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Maija Lahtinen

DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE AND PAEDIATRIC DBS SERVICE

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UNIVERSITY OF OULU,
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Abstract

Idiopathic Parkinson's disease (PD) is globally the most common neurodegenerative movement disorder and it affects not only physical and cognition but also the activities of daily living and social life. Deep brain stimulation (DBS) is the neurosurgical treatment in advanced PD and it is the most common indication of DBS surgery. In PD, the most common target area of stimulation is the subthalamic nucleus (STN) in order to alleviate motor symptoms, e.g., rigidity, tremor and bradykinesia. After STN DBS, PD-medication, which includes levodopa, can be reduced. Thus, levodopa-induced involuntary hyperkinetic movements, i.e., dyskinesias are alleviated and the PD patient's condition becomes more stable.

Studies I-II were undertaken to evaluate the beneficial effects of bilateral STN DBS stimulation on PD patient's motor symptoms and levodopa reduction 12 months after DBS surgery, when the DBS surgery was based on high-quality 3T MRI and the follow-up was conducted by the same DBS team. The results were compared with a previous study from OUH, which was presented by Tuomo Erola in his 2006 thesis. In Study II, the main interest was to study whether stimulation of the hyperdirective pathways between the lateral border of the STN and prefrontal cortex correlated with the motor outcome and levodopa reduction. The study implicated that diffusion tensor images (DTI) -based tractography can be applied in a clinically reasonable way for DBS targeting.

The paediatric population is the smallest and the most fragile DBS patient group and the usual indication is severe hyperkinetic movement disorder, e.g., dystonia. Paediatric DBS surgery (pDBS) is not an everyday procedure and the pre- and postoperative preparations are as important as the surgery itself. For this reason practical instructions are required when starting a pDBS centre. This is the topic of Study III.

Keywords: deep brain stimulation, diffusion tensor imaging, levodopa, magnetic resonance imaging, Parkinson's disease, pediatric dystonia, subthalamic nucleus

Lahtinen, Maija, Syväaivostimulaatio Parkinsonin taudin hoidossa ja lasten syväaivostimulaatiopalvelu.

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Tiivistelmä

Parkinsonin tauti on maailmanlaajuisesti yleisin aivoja rappeuttava liikehäiriösairaus. Se ei vaikuta ainoastaan ruumiillisesti ja tietotaidollisesti, vaan myös potilaan ja hänen läheisten koko arkielämään. Syväaivostimulaatio (engl. deep brain stimulation, DBS) on neurokirurginen hoitomuoto, jonka käytön yleisin peruste on edennyt Parkinsonin tauti. Tavallisimmin stimulaation kohdealueena käytetään aivojen näkökukkulan alapuolista hermosolukertymää (lat. subthalamic nucleus, STN). Tämän alueen stimulointi lievittää parkinsonintaudin liikehäiriöitä (jäykkyyttä, vapinaa ja liikkeiden hitautta). Stimulaation aloituksen jälkeen levodopalääkitystä päästään keventämään, jolloin lääkityksen haittavaikutukset lievittyvät ja potilaan voinnista tulee vakaampi.

Tämän tutkimuksen I ja II osatyön aiheena oli arvioida parkinsonpotilaiden liikehäiriöoireiden ja levodopalääkityksen muutoksia 12 kuukauden seuranta-aikana STN DBS leikkauksen jälkeen. Leikkaustoimenpide perustui aivojen korkealaatuiseen korkeakenttämagneettikuvaukseen (3 tesla), ja leikkauksen jälkeinen yhden vuoden pituinen seuranta toteutettiin saman DBS-ryhmän toimesta. Tutkimustuloksia verrattiin Oulun yliopistossa vuonna 2006 julkaistuun Tuomo Erolan väitöskirjan tuloksiin. Lisäksi II osatyössä mielenkiinnon kohteena oli tutkia STN-ulkoreunan sekä otsalohkon etummaisen osan välisiä erityisen nopeita valkeanaivoaineen ratoja sekä sitä, onko ratojen eri osien stimuloinnilla vaikutusta potilaan liikehäiriön tai levodopalääkityksen muutokseen.

Tutkimuksen III osatyössä käsiteltiin lasten DBS-hoitoa. Tämän ryhmän potilailla on yleensä vaikea liikehäiriö, kuten esimerkiksi lihasvääntötauti (dystonia), mikä tekee heistä erityisen hauraan potilasryhmän. Lapsipotilaiden DBS-hoito vaatii hyvän ennakkovalmistelun sekä leikkauksen hyvän jälkihoidon ja seurannan. Tämän vuoksi oli tarpeellista luoda ohjeistus lasten DBS-hoidolle.

Asiasanat: diffuusiotensorikuvaus, lasten dystonia, levodopa, magneettikuvaus, Parkinsonin tauti, subthalaaminen tumake, syväaivostimulaatio

To my grandfather Toivo (eng. hope)

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The present study was carried in the Clinic of Neurosurgery, Neurocenter, Oulu University Hospital (OUH) headed by Docent Niina Salokorpi MD, PhD; the Division of Orthopedics and Neurosurgery, OUH headed by Susanna Yli-Luukko MD; the Unit of Neurosurgery, OUH headed by previous Professors John Koivukangas, Ville Leinonen, Aki Laakso and present Professor Mikael von und zu Fraunberg; Oulu Research Group of Advanced Surgical Technologies and Physics (ORGASTP); and Medical Research Center (MRC) at the University of Oulu from 2013 to 2023. I thank them all for the opportunity to use the facilities of their units.

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This study was inspired by Tuomo Erola's doctoral thesis *Deep brain stimulation of the subthalamic nucleus on Parkinson's disease* from 2006 published by the University of Oulu and supervised by Professor h.c. Esa Heikkinen, the pioneer of the DBS surgery in Finland.

First, I would like to express my gratitude and appreciation to my supervisors, Docent Jani Katisko, medical physicist, PhD; and Professor h.c. Esa Heikkinen, MD, PhD for their continuous support and guidance. Jani is the bright brains behind this study, constantly producing innovative ideas for research and clinical practice. He is one of the few who understands deeply the mechanisms of deep brain stimulation and the brain based on physical laws. Esa is the heart behind this study who remembers his DBS patients from many years ago in detail and knows the power of positive encouragement and feedback.

Second, I would like to express my gratitude to Professor Emeritus Willy Serlo, MD, PhD and Professor Mikael von und zu Fraunberg, MD, PhD from my follow-up group. Willy has been a driving force for the past year and without his enthusiastic encouragement this thesis would never have seen a printer. I also warmly thank him for guidance and support in the field of paediatric surgery. Mikael is a balancing force in our neurosurgical unit and we are happy to have a captain on board.

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thank paediatric neurologist Dr. Jean-Pierre Lin MD, PhD and the whole team of Complex Motor Disorders Service at the Evelina London Children's Hospital, London, UK, which our paediatric DBS team was honoured to visit in 2016. JP, your enthusiasm towards paediatric DBS treatment and your commitment to patients and their caregivers is inspiring. In the academic field, I would like to thank Professor Marwan Hariz MD, PhD who sent me a personal congratulatory e-mail when my first editorial was published in an academic journal in 2017. That message is posted on my office wall.

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Finally (before I get too sentimental), I would like to express my sincere thanks to the patients and their families who entrusted themselves into our hands.

Oulu, July 2023 Maija Lahtinen

List of Abbreviations

AC-PC	line between anterior commissure and posterior commissure
ADL	activities of daily living
ANT	anterior nuclei of the thalamus
ANT DBS	deep brain stimulation of anterior nuclei of the thalamus
BA	Broadman area
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
CFCS	Communication Function Classification System
CMCT	cortical motor conduction time
COMP	Canadian Occupational Performance Measure
COMT	Catechol-O-methyltransferase inhibitors
CP	cerebral palsy
CPCHILD	Caregiver Priorities & Child Health Index of Life with Disabilities
CT	computed tomography
cZI	caudal zona incerta
DBS	deep brain stimulation
dlPMC	dorsolateral premotor cortex
DRTC	dentato-rubro-thalamo-cortical tract
DTI	diffusion tensor imaging
EDACS	Eating and Drinking Ability Classification System
ET	essential tremor
FA	fractional anisotrophy
FDA	The United States Food and Drug Administration
FGATIR	fast gray matter acquisition T1 inversion recovery
GAS	Goal Attainment Scaling
GMFCS	Gross Motor Function Classification System
GPe	globus pallidus externa
GPi	globus pallidus interna
GPi DBS	deep brain stimulation of globus pallidus interna
HUS	Helsinki University Hospital
iMRI	interventional magnetic resonance imaging
IPG	implantable pulse generator
iTM	indirect targeting method
iv	intravenous
KELA	The Social Insurance Institution of Finland

LCT	levodopa challenge test
LEDD	levodopa equivalent daily dose (mg)
LESU	Enterprise resource planning for surgical procedures in Oulu University Hospital (Esko Systems Oy, Oulu, Finland)
LFP	local field potential
LITT	laser interstitial thermal therapy
MACS	Manual Ability Classification System
MCP	midcommissural point
medON	the best phase of levodopa medication
MEP	motor-evoked potentials
MER	microelectrode recording
MPRAGE	magnetization prepared rapid gradient echo
MRgFUS	magnetic resonance guided focused ultrasound
MRI	magnetic resonance imaging
M1	motor cortex
NPT	neuropsychological test
OCD	obsessive-complusive disorder
ORGASTP	Oulu Research Group of Advanced Surgical Technologies and Physics
OUH	Oulu University Hospital
PD	Parkinson's disease
pDBS	deep brain stimulation for paediatric patients
PKAN	pantothenate kinase-associated neurodegeneration
preSMA	presupplementary motor area
PVP	posteroventral pallidotomy
QoL	quality of life
RF	radio frequency
ROI	region of interest
rZI	rostral zona incerta
SCS	spinal cord stimulation
SEP	somatosensory evoked potentials
SF-36	Short-Form-36
SMA	supplementary motor area
SN	substantia nigra
SNr	substantia nigra pars reticulata
SSI	surgical-site infection
STIR	short-T1 inversion recovery

STN	subthalamic nucleus
STN DBS	deep brain stimulation of the subthalamic nucleus
SWI	susceptibility weighted imaging
T	tesla
TRD	treatment resistent depression
TS	Gilles de la Tourette syndrome
UMS	unilateral motor score
UPDRS	Unified Parkinson's Disease Rating Scale
USD	dollar of United States
VAT	volume of activated tissue
VIM	ventral intermediate nucleus of thalamus
VLT	ventrolateral thalamus
VNS	vagus nerve stimulation

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Lahtinen, M., Haapaniemi, T., Kauppinen, M., Salokorpi, N., Heikkinen, E. & Katisko, J. (2020). A comparison of indirect and direct targeted STN DBS in the treatment of Parkinson's disease-surgical method and clinical outcome over 15-year timespan. *Acta Neurochirurgica (Wien), 162*(5):1067–1076.

II Kähkölä, J.*, Lahtinen, M.*, Keinänen, T. & Katisko, J. (2023). Stimulation of the presupplementary motor area cluster of the subthalamic nucleus predicts more consistent clinical outcomes. *Neurosurgery*, 92(5):1058–1065.

III Lahtinen, M.*, Helander, H.*, Vieira, P., Uusimaa, J.** & Katisko, J.**(2021). Starting a DBS service for children: It's not the latitude but the attitude - Establishment of the paediatric DBS centre in Northern Finland. *European Journal of Paediatric Neurology, 36*:107–114.

* shared first authorship

** shared last authorship

Contents

1 Introduction

Everyone knows someone with Parkinson's disease (PD), or at least one later realized or heard that the difference in an encounter was related to PD. My grandfather Toivo (eng. hope; b. 1921 – d. 1995) had PD in my childhood and I remember how the communication with him was noticeably different compared with others, and mainly due to hypomimia and a slowed response to my questions and participation in conversation. Quickly, I learned that Papa's answers will come after a couple of minutes depending on his daily condition. Later this was a familiar feature of the PD patients, and easily recognizable in clinical work.

Idiopathic PD is globally the most common neurodegenerative movement disorder (Balestrino & Schapira, 2020). It affects not only physically, but also mentally, socially and economically the patient's life and relations with family and social participation. PD patients' differences from others and the lack of functional capacity can cause shame and stigma. It has been shown that patients with PD suffer self-stigma particularly when in unfamiliar places, in the work place or in contact with people without PD (Hanff et al., 2022).

Currently, there is no curative treatment for PD and the aethiology of the disease in not known. It has been suggested that the aethiology is multifactorial, which means that there must be more than one treatment method. The primary method of treatment is pharmacological therapy and rehabilitation. Despite the fact that medication can relieve symptoms, it can cause side-effects, e.g., unwanted motor complications (dyskinesias) or psychiatric side-effects. In advanced PD, neurosurgical treatments can be considered: deep brain stimulation (DBS) or ablative, i.e., lesional procedure. The latter can be divided into two categories: surgical ablative procedure, which is carried out traditionally by radiofrequency (RF) or novel laser interstitial thermal therapy (LITT) and non-surgical ablative procedure, which is carried out by radiosurgery, e.g., Gamma Knife, or magnetic resonance guided focused ultrasound (MRgFUS).

The most commonly used neurosurgical method is DBS and in PD the most commonly used treatment focus, i.e., target, is the subthalamic nucleus (STN) bilaterally. Notably, DBS is the only neurosurgical method which is adjustable and reversible, and this is the overriding advantage of DBS considering the degenerative and progressive nature of the disease.

This thesis was designed to provide information of DBS treatment in the PD population when using 3 tesla (T) MR imaging methods combined with neurophysiological methods and clinical 12-months follow-up of PD patients by

the caring DBS team. Also, to provide new information on the white matter connections between the STN and the frontal cortex and their correlation with clinical outcome, and consider whether white matter connections could be used as an aiding targeting tool in DBS or ablative surgery. Last but not least, to develop a DBS protocol for children with movement disorders based on over 25 years of experience in adult DBS treatment in Oulu University Hospital (OUH).

2 Review of literature

2.1 Deep brain stimulation (DBS) in general

The vast majority of PD patients are treated with medication and rehabilitation. It has been estimated that at a tertiary-referral centre 1 in 34 patients with essential tremor (ET), and 1 in 72 PD patients, will undergo DBS-surgery (Kestenbaum et al., 2015). DBS is an effective and well-established neurosurgical treatment for medically-refractory hypokinetic and hyperkinetic movement disorders, and it is being explored for a variety of other neurological and psychiatric diseases (Miocinovic et al., 2013). DBS is the application of implantable electrical stimulation technology and the system is based on electrodes, which have four or more stimulating contacts. The electrodes are stereotactically implanted uni- or bilaterally in the treatment area of the deep brain structures (i.e., target) during the neurosurgical operation (Coffey, 2009). The electrodes are connected via two subcutaneous extension wires to an implantable pulse generator (IPG) that is placed on the chest wall under the collarbone or on the abdominal subcutaneous fat tissue (see Fig.1.). The weak electric current is conducted from the IPG along the electrodes to the brain target area to alleviate the symptoms. (Herrington et al., 2016). DBS differs from functional electrical stimulation and sensory prosthetics (cochlear implants etc.) in that DBS does not substitute for or replace injured tissues, organs or body functions. DBS is targeted at particular brain nuclei or pathways that are specific for disorder, thus relieve symptoms and improve the overall functioning of the patient (Coffey, 2009). A clinician uses a handheld device to wirelessly communicate with the IPG and adjust the parameters of stimulation (amplitude, voltage, pulse width, frequency) to maximize symptom relief and to minimize side effects (Herrington et al., 2016).

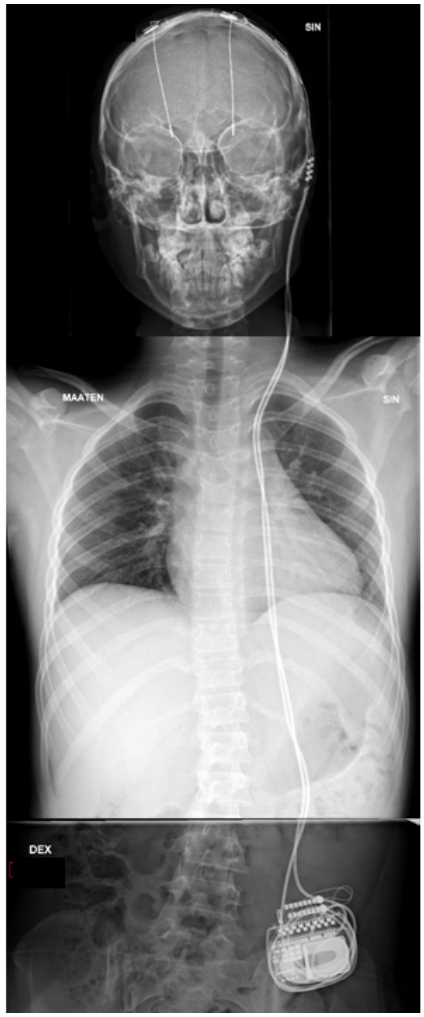

Fig. 1. Implanted deep brain stimulation (DBS) device is shown in x-rays. This is a paediatric DBS device and its implantable pulse generator (IPG) is placed in abdominal fat tissue. Figure by Jani Katisko.

2.1.1 Principles of DBS

The use of DBS to intervene directly in pathological neural circuits has changed the way that brain disorders are treated and understood (Lozano et al., 2019). Depending on the indications, target in the brain and the stimulation parameters,

DBS may facilitate neural conduction of activity (excitatory), or block neuronal activity of conduction (inhibitory) (Coffey, 2009). The different symptoms of diseases have different latencies in response to DBS treatment, for example, tremor response in seconds to minutes and dystonia in weeks to months. This supports the theory that different mechanisms of DBS are responsible, including immediate neuromodulation effects, synaptic plasticity, and long-term effects that may involve anatomical reorganization. A high-frequency stimulation has a therapeutic effect similar to that of ablative surgery and DBS is thought to function as a reversible lesion by inhibiting neurons near the stimulating electrode (i.e., the reversible lesion hypothesis) (Herrington et al., 2016). In 2019, Lozano et al gathered together different mechanisms of action of DBS: direct inhibition of neural activity, direct excitation of neural activity, information lesion (jamming) and synaptic filtering. However, the exact mechanism of action is unclear. In addition to stimulation, DBS provides a tool which can directly measure pathological brain activity and can deliver adjustable stimulation for therapeutic effect, thus DBS opens brand new opportunities to access and interrogate malfunctioning brain circuits.

2.1.2 Costs and General availability

When estimating the cost-effectiveness of DBS treatment in PD, it is necessary to include direct, indirect and intangible costs on both a short-term and also a long-term basis. It should be noted that the cost of DBS in PD varies considerably from country to country and costs also depends on how health care is financed. The first and, to the best knowledge, only study of the cost-effectiveness of DBS of the subthalamic nucleus (STN DBS) in PD in Finland was published in 2005. This study showed that the cost of STN DBS in the first postoperative year was 25 591€ (Erola et al., 2005a). According to a more recent study, the average cost of DBS for a patient with PD in 5 years is 186 244USD (168 257€, exchange rate according to The Bank of Finland in 2016). The costs in the first year are higher with DBS due to direct costs related to the surgical procedure, the device, and the more frequent controls (Becerra et al., 2016).

When comparing all device-aided therapies (DBS, levodopa-carbidopa intestinal gel, continuous subcutaneous apomorphine infusion), all devices improved quality of life compared to the best medical treatment, with improvements in quality-adjusted life year between 0.88 and 1.26 in studies with long temporal horizons (Smilowska et al., 2021).

In 2021, the number of patients that received DBS was estimated to be 208 000 worldwide (Vedam-Mai et al., 2021). However, exact literature on global availability does not exist. The high costs of DBS treatment and the lack of movement disorder neurologists makes the availability of DBS treatment in low-economy countries relatively impossible (Jamora & Miyasaki, 2017).

2.1.3 Global burden of Parkinson's disease (PD)

PD is the most common neurodegenerative movement disorder and common cause of disability. PD's aethiology in unknown. Its cardinal motor symptoms are tremor, rigidity, bradykinesia/akinesia and postural instability. Risk factors are age, male gender and some environmental factors (toxicants such as pesticides, solvents, metals and other pollutants). Family history is a risk factor for PD and the relative risk in first-degree relatives of PD cases increases by approximately 2–3 fold compared to controls. Familial forms of PD cover 5–15% of cases (Goldman, 2014). In Finland, monogenetic PD is very rare (Valtteri Kaasinen personal communications).

In industrial countries the estimated prevalence of PD is 0.3% in the general population, 1.0% in people aged over 60 and 3.0% in people aged over 80; incidence rates of PD are estimated to range between 8 to 18 per 100 000 persons-years (Balestrino & Schapira, 2020). In an earlier study, the estimated prevalence and incidence rates for PD are approx. 108–257/100 000 and 11–19/100 000 per year, respectively in Europe (Goldman, 2014). Overall, PD affects 1–2 per 1000 of the population at any time and the prevalence increases with age affecting 1% of the population above 60 years (Tysnes & Storstein, 2017). The Global Burden of Disease Study 2016 revealed that from 1990 to 2016 the global burden of PD has more than doubled, not only due to the ageing populations, but also the increased disease duration and environmental factors (Dorsey et al., 2018). In Finland, from 1995 to 2000 the annual incidence of PD was 32.6/100 000 person-years and the prevalence was 268/100 000 persons among citizens aged 30 and over, based on data from the Social Insurance Institution of Finland (KELA) (Sipilä & Kaasinen, 2022).

2.2 History of DBS

2.2.1 Surgery of pyramidal system in pre-stereotactic era

Neurologist James Parkinson was the first to published and described six patients who suffered a shaking palsy in 1817 (see Fig.2.). He also noticed that with patient no.6, tremor disappeared unilaterally after hemiparetic stroke (Parkinson, 1817). This led to the invention of pyramidal system surgery for PD in the pre-stereotactic era firstly introduced by neurosurgeon Victor Horsley 1906. Pyramidal system surgery included a subpial resection of the premotor cortex (Broadman area (BA) 6) and motor cortex (BA 4), a resection of anterior internal capsule, a lateral pyramidal tractotomy and a mesencephalic pedunculotomy. All these procedures reduced tremor but, in addition, led to hemiparesis and increased spasticity (Cozzens, 2007; Hariz et al., 2022).

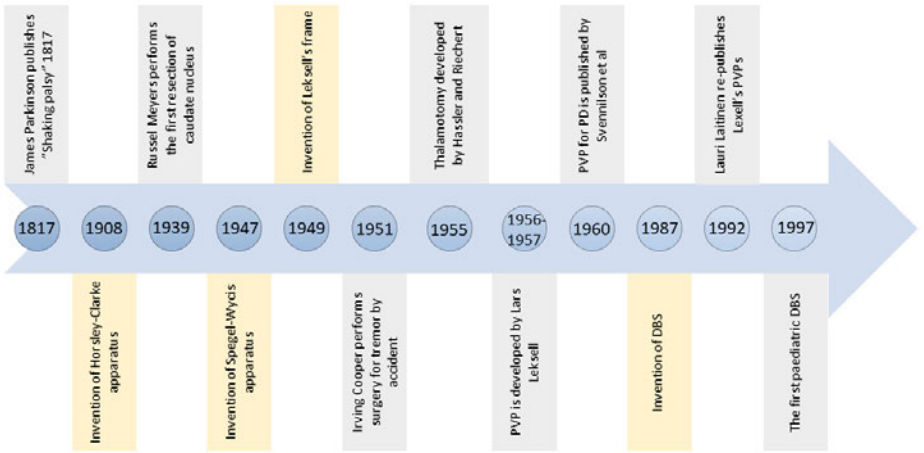

Fig. 2. Timeline of surgical and technological development in pre-DBS era. Abbreviations: DBS, deep brain stimulation; PVP, posteroventral pallidotomy. Figure by Maija Lahtinen.

2.2.2 Surgery of extrapyramidal system in the pre-stereotactic era

In 1930 neurosurgeon Walter Dandy was the first to introduced the concept of extrapyramidal system, later known as basal ganglia. He called it the centre of consciousness, thus a "no-man-land" of neurosurgeons, based on the experiences

of ligating arteries of anterior circulation. In 1939 neurosurgeon Russel Meyers was the first to purposely resected the caudate nucleus of patients with PD to relieve tremor and rigidity successfully. The surgery was based on previous experiences with lobotomies (Meyers, 1951). In 1951 neurosurgeon Irving Cooper made the discovery by chance whilst performing a pedunculotomy on a PD patient. He accidentally damaged the anterior choroidal artery and was obliged to occlude the artery without proceeding to pedunculotomy. After the surgery, the patient woke up without any neurological deficits and no tremor. This observation led to the conclusion that occluding the precise artery could provide a treatment for PD (Cooper, 1954). Afterwards, autopsies revealed degeneration of the internal globus pallidus (GPi) and led Cooper to try direct lesioning of GPi through a medial approach using a specific probe and to further investigate lesioning the ventrolateral thalamus (VLT) (Das et al., 1998).

2.2.3 Surgery of extrapyramidal system in the stereotactic era

The first stereotactic system was described in 1908 by neurophysiologist and neurosurgeon Victor Horsley and mathematician Robert H. Clarke. It was known as the Horsley-Clarke apparatus, and was mainly used in animal experiments (Horsley & Clarke, 1908). They also coined the term stereotaxis (Jensen et al., 1996; Rahman et al., 2009).

The first human stereotactic system was introduced by experimental neurologist Ernest A. Spiegel and neurosurgeon Henry T. Wycis in 1947 (Spiegel et al., 1947). Its development was based on the Horsley-Clarke apparatus and was accurate enough to be used in humans. The human use of the Spiegel-Wycis apparatus also required the development of human neurophysiology, pneumoencephalography, radiology and electrophysiology and was used for surgery of psychiatric illness, pain, movement disorders and aspiration of tumour cysts (Gildenberg, 2001).

Thalamotomy

The VLT was developed by R Hassler and T Riechert in Germany in 1955 to eliminate specific deep brain structures without injury to neighbouring structures for therapeutic purposes. They used ring-based stereotactic apparatus developed by Reichert and M. Wolff to stimulate, record and coagulate with a specific needle (Hassler & Riechert, 1954, 1955). In 1959 Bravo and Cooper published the analysis

and results of 300 PD patients who underwent the lesional procedure of pallidotomy or thalamotomy (Bravo & Cooper, 1959).

Pallidotomy

The first pallidotomy was performed in 1947 on a patient who suffered from Huntington's disease. Pallidotomy achieved wider acceptance as the treatment for PD but was abandoned, first by thalamotomy and then by levodopa in the 60s (Cif & Hariz, 2017). The pioneer of posteroventral pallidotomies (PVP) was neurosurgeon Lars Leksell who invented the approach in 1956–1957. The first study of 81 patients was published in 1960 but did not achieve the attention it deserved (Svennilson et al., 1960). The patient data for pallidotomies between 1958–1962 was re-published by Lauri Laitinen (Laitinen, 2000).

In the mid-1980s, Leksell's PVP was reintroduced and the results of 38 PD patients was published in 1992 by Laitinen. The result was that parkinsonian tremor, rigidity and hypokinesia can be effectively treated by PVP. The response was expected to come from the discontinuation of the striopallidal or subthalamopallidal pathways (Laitinen et al., 1992). Today PVP has a place in the armanterium of neurosurgical procedures mainly in those situations when DBS is not possible, or as a rescue surgery when a sudden cessation of stimulation occurs (so called DBS withdrawal syndrome). With new technologies such as MRgFUS and LITT, interest in uni- and bilateral PVP may have risen (Hariz & Blomstedt, 2022).

2.2.4 Inventing DBS

In 1987, in the hospital of Universite Joseph Fourier, Grenoble, France, neurosurgeon and physicist Alim-Louis Benabid tested stimulation at different frequencies during a thalamotomy operation. He discovered that high-frequency stimulation reduces tremor mimicking reversible lesions (Williams, 2010). Since the 1960s, DBS and spinal cord stimulation (SCS) devices have been developed for the treatment of intractable pain of various origins. These hardware solutions: electrodes, extensions and IPGs were extended to the treatment of movement disorders (Benabid et al., 2009). At first, DBS was used as a combined therapy: unilateral thalamotomy at the dominant hemisphere and unilateral DBS of ventral intermediate nucleus of thalamus (VIM) for the non-dominant hemisphere. This treatment protocol was published in 1987 (Benabid et al., 1987a).

2.2.5 History of DBS devices

The development of DBS devices has emerged as features of cardiac pacemakers and SCS devices and then incorporated into DBS systems. The first commercially marketed implantable human DBS device was introduced in the mid-1970s. They were initially designed for pain but the results were not encouraging. By the late 1980s, the potential use of DBS was for movement disorders: essential tremor (ET), PD and dystonia. Later for selected psychiatric disorders: obsessive-compulsive disorder (OCD), treatment-resistant depression (TRD), Gilles de la Tourette syndrome (TS), as well as other indications: epilepsy, obesity and cluster headache (Coffey, 2009). The appearance of multiple manufacturers of DBS technology on the global market has sparked international competition and has accelerated the development of DBS technology. In the future, the implementation of new hardware designs, improved technology and refined stimulation algorithms can be expected (Krauss et al., 2021) (see Fig.3.).

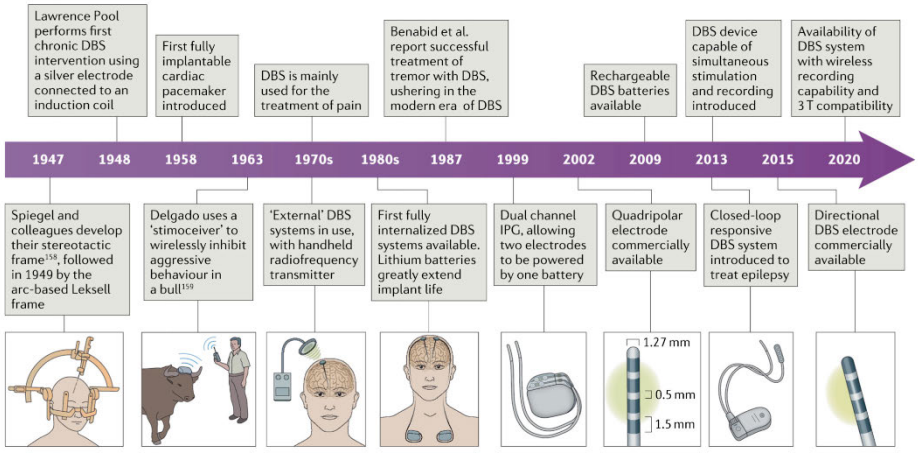

Fig. 3. Timeline of technology development for DBS. Adapted from Krauss et al. (2021). Reproduced with permission from Nature Reviews Neurology, Springer Nature.

2.2.6 Establishment of DBS treatment

At first, DBS was used as a combined therapy for PD patients with bilateral tremor resistant to drug therapy: RF thalamotomy of VIM for the most disabled side and a continuous VIM stimulation with DBS for the other side (Benabid et al., 1987b).

By the mid-1990s, there was evidence that bilateral VIM DBS was superior and should replace thalamotomy in regular surgical treatment of PD and ET (Benabid et al., 1996). In 1997, the US Food and Drug Administration (FDA) approved indications for DBS included unilateral thalamic stimulation for the suppression of upper extremity tremor in ET or PD; conditional approval in 2002 for bilateral stimulation of globus pallidus internus (GPi DBS) or STN DBS for adjunctive therapy in levodopa-responsive PD; in 2003 uni- or bilateral stimulation of the GPi or STN in chronic, intractable, drug refractory, primary dystonia (generalized and segmental dystonia, hemidystonia and cervical dystonia) (Coffey, 2009).

2.2.7 History of DBS in Finland

The pioneers of DBS surgery of Finland were neurosurgeons Esa Heikkinen in OUH and Juha Pohjola in Helsinki University Hospital (HUS) (Esa Heikkinen personal communications). The first DBS implantation in OUH was performed in 1997 (data retrieved from enterprise resource planning for surgical procedures in Oulu University Hospital (LESU), Esko Systems, Oulu, Finland). DBS-operations were started in HUS 1997 (Riku Kivisaari personal communications), Tampere University Hospital 2009 (Kai Lehtimäki personal communications), Kuopio University Hospital 2012 (Mikael von und zu Fraunberg personal comminications) and Turku University Hospital 2014 (Janek Frantzén personal communications).

2.2.8 Previous DBS study in Oulu University Hospital (OUH)

Tuomo Erola published his thesis *Deep brain stimulation of the subthalamic nucleus in Parkinson's disease* in 2006 in the University of Oulu (Erola, 2006). The thesis included four publications and the first study (Erola et al., 2006a) consisted of 24 PD patients treated with STN DBS, which was performed by an indirect targeting method (iTM) using constant co-ordinates and the follow-up time was 12 months. At twelve months after DBS surgery Unified Parkinson's Disease Rating Scale (UPDRS) scores of dyskinesia were 53% lower than preoperative values. Motor scores improved 31.4% and ADL scores increased 19% compared to the preoperative values. Levodopa medication was 22% lower 12 months after DBS surgery. He also studied whether STN DBS improves health-related quality of life in PD patients (Erola et al. 2005b). The third study (Erola et al., 2005a) examined the direct costs compared to the results and the fourth study (Erola et al., 2006b)

concerned the stability of long-term heart rate variability after STN DBS in PD patients.

2.3 Traditional indications of DBS

2.3.1 Parkinson's disease

PD is a progressive disease which is caused by destruction of dopaminergic neurons in the pars compacta of the substantia nigra (SN) and by accumulation of misfolded α-synuclein in intra-cytoplasmic inclusions (Lewy bodies). This leads to disruption of the dopaminergic pathway to the Striatum leading to typical motor symptoms of PD: rigidity (stiffness), hypokinesia (slowness) of movement, resting tremor and impaired balance. Dopaminergic cell destruction outside this pathway causes the non-motor symptoms of PD such as depression, cognitive decline, delusions, urinary problems, constipation, excessive saliva drainage, sleeping problems, loss of sense of smell (Tysnes & Storstein, 2017). The diagnosis of idiopathic PD is set according to the Movement Disorder Society Clinical Diagnostic Criteria for PD (Postuma et al., 2015).

The treatment of PD is symptomatic: medical treatment, rehabilitation and device-aided therapies. PD is an official indication for DBS. The international guidelines for the invasive treatment of PD have been published by the European Academy of Neurology and the European section of the Movement Disorder Society in 2022 (Deuschl et al., 2022). In the mid-1990s, based on encouraging experiences in animal models and results in unilateral, human pallidotomy surgery, the positive effect of the bilateral STN DBS for motor symptoms of PD was published (Limousin et al., 1998). A follow-up study revealed that the STN DBS efficacy lasts over a five-year follow-up (Krack et al., 2003). Since the mid-2000s, there has been Level I evidence that STN DBS is an effective treatment for PD (Goetz et al., 2005). Long-term outcome studies have shown that STN DBS maintains its effect for motor OFF-symptoms over a ten-year follow-up (Aviles-Olmos et al., 2014; Castrioto, 2011). Today STN DBS is a well established surgical treatment for medically refractory advanced idiopathic PD (Fox et al., 2018). The STN and GPi are the main brain targets for PD (Peng et al., 2018), thus STN has been the most commonly used target for PD DBS over the past 10 years (Deuschl et al., 2013). Previous studies have shown that STN DBS provides persistent symptom improvement even 5 to 10 years after DBS surgery, albeit with

deteriorations of cognition and gait due to nature of the degenerative disease (Rizzone et al., 2014).

According to an international expert consensus statement: DBS should be considered if the PD patient has medically intractable motor fluctuations, tremor or intolerance of medication without significant active cognitive or psychiatric problems. DBS should be performed by a neurosurgeon with expertise in stereotactic neurosurgery and supported by a multidisciplinary team. The DBS programming should be performed by an experienced clinician and can take 3–6 months to obtain optimal results (Bronstein et al., 2011). In addition to accurate patient selection, electrode implantation and stimulation parameters, the outcome can be improved with new technological methods (Bari et al., 2015).

2.3.2 Tremor

Tremor is a hyperkinetic movement disorder with an involuntary movement that is both rhythmic and oscillatory and upper limbs tend to be the most symptomatic. The most common aetiologies are ET and PD. Tremor was the first indication for DBS, together with chronic pain, mainly encouraged by the results of RF ablations of VIM (Chandra et al., 2022). Today, tremor is an official indication for DBS. There are a handful of novel targets for tremor: rostral zona incerta (rZI), caudal zona incerta (cZI) and dentato-rubro-thalamo-cortical tract (DRTC) (Baumgartner et al., 2022).

2.3.3 Dystonia

Dystonia is a hyperkinetic movement disorder characterised by painful, involuntary posturing due to inappropriate muscle contractions of the affected body region(s). DBS is an intervention typically reserved for severe and drug-refractory cases, although uncertainty exists regarding its efficacy, safety and tolerability (Rodrigues et al., 2019). Dystonia can be classified as primary or secondary, but the most recommended method of classification was published in 2013 (Albanese et al., 2013). One example of late-onset dystonia is cervical dystonia in the adult population (Evatt et al., 2011). Dystonia is an official indication for DBS.

2.3.4 Dystonia in the paediatric population

DBS treatment for the paediatric population (pDBS) is less common, thus it is an official indication for DBS from the age of 7 years. The youngest child to have been DBS-implanted was 2 years and 8 months old girl who suffered painful dystonia (personal communication Jean-Pierre Lin, the Complex Motor Disorders Service at the Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, Great Britain). The indication for pDBS is mainly generalized dystonia due to genetic abnormality or cerebral palsy (CP), though there are several aetiologies. Results vary considerably and are dependent on the fenotype and aethiology (Hale et al., 2020). The most frequently used target for pediatric dystonia is GPi but there are also encouraging results from STN stimulation, especially in the cases when GPi does not delineate from magnetic resonance imaging (MRI), for example, pantothenate kinase-associated neurodegeneration (PKAN) (Li et al., 2022). The decision to proceed towards pDBS is viewed as a significant life altering decision by the parents. The risks of pDBS, what the child might lose and the uncertainty of pDBS outcome, should be given clinical importance (Austin et al., 2017). Taking into account a small number of the paediatric patients, paediatric DBS benefits from national centralization (Helander et al., 2020).

2.4 Novel indications of DBS

2.4.1 Epilepsy

Bilateral deep brain stimulation of the anterior nuclei of the thalamus (ANT DBS) reduces seizures and is generally safe therapy. According to one study, benefits persisted for 10 years and the complication rate was modest. ANT DBS is useful for some people with medically refractory epilepsy with partial and secondarily generalized seizures (Fisher et al., 2010; Salanova et al., 2021). ANT DBS appears to be especially effective in reducing focal impaired awareness, when the appropriately chosen contacts are activated (Järvenpää et al., 2020). ANT DBS can be implanted in patients with previous vagus nerve stimulation (VNS), and the response to VNS appears similar to that in DBS therapy (Kulju et al., 2018). Transventricular lead placement has been found to be a safe and accurate surgical method when implanting ANT DBS (Lehtimäki et al., 2019). Epilepsy is the official indication for DBS for one of the device manufacturer.

2.4.2 Psychiatric indications

DBS has been used for psychiatric disorders and behavioural/cognitive symptoms, e.g., TRD, OCD, addictions (substance-use related disorders), Alzheimer's dementia, eating disorders (anorexia, obesity), schizophrenia and post-traumatic stress disorder. Several targets have been used in investigational studies and OFF-label use (Mahoney et al., 2022).

Obsessive compulsive disorder (OCD)

There is no consensus where DBS for OCD is an established therapy. Two blinded randomized controlled trials have been published, one with level I evidence (Yale-Brown Obsessive Compulsive Scale score improved 37% during stimulation on), the other with level II evidence (25% improvement) (Wu et al., 2021). DBS showed best results when targeting the crossroad between the nucleus accumbens and the ventral capsule or the STN (Rapinesi et al., 2019). OCD is the official indication for DBS for one device manufacturer.

Depression

DBS literature demonstrates that DBS can reduce symptoms in patients with TRD, though is similar to DBS for other psychiatric diagnoses, DBS for depression still requires more thorough investigation via well-controlled clinical trials. Depression isn't the official indication for DBS and device implantations should be combined with the study protocol (Mahoney et al., 2022).

2.4.3 Gilles de la Tourette (TS)

The data on DBS for TS is still open to debate regarding its efficacy and tolerability. Therefore, it is considered that DBS for TS is an experimental treatment that should be used only in carefully selected, severely-affected and otherwise treatment-resistant patients (Szejko et al., 2022).

2.5 Present technique of DBS in the 2020s

2.5.1 Magnetic resonance imaging (MRI) for DBS

As imaging technology developed, it became possible to measure the midcommissural point (MCP) from CT or MRI scans and subsequent development of MR imaging enabled the possibility of defining patient-specific anatomy of the brain structures (Machado et al., 2006; Chandran et al., 2016; Hertel et al., 2015). Alongside, the development of imaging has enabled precise postoperative analysis of the lead location, thus facilitating the optimal programming (Katisko et al., 2012). Today in DBS surgery, target and trajectory planning are based on high-resolution MR imaging, which delineate basal ganglia and thalamic internal anatomy very well (see Fig.4.). MR imaging describes anatomic locations but not specific functional structures. The clinical MR imaging sequences for DBS improves the visualization of normal anatomy and may increase our understanding of basal ganglia and thalamic function. Better visualization may also improve treatments for movement disorders (Hoch & Shepherd, 2022).

Interventional MRI (iMRI)-guided DBS surgery enables real-time image guidance in asleep surgery, obviating the need for patients to be awake during lead placement (LaHue et al., 2017). In a recent study, asleep iMRI-guided implantation of DBS was more accurate in a lead placement for the intended target compared with awake-DBS, but clinical outcomes of PD patients were similar between surgical approaches. The iMRI cohort had smaller errors between intended and actual lead locations (1.27 ± 0.72 mm) compared to an awake surgery (1.59 ± 0.96 mm, $p < .01$) (Lee et al., 2022).

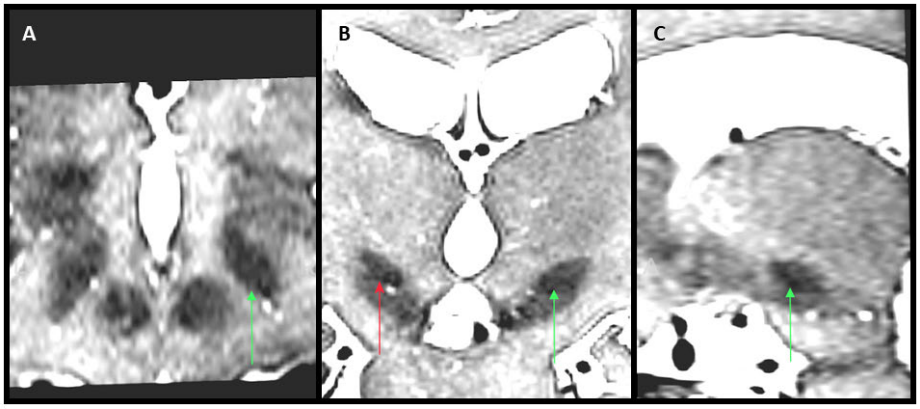

Fig. 4. Subthalamic nucleus (STN) delineates from MRI and is marked with arrows (green arrow = right STN, red arrow = left STN). Figure by Jani Katisko and Maija Lahtinen.

2.5.2 Diffusion tensor imaging (DTI) for DBS

Alongside high-quality MR imaging, other imaging methods have been introduced, for example, diffusion tensor imaging (Hoch & Shepherd, 2022). DTI is an MRI technique that allows non-invasive measurement of the translational motion of water, providing information about its anisotropy in different tissues (Lope-Piedrafita, 2018). DTI is an MRI technique that can measure micronisation (Mori & Zhang, 2006) in nervous system tissue (Mori & Zhang, 2006). The white matter tracts in the brain can be reconstructed using DTI tractography and is an emerging method for targeting specific brain regions, which does not delineate on conventional MRI, for example, VIM. Another tract, which can be perceived from MRI using tractography, for example, DRTC, can be used as a tool for targeting the DBS electrodes. The technology of DTI is demanding and is vulnerable to inaccuracies especially since it is performed on an individual level, and tremor and psychiatric indications are the main targets when using DTI as an aid (Coenen & Reisert, 2021).

2.5.3 Planning software

Of the software currently on the market, there are two leading planning software in clinical use: Elements 2.0 (Brainlab, Munich, Germany) and Stealth FrameLink

(Medtronic, Minneapolis, USA). They both include deterministic tractography software for clinician use. (Frey et al., 2022). It has been found that multi-fiber deterministic tractography is well suited to connectome reconstructions, while probabilistic algorithms are hampered by an abundance of false-positive connections, thus connectome thresholding is essential (Sarwar et al., 2019).

2.5.4 Devices used in DBS surgery

Bilateral DBS devices are made up of three main parts: paired DBS electrodes, paired extension wires and single IPG, which can be implanted in the subcutaneous fat tissue of the subclavicular or abdominal area. A bilateral DBS device with two IPG is possible but less common. Unilateral DBS devices include a single DBS electrode, single extension wire and single IPG.

DBS electrodes include four or more metallic contacts through which low-intensity electrical impulses are supplied to the nervous system. The contacts can be conventional or directional, the latter means that the direction of the electric current can be modified. The possibilities to modify the stimulation field are device-specific as well as indications for the use of devices in diseases. Sensing technology means that IPG can record brain signals, known as local field potentials (LFP), simultaneously while delivering therapeutic stimulation. Two types of batteries for IPGs are available: disposable and rechargeable. The three largest manufacturers on the market are (in alphabetical order): Abbott (Abbott, Abbott Park, Illinois, USA), Boston Scientific (Boston Scientific, Marlborough, Massachusetts, USA) and Medtronic (Medtronic, Minneapolis, USA) (retrieved February 4, 2023, from www.abbott.com, www.bostonscientific.com, www.medtronic.com).

2.5.5 Targeting

Targeting is the pre-operative planning of the insertion and location of the DBS electrode. In the early stages of its development, DBS targeting was based on constant coordinates obtained from the brain atlases (Schaltenbrand & Wahren, 1977; Talairach, 1988), thus called indirect targeting. The constant coordinates were measured from the line between the anterior commissure and posterior commissure (AC-PC), which was obtained from ventriculography images (Khan & Henderson, 2013).

As imaging developed, MRI based targeting was proven to be superior, especially using 3T MRI (Patel et al., 2008). The location of a DBS electrode in the desired brain area is determined solely on the basis of 1.5–3 T MR images, this is called direct targeting. Novel imaging technology, e.g., DTI based tractography, can be used as an aid to target DBS electrodes, e.g., when targeting VIM with the aid of DRTC (Boutet et al., 2019). However, despite advanced imaging, the optimal surgical target within the STN remains unclear and specialists vary in their approach (Hamel et al., 2017). Some estimates have stated that the dorsolateral part of the STN would yield the best results (Johnsen et al., 2010; Welter et al., 2014). The cadaver dissection of the STN and its correlation to fibre tracts in MRI emphasizes the complex anatomy and connections of the STN (Güngör et al., 2019). In the MRI, anatomical variation exists in the shape and spatial position of the STN within and between individuals. Also, it has been shown that STN morphology changes in PD (Daniluk et al., 2010; den Dunnen & Staal, 2005).

Furthermore, the STN has been shown to have specific functional structures connecting to cortical regions which participate in movement control (Akram et al., 2017). Finding the optimal stimulation region should thus consider individual STN structures and connectivity (Coenen & Reisert, 2021).

2.5.6 Surgical considerations

Expert consensus recommends that DBS surgery is best performed by an experienced neurosurgeon with expertise in stereotactic neurosurgery and working as part of an interprofessional team (Bronstein et al., 2011). DBS surgery can be performed using local anaesthesia (awake DBS) or under general anaesthesia (asleep DBS). There is no difference in outcome but asleep DBS in less burdensome for patients and the operation is shorter (Holewijn et al., 2021).

DBS surgery is performed with a stereotactic frame. Apparently, the Leksell's frame (Elekta, Stockholm, Sweden) is the most widely used frame and was invented by the Swedish neurosurgeon Lars Leksell 1947 (Bergenheim & Bergenheim, 2021). In a large patient cohort analysis, using frame-based MRI-targeted and -verified DBS surgery, anatomically acceptable lead placement was achieved with a single brain pass for 97% of leads. The mean ± SD of the final targeting error was 0.9 mm ± 0.3 (Rajabian et al., 2022). In the frameless DBS surgery, the global vector error was found to be 1.43 mm ± 0.37 and the study concluded that frameless DBS surgery appears to be reliable and accurate (Rajabian et al., 2022).

2.5.7 Microelectrode recording (MER) and test stimulation

Microelectrode recording (MER) is one of the methods used to measure brain anatomy intraoperatively. MER is based on registering neuronal activity at the cellular level. The registration is performed along 1–5 trajectories in the volume of interest to identify the different structure boundaries (Hemm & Wårdell, 2010). MER is performed in 1-mm steps from 10 mm above the target for the first 5mm, then in 0.25–0.5 mm steps until the end of STN activity and the start of substantia nigra pars reticulata (SNr) activity. The length of these steps and the duration of MER at each step might differ from centre to centre. The STN has a typical electrophysiological activity consisting of high-voltage spikes, cells firing in the burst mode and an obvious widening of the background. MER ends when STN activity disappears and SN activity appears (Kocabicak & Temel, 2013).

2.5.8 Follow-up and programming

An expert consensus recommended, that DBS programming is best accomplished by an experienced clinician and can take 3 to 6 months to obtain optimal results (Bronstein et al., 2011). The use of an evaluation rating scale such as UPDRS, Dyskinesias Rating Scale and the Self-Reporting Questionnaire usually administrated on PD patients are advised (Broggi et al., 2003).

The effects of DBS on clinical symptoms are time-dependent. PD signs and symptoms respond to STN DBS variably. Axial symptoms may take hours or days to improve, whereas tremor typically disappears almost instantly with STN or VIM DBS. A similar temporal disparity occurs with dystonia, where phasic dystonic symptoms respond quickly within minutes to GPi DBS, and tonic dystonic movements may take much longer to resolve (Koeglsperger et al., 2019). Thus, the programming of DBS is patient specific. DBS programming algorithms have been developed for PD to standardise the programming, for example, Toronto Western Hospital Algorithms (Picillo et al., 2016). After the introduction of directional electrodes, the directivity has been used more and more in stimulation settings (Koivu et al., 2022).

Most of the DBS guidelines for dystonia are for adults and there is lack of evidence-based or consensus statements for pDBS. A recent review proposed programming algorithms and a follow-up program for pDBS (Gelineau-Morel et al., 2022).

2.5.9 Complications of DBS

Infections

The most common complication in DBS surgery for adults is surgical-site infection (SSI). In a recent review study, the summary prevalence of SSI was estimated at 5.0% with higher rates for dystonia (6.5%) and novel indications: epilepsy (9.5%), TS (5.9%) and OCD (4.5%) (Kantzanou et al., 2021). According to another recent review article, which analysed studies from 2008 to 2020, the estimated infection and erosion rate in adult DBS surgery was 3.0% (Koh et al., 2021). A third study estimated SSIs (which needed revision surgery), as low as 1.7% (Bronstein et al., 2011).

In the paediatric population the SSIs rate is higher than in adults. In a study from 2011 with a small number of patients (22), the SSI was 14% (Haridas et al., 2011). In 2017, a study from a large paediatric DBS centre with a high number of pDBS patients (129), found an SSI rate of 10.3% for primary implantations and 8.6% for revisions (Kaminska et al., 2017).

Cerebral haemorrhage

The amount of cerebral haemorraghe varies depending on whether asymptomatic imaging findings are included. According to a recent study, the risk of intracranial complication rate (including intracranial haemorraghes) in adult DBS was found to be 2.7% (Koh et al., 2021). Another study found the risk of intracranial symptomatic hemorraghe to be 1.1% and asymptomatic (diagnosed by postoperative CT) 0.5% (Fenoy & Simpson, 2014).

In pDBS the risk of intracerebral haemorrhage is very low. In a larger patient cohort (129 patients) only one had cerebral haemorrhage and it was asymptomatic (Kaminska et al., 2017).

Hardware complication

According to Koh et al, the risk of technical hardware complication in adult DBS is 2.2% (Koh et al., 2021). Another study found the hardware-related complications requiring surgical revision (including wound infections) was 1.7%, lead malposition and/or migration 1.7%, component fracture 1.4%, component malfunction 0.5%, and loss of effect 2.6% (Fenoy & Simpson, 2014).

In pDBS, the risk of hardware complication is greater, electrode/extension problems were recorded in 18.4% of patients, fracture in 4.6%, malfunction in 7.7%, short extension 3.8% and electrode migration in 2.3% (Kaminska et al., 2017).

2.6 Results of DBS in Parkinson's disease

2.6.1 Results in Parkinson's disease

A study in 2011 showed a mean improvement in the off-medication motor part of UPDRS (UPDRS 3) of 27.7 points (SD ± 13.8) equivalent to a mean improvement of 52% during a median follow-up time of 12–14 months. In addition, there were significant improvements in dyskinesia duration, disability and pain, with a mean reduction in on-medication dyskinesia severity and also Quality of life (QoL). This result suggested that MRI-guided STN DBS without microelectrode recording can lead to substantial improvements in motor disability with accompanying improvements in QoL and, most importantly, with very low morbidity (Foltynie et al., 2011). The adverse effects of STN DBS may be increased depression, apathy, impulsivity, worsened verbal fluency, and executive dysfunction in a subset of patients (Bronstein et al., 2011).

A recent study provides class IV evidence (case reports and series, consensus expert opinion; American Academy of Neurology Classification of Evidence) that, for patients with PD, STN DBS remains effective at treating motor complications of PD as long as 15 years after surgery. Compared to baseline, dyskinesia and the off-state time were reduced by 75% and by 58.7%, respectively. Moreover, dopaminergic drugs were reduced by 50.6% and the QoL was maintained (Bove et al., 2021). A retrospective analysis of 400 PD patients, treated with DBS and at least 10 years of follow-up, revealed a survival probability of 51% and medical co-morbidities were not significantly associated with survival. Tremor responded best to DBS (72.5% improved) while other motor symptoms remained stable. Ability to conduct ADLs remained stable (dressing 78% of patients, running errands 52.5% of patients) or worsened (preparing meals 50% of patients). Patient satisfaction remained high (happy with DBS 92.5% of patients, would recommend DBS 95%, felt it improved symptom control 75%) (Hitti et al., 2020).

2.6.2 Results of DBS in paediatric dystonia

Primary dystonia

A study from 2011 revealed that in a median follow-up of 2 years (range 1–8 years), the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor subscores were improved 84%, 93%, and 94% (median) at the timepoints 1, 2 and 3 years in patients with primary dystonia. The response to DBS resulted in significant reductions in oral and intrathecal medication requirements after 12 and 24 months of stimulation. There were no haemorrhages or neurological complications related to surgery and no adverse effects from stimulation. Significant hardware-related complications were noted, in particular, infection (14%), which delayed clinical improvement (Haridas et al., 2011).

Secondary dystonia

The most common secondary dystonia in the paediatric population is due to CP. A study from 2022 revealed, that after 12-months follow-up mean improvement of Caregiver Priorities & Child Health Index of Life with Disabilities (CPCHILD) was 4.2 ± 10.4 points, and among secondary outcomes: improvement in Canadian Occupational Performance Measure (COPM) performance improved 1.1 ± 1.5 points and in the Short-Form-36 (SF-36) physical health component improved by 5.1 ± 6.2 points. The resulting conclusion was that evidence to recommend DBS as a routine treatment to improve QoL in paediatric patients with dyskinetic CP is not yet sufficient (Koy et al., 2022).

3 Aims of the study

The aim of this thesis was:

1. To study whether the demographic data of PD DBS patients has changed over 20 years in our hospital district. (I)
2. To investigate how direct MRI targeted and MER verified STN DBS treatment improves the outcome of PD patients compared to indirect constant co-ordinate targeted and MER verified STN DBS. (I)
3. To explore the hyperdirective white matter pathways between the cluster of stimulated STN and prefrontal cortex and to study how their stimulation correlates with the motor response and levodopa intake in PD patients. (II)
4. To create a DBS-protocol for the paediatric population. (III)

4 Materials and Methods

4.1 DBS database

The data for the DBS database was collected from LESU from 1997 to 2021 retrospectively. The hospital serves as the only tertiary care centre facility providing DBS-surgery in Northern Finland, thus all DBS related surgery is carried out in OUH. The population base in the catchment area is approx. 740 000 people (Kuntaliitto, 2021). All DBS operations were collected including primary operations and revision. The data was checked from the patient records to ensure that information was correct in the database.

Several items were added to the database: DBS-patient's name and social security number, operation date, diagnosis, therapy, target, uni- and bilateral operations and the DBS device used. Primary DBS implantations were documented as two separate surgeries: electrode and IPG implantation.

Three patient groups were selected from the DBS database: two groups of PD patients and one group of paediatric DBS patients. The first patient group formed Study I and included 25 PD patients operated on from 2014 to 2017. The second patient group formed Study II and included 22 PD patients which were operated on from 2017 to 2020. All these PD patients received bilateral STN DBS: a voltage-controlled device in Study I and a current-controlled device in Study II. The third patient group formed Study III and they were paediatric patients operated on from 2016 to 2021. Demographic data is depicted in details in Table 1, in addition to previous study (Erola et al., 2006a).

Table 1. Demographic data of DBS Studies I-III compared with the previous study in Oulu University Hospital.

Demographic data	Erola et al 2006a	Study I	Study II	Study III
Operating years	2000–2003	2014–2017	2017–2020	2016–2021
Diagnosis	PD	PD	PD	CMD
Number of patients	29	30	24	5
Sex (female:male)	9:20	8:22	5:19	2:3
Excluded patients	5	5	2	1
Total patient number	24	25	22	4
Age at implantation (y/m±SD)	60y±8	61y±5	62y±6	144m±50
Disease duration (y/m±SD)	13y±7	13y±5	10y±5	136m±53

Demographic data	Erola et al 2006a	Study I	Study II	Study III
pLEDD (mg±SD)	585±293	851±368	951±374	No
Stereotactic frame	Laitinen	Leksell G-frame	Leksell Vantage	Leksell G-frame
Targeting method	Constant coordinates	Direct MRI	Direct MRI	Direct MRI
Planning image	Ventriculography	Preop 3T MRI	Preop 3T MRI	Preop 3T MRI
Intraop imaging	X-ray (AP, lateral)	ioCT (2D, 3D)	ioCT (2D, 3D)	ioCT (2D, 3D)
Surgery	Awake	Awake	Awake	Asleep
MER	Yes	Yes	Yes	Yes/No
Intraop stimulation	Permanent electrode	MER-electrode	MER-electrode	No
Temporary stimulation	Yes	No	No	No
Permanent electrode	M 3387	M 3389	BS VC	M 3389, BS VC
IPG	M Kinetra	M Activa PC/RC	BS Vercise Gevia	BS Vercise Gevia
Stimulation control	voltage	voltage	current	current
Postop follow-up (m)	12	12	12	31

Abbreviations: AP, anterior-posterior; BS, Boston Scientific; BS VC, Boston Scientific Vercise Cartesia; CMD, complex movement disorder; DBS, deep brain stimulation; IPG, implantable pulse generator; y/m±SD, years or months ± mean standard deviation; pLEDD, preoperative levodopa equivalent daily dose (mg); MER, microelectrode recording; M, Medtronic; MRI, magnetic resonance imaging; PC, non-rechargeable battery; PD, Parkinson's disease; RC, rechargeable battery; 3T MRI, 3 tesla head MRI for deep brain stimulation; ioCT (2D, 3D), intraoperative CT performed by O-arm (Medtronic, Minneapolis, USA) with 2 and 3 dimensional images.

4.1.1 Inclusion criteria and clinical data (I-II)

The inclusion criteria for Studies I and II were as follows: idiopathic PD, at least 5 years from the diagnosis and no signs of marked decline in cognitive functions or memory. All the patients had a good response to levodopa with at least 30% decrease in motor symptoms as measured with the motor UPDRS in the levodopa challenge test (LCT), which was completed by neurologists before referral. Preoperative evaluation protocol for adult DBS patients in OUH is depicted in detail in Fig.5.

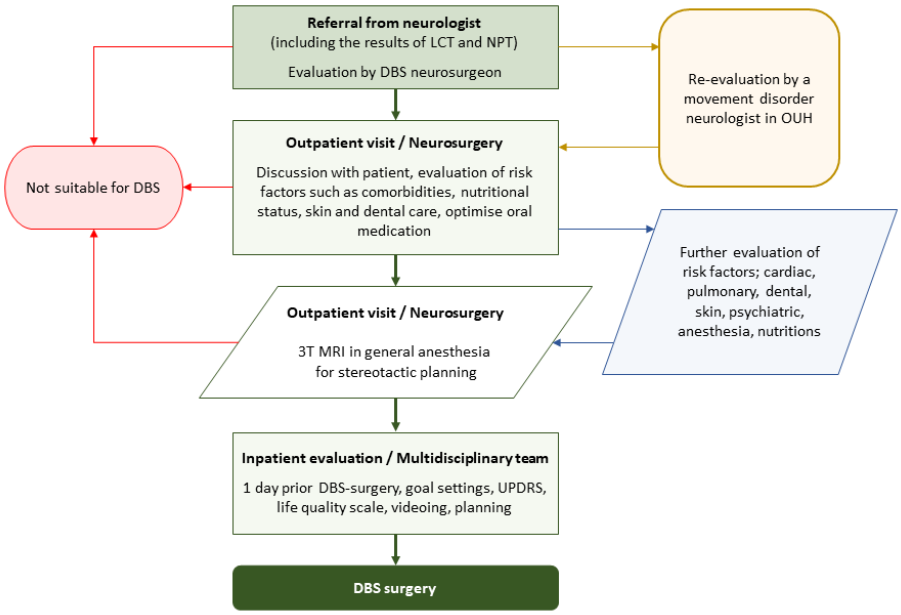

Fig. 5. Preoperative evaluation protocol for adult DBS patients with PD at Oulu University Hospital. DBS deep brain stimulation, PD Parkinson's disease, LCT levodopa challenge test, NPT neuropsychological test, 3T MRI 3 tesla magnetic resonance imaging, OUH Oulu University Hospital, UPDRS Unified Parkinson's Disease Rating Scale.

In Study I, five patients were excluded from the data: one patient suffered from an additional neurological disease, which interfered with the analysis of movement; two patients suffered early SSI leading to DBS explantation; two patients suffered technical failure (lead fracture) and cessation of stimulation before 12-months evaluation. One patient suffered bilateral haemorrhage alongside brain electrodes and due to ongoing rehabilitation, the patient was lost from the 12-months follow-up. However, medication data was included. In Study II, two patients were excluded as their DTI was not technically successful.

Clinical data and PD-related medications were collected from patient records retrospectively by the same clinician (author). The PD DBS-protocol of OUH includes clinical assessment carried out by UPDRS parts 3–5 with the best medical response (medON), at least 30–60 minutes after the latest levodopa intake. The assessment was carried out the day before the operation (baseline) and 12-months after the DBS operation by the same clinician (author) at both timepoints. The

clinical symptoms were also documented by video recordings. Patient themselves, or with the help of their caregivers, filled out UPDRS parts 1–2 in a self-assessed manner. In Study II, unilateral motor scores (UMS) were calculated separately for the right and left sides of the body, adding UPDRS items 20–26. PD-related medication which included levodopa was collected from patient records and was converted into levodopa equivalents daily dose (LEDD) (Tomlinson et al., 2010).

4.1.2 Inclusion criteria and clinical data (III)

In Study III all patients were under 18 years. All patients were evaluated for DBS surgery by the paediatric DBS core team including: two paediatric neurologists, one neurosurgeon (author), one medical physicist and thereafter by the multidisciplinary paediatric DBS Team. The clinical evaluation on movement disorder was done by BFMDRS by the same two paediatric neurologists. A total of 12 patients were evaluated and five patients were selected for pDBS surgery and four pDBS operations were performed. For one patient, the pDBS operation was postponed due to infection.

Inclusion criteria comprised complex movement disorder (mainly dystonia and/or hyperkinesia), realistic and achievable individual goals set up by the patient and parents and favourable results in preoperative structural examination: brain 3T MRI and somatosensory evoked potentials (SEP), motor evoked potentials (MEP) or central motor conduction time (CMCT). Developmental delay, mental retardation, or stable epilepsy was not an exclusion criteria for pDBS. Clinical data was collected retrospectively from patient records. Preoperative evaluation protocol for pDBS patients in OUH is depicted in detail in Fig.6.

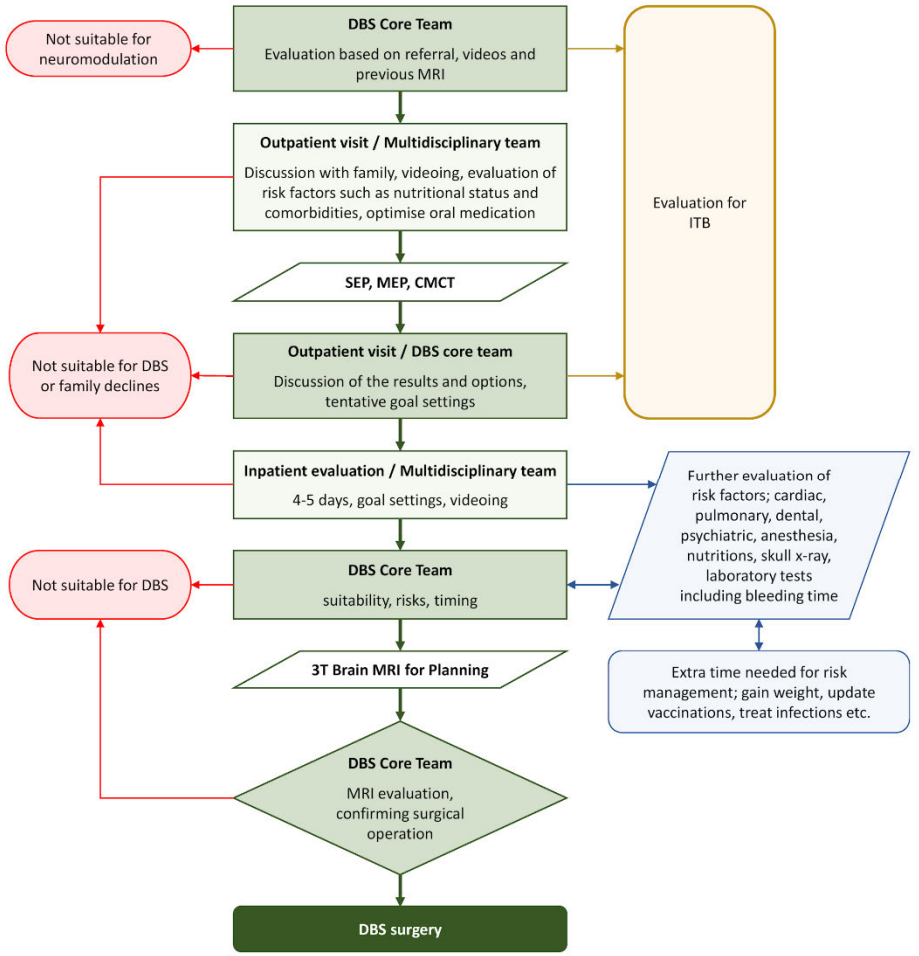

Fig. 6. Preoperative evaluation protocol for paediatric DBS patients with complex movement disorder at Oulu University Hospital. CMCT central motor conduction time, DBS deep brain stimulation, ITP intrathecal baclofen pump, MEP motor evoked potentials, 3T MRI 3 tesla magnetic resonance imaging, SEP somatosensory evoked potentials. Adapted from Lahtinen et al., 2021. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

4.2 Preoperative preparations (I-III)

In Studies I-II patients were admitted one day prior to their DBS operation to the neurosurgical ward for surgical preparations: preoperative interview, skin examination and care (chlorhexide skin washes), laboratory tests and considerations of the anaesthetists. After the DBS operation, immediate postoperative care was given overnight in the awakening room next to operating theatre and patients were transferred back to the neurosurgical ward on postoperative day one.

In Study III paediatric patients were admitted five days prior to their DBS operation to the paediatric neurological ward for the same kind of surgical preparations as adult patients, though chlorhexidine washes were done for five consecutive days prior to DBS surgery. For pDBS patients, postoperative care was given in the intensive care unit for approximately three days and thereafter pDBS patients were transferred back to the paediatric neurological ward.

All DBS surgeries were performed in accordance with the established customs of the OUH: the same surgical DBS team of two neurosurgeons, physicist, anaesthetist, anaesthetist nurse, instrument nurses and technical nurse.

4.2.1 MR imaging (I-III)

Preoperative stereotactic head MRI was performed using the hospital's established method for DBS surgery. MRI was done 1–8 weeks prior to the operation using 3T MRI under general anaesthesia supervised by the medical physicist of the DBS team. MRI was performed using the protocol of 64-channels head coil with the highest filling factor to achieve the highest signal-to-noise ratio in a reasonable imaging time (Skyra 3T and Vida 3T, Siemens Healthcare GmBH, Erlangen, Germany). The reference dataset was used to visualize overall brain structures, the sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) 3D sequence with the contrast agent. Multiple sequences were obtained to demarcate the target region: the coronal (perpendicular to the AC-PC -line) T2-weighted space sequence, the magnitude part of the coronal susceptibility-weighted imaging (SWI) sequence, the axial short tau inversion recovery sequence and for tractography, diffusion tensor images (DTI) were collected from 64 directions. In addition, for Study III the isotropic Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence was done to visualize pallidal and thalamic structures. Metadata for MRI sequences is depicted in table 2.

Table 2. Metadata for preoperative stereotactic head magnetic resonance imaging in Oulu University Hospital.

Parameter	3D+C	cor T2	SWI	ax STIR	DTI	FAGATIR
Repetition time (ms)	2200	1000	26	8000	5000	3000
Echo time (ms)	2.62	68	19	22	79	2.52
Inversion time (ms)				120		400
Flip angle (°)	90	120	15	120	90	6
Average	2	4	1	2	1	1
field of view (mm)	230x230	202x202	183x220	235x235	230x230	230x230
Matric (px)	384x384	380x384	240x288	256x256	130x130	256x256
Slice thickness (mm)	0.6	0.7	1.5	2.0	2.0	0.9
Imaging time	14min 52s	7min 10s	5min 16s	13min 36s	7min 37s	10min 6s

Abbreviations: 3D+C, sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) 3D sequence with the contrast agent; cor T2, coronal (perpendicular to the AC-PC -line) T2-weighted space sequence; SWI, magnitude part of the coronal susceptibility-weighted imaging (SWI) sequence; ax STIR, axial short tau inversion recovery sequence; DTI, diffusion tensor images (DTI) collected from 64 directions; FAGATIR, isotropic Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence (Study III).

4.2.2 Targeting (I-III)

The targeting of DBS electrodes was done one week prior to DBS surgery using planning software (Elements 2.0, Brainlab, Munich, Germany or Stealth FrameLink, Medtronic, Minneapolis, USA) and was directly based on brain 3T MRI. Two neurosurgeons and a medical physicist evaluated the targeting plan in the preoperative meeting.

In Studies I-II the target was the STN, and the target and its surrounding structures were outlined using MRI in three planes (axial, coronal, sagittal). The second most proximal contact of the lead was planned within the dorsolateral border of the STN so that the most distal contact was in the SN and the most proximal contact above the STN. The trajectory was planned to avoid vascular structures and ventricles. Entry points were planned near to the coronal suture.

In Study III, the target was GPi bilaterally. The aim of the plan was to define the target region of the stimulation, which included hyperdirect connections from the sensorimotor cortex to the GPi and thalamopallidal connections, especially ansa lenticularis and subthalamic fasciculus. The intent was to stimulate a wider region with neural connections as opposed to one specific location. The sequences of T1 were not feasible in order to demarcate the target region itself. Therefore, the Short-T1 Inversion Recovery (STIR) and the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequences were used to delineate the anatomical GPi and its inner laminar structure. The GPi and its surrounding structures are outlined in the pDBS-MRI shown in Fig.7.

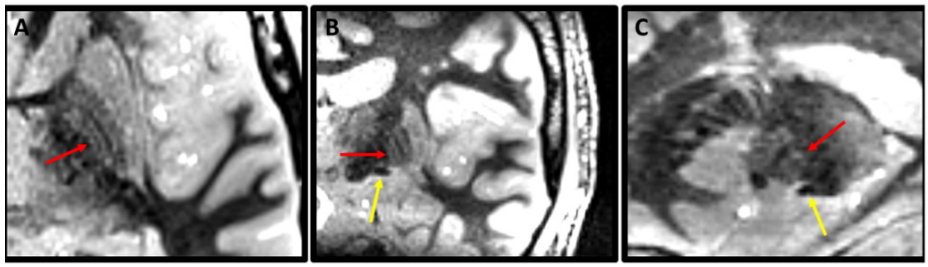

Fig. 7. Globus Pallidus interna (GPi) is a common target for deep brain stimulation (DBS) to alleviate dystonic symptoms. Visualisation of GPi and its surrounding brain structures in magnetic resonance images (MRI) is an important part of paediatric deep brain stimulation (pDBS). Optimised pDBS MRI protocol includes isotropic Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence delineate, especially pallidal anatomy and surrounding anatomy in all radiological directions; axial (A), coronal (B) and sagittal (C). The ventroposterior part of the GPi (red arrow) and its inner lamina structure can be clearly demarcated from capsular and Globus Pallidus externa (GPe) anatomy. Optic tract (yellow arrow) visualise inferiorly to GPi. Adapted from Lahtinen et al., 2021. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

Tractography, based on DTI, was used to study the white matter connections from the GPi to the neocortex and to other basal ganglia, for example, STN and subthalamic fasciculus (see Fig.8.).

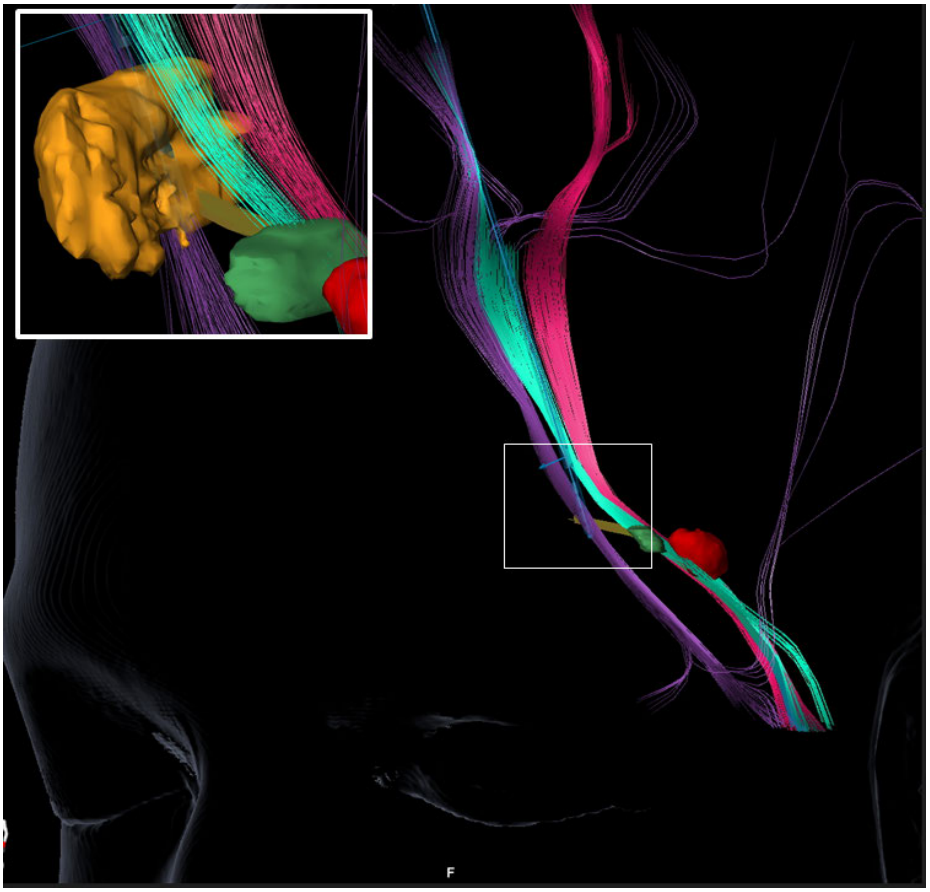

Fig. 8. Tractography was used to study the white matter connections from the sensorimotor, i.e., the posterior part of the Globus Pallidus interna (GPi) (yellow 3D model) and subthalamic nucleus (STN) (green 3D model) to the prefrontal cortex. The hyperdirect connections between: GPi and motorcortex are shown in purple fibre, STN and motorcortex in red fibre, STN and premotorcortex in turquoise fibre. The subthalamic fasciculus which connects GPi and STN is shown in yellow fibre. Adapted from Lahtinen et al., 2021. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

4.2.3 Tractography analysis (II)

In Study II, the DTI data was analysed retrospectively using deterministic calculation software (Elements 2.0, Brainlab, Munich, Germany). Patient image sets were fused into a dataset containing preoperative 3T DBS images and 1-month postoperative CT scans. Anatomical cortical regions of interest (ROI) were manually segmented: STN, motor cortex (M1, BA 4), supplementary motor area (SMA, BA6) and presupplementary motor area (preSMA, BA6 and 8) and dorsolateral premotor cortex (dlPMC, BA6). The STN was visible in all cases and was manually delineated from T2 coronal and SWI sequences. A vertical plane through the anterior commissure at the level of superior frontal gyrus was used to distinguish SMA and preSMA. The dlPMC was located lateral to the SMA and preSMA. Standardized anatomical templates were not used to allow for a more detailed segmentation of the structures and to avoid warping of the image.

Fibres were calculated using fractional anisotropy (FA) value of 0.2–0.3, minimum length 50 mm and minimum angulation 45°. Segmented cortical areas (M1, SMA, preSMA and dlPMC) were used singly as one seed and 2 mm diameter sphere (Interactive Tool) as another. Sphere seed was manually explored through the lateral region of the STN where hyperdirect pathways, except the limbic pathway, are known to be located. To avoid false positive tracts, only tracts that reached to the subcortical area of the seed were included (see Fig. 9.).

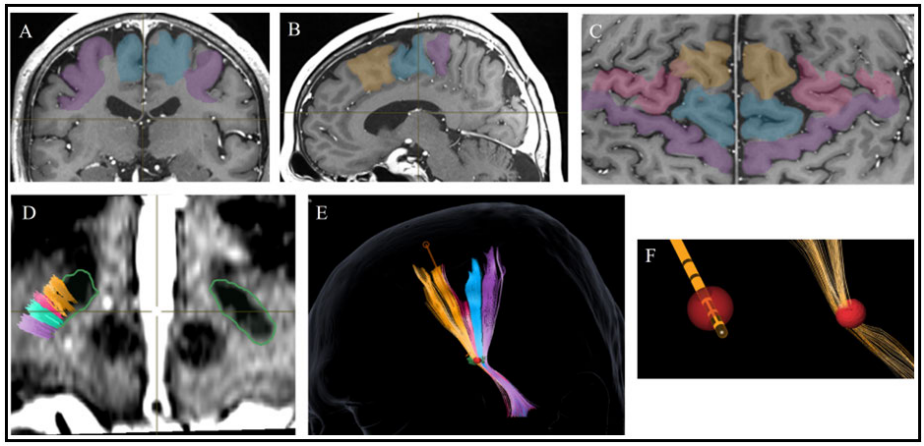

Fig. 9. Upper row subfigures A, B and C. Cortical areas were manually segmented as shown: purple is motor cortex (M1); blue supplementary motor area (SMA); orange presupplementary motor area (preSMA); pink dorsolateral premotor cortex (dlPMC).

Lower row subfigures D and E. Subthalamic nucleus (STN, green) was outlined from MRI in three planes: axial, coronal, and sagittal. The hyperdirect pathways were determined form the lateral border of the STN. The hyperdirect pathways project between the STN and the subcortical areas of the prefrontal cortex. Subfigure F. The volume of activated tissue (VAT, red) was calculated from the stimulation parameters of 12 months follow-up visit and VAT was edited to include the volume of the electrode. Intersectional volumes of VAT and the volumes of hyperdirect pathways were analysed. Adapted from Kähkölä et al., 2023 (Study II). Reproduced with permission from Neurosurgery, Wolters Kluwer Health, Inc.

Volume of activated tissue (VAT) and intersectional volumes (II)

The volume of activated tissue (VAT) was calculated with GuideTX (Elements 2.0, Brainlab, Munich, Germany) from 12-months postoperative parameters and active contacts of the lead. The objects of VAT were spherically edited to include the brain tissue displaced by the electrode and the volume was converted to cubic millimetres (mm^3).

Intersectional volumes of the VAT and the hyperdirect pathways (M1, SMA, preSMA and dlPMC) were calculated, and the results were divided by VAT to represent the percentage of which subvolume of VAT stimulates the fibre tracts projecting from a specific cortical area (m1VAT%, smaVAT%, presmaVAT% and dlpmcVAT%).

4.2.4 Surgical method (I-III)

In adult cases, the intracranial leads were implanted under local anaesthesia and extension wires as well as IPG's were implanted under general anaesthesia on the same day. The paediatric patients were implanted under general anaesthesia. For antibiotic prophylaxy: cefuroxime 1.5 g x 1 intra venous (iv) was administered to the adult patients and ceftriaxone 60 mg/kg (max 2 g) iv to the paediatric patients, and both patient groups were administered vancomycin 1–1.5 g iv (adults) or vancomycin 15 mg/kg iv (max 1 g, paediatrics).

First, the frame (Leksell G-frame or Vantage, Elekta, Stockholm, Sweden) was fixed to the patient's head under local anaesthesia. The CT coordinate indicator box (Leksell, Elekta, Stockholm, Sweden) was attached to the frame and intra-operative stereotactic head CT scans (Toshiba Aquilion One Vision Edition CT-scanner, Canon Medical Systems, Otawara, Tochigi, Japan) were taken. The scanning parameters were 120 kVp, 350 mAs, slice thickness 0.5 mm, pixel size 0.48 x 0.48

mm, matrix size 512 x 512 px and 320 slices. Contrast enhancement was used to highlight the vascular structures and improve the image fusion. The stereotactic CT scans and preoperative stereotactic 3T-MRI scans were fused by a medical physicist in the planning software to obtain stereotactic coordinates X, Y and Z.

After imaging, the patient was placed in a supine position on a conventional surgical operating table. The frame was fixed to the table. Next, patients in awake surgery were given slightly sedative medication, dexmedetomidine infusion (Dexdor, Orion, Espoo, Finland), was initiated to the patient. Surgical draping was done in a conventional manner using ethanol cum chlorhexidine scrubs, iodine film wrapping and local anaesthesia with chirochain cum adrenalin.

The stereotactic arc (Leksell Multipurpose Stereotactic Arc, Elekta, Stockholm, Sweden) was attached to the frame and stereotactic coordinates X, Y and Z were set, double-checked and the entry point located. A bifrontal skin incision and burr hole at the entry point were made, starting from the dominant or more symptomatic hemisphere. After placing the lower ring of the burr hole cover (SureTek Burr Hole Cover, Boston Scientific, Marlborough, Massachusetts and StimLoc, Medtronic, Minneapolis, USA or Guardian, Abbott, Illinois, USA), a dural incision was made and the stereotactic coordinates were again set to the stereotactic arc.

Microelectrode recording (MER)

MER was performed in awake DBS surgery, due to fact that under general anaesthesia the drugs may suppress the measurable electrical response. One, in the main, but up to a maximum of three guiding tubes 10 mm before the target point (Universal Guide Tube, Elekta, Stockholm, Sweden) were positioned. One to three microelectrodes (Elekta, Stockholm, Sweden) were inserted through the guiding tubes. For patients undergoing awake surgery, MER was performed (Leadpoint, Alpine Biomed, Skovlunde, Denmark). MER was used to evaluate electrical activity from 10 mm above to 2–3 mm below the target point in order to identify the borders of the target and the electrical firing abnormalities of the target area. Test stimulation was performed after MER: three levels were chosen and test stimulation was done using the same MER-electrodes. Stimulation was given with 0–4.0 mA, high frequency 130 Hz current with pulse width 60 µs. Clinical effects and side effects of the stimulation were evaluated and documented.

Permanent DBS electrodes and IPG

Two DBS devices with different principles of stimulation control were used: voltage-controlled (Activa RC, Medtronic, Minneapolis, USA) and current-controlled (Vercise Gevia, Boston Scientific, Marlborough, Massachusetts, USA). All DBS devices were rechargeable and MRI conditional. Two types of brain electrodes were used: conventional lead with 4-contacts (3389, Medtronic, Minneapolis, USA) and directional leads with 8-contacts (Vercise Cartesia, Boston Scientific Marlborough, Massachusetts, USA). After the evaluation of the location, the microelectrode was replaced with a permanent lead. Two centre-most contacts were inserted in the middle of the target area and adjustments of the permanent lead and its depth were made using 2D skull x-rays taken intraoperatively (O-arm, Medtronic, Louisville, CO, USA). The guiding tubes were removed and a permanent lead was secured in place using the burr hole cover (StimLoc, Medtronic, Minneapolis, USA and SureTek, Boston Scientific, Marlborough, USA). The distal end of the lead was inserted subcutaneously behind the contralateral ear. The operation was continued repeating the same surgical procedures on the other hemisphere in the same manner. Skin closure was performed in two layers. Finally, 3D head CT-scanning was done by O-arm (Medtronic, Minneapolis, USA) to visualize the lead positioning, amount of intracranial air, to rule out intraoperative haemorrhage and to perform immediate image fusion with preoperative stereotactic 3T-MRI-scans in order to investigate the lead and contact localization.

In the second phase, under general anaesthesia for every patient; the double extension wires (model 37086-40 cm, Medtronic, Minneapolis, USA and 55 cm, Boston Scientific, Marlborough, Massachusetts, USA) were placed subcutaneously on the neck area and a rechargeable pulse generator (Activa RC, Medtronic, Minneapolis, USA and Vercise Gevia, Boston Scientific, Marlborough, Massachusetts, USA) was implanted subfascially on the subclavicular or abdominal area.

4.2.5 Postoperative follow-up (I-II)

Postoperative follow-up was carried out in a structural form: 1, 3, 6 and 12 months after DBS surgery. The first control visit was an overnight visit in a neurosurgical ward and included head CT (Toshiba Aquilion One Vision Edition CT-scanner, Canon Medical Systems, Otawara, Tochigi, Japan) and image fusion with preoperative 3T stereotactic head MRI and targeting plan. During every follow-up

visit fine adjustment of the DBS programming was done and PD medication was evaluated. All control visits were carried out by the surgical DBS team. 12-months postoperative control was performed solely by the author in the same manner as the preoperative baseline evaluation (UPDRS, videos).

4.2.6 Postoperative follow-up (III)

Paediatric DBS patients were followed-up by the multidisciplinary DBS team to control the visits and consultations. The follow-up programme for paediatric patients is depicted in detail in Table 3.

Table 3. Long-term multidisciplinary postoperative follow-up protocol for paediatric deep brain stimulation patients for movement disorder in Oulu University Hospital. Adapted from Lahtinen et al., 2021. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

Data	1m	2m	3m	6m	9m	12m	18m	annual visit
Paediatric neurologist	x	x	x	x	x	x	x	x
Neurosurgeon+physicist	x	x	x	x	x	x	x	x
Nurse	x	x	x	x	x	x	x	x
Physiotherapist			x	x	x	x	x	x
Speech therapist	(x)	(x)	(x)	(x)	(x)	x	(x)	x
Occupational therapist			(x)	(x)	(x)	x	(x)	x
BFMDRS			x	x	x	x	x	x
QoL						x		x
COMP						x		x
GAS						x		x
GMFCS						x		x
CFCS						x		x
MACS						x		x
EDACS						x		x
Head CT-C+	x							
X-ray						x[1]		

Abbreviations: DBS, deep brain stimulation; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; QoL, Quality of Life; COMP, Canadian Occupational Performance Measure; GAS, Goal Attainment Scaling; GMFCS, Gross Motor Function Classification System; CFCS, Communication Function Classification System; MACS, Manual Ability Classification System; EDACS, Eating and Drinking Ability Classification System; CT-C+, Computed Tomography with contrast-enhancement.

[1] Specific indications for X-ray of DBS device: patient has a migration of the extension lead connectors during the growth spurt, suspicion of hardware breakage or planned scoliosis surgery.

4.3 Statistical analysis

All statistical analyses were performed using commercially available software: SPSS for Windows 23.0 (Study I) and 27.0 (Study II), IBM, New York, USA and Excel 2016, Microsoft, Redmond, WA, USA. The paired samples T-test was used when comparing the change between preoperative and 12-months postoperative data. Statistical significance was set to $p < 0.05$ (Studies I and II). Linear regression analysis was used to calculate regression coefficients (β-coefficients) and scatterplot graphs were used for analyses (Study II).

4.4 Ethical considerations

This study was carried out in accordance with the Declaration of Helsinki and its later amendments (World Medical Association Declaration of Helsinki, 2013). Studies I and II were approved by the administration of OUH (Registry number 7/2013) and the Ethics Committee of the Northern Ostrobothnia Hospital District approved the work (Ethical Approval number 1/2013 and amendment 1/2014). Study III was approved by the administration of OUH (Registry number 272/2016) and the regional Ethics Committee of the Northern Ostrobothnia Hospital District of Finland (Ethical approval number 107/2016). Studies I-III were conducted as a registry studies. In Study III, a written informed consent was obtained from patients or guardians of the patients to whom DBS was implanted due to the rarity of the disease (patients may be identified from the publication).

5 Results

5.1 DBS database

A total of 920 DBS-related operations were recognized from 1997 to 2021 and included in the OUH DBS database: 333 primary or re-implantations of deep brain electrodes uni or bilateral (Therapy: AAG20), 515 primary or re-implantations of IPG (Therapy: AEA00), 30 DBS related surgical revisions due to technical problems or device migration (Therapy: AAG99), 36 revisions due to infection (Therapy: AAM99) and 3 revisions due to haematoma (Therapy: AWE00) (see Fig.10.). The majority of the patients (81%, 269 patients) had a PD diagnosis (see Fig.11.).

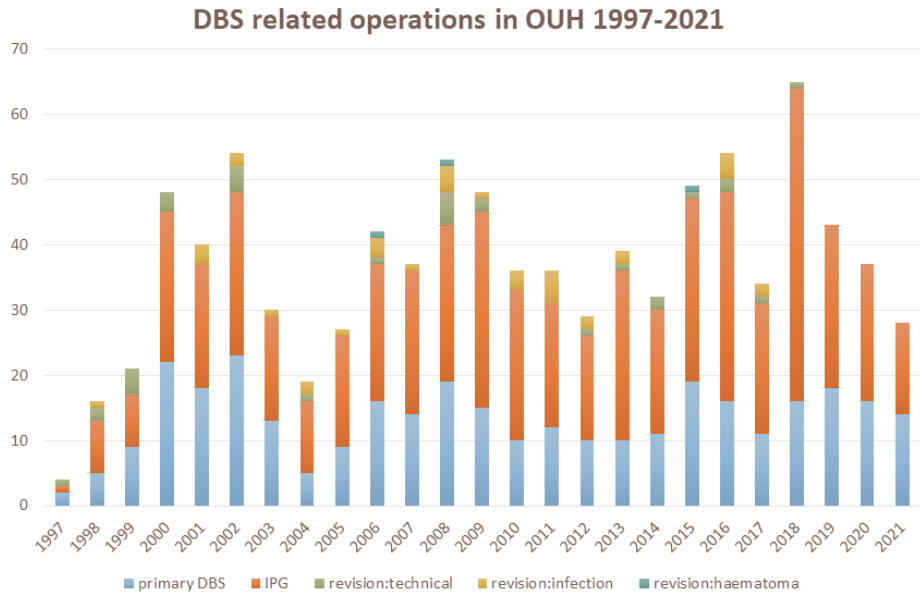

Fig. 10. Deep brain stimulation related operations in Oulu University Hospital 1997–2021. Figure by Maija Lahtinen.

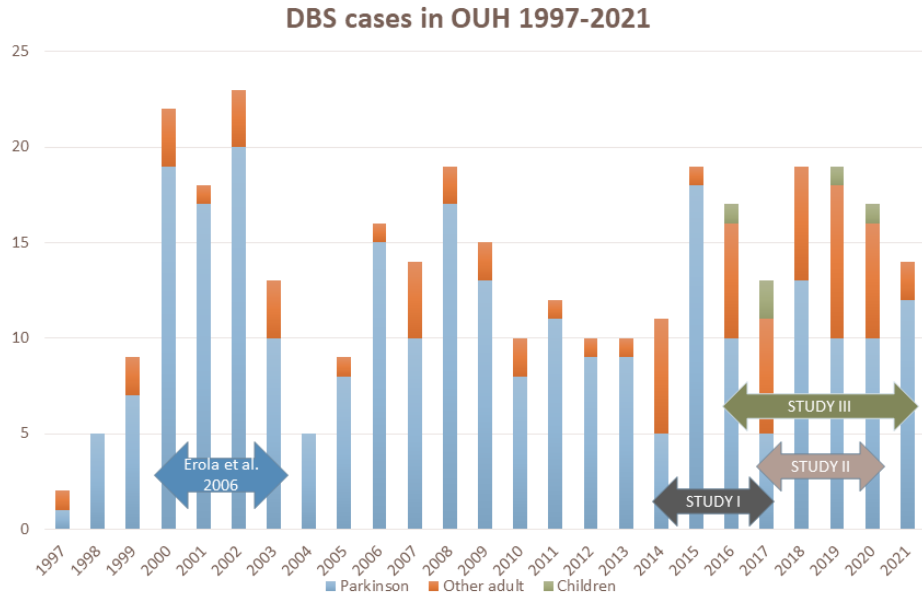

Fig. 11. Deep brain stimulation cases in Oulu University Hospital 1997–2021. Figure by Maija Lahtinen.

5.2 Patient data (I-III)

Study I consisted of 30 consecutive PD patients who underwent DBS surgery from June 2014 to January 2017. Five patients were excluded for reasons described previously in Methods. One male patient had previously undergone unilateral thalamotomy due to PD tremor. A total of 25 patients were included (7 female and 18 male) in Study I. Their mean age at the time of the DBS operation was 61 years (SD ± 5) and the mean disease duration (time from the PD diagnosis to surgery) was 13 years (SD ± 5).

Study II consisted of 24 consecutive PD patients from August 2017 to November 2020. Two patients were excluded from the study (see Methods). In total, 22 patients were included (5 female and 17 male) in Study II. Their mean age at the time of the DBS operation was 62 years (SD ± 6) and the mean disease duration was 10 years (SD ± 5).

Study III consisted of 4 consecutive paediatric DBS patients from November 2016 to March 2020. One patient was evaluated but the DBS surgery was postponed due to infection.

5.3 Outcome in Unified Parkinson's Disease Rating Scale (UPDRS) (I-II)

In Study I, statistical improvement ($p < 0.05$) was seen in six out of seven parameters of UPDRS measured with the best medication response. The change was statistically highly significant in four parameters: activities of daily living (UPDRS 2), motor score (UPDRS 3), dyskinesias (UPDRS 4a) and fluctuations (UPDRS 4b). The 12-months follow-up improvements compared to the baseline were 41%, 62%, 81% and 81%, respectively.

In Study II, statistical improvement was seen in six out of seven parameters of UPDRS. The reduction was statistically highly significant in two parameters: motor score 58% and fluctuations 78%. The change was statistically significant in two subscores: dyskinesias 69% and Hoehn&Yahr classification (UPDRS 5) 19% (see Table 4).

Table 4. UPDRS baseline and 12-months postoperative scores of PD patients treated by STN DBS (Studies I-II).

UPDRS (min-max)	Study	preDBS	PostDBS		95% CI*		Sig.(2-tailed)
		Mean ±SD	Mean ±SD	Mean diff.±SD	Lower	Upper	p**
1 (0–16)	I	1.8±1.8	2.2±2.1	- .4±1.4	-1.1	0.3	0.215
2 (0–52)	I	16.6±7.1	9.8±7.4	6.8±7.4	3.2	10.3	< .001
3 (0–108)	I	30.1±16.6	11.8±8.5	19.0±14.8	12.8	25.2	< .001
4a (0–13)	I	5.2±3.5	1.0±1.4	4.3±4.0	2.5	6.1	< .001
4b (0–7)	I	3.1±1.1	0.6±1.2	2.5±1.2	2.0	3.1	< .001
4c (0–3)	I	1.6±1.0	0.8±0.9	0.8±1.1	0.4	1.3	.002
5 (0–5)	I	2.7±0.7	2.2±0.7	0.5±0.8	0.2	0.9	.003
1 (0–16)	II	2.4±1.8	2.2±1.6	0.2±1.6	-0.5	0.9	.584
2 (0–52)	II	11.9±3.0	9.1±4.8	2.7±5.1	0.4	5.0	.025
3 (0–108)	II	36.0±10.2	15.1±6.2	21.0±10.1	16.5	25.4	< .001
4a (0–13)	II	3.6±2.6	1.1±2.5	2.5±4.0	0.7	4.2	.008
4b (0–7)	II	2.7±1.4	0.6±1.0	2.0±1.9	1.2	2.9	< .001
4c (0–3)	II	1.5±1.0	1.0±0.7	0.5±0.9	0.1	0.9	.013
5 (0–5)	II	2.6±0.5	2.1±0.6	0.5±0.6	0.2	0.9	.004

Abbreviations: CI, Confidence Interval of the Difference; **p, postoperative (12 months) p-value between pre- and post-DBS operation (Paired Samples t-test); DBS, deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale: 1 Mentation, Behaviour & Mood, 2 Activities of daily living, 3 Motor, 4a Dyskinesias, 4b Fluctuations, 4c Complications, 5 Hoehn & Yahr.

5.4 Outcome in levodopa reduction (I-II)

Patients PD-related LEDD is shown in Table 5. In Study I, LEDD reduction was 62% comparing baseline and 12-months postoperative medication. Five patients (20%) were without levodopa medication 12 months after DBS initiation. In Study II, the reduction was 75% and five patients were without levodopa medication 12 months after DBS initiation.

Table 5. Levodopa medication of PD patients: baseline and 12 months after STN DBS operation.

Data	Preop LEDD	Postop LEDD	Mean diff	95% CI*		p**
	Mean (±SD)	Mean (±SD)	(±SD)	Lower	Upper	
Study I	851±368	327±241	524±269	413	635	< .001
Study II	951±374	237±187	714±376	547	880	< .001

Abbreviations: CI*, Confidence Interval of the Difference; p**, postoperative (12 months) p-value between pre- and post-DBS operation (Paired Samples t-test); DBS, deep brain stimulation; LEDD, levodopa equivalent daily dose (mg); PD, Parkinson's disease; STN, subthalamic nucleus.

5.5 Stimulation parameters (I-II)

In Study I, all patients had the DBS device with conventional 4-contacts leads and rechargeable IPG (lead model 3389, extensions model 37086-40 cm, IPG model Activa RC; Medtronic, Minneapolis, USA) and the stimulation was voltage-controlled (V). 12 months after the DBS operation the mean stimulation parameters were: amplitude 2.4 V (SD ± 0.5), pulse width 71 μs (SD ± 19) and frequency 142 Hz (SD ± 25). Twenty-one patients had bilateral monopolar stimulation, three patients had bilateral bipolar stimulation, and one patient had unilateral monopolar and unilateral bipolar stimulation. Eleven patients had two contacts of the electrode activated, and one patient had three contacts activated in the left hemisphere's lead. Eight patients had two active contacts, and one had three active contacts in the right hemisphere's lead.

In Study II, all patients had the same DBS device with directional 8-contacts leads and rechargeable IPG (lead model Vercise Cartesia, extension model 55 cm and IPG model Vercise Gevia; Boston Scientific, Marlborough, Massachusetts, USA) and the stimulation was current-controlled (mA). 12 months after the DBS operation the mean stimulation parameters were: amplitude 2.4 mA (SD ± 0.5), pulse width 67 μs (SD ± 12) and frequency 146 Hz (SD ± 27). Fifteen patients had

the primary contact (second proximal contact) active, seven patients had directional stimulation and two patients had bipolar stimulation. The most common reason for directional stimulation was postural instability.

VAT analysis (II)

The mean VAT in the left hemisphere was 70.5 mm^3 (SD ± 21.9) and in the right 75.0 mm^3 (SD ± 24.4). Larger VAT values did not correlate with better motor improvements.

5.6 Tractography analysis of hyperdirective pathways of the subthalamic nucleus (STN) and clinical outcome (II)

The stimulated clusters of STN were mostly connected via hyperdirect pathways with the cortical SMA and preSMA regions. Stimulation of the M1 cluster was minor with only 4 electrodes, therefore, M1 tracts were excluded. The FA values used in this study did not reliably show hyperdirect fibre tracts from the dlPMC (16 of the 44 electrodes studied), thus dlPMC was excluded.

Stimulation in the preSMA cluster proximity was predictive of a better and more consistent treatment response. Patients with predominantly preSMA cluster stimulation (presmaVAT% ≥ 50%) had a good response to the treatment with contralateral UMS improvement over 40% and LEDD reduction over 60%. Moreover, three out of five patients, who were completely without levodopa 12-months postoperatively, had presmaVAT% ≥ 50%. Conversely, patients with less or no preSMA cluster stimulation (presma < 50%) had varied results in UMS and LEDD reduction.

5.7 The first pedDBS patients: clinical outcome, surgical safety (III)

Twelve paediatric (0–18 years) patients were evaluated according to the pDBS protocol and the decision to proceed with pDBS surgery was made for five patients (41.7%). One operation was postponed due to infection and one pDBS was re-implanted due to technical failure (fracture in both leads). A total of five pDBS implantations on four patients were performed during the follow-up time. All patients had known aetiology of hyperkinetic movement disorder, the main feature was dystonia (see Table 6.).

Table 6. The demographic data of the first paediatric DBS patients in Oulu University Hospital. Adapted from Lahtinen et al., 2021. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

Patient	Sex	Age of onset	Age at operation	Time for preop evaluation	Follow-up	Complications
P1	male	4m	10y 8m	6m	48m	haematoma around IPG (conservative treatment)
P2	male	2y	11y 6m	8m	42m	no
P3	male	2m	6y 4m reop at 8y	12m	20m	bilateral lead fracture within 3m of surgery resulting DBS re-implantation
P4	female	at birth	17y 9m	14m	12m	no
P5	female	at birth	14y, but postponed	8m		

Abbreviations: DBS, deep brain stimulation; IPG implantable pulse generator; m, months; y years.

All the patients benefitted from DBS treatment. Even when BFMDRS disability scores failed to show any measurable change, the quality of life improved in the form of easier dressing and hygiene (P3) and improved eating (P4). In the case of progressive dystonia due to a metabolic defect (p2) the rate of disease progression halted for a considerable time enabling independent ADL. With this patient, an Influenza A infection affected the BFMDRS motor scores (see Fig.12.).

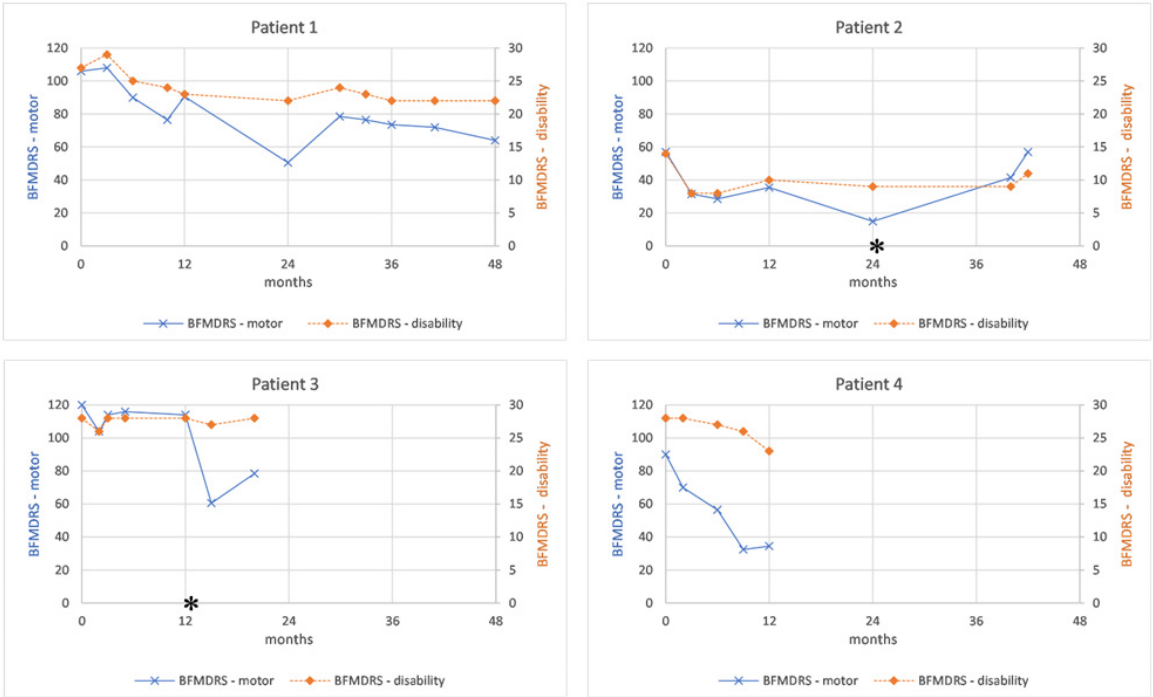

Fig. 12. Deep brain stimulation (DBS) implanted paediatric patients and their follow-up data presented as a graph of time by Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor and disability scores. Patient 2* Influenza A infection resulted in a deterioration of motor symptoms. Patient 3* Initiation of diazepam medication, BFMDRS scores obtained after DBS re-implantation. Adapted from Lahtinen et al., 2022. Reproduced with permission from European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society, Elsevier Science & Technology Journals.

6 Discussion

The principles of DBS have remained the same, but the imaging, hardware and software have evolved significantly. The basic idea behind this work was to study whether the outcome of patients with PD, who underwent STN DBS, changed over the years. The hypothesis explored is that advanced imaging and software, as well as precise and individual targeting and follow-up, will improve the outcomes of DBS surgery in PD. In this respect, the author is grateful to a previous thesis conducted by Professor h.c. Esa Heikkinen and carried on by Tuomo Erola (Erola, 2006). Consequently, we have reference data from almost 20 years ago with which to compare our results.

OUH serves as the only tertiary centre in Northern Finland for a population of approx. 740 000 (Kuntaliitto, 2021), which is 13.6% of the Finland population (total 5.5 million) (StatFin, 2023). OUH is the smallest tertiary hospital in Finland in terms of population catchment area yet the largest in terms of area. As a small-size tertiary hospital, the number of the patients is relatively modest, but the material is even more accurate considering that all DBS-related surgery for the area is centralized in OUH and DBS patients are easily accessible and able to be followed-up. The DBS database includes all DBS related operations from 1997 to 2021 and it is a unique and valuable database for further study both nationally and also internationally. In this work, all patient data was drawn from this DBS database. In the future, a national registry for therapeutic DBS patients and trials is essential (Lozano et al., 2019).

6.1 Parkinson's patients in Studies I-II

From the DBS database we selected consecutive PD patients undergoing primary DBS surgery for Studies I and II. The DBS database revealed that the number of PD patients undergoing DBS-surgery of the STN has remained constant over twenty years of follow-up when comparing the age, disease duration and sex ratio to the earlier study (Erola et al., 2006a). The main difference was the amount of preoperative levodopa medication, which was 31% and 38% greater when comparing the results of Study I and II, respectively, to the previous study where PD patients were operated on between 2000–2003. This is likely due to the introduction of Catechol-O-methyl transferase, i.e., COMT-inhibitors such as entacapone, opicapone or tolcapone (Fabbri et al., 2022). The triple combination drug for PD with peripheral-COMT-inhibitor (Stalevo, Orion Pharma, Espoo,

Finland) was proven to be efficient, safety and well tolerated and was approved by the FDA in 2003 (Solla, 2010). From this it can be understood that PD patients tolerate a higher dose of levodopa with the least adverse complications from the medication such as levodopa-induced dyskinesias and fluctuations.

These findings underline the conclusion, that the patient selection, indication and the time window for DBS surgery have remained the same over the past 20 years, thus the number of DBS-operated PD patients has remained relatively constant. Although the numbers of PD patients and the awareness of DBS-treatment have risen, DBS-surgery has developed towards individual treatment and it is well tolerated, safe and effective. There is Class II evidence (A randomized controlled clinical trial or a prospective matched cohort study, American Academy of Neurology Classification of Evidence) that DBS surgery in early-stage of PD decreases the risk of PD progression and polypharmacy compared to optimal medical therapy alone (Hacker et al., 2020). A recent study revealed that the higher (> 50%) total levodopa response strongly correlates with postoperative motor scores (UPDRS 3) and PD specific QoL (Zheng et al., 2021). Also, there is evidence that early STN DBS in PD reduces long-term medication costs (M. Hacker et al., 2021). The most recent publication from our DBS research group (ORGASTP) will consider the impact of DBS on the QoL of PD patients, and raises the question of the earlier timing of DBS (Kähkölä et al., 2023). Thus, the questions are: whether certain patient groups should be operated on earlier to restore the quality of life? Can we identify these patients early before the disease is medically-refractory?

Studies I and II confirm that STN DBS in advanced PD is an effective treatment to substantially reduce motor symptoms and complications associated with levodopa medication. These studies provide updated information concerning STN DBS in PD patients in Finland, and describes the use of the direct targeting method and MER in DBS-surgery as well as standardized and predictable programming method and follow-up in detail. These findings can be contrasted with a study from HUS (Koivu et al., 2018a) and these studies can give an overview of the current state of DBS in Finland. This study also emphasises the progress that has been made in DBS-surgery and the imaging technology.

6.2 Levodopa reduction and motor outcome

After surgery, DBS treatment continues as a chronic stimulation and levodopa medication is reduced in order to minimize its side effects. The challenge is not to reduce medication too much at the expense of the motor response. For this reason,

LEDD and clinical tests of PD (UPDRS) should be evaluated at the same timepoints. In the future, the questionnaire on dyskinesias which was recently validated in the Finnish language (Kaasinen et al., 2021), could be included in the follow-up protocol of PD DBS patients who have dyskinesias despite attempts to DBS adjustments.

In Studies I and II, the direct MRI based STN DBS resulted in greater reduction in levodopa medication compared to indirect constant-coordinate based DBS surgery (Erola et al., 2006a): 62%, 75% and 22% respectively. In addition, it is notable that in the direct STM DBS group 20 % of the PD patients were without levodopa medication 12 months after the operation, i.e., “super-responders”. Previous studies have shown that reduction in antiparkinsonian medication can be long lasting (Hertel et al., 2015). However, it should be noted that in Studies I and II, patients had a higher preoperative dose of antiparkinsonian medication than in the previous study (Erola et al., 2006a): 851 mg (SD ± 368), 951 mg (SD ± 374) and 585 mg (SD ± 293) respectively.

Also of note is that in all three studies, the reduction of levodopa medication did not negatively affect UPDRS subsections: ADL (UPDRS2), motor response (UPDRS3), dyskinesias (UPDRS4a) and fluctuation (UPDRS4b) 12 months after the operation. However, the improvement was greater in direct MRI based STN DBS Studies (I-II) compared to the earlier one (Erola et al., 2006a): ADL 41%, 24% and 19%; motor response 62%, 58% and 31%; dyskinesias 81%, 69% and 53%; fluctuations 81%, 78% and 39%, respectively in all subsections.

Similar results have been obtained in another Finnish study (Koivu et al., 2018b) of STN DBS in PD patients. The follow-up time was 6 months after STN DBS surgery and the outcome was measured in OFF-medication. The improvement in motor response (UPDRS3) was 41% and reduction in LEDD was 40%.

It is predictable that patients with an exceptionally good stimulation response have the active contact of the lead near the hyperdirect pathways, which run between the STN and prefrontal cortex, i.e., "sweet spot”. This followed the idea of Study II: to establish whether there is a correlation between the hyperdirect pathways running between the lateral border of the STN and stimulation field (VAT) and the clinical response and LEDD reduction. Thereby, to study which part of the STN cluster is the “sweet spot”. Study II reinforced the preassumption that the “sweet spot” is anterior to the M1 and lies somewhere between the clusters of preSMA and SMA. This finding confirms the results of a previous study where it was found that stimulation of the M1 cluster does not predict a better clinical outcome (Avecillas-Chasin et al., 2019).

In Studies I and II it must also be highlighted that two different DBS devices (voltage- and current-controlled) were used. A recent study suggested that in voltage- and current-controlled DBS, the stimulation activates different pathways (Evers et al., 2022), and thus produce mixed results and bias the study. Further studies are needed to understand which method of stimulation is better for each patient.

6.3 The role of MER

The role of MER in determining the lead position has decreased over the years to the same extent that the importance of imaging has increased. Notably, the transition to asleep DBS-surgery has reduced the use of MER, thus it is known that MER is less reliable when the patient is under general anaesthesia (Bos et al., 2021).

In Study I, MER was initiated through one to three channels but in Study II only one channel was measured so the result of MER affected only the depth of the lead. Thus, the question is raised, have we come to the end of MER in DBS surgery? However, if we want to treat brain diseases and their underlying pathophysiology an to treat the cause instead of the symptom, then we need more information about the electrical activity at the cellular level in patients with movement disorders. Further studies are needed to analyse the information of MER with the information of the LFP gained from the recordings of the DBS devices.

6.4 The role of stimulation parameters

DBS requires appropriate dosing, thus using electrical stimulation parameters to control the shape and the extent of the electrical field and different types of neural elements and circuits (Lozano et al., 2019).

In Study I, stimulation parameters in the direct STN DBS group were quite equal compared to the indirect STN DBS group. However, the latter had a wider range of parameters which demonstrates the heterogeneity of programming parameters. The heterogeneity in stimulation parameters may be due to inaccurate positioning of the electrodes in the STN region and the slight variations of normal brain structures.

In Study II, stimulation currents and VAT values used were moderate compared to a similar study (Avecillas-Chasin et al., 2019). It seems that if the distance to the "sweet spot" is kept to a minimum, there is no need to increase the stimulation current. This reinforces the findings of previous studies (Prent et al., 2020)

(Mahlknecht et al., 2017). Study II shows that larger VAT does not improve the contralateral motor outcome, thus we suggest that suboptimal targeting cannot be compensated with larger VAT and unwanted side effects of the stimulation. In the future, anatomical MR imaging can be routinely used for targeting together with the tractography.

6.5 Paediatric DBS service

In our experience, the first pDBS patients formed a heterogenous group in terms of aetiology and also presented with very severe phenotype. This is likely to be common when starting a DBS service for a novel patient group, also in adults.

From a paediatric neurological point of view, one important consideration is to have a team with extensive experience in the classification of paediatric movement disorders and to have a direct contact with the families. The pDBS is an excellent tool to alleviate symptoms as long as the patient selection is right.

From a neurosurgical point of view, pDBS service must be based on long term experience of DBS-surgery, including high-quality brain imaging, technical nuances of stereotactic neurosurgery and quality control of targeting. One should be aware of the technical differences and their capabilities between DBS devices from different manufacturers, e.g., electrodes for directional stimulation. Experience in paediatric neurosurgery is an advantage.

In addition, there needs to be an awareness that a sudden cessation of DBS can lead to a dramatic deterioration in the patient, such as status dystonicus. In which case the neurosurgical team should be able to proceed to lesional surgery such as pallidotomy (Garone et al., 2020).

From the patient and family point of view, the pDBS service offers an alleviating treatment for severe movement disorder and hopefully raise the QoL. However, pDBS service requires a long-term commitment from the patients and families. There is also considerable unmet need in a population where DBS service has not been previously available, and it is important to spend time informing the patients with dyskinetic movement disorders so they are aware of this treatment option.

6.6 Strengths and limitations

The strength of this thesis is that the patients were evaluated and operated on by the same DBS team. Preoperative and postoperative clinical assessments (UPDRS,

BFMDRS) were carried out by the same clinicians (author in Study I-II and two paediatric neurologists in Study III) and all assessments were complited according to the same protocol. The limitation of this study is that the evaluation of motor response was conducted with the best medication on, not medication off. During follow-up there were no missing patients due to non-medical reasons. Thus, one limitation is that it is based on retrospective data with non-blinded evaluation and the patient size is rather small and in Study III individual patients.

6.7 Future aspects

The future we will see more personalized DBS treatment, which is targeted based on MR images, tractography and functional imaging of the brain. The stimulation is delivered by closed-loop DBS systems, which will enable more personal DBS treatment for the patient and also analyse the mechanisms of underlying circuit pathology. With the aid of prognostic computing models, we will be able to identify the super-responders at an early stage of the PD and thus affect PD patients clinical symptoms at an earlier stage, and potentially delay some of the late-stage disability and prolong survival, of which there have been signs in previous studies (Mahlknecht et al., 2022). With the development of technology, DBS devices will also benefit from miniaturization. DBS devices may also become more common, for example, in restoring memory (Bick & Eskandar, 2016). Instead of clinical screening tests (like UPDRS) the computerised analysis of movements will become as a routine.

Paediatric DBS treatment will be few in numbers, but in future the aim is to be able to assess all possible candidates for pDBS treatment. Paediatric patients, especially, will benefit from miniaturisation of DBS devices.

Lesional neurosurgery has experienced a renaissance in the recent years. Some patients, for example, older unilateral tremor patients with mild-moderate memory loss, will benefit from lesional surgery performed by RF-technique, which is the fastest and most economical method to perform a lesion. In recent years, there has been a rising interest in non-surgical lesional methods such as MRgFUS in PD (Meng et al., 2018; Martínez-Fernández et al., 2020). Moreover, in recent years non-surgical treatment methods have achieved a prominence in the field, taking the interest away from reversible DBS surgery. On the other hand, MRgFUS enables treatment for those patients who are not suitable for invasive surgery and might otherwise be rejected completely from neurosurgical treatments of movement

disorders. However, these treatment methods require a large financial investment in equipment compared to RF-ablation.

A recent prospective double-blinded study of unilateral pallidotomy in PD patients treated by MRgFUS (Krishna et al., 2023) revealed that 69% of MRgFUS-operated patients had response after 3 months follow-up, and 77% of those who were continued follow-up until 12 months had response, although the mean improvements compared to baseline were quite modest: in the off-medication UPDRS3 score for the treated side was 4.9 points (27%) compared to 1.0 points (6%) in a sham-group. Notably, after 3 months, one third of the patients were non-respondents in MRgFUS 31% compared to 68% in the sham-group. Pallidotomy is not a new idea for PD, as we know it has been presented two times before. RF-pallidotomy was first presented in 1960 (Svennilson et al., 1960) and was named after Lars Lexell. The target was the same as today, the posteroventral lateral part of globus pallidus interna. The second coming of pallidotomy was in 1992 (Laitinen et al., 1992). At that time before levodopa and MRI, this neurosurgical technique and Svennilson's paper were revolutionary in the treatment of PD but was fell into oblivion with the invention of DBS (Krauss & Wolff Fernandes, 2022). Nonetheless, it remains possible that after over 60 years Leksell's pallidotomy (Svennilson et al., 1960) may experience a third coming whether the procedure method is RF-ablation, radiosurgery or MRgFUS. However, DBS is still the only reversible neurosurgical method whose efficacy, i.e., dosage of stimulation, can be adjusted as the disease progresses. It is also the only treatment method by which neural connections and their abnormalities can be measured and studied. However, further study of short- and long-term outcomes is needed for both reversible and irreversible neurosurgical procedures in PD and underknown neural connections in all movement disorders.

7 Conclusions

The aim of this work was to analyse the clinical results of DBS in Parkinson patients based on the DBS database and to create a DBS-protocol for the paediatric population. The findings facilitate the planning of future clinical trials of DBS treatment and, in addition, developing a clinical workflow, surgical methods and follow-up among adult and paediatric patients. The following conclusions can be drawn from this work:

1. Our DBS database shows that the demographic data of DBS patients with PD has remained similar for the follow-up period, excepting the amount of preoperative levodopa, which, it can be assumed, is due to the introduction of combination drugs, for example, dopamine agonists and entacapone.
2. In idiopathic PD, direct 3T-MRI-based DBS targeting, when combined with MER and test stimulation, improves the outcome significantly at the 12-month follow-up in four subscores of the UPDRS (ADL, motor score, dyskinesias and fluctuation). Furthermore, results were superior compared to the MER-verified indirect constant co-ordinate DBS targeting: ADL 41% vs 19%, motor score 62% vs 31%, dyskinesias 81% vs 53% and fluctuations 81% vs 39%, respectively. Direct DBS targeting decreases the need for levodopa-medication compared to indirect DBS targeting: levodopa 62–74% vs 28%.
3. Manual segmentation of STN to functional clusters using deterministic tractography is possible and could be used in everyday clinical practice. When stimulating the cluster of the STN which project the hyperdirect pathways to and from the preSMA, the 12 months outcome of Parkinson-related motor symptoms and levodopa reduction are better and more predictable.
4. The establishment of a paediatric DBS centre requires expertise in classification of paediatric movement disorders, longstanding experience in adult DBS, a committed multidisciplinary team, high quality imaging, a skilled neurosurgery team, careful patient selection, realistic treatment goals and experience in rehabilitation. The protocol of paediatric DBS-service depicted in detail in the original publication III proved to be feasible and reliable.

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