



Diffusion tensor imaging in pediatric patients with dystonia

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ABSTRACT

Background: Childhood-onset dystonia is often progressive and severely impairs a child's life. The pathophysiology is very heterogeneous and treatment responses vary in patients with dystonia. Factors influencing treatment effects remain to be elucidated. We hypothesize that differences in brain connectivity and fiber coherence contribute to the heterogeneity in treatment response among pediatric patients with inherited and acquired dystonia.

Methods: Twenty patients with childhood-onset dystonia were retrospectively recruited including twelve patients with inherited or idiopathic, and eight patients with acquired dystonia (mean age 10 years; 8 female/12 male). Fiber density between the internal part of the globus pallidus and selective target regions, as well as the diffusion measures of fractional anisotropy (FA) and mean diffusivity (MD) were analyzed and compared between different etiologies.

Results: Patients with acquired dystonia presented higher fiber density to the premotor cortex and putamen and lower FA values in the thalamus compared to patients with inherited/idiopathic dystonia. MD in the premotor cortex was higher in patients with acquired dystonia, while it was lower in the thalamus.

Conclusion: Diffusion MRI reveals microstructural and network alterations in patients with dystonia of different etiologies.

1. Introduction

Dystonia is a movement disorder characterized by involuntary muscle contractions causing abnormal repetitive movements and/or postures. Dystonia can manifest as an isolated symptom or in association with additional neurological signs. Its etiology can be categorized into inherited, acquired, or idiopathic dystonia (Albanese et al., 2013). The most common forms of early-onset inherited dystonia are caused by *TOR1A*, *KMT2B*, or *THAP1* mutations, leading to abnormalities in various biological pathways such as cellular signal transduction and transcriptional regulation (Balint et al., 2018). Several other genes have been discovered since then, most of them affecting different pathways.

Conversely, acquired dystonia is caused by damage to the brain by hypoxia, infections, autoimmune vasculitis, stroke, trauma, or toxic reactions to drugs or heavy metal (Jinnah et al., 2017; Sharma, 2019). The most common form of acquired dystonia in childhood is dyskinetic cerebral palsy (DCP) (Monbaliu et al., 2016).

The three main abnormalities leading to the pathophysiological changes in dystonia are alterations of inhibitory circuits, abnormal synaptic plasticity and sensory dysfunction (Quartarone et al., 2013). Clinically, the phenotypic characterization of dystonia can be very heterogeneous and its correlation with the etiologies often remains unclear as the pathophysiology has not yet been fully understood. Imaging studies of patients with DCP often show lesions of the putamen, the globus pallidus, and the thalamus (Krägeloh-Mann et al., 2002).

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Abbreviations	
DBS	deep brain stimulation
DTI	diffusion tensor imaging
FA	fractional anisotropy
GPI	globus pallidus internus
M1	primary motor cortex
MD	mean diffusivity
MRI	magnetic resonance imaging
S1	primary sensory cortex
SMA	supplementary motor area
STN	subthalamic nucleus
SN	substantia nigra

implying that these structures play a key role in the pathophysiology of dystonia (Eltahawy et al., 2004; Tierney and Lozano, 2012). Further studies on adult patients with isolated monogenetic forms of dystonia also show alterations of fiber architecture assessed by diffusion tensor imaging (DTI) in the cortex, basal ganglia, cerebellum, the cerebello-thalamic and thalamocortical pathways (Carbon et al., 2004, 2008; Argyelan et al., 2009).

As effects of pharmacotherapy are often limited, deep brain stimulation (DBS) of the globus pallidus internus (GPI) has been established as a safe and effective treatment option for certain forms of pharmacorefractory dystonia (Volkman et al., 2012). Patients with inherited dystonia tend to respond better to DBS than patients with acquired dystonia (Eltahawy et al., 2004; Koy et al., 2013; Vidailhet et al., 2013; Elkaim et al., 2018). Nonetheless, some cases of inherited dystonia are still classified as “non-responders” to DBS therapy. Of note, the clinical effects of DBS can be variable and motor improvements can sometimes take weeks to months to evolve (Ruge et al., 2011). The reason for this heterogeneity in treatment outcome is not yet fully understood. In the case of acquired dystonia, multiple variables seem to play a role and should be further investigated. These include heterogeneity in etiology and clinical phenotype, disease duration, age at surgery, differences in stimulation settings or in electrode location, and extent and pattern of the structural lesions (Al-Fatly et al., 2023; Jinnah et al., 2017; Pauls et al., 2017; Coblenz et al., 2021; Isaias et al., 2011; Lumsden et al., 2013).

One approach to investigate the differences in clinical phenotype and response to DBS is to investigate the structural connectivity between brain areas in patients with dystonia. Based on the diffusion of water molecules, microstructural changes and fiber connections within the brain can be visualized by DTI and tractography. Common measures derived from DTI are fractional anisotropy (FA) and mean diffusivity (MD). The former is an estimation of directionality of diffusion and represents the integrity and/or coherence of the nerve fiber. The latter is an indicator of cell density and distribution of extracellular space (Clark et al., 2011).

The aim of this study was to analyze DTI data of pediatric patients with dystonia of various etiologies using a region-of-interest (ROI)-based analysis to investigate if differences in network architecture and microstructural integrity can be identified between different dystonia etiologies and clinical phenotypes. Due to structural changes of the brain in patients with acquired dystonia, we hypothesized that these patients will present lower fiber coherence and lower cell density in the basal ganglia and structures functionally related to them.

2. Methods

2.1. Participants

Data from 20 childhood-onset dystonia patients (8 females; 12

males) of heterogeneous etiology was retrospectively investigated in a monocenter setting. Twelve patients presented with various forms of inherited dystonia: in six patients a genetic cause could be identified. Affected genes were: *SGCE* ($n = 1$), *TOR1A* ($n = 2$), *GNAO1* ($n = 2$), and *PANK2* ($n = 1$). In six patients, a genetic etiology was suspected, but the genetic testing at the time of investigation had not revealed any pathogenic variant, therefore they were classified as idiopathic. Eight patients presented with dyskinetic cerebral palsy due to perinatal asphyxia. The overall age at cranial MRI ranged from 2 to 20 years.

Ten of the patients with inherited or idiopathic dystonia and three of the patients with acquired dystonia underwent bilateral DBS of the GPI. Mean improvement of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) at the 12 or 24-month follow-up was assessed.

2.2. Image acquisition and preprocessing

Imaging was performed according to clinical routine either for diagnostic reasons or in preparation for a planned DBS. Due to the young age of some patients and the hyperkinetic movement disorder, imaging was performed under sedation in all patients.

Imaging data were acquired on a Phillips Achieva 3T scanner (Amsterdam, The Netherlands). These included high-resolution structural T1-, and T2-weighted images, diffusion-weighted images and STIR images. Acquisition parameters for all the sequences are summarised in Table 1.

Preprocessing of diffusion data including corrections for patient movements, susceptibility-induced distortions of echo planar imaging data, and eddy currents was performed using the tools *topup* and *eddy* from the FSL Diffusion Toolbox (Andersson et al., 2003, 2016; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). Following that, the diffusion tensor was estimated, from which maps of FA and MD were calculated, using *dtifit*.

Intra-patient imaging data was co-registered to the respective patient’s T2-weighted image, and the patients’ imaging data was then normalised to the ICBM 2009b non-linear asymmetric template in two steps. First, linear transformations were carried out using the FMRIB’s Linear Image Registration Tool (FLIRT, Jenkinson et al., 2002). Then, non-linear transformations were computed with the Advanced Normalization Tools (ANTs, Avants et al., 2008; <https://github.com/ANTsX/ANTs>).

2.3. Regions of interest

Eight brain regions were defined as target ROIs. The target ROIs were divided into two groups: deep grey matter targets and cortical targets. The former consisted of the caudate nucleus, putamen, subthalamic nucleus (STN), substantia nigra (SN) and thalamus, while the latter included the primary motor area (M1), primary sensory area (S1) and supplementary motor area (SMA). Masks of all deep grey matter ROIs

Table 1
Imaging parameters.

Protocol	TR/TE (ms)	Voxel size (mm ³)	Acquisition matrix	Nr. Slices	Further parameters
T1	9.75 / 4.86	0.49 × 0.49 × 1	252 × 249	165	
T2	3000 / 80	0.50 × 0.50 × 2	400 × 15	80	
STIR	3481 / 15	0.41 × 0.41 × 2	300 × 204	28	
DWI	8218 / 103	2 × 2 × 2	112 × 110	60	40 diffusion directions with AP phase encode direction; 1 b0 with AP phase encode; 1 b0 with PA phase encode.

except for the STN were derived from the Harvard-Oxford subcortical atlas (Frazier et al., 2005). The STN was derived from the DISTAL atlas (Chakravarty et al., 2006; Ewert et al., 2018), while the cortical ROIs were derived from the Desikan-Killiany atlas (Desikan et al., 2006). Manual correction after transformation of the ROIs from MNI space into the patients' T2 space was performed when needed (Fig. 1).

The GPI served as seed mask as it is the common DBS target in dystonia (Koy et al., 2017; Volkmann et al., 2012) and was also derived from the DISTAL atlas. Since the GPI can be hard to discriminate on normal T2-weighted images, even more when further hampered by lesions within this nucleus, an additional high-resolution imaging, like STIR sequences, was acquired. Experts in neuroradiology (C. K.) and neurosurgery (J. W.) were consulted for imaging assessment to improve placement of the GPI seed. An example of such correction is shown in Fig. 1.

2.4. Probabilistic tractography

Probabilistic fiber tracking was used to model white matter fiber pathways between GPI and the eight defined target areas. Tractography was run from the seed region to the ROIs of the ipsilateral hemisphere. The probtrackX algorithm was used to produce voxel-wise sample streamlines from the GPI mask by drawing an orientation from the voxel-wise distributions provided by bedpostX (Behrens et al., 2007). The algorithm then moves along this orientation and checks for predefined termination criteria, like low fractional anisotropy or high angulation between two consecutive orientations. These steps iterate until all fibers have terminated. For the cortical ROIs, the tractography reconstruction was performed using additional exclusion regions (the deep grey matter ROIs), so that only direct connections were reconstructed. After fiber connections between the GPI and ROIs were reconstructed, connections between the GPI and the whole brain, i.e. without any inclusion or exclusion ROIs, were also reconstructed. This was used to calculate relative connectivity - see Section 2.5.

2.5. Statistical analyses

Patients were divided into two sets of two groups each according to age and etiology. The first set divided the patients by etiology, where patients with inherited or idiopathic dystonia were compared to those with acquired dystonia. The second set divided the patients by age according to age, in order to distinguish between children and adolescents, where patients younger than 12 years old were compared to patients

older than 12 years old. All metrics were gathered in the patient's native space.

Firstly, the mean fiber count per voxel between the GPI and the respective target ROI was evaluated.

Additionally, relative connectivities (RC) of the ROIs compared to the whole fiber connections of the GPI were calculated with the following formula:

$$RC[\%] = \frac{C_{ROI}}{C_{GPI}} \times 100$$

where C_{ROI} is the connectivity between the GPI and the target region and C_{GPI} is the whole fiber in- and output from the GPI.

Finally, we compared FA and MD of the gray matter ROIs between the groups. The groups were compared using the Mann-Whitney-U test with a significance level of $p < 0.05$ and Bonferroni correction for multiple comparison. All statistical tests were carried out in R (Version 3.6.3; <http://www.r-project.org>).

3. Results

Regarding etiology, there were 12 patients with inherited or idiopathic dystonia (four female, mean age 11 years) compared to eight patients with acquired dystonia (four female, mean age 10 years). A summary of MRI findings for the acquired dystonia group is available in Supplementary Table I. As for age, in the group of patients aged under 12 years ($n = 13$, five female) the mean age was 8.4 ± 2.6 years versus 15.0 ± 2.4 years ($p < 0.05$) in the group of patients older than 12 years ($n = 7$, three female). Of the 13 patients who underwent DBS, 11 had clinical follow-up at 12 or 24 month. The mean improvement of the BFMDRS-M ($\pm$ SD, 95 % CI) was 28 % (± 32.4 , [-3.36, 43.5]) in the group of inherited or idiopathic dystonia and 4.82 % (± 6.99 [-3.93, 52.27]) in patients with acquired dystonia. A table with the individual scores is available in Supplementary Table II and in Supplementary Fig. 1 are shown exemplary electrode locations for 6 patients.

3.1. Mean fiber density

Overall, fibers were densest between the GPI and adjacent structures like the SN and STN (Fig. 2A). Fiber density to the PMC and putamen were higher in patients with acquired dystonia compared to patients with inherited or idiopathic forms (GPI-PMC: 250 ± 131 versus 119 ± 115 , mean $\pm$ SD, $p = 0.022$; GPI-putamen 472 ± 351 versus 217 ± 377 , $p = 0.029$).

Regarding age, patients under 12 years presented higher fiber densities to most ROIs compared to patients over 12 years (Fig. 2B), except to the S1 although no significant differences were found.

3.2. Relative GPI output

We compared the fiber count between the GPI and the respective ROIs to the fiber count between the GPI and the whole brain to calculate relative connectivities between the functionally related structures. There were no significant differences found between inherited and acquired dystonia (Fig. 3A). When patients were compared by age, patients under 12 years showed significantly lower relative connections compared to patients over 12 years to the SMA (37 ± 8 % versus 47 ± 10 %, $p = 0.019$) and the thalamus (22 ± 7 versus 30 ± 6 %, $p = 0.025$) (Fig. 3B).

3.3. FA and MD

The FA values of grey matter ROIs were evaluated to examine possible microstructural alterations and are shown in Fig. 4. Patients with inherited or idiopathic presented significantly higher FA in the thalamus ($p = 0.006$). On the other hand, age-group analysis revealed

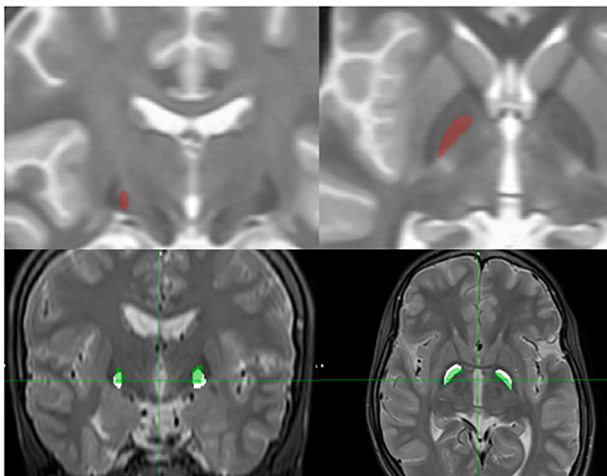


Fig. 1. Top: Coronal and axial slice of GPI mask derived from the DISTAL atlas in MNI space (in red). Bottom: Coronal and axial slice of GPI mask transposed into patient space without correction (in white) and after manual correction (in green).

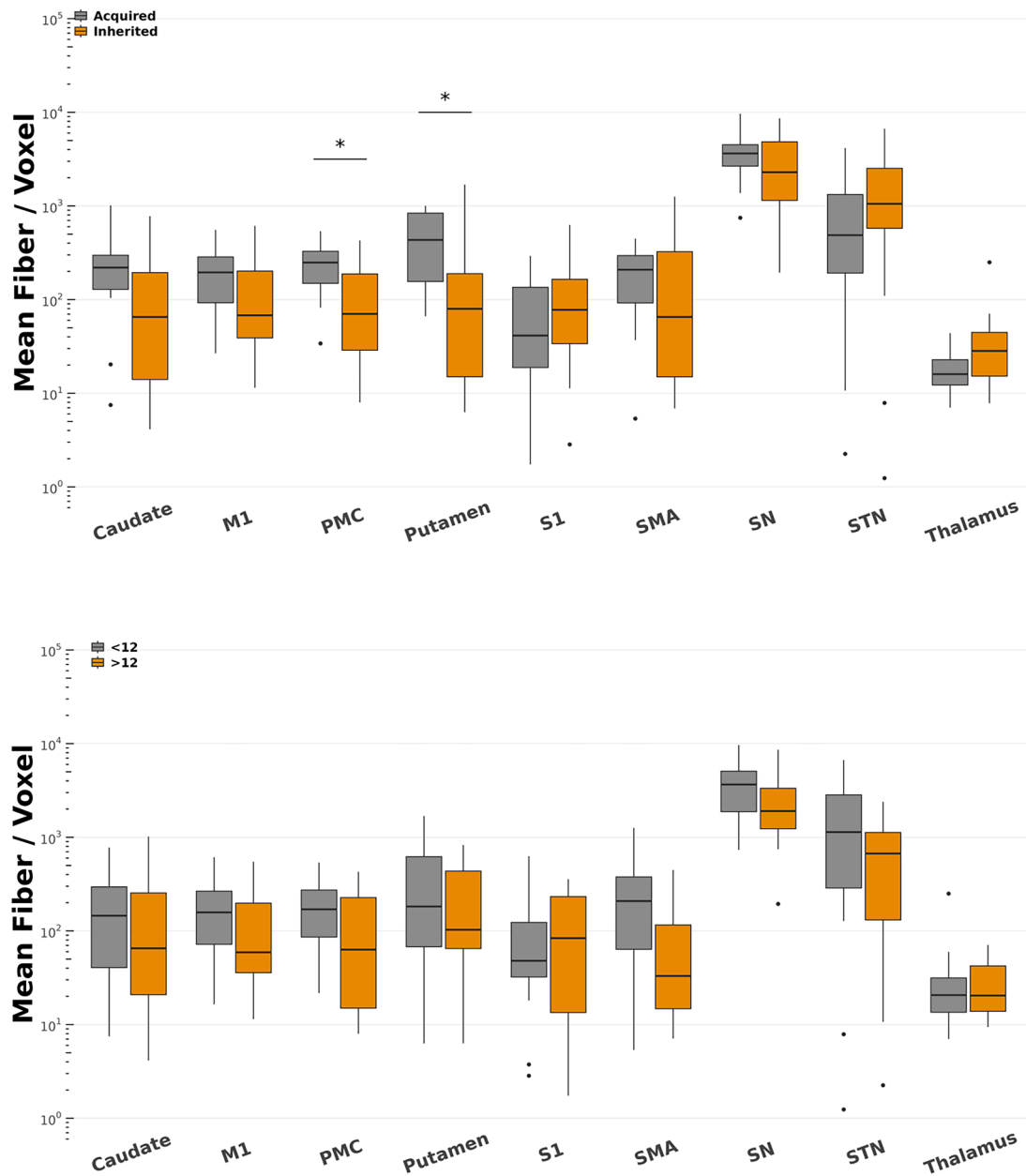


Fig. 2. Boxplot of the fiber density between the GPi and the different ROIs compared between inherited and acquired dystonia (top), and child and adolescent dystonia patients (bottom). The y-axis is in logarithmic scale. Abbreviations: M1: primary motor cortex, S1: primary sensory cortex; SMA: supplementary motor area; SN: substantia nigra; STN: subthalamic nucleus. Significance level (corrected): * - $p < 0.05$.

overall higher FA values of all ROIs in the older patients (>12 years) than those of younger than 12 years (Fig. 4B). Significant differences were seen in the caudate nucleus ($p < 0.001$), the PMC ($p = 0.017$), the putamen ($p = 0.036$), and the thalamus ($p = 0.006$).

Regarding MD, shown in Fig. 5, comparing patients with different etiologies showed significantly higher MD in patients with acquired dystonia compared to those of patients with inherited/idiopathic dystonia in the PMC ($p = 0.025$) and significantly lower in the thalamus ($p = 0.023$). Additionally, differences in the MD value in the putamen showed a trend to significance, with MD of patients with acquired dystonia being lower than that of patients with inherited dystonia ($p = 0.058$). As for age groups, differences were only seen at the subcortical level. Significantly higher MD values were seen in patients younger than 12 years compared to patients older than 12 years in the SN ($p = 0.005$).

4. Discussion

This study demonstrates differences in fiber density, relative connectivity, FA, and MD in specific brain regions between inherited/idiopathic and acquired dystonia in patients with childhood-onset dystonia. Furthermore, differences in the aforementioned DTI metrics and structural connectivity were also observed when splitting the cohort into two specific age groups.

4.1. ROI-based approach

The pathogenesis of dystonia is still not yet fully understood (Kaji et al., 2018). The GPi is a key structure due to the relative efficacy of DBS to this region in patients with various forms of dystonia (Koy et al., 2017; Volkman et al., 2012). However, beyond the basal ganglia, other structures have been linked to the pathophysiology of dystonia, like the

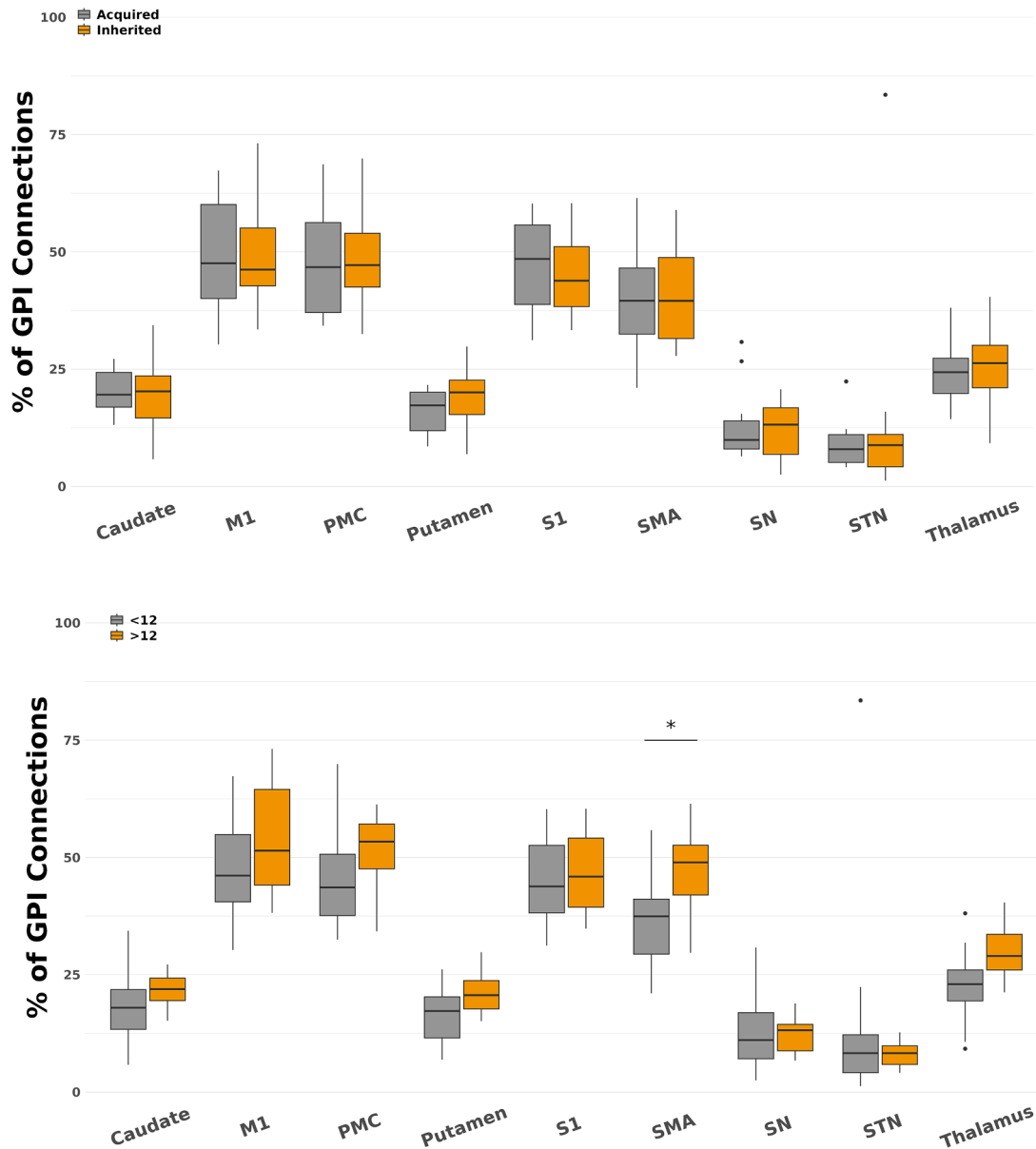


Fig. 3. Boxplots of the relative connectivity of ROIs to whole GPI output in inherited and acquired dystonia (top), and in young and adolescent dystonia patients (bottom). Abbreviations: M1: primary motor cortex; S1: primary sensory cortex; SMA: supplementary motor area; SN: substantia nigra; STN: subthalamic nucleus. Significance level (corrected): * - $p < 0.05$.

cerebellum, the thalamus and the dentato-rubro-thalamic tract (Argyelan et al., 2009; Morigaki et al., 2021), and even cortical areas (Carbon et al., 2004; Merhar et al., 2020). Dystonia can be therefore considered as network disorder of the brain. In this study, we chose to use the GPI as the reference node within this network, as it is the most common target for DBS in dystonia.

The study design depends on the accuracy of the masks for the ROIs. All structures were derived from atlases that were designed for adult MNI space. To our knowledge, only the DISTAL atlas includes subcortical structures that are adjusted to the pediatric MNI template. Transposing these structures onto the pediatric patients' images had to be adjusted manually in every patient when anatomical structures did not fit. Special accuracy was given to the seed ROI, the GPI (Fig. 1). The nucleus is located laterally to the internal capsule and the atlas-based masks would always overlap with this fiber bundle when not adjusted and thus lead to incorrect fiber reconstructions. One strength of this study is therefore the precise delineation of the ROIs according to the pediatric anatomy.

4.2. Network architecture

Fiber density between the GPI and the putamen was higher in the patients with acquired dystonia of our cohort (Fig. 2). The connection between the striatum and the GPI is part of the direct pathway, in which the striatum inhibits the GPI, which in turn loosens its inhibitory effect on the thalamus, enabling the motor cortex to facilitate movement (Alexander and Crutcher, 1990). Our findings indicate that the striato-pallidal connections are enhanced in patients with acquired dystonia. This may lead to an overexpression of the direct pathway with loss of inhibition, resulting in hyperkinetic/hypertonic movements that are observed in dyskinetic cerebral palsy patients, where mobile dystonia and choreoathetosis dominate (Monbaliu et al., 2017).

Furthermore, Raghu et al. (2021) conducted a study on adult patients with cervical dystonia demonstrating that connectivity strength to the putamen correlated with clinical improvement after DBS, and that the primary motor putamen can be identified as a key node according to a series of cortical connectivity-based putaminal parcellations. More

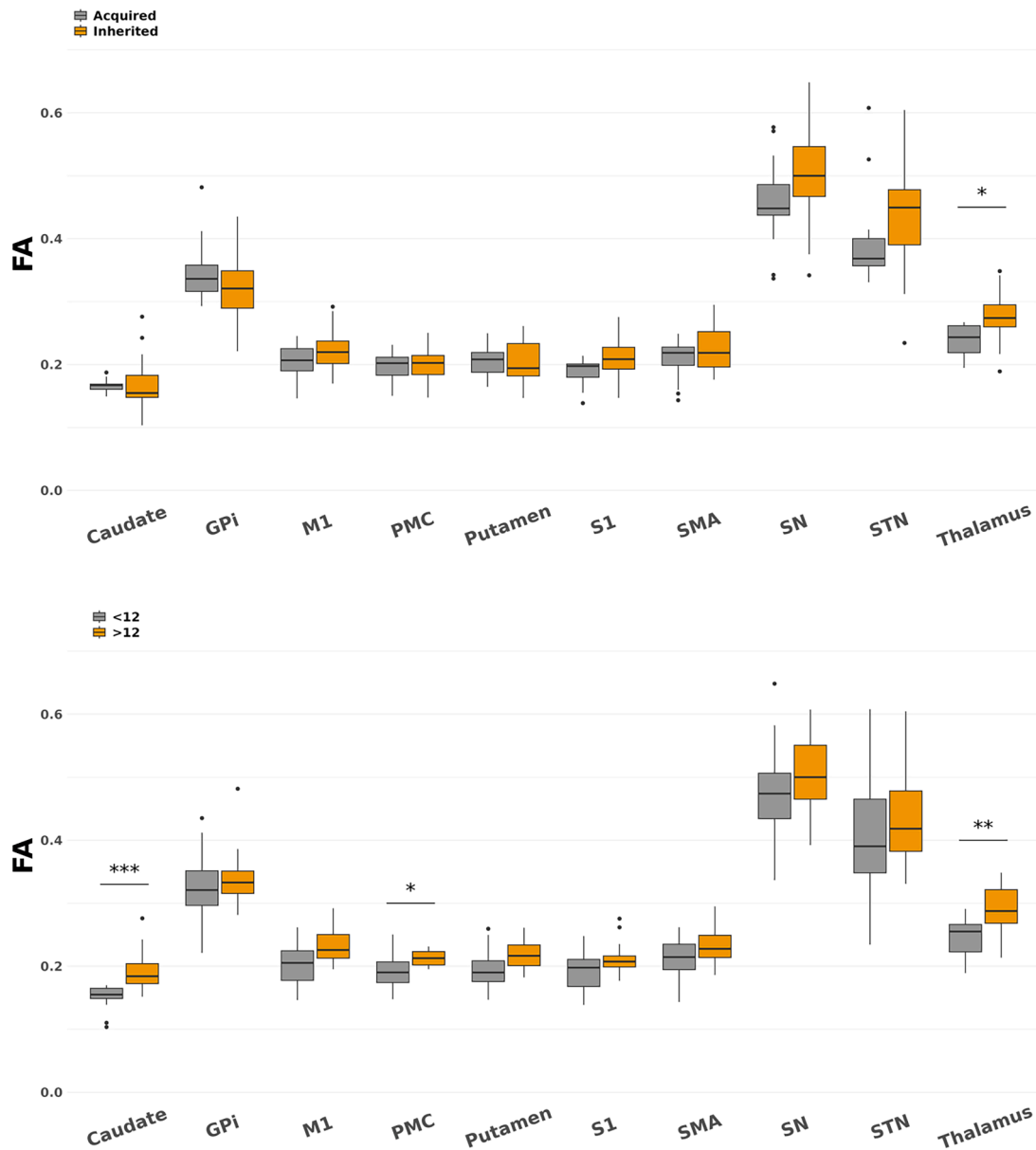


Fig. 4. Boxplots of the fractional anisotropy of the different ROIs in inherited and acquired dystonia (top), and in young and adolescent dystonia patients (bottom). Abbreviations: M1: primary motor cortex, S1: primary sensory cortex; SMA: supplementary motor area; SN: substantia nigra; STN: subthalamic nucleus. Significance levels (corrected): * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$.

recently, [Horn et al. \(2022\)](#) performed a multi-center retrospective study of adult cervical and generalized dystonia patients which showed that stimulating the fibers linking the putamen-GPe-GPi were correlated with symptom improvement in generalized dystonia, while negatively correlated in cervical dystonia. Therefore, certain connectivity patterns can also add additional information on outcome prediction and individualized targeting.

4.3. Microstructural alterations

Our results showed that patients with acquired dystonia have lower FA and higher MD in the thalamus than patients with inherited dystonia, which could be a result of neuronal damage due to perinatal asphyxia. [Berman et al. \(2018\)](#) have reported altered diffusion parameters in different brain regions of patients with cervical dystonia and blepharospasm as the most common adult-onset focal dystonia forms. Reduced FA in the right cerebellar cortex, and increased MD in the left caudate

nucleus in patients with cervical dystonia compared to healthy controls could be identified. When looking at the literature about inherited forms of dystonia, it has been shown that TOR1A carriers with cervical dystonia have reduced FA in the pontine brainstem and increased FA in the left STN compared to healthy controls ([Blood et al., 2012](#)).

Beyond the basal ganglia, our cohort only showed a lower in MD in the PMC of patients with acquired dystonia compared to those with inherited/idiopathic etiology, despite the literature showing a broader range of alterations in the cortex and white matter. In the study from [Berman et al. \(2018\)](#), FA was lower in the right cerebellar cortex, left supramarginal gyrus, and right inferior frontal gyrus in patients with cervical dystonia compared to patients with blepharospasm. A study in infants showed that infants with cerebral palsy due to perinatal brain injury showed significantly reduced FA in white matter pathways in the corpus callosum, the corticospinal tract, and, at the cortical level, the PMC and M1, compared to infants who did not develop cerebral palsy despite their brain injury ([Merhar et al., 2020](#)). Conversely, in our

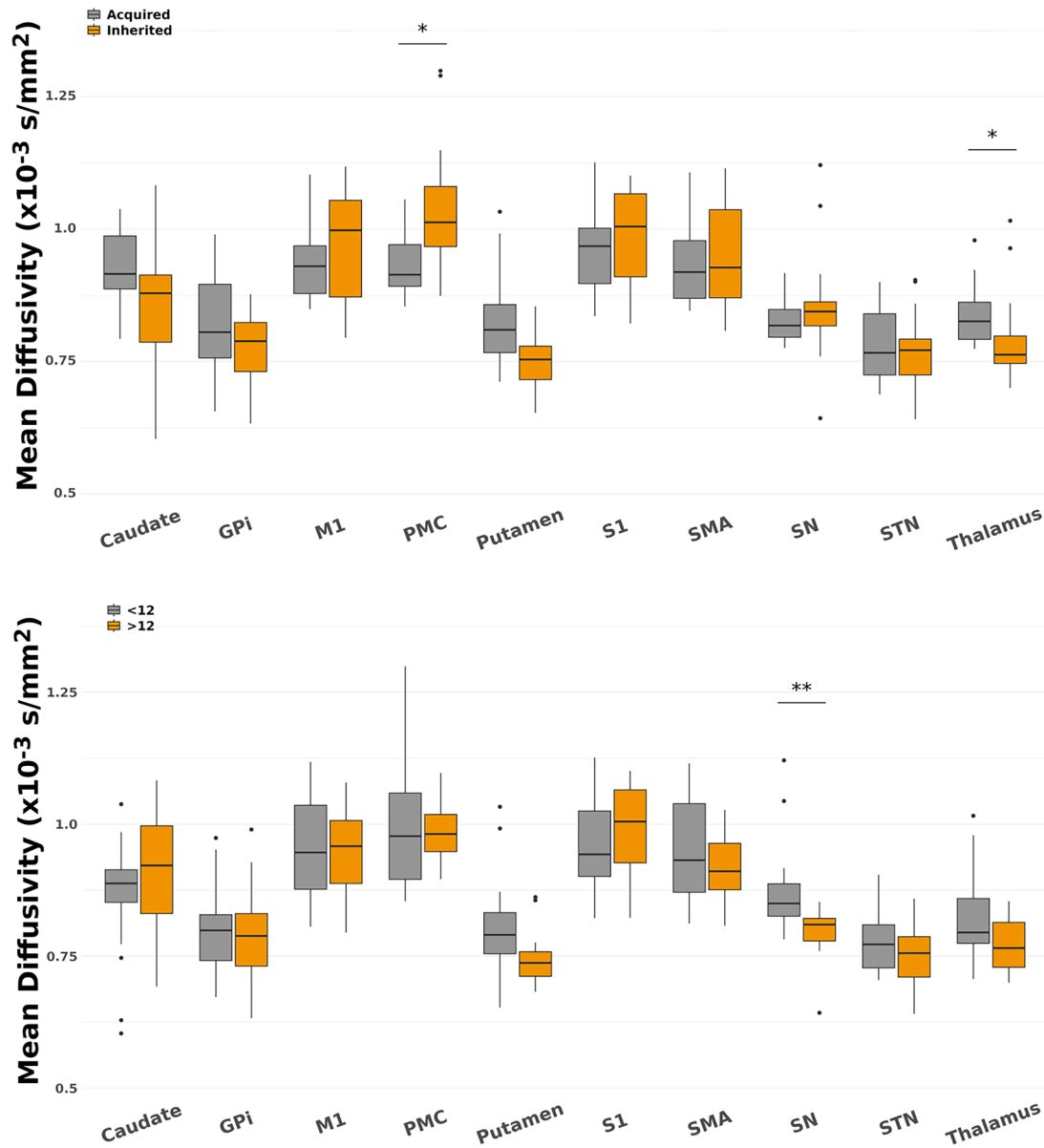


Fig. 5. Boxplots of the mean diffusivity of the different ROIs in inherited and acquired dystonia (top), and in young and adolescent dystonia patients (bottom). Abbreviations: M1: primary motor cortex, S1: primary sensory cortex; SMA: supplementary motor area; SN: substantia nigra; STN: subthalamic nucleus. Significance levels (corrected): * - $p < 0.05$; ** - $p < 0.01$.

cohort, the only changes identified at the cortical level was a higher MD in the PMC in patients with inherited/idiopathic dystonia. In adults with inherited dystonia, reduced FA in the sensorimotor cortex has been shown in manifesting TOR1A carriers compared to healthy controls and non-manifesting TOR1A carriers (Carbon et al., 2004). Taken as a whole, the literature seems to suggest that acquired and inherited dystonia have different patterns of altered microstructure and our results point in the same direction.

Regarding age, dystonia patients under the age of 12 years showed overall lower FA in all ROIs and higher MD in the SN than patients over 12 years. While these alterations can be indicative of neurodegenerative processes (Berman et al., 2018; Kotian et al., 2020), it is known that the brain naturally undergoes structural changes during maturation, which include an increase in overall FA and reduction in overall MD over the years (Coll et al., 2020; Verhoeven et al., 2010; Hermoye et al., 2006; Huang et al., 2006). Since neurodegeneration is only common in certain types of dystonia (Salomão et al., 2016), separating the effects of age and pathology in our cohort is not straightforward.

4.4. Limitations

This study suffers from some limitations, one being the heterogeneity of etiology. The genetic group included patients with idiopathic dystonia, as well as patients with various known genetic mutations. These genes do not share most of their cellular functions (Jinnah and Sun, 2019), so one may question if it is applicable to group these individuals together. As dystonia is an ultra-rare disorder with several underlying causes, multicenter collaboration projects could help to increase sample sizes to investigate different genetic entities.

Most of the patients with cerebral palsy due to perinatal asphyxia showed lesions within the basal ganglia and the thalamus to various extents (Krägeloh-Mann et al., 2002). This implies that the amount of neuronal loss may strongly differ, resulting in differences in treatment outcomes such as DBS (Tierney and Lozano, 2012). Therefore, data must be interpreted in the context of the various extent of structural brain abnormalities. For further investigation, a group stratification according to certain lesional patterns might be a valuable attempt to limit

structural heterogeneity.

Furthermore, in this study, a control group of healthy individuals was lacking. Pediatric diffusion MRI data is not as abundantly available at our centre. An adult control group is not an option due to the fact that diffusion parameters are known to change with age (Verhoeven et al., 2010; Hermoye et al., 2006; Huang et al., 2006). Resorting to external datasets like, for example, the Human Connectome Project – Development (Harms et al., 2018) was also not an option, as the sequence parameters do not match those in this study and it has been shown that such differences can lead to biases in the estimated DTI metrics (Qin et al., 2009; Chou et al., 2012). In order to unravel the pathology behind dystonias, healthy comparisons are essential. The present examinations demonstrated for example, that cerebral palsy is generally associated with lower FA in the thalamus and higher connectivity values between the GPi and the putamen compared to patients with genetic dystonia. The next step would be to investigate, how patients with dystonia would fare against healthy subjects, i.e., if inherited and acquired dystonia have impaired FA and/or MD, or if one of the groups levels with controls. Therefore, DTI data of an age-matched healthy control group assessed by the same scanner and protocol would be required to further investigate the pilot data acquired in this study.

Finally, we considered the thalamus as a whole, although it is a large structure with multiple nuclei, each of which carrying specific functions. While the GPi is the preferred target for DBS in inherited and acquired dystonia, thalamic DBS targeting the ventralis oralis anterior nucleus has been shown to perform better in cases of focal dystonia (Yamada, 2021). It would have been, therefore, interesting to investigate the thalamic nuclei individually, further advancing the understanding of their involvement in the pathology of different forms of dystonia.

5. Conclusion

This mono-center retrospective study investigated connectivity data of exclusively young patients with dystonia as the leading clinical symptom during childhood and adolescence.

One main finding of the study was the different structural integrity of the thalamus between patients with inherited and acquired dystonia. Pallido-thalamic connectivity and the anatomical integrity of the thalamus itself may be relevant for effective DBS therapy. Unraveling the pathophysiological differences in inherited and acquired dystonia is an important step to improve patient selection and precise targeting by DBS. Due to the limited response to DBS of patients with acquired or certain inherited forms of dystonia, the exploration of possible alternative DBS targets would be of great interest to improve treatment of these often severely impaired patients. Therefore, DTI metrics of larger cohorts of pediatric patients grouped according to etiology need to be investigated further in order to identify DTI-based biomarkers in relation to treatment outcome aiming at improving patient selection and targeting in the future.

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Ethics statement

This study was registered and approved by the Local Ethical Committee, Ethics Commission of Cologne University's Faculty of Medicine, under the registration number 22–1045-retro. Written informed consent from the participants was not required for this retrospective study in accordance with local/national guidelines.

Data and code availability statement

For all proposals of data sharing or analysis outside of the study team, the strict regulations of the German and European data protection

laws have to be fulfilled. Upon request to the author, data can be made available in an anonymous form if a formal data sharing agreement has been signed and the data requestor will assure to take full responsibility by ascertaining that the above-mentioned legal premises will be fulfilled.

CRediT authorship contribution statement

Ricardo Loução: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Julia Burkhardt:** Writing – original draft, Investigation, Formal analysis. **Jochen Wirths:** Writing – review & editing, Resources, Data curation. **Christoph Kabbasch:** Writing – review & editing, Resources, Data curation. **Till A. Dembek:** Resources, Data curation, Writing – review & editing. **Petra Heiden:** Writing – review & editing, Resources, Data curation. **Sebahattin Cirak:** Writing – review & editing, Resources, Data curation. **Bassam Al-Fatly:** Writing – review & editing, Resources, Data curation. **Harald Treuer:** Writing – review & editing, Supervision, Conceptualization. **Veerle Visser-Vandewalle:** Writing – review & editing, Supervision, Funding acquisition. **Mauritius Hoevels:** Writing – review & editing, Software, Methodology, Conceptualization. **Anne Koy:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anne Koy reports financial support was provided by Dr. Hans Günther and Dr. Rita Herfort Foundation. Anne Koy reports financial support was provided by Boston Scientific Neuromodulation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data sharing is possible upon reasonable request to anne.koy@uk-koeln.de, provided the regulations of the German and European data protection laws have been fulfilled.

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