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CORTICAL FEATURES IN CHILD AND ADOLESCENT CARRIERS OF MUTANT HUNTINGTIN (MHTT)

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Abstract

BACKGROUND: Molecular studies provide evidence that mutant huntingtin (*mHTT*) affects early cortical development; however, cortical development has not been evaluated in child and adolescent carriers of *mHTT*.

OBJECTIVE: To evaluate the impact of *mHTT* on the developmental trajectories of cortical thickness and surface area.

METHODS: Children and adolescents (6–18 years) participated in the KidsHD study. *mHTT* carrier status was determined for research purposes only to classify participants as gene expanded (GE) and gene non-expanded (GNE). Cortical features were extracted from 3T neuroimaging using FreeSurfer. Nonlinear mixed effects models were conducted to determine if age, group, and CAG repeat were associated with cortical morphometry.

RESULTS: Age-related changes in cortical morphometry were similar across groups. Expanded CAG repeat was not significantly associated with cortical features.

CONCLUSIONS: While striatal development is markedly different in GE and GNE, developmental change of the cortex appears grossly normal among child and adolescent carrier of mHTT.

Keywords

Huntington's disease; cortical development; children at risk for HD; magnetic resonance imaging; trinucleotide repeat disorder

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Conflict of Interest

The authors report no other conflicts of interest relevant to this work.

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Introduction

Huntington's disease (HD) is a fatal neurodegenerative disease caused by a CAG repeat expansion in the Huntingtin gene (*HTT;* OMIM 143100). The neuropathology of HD is characterized by atrophy of the striatum and surrounding white matter, beginning roughly 15–20 years prior to motor onset [1–3]. This appears to be followed by a progressive loss of cortical volume, which has also been identified around 10–15 years prior to estimated motor onset. Although the primary disease process is neurodegeneration, the origins of disease pathology may lie in neurodevelopmental changes in the growth and development of the striatum, driven by the gene expansion [4].

Robust findings from histopathological research and human neuroimaging studies link mHTT with abnormal cortical development. Evidence of abnormal neuronal migration has been documented in both mouse and human embryos carrying mHTT [5], as well as in adult HD patients through post-mortem analyses [6]. Similarly, Cepeda and colleagues reported evidence of cortical dysplasia and hyperexcitability in R2/6 mice shortly after birth [7]. On a structural level, these disruptions to normal corticogenesis likely contribute to smaller intercranial volume [8], cortical enlargement [9], and abnormal cortical folding [10], all which have been observed in adult patients. Despite these reports, the effects of mHTT on development of cortex morphology have not yet been assessed via neuroimaging.

The Kids-HD study was designed to characterize brain development in children and adolescents at-risk for adult-onset HD. Subjects ages 6–18 who have a family history of HD are genotyped for research purposes and grouped into a Gene-Expanded (GE) group – individuals who will develop HD later in life (CAG ≥ 36) – or a Gene Non-Expanded (GNE) – individuals who will not develop the disease (CAG < 35). We previously reported that GE subjects had significantly different growth and development of the striatum compared to the GNE group with early striatal hypertrophy and a significant decline in volume seen in GE individuals throughout the 6–18 year age range [11]. Using the Kids-HD sample, the goals of the current study were to evaluate differences in cortical morphology (thickness and surface area) between GE and GNE subjects.

Materials and Methods

Participants

Details regarding study methods were published previously [11]. Briefly, participants between the ages of 6–18 with a parent and/or grandparent with HD were recruited. CAG repeat was determined through PCR analysis on saliva or blood samples that were collected for research purposes only. Written informed consent was obtained from either the participant or their parent/guardian (for those under 18). Study procedures were approved by the University of Iowa Institutional Review Board.

Following an accelerated longitudinal design (ALD), participants were assessed across a wide age range, with some participants returning for multiple visits and others contributing only a single data point [12]. Since we were interested in evaluating development rather than

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disease progression, we excluded 11 GE observations from 8 participants estimated to be within 15 years from onset, based a model developed by Langbehn and colleagues [13].

MRI acquisition and processing

Neuroimaging data was acquired on either a 3T Siemens Trio TIM (Siemens AG, Munich, Germany) or a 3T General Electric Discovery MR750w (GE Medical Systems, Chicago, IL). Cortical features were extracted using FreeSurfer and regions of interest were labeled with the Desikan-Killiany atlas.[11] Inter-scanner variation was removed using ComBat Harmonization as implemented in ez.combat 1.0.0 package in R [14].

Statistical Analysis

The development of regional cortical thickness (in mm) and cortical surface area (mm^2) were explored using mixed regression analyses. We first evaluated the group*age interaction for each region of interest (ROI), including whole brain, and frontal, parietal, temporal, and occipital lobes. Since cortical development is known to be non-linear [15], we considered varying degrees of non-linearity with natural cubic spline transformations of age. Linear and non-linear models with up to 3 spline knots were compared by calculating Akaiki information criteria corrected for small sample size (AICc) using the AICcmodavg (2.30–1) package. Lower AICc was considered an indicator of better fit. Type III ANOVA was performed to estimate joint significance of the group*age interaction. All models included sex as a covariate and controlled for random effects of both family relations and participants. The false discovery rate (FDR) was calculated to account for repeated analysis and FDR < 0.05 was considered statistically significant. Results were visualized by standardizing and mean-centering cortical variables (mean = 0, units = standard deviation).

We also evaluated the effect of expanded CAG repeat length on cortical features in the GE group using linear mixed-effects models fit by restricted maximum likelihood. All models included sex and age as covariates and controlled for random effects of both family relations and participants.

Results

The sample included 285 total observations from 71 GE participants and 101 GNE participants. Demographics, including age (Mean = 13.6, SD = 3.7), sex (59.3% female), and total motor score (Mean = 1.12, SD = 2.41), were comparable between groups (all $p > 0.05$); Table 1). GE participants were, on average, 35.4 years from predicted onset.

There were no significant group-by-age interactions across any ROIs for cortical thickness or surface area (Figure 1, Table 2). Both GE and GNE groups demonstrated comparable thinning of the cortex with increased age ($F(3, 246) = 2.34$, FDR = 0.185). Both groups also showed similar non-linear change in whole brain cortical surface area with age ($F(3,84.5) = 3.16$, FDR = 0.095; Figure 1). Details on model selection (Supplemental Table 1) and main effects of group, sex, and age (Supplemental Table 2) are described in the supplemental materials.

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Similarly, we found no association between CAG repeat length overall and overall cortical thickness ($F(1,69.5) = 0.917$, FDR = 0.85) or surface area ($F(1,79.3) = 4.35$, FDR = 0.108; Table 3).

Discussion

Morphological development of major cortical areas were compared in children and adolescents with and without *mHTT*. GE and GNE groups demonstrated no significant differences in age-dependent change of cortical thickness and surface area across all lobes of the brain. Dynamic changes in cortical thickness and relatively smaller global decrease in cortical surface area likely reflects normal synaptic pruning [15]. We also found no significant association between cortical morphology and CAG repeat length within individuals at-risk for adult-onset HD.

Numerous studies have demonstrated that mHTT affects early differentiation of neural progenitors in rodent models [5, 16], cortical cell cultures [17, 18], and human fetal tissue samples [5, 6]. The current predominating theory of corticogenesis—the radial unit lineage model—suggests that neuronal proliferation within each radial column determines cortical thickness [19]. Based on this model, it follows that the lower levels of proliferation observed in early cortical tissues carrying *mHTT* would lead to a thinner cortex in GE individuals. Despite this, we observed no effect of gene status on cortical development in the Kids-HD cohort. Our findings were consistent with recent assessment of brain development in juvenile zQ175 mice, where a pathological CAG expansion did not appear to significantly alter neocortical volume [20]. These findings alongside our own are not sufficient to refute the clear impact of *mHTT* on corticogenesis, as it is possible that current neuroimaging methods do not adequately capture cortical changes associated with *mHTT*. However, the lack of group difference in our sample suggests that early differences in cytoarchitecture may not translate into detectable differences in cortical morphology.

While mHTT does not seem to significantly impact cortex size, its effects may be detectable through changes in other measures, such as cortical connectivity, plasticity, and excitability. For example, GE subjects in this cohort display altered connectivity in striatal-cerebellar circuitry [21] and we have yet to explore how these changes relate to striatal-cortical connectivity. Based on findings from the Young Adult Study, altered functional connectivity of front-striatal circuits and associated with cognitive impairments are present up to two decades prior to motor onset [22]. Likewise, transmagnetic stimulation (TMS) studies demonstrate reduced cortical inhibition prior to motor onset [23, 24]. These findings demonstrate the sensitivity of resting-state functional MRI (rs-fMRI) and TMS [25] in detecting cortical changes prior to motor onset, however neither have been used to look at pediatric carriers. As such, it is not yet clear whether altered signaling is a consequence of early neurodegeneration, a direct result of mHTT-associated developmental abnormalities, or some combination of the two. Intracortical functional connectivity appears to increase as patients near motor onset, supporting a compensation model [26], yet R6/2 mice demonstrate altered excitatory/inhibitory balance early in development [7]. Considering the importance of the fronto-striatal pathways to executive functioning [27], it is crucial that

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future studies continue to characterize their structure and functioning in child and adolescent carriers of the *mHTT* mutation.

The present study is the first to evaluate cortical development in child and adolescent carriers of *mHTT* decades from disease onset. While previous analyses have shown differences in striatal development between GE and GNE, we did not observe differences in developmental trajectories of the cortex. Given the reported impact of mHTT on cortical neurogenesis, it is imperative that future studies bridge the gap between basic science and clinical findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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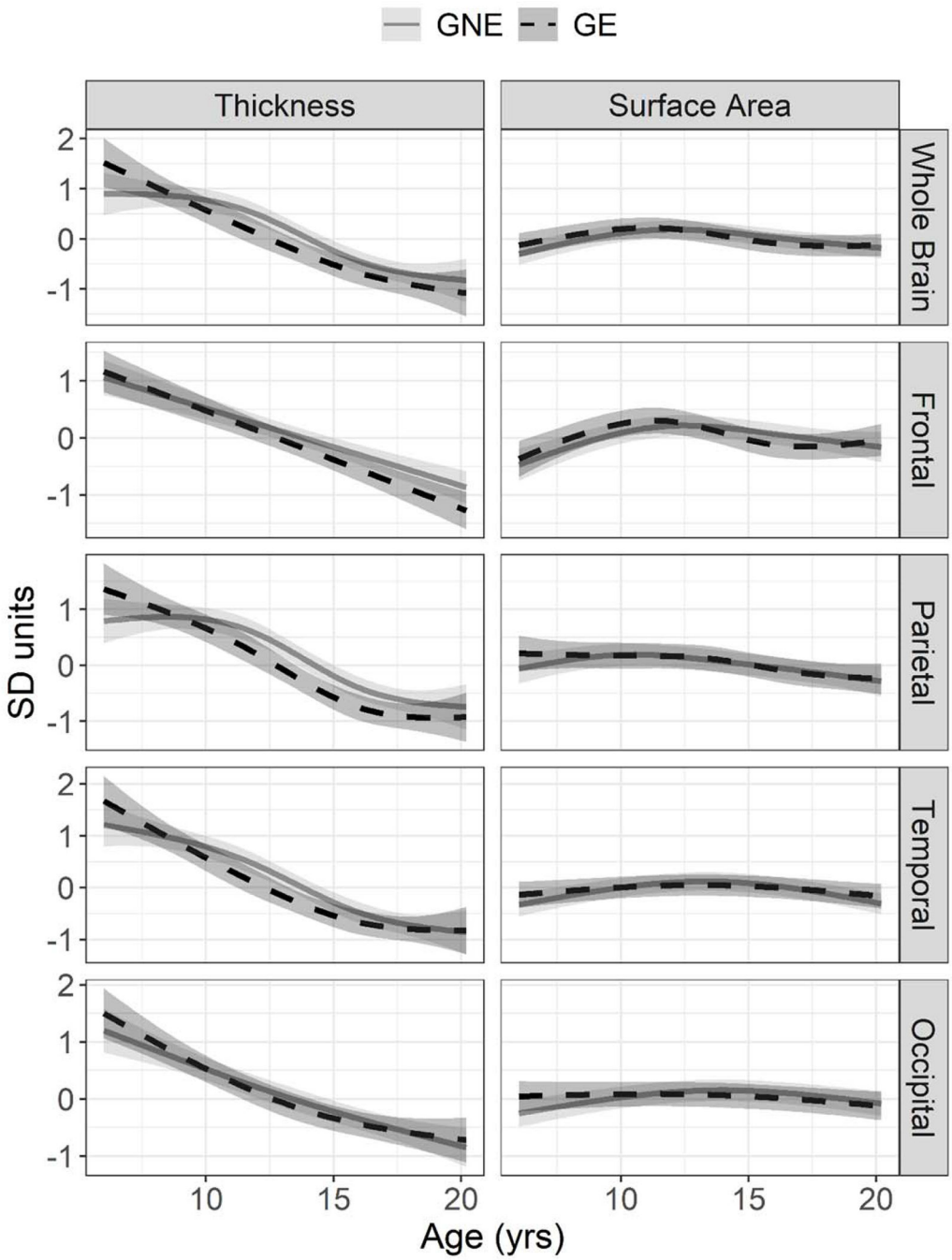

Figure 1. Developmental trajectory of cortical thickness and surface area by group.

Mean estimated age-dependent change in cortical features in the gene non-expanded (GNE; grey) and gene-expanded (GE; black) groups. On the y-axis, cortical thickness (left) and surface area (right) are centered around sex-adjusted estimates from mixed effects models with natural cubic spline transformations of age.

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Table 1

Demographics of Sample Observations

	GNE (N=168)	GE (N=117)	p-value
Age (yrs)			
Mean (SD)	13.5 (3.70)	13.7 (3.74)	0.708
Median [Min, Max]	13.7 [6.08, 20.3]	14.0 [6.00, 20.2]	
Sex			
Female	94.0 (56.0%)	75.0 (64.1%)	0.209
Male	74.0 (44.0%)	42.0 (35.9%)	
CAG repeat length			
Mean (SD)	20.2 (4.01)	44.0 (4.26)	
Median [Min, Max]	18.5 [15.0, 34.0]	43.0 [36.0, 58.0]	
UHDRS total motor score			
Mean (SD)	1.13 (2.32)	1.12 (2.56)	0.986
Median [Min, Max]	0 [0, 14.0]	0 [0, 15.0]	

Abbreviations: GNE, Gene-Non-Expanded; GE, Gene-Expanded.

Note: Welch two sample t-tests were performed to compare UHDRS and age between groups. Chi-square test of independence was used to compare sex distribution between groups.

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Table 2

Age-dependent effect of group on cortical morphology

Variable	Region	F-Statistic	dfn, dfd	p-value	FDR
Cortical Thickness	Whole Brain	2.34	3, 246	0.074	0.185
	Frontal	1.76	1, 256	0.186	0.233
	Parietal	4.05	2, 260	0.0186	0.0928
	Temporal	1.82	3, 243	0.143	0.233
	Occipital	0.905	2, 242	0.406	0.406
Cortical Surface Area	Whole Brain	3.16	3, 84.5	0.0287	0.095
	Frontal	2.9	3, 110	0.038	0.095
	Parietal	0.737	4, 94.7	0.569	0.569
	Temporal	2.62	2, 263	0.0745	0.124
	Occipital	0.905	2, 242	0.406	0.508

Abbreviations: GNE, Gene-Non-Expanded; GE, Gene-Expanded; dfn, degrees of freedom numerator; dfd, degrees of freedom denominator

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Table 3

Effect of expanded CAG repeat length on cortical morphology

Variable	Region	F-Statistic	dfn, dfd	p-value	FDR
Cortical Thickness	Whole Brain	0.0342	1, 69.5	0.85	0.917
	Frontal	0.0109	1, 68.3	0.92	0.917
	Parietal	0.118	1, 71.1	0.73	0.917
	Temporal	0.0368	1, 65.8	0.85	0.917
	Occipital	0.0587	1, 71	0.81	0.917
Cortical Surface Area	Whole Brain	4.35	1, 79.3	0.04	0.108
	Frontal	2.82	1, 79.6	0.10	0.108
	Parietal	2.98	1, 74.4	0.09	0.108
	Temporal	4.17	1, 77.6	0.04	0.108
	Occipital	2.64	1, 74	0.11	0.108

Abbreviations: dfn, degrees of freedom numerator; dfd, degrees of freedom denominator