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T1ρ Imaging in Premanifest Huntington Disease Reveals Changes Associated with Disease Progression

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Abstract

Background—Imaging biomarkers sensitive to Huntington’s disease (HD) during the premanifest phase preceding motor diagnosis may accelerate identification and evaluation of potential therapies. For this purpose, quantitative MRI sensitive to tissue microstructure and metabolism may hold great potential. We investigated the potential value of T1ρ relaxation to detect pathological changes in premanifest HD (preHD) relative to other quantitative relaxation parameters.

Methods—Quantitative MR parametric mapping was used to assess differences between 50 preHD subjects and 26 age- and sex-matched controls. Subjects with preHD were classified into two progression groups based on their CAG-age product (CAP) score; a high and a low/moderate CAP group. Voxel-wise and region-of-interest analyses were used to assess changes in the quantitative relaxation times.

Results—T1ρ showed a significant increase in the relaxation times in the high-CAP group, as compared to controls, largely in the striatum. The T1ρ changes in the preHD subjects showed a significant relationship with CAP score. No significant changes in T2 or T2* relaxation times

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were found in the striatum. T2* relaxation changes were found in the globus pallidus, but no significant changes with disease progression were found.

Conclusion—These data suggest that quantitative T1ρ mapping may provide a useful marker for assessing disease progression in HD. The absence of T2 changes suggests that the T1ρ abnormalities are unlikely owing to altered water content or tissue structure. The established sensitivity of T1ρ to pH and glucose suggests that these factors are altered in HD perhaps owing to abnormal mitochondrial function.

Keywords

premanifest Huntington disease; magnetic resonance imaging; imaging biomarkers; T1ρ; quantitative imaging

Huntington's disease (HD) is a progressive, fatal, autosomal-dominant, neurodegenerative disease with no disease-modifying treatment. The disease is caused by an abnormal trinucleotide cytosine-adenine-guanine (CAG) expansion in the huntingtin gene. Detecting pathophysiological processes underlying HD before a clinical motor diagnosis offers hope for assessment of treatments and allows for early intervention, which ultimately will result in improved outcomes.¹ To evaluate treatments before a clinical motor diagnosis is given, biomarkers are needed that can be objectively measured, are an indicator of disease progression, and measure a pharmacological response. To date, there are no proven biomarkers in HD and continued evaluation of potential biomarkers is needed.²

MRI provides a number of modalities that have been studied as potential biomarkers for HD progression during the premanifest phase preceding motor diagnosis, including structural imaging, diffusion imaging, magnetization transfer imaging, spectroscopy, and functional imaging, as previously reviewed in Bohanna et al.³ Weir et al.⁴ and van Den Bogaard et al.⁵ The size of the caudate and putamen have been shown to be potential biomarkers for disease progression.^{6,7} Based on the PREDICT-HD study, decreased volume of the striatum and white matter (WM) are detectable years to decades before estimated motor diagnosis of HD⁸ and are significantly atrophied close to clinical manifestation.⁹ The change in volume has been found to be approximately linear during the premanifest phase of the illness. Changes in brain metabolism^{10,11} and function^{12–15} have also been reported.

There has been growing interest in using quantitative parametric MRI as a biomarker for neurodegenerative disorders.^{16–22} Quantitative imaging has a number of advantages over existing MRI techniques, including the ability to study changes in the relaxation time without the need to normalize to a standard (e.g., volumetric normalized to intracranial volume). Quantitative measurements offer the possibility to relate these changes back to pathological processes given that they reflect tissue properties at the microscopic level, instead of the macroscopic level, such as striatal volume. Coupling of multiple quantitative parametric imaging techniques facilitates the identification of the underlying mechanisms that may be responsible for the relaxation time changes.

Previous studies have employed quantitative T2 and T2* mapping to study how these relaxation times change in HD^{19,23–25} These studies were motivated by the findings that

subjects with HD have an increased iron concentration in the striatum postmortem^{16,26} and the known sensitivity of these relaxation parameters to metal ion concentrations. These studies have largely found decreased T2* relaxation rates within the globus pallidus (GP) and nonsignificant changes in the striatum.^{19,23–25} WM T2* relaxation times have been found to increase only during the early manifest stage.²³ T2 mapping has been shown to largely disassociate from iron concentrations in HD,¹⁹ suggesting that other microstructural changes are largely driving the changes in T2 relaxation times.

Recently, another quantitative MR parameter, T1 relaxation in the rotating frame (T1ρ), has been used to study progressive changes in Parkinson's and Alzheimer's disease.^{21,27,28} T1ρ measures proton exchange, which is influenced by metabolism (pH and glucose)^{29–31} and protein concentrations.³² However, T1ρ relaxation is sensitive to a number of microscopic environmental factors, including water content, which can be measured using T2 measurements. Therefore, this study was designed to collect multiple quantitative imaging parameters to better understand the underlying microscopic changes that are occurring associated with disease progression.

The aims of this study were to apply multiple quantitative MRI techniques to determine whether T1ρ can serve as a unique quantitative biomarker for disease progression and examine whether T1ρ changes occur in the absence of T2 changes in terms of regional specificity and proximity to disease onset.

Patients and Methods

Participants

All participants in this study were enrolled in the PREDICT-HD study at the University of Iowa (Iowa City, IA). Participants were at risk for HD (had a parent with HD) and had previously undergone elective presymptomatic genetic testing. Those who were gene expanded (CAG length greater than or equal to 36), but had not yet received a motor diagnosis, were referred to as preHD participants. Those who were nongene expanded (CAG at or below 30) were enrolled as control participants. Subjects who were selected for this study were age and sex matched. Participant demographics are summarized in Table 1. The University of Iowa Institutional Review Board approved this study and written informed consent was obtained from all participants. Participants recruited underwent detailed neurological motor examination, cognitive assessment, brain MRI, and psychiatric and functional assessment, with blood samples for genetic and biochemical analyses. Summary variables for the motor and cognitive assessments are provided in Tables 1 and 2 for the total motor score (TMS), Symbol Digit Modalities Test (SDMT), and the SCL90 Global Severity Index (GSI) given that these variables have shown the greatest change with disease progression in previous analyses.⁶ For participants with the HD CAG gene expansion, the CAG-Age Product (CAP) score was computed as CAP=Age X (CAG-33.66).³³ CAP purports to measure the cumulative toxicity with the huntingtin protein and has previously been used by Rao et al. to identify progressive changes in brain circuits using functional MRI.¹⁵

In the analysis of the quantitative imaging data described below, two distinct groupings of the participants were created, both consistent with the validation analysis of Zhang et al.³³ The first grouping consisted of three groups. Participants with a high CAP score (>368) were included in the HiCAP group, participants with low or moderate CAP score (<368) were included in the LoMoCAP group, and controls constituted the third group. Based on the model of Zhang et al.,³³ the HiCAP participants are estimated to have less than 7.62 years to motor diagnosis, whereas the LoMoCAP participants are estimated to have at least 12.78 years to diagnosis. The second grouping combined all of the gene-expanded participants and excluded controls.

Image Acquisition

For this study high-resolution anatomical images were collected on a Siemens TIM Trio 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) as part of the standard PREDICT-HD imaging protocol. High-resolution anatomical imaging consisted of T1- and T2-weighted images. In addition, quantitative parametric imaging was conducted to compute T2, T2*, and T1ρ relaxation times. For T2 mapping, a two-dimensional (2D) spin-echo sequence was acquired in the axial plane (echo time [TE]=13.1, 26.2, 39.3, 52.4, and 65.5 ms; repetition time [TR]=3,000 ms; field of view [FOV]=240 x 192 mm; matrix=256 x 204; slice thickness/gap=2.0/0.0mm; integrated parallel acquisition technique [IPAT]=2). T2* mapping was performed using a 2D gradient-echo sequence collected in the axial plane (TE=4.63, 20.0, 30.0, and 40.0 ms; TR=2,300 ms; flip angle [FA]=50 degrees; FOV=240 x 192 mm; matrix=512 x 410; slice thickness/gap=2.0/0.0 mm; IPAT=2). Quantitative T1ρ mapping was performed using a coronal segmented three-dimensional (3D) gradient echo sequence with spin-lock pulses (TE=2.5 ms; TR=5.6 ms, FOV=220 x 220 x 200 mm³; sampling matrix=128 x 128 x 40; FA=10 degrees; IPAT =2; spin-lock frequency=330 Hz; spin-lock times=10 and 55 ms).

Image Analysis

Anatomical image analysis was performed using the BRAINS AutoWorkup³⁴ pipeline with the high-resolution anatomical images (3D T1- and T2-weighted scans). The pipeline performs the following steps: (1) alignment of the participant image into a standard anterior commissure and posterior commissure orientation; (2) bias field correction; (3) tissue classification; and (4) anatomical segmentation.^{35, 36} As part of the tissue classification procedure, the anatomical priors were registered to the individual participant using a symmetric diffeomorphic image registration from the Advanced Normalization Toolkit.³⁷

The multiple spin-lock images acquired for T1ρ mapping were coregistered using a rigid body registration and a mutual information image metric. The images for each echo for T2 and T2* mapping were already coregistered because they were collected as multiple echoes within a single acquisition. The images for each technique were then fit to a monoexponential decay model shown in Equation 1:

$$S = S_0 e^{-\frac{t}{T}}$$

to quantify the relaxation parameter T. The resulting relaxation maps were then brought into correspondence with the T2-weighted scan for the participant using a rigid body registration, and the resulting transform was applied to the quantitative parametric images, which were resampled to 1-mm isotropic resolution. The resulting images were then analyzed using a region-of-interest (ROI) analysis in subject space. The parametric images were also transformed to a common coordinate system using the inverse transformation estimated during tissue classification, which maps the images from subject space into Neuroimaging Analysis Center atlas³⁸ (1-mm isotropic resolution) space. The parametric images were then analyzed using a voxel-wise statistical analysis approach. The voxel-based analysis was restricted to voxels containing more than 50% brain tissue (gray matter [GM] or WM),³⁹ thus minimizing partial volume artifacts with cerebrospinal fluid.

Voxel-wise Statistical Analysis

Using the Functional MRI Expert Analysis tool from the FSL neuroimaging toolkit,⁴⁰ a two-tailed unpaired t test was performed comparing the following groups: (1) HiCAP versus controls; (2) LoMoCAP versus controls; and (3) HiCAP versus LoMoCAP groups. We then conducted a linear regression analysis using the CAP score as an explanatory variable for the T1 ρ , T2, and T2* mapping with the single group of preHD participants. A significance level of P<0.05 with a family-wise error correction was used to identify voxels of interest for all of the analyses conducted.

Region of Interest Analysis

A follow-up ROI based analysis was performed. Mean relaxation times within subcortical labels (caudate, putamen, thalamus, and GP) created from the BRAINS AutoWorkup were measured for the right and left hemisphere separately. An unpaired t test (unequal variance, single tailed) was calculated between (1) the HiCAP and control groups, (2) the LoMoCAP and control groups, and (3) the HiCAP and LoMoCAP score groups.

Results

Voxel-wise Statistical Analysis

The voxel-wise analysis of the T1 ρ parametric images showed a significant increase in T1 ρ relaxation times in the posterior regions of the putamen and in the nucleus accumbens bilaterally in the HiCAP group, as compared to controls (Fig. 1A). Increased T1 ρ relaxation times were also observed in cortical areas, including the insula and superior and transverse temporal gyri. The LoMoCAP group, in comparison to controls, showed no regions with significantly elevated T1 ρ relaxation times, but showed a decrease in T1 ρ relaxation times within the anterior cingulate (Fig. 1B). A direct comparison between the HiCAP and LoMoCAP groups found a statistically significant increase in T1 ρ relaxation times within the striatum (Fig. 1C). In the huntingtin gene expanded group, the linear regression with CAP score revealed a significant positive correlation with T1 ρ relaxation times in the left putamen and right caudate (Fig. 2A).

The voxel-wise analysis of the T2 relaxation times showed a statistically significant increase in the left external capsule in HiCAP, compared to controls (Fig. 1D). A direct comparison

between the HiCAP and LoMoCAP groups also showed the finding in the left external capsule (Fig. 1F). The LoMoCAP group had only one small statistically significant region ($P < 0.05$) in the lateral aspect of the left thalamus (Fig. 1E), as compared to control subjects. A significant relationship between T2 relaxation times and CAP score was found in the left external capsule (Fig. 2B) in participants with the huntingtin gene expansion.

Quantitative T2* mapping showed a very different pattern of changes, as compared to T1 ρ and T2 results. The T2* relaxation changes were almost exclusively confined to the GP and were evident when comparing both the LoMoCAP and HiCAP groups to controls (Fig. 1G,H). No differences were observed when comparing the HiCAP and LoMoCAP groups (Fig. 1I) and no significant relationship with CAP score was found. All of the findings showed a decrease in the T2* relaxation times (i.e., increased magnetic field inhomogeneity) associated with huntingtin gene expansion.

ROI Statistical Analysis

The ROI analysis of the T1 ρ parametric scans confirmed the statistically significant changes within the striatum found in the voxel-wise analysis (Table 3). T1 ρ relaxation times were significantly elevated in the putamen bilaterally in the HiCAP group, as compared to controls or the LoMoCAP group ($P < 0.05$). In addition, the HiCAP group had statistically significant ($P < 0.05$) prolonged T1 ρ relaxation in the left caudate and a trend in the right caudate, when compared to controls. No significant changes in T2 relaxation time changes were found in the striatum. The ROI analysis of the T2* relaxation times confirmed the statistically significant changes within the GP ($P < 0.05$), when comparing the HiCAP and LoMoCAP groups to controls. In addition, no statistically significant changes were found between the HiCAP and LoMoCAP groups.

Discussion

This study employed multiple quantitative MR parametric imaging approaches to study changes in tissue properties of subjects in the premanifest stage of HD. Using these quantitative imaging sequences, changes in T1 ρ relaxation times were found, predominately in the striatum, and showed a significant relationship with disease progression in premanifest HD, as measured by CAP score. T2* relaxation times showed significant changes in the premanifest HD subjects, but no significant relationship with disease progression was found. T2 mapping showed relatively few changes, as compared to T1 ρ . These changes did not overlap with any significant changes in T2 relaxation times, which appeared in the external capsule using a voxel-based analysis. However, the location of the T2 relaxation changes could be the result of atrophy of the putamen, which is known to occur during the premanifest phase of the illness.

T1 ρ relaxation time is sensitive to both relaxation related to chemical exchange (T_{ex}) and T2 relaxation in the absence of chemical exchange (T_{20}),²⁹ as shown by Equation (2).

$$\frac{1}{T1\rho} = \frac{1}{T2_0} + \frac{1}{T_{ex}}$$

The T_{20} component is related to tissue microstructure and water content. In this current study, quantitative T2 mapping was also performed (i.e., measurement of T_{20} in Equation (2)) and no significant differences (Table 3) were observed in the caudate and putamen, suggesting that the low-frequency proton exchange (T_{ex}) is responsible for the observed changes in T1 ρ relaxation times. We did not directly compute the T_{ex} parameter because different imaging sequences, 2D spin-echo and 3D segmented gradient-echo, were used to collect the data for T2 and T1 ρ , respectively. However, future studies that utilize a T2 preparation pulse⁴¹ in the 3D segmented gradient-echo sequence for measurement of T2 relaxation times would facilitate such measurements.

The observed elevation of T1 ρ relaxation times is consistent with evidence for metabolic abnormalities in HD. Glucose and pH have emerged as two of the leading metabolic factors to influence T1 ρ relaxation times by changing proton exchange.^{29–31} An increase in T1 ρ relaxation times is consistent with a decreased glucose concentration. Premanifest HD subjects have been shown to have a decreased glucose uptake in the striatum.^{42–44} The increased T1 ρ relaxation times in the striatum would also be consistent with an acidosis within this region possibly resulting from impaired energy metabolism in HD^{45–47} and/or lactate accumulation.⁴⁸ Interestingly, acidosis has been suggested to contribute to HD-related pathology and blocking acid-sensing ion channel 1 might alleviate HD pathology.⁴⁹ However, the only previous study to measure pH in HD found an alkalosis using ³¹P spectroscopy.⁵⁰ In that study, pH estimates were for the whole brain and acquired 7 years after HD diagnosis, and not specifically in the striatum.

The current study did not find a significant change in T2* relaxation times associated with disease progression, suggesting that the increased iron deposition may be a developmental phenomenon and not a measure of disease progression. These findings contradict a couple of recent studies that have shown progressive changes in iron deposition within the basal ganglia.^{20,25} Recent work by Dumas et al. found progressive changes in magnetic field correlation maps from premanifest and early HD subjects. However, other studies that employ T2* mapping have found conflicting findings within the nuclei of the basal ganglia.^{24,25} A recent study by Di Paola et al. found WM progression of T2* changes in the corpus callosum, when comparing preHD subjects to HD subjects,²³ but did not detect any progressive changes in preHD subjects. The present study did not find any progression of T2* relaxation rates in preHD subjects within the WM and is in agreement with the study by Di Paola et al.²³

This study employed two strategies for analysis of the quantitative imaging parameters that have well-known strengths and weaknesses. The use of voxel-based statistical analysis allows for whole-brain analysis of the data, but may be sensitive to atrophy of anatomical regions. The ROI-based analysis defined the ROIs based on the anatomical images acquired for the corresponding subject collected at the same time as the quantitative parametric images. This allowed us to verify that the changes in relaxation times found in the voxel-wise analysis were not the result of striatal atrophy.

There are some potential limitations of the current study. The first is that we cannot attribute the T1 ρ abnormalities in preHD to a single molecular phenomenon. T1 ρ is very sensitive to

pH and glucose, but it is also sensitive to other factors, such as water and protein content. However, water content is not likely to be responsible because we found no significant differences in T2 relaxation, which is sensitive to water. Future work employing T1ρ dispersion or chemical exchange saturation transfer imaging and magnetic resonance spectroscopy could help to further identify mechanisms underlying T1ρ abnormalities in HD. Second, the selection of echo times was not optimal for GM T2 values. We used a shorter maximum TE (65.5 ms) than is optimal for a GM.⁵¹ This was done to help reduce the scan time while collecting all three parametric image sets. A third limitation is the cross-sectional design. In future studies, a longitudinal design may help reveal the rate of T1ρ change over time and detect specifically when the T1ρ changes begin. Finally, increasing the sample size would help us learn whether there might also be differences in T1ρ between the low- and mid-CAP groups.

In conclusion, T1ρ mapping may be a valuable biomarker for assessing disease progression and therapeutic responses in premanifest HD. The T1ρ changes were predominately within the striatum and exhibited a significant relationship to disease progression, as estimated by CAP score. The quantitative nature of T1ρ may allow future studies to set thresholds to help define transitions between various stages of the illness. Furthermore, T1ρ imaging may provide a tool to study metabolic changes in HD with high spatial resolution and sensitivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

T1 ρ differences between (A) HiCAP subjects and controls, (B) LoMoCAP subjects and controls, and (C) HiCAP and LoMoCAP subjects. T2 differences between (D) HiCAP subjects and controls, (E) LoMoCAP subjects and controls, and (F) HiCAP and LoMoCAP subjects. T2* differences between (G) HiCAP subjects and controls, (H) LoMoCAP subjects and controls, and (I) HiCAP and LoMoCAP subjects. The Z value maps thresholded at a Z value of 2.3 ($P < 0.05$, corrected at the cluster level) are overlaid on the NAC atlas for reference. The yellow color indicates prolonged relaxation times, while the blue color indicates a shorter relaxation times.

TABLE 1

Participant demographics

Participants	N	Sex (male:female)	Age* (Years)	TMS*	SDMT*	SLC90 GSI*
Prenamifest	50	19:31	47 ± 21 (20–91)	5.7 ± 4.7 (0–24)	51.1 ± 10.5 (24–73)	50.2 ± 10.1 (40–83)
Control	26	7:19	48 ± 10 (26–66)	5.6 ± 3.7 (0–13)	55.7 ± 8.2 (39–75)	47.2 ± 6.7 (40–63)

* Mean ± standard deviation (range).
** Mean ± standard deviation.

TABLE 2

Demographics of the HiCAP and LoMoCAP groups

Group	N	Sex (male:female)	Age* (Years)	CAG Age Product**	TMS*	SDMT*	SLC90 GSI*
HiCAP	24	8:16	53 ± 13 (20–73)	429.5 ± 39.9	10.4 ± 6.2 (1–24)	42.9 ± 8.8 (24–56)	49.9 ± 8.2 (40–62)
LoMoCAP	26	11:15	40 ± 13 (21–81)	295.6 ± 53.6	4.4 ± 3.1 (0–11)	53.4 ± 9.9 (30–73)	50.2 ± 10.7 (40–83)

* Mean ± standard deviation (range).

** Mean ± standard deviation.

TABLE 3

Subcortical ROI-based relaxation time measurements

		T1ρ					
Region	Hemisphere	HiCAP (ms)*	LoMoCAP (ms)*	Controls (ms)*	HiCAP Controls (P Value)	LoMoCAP Controls (P Value)	HiCAP-LoMoCAP (P Value)
Caudate	Left	88.40 (18.26)	81.47 (6.09)	86.79 (17.83)	0.75	0.37	0.04
	Right	87.37 (14.63)	82.19 (7.34)	82.05 (10.39)	0.07	0.48	0.06
Putamen	Left	67.17 (3.07)	64.93 (2.37)	65.42 (2.71)	0.02	0.24	0.003
	Right	66.99 (3.94)	64.90 (2.98)	65.34 (2.49)	0.04	0.28	0.02
GP	Left	61.44 (3.62)	59.35 (2.25)	60.75 (3.10)	0.24	0.03	0.01
	Right	61.89 (4.28)	59.00 (2.54)	60.66 (3.03)	0.12	0.02	0.003
T2*							
Caudate	Left	49.22 (18.17)	54.68 (18.28)	54.68 (18.28)	0.30	0.26	0.96
	Right	49.42 (21.36)	53.43 (15.81)	53.43 (15.81)	0.46	0.14	0.67
Putamen	Left	34.26 (10.22)	34.72 (9.44)	37.62 (6.83)	0.18	0.21	0.87
	Right	34.18 (9.59)	37.56 (6.44)	37.56 (6.44)	0.15	0.37	0.63
GP	Left	24.86 (7.91)	25.24 (6.94)	28.84 (6.14)	0.03	0.03	0.42
	Right	25.82 (9.07)	24.70 (6.89)	28.95 (5.72)	0.07	0.009	0.31
T2							
Caudate	Left	117.39 (13.53)	120.93 (11.20)	120.94 (14.60)	0.19	0.50	0.16
	Right	123.55 (12.15)	125.14 (12.17)	127.56 (13.19)	0.14	0.25	0.33
Putamen	Left	106.88 (13.82)	100.98 (11.35)	102.06 (12.84)	0.11	0.38	0.06
	Right	105.23 (19.31)	101.12 (11.95)	101.24 (12.60)	0.20	0.49	0.19
GP	Left	85.17 (17.00)	79.97 (9.22)	83.17 (17.18)	0.34	0.21	0.09
	Right	87.56 (21.79)	80.12 (10.34)	82.90 (16.85)	0.20	0.24	0.07

Mean and (standard deviation) for the relaxation times are reported.

Statistical tests with $P < 0.05$ are shown in bold.