Imaging Gradual Neurodegeneration in a Basal Ganglia Model Disease

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Objective: X-linked dystonia-parkinsonism (XDP) is a neurodegenerative disease with adult onset dystonia and subsequent parkinsonism. Postmortem and imaging studies revealed remarkable striatal pathology, with a predominant involvement of the striosomal compartment in the early phase. Here, we aimed to disentangle sequential neurodegeneration in the striatum of XDP patients, provide evidence for preferential loss of distinct striatal areas in the early phase, and investigate whether iron accumulation is present.

Methods: We used multimodal structural magnetic resonance imaging (voxel-based morphometry and relaxometry) in 18 male XDP patients carrying a TAF1 mutation and 19 age-matched male controls.

Results: Voxel-based relaxometry and morphometry revealed (1) a cluster in the anteromedial putamen showing high iron content and severe atrophy (−55%) and (2) a cluster with reduced relaxation rates as a marker for increased water levels and a lower degree of atrophy (−20%) in the dorsolateral putamen. Iron deposition correlated with the degree of atrophy (p = −0.585, p = 0.011) and disease duration (p = 0.632, p = 0.005) in the anteromedial putamen. In the dorsolateral putamen, sensorimotor putamen atrophy correlated with disease severity (p = −0.649, p = 0.004).

Interpretation: This multimodal approach identified a patchy pattern of atrophy within the putamen. Atrophy is advanced and associated with iron accumulation in rostral regions of the striatum, whereas neurodegeneration is moderate and still ongoing in dorsolateral areas. Given the short disease duration and predominant dystonic phenotype, these results are well in line with early and preferential degeneration of striosome-rich striatal areas in XDP.

X-linked dystonia-parkinsonism (XDP) is a hereditary movement disorder that has been attracting increasing attention as a basal ganglia model disease. XDP is characterized by rapidly progressive dystonia and subsequent parkinsonism in later disease stages caused by an SVA (short interspersed elements [SINE]–variable number of tandem repeats [VNTR]–Alus) retrotransposon in the TAF1 gene. Initial symptoms usually appear during the 3rd or 4th decade and typically manifest as focal dystonia. Dystonia often generalizes within the first 2 to 5 years and usually becomes less severe after a disease duration of 10 or more years. Parkinsonian signs may...
already coexist in the dystonic phase of XDP, but they clearly grow more prominent as the dystonia diminishes. Postmortem investigations of brains of deceased XDP patients revealed extensive striatal atrophy, with a consistent loss of striosomal medium spiny neurons in the early phase of XDP, whereas degeneration of the matrix is additionally present in later disease stages. Quantitative magnetic resonance imaging (MRI) studies in XDP confirmed the distinct striatal atrophy and identified additional tissue loss in the globus pallidus, white matter, and associative part of the cerebellum, but also increased gray matter volume in the motor part of the cerebellum and increased connectivity between the insula and putamen.

Aside from the aforementioned classical motor signs, recent clinical reports and electrophysiological studies provide evidence for an impairment of executive functions in early XDP with an involvement of multiple cognitive processes that are relevant for goal-directed behavior. In detail, XDP patients showed problems in attentional shifting, conflict monitoring, response selection, behavioral adaptation, and error processing. These studies corroborate the involvement of frontostriatal circuits and a potential contribution of striosomal dysfunction in patients with early XDP.

The striatum is the input nucleus of the basal ganglia and receives abundant projections from limbic, associative, and sensorimotor cortical regions. The topographical organization of the striatum into subregions is related to a functional segregation of corticostriatal circuits. The rostral striatum is anatomically connected to the limbic and prefrontal areas, and thus, implicated in the regulation of mood and cognitive functions, whereas the dorsolateral putamen has projections to sensorimotor cortex areas, which explains the impact on motor control. The striatal microstructure comprises 2 neurochemically defined compartments, the striosome and the matrix. Histopathological studies across species including mice, rats, monkeys, and humans consistently demonstrate that the striosome occupies 10% to 15% of the entire striatal volume. The striosome and matrix are distributed across the striatum in a patchy fashion; however, the density of striosomes appears to follow a caudorostral gradient, with the rostral striatum being considered striosome rich and the dorsolateral putamen mainly comprising matrix. However, data on the distribution of striosomes in the dorsolateral putamen in humans are lacking. Striosomal dysfunction which has been implicated in early stages of Huntington disease (HD), and imbalance between striosomal and matrix function are discussed as potential disease mechanisms in dystonia and levodopa-induced dyskinesia in patients with advanced Parkinson disease (PD). Tissue loss, however, is more widespread in HD, and the distribution of neurodegeneration is more heterogeneous in early HD than previously thought, making it difficult to exploit early HD as a model for striosomal dysfunction.

Lastly, iron deposition plays a crucial role in neurodegenerative diseases such as PD and HD, most likely as the consequence of neurodegeneration. Distribution of iron in the brains of XDP patients has not yet been investigated.

In the present study, we used multimodal MRI to investigate whether neurodegeneration is homogenous or heterogeneous in the striatum of patients with early XDP. We hypothesized that (1) iron accumulation is present in the brains of XDP patients and most pronounced in the striosome-rich rostral part of the striatum, and that (2) the degree of atrophy is less striking in the dorsolateral striatum.

Subjects and Methods

Participants and MRI Acquisition

Eighteen male XDP patients (aged 40.1 ± 7.3 years, Table 1) from the Philippines were asked to participate in a multimodal cliniconeuroimaging study at the University of Lübeck, Lübeck, Germany. Results on structural changes of the gray matter were recently published. Sixteen of these 18 XDP patients underwent deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPI) after the MRI scan. They were recruited by their attending Filipino movement disorders specialists in collaboration with the Department of Neurology and the Institute of Neurogenetics at the University of Lübeck.

The control group (n = 19) was composed of relatives of the patients (n = 8) and other volunteers (n = 11) gathered by study advertisement (aged 36.4 ± 8.1 years). All controls tested negative for genetic markers in the XDP-associated locus in TAF1, were neurologically healthy, male, and of Filipino ancestry.

The study was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the local ethics committee (AZ12-219). Before participation, written informed consent was obtained from all participants or their caregivers, respectively. Materials were provided in English and Tagalog, and the study was explained by a Tagalog native speaker.

Clinical Assessment

Clinical assessment included a video-recorded neurological examination. Motor function was assessed by the motor score of the Burke–Fahn–Marsden–Dystonia Rating Scale (BFMDRS) and the Unified Parkinson Disease Rating Scale: Part III: Evaluation of Motor Function (UPDRS-III). The Montreal Cognitive Assessment–Filipino version (MoCA-P) was applied to test global cognitive function and was administered by a Tagalog speaking physician.

Structural MRI

Multiecho T2* and T1 images were acquired on a 3T Achieva (13 patients, 17 controls; 8-channel head coil; Philips, Best, the
Netherlands) and a 3T Ingenia scanner (5 patients, 2 controls; 32-channel head coil; Philips), respectively. In 4 patients, scans were acquired under general anesthesia during acquisition of a preoperative (DBS surgery) stereotactic planning MRI. The stereotactic frame visible on the scans did not cause any artifacts or otherwise affected data quality. The analyst was not involved in the process of image acquisition.

**Multiecho T2* Imaging**

T2* relaxometry enables determining the tissue water content, integrity, and iron deposition depending on the relaxation rate (R2*). Increased relaxation rates are indicative of higher tissue iron levels, whereas decreased relaxation rates are associated with an increased water content of the underlying tissue, inflammation, or demyelination. To detect altered iron or tissue water concentrations in brains of XDP patients, we acquired multiecho T2*-weighted images using the following settings: fast field echo (FFE) sequence; transverse orientation; 24 slices; 1 mm gap; field-of-view (FOV) = 230 × 183.3 × 119 mm; 0.45 × 0.45 × 4 mm3 voxel size; flip angle = 18°; 6 volumes; echo time (TE) = 6.9, 13.8, 20.7, 27.6, 34.5, 41.5 milliseconds; repetition time (TR) = 1,200 milliseconds. Voxel-based relaxometry (VBR) was performed with an in-house software tool based on MATLAB (MathWorks, Natick, MA) and SPM 12 (University College London, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). After visual inspection by 2 independent researchers (H.H. and M.H.) for motion artifacts and manual reorientation of all images to the anterior commissure (AC), the T1 scan was coregistered to the first T2* image because of the best signal-to-noise ratio and segmented using the a priori tissue probability maps of SPM 12 with affine regularization to the International Consortium for Brain Mapping (ICBM) space. Multiecho T2*-weighted scans were resliced to a voxel size of 1 × 1 × 5 mm3 and smoothed with a full-width–half-maximum isotropic Gaussian kernel of 1.5 × 1.5 mm2 in plane. After applying a brain mask including segmented images of gray matter, white matter, and cerebrospinal fluid onto the T2* images, relaxation rate maps were calculated. Voxel-wise relaxation rates were estimated assuming a monoexponential signal decay (S = S0e−VT2*) by performing a straight-line fit to ln(S) = ln(S0)−TE × R2*. R2* maps were brought to the Montreal Neurological Institute (MNI) space by applying the deformation fields of the T1 segmentation process.

Group analysis was performed with an independent 2-sample t test in SPM 12, with age as a potential nuisance covariate. According to the neurodegenerative pattern in XDP, 5 regions of interest (ROI) were defined (caudate head and body, putamen, GPi, and external globus pallidus). Additionally, a ROI of the substantia nigra was included due to known relaxation rate increase in patients with PD. Masks were generated in the Wake Forest University PickAtlas Toolbox based on the Talairach demon (converted to MNI space by the best-fit transformation [icbm2tal]). Differences were considered significant if exceeding the threshold of p < 0.05 familywise error for the ROI analysis and if exceeding the threshold of p < 0.05 familywise error corrected at the cluster (cluster-defining threshold p < 0.001) for the whole brain analysis. Mean relaxation rates of the significant clusters were subsequently extracted with fslstats (Fslutils; Oxford Centre for Functional MRI of the Brain [FMRI] Software Library v5.0, created by the Analysis Group, Oxford Centre for FMRI, Oxford, United Kingdom).

**Voxel-Based Morphometry**

To correlate gray matter density with alterations of iron or tissue water concentrations in XDP, voxel-based morphometry (VBM) was additionally performed in SPM 12 on MATLAB. T1-weighted images were acquired using an FFE 3-dimensional magnetization-prepared rapid acquisition gradient echo sequence ( sagittal orientation, 180 slices without gaps, matrix = 240 × 240, 1 × 1 × 1 mm3 voxel size, FOV = 240 × 240 × 180 mm, flip angle = 9°, TR = 6.6 milliseconds, TE = 3.0 milliseconds).

After visual inspection by 2 independent researchers (H.H. and M.H.) for motion artifacts and manual reorientation to the AC, T1-weighted images were segmented, further aligned with Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL), normalized to the MNI space, and smoothed with a full-width–half-maximum isotropic Gaussian kernel of 6 mm. Mean voxel intensities of putaminal clusters where significant differences in relaxation rates between XDP patients and controls could be identified were subsequently extracted with fslstats and used for correlation analysis. One

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**TABLE 1. Demographic and Clinical Characteristics**

| Controls | Patients |
|----------|----------|
| **Mean** | **SD** | **n** | **Mean** | **SD** | **n** |
| Age, yr  | 36.4     | 8.1   | 19       | 40.1     | 7.3   | 18   |
| Disease duration, yr | 3 | 1.7 | 18 |
| BFMDRS  | 48.6 | 25.4 | 18 |
| UPDRS-III | 36.7 | 16.5 | 18 |

The table displays the demographic details and the scores of the clinical assessments.

BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale; SD = standard deviation; UPDRS-III = Unified Parkinson Disease Rating Scale: Part III: Evaluation of Motor Function.
patient had to be excluded due to severe movement artifacts in both T1- and T2*-weighted images, resulting in a total number of 18 patients as described above.

**Statistical Analysis and Figure Creation**

Statistical analysis was performed in SPSS (v21.0; IBM, Armonk, NY). Age-corrected mixed model analysis of covariance and correlation analysis (Spearman ρ) were conducted. To preserve the transparency of the model, uncorrected degrees of freedom but sphericity-corrected $F$ and $p$ values are reported (Greenhouse–Geisser or Huynh–Feldt where applicable). Visualization of clusters on MRI scans was performed with MRicroGL (32-bit version for Windows, May 5, 2016; http://www.mccauslandcenter.sc.edu/mricrogl/).

**Results**

Dystonia was severe in most patients, with a maximum of 88/120 points in the BFMDRS (average 48.6 ± 25.4 points) despite a short disease duration of 1 to 7 years (Table 1). The mean UPDRS-III score was 36.7 ± 16.5 of 108 points. Global cognitive function was impaired in most patients (MoCA-P = 21.4 ± 3.8, range = 14–27, n = 14). Thirteen patients received medication at the time point of the MRI scan with limited response. The following drugs were prescribed: clonazepam (n = 10), biperiden (n = 8), zolpidem (n = 5), levodopa (n = 3), and diazepam (n = 1).

In both hemispheres, VBR revealed higher relaxation rates as a surrogate marker for iron deposition in the anteromedial part (Cluster 1) and reduced relaxation rates in the dorsolateral part of the putamen (Cluster 2) in patients (Fig 1A, Table 2). In XDP patients, gray matter atrophy was present in both putaminal clusters using ROI-based VBM (~55% and ~20% respectively, $p < 0.001$). The degree of atrophy was, however, clearly larger in Cluster 1, with a significant interaction of cluster and degree of atrophy ($F_{1,33} = 92.17, p < 0.001$; Fig 2).

In Cluster 1 (anteromedial putamen), relaxation rates (ie, higher iron levels) correlated with disease duration ($p = 0.623, p = 0.005, n = 18$) and regional atrophy levels ($p = -0.585, p = 0.011, n = 18$). In Cluster 2 (dorsolateral putamen), the degree of atrophy correlated with the motor part of the UPDRS-III score ($p = -0.649, p = 0.004, n = 18$), the BFMDRS score ($p = -0.598, p = 0.009, n = 18$), and the MoCA score ($p = 0.534, p = 0.049, n = 14$). Furthermore, relaxation rates in Cluster 2 correlated with the MoCA score ($p = 0.637, p = 0.014, n = 14$). There was a trend that relaxation rates correlated with signal intensity in Cluster 2 ($p = 0.461, p = 0.054, n = 18$), suggesting that a higher degree of atrophy was associated with lower relaxation rates, which could correspond to a higher tissue water content rather than decreased iron levels in patients. In both putaminal clusters, atrophy levels correlated with disease duration (Table 3). Relaxation rates did not correlate with VBM-derived voxel intensities in controls; thus, a direct influence of relaxation rates on signal intensity was unlikely.

In addition to the putaminal findings, relaxation rates were significantly reduced in the caudate nucleus bilaterally (Table 1). In the pallidum, small clusters with increased and reduced relaxation rates were both present (Table 1). Relaxation rates were not different between groups in the substantia nigra, even when lowering the statistical threshold to $p < 0.05$ uncorrected.

Whole-brain analysis corroborated our ROI-based approach, with higher relaxation rates in the anteromedial putamen, pallidum, and caudate, as well as lower relaxation rates in the dorsolateral putamen and caudate nucleus of the patient group. Moreover, another small cluster in the left precentral gyrus showed increased relaxation rates. Furthermore, reduced relaxation rates were identified in small clusters in the thalamus, insula, calcarine sulcus, cerebellum, postcentral gyrus, frontal, temporal and occipital lobes, and supplementary motor area (Supplementary Table). According to the Thalamic Connectivity Atlas, the thalamic peak coordinates (MNI [xyz] 2, −16, 6 and −8, −26, 10) were most likely connected to the temporal (0.36 and 0.72, respectively) and prefrontal (0.39 and 0.28, respectively) cortex. This is in keeping with what we observed using visual inspection (see Fig 1), namely, that both thalamic clusters were situated in the medial thalamic nuclei and the medial thalamic pulvinar. In the healthy control group, relaxation rates matched values of previous studies for the putamen, caudate nucleus, and pallidum.

The results were not significantly different regarding cluster size, location, or significance after including the 2 different scanners as an additional nuisance factor into the general linear model.

**Discussion**

In the present study, we performed multimodal structural MRI to explore neurodegenerative changes that may explain underlying disease mechanisms including predominant striosomal pathology in early XDP. We found increased iron levels in the striosome-rich part of the striatum and a correlation of iron deposition with disease duration. Tissue loss was severe in this region and much more pronounced than in the dorsolateral putamen. The missing correlation of iron deposition and severity of motor symptoms, as well as severe focal atrophy in this region, argue for a long-lasting neurodegenerative process that is not or no longer related to the clinical motor phenotype of XDP. This is in line with the widespread hypothesis that iron accumulates secondary to neurodegeneration.
In contrast to the anteromedial cluster, in the dorso-lateral putamen, relaxometry was indicative of an active disease process, with evidence of water retention as measured by means of decreased relaxation rates. In keeping with these results, clinical scores correlated with the degree of atrophy, pointing to a relationship between clinical severity and dynamic tissue changes in this region.

These findings collectively provide evidence for advanced neuronal loss in striosome-rich striatal regions despite a relatively short disease duration of 1 to 7 years, and a rostrocaudal gradient of putaminal neurodegeneration.

FIGURE 1: Results from voxel-based relaxometry. Voxels that exceed the statistical threshold are color coded; color intensity represents t values at the voxel level. Color maps are superimposed on a T1-weighted 152-MNI template in neurological convention. Peak voxel coordinates are shown in Table 1 (A) and Supplementary Table (B). (A) Putamen: green, controls > patients; red, patients > controls. (B) Whole brain: green, controls > patients; red, patients > controls. FWE = familywise error; FWEc = familywise error corrected at the cluster; MNI = Montreal Neurological Institute.
Striatonigral and Nigrostriatal Pathways

Striosomal medium spiny neurons are the origin of GABAergic striatonigral projections that form bouquetlike arborizations that target dopamine-containing neurons in the substantia nigra. These dopaminergic neurons in turn project to the striatum via the classical nigrostriatal pathway, with most of the fibers targeting the dorsolateral putamen. As a consequence, impairment of inhibitory striatonigral projections due to striosomal degeneration results in nigral disinhibition and presumed overactivity of dopaminergic nigrostriatal projections. Dopamine excess in the dorsolateral putamen could give rise to an imbalance of the direct and indirect pathway, which may result in dystonia during the first years of the disease. Accordingly, dopaminergic dysregulation has been associated with dystonia in a DYT1 dystonia animal model. Dopamine itself may also have neurotoxic effects, either directly by inducing apoptotic death of striatal neurons, mediating mitochondrial and lysosomal dysfunction in PD, or indirectly by enhancing striatal toxicity of 3-nitropropionic acid. It remains, however, speculative whether an increased dopamine concentration in the synaptic cleft may predispose or enhance neurodegeneration. It is more likely that neurodegeneration in XDP predominantly affects the striosomal compartment in the early phase of the disease and becomes less selective.

| Cluster No. | t  | Size, k | MNI Coordinates, X, Y, Z | Label                      |
|-------------|----|---------|---------------------------|---------------------------|
| Putamen     |    |         |                           |                           |
| Controls > patients |    |         |                           |                           |
| 1           | 7.22 | 47     | −30, −2, −4               | Putamen (L)               |
| 2           | 5.26 | 8      | −32, −10, −3              | Putamen (L)               |
| 3           | 5.08 | 19     | 32, 0, −3                 | Putamen (R)               |
| 4           | 4.84 | 2      | −30, −18, −3              | Lentiform nucleus (L)     |
| 5           | 4.61 | 2      | 28, 4, −8                 | Putamen (R)               |
| Patients > controls |    |         |                           |                           |
| 1           | 6.93 | 93     | 22, 4, 4                  | Pallidum (R)              |
| 2           | 6.71 | 73     | −22, 6, 0                 | Putamen (L)               |
| 3           | 4.52 | 1      | −26, −8, 3                | Putamen (L)               |
| Caudate     |    |         |                           |                           |
| Controls > patients |    |         |                           |                           |
| 1           | 6.99 | 119    | 9, 10, 12                 | Caudate (R)               |
| 2           | 6.72 | 136    | −9, 4, 15                 | Caudate (L)               |
| 3           | 4.45 | 3      | −9, 18, 4                 | Caudate (L)               |
| Pallidum    |    |         |                           |                           |
| Controls > patients |    |         |                           |                           |
| 1           | 6.27 | 20     | −22, −14, −4              | Sublobar (left cerebrum)  |
| Patients > Controls |    |         |                           |                           |
| 1           | 6.98 | 11     | 22, 0, 3                  | Pallidum (R)              |
| 2           | 4.59 | 2      | −21, −2, 3                | Putamen (L)               |

The table depicts clusters with significant differences (p < 0.05 FWE) in each ROI with t values, cluster size in number of voxels (k), MNI coordinates of the peak voxel, and labeling according to the Automated Anatomical Labeling atlas. FWE = familywise error; L = left; MNI = Montreal Neurological Institute; R = right; ROI = regions of interest.
in involving other parts of the striatum including the dor-
solateral putamen over the disease course.

Iron Deposition in XDP
Iron deposition as found here in the anteromedial putamen,
pallidum, and caudate head is common in neurodegenerative
disorders. Across different iron-sensitive MRI modalities,
basal ganglia iron deposition could be demonstrated in symp-
tomatic but also premanifesting carriers of the HD-causing
mutation, even in individuals far from the expected onset of
motor symptoms. The extent of iron levels in the basal
ganglia were in part correlated with volume reduction, and

![FIGURE 2: Quantitative analysis of voxel-based morphometry and correlations. (Top) Scatter plot of the mean voxel intensity in
the significant clusters of the putamen. (Middle) Significant clusters of relaxometry in the putamen: anteromedial (Cluster 1, left)
and dorsolateral (Cluster 2, right). (Bottom) Correlation of relaxation rates with disease duration in Cluster 1 (left) and correlation
of mean voxel intensity in Cluster 2 with the UPDRS-III score (right). UPDRS-III = Unified Parkinson Disease Rating Scale: Part III:
Evaluation of Motor Function.]

| TABLE 3. Correlation of Clinical and Magnetic Resonance Imaging Data |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Disease Duration | UPDRS-III | BFMDRS | MoCA, n = 14 |
| R2* Cluster 1    | 0.632*        | 0.005*        | 0.281           | 0.258           | 0.224           | 0.372           | −0.62           | 0.834           |
| MVI Cluster 1    | −0.552*       | 0.018*        | −0.294          | 0.237           | −0.104          | 0.681           | −0.247          | 0.395           |
| R2* Cluster 2    | −0.179        | 0.478         | −0.333          | 0.177           | −0.379          | 0.121           | 0.637*          | 0.014*          |
| MVI Cluster 2    | −0.579*       | 0.012*        | −0.649*         | 0.004*          | −0.598*         | 0.009*          | 0.534*          | 0.049*          |

The table shows the correlation analysis of clinical and MRI data with Spearman $\rho$.

*Statistically significant.

BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale (motor part); Cluster 1 = anteromedial putamen; Cluster 2 = dorsolateral putamen;
MRI = magnetic resonance imaging; MoCA = Montreal Cognitive Assessment; MVI = mean voxel intensity (indicating grey matter density); UPDRS-III = UPDRS-III = Unified Parkinson Disease Rating Scale: Part III: Evaluation of Motor Function.
the number of cytosine, adenine, and guanine (CAG) repeats indicating a potential role of iron imaging as a progression marker for HD brain pathology. Other studies reported conflicting results without evidence of iron accumulation in premanifest HD, and they could not verify a relationship between basal ganglia volume and regional iron levels in symptomatic HD. These inconclusive results on basal ganglia iron deposition in (premanifest) HD and PD may result from measuring average relaxation rates of the entire putamen, which ignores differential alterations of relaxation rates throughout the putamen and its anatomical subdivisions.

Longitudinal studies evaluating dynamic changes of brain iron levels in combination with other structural alterations are scarce in HD as well as other neurodegenerative disorders. This is an important limitation with regard to the time point of the first occurrence of iron deposition and the significance of iron as a contributor to the pathological cascade. In a longitudinal study in which relaxation rates in the substantia nigra pars compacta of PD patients were measured, increasing values correlated with faster disease progression, whereas decreasing values were associated with slower disease progression. The authors hypothesized that an increased tissue water content may dominate in early disease stages, thereby concealing a lesser change of iron content.

Another important finding of the present study is the patchy distribution of striatal iron accumulation in XDP as compared to HD. Again, the results suggest that degeneration in XDP is differentially progressing in different parts of the striatum, whereas the underlying pathology and iron deposition may be more uniform, at least in the symptomatic phase of HD. Loss of striosomal neurons, however, has also been considered an early event in HD in keeping with autopsy studies of early HD patients. Furthermore, accentuated striosome pathology was associated with more pronounced mood dysfunction in a postmortem study of 35 brains of deceased HD patients. Patients with prominent striosomal abnormalities exhibited an earlier age at onset, lower disease stage, and lower CAG repeat length. The association of striosomal cell loss and mood dysfunction regardless of disease duration may be the explanation for the prominent limbic phenotype of this subgroup of HD patients. The pattern of striatal involvement and cell loss is, however, highly variable, and there is considerable variation in the pattern of neurodegeneration between striosome and matrix across HD patients. Furthermore, in contrast to the current concept of XDP, the pathology goes beyond the basal ganglia and also largely involves white matter and the cerebral cortex. Involvement of these regions additionally explains the observed variability of clinical symptoms in HD.

Unexpectedly, in addition to subcortical alterations, we also found evidence for a widespread but mild cortical and cerebellar involvement in terms of reduced relaxation rates in various regions in XDP patients. There are different ways to interpret reduced relaxation rates upon T2* relaxometry: (1) the tissue iron content is reduced in comparison to healthy controls, (2) the tissue water content is increased, or (3) the underlying tissue is subjected to a demyelinating process. Reduced relaxation rates (ie, prolonged T2* times) have been reported for various cortical regions in multiple-system atrophy and were considered to correspond to possible water retention, which may indicate ongoing cortical neurodegeneration. In HD, reduced relaxation rates have likewise been described in the premotor and parieto-temporo-occipital cortex, but were, however, interpreted as lowered tissue iron content, which may be counterintuitive in a neurodegenerative disease that affects both subcortical and cortical regions. The authors’ interpretation is further challenged by the fact that gray matter atrophy correlated negatively with relaxation rates in these cortical areas, whereas there was a positive correlation in the basal ganglia. Taking these observations together, water retention possibly indicating active neurodegeneration is, in our opinion, the most likely explanation for this finding. Accordingly, widespread white matter involvement, mild cortical thinning, especially of the frontal and temporal lobes, and cerebellar involvement have been demonstrated in XDP.

Reduced relaxation rates were not only seen in the striatum and cortical regions but also in the pallidum and thalamus, the latter not being implicated in the disease process to date. Intriguingly and in keeping with cortical thinning of the frontal and temporal lobe in XDP, these clusters were located in the medial thalamic group and the medial pulvinar, both being strongly connected to the prefrontal and temporal lobes. Recent research considers the mediadorsal nucleus as an important structure in associative learning and decision making, whereas the pulvinar is implicated in spatial attention but also planning, selection, and initiation of voluntary (especially visually guided) actions.

In contrast to idiopathic PD, iron deposition in the substantia nigra could be excluded in this group of XDP patients, supporting the concept of its extranigral form of parkinsonism.

Taken together, our multimodal imaging study in patients with early XDP provides evidence for sequential neurodegeneration in XDP, with more pronounced atrophy and iron accumulation of the anterior putamen. The prominent involvement of this associative striatal subdivision could explain impaired executive functions in XDP patients, even with a short disease duration. Nigrostriatal...
projections may be disinhibited due to the loss of inhibitory striosomal projections to the substantia nigra. Neurodegeneration appears to be ongoing in the dorsolateral putamen, possibly due to dopamine toxicity as a consequence of increased dopamine release to the striatum.

In the future, longitudinal imaging studies in asymptomatic and symptomatic carriers, and cross-sectional comparisons between asymptomatic carriers and XDP patients are warranted to better understand the propagation of neurodegeneration in the striatum and the role of iron deposition and water retention. These studies should be combined with electroencephalogram and clinical studies to determine whether the structural impairment of the anterior striatum and its cortical projections are related to an impairment of limbic and executive functions, and electrophysiological findings in prodromal and manifest XDP. This will provide a better insight into striosomal dysfunction.

Finally, XDP as a basal ganglia model disease may offer the unique possibility to develop disease-modifying therapies potentially by modulating dopaminergic neurotransmission in the striatal synaptic cleft. It may illustrate the translational approach in genetically defined disorders.

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Author Contributions
M.H., C.C.D., A.D., R.L.R., R.D.G.J., T.F.M., C.K., and N.B. contributed to the conceptualization and the design of this study. H.H., J.P., M.H., A.D., M.G., A.J.B., C.K., and N.B. contributed to the acquisition and analysis of the data. H.H. and N.B. drafted the manuscript and figures.

Potential Conflicts of Interest
Nothing to report.

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