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Outcome Predictors for Deep Brain Stimulation in Patients With Childhood-Onset Dystonia: Short- and Long-Term Evaluation of the GEPESTIM Registry

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Erklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertationsschrift ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskriptes habe ich Unterstützungsleistungen von folgenden Personen erhalten:

1) **Frau Priv.-Doz. Dr. Anne Koy** (Leiterin des Zentrums für dystone Bewegungsstörungen im Kindesalter aus der Klinik für Kinder- und Jugendmedizin des Universitätsklinikums Köln)
2) **Herr Prof. Dr. Martin Hellmich** (Institut für Medizinische Statistik und Bioinformatik der Universität zu Köln)

Weitere Personen waren an der Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe einer Promotionsberaterin/eines Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertationsschrift stehen.

Die Dissertationsschrift wurde von mir bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Der dieser Arbeit zugrunde liegende Datensatz wurde zu einem großen Teil von mir selbst erhoben. Ich benutzte für meine Auswertungen jedoch auch Daten, die ohne meine Mitarbeit von Milena Weinsheimer und Nina Bockhorn unter der Anleitung und Aufsicht von Frau Priv.-Doz. Dr. Anne Koy und Herrn Univ.-Prof. Dr. med. Lars Timmermann aus der Klinik für Kinder- und Jugendmedizin beziehungsweise Klinik für Neurologie des Universitätsklinikums Köln und des Universitätsklinikums Gießen-Marburg erhoben worden sind. Die bereits erhobenen Daten sind mir mittels Online-Datenbank (RedCap) von Frau Priv.-Doz. Dr. Anne Koy zur Verfügung gestellt worden. Die Arbeitshypothesen für mein Dissertationsprojekt entwickelte ich gemeinsam mit Frau Priv.-Doz. Dr. Anne Koy.

Die statistische Auswertung komplexer Studiendaten mittels Regressionsanalysen und die Erstellung von Graphiken zur bildlichen Veranschaulichung der Regressionsanalysen führte Herr Prof. Hellmich mithilfe des Programms IBM SPSS Statistics 27.0 durch. Im Detail zählen dazu folgende Graphiken/ statistische Auswertungen:

- Figure 7 (Results): Absolute postoperative reduction of prescribed drugs for treatment of movement disorder and direct sequelae
- Figure 8 (Results): Postoperative change in BMI measured by percentile curve
- Figure 9 (Results): Scatterplots of percentage change in BFMDRS score compared with baseline at follow-up 1, 2 and 3 against years of life lived with dystonia before surgery in years, age at onset in years and age at implantation in years for all paediatric patients with 1) isolated inherited and idiopathic, 2) combined inherited and idiopathic and 3) acquired dystonia
- Figure 10 (Results): Bar chart showing the relative (see y-axis) and absolute (see labels in the bars) proportion of preoperative physiological and pathological cMRI findings of the deteriorated group and the insufficient, moderate and superior outcome group
- Figure 11 (Results): Bar chart showing the relative (see y-axis) and absolute (see labels in the bars) proportion of patients for whom at least one or no orthopaedic deformity in the left or right arm, hip, knee, ankle, and spine area was diagnosed preoperatively, or an orthopaedic deformity was detected but had been successfully treated with surgery before DBS implantation

Die Zusammenstellung der Daten für die Analysen für Herrn Prof. Hellmich und die Ausarbeitung der statistischen Auswertungen von Herrn Prof. Hellmich (hierzu zählt zum Beispiel die Modifikation/ Bearbeitung der Graphiken, ohne Rohdaten und statistische Aussagen zu verändern) führte ich selbstständig durch. Die Anfertigung rein deskriptiver Statistik führte ich mittels Microsoft Excel 2021 selbstständig durch, insbesondere ohne eine statistische Beratung in Anspruch zu nehmen. Von mir ohne Hilfe oder Beratung durch weitere Personen durchgeführte statistische Berechnungen sind in folgenden Tabellen aufgelistet:

- Table 3 (Results): Demographic and clinical data of the registry cohort.
- Table 4 (Results): Perioperative AEs (<1 month postoperative) associated with DBS in paediatric patients (adopted, updated and added to from Koy et al., 2019, p.1114)
- Table 5 (Results): Short-term adverse events (1-6 months postoperative) associated with DBS in paediatric patients (adopted, updated and added to from Koy et al., 2019, pp.1114-1115)
- Table 6 (Results): Long-term adverse events (>6 months postoperative) associated with DBS (adopted, updated and added to from Koy et al., 2019, pp.1114-1115)
- Table 7 (Results): Mean pre- and postoperative BFMDRS scores of the registry cohort, listed separately according to group
- Table 8 (Results): T-test comparison of mean pre- and postoperative BFMDRS scores, classified according to aetiology
- Table 9 (Results): T-test comparison of preoperative and postoperative BFMDRS scores classified according to preoperative cMRI findings as well as preoperative presence/absence of orthopaedic deformities

Erklärung zur guten wissenschaftlichen Praxis

Ich erkläre hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten (Amtliche Mitteilung der Universität zu Köln AM 132/2020) der Universität zu Köln gelesen habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Hannover, den 19.01.2025

Unterschrift: .....

Zusatz

Im Rahmen des in deutscher Sprache formulierten Anteils meiner Doktorarbeit bemühte ich mich, eine geschlechtersensible und inklusive Sprache zu benutzen. Ich entschied mich in Situationen, in denen die Formulierung genderneutraler Personenbezeichnungen nicht möglich war, für die Benutzung des Gender-Sternchens, wie es offiziell von der Antidiskriminierungsstelle des Bundes sowie der Medizinischen Fakultät der Universität zu Köln empfohlen wird (Stand 01/2025).

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For the children of the GEPESTIM cohort and their caregivers.

Table of Contents

List of Abbreviations

AE/AEs	Adverse Event/Adverse Events
AM	Alleviating Manoeuvre/s
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
BMI	Body Mass Index
BoNT/BT	Botulinum Toxin
BoNT-A	Botulinum Toxin Type A
CCT/cCT	Cranial Computed Tomography
CMRI/cMRI	Cranial Magnetic Resonance Imaging
cMRT	Magnetresonanztomographie des Schädels
CP	Cerebral Palsy
CNS	Central Nervous System
DBS	Deep Brain Stimulation
DCP	Dyskinetic Cerebral Palsy
DRD	Dopa-Responsive Dystonia
e.g.	Exempli gratia
FDA	Food and Drug Administration
GPi	Internal Globus Pallidus/Globus Pallidus Pars Interna
GPe	External Globus Pallidus/Globus Pallidus Pars Externa
IMSB	Institut für Medizinische Statistik und Bioinformatik
IPG	Implanted Pulse Generator, Implantable Pulse Generator
IV	Intravenous
i.e.	Id est
LAE/LAEs	Long-term Adverse Event/Long-term Adverse Events
MRSA	Methicillin-resistant Staphylococcus Aureus
NBIA	Neurodegeneration with Brain Iron Accumulation
NIBS	Non-Invasive Brain Stimulation
PKAN	Pantothenate Kinase-Associated Neurodegeneration
PNS	Peripheral Nervous System
PVP	Posteroventral Pallidotomy
p./pp.	Page/Pages
SAE/SAEs	Short-term Adverse Event/Short-term Adverse Events
STN	Subthalamic Nucleus
THS	Tiefe Hirnstimulation
VIM	Ventral Intermediate Nucleus of the Thalamus
VOA	Ventral Oral Anterior Nucleus of the Thalamus
VTA	Volume of Tissue Activation/ Volume of Tissue Activated
z. B.	Zum Beispiel

1. Summary

1.1. Summary in German (Zusammenfassung in deutscher Sprache)

Hintergrund: Die sorgfältige Auswahl der pädiatrischen Dystonie-Patient*innen ist von entscheidender Bedeutung für den Behandlungserfolg mit Tiefer Hirnstimulation (THS). Die Genotypisierung von Dystonien und umfassende Diagnostik helfen Patient*innen und Ärzt*innen bei der Entscheidungsfindung, da sie nützliche Prädiktoren für das Ergebnis der THS liefern[2,3]. Kinder und Jugendliche mit monogenetisch vererbter, isolierter Dystonie sprechen besser auf die THS an als pädiatrische Patient*innen, die unter anderen Formen der Dystonie leiden[2,4,5]. In einigen Studien werden mögliche Einflussfaktoren auf das Therapieansprechen nach THS-Implantation bei Dystonie diskutiert. Ein junges Implantationsalter und eine kürzere Symptomdauer zum Zeitpunkt der Operation gelten als etablierte Prädiktoren für bessere postoperative klinische Ergebnisse bei Dystonie im Erwachsenenalter[2,4,6-11]. Neben genetischen, phänotypischen und zeitlichen Merkmalen spielen der Schweregrad der Dystonie und assoziierte Komorbiditäten wie fixierte orthopädische Deformitäten eine Rolle für die Erfolgschancen der THS[2,8]. Nach wie vor fehlt in der Literatur eine systematische, ausführliche Zusammenstellung und Analyse von präoperativ quanti- und qualifizierbaren Prädiktoren, die, wenn sie bei der Indikationsstellung der THS berücksichtigt werden, den größtmöglichen individuellen THS-Erfolg bei pädiatrischen Patient*innen mit Dystonie ermöglichen.

Zielsetzungen: Ziel dieser Arbeit war es, in einer großen Multicenterkohorte Dystonie-Patient*innen, die eine THS bis zum 18. Lebensjahr erhalten haben, im Kurz- und Langzeitverlauf systematisch zu charakterisieren und potenzielle Faktoren, die das Therapieansprechen beeinflussen, zu identifizieren. Wir quantifizierten die Therapieeffekte anhand der Schwere der Dystonie mit Hilfe der Burke-Fahn-Marsden Dystoniebewertungsskala (BFMDRS) sowie an Effekten auf die körperliche Entwicklung der Kinder anhand von Gewichts- und Längenwachstum sowie an der Anzahl der postoperativen Medikamente. Durch die Identifizierung von Prädiktoren für das Therapieansprechen wird die Patientenselektion und Beratung der betroffenen Familien verbessert.

Methoden: Die Analyse basierte auf einem retrospektiven, beobachtendem Studiendesign. Zur Identifizierung und Neubewertung der klinischen Faktoren und potenziellen Prädiktoren nutzten wir die Online-Datenbank des multizentrischen GEPESTIM-Registers (DRKS-Nummer: 00006778). Zur Erstellung und Verwaltung dieser Datenbank setzten wir die sichere Webanwendung „REDCap“ ein. In die Datenbank des GEPESTIM-Registers werden regelmäßig neue Informationen und Daten aus präoperativen Assessments, OP-Protokollen, Nachuntersuchungen, Arztbriefen im Allgemeinen und weiteren Informationsquellen eingebettet. Die Patient*innen wurden auf der Grundlage der von Albanese et al. vorgeschlagenen aktuellen internationalen Dystonie-Klassifikation in drei Gruppen eingeteilt[1]. Grundsätzlich werden isolierte Dystonien von kombinierten Dystonien, bei denen zusätzliche Bewegungsstörungen wie ein Myoklonus oder Parkinsonismus vorliegen, unterschieden[1]. Gruppe 1 bildeten die isolierten vererbten und idiopathischen Dystonien, Gruppe 2 bestand aus Patient*innen mit kombinierter vererbter und idiopathischer Dystonie und Gruppe 3 inkludierte Patient*innen mit erworbener Dystonie.

Die klinische Bewertung der Bewegungsstörung der Patient*innen wurde jeweils präoperativ und nach Implantation des THS-Systems durchgeführt. Die postoperativen klinischen Ergebnisse wurden in drei Follow-up-Intervallen zusammengefasst: „Follow-up 1“ (null bis sechs Monate postoperativ), „Follow-up 2“ (ein Jahr +/- sechs Monate bis zwei Jahre +/- sechs Monate postoperativ) und „Follow-up 3“ (drei Jahre +/- sechs Monate bis sechs Jahre +/- sechs Monate postoperativ). Es wurde untersucht, ob und inwiefern die präoperativ bekannten Kriterien Geschlecht, Alter bei Erstmanifestation der Dystonie in Jahren, Implantationsalter in Jahren und Krankheitsdauer zum Zeitpunkt der Operation in Jahren mit dem kurz-, mittel- und langfristigen Ergebnis, quantifiziert mithilfe der prä- und postoperativ ermittelten individuellen BFMDRS-Punktezahl, korrelierten.

Ergebnisse: Elf THS-Zentren aus Deutschland und Österreich stellten Daten von 89 Patient*innen zur Verfügung, die sich zwischen 1998 und 2020 im Alter von drei bis 18 Jahren einer THS-Implantation unterzogen (Stand 01.01.2023). In unserer Kohorte von 53 männlichen und 36 weiblichen Proband*innen wurden 29 Patient*innen in Gruppe 1 (isolierte vererbte und idiopathische Dystonie), 29 Patient*innen in Gruppe 2 (kombinierte vererbte und idiopathische Dystonie) und 31 Patient*innen in Gruppe 3 (erworbene Dystonie) eingeteilt. In der Gruppe der Patient*innen mit isolierter vererbter oder idiopathischer Dystonie kam für jede Nachuntersuchung bis zu vier Jahren postoperativ eine signifikante Verbesserung der mittleren BFMDRS-Werte im Vergleich zu den präoperativen Ausgangswerten zur Darstellung, wohingegen in der zweiten Gruppe (kombinierte vererbte und idiopathische Dystonie) nur eine leichte Verbesserung der durchschnittlichen BFMDRS-Werte nach THS-Implantation festgestellt werden konnte; dieser positive Trend erreichte keine statistische Signifikanz. Für die Gruppe der erworbenen Dystonien konnte im zweiten Follow-up, also ein bis zwei Jahre +/- sechs Monate postoperativ, im Durchschnitt eine statistisch signifikante Verbesserung der Dystonie gezeigt werden, während in den anderen Nachuntersuchungen nur eine geringe, nicht signifikante Verbesserung der BFMDRS-Werte festgestellt werden konnte.

Insgesamt betrug die durchschnittliche Reduktion der Anzahl der verordneten Medikamente, die zur direkten Behandlung der Bewegungsstörung sowie zur Behandlung der nicht-motorischen Symptome der Dystonie eingenommen wurden mindestens ein Medikament, meistens jedoch mehr als ein Medikament. Die Analyse der Daten zeigt außerdem einen überwiegend positiven Einfluss der THS auf die körperliche Entwicklung der Patient*innen, respektive auf den alters- und geschlechtsspezifischen Body Mass Index (BMI) an. So haben sich von 15 Patient*innen, die vor der Operation als untergewichtig oder extrem untergewichtig eingestuft worden sind, zehn Patient*innen (= 66,7 %) in einem, zwei oder allen der Follow-ups 1, 2 und 3 im Vergleich zu präoperativ einem gesundheitsförderlichen BMI angenähert. Darüber hinaus erwiesen sich ein möglichst junges Implantationsalter und eine möglichst kurze Krankheitsdauer vor THS-OP als signifikante unabhängige Prädiktoren für eine prozentuale Verbesserung in der BFMDR-Skala in unserer Regressionsanalyse, allerdings gilt dies nur für die Gruppe der isolierten Dystonien und konnte lediglich im kurz- und mittelfristigen Follow-up dargestellt werden. Im Gegensatz dazu war die relative postoperative Verbesserung der BFMDRS in Follow-up 2 umso größer, je älter die Patient*innen der kombinierten Dystonie-Gruppe in unserer Kohorte bei der THS-Operation waren.

Diskussion: Patient*innen mit isolierter kongenitaler und idiopathischer Dystonie zeigten im Vergleich zu Patient*innen mit kombinierter oder erworbener Dystonie in allen Follow-ups die größte postoperative Verbesserung der Bewegungsstörung. Im Vergleich zu den Ergebnissen bereits publizierter Studien, in denen der postoperative Effekt der THS bei kombinierter und erworbener Dystonie untersucht wurde, konnten wir in unserer Kohorte in diesen Gruppen eine ähnlich geringe und weitgehend nicht signifikante mittlere postoperative Reduktion der BFMDRS-Punktezahl, sprich Verbesserung der Dystonie, feststellen[9,12,13]. Ein Grund, warum in der Gruppe der erworbenen Dystonie sowie der kombinierten angeborenen und idiopathischen Dystonie ein geringerer Effekt auf den Dystonie-Schweregrad festgestellt werden konnte, kann damit zusammenhängen, dass gerade in diesen Gruppen die Prävalenz von präoperativ diagnostizierten fixierten Kontrakturen oder orthopädischen Deformitäten deutlich höher war als in der Gruppe der isolierten angeborenen und idiopathischen Dystonie.

Die Verwendung einer validierten Dystonie-Schweregradskala wie der BFMDRS zur Beurteilung des THS-Effekts liefert objektive Ergebnisse in Bezug auf die postoperative Verbesserung der Dystonie. Patient*innen und ihre Kontaktpersonen haben jedoch über die Verbesserung der Dystonie hinaus weitere Erwartungen an die THS, zum Beispiel in Bezug auf Veränderungen in ihrem täglichen Leben. Die signifikante durchschnittliche Verringerung der für die direkte Behandlung der Dystonie sowie der indirekten Folgen der Mobilitätseinschränkung verschriebenen Medikamente beeinflusst die Zufriedenheit und Lebensqualität der THS-Patient*innen und ihrer Angehörigen[14-16]. Die Tatsache, dass die durchschnittliche Anzahl der täglich eingenommenen Medikamente nach der Operation reduziert werden konnte, kann als Erfolg der pallidalen THS gewertet werden.

Untergewicht im Kindesalter ist eine der Hauptursachen für die weltweite Krankheitsbelastung und stellt nach wie vor einen ernsthaften Risikofaktor für den Erwerb einer Immunschwäche dar, die zu schweren Verläufen von Infektionskrankheiten führen kann[17]. Aus diesem Grund ist es erfreulich, dass die Patient*innen der GEPESTIM-Kohorte nach THS-Implantation im Durchschnitt eine gesundheitsförderliche Verbesserung ihres alters- und geschlechtsspezifischen BMI erfuhren. Zu den möglichen Mechanismen, die eine Gewichtsveränderung bei Dystonie-Patient*innen nach einer THS-Implantation erklären, gehört die Reduktion der intermittierenden oder anhaltenden Muskelkontraktionen, die zu einer Abnahme des Energieverbrauchs führt[18,19].

Die Ergebnisse des GEPESTIM-Registers unterstützen den Einsatz der pallidalen THS zur Therapie der isolierten vererbten und idiopathischen Dystonie und zweifellos insbesondere der DYT-TOR1A Dystonie im Kindes- und Jugendalter. Da die Ergebnisse nach einer pallidalen THS bei pädiatrischen Patient*innen mit erworbener oder kombinierter Dystonie viel variabler sind, ist es bei der individuellen Beurteilung, ob eine THS-Operation indiziert ist, umso wichtiger, die Prädiktoren für ein gutes Ansprechen auf die THS zu kennen. Die THS als Behandlungsoption der Dystonie sollte in Erwägung gezogen werden, bevor die oft progredient verlaufende Bewegungsstörung gesundheitliche Folgeschäden, wie z. B. fixierte Kontrakturen oder skelettale Deformitäten, verursacht hat, und bevor das Zeitfenster für die Entwicklung der Neuroplastizität verpasst wurde[20].

Die Krankheitsdauer vor THS-Implantation und das Alter bei Implantation scheinen für die Gruppe der kombinierten und erworbenen Dystonien keine geeigneten präoperativen Faktoren darzustellen, die ein besseres Ansprechen auf die THS vorhersagen. Infolgedessen sollte eine THS nicht bei jedem Kind mit diagnostizierter Dystonie frühzeitig in Betracht gezogen werden, da eine kurze Krankheitsdauer vor der Implantation nur in der Gruppe der isolierten Dystonie zu einem maximalen postoperativen Nutzen und in der Gruppe der erworbenen Dystonie zu einem kurzfristigen maximalen postoperativen Nutzen führte. Aus Studien zur THS bei erwachsenen Patient*innen mit Dystonie ist bekannt, dass das präoperative Vorhandensein von Kontrakturen oder Skoliose infolge einer langen Krankheitsdauer zu den Prädiktoren für ein unzureichendes THS-Ergebnis gehört[8]. In einer anderen Studie konnte gezeigt werden, dass Patient*innen mit Atrophien oder Läsionen in einem Netzwerk von assoziativen, senso- und visuomotorischen Hirnarealen eine gestörte Netzwerkarchitektur und infolgedessen ein unzureichendes THS-Outcome aufwiesen[21]. Daran anknüpfend konnte im Rahmen der GEPESTIM-Studie gezeigt werden, dass bei pädiatrischen Patient*innen wichtige Prädiktoren für das Ansprechen auf die THS ein präoperatives cMRT ohne strukturelle Auffälligkeiten, wie z.B. strukturelle Läsionen in den Basalganglien, sowie das Fehlen oder die bestmögliche Vorbehandlung orthopädischer Deformitäten und Kontrakturen vor der Operation sind. Aufgrund der Komplexität der Dystonie und der großen Anzahl von Variablen, die für den letztendlichen Erfolg der THS eine Rolle zu spielen scheinen, kann es schwierig sein, rückblickend und im Detail zu bewerten, warum postoperative THS-Ergebnisse individuell variieren. Die Genauigkeit der Elektrodenplatzierung in den "Sweet Spot" hat einen wesentlichen Einfluss auf den Grad der klinischen Verbesserung nach einer THS-Operation[22-24]. Auch wenn es validierte Einschluss- und Ausschlusskriterien für die THS bei Dystonie gibt[25], ist es notwendig, nach den Grundsätzen der personalisierten Medizin zu handeln. Die Indikation für eine THS muss unter Abwägung des individuellen Nutzen-Risiko-Verhältnisses geprüft werden, die Sicherheit und das Wohlbefinden der Patient*innen sollte bei der Indikationsstellung im Vordergrund stehen. Mit Hilfe des GEPESTIM-Registers war es möglich, die Auswirkungen und Faktoren, die eine Verbesserung nach pallidaler THS vorhersagen, in einer großen pädiatrischen Kohorte zu bewerten und so valide Informationen zur Verbesserung der Behandlung dieser Patient*innen zu erhalten. In Zukunft müssen die gesammelten Daten durch eine noch größere Anzahl von Patient*innen bestätigt werden.

Fazit: Die THS stellt eine wirksame Behandlungsoption für medikamentenrefraktäre Dystonien im Kindes- und Jugendalter dar. Jüngere Patient*innen mit kürzerer Krankheitsdauer vor Implantation und höherem Alter bei Krankheitsbeginn, die eine isolierte angeborene oder idiopathische Dystonie haben, profitieren am meisten von der pallidalen THS. Basierend auf unseren Ergebnissen gilt diese These nicht uneingeschränkt für die Gruppe der kombinierten angeborenen und idiopathischen und erworbenen Dystonien. Daher spielt eine gute klinische Phäno- und Genotypisierung eine wichtige Rolle bei der Patientenselektion. Weitere multizentrische Studien sind notwendig, um die mittel- und langfristige Rolle der pallidalen THS, sowie den Einfluss von neurophysiologischen/ Netzwerk-Biomarkern und Erkenntnissen aus der "Sweet Spot"-Analyse als Prädiktoren für die Behandlungseffektivität im Therapiemanagement der Dystonie zu bestimmen.

1.2. Abstract

Background: Diligent patient selection is of key importance for the treatment success with deep brain stimulation (DBS). Previous studies suggest that a shorter duration of dystonia and a young implantation age may improve the prospects of DBS success[2,4,6-11]. Children with inherited, isolated dystonia without nervous system pathology and fixed contractures seem to respond better to DBS than patients with other forms of dystonia or patients with structural lesions/neurodegeneration detected in pre-surgery cranial magnetic resonance imaging (cMRI) or patients with diagnoses of orthopaedic deformations[2,26]. However, little data are available beyond these populations.

Objectives: We aim to gain a better understanding as to which patients with dystonia will most benefit from DBS. We measure individual outcomes not only by quantifying motor improvement with the help of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) but also by taking into account the child's physical development and the question whether and to which extent it was possible to reduce medication postoperatively. In the present study, we sought to identify and re-evaluate clinical factors that might predict the initial, medium-term and long-term responses as well as the maintenance of the benefits over time in paediatric patients undergoing DBS due to various aetiologies and subgroups of dystonia.

Methods: For the identification and re-evaluation of these clinical factors, we used the steadily growing online database of the multicentre GEPESTIM registry, which is constantly fed with new information on paediatric DBS. Patients were divided into three groups based on the current international dystonia classification proposed by Albanese et al.: group 1 – isolated inherited and idiopathic dystonia, group 2 – combined inherited and idiopathic dystonia, and group 3 – acquired dystonia[1]. Clinical evaluation was performed preoperatively, and the postoperative clinical results were summarised in 3 follow-up intervals: follow-up 1 (short-term), follow-up 2 (medium-term) and follow-up 3 (long-term). A multiple linear regression model was used to evaluate whether preoperatively known criteria of sex, age at onset of dystonia, age at implantation and duration of disease at the time of surgery were related to short-term, medium-term, and long-term outcomes.

Results: Eleven DBS centres from Germany and Austria provided data on 89 patients between the ages of three and 18 years who underwent DBS in the years from 1998 to 2020. In our cohort of 53 male and 36 female subjects, 29 patients were classified into group 1, 29 patients into group 2 and 31 patients into group 3. The group of isolated inherited and idiopathic dystonia showed a significant improvement in the mean BFMDRS values compared to preoperative baseline scores in every follow-up until 4 years after surgery, whereas group 2 showed only mild improvement of BFMDRS values after DBS. For the acquired dystonia cohort, a statistically significant improvement could be displayed in follow-up 2, whereas in the other follow-ups only a minor, non-significant improvement of the BFMDRS values could be detected. In total, mean reduction of pharmaceutical substances prescribed for direct treatment of the movement disorder as well as for non-motor symptoms amounted to 1.5 in short-term follow-up and 1.4 in medium-term and long-term follow-up. DBS also has a statistically significant influence on the physical development of the patients, more precisely, on the age- and gender-specific BMI. Furthermore,

age at implantation turned out to be a significant independent predictor of percentage improvement in our regression analysis for the group of patients with isolated dystonia in short-term and medium-term follow-ups. Additionally, in group 1, years of life lived with dystonia before the implantation of DBS correlated negatively with the clinical outcome expressed by the change of the BFMDRS percentage at all follow-ups. Moreover, important predictors of patient response to pallidal DBS are a preoperative cerebral MRI without any structural abnormalities, such as structural lesions in the basal ganglia, and the absence of orthopaedic deformities before surgery.

Discussion: Our results support the use of pallidal DBS in the treatment of isolated inherited and idiopathic dystonia in childhood. Since outcomes following pallidal DBS in paediatric patients with acquired or combined inherited and idiopathic dystonia are much more variable, within these patient cohorts, it is even more pivotal to know the predictors of good DBS response when individually assessing whether DBS surgery is indicated.

Novel findings of this registry-based analysis are that years of life lived with dystonia before implantation and age at implantation do not seem to serve as preoperative factors aimed at predicting a better response to DBS for the combined inherited and idiopathic dystonia as well as for the acquired dystonia group. As a result, DBS might not be considered early in every patient diagnosed with dystonia since short disease duration before implantation only led to maximised benefits in the group of isolated dystonia, and short-term maximised benefits in the group of acquired dystonia. Invasive neuromodulation for dystonia management should be performed before the often progressive clinical course of dystonia has caused consequential health damage, for example fixed contractures or skeletal deformities[20]. The accuracy of electrode placement is considered a key determinant of clinical improvement following DBS surgery[23]. By locating reliable 'sweet spots' and using them as implant sites, the efficiency of DBS can be increased, and computer-guided DBS programming might provide optimal stimulation settings[27].

Even if selection criteria for DBS procedures exist[25], it is necessary to act according to the principles of personalised medicine. The indication for DBS needs to be considered individually with weighing up the risk to benefit ratio, and the patient’s safety and comfort should always be given priority in the individual decision on the optimal time for DBS implantation. In the future, the collected data need to be confirmed by an even greater number of patients.

Conclusion: DBS can be an efficacious treatment option for medication-refractory childhood-onset dystonia. Younger patients with shorter disease duration and late age at onset suffering from isolated inherited and idiopathic dystonia fare best after pallidal DBS. Based on our results, this thesis does not necessarily hold for the group of combined inherited and idiopathic as well as for the group of acquired dystonia. Hence, good clinical pheno- and genotyping plays an important role in patient selection. Further multicentre studies are essential to determine the medium- and long-term role of pallidal DBS as well as the impact of neurophysiological/network biomarkers and findings from probabilistic 'sweet spot' analysis as predictors of treatment efficacy in the therapy management of dystonia.

2. Introduction

2.1. Dystonia – Definition and Overview

Dystonia is a heterogeneous group of disorders which often start during early childhood and are characterised by involuntary intermittent or sustained muscle contraction causing abnormal postures, repetitive and twisting movements, or both[1,28,29]. Dystonic movements are caused by co-contraction of agonist and antagonist muscles and can manifest not only as abnormal postures but also as slow writhing movements or as dystonic tremor[30,31]. Dystonic postures and postural changes can be mobile, tonic, fixed, or any combination[1].

Dystonia is categorised as a hypertonic movement disorder[1,29]. It is a clinically and aetiologically manifold condition that occurs as an isolated symptom, in combination with other movement disorders, or in association with other neurological or non-neurological symptoms[32]. Isolated dystonia describes phenotypes in which dystonia is the only neurological symptom[1]. When dystonia manifests with other movement disorders, it is defined as combined dystonia[1,33]. In combined dystonia, e.g. spasticity, myoclonus, or dyskinesia, can be present[1,34]. Recently, dystonia has also been categorised as complex dystonia, which means that dystonia occurs as a motor feature in combination with non-neurological symptoms, such as liver insufficiency or dermatological features[34]. Regarding the evaluations of the GEPESTIM study, however, I only distinguished between isolated and combined dystonia.

Dystonia can lead to severe disablement with irreversible fixed muscular contractures and skeletal deformations[35]. Severe dystonia can lead to status dystonicus – a life-threatening condition with high mortality[36]. Dystonia is the third most common movement disorder after essential tremor and Parkinson's disease among adults considerably affecting the quality of life and ability to work[37,38].

2.1.1. Historical Background

Since the first descriptions of dystonia and dystonia syndromes, which can be dated back to the late 19th century, there has been a continuous debate about the nosological classification and aetiology of dystonia syndromes[39]. As early as 1897, the Spanish neurologist Barraquer-Roviralta described a patient who presented to him with a clinical symptomatology which would be retrospectively classified as generalised dystonia[40,41]. Back then, he described the clinical picture as 'athetosis'[40,41]. His static photographs remain compelling visual documents of a disorder that was poorly understood at the time and could not be classified pathophysiologically[41].

Furthermore, in 1908, the Berlin-based neurologist Markus Walter Schwalbe, as part of his dissertation, reported on a family that seemed to be affected by dystonia[29,39]. At the time, Schwalbe described this family as suffering from odd tonic contractions with hysterical symptoms[29,42,43]. Presumably, it was assumed quite early that the disease might have a genetic component, whereas Mr Schwalbe surmised a psychiatric cause due to the anomalous and hysterical symptoms he had observed[39]. According to the Italian professor and renowned expert on movement disorders Alberto Albanese, the first reports of the medical term 'dystonia' date back to 1911[1]. Apparently, the term 'dystonia' originates from Hermann Oppenheim, who was a neurologist from Berlin (1858–1919)[1]. In 1911, he documented the previously

unknown syndrome and described it as ‘dystonia musculorum deformans’ (Oppenheim, 1911, p. 1090)[44]. He described a peculiar spasmodic disease of infancy and adolescence, which he observed in four unrelated Jewish children and could not assign to any other movement disorder[44,45].
In 1975, the first international conference on dystonia was held in New York[46]. After information on dystonia has been put together on an international level, it turned out that dystonia phenotype included not only severe generalised forms but also slowly progressive focal and segmental cases with onset in adulthood such as blepharospasm, torticollis and writer's cramp[1]. As early as 30 years ago, it had become evident that as varied as clinical presentation and aetiology of dystonia appeared to be, the respective treatment options were just as heterogeneous[1].

Yet, treatment options for dystonia are often limited[35]. Dystonia is oftentimes refractory to enterally or parenterally administered drugs, especially on the long-term, and unwanted side effects are common[35]. Thus, symptomatic surgical options, e.g. intrathecal insertion of baclofen, and neuromodulation interventions, such as DBS, have been increasingly applied in patients with dystonia[47,48]. In 1996, bilateral DBS to the globus pallidus internus (GPi) was performed for the first time on a child with DYT-TOR1A dystonia, thus marking the inception of paediatric DBS applications in the management of dystonia[20,49,50]. The surgery was performed in Montpellier, France[20,49]. This case subsequently led to the publication of the first paediatric case series documenting successful dystonia management with DBS by Philippe Coubes et al[49,51]. Ten years ago, the multicentre GEPESTIM registry was founded in Germany[35]. The registry was established with the aim of systematically analysing the clinical outcomes of paediatric patients undergoing DBS and thus facilitating the counselling of patients and their families with regard to DBS[35]. According to Newby et al., “we are still in a period of ‘living history’ of dystonia with much yet to be understood about pathophysiology [and treatment options]” (Newby et al., 2017, p. 478)[46], and so the GEPESTIM database and findings evolving from the registry have been growing to date. A more detailed background on the history of dystonia is provided in Chapter 7.3. in the Appendix.

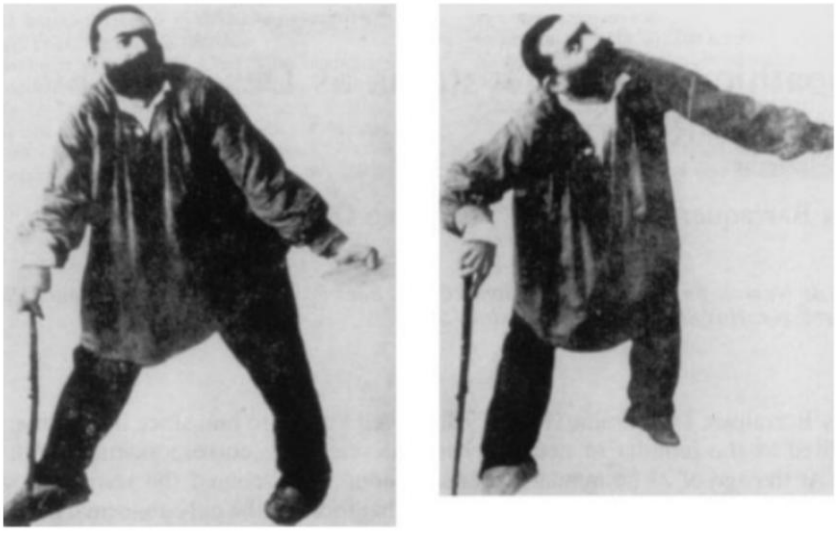


Figure 1 (Introduction): *Historical photographs taken by the Spanish neurologist Barraquer-Roviralta in 1897 showing a clinical case of generalised dystonia, although Barraquer-Roviralta used the term 'athetosis' (adopted and modified from Goetz & Vilensky, 2006, p.1562)[41].*

2.1.2. Epidemiology

Up until today, there is insufficient data on the epidemiology of dystonia[52]. In a meta-analysis that incorporated data from nine different studies examining the prevalence of dystonia in European clinics and hospitals, the prevalence of dystonia for primary, i.e. inherited, dystonia was estimated to be 16.4/100,000[52]. In addition, an overall prevalence of focal and segmental dystonia was described as 15.36 per 100,000[52]. For cervical dystonia, Steeves et al. calculated an overall prevalence of 4.98 per 100,000[52]. According to Lauritsch, the prevalence of isolated infantile or juvenile forms of dystonia varies in different studies between 0.2 and 5 per 100,000 inhabitants[39].

Dyskinetic cerebral palsy (DCP) is the most common cause of acquired dystonia in children and has a total incidence of 15–25 per 100 000 in Western countries[12,53,54]. Infantile cerebral palsy (CP) has a prevalence of 2 to 3 per 1,000 live births; 6–15% of patients with CP develop a dyskinetic movement disorder which manifests in early childhood[12,54,55].

Although the terminology and prevalence thresholds for defining rare diseases vary from country to country and organisation to organisation, the term 'rare disease' is commonly used when the prevalence is less than 40–50 cases/100,000 inhabitants[56]. According to the usually applied definition of a rare disease, dystonia can accordingly be classified as such. Yet, what is crucial to consider is the fact that dystonia is believed to be underdiagnosed or misdiagnosed due to its broad clinical spectrum and the difficult differentiation from other movement disorders, especially for non-specialists[57].

2.1.3. Pathophysiology

To date, the pathophysiological basis of dystonia is only understood incompletely[39]. In literature, multiple concepts about aetiopathogenesis of dystonia can be found – corresponding to the complexity of the neuroanatomy and neurophysiology of the human central nervous system (CNS). In the last 35 years, important neurophysiological abnormalities that explain the development of dystonia have been identified[58,59].

Crucial and well-established pathophysiological concepts regarding aetiopathogenesis of dystonia are:

- Loss of inhibitory control on several levels of the CNS, in particular within the motor basal ganglia-cortex circuitry[58,60,61]
- Impairment of sensorimotor integration[58,60]
- Changes in synaptic plasticity[39,58,60]

In combination, these mechanisms contribute to an impairment of the gating function of the basal nuclei resulting in inadequate suppression of overshooting activity and excessive activation of cortex areas[60,62].

In a strictly anatomical sense, the basal ganglia are defined as the nuclei listed below that are located in the white matter of the encephalon:

- Striatum, which is composed of caudate nucleus and putamen, and
- Pallidum (globus pallidus externus and internus, GPe and GPi)[63],
- Nucleus subthalamicus (STN) and substantia nigra (SN).

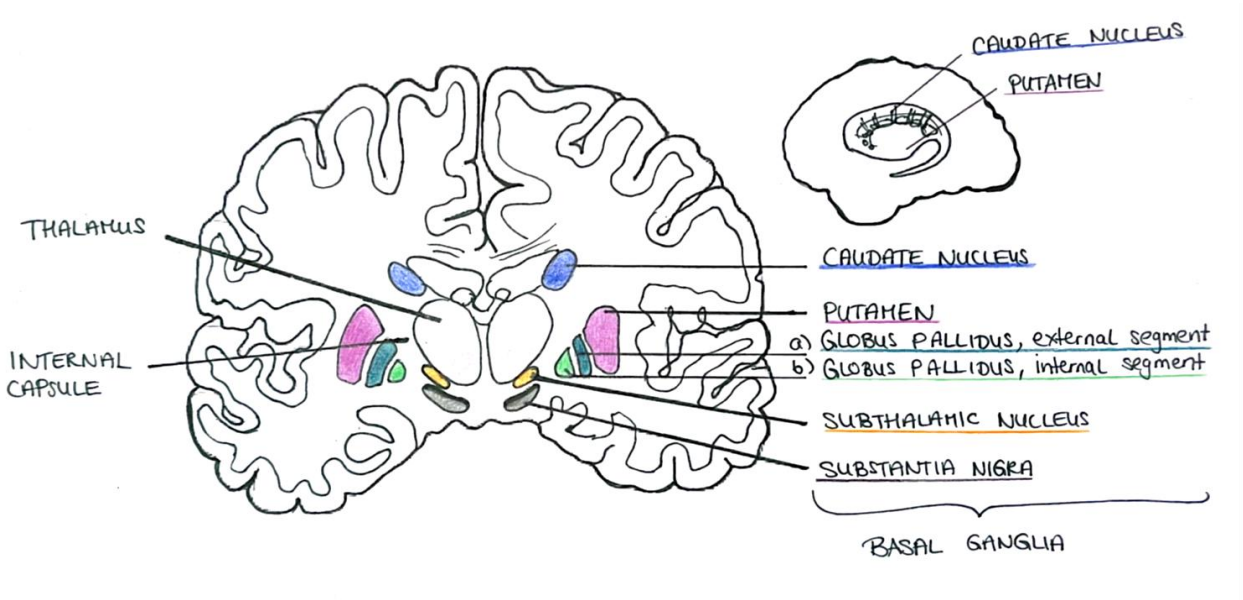


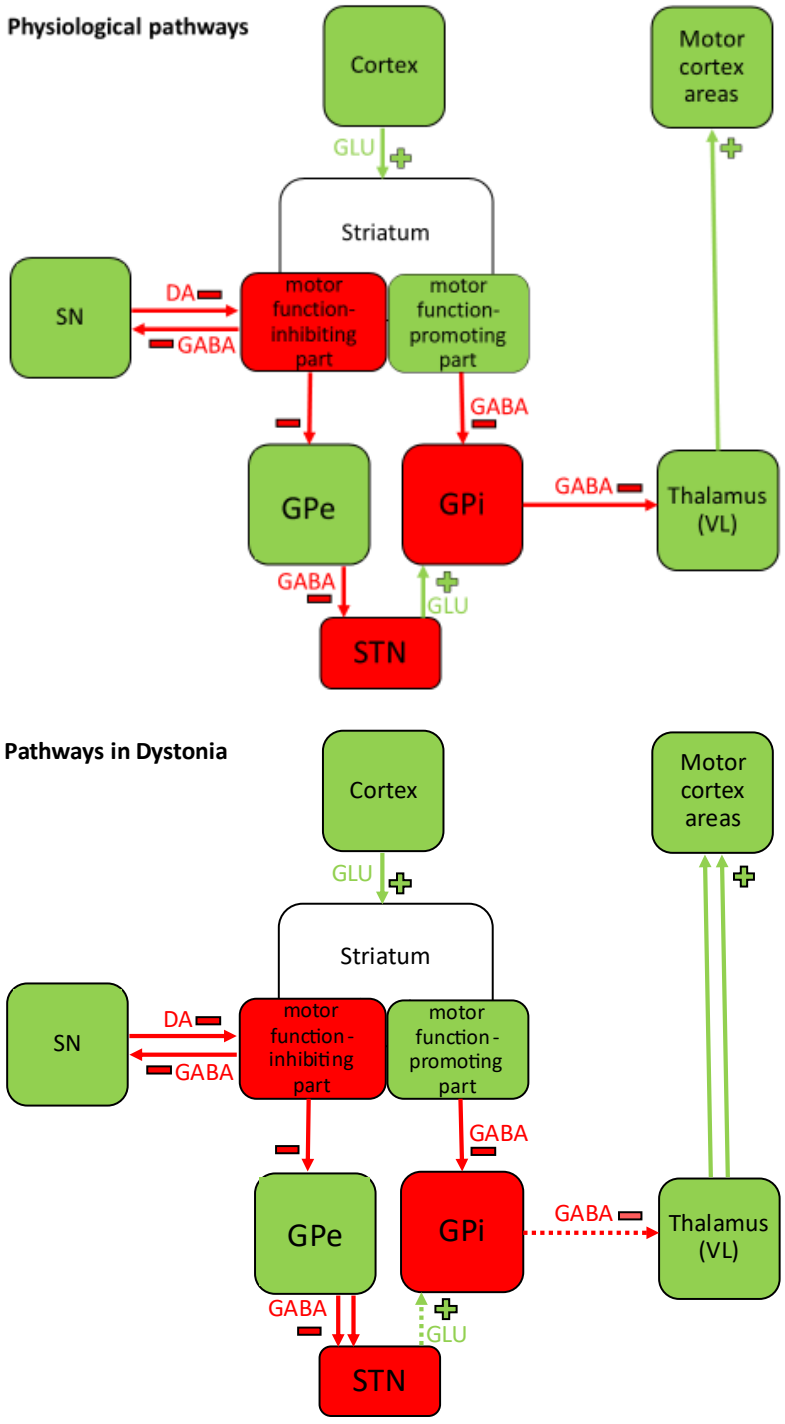
Figure 2 (Introduction): *The basal ganglia and surrounding structures, coronal section (adopted and modified from Van Kan, year n/a)*[64]

The basal ganglia play an essential role in the regulation of motor function[63]. They obtain stimuli from all areas of the cerebral cortex and connect this input through relays in the thalamic nuclei to prefrontal, premotor and motor areas of cerebral cortex[64]. In their interaction, the basal nuclei are responsible for the fine tuning of all movement impulses[63]. Those impulses are designed in the association cortex and either executed in the agonistic and antagonistic muscles or suppressed by the basal ganglia according to the situation[63]. The most important task of the basal ganglia is thus to control the degree, direction, force, and speed of a movement[63].

The aetiopathogenesis of dystonia is based on a dysfunction of the basal ganglia, or rather a disbalance of the basal ganglia-thalamocortical circuitry[65]. Within the basal ganglia-thalamocortical circuitry there are two essential pathways that balance each other under physiological conditions[39]. The direct pathway promotes desired movements by mediating inhibition of the movement-inhibiting GPi via the motor-promoting part of the striatum[63]. Neuronal inhibition is the diminution of activity of a neuron by another neuron in neuronal networks[66]. Disinhibition refers to an activating process through the removal or inhibition of an inhibition[67]. If the inhibition emanating from the GPi is inhibited by a part of the striatum that promotes motor activity, this results in disinhibition, so the effect is stimulating or movement-promoting[63]. Hence, disinhibition of the ventral anterolateral nucleus of the thalamus originating in the striatum and GPi leads to increased thalamocortical excitation[63]. In contrast, the inhibitory indirect pathway blocks unwanted movements, such as the movement of antagonistically working muscles[39]. By inhibiting the GPe through the motor inhibitory part of the striatum, the STN is inhibited more strongly, which in turn leads to increased activity of the GPi and thus increased inhibition of the thalamus; in other words, inhibition of motion[68]. In dystonia, the balance between the direct and indirect pathway and, hence, the balance within the basal ganglia – thalamus – cortex circuitry is distorted, all of which leads to a surplus

of muscle activity[65]. It is not yet fully understood whether this imbalance is (co)caused by a relative overactivity of the direct pathway or a relative underactivity of the indirect pathway, or both[39].

The objectifiable, pathologically reduced neuronal activity in the GPi in dystonia leads to a reduced inhibition of the excitatory neurons of the thalamus, thus to an excitation of the thalamic neurons that exceeds the normal level[69]. This results in increased thalamo-cortical excitation and the development of hyperkinetic/hypertonic movement disorders[69]. Figure 3 shows the basal ganglia-thalamocortical circuitry in a very simplified way in healthy individuals and in patients with dystonia.



Legend:
- and + indicate whether the corresponding projections are of inhibitory or excitatory nature, with inhibitory pathways highlighted in red and excitatory pathways in green. Boxes highlighted in red represent a motor-inhibitory centre, boxes highlighted in green represent a motor-enhancing centre.
Abbreviations:
DA = dopamine, GPe = external globus pallidus, GABA = gamma-aminobutyric acid, GLU = glutamate, GPi = internal globus pallidus, SN = substantia nigra, STN = subthalamic nucleus, VL = ventral lateral nucleus of

Figure 3 (Introduction): *Simplified schematic illustration of physiological connectivity patterns of the basal ganglia (top diagram) and pathological alterations in the direct and indirect pathway in dystonia (bottom diagram), illustrated together with the involved transmitters (adopted and modified from Trepel, 2015, p.209)[63]*

A closer look at the complex system of the basal ganglia circuits reveals that various neurotransmitters are necessary for the functioning of the circuits. Thus, as early as 1987, it was suspected that certain forms of dystonia may result from modifications of the dopaminergic/ noradrenergic balance within the basal ganglia circuits[70]. This hypothesis is supported by the fact that the activity of dopamine beta-hydroxylase, an enzyme that catalyses the conversion of dopamine to noradrenaline, is often increased in patients with a specific form of torsional dystonia[70]. Relative noradrenaline hyperactivity may either be caused by increased release of noradrenaline or, as occurs in drug-induced dystonia, dopaminergic blockade[70]. Other studies emphasise the role of dopamine imbalances within the basal ganglia circuitry leading to dystonia[71,72]. The role of dopamine within the basal ganglia pathways consists of regulating the balance between the two striato-pallidal pathways by modulating the cortico-striatal synapses[71]. This process allows the selection of specific action-adopted routines, e.g. to navigate activation of agonist muscles (direct pathway) while inhibiting their antagonists (indirect pathway) when performing a movement[71]. Failure of this mechanism leads to two hallmarks of dystonia: muscular co-contractions and overshooting of muscle activity. According to Ribot et al., there is evidence for the causal role of reduced dopamine levels in the pathophysiology of dystonia pattern, such as rigidity or severe bradykinesia, both leading to fixed dystonic postures[71]. There are many mechanisms that influence the dopaminergic system and are involved in the pathophysiology of dystonia such as complete loss of dopamine transporter activity in the basal nuclei, alterations in postsynaptic dopaminergic expression, overactivity of specific ion channels and modifications in adenylyl cyclase function or DNA synthesis[71,72].

Pathophysiology of dystonia cannot be exclusively explained by the presence of pathological imbalances in the motor system. An abnormal integration of sensory information is associated with the occurrence of dystonic symptoms[73]. Hence, the brain response to somatosensory input may be abnormal in dystonia[73]. Aberrant sensorimotor processing and integration may involve dysfunction within the cortex, cerebellum, and basal ganglia, or their inter-connections as part of the sensorimotor network[74]. Distorted perception of afferent information and its abnormal integration with motor commands may be partly responsible for the development of overshooting and voluntary dystonic movements, though patients with dystonia usually do not present with obvious sensory deficits[74]. For example, the presence of an alleviating manoeuvre (AM) in patients with cervical dystonia suggests that alterations in sensorimotor integration can lead to dystonia[60,75]. Some patients with dystonia adopt a variety of AM or 'gestes antagonistes', such as a light touch of the cheek, to correct the dystonic posture or stop the abnormal movement[75]. AM produce a combination of tactile and proprioceptive sensory feedback from the body region chiefly affected by dystonia and may involve visual, auditory or thermal stimuli[76]. AM seem to improve dystonic muscle contraction and the efficiency of voluntary movements[76]. This suggests that AM have a broad influence at the premotor control stage[76]. AM can be observed in other disorders affecting the CNS as well, and abnormalities in the sensorimotor system may therefore not be causative but rather a consequence of dystonic muscle activity[60]. Although the development of neuronal processes

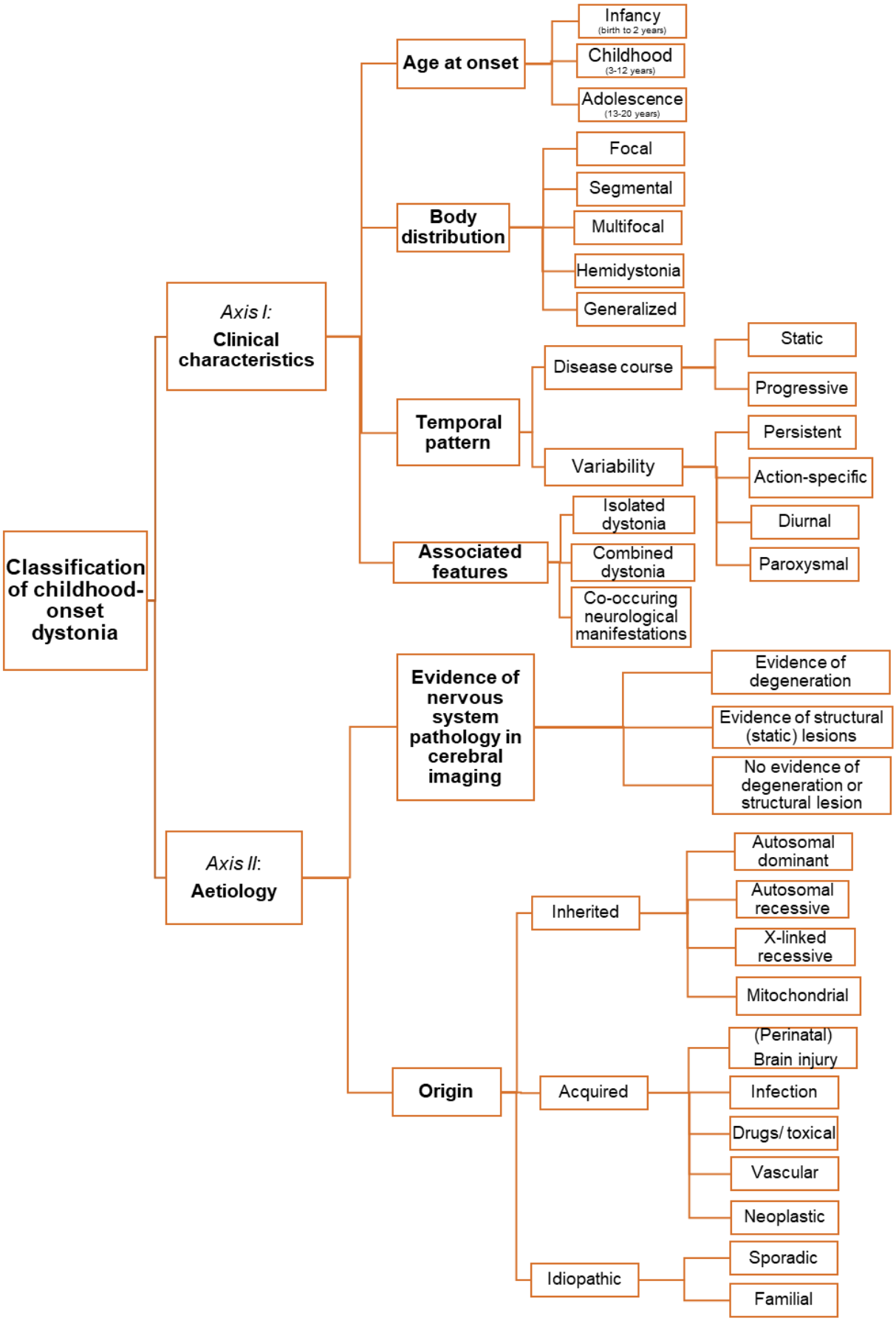
underlying sensorimotor integration is not completely understood, it is believed to involve activity-dependent modelling and refining of sensorimotor circuits through processes that are already taking place in utero and which continue through infancy, childhood and into adolescence[77].

Another important aspect contributing to the pathophysiology of dystonia is the maladaptive neuronal plasticity in the sensorimotor cortex[39,58]. The term 'neuroplasticity' describes the dynamic physiological ability of the CNS to undergo structural and functional change in response to experience and to adapt after damages have occurred[74]. These experience-driven alterations are mediated by a multitude of mechanisms, including apoptosis, neurogenesis, synaptogenesis and synaptic pruning[74]. Thus, neuroplasticity creates the foundation for learning processes[39]. Two main forms of neuroplasticity are defined – homeostatic and Hebbian – and both play a key role in the maturation of the nervous system[74]. Homeostatic mechanisms regulate both the number and the strength of synapses and serve to adapt neuronal firing in response to changes in postsynaptic activity[74]. Hebbian mechanisms include synaptic strength changes which are caused by long-term potentiation or depression following high frequency or prolonged, patterned presynaptic stimulation[74]. Neuronal plasticity has been suspected to be altered in dystonia based on the observation that task-specific dystonia occurred in patients during highly skilled repetitive movements[78]. Evidence from animal models of dystonia and from patients has revealed significant “alterations of synaptic plasticity characterised by a disruption of homeostatic plasticity, with a prevailing facilitation of synaptic potentiation, together with the loss of synaptic inhibitory processes” (Quartarone & Hallett, 2013, p.1)[58]. Quartarone and Hallett suggested that during motor learning, abnormal plasticity may lead to an abnormal sensorimotor integration, leading to consolidation of abnormal motor patterns as observed in dystonia[58]. Data published by Sadnicka and Hamada failed to confirm the thesis that excessive neuronal plasticity leads to dystonic symptoms manifestation[79]. The scientists were able to quantify neuroplasticity in patients with dystonia by using non-invasive brain stimulation (NIBS) techniques and by taking a mean measure of the motor evoked potential before and after the session[79]. Sadnicka and Hamada concluded that “as a fundamental mechanism within the brain, synaptic plasticity will never be irrelevant to the mechanism, manifestation, or treatment of dystonia” (Sadnicka & Hamada, 2020, p.1615)[79]. However, the researchers were unable to confirm the hypothesis that neuronal plasticity is excessive in dystonia because a high variability of response to NIBS techniques among patients and healthy subjects made a distinct interpretation of the results impossible[79].

2.1.4. Classification

Albanese et al. classify dystonia along two axes[1]. The first axis comprises clinical characteristics, including age at onset, temporal pattern, body distribution and associated features (neurological features or additional movement disorders); the second axis includes aetiology with respect to nervous system pathology (measured by findings in the cMRI or cCT) and inheritance[1]. With regard to the second axis, a distinction is drawn between inherited (autosomal dominant, autosomal recessive, x-linked recessive, mitochondrial), acquired (perinatal brain injury, infection, neoplastic, etc.) and idiopathic (sporadic, familial) forms of dystonia[1].

Figure 4 (Introduction): *Classification of childhood-onset dystonia (adopted and modified from Albanese et al., 2013, p. 868)*[1]



2.1.5. Aetiology

With the development of next generation sequencing (NGS) techniques, the field of genetics of dystonia has rapidly expanded in recent years[80-82]. Chiefly, whole-exome sequencing coupled with bioinformatics analysis and detailed phenotyping of mutation carriers has made it much easier to arrive at a genetic diagnosis, especially in heterogeneous disorders[83]. In the past three decades, more than 200 genes have been linked to different, mainly childhood-onset generalised forms of dystonia[81-83]. In addition, in the 'Online Mendelian Inheritance in Man' (OMIM) database multiple rare genetic traits that can demonstrate dystonia as part of their phenotypic spectrum have been published[83]. The most common aetiological forms of dystonia and those that are represented in the GEPESTIM cohort will be introduced below.

The mutations in TOR1A are the most common causes for inherited dystonia in childhood and adolesce[39]. The first symptoms of DYT-TOR1A dystonia typically appear between the ages of eight and twelve[39,84]. Initially, patients usually present with focal symptoms, and often one of the lower extremities is affected[85]. Within a few years, the symptoms can spread to the whole body and therefore become generalised; dystonia is usually chronic-progressive[39,81]. In over 70%, a genetic alteration caused by the deletion of a GAG base pair on chromosome 9q34 in the TOR1A gene leads to DYT-TOR1A dystonia[81,86]. The TOR1A gene encodes an ATP-binding protein that has been named torsin A[39,87]. TOR1A dystonia follows an autosomal dominant pattern of inheritance with a penetrance rate of approximately 30% but variable expressivity[81,86]. This means that the disease, the phenotype, will be clinically manifest in only about one third of the mutation carriers. The patients in whom the disease manifests present with different degrees of disease severity, with some patients developing only mild, focal dystonia symptoms[81]. After a longer period of illness and in an advanced stage of the disease, other patients with DYT-TOR1A dystonia, or with many forms of inherited dystonia in general, develop skeletal deformities, which, as also seen in patients participating in the GEPESTIM study, can lead to less functionality and immobility[39].

DYT-THAP1 dystonia is another isolated dystonia syndrome clinically characterised by an age of onset in late childhood, with symptoms that frequently start in craniocervical muscles and tend to spread to adjacent body regions[88]. In DYT-THAP1 dystonia, laryngeal dystonia that causes speech difficulties is particularly common[88]. It usually presents with dysphonia or writer's cramp in late childhood or adolescence[82]. About 100 missense, nonsense and frameshift mutations in the THAP1 gene encoding the transcription factor THAP1 cause this type of dystonia with mixed phenotype[82,89-91].

Furthermore, multiple syndromes in which dystonia co-occurs with another movement disorder such as myoclonus or parkinsonism (combined dystonia) have a distinct genetic origin. For example, more than 100 different heterozygous mutations in the GCH1 gene (GTP cyclohydrolase 1), which encodes the rate-limiting enzyme in the biosynthesis of dopamine via the biopterin pathway, are a cause of childhood-onset dopa-responsive dystonia (DRD) with diurnal fluctuation (DYT-GCH1 dystonia)[82,92]. Because DRD

subjects may also exhibit parkinsonism that begins simultaneously to or after dystonia onset, it is considered a combined form of dystonia[93].
Apart from the group of monogenetic isolated or combined dystonia, the subgroup composed of different neurometabolic, or neurodegenerative, disorders leading to dystonia should also be mentioned here. This subgroup encompasses diseases such as DYT-ATP7B (Wilson disease), NBIA/DYT/PARKa-PLA2G6 or PLA2G6-associated neurodegeneration (PLAN), NBIA/DYT-PANK2 or pantothenate kinase-associated neurodegeneration (PKAN), Lesch-Nyhan syndrome and glutaric aciduria type 1 that are all inherited in an autosomal recessive or x-linked recessive (X-chromosomal) fashion[1,34]. Indeed, multiple metabolic disorders can be allocated to this category[34]. Overall, a large proportion of the autosomal and X-linked recessively inherited dystonia syndromes are mostly classified as complex or combined dystonia, whereas forms of isolated dystonia with a known genetic causality are usually inherited in an autosomal dominant fashion[34].

The genetic locus symbols (e.g. DYT1) have been used as synonyms for the respective phenotype such as 'DYT-1 dystonia' or the underlying genetic origin (mutation in the DYT1 gene) for a long time. This nomenclature, however, is not recommended by the official HUGO Gene Nomenclature Committee[82]. Therefore, a new genetic classification and nomenclature scheme based on the gene mutations which have been confirmed as a genetic cause of dystonia has been proposed[94]. According to the Committee's recommendations, the phenotype prefix 'DYT' for dystonia is followed by the gene name. In the case of DYT1/DYT6/DYT28 dystonia, the disease designations would, for example, be replaced by DYT-TOR1A/DYT-GCH1/DYT-KMT2B dystonia, respectively[82,94].

CP is the most common reason for severe physical impairment in infancy[12,47]. Infantile CP describes a group of persistent disorders of the development of movement and posture revolving from foetal or early childhood damage to the immature, developing brain[95,96]. Patients with CP show varying degrees of motor dysfunction, and movement malfunction is usually accompanied by disturbances of perception, sensation, cognition, communication, and behaviour[95,96]. DCP is the second most frequent type of cerebral palsy after spastic forms[47]. DCP is usually caused by non-progressive lesions to the thalamus or basal ganglia, or both[47]. Injuries to the basal ganglia due to hypoxic-ischaemic damage in the perinatal or infantile period lead to abnormal postures or movements associated with impaired tone regulation or movement coordination[47,97]. Causes of CP and consequently acquired dystonia include kernicterus, infections, strokes, autoimmune disorders, tumours, trauma, cerebral malformations, and neurodegenerative pathologies[1,98]. Acquired dystonia usually presents together with other motor and non-motor (cognitive, language, behavioural) impairments[99]. Therefore, acquired dystonia is most often referred to as combined dystonia and rarely manifests as isolated dystonia[99]. In DCP, two major movement disorders, dystonia and choreoathetosis, are present together in most cases[47,100].

The term 'idiopathic dystonia' basically means that the disease has an unknown cause or aetiology[1]. Idiopathic dystonia may occur sporadically or familial[1]. This implies that idiopathic forms can be categorised as inherited if new dystonia genes are identified[1]. In our study cohort, patients whose dystonia was formerly classified as idiopathic were reclassified into both the acquired and inherited dystonia categories after new information could be obtained. For instance, some patients were reclassified into acquired dystonia category by reviewing postnatal medical reports or brain imagery.

Table 1 (Introduction): *Inherited dystonia variants in which dystonia is the only feature (isolated dystonia) or combined with differing motor symptoms or non-motor symptoms (complex dystonia) (adopted and modified from Ip et al., 2021, p. 12-13)*[101]

Name of Dystonia	Characteristics	Inheritance
Isolated dystonia		
DYT-TOR1A	Typically presents in childhood or adolescence[102,101]. Dystonic muscle contractions leading to abnormal posture or irregular tremor of a leg (or arm) are the most common first symptoms[102]. Dystonia is typically first apparent with specific actions such as walking or writing. In the progress of the disease, the contractions frequently (but not invariably) occur with less specific actions and spread to other body regions (generalised dystonia)[102].	Autosomal dominant
DYT-THAP1	Torsion dystonia with onset in adolescence or early adulthood. Segmental or generalised Dystonia, symptoms frequently involve the craniocervical region[88]. Presents often with prominent (spasmodic) dysphonia[88].	Autosomal dominant
DYT-ANO3	Mostly focal (cervical) or segmental dystonia that manifests in childhood and adulthood[103]. Cervical dystonia is the most common site of onset followed by laryngeal dystonia. Often presence of tremor[103].	Autosomal dominant
DYT-GNAL	Adult-onset dystonia, which mostly manifests focally and segmentally, motor symptoms are rarely generalised[104]. Dystonia usually begins in the cervical spine area and commonly spreads to the cranial region (oromandibular/jaw, larynx, eyelids) and/or to one arm[104].	Autosomal dominant
DYT-VPS16	Adolescence-onset focal/segmental dystonia that manifests oromandibularly, cervically, bulbarly, or in the upper limb[105]. It usually shows slow progression to generalised dystonia[105]. A subset of patients may have neurocognitive impairment, including mild intellectual disability or psychiatric manifestations[105].	Autosomal dominant (Autosomal recessive[106])
Complex dystonia		
DYT-KMT2B	Complex childhood-onset (mean age 7 years) dystonia characterised by a progressive disease course evolving from lower-limb focal dystonia into generalised dystonia with prominent cervical, cranial, and laryngeal involvement[107]. Intellectual disability and developmental delay are commonly reported[107]. Additional findings include skin changes, psychiatric comorbidities, myoclonus, seizures, spasticity, and sensorineural hearing loss when larger deletions of DNA segments exist[107].	Autosomal dominant

Table 2 (Introduction): *Inherited varieties of dystonia in which dystonia is a prominent and consistent feature (combined dystonia) (adopted and modified from Ip et al., 2021, p. 12-13)*[101]

Name of Dystonia	Characteristics	Inheritance
Combined dystonia		
DYT/PARK-GCH1	Generalised dystonia with diurnal fluctuation of symptoms, and a very good therapeutic response to L-dopa[108]. The clinical spectrum can range from subtle neurologic symptoms (e.g. abnormal writing tests) to orthopedic signs (e.g. pes equinovarus)[108]. Parkinsonism and psychiatric manifestations possible[108].	Autosomal dominant
DYT/PARK-TH	Dopa-responsive childhood-onset dystonia with additional clinical signs such as developmental delay, axial hypotonia, autonomic dysfunction, spasticity[101].	Autosomal recessive
DYT/PARK-SPR	Dopa-responsive childhood-onset dystonia with possible additional hyperreflexia, axial hypotonia, developmental delay and autonomic dysfunctions[55,109].	Autosomal recessive
DYT/PARK-ATP1A3	Rapid-onset dystonia-parkinsonism characterised by abrupt onset of asymmetric dystonia and parkinsonism[110]. Manifests usually in young adulthood, often after a trigger such as physical overexertion, trauma, heat, or fever[110].	Autosomal dominant
DYT/PARK-TAF1	Childhood- and adulthood-onset dystonia-parkinsonism[111]. Homogeneous disorder introduced by a founder effect in the Filipino population[111]. Spasmodic eye blinking may be first symptom, movement disorder tends to generalise[111].	X-linked recessive
DYT/PARK-PRKRA	Dystonia-parkinsonism syndrome that manifests in adolescence. First symptom commonly begin in the lower limbs, movement disorder tends to generalise[101].	Autosomal recessive
DYT/MYOC-SGCE	Childhood- and adolescence-onset (onset in first or second decade) myoclonus-dystonia[112]. The movement disorder is characterised by myoclonic jerks affecting rather proximal muscles[113,114]. Dystonic symptoms such as torticollis or writer's cramp are observed in most patients[114]. Symptoms often respond to alcohol[113]. Patients may also have psychiatric abnormalities[114].	Autosomal dominant
DYT/MYOC-KCTD17	Childhood- and adolescence-onset (onset in first or second decade) myoclonus-dystonia[115]. Myoclonic jerks affecting the upper limbs regularly present as first symptom[115]. It is a progressive movement disorder, and patients later develop dystonia with predominant involvement of the craniocervical regions and sometimes the trunk and/or lower limbs[115]. Dystonia then dominates the clinical picture[115].	Autosomal dominant

2.1.6. Treatment Options

Symptomatic treatment of childhood-onset dystonia consists of enterally or parenterally applied drugs, botulinum toxin injections, (neuro)surgical approaches such as DBS as well as physical therapy and rehabilitation. When considering treatment options, the question as to how many and which body regions are affected by the movement disorder should be answered. Only then is it possible to decide on the ideal approach to therapy for the individual patient. In segmental or generalised dystonia, systemic pharmacological interventions represent the basic framework of symptomatic dystonia therapy, while BoNT therapy is reserved for the treatment of particularly bothersome focal symptoms[101]. Neurosurgical treatment procedures such as pallidotomy, peripheral denervation surgery, the implantation of intrathecal baclofen pumps and, most importantly, DBS, can be indicated in cases of focal, segmental or generalised dystonia with severe disability that are refractory to conservative treatment[116,117].

Among the group of combined dystonia, only DYT/PARK-GCH1 dystonia is amenable to causal treatment with drugs[101]. This form of dystonia is based on an inherited disorder of the 6-pyrvoyl-tetrahydrobiopterin synthesis, which impairs the dopamine metabolism[81,101,118]. Under lifetime substitution of L-dopa combined with dopa-decarboxylase inhibitors, affected patients can become asymptomatic[101,119]. Since other forms of dystonia than DYT/PARK-GCH1, such as myoclonus dystonia, or symptomatic dystonia may improve through therapy with L-Dopa as well, the current German AWMF guideline for dystonia suggests that an L-dopa treatment trial should be initialized for all forms of childhood- and adolescence-onset dystonia[101].Other drugs indicated for segmental or generalised dystonia are listed in the bar chart below (see Figure 5). Certain drugs are discussed in more detail in the following as I observed that patients of the GEPESTIM study resorted to these drugs particularly frequently.

Trihexyphenidyl is the anticholinergic drug with which most experience has been gained in patients with dystonia[101,120-123]. It is a muscarinic receptor antagonist that acts on receptors to produce an anticholinergic effect[124]. Those receptors are located throughout the body, including the CNS[124]. Rebalancing of cholinergic to dopaminergic inter-neuronal drive in the basal ganglia and associated structures is believed to lead to dystonia reduction[125]. The use of anticholinergic agents such as trihexyphenidyl should be considered in paediatric patients with inherited or idiopathic severe generalised dystonia[101]. Trihexyphenidyl is not recommended for managing certain types of acquired dystonia as it is less effective in reducing dystonia symptoms, improving motor function and easing caregiving in DCP leading to dystonia[124]. Common side effects of trihexyphenidyl are mouth and eye dryness, nausea, confusion, memory loss, hallucinations, constipation, and urinary retention[30]. Yet, children who are immobile and bedridden due to severe dystonic symptoms tend to suffer from constipation, so the use of anticholinergics probably does not increase the children's individual comfort even though it may lead to improvement of the movement disorder.

Figure 5 (Introduction): *Symptomatic treatment of childhood-onset dystonia (content adopted and modified from Richardson et al., 2017[126], Albanese et al., 2011[117] and Prudente et al., 2018[127])*

Drugs	BoNT	(Neuro)surgical interventions	Physical therapy and rehabilitation
•Anticholinergics (e.g. trihexyphenidyl) • Dopaminergic substances (e.g. levodopa) • Antidopaminergic substances or dopamine-depleting drugs (e.g. tetrabenazine) • α-adrenergic agonists (e.g. clonidine) •Muscle relaxants (e.g. cyclobenzaprine) •Benzodiazepines (clonazepam, lorazepam, diazepam) •Non-benzo hypnotics (zolpidem) •Herbal substances (cannabinoids)	•Onabotulinumtoxin A •Abobotulinumtoxin A •Incobotulinumtoxin A •Daxibotulinumtoxin A •Rimabotulinumtoxin B	•DBS (GPi-DBS, STN-DBS, VIM-DBS, VOA-DBS) •Intrathecal baclofen •Pallidotomy (bilateral posteroventral pallidotomy) • Selective peripheral denervation •Myectomy •Myotomy •Radiofrequency lesioning	•Categories of interventional approaches: -Movement practise -Training with constraint - Sensory reorganization - Normalisation of muscle activity with external techniques - Neuromodulation with training -Compensatory strategies

Another group of drugs, particularly used for the treatment of dystonic crisis, will be introduced here to illustrate the narrow ridge between risk and benefit in dystonia therapy. Benzodiazepines act at the benzodiazepine receptor, which is linked to the GABA-A-receptor and potentiates the inhibitory postsynaptic action of GABA[124]. This results in anxiolytic, hypnotic, anticonvulsant, and muscle-relaxing effects[128]. Yet, usage of benzodiazepines is favoured for the acute treatment of status dystonicus or dystonic storms, including those related to acute failure of the baclofen pump or DBS and for short-term management of dystonia[124,129]. Studies have revealed multiple side effects associated with treatment with benzodiazepines. The main side effect is sedation, and in higher doses benzodiazepines depress respiratory drive[30,124,130]. In addition, cognitive and psychomotor impairments can be observed[131]. Titration of benzodiazepines should be done gradually and carefully[124]. Stepwise weaning is essential since sudden withdrawal of benzodiazepines can cause seizures, anxiety and dystonic storms[124]. Thus, the dilemma is that on the one hand the administration of benzodiazepines is a good option to alleviate hyperkinetic symptoms[129]. On the other hand, the use of benzodiazepines entails serious risks in terms of potential side effects and high addiction potential[132]. A high level of patient's adherence and close monitoring of therapy must therefore be ensured. In addition, in many developed countries, such as Germany, several of the above-mentioned drugs do not have a Food and Drug Administration (FDA)-approved indication for dystonia and are used off-label, especially in children. This places an additional

burden on treating physicians (e.g. physicians need more time for drug education, parents are uncertain and sometimes reluctant to consent to the use of the drugs, liability issues)[126].

Especially in focal dystonia, including cranial, cervical and limb dystonia, intramuscular injections with botulinum toxin type A (BoNT-A) is the preferred therapy option[133,134,117,135,136]. Moreover, the recent introduction of BoNT high dose therapy allows to treat more wide-spread dystonia, such as segmental and generalised dystonia[135]. BoNT is a neurotoxin that is isolated and purified from Clostridium botulinum bacteria[137]. It temporarily inhibits the release of acetylcholine at the neuromuscular junction, resulting in a focal chemical denervation at the injection sites[124]. Selective peripheral denervation of the affected muscle group by local injection of BoNT leads to a dose-dependent and temporary paralysis or relaxation of the affected muscle, resulting in symptom relief[39,101]. The effects of the BoNT products typically wear off about three to five months after injection[135]. Hence, the injections must be repeated regularly to maintain stable clinical effects. This may be particularly burdensome for paediatric patients and their caregivers and may present a logistical challenge. According to a Cochrane Review, dysphagia and diffuse muscle weakness/tiredness are the most common BoNT treatment-related AEs[138,139]. Further AEs include dysphagia, ptosis, neck weakness, nausea/vomiting, blurred vision, chewing difficulties, edema, dysarthria, palpitations, and general weakness[140,141]. Nonetheless, AEs of BoNT treatment are transient and usually mild and long-term BoNT application is described to be safe[135,140]. Resistance to BoNT due to the development of antibodies to the toxin may limit therapeutic options in the long term[140,141]. BoNT can easily be combined with further anti-dystonic treatment options such as DBS and intrathecal baclofen application[135]. Best therapy results are obtained when BoNT treatment is integrated in a multimodal and long-term multifaceted concept of dystonia treatment[135].

2.2. Deep Brain Stimulation

DBS has been increasingly applied for the treatment for medication-refractory movement disorders over the last three decades[20,142]. Applying high-frequency electrical stimulation to deep brain structures such as the GPi, chronic disabling movement disorders such as dystonia have become amenable to long-term neuromodulation[20,143].

How does DBS work? Recent studies have suggested that DBS activates the output of the stimulated nuclei[142]. It is assumed that this very regular, time-locked output activated by DBS reduces or abolishes the transmission of pathological bursts and oscillatory activity through the stimulated nuclei, as well as it induces network reorganization and synaptic plasticity[142].

DBS systems consist of one or two intracranial electrode(s), depending on whether unilateral or bilateral implantation was performed, extension wires and a pulse generator[143]. It is a neurosurgical procedure comprised of three sub-steps: the stereotactic implantation of the stimulation electrode(s), the implantation of a pulse generator or 'pacemaker', and their connection[39]. The optimal position of the electrode(s) is calculated preoperatively based on cMRI scans and is verified intraoperatively by electrophysiological recordings and clinical testing[39,144]. Through the guidance of a stereotactic frame allowing

the highest precision of electrode implantation, the electrode(s) is/are placed unilaterally or bilaterally into the target region(s), for instance into the posteroventral part(s) of the GPi[39].
The implantable pulse generator (IPG) is then placed either in upper abdomen, alternatively under the clavicle, and will be connected to the electrode(s) either in the same session or in a second procedure[39].
In paediatric patients, DBS is notably challenging and bears particularities compared to DBS in adult patients[39,144]. During DBS surgery preparation for adult patients, the question whether the surgery should be performed with the patient awake (only mask anaesthesia and IV-sedation) or asleep (general anaesthesia plus intubation) must be answered[144]. Intraoperative test stimulation in the patient being awake is only one of various elements used to determine accurate electrode placement in the target nucleus[144,145]. Particularly in paediatric, anxious, or agitated patients, as well as patients presenting with strong hyperkinetic movements, it is not possible to perform the procedure unless general anaesthesia is applied. Placement of the electrode(s) must then be based on anatomic targeting, e.g. with the help of intraoperative MRI, and neurophysiological target confirmation by intraoperative microelectrode recordings[144,145]. Overall, general anaesthesia DBS is believed to be a safe option; the surgical risks are small[146].

In general, the most feared intra- or perioperative adverse events (AEs) include haemorrhage, infection, and stroke[144]. Two studies based on large paediatric cohorts, reported very low rates of perioperative intracerebral haemorrhage[42,147]. Much more frequently, AEs may develop some time after DBS surgery[39]. Recording to Marks et al., postoperative infection has been the most prevalent complication in the majority of series, with incidence rates of 5%–33%, with higher rates being reported among paediatric patients[144]. Data originating from the german multicentre GEPESTIM registry published in 2019 confirm that a noticeable rate of AEs is associated with DBS in paediatric patients[42]. Albeit, hard-ware-related AEs, closely followed by stimulation-induced AEs, were the most common long-term AEs (LAEs) appearing in almost 30% of the study cohort[42]. The summarised number of peri- and postoperative DBS-related (wound) infections requiring surgical interventions was with n=14 in nine patients (12.5%) lower than, based on the evidence available from earlier published studies, expected[42]. Furthermore, the GEPESTIM registry-analysis from 2019 proved that age at DBS implantation had a relevant impact on the complication rate[42]. Patients aged seven to nine years had the highest rate of AEs per follow-up year, whereas patients aged ten to twelve years had the lowest[42]. Moreover, there is a trend of a higher complication rate in patients aged under six years[42].

DBS has been established as a safe and effective treatment option for some inherited forms of dystonia[48]. DBS, which targets the internal segment of the globus pallidus, subthalamic nucleus or thalamus, has been proven to be a therapeutic option for patients with pharmacorefractory isolated inherited dystonia over the last two decades, especially for patients with DYT-TOR1A and DYT-THAP1. Among other reports, two independent meta-analyses from 2006 and 2018 state that dystonia in children with isolated

inherited dystonia improved by an average of 67.8% (range, 12.5–100%) postoperatively[4] and that patients suffering from isolated inherited dystonia without nervous system pathologies in the preoperative cMRI even showed an average improvement of 78.1% 15 months postoperatively as measured by the BFMDRS motor score[26]. DBS has also been increasingly applied in patients with acquired dystonia, due to a lack of efficacious other treatment options[35]. The effects in patients with acquired dystonia are less prominent and more heterogeneous than those in patients with monogenetic isolated dystonia[53]. Studies suggest that patients with acquired dystonia benefit least from DBS; an average postoperative improvement of 23% in the BFMDRS was described by Koy et al. in a meta-analysis[4,35,148]. In contrast, Elkaim et al. report that in cohorts of CP patients undergoing DBS there was only a 11.1% improvement in BFMDRS, whereas idiopathic dystonia improved by 50.5%[26]. The category of combined dystonia is very heterogeneous and includes various dystonia syndromes concomitant with other movement disorders, making it difficult to summarise the results of DBS in patients with combined (inherited or idiopathic) dystonia. The term 'combined dystonia' is still rare in DBS outcome literature. For instance, Holloway et al. refers to familial myoclonic dystonia, or Huntington's chorea as secondary hereditary dystonia[4]. In their meta-analysis, patients divided into this category showed improvement of 46.5% (range 16.8–91.5%) in BFMDRS motor score[4].

To summarize: Although DBS can be highly effective in some patients, it is increasingly recognised that response to DBS can be variable and difficult to predict[26,35,42]. Paediatric patients with isolated inherited dystonia without nervous system pathology seem to respond better to DBS than those with other forms of dystonia. Little data is available for DBS outcome in paediatric patients beyond the cohort of isolated, inherited dystonia. Analysis of DBS outcome in the comprehensive category of combined dystonia is needed. The reasons for the different DBS-responses have not yet been sufficiently clarified.

However, given the large number of patients suffering from dystonia, the significant burden on the patients and their families, and the potential for DBS to improve their functional status and comfort level, there is a need to identify the best candidates for surgery in all forms of dystonia[149]. In this context, it is immensely important to take into consideration what matters most to paediatric patients and their caregivers. Although dystonia severity reduction measured by movement scores is a highly useful variable to evaluate the effect of DBS, it may, on occasion, fail to adequately reflect what might be most crucial to children and their caregivers in terms of their personal perception of DBS efficacy.
There is limited knowledge about the impact of paediatric DBS on the cognitive functioning of the children, the patients and their families participation in the daily life, medical and nursery care, or on dystonic pain reduction in these patients[150,151]. Within a retrospective case series study, Owen et al. analysed change in global cognitive ability by using standardised measures of intellectual ability and memory in a cohort of 13 children with dystonia undergoing DBS implantation[150]. In all subjects, cognitive profiles were either found to remain stable or cognitive function improved one year before and after DBS implantation[150]. Owen et al. discuss that improvements may be, next to the impact of DBS on non-motor

functioning, attributable to medication reduction made possible by the motor benefits of DBS surgery[150]. In their pilot study on dystonic pain reduction through DBS, based on a cohort of 140 paediatric patients, Perides et al. observed that dystonic pain improved in 90% of the study cohort and in all aetiological subgroups one year after DBS implantation[151]. They noted reduction of pain severity, frequency, and analgesia requirement[151]. According to Perides et al., pain reduction, which is often refractory to pharmacological interventions, can be directly linked to improved quality of life as a goal for paediatric DBS[151].

2.3. Research Questions and Objectives

Diligent patient selection is of key importance for the best DBS treatment results. In the present study, I sought to identify and re-evaluate clinical factors that might predict the short-, medium-term and long-term responses as well as the maintenance of the benefits over time in paediatric patients undergoing DBS due to various aetiologies of dystonia by differentiating between isolated inherited and idiopathic dystonia, combined inherited and idiopathic dystonia as well as acquired dystonia. For the identification and re-evaluation of these clinical factors, I used the expanding online database of the multicentre national GEPESTIM registry, where data of patients with childhood-onset dystonia undergoing DBS up to the age of 18 years is regularly documented.

Previous studies suggest that a shorter duration of dystonia and a young implantation age may improve the prospects of DBS success[6,10,11]. Indeed, timing of DBS surgery is an important issue for the management of dystonia, particularly as dystonia duration may affect the outcome adversely[11]. But should DBS really be considered early in all paediatric patients suffering from dystonia to maximise the benefit, minimise the subsequent orthopaedic dysfunction and deformity and reduce the distressing experience of dystonia in childhood? A satisfactory answer to this question should take into account the risk-benefit ratio of early DBS since most of the data suggest that children undergoing DBS have a higher infection rate compared to adults, especially those patients with acquired forms of dystonia such as cerebral palsy[42,152,153].

My aim is to exemplify that in many cases of dystonia, the sole use of dystonia scores, such as the BFMDRS, may be insufficient to fully evaluate and demonstrate outcome after DBS implantation in certain patient cohorts[154]. Beyond assessing the BFMDRS motor score, I decided to assess other parameters beyond the clinical impairment scales to detect subtle but relevant effects to the patient. I therefore chose to link the effect of DBS to the absolute reduction in medication and to the impact on the children's physical development, including weight regulation.

I hypothesise that:

- Response to pallidal DBS in the treatment of dystonia declines with the years of live lived with dystonia before GPi implantation. Within the different subgroups of dystonia, however, mixed results with regard to this hypothesis are expected.

- Patients without or with only minor orthopaedic deformities as well as patients without pathologies in the basal ganglia or thalamus diagnosed in preoperative cMRI respond best.
- DBS yields benefit for paediatric patients as the number of antidystonic drugs with potential unwanted side effects can be reduced after implantation.
- DBS exerts influence on girls' and boys' physical development. This influence can be objectively quantified by evaluating changes in gender- and age-adjusted BMI over time.

Furthermore, my objective is to gain a better understanding of which patients with dystonia will most benefit from DBS, taking into consideration the principles of personalised medicine as a key to surgical candidate selection. From a medical ethics point of view, the physicians in charge should be able to ensure that paediatric patients likely to benefit are offered the procedure, while invasive and potentially harmful operations in young and vulnerable patients who are unlikely to benefit should be avoided.

3. Material and Methods

3.1. Data Collection and Data Documentation

With permission from the ethics committee of the University of Cologne (13–168), the German DBS centres of Berlin, Düsseldorf, Freiburg, Hanover, Heidelberg, Kiel, Lübeck, Magdeburg, Munich and the Austrian DBS centre of Vienna were contacted. After attaining approval of the local ethics committees and obtaining the written consents of patients and their parents or guardians, all patients who had received DBS up to the age of 18 years due to childhood-onset dystonia in those centres and the DBS centre of Cologne were recruited. From 2014–2021, retrospective data documentation of the pseudonymised patients took place in each centre during an annual on-site visit. Patients' pseudonymised medical histories and statuses were obtained by reviewing medical records supplied by the patients and the cooperating centres.

For the retrospective data collection, a full chart review using a broad data set was performed for each patient. The collected data included demographics such as date of birth, gender, aetiology of dystonia, birth and childhood as well as physical development, age and site of onset of dystonia; clinical characteristics such as course of dystonia over time, psychiatric comorbidities, family and clinical history, other neurological symptoms and diagnoses, genetics if available; pharmacological management and type of school; supportive therapy; details of the surgical procedure; stimulation settings; DBS outcome on dystonia severity assessed by clinical ratings scales and subjective perception; and adverse events. Available clinical information was documented in an online data base programmed by the Research Electronic Data Capture (REDCap) system in cooperation with the Institute of Medical Statistics and Computational Biology (IMSB) of the University of Cologne. Data were documented at various follow-up intervals for each patient, with the last data documented in the clinical chart record before DBS implantation being considered as preoperative and postoperative data being collected in follow-up examinations according to specified time intervals[42]. The time intervals are defined as follows: preoperative assessment, intra- or perioperative assessment including neurosurgical details, 0–3 months postoperative

follow-up, 4–6 months postoperative assessment, 1 year +/- 6 months follow-up, 2 years +/- 6 months follow-up, 3 year +/- 6 months follow-up, 4 years +/- 6 months follow-up, 5 years +/- 6 months follow-up, 7 years +/- 6 months follow-up, 8 years +/- 6 months follow-up, 9 years +/- 6 months follow-up, 10 years +/- 6 months follow-up, 11 years +/- 6 months follow-up, 12 years +/- 6 months follow-up, 13 years +/- 6 months follow-up, 14 years +/- 6 months follow-up and 15 years +/- 6 months postoperative follow-up.

3.2. Surgical and Medical Procedures

DBS surgery was performed following the surgical protocols according to internal standards of the participating centres with intra-cranial electrodes being inserted bilaterally or sometimes unilaterally into the GPi, STN, ventral intermediate nucleus of the thalamus (VIM) and the ventral oral anterior nucleus of the thalamus (VOA) under stereotactic guidance (frame-based or frame-less stereotaxy) or with the help of intraoperative cMRI monitoring. In all cases, the procedure was performed under general anaesthesia, and perioperative antibiotic prophylaxis was administered, e.g. with first, second or third generation cephalosporins or glycopeptides such as vancomycin, depending on the patient's individual risk profile. Generally, the implantation of the electrode(s) and the placement of the pulse generator were carried out in one single session.

3.3. Outcome Measures

Patients were assessed on their regular visits. Clinical evaluation was performed preoperatively, and the postoperative clinical results were summarised in three follow-up intervals: follow-up 1 (short-term follow up) includes data that were collected 0–3 months and 4–6 months postoperatively, follow-up 2 (medium-term follow-up) contains information from the 1 year +/- 6 months examination as well as the 2 year +/- 6 months postoperative follow-up, follow-up 3 (long-term follow-up) comprises data from the 3 years +/- 6 months follow-up up to the clinical presentation of the patient that took place 6 years +/- 6 months postoperatively (see figure 6).

The BFMDRS is a universally applied and reliable impairment scale used to test the severity of dystonia in nine body regions (including the eyes, mouth, speech and swallowing, neck, trunk, arms, and legs)[155,156]. It was initially developed for patients with inherited dystonia and has often been used as the primary outcome measure to allow comparison with published DBS literature[155]. It is a 120-point rating scale that takes into account the severity and frequency of the dystonic movements, with a higher score meaning greater impairment[155]. The scale consists of a movement and disability subscale[155,156]. We only used the movement subscale for our statistical analysis of DBS outcome and predictors of response. If available, pre-, and postoperative videos demonstrating the movement disorder of the patients were rated according to the BFMDRS protocol by experts for movement disorders.

To be able to calculate whether there is a postoperative reduction of drugs for the treatment of dystonia after DBS or not, these drugs needed to be precisely defined. In our analysis, we documented the fol-

lowing drugs for the treatment of dystonia and its direct sequelae such as sleep disturbance and musculoskeletal pain: anticholinergic and dopaminergic drugs, dopamine-depleting drugs, benzodiazepines, sedatives, muscle relaxants, antipsychotics, anticonvulsants, analgesics, regular botulinum toxin injections into at least one muscle. With regard to the administration of drugs like seizure supressing medication, e.g. topiramate, gabapentin, pregabalin, I explicitly researched whether they had been used to treat the movement disorder or a co-existing epilepsy. If patients had no history of epilepsy or epilepsy was not listed as a diagnosis in the medical reports, I included the relevant drugs among those used to treat the movement disorder and its associated symptoms.

To assign the pre- and postoperative BMIs to the age- and gender-specific percentile values, we used the percentile curves from the publication 'Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutschen Stichproben' by Kromeyer-Hauschild et al.[157]. For the exact determination of the percentile position of the children, we utilised an online calculator designed by the paediatrician Dr. Daniel Gräfe that outputs the BMI percentiles after entering the age, sex, weight, and height of the patient[158]. Pursuant to the reference system according to Kromeyer-Hauschild et al. used in Germany to define underweight, overweight and obesity, children and adolescents are classified as underweight if their age- and gender-specific BMI value is below the tenth percentile, whereby this includes cases of severe underweight (below the third percentile). A BMI value above the 90th percentile is considered overweight and one above the 97th percentile is defined as obesity[157,159].

3.4. Statistical Evaluation

The BFMDRS baseline scores were compared with scores at 0–3 months, 4–6 months, 1 year +/- 6 months, 2 years +/- 6 months and then each year up to 15 years +/- 6 months postoperatively using the Wilcoxon paired-rank test for significance. To assess changes over fixed time periods and because there were some missing BFMDRS values, comparisons were also performed by taking the arithmetical mean of two, three or four BFMDRS scores. This means for example: if a 0–3 months-postoperative follow-up BFMDRS score was not recorded but a 4–6-months follow-up BFMDRS value was documented, we used the 4–6 months follow-up value as the counting value for follow-up 1 (short-term follow-up). If both the 0–3 months postoperative BFMDRS score and the BFMDRS score that captured the patient's movement disability status 4–6 months postoperatively were available, the arithmetic mean of the scores was calculated and set as follow-up 1 (short-term) BFMDRS. We continued this method of calculating the average BFMDRS also for the evaluation of follow-up 2 (medium-term follow-up) and follow-up 3 (long-term follow-up) (for further details, see Figure 6).

Results for the BFMDRS are described by percentage change calculated by: $\%\text{change} = \frac{\text{preoperative score} - \text{postoperative score}}{\text{preoperative score}} \text{ x } 100$[154]. Patients were assigned to the 'superior outcome' group or 'moderate outcome' group, depending on whether they showed a motor improvement measured by percentage change in BFMDRS above or below 60%, respectively. When patients had motor improvement below 20% in BFMDRS percentage change but still showed little improvement (>0% improvement in

BFMDRS), they were assigned to the 'insufficient outcome' group. Patients who showed a worsening of postoperative scores compared to the preoperative ones were assigned to the 'deteriorated' group. Quantitative variables were summarised by mean +/- standard deviation and range, qualitative variables by count and percentage. Change over time in quantitative measures was evaluated by the paired t-test, comparison of subgroups was done with the two-sample t-test. A multiple linear regression model was used to evaluate whether preoperative criteria of sex, age at onset of dystonia, age at implantation and duration of disease at the time of surgery were related to short-term, medium-term and long-term outcome (Figure 9). P=<0.05 was considered significant. To create the individual trajectories in Figure 8 (BMI-percentile progressions and trends), we interpolated missing values. All statistical calculations were done with the software SPSS Statistics (Version 23, IBM Corp., Armonk, NY, USA), the descriptive statistics were supplemented by calculations made in Excel.

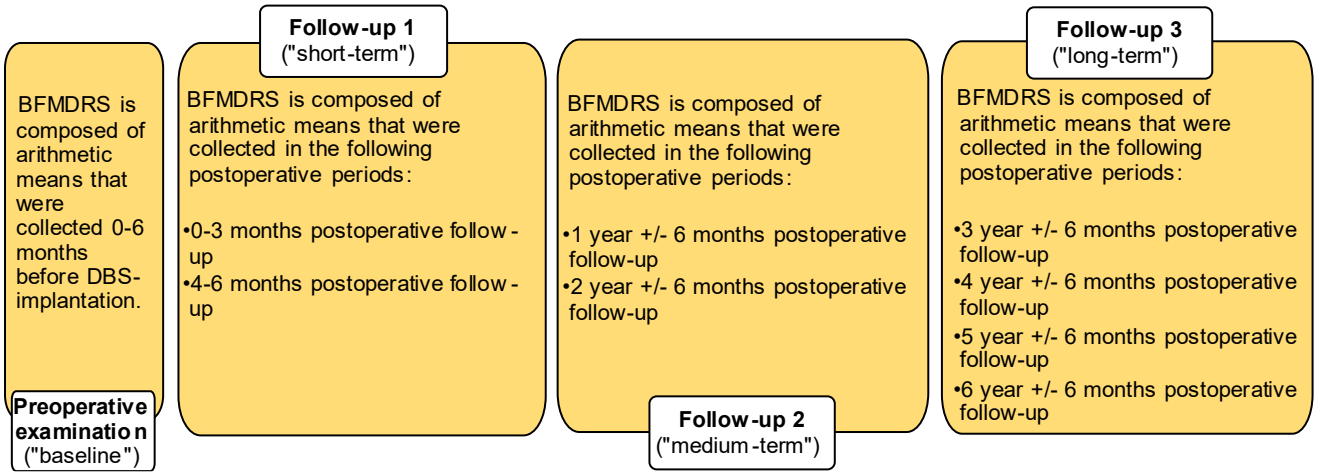


Figure 6 (Methods): *Overview of the different intervals in which BFMDRS scores were assessed and documented, classified as preoperative examination, short-term, medium-term and long-term follow-up*

3.5. 'Sweet Spot' and Functional Network Analysis

As part of a collaboration with scientists from the Charité University Hospital Berlin, 'sweet spot' and functional network analysis was performed on the basis of data from 20 patients from the GEPESTIM study[27]. With the help of the intelligent open-source software 'Lead-DBS' and information on the individual stimulation parameters, plus pre- and postoperative cerebral imaging (MRIs or CTs), the positions of the stimulation electrodes were analysed[27]. First, an average paediatric brain template was implemented and used to localize the DBS-electrodes in patients from the GEPESTIM registry cohort[27]. Then, a paediatric subcortical atlas was employed to highlight the anatomical structures of interest[27]. The next important step was to define the patient-specific 'Volume of Tissue Activated' (VTA) that can be derived from the individual stimulation settings of the patients. The VTA estimates the region activated by electrical stimulation, whereas different estimation approaches exist[160]. In simplified terms and leaving out explanation of further adjustment steps, that have been carried out with the help of Lead DBS and are already integrated in the programme, the VTAs were then normalised to MNI space and weighted with the percentage postoperative improvement of the BFMDRS. Next, the average improvement for each

voxel was calculated. A voxel is a volume element (volumetric pixel) that represents a value in the three-dimensional space[161].

When a statistically significant accumulation of certain VTA localisations that can be linked to excellent postoperative improvements have been identified, these clinically favourable stimulation positions (consisting of voxels with the highest clinical efficacy values) are usually described as 'sweet spots'[23]. In our cohort, every binarized mask of each stimulation volume was weighted by its corresponding improvement in BFMDRS motor score[27].

4. Results

4.1. Demographics, Classification and Aetiology of Dystonia

Eleven DBS centres from Germany and Vienna/Austria provided data on 89 patients who underwent DBS until the age of 18 years between 1998 and 2020. In our cohort of 53 male and 36 female subjects, the mean age of dystonia onset was 3.6 +/- 3.6 years (range, 0–11 years), the mean number of years lived with dystonia before surgery (i.e. duration of disease at time of surgery) was 8.8 +/- 5 years (range, 1–18 years) and the mean age at DBS implantation was 12.2 +/- 3.6 years (range, 3–18 years). 29 patients were classified into group 1 – isolated inherited and idiopathic dystonia, 29 patients into group 2 – combined inherited and idiopathic dystonia, and 31 patients into group 3 – acquired dystonia. Dystonia aetiology within group 1 and group 2 was as follows: 16 patients were diagnosed with DYT-TOR1A dystonia, DYT-KMT2B n=2, DYT-SGCE n=2, DYT-ATP1A3 n=1, DYT-PRKRA n=1 and DYT-ANO3 n=1. Six patients showed mutations in the GNAO1 gene leading to movement disorders; one child with TSEN54 associated pontocerebellar hypoplasia (TSEN54-PCH) type II, three patients with Lesch-Nyhan-Syndrome, and eight patients with inherited forms of Neurodegeneration with Brain Iron Accumulation (NBIA) were included in the registry. Among the group of patients with acquired dystonia, 22 patients experienced perinatal brain injury due to perinatal asphyxia leading to dystonia, three patients had traumatic brain injury during childhood, two patients were diagnosed with infection of the CNS during early childhood, one patient with intracerebral haemorrhage and two patients with kernicterus. 17 patients with generalised dystonia of unknown cause (idiopathic dystonia) were included in the GEPESTIM registry. Generally, data could be documented for up to 5.3 +/- 4.1 years (range, 0.3–15 years) after initial implantation, which implies that an average of seven postoperative follow-up visits per patient could be documented in the data base (within the first year after implantation of the DBS system, the documentation of three follow-ups is intended, afterwards the patients are seen on an annual basis). For further details on demographic data, clinical characteristics, aetiology as well as DBS targets see Table 3 (Results).

4.2. Medication

Based on previous studies, I defined 'minor polypharmacy' as taking two to four antidystonic drugs a day, 'moderate polypharmacy' as taking five drugs daily, and the term 'major polypharmacy' is used for patients taking over five drugs per day[162,163]. Preoperatively, 45 paediatric patients of our cohort took

two to four different drugs prescribed for treatment of the movement disorder per day (minor polypharmacy), whereas nine patients took five drugs daily (moderate polypharmacy). Four patients took at least six drugs per day (major polypharmacy), and for 11 patients data were missing. In the short-term follow-up, there were 20 subjects who can be classified into the minor polypharmacy category, one patient took five drugs a day (moderate polypharmacy) and another patient at least six a day (major polypharmacy). The medium-term follow-up/long-term follow-up revealed that 16 patients/15 patients took two to four drugs a day and none of the subjects took over four drugs daily (missing data for 33 patients in follow-up 2, missing data for 38 patients in follow-up 3).

4.3. Body Mass Indexes (BMI)

Preoperatively, 15 patients (41.7%) were underweight, including 11 patients (30.6%) who were severely underweight. 17 patients (47.2%) had normal weight and four children (11.1%) were overweight with one child (2.8%) having obesity (missing data for 53 patients; percentages refer to the proportion of patients for whom data were available). At short-term/medium-term/long-term follow-up, it was documented that 13 (52%)/13 (44.8%)/12 (44.4%) patients were underweighted, with 8 (32%)/6 (24%)/8 (29.6%) children showing severe underweight. 15 (60%)/12 (48%)/13 (48.2%) patients had normal weight in the first/second/third follow-up, 2 (8%)/4 (13.8%)/2 (7.4%) children were overweight, and 1 child had obesity in each of the follow-ups (4%/3.5%/3.7%; missing data for 64 patients in follow-up 1, 60 patients in the second follow-up and 62 patients in the third follow-up).

Table 3 (Results): *Demographic and clinical data of the registry cohort*

	Total (N=89)	**Group 1:** Isolated dystonia* (N=29)	**Group 2:** Combined dystonia** (N=29)	**Group 3:** Acquired dystonia (N=31)
Gender (male/female)	53 (59.6%)/ 36 (40.5%)	18 (62.1%)/ 11 (37.9%)	16 (55.2%)/ 13 (44.8%)	19 (61.3%)/ 12 (38.7%)
Age at onset (mean age, SD)	3.6 +/- 3.6[a]	5.7 +/- 2.9	3.4 +/- 3.7[b]	1.9 +/- 3.1[c]
Age at implantation of DBS system (mean age, SD)	12.2 +/- 3.6	11.8 +/- 3.5	11.9 +/- 3.8	12.8 +/- 3.6
GPi (unilat./bilat.)	0/86[d]	0/28[e]	0/29[f]	0/29[g]
STN (unilat./bilat.)	1/1	0/1[h]	0/0	1/0[i]
VIM (unilat./bilat.)	0/3	0/1[h]	0/0	0/2[j]
VOA (unilat./bilat.)	0/1	0/1[h]	0/0	0/0
Patients' status (alive/deceased)	87/2[k]	28/1[l]	28/1[m]	31/0
Preoperative cMRI (evidence of degeneration/evidence of structural lesions/no evidence of degeneration or structural lesion)	11 (12.4%)/ 35 (39.3%)/ 43 (48.3%)	1 (3.5%)/ 4 (13.8%)/ 24 (82.8%)	9 (31.0%)/ 6 (20.7%)/ 14 (48.3%)	1 (3.2%)/ 25 (80.7%)/ 5 (16.1%)
Diagnosis of fixed orthopaedic deformities or contractures (yes/none/yes, but condition after tendon surgery or osteotomy)	49 (57.7%)/ 30 (35.3%)/ 6 (7.1%)[n]	13 (44.8%)/ 12 (41.4%)/ 4 (13.8%)	15 (57.7%)/ 10 (38.5%)/ 1 (3.9%)[o]	21 (70.0%)/ 8 (26.7%)/ 1 (3.3%)[p]

Legend:*Isolated inherited and idiopathic dystonia. **Combined inherited and idiopathic dystonia. SD = standard deviation, GPi = internal globus pallidus, STN = subthalamic nucleus, VIM = ventral intermediate nucleus of the thalamus, VOA = ventral oral anterior nucleus of the thalamus. [a]3 patients with missing data. [b]2 patients with missing data. [c]1 patient with missing data. [d]6 patients with 2nd GPi implantation (6 bilateral/0 unilateral) after initial GPi-DBS. [e]1 patient with 2nd GPi implantation bilateral after initial GPi-DBS. [f]3 patients with 2nd GPi implantation (3 bilateral/0 unilateral) after initial GPi-DBS. [g]1 patient with GPi implantation (bilateral) after initial STN implantation (unilateral), 2 patients with 2nd GPi implantation (bilateral) after initial GPi-DBS (bilateral). 1 patient with GPi implantation (bilateral) and VIM-DBS (bilateral, 4 electrodes in total). [h]1 patient with STN and VOA implantation after initial GPi and VIM implantation. [i]1 patient with GPi implantation both-sided after initial STN implantation one-sided. [j]1 patient with GPi and VIM-DBS and 1 patient with 2nd VIM implantation after initial VIM implantation. [k]6 patients are lost to follow up. [l]Cause of death: pulmonary embolism during myofasciotomy. [m]Cause of death: SUDEP/death during epileptic seizure. [n]4 patients with missing data. [o]3 patients with missing data. [p]1 patient with missing data.

4.4. Implantation, Target and Stimulation Parameters

89 patients received a total number of 201 DBS electrodes and 171 IPGs in 194 surgical procedures. In total, 86 patients received bilateral GPi-DBS as first procedure. Thereof, one patient got implanted both into the GPi and VIM, each bilaterally. Six patients needed a second bilateral GPi implantation (revision surgery) after initial both-sided GPi implantation. In one patient, the DBS electrodes were implanted bilaterally into the STN and VOA after initial both-sided GPi and VIM implantation. One patient with both-sided GPi implantation after initially receiving one-sided STN implantation was added to the registry. One patient needed a second (revision) bilateral VIM implantation after receiving both-sided

VIM implantation at first. In our cohort, the IPG was placed in 23 cases (25.8%) infraclavicular right, in 12 cases (13.5%) infraclavicular left, in 25 subjects (28.1%) the generator was placed into the subcutaneous tissue of the left abdomen, and in nine patients (10.1%) the generator was positioned in the right abdomen-area (missing data for 20 patients). 19 IPGs in 18 patients (20.2%) were implanted in a second surgical session a few days after implanting the electrodes (missing data for 13 patients). At initial DBS implantation, 39 patients (43.8%) received a rechargeable IPG, whereas an equal number of patients (43.8%) received a non-rechargeable IPG (missing data for 11 patients).

The registry data unveil a wide spectrum of stimulation parameters used (mean values for voltage in short-term/medium-term/long-term follow-up: 2.4 V [range, 0.6–5.3]/ 2.9 V [range, 1–6.8]/ 3.1 V [0.5–5.9]; frequency: 129.5 Hz [range, 95–180]/ 132.3 Hz [range,60–210]/ 133.1 Hz [range,74–210]; pulse width: 117.6 µs [range, 60–300]/ 126.4 µs [range, 30–300]/ 129 µs [range, 60–420]. On average, 3.6 (range, 2–8) contacts per patient were stimulated in short-term follow-up, 3.8 (range, 2–8) in medium-term follow-up and 3.4 (range, 2–8) in final follow-up (missing stimulation settings for 26 patients in follow-up 1, 27 patients in follow-up 2 and 29 patients in follow-up 3). Stimulator settings were bipolar for 16 patients, of which six patients changed to monopolar settings during postoperative follow-ups. 64 patients initially had monopolar stimulation, of which five patients switched to bipolar stimulation in the course of postoperative monitoring. Four patients changed between monopolar and bipolar settings up to four times during follow-ups (missing data for nine patients).

4.5. Adverse Events

During a median follow-up period of 5.5 years, 21 extension lead revisions in 20 patients (22.5%) and four electrode revisions in four patients (4.5%) were performed in this cohort. Two electrode revisions and one lead extension revision were unilateral procedures only. Extension lead revision within the first six months after DBS implantation (SAE) was necessary in one case because of a wound infection caused by a cable protruding into the wound. Another patient had a foreign body associated infection with seroma and one patient of the cohort needed extension lead revision due to a technical defect of the extension lead.

Long-term adverse events (LAEs) included technical failure of the extension lead in two cases, extension lead fracture/disconnection in four cases and extension lead dislocation/migration in four cases. In two patients, combined reasons from those mentioned above were rationale for extension lead revision. In five patients or six cases, extension lead shortness due to growth and/or malposition of the IPG was present. In one patient, extension lead revision was performed due to loss of effect, in another patient due to combined reasons consisting of discomfort/pain/loss of effect and dystonic crisis. Due to wound or foreign body associated infections, revision of the extension lead had to be performed three times. Revision of the electrodes was required because of dislocation/migration of the electrodes in two patients. In one patient, both DBS electrodes developed a technical defect, which is why they had to be revised.

Furthermore, 77 IPG replacements in 46 patients (51.7%) were performed in this cohort (if the entire DBS system was replaced, then the IPG replacement has not been included in this number). Based on our study cohort, hardware-related AEs can be assigned to the category of LAEs for the most part. In the follow-up period starting over six months after DBS implantation (LAE), 56 IPG replacements in 28 patients (31.5%) were scheduled interventions due to battery failure (generator expired). In four cases (three patients, one patient was affected twice, 3.4%), the IPG was dislocated or misplaced. A technical defect of the IPG leading to IPG replacement occurred 13 times in eleven patients (12.4%). Two IPG hardware revisions were carried out (2.2%), without the reason for this being identifiable (missing information on the indication for IPG replacement). In four patients (4.5%), IPG arrested accidentally, but no operative intervention was needed to service the IPG. Within the first six months after DBS surgery (SAE), IPG removal or replacement (combined with extension lead revision or removal) was urgent in three cases (three patients, 3.4%) because of infection of the subcutaneous pocket where the IPG was inserted, wound infection, or wound healing impairment. Mean implantable pulse generator time to first replacement was 3.3 +/- 1.6 years (range, 0.3–8 years)[10].

On average 2.5 +/- 1.5 years after initial DBS implantation, the DBS System had to be explanted in 13 patients (14.6%); whereby a two-stage procedure was chosen for two patients (2.2%). These patients initially underwent extension lead revision and/or explantation of IPG and received explantation of extension lead and/or electrodes one/four years later. However, reimplantation of the DBS-system took place in five patients (5.6%). Reimplantation of DBS electrodes into the same nucleus as prior to explantation was performed in four patients (4.5%), and in one patient, DBS electrodes were implanted into the VOA and STN both-sided (whereas initially, the GPi and VIM were stimulated both-sided).

The reasons for DBS explantation within the first six months after DBS implantation (SAEs) were foreign body infections in two patients and a severe wound infection that developed into a systemic infection in one patient (in total three patients, 3.4%). In the patient mentioned last, methicillin-resistant staphylococcus aureus (MRSA) was cultured from the wound. Looking at the LAEs, infections were the most common cause leading to explantation of the DBS system. In six cases, the DBS system was explanted due to either wound infection or foreign body associated infection. In two of these patients the infection was localised to the wound and in one patient the wound infection progressed to a systemic infection. In this patient, staphylococcus aureus was identified by wound swab. Four patients had foreign body associated infections (4.5%), including one patient with focal encephalitis (right frontal cerebritis). In one patient with foreign body associated infection leading to DBS explantation, MRSA was detected on the IPG and both electrodes, and cutibacterium acnes was identified in the microbiological analysis of the left electrode. In one patient, a technical failure occurred and led to DBS explantation in addition to infection (a cable was torn out of its connector, leading to disconnection of the DBS system). Furthermore, rationale for DBS explantation were lack or loss of effect in three patients (3.4%), of which one

patient reported stimulation-related pain/headache in addition to loss of effect. Moreover, one patient (1.1%) wished for removal of their IPG and in one patient (1.1%), DBS stimulation was discontinued without intraoperative removal of the DBS system due to loss or lack of effect. Explantation and reimplantation of the DBS system due to electrode fracture was performed once (1.1%). Tables 4, 5 and 6 provide a detailed overview of all documented AEs in the registry cohort, categorised as perioperative, short-term and long-term AEs.

Table 4 (Results): *Perioperative AEs (<1 month postoperative) associated with DBS in paediatric patients (adopted, updated and added to from Koy et al., 2019, p.1114[42]) .*

Perioperative AE	AE/Patient	Intervention
DBS-surgery related AEs:		
Fever[a,f]	5/5	
Stridor after IPG revision[a]	1/1	
Respiratory distress/respiratory infection[a]	2/2	
Pneumonia[a,g]	1/1	
Intracerebral haemorrhage[a,h]	1/1	
Wound complications/infections:		
Reversible		
Impaired wound healing[a]	1/1	
Wound infection[a,i]	1/1	
Seroma[a]	5/5	
Irreversible		
Impaired wound healing	3/3	
Wound dehiscence[b,j]	1/1	Wound revision
Wound infection[b,c,k]	1/1	Intervention 8 weeks after implantation
Foreign body associated infection[b,c,k]	1/1	Intervention 5 weeks after implantation
Other or unspecified[l] AEs:		
Dysarthria[a,d]	1/1	
Paraesthesia/sensory dysfunction[a,l]	2/1	
Agitation[a,l]	1/1	
Vertigo[a,b,c,d,e,m]	2/2	
Seizure[n]	1/1	

Legend: Ongoing AEs are displayed in every time interval during which they were documented. Ongoing AEs were only counted once per time interval when calculating the absolute number of AEs per patient. [a]Reversible. [b]Irreversible. [c]Ongoing. [d]Not stimulation-induced (non-DBS associated disease-related). [e]Stimulation-induced side effect. [f]1 patient with fever after DBS explantation. [g]Associated with anaesthesia, mild respiratory infection before DBS-implantation. [h]Perioperative intracerebral hemorrhage after pallidotomy on the right side and subsequent removal of DBS-system in one session. [i]Wound infection with soft tissue involvement, MRSA detected in microbiological wound sample. [j]Impaired wound healing combined with wound dehiscence, intervention: intraoperative wound revision and closure of the wound with additional sutures. [k]See SAEs in Table 5. [l]Information whether AE is stimulation-induced or not is not available. [m]1 patient with reversible, not stimulation-induced vertigo; 1 patient with ongoing, irreversible and stimulation-induced vertigo, see SAEs in Table 5. [n]Known epilepsy.

Table 5 (Results): *Short-term adverse events (1-6 months postoperative) associated with DBS in paediatric patients (adopted, updated and added to from Koy et al., 2019, pp.1114-1115[42])*

SAE	AE/ Patient	Intervention
Dysarthria[a,e]	5/4	
Increased dystonic posturing[a,e]	6/4	
Increased hyperkinesia[a,e]	4/3	
Fasciculations/spasms[a,e]	1/1	
Reduction of mobility[a,e]	1/1	
Worsening of coordination[a,e]	1/1	
Paraesthesia[a,e]	1/1	
Pain/headache[a,e]	3/2	
Increased weakness[a,d,e,p]	2/2	
Vertigo[b,e]	1/1	Stimulation off[f]
Psychiatric symptoms[b,c,e,m]	1/1	Stimulation off[f]
Wound-related AEs/ infections (all):	13/13	
1. Reversible		
Wound healing impaired[a]	1/1	
Wound infection[a,g]	1/1	
Papilloma[a]	1/1	
Seroma[a]	4/4	
Infection[a,h]	1/1	
2. Irreversible		
Wound infection, wound healing impaired[b,i]	1/1	Extension lead revision and explantation of IPG[j]
Foreign body associated infection[b]	3/3	Explantation of DBS system or extension lead revision and IPG replacement
Foreign body associated infection and Seroma[b]	1/1	Extension lead revision and IPG replacement[k]
Other or unspecified[l] AEs:		
Extension lead technical defect[b]	1/1	Extension lead revision
Lack/loss of effect[b,n]	1/1	
Pain/headache[a]	1/1	
Increased seizure frequency[a,o]	1/1	
Enuresis[a]	1/1	
Weakness[b,c]	1/1	

Legend: Ongoing AEs are displayed in every time interval during which they were documented. Ongoing AEs were only counted once per time interval when calculating the absolute number of AEs per patient. [a]Reversible. [b]Irreversible. [c]Ongoing. [d]Not stimulation-induced (non-DBS associated disease-related) side effect. [e]Stimulation-induced side effect. [f]Intermittent electrode revision was performed later (see electrode dislocation section in Table 6). [g]Wound infection with soft tissue involvement and MRSA detected in microbiological wound sample. [h]Unspecified infection due to missing information, Escherichia coli detected in microbiological wound sample. [i]Caused by a cable protruding into the wound. [j]6 months later explantation of extension lead and electrodes, DBS reimplantation 4 years after explantation, MRSA detected in microbiological wound sample. [k]2 patients received explantation of DBS system, one patient got reimplanted 2 years after initial DBS-implantation, one patient with IPG replacement and lead extension revision and pseudomonas aerugionosa detected in microbiological wound sample. [l]Information whether AE is stimulation-induced or not is missing. [m]Depression. [n]Patient lost to follow-up. [o]Known epilepsy. [p]1 patient with stimulation-induced, reversible increased weakness, 1 patient with not stimulation-induced, reversible increased weakness.

Table 6 (Results): *Long-term adverse events (>6 months postoperative) associated with DBS in paediatric patients (adopted, updated and added to from Koy et al., 2019, pp.1114-1115[42])*

LAE	AE/Patient	Intervention
Not stimulation-induced[d]		
Increased dystonic posturing[a,b,d,f]	11/10	
Increased hyperkinesia[a,d]	1/1	
Pain/headache[a,d]	2/1	
Paraesthesia[a,d]	2/2	
Transient cognitive impairment[a,d]	1/1	
Impaired vision[b,c,x]	1/1	
Vomiting[b]	1/1	
Hip dislocation (one-sided)[a]	1/1	
Stimulation-induced		
Dysarthria/swallowing problems[a,b,h]	10/8	
	1/1	Stimulation off
Increased dystonic posturing[a]	10/10	
Increased hyperkinesia[a]	4/4	
Muscular hypotonia[a], reduction of spontaneous motion[a]	3/1	
Paraesthesia[a]	2/2	
Sleep disorder[a]	2/2	
Pain/ headache[a,b,g]	2/2	
	1/1	Explantation of DBS system
Vertigo[a]	1/1	
Increased seizure frequency[a,i]	1/1	
Psychiatric symptoms[a,j]	1/1	
Wound-related AEs/ infections (all):	14/13	
1. Reversible		
Wound infection[a,k]	1/1	
Systemic infection[a]	3/3	
2. Irreversible		
Wound infection[b,l]	3/3	Explantation of DBS system or extension lead revision and explantation of IPG
Foreign body associated infection[m]	6/5	Extension lead revision and/or IPG replacement and/or explantation of DBS-system
Wound healing impaired[n,y]	1/1	
Hardware-related AEs (all):	101/68	
1. IPG		
Accidental arrest[a]	4/4	
Cable defect[b]	1/1	Replacement of the power supply cable
Battery expired[b]	56/28	IPG replacement
Technical defect[b]	13/11	IPG replacement
Dislocation/malposition[b]	4/3	IPG replacement and repositioning
Hardware revision[b,o]	2/2	IPG replacement
2. Extension lead/s		
Technical defect[b]	2/2	Extension lead revision
Fracture/disconnection[b,p]	5/4	Extension lead revision/explantation of DBS-system/stimulation off

Dislocation/ migration[b,q]	4/4	Extension lead revision
Shortness due to growth and/or mal-position of IPG[b,r]	6/5	Extension lead revision (and IPG repositioning or replacement)
3. Electrode/s		
Technical defect[b]	1/1	Electrode revision
Dislocation/migration[b]	2/2	One-sided electrode revision
Fracture/ disconnection[b,s]	1/1	Explantation and reimplantation of DBS system
Lack/loss of effect[a,b,t]	2/2	
	6/6	Explantation of DBS system and/or lead revision and implantation of additional electrodes
Other or unspecified[u] AEs**:**		
Dysarthria/swallowing problems[a,b,c,v]	3/3	
Increased dystonic posturing[a,b,c,w]	6/4	
Increased hyperkinesia[a]	2/2	
Pain/headache[a]	2/2	
Seizure[a]	2/2	
Shortening of tendons[a,z]	1/1	
Psychiatric symptoms[b,c,aa]	2/1	
Discomfort/pain/lack of effect/dystonic crisis[y]	1/1	Extension lead revision, implantation of two additional electrodes, change of IPG position
Weight loss[y,aa]	1/1	

Legend: Ongoing AEs are displayed in every time interval during which they were documented. Ongoing AEs were only counted once per time interval when calculating the absolute number of AEs per patient. [a]Reversible. [b]Irreversible. [c]Ongoing. [d]Not stimulation-induced (non-DBS associated disease-related) AE. [e]Stimulation-induced AE. [f]1 patient with ongoing, irreversible increased dystonic posturing. [g]1 Patient with coexisting loss/lack of effect leading to explantation of DBS system. [h]1 Patient with irreversible swallowing problems leading to switch off stimulation. [i]Known epilepsy. [j]Psychosis, visual hallucinations. [k]Staphylococcus epidermidis detected in microbiological wound sample. [l]Wound infection combined with wound healing impairment; 1 patient with explantation of DBS system in 3 surgeries over 2 years; 1 Patient with explantation and reimplantation of DBS system, staphylococcus aureus detected in microbiological wound sample; 1 patient with extension lead revision and explantation of IPG, wound infection was caused by a cable protruding into the wound, MRSA detected in microbiological wound sample. [m]1 Patient with extension lead revision and explantation of DBS-system after second infection (coexisting extension lead fracture/ disconnection); 1 patient received extension lead revision and IPG replacement (coexisting extension lead shortness due to growth); 1 Patient with explantation of DBS system, MRSA (IPG, electrodes) and cutibacterium acnes (left electrode) detected in microbiological wound sample; 1 Patient with encephalitis. [n]Concerns wound on IPG pocket. [o]Exact reason for IPG replacement not applicable. [p]1 Patient with extension lead revision due to coexisting extension lead dislocation/migration; 1 patient with explantation of DBS-system and coexisting infection. [q]2 patient with one-sided extension lead revision; 1 patient with extension lead revision and coexisting extension lead fracture. [r]1 Patient with extension lead revision and IPG repositioning; 1 patient with extension lead revision and IPG replacement (coexisting infection). [s]Combined with IPG dislocation. [t]2 AEs/2 patients with reversible and 6 AEs/6patients with irreversible lack/loss of effect; 1 patient with coexisting stimulation-induced pain/headache (explantation of DBS system); 1 patient with lead revision and implantation of two additional DBS-electrodes into different nucleus (GPi); 1 patient with explantation of IPG only; 1 patient switched off stimulation. [u]Information whether AE is stimulation-induced or not is missing. [v]1 patient with irreversible, ongoing dysarthria; 1 patient with missing information on reversibility of swallowing problems. [w]2 AEs/2 patients with irreversible, ongoing increased dystonic posturing. [x]Due to optic disc drusen. [y]Missing information on reversibility of AE. [z]Reversible after myofasciotomy. [aa]Anxiety disorder, depressive episode.

4.6. DBS Outcome

4.6.1. Dystonia

The effect of DBS was assessed by analysing relative and absolute improvement in the BFMDRS movement score, by measuring the quantitative reduction of medication and by evaluating the physical development of each patient and within each subgroup. Pre- and postoperative BFMDRS scores were available for 63 patients. Group 1, representing the patients with isolated inherited and idiopathic dystonia undergoing DBS, showed a significant improvement in the mean BFMDRS compared to preoperative baseline scores in every follow-up until four years postoperatively, whereas group 2 (combined inherited and idiopathic dystonia) showed only mild improvement from the zero to three months postoperative follow-up up to the three years postoperative follow-up without reaching statistical significance. For group 3 (acquired dystonia), a statistically significant improvement could be shown in follow-up 2 (one year +/- six months to two years +/- six months postoperative), whereas in the zero to three months postoperative follow-up up to the two years postoperative follow-up only a minor, non-significant improvement in the BFMDRS was detected. In general, the mean BFMDRS score percentage change, or improvement in postoperative score from baseline, was 21.6% for the zero to six months postoperative follow-up, 22.4% for follow up 2 and 23.6% for follow-up 3 (three years +/- six months to six years +/- six months) with a range of -22.9% to 94.1% for follow-up 1, -135% to 96.3% for follow-up 2 and -75.6% to 91.3% for follow-up 3. Looking at Group 1 only, the mean BFMDRS score percentage change was 48% (range, 1,79%–94.12%) for the first follow-up and 55.9% (range, 8.6%–96.3%) for the second follow-up, and the improvement in postoperative score from baseline was 49.8% (range, 11.7%–91.3%) for the last follow-up. The relative improvement of dystonia severity represented by percentage change in BFMDRS scores for group 2 and group 3 was as follows: group 2 – follow-up 1 10.1% (range, -22.9%–70.2%), follow-up 2 1.2% (range, -135.2%-72.3%), follow-up 3 7.7% (range, -57.5%-38.5%); group 3 – follow-up 1 5% (range, -20.9-47.1%), follow-up 2 7.3% (range, -13.7-44.5%) and follow-up 3 7.9% (range, -75.6–80.5%). More responses to pallidal DBS depending on subgroup distribution and aetiology are provided in Tables 7 and 8 (Results).

Table 7 (Results): *Mean pre- and postoperative BFMDRS scores of the registry cohort, listed separately according to group*

	Baseline +/- SD	0-3 m. po. +/- SD	4-6 m. po. +/- SD	**FU1** +/- SD	1 y. +/- 6 m. po. +/- SD	2 y. +/- 6 m. po. +/- SD	**FU2** +/- SD	3 y. +/- 6 m. po. +/- SD	4 y. +/- 6 m. po. +/- SD	5 y. +/- 6 m. po. +/- SD	6 y. +/- 6 m. po. +/- SD	**FU3** +/- SD
Total (N=89)	68.0 +/- 27.8[a]	52.7 +/- 31.0[e**]	54.4 +/- 33.6[i**]	54.3 +/- 31.5[m**]	49.7 +/- 33.9[q**]	48.4 +/- 29.7[u**]	50.8 +/- 33.1[y**]	48.2 +/- 29.9[cc**]	50.8 +/- 29.5[gg**]	76.0 +/- 11.3[kk]	63.3 +/- 20.1[oo]	50.1 +/- 27.6[ss**]
Group 1: Isolated dystonia[+] (N=29)	66.3 +/- 28.4[b]	40.8 +/- 31.4[f**]	37.6 +/- 43.8[j**]	37.7 +/- 29.8[n**]	26.4 +/- 25.1[r**]	35.1 +/- 27.8[v**]	30.6 +/- 29.5[**z]	32.1 +/- 25.7[dd**]	35.7 +/- 22.5[hh**]	84[ll]	56.8 +/- 26.1[pp]	33.9 +/- 21.7[tt**]
Group 2: Combined dystonia[++] (N=29)	64.3 +/- 30.9[c]	55.7 +/- 31.9[g]	50,2 +/- 37.9[k]	55.5 +/- 33.4[o]	57.4 +/- 35.0[s]	40.1 +/- 34.1[w]	55.1 +/- 33.4[aa]	49.4 +/- 37.6[ee]	68.5 +/- 35.0[ii]	[mm]	86 +/- 0[qq]	57.9 +/- 33.9[uu]
Group 3: Acquired dystonia (N=31)	72.4 +/- 25.2[d]	66.4 +/- 25.3[h]	69.8+/- 26.0[l]	69.7 +/- 24.0[p]	67.0 +/- 28.5[t]	63.0 +/- 24.6[x]	66.5 +/- 27.2[bb**]	59.6 +/- 25.3[ff]	77.0 +/- 12.7[jj]	68[nn]	61.5 +/- 2.1[rr]	60.8 +/- 23.3[vv]

The preoperative and postoperative BFMDRS scores for the cohort and each subgroup were compared by paired t-test (** = p<0.05). [+]Isolated inherited and idiopathic dystonia. [++]Combined inherited and idiopathic dystonia. FU1 = follow-up 1, FU2 = follow-up 2, FU3 = follow-up 3, m. = months, po. = postoperative, SD = standard deviation, y. = years. [a]26 patients with missing scores. [b]9 patients with missing scores. [c]10 patients with missing scores. [d]7 patients with missing scores. [e]58 patients with missing scores. [f]17 patients with missing scores. [g]18 patients with missing scores. [h]23 patients with missing scores. [i]68 patients with missing scores. [j]22 patients with missing scores. [k]24 patients with missing scores. [l]22 patients with missing scores. [m]46 patients with missing scores. [n]14 patients with missing scores. [o]16 patients with missing scores. [p]16 patients with missing scores. [q]42 patients with missing scores. [r]12 patients with missing scores. [s]16 patients with missing scores. [t]14 patients with missing scores. [u]64 patients with missing scores. [v]20 patients with missing scores. [w]24 patients with missing scores. [x]20 patients with missing scores. [y]37 patients with missing scores. [z]11 patients with missing scores. [aa]14 patients with missing scores. [bb]12 patients with missing scores. [cc]62 patients with missing scores. [dd]20 patients with missing scores. [ee]23 patients with missing scores. [ff]19 patients with missing scores. [gg]77 patients with missing scores. [hh]22 patients with missing scores. [ii]26 patients with missing scores. [jj]29 patients with missing scores. [kk]87 patients with missing scores. [ll]28 patients with missing scores. [mm]No data available. 29 patients with missing scores. [nn]30 patients with missing scores. [oo]83 patients with missing scores. [pp]26 patients with missing scores. [qq]28 patients with missing scores. [rr]29 patients with missing scores. [ss]57 patients with missing scores. [tt]17 patients with missing scores. [uu]22 patients with missing scores. [vv]18 patients with missing scores.

Table 8 (Results): *T-test comparison of mean pre- and postoperative BFMDRS scores, classified according to aetiology*

Aetiology	N[+]	**Baseline** +/- SD	Po. **FU1** (Score +/- SD/ Change*)	Po. **FU2** (Score +/- SD/ Change*)	Po. **FU3** (Score +/- SD/ Change*)	**P value** (FU1/FU2/FU3)
DYT-TOR1A dystonia	12	53 +/- 25.9	19.8 +/- 11.1/ 56.0%[a]	20.3 +/- 25.6/ 62.9%	23.6 +/- 13.5/ 55.2%[b]	0.000/ 0.000/ 0.000
Other DYT forms**	12	74.3 +/- 26.7	62.3 +/- 28.9/ 25.3%[c]	55.9 +/- 27.9/ 14.7%[d]	35.7 +/- 20.6/ 44.8%[e]	0.054/ 0.105/ 0.048
PKAN	4	59.1 +/- 26	50.0 +/- 29.4/ 18.6%[f]	47.3 +/- 23.9/ -9.9%[g]	74.0 +/- n/a -57.5%[h]	0.368/ 0.862/ n/a
Perinatal brain injury	18	76.4 +/- 25.9	77.2 +/- 20.7/ 1.7%[i]	68.6 +/- 29/ 7.3%[j]	59.9 +/- 25.4/ 16.1%[k]	0.478/ 0.114/ 0.043
Acquired, except perinatal brain injury	5	57.2 +/- 20.7	39.5 +/- 4.9/ 3.9%[l]	56.9 +/- 24.1/ 4.1%[m]	65.8 +/- 3.9/ -74.1%[n]	0.5/ 0.368/ 0.522
Idiopathic	12	71.7 +/- 33	66.4 +/- 34.4/ -0.1%[o]	55.1 +/- 37.4/ 18.8%[p]	65.7 +/- 31.3/ 16.5%[q]	0.361/ 0.101/ 0.026
Overall	63	68.0 +/- 27.8	54.3 +/- 31.5/ 21.6%[r]	50.8 +/- 33.1/ 22.4[s]	50.1 +/- 27.6/ 23.6%[t]	0.000/0.000/ 0.000

Legend: The preoperative and postoperative BFMDRS scores for each aetiology were compared by paired t-test. FU1 = follow-up 1, FU2 = follow-up 2, FU3 = follow-up 3, n/a = not applicable/not available, po. = postoperative. Follow-up 1 = 0–6 months postoperative, follow-up 2 = 1 year +/- 6 months to 2 years +/- 6 months, follow-up 3 = 3 years +/- 6 months to 6 years +/- 6 months postoperative *Percentage change (improvement) compared to baseline score. **Other inherited monogenetic forms of dystonia = DYT-TOR1A negative inherited dystonia including DYT-KMT2B, DYT-SGCE, DYT-ATP1A3, DYT-PRKRA, DYT-ANO3, dystonia due to GNAO1 gene mutation, Lesch-Nyhan-syndrome. PKAN = pantothenate kinase-associated neurodegeneration dystonia. Acquired, except perinatal brain injury includes encephalitis (1x), traumatic brain injury (3x), Kernicterus (1x). [+]Only those patients from our cohort were counted for whom preoperative scores and at least one postoperative score were available. [a]1 missing score. [b]5 missing scores. [c]3 missing scores. [d]2 missing scores. [e]7 missing scores. [f]1 missing score. [g]1 missing score. [h]3 missing scores. [i]6 missing scores. [j]3 missing scores. [k]7 missing scores. [l]3 missing scores. [m]2 missing scores. [n]3 missing scores. [o]6 missing scores. [p]3 missing scores. [q]6 missing scores. [r]20 missing scores. [s]11 missing scores. [t]31 missing scores.

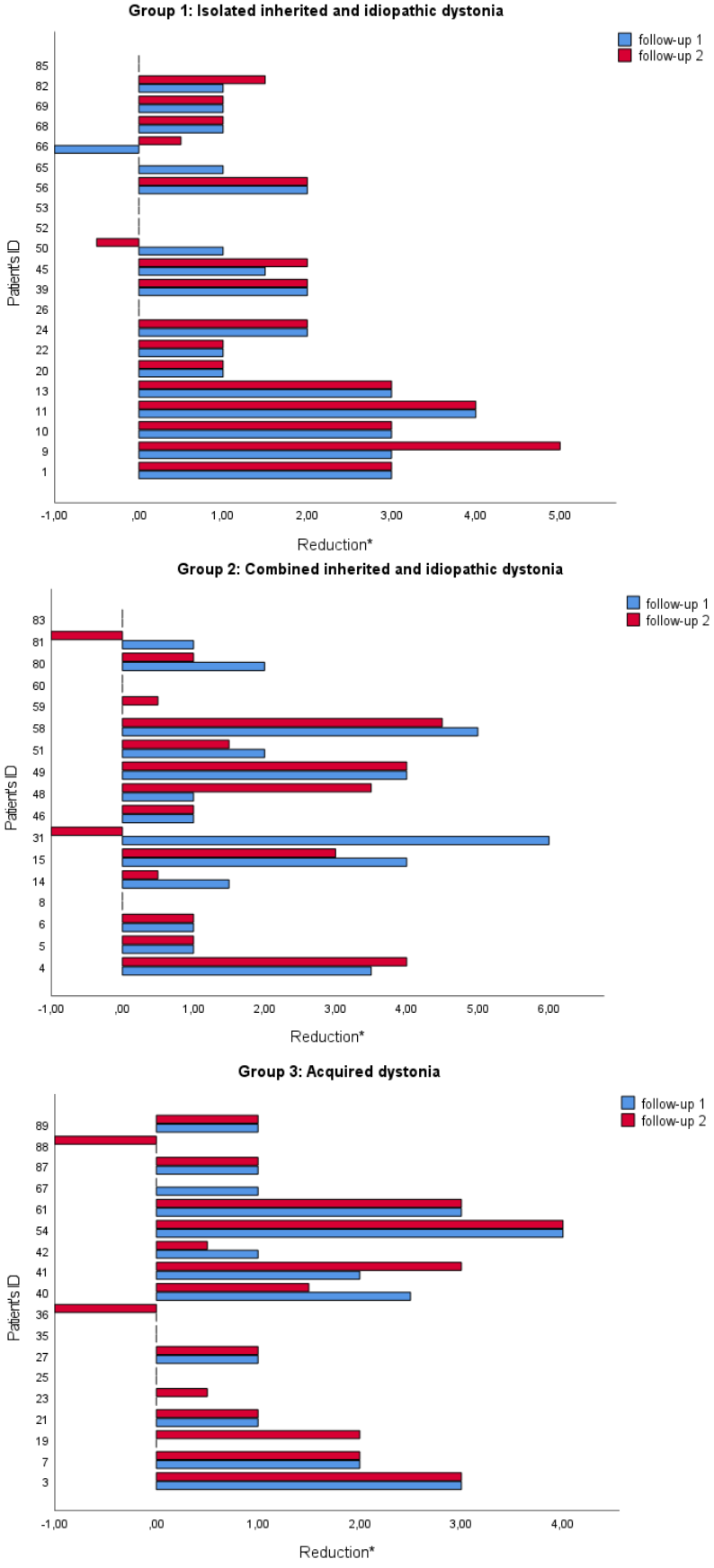
4.6.1. Effects on Pharmacotherapy and BMI

In total, mean reduction in medication prescribed for the treatment of dystonia was 1.5 in short-term follow-up (range, -4–6, missing data for 20 patients) and 1.4 in medium-term and long-term follow-up (medium-term and long-term follow-up range, -1–5, missing data for 30 patients in follow-up 2, missing data for 34 patients in follow-up 3). Looking at the different subgroups, there is only a slight difference between the number of drugs that could be discontinued within the various follow-ups. Thus, for group 1, an average of 1.4 pharmaceuticals were discontinued in the first follow-up (range, -1–4, missing data for five patients), 1.5 drugs in the second follow-up (range, -0.5–5, missing data for seven patients), and 1.5 drugs in the last follow-up (range, -0.5–5, missing data for 9 patients). In the group of patients diagnosed with combined inherited and idiopathic dystonia, an average of 1.7 drugs were discontinued in the short-term follow-up (range, -4–6, missing data for seven patients), an average of 1.4 pharmaceuticals in follow-up 2 (range, -1–4.5, missing data for 12 subjects) and 1.7 drugs in follow-up 3 (range, 0–5, missing data for 13 patients). The number of medications that could be reduced postoperatively compared to baseline for the acquired dystonia group was as follows: short-term follow-up 1.5 (range, -5–5, missing data for eight subjects), medium-term follow-up 1.3 (range, -1–5, missing data for 11 patients), long-term follow-up 1.1 (range, -0,5–4, missing data for ten patients). Absolute reduction of drugs 0–6 months and 1 year +/- 6 months to 2 years +/- 6 months postoperatively compared to baseline per individual subject is provided in Figure 7 (Results).

For 15 patients in the GEPESTIM cohort who were below the tenth percentile for BMI (range, below the first to eighth percentile), both pre- and post-operative BMIs could be collected. Of these 15 patients who were considered to be underweight or extremely underweight preoperatively, ten patients (=66.7%) improved in their age- and sex-specific BMI percentile position at either one, two or all of the follow-up visits compared to the preoperative visit and thus approached a healthier BMI (missing data for three patients in follow-up 1 and two patients in follow-up 2). Two patients who were underweight or severely underweight before DBS implantation showed no change in percentile position (13.3%), and three patients (20%) were below their preoperative BMI percentile position at one, two or all postoperative follow-ups (missing data for one patient in follow-up 1 and 2, missing data for three patients in follow-up 3).
The individual percentiles of those patients for whom pre- and postoperative BMIs could be collected are depicted in Figure 8 (Results). As the average pre- to postoperative course of the BMI percentile curves, shown by the black dashed regression line in Figure 8, shows, DBS does have a statistically significant influence on the physical development of the patients, more precisely, on the age- and gender-specific BMIs (type III tests of fixed effects: p=0.023 for visit 1,2,3,4; p=0.000 for intercept, see Table 11 in the Appendix). In the group analysis, only positive trends can be reported for groups 1 and 3 (see Figure 8); merely in group 2 the regression line, which is formed from the arithmetic mean of the percentile positions of the individual patients, showed statistical significance (p-value for interception: p=0.001).

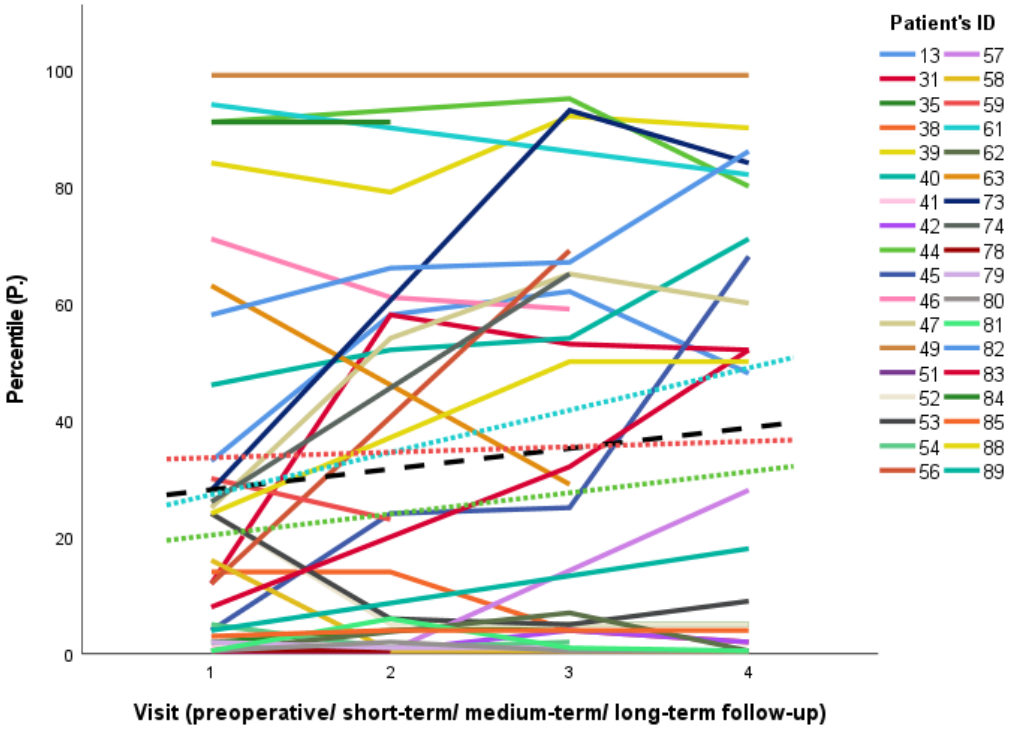
Figure 7 (Results):

Absolute postoperative reduction of prescribed drugs for treatment of movement disorder and direct sequelae



Legend: *Reduction of prescribed medication required for treatment of the movement disorder in absolute numbers. Recorded drugs that could be reduced in number include for example: anticholinergic and dopaminergic medication, dopamine depleting drugs, benzodiazepines, muscle relaxants, antipsychotics, anticonvulsants, regular botulinum toxin injections in at least one muscle (see Methods).

Figure 8 (Results): *Postoperative change in BMI measured by percentile curve*



Legend: The dashed black line represents the average course of BMI change of all patients, shown in percentile curves. The dotted turquoise curve depicts the mean change in BMI percentiles for group 1. The pink dotted line illustrates the average percentile change for all patients in group 2, and the light green dotted line demonstrates the average BMI change for group 3. Number '1' on the horizontal axis indicates the preoperative examination, number '2' represents the 0–6 months postoperative follow-up, number '3' the 1 year +/- 6 months to 2 years +/- 6 months postoperative follow-up, and number '4' displays the 3 years +/- 6 months to 6 years +/- 6 months postoperative follow-up. The percentiles are shown on the vertical axis.

4.7. Outcome Predictors

4.7.1. Gender

Figure 9 (Results) shows the correlation analysis between the outcome of DBS and pre-operative variables. No significant differences were detected between the mean postoperative BFMDRS motor scores in terms of gender (p-value follow-up 1/2/3= 0.579/0.992/0.951).

4.7.2. Age at Onset, Age at Implantation and Years of Life Lived With Dystonia Before Implantation of DBS System

Among other demographic features, there is a positive trend towards correlation of age at onset with clinical outcome, both at first follow-up (r^2=0.213; p=0.055) and second follow-up (r^2=0.217, p=0.056) in the group of patients with isolated inherited and idiopathic dystonia. However, statistical significance could not be reached. This positive trend does not apply for the change in DBS effects 3 years +/- 6 months to 6 years +/- 6 months after DBS surgery (r2=0.264, p=0.164). Within the linear regression model for follow-up 3, it is noticeable that in the group of patients with acquired dystonia, we found a statistically significant negative linear correlation between the dependent variable 'DBS outcome measured in BFMDRS motor score' and the independent variable 'age of onset' (r^2=0.314, p=0.022). This

suggests that the lower the age of onset of paediatric patients suffering from acquired dystonia, the better the long-term effect of DBS. For the group of combined dystonia, no linear correlation between age at onset and effect of DBS could be shown.

Furthermore, age at implantation turned out to be a significant independent predictor of percentage improvement in our regression analysis for group 1 in short-term and medium-term follow-up. For the group of patients with isolated inherited and idiopathic dystonia, a statistically significant negative correlation between the independent variable 'age at implantation' and the dependent variable 'improvement in BFMDRS at follow-up 1 (%)' (r^2=0.348, p=0.011) as well as 'improvement in BFMDRS at follow-up 2 (%)' (r^2=0.378, p=0.009) could be shown. In other terms, for the group of isolated inherited and idiopathic dystonia, we obtained the following result: the younger the patients were at DBS surgery, the greater the relative postoperative improvement in BFMDRS in the short-term and medium-term follow-up. In contrast, a statistically significant positive linear correlation between age at implantation and percentage improvement in BFMDRS at medium-term follow-up could be demonstrated for the group of combined inherited and idiopathic dystonia (r^2=0,157, p=0.027). Hence, the older the patients of the combined dystonia group in our cohort were at DBS surgery, the greater was the relative postoperative improvement in BFMDRS in the medium-term follow-up. For the group of patients with acquired dystonia, age at implantation does not seem to be a suitable predictor for the outcome of DBS (r^2=0.019, r^2=006, r^2=0.002 for follow-up 1, 2, 3).

Among clinical variables, in group 1 (isolated inherited and idiopathic dystonia) years of life lived with dystonia before DBS implantation (disease duration) negatively correlated with clinical outcome in BFMDRS percentage change at short-term, medium-term, and long-term follow-up (r^2=0.416/0.470/0.157). Years of life lived with dystonia before implantation was found to be a significant independent predictor of percent improvement in our regression at follow-up 1 and follow-up 2 for group 1 (p-value for follow-up 1: p=0.006, for follow-up 2: p=0.005). Additionally, we discern a trend towards positive correlations, without reaching statistical significance, between years of life lived with dystonia before implantation and improvement in BFMDRS percentage change in group 2 and follow-up 1, 2 and 3 (r^2=0.025/0.001/0.054). The group of acquired dystonia shows varying and highly volatile trends with regard to the relationship between duration of disease and outcome, depending on the follow-up. For group 3 and follow-up 1, the trend shows that the earlier in the course of the disease surgery was performed, the greater the effect of DBS (r^2=0.053). The almost non-existent linear correlation in follow-up 2 implies that the time of surgery in the course of the disease does not play a role in the relative effect of DBS (r^2=0.002). In follow-up 3, on the other hand, there is a positive correlation between years of life lived with dystonia before surgery and the relative effect of DBS for the group of acquired dystonia (0.124). The trends that emerge for group 3 are not of statistical significance. For all parameter estimates of our linear regression models, please refer to Table 10 in the Appendix.

4.7.3. Preoperative Cerebral Imaging and Orthopaedic Deformations

As demonstrated by the results presented in Figures 10, 11 and Table 9, important predictors of patient response to pallidal DBS are a preoperative cerebral MRI/CT without any structural abnormalities and the absence of orthopaedic deformities and fixed contractions before surgery. Figure 10 shows that all patients with a superior outcome after DBS implantation at follow-ups 1 and 2 had no evidence of degeneration or structural lesions on preoperative cerebral imaging. With a few exceptions (one patient at each follow-up), patients classified as having an insufficient or deteriorated outcome based on postoperative outcome measured by the BFMDRS had markedly more structural lesions or signs of degeneration on preoperative cMRI or cCT. Consequently, patients demonstrating no evidence of degeneration or structural lesions in preoperative brain imaging, in addition to subjects with preoperative absence of fixed orthopaedic deformations, exhibited a significant improvement in the mean BFMDRS compared to preoperative baseline scores in every follow-up (see Table 9 for details including p-values).

We looked separately at patients with preoperatively documented orthopaedic deformations who had been successfully treated surgically prior to DBS implantation, e.g. tendon releases and osteotomies. These patients also experienced a statistically significant relative improvement in BFMDRS motor score when comparing mean preoperative scores with postoperative scores for all follow-ups (p=0.003, p=0.013 and p=0.037 for short-term, medium-term and long-term follow-up scores; for missing values and more information see Table 9 as well as Figures 10 and 11).

4.7.4. Overlap of Stimulation Volumes with the 'Sweet Spot'

'Sweet spot' analysis of our cohort revealed that the calculated statistical model (T-model) of the 'sweet spot' was found to lie in the ventral and lateral region of the GPi[27]. In detail, the 'sweet spot' spanned a region within the GPi that interfaces with the GPe and extends toward the pallidal region. In our GEPESTIM cohort, “overlap of each combined bilateral stimulation volumes’’ with the 'sweet spot' “correlated with the corresponding DBS-associated clinical improvement (R = 0.46, permuted p = 0.019 […]” (Al-Fatly, 2023, p. 5)[27]. Additionally, a group analysis was performed and the degree of overlap with the DBS 'sweet spot', which correlates with clinical improvement, was stable when comparing the subgroup of patients with inherited or idiopathic dystonia with the group of all patients[27]. Furthermore, a connectivity analysis was performed in order to obtain further insight from a network perspective. Based on our study cohort, connectivity of the electrode location to the parietal and anterior cingulate cortices, the brainstem and the medial/ superior parts of the cerebellum were positively correlated with postoperative improvement, whereas connectivity to the sensorimotor cortex, frontal cortex or posterior cerebellum was negatively correlated with the DBS effects measured by change in BFMDRS[27].

Figure 9 (Results):

Scatterplots of percentage change in BFMDRS score compared with baseline at follow-up 1, 2 and 3 against years of life lived with dystonia before surgery in years, age at onset in years and age at implantation in years for all paediatric patients with 1) isolated inherited and idiopathic, 2) combined inherited and idiopathic and 3) acquired dystonia

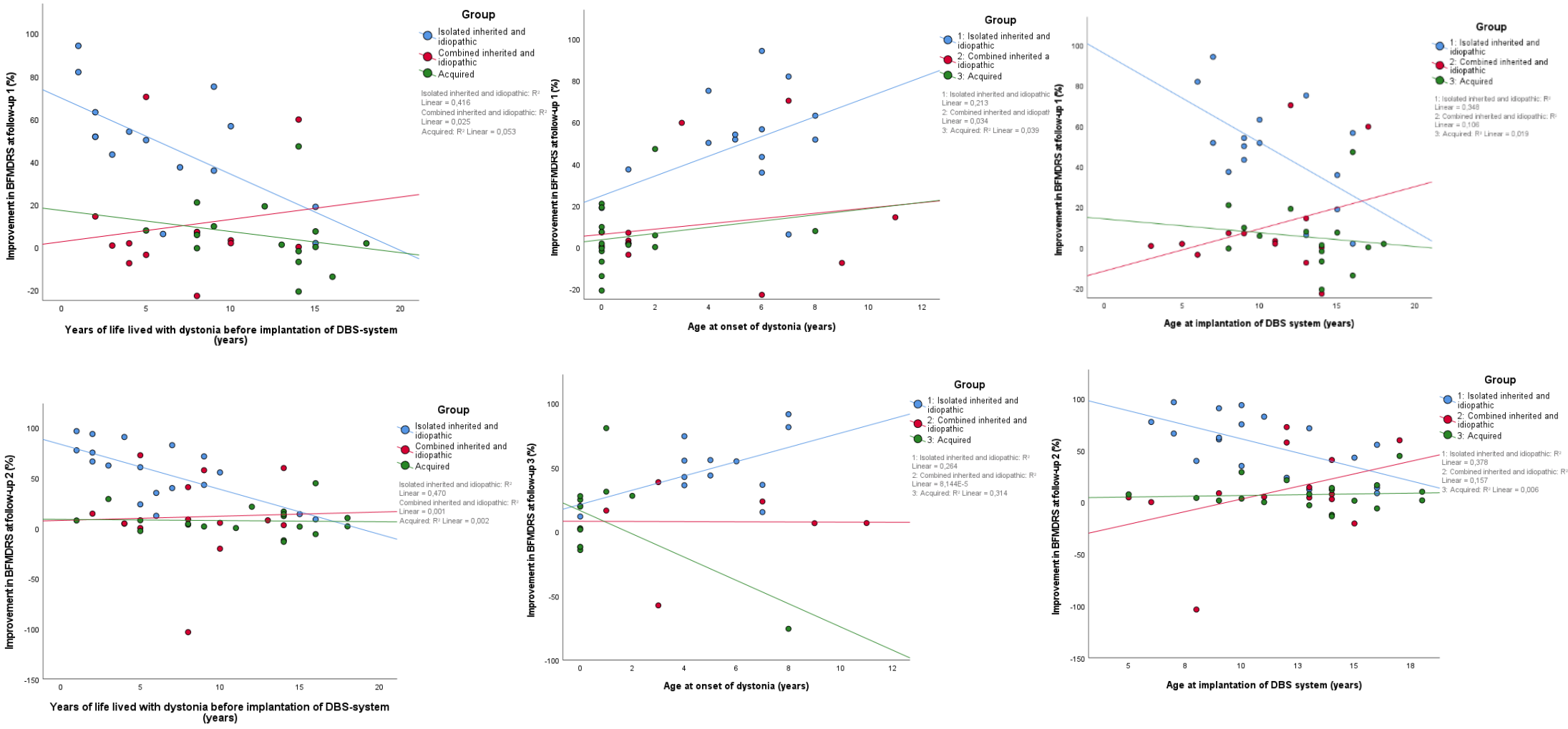
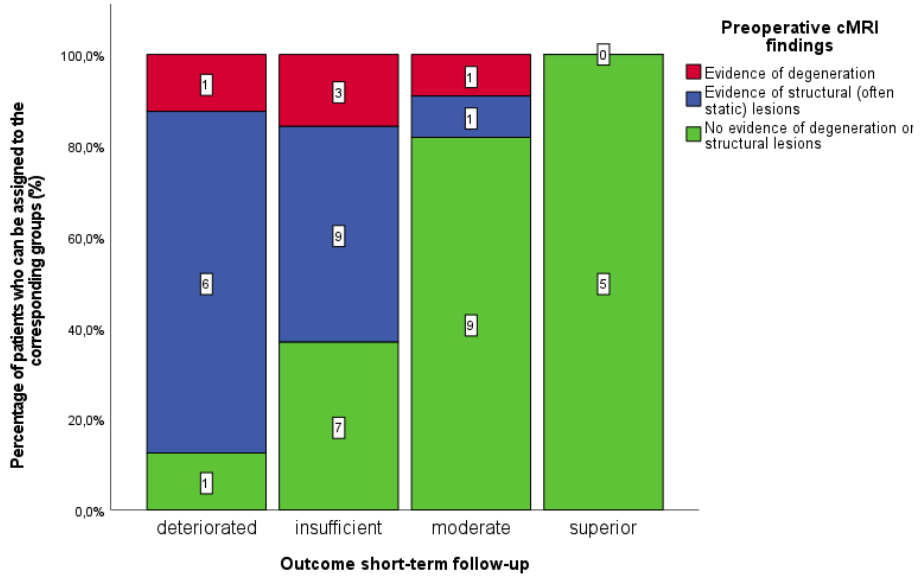
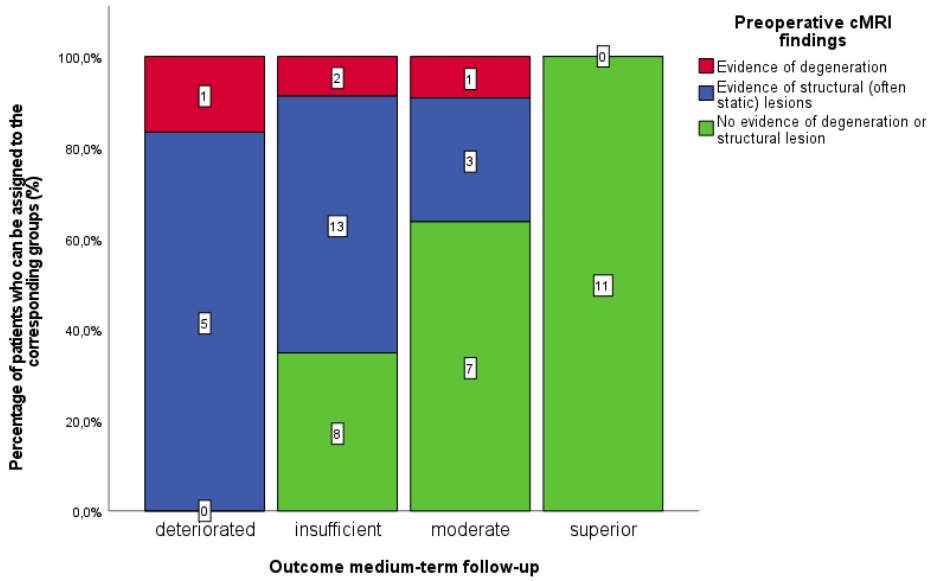
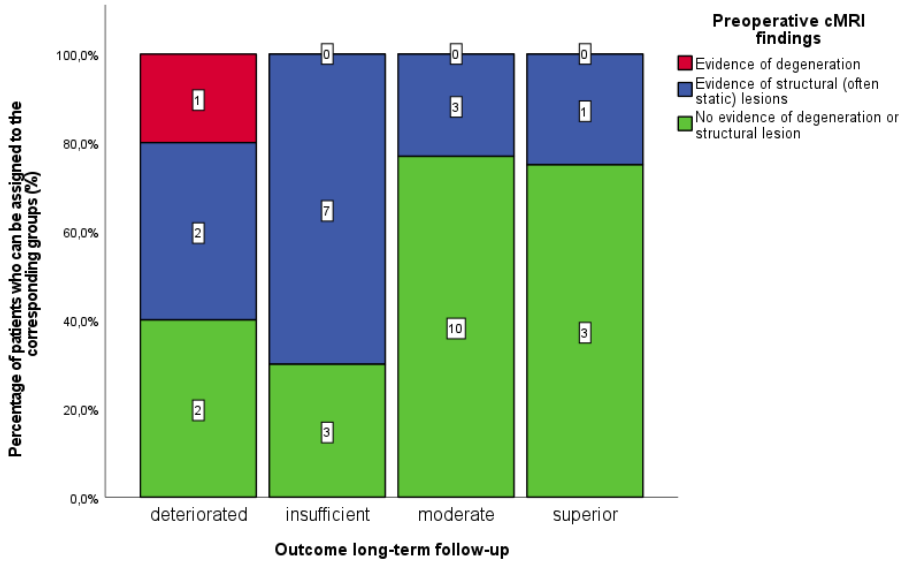


Figure 10 (Results):

Bar chart showing the relative (see y-axis) and absolute (see labels in the bars) proportion of preoperative physiological and pathological cMRI findings of the deteriorated group and the insufficient, moderate and superior outcome group



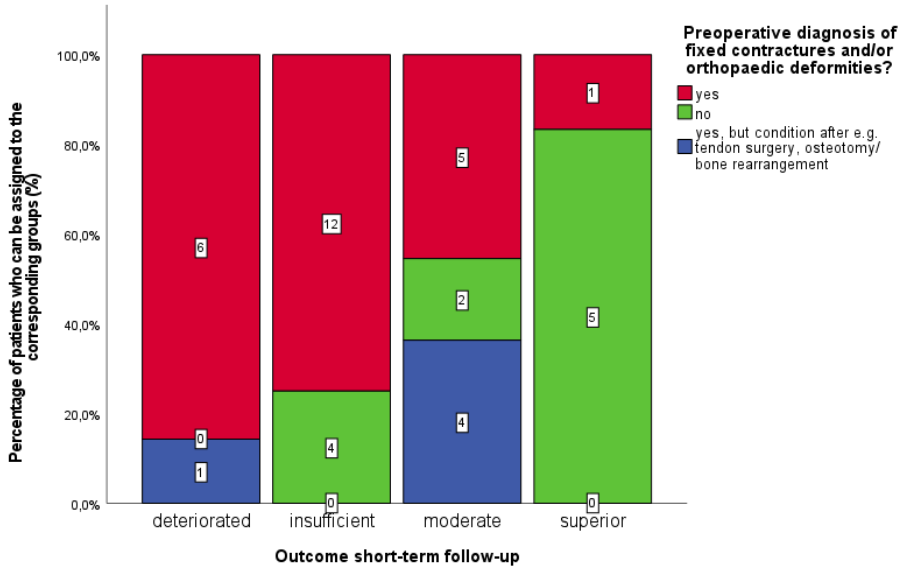


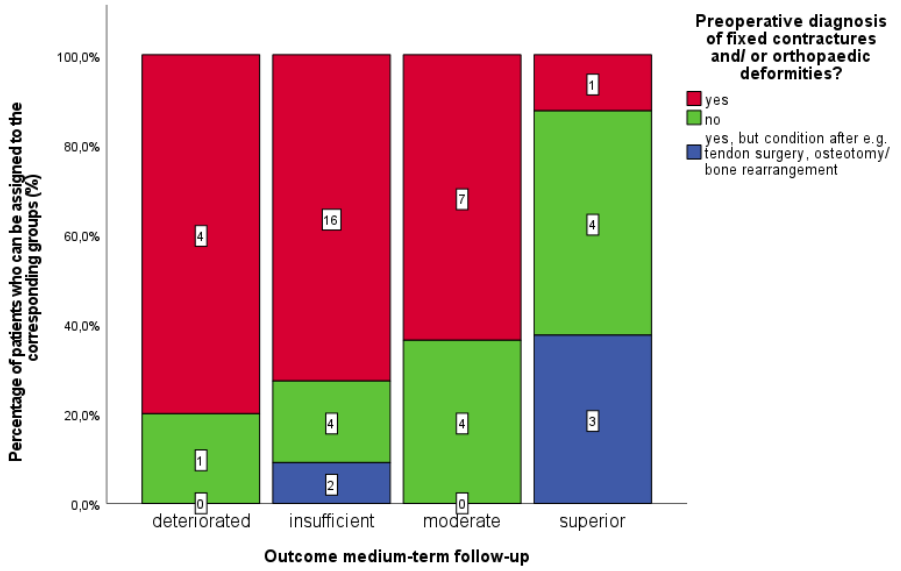


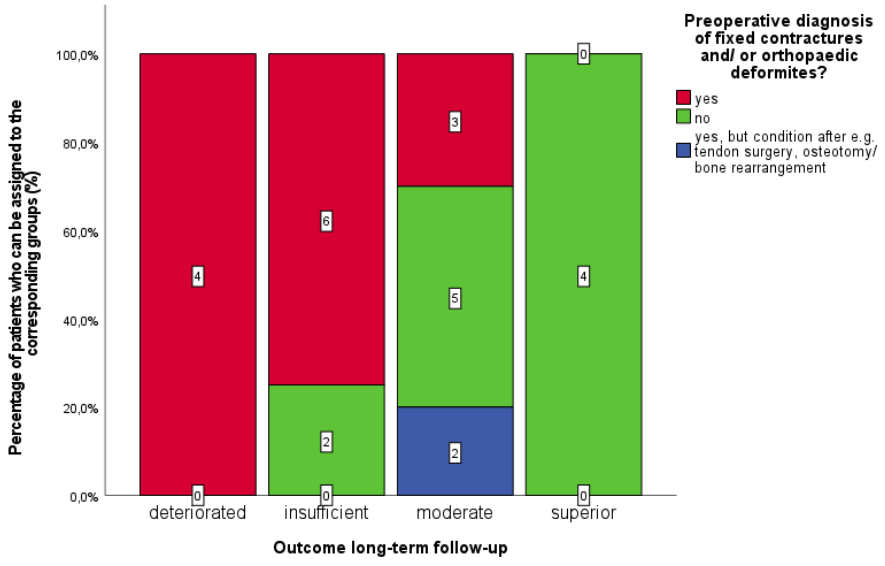
Additional information: Patients were assigned to the superior outcome/moderate outcome/insufficient outcome/deteriorated group, depending on whether they had above 60%/below 60% and above 20%/below 20%/below 0% motor improvement measured by percentage change in BFMDRS motor score and for each follow-up. Missing values and/or missing preoperative cMRI findings for 46 patients in short-term follow-up, 38 patients in medium-term follow-up and 58 patients in long-term follow-up.

Figure 11 (Results):

Bar chart showing the relative (see y-axis) and absolute (see labels in the bars) proportion of patients for whom at least one or no orthopaedic deformity in the left or right arm, hip, knee, ankle, and spine area was diagnosed preoperatively, or an orthopaedic deformity was detected but had been successfully treated with surgery before DBS implantation







Additional information: Patients were allocated to the superior outcome/moderate outcome/insufficient outcome group and to the deteriorated category, depending on whether they had above 60%/below 60% and above 20%/below 20%/below 0% motor improvement measured by percentage change in BFMDRS motor score and for each follow-up. Missing values and/or missing information about the presence or absence of fixed contractures and deformities for 49 patients in short-term follow-up, 43 patients in medium-term follow-up and 63 patients in long-term follow-up.

***Table 9 (Results)**: T-test comparison of preoperative and postoperative BFMDRS scores classified according to preoperative cMRI findings as well as preoperative presence/absence of orthopaedic deformations*

Predictors of response	N*	Mean preop.	Mean postop. **FU1** (Score/ Change**)	Mean postop. **FU2** (Score/ Change**)	Mean postop. **FU3** (Score/ Change**)	**P value** (FU1/FU2/FU3)
Preop. cMRI: No evidence of degeneration or structural lesion	30	63.6	37.3/ 39%[a]	33.3/ 46.4%[b]	39/ 38%[c]	0.000/0.000/0.000
Preop. cMRI: Evidence of structural (often static) lesions	26	75.3	75.1/ 17%[d]	70.9/ 5.7%[e]	63.5/ 9.9%[f]	0.484/ 0.1/ 0.114
Preop. cMRI: Evidence of degeneration	6	65.6	61.9/ 10.6%[g]	55.9/ -7.4%[h]	74/ -57.5%[i]	0.362/ 0.848/ n.a.
Preop. absence of fixed orthopaedic deformities or contractures	18	68.9	34.3/ 48.5%[j]	33.7/ 51.6%[k]	36.7/ 37.9%[l]	0.001/ 0.000/ 0.003
Preop. presence of fixed orthopaedic deformities or contractures	36	66	65.2/ 5.8%[m]	62.3/ 2.9%[n]	60.8/ 7.1%[o]	0.142/ 0.354/ 0.19
Preop. condition after tendon surgery, osteotomy (bone rearrangement)***	5	66.9	33.7/ 49.2%	28.6/ 59.1%	35.3/ 51.5%[p]	0.003/ 0.013/ 0.037

Legend: The preoperative and postoperative BFMDRS scores for each predictor of response were compared by paired t-test. *Only those patients from our cohort were counted for whom preoperative scores and at least one postoperative score were available. **Percentage change (improvement) compared to baseline score. ***Preoperative presence of fixed orthopaedic deformities or contractures but pretreatment of deformities and contractures before DBS-surgery (e.g. condition after tendon surgery, osteotomy). Follow-up 1 = 0–6 months postoperative, follow-up 2 = 1 year +/- 6 months to 2 years +/- 6 months postoperative, follow-up 3 = 3 years +/- 6 months to 6 years +/- 6 months postoperative. [a]8 missing scores. [b]4 missing scores. [c]12 missing scores. [d]10 missing scores. [e]5 missing scores. [f]13 missing scores. [g]1 missing score. [h]2 missing scores. [i]5 missing scores. [j]7 missing scores. [k]3 missing scores. [l]5 missing scores. [m]11 missing scores. [n]4 missing scores. [o]12 missing scores. [p]2 missing scores.

5. Discussion

5.1. Outcome Measured by the BFMDRS

We assessed the effects of DBS in patients implanted up to the age of 18 years in 89 patients with childhood-onset dystonia recruited by the GEPESTIM registry. We discriminated between aetiology of dystonia, isolated inherited and idiopathic, combined inherited and idiopathic dystonia and acquired dystonia, time of implantation in the course of disease, age at onset of dystonic symptoms, age at implantation, and whether intracerebral abnormalities/pathologies as well as orthopaedic deformities were diagnosed preoperatively.

Using our cohort, we confirmed that patients with isolated inherited and idiopathic dystonia showed the greatest and statistically most significant reduction, i.e. improvement, in the BFMDRS motor score at short-term, medium-term and long-term follow-up, both in absolute and relative numbers, compared to patients with combined and acquired dystonia.

To the best of my knowledge, to date there is no other multicentre study published that has explicitly compared DBS outcome in BFMDRS change between paediatric patients with isolated and combined dystonia, including both inherited and idiopathic dystonia in each subgroup. Data on efficacy of GPi-DBS in isolated inherited and idiopathic dystonia in adult populations is available. The mean postoperative improvement of 51.2% in short, medium- and long-term follow-up obtained in group 1 is in line with findings from Moro et al. who included 24 studies comprising 523 adult patients in their meta-analysis and found a mean percentage improvement between 59.0% (range, 51.2%–66.7%) at 6 months after DBS implantation and 65.2% (range, 59.6%–70.7%) at the last follow-up (mean 32.5 months after surgery)[164]. Furthermore, results from Group 1 correspond with postoperative outcome disclosures for inherited generalised dystonia established by the first meta-regression study of GPi-DBS in dystonia[9]. In this meta-analysis, 209 patients adult patients who received DBS for primary generalised dystonia from 20 centres were identified, and the mean percentage improvement of the group was 60.7% (range, 43.4%–83.3%)[9].

In our cohort, the relative and quantitative reduction in dystonia severity was even greater when analysing postoperative results of the DYT-TOR1A dystonia subgroup in isolation. In fact, in our cohort the DYT-TOR1A dystonia group achieved the best DBS effects measured by BFMDRS, with an average percentage improvement of 58% (arithmetic mean of the effects achieved in each of the three follow-ups). DYT-TOR1A positive status is associated with greater improvement compared to other group effects; this statement indeed is not a novelty in DBS research[7,9]. However, I was able to confirm this using a large paediatric cohort from the GEPESTIM registry, and long-term outcomes have been reported. Data published by Isaias et al. suggest that DYT-TOR1A status may not be an independent outcome predictor[7]. According to them and various other scientists that have come to share their view, the superior DBS outcomes in DYT-TOR1A positive subjects appear to be correlated with their younger age and shorter disease duration at the time of surgery[6,7,39]. Within our cohort of DYT-TOR1A positive

patients, the average age at implant in this group was 10.8 years, which is younger than the average age of the total cohort at surgery (average age at implant for the entire cohort was 12.2 years). The duration of disease before implant in the DYT-TOR1A positive subgroup amounted to 4.8 years, which was almost half of the average of 8.8 years that the entire cohort lived with the disease. Thus, the patients with DYT-TOR1A positive status were obviously implanted earlier in the course of disease than the average of our cohort. In addition, none of our twelve children with DYT-TOR1A dystonia were preoperatively presented with a pathological cMRI or cCT. Therefore, it can be assumed that the DYT-TOR1A status per se may not be an independent outcome predictor. However, the satisfactory DBS outcome in patients with DYT-TOR1A dystonia may be attributable to a shorter duration of disease before implantation and the absence of lesions in the basal ganglia and surrounding structures, as well as the lack of detectable degeneration in the preoperative cerebral imaging. Moreover, Isaias et al. conjectured that "DYT1-positive subjects [preoperatively] present with a low burden of SS [=speech and swallowing] symptoms, which are less responsive to pallidal DBS" (Isaias et al., 2011, p.1475)[7]. Presumably, other clinical features which we did not explicitly assess in our GEPESTIM study may be the reason for DYT-TOR1A positive subjects showing the observed DBS outcome advantage. Yet another interesting study published by Vasques et al. in 2009 concluded that patients who responded well to treatment "were found to have significantly larger mean stimulated volumes (isofield value 0.2 V/mm) in the […] GPi than those who were less improved" (Vasques et al., 2009, p. 227)[165]. Additionally, the better DBS response of patients with DYT-TOR1A positive dystonia may correlate with generally larger GPi volumes in those patients compared to patients with other aetiologies[20,165].

A further controversial question to be addressed is, whether the effect of DBS diminishes over time. Pursuant to a study on DBS effects in adult patients with dystonic tremor authored by Peters and Tisch, the long-term benefit of DBS waned over time, a phenomenon they referred to as stimulation tolerance or habituation[166]. While habituation, presenting as substantial loss of initial DBS benefit occurring as early as a few months after initial stimulation, is accepted to exist by some authors, it remains controversial since attempts to quantify habituation have revealed conflicting reports[166]. In the isolated dystonia group of our paediatric cohort, a statistically significant decrease in relative postoperative improvement in BFMDRS of about six percentage points from follow-up 2 to follow-up 3 could be seen. Moreover, the average effect of DBS decreased by 7.7 absolute points in the BFMDRS during post-surgery monitoring in the subgroup of DYT-TOR1A dystonia. These results suggest but do not proof that the effect of pallidal DBS in patients with isolated dystonia may be likely to lightly diminish over time, which may be the result of a combination of factors[167]. First, the potential loss of DBS benefit over time is probably attributable to the progressive nature of certain dystonia types, such as the DYT-TOR1A dystonia[166]. Next to disease related progression, placebo effects, suboptimal stimulation through maladjustment of stimulation parameters in the course of the disease and stimulation related side-effects may contribute to the loss of sustained long-term therapeutic effects after DBS[166].

Compared with results from previous trials examining the effect of DBS on combined and acquired dystonia, we saw a similarly small and largely non-significant mean postoperative reduction, i.e. improvement, in BFMDRS in our cohort in these groups[9,12,13]. Minor postoperative improvement in combined and acquired dystonia may be due to the fact that, among other things to be discussed below, our combined and acquired dystonia cohorts represent heterogeneous patients. As listed in the results section (see Chapter 4.6.1.), the range of the average relative improvement in the combined inherited and idiopathic and acquired dystonia group is very broad, with some responders and some non-responders in both groups, which may account for the lower median improvement in BFMDRS motor score as compared to some reports[9,11].

My results support the use of pallidal DBS in the treatment of isolated inherited and idiopathic dystonia and, undoubtedly, DYT-TOR1A dystonia in childhood. However, especially for paediatric patients suffering from combined inherited and idiopathic and acquired dystonia, it seems to be of great relevance to carefully explore whether the patient is likely to benefit from DBS surgery. Since outcomes following pallidal DBS in paediatric patients with acquired or combined inherited and idiopathic dystonia are much more variable, within these patient cohorts, it is even more pivotal to know the predictors of good DBS response when individually assessing whether DBS surgery is indicated.

5.2. Outcome Measured by Reduction of Medication and Physical Development

Obviously, using one of the validated dystonia severity scales such as the BFMDRS to gauge outcome following DBS for isolated inherited and idiopathic, combined inherited and idiopathic and acquired dystonia provides objective results, but the resulting scores do not necessarily reflect the patients' and caregivers' subjective perceptions of changes in their daily lives. Chronically ill patients, such as patients with movement disorders, tend to have, depending on disease severity, a high risk of multimorbidity; hence, multiple drug use is common[16]. The resulting polypharmacy increases the risk of adverse drug–drug or drug–disease interactions, which is known to affect adult patients' health-related quality of life negatively[14-16]. Additionally, polypharmacy is associated with poor health outcomes, including lack of treatment adherence and adverse side effects in population- and general practitioner (GP-)based cohorts[14,15]. For our paediatric cohort, we can only guess to what extent the mean reduction of drugs prescribed for direct treatment of the movement disorder as well as for the treatment of indirect consequences of mobility impairment of 1.51 in short-term follow-up (range, -4–6), 1.41 in medium-term and long-term follow-up (medium-term and long-term follow-up range, -1–5) affects the satisfaction and quality of life of DBS patients and their relatives. Nevertheless, the fact that the average consumption of medication could be reduced postoperatively can be considered as a success of pallidal DBS in paediatric patients.

So far, little is known about the effects of GPi-/STN-/VIM-/VOA-DBS on non-motor symptoms such as growth and thrive or BMI changes in dystonia patients. A thorough review of the available literature revealed two studies that investigated weight gain in patients with isolated dystonia and Parkinson's

disease after surgery[18,19]. In one of the two studies, data from 47 adults diagnosed with isolated dystonia who underwent bilateral STN-DBS surgery between 2012 and 2019 was analysed, and postoperative weight gain had been observed in almost eighty percent of the patient cohort[18]. Interestingly, weight gain had been noted to be more prominent in female patients and had been associated with preoperative existing overweight but not with the effects of STN-DBS on motor-symptoms[18].

Childhood underweight is one of the leading causes of the global burden of disease[17]. Despite the distinction between underweight and micronutrient deficiencies, malnutrition remains the leading cause of health loss worldwide and is a serious risk factor for acquiring immunodeficiency, resulting in severe courses of infectious diseases[17]. For this reason, it is extremely gratifying that, on average, the patients in our cohort experienced a trend towards increase in percentile position in relation to their age- and gender-specific BMIs under the treatment of DBS. Of course, the different groups must be considered isolated from each other; in the group analysis, a statistically significant positive slope in the regression line can only be observed for group 2. For groups 1 and 3, we can merely report positive trends, which can, however, be clearly discerned in the graph (see Figure 8 in Results). These results pose the question of why group 1 and 3 did not improve significantly, when group 2 did. According to Nayak, this may be attributable to the fact that null studies may be underpowered to detect the desired difference when the sample size is too small[168]. Due to missing data, only ten people from group 1 and ten people from group 3 were able to be included in the BMI subgroup analysis, while group 2 comprised of 16 subjects. Yet the remaining question is, why do the paediatric patients of our cohort on average tend to climb up the age- and gender-specific BMI percentile curves? Some potential mechanisms explaining weight change in patients with dystonia and Parkinson's disease after DBS treatment have been suggested, including the improvement of dyskinesias and the reduction of resting tremor as well as dysphagia leading to mitigation in energy expenditure, changes in eating behaviour and food intake, and alterations in hormone and neurotransmitter systems[18,19]. Further explanations may include: The children and adolescents are not only experiencing more functionality during the eating process after surgery, but they also have greater appetite due to improved participation in social eating, e.g. in the context of postoperative social and neuro-rehabilitative integration programmes, childcare facilities, (pre-)school, etc. A decrease in energy expenditure may be attributable to the reduction in intermittent or sustained muscle contractions. However, the exact mechanism underlying weight gain after DBS implantation remains unknown and is certainly attributable to many factors.

5.3. Improving Patient Selection for DBS in Paediatric Patients

The challenge for neuromodulation in paediatric patients with dystonia is to unlock the full potential of this technique and to apply it at the ideal time in the child's development and, of course, in the child best condition for the procedure[20]. Invasive neuromodulation for dystonia management should be performed before the often progressive movement disorder has caused consequential health damage, for example orthopaedic deformations, and before the window of opportunity for developmental neuroplasticity has been missed[20]. In childhood, the timing of surgery is even more crucial, as successful intervention could,

in addition to the outright benefits of reducing unwanted movement, lead to pain reduction, reduced use of sedative medication, mood improvement and increased access to and participation in social and educational life which may improve quality of life[11,169].

According to Speelman et al., negative outcome predictors are, aside from neurosurgical technical issues, long duration of disease, fixed joint contractures, and additional motor disorders such as spasticity and cerebellar dysfunction[8,20]. A 2006 meta-analysis demonstrated that a longer duration of dystonia symptoms in general correlates negatively with surgical outcome[4]. Later, Isaias et al. delved more into details and stated that "disease duration [of patients with isolated dystonia] is inversely correlated with the magnitude of the response to DBS as measured by the percent change in the BFMDRS motor score" (Isaias et al., 2011, p. 1473)[7]. In addition, "age at surgery directly correlated with continued BFMDRS improvements […] between years 1- and 3-year of follow-up, suggesting that older dystonia patients (independent of their duration of disease) may require more time to achieve their maximal response to pallidal stimulation" (Isaias et al., 2011, p.1473)[7]. In 2013, Lumsden et al. went even one step further and postulated that the response to pallidal DBS in the treatment of dystonia decreases with the proportion of years of life spent with dystonia in isolated, combined and acquired dystonia (from Lumsden et al. referred to as primary and secondary dystonia)[11]. This conclusion was based on a retrospective study of a cohort of 63 paediatric patients[11]. If one pursues this thesis, one could explain the worse average outcome of groups 2 and 3 of our cohort as follows: the years of life lived with dystonia before implantation are about two years higher in the group of combined dystonia and about an average of five years higher in the group of acquired dystonia as compared to the average duration of disease before implantation in group 1. Since the duration of disease in groups 2 and 3 is generally larger than in group 1, this could have led to an average worse outcome in those groups.

Eventually, the above-mentioned study by Lumsden et al. confirms and extends previous findings indicating that less years of life lived with dystonia before DBS implantation as well as a lower age at implantation predict better clinical outcomes in patients with isolated inherited and idiopathic dystonia in the short-and medium-term follow-up[4,6,7,10,11,170,171].

Markun et al. published their study on the correlation between shorter disease duration in patients with isolated dystonia and improved long-term DBS outcomes in 2012. The study described that especially at long-term follow-up, multiple linear regression analysis revealed a significant influence of duration of disease as a predictor of percent improvement in BFMDRS in the cohort[10]. Interestingly, we did not see a significant negative correlation in our multiple regression analysis for the group of patients with isolated inherited and idiopathic dystonia and A) years of life lived with dystonia as well as B) age at implantation to predict percentage change in BFMDRS after 3 years +/- 6 months to 6 years +/- 6 months postoperatively. This may be due to the fact that the sample of group 1 in the long-term follow-up is smaller than in follow-up 1 and 2 (missing data from 17 out of 29 patients in follow-up 3 vs. missing data from 14/11 patients in follow-up 1/2, respectively) and that the results in BFMDRS motor score are more heterogeneous.

However, on the basis of my findings, I cannot confirm the hypothesis that all children with dystonia, regardless of whether they suffer from isolated, combined or acquired dystonia, benefit from surgery early in the course of the disease or at a young age independently of the duration of the disease[11]. For instance, our medium-term multicentre analysis showed that patients with combined inherited and idiopathic dystonia even responded significantly better to DBS assessed by the BFMDRS motor score percentage changes the higher the age at implantation was. For the group of acquired dystonia, however, it is considered certain that the lower the age of onset of dystonia in paediatric patients, the better the long-term effect of DBS. Within the framework of the analysis of the correlation between 'years of life lived with dystonia' and 'outcome', no statistically significant result was obtained for the group of combined inherited and idiopathic dystonia.

Additionally, novel findings of this registry-based analysis are that age at implantation and years of life lived with dystonia before DBS implantation (disease duration) likewise do not appear to play complementary roles in predicting clinical outcomes in patients with acquired dystonia undergoing GPi-DBS. Years of life lived with dystonia before implantation and age at implantation do not seem to serve as preoperative factors aimed at predicting a better response to DBS for the combined inherited and idiopathic dystonia as well as for the acquired dystonia group. As a result, DBS might not be considered early in every patient diagnosed with dystonia since short disease duration before implantation only led to maximised benefits in the group of isolated dystonia, and short-term maximised benefits in the group of acquired dystonia[11]. Even if selection criteria for DBS procedures exist[25], it is necessary to act according to the principles of personalised medicine. The indication for DBS needs to be considered individually with weighing up the risk to benefit ratio.

The goal of pallidal DBS should be to maximise individual clinical efficacy while minimising adverse effects[172]. Overall, the perioperative risks of DBS surgery are low, and postoperative complications are manageable in most cases, with DBS lead infection and infection of the IPG being the biggest postoperative adverse events[20,42]. Previous studies suggest that the occurrence of serious adverse events such as infections is higher in approximately 60 percent of the children implanted at an age younger than ten years, with the rate of adverse events being the highest at the age of seven to nine years at implantation[42,152]. Keen et al. suggest that young children may have increased infection risk after reporting a 40% rate in a small group of five patients aged eight to 17 years[153]. Air et al. even published a 57% infection rate in patients younger than ten years[152]. Those disclosures contrast with findings of a large single-centre study published by Kaminska et al[147]. In this study, data was collected as a prospective audit and additionally from a questionnaire on recharging of the stimulators. Kaminska et al. reported lower infection rates following DBS for dystonia than in comparable literature[147]. Especially in patients aged under seven years, no increased risk for postoperative infections has been detected (infection rate amounted to 7.6% in patients under seven years)[147]. Although Kaminska et al. reported lower than previously described DBS infection rates particularly for patients under seven years, they identified relatively high incidence of technical problems with electrodes, extensions and recharging (18.4%, with the

latter analysis not explicitly referring to patients under seven years of age but summarising the entire cohort with mean age at the DBS implantation of 10.8 years with a range from three to 18.8 years)[147].

Moreover, even if DBS implantation for isolated inherited and idiopathic dystonia achieves a better post-operative outcome at a younger age as shown in this study, there may be certainly physical limitations to DBS placement, and additional expenditure in the scope of post-operative monitoring may occur. Indeed, implanting a DBS system in paediatric patients whose brains are still growing may lead to electrode dislocation or tension of the extension lead over time[20]. Nevertheless, one study that focussed on modelling this using skull and brain growth deduced that it is unlikely that growth will cause significant electrode motion until after the age of seven[173].

Taking a potentially increased risk of side effects into account with younger age or shorter duration of disease before implantation is important for the indication of DBS surgery. Based on the current available evidence, however, no consensus can be found and a potentially increased incidence of AEs or an altered side effect profile with younger implantation age or shorter duration of disease before implantation cannot be depicted. Nonetheless, in addition to taking heed of prognostically favourable factors for the postoperative effect of DBS such as less years of life lived with dystonia before DBS implantation and an earlier age at implantation, the patient's safety and comfort should always be given priority in the individual decision on the optimal time for DBS implantation.

Insufficient outcomes were also related to structural lesions and degeneration of the GPi and neighbouring structures in the preoperative cMRI as well as to the preoperative presence of surgically untreated musculoskeletal deformities.

In the combined inherited and idiopathic dystonia group only just under half of the patients and in the acquired dystonia group only approximately 16% had a preoperative cMRI without degeneration or structural lesion in the basal ganglia. Although neuroimaging may not at all times correlate with physiological findings[20], we know that the presence of lesions in both hemispheres [negatively] impacts the extent cortical reorganisation[174]. Indeed, the presence of bilateral brain injury in patients with cerebral palsy (CP) can impair neuroplasticity [174]. Poorer response to DBS in patients with dystonia may consistently be rooted in the theory that the greater the neuroplasticity, the greater the response to DBS – hence, the smaller the cerebral plasticity, the worse the response to DBS[20,175,176]. Moreover, Horn et al. found out that structural and functional connectivity were independent predictors of clinical improvement after DBS[177]. Presumably, structural lesions and neurodegenerative alterations in the basal ganglia indicate that this structural and functional connectivity may be disturbed. Bari et al. defined the selection criteria for DBS of the subthalamic nucleus (STN-DBS) in Parkinson's patients which are intended to optimise the efficiency of STN-DBS[172]. In their work, they even go so far as to state that for optimal patient selection, a normal preoperative cMRI of the brain must be available as well as it is mandatory to exclude structural lesions, diffuse ischaemic changes or severe atrophy in the cMRI before DBS surgery[172].

Accordingly, another reason why our cohort of acquired dystonia as well as the group of combined inherited and idiopathic dystonia showed a lower postoperative effect on dystonia severity can be linked to the fact that particularly in those groups, the prevalence of preoperatively diagnosed fixed contractures or orthopaedic deformities is higher than in our group of isolated dystonia (see Table 9). The reasons for this may be that more effective symptomatic treatments, for example intramuscular botulinum toxin injections, are available for isolated dystonia than for acquired or combined dystonia. Furthermore, in isolated dystonia, less other (movement or neurodegenerative) disorders restricting mobility and increasing prevalence of fixed contractures occur than in combined dystonia. Preoperative presence of fixed contractures as well as orthopaedic deformities such as hip dysplasia or scoliosis has been unanimously anticipated to be a predictor of poor DBS outcome in the literature[8,178]. Alterman et al. state for example that the presence of static dystonic postures and/or fixed orthopaedic contractures may limit the functional response to DBS and may require additional surgery[178]. However, it should be emphasised again at this point that based on the GEPESTIM cohort, one may assume that orthopaedic deformities that had been pre-treated (surgically), might be no longer a predictor of poor response to DBS in all cases. Patients of the GEPESTIM cohort with preoperatively documented orthopaedic deformities who had been successfully treated surgically prior to DBS implantation, e.g. tendon releases and osteotomies, experienced a statistically significant relative improvement in BFMDRS motor score when comparing mean preoperative scores with mean postoperative scores for all follow-ups (mean preoperative BFMDRS was 66.9, mean postoperative scores were in absolute numbers/ in relative improvement compared to preoperative scores: 33.7/ 49.2, 28.6/ 59.1, 35.3/ 51.5, with p=0.003, p=0.013 and p=0.037 for short-term, medium-term and long-term follow-up scores, for more details see Table 9). However, the small sample size of N=six patients who underwent surgery to improve fixed contractures or orthopaedic deformities, of which only N=five subjects had documented pre- and postoperative BFMDRS scores, limit the statistical validity of this thesis.

5.4. Probabilistic 'Sweet Spot' Analysis

Due to the complexity of the disease and to the high number of variables that seem to play a role for the ultimate DBS success, it can be difficult to evaluate retrospectively and in detail why a particular patient has a poor DBS outcome. Recently, one variable has been the subject of intensive research: the 'sweet spot'. Based on adult patient data, a “positive and statistically significant correlation between the overlap ratio of a patient's individual stimulation volume and the probabilistic map's sweet spot” was reported[22] (Nguyen et al., 2019, p. 1127). In accordance to 'sweet spot' analysis on adult populations, “overlap of each combined bilateral stimulation volumes with the sweet spot correlated with the corresponding DBS-associated clinical improvement” in our paediatric cohort, either (Al-Fatly, 2023, p. 5)[27].

The accuracy of electrode placement is considered a key determinant of clinical improvement following DBS surgery[23]. As a result, one potential contributor to the poorer outcomes observed in paediatric

patients with acquired forms of dystonia may be sub-optimal electrode placement. Furthermore, 'sweet spots' need to be stimulated to achieve the greatest possible DBS success[22,23,179].

'Probabilistic Stimulation Mapping' (PSM) is a technique for understanding, and consequently reducing, the variability in outcome following DBS in paediatric patients with dystonia by defining voxels within the GPi/thalamus that seem to be associated with the largest improvement in BFMDRS motor score[23]. A probabilistic map's 'sweet spot' is commonly defined as "the ten percent of voxels with the highest clinical efficacy values" (Nguyen et al., 2019, p. 1127)[22].
Lumsden et al. recently published results from a novel PSM study, too. The researchers were able to show that in young patients with inherited or idiopathic dystonia who underwent DBS and presented with good postoperative effects, voxels clustered in a small region of the posteroventrolateral GPi had been identified to be consistent with anti-dystonic 'sweet spots' defined by two previous studies[23]. For the genetic/idiopathic dystonia group, BFMDRS improvement had been associated with stimulation across a broad volume of the GPi (VTA)[23]. The CP group of their cohort presented with minimal BFMDRS improvement after surgery and, in contrast to their inherited or idiopathic dystonia group, no spatial clustering of efficacious clusters or correlation between established 'sweet spot' could be identified[23]. Lumsden et al. concluded that PSM in paediatric patients with genetic/idiopathic dystonia but not with acquired dystonia demonstrated the presence of a definable 'sweet spot' for electrode placement within the GPi[23].

Overall, this concept of a computer-based prediction of optimal initial lead placement combined with best stimulation parameters for patients with dystonia is promising. With the help of 'sweet spot' analysis, we were able to look at the clinical effects of paediatric DBS from an electrode localisation perspective. With functional network analysis, the concept of the 'sweet spot' was extended, and related information from whole-brain regions that are indirectly, or through polysynaptic links, connected to the DBS electrode location has been extracted[27]. By locating reliable 'sweet spots' and using them as implant sites, the efficiency of DBS can be increased on the one hand. On the other hand, computer-guided DBS programming might provide optimal stimulation settings for patients on remote and without the burden of months of programming sessions[180].

5.5. Limitations

Methodologically, the BFMDRS movement score has limitations in the assessment of dystonia severity in patients with complex motor disabilities[154]. The most overt limitation is that when choosing to measure a percentage change between baseline BFMDRS and postoperative BFMDRS motor score, more severe cases seem to respond less well than mild cases[20]. But especially in the combined inherited and idiopathic and acquired dystonia group, patients tend to have a much more complex movement disorder. This makes the treatment of combined inherited and idiopathic and acquired dystonia with DBS more challenging, as there is a wide spectrum of degree in motor impairment and fixed abnormalities. The

effect of DBS may not be fully captured by the BFMDRS motor score in these patients due to its lower validity for acquired and combined dystonia. Trials indicate that a small improvement in movement dysfunction after pallidal DBS releases a measurable level of activity and participation in the patient's everyday life[181], which needs to be assessed by other scores such as the Canadian Occupational Performance Measure (COPM) , a subjective scale of performance and satisfaction in personalised objectives[20,154,181]. Therefore, the sole use of this impairment score may not fully reflect DBS effects in patients with combined and acquired dystonia.

Despite their high ranking in the hierarchy of clinical studies, the implementation of intervention studies such as placebo-controlled, randomised clinical trials is often not possible in a neuropaediatric field of research which is mainly due to ethical constraints and the rare prevalence of the diseases[182]. Therefore, prospective or retrospective cohort studies are frequently used to answer research questions[182].
Nevertheless, limitations of the GEPESTIM study arising from its retrospective study design need to be discussed. Although Talari and Goyal postulate that retrospective studies are an essential instrument to study rare diseases, manifestations and outcomes, and the results of these studies commonly form the basis on which prospective studies are planned and designed, retrospective cohort studies come with disadvantages[183]. For instance, some key statistics cannot be measured due to the unavailability of data. Since retrospective data collection depend on the review of charts and surgery protocols that were originally not designed to collect data for systematic research, information is inevitably missing[183]. Regarding the GEPESTIM study, it proved difficult to collect missing but essential data in a post-hoc analysis. This was particularly a matter of concern with regard to missing baseline BFMDRS scores. Thus, some patients had to be excluded from evaluation because of missing preoperative BFMDRS scores, leading to a substantial reduction in sample size, and moreover, to a reduction of the quality of the analysis. Additionally, with smaller sample sizes, the p-values deviate from significance[184]. Besides, retrospective studies generally need larger sample sizes for exposing rare outcomes. Furthermore, researchers are not able to control exposure or outcome assessment in retrospective studies[185].
Another disadvantage of the retrospective study design: When gathering data within a retrospective study design, one must rely on the “accuracy of written record or recall of individuals [recall bias]” (Hess, 2004, p. 1174)[185]. Finally, information bias must be taken into consideration. Information bias occurs when information used for data analysis is either measured or recorded inaccurately[186]. These measurements can be in various forms, such as responses to self-administered questionnaires, physical measurements or information in medical records[186]. To prevent information bias, it is necessary to use standard measurement instruments, e.g. questionnaires or national-wide standardised diagnostical tests, and the person collecting the data should be non-informed about the intervention’s outcome (double blinding). Information biases often occur during the data collection phase, and an essential type of information bias is the misclassification bias[187]. According to Tripepi et al., a “misclassification bias is present when the detection of the exposure status (exposure identification bias) and/or the disease assessment (disease identification bias) is biased” (Tripepi et al., 2010, p.98)[187].

A case in point: During the data analysis of the GEPESTIM study, it was noticed that two patients had been incorrectly classified. Based on data from medical reports, two patients were assigned to the combined dystonia group. Given that the documented symptom complex of each of the two patients did not fit the combined dystonia criteria, we initiated a differentiated evaluation of the symptoms and consultation with two independent dystonia experts who revised the status of combined dystonia; the patients were then recategorized into the group of isolated dystonia. Unfortunately, subgrouping may occasionally be challenging due to the complexity and versatility of dystonia and since the definitions and classifications of dystonia are constantly being revised.

5.6. Future Perspectives

In our analysis, we primarily identified which preoperative factors play a role in achieving the best possible outcome of DBS. What we did not investigate further, but which we find important to mention here, is the assumption that the structural formation of the GPi in terms of volume and tissue integrity, could also impact the varying benefits of DBS[165]. In addition to neuroimaging, it might also be important to measure neurophysiological biomarkers in children who may be candidates for DBS and to determine if responsiveness to DBS can be more accurately predicted by using for example neurophysiological imaging such as transcranial magnetic stimulation for central motor conduction time evaluation[20,77]. While DBS surgery makes it possible to both record brain activity and stimulate parts of the brain that are difficult to reach with non-invasive techniques, electroencephalography for example provides complementary information from other brain areas, which can be used to preoperatively characterise brain networks targeted through DBS[188]. Moreover, some preoperative factors are difficult to quantify, for which reason we did not include them in our analysis. For example, experience and commitment of the stereotactic team are considered predictors of a good response to DBS by some authors[8].

We were also not able to analyse the quality of postoperative care as a predictor for a good DBS outcome, which probably is a key determinant for long-term treatment response. Once the ideal patient is selected and the optimal surgical target has been appropriately accessed, the post-surgery care then lies in the physician’s ability to select the best contacts and programming[20]. One aim for improvement of treatment would be to identify biomarkers for network responses that can be adapted to guide stereotactic implantation or optimisation of stimulation parameters, which is especially important for diseases where the clinical effect of DBS is delayed or develops slowly over time[188].

A software-based, individualised calculation of the best stimulation parameters, based on optimal electrode placement and the patient's current symptoms, would improve postoperative patient care. Lead-DBS already provides as innovative toolbox that facilitates reconstruction of the lead electrode trajectory and contact placement and may also be a key element in improving postoperative care[189]. The programme may help clinicians to identify the best stimulation contacts based on anatomical target areas but is has not yet been approved for clinical practice[189]. Intelligent programmes such as Lead-DBS or AI-based software may simplify and customise optimal programming and may shorten test stimulation protocols in the future[189]. Moreover, Al-Fatly et al. were able to implement a paediatric neuroimaging

dataset that is available for public use as a tool for paediatric DBS analysis[27]. However, further work is required to validate 'sweet spots' and functional connectivity fingerprints of DBS outcomes across different and larger cohorts of patients, and particularly those with differing dystonia aetiology including paediatric patients with acquired dystonia[23].

With the aid of the GEPESTIM registry, it became feasible to thoroughly assess the effects and factors predicting protracted improvement after pallidal DBS in a sizeable paediatric cohort, providing valid information to improve the management of these patients. Moreover, one option helping to minimise the incidence of certain biases, such as selection or information bias, may be to employ a prospective study design for advanced studies. In the future, the collected data need to be confirmed by an even greater number of patients. According to Marks et al. this can be accomplished through an organised platform for international data sharing called 'PEDiDBS'[190]. PEDiDBS is managed by an executive committee and administered by a project manager[190]. The goal of the project is to foster collaborative research and develop evidence- and practice-based guidelines elucidating the role of DBS in a paediatric population by using internationally prospectively and retrospectively collected data[190].

6. Conclusion

DBS can be an efficacious treatment option for medication-refractory childhood-onset inherited, idiopathic and acquired dystonia. 21 years after GPi-DBS was officially approved for dystonia in the European Union[191], it is now possible to discuss not only short-, medium- and long-term outcome within the various aetiologies of dystonia but also patient selection in routine clinical practise. Younger patients with shorter disease duration and late age at onset suffering from isolated inherited and idiopathic dystonia fare best after pallidal DBS. Based on our results, this thesis does not necessarily hold for the group of combined inherited and idiopathic as well as for the group of acquired dystonia. Hence, good clinical phenotyping and genotyping plays an important role in patient selection, in addition to the assessment of preoperative cMRI findings and a detailed paediatric orthopaedic-neurological preliminary examination to exclude or detect fixed contractures and skeletal deformities, which should be subjected to treatment. Further multicentre studies are essential to determine the medium- and long-term role of pallidal DBS as well as the impact of neurophysiological/network biomarkers and findings from probabilistic 'sweet spot' analysis as predictors of treatment efficacy in the therapy management of isolated, combined and acquired dystonia.

7. Appendix

7.1. Table of Figures

7.2. List of Tables

7.3. Additional Information on the Historical Background of Dystonia

The term 'dystonia' (Ancient Greek δύς- dys- 'bad', 'wrong'; τόνος tonos 'tension') derives from Latin and ancient Greek and was used to describe abnormal postures and misregulated, pathological muscular toni observed in some patients with corresponding movement disorders[29]. Accordingly, Oppenheim used the term “dystonia musculorum deformans” to portray that the children's muscle tone was occasionally as much hypotonic as it was hypertonic (Oppenheim, 1911, p. 1090)[44]. Tonic muscle spasms, partly but not exclusively triggered by voluntary movements, followed episodes of poor strength and tension of the same skeletal muscles[1,41].

In a publication published in 1911, the Polish neurologists Flatau and Sterling described the occurrence of torsional spasms as the main clinical symptom of dystonia; varying muscle tone was not an essential element in their definition of dystonia[192]. As an alternative term to dystonia, they proposed “Progressiver Torsionsspasmus bei Kindern [=progressive torsional spasm in children]” (Flatau & Sterling, 1911, p. 586)[192]. Thus, Oppenheim, Flatau and Sterling described that different characteristics of the symptom complex of dystonia can present themselves in very different ways and in varying severity in different individuals, a finding that has meanwhile become consensus. Oppenheim's term for dystonia has prevailed until now, and some of the clinical features and characteristics depicted by Flatau and Sterling have been integrated into the phenomenological disease description of dystonia.

The aetiology of dystonia has always been controversially discussed. As a body of knowledge about dystonia emerged during the late 19th to early 20th centuries, two intellectual undercurrents shaped the development of modern neurology, both of which had a lasting impact on the classification, categorisation and further approach to the study of dystonia[46]. From an aetiopathogenetic point of view, dystonia has long been seen on the fine line between a functional and an organic disease[193]. With his 'methode clinico-anatomique', Jean-Martin Charcot (1825–1893) postulated that a clear neuroscientific distinction should be made between organic diseases that could be attributed to structural changes in the central and peripheral nervous system and functional syndromes whose aetiopathogenesis could not be explained on the basis of lesions and other pathologies in the CNS and PNS[46].

As various forms of dystonia were described over the next few decades, they were first classified by Charcot as 'névroses': his term for disorders with no detectable neuroanatomical cause at the time[46,194]. However, Charcot believed that dystonia was of organic aetiology, but since the possibilities of imaging and electrophysiological diagnostics were unavailable at the time, this theory could not be objectively confirmed[194]. Although Charcot went so far as to believe that even hysteria, now classified as a somatoform or dissociative disorder, was also purely organic, the dichotomy of neurology and psychiatry he called for accelerated research into the potential neuroanatomical basis of dystonia[46].

Another person who influenced the development of modern neurology, and consecutively on dystonia research, was psychoanalyst Sigmund Freud (1856–1939)[46]. He published theories about early life experiences and resulting psychological stresses that would be transformed into physical symptoms[46].

Freud's theories were soon applied to the theory of why and how dystonia might manifest, which subsequently occupied a borderline area between neurology and psychiatry for many years[46].

Not only Oppenheim but also Flatau and Sterling described the clinical features of dystonia in some Jewish children affected by a syndrome that was retrospectively considered a familial case of DYT-TOR1A dystonia[44,192]. While Oppenheim, who examined numerous Jewish children as well as other patients with dystonic movement disorder, suspected an organic disorder early on, Schwalbe attributed the development of dystonia to a psychogenic aetiopathogenesis with a hereditary component based on a familial cluster of symptoms which he described as hysterical[39].
In 1944, Ernst Herz, a German physician, did research in the field of dystonic movement patterns and muscle excitation using electrophysiological and cinematographic methods[39,41]. Using image sequencing, Herz was able to quantify abnormal muscle contractions in patients with dystonia and defined the presence of persistent abnormal postures and positioning as an essential diagnosis criteria for dystonia[39]. Not only the electrophysiological method to quantify abnormal muscle movements detected by Herz but also the description of several hereditary cases at the end of the 1950s plus the insufficient effects of psychotherapy in torsional dystonia contributed to the fact that the organic genesis of dystonia could be verified[39,195,196].

A few years later, in 1975, the first international conference on dystonia was held in New York[46]. After information on dystonia has been put together on an international level, it turned out that dystonia phenotype included not only severe generalised forms but also slowly progressive focal and segmental cases with onset in adulthood such as blepharospasm, torticollis and writer's cramp[1]. In 1985, the English neurologist Marsden published a journal article describing his findings after conducting a cohort study with 28 patients suffering from focal dystonia or hemi-dystonia who had a history of tumorous masses, arteriovenous malformations, infarction, haemorrhage or hemiatrophy of the brain. He found that the core cause of dystonia was abnormal input from the thalamus to the premotor cortex leading to disturbed circuitry within the basal ganglia[197]. If this circuitry is disturbed, e.g. caused by direct lesions in the thalamus or by lesions in the striatum, abnormal or dysregulated stimulus transmission from the thalamus to the premotor cortex is the consequence, which in Marsden's cohort manifested clinically as dystonia[197]. The lesions responsible for dystonia were detected by computed tomography and pathological examination and were located in the contralateral caudate nucleus, lentiform nucleus (especially in the putamen), thalamus or a combination of these structures[197]. In 1997, Ozelius and colleagues identified a gene mapping technique via linkage analysis and discovered the DYT-TOR1A gene, which is located on chromosome 9q34 and is responsible for most cases of early-onset torsional dystonia in both Ashkenazi Jewish (AJ) and non-Jewish families[86]. This disease is inherited in an autosomal dominant mode with reduced penetrance (30%–40%)[85]. The identification of the gene solidified the thesis that dystonia can not only be acquired, but also congenital through gene mutation.

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7.5. Publication List (Pre-published Results)

Al-Fatly, B., Giesler, S. J., Oxenford, S., Li, N., Dembek, T. A., Achtzehn, J., Krause, P., Visser-Vandewalle, V., Krauss, J. K., Runge, J., Tadic, V., Bäumer, T., Schnitzler, A., Vesper, J., Wirths, J., Timmermann, L., Kühn, A. A., Koy, A., & GEPESTIM consortium (2023). Neuroimaging-based analysis of DBS outcomes in pediatric dystonia: Insights from the GEPESTIM registry. NeuroImage: Clinical, 39, 103449. Doi: 10.1016/j.nicl.2023.103449. PMID: 37321142; PMCID: PMC10275720.

7.6. Additional Material

Table 10 a) – i) (Appendix): *Linear regression model – parameter estimates for follow-up 1, 2 and 3*

a) Dependent Variable: Relative improvement in BFMDRS 0–6 months postoperative (follow-up 1)

					95% Confidence Interval	
Parameter	B	Std. Error	t	p-values	Lower Bound	Upper Bound
[group=1]	,696	,092	7,597	,000	,511	,882
[group=2]	,024	,129	,190	,851	-,236	,285
[group=3]	,171	,195	,875	,387	-,224	,565
[group=1] * lifetime**	-,036	,012	-2,943	,006	-,060	-,011
[group=2] * lifetime**	,010	,016	,668	,508	-,021	,042
[group=3] * lifetime**	-,010	,015	-,643	,524	-,041	,021

b) Dependent Variable: Relative improvement in BFMDRS 1 years +/- 6 months to 2 years +/- 6 months postoperative (follow-up 2)

					95% Confidence Interval	
Parameter	B	Std. Error	t	Sig.	Lower Bound	Upper Bound
[group=1]	,832	,114	7,315	,000	,603	1,061
[group=2]	,076	,179	,423	,674	-,284	,436
[group=3]	,086	,158	,544	,589	-,233	,405
[group=1] * lifetime**	-,045	,015	-2,932	,005	-,075	-,014
[group=2] * lifetime**	,004	,020	,208	,836	-,036	,044
[group=3] * lifetime**	-,001	,013	-,091	,928	-,027	,025

c) Dependent Variable: Relative improvement in BFMDRS 3 years +/- 6 months to 6 years +/- 6 months postoperative

					95% Confidence Interval	
Parameter	B	Std. Error	t	Sig.	Lower Bound	Upper Bound
[group=1]	,616	,143	4,299	,000	,321	,911
[group=2]	-,044	,240	-,182	,857	-,538	,450
[group=3]	-,347	,310	-1,120	,273	-,984	,290
[group=1] * lifetime**	-,022	,022	-1,045	,306	-,067	,022
[group=2] * lifetime**	,013	,023	,573	,571	-,034	,060
[group=3] * lifetime**	,033	,023	1,430	,165	-,014	,080

**years of life lived with dystonia before implantation of DBS system (in years).

e) Dependent Variable: Relative improvement in BFMDRS 7 months to 2 years +/- 6 months post-operative

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound	Upper Bound
[group=1]	,279	,156	1,784	,081	-,036	,593
[group=2]	-,037	,107	-,345	,732	-,252	,178
[group=3]	,059	,075	,793	,432	-,091	,210
[group=1] * Age at onset of Dystonia in years	,057	,029	1,976	,054	-,001	,114
[group=2] * Age at onset of Dystonia in years	,042	,022	1,916	,062	-,002	,086
[group=3] * Age at onset of Dystonia in years	,008	,023	,353	,726	-,038	,054

f) Dependent Variable: Relative improvement in BFMDRS 3 years +/- 6 months to 6 years +/- 6 months postoperative

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound	Upper Bound
[group=1]	,211	,213	,989	,332	-,227	,649
[group=2]	,080	,172	,465	,646	-,274	,435
[group=3]	,163	,086	1,894	,069	-,014	,339
[group=1] * Age at onset of Dystonia in years	,056	,038	1,458	,157	-,023	,134
[group=2] * Age at onset of Dystonia in years	-,001	,028	-,024	,981	-,058	,056
[group=3] * Age at onset of Dystonia in years	-,090	,037	-2,443	,022	-,167	-,014

g) Dependent Variable: Relative improvement in BFMDRS 0–6 months postoperative

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound	Upper Bound
[group=1]	,957	,186	5,140	,000	,580	1,335
[group=2]	-,117	,170	-,692	,493	-,461	,226
[group=3]	,140	,242	,579	,566	-,351	,631
[group=1] * AgeatImplantation-ofDBSsystem	-,044	,016	-2,682	,011	-,077	-,011
[group=2] * AgeatImplantation-ofDBSsystem	,021	,015	1,373	,178	-,010	,052
[group=3] * AgeatImplantation-ofDBSsystem	-,007	,018	-,382	,705	-,043	,029

h) Dependent Variable: Relative improvement in BFMDRS 7 months to 2 years +/- 6 months post-operative

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
[group=1]	1,151	,226	5,089	,000	,695	1,606
[group=2]	-,456	,258	-1,768	,084	-,975	,064
[group=3]	,034	,242	,141	,888	-,453	,521
[group=1] * AgeatImplantation-ofDBSsystem	-,054	,020	-2,725	,009	-,094	-,014
[group=2] * AgeatImplantation-ofDBSsystem	,049	,021	2,281	,027	,006	,091
[group=3] * AgeatImplantation-ofDBSsystem	,003	,018	,166	,869	-,033	,039

i) Dependent Variable: Relative improvement in BFMDRS 3 years +/- 6 months to 6 years +/- 6 months postoperative

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
[group=1]	,591	,295	2,003	,056	-,016	1,198
[group=2]	-1,130	,862	-1,311	,201	-2,902	,642
[group=3]	,005	,456	,012	,991	-,931	,942
[group=1] * Age at Implantation of DBS system	-,009	,027	-,332	,743	-,065	,047
[group=2] * Age at Implantation of DBS system	,085	,060	1,414	,169	-,039	,209
[group=3] * Age at Implantation of DBS system	,005	,032	,165	,870	-,061	,071

Table 11 (Appendix): *Estimates of fixed effects[a], Type III Tests of fixed effects (change in BMI measured by percentiles)*

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept (group 1, 2, 3)	24.551114	5.772666	34.462	4.253	.000	12.825429	36.276799
visit	3.533005	1.476367	30.867	2.393	.023	.521407	6.544603

[a]Dependent Variable: perc.

Estimates of Fixed Effects[a] (Change in BMI measured by percentiles)

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
[Classification_Of_Dystonia=1,00]	20.262822	11.038819	32.134	1.836	.076	-2.218840	42.744484
[Classification_Of_Dystonia=2,00]	32.622918	8.780591	32.883	3.715	.001	14.756263	50.489574
[Classification_Of_Dystonia=3,00]	16.444579	11.130914	33.192	1.477	.149	-6.196453	39.085610
visit	3.775196	2.826507	31.281	1.336	.191	-1.987409	9.537801
[Classification_Of_Dystonia=1,00] * visit	3.288068	3.906279	29.631	.842	.407	-4.693790	11.269927
[Classification_Of_Dystonia=2,00] * visit	-2.846138	3.610596	31.316	-.788	.436	-10.206991	4.514715
[Classification_Of_Dystonia=3,00] * visit	0[b]	0	.	.	.	.	.

[a]Dependent Variable: perc.

[b]This parameter is set to zero because it is redundant.