Aus der Klinik für Neurochirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Untersuchung der morphologischen Unterschiede der Basalganglien bei Dystonie-Patienten / examination of the morphological abnormalities in the basal ganglia of dystonia patients

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List of abbreviations

18F-FDG PET	18F-fluorodeoxyglucose positron emission tomography
2 D	two-dimensional
3 D	three-dimensional
ATN	anterior thalamic nucleus
BoNTs	botulinum toxin injection
CT	computer tomography
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
EEG	electroencephalography
EMG	electromyography
GABA	γ-Aminobutyric acid
GP	globus pallidus
GPe	globus pallidus externus
GPi	globus pallidus internus
MRI	magnetic resonance imaging
MSNs	medium spiny neurons
PPN	pedunculopontine nucleus
SA	signal alterations
SD	standard deviation
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
VIM	ventral intermediate
VRS	Virchow-Robin spaces

Zusammenfassung

Ziel: Mit dem Begriff „primäre Dystonie“ werden idiopathische oder genetisch bedingte Fälle von Dystonie bezeichnet, die isoliert und ohne pathologische Veränderungen auftreten. Bei der primären Dystonie ist im Gegensatz zur sekundären Dystonie seit langem bekannt, dass kein anatomisches Substrat vorhanden ist. Während der Trajektorienplanung der tiefen Hirnstimulation entdeckten wir jedoch T2-hyperinstensive Signalveränderungen in der Zielregion, selbst bei jungen Patienten, bei denen Ischämie selten ist.

Methoden: 50 MRTs von Patienten mit primärer Dystonie, für die tiefe Hirnstimulation geplant war, wurden untersucht. Die Gesamtvolumina der Basalganglien und der Signalveränderungen wurden bewertet und dann mit 50 altersentsprechenden Kontrollgruppen-Personen verglichen.

Ergebnisse: Die Dystonie-Gruppe hatte eine 10-fache Prävalenz von Signalveränderungen innerhalb des Globus pallidus (GP). Der größte Unterschied wurde in der Gruppe unter 25 Jahren beobachtet. In der Dystonie-Gruppe wurde eine Gesamtvariation des Basal Ganglien-Volumens mit größerem GP und signifikant kleinerem Putamen und Caudatum beobachtet.

Schlussfolgerungen: Die Anatomie der Basal-Ganglien mit primärer Dystonie unterschied sich von der einer Kontrollgruppe. Eine Abnahme des Putamen- und Caudatvolumens kann auf eine funktionelle Degeneration hinweisen, während ein größeres Putamen- und Caudatumvolumen eine Überaktivität bedeuten kann. Die T2-hyperintensive Signalveränderung im GP junger Patienten ist interessant, da mikrovaskuläre Läsionen sehr selten sind. Ihre pathogene Natur ist unbekannt.

Abstract

Objective: The term ‘primary dystonia’ is used to describe idiopathic or genetic cases of dystonia that are isolated and do not entail pathological changes. Primary dystonia, as opposed to secondary dystonia, has long been known to be lacking of any anatomical substrate. During deep brain stimulation (DBS) trajectory planning, however, we discovered T2-hyperinstensive signal alterations (SA) in the target area, especially within young patients with dystonia. Those young patients normally should not have SA.

Methods: We studied 50 MRIs from patients with primary dystonia who were implanted with DBS. An evaluation of SA volumes and total basal ganglia volumes took place, followed by 50 age-matched controls.

Results: The dystonia group has a 10-fold prevalence of SA inside the globus pallidus (GP). The biggest difference was observed in the age group that was younger than 25-year-old. A total basal ganglia volume variation was observed in the dystonia group, with larger GP and significantly smaller putamen and caudate.

Conclusions: We observed differences in the basal ganglia anatomy between primary dystonia patients and the control group. Decreases in putamen and caudate volume may indicate functional degeneration, meanwhile a bigger volume of putamen and caudate might imply overactivity. The novel result of T2-hyperintensive SA in the GP of young patients was a productive discovery, considering the fact that microvascular lesions are very rare. Their pathogenic nature is unknown.

1 Introduction

1.1 Dystonia

1.1.1 Definition

Dystonia is a neurological movement disorder. Hermann Oppenheim, a famous neurologist who studied and worked in Charité Hospital, University of Medicine Berlin, was the first to describe the concept of dystonia in 1911 [1].

Dystonia is the third most common movement disorder, ranking after Parkinson's disease and tremor. A systematic review and analysis based on 15 studies on the epidemiology of primary dystonia yielded an occurrence rate of 164.3 per million. In contrast to the term primary dystonia, secondary dystonia is caused by birth injury of brain, neurodegeneration, metabolic disease, infections, stroke, trauma, previous exposure to drugs or toxins, among other factors [2]. An exact number of dystonia patients in the world is yet to be determined.

Dystonia is a term that defines a large hyperkinetic group of disorders caused by involuntary muscle contractions. The symptoms are highly complex. The inability to regulate muscle contractions results in abnormal movements or postures in one or more areas of the entire body [3]. It may cause pain in the affected areas of the body. Moreover, the symptoms affect not only the physical body but can also impact the mental health of the patient in turn. The disease may also lead to secondary complications and may worsen into a life-threatening condition [4].

Dystonia can begin at any age, ranging from infancy to late age. Symptoms can impact muscles in nearly any part of the body. The symptoms are not random and tend to occur repetitively. Many dystonias are chronic, a few are progressing, some have changed symptoms over time. Some patients have only dystonia, while others have dystonia combined with various complicated syndromes [5]. Patients with abnormal movement and posture are in pain and can have trouble at school, at work, in everyday life, which burdens them and their families.

The symptoms vary widely, and the definition and classification of dystonia have been subject to change several times over the past hundred years. Dystonia used to be defined as a psychological disease in the past, instead of a neurological disease. Its consideration as a psychological disorder was partially related to the worsening of symptoms by stress and the alleviation of symptoms by sensory tricks. Moreover, the lack of any specific structural defects in patients with primary dystonia prevented the discovery of the organic existence of this condition [6, 7].

Some new developments to the consideration of dystonia have taken place over the past 20 years. In 2013, the International Parkinson and Movement Disorder Society published the new advances in dystonia [3, 8]. Additionally, the dystonia guidelines were renewed by the German Neurological Society in 2021 [9].

The general definition and classification of dystonia were revised in 2013. Dystonia is a neurological movement disorder characterized by sustained or intermittent muscle contractions that cause abnormal, often repetitive movements, postures (of face, trunk, neck, limbs or among other muscles) or both. Dystonia is often initiated or worsened by voluntary action and associated with an overflow of muscle activation. Dystonic movements are typically patterned and tend to occur in a twisting manner, in addition to also being tremulous [3, 10].

More genes of inherited dystonia have been discovered recently. This development resulted in the definition of new genes, a new nomenclacture and classification [11]. In the past, the genes of inherited dystonias were named by way of the DYTn system, and DYT is short for dystonia, e.g., DYT1, DYT2, DYT 3, etc. However, the names do not indicate the specific gene in a definitive manner. For example, DYT1 has been redefined as DYT-Tor1A, which addresses the mutations in gene Tor1A. Combined dystonia is a type that combines with other movement disorders like Parkinson symptoms. For example, instead of the old name DTY in addition to a number, the new name DYT/PARK-GCH1 directly describes dystonia and Parkinson symptoms and the mutation in gene GCH1 [3, 9].

1.1.2 Etiology and classification

Dystonia's basic neuroanatomical structure and neuropathological factors on a molecular level remain unclear as of yet. No evidence of neuron loss, inflammation, DNA strand breakage, or altered distribution of torsine-like immunoreactivity to help functional and not degenerative pathology of early onset torsion dystonia could be found [12]. According to the classical concepts, the difference between primary dystonia and secondary dystonia is significant. An imaging correlation such as ischemia or basal ganglia bleeding may be discovered in secondary dystonia, yet primary dystonia is characterized by the absence of a morphological base. Some genetic factors have been found among patients with primary dystonia, although most primary dystonias remained idiopathic.

This being said, the old definition has led to missunderstadings:

- The term ‘primary dystonia’ was used consistently to explain the charateristics of pure forms of dystonia void of other neurological symptoms and not subject to pathological changes. However, tremor occurs in a great number of primary dystonias.
- The term ‘secondary dystonia’ indicates non-pure dystonia, a known etiology or a known pathology. It sometimes refers to any type of dystonia with a pathology, sometimes any dystonia that is not primary and sometimes even only acquired dystonia [3].

In fact, the classification of dystonia has been subject to change over time. The developments reflect an improved unterstanding of etiologies and clinical characters as well as the alterations to opinion on criteria used for categorizing the same disorders together [3].

The biggest change in the newest 2013 update is the classification of dystonia. Two important goals are important in this new classification. One goal is to organize the patients into clinical groups in order to allow for diagnosis, followed by treatment and further research. Another goal is a biological information guide, a development based on etiology and design new treatment, so as to classify those disorders based on two separate axes [3].

Axis I highlights the clinical features and is divided into four different dimensions: age at onset, body region, temporal aspects, and associated clinical features. Body distribution, which entails the affected body region, includes [3]:

- Generalized dystonia: the trunk plus at least two additional locations
- Hemidystonia: more body areas on only one side of the body
- Multifocal dystonia: two or more non-contiguous body areas
- Segmental dystonia: two or more contiguous body areas
- Focal dystonia: one body area

The below examples of dystonia provide a brief illustration of various subtypes of dystonia:

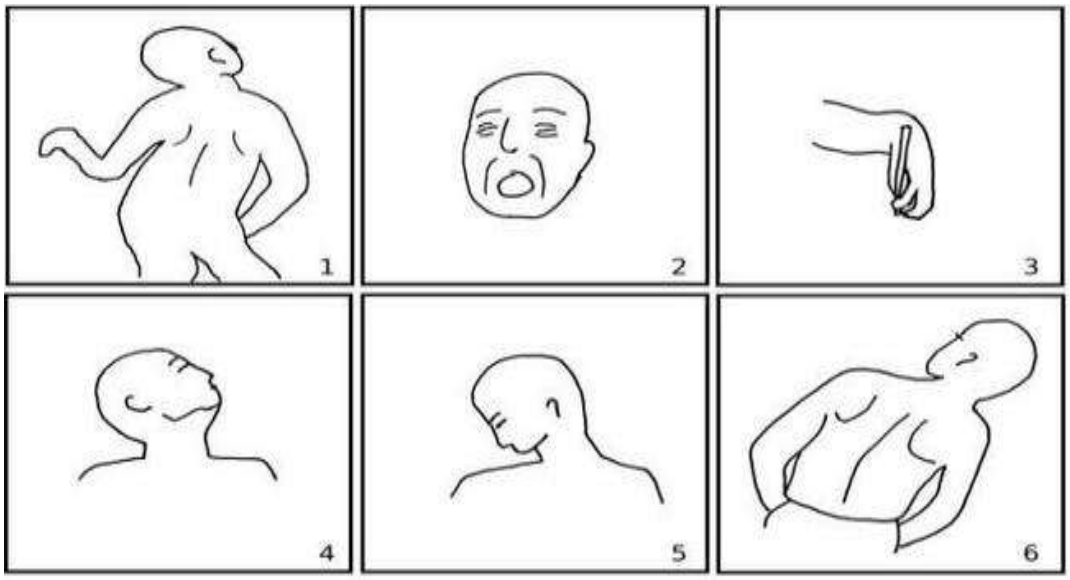

Figure 1. Different subtypes of dystonia: 1) generalized dystonia 2) Meige's syndrome 3) Writer's cramp 4) cervical dystonia 5) cervical dystonia 6) axial dystonia. Source: All pictures are drawn by Xi Bai.

Axis II is concerned with etiology, yet the etiology of many types of dystonia is still unknown. This is a developing area that will be updated when new information becomes available.

The etiology is classified into the following categories:

- Nervous system pathology: degeneration, structural lesions, no evidence of structural lesions or degeneration.

- Inherited or acquired: inherited (evidence of genetic origin), acquired (due to infection, toxic, drug, brain injury, perinatal brain injury, vascular, neoplastic and psychogenic), idiopathic (unknown cause) [3].

1.1.3 Diagnosis

The diagnosis of dystonia is a multiphase procedure. A detailed clinical examination is necessary for leading therapy options. No easy diagnostic methods that can cover all different dystonia subtypes exist, since clinical symptoms and different etiology vary immensely. A careful physical exam and medical history as well as family history should be examined firstly by neurologists [13]. The following tests can be used to help diagnosis and to exclude differential disorders: exam of cerebrospinal fluid, blood and urine, brain magnetic resonance imaging (MRI) and computer tomography (CT), electromyography (EMG), electroencephalography (EEG), laryngoscopy, genetics tests.

1.1.4 Treatment

Dystonia can not be cured at this stage in time, but the symptoms of dystonia could be relieved by some treatments. The most prevalent treaments are botulinum toxin injections (BoNTs), oral medication and surgical interventions.

BoNTs are used commonly as treatment for two or more contiguous body areas like focal and segmental dystonias. However, it is not effective for all kinds of dystonia [14].

Many oral medications are used for dystonias: benzodiazepines, muscle relaxants, anticholinergics, anti-spasticity drugs, dopamine-related drugs, among others. Unfortunately, oral medications have several side effects and a limited success for most dystonias [14].

When BoNT and medications fail to achieve the desired effect, surgical treatments could be considered.

Surgical ablation like pallidotomy and thalamotomy was a common method in the past. The ablation procedure includes creating an electrolytic lesion in the target area in basal

ganglia or peripheral nerves with a temporarily implanted electrode. The lesion can lead to permanent side effects.

Deep brain stimulation (DBS) was approved to treat primary dystonia in Europe and the United States in 2003. Compared to the ablation operation, DBS is reversible and programmable individually and rarely leads to permanent side effects. Due to its positive outcomes following careful patient selection, DBS has become the most widely utilized new surgical technique for dystonia in the last 20 years [15].

1.2 Basal ganglia

1.2.1 Anatomy

Basal ganglia are anatomical structures, also known as the basal nuclei. The term ‘basal’ describes characteristics related to a structure's base. The basal ganglia are a group of gray matter that are located deep in the brain [16].

The definitions of anatomical structures of basal ganglia differ depending on various expert opinions. The basal ganglia could be functionally classified as three different nuclei: input nuclei, intermediate nuclei, and output nuclei.

- input nuclei:	striatum: caudate nucleus and putamen
	nucleus accumbens
	olfactory tubercle
- intermediate nuclei:	globus pallidus externus (GPe)
	subthalamic nucleus (STN)
	substantia nigra pars compacta (SNc)
- output nuclei:	globus pallidus internus (GPi)
	substantia nigra pars reticulata (Snr)

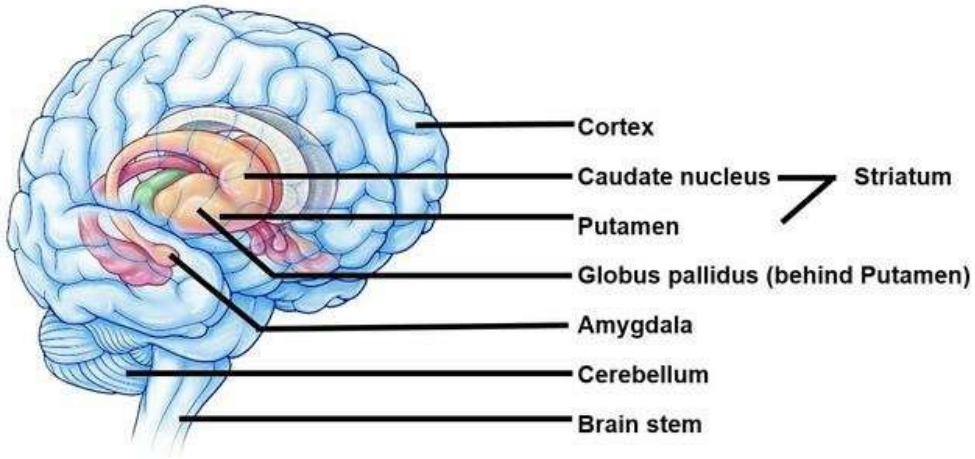

Figure 2. Anatomy of basal ganglia and other areas in the brain. Source: Oto, Evan in Science Photo Library (https://www.science-photo.de/bilder/12641402-Limbic-System-illustration). The picture is used with permission from Science Photo Library Deutschland. Annotations by Xi Bai.

Every structure of basal ganglia entails its own complicated anatomical and chemical functions. The input nuclei receive signals from the cortex, thalamus, and nigral nuclei. The output nuclei regulate the thalamus, which transmits inputs to the cortex, completing the corticobasal ganglia-thalamo-cortical loop [17].

1.2.2 Mechanism

The basal ganglia play a pivotal role in brain function; many tasks are related to basal ganglia, e.g., control of voluntary movements, eye movements, decision selection, behavior, learning, and emotions [18, 19].

The classic theories of direct and indirect pathways reported by Albin, Young and DeLong in 1989 and 1990 made for the basis of hypothesized explanations of basal ganglia activity [20]. The dopamine D1 receptors are often connected with the direct pathway, and dopamine D2 receptors are connected with the indirect pathway. The direct pathway activates the thalamus and the cortex thereafter, by inhibiting GPi first via a direct striatal-pallidal-thalamic loop. Conversely, the indirect pathway delivers an inhibitor to the GPe first, resulting in less inhibition of the STN and an increased activation of the GPi. The activated GPi inhibits the thalamus, and the thalamus activates the cortex less [21, 22].

Endogenously produced striatal dopamine regulates direct and indirect pathways, and also connects collaterals between these two pathways, providing a dynamic regulation of thalamo-cortical neurons for physiologically correct facilitation of motor cortex-initiated movements [23].

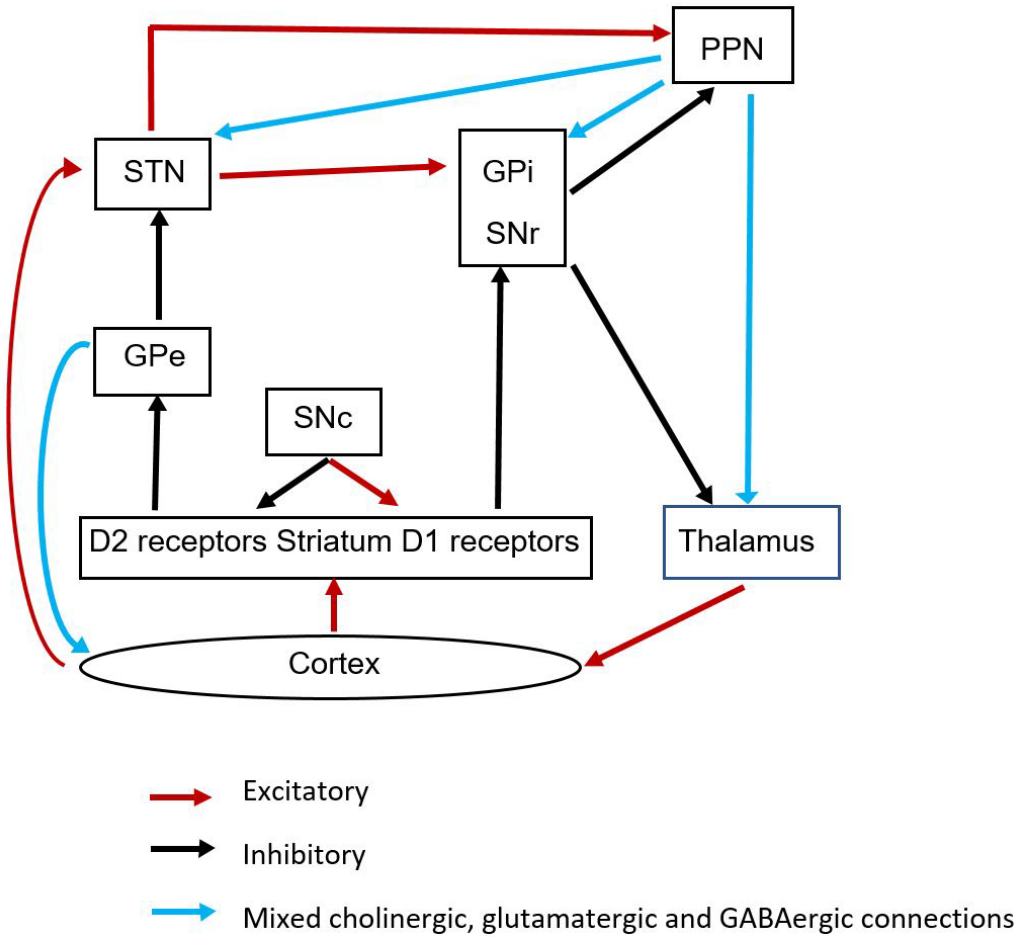

Figure 3. Mechanism of basal ganglia. Source: The picture is made by Xi Bai according to the article by Herrington TM, Cheng JJ, Eskandar E [24].

The current model for the mechanism of basal ganglia was proposed about 20 years ago, yet many problems are not attended by this model [25]. Its simplicity of the basal ganglia provides only little information about the actual interaction of the different cells. The physiological processes at the cellular level remain unknown [16]. However, some new developments have occurred that may contribute to the improvement of defining this mechanism.

The direct and indirect pathways come from diverse groups of striatal medium spiny neurons (MSNs) and transmit to various output areas. The two pathways are defined as having completely opposite impacts. The direct pathway is thought to stimulate movement, while the indirect pathway is said to inhibit it. However, recent research suggests that this is not the case. All MSNs may either stimulate or inhibit movement at the same time [26]. The network in basal ganglia would be a number of parallel loops and re-entering loops [18]. Yet, these loops are not always closed per se [27, 28]. The recent 10 years have provided more understanding that, in addition to the direct, indirect and hyperdirect pathways, numerous additional circuits can also influence basal ganglia [25]. These findings imply that the basal ganglia, cortex, and cerebellum comprise a connected and separated network that controls ample motor and non-motor activities. Despite this complicated interaction not having been investigated fully, researchers expect it to be the focus of optogenetic, behavioral, physiological, and neuroimaging research in the future [29].

1.2.3 Basal ganglia and dystonia

Basal ganglia diseases are one heterogeneous group of symptoms that have a similar anatomical location inside the basal ganglia [20]. The dysfunction in basal ganglia causes a variety of neurological disorders including hypokinetic movement disorders, hyperkinetic movement disorders, and other basal ganglia diseases: Parkinson's disease, dystonia, tremor, chorea, hemiballismus, dyskinesia, athetosis, myoclonus and so on [30, 31]. Even though the specific etiology of dystonia is unknown, a relationship between dystonia and basal ganglia disorders exists [32]. By way of balancing the excitation and inhibition inside the thalamo-cortical loop, the basal ganglia provide the rhythm for stimulation of voluntary movements. Dystonia appears when this balance is no longer given.

The classical potential mechanism of dystonia entails that abnormal reductions occur in cortical inhibition, followed by abnormal gains in motor cortical activities due to the following reasons:

(1) Decreased function of the indirect pathway is suggested as a potential reason based on findings of reduced supply of dopamine D2 receptors and striatal dopaminergic disorder.

(2) Hyperfunctional activity of the direct pathway is likely to lead to more cortical excitability [17, 22, 23].

More and more studies focus on the mechanism of dystonia. The common theory of thalamo-cortical loop is most likely not the only cause of dystonia.
Several focal dystonias, such as musician's dystonia and writer's cramp, have been related to plasticity and relevant abnormal somatosensory disorder. The synaptic systems that control plasticity are highly complicated and involve dopamine, acetylcholine, some other neurochemicals, calcium-mediated changes, among other factors [33, 34].

Cerebellar pathways implicated in the plasticity have been proposed in parallel to or in combination with the basal ganglia [17]. Neuroimaging studies of 18F-FDG PET show some new evidence that supports the idea that basal ganglia are not the only region that causes dystonia. The greater excitability of the premotor and prefrontal regions as well as lesser activity of the major sensorimotor areas were emphasized [35].

Primary dystonia is now known to be caused by an impairment of a large network of brain regions, including basal ganglia, motor cortex, cerebellum, and brainstem, instead of an isolated disorder of a single system. Experimental stimulation of brain areas provides clear evidence of the presence of basal ganglia, cerebellum, thalamus and other areas [36].

Different mechanisms in various types of dystonia are probable as a result. Any of these pathways might be a potential treatment option [34].

1.3 Deep brain stimulation

1.3.1 History of deep brain stimulation

The brain functions based on the communications of neurons, and receives and sends electrical and chemical signals through synapses of one neuron to others [37]. In fact, electrical stimulation has been utilized to influence the neurological system as early as the times of ancient Rome and ancient Greece [38]. In 46 C.E., Scribonius Largus used a ray to stimulate the head of a person suffering from a headache. Electric fish were utilized to treat pain in the 18th century [39]. The observation that the brain is an electrical organ which is not homogeneous were the first key advances [40]. Moreover, Horsley carried out brain ablations for movement problems in 1890, however, the participants suffered extreme paresis as a side effect [41].

This technique was improved by Spiegel and Wycis in 1947. They created stereotactic head equipment which provided an XYZ coordinate system to locate the targets in the deep brain and used it for ablative operations [42]. Chronic stimulation of the brain was successfully implemented in 1950. DBS developed from ablative operations [43] and the team of Benabid and Pollak in 1987 France announced the modern form of DBS modelled for tremor patients [44]. DBS for cervical dystonia was reported by Mundinger in 1977 [45]. As mentioned above, DBS was approved for dystonia in Europe and the USA in 2003 after the approval for tremor and Parkison's disease in 1995 and 1998. In 2009 and 2010, obsessive-compulsive disorder and epilepsy were also approved in Europe.

DBS is a promising technique and the latest trend in the neurosurgical field. Movement disorders are already good indications for DBS and other neurological and psychiatric uses for Tourette's syndrome, chorea, chronic pain, Alzheimer's disease, depression and so on are being researched [24, 46].

1.3.2 Introduction of deep brain stimulation

Definition of DBS: DBS is a deep intracerebral stimulation that contains implanted electrodes which deliver a constant tiny electrical current to a deep brain target area. The target planning is important for the success of the treatment. Pre-operative MRI and CT imaging volumes are required to accurately locate the subcortical structures. A

stereotactic head frame is attached to the head of the patient and a CT scan is performed. The CT scans and preoperative MRI are co-registered in the stereotactic software, which is used to reference the stimulation targets on the MRI to the stereotactic head frame coordinates. Microelectrode recording is applied as confirmation in electrodes implantation procedures and in order to detect side effects [47]. The implanted electrodes are inserted deep inside the brain via small holes in the skull. An extension wire connects the electrodes to an implantable pulse generator placed under the skin of the patient's chest [48].

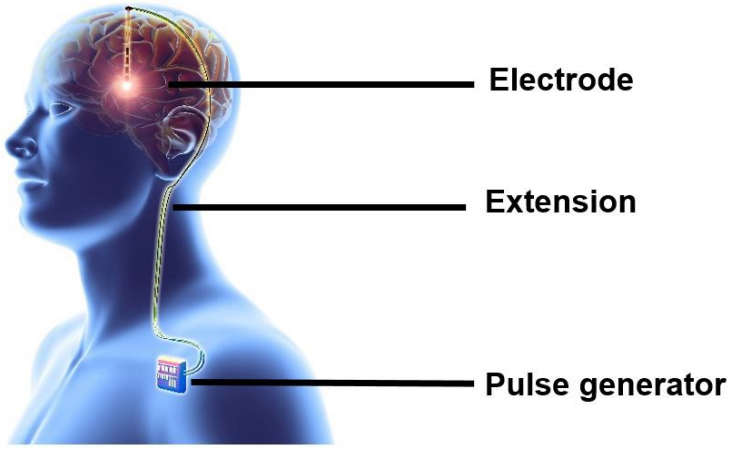

Figure 4. An introduction picture of DBS. Source: Pasieka, Alfred in Science Photo Library (https://www.science-photo.de/bilder/11721786-Deep-brain-stimulation-artwork).
The picture is used with permission from Science Photo Library Deutschland. Annotations by Xi Bai.

After a DBS operation, the parameters could be changed to ensure the best therapeutic results. Changes are made to the stimulation parameters (frequency, voltage, and pulse width) to ensure the results during ambulatory follow-up tests. During programming sessions, thousands of parameter settings may change, which is important for individual therapy [49].

Mechanism of DBS: DBS has been used as treatment for different diseases for more than thirty years, however, the mechanism of DBS still remains unknown. This being said, numerous hypotheses circulate about how DBS could work. A common mechanism of DBS has been proposed as follows: DBS separates input and output signals in the nucleus and disrupts abnormal flow of information in pathological conditions by way of

the cortico-basal ganglia loop [50, 51]. Some studies discuss the changes of neuronal transmission after DBS. The latter stimulates the axon terminals in the nucleus, causing the release of significant amounts of neurotransmitters like GABA and glutamate, and dissociates the inputs and outputs of the stimulated nucleus, thus disrupting the irregular flow of information through the loop of the cortico-basal ganglia [50].

Target areas of DBS: DBS presupposes an application of an electrical current to subcortical nuclei in the brain. The stimulation of some subcortical nuclei has had an effect on the motor and non-motor symptoms. The common target areas can be STN, GPi, ventral intermediate (VIM), pedunculopontine nucleus (PPN), anterior thalamic nucleus (ATN) etc. The suitable target areas are different depending on the disease. DBS improves non-motor symptoms, which benefit from motor effect and the reduction of drugs [24].

Target area of DBS in dystonia: GPi is currently the target area of DBS in dystonia. The studies suggest that the key functional effect of GPi-DBS in these patients will be to motor activation responses and normalize pathologically overactive responses. However, other subcortical nuclei in the brain for DBS are also studied in patients with dystonia, including the STN and the VIM, with the aim of modulating the excitability of the cortex [22, 51, 52, 53].

New technical developments of DBS: Developments of DBS technology will expand the range of its application and help to understand the brain's network, e.g., smaller and more effective implantable pulse generators and electrodes, better control of the current and waveform shape, closed-loop designs that cater to the adjustment of the stimulation in relation to the disease, better target areas, and stimulation of individual brain areas. Online control by doctors is also possibe, given that DBS systems adapt to wireless networks [54].

1.3.3 Treatment outcome of DBS in dystonia

DBS has been used for primary dystonia as a new surgical treatment for more than 20 years [55]. The safety and benefit of DBS for primary dystonia have been proven by several clinical studies. Evidence reveals that young-aged patients with shorter durations of the disease report strong benefits after DBS [56].

A follow-up study of a group of 36 patients who suffered from dystonia and were operated between 2000 and 2007, carried out at Charité Hospital, University of Medicine Berlin, examined the long-term effects on mood, motor symptoms and quality of life after a DBS implant. The team concluded that DBS is a long-term therapy for dystonia that is both safe and effective, with a beneficial long-term impact on the motor dysfunction and injury, as well as an important improvement to the quality of life and mood [57]. The study was published in 2020 and the results of long-term benefits of DBS were added to the newest German dystonia guidelines in 2021 [9].

DBS was used mainly for primary generalized dystonia in the past. Because of its success in treating primary generalized dystonia, DBS is used to treat patients with focal or segmental dystonia who are less severely afflicted, yet did not respond well to treatment with BoNT or oral medicines [9].

1.4 Questions and topic of the study

We found a large amount of lesions inside the basal ganglia, especially in younger patients, while reading MRI of dystonia patients before a DBS operation. However, microvascular lesions or ischemia injury seemed to be very unlikely with young people. This new discovery led us to measure lesions that we observed in primary dystonia patients and compare these results with a control group [58].

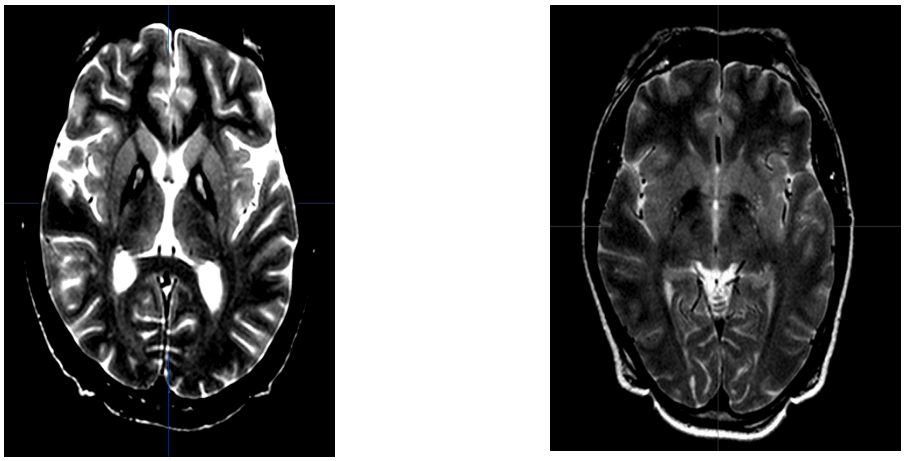

Figure 5. An MRI of lesions in basal ganglia of a 25-year-old and a 29-year-old patient. Source: from Xi Bai's study.

We assumed two hypotheses: (1) signal alterations (SA) in T2 could be more common and of higher volumes in the dystonia group; (2) SA could be identified in the dystonia group at younger ages of the patients [58].

We challenged the common conception that no lesions are found in the basal ganglia of primary dystonia and that a change of anatomy is present in the GP area. We collected the data from the neurosurgery department of the Charité hospital of dystonia patients with a DBS operation since 2000. The time predates the time of the update of the newest definition and classification in 2013, and we also cite literature published before 2013. The neurology department provides the patients' diagnosis and treatments and transfers those who have a DBS indication to the neurosurgery department for further evaluation and operation. Hence, this paper indicates the terms from the old classification - primary dystonia and secondary dystonia.

2 Method

2.1 Patient selection

50 patients with DBS-treated primary dystonia in the Charité neurosurgery department were recorded in this study over a 10-year period. Patients with secondary dystonia, related to bleeding or stroke in the basal ganglia area, and MR-SA dystonia within the target area (for example neurodegeneration with brain iron accumulation syndrome) were removed from the data. All patients with dystonia have been genetically checked prior to the operation [58].

The dystonia group was assigned to 50 age-matched patients present in the same neurosurgery department for other purposes. Exclusion factors included basal ganglia tumor or bleeding, hydrocephalus, inflammatory central nervous system disease, moyamoya disease and other cerebrovascular disorders [58].

Due to compensation for possible singularities in the section of dystonia in individuals with a genetic defect, all volumetric figures for the whole dystonia cohort were replicated in the dystonia cohort, thereby excluding genetic causes. Additionally, data from people with and without a genetic history of dystonia were compared within the dystonia group [58].

Neurosurgical patients were part of the control group. Tumorous lesions were present in the control patients, but none of them were located near the basal ganglia or in the central area. None of the diagnoses were thought to have a direct or indirect effect of basal ganglia metabolism or perfusion [58].

2.2 MRI

Both groups had 1.5 Tesla MR images. The T2 was done for all subsequent analyses during the process of diagnosis. For the dystonia cohort, T2 were produced as part of the preoperative image sets needed 0° gantry for preparing the trajectory prior to the operation, although the control group was not 0° gantry [58].

2.3 Measuring volume of basal ganglia and lesions

The evaluation of T2 hypertensities inside the GP was performed using Brainlab's iPlan 3.0 navigation program to measure volume. The researcher was blinded to the two groups. The MRI's borders were defined on every axial slice and defined as the region with the clearest inclination of signal intensity.

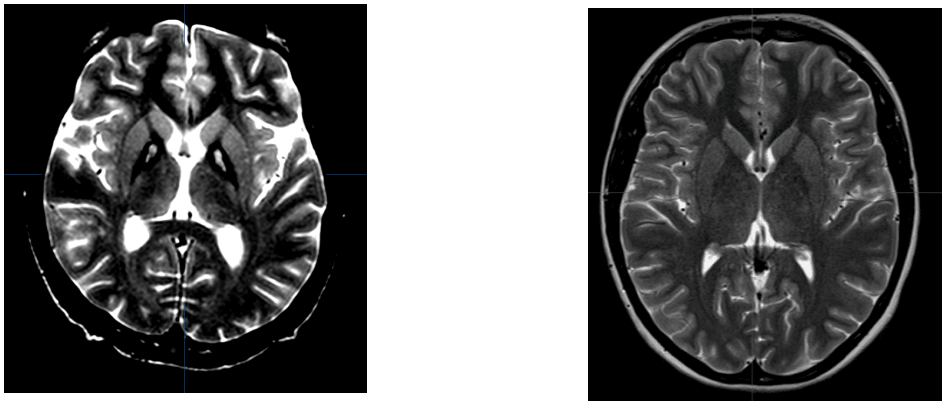

Figure 6. An MRI slice of a 25-year-old patient vs an MRI of a 24-year-old control. Source: from Xi Bai's study.

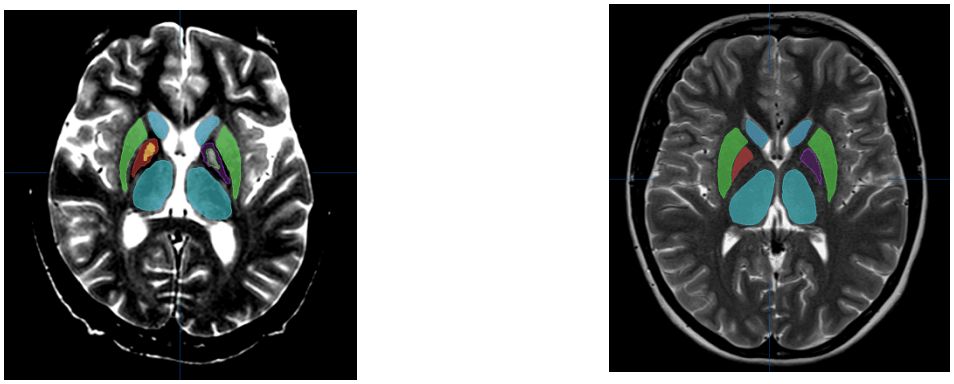

Figure 7. Measurement of the two slices with Brainlab's iPlan 3.0. Source: made by Xi Bai

The two-dimensional (2D) contours of each slice were then transformed into the three-dimensional (3D) object, the volume of which was measured in mm^3. SA borders were also identified as the clearest decline. Complete GP volumes and SA volumes inside the GP were evaluated by utilizing the iPlan software's functions: "create object" and "object volume". Although the border between GPi and globus pallidus externus (GPe) can not always be defined clearly, the GP (i.e. GPi + GPe) was defined as a separate unit. The

SA volume ratio: total GP volume was measured for every brain and hemisphere. GP volume(s): lesion ratios between groups were compared therafter [58].

The same analysis was conducted for the comparison between different structures (the putamen, the caudate, and the thalamus) in basal ganglia. In addition, measurements of the whole brain were carried out in order to detect possible changes in basal ganglia volumes over a lifetime. Here, the whole brain volume entails the cerebrum without cerebellum, because the latter possibly plays an important role in pathogenesis [59].

2.4 Group design

2.4.1 According to age

The newest scheme dividing the age at onset by Albanesel in 2013 [3]:

0-2 years old	infancy
3-12 years old	childhood
13-20 years old	adolescence
21-40 years old	early adulthood
older than 40 years old	late adulthood

We divided 50 primary dystonia patients according to the scheme into 2 groups at the very beginning: 27 patients younger than 40 years old were placed in one group and 23 patients older than 40 years old in another group.

As we began to detect the volumes and lesions of basal ganglia, templated them in the software and analyzed the data for a small group of patients, one striking factor was that the changes in volume in basal ganglia reduced more in the younger group than was the case in the older group. This phenomenon is not normal and unlikely for the younger people because generally, the reduction of brain volume and weight occurs in the older people and is subject to age-related changes [60]. We supposed that this abnormal phenomenon was perhaps a special alteration of the young group, and we applied the procedure to a very young group, e.g., younger than 20 years old or 25 years old from the group younger than 40 years old. However, our samples did not contain enough cases

younger than 20 years old to compare with other groups, and we decided on a very young group, younger than 25 years old, comprised of 12 patients.

2.4.2 According to genes test

Prior to the DBS operation, genetic testing was performed on all 50 patients in the dystonia group. According to the genetic result, the patients were divided into 2 groups: one group with a genetic mutation and another group with no genetic mutation. We wanted to explore whether some difference of volumes and SA could be found between the two groups.

2.5 Statistics

We used Graph Pad's Instat 3 program for the data analysis. Graph Pad's Prism 7 program was used to plot images and volume findings were compared with 3 clinical characteristics. (1) elevation of symptoms (segmental versus generalized); (2) analysis of symptoms; (3) reaction to DBS therapy (<60 percent improvement compared to >60 percent improved after 1 year). ANOVA was done with Bonferroni correction for various volume comparisons [58].

3. Results

3.1 General patient data

The mean age was 39 ± 16 years and the sex was fairly distributed. A little more than 50% of the patients had generalized dystonia, 44% had a segmental or focal type. Symptoms were correlated to one half of the body in 56% of patients [58]. The dystonia group was divided into groups according to age and gene test, and the characteristics are shown in the following picture:

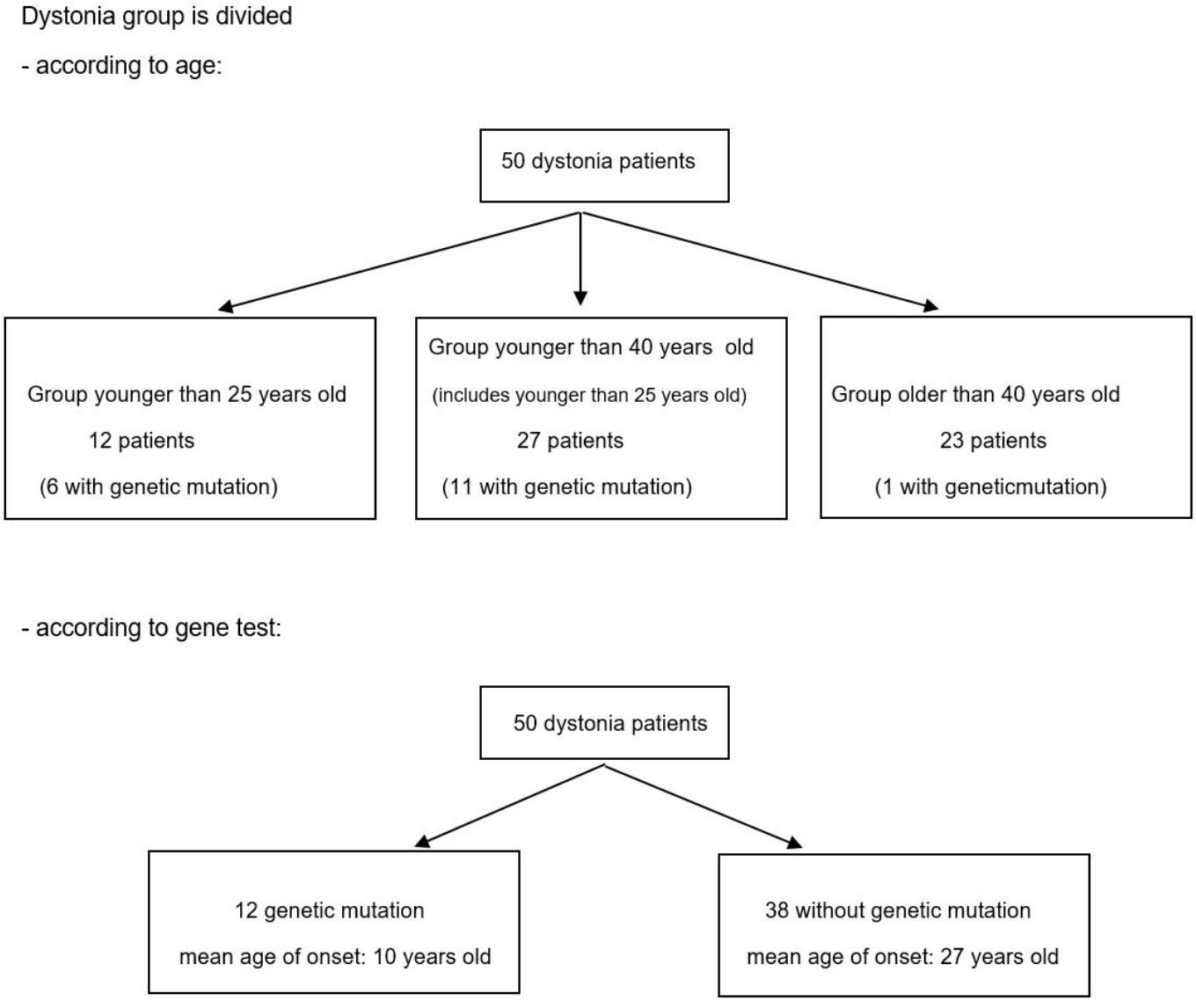

Figure 8. General patient data. Source: made by Xi Bai with MS Word 2019.

3.2 Lesions

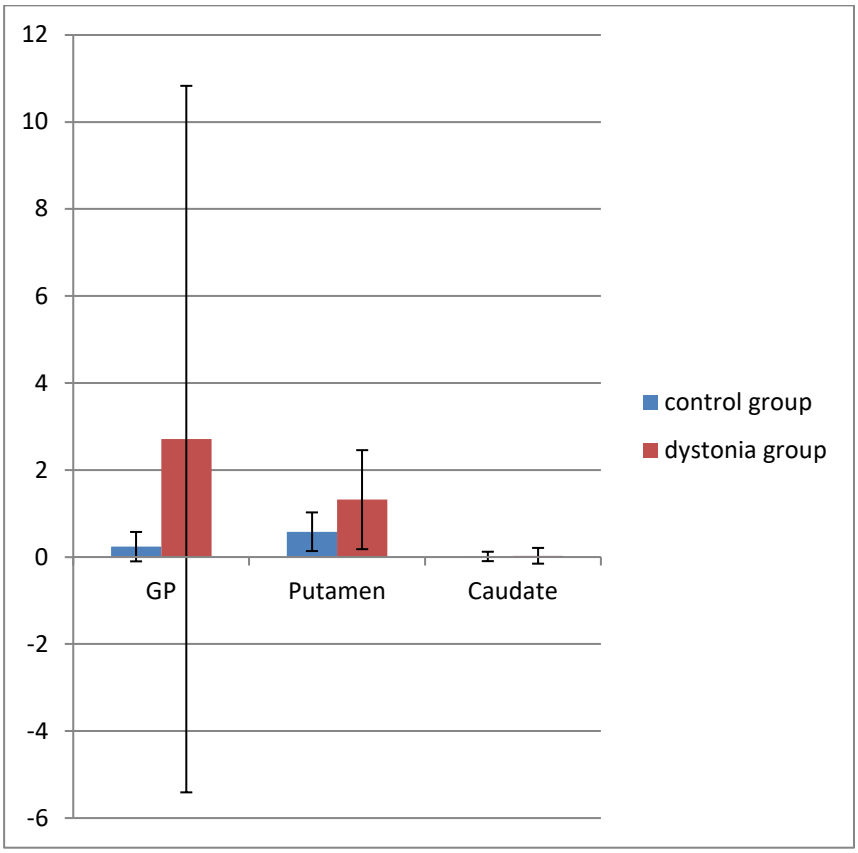

Figure 9. Fraction of lesions, all dystonia patients included. Source: made by Xi Bai with MS Excel 2019.

All patients had lesions in the GP in the dystonia group, whereas 16% of the patients in the control group had lesions. The lesion volumes are tenfold higher in the dystonia group than in the control group, 2.711 vs. 0.239, $p<0.001$. Interestingly, the greatest difference of lesion volumes showed fiftyfold higher in patients younger than 25 years old than the control group, 3.662 vs. 0.068, $p<0.01$ (data shown in the publication). We also saw that the lesion volumes in the putamen were higher in the dystonia group, but there was no statistically significant difference [58].

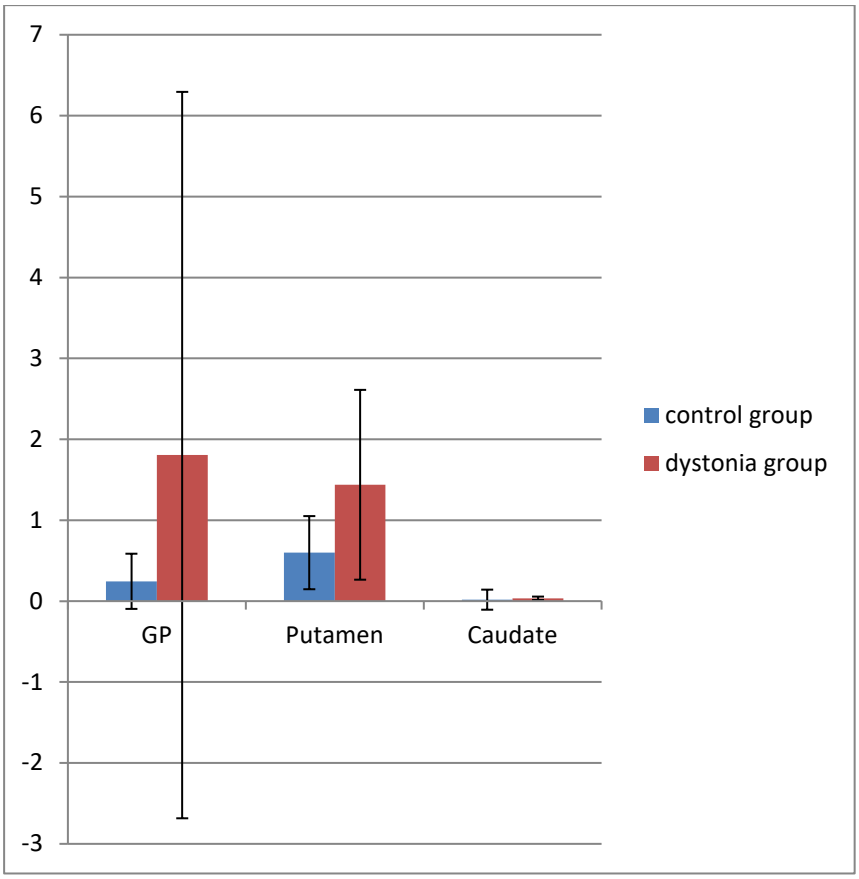

Figure 10. Fraction of lesions, patients without genetic mutation. Source: made by Xi Bai with MS Excel 2019.

We excluded the 12 genetic patients from the whole dystonia group and compared the lesion volumes between the nongenetic group and the control group. The difference in the GP was smaller but remained significant. However, a difference in the putamen appeared as well. In the whole dystonia group, no significant difference showed in the putamen, but in terms of the nongenetic group, a difference was detected in the dystonia group younger than 25 years old 0.573 vs. 2.091, $p<0.01$, and in the dystonia group younger than 40 years old, 0.537 vs. 1.181, $p<0.001$ [58].

The SD in figure 9 and figure 10 shows a high scatter. It is so high because there were five patients in our dystonia group whose values are much higher than those of the other patients. The statistics imply that the dystonia group, which includes many of different subtypes of dystonia, may include an unusually heterogeneous population: There is a chance that various types of dystonia with various clinical symptoms and pathogenetic backgrounds could have various disease pathogeneses and consequently display various function-anatomical results [58].

3.3 Age-dependent volume changes in basal ganglia

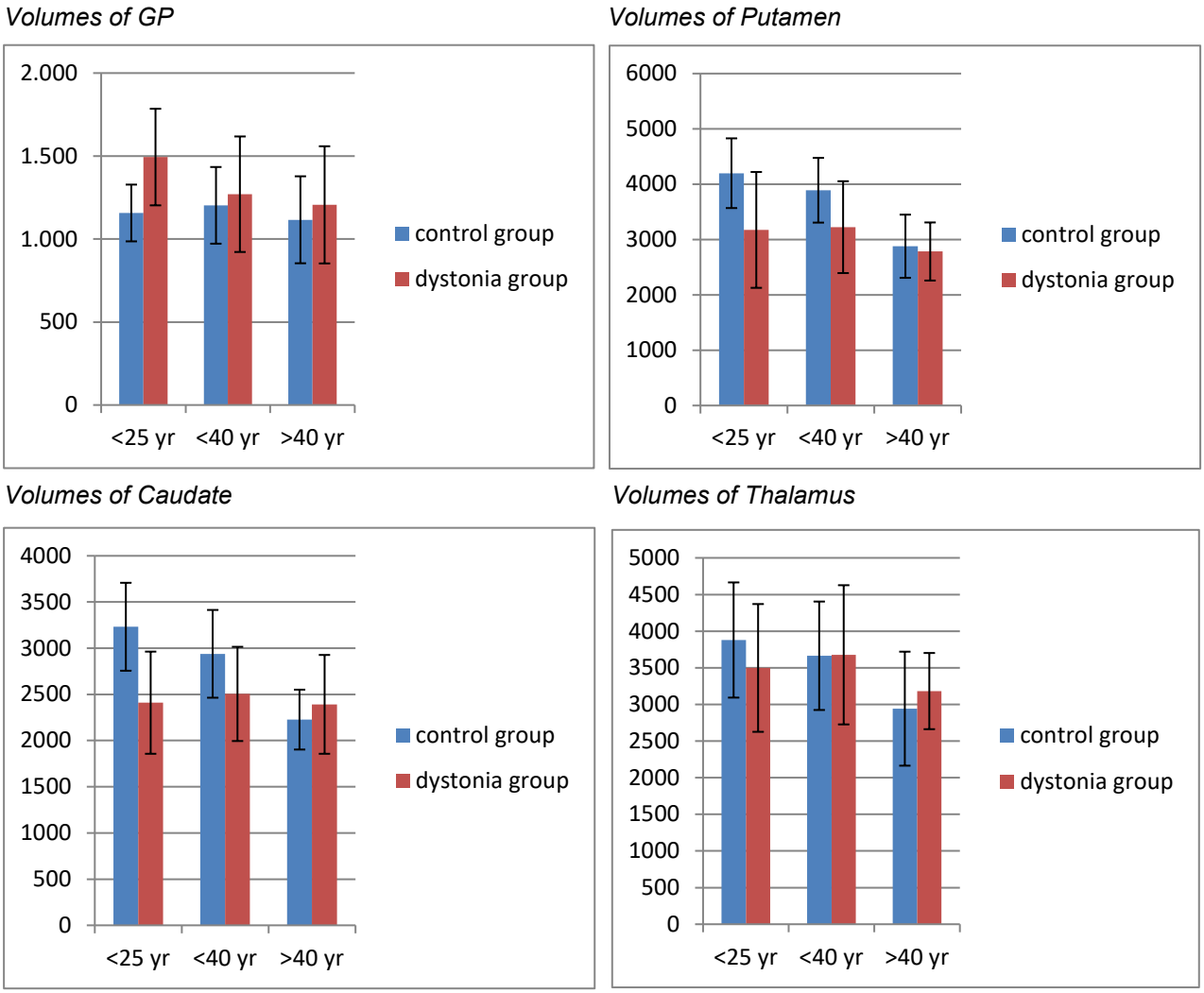

Figure 11. Volumes of different BG structures. Source: made by Xi Bai with MS Excel 2019.

Once the patient cohort was separated into respective age groups, a reduction of BG volumes over a lifetime was seen, reflecting the process of degeneration. When analyzing patient subgroups both younger and older than 40 years, the age-dependent decrease in volume for putamen and thalamus was statistically significant in both the dystonia and control cohorts.

Nevertheless, the measured loss of BG volume was not paralleled by a general loss of cerebral volume over time. At any given period, the whole-brain volume indicated no significant differences between the various age groups.

Curiously, GP volumes were much higher when patients younger than 25 years were examined in contrast to the control group. It was also obvious that the GP's shape altered over time, with younger patients having a fuller, more roundish appearance and the elderly having a slimmer appearance [58].

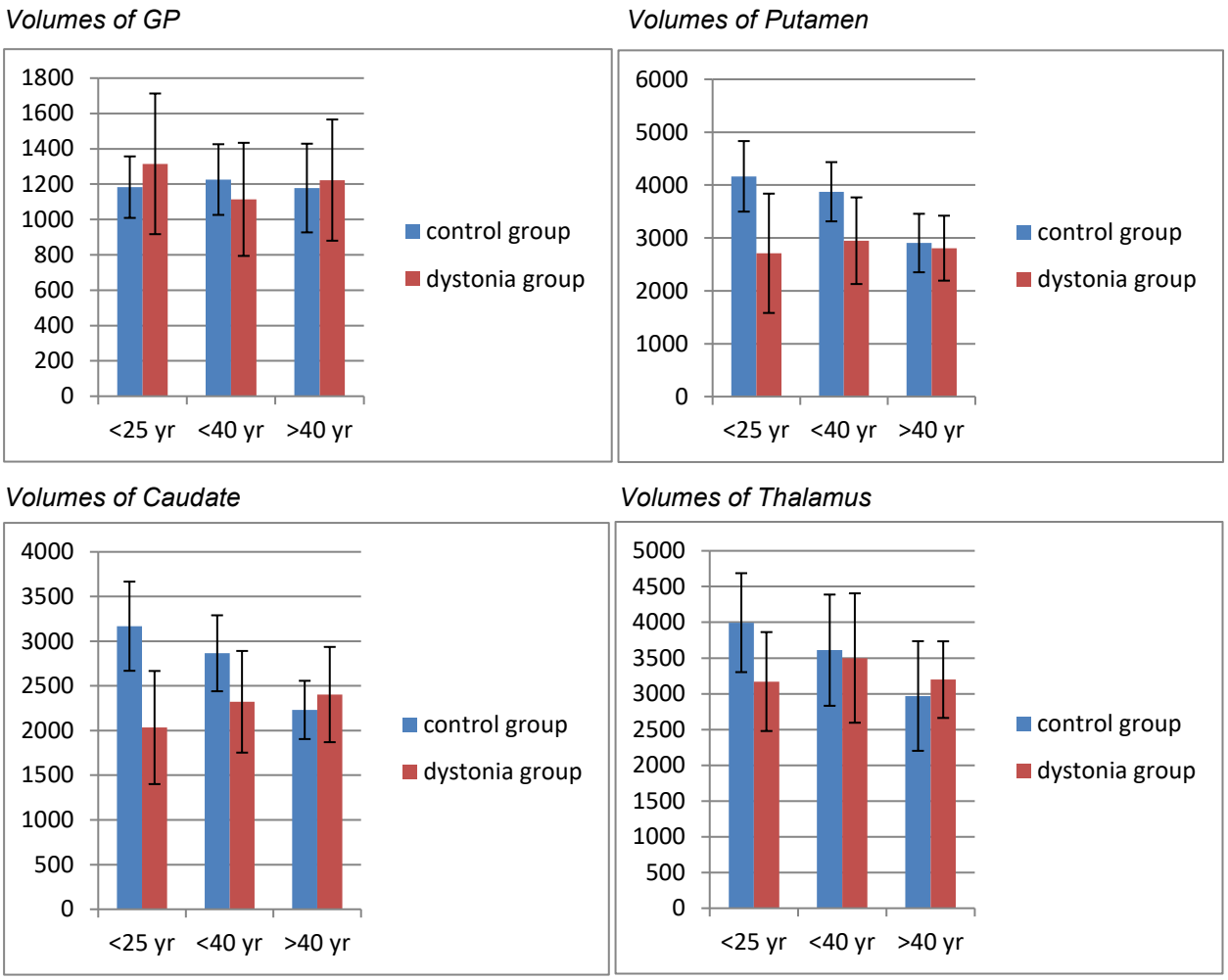

Figure 12. Volumes of different basal ganglia structures patients without genetic mutation. Source: made by Xi Bai with MS Excel 2019.

When genetic dystonia patients were excluded, the difference became slightly smaller but was still significant.

The comparison of the volume difference of different basal ganglia structures between the 38 patients without genetic mutation in the dystonia group and the control group yielded a statistically significant difference in the putamen. 3346 vs. 2850, $p<0.001$. The

difference in the putamen between these two groups was defined in the young groups, the group younger than 25 years old, by 4165 vs. 2710, $p<0.001$, and the group younger than 40 years old, as 3874 vs. 2948, $p<0.001$. However, no significant difference occurred in the group older than 40 years old, the volumes of putamen in the control group reduced faster than was the case for the dystonia group. There was also significant difference in the caudate, but only in the group younger than 25 years old, 3168 vs. 2034, $p<0.05$, and in the group younger than 40 years old, 2865 vs. 2322, $p<0.05$. Moreover, no difference was found in the GP and thalamus.

We analyzed the clinical factors (disease duration, topography and lateralization of symptoms, response to DBS), yet a correlation to volumes of different BG structures or lesion volumes could not be seen (data not shown). However, a few differences appeared when analyzing nongenetic group and genetic group. A loss of volumes over life span took place in all BG groups in the whole dystonia group (all dystonia patients included), the control group as well as nongenetic dystonia group, except in the caudate of the nongenetic dystonia group. On the contrary, the volumes of caudate of the nongenetic group were slightly bigger over a life span [58].

4. Discussion

4.1 Short summary of results

Our study resulted in two important findings [58]:
1) Dystonia patients have different basal ganglia gray matter volumes and a different age-dependent volume reduction in contrast to the age-matched control group.
2) Dystonia patients have more T2-hyperintense in MRI.

4.2 Interpretation of the results

4.2.1 Nature of lesions

It is unclear if the SA in our study is primary or secondary to the cause of dystonia. Secondary dystonia has been reported as a result of pallidum lesions, as well as lesions in other parts of the BG circuit and the cerebellum [61]. Even if the nature of the SA is unclear, some data from basic research indicates that they may represent a microanatomical correlate of neurodegeneration, which could become visible with the development of high-resolution MR imaging.

However, the SA noticed in our dystonia group are not probable to be traumatic, vascular, or infectious lesions. In T1, the T2 hyperintensities are hypointense. They appear isointense to cerebrospinal fluid in all MR weightings. We considered that SA may be Virchow-Robin spaces (VRS, perivascular spaces), given that their diameter reaches 5 mm and they are also detected in very young patients.

Normal VRS functions include signal transduction, the blood-brain barrier, extracellular fluid regulation. VRS dilatation has been related to a variety of illnesses, including Parkinson's disease, multiple sclerosis, autism, and dementia [62].

A 2021 systematic review of structural MRI in dystonia collected the studies of the recent 15 years (our study included) and showed that imaging of dystonia is still a relatively unexplored topic. Most studies have only a small cohort with different methods and conflicting results [63]. Although many aspects of the pathogeneses of the various disorders associated with increased VRS remain unknown, they all share similar

pathogenic procedures including neurodegeneration, oxidative stress, and inflammation. We considered that it is possible that some of the pathological factors may also play a role in the development of primary dystonia.

Although the different types of dystonia are classified as only one single disease entity, they could be caused by different disease pathologies and, as a result, exhibit different function-anatomical outcomes. Because dystonia is an uncommon and heterogeneous disease with several subtypes, further research may require different analysis for one single subtype and a large dystonia database from multicenter collecting with enough patients for each subtype.

4.2.2 Volume changes

The putamen and caudate are much smaller in dystonia in our study, but the GP is a little bigger in the early stages of dystonia. Surprisingly, although volume loss was found in the BG in dystonia group and control group, the whole cerebral volume had no volume loss. If volume loss is a symptom of age-related degeneration, it may occur earlier or selectively in the BG than in other areas of the brain.
The increase in gray matter volume could be an effect of an increased metabolism, connectivity or cellularity. The decrease in gray matter volume is often associated with atrophy and degeneration [64].

The small volume increases in the GP of our dystonia group might be related to a compensatory mechanism, which often happens in the case of motor disbalance. The volume decreases in the putamen and caudate in our study may imply that dystonia is a neurodegenerative disease like Parkinson’s disease, which is considered as a disease of selective neurodegeneration that may occur in a specific area of the brain [65].

This being said, the results of brain morphometric studies are always conflicting. Some literatures reported similar results, others revealed no differences between the dystonia group and the control group, while others showed exactly the opposite results.

The various findings in different literatures may be attributed to two heterogeneities in the various study designs:

(1) Differences in the method of analysis. The method of analysis may be individually designed. The methods have shown to provide diverging volumetric findings when image processing settings, software designs, or even software updates are changed. In our study, we used a traditional morphometric method to measure the volumes, given its accuracy, but a systematic bias could be the result thereof, since the measurement depends on the experience and visual judgement of the researchers [58].

(2) Differences between the patient sample. A study group selection bias between the studies is present. In our study, we had cases of 56% with generalized dystonia and 44% with foal or segmental dystonia. The mean patient age was 39 years old. The dystonia group in a study by Egger et al [66], including generalized dystonia and hereditary type, showed similar results to our study and its mean age of the patients was likewise roughly 40 years of age. Yet the studies by Vilany et al [67], Piccinin et al [68] and Gracien et al [69] showed no volume difference in the dystonia groups. The mean age in those studies was consistently above 50 years. However, the subgroups older than 40 years in our study likewise resulted in no volume difference. Thus, our results did not contradict the above-mentioned studies [58].

4.2.3 Etiology discussion

A variety of genetic types have been identified, although the majority of cases have an unknown etiology. Very few autopsy examinations of primary dystonia have been carried out, and the findings for recognizable neuropathological lesions are varied and unclear [70].

According to our data, we found the abnormal changes of volumes and lesions in basal ganglia and challenged the classical concept that no substantial neurodegeneration or morphological damage can be detected with routine methods [12]. This being said, the complicated questions can only be explained by pathological researches.

4.3 Embedding the results in the current state of research

Currently, the mechanisms of basal ganglia pathology in dystonia remain unclear. So do the detailed mechanisms of action of DBS. Any new finding about one mechanism could contribute to the others.

Compared to other MRI studies of dystonia, the scope of our dystonia group is large. As dystonia has many subtypes caused by different pathological reasons, the findings of studies are always conflicting. More studies with more cases could be helpful to explain this conflicting situation.

4.3.1 MRI for dystonia

Because the patients in our study obligatorily received a thin sliced MRI (1-2mm) for DBS planning, potentially more lesions may have been detected than in thicker sliced MRIs. One surprising finding was that all dystonia patients included in this study showed small lesions in the basal ganglia. Further data from neurosurgery and neurology departments are required, in order to discuss if the occurrence of lesions in the basal ganglia in primary dystonia is a coincidence or a particularity of patient selection within a surgical cohort. It may be productive to examine more primary dystonia patients, including those, not scheduled for surgery. Are dystonia patients exibiting lesions potentially more eligible for DBS implantation?

4.3.2 Other neurological movement disorders

The most common neurological movement disorders are Parkinson’s disease, tremor, and dystonia. Patients who suffer from Parkinson’s disease are relatively old in comparison to patients who suffer from tremor or dystonia, and they may have a higher likelihood of having lesions in the brain in the first place. The relatively young patient ages in tremor and dystonia patients make degenerative or vascular lesions unlikely. Therefore, after discovering the interesting findings about our dystonia patients, we also collected the data of the tremor patients in the neurosurgery department of the Charité Hospital, and evaluated about 20 patients with essential tremor using the same method we applied for the dystonia patients. Although we have not completed this second study of tremor, one important aspect is that we found similar results compared with our

dystonia study. Does it mean that lesions are possibly the common reason for neurological movement disorders? This needs further research and data from more patients.

4.4 Strengths and weaknesses of the study

4.4.1 Strengths

Several studies using MRI techniques have been published over the last 20 years discussing gray matter volume in a variety of dystonia subtypes. However, the results were conflicting. For the BG, some researchers have noted a decrease of volume of putamen, while others were unable to find any volumetric difference. In a cohort of DYT-1 patients in 2009, Gavarini et al. reported the first mention of signal alterations in the BG [71]. The research remains descriptive, since the writers did not quantify the SA's [58].

Our study is a collection of almost all dystonia patients with DBS treatment in Charité Hospital since 2000. At that time, DBS was a completely new surgical treatment after its approval in Europe, and research about dystonia with DBS was required. We have collected a large number of cases over a long period of time and in so doing, are the first to quantify the volumes and lesions in basal ganglia. The promising results may incite efforts to further explore the pathophysiological mechanisms in dystonia and other movement disorders. It also led us to challenge the classical conception of primary dystonia.

4.4.2 Weaknesses

Retrospective study: we apply a retrospective analysis with a case control design. The cases in the control group are not totally healthy, however, we have confined the control cohort to cases excluding disease related to basal ganglia or the central area [58].

Different gantry: the MRI modalities in the patient group and control group were not same. The measured volume may thus have varied slightly, due to section phenomena caused by different gantries: the MRIs in the patient group had 0° gantry scans, whereas the control group MRIs were of physiological gantry. However, a systematic bias based on

section phenomena is very unlikely, because we see antidromic volume behaviors in different BG areas in the two groups (GP is larger and the putamen is smaller in the dystonia group). In general, heads are hardly angled exactly the same in MRI research. Although the skull may be in the same gantry, the anatomic position and shape of the BG vary even within the same gantry [58].

Development of gene testing: due to the development of gene testing, more and more new genetic mutations of the dystonia patients will be discovered in the next several decades. The implication is that our dystonia patients currently in the group with no genetic mutation could be identified with a new genetic mutation in the future and will then be placed in the group with genetic mutations after new technical gene testing has been carried out. However, research should not wait until all genetic mutations will be discovered and instead begin to study the old cases. It may be worthwhile looking into more cases, or also re-evaluating the present data again, once further genetic forms will be identified in the future.

Subtypes in the dystonia group: Dystonia is a disease that includes a large hyperkinetic group of disorders. It shows highly various symptoms in different body parts, and the classification was changed several times during the past century. Different subtypes of dystonia can be caused by individual anatomical and pathological reasons. The number of our patients was not exhaustive enough for dividing them into more subtype groups. Here, carrying out the research in multicenters with more cases to be divided into different subgroups would have been a more productive setting.

Measuring substructures: volumes of different structures of basal ganglia and lesions were measured in this study. The same MRI equipment has been used in the hospital for 10 years. Due to the limitation of MRI image quality, we could not differentiate the GPi and GPe substructures within GP sufficiently. GPi and GPe are functionally two different anatomical structures, which partake in two separate pathways: direct and indirect pathways in basal ganglia. With the development of MRI images, smaller substructures will be identified and the changes of volumes could be compared. These analyses may then contribute to more detailed findings.

4.5 Implications for clinic and/or future research

4.5.1 For clinic

The previous concept of primary dystonia without an imaging relation may be outdated. Prospectively, MRIs may be evaluated in the early diagnostic workup for lesions and volume alterations. Those criteria may support future decision making. Our findings are in line with the theory that different forms of dystonia share similar patterns of structural brain alterations, and they could lead to more research in imaging studies of different forms of dystonia in the future.

4.5.2 For research

Are the lesions different on a molecular level from healthy tissue? Are the lesions caused by an abnormality in sensorimotor integration and excitability of the cortex? Are there neurophysiologic and bio-chemical changes? Do the lesions influence the network in the brain?

We hope that more research can focus on the pathology of the lesions of dystonia patients in the future. This may shed light on the yet unknown etiology of dystonia and other neurological movement disorders. With further knowledge of the etiology of the disease, the way may be paved for a causal treatment approach.

5. Conclusion

In this study, we found and quantified volume changes of substructures and lesions in basal ganglia in primary dystonia, particularly in very young patients: (1) volumes of caudate and putamen werere decreased; (2) ten times more lesions were present in the dystonia group than in the control group. The decreased volumes may relate to degeneration and atrophy, while thelesions may be a potential contributor to the cause of primary dystonia. The results may challenge the common definition of primary dystonia as having no anatomical sbstrate. They may explain the dysfunction in the indirect pathway, as well as relate to plasticity changes.

We hope that more research will focus on the morphological changes of dystonia patients, in future also including patients not scheduled for DBS surgery. After all, the described volume changes and lesions remain unclear on a molecular level. More radiological studies are necessary to further specify the details of dystonia and other movement disorders.

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Eidesstattliche Versicherung

„Ich, Xi Bai, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *Untersuchung der morphologischen Unterschiede der Basalganglien bei Dystonie-Patienten / examination of the morpological abnormalities in the basal ganglia of dystonia patients* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Ich, Xi Bai, hatte folgenden Anteil an der Publikation

„Morphologische Unterschiede der Basalganglien bei Dystonie-Patienten / morpological abnormalities in the basal ganglia of dystonia patients“

(https://www.karger.com/Article/Pdf/512599):

Methodische Durchführung, hauptverantwortliche Datengewinnung und Datenanalyse, insbesondere:

- bildgebende Studien zur Genese von Bewegungsstörungen und potentiellen anatomisch-morphologischen Substraten für ein verbessertes Ansprechen auf die tiefe Hirnstimulation.
  Daraus habe ich die Tabellen 1, 2, die Abbildung Fig. 1 und Seiten 352-355 Methods (Patient Cohort, Image Acquisition Details, Volumetry of BG and T2 Hyperintersities, Statistic) erstellt.

- Durchführung extensiver Volumetrien und Bilddatenanalysen.
  - Aus meiner statistischen Auswertung habe ich die Tabellen 3 und 4 erstellt.
  - Meine Daten wurden zur Erstellung genutzt für die Tabellen 5 und 6.

- insbesondere: hervorheben und messen der für die Untersuchung relevanten Areale des Gehirns aus den MRT-Bildern einer Patientengruppe und einer Kontrollgruppe von je 50 Personen in Brainlab’s iPlan 3.0, Vergleich der beiden Kollektive hinsichtlich Auffälligkeiten in den markierten Bereichen.

  Aus meiner statistischen Auswertung habe ich erstellt:
  - die Abbildung Fig. 2,
  - Seiten 355-356 Results (General Patient Characteristics, Volume Differences),
  - Seiten 358-359 Discussion (Volumetric Findings).

  Meine Daten wurden zur Erstellung genutzt für:
  - Seiten 356-357 Results (Age-Dependent Volume Changes, Signal Alterations, Influence of Genetic Status and Clinical Features),
  - Seiten 360-361 Discussion (Nature of the SA, Limitations to the Study, Conclusion).

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Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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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-hyperinstensive 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 percentaged 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].

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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 panning, 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.

Table 1. Patient characteristics of the study group

General	
Mean age (±SD)	39±16 yr
Age range	6–70 yr
Male:female	23 (46%):27 (54%)
Mean age of onset	27±21 yr
Age range of onset	0–72 yr
Mean disease duration (±SD)	13±10 yr
Age range of disease duration	2–37 yr
Manifestation	
Generalized	28/50 (56%)
Focal/segmental	22/50 (44%)
Symptom lateralization	
No dominance	22/50 (44%)
Dominance	28/50 (56%)
Right side	16/28 (57%)
Left side	12/28 (43%)
Genetic background	
None	38 (76%)
Yes	12 (24%)
DYT-1	5 (10%)
DYT-11	4 (8%)
DYT-12	1 (2%)
DYT-16	1 (2%)
Sepiapterin reductase deficiency	1 (2%)
Correlation: clinical dominance/lesion dominance	
Correct correlation	14/28 (50%)
False correlation	14/28 (50%)

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-

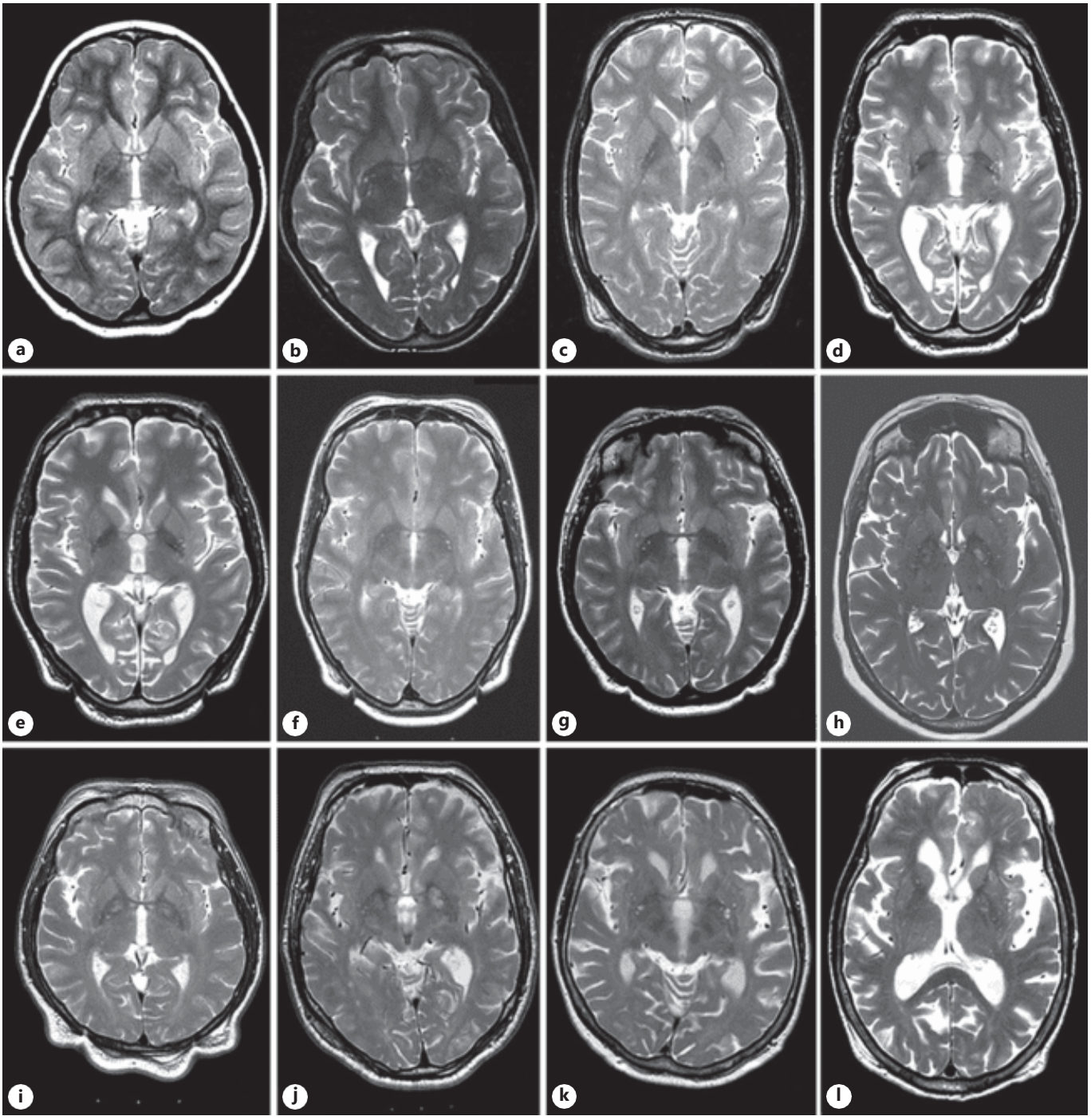

Fig. 1. MRIs of patients of different ages with diagnosis of primary dystonia scheduled for DBS treatment. All T2 axial sections. Evidence of hyperintense SA within the GP. Patient ages: 6 years (**a**), 23 years (**b**), 25 years (**c**), 29 years (**d**), 32 years (**e**), 45 years (**f**), 47 years (**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			
	means (±SD)		*T* (Bonferroni)	*p* value
	control group	dystonia group		
GP				
All	1,167 (±249)	1,224 (±352)	0.58	ns
<25 yr	1,157 (±171)	1,494 (±291)	2.10	ns
<40 yr	1,203 (±231)	1,270 (±348)	0.14	ns
>40 yr	1,116 (±262)	1,206 (±353)	0.90	ns
Putamen				
All	3,455 (±765)	2,970 (±752)	5.53	<0.001
<25 yr	4,199 (±630)	3,174 (±1,047)	4.94	<0.001
<40 yr	3,891 (±585)	3,224 (±830)	5.47	<0.001
>40 yr	2,879 (±571)	2,784 (±525)	0.92	ns
Caudate				
All	2,632 (±545)	2,440 (±525)	2.19	ns
<25 yr	3,232 (±476)	2,410 (±553)	3.96	<0.01
<40 yr	2,939 (±475)	2,505 (±510)	3.55	<0.05
>40 yr	2,227 (±324)	2,392 (±535)	1.59	ns
Thalamus				
All	3,352 (±834)	3,392 (±779)	0.45	ns
<25 yr	3,879 (±786)	3,498 (±872)	1.84	ns
<40 yr	3,664 (±740)	3,677 (±950)	0.11	ns
>40 yr	2,942 (±778)	3,182 (±520)	2.317	ns

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 is <0.05, if $T > 3.134$; cohort <25 years: p is <0.05, if $T > 3.180$; cohort <40 years: p is <0.05, if $T > 3.145$; and cohort >40 years: p is <0.05, if $T > 3.144$. BG, basal ganglia; GP, globus pallidus.

cluded. All dystonia patients were genetically tested. In 12 of the patients, an underlying genetic mutation was identified; the remaining 38 patients were classified as idiopathic dystonia. Dystonia patients were paired to 50 age-matched controls, who were also treated in the department of neurosurgery within the respective time period for other reasons. Exclusion criteria in the control group were tumor or bleeding within the BG, moyamoya disease or other cerebrovascular abnormality, inflammatory CNS disease, and hydrocephalus. Patient characteristics of the dystonia group and the control group are summarized in Tables 1 and 2. For subsequent analysis of possible age-dependent differences, the patient cohort was subdivided into 3 age groups: (1) cohort younger than 25 years; (2) cohort younger than 40 years (also containing the 1st cohort's patients); and (3) group older than 40 years (see Tables 3–6). In order to account for potential singularities within the portion of dystonia patients bearing a genetic mutation, all volumetric statistics that were done on the entire dystonia cohort were repeated on the dystonia cohort excluding genetic forms (see Tables 5, 6). Also, data of patients with and without a genetic background were compared within the dystonia cohort.

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 × 0.7 × 2 mm, 2-mm slice thickness, and field of view was 250 × 250 mm; matrix 288 × 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 preoperative image sets required for trajectory planning in DBS with 0° gantry, while the control group was not 0° gantry.

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 GPi and GPe often could not be outlined with certainty, the GP (i.e., GPi + 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-

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

	Means (±SD)		% SA	
	control group	dystonia group	*T* (Bonferroni)	*p* value
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. ** $p < 0.01$, *** $p < 0.001$.

ebellum since the cerebellum has been discussed to potentially play a further specific role in dystonia pathogenesis [16].

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. Volumetry 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 (seeTable 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

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

	Volumes, mm^3			
	means (±SD)		*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

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 hemisphere plotted separately. Cohort all: p is <0.05, if $T > 3.136$; cohort <25 years: p is <0.05, if $T > 3.241$; cohort <40 years: p is <0.05, if $T > 3.158$; and cohort >40 years: p is <0.05, if $T > 3.145$. BG, basal ganglia; GP, globus pallidus.

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 thalami) in the dystonia group with 100 GPs (putamens, caudates, and thalami) 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] mm^3 vs. 3,455 [±765] mm^3, $p < 0.001$) 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] mm^3 vs. 3,352 [±834] mm^3; 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] mm^3 vs. 2,879 [±571] mm^3, $p < 0.001$; dystonia: 3,224 [±830] mm^3 vs. 2,784 [±525] mm^3, $p < 0.001$) and thalamus (control: 3,664 [±740] mm^3 vs. 2,942 [±778] mm^3, $p < 0.001$; dystonia: 3,677 [±950] mm^3 vs. 3,182 [±520] mm^3, $p < 0.001$), as well as for caudate in the control group (2,939 [±475] mm^3 vs. 2,227 [±324] mm^3, $p < 0.001$). For caudate in the dystonia group (2,505 [±510] mm^3 vs. 2,392 [±535] mm^3, $p > 0.05$), as well as for GP in both groups (control: 1,203 [±231] mm^3 vs. 1,116 [±262] mm^3, $p > 0.05$; dystonia: 1,270 [±348] mm^3 vs. 1,206 [±353] mm^3, $p > 0.05$), 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 cm^3; control <25 years: 924 ± 112 cm^3; dystonia <40 years: 925 ± 69 cm^3; control <40 years: 918 ± 98 cm^3; and dystonia >40 years: 874 ± 88 cm^3; control >40 years: 878 ± 93 cm^3.

Table 6. Fraction of T2-hyperintense SA, patients with genetic mutation excluded

	Means (±SD)		% SA	
	control group	dystonia group	*T* (Bonferroni)	*p* value
GP				
All	0.245 (±0.341)	1.805 (±4.489)	5.20	<0.001 (***)
<25 yr	0.088 (±0.120)	0.723 (±1.109)	1.92	ns
<40 yr	0.201 (±0.256)	1.505 (±2.402)	5.04	<0.001 (***)
>40 yr	0.283 (±0.399)	1.974 (±5.148)	3.60	<0.01 (**)
Putamen				
All	0.599 (±0.452)	1.438 (±1.173)	2.66	ns
<25 yr	0.573 (±0.495)	2.091 (±1.668)	4.31	<0.01 (**)
<40 yr	0.537 (±0.430)	1.818 (±1.260)	4.70	<0.001 (***)
>40 yr	0.653 (±0.468)	1.267 (±1.102)	1.25	ns
Caudate				
All	0.018 (±0.124)	0.035 (±0.201)	0.06	ns
<25 yr	0	0	–	–
<40 yr	0	0	–	–
>40 yr	0.033 (±0.168)	0.051 (±0.240)	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. Thirty-eight idiopathic dystonia patients compared to 38 age-matched controls. Cohort all: p is <0.05, if $T > 2.947$; 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 $T > 2.958$. BG, basal ganglia; GP, globus pallidus; SA, signal alterations. ** $p < 0.01$, *** $p < 0.001$.

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] mm^3 vs. 1,494 [±291] mm^3, $p < 0.05$, 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 (lateralization 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 nongenetic forms within the dystonia cohort, a few conspicuities

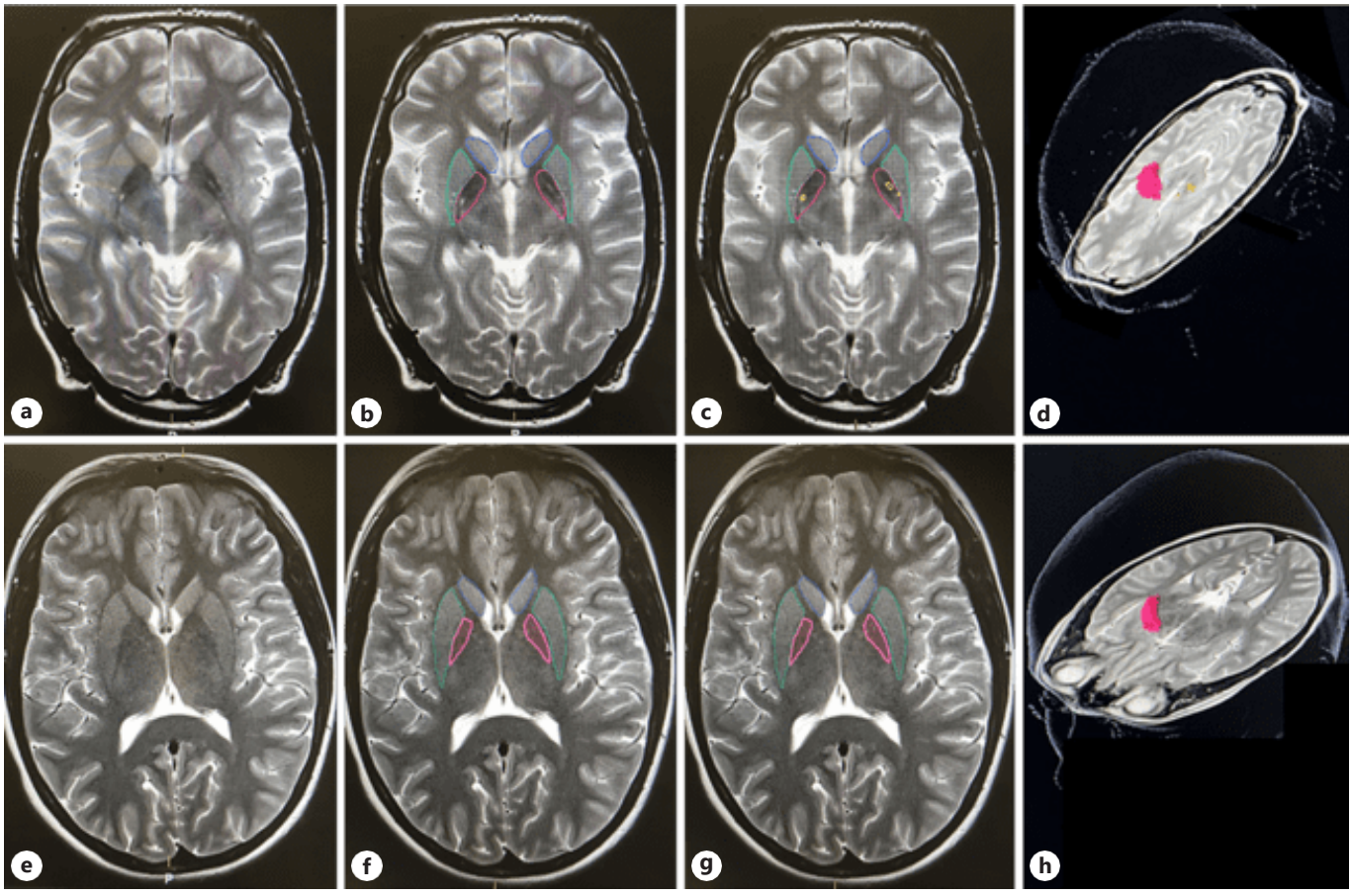

Fig. 2. Volumetry of the BG and of the SA in T2 weight MRI. **a–d** Dystonia patient, 25 years old. **e–h** Control patient, 25 yearsold. Native images (**a**, **e**); outlining the BG for volumetry, GP (pink), putamen (green), and caudate (blue) (**b**, **f**); and outlining the SA within the GP (yellow) (**c**, **g**). **d**, **h** Volume objects of the GP (left hemisphere) and SA (right hemisphere). BG, basal ganglia; SA, signal alterations; GP, globus pallidus.

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.

Nature of the SA

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

gantry, 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.

Statement of Ethics

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.

Conflict of Interest Statement

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Author Contributions

K.F. conceived the study. X.B. performed the quantitative volume measurements. K.F. analyzed the data and drafted the manuscript. P.V. contributed in the study's coordination and execution. All authors have read and approved the final manuscript.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Komplette Publikationsliste

Bai, X, Vajkoczy, P, Faust, K. Morphological abnormalities in the basal ganglia of dystonia patients. Stereotact Funct Neurosurg. 2021 Jan 20; 1-12
Journal Impact Factor: 1.905
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Faust, K, Vajkoczy, P, Bai, X, Harnack D. The effects of deep brain stimulation of the subthalamic nucleus on vascular endothelial growth factor, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor in a rat model of Parkinson’s Disease. Stereotact Funct Neurosurg. 2020 Nov 5;1-11.
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