Morphological Abnormalities in the Basal Ganglia of Dystonia Patients

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Keywords
Dystonia · Globus pallidus · Basal ganglia · Magnetic resonance imaging · Volumetry

Abstract
Objective: The pathophysiology of dystonia is poorly understood. As opposed to secondary forms of dystonia, primary dystonia has long been believed to lack any neuroanatomical substrate. During trajectory planning for DBS, however, conspicuous T2-hyperintensive signal alterations (SA) were registered within the target region, even in young patients, where ischemia is rare.

Methods: Fifty MRIs of primary dystonia patients scheduled for DBS were analyzed. Total basal ganglia (BG) volumes, as well as proportionate SA volumes, were measured and compared to 50 age-matched control patients.

Results: There was a 10-fold preponderance of percentage SA within the globus pallidus (GP) in dystonia patients. The greatest disparity was in young patients <25 years. Also, total BG volume differences were observed with larger GP and markedly smaller putamen and caudate in the dystonia group.

Conclusions: BG morphology in primary dystonia differed from a control population. Volume reductions of the putamen and caudate may reflect functional degeneration, while volume increases of the GP may indicate overactivity. T2-hyperintensive SA in the GP of young primary dystonia patients, where microvascular lesions are highly unlikely, are striking. Their pathogenic role remains unclear.

Introduction
The term dystonia is applied to a heterogenous group of movement disorders characterized by hyperkinetic involuntary muscle contractions or sustained abnormal limb postures [1]. The underlying neuroanatomical substrate for dystonia is poorly understood and so are its neuropathological causes on a molecular basis. However, a defect in the motor circuit connecting the basal ganglia (BG) with the motor cortex and the cerebellum is hypothesized, leading to an imbalance of direct excitatory and indirect inhibitory pathways [2].

The hitherto existing distinction between primary dystonia and secondary acquired forms of dystonia is important. In secondary dystonia, a clear imaging correlate such as ischemia or bleeding in the BG can be identified, whereas primary dystonia is defined to lack any morphological substrate [3]. Within primary dystonia, a number of genetic causes have been identified, while the majority of primary dystonias have remained idiopathic [2,4].
Clinically, classifications based on the topography of symptoms are relevant, distinguishing focal and segmental from generalized forms [5].

Deep brain stimulation (DBS) of the globus pallidus pars internus (GPI) has evolved as an effective and now commonly used therapy for dystonic syndromes otherwise refractive to pharmacological treatment. For stereotactic planning of the trajectories targeting the GPi, thinly sliced T2 weight images are routinely generated.

While working with the T2 images during DBS planning, we observed a strikingly high amount of hyperintensities within the target region even in very young patients, where ischemia or microvascular lesions appeared highly unlikely (see Fig. 1). This observation prompted us to aim at quantifying the T2-hyperintensive lesions found in primary dystonia patients within the GP and other BG regions with relation to the total BG volumes and to compare the findings to age-matched control patients. We questioned the widely accepted notion that there are no lesions within the BG in primary dystonia and hypothesized there may in fact be an anatomical substrate within the GP.

There has been one prior and first-time mention of signal alterations (SA) within the BG in a cohort of DYT-1 patients in 2009 by Gavarini et al. [6]. The authors did not perform a comparative quantification of the SA; therefore, the report has remained descriptive.

As concerns gray matter volumetry, there have been a number of reports in various subtypes of dystonia over the last 2 decades, using quantitative magnetic resonance imaging (MRI) techniques. They have produced diverging, sometimes even contradicting, results. More recent reports using voxel-based morphometry (VBM) have focused on craniocervical dystonias (CCD) [7–9] and other forms of focal dystonias [10–13]. A majority of these data suggest a volume reduction in the motor, sensory, and visual cortices of the brain’s convexity [3, 10, 13, 14], while also some reports of gray matter increases in these areas exist [15]. As concerns the BG, several authors have reported a reduction of putaminal volumes [3, 12], while others could not detect any volumetric changes in the BG [7, 13, 14].

The aim of our study was to quantify the volumes of these conspicuous SA features as a portion of total BG volumes in a dystonia cohort and then to compare these values to a control cohort. We hypothesized that (1) SA would be more frequent and of larger total volumes in the dystonia cohort and that (2) SA would be registered at younger patient ages in the dystonia group.

We assume that providing evidence of abnormal SA within the BG of dystonia brains may eventually entail their etiological attribution. The study may thus potentially aid in shedding further light into understanding the currently fragmentary pathophysiology of dystonia.

### Methods

**Ethical Standards**

The study protocol was approved by the local ethics committee (Landesamt fuer Gesundheit und Soziales [LAGeSo], Berlin), in accordance with the Declaration of Helsinki. All patients included have given informed consent to the scientific analysis of their MRI data.

**Patient Cohort**

Over a period of 10 years, 50 patients with a diagnosis of primary dystonia treated with DBS were collected. Patients with secondary dystonia due to stroke or bleeding in the BG region as well as dystonias with known MR-SA in the target region (such as neurodegeneration with brain iron accumulation syndrome) were ex-
Fig. 1. MRIs of patients of different ages with diagnosis of primary dystonia scheduled for DBS treatment. All T2 axial sections. Evidence of hyperintense SA within the GP. Patient ages: 6 years (a), 23 years (b), 25 years (c), 29 years (d), 32 years (e), 45 years (f), 47 years (g), 49 years (h), 56 years (i), 69 years (j), 74 years (k), and 79 years (l). DBS, deep brain stimulation; SA, signal alterations; GP, globus pallidus.
Table 2. Neurosurgical diagnoses of the control group

| Diagnoses of control group | $N$ |
|-----------------------------|-----|
| AVM                         | 2   |
| cavernoma                   | 2   |
| Arachnoid cyst              | 2   |
| Pituitary adenoma           | 7   |
| Craniopharyngioma           | 1   |
| Meningioma                  | 9   |
| Colloid cyst                | 2   |
| Low-grade glioma (WHO I–II) | 3   |
| High-grade glioma (WHO III–IV) | 10 |
| Medulloblastoma             | 1   |
| Abscess                     | 2   |
| Skull bone lesion           | 3   |
| Trigeminal neuralgia        | 4   |
| ACN                         | 1   |
| Aqueduct stenosis           | 1   |

Table 3. Volumetric results of various BG structures

|                      | Volumes, mm$^3$ | $T$ (Bonferroni) | $p$ value |
|----------------------|-----------------|------------------|-----------|
|                      | control group   | dystonia group   |            |
| GP                   |                 |                  | ns        |
| All                  | 1,167 (±249)    | 1,224 (±352)     | 0.58      |
| <25 yr               | 1,157 (±171)    | 1,494 (±291)     | 2.10      |
| <40 yr               | 1,203 (±231)    | 1,270 (±348)     | 0.14      |
| >40 yr               | 1,116 (±262)    | 1,206 (±353)     | 0.90      |
| Putamen              |                 |                  | ns        |
| All                  | 3,455 (±765)    | 2,970 (±752)     | 5.53      |
| <25 yr               | 4,199 (±630)    | 3,174 (±1,047)   | <0.001    |
| <40 yr               | 3,891 (±585)    | 3,224 (±830)     | <0.001    |
| >40 yr               | 2,879 (±571)    | 2,784 (±525)     | 0.92      |
| Caudate              |                 |                  | ns        |
| All                  | 2,632 (±545)    | 2,440 (±525)     | 2.19      |
| <25 yr               | 3,232 (±476)    | 2,410 (±553)     | 3.96      |
| <40 yr               | 2,939 (±475)    | 2,505 (±510)     | <0.05     |
| >40 yr               | 2,227 (±324)    | 2,392 (±535)     | 1.59      |
| Thalamus             |                 |                  | ns        |
| All                  | 3,352 (±834)    | 3,392 (±779)     | 0.45      |
| <25 yr               | 3,879 (±786)    | 3,498 (±872)     | 1.84      |
| <40 yr               | 3,664 (±740)    | 3,677 (±950)     | 0.11      |
| >40 yr               | 2,942 (±778)    | 3,182 (±520)     | 2.317     |

GP, putamen, caudate, and thalamus in the dystonia versus the control group and then also subdivided into different age ranges, with the respective statistical relevance. Left and right hemispheres plotted separately, Cohort all: $p < 0.05$, if $T > 3.143$; cohort $<25$ years: $p < 0.05$, if $T > 3.180$; cohort $<40$ years: $p < 0.05$, if $T > 3.145$; and cohort $>40$ years: $p < 0.05$, if $T > 3.144$. BG, basal ganglia; GP, globus pallidus.

Image Acquisition Details

Both dystonia and control patients were imaged at the same 1.5 Tesla MR imaging unit (GE Healthcare, Milwaukee, WI, USA). As part of the usual diagnostic sequences, the T2-weighted sequence was used for all subsequent analysis. T2 was acquired in the transversal plane with isotropic voxels of $0.7 \times 0.7 \times 2$ mm, 2-mm slice thickness, and field of view was $250 \times 250$ mm; matrix $288 \times 384$; echo time 101 ms; repetition time 13,320 ms; and flip angle 150°. For the dystonia group, T2 images were generated as part of the usual diagnostic sequences, the T2-weighted sequence.

Volumetry of BG and T2 Hyperintensities

Analysis of the observed T2 hyperintensities within the GP was done with Brainlab’s iPlan 3.0 navigation software (Brainlab®, Heimstetten, Germany) by volumetry. The analyst was blinded to the group status of the patients. On all axial slices depicting the GP, its borders were delineated sequentially. The borders of the GP were defined as area of the sharpest incline of signal intensity to the surrounding tissue. The 2D contours of each single slice throughout the GP were then fused by the software to a 3D object of the GP, whose total volume was then calculated in mm$^3$. The borders of the SA were equally defined as the sharpest decline of signal intensity within the GP tissue. Volumes of total GP as well as volumes of the SA within the GP were calculated applying iPlan’s “create object” function and then “volume of object” function (see Fig. 2). Since the border between GPe and GPe often could not be outlined with certainty, the GP (i.e., GPe + GPe) was handled as one entity. A ratio of SA volume: total GP volume was calculated for each patient and for each hemisphere. Total GP volumes and volume: lesion ratios were compared between the groups.

For reasons of comparison, the same analysis was done for other BG structures, namely, the putamen, the caudate, and the thalamus. To evaluate potential changes of BG volumes over lifespan, whole brain measures were performed in addition. For whole brain volumetry, only the cerebrum was outlined without the cer-
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Statistics
Volumes were always specified as mean ± standard deviation (SD). For statistical analysis, Graph Pad’s Instat 3 software was used. To plot graphs, Graph Pad’s Prism 7 software was used. Volume results were then correlated with 3 clinical features of the patients: (1) topography of symptoms (segmental vs. generalized); (2) lateralization of symptoms (in those with one-sided symptoms, lateralization of SA is defined as the hemisphere where the total volume of all SA within the respective target region was bigger than the total volume on the other hemisphere); (3) response to DBS treatment (<60% improved vs. >60% improved after 1 year). For multiple comparisons of volumes, ANOVA was done with Bonferroni correction.

Results

General Patient Characteristics
Ages and age distribution were identical between the groups, as a matter of course. Mean age (±SD) was 39 ± 16. Sexes were evenly distributed. General patient characteristics of the dystonia group are shown in Table 1.

Slightly more than half of the patients suffered from generalized dystonia, 44% from segmental or focal forms, such as meige syndrome or torticollis. In 56% of the patients, symptoms were lateralized to one half of the body. In one-quarter of the dystonia group, a mutation had been identified as the underlying cause of the disease (see Table 1), and in three-quarters, the dystonia was classified as idiopathic. Mean age of symptom onset was 27 years; in the subgroup of genetic dystonias, mean age of onset was 10 years. Within the dystonia group, 12 patients were younger than 25 years (6 of which with a genetic mutation), 27 were younger than 40 years (11 of which with a genetic mutation), and 23 were older than 40 years (one of which with a mutation).

The neurosurgical diagnoses of the patients in the control group are shown in Table 2. In the majority of the control patients, a tumorous lesion was present, however, none of which in the proximity of the BG or in the central
ebellum since the cerebellum has been discussed to potentially play a further specific role in dystonia pathogenesis [16].

Table 4. Fraction of T2-hyperintense SA, all forms of dystonia included

|          | Means (±SD)                  | % SA | T (Bonferroni) | p value |
|----------|------------------------------|------|----------------|---------|
|          | control group                | dystonia group |                 |
| GP       |                              |      |                |         |
| All      | 0.239 (±0.338)               | 2.711 (±8.120) | 5.73           | <0.001 (***)|
| <25 yr   | 0.068 (±0.109)               | 3.662 (±7.721) | 3.80           | <0.01 (**) |
| <40 yr   | 0.185 (±0.259)               | 2.384 (±5.289) | 5.30           | <0.001 (***)|
| >40 yr   | 0.309 (±0.412)               | 1.926 (±5.148) | 3.56           | <0.01 (**) |
| Putamen  |                              |      |                |         |
| All      | 0.582 (±0.444)               | 1.319 (±1.138) | 1.64           | ns      |
| <25 yr   | 0.577 (±0.446)               | 1.286 (±1.412) | 0.77           | ns      |
| <40 yr   | 0.509 (±0.413)               | 1.467 (±1.213) | 2.181          | ns      |
| >40 yr   | 0.668 (±0.473)               | 1.247 (±1.089) | 1.21           | ns      |
| Caudate  |                              |      |                |         |
| All      | 0.0139 (±0.108)              | 0.029 (±0.181) | 0.031          | ns      |
| <25 yr   | 0                          | 0      | –              | –       |
| <40 yr   | 0                          | 0      | –              | –       |
| >40 yr   | 0.032 (±0.164)               | 0.050 (±0.264) | 0.04           | ns      |
| Thalamus |                              |      |                |         |
| All      | 0                          | 0      | –              | –       |
| <25 yr   | 0                          | 0      | –              | –       |
| <40 yr   | 0                          | 0      | –              | –       |
| >40 yr   | 0                          | 0      | –              | –       |

Within the various BG structures (GP, putamen, caudate, and thalamus) as percentage of total BG volume and then also subdivided into different age ranges, with the respective statistical relevance. Fifty dystonia patients compared to 50 age-matched controls. Cohort all: p is <0.05, if T > 3.135; cohort <25 years: p is <0.05, if T > 2.991; cohort <40 years: p is <0.05, if T > 2.959; and cohort >40 years: p is <0.05, if T > 2.958. SA, signal alterations; BG, basal ganglia; GP, globus pallidus. ** p < 0.01, *** p < 0.001.
region. It was assumed that none of the diagnoses exerts direct or indirect influence on metabolism or perfusion of the BG.

**Volume Differences**

In Table 3, the respective volumes of the GP, as well as of the other BG: putamen, caudate, and thalamus, are depicted for all groups and age ranges. For none of the BG regions, the left and right volume differed significantly from each other. This symmetry between the hemispheres applied both to the dystonia group and to the control group (see Table 3), as assessed both by ANOVA and by unpaired t tests. Therefore, for comparison of total volumes, both respective hemispheres were combined, resulting in the comparison of 100 GPs (putamens, caudates, and thalamus) in the dystonia group with 100 GPs (putamens, caudates, and thalamus) in the control group.

GP volumes were overall slightly larger in the dystonia group than in the control group, especially in younger patients; yet, there was no significant statistical difference. However, there was a highly significant difference in putamen volumes (always means ± SD: 2,970 ± 752 mm³ vs. 3,455 ± 765 mm³, p < 0.001) with putamen volumes being considerably smaller in the dystonia group (see Table 3). Caudates were also slightly smaller in the dystonia group, with a significant difference only in the younger patient cohort. There was no difference in thalamus size (means ± SD: 3,392 ± 779 mm³ vs. 3,352 ± 834 mm³; see Table 3).

**Age-Dependent Volume Changes**

When dividing the patient cohort into different age groups, a loss of BG volumes over life span became apparent, mirroring the degenerative process. This applied to both groups and all analyzed areas (see Table 3). When comparing patient subgroups <40 years and >40 years, the age-dependent volume reduction was statistically highly significant in both the dystonia and control cohorts for putamen (always means ± SD, control: 3,891 ± 585 mm³ vs. 2,879 ± 571 mm³, p < 0.001; dystonia: 3,224 ± 830 mm³ vs. 2,784 ± 525 mm³, p < 0.001) and thalamus (control: 3,664 ± 740 mm³ vs. 2,942 ± 778 mm³, p < 0.001; dystonia: 3,677 ± 950 mm³ vs. 3,182 ± 520 mm³, p < 0.001), as well as for caudate in the control group (2,939 ± 475 mm³ vs. 2,227 ± 324 mm³, p < 0.001). For caudate in the dystonia group (2,505 ± 510 mm³ vs. 2,392 ± 535 mm³, p < 0.05), as well as for GP in both groups (control: 1,270 ± 321 mm³ vs. 1,206 ± 362 mm³, p > 0.05; dystonia: 1,270 ± 348 mm³ vs. 1,206 ± 353 mm³, p > 0.05), there was no statistical relevance (using multiple testing comparing all regions of interest and groups using ANOVA and Bonferroni posttest).

However, the observed loss of BG volume was not mirrored by a general cerebral volume loss over time. Whole brain volumetry revealed no significant difference between age groups and/or study groups at any given time. There were, however, slightly smaller whole brain volumes measured in the dystonia group than in the control group within the age range <25 years. Also, there were slightly smaller whole brain volumes registered in the group >40 years, as compared to the younger groups, in both study cohorts. Whole brain measures were as follows (always mean ± SD): dystonia <25 years: 848 ± 120 cm³; control <25 years: 924 ± 112 cm³; dystonia <40 years: 925 ± 69 cm³; control <40 years: 918 ± 98 cm³; and dystonia >40 years: 874 ± 88 cm³; control >40 years: 878 ± 93 cm³.

### Table 5. Volumetric results of various BG structures, patients with genetic mutation excluded

|               | Volumes, mm³ | T (Bonferroni) | p value |
|---------------|--------------|----------------|---------|
|               | control group | dystonia group |         |
| **GP**        |              |                |         |
| All           | 1,200 (±229) | 1,187 (±338)   | 0.14    | ns      |
| <25 yr        | 1,183 (±174) | 1,315 (±398)   | 0.46    | ns      |
| <40 yr        | 1,226 (±200) | 1,114 (±320)   | 0.78    | ns      |
| >40 yr        | 1,178 (±251) | 1,223 (±343)   | 0.46    | ns      |
| **Putamen**   |              |                |         |
| All           | 3,346 (±736) | 2,850 (±681)   | 5.37    | <0.001  |
| <25 yr        | 4,165 (±667) | 2,710 (±1,128) | 4.76    | <0.001  |
| <40 yr        | 3,874 (±560) | 2,948 (±819)   | 6.03    | <0.001  |
| >40 yr        | 2,904 (±553) | 2,807 (±614)   | 0.95    | ns      |
| **Caudate**   |              |                |         |
| All           | 2,520 (±489) | 2,378 (±542)   | 1.54    | ns      |
| <25 yr        | 3,168 (±499) | 2,034 (±633)   | 3.71    | <0.05   |
| <40 yr        | 2,865 (±425) | 2,322 (±569)   | 3.54    | <0.05   |
| >40 yr        | 2,231 (±326) | 2,403 (±533)   | 1.67    | ns      |
| **Thalamus**  |              |                |         |
| All           | 3,261 (±832) | 3,291 (±679)   | 0.32    | ns      |
| <25 yr        | 3,995 (±692) | 3,171 (±692)   | 2.70    | ns      |
| <40 yr        | 3,610 (±778) | 3,500 (±905)   | 0.72    | ns      |
| >40 yr        | 2,969 (±767) | 3,198 (±536)   | 2.23    | ns      |
Interestingly, when looking at young patients separately (age <25 years), GP volumes were noticeably larger than in the control group (mean ± SD: 1,157 ± 171 mm³ vs. 1,494 ± 291 mm³, p < 0.05, see Table 3). In the complete cohort, however, including all ages, GP volumes were only slightly larger in dystonia patients. The difference leveled out with age due to a faster reduction of GP volumes over time in the dystonia group.

It was also perceivable that the GP changed shape over time, with a fuller, more roundish appearance in younger patients and a sharper-edged, slim appearance in the elderly. When looking at the caudate and putamen, the previously described volume differences were also more prominent in the young patient fraction (see Table 3). The thalamus showed no difference in size at any given age period.

**Signal Alterations**

100% of the dystonia patients (50/50) showed T2-hyperintense SA in the GP, of those 94% bilaterally (47/59), while only 16% (8/50) of the control patients showed SA, here 75% (6/8) bilaterally. The fraction of SA within the GP was up to 10-fold higher in dystonia patients, 2.7 versus 0.2% in the control population, p < 0.001. The difference in lesion volumes was greatest in younger patients <25 years; here, the mean percentage of lesions within the GP was up to 50-fold higher than in the control population: 3.7% versus 0.07 (see Table 4). We also observed slightly higher percentages of SA in the putamina of dystonia patients. This predominance was only approximately 2-fold and not statistically significant (see Table 4).

**Influence of Genetic Status and Clinical Features**

With none of the analyzed clinical attributes (latenalization of symptoms, topography of symptoms, disease duration, and response to DBS treatment), a clear correlation to volumes or %SA could be retraced (data not shown). When comparing genetic versus non-genetic forms within the dystonia cohort, a few conspicuities...
became apparent. As concerns volumes, the GP of the genetic forms was only slightly bigger (1,555 vs. 1,432 mm$^3$ in the <25-year group; 1,340 vs. 1,222 mm$^3$ in the <40-year group); however, the fraction of SA was quite considerably larger in the genetic group (6.6 vs. 0.94 in the <25-year group and 4.0 vs. 1.52 in the <40-year group). These differences did not (quite) reach statistical significance, possibly due to small group sizes and a large SD (in the groups >40 years, there was only 1 patient with a genetic form; therefore, statistics were only possible within the younger patient groups). When excluding the genetic forms of dystonia from the analysis (comparing the 38 nongenetic/idiopathic forms to their 38 respective age-matched controls), differences became smaller but remained significant for the most part (see Tables 5, 6).

**Discussion**

There are 2 relevant findings in the present study:
1. Dystonia patients exhibit altered BG gray matter volumes as compared to age-matched controls, as well as an altered age-dependent volume reduction.
2. Dystonia patients exhibit more prominent T2-hyperintense SA within the GP than age-matched controls.

**Volumetric Findings**

The literature on brain morphometric studies in primary dystonia is sparse and of varying results [17]. According to our data, the putamen and caudate are considerably smaller in dystonia, while the GP is slightly larger (at least in the early stages of the disease).

An increase in GP volume in dystonia has been suggested before [18]. In this respect, our results are largely
conformable with those of Egger et al. [18] who describe an increase in gray matter volume of the GP, based on VBM in 31 patients. Draganski et al. [15] also report an (unilateral) increase of GP volume in 10 patients with cervical dystonia. There are also a few PET studies (with small patient numbers though) that suggest increased perfusion within the lentiform nucleus [19, 20], supporting the hypothesis of pallidal (over-) activation in dystonia.

A few accounts of putaminal volume alterations exist with rather diverging results [3, 11, 12, 21, 22]. Pantano et al. [3] describe a volume reduction in the putamen and caudate similar to our data, and Obermann et al. [12] also describe a volume reduction in the putamen. However, there are several more recent studies reporting no volumetric difference in the BG at all [7, 13, 14]. Some studies even account of a putaminal volume increase [21, 22]. The considerable differences in results between the authors may be traced back to 2 fundamental heterogeneities in the different study designs: (1) dissimilarity in the patient sample; (2) dissimilarity in the analytic method applied.

Ad 1. What may be important is that in those studies that did not register any volume differences within the BG [7, 13, 14], mean patient age was above 50 years (in Vilany et al. [13]: 60 years, in Gracien et al. [7]: 51 years, and in Piccinin et al. [14]: 54 years). Also, their accounts focus on CCD, exclusively. CCD is the most common form of idiopathic focal dystonia that typically presents at a later age, between 40 and 60 years [1, 4]. Our mean patient age was 39 years, which is considerably younger, and we have also included over 50% generalized dystonias. If we look at our data in more detail (see Tables 3, 5), we also did not register any volumetric difference in the older patient cohort (patients >40 years). Thus, our data are not contradicting to the abovementioned reports. Interestingly, the cohort in the study by Egger et al. [18], who showed similar volume alterations to ours, was of a similar mean patient age (around 40 years). Also, like us, Egger et al. [18] included generalized dystonias and genetic forms. Thus, there is a study group selection bias between the studies since age of onset and clinical presentation of genetic forms differ from nongenetic forms. Genetic forms generally present at younger ages and are more often generalized [4].

Ad 2. There are also methodological differences between the studies. The majority of the more recent studies have used tools for automated computerized image-based brain morphometry, either VBM or surface-based morphometry, which use different imaging biomarkers. These techniques are vulnerable to a number of factors that can influence the results: It has been shown that changes in the image processing steps, the software settings, or even the software updates were yielding diverging volumetric results with these techniques [23, 24]. Image processing steps varied across the authors, and they have also used different software providers. We have used conventional morphometry, which is often believed to be more accurate, while bearing the disadvantage of being time-consuming. However, results in conventional morphometry may also be subject to potential systematic bias since they can vary depending on visual judgment, experience, and diligence of the investigator.

Regional increase of gray matter volume may be the result of either increased connectivity, increased metabolism, or increased cellularity, while decrease in volume may congruously indicate the opposite. Reduced gray matter volume is generally a correlate for degeneration and atrophy [25]. Clearly, there is an age-dependent loss of BG volume due to senescence in all humans. However, here, the brains of juvenile dystonia patients exhibit putamen and caudate volumes otherwise found in the ancient. This may entail a discussion as to whether dystonia may in fact be a neurodegenerative disease. After all, comparable to Parkinson’s disease (PD), “selective neurodegeneration” may occur in a circumscribed region of the brain [26]. Our data may be suggestive that degeneration in certain BG structures occurs earlier in dystonia than in controls. Interestingly, the observed volume loss of the BG over time in both study groups was not mirrored by a loss of total cerebral volume. If volume loss is a sign of age-dependent degeneration, degeneration may occur either earlier or preferentially in the BG than in other regions of the brain.

It is not clear, how a regional increase in volume in a potentially degenerative process may be explained. However, for example, in PD, there is evidence that at certain stages of the disease, neural hypertrophy within the substantia nigra occurs, and it is hypothesized that this represents a compensatory effect that aims at sustaining normal motor function after dopamine depletion has already commenced [27]. The volume increase that we observed in younger dystonia patients may analogously be suggestive for a compensatory mechanism in an already disturbed motor equilibrium. Potentially, neuronal hypertrophy of a portion of the GP cells, leading to volume increase, occurs partly in parallel to cell degeneration, which in turn may lead to decreased cellular density and increased extracellular spaces. Thus, seemingly contrarious anatomical phenomena may be observed simultaneously.
Lesions in the pallidum have been described to induce secondary dystonia [28, 29] and so have lesions in other regions of the BG circuit and of the cerebellum [9]. It is not entirely clear whether the observed SA are primary or secondary in the course of the disease. However, it is highly unlikely that the SA described in our dystonia cohort represent vascular, traumatic, or infectious lesions. The T2 hyperintensities are hypointense in T1. They appear isointense to cerebrospinal fluid in all of the MR weightings. Therefore, their signal behavior does not correspond to ischemia or scar tissue. Most probably, they are conformable with enlarged Virchow-Robin spaces (VRS, perivascular spaces). Because their diameter often exceeds 5 mm and they are also prominent in very young patients, they must be considered at least an anatomical abnormality, of not pathological.

Normal functions of the VRS include regulation of extracellular fluid, the blood-brain barrier, signal transduction, and immunological responses such as regulation of microglia [30, 31]. Hypothesized pathogenetic mechanisms to result in enlarged VRS are abnormal perivascular permeability or atrophy of the surrounding brain tissue, amongst others [32]. Interestingly, dilation of VRS has been associated with many diseases, including MS, autism, dementia, and PD [33].

Those other diseases described to be accompanied by enlarged VRS – although large parts of their respective pathogeneses have remained unclear to the present date – share common pathological mechanisms, including neurodegeneration, inflammation, and oxidative stress. Hence, it might be hypothesized that some of those pathophysiological contributors may play a role in the pathogenesis of primary dystonia, as well.

Even though the nature of the described SA is not entirely clear, there is some evidence from basic science that these may constitute a macroanatomical correlate of neurodegeneration and cell loss, which may now have become tangible with the advent of modern high-resolution MR imaging. For example, Goto et al. [34], who have performed histological staining on postmortem brains of DYT-3 dystonia patients, have described neuronal loss and astrogliosis within the neostriatum of DYT-3 patients. In this report, the cell loss was mosaic like and cell-type specific with a preferential loss of medium spiny neurons and sparing of cholinergic neurons. Since the selective cell loss resulted in an imbalance between striosomal and matrix-based pathways within the striatum, the authors found a possible histological explanation for the distinctive motor features in dystonia [34].

Interestingly, already in 2008, Gavarini et al. [6] report on focal signal abnormalities within the BG on MRI scans. Even though their account remains descriptive, as it is lacking a control group to compare to, the authors already surmise these SA to be part of a structural abnormality [6]. According to our data, the SA are more prevalent in young patients with genetic forms of dystonia. Notably, the Gavarini et al. [6] data stem from a cohort of genetically confirmed DYT-1 patients exclusively, with a mean age of 22 years.

In synopsis, our data suggest that our dystonia cohort, which includes multiple different subtypes of dystonia, may consist of a heterogenous population to some extent: It is possible that different forms of dystonia with different clinical presentations and different underlying pathogenetic backgrounds – even though grouped together to one disease entity – may in fact have differing disease pathogeneses and thus exhibit different function-anatomical findings. Since dystonia is a rare and at the same time heterogenous entity with many subtypes [5] that might require individual analyses, patient numbers in our report (as in previous) may be considerably too low. A large multicentric dystonia database, which could eventually generate sufficient numbers to each single genetic subtype, would be much desired.

Limitations to the Study

There are a few weaknesses in this paper: Clearly, this study is retrospective with a case control design. For the age-matched control patients, not entirely healthy individuals were employed. However, patients with any potential affection of the BG or motor circuit, as well as any patients with chronic disease of the brain (be it degenerative or vascular), were carefully excluded to minimize systematic bias within the control group [8,35]. Secondly, MR imaging modalities were not exactly the same since all MRIs of the patient cohort were 0° gantry scans, while the control cohort was of arbitrary/physiological gantry: Section phenomena as a result of different gantries may result in slightly altered volume measurements. However, since we observe antidromic volume behaviors in different BG regions between the 2 groups (i.e., GP larger in dystonia and striatum smaller in dystonia), a systematic bias based on section phenomena is highly unlikely. As concerns the SA, entry slice phenomena could have occurred. Since we analyzed axial sections of 2-mm thickness, it is possible that very small SA at the rim of the GP may be depicted with 1 gantry angle and with another one not. However, by nature, heads are never tilted exactly the same in comparative MRI studies. Even within the same
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Gantery, the anatomic shape and orientation of the GP varies from brain to brain, despite the skull being in the same gantry. This largely unavoidable bias can be reduced through thinner image slicing though.

**Conclusion**

What may be drawn from morphometric studies like the present one is that the previous notion of primary dystonia having no imaging correlate may be obsolete. As chronic pathophysiological changes can result in anatomic alterations, macroscopic findings may in turn mirror functional modification and give clues to underlying pathophysiology. With the current advent of technical progress in all imaging modalities and higher MRI resolutions, disease-associated phenomena that were previously not discernable with the naked eye may now be detected and even quantified. More advanced imaging techniques and analyses than employed in the current study may contribute supplementary information on disease pathology. Our findings support the hypothesis of common patterns of structural brain alterations in different forms of dystonia and may hopefully encourage further-reaching imaging studies.

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