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Differential Changes in Functional Connectivity of Striatum-Prefrontal and Striatum-Motor Circuits in Premanifest Huntington's Disease

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Keywords

Functional connectivity · Prefrontal cortex · Chorea · Premanifest period · Magnetic resonance imaging, 7 T

Abstract

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder. The striatum is one of the first brain regions that show detectable atrophy in HD. Previous studies using functional magnetic resonance imaging (fMRI) at 3 tesla (3 T) revealed reduced functional connectivity between striatum and motor cortex in the prodromal period of HD. Neuroanatomical and neurophysiological studies have suggested segregated corticostriatal pathways with distinct loops involving different cortical regions, which may be investigated using fMRI at an ultra-high field (7 T) with enhanced sensitivity compared to lower fields. ***Objectives:*** We performed fMRI at 7 T to assess functional connectivity between the striatum and several chosen cortical areas including the motor and prefrontal cortex, in order to better understand brain changes in the striatum-cortical pathways. ***Method:*** 13 manifest subjects (age 51 ± 13 years, cytosine-adenine-guanine [CAG] repeat 45 ± 5, Unified Huntington's Disease Rating Scale [UHDRS] motor score 32 ± 17), 8 subjects in the close-to-onset premanifest period (age 38 ± 10 years, CAG repeat 44 ± 2, UHDRS motor score 8 ± 2), 11 subjects in the far-from-onset premanifest period (age 38 ± 11 years, CAG repeat 42 ± 2, UHDRS motor score 1 ± 2), and 16 healthy controls (age 44 ± 15 years) were studied. The functional connectivity between the striatum and several cortical areas was measured by resting state fMRI at 7 T and analyzed in all participants. ***Results:*** Compared to controls, functional connectivity between striatum and premotor area, supplementary motor area, inferior frontal as well as middle frontal regions was altered in HD (all p values <0.001). Specifically, decreased striatum-motor connectivity but increased striatum-prefrontal connectivity were found in premanifest HD subjects. Altered functional connec-

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tivity correlated consistently with genetic burden, but not with clinical scores. ***Conclusions:*** Differential changes in functional connectivity of striatum-prefrontal and striatum-motor circuits can be found in early and premanifest HD. This may imply a compensatory mechanism, where additional cortical regions are recruited to subserve functions that have been impaired due to HD pathology. Our results suggest the potential value of functional connectivity as a marker for future clinical trials in HD.

Introduction

Huntington's disease (HD) is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat length expansion in the Huntingtin gene on chromosome 4 [1]. Mutant Huntingtin protein causes cell toxicity leading to neurodegeneration and regional brain atrophy [2]. Genetic testing allows for the identification of subjects at risk for HD and their estimated time of symptom onset [3].

Clinical symptoms of HD evolve insidiously [2, 4, 5]. First, individuals are in the "far-from-onset premanifest" period of HD (farpremHD), when they are indistinguishable from the general population. Then, subtle motor, cognitive, and behavioral changes develop in the "close-to-onset premanifest" period of HD (closepremHD). These two periods together constitute the premanifest period [5]. Thereafter, individuals transition into the "manifest" period of HD, when the clinical diagnosis can be made based on the "unequivocal presence of an otherwise unexplained extrapyramidal movement disorder" [4].

Postmortem studies of subjects who died in the "manifest" stage of HD revealed disease-specific neuronal loss in the striatum and cortical areas leading to atrophy [6]. Structural magnetic resonance imaging (MRI) studies have replicated neuropathological findings and also revealed atrophy of the striatum and cortical areas already in the premanifest period of HD [7–9]. Dysfunction of neurons and their connections is believed to occur prior to actual neuronal cell death [2, 10]. Functional MRI (fMRI) can map altered brain activity before cell death occurs [2, 10, 11]. For instance, a previous study of our center revealed altered corticostriatal functional connectivity in motor loops in prodromal HD subjects [12]. Such impaired functional connectivity between striatum and motor cortex has also been reported by other groups [11, 13–16], linking the pathophysiological changes in the striatum and the clinical signs and symptoms in manifest HD.

Neuroanatomical and neurophysiological studies have suggested segregated striatum-cortical pathways that consist of distinct loops through the striatum, including a motor loop connecting to the premotor regions, and a prefrontal loop linking the striatum and the prefrontal cortex [17]. In this study, we investigated the possible occurrence of changes in functional connectivity between striatum and several chosen cortical regions other than the motor cortex in HD. We performed our study at the ultra-high magnetic field (7 tesla or 7 T), as higher field strength allows for a higher signal-to-noise ratio and thus a finer spatial resolution [18, 19]. This is important for seed-based analysis of resting state fMRI data for the evaluation of changes in separate neuronal pathways. We assessed HD subjects in the early "manifest" period, the "closepremHD" period and the "farpremHD" period to investigate potential progressive changes in these pathways. We hypothesized that functional connectivity between striatum and different cortical regions may be affected differentially by the HD disease process.

Methods

Study Participants

Study participants were recruited from the Johns Hopkins Huntington's Disease Center. Thirty-two participants with an increased CAG expansion of 36 and higher in the Huntingtin gene were recruited and subdivided into three groups (Table 1). In the first group there were 11 farpremHD subjects, who had a Unified Huntington's Disease Rating Scale (UHDRS) total motor score of 4 or less and had a diagnostic confidence level of 0 or 1 (<50% certainty) on the UHDRS. The second group comprised 8 closepremHD subjects, with subtle motor, cognitive, or behavioral alterations and a diagnostic confidence level of less than 4 on the UHDRS, but a score on the UHDRS motor score of 5 or higher. In the third group there were 13 subjects with early, but manifest HD (earlyHD) with a diagnostic confidence level of 4 (≥99% certainty) on the UHDRS. The control group consisted of 16 healthy subjects, who were consanguineous family members of people with HD but who had a normal number of CAG repeats (≤24) or were the unaffected spouse to subjects with HD. Individuals with a condition which would preclude them to have an MRI, a history of substance abuse, head trauma, a neurological illness, severe mood disorder, obsessive-compulsive disorder, or psychiatric disorder other than HD were excluded from this study.

All participants were examined using the UHDRS including all subscales [20], the Montreal Cognitive Assessment [21] and the Edinburgh Inventory to assess handiness [22] (Table 1). The CAG-Age Product (CAP) score as age × (CAG-33.66) [23] was calculated. We estimated years to symptom onset (YTO) of motor symptoms in HD with a 50% certainty according to an established formula [3].

Table 1. Demographic data and clinical assessment of the study populations

Subject groups	Controls	farpremHD	closepremHD	earlyHD	*p*	Post hoc tests
Demographics						
Subjects, *n*	16	11	8	13		
Age, years	44±15	39±11	39±11	51±13	0.077	
Gender (F/M)	10:6	5:6	6:2	7:6	0.396[a]	
Education, years	16±2	14±2	15±2	15±2	0.346	
MoCA score	29±1	29±2	29±2	27±3	0.005	
Handedness (R/L)	15/1	11/0	10/0	13/1	0.732[a]	
Disease characteristics						
CAG repeat size	NA	42±2	44±2	45±5	0.113	
CAP score	NA	293±93	378±46	537±98	<0.001	farpremHD < earlyHD
YTO, 50% certainty	NA	18±12	7±5	−7±8	<0.001	farpremHD < earlyHD
Clinical scores						
UHDRS-motor	1±3	1±2	8±2	32±17	<0.001	controls, farpremHD, closepremHD < earlyHD
UHDRS-behavior	3±4	6±6	5±4	14±15	0.011	
UHDRS TFC	13±0	13±0	13±0	10±4	<0.001	earlyHD < closepremHD, farpremHD, controls
SDMT	53±12	58±18	62±8	34±14	<0.001	earlyHD < closepremHD
Verbal fluency	42±10	44±12	53±15	31±17	0.003	earlyHD < closepremHD
Stroop total	235±32	215±44	223±39	144±52	<0.001	earlyHD < farpremHD, closepremHD, controls

Values are means ± standard deviation; HD, Huntington's disease; MoCA, Montreal Cognitive Assessment; YTO, estimated years to onset according to Langbehn et al. [3], 2004; CAG repeat, cytosine-adenine-guanine repeat; CAP score, age × (CAG-33.66); UHDRS, Unified Huntington's Disease Rating Scale; TMS, total motor score; TFC, total functional capacity; SDMT, Symbol Digit Modalities Task; verbal fluency, sum of the three parts of the FAS test; Stroop total, sum of color naming, color reading, and interference section. Please see Methods on details regarding the test applied. Controls, control subjects; farpremHD, HD subjects in the far-from-onset premanifest period; closepremHD, HD subjects in the close-to-onset premanifest period; earlyHD, HD subjects in the early manifest period of HD; *p* values based on ANOVA (correction for multiple testing according to Bonferroni as applied; critical *p* value is 0.004); post hoc tests, post hoc testing using Tukey's honest significant difference criterion. [a] Assessed with χ^2 test.

The study was approved by the local ethics board at Johns Hopkins University. All participants in this study gave written informed consent prior to participation.

Magnetic Resonance Imaging

Experiments were performed on a 7-T MRI Philips scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil at the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute.

Whole-brain anatomy was assessed using a T1-weighted, 3-dimensional (voxel = 1 mm isotropic) magnetization prepared rapid gradient echo MRI sequence. A resting state fMRI scan was performed with gradient-echo echo-planar imaging with the following parameters: time of repetition = 2,000 ms, time of echo = 22 ms, flip angle = 60°, 150 slices (no gap), field of view = 256 × 256 mm^2, voxel = 2.5 mm isotropic, total scan time = 7 min. Optimal high-order shimming techniques [24] were used to minimize image artifacts due to magnetic susceptibility effects and field inhomogeneity.

Data Analysis

Analysis of T1-weighted magnetization prepared rapid gradient echo images was performed using topology-preserving, anatomy-driven segmentation [25]. Resulting volumes of main cerebral structures were used for subsequent analysis.

Each fMRI analysis was performed using the Statistical Parametric Mapping (SPM) software package (http://www.fil.ion.ucl.ac.uk/spm/) and the MatLab software (MathWorks Inc., Natick, MA, USA). Individual fMRI data were preprocessed by an initial correction for timing differences between slices, realignment, coregistration to anatomical images, spatial normalization to Montreal Neurological Institute template space, nuisance removal (CompCor) [26], regression of global mean, and motion parameters (six rigid body motion correction parameters computed from the realignment routine and the first derivative of each parameter). A bandpass filter (0.1–0.01 Hz) was applied as a final step of preprocessing. We also applied an additional "scrubbing" procedure [26, 27] to correct for micromovements after the standard realignment procedure that can affect functional connectivity data [27–29]. Each analysis was also repeated without the global signal regression (GSR) step.

Seed-based functional connectivity analysis between the striatum (seed) and four chosen cortical regions ("premotor," supplementary motor area ("SMA"), "frontal interior," and "frontal middle") were performed. Anatomical regions were identified using the Individual Brain Atlases using the Statistical Parametric Mapping atlas [30–34] provided in the PickAtlas software (Wake Forest University, NC, USA). Functional connectivity was calculated between the striatum and each cortical region and converted to normal distribution using Fisher r-to-z transformation.

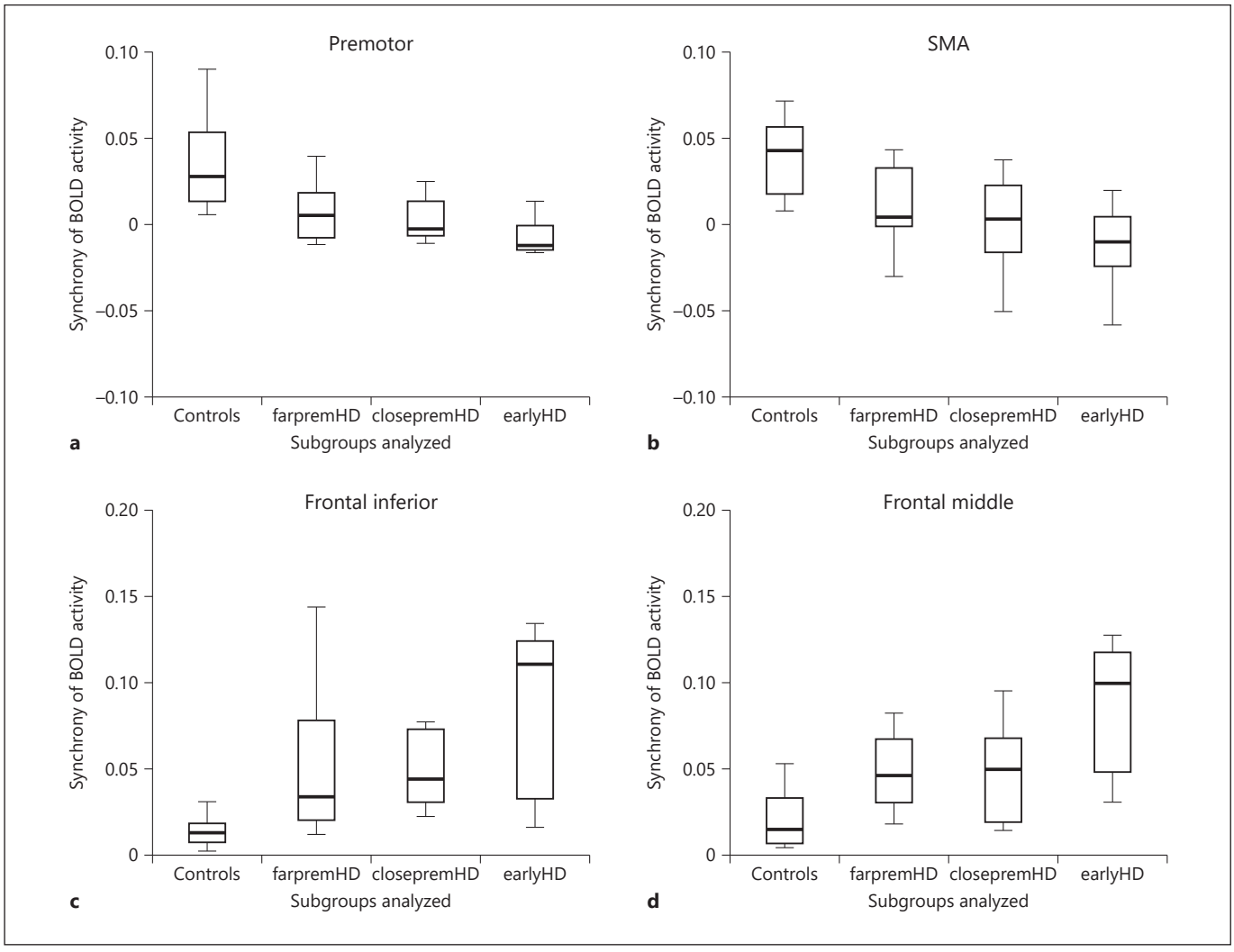


Fig. 1. Functional connectivity measured in HD subjects and controls. Box and whisker plots show degree of synchrony of blood oxygenation level dependent (BOLD) activity between cortical regions and striatum (seed) in the different subject groups analyzed. Functional connectivity was converted to normal distribution using Fisher *r*-to-*z* transformation. Controls, control subjects; farpremHD, HD subjects in the far-from-onset premanifest period; closepremHD, HD subjects in the close-to-onset premanifest period; earlyHD, HD subjects in the manifest period of HD. **a** Functional connectivity between the "premotor" region and striatum. **b** Functional connectivity between the supplementary motor area (SMA) and striatum. **c** Functional connectivity between the "frontal inferior" region and striatum. **d** Functional connectivity between the "frontal middle" region and striatum.

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences 25 software (SPSS Inc., Chicago, IL, USA). One-way analysis of variance followed by post hoc testing using Tukey's honestly significant difference criterion was performed to do group and subgroup comparisons, respectively. The χ^2 test was applied for comparing the categorical variables including gender and handedness. Correlations between functional connectivity and clinical scores as well as CAP score and YTO were analyzed using Pearson's correlation coefficient. Age, gender, regional gray matter volume from anatomical scans, motion, and differential motion parameters were all accounted for as covariates in the analysis. Alpha error was adjusted for multiple comparisons using the Bonferroni method (critical *p* value 0.004).

Results

Demographic information for the study participants is summarized in Table 1. Age and gender were matched between groups ($p > 0.1$). The farpremHD, closepremHD

and early HD patient subgroups showed significant differences in the CAP score ($p < 0.001$) and YTO ($p < 0.001$), and UHDRS motor score ($p < 0.001$), UHDRS behavior score ($p < 0.01$), and UHDRS total functional capacity ($p < 0.001$). Involuntary movements and related image artifacts were minimal during all MRI scans. This is reflected in the head motion parameters quantified using the SPM realignment routine (control: 0.33 ± 0.12 mm translation, 0.05 ± 0.05° rotation; HD: 0.32 ± 0.16 mm translation, 0.05 ± 0.06° rotation; $p > 0.1$).

Analysis of synchrony of blood oxygenation level dependent (BOLD) activity showed statistically significantly altered functional connectivity in HD subjects compared to controls between the striatum and "premotor" region ($p < 0.001$, $F = 11.4$), "SMA" region ($p < 0.001$, $F = 11.9$), "frontal inferior" region ($p < 0.001$, $F = 10.3$), and "frontal middle" region ($p < 0.001$, $F = 13.7$) (Fig. 1).

Specifically, functional connectivity between the "premotor" region and the striatum as well as between the "SMA" region and the striatum was diminished in all three HD groups compared to controls (Fig. 1a, b). This finding proved to be statistically significant in the post hoc testing. In contrast, functional connectivity between the "frontal inferior" region and the striatum as well as the "frontal middle" region and the striatum was increased in all three HD subgroups compared to controls (Fig. 1c, d). Post hoc testing revealed that functional connectivity between the "frontal inferior" region and the striatum was significantly smaller in controls than in the three HD subgroups. The functional connectivity between the "frontal middle" region and the striatum was significantly smaller in controls compared with early HD subjects as revealed by post hoc testing, but results of the farpremHD subjects and the closepremHD subjects did not differ significantly from controls or early HD subjects based on post hoc test applied.

Correlation Analysis between Functional Connectivity and Clinical Data

There was a significant correlation between UHDRS motor score and the "premotor" region as well as a significant correlation between UHDRS behavioral score and the "frontal middle" region. Other clinical scores did not correlate with the impaired functional connectivity found (p values >0.03).

The CAP scores and YTO correlated statistically significantly with altered functional connectivity between the striatum and the "frontal middle" region, "frontal inferior" region, "premotor" region, and "SMA" region (all p values <0.001 of Pearson's correlation coefficients). The CAP scores showed a positive correlation with the altered functional connectivity found, while the YTO showed a negative correlation with the altered functional connectivity (Fig. 2).

Functional connectivity between the striatum and the cortical regions that showed changes of the same directions in HD (increase or decrease compared to controls) showed significant positive correlations (Fig. 3). Functional connectivity between the striatum and the cortical regions that showed opposite changes in HD (increase or decrease compared to controls) showed significant negative correlations (Fig. 3).

All key findings including group differences and correlations remained significant when the functional connectivity analysis was repeated without GSR.

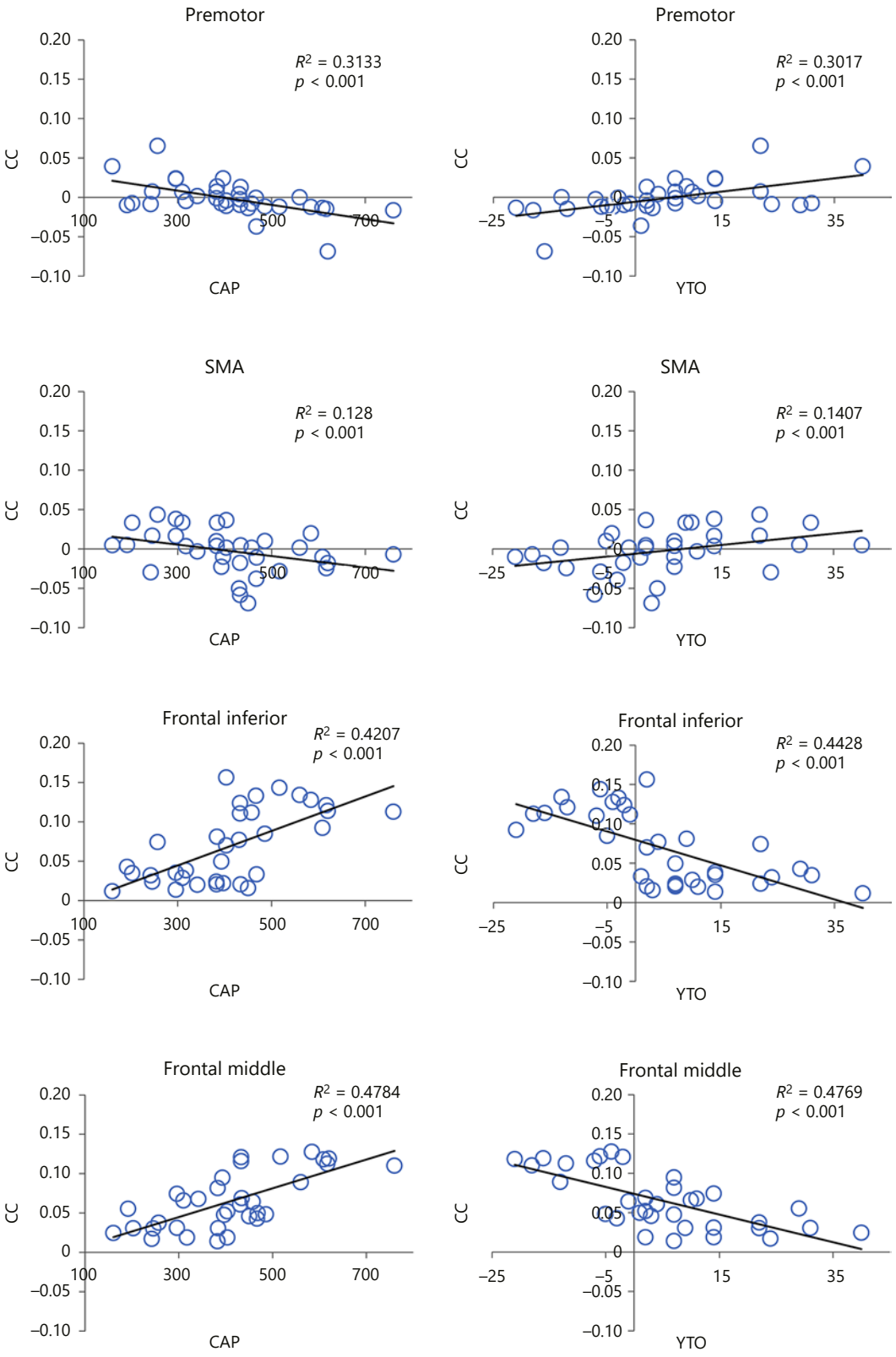
Discussion

In the current study, functional connectivity between the striatum and several cortical regions was examined using resting state fMRI performed at 7 T in HD subjects of different stages. Our results confirmed our previous finding of impaired striatal connectivity to the motor cortex but revealed enhanced striatal connectivity with the prefrontal cortex in HD [12]. The reduction in functional connectivity of the striatum-motor circuit in HD subjects is consistent with previous studies at 3 T and lower fields [11–16]. We speculate that the enhanced functional connectivity of the striatum-prefrontal circuit in HD may imply a compensatory mechanism, in which cortical regions other than motor areas are recruited to subserve functions that have been impaired due to pathological changes in HD [10].

The significant correlations between altered functional connectivity and genetic measures (CAP and YTO) suggest its potential value as a biomarker for tracking disease progression in HD. The CAG-age product or "CAP score" can be used to estimate the degree of genetic exposure to the HD mutation in HD subjects [23].

Fig. 2. Correlation between functional connectivity between the striatum and various cortical regions (measured with correlation coefficient or CC) and genetic data in early and premanifest HD subjects ($n = 34$). The CAG-age product (CAP) score and estimated year to onset (YTO, approximate) are both quantities derived from genetic exposure of the HD subjects. R^2, adjusted R^2 in multiple regression.

(For figure see next page.)



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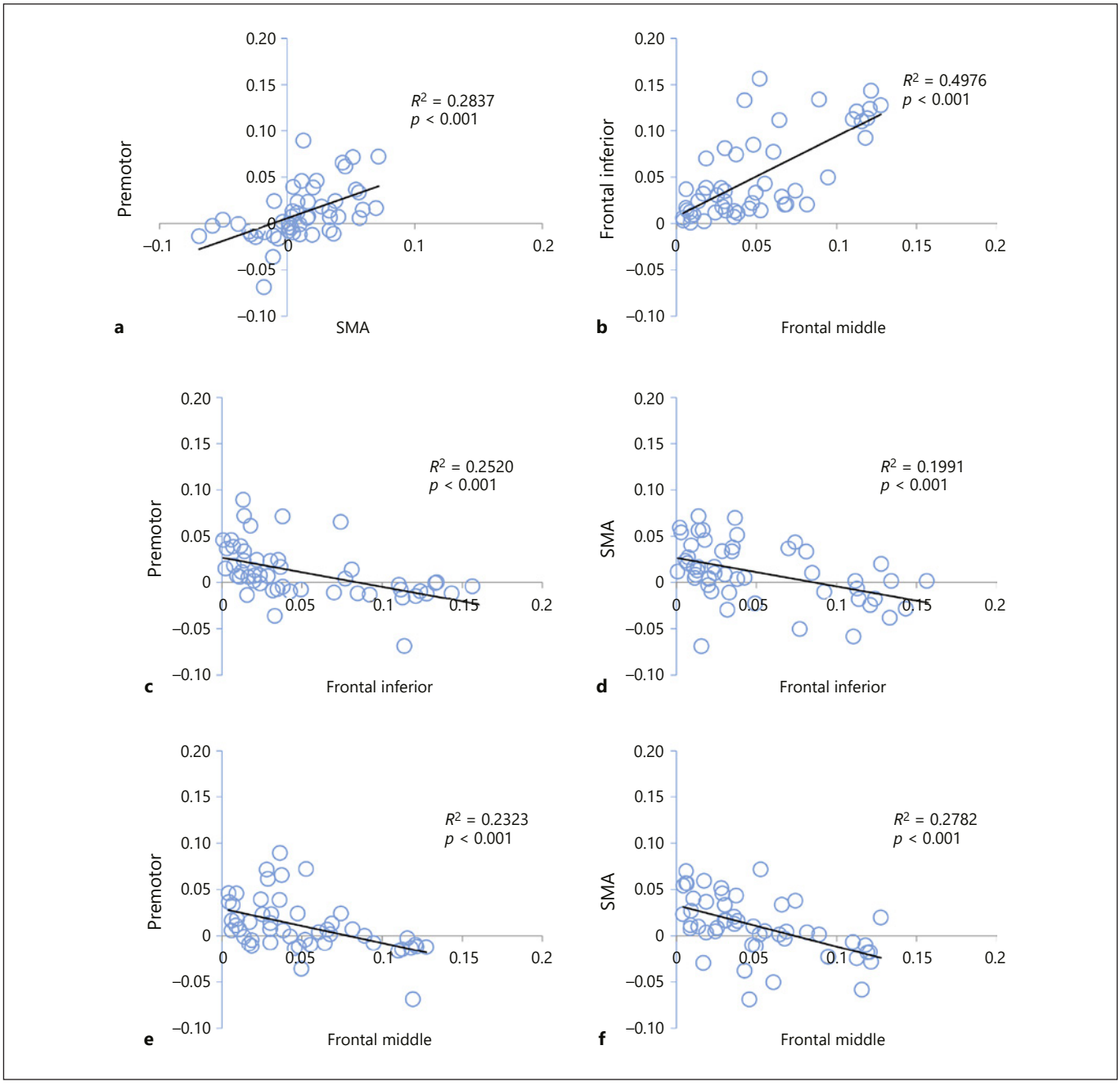

Fig. 3. a–f Correlation between functional connectivity between the striatum and various cortical regions (measured with correlation coefficient) in all subjects including healthy controls and HD subjects (n = 51). R^2, adjusted R^2 in multiple regression.

In line with the group comparison results, functional connectivity between the striatum and motor regions showed negative correlation with genetic exposure, whereas striatum-prefrontal functional connectivity showed the opposite.

The current study was performed at the ultra-high field strength of 7 T, which is expected to benefit from higher signal-to-noise ratio, thus increased sensitivity and spatial resolution compared to lower fields such as 3 T [18]. In addition to an approximately linear increase

in signal-to-noise ratio with field strength, ultra-high field is particularly attractive to BOLD fMRI as the BOLD contrast shows supra-linear increase with field [35]. The spatial specificity of BOLD fMRI also improves at ultra-high field since the BOLD signal predominantly originates from microvessels close to neuronal parenchyma due to shortened venous blood T2*-weighted relaxation time, whereas at 3 T and lower fields, macrovessels can have significant contributions to the BOLD signals [36–39]. For functional connectivity measured by resting state BOLD fMRI, 7 T can improve spatial specificity and is capable of detecting subtle correlations between brain regions not detected at 3 T [40]. MRI at 7 T also presents technical challenges in terms of increased magnetic susceptibility effects and field inhomogeneity. However, optimal high-order shimming techniques [24] were employed in the current study to minimize these problems. No substantial image artifacts were observed in our fMRI data using the optimized methodology. In a recent study conducted with the same fMRI approaches on the same scanner in our center on subjects with schizophrenia, we showed that comparable effect sizes in changes in functional connectivity from large-scale 3-T studies can be detected with a much smaller cohort at 7 T [41]. Therefore, we believe that the results from this study may aid the development of therapeutic biomarkers using functional connectivity measures at ultra-high field to detect functional changes in the brain with substantially fewer subjects in HD clinical trials.

Given the growing concerns that the GSR step in functional connectivity analysis may introduce additional negative correlations in the data, and thus may confound group comparison results [42], all functional connectivity analysis in the study was repeated without the GSR step in preprocessing. Indeed, we found that the results without GSR seemed to show somewhat fewer negative correlations compared to results with GSR, consistent with previous reports [42]. However, the main findings in our data including the group level differences in functional connectivity and correlations were comparable with or without the GSR step.

Although significant effects were detected in our data, we believe that the relatively small sample size and the cross-sectional design remain fundamental limitations of the current study. The sample size was estimated based on the effect size of functional connectivity changes in the striatum-motor circuit reported in our previous study [12]. The data from the current study will serve as the basis for designing future studies with larger cohorts and longitudinal components to validate our current findings.

In summary, differential changes in functional connectivity were detected in the striatum-motor and striatum-prefrontal pathways in the brains of premanifest and early manifest HD subjects using ultra-high field (7-T) BOLD fMRI. The functional connectivity changes correlated strongly with the CAP score in HD subjects. Our data are consistent with a compensatory mechanism in the HD brain attempting to restore the impaired motor functions by recruiting additional cortical regions such as the prefrontal cortex. This hypothesis should be further explored and validated in subsequent studies to help us better understand the functional changes in the brain in HD. This may help with the development of useful biomarkers to track disease progression and to evaluate responses to therapeutic interventions in HD.

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Statement of Ethics

All participants of this study have given their written informed consent. The study protocol has been approved by the committee on human research at Johns Hopkins.

Disclosure Statement

This study was performed on a human MRI scanner manufactured by Philips Healthcare. Dr. van Zijl is a paid lecturer and has a grant from Philips Healthcare. He is also the inventor of technology licensed to Philips. This arrangement has been approved by Johns Hopkins University in accordance with its conflict of interest policies. All the other authors have no conflicts of interest to declare.

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Author Contributions

M.K. (equal contribution): organization and execution of the study, statistical analysis, writing of the manuscript, review and critique of the manuscript; J.H. (equal contribution): conception and design, organization and execution of the study, statistical analysis, writing of the manuscript, review and critique of the manuscript; J.Y.A.B.: review and critique of the manuscript; K.E.U.: organization and execution of the study, review and critique of the manuscript; X.M.: execution of the study, statistical analysis, review and critique of the manuscript; X.Z.: statistical analysis, review and critique of the manuscript; J.J.P.: conception and design, statistical analysis, review and critique of the manuscript; P.C.M.Z.: conception, review and critique of the manuscript; W.D.: conception and design, review and critique of the manuscript; C.A.R.: conception and design, organization and execution of the study, statistical analysis, review and critique of the manuscript.

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