249 trace through crossing fiber regions. The multi-tensor unscented Kalman filter tractography (UKFt) method  
250 consisted of two anisotropic tensors along with an isotropic volume compartment to model fast extracellular water  
251 diffusion (Malcolm et al., 2010; Baumgartner et al., 2012; Reddy and Rathi, 2016). The model estimated a convex  
252 combination of weights for the anisotropic fiber compartment and the isotropic volume compartment with the  
253 diffusivity of the isotropic volume set to  $3 \times 10^{-3}$  s/mm<sup>2</sup> as in our previous work (Pasternak et al., 2009;  
254 Baumgartner et al., 2012). UKFt parameter settings were determined via empirical testing on a subset of the dataset.  
255 To maximize sensitivity to the cortico-striatal connections, the fractional anisotropy and generalized anisotropy  
256 thresholds for seeding/stopping tractography were set to 0.06, and 10 fiber seeds were initiated per voxel. All  
257 tractography results (for all subjects) underwent a quality check using the white matter analysis (O'Donnell and  
258 Westin, 2007) quality control tool, which enables rapid visual inspections of tractography results by human experts.  
259 Subjects that failed this quality control check were excluded.

260 **Extracting cortico-striatal tracts for hand, face, trunk, and leg regions.** The extraction of the tracts under  
261 investigation in the present study requires a cortical atlas that defines the hand, leg, face and trunk functional sub-  
262 regions of the motor cortex. However, the standard Desikan-Killany atlas (Desikan et al., 2006) typically used with  
263 FreeSurfer does not distinguish between different sub-regions of the motor cortex. However, the FreeSurfer  
264 processing pipeline allows users to create custom-made cortical atlases (Fischl et al., 2004).

265 To that effect, under the guidance of an expert neuroanatomist (Dr. Makris), we manually delineated the hand, leg,  
266 face and trunk sub-regions of the motor cortex on the anatomical (T1) MRI images of six healthy control subjects  
267 that were not part of the present study. We then used the “mris\_ca\_train” FreeSurfer command to create a new atlas  
268 which augments the standard Desikan-Killany atlas with these new four regions. Then, the “mris\_ca\_label” and  
269 “mri\_aparc2aseg” FreeSurfer commands were used to individually map this new atlas to all the subjects used in the  
270 present study.

271 This newly created, custom-made cortical parcellation was used in conjunction with the White Matter Query  
272 Language (WMQL) (Wassermann et al., 2016), in order to perform tract extraction. WMQL is a powerful,  
273 automated tract extraction method that uses gray matter regions of interest from the cortical parcellation as

274 anatomical queries for constructing white matter tracts. Specifically, for each cerebral hemisphere in each subject,  
275 we used WMQL to extract the tracts that connect each of the four motor cortex subregions (hand, face, trunk, and  
276 leg) to one of the two subcortical nuclei (caudate, putamen), for a total of eight tracts for each hemisphere.

277

### 278 **3. Results**

279 **Caudate/Putamen volume loss.** To confirm the reported decrease in volume size of caudate and putamen (Paulsen  
280 et al., 2008) in our data set, we investigated the volume size changes in both normal control and prodromal-HD  
281 groups. The changes were captured by using a linear mixed-effects model as in Equation (2), where the explanatory  
282 variable is the age and the response variable is the volume size). By applying this model to the longitudinal data for  
283 the caudate and putamen, we estimated a global intercept  $\beta_0$  and slope  $\beta_1$  for each structure in each group. A p-value  
284 for each parameter was also obtained and adjusted by the use of linear step-up (LSU) procedure originally  
285 introduced by Benjamini and Hochberg (Benjamini and Hochberg, 1995) to indicate the significance of the estimate.  
286 As shown in **Fig. 2**, the solid lines depict the global trend of volume loss over age, and the bars depict the FDR-  
287 adjusted p-values of the global estimate of the slope. The adjusted p-values for the intercept estimates are all close to  
288 zero, which are not shown in **Fig. 2**. Considering a significance level of 0.05, all estimates for global intercepts and  
289 slopes are statistically significant (see **Supplementary material, Table 1** for the actual p-values). That is, there is a  
290 correlation between volume size of caudate and putamen with age. Compared with the normal control group, the  
291 prodromal-HD group had a reduced volume size for the caudate and the putamen and a significantly faster  
292 degeneration rate as expected.

293

294 **Isotropic volume fraction changes over age for different sensorimotor areas.** To investigate longitudinal  
295 changes in the isotropic volume fraction (related to tissue atrophy), we leverage the longitudinal data and use the  
296 linear mixed-effects model to estimate group trends for both normal controls and prodromal-HD groups. **Fig. 3**  
297 shows the isotropic volume fraction changes in fiber bundles from hand, face, trunk, and leg sensorimotor areas to  
298 left and right caudate and putamen, respectively. Overall, most of the estimated trends suggest an increase in the  
299 isotropic volume fraction with age, from the four cortical areas to the caudate and putamen. Based on the estimated  
300 p-values (after FDR correction) for the intercept (not shown in **Fig. 3**) and slope, the prodromal-HD group trends are  
301 all significant at the level of 0.05 (also see **Supplementary material, Table 2** for the actual p-values). For the

302 normal control group, while fiber bundles associated with the caudate have no significant increase in the isotropic  
303 volume fraction, some fiber bundles associated with the putamen show significant changes in the isotropic volume  
304 fraction, including the left putamen to hand, face, and leg areas, as well as the right putamen to hand, trunk, and leg  
305 regions (see **Fig. 3**). These results indicate that for Huntington's disease, significant isotropic volume fraction  
306 changes were detected in all cortico-striatal pathways, while for healthy controls the pathways connecting the  
307 putamen show more significant isotropic volume fraction changes than those connected to the caudate.

308 It is worth to mention that the isotropic volume fraction contributes only about 10-15% (0.1-0.15) of the total signal  
309 volume fraction, as shown in Fig.3. This is small and in-line with that expected in white matter tissue. However, it is  
310 elevated in HD due to tissue atrophy. In light of the histology work of (Wang et al. 2011), it is likely that there exist  
311 small pockets of fast moving water within the tissue, which indicate tissue atrophy as is known to exist in HD.

312 **Differential rate of increase in the isotropic volume fraction with age.** To further investigate which region  
313 shows a faster rate of increase in the isotropic volume fraction (or atrophy), we estimated group trends in different  
314 regions for both normal control and prodromal-HD subjects. In particular, we compared the isotropic volume  
315 fraction difference between these two groups at age 50 (years), as the fit from linear regression has the lowest  
316 uncertainty at this age. Specifically, we estimated the isotropic volume fraction at age 50 for both groups and then  
317 computed their difference. To ensure robustness of the results, we color coded the rates such that the blue bars  
318 indicate connections for which the slope was statistically significant (after FDR correction). As shown in **Fig. 4** (top  
319 row), at the age of 50 years, the average isotropic volume fraction in the prodromal-HD group is larger than that for  
320 the normal control group in almost all cortico-striatal pathways. The top two significant fiber connections on the list  
321 are hand to the bilateral putamen, as shown on the top right of **Fig.4**.

322 In addition, the rate of increase in the isotropic volume fraction in prodromal-HD subjects is also faster than  
323 controls in almost all pathways. By discarding estimates with adjusted p-value larger than 0.05 (the gray bars in **Fig.**  
324 **4**), the fiber bundles connecting hand and leg to right putamen show the fastest increase in the isotropic volume  
325 fraction (i.e., fastest rate of atrophy). The fiber bundle connecting hand to left putamen also shows similar rate of  
326 atrophy. **Thus, after accounting for the normal degeneration rate (from healthy controls), the cortico-striatal**  
327 **hand motor fibers seem to degenerate faster than other fiber tracts in Huntington's disease.**

328

329 **Isotropic volume fraction correlation with genetic load.** The number of CAG repeats determines whether a  
330 subject will develop Huntington's disease during his or her lifetime. We aim to find the correlation between this  
331 genetic load and isotropic volume fraction in the prodromal-HD group. To achieve this goal, we first regress out the  
332 effects of normal aging on changes in the isotropic volume fraction, and then estimate the relationship between the  
333 isotropic volume residuals and CAG repeats in prodromal-HD subjects. Although no significant correlations are  
334 found in caudal connections, motor regions connected to the putamen show significant correlations, for example,  
335 hand to the left and right putamen and leg to the right putamen, as shown in **Fig. 5** (also see **Supplementary**  
336 **material, Table 3** for the actual p-values). In addition, face to the left putamen and trunk to the right putamen (in  
337 **Fig. 5**) also show a significant change in the slope, indicating strong correlation between the isotropic volume  
338 fraction and CAG repeats in these regions. These results indicate that the isotropic volume fraction correlates with  
339 the genetic load in prodromal-HD subjects, and it further confirms that the putamen (and its motor connections)  
340 could play a critical role in early assessment of degeneration in Huntington's disease.

341 **Isotropic volume fraction correlates with clinical scores.** To further explore the relationship of the isotropic  
342 volume fraction with clinical scores, we used total motor scores and diagnostic confidence levels of prodromal-HD  
343 subjects using linear mixed-effects models. These scores are used to define motor diagnosis in at-risk individuals,  
344 and we study them only in prodromal-HD subjects. In addition, for each motor area we average the isotropic volume  
345 fraction from the bilateral tracts of the caudate or the putamen. The experimental results are shown in **Fig. 6**. In all  
346 regions except for trunk to the caudate for testing total motor scores correlation, the isotropic volume fraction was  
347 significantly correlated with both total motor scores and diagnostic confidence level with  $p < 0.05$  (see FDR  
348 corrected p-values in **Supplementary material, Table 4**).

349 **Exploratory tissue fractional anisotropy (FA<sub>t</sub>) and mean diffusivity analyses.** We also investigated if white  
350 matter integrity as measured by tract-specific fractional anisotropy (FA<sub>t</sub>) was affected in prodromal-HD, as has been  
351 reported in several works using the standard DTI model (Poudel et al., 2015; Liu et al., 2016). Using our multi-  
352 tensor and isotropic volume compartment model, we found no statistically significant differences in the rate of  
353 change of FA<sub>t</sub> (slope) with age between the prodromal-HD and normal control group. We note that the FA<sub>t</sub> measure  
354 used in this work is obtained from the principal diffusion tensor estimated and oriented along the fiber tracts and  
355 thus is different than the standard DTI-based fractional anisotropy measure (which does not account for crossing  
356 fibers). Further, FA<sub>t</sub> also did not correlate with CAG-repeats in the prodromal-HD subjects. The change in mean

357 diffusivity (proportional to the trace of the principal diffusion tensor) with age also did not differ between the two  
358 groups, except for the fiber bundle connecting the putamen with the hand motor areas. Thus, when using a different  
359 model of diffusion, we find that only the atrophy-related measure of the isotropic volume fraction to be statistically  
360 different between the groups.

361

#### 362 **4. Discussion**

363 In this paper, we present a unique longitudinal study of Huntington's disease in a large cohort of subjects by  
364 delineating specific fiber tracts connecting the striatum with four cortical motor regions, i.e., hand, face, trunk, and  
365 leg. Our approach utilizes the dependency in the longitudinal data by using linear mixed-effects models. We  
366 analyzed the isotropic volume fraction, a measure of tissue atrophy, in the cortico-striatal pathways and determined  
367 its correlation with age, genetic load, and clinical severity scores.

368 Previous studies on Huntington's disease often performed group comparison between Huntington's disease (or  
369 prodromal-HD) subjects and normal controls based on CAP scores (Zhang et al., 2011; Shaffer et al., 2016). The  
370 CAP score is computed using the number of CAG repeats and the subject's age. Here, instead of using the CAP  
371 score, we demonstrate a direct correlation of the isotropic volume fraction with CAG-repeats, by removing aging  
372 related effects in our longitudinal data. To the best of our knowledge, this is the first time that the genetic load in the  
373 prodromal-HD group has been shown to correlate with abnormality in specific cortico-striatal white matter tracts  
374 using an image-based marker. Significant correlations of the isotropic volume fraction (indicating atrophy) with  
375 CAG repeats are seen in connections to the four motor areas, especially to the hand motor areas (**Fig. 5**). The fibers  
376 connecting the cortical hand motor area demonstrate more atrophy than other motor areas. While our study connects  
377 the imaging, genetic and behavioral measures (motor scores), a recent study (Collins et al., 2014) showed that hand  
378 tapping performance was correlated with CAG-repeats and could be used as a longitudinal behavioral marker to  
379 assess progression of Huntington's disease. In a similar spirit, we believe that the proposed isotropic volume fraction  
380 estimated in the white matter tracts connecting the hand motor area could be used as an imaging marker of disease  
381 severity with possible use to monitor therapeutic interventions.

382 Furthermore, our results confirm earlier results on the volumetric loss in both caudate and putamen (Niccolini and  
383 Politis, 2014). A faster volume loss rate is detected in the caudate in prodromal-HD, as shown in **Fig. 2**. This result  
384 is consistent with the previous studies on longitudinal change in basal ganglia volume and studies on rate of caudate

385 atrophy in patients with Huntington's disease (Aylward et al., 1997; Aylward et al., 2000). This previous study  
386 suggested that change in caudate volume may be useful for assessing treatment effectiveness in both pre-  
387 symptomatic and symptomatic subjects. However, our analysis of white matter microstructure from dMRI measures  
388 in the cortico-striatal pathways shows that the fibers connecting motor areas to the putamen are more affected in  
389 prodromal-HD than those to the caudate, especially as demonstrated by the isotropic volume fraction changes over  
390 age (**Fig. 3**) and the correlation of the isotropic volume residuals with CAG-repeats (**Fig. 5**). A recent study (Singhal  
391 et al., 2017) also shows that caudate has a less degree of involvement in Huntington's disease and putaminal  
392 hypometabolism exceeds caudate changes on 18F-FDG PET imaging. Thus, the motor fibers connected to the  
393 putamen may be a better imaging marker for assessing structural changes in prodromal-HD.

394 Previous DTI studies on Huntington's disease suggested that fractional anisotropy is more sensitive than mean  
395 diffusivity in detecting structural changes in prodromal-HD (Liu et al., 2016). However, in our experiments, the  
396 isotropic volume fraction outperforms both fractional anisotropy and mean diffusivity by demonstrating stronger  
397 correlation with age and CAG-repeats. We should note that, using a more advanced model of diffusion that  
398 incorporates multiple crossing fibers and an isotropic volume compartment lends increased specificity and  
399 sensitivity to the obtained results as seen in studies on other neurodegenerative disorders such as Parkinson's disease  
400 (Planetta et al., 2016; Lyall et al., 2017). Our results indicate that the isotropic volume fraction could be a potential  
401 imaging maker for monitoring the progression of Huntington's disease.

402

#### 403 **Figure legend list:**

404 Fig 1. White matter tracts connecting the striatum (top: caudate and bottom: putamen) with four cortical motor  
405 regions (left to right: hand, face, trunk, and leg).

406

407 Fig 2. Volume loss of the caudate and putamen over age. Lines illustrate estimates of the group trend for each  
408 population, normal controls (NC) or subjects with Huntington's disease (prodromal-HD). Grey areas show the 95%  
409 confidence intervals for the estimated group trends. Bars indicate the FDR-corrected p-values for the estimation of  
410 slope (decay rate).

411 Fig 3. Longitudinal analysis of the isotropic volume fraction of the caudate and putamen, connected with four motor  
412 regions, i.e., hand, face, trunk, and leg. Lines show the estimated group trend for each population, normal control

413 (NC) and prodromal-HD. Grey areas show the 95% confidence intervals for the estimated group trends. Bars present  
414 the FDR-adjusted p-values for the estimation of slope using the linear mixed-effects model. An adjusted p-value less  
415 than 0.05 indicates the estimate is significant and reliable. The title of each sub-figure details tractography  
416 connections that were reliably traced from the total scans in each group.

417

418 Fig 4. Comparison of the isotropic volume fraction between Normal Control (NC) and prodromal-HD groups. Top:  
419 the averaged isotropic volume fraction values estimated at the age of 50 years old for different regions. Bottom: the  
420 degeneration rates (slopes of estimated group trends) for different regions. From left to right: NC group, HD group,  
421 and their differences. Gray bars were used in those regions where estimate for the slope is not significant at the level  
422 of 0.05 (i.e., no significant correlation between isotropic volume fraction and age), while blue bars indicate that the  
423 results are significant at the level of 0.05. (Cau: Caudate, Put: Putamen).

424

425 Fig 5. Correlations between the isotropic volume fraction residuals (after regressing out the effect of age) and CAG  
426 repeats in prodromal-HD group for white matter connections to left caudate, left putamen, right caudate, and right  
427 putamen (from top to bottom). Lines depict estimates of group trends, gray areas indicate their 95% confidence  
428 intervals, and bars indicate the corresponding p-values of the estimated intercepts ( $\beta_0$ ) and slopes ( $\beta_1$ ). The title of  
429 each sub-figure details tractography connections and the number of scans for which robust connections were  
430 obtained out of total scans in prodromal-HD group.

431

432 Fig 6. Correlations between the isotropic volume fraction and (a) total motor scores (TMS), (b) diagnostic  
433 confidence level (DCL) in prodromal-HD group for caudate (top) and putamen (bottom). Lines show estimates of  
434 group trends, gray areas indicate their 95% confidence intervals, and bars present the corresponding FDR-corrected  
435 p-values of the estimated intercepts ( $\beta_0$ ) and slopes ( $\beta_1$ ).

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440

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**Table 1 Demographic and clinical information of the PREDICT-HD sample used in the experiments.** \*The corresponding parameters were not available for some subjects. SD: standard deviation.

	Normal Control (N = 88, total scans: 219)	Huntington's Disease (N = 243, total scans: 611)
# Male	35 (39.77%)	75 (30.86%)
# Female	53 (60.23%)	168 (69.14%)
Age (Mean $\pm$ SD, [Min, Max])	48.58 $\pm$ 12.61, [23.19, 87.73]	45.62 $\pm$ 12.48, [18.84, 82.72]
Maximum Education Years	15.08 $\pm$ 2.56, [9, 20]	14.82 $\pm$ 2.47, [9, 20] (3 unavailable*)
CAG Repeats	20.68 $\pm$ 3.80, [15, 35]	42.10 $\pm$ 2.70, [37, 58]
Total Motor Scores	3.08 $\pm$ 4.15, [0, 30] (10 unavailable*)	9.11 $\pm$ 11.21, [0, 77] (8 unavailable*)
Diagnostic Confidence Level	0.58 $\pm$ 0.66, [0, 3] (10 unavailable*)	1.32 $\pm$ 1.29, [0, 4] (8 unavailable*)

**Table 2 Summary of the representative MRI parameters used by each manufacturer.** Diffusion-weighted imaging (DWI) data was acquired with 32 – 237 directions; TR: repetition time; TE: echo time; TI: inversion time.

Mode	Manufacturer	TR (ms)	TE (ms)	TI (ms)	Thickness (mm)	Acquisition Matrix	Bandwidth (Hz/pixel)	Flip Angle
T1	GE	6.5	2.8	400	1	256, 256, 216	244.1	12
	Philips	7.7	3.5		1.1	220, 218, 164	241	8
	Siemens	2,300	2.87	900	1.1	256, 256, 240	238	10
T2	GE	3,000	82.5		1.4	288, 288, 160	244.1	90
	Philips	2,500	183.6		1.1	220, 218, 164	583	90
	Siemens	4,800	430		1.4	256, 250, 160	592	90
DWI	GE	17,000	87.2		2.4	128, 128	1,953.12	90
	Philips	9,679	92		2	128, 128	1,566.02	90
	Siemens	12,000	92		2	128, 128	1,565	90

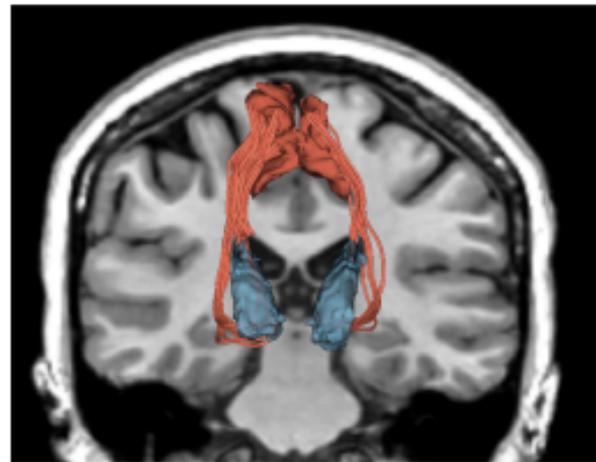
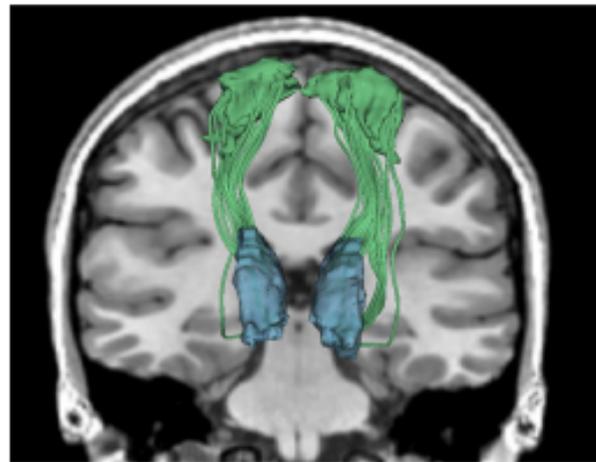
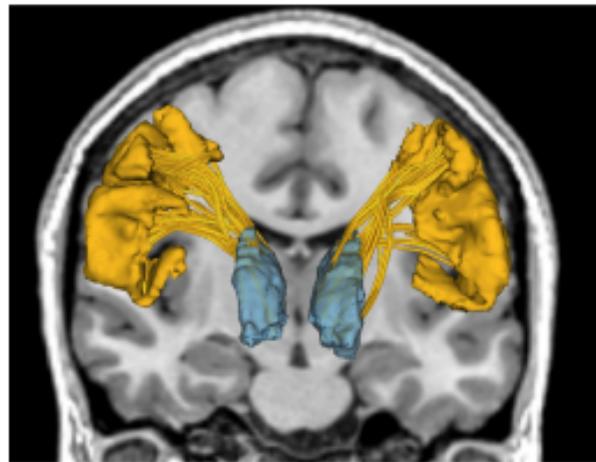
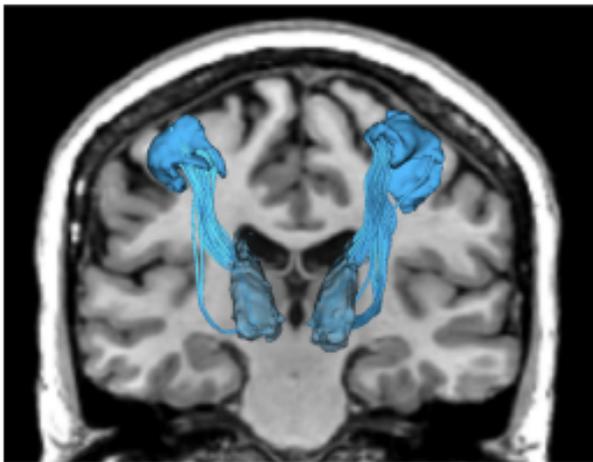
Hand

Face

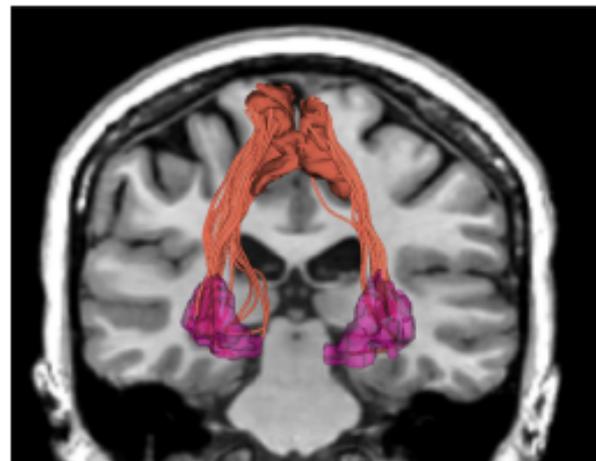
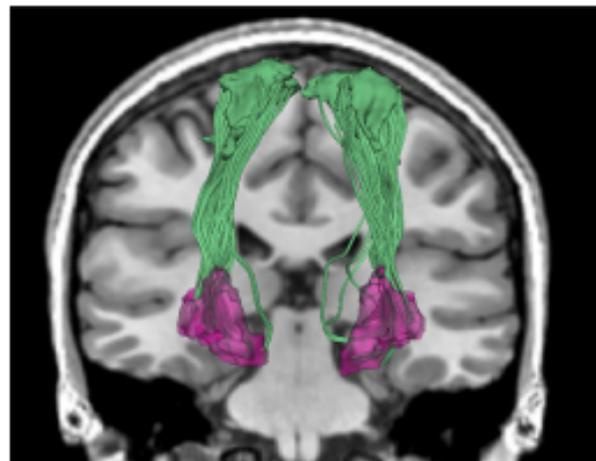
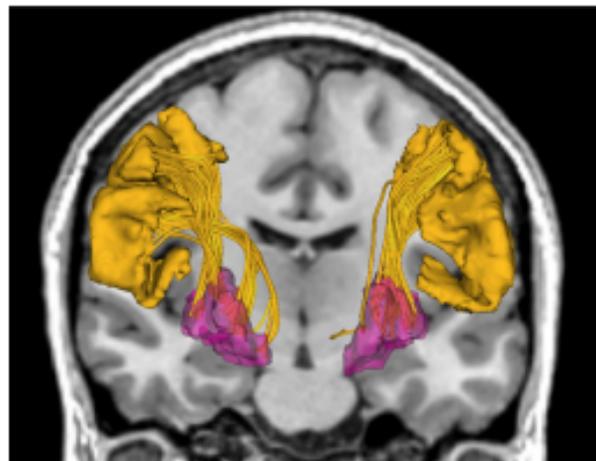
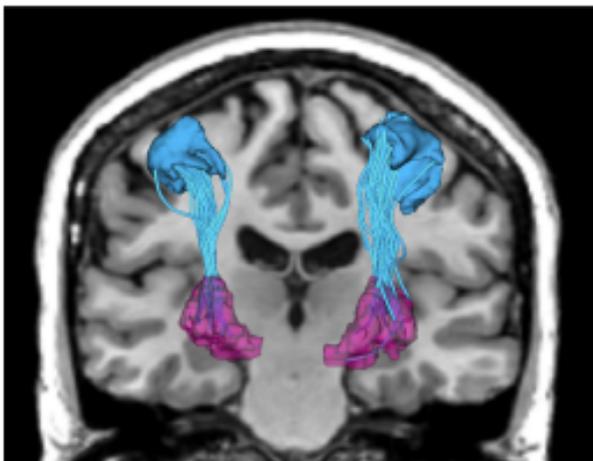
Trunk

Leg

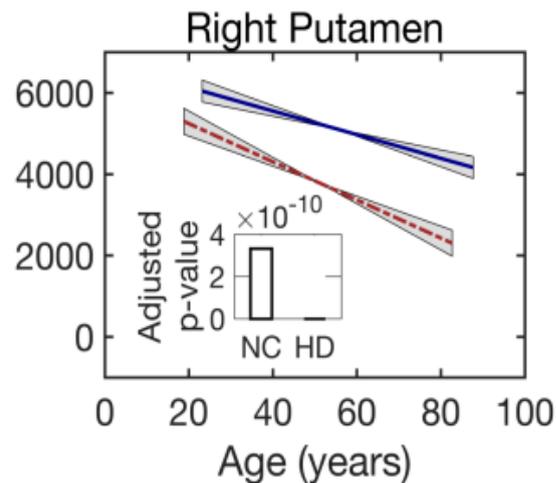
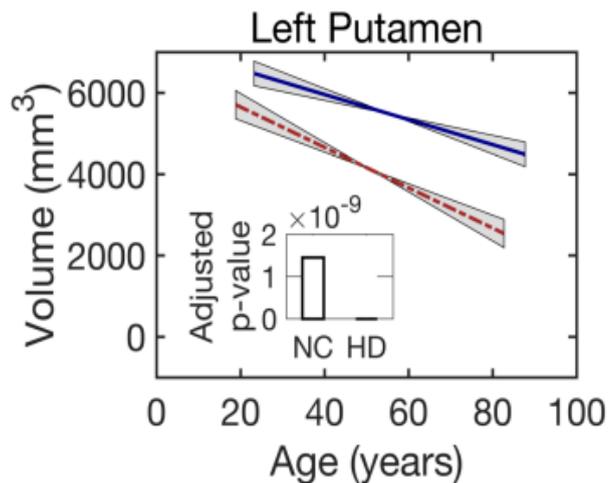
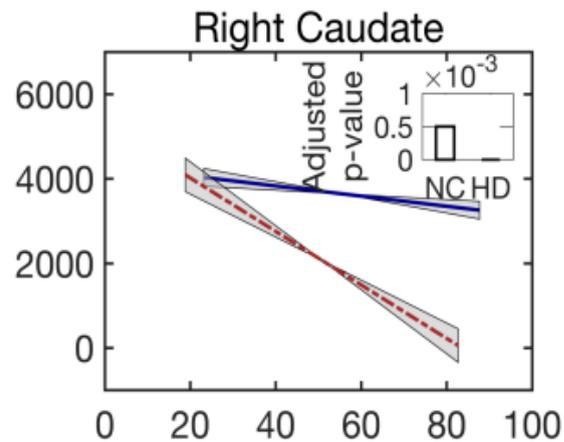
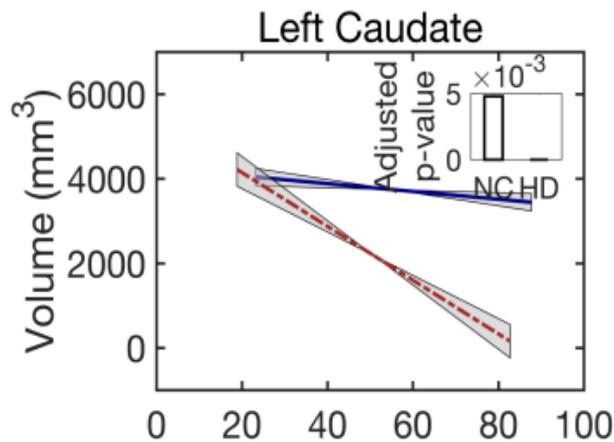
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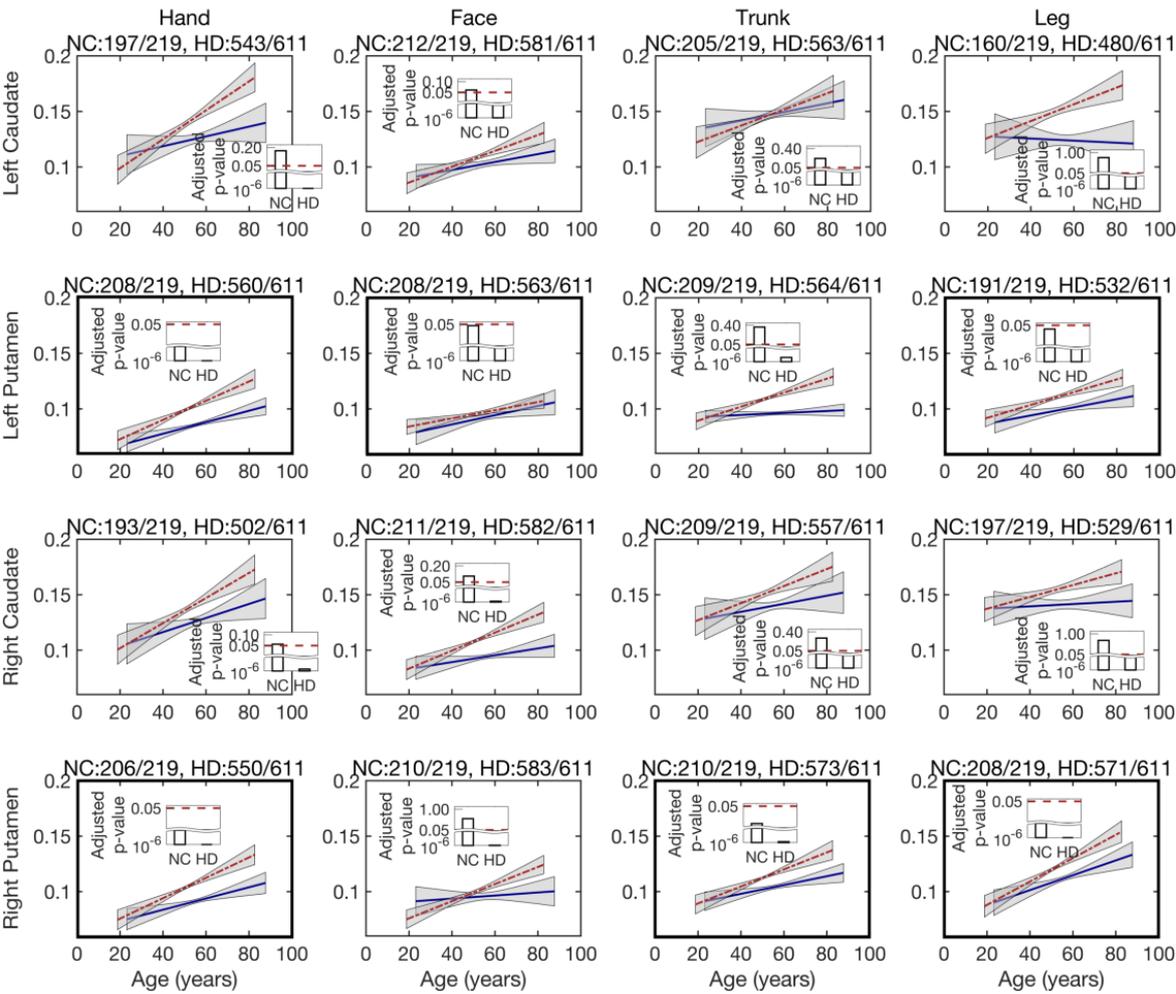
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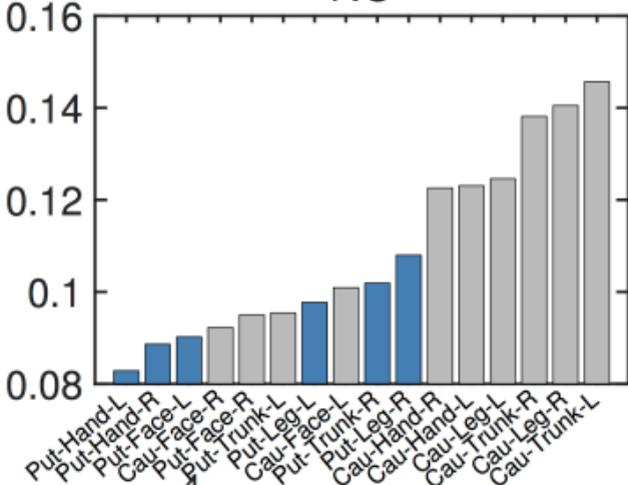
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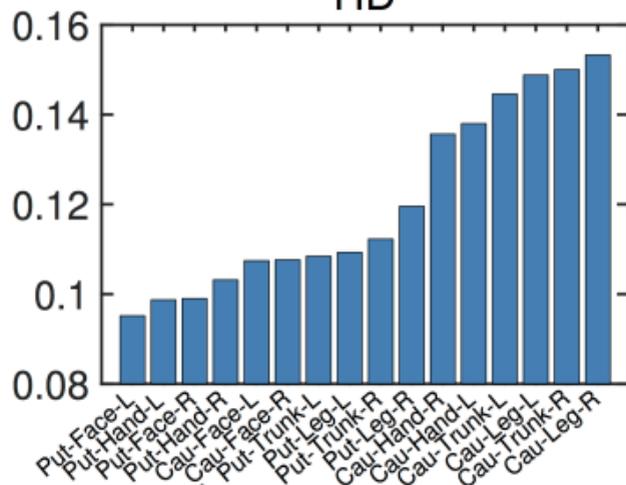
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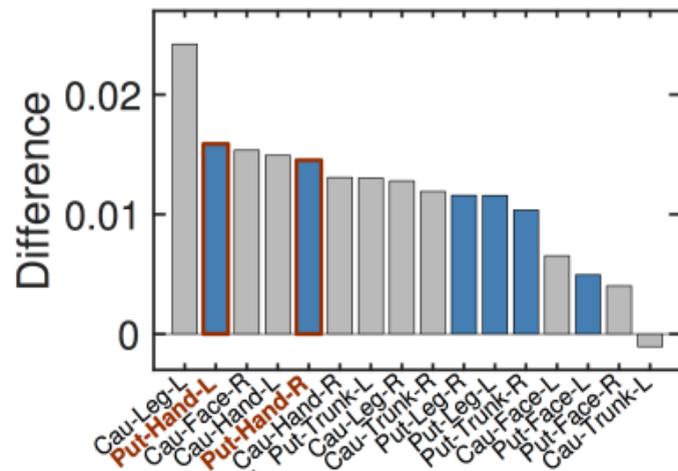
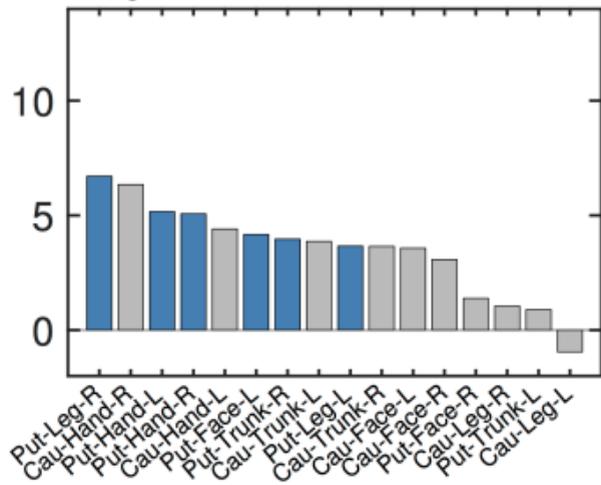
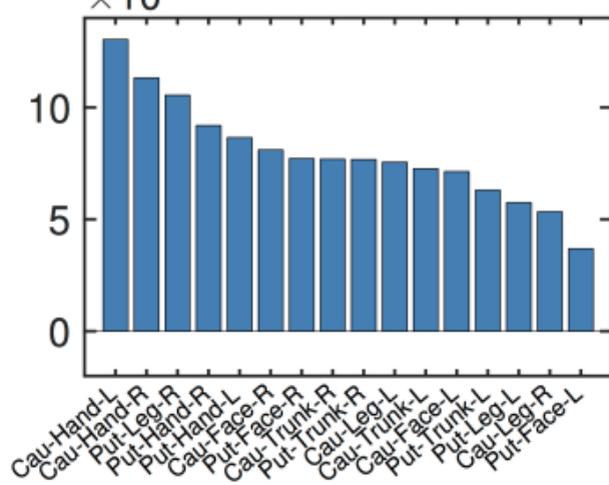
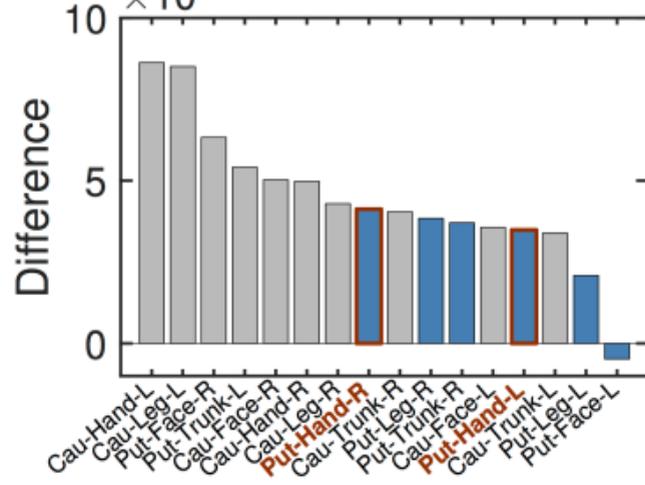
NC

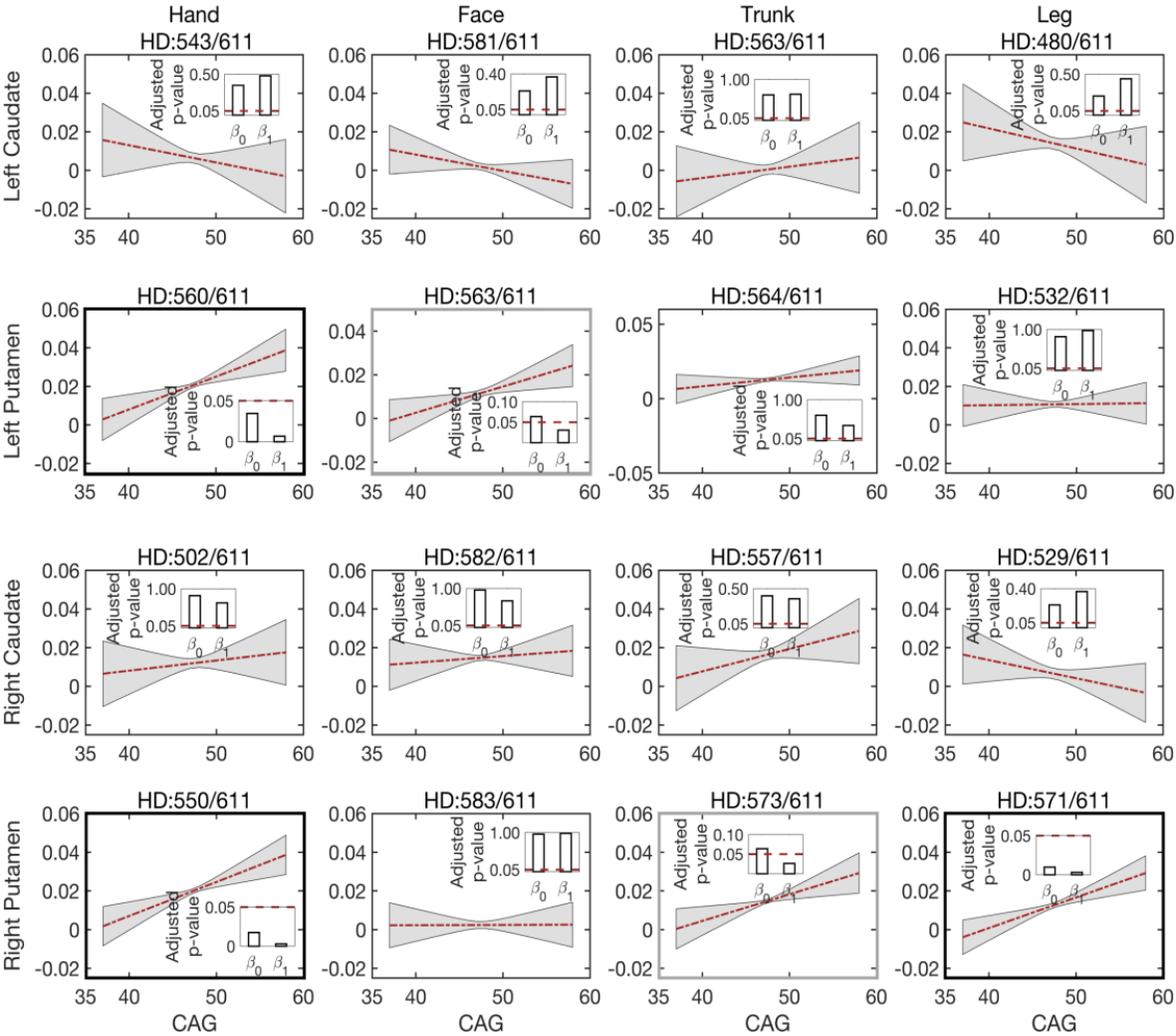


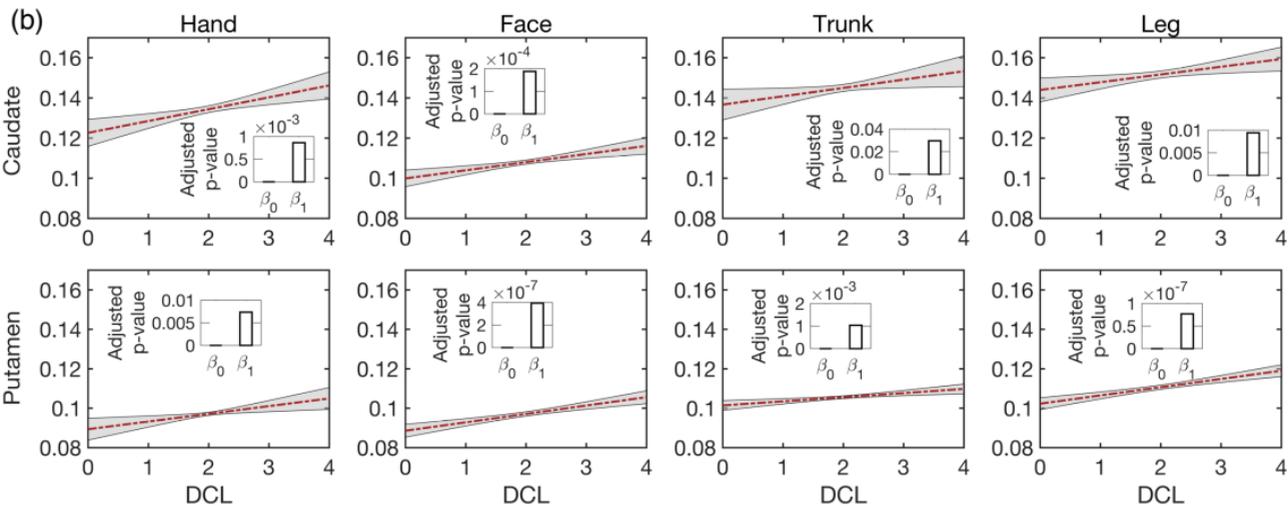
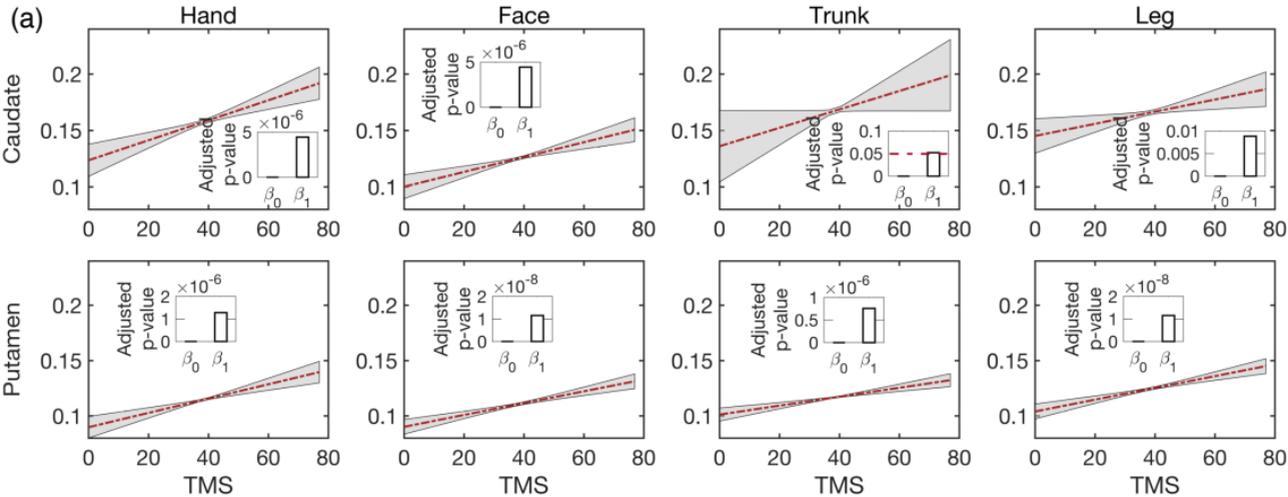
HD



HD - NC

 $\times 10^{-4}$  $\times 10^{-4}$  $\times 10^{-4}$ 





## Supplementary material

**Table 1** The slope, t-statistic, estimated degrees of freedom (DF), and associated FDR-corrected p-values for correlation between caudate and putamen volume loss and age (cf. Fig. 2). All correlations are significant at a significance level of 0.05.

	Normal Control				Huntington's Disease			
	Slope	t-Stat	DF	p-Value	Slope	t-Stat	DF	p-Value
Left Caudate	-9.2347	-2.8497	216	4.7991e <sup>-3</sup>	-63.6013	-10.075	603	1.4442e <sup>-21</sup>
Right Caudate	-12.0076	-3.6132	214	5.0257e <sup>-4</sup>	-63.2369	-9.9663	607	1.8083e <sup>-21</sup>
Left Putamen	-30.8260	-6.4565	211	1.4495e <sup>-9</sup>	-49.6062	-8.9647	603	3.8796e <sup>-18</sup>
Right Putamen	-29.0864	-6.8354	215	3.3251e <sup>-10</sup>	-46.8855	-9.1738	602	9.6031e <sup>-19</sup>

**Table 2** The slope, t-statistic, estimated degrees of freedom (DF), and associated FDR-corrected p-values for correlation between isotropic volume fraction and age (cf. Fig. 3). \*In these regions, normal control or Huntington's disease groups show significant changes in free water fraction at a significance level of 0.05.

		Normal Control				Huntington's Disease			
		Slope (10 <sup>-3</sup> )	t-Stat	DF	p-Values	Slope (10 <sup>-3</sup> )	t-Stat	DF	p-Values
	Hand	0.4410	1.6148	194	0.1728	1.3038	6.4163	539	1.3002e <sup>-9*</sup>
Left	Face	0.3571	2.1778	210	0.0611	0.7133	4.8499	575	2.3160e <sup>-6*</sup>
Caudate	Trunk	0.3868	1.4445	203	0.2184	0.7259	3.2555	561	0.0013*
	Leg	-0.0953	-0.2988	157	0.7655	0.7553	3.7125	476	0.0003*
	Hand	0.5166	4.3121	202	0.0004*	0.8653	6.4029	555	1.3002e <sup>-9*</sup>
Left	Face	0.4167	2.3924	205	0.0470*	0.3687	3.5611	558	0.0005*
Putamen	Trunk	0.0893	1.0394	201	0.3691	0.6306	5.3025	558	2.9310e <sup>-7*</sup>
	Leg	0.3662	2.5095	182	0.0415*	0.5750	4.8706	524	2.3160e <sup>-6*</sup>

	Hand	0.6344	2.2620	188	0.0568	1.1323	5.4890	496	1.2921e <sup>-7*</sup>
Right	Face	0.3077	1.8964	206	0.1054	0.8103	5.6908	573	5.3852e <sup>-8*</sup>
Caudate	Trunk	0.3650	1.2484	204	0.2844	0.7693	3.7406	555	0.0003*
	Leg	0.1047	0.4490	194	0.6975	0.5340	3.1855	526	0.0015*
	Hand	0.5069	3.4185	200	0.0041*	0.9193	6.5131	546	1.3002e <sup>-9*</sup>
Right	Face	0.1388	0.6830	205	0.5662	0.7718	5.9120	578	1.8502e <sup>-8*</sup>
Putamen	Trunk	0.3968	3.0431	206	0.0106*	0.7675	5.6617	561	5.4746e <sup>-8*</sup>
	Leg	0.6707	3.7390	205	0.0019*	1.0549	6.8896	561	2.4118e <sup>-10*</sup>

**Table 3** The intercept and slope with their t-statistic, estimated degrees of freedom (DF), and associated FDR-corrected p-values for correlation between isotropic volume fraction and the genetic load, CAG (cf. Fig. 5).

\*indicates significant correlations (FDR corrected p-value < 0.05).

		$\beta_0$				$\beta_1$			
		Intercept	t-Stat	DF	P-Values	Slope (10 <sup>-3</sup> )	t-Stat	DF	p-Values
	Hand	0.0489	1.2676	538	0.3653	-0.8964	-0.9734	538	0.4812
Left	Face	0.0420	1.6034	575	0.2334	-0.8452	-1.3806	575	0.3704
Caudate	Trunk	-0.0275	-0.7290	561	0.6217	0.5862	0.6585	561	0.6383
	Leg	0.06341	1.5716	472	0.2334	-1.0428	-1.0868	472	0.4443
	Hand	-0.0605	-2.7329	556	0.0345*	1.7114	3.2387	556	0.0068*
Left	Face	-0.0454	-2.3334	558	0.0639	1.2007	2.5994	558	0.0307*
Putamen	Trunk	-0.0155	-0.7814	558	0.6217	0.5938	1.2595	558	0.3704
	Leg	0.0079	0.3586	524	0.8229	0.0575	0.1094	524	0.9738
	Hand	-0.0130	-0.3780	496	0.8229	0.5266	0.6459	496	0.6383
Right	Face	-0.0014	-0.0503	574	0.9599	0.3392	0.5299	574	0.6816
Caudate	Trunk	-0.0387	-1.1404	555	0.4074	1.1603	1.4335	555	0.3704
	Leg	0.0512	1.6662	526	0.2334	0.9404	-1.2840	526	0.3704

	Hand	-0.0633	-3.0764	546	0.0176*	1.7583	3.5795	546	0.0030*
Right	Face	0.0017	0.0739	579	0.9599	0.0138	0.0247	579	0.9803
Putamen	Trunk	-0.0505	-2.3971	562	0.0639	1.3746	2.7283	562	0.0263*
	Leg	-0.0624	-3.4471	561	0.0097	1.5809	3.7022	561	0.0030*

**Table 4** The slope, t-statistic, estimated degrees of freedom (DF), and associated FDR-corrected p-values for correlation of isotropic volume fraction and clinical scores (total motor scores and diagnostic confidence level, cf. Fig. 6). Except for the connection from trunk to the caudate (colored in red), isotropic volume fractions in other regions are significantly correlated with total motor scores /diagnostic confidence level.

		Total Motor Scores				Diagnostic Confidence Level			
		Slope ( $10^{-3}$ )	t-Stat	DF	p-Values	Slope	t-Stat	DF	p-Values
Caudate	Hand	0.8886	4.7418	461	4.4355e <sup>-6</sup>	0.0059	3.5451	460	0.0009
	Face	0.6563	4.6976	552	4.4355e <sup>-6</sup>	0.0041	4.0057	552	0.0002
	Trunk	0.8182	1.9485	521	<b>0.0519</b>	0.0041	2.1821	521	0.0296
	Leg	0.5393	2.6763	432	0.0088	0.0038	2.6551	432	0.0094
Putamen	Hand	0.6479	5.0405	527	1.2785e <sup>-6</sup>	0.0039	2.7872	526	0.0073
	Face	0.5353	6.1561	537	1.1525e <sup>-8</sup>	0.0043	5.4032	539	3.9358e <sup>-7</sup>
	Trunk	0.4044	5.1996	539	7.5747e <sup>-7</sup>	0.0021	3.4316	537	0.0010
	Leg	0.5330	6.0492	493	1.1528e <sup>-8</sup>	0.0042	5.8373	495	7.6851e <sup>-8</sup>