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Impaired cortico-striatal functional connectivity in prodromal Huntington's Disease

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Abstract

Huntington's Disease (HD) is a neurodegenerative disease caused by a CAG triplet-repeat expansion-mutation in the Huntingtin gene. Subjects at risk for HD can be identified by genetic testing in the prodromal phase. Structural changes of basal-ganglia nuclei such as the caudate nucleus are well-replicated findings observable early in prodromal-HD subjects and may be preceded by distinct functional alterations of cortico-striatal circuits. This study aims to assess functional integrity of the motor system as a cortico-striatal circuit with particular clinical relevance in HD.

Ten subjects in the prodromal phase of HD and ten matched controls were administered blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) at rest (3 Tesla). Functional connectivity was measured as synchrony of BOLD activity between the caudate nucleus and thirteen cortical brain regions (seeds). Basal-ganglia volumes were assessed as established markers of disease progression in prodromal-HD. Linear regression analysis was

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performed to test for a relationship between structural changes and group differences in functional connectivity.

Prodromal-HD subjects showed reduced BOLD synchrony between two seeds in the premotor cortex (BA6) and the caudate nucleus. While similar effect sizes could be observed for reduced basal-ganglia volumes and differences in functional connectivity, coefficients of determination indicate a moderate relationship between functional connectivity and striatal atrophy.

Our data show reduced cortico-striatal functional connectivity at rest in prodromal-HD and suggest a relation to early structural brain changes. Additional longitudinal studies are necessary to elucidate the temporal relationship between functional alterations and earliest structural brain changes in prodromal-HD.

Introduction

Huntington's Disease (HD) is a neurodegenerative disease caused by a CAG repeat length expansion mutation in the *Huntingtin* Gene [20, 21]. After an initial prodromal phase, HD manifests with a characteristic triad of progressive motor-, cognitive and behavioral symptoms [39]. HD motor-symptoms are characterized early by chorea, incoordination and motor impersistence and later by dystonia, bradykinesia and rigidity [37, 45].

Neuropathological studies show damage of cortico-striatal components with neuronal loss in the cortex and the caudate nucleus in particular [44]. Neuroimaging studies using magnetic resonance imaging (MRI) are consistent with these data, indicating early characteristic structural alterations of striatal and cortical structures already in the prodromal phase [2, 33]. Particularly volume loss of the caudate and putamen have been demonstrated to be valid markers of disease progression [3-5], which is characterized by a general impairment of neural circuits linking basal ganglia and cortex [1, 11, 13]. This may be consistent with functional MRI (fMRI) data, demonstrating significant changes in neuronal activity in prodromal-HD [32, 36] involving distinct alterations of the motor system [25]. Functional connectivity is defined as synchronous blood oxygen level dependent (BOLD) activity of spatially segregated brain regions [19, 42] and distinct patterns of both positive and negative BOLD correlation are active at rest [7, 10, 12, 24]. In this context spontaneous fluctuations in the BOLD signal of resting state fMRI has been suggested to reflect basal neuronal activity within various networks involved in intrinsic brain function [18, 35]. In addition, altered interactions of neuronal populations measurable based on intrinsic functional connectivity may be a physiological correlate of various neuropsychiatric disorders [17, 43]. Altered functional connectivity has been reported for prodromal HD [46] and cortico-striatal BOLD synchrony in particular has been suggested to reflect early HD related pathology [28]. Functional connectivity analysis at rest appears particularly promising in HD, as it remains a central question whether there is independent degeneration in different brain regions or system degeneration due to functional connections [39]. However, at this point most fMRI studies on HD were performed during activation and to our knowledge no resting-state data has been published on functional integrity of cortico-striatal motor circuits.

We hypothesize that measuring functional connectivity at rest will reveal impaired interaction between the caudate nucleus and cortical regions in prodromal-HD versus unaffected healthy controls as a reflection of earliest disease related brain alterations. This study therefore focuses on probing functional integrity of the motor system as a cortico-striatal circuit with particular clinical relevance in HD and will assess its relationship with striatal atrophy.

Methods

Study population

Ten subjects CAG-expansion-positive for HD that were still in the prodromal phase of the disease, were recruited through the Huntington's Disease Center at Johns Hopkins University School of Medicine. All prodromal-HD subjects received standardized neurological examination, using Quantified Neurological Exam-scores [16]. Estimated time to onset of motor symptoms was calculated based on CAG-repeat length of the mutated HTT allele and age [26], disease burden score (DBS) was calculated as $[(\text{CAG-repeat length} - 35.5) * \text{age}]$ [34]. Additionally ten age- and gender-matched control subjects were recruited through Johns Hopkins University. None of the 20 participants had a history of severe mood-, obsessive compulsive-, or psychotic disorders or substance abuse. Consent was obtained according to the Declaration of Helsinki [47] and approved by the Johns Hopkins University Institutional Review Board.

MRI and fMRI acquisition

MRI data was acquired at the FM Kirby Research Center for Functional Brain Imaging at Kennedy Krieger Institute on a Philips Intera 3T scanner (Philips Medical Systems, Best, the Netherlands) equipped with a SENSE head coil (eight elements radially positioned around the head).

Whole-brain anatomy was assessed using T1-weighted, three-dimensional Magnetization Prepared Rapid Gradient Echo (MP-RAGE) using the following parameters: TR=8.2ms; TE=3.8ms; flip angle=8°; 150 slices (no gap); FOV=256mm; nominal resolution=1×1×1mm; no gap; SENSE factor=2.0; total acquisition time=278 seconds.

Functional acquisitions were performed at 440 seconds open eye resting state using partially parallel accelerated gradient-echo (GE) echo planar imaging (EPI). They consisted of 37 slices in the axial plane, aligned parallel to the line from the anterior commissure to the posterior commissure using the following parameters: TR=2000ms; TE=30ms; flip angle=75°; FOV=240mm; nominal resolution = 3mm; no gap; SENSE factor = 2.0.

Post image acquisition analysis

Analysis of T1 MP-RAGE images was performed using TOPOLOGY-preserving, Anatomy-Driven Segmentation (TOADS) with desired topology and relationships as given by a template (<http://medic.rad.jhmi.edu/download/public/index.shtml>) [6]. Resulting volumes of main cerebral structures were used for subsequent group comparisons of regional brain morphology.

Individual fMRI data were preprocessed by an initial correction for timing differences between slices, realignment, spatial normalization to Montreal Neurological Institute (MNI) template space. To minimize nuisance and partial volume bias, nuisance masks reflecting white matter (WM), cerebro spinal fluid (CSF) signal and motion were calculated. Residual volumes were generated by performing regression based on these masks and then smoothed with a 6mm3 full width half-maximum Gaussian kernel. A bandpass-filter (0.1-0.01Hz) was applied as a final step of preprocessing. Preprocessing was performed using the Statistical Parametric Mapping (SPM5) software package (<http://www.fil.ion.ucl.ac.uk/spm/>) and the MatLab with signal processing toolbox (Version 7.12, MathWorks Inc., Natick, Massachusetts, United States). The concept of measuring functional connectivity between regions of interest using anatomically defined seeds has been reviewed recently [24]. A total of thirteen 6mm diameter spherical gray matter regions of interest (referred to as "seeds" to test for connectivity with other regions) were generated based on anatomical information in

talairach space [40] including eleven cortical and subcortical-regions in the motor-system (Caudate Nucleus, Globus Pallidus (G.P.), Thalamus (Pulvinar), premotor area (Brodmann Area (BA) 6 (1,2) and anterior cingulate cortex (BA 32), supplementary motor area (BA 6 (3-5), primary motor cortex (BA 4 (1-2)). As negative controls, two additional tests were performed with seeds located in brain regions not primarily involved in motor control and not expected to be mainly affected in early HD [4] (Cuneus, BA 18 and parahippocampal gyrus, BA 35). These regions of interest (seeds) were used to test for BOLD-synchrony with the Caudate Nucleus (26,45) (Figure 1). All included cortical regions are well known to connect to the striatum [1, 14].

Statistics

Statistical analyses were performed using SPSS for Windows (version 17.0, SPSS Inc, Chicago, IL, USA). Group differences of BOLD-synchrony were assessed using Fisher r to z transformation of the individuals correlation coefficients to normal distribution [15], followed by independent sample t -tests (MatLab 7.12, statistics toolbox). Effect sizes were estimated as Cohen's d . We predicted that BOLD-synchrony would be lower between components of the motor system and compared BOLD synchrony between seeds in the caudate nucleus and motor system, adjusting alpha (5%) by applying Bonferroni correction for performing twelve tests [22]. Linear regression analysis was performed to estimate coefficients of determination (r^2) for striatal atrophy (putamen and caudate-volumes) and significantly differing BOLD correlation coefficients of HD-subjects, using z -scores in reference to the mean values of the healthy control group. Age and sex were used as covariates and did not affect measures of correlation significantly.

Results

Subject characteristics

Group demographics for the 20 individuals included in this study (ten unaffected controls, ten expansion positive individuals in the prodromal phase of HD) are displayed in table 1. The mean total QNE and also chorea subscore reflect only non-HD specific neurological symptoms, subjects with manifest HD usually have total QNE scores significantly above 20 [9, 16].

Group comparisons of brain morphology between controls and HD subjects

Measures of brain morphology as assessed by cortical and subcortical segmentation indicate significantly reduced caudate ($p=0.01$, effect size=1.9) and putaminal volumes ($p=0.03$, effect size=1.9) in prodromal-HD subjects compared to controls. While cerebral gray- and white matter volumes tend to be lower in prodromal-HD, differences are not significant. None of the other measured cerebral structures and brain tissue components differed significantly between prodromal-HD and controls (Table 1).

Reduced cortico-striatal BOLD synchrony in prodromal-HD subjects

Seed based BOLD synchrony with the Caudate Nucleus was assessed for a total of twelve brain regions (figure 1), correlation coefficients were converted to z -values using Fisher r to z transformation [15]. Independent samples t -tests of the converted z -values of all twelve regions revealed significantly lower BOLD synchrony in prodromal-HD between the caudate nucleus and seeds in BA6, which remained significant after correction for multiple testing and indicate reduced cortico-striatal functional connectivity compared to controls, with a moderate degree of variance explained by caudate atrophy (BA 6_2: controls 0.28 (SE:0.05), prodromal-HD -0.08 (SE:0.08), $p=0.001$, effect size=1.8, caudate $r^2=0.3$, $p=0.09$, putamen $r^2=0.13$, $p=0.30$; BA 6_3: controls 0.21 (SE:0.04), prodromal-HD 0.02 (SE:0.04),

$p=0.004$, effect size=1.6, caudate $r^2=0.4$, $p=0.04$, putamen $r^2=0.2$, $p=0.25$) (figure 2). Seeds in adjacent regions showed trends of lower BOLD synchrony in prodromal-HD subjects (BA 6_1: controls 0.21 (SE:0.06), prodromal-HD 0.01 (SE:0.08), $p=0.054$, effect size=0.9; BA 4_1: controls 0.12 (SE:0.06), prodromal-HD -0.09 (SE:0.08), $p=0.051$, effect size=1.0). Also correlation analysis between the caudate and the globus pallidus showed a trend of reduced BOLD synchrony in prodromal-HD subjects (G.P.: controls 0.11 (SE:0.06), prodromal-HD -0.09 (SE:0.09), $p=0.07$, effect size=0.9). This trend of reduced BOLD synchrony between cortico-striatal structures of the motor system in prodromal-HD subjects could not be observed for seeds in parahippocampal gyrus (BA 35), Anterior Cingulate (BA 32) and Cuneus (BA18) (BA 35: controls -0.19 (SE:0.08), prodromal-HD -0.13 (SE:0.05), $p=0.57$, effect size=-0.3; BA 32: controls 0.12 (SE:0.08), prodromal-HD 0.18 (SE:0.06), $p=0.53$, effect size=-0.3; BA 18: controls -0.12 (SE:0.08), prodromal-HD -0.10 (SE:0.06), $p=0.82$, effect size=-0.1).

Discussion

Our data show significantly reduced BOLD synchrony between seeds representing the caudate nucleus and lateral premotor area, indicating impaired cortico-striatal functional connectivity as a correlate of brain changes in prodromal-HD.

To our knowledge this is the first study reporting impaired functional connectivity at rest between motor cortex and the caudate nucleus in prodromal-HD subjects. Relevance for motor circuits is indicated by the fact that functional connectivity between the caudate and cortical regions not involved in motor control (parahippocampal gyrus and cuneus) did not differ significantly between controls and prodromal-HD subjects. Our data is consistent with earlier reports on brain network alterations in early HD that involve impaired cortico-striatal circuit integrity at early disease stages both in humans and also genetic mice models [8, 11, 14, 23]. Functional connectivity analysis appears to be particularly suited to address the question of HD related alterations of brain networks at rest [7, 12]. We have used a seed based approach, allowing us to address the specific hypothesis of altered cortico-striatal interaction in prodromal-HD, reflected in particular by reduced BOLD synchrony between cortical and striatal components of the motor system.

While there are significant conceptual differences to multivariate approaches of measuring functional connectivity such as independent component analysis (ICA), results from seed-based and ICA methodologies are generally similar [24]. While there is consistent evidence for characteristic structural changes developing early in prodromal-HD [2, 4, 33, 38], functional markers of disease progression have been speculated to reflect even earlier pathological processes [32, 36]. In our sample both functional alterations and the earlier reported characteristic structural changes involving reduced volumes of the caudate nucleus and putamen were observable with similar effect sizes in prodromal-HD. As striatal atrophy explained only a moderate degree of the differences in functional connectivity, this might reflect different pathological processes active in parallel. However, the temporal relationship between functional and structural brain alterations observable in our data remains unclear due to the cross-sectional design of this study. While the biological underpinnings of reduced BOLD synchrony between spatially distinct brain regions in prodromal HD still remain largely unclear, it may reflect disease related biochemical processes affecting cellular viability such as decreased transport and release of brain derived neurotrophic factor (BDNF) but also excitotoxic effects in cortico-striatal neurons in a context of dysregulated glutamate metabolism [11, 39]. Impaired function of affected neuronal populations may go along with reduced BOLD synchrony [48] within cortico-striatal loops of the motor-system, progressing to sensorimotor striatal degeneration at later disease stages [8]. On a systems level this may result in clinical symptoms such as cognitive and behavioral deficits, which

are observable in the prodromal phase of HD and have been demonstrated to be associated with cortico-striatal dysfunction, which may be consistent with the lower degree of spontaneous BOLD synchrony observable in our data [27, 29, 31, 39].

A limitation of our study is the small sample size, which limited power for secondary regression analysis of relevant clinical parameters. Furthermore the fact, that beyond the standardized neurologic examination no neuropsychological and behavioral assessment was performed. This may be a promising approach of expanding the here presented study on earliest functional alterations in prodromal HD, as dysfunction of loops involving cortical regions and the caudate have been shown to relate to behavioral manifestations of brain pathology in HD [29, 30, 41].

Conclusion

By measuring BOLD-synchrony between the caudate nucleus and the motor cortex, we find evidence for impaired cortico-striatal functional connectivity in prodromal-HD subjects which shows similar effect size as striatal atrophy. Further longitudinal studies may help to elucidate temporal aspects of the relationship between functional and structural brain alterations in prodromal-HD.

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Highlights

Dysfunction of cortico-striatal circuits may precede structural changes in prodromal HD

This is the first report on dysfunctional cortico-striatal connectivity at rest in HD

Particularly the caudate nucleus and the premotor cortex appear affected

These measures may serve as response markers for neuroprotective treatment approaches

Figure 1.

Overview of the brain regions included by the seeds used for analysis of BOLD synchrony (talairach coordinates: x;y;z): A) Caudate Nucleus, body (-12;10;16), B) BA 6_1, Lateral Premotor Area (-57;3;16), C) BA 6_2, Lateral Premotor Area (-57;2;28), D) BA 6_3, Premotor Area (-42;-15;44), E) BA 6_4, Supplementary Motor Area (-33;-14;63), F) BA 6_5, Supplementary Motor Area (-12;-17;65), G) BA 4_1, Primary Motor Cortex (-42;-15;44), H) BA 4_2, Primary Motor Cortex (-18;-26;65), I) Globus Pallidus (-15;-4;-2), J) BA 32, Anterior Cingulate (-5, 29, 25), K) Thalamus (-7;-15;14), L) BA 35, Parahippocampal Gyrus (-20;-27;-11), M) BA 18, Cuneus (-5; -100; 8).

Figure 2.
Correlation coefficients (pearson r) for 11 brain regions (B-M) reflecting group averages of BOLD synchrony at rest with the Caudate Nucleus.

Table 1

a) Demographics of the study populations and b) volumes (ml) of brain tissues and regions (group averages, standard deviations).

	Controls	Prodromal HD	T-test (<i>p</i>)
a) Demographics			
<i>N</i>	10	10	-
<i>Females; Males</i>	6; 4	4; 6	-
<i>Age</i>	42.3 (11)	44 (9.2)	0.71
<i>CAG repeat length</i>	-	42.8 (1.5)	-
<i>Estimated Years to onset (YTO)</i>	-	10.4 (6.3)	-
<i>Disease Burden Score (DBS)</i>	-	316.6 (71.7)	-
<i>QNE, total score</i>	-	4 (8.7)	-
<i>QNE, chorea subscore</i>	-	0.9 (2.5)	-
b) Volumes			
<i>Sulcal CSF</i>	281 (40)	274 (27)	0.64
<i>Ventricles</i>	22 (11)	22 (12)	0.93
<i>Cerebellar GM</i>	84 (8.7)	83 (8.4)	0.79
<i>Cerebral GM</i>	524 (53)	510 (44)	0.53
<i>Caudate</i>	9.5 (0.6)	7.5 (1.4)	* 0.01
<i>Thalamus</i>	19 (1.3)	19 (1.1)	0.59
<i>Putamen</i>	12 (1)	10 (1.1)	* 0.03
<i>Brainstem</i>	21 (2.5)	21 (2.8)	0.91
<i>Cerebellar WM</i>	31 (5.1)	30 (3.9)	0.48
<i>Cerebral WM</i>	467 (71)	450 (25)	0.48