Aus dem Zentrum für Neurologie und Psychiatrie der Universität zu Köln
Klinik und Poliklinik für Neurologie
Direktor: Universitätsprofessor Dr. med. G. R. Fink

Wirksamkeit der Tiefen Hirnstimulation im Globus Pallidus internus bei NBIA – Dystonie

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Hohen Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Karolin Wieland
aus Kaufbeuren

Promoviert am 07. März 2012

Dekan: Universitätsprofessor Dr. med. Dr. h. c. Th. Krieg

1. Berichterstatter: Universitätsprofessor Dr. med. L. Timmermann
2. Berichterstatter: Universitätsprofessor Dr. med. R. Goldbrunner

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

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

Univ.-Prof. Dr. Lars Timmermann
Dr. med. Amande Pauls
Dr. rer. nat. Christiane Reck
Dr. Carmen Schade-Brittinger
Frau Selma Wieland

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Die dieser Arbeit zugrunde liegenden Daten wurden von mir mit der Unterstützung von Univ.-Prof. Dr. Lars Timmermann, der deutschen Selbsthilfegruppe „Hoffnungsbaum e.V.“ und der amerikanischen Selbsthilfegruppe „NBIA Disorders Association“ zusammengetragen. Folgende Personen haben die von ihnen ermittelten Daten zu dieser Arbeit beigetragen:

Gill S. S., *Institute of Neurosciences, Frenchay Hospital, Bristol, UK*
Haenggeli, C. A., *Hopital des Enfants, Geneve, Switzerland*
Jech, R., *Department of Neurology, 1st Medical Faculty, Charles University, Katerinská 30, 120 00 Prague 2, Czech Republic*
Kurlemann, G., *University Children's Hospital, Department of Paediatric Neurology, Muenster, Germany*
Leenders, K. L., *Department of Neurology, University Medical Centre Groningen, Groningen, the Netherlands*
Limousin, P., *Unit of Functional Neurosurgery, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, England, United Kingdom*
Malanga, C.J., *Department of Neurology, Division of Child Neurology, University of North Carolina at Chapel Hill, USA*
Ostrem, J. L., *Department of Neurology, University of California, San Francisco, California 94143, USA*
Pauls, A., *Department of Neurology, University of Cologne, Cologne, Germany*
Peker, S., *Department of Neurosurgery, Hospital for Neurological Sciences, Acibadem University School of Medicine, Istanbul, Turkey*
Revilla, F. J., *Department of Neurology, Movement Disorders Center, University of Cincinnati, 231 Albert Sabin Way, MSB 4503, Cincinnati, OH 45267-0525, USA*
Santens, P., *Department of Neurology, Gent University Hospital, Ghent, Belgium*
Sharma, N., *Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*
Tisch, S., *Unit of Functional Neurosurgery, Sobell Department Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London, United Kingdom*
Valldeoriola, F., *Hospital Clinic, Institut de Neurosciences Universitat de Barcelona, Barcelona, Spain*
Vesper, J., *Functional Neurosurgery, Department of Neurosurgery, Heinrich Heine University, Düsseldorf, Germany*
Volkmann, J., *Department of Neurology, Christian-Albrechts-University, Kiel, Germany*
Woitalla, D., *Department of Neurology, St. Josef Hospital, Ruhr University, Bochum, Germany*
Wojtecki, L., *Department of Neurology, Heinrich Heine University, Düsseldorf, Germany*

Das Datenmaterial ist nach entsprechender Anleitung durch Univ.-Prof. Dr. Lars Timmermann, durch Dr. med. Amande Pauls, durch Dr. rer. nat. Christiane Reck und durch Dr. Carmen Schade-Brittinger von mir selbst ausgewertet worden. Der Text ist von mir selbst in englischer Fachsprache verfasst und von Frau Selma Wieland Korrektur gelesen worden.

Acknowledgements

First, I would like to express my gratitude to Univ.-Prof. Lars Timmermann for his professional and excellent guidance and supervision.

Furthermore, I would like to thank all members of the group „Deep Brain Stimulation and Movement Disorders“ at the Department of Neurology of the University Hospital of Cologne who always offered me, in whatever manner, advice and support.

I am grateful to the many patients, families, and physicians, who contributed to this work. In particular I would like to mention the effective and encouraging collaboration with the patient organisations, most notably Mrs Angelika Klucken, chairwoman of the German “Hoffnungsbaum e. V.” as well as Mrs Patricia Wood, president of the NBIA Disorders Association in the United States.

This work is dedicated to all NBIA-patients

and their families.

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Glossary

BFM	Burke-Fahn-Marsden
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
BFMDRS-D	Burke-Fahn-Marsden Dystonia Rating Scale – Disability Scale
BFMDRS-M	Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale
CCHQ	Care and Comfort Hypertonicity Questionnaire
CD	cervical dystonia
CoA	Coenzyme A
DBS	Deep Brain Stimulation
dd	day
DNA	deoxyribonucleic acid
DVD	digital versatile disc
DYT1	Torsion Dystonia gene
e.g.	for example (Latin: exempli gratia)
eots-neg	negative for the “eye of the tiger sign”
eots-pos	positive for the “eye of the tiger sign”
etc.	et cetera
GDS	Global Dystonia Scale
GPe	Globus Pallidus pars externus
GPi	Globus Pallidus pars internus
GPi-DBS	Globus Pallidus pars internus – Deep Brain Stimulation
GPi-THS	Globus Pallidus pars internus – Tiefe Hirnstimulation
Hz	Hertz
i.e.	that is (Latin: id est)
IPG	internal pulse generator
INAD	infantile neuroaxonal dystrophy
min	minutes
mm	month
MRI	magnetic resonance imaging
µsec	microsecond
n	number of patients
NBIA	Neurodegeneration with Brain Iron Accumulation

n. s.	not significant
PANK2	Pantothenate Kinase 2
PET	positron emission tomography
PKAN	Pantothenate Kinase-Associated Neurodegeneration
PLA2	Phospholipase A2
PLA2G6	Phosphoplipase A2G6
SD	standard deviation
sec	seconds
SNr	Substantia Nigra pars reticulata
SPECT	single photon emission computed tomography
STN	Nucleus subthalamicus
THS	Tiefe Hirnstimulation
UDRS	Unified Dystonia Rating Scale
V	Volt
Vim	ventral intermediate nucleus of the thalamus
VL	nucleus ventralis lateralis
WeeFIM	Functional Independence Measure for children
yy	year

1. Introduction

1.1. Neurodegeneration with Brain Iron Accumulation (NBIA)

Neurodegeneration with Brain Iron Accumulation (NBIA, previously known as Hallervorden-Spatz Syndrome) describes a group of rare disorders involving a series of severe and sometimes even life-threatening neurological features, associated with focal iron accumulation particularly in the area of the basal ganglia (Hallervorden and Spatz, 1922; Dooling et al., 1974). Depending on the subtype of the disease, symptoms can occur in early childhood with fast episodic or progressive course or later in adolescence most commonly affiliated with a milder devolution (Gregory and Hayflick, 2005; Gregory et al., 2009). Its prevalence is projected at 1-3 per million based on observed cases in a population (Gregory et al., 2004)

Several approaches have been made to establish a nosology for the syndrome, which is nowadays defined as NBIA (Appendix 1).

Due to cumulative familial occurrence which had been observed apart from the cases described by Hallervorden and Spatz (Wigboldus and Bruyn, 1968), an autosomal recessive mode of inheritance was hypothesized (Hallervorden, 1924; Elejalde et al., 1979). In NBIA, different causal gene defects are presently revealed.
Taylor and colleagues defined the most common genetic subtype, a defect on the Pantothenate Kinase 2 gene (PANK2) on chromosome 20p12.3-p13, which is aetiologic of panthotenate kinase - associated neurodegeneration (PKAN) (Taylor et al., 1996; Zhou et al., 2001) (Appendix 2).
Recently a Phospholipase A2G6 (PLA2G6) - gene-mutation was discovered on chromosome 22q12-q13 being positive both in several NBIA-individuals and in some patients suffering from Infantile neuroaxonal dystrophy (INAD) (Morgan et al., 2006). PLA2G6 encodes the enzyme Phospholipase A2 (PLA2) which is known to be critical in lipid metabolism (Balsinde and Balboa, 2005) and which plays a key role in cell membrane homeostasis (Baburina and Jackowski, 1999). Among the PLA2G6-mutation-positive INAD-population, a remarkable part of 40 % showed high iron content in the Globus Pallidus as evident on brain magnetic resonance imaging (MRI) whereas classical INAD does not involve brain iron accumulation. A clear correlation between PLA2

dysfunction and neurodegeneration associated with high brain iron could be demonstrated (Morgan et al., 2006) and it is recommended to conduct molecular diagnostic testing for PLA2G6 mutation if the clinical picture is suspicious of INAD and if high brain iron is shown besides cerebellar atrophy on brain MRI (Gregory et al., 2009).
Other genetic aberrations resulting in disorders of iron metabolism, which are associated with NBIA, are neuroferritinopathy and aceruloplasminemia. Neuroferritinopathy is based on a mutation in the ferritin light chain (Curtis et al., 2001) and aceruloplasminemia is a disorder correlated with mutations in the ceruloplasmin gene (Yoshida et al., 1995; Harris et al., 1995; Gitlin, 1998).
NBIA- patients without determined gene mutation but showing typical clinical signs are considered as idiopathic and other, yet unknown, causative gene defects are believed to underlie this form (Gregory et al., 2009).

Consequently the common term NBIA describes a genotypically and phenotypically heterogeneous disease pattern of progressive extrapyramidal disorders associated with brain iron accumulation particularly within the basal ganglia (Hayflick et al., 2003; Gregory and Hayflick, 2005; Gregory et al., 2009).

Prior to our excellent diagnostic options such as MRI and gene analysis, NBIA had been a post mortem diagnosis (Gregory and Hayflick, 2005) (Appendix 3).
In order to allow the clinical diagnosis, onset of the disease in the first two decades of a patient's life, progression of symptoms and evidence of at least one extrapyramidal sign (dystonia, rigidity or choreoathetosis) must be observed (Swaiman, 2001; Gregory and Hayflick, 2005). Today, the realisation of a brain MRI scan is standard within the diagnostic procedure (Gregory et al., 2009). On T2-weighted MRI, hypointense lesions result from high iron in the pallidum (Drayer et al., 1987; Mutoh et al., 1988; Sethi et al., 1988; Tanfani et al., 1987). The "eye of the tiger sign" is presumed to be pathognomonic for the disease (Sethi et al., 1988) (Appendix 3).

Although most of attention is given to structural changes within the basal ganglia, primarily to those of the Globus Pallidus pars internus (GPi), the pathophysiological mechanisms which lead to the symptomatology in NBIA are not clearly understood yet (Ford, 2004) (Appendix 4).

One of the leading symptoms in NBIA is generalized dystonia and in the course of the disease truncal involvement becomes most obvious (Hayflick et al., 2003). According to this, disability may result with gait impairment, pain and difficulty with speech and swallowing. A severe complication which might appear in the context of the disease is the status dystonicus (Kyriagis et al., 2004). This state is accompanied by increasingly frequent episodes of painful spasms and generalized dystonia that might lead to respiratory failure and renal insufficiency due to rhabdomyolysis (Manji et al., 1998). As dystonia plays an important role in the clinical presentation of NBIA (Dooling et al., 1974; Gregory and Hayflick, 2005) many methods of treatment concentrate on this severe and sometimes even life threatening symptom.

The first step in treatment for all types of disabling dystonia is systemic pharmacotherapy. Specific agents and combinations of those show positive results depending on the entity. Frequent use is made of anticholinergics, such as Trihexiphenidyl and Ethopropazine, of dopaminergics, i.e. Levodopa and dopamine agonists as well as of antidopaminergics, such as Phenothiazines or Haloperidol, and of benzodiazepines such as Clonazepam (Fahn, 1987). Anticholinergics, such as Trihexiphenidyl (Burke et al., 1986) and oral or continuous intrathecal Baclofen (Albright et al., 1996), however, are reported to be exceedingly effective drugs to release the dystonia-associated affliction. Intrathecal Baclofen is in particular effective in life-threatening status dystonicus (Kyriagis et al., 2004).
Drugs such as Levodopa have been reported to have a positive effect on disabling movement disorders in some NBIA-patients (Singhi and Mitra, 1997; Gregory and Hayflick, 2005; Clement et al., 2007).
Another option to disrupt sustained regional muscle contractions persists in local Botulinum Toxin application (Dressler et al., 2001).

Nevertheless, pharmacotherapy in secondary generalized dystonia in NBIA is basically presumed to be limited (Justesen et al., 1999). Therefore several surgical approaches have been performed successfully to control severe dystonia in NBIA by bilateral thalamotomy (Tsukamoto et al., 1992) as well as by unilateral (Justesen et al., 1999) or bilateral pallidotomy (Kyriagis et al., 2004) or by bilateral pallidothalamotomy (Balas et al., 2006). Deep Brain Stimulation (DBS) (Appendix 5) which is considered as an

effective and reversible treatment option in dystonia appreciably replaces these highly invasive and irreversible procedures.

1.2. Lesion based surgery and DBS in dystonia and in NBIA-dystonia

1.2.1. Thalamotomy and Pallidotomy in different forms of dystonia and in NBIA-dystonia

It was demonstrated between 1960 and 1990 that surgically placed lesions in the thalamus showed distinct effectiveness in many cases of dystonia (Andrew et al., 1974; Cooper, 1976a; Tasker et al., 1988). At the same time clear positive results for the inner pallidotomy in dystonia were missing (Hassler et al., 1960; Burzaco, 1985).
Since thalamotomy could be demonstrated as a promising treatment option in dystonia (Andrew et al., 1974; Cooper, 1976a; Tasker et al., 1988), this procedure was the first reported surgical approach being performed in a 10 year old patient diagnosed with Hallervorden-Spatz Disease (Tsukamoto et al., 1992). After the patient had undergone repeated thalamotomy within the thalamic nucleus ventralis lateralis (VL) on both sides, the authors demonstrated a significant improvement of dystonic symptoms while hypnotic and sedative medication was reduced. Up to 21 months after the last operation, no progression of symptoms had been found.

Later, striking effectiveness of Leksell`s pallidotomy could be demonstrated in Levodopa-induced dystonia (Laitinen et al., 1992) and advantages of the pallidal approach both in terms of efficacy in dystonia and safety as compared to thalamotomy became obvious (Yoshor et al., 2001; Ford, 2004).
In modern pallidotomy for dystonia, surgeons target to the pallidal nucleus posteroventralis within the GPi (Laitinen et al., 1992). Having regard to this concept, a dramatic improvement in severity of different types of dystonia could be demonstrated in numerous reports (Iacono et al., 1996; Lozano et al., 1997; Ondo et al., 1998). Lin and colleagues showed the benefit of bilateral pallidotomy in a series of 18 patients who suffered from pharmacotherapy-resistant, secondary dystonia due to various reasons such as cerebral palsy, hypoxic encephalopathy, carbon monoxide poisoning, encephalitis, and post infectious encephalopathy. They found a delayed improvement of symptoms being highest six months after the operation and decreasing thereafter. The mean improvement

of dystonia of only 13 % at the one-year-follow-up points to the inferiority of surgical effectiveness in forms of secondary dystonia as compared to pallidotomy in primary dystonia (Lin et al., 1999).

In 1999, the first unilateral pallidotomy was performed in a 10 year old Hallervorden-Spatz-patient, diagnosed clinically and by T2-weighted MRI (Justesen et al., 1999). After surgery, reduction of the contralateral disabling dystonia could immediately be observed and respiratory problems due to severe muscle contractions decreased. This condition remained unchanged up to six months after pallidotomy.
In a PKAN-patient the effectiveness of bilateral pallidotomy combined with the application of intrathecal baclofen could be demonstrated in the emergency of a status dystonicus (Kyriagis et al., 2004). The authors postulate the superiority of pallidotomy on pallidal stimulation within palliative, advanced, and severe generalized dystonia. Likewise, Balas and colleagues performed a multitarget ablation (bilateral pallidothalamotomy) in the urgent case of a status dystonicus in a Hallervorden-Spatz patient with good and enduring results (Balas et al., 2006).

Although pallidotomy is considered to be quite safe among other lesion-based procedures for dystonia, it is an invasive procedure which is related to several risks, among which hemiparesis and visual field deficit are the most cited ones (Ford, 2004). Intracerebral haemorrhage has been monitored in 3.3 % of thalamic and pallidal lesions respectively (Rowe et al., 1999).

1.2.2. DBS in dystonia

Thalamic DBS in dystonia

A first approach of DBS in cervical dystonia was made by Mundinger targeting unilaterally to the motor thalamus as well as to the subthalamic area (Mundinger, 1977).
Thalamic stimulation has been applied in generalized primary and secondary dystonia with various treatment results.
Cooper published a series of reports about patients suffering from different movement disorders who were treated with thalamic DBS whereby dystonia patients seemed to have the poorest benefit (Cooper et al., 1982).

Sellal (Sellal et al., 1993) and Loher and colleagues (Loher et al., 2001) on the other hand reported good to excellent outcomes for continuous thalamic stimulation in primary or secondary dystonia, whereas Trottenberg and colleagues did not achieve any positive results applying this technique in dystonia (Trottenberg et al., 2001).
After thalamic DBS, Vercueil and colleagues (Vercueil et al., 2001) found dystonia scores in four primary and eight secondary dystonia-patients unchanged, but in eight of them, good functional results were observed. In three of Vercueil`s patients affected by primary as well as by secondary dystonia respectively, progression of dystonia led to a surgical re-intervention targeting to the GPi, which showed favourable results. These cases are uncommon examples, alluding to the superiority of the pallidal target in dystonia by comparing both approaches in one individual.
On the other hand, there is a series of post-anoxic dystonia patients who did not improve after pallidal DBS, but one of them showed marked amelioration after thalamic stimulation (Ghika et al., 2000).

Pallidal DBS in dystonia

The identification of the posteroventral GPi as a reasonable and promising target-point for pallidotomy in dystonia gave direction for Globus Pallidus pars internus - Deep Brain Stimulation (GPi-DBS) (Ford, 2004).
Pallidal DBS for dystonia was introduced only in the late 1990s (Coubes et al., 1999; Kumar et al., 1999; Krauss et al., 1999). The idea is based on animal experiments of Hassler and Hess in the early 1950s leading to a first explanation of the physiology and pathophsiology of cervical dystonia (CD) (Hassler and Dieckmann, 1970). Patients suffering from akinetic hypertonic disorders (Volkmann et al., 1998; Siegfried and Lippitz, 1994a) as well as patients affected by Levodopa-induced dyskinesia in Parkinson`s Disease were reported to show high response to this treatment (Siegfried and Lippitz, 1994a; Tronnier et al., 1997; Volkmann et al., 1998; Benabid et al., 1998).

Referring to several recent publications, continuous stimulation of the GPi in dystonia is a very promising treatment option (Cif et al., 2003; Krauss et al., 2004; Trottenberg et al., 2005), although thalamic DBS has always been a competing approach, particularly in forms of secondary dystonia (Vercueil et al., 2001).

Generally, it is argued to apply DBS as long as orthopaedic problems do not interfere with the symptomatology yet, in order to achieve outcomes that are not superposed by irreversible disabling neurological and musculoskeletal injuries (Vercueil et al., 2002; Coubes et al., 2004).

Most commonly, pallidal stimulation for dystonia is applied bilaterally (Krauss et al., 2004). The interruption of pallidal output by performing pallidal functional surgery seems to remodulate pathologic neuronal activity within the GPi (Lozano et al., 1997; Vitek et al., 1999) according to the theory that pathologic excitatory patterns within the pallido-thalamocortical pathway are responsible for dystonia and other hyperkinetic movement disorders (Vitek et al., 1999; Vitek and Giroux, 2000; Ford, 2004).

Pallidal DBS has been reported to ameliorate dystonic features and associated functional disability progressively over a time-course of weeks or months (Yianni et al., 2003). An early improvement of phasic or myoclonic dystonic movements has been observed in some patients (Vercueil et al., 2002) whereas improvement of dystonic tonus is expected to be delayed after DBS activation (Krauss et al., 2004). Advancing improvement over time might be correlated with a subsequent slow and broad reorganisation of neuronal interaction (Lozano et al., 1997).

So far, there are first hints being suggestive of a somatotopic organisation of the sensorimotor GPi, which prospectively might gain importance within the treatment for dystonic syndromes involving different body parts (Vayssiere et al., 2004).

Interestingly, it had already been described in the 1960s that low-frequency pallidal stimulation (4 - 8 Hertz (Hz)) might trigger abnormal hyperkinetic movements in the contralateral extremities in patients suffering from torsion dystonia and athetosis, whereas high-frequency stimulation might worsen or suppress them (Hassler et al., 1960). Increasing voltage, high pulse width, and high frequency have been shown to alleviate dystonia (Coubes et al., 2002; Krauss et al., 2004).

This comprises the challenge of short battery life. Battery failure or other system complications in dystonia patients sometimes lead to severe worsening of symptoms or even life-threatening situations, which makes a close follow-up-care indispensable (Krauss et al., 2004). Internal pulse generator (IPG) switch-off, which has been observed to be a frequent problem among software complications, may expeditiously lead to impairment of dystonic features (Coubes et al., 2002). IPG malfunction, lead fracture, lead erosion and transventricular misplacement of lead are reported to be among device related problems. Since reduction of these events seems to correlate with increasing

surgical experience, DBS appears to be a safe procedure if conducted within specialist centres (Joint et al., 2002). The striking tolerance of the IPG in children has been reported (Cif et al., 2003). Since the growth potential of the brain and cranium seems to be limited after the age of three, complications due to electrode displacement are not expected (Coubes et al., 2004).

Though, deep brain surgery bears low risks of infection and surgery-related intracranial haemorrhage (Benabid et al., 1998; Coubes et al., 2002). Postoperative infections, seroma, lead dislodgement, or lead breakage appear to be more frequent in dystonia patients than it has been reported for Parkinson's Disease-patients (Kupsch et al., 2006). But in experienced hands the perioperative risk of GPi-DBS is quite low with 2 % of permanent severe morbidity and with 3 - 4 % of infection or damage of the stimulation system (Vercueil et al., 2002).
DBS is considered to be a reversible and adaptable treatment for severe medical refractory dystonia (Benabid et al., 1998; Coubes et al., 2002). Side effects are mainly suggested to be corrigible and postoperative morbidity seems to occur less than in lesion-surgery (Krauss et al., 2004). Features such as dysarthria, worsening of dystonia or dysesthesias have been defined as typically related to DBS whereas they are likely to disappear or improve by adjusting stimulation parameters (Kupsch et al., 2006).

GPi-DBS in dystonia has been proven to have no negative effects on cognition, mood and neuropsychiatric status (Halbig et al., 2005). According to an anatomic division of the GPi in different functional parts, the dorsomedial region of the GPi has been determined for cognitive function (Middleton and Strick, 1994). Since GPi-DBS in dystonia targets to the pars posteroventralis lateralis, there should be no risk considering neuropsychological and cognitive side effects (Halbig et al., 2005). A significant improvement of mood without any other behavioural abnormalities could be observed among dystonia patients under continuous GPi-DBS (Kupsch et al., 2006).

An increasing number of studies shows the efficacy of GPi-DBS in medical refractory dystonia (Coubes et al., 1999; Kumar et al., 1999; Coubes et al., 2000; Tronnier and Fogel, 2000; Cif et al., 2003; Krauss et al., 2003; Krause et al., 2004; Krauss et al., 2004; Trottenberg et al., 2005; Vidailhet et al., 2005; Halbig et al., 2005; Zorzi et al., 2005; Kupsch et al., 2006).

In a group of 22 selected patients suffering from primary dystonia, efficacy of GPi-DBS has been proven within a prospective and video-controlled, double-blind trial regarding change in dystonia (Vidailhet et al., 2005). In a further double blind prospective study including 40 patients who were affected by primary generalized and segmental dystonia, the effectiveness of pallidal DBS was verified. Kupsch et al. documented a favourable outcome after 3 months of stimulation, which was significantly superior to the values of the sham stimulation group (Kupsch et al., 2006).
Coubes and colleagues published a report about seven patients with Torsion Dystonia gene (DYT1) - positive generalized dystonia and showed a mean improvement by 90 % in dystonia (Coubes et al., 2000).
Krauss and colleagues likewise reported good results over a time course of two years in two patients being affected by DYT1-negative primary generalized dystonia (Krauss et al., 2003).
With growing long-term-experience, there are references that point at a reduction of effectiveness of GPi-DBS in generalized dystonia over time (Krause et al., 2004). A higher response to DBS among young children is ascribed to permanent orthopaedic disadvantages occurring after long-lasting generalized dystonia in older patients (Coubes et al., 2004).

At the same time, other analyses have detected the efficacy of pallidal DBS in some cases of secondary dystonia, such as post-traumatic, post-anoxic or cerebral palsy associated dystonia (Loher et al., 2000; Vercueil et al., 2001; Krause et al., 2004; Vidailhet et al., 2009). To date patients with tardive dystonia have been shown to considerably profit from GPi-DBS (Trottenberg et al., 2005). It is assumed that location, quantity and nature of lesions which lead to dystonic symptoms play an important role within responsiveness to pallidal DBS (Vercueil et al., 2002).

1.2.3. DBS in NBIA-dystonia

As in many NBIA-patients pharmacologic anti-dystonic treatment remains insufficient, the implantation of intracerebral stimulation electrodes for electrical high-frequency stimulation, as applied in other forms of medical refractory generalized dystonia, turned out to be a promising therapy.

Vercueil observed two sisters, diagnosed retrospectively as having NBIA, who had been treated by thalamic DBS and who were reported with considerable long-term benefit (Vercueil et al., 2001).
Today pallidal surgery for dystonia is believed to be superior to the thalamic approach in terms of efficacy and perioperative risk (Yoshor et al., 2001; Vercueil et al., 2001; Ford, 2004) and GPi-DBS has been applied in the treatment of NBIA-dystonia for a few years. Up to now several case reports (Umemura et al., 2004; Sharma et al., 2005; Krause et al., 2006; Koyama and Yagishita, 2006; Clement et al., 2007; Shields et al., 2007; Mikati et al., 2009) and a scientific trial including six patients (Castelnau et al., 2005) have been published giving an account of the observed, predominantly high effectiveness of bilateral GPi-DBS in NBIA-dystonia.

First of all, Umemura and colleagues showed the positive outcome of high-frequency GPi-DBS in a 36-year-old male diagnosed with Hallervorden-Spatz Syndrome with symptom onset at the age of 8 (patient number 11) (Umemura et al., 2004). The patient, who preoperatively was wheelchair-bound, was able to stand up independently and walk with according devices 3 months after the surgical treatment. He showed an 80 % - improvement within the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the benefit of DBS was still evident at the 1-year-follow-up.
Sharma and colleagues reported about a severely affected 8-year-old boy diagnosed with Hallervorden-Spatz Disease. Due to his pharmacologically intractable generalized dystonia, he was treated by GPi-DBS. The patient did not show any postoperative improvement and unfortunately succumbed to his disease three months after surgery (Sharma et al., 2005).
Koyama and colleagues described the positive effect of bilateral pallidal DBS in a 6-year-old early-onset PKAN patient in conjunction with brain perfusion studies on photon-emission computed tomography (SPECT). DBS considerably reduced opisthotonus and after 19 weeks, hypoperfusion could be observed by SPECT in the basal ganglia most notably on the right and in the right frontotemporal region (Koyama and Yagishita, 2006).
The long-term benefit of pallidal DBS in genetically defined PKAN-dystonia could be demonstrated in a 13-year-old patient who still showed marked improvement 5 years after he had undergone surgery (patient number 9) (Krause et al., 2006). Although the patient suffered a dystonic exacerbation two days after electrode implantation (Krause et

al., 2004), DBS made a beneficial effect shortly after the stimulation had been started and the anticholinergic medication could be ceased. The BFMDRS motor score decreased from 92/120 points preoperatively to 30/120 points (approximately 70 %) one year after having started with DBS, but thereafter impaired to 70/120 points at the 5-year-follow-up. These results, though, still show an important long-term improvement of disabling symptoms. Krause and colleagues concluded that the re-aggravation of disabling symptoms was not the effect of decreased DBS-efficacy but was most likely due to disease-related progression of the movement disorder in PKAN, which consists of various components.

Clement and colleagues emphasized the heterogeneity of NBIA describing two cases being affected by the disease (Clement et al., 2007). One of them presented with the classical PKAN-form with onset in childhood and the patient was treated successfully with GPi-DBS. The other individual started to show first symptoms in adulthood with akinesia, rigidity and involuntary buccolingual and facial movements including difficulty in swallowing and dysarthria as predominant features. These signs appeared to be Levodopa-responsive. In this way, the authors alluded to different therapy approaches being required within the treatment of different entities of NBIA.

Recently the positive outcome of pallidal DBS was reported in an 18-year-old male who had PKAN (patient number 10) (Shields et al., 2007). After the patient had received bilateral, stereotactic, microelectrode-guided placement of pallidal deep brain stimulators, an improvement could be observed within the BFMDRS: the movement score ameliorated from 86/120 points to 66/120 points whereas the disability score remained more or less unchanged. However, after surgery a gastrostomy-tube for nutritional supplementation was no more needed and with physical therapy the patient succeeded in ambulating with the help of certain devices and later independently.
Another case report about pallidal DBS in PKAN was published by Mikati and colleagues in which they described the therapy outcome in an 11-year-old female suffering from the early onset form (Mikati et al., 2009). The authors used the Barry-Abright Dystonia Scale and the Functional Independence Measure for children (WeeFIM) to assess therapy-outcome and found an improvement from 24/36 points to 8/36 points and from 1/7 points to 5/7 points respectively. Unfortunately, due to infection surgeons had to withdraw the device three months after surgery. Subsequently, a slow

deterioration of the patient's status was noted until symptoms returned to the preoperative level four months after the electrodes had been removed.

Certainly, the most comprehensive and accurate study about bilateral GPi-DBS-effectiveness in NBIA-dystonia was published by Castelnau and colleagues, who documented the results of 4 classical and 2 atypical PKAN-cases in a period of 6 to 42 months after surgery applying the BFMDRS (Castelnau et al., 2005). They found dramatic improvements in the motor score of on average 74.4 % and in the disability score of on average 53 %. These results turned out to be significant. Furthermore, they showed that the benefit of this therapy does not rely on preoperative severity of disease and that improving motor capabilities helps significantly to alleviate difficulties in daily living. DBS effectiveness could be observed in all patients within four months after surgery and continued to be unchanged up to an average follow-up of 20.6 months. Castelnau and colleagues described the entire disappearance of painful muscle spasms and a prominent decrease of dystonic postures and abnormal movements in all six PKAN-patients. They depicted GPi-stimulation as an effective, long-lasting and low-risk treatment option within PKAN-associated movement disorders. Interestingly, they used stimulation parameters (pulse width 450 microseconds (μsec), voltage 1.3 – 1.7 Volt (V), frequency 130 Hz) that differ from those being efficient in forms of primary dystonia (Krause et al., 2004; Vidailhet et al., 2005).

1.3. Central issue

With this retrospective multi-centre study about GPi-DBS effectiveness in NBIA-dystonia, we would like to gain some further answers to a series of still open questions, analyzing worldwide experience and treatment results in this field. Since NBIA is a rare disorder, there has always been the burden of the small number of patients and case reports bear the risk of a reporting bias in favour of positive results. Published data lack a detailed, standardized meta-analysis, pooling patient-data from different international centres. Beyond that, investigations on small series do scarcely allow the determination of selection criteria for DBS in NBIA-patients.

DBS remains an invasive therapy, which is associated with several perioperative risks. Therefore, it is even more important to accurately define indications for this potentially harmful but highly effective treatment option, especially in young, mainly minor NBIA-patients. Focussing on effectiveness of treatment, on the time course of responsiveness

and on predisposing factors, we performed a detailed international trial with the intent to provide evidence-based data for patients, relatives and clinicians. For this purpose, we started to collect all available data of NBIA-patients under GPi-DBS planning to provide an unselected summary of treatment results, which have been observed so far. Applying the Burke-Fahn-Marsden Dystonia Rating Scale, we hypothesized the palliation of dystonia, which however, is not as distinct as it has been reported in to date known single cases and small series.

This retrospective analysis is a first approach in order to create a treatment algorithm for GPi-DBS in NBIA-dystonia, but it has to be pursued in further well-controlled prospective studies. In detail, we aimed to answer the following questions:

- Is there a significant change of dystonia observable 2-6 months post-operatively and how do symptoms develop 9-15 months after surgery?

- Is there a significant change of disability observable 2-6 months post-operatively and how does disability present 9-15 months after surgery according to the BFMDRS Disability Scale?

- Is there a significant improvement of quality of life detectable, comparing the pre-operative situation and the status of 2-6 months and 9-15 months after surgery respectively?

- To what extent does improvement of disability depend on improvement of motor function?

- To what extent does improvement of quality of life depend on improvement of motor function?

- Are there factors that have predictive value in terms of therapy outcome (e.g. age at onset of symptoms, duration of disease, pre-operative severity of dystonia, age at time of operation)?

- Do different settings of stimulation parameters have any influence on therapy outcome?

- Does a preferred stereotactic target point exist among NBIA-patients undergoing GPi-DBS?

- What is the incidence of adverse events, side-effects and system complications?

- Could anti-dystonic medication be reduced?

- To what extent do the results of the blinded video rating overlap with results provided by the treating physicians?

2. Materials and methods

2.1. Recruitment

With the aim of collecting the highest possible number of patient data sets, we contacted different centres and patient organisations to reach NBIA-patients worldwide who had received GPi-DBS. Each appropriate data set, irrespective of outcome, was explicitly requested.

2.1.1. Collaboration with the German "Hoffnungsbaum e.V." and the American "NBIA Disorders Association"

Establishing of contacts with patients has been coordinated by collaboration with the US-American patient organisation "NBIA Disorders Association" and with its German sister organisation "Hoffnungsbaum e.V."

2.1.2. Contact with national and international DBS centres

Our group at the department of Neurology at the University Hospital of Cologne "Deep Brain Stimulation and Movement Disorders" has several intensive connections to DBS centres worldwide. Additionally we tried to contact as many centres as possible referring to a list of national and international centres known to implant DBS devices, provided by the only manufacturer at the time (Medtronic Inc.). All these centres were contacted at least two times, either by Email, fax or phone. A comparable mode of data collection has already been applied in other retrospective multi-centre studies (Voon et al., 2008).

2.1.3. Citations

Data of 3 patients were either completely (Umemura et al., 2004) or partially (Krause et al., 2006; Kurlemann et al., 1991) extracted from literature.

2.2. Inclusion criteria

Inclusion criteria were the diagnosis of NBIA as attested within a specialized centre, presentation of moderate to severe dystonia and performance of bilateral GPi-DBS to treat dystonia. In order to allow the diagnosis NBIA, onset of progressive symptoms in the first two decades, evidence of at least one extrapyramidal sign (dystonia, rigidity or choreoathetosis) and an abnormal MRI scan must be observed (Swaiman, 2001; Gregory and Hayflick, 2005).

2.3. Protocol

We designed the study as an international retrospective trial analyzing post-hoc clinical data with high data quality.
In order to achieve good data reliability a standardized scale was sent to all participating DBS centres, which contained all parameters to be included in the analysis (Appendix 6). On the one hand, the scheme aimed at points that should be answered by the treating physicians; on the other hand, there were issues that asked for the patients´ and caregivers´ evaluation.
Apart from patient characteristics, we primarily focused on the assessment of severity of dystonia, degree of disability and quality of life. We used different scales in order to have these realms quantified.
Progression parameters were assessed before operation, 2-6 months and 9-15 months thereafter to evaluate DBS effectiveness in NBIA-dystonia over time.

2.3.1. Patient characteristics

First, we documented patient characteristics that included patients´ age at time of primary symptoms, age at diagnosis and age at electrode implantation. From this follows the duration of disease, in the case of this study defined as the period from the beginning of symptoms until surgical therapy. Furthermore, we registered the patients´ gender. Genetic findings in patients referred to whether the PANK2 gene mutation (see Appendix 2) was present or not. We did neither protocol the kind of mutation nor the eventual residual enzyme activity.

We registered if patients were positive for the presentation of the “eye of the tiger sign” (see Appendix 3) in T2-weighted MRI. Furthermore, we asked for other abnormalities detected by MRI.

2.3.2. Dystonia

It was a matter of particular interest in this retrospective analysis to find out whether DBS helps in NBIA-dystonia and whether DBS leads to a significant improvement of dystonic features. We therefore utilized different scales in order to quantify severity of dystonia and compared the preoperative scores with those assessed 2-6 months and 9-15 months after DBS activation.

2.3.2.1. Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)

The BFMDRS is subdivided in two sections, the “Dystonia movement scale” (BFMDRS-M) and the “Disability scale” (BFMDRS-D), and has been validated for primary torsion dystonia (Burke et al., 1985), but according to Burke and colleagues the scale can also be applied for the assessment of secondary dystonia.
We included scores of the BFMDRS-M, if available, before electrode implantation, 2-6 months and 9-15 months thereafter in order to utilize these data in a first step to find out whether an improvement of motor capabilities was detectable 2-6 months and 9-15 months after surgery in comparison to the preoperative situation. Furthermore, we analyzed the difference between the values measured during 2-6 months and during 9-15 months after surgery.
The BFMDRS-M is based on physical examination considering severity of dystonia, and the disability scale is based on the patient’s appraisal of feasibility of seven items of daily living (Appendix 7). The sum of nine items for nine body regions scores the Dystonia movement scale, whereas speech and swallowing are considered as one body region. The value of each item is the product of the provoking factor, the severity factor (each one rated on a scale from zero to four) and the weight factor (fixed value defined for each body region). The provoking factor gives evidence about circumstances leading to dystonic postures (e.g. intended movement of one hand), whereas the severity factor describes the extent of involuntary dystonic movements.

The summary score of the Disability scale is the sum of scores of the seven items concerning daily living.
Since the BFMDRS has been utilized in several former publications to validate motor function and disability before and after the implantation of GPi-electrodes in primary as well as in secondary forms of dystonia (Krauss et al., 2003; Cif et al., 2003; Castelnau et al., 2005; Kupsch et al., 2006), so far it seems to be established as a very reliable international measure to assess effectiveness of DBS in different forms of dystonia. Nevertheless, the BFMDRS might contain several difficulties for secondary forms of dystonia, such as NBIA, that are characterized by additional neurological impairment, which might interfere with the dystonic component.

Blinded video rating

All centres and patients were encouraged to send video tapes or digital versatile discs (DVDs) documenting the patients` individual situations before and after surgery. Whenever possible, we asked the participants of this multi-centre-trial to use the Videotape examination protocol provided by the Dystonia Study Group (Appendix 10) (Comella et al., 2003).
Since this study is a retrospective analysis, we included all videos provided by our co-investigators, even those being filmed without reference to this standardized protocol.
The intent of the collection of videotaped patient documentation was to have these videos assessed by independent blinded raters using the BFMDRS-M (Burke et al., 1985).

2.3.2.2. Barry-Albright Dystonia Scale (BADS)

In addition to the BFMDRS we used the Barry-Albright Dystonia Scale (Barry et al., 1999) to assess severity of dystonia.
The questionnaire includes five sections referring to eight different body parts (eyes, mouth, neck, trunk, four extremities) being assessed in terms of severity of dystonia respectively (Appendix 8). Dystonia is rated as none (0), slight (1), mild (2), moderate (3), or severe (4) and the summary score results from adding the single values.

2.3.2.3. Global rating of severity of dystonia by the treating physician

Likewise, subjective impressions of DBS efficacy in NBIA-dystonia should enter this statistical trial. The intent was to find out whether there were any significant improvements within severity of dystonia according to the treating physician and to compare global clinical ratings by physicians with those equally assessed by patients and caregivers.
Treating neurologists and neurosurgeons rated severity of dystonia on a scale from 0-10, 0 being no dystonia at all, and 10 being the most severe generalized dystonia.

2.3.2.4. Global rating of dystonia by the patient and by the caregiver

The key interest of these scores was to find out whether patients and caregivers had registered any significant changes within severity of dystonia and to compare ratings of treating physicians (2.3.2.3.), patients and caregivers.
In order to collect data of subjective impressions of DBS efficacy in NBIA-dystonia, patients and caregivers were asked respectively to assess severity of dystonia on a scale from 0-10, 0 being no dystonia at all and 10 being the most severe generalized dystonia.

2.3.3. Disability

The purpose of evaluation of disability was to find out whether there was any significant difference before and after operation in abilities of daily living and whether there was a correlation between motor- and disability improvement.
In order to assess the degree of disability, we used the BFMDRS Disability scale (2.3.2.1. and Appendix 7).

2.3.4. Quality of life

It is a major concern of this trial to find out if DBS leads to a significant improvement of quality of life and to provide information about whether an improvement of dystonia might be associated with higher quality of life.

2.3.4.1. Care and Comfort Hypertonicity Questionnaire (CCHQ)

In order to measure quality of life objectively, we used the CCHQ, which primarily has been validated among patients with spastic/dystonic cerebral palsy and which is supposed to be applied within trials that document the efficacy of therapies in diseases with severe muscle hypertonicity (Nemer McCoy et al., 2006). The purpose of this questionnaire is to reflect accurately the changes in everyday life, noted by patients who are referred to a certain treatment and by their caregivers. In this way, this test analyzes the subsequent influence on the patients` and caregivers` quality of life and on the patients` functional abilities.

The standardized questionnaire consists of 27 questions being addressed to the caregiver, including the four sections “personal care”, “positioning/transferring”, “comfort” and “interaction/communication” (Appendix 9). Each item is rated on a scale from 1-7, 1 being “very easy/no problem” and 7 being extremely “difficult/impossible”. To evaluate the CCHQ summary score, the mean of the four section means has to be assessed. If a question is indicated as “not applicable”, it is excluded from the calculation of the mean value of the respective section.

2.3.4.2. Global rating of quality of life by the patient and by the caregiver

Within assessment of therapeutic outcome, quantification of changes within quality of life plays a very important role. Patients and caregivers were asked to rate quality of life on a scale from 0-10, 0 being no quality of life at all and 10 being the best imaginable quality of life. For analysis, these data are of great interest to find out whether a significant improvement within quality of life occurred according to patients or caregivers and to compare the patients` subjective impressions with those of the caregivers.

2.3.5. Surgical target point

The planned surgical target point of every patient was recorded with reference to the Schaltenbrand-Wahren atlas (Schaltenbrand and Wahren, 1977).

2.3.6. Stimulation parameters

We registered voltage, pulse width and pulse frequency of every patient within both GPi 2-6 months and 9-15 months after electrode implantation.

2.3.7. Adverse events

In order to estimate the risk potential of this effective but invasive therapy, we accurately documented all side effects of stimulation as well as system complications and asked about the circumstances, which led to these events.
We registered all severe adverse events in the perioperative and postoperative phase up to 15 months after surgery including all events leading to hospitalisation or death.

2.3.8. Accompanying medication

Anti-dystonic medication was recorded in detail to find out conditions leading to reduction or increase of pharmacological therapy.

2.4. Outcome measures

We chose to use change in severity of dystonia as assessed by the BFMDRS-M as our primary outcome parameter within the analysis. A clinically relevant improvement was presumed at a positive change of 20 % or more in BFMDRS-M, accordant to prior studies investigating on therapy outcome in secondary dystonia (Vidailhet et al., 2009). Furthermore, as different raters in different centres raised BFMDRS-M data, our intent was to have the results of our primary outcome measure confirmed by blinded video rating.
Additively, the Barry-Albright Dystonia Scale was used as a second dystonia measure, in order to verify the results of our first outcome parameter in this heterogeneous cohort. Its reliability and responsiveness have been validated for forms of secondary dystonia considering various cognitive and physical impairment.

Secondary outcome parameters were disability according to the BFMDRS-D and quality of life according to global ratings by the caregivers. Following the principle stated for the

first outcome measure, clinically relevant change was determined as a minimum of a 20 % improvement respectively.

2.5. Statistics

One patient had to be excluded from data analysis because DBS electrodes had not been implanted in the GPi.

Normality of data distribution was tested applying the Kolmogorov-Smirnov-Test and all data, which have been included for analysis in this trial, were normally distributed.

Descriptive statistics have been performed calculating means and standard deviations for all preoperative parameters and for all progression parameters.
Furthermore, the frequency of side effects, system complications and adverse events were described.

Percentages of patients reaching the clinically relevant therapy result regarding dystonia according to the BFMDRS-M, disability according to the BFMDRS-D and quality of life according to the global rating by caregivers were calculated accounting for findings both 2-6 months and 9-15 months after DBS. Percentaged relevant therapy outcome (at least 20 % or more) was calculated applying the formula ((baseline – actual value)/baseline) x 100.

In another step, t-tests for dependent samples were conducted in order to determine the difference between preoperative severity of dystonia, disability and quality of life and corresponding values at both 2-6 months and 9-15 months postoperatively. For calculation, we solely used series containing data at all three time points, as in some cases data have not been available. Accordingly, different data sets may have been applied for different categories. Evaluation of dystonia was performed by using the BFMDRS-M, the Barry-Albright Dystonia Scale and global ratings by treating physicians, patients and caregivers. Disability was validated by applying the BFMDRS-D and Quality of life was assessed according to the CCHQ and according to global ratings by caregivers and patients.

As we performed multiple t-tests for dependent samples, for secondary outcome measures a Bonferroni correction was applied.

Furthermore, we tested different variables in order to find out, if possible, factors of predictive value in terms of therapy outcome. According to this, we tested age at time of onset, duration of disease, age at operation and preoperative severity of dystonia with regard to improvement in dystonia by performing linear regressions. Likewise, we tested the relation between change in severity of dystonia and change in disability. At last, we examined if the amount of the effective voltage (Rehncrona et al., 2003) being applied had any influence on therapy outcome in terms of change in dystonia. As several linear regressions were performed, we applied a Bonferroni correction in order to adjust the level of significance accordingly.

Data analysis was conducted using Statistical Package for the Social Sciences 17.0.

2.6. Vote of the local ethics committee

We had a master vote of the ethics committee in Düsseldorf covering national and international informed consent forms (Appendix 11) and study procedures as well as data protection. All patients or rather their parents, when patients themselves were either minor or not able to consent in written form, gave informed consent agreeing to their data being used anonymously within this retrospective trial.

3. Results

3.1. Descriptive statistics

We included 23 patients diagnosed with NBIA who underwent pallidal deep brain electrode implantation in different international DBS centres within this post-hoc analysis of clinical data.

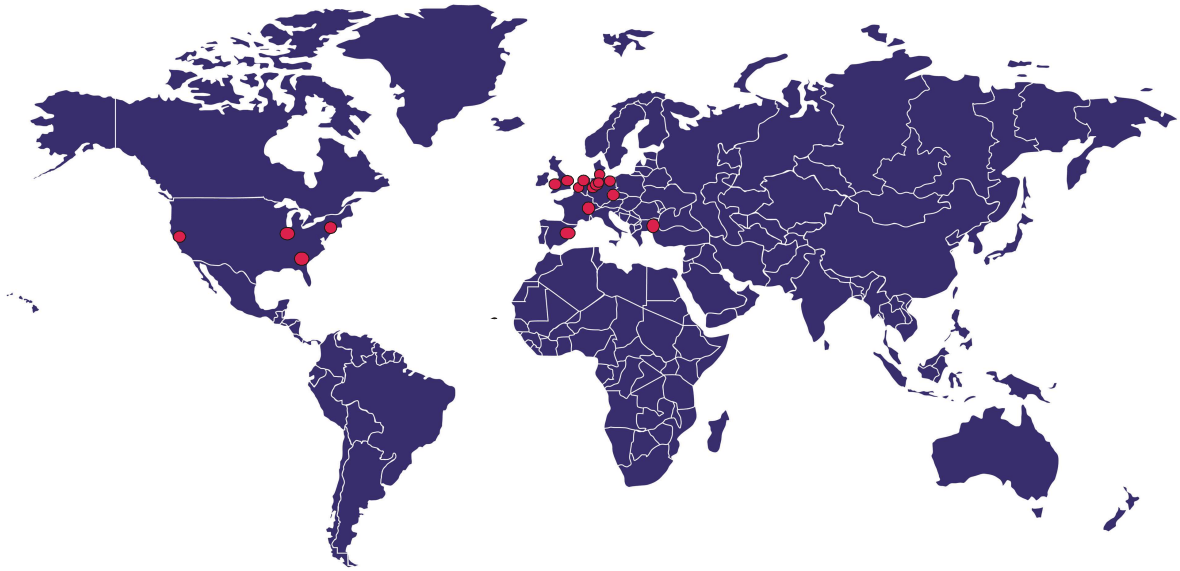

Figure 1: World map showing the worldwide allocation of DBS centres which participated within this international trial.
Modified Image "iStock_000000522732Illustra", acquired at
http://deutsch.istockphoto.com/search/text/Weltkarte/filetype/illustrations/source/basic#127313d9

Data of patient 11 are completely extracted from literature (Umemura et al., 2004) and data of patient 9 and patient 16 are partially cited from other publications (Krause et al., 2006; Kurlemann et al., 1991). Data of patient 10 have already been published elsewhere (Shields et al., 2007).

Patient 10 and patient 18, patient 13 and patient 14 as well as patient 20 and patient 23 are siblings.

Unfortunately, patient 4 and patient 7 succumbed to their disease after being implanted. One of them suffered a dystonic crisis shortly before surgery was performed and did not recover under DBS. He died 6 weeks after the operation.

The other patient died formally outside of the observation period due to severe aspiration pneumonia.
Following the surgical principals stated in Appendix 5, all patients underwent bilateral continuous DBS, targeting to the nucleus posteroventralis lateralis of the GPi.

Mean age at onset of symptoms was 7.8 years (n = 23, SD = 4.8) and mean age at time of diagnosis was 12.7 years (n = 23, SD = 8.0). At the time of electrode implantation the average age of included patients was 18.0 years (n = 23, SD = 8.8) and mean duration of the disease (period between onset of first symptoms and surgical therapy) was then 10.2 years (n = 23, SD = 6.4). Nine patients of our study population (n = 23) were female (39.1 %) and 14 patients were male (60.9 %).
Genetic examination was performed in 15 patients (n = 15), among which 14 individuals were positive for a Pantothenate-Kinase 2 gene mutation (93.3 %) and one subject was negative for the mutation (6.6 %).
MRI results were available in 23 patients (n = 23). All examined individuals showed the “eye of the tiger sign” within both GPi (100 %). No other radiological signs were reported in anyone of the study population.
These data are summarized as patient characteristics in Table 1.

Averaged preoperative patient characteristics and averaged preoperative basic parameters are listed in Table 2.

Patient Number	Age at onset of symptoms (years)	Age at time of diagnosis (years)	Age at Operation (years)	Duration of disease (years)	Gender	Genetics	MRI
1	1	5	6	5	female	PKAN	eye of the tiger sign
2	1	6	9	8	male	PKAN	eye of the tiger sign
3	2	11	16	14	male	PKAN	eye of the tiger sign
4	2	5	12	10	female	unknown	eye of the tiger sign
5	2	5	6	4	female	PKAN	eye of the tiger sign
6	2	5	9	7	female	unknown	eye of the tiger sign
7	3	5	12	9	male	unknown	eye of the tiger sign
8	4	8	14	10	male	PKAN	eye of the tiger sign
9*	6	10	13	7	male	PKAN	eye of the tiger sign
10**	8	10	17	9	male	PKAN	eye of the tiger sign
11***	8	36	36	28	male	unknown	eye of the tiger sign
12	9	11	13	4	male	PKAN	eye of the tiger sign
13	9	11	16	7	female	PKAN	eye of the tiger sign
14	9	13	17	8	male	PKAN	eye of the tiger sign
15	10	13	17	7	male	unknown	eye of the tiger sign
16****	11	13	29	18	female	non-PKAN	eye of the tiger sign
17	12	16	32	20	female	PKAN	eye of the tiger sign
18	12	12	15	3	male	PKAN	eye of the tiger sign
19	12	13	24	12	female	PKAN	eye of the tiger sign
20	14	16	20	6	female	unknown	eye of the tiger sign
21	14	33	36	22	male	PKAN	eye of the tiger sign
22	14	19	27	13	male	unknown	eye of the tiger sign
23	15	15	19	4	male	unknown	eye of the tiger sign
	(n = 23) Mean = 7.8 SD = 4.8	(n = 23) Mean = 12.7 SD = 8.0	(n = 23) Mean = 18.0 SD = 8.8	(n = 23) Mean = 10.2 SD = 6.4	(n = 23) male = 14 (60.9 %) female = 9 (39.1%)	(n = 15) PKAN = 14 (93.3 %) non-PKAN = 1 (6.6 %)	(n = 23) eots-pos = 24 (100%) eots-neg = 0 (0 %)

Table 1: Patient Characteristics
eots-neg: negative for the eye of the tiger sign
eots-pos: positive for the eye of the tiger sign
MRI: magnetic resonance imaging
non-PKAN: non-Pantothenate Kinase-Associated Neurodegeneration
PKAN: Pantothenate Kinase-Associated Neurodegeneration
SD: standard deviation
n: number of patients

* partially cited from (Krause et al., 2006)
** referred to in (Shields et al., 2007)
*** cited from (Umemura et al., 2004)
**** partially cited from (Kurlemann et al., 1991)

	n	Mean ± SD	Range
Age at onset (years)	23	7.8 ± 4.8	1.0 – 15.0
Age at diagnosis (years)	23	12.7 ± 8.0	5.0 – 36.0
Age at operation (years)	23	18.0 ± 8.8	6.0 – 36.0
Disease duration (years)	23	10.2 ± 6.4	3.0 – 28.0
BFMDRS-M (out of 120)	21	71.4 ± 26.1	21.0 – 112.0
BFMDRS-D (out of 30)	22	21.0 ± 5.7	9.0 – 30.0
Barry-Albright-Dystonia Scale (out of 32)	21	21.0 ± 6.3	6.0 – 30.0
Global dystonia – doctor (out of 10)	17	7.7 ± 1.7	5.0 – 10.0
Global dystonia – patient (out of 10)	16	8.2 ± 1.6	5.0 – 10.0
Global dystonia – caregiver (out of 10)	21	8.4 ± 1.4	6.0 – 10.0
Global quality of life – patient (out of 10)	16	3.7 ± 2.8	0.0 – 9.0
Global quality of life – caregiver (out of 10)	21	3.0 ± 2.5	0.0 – 9.0
Care and Comfort Hypertonicity Questionnaire (out of 189)	17	104.1 ± 41.8	31.0 – 177.0

Table 2: Mean preoperative patient characteristics and mean preoperative basic parameters
n: number of patients
SD: standard deviation

3.2. Primary outcome measure

Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale (BFMDRS-M)

At all three times of assessment, we collected values for the BFMDRS-M in 14 patients. Preoperatively, the mean BFMDRS-M was 74.3 ± 24.0 out of 120 (n = 14), 2-6 months after surgery patients showed a mean BFMDRS-M of 47.8 ± 28.7 (n = 14) and 9-15 months after DBS they showed a mean BFMDRS-M of 51.0 ± 29.7 (n = 14). Accordingly, mean severity of dystonia was significantly improved by 26.5 points (35.7 %) at the 2-6 months interval (T = 3.6, P < 0.01) and 9-15 months after continuous neurostimulation dystonia was still improved by 23.3 points (31.4 %) which turned out to be significant (T = 2.7, P < 0.05). Mean dystonia impaired by 3.2 points (6.6 %) between 2-6 months and 9-15 months after DBS but this change was not significant (Figure 2).

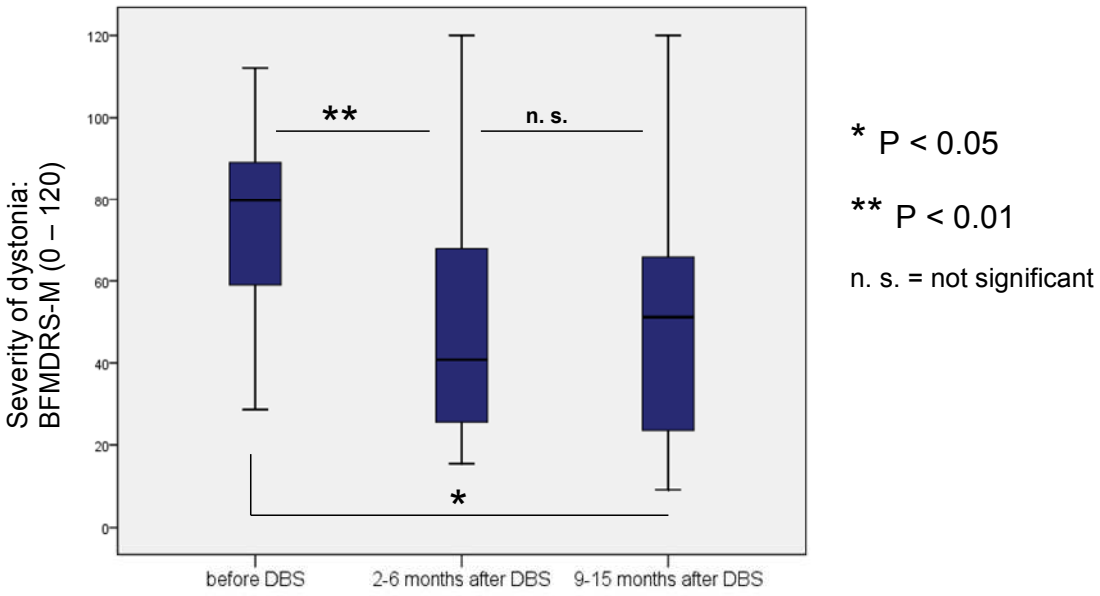

Figure 2: Box plots depicting mean scores of the BFMDRS-M (0 – 120) before DBS, 2-6 months after DBS and 9-15 months after DBS.
BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale
DBS: Deep Brain Stimulation
P Values according to the unadjusted t-test for dependent samples

At the 2-6 months interval, values for the BFMDRS-M were available in 19 patients and 11 of them (57.9 %) showed a clinical improvement of more than 20 % (Figure 3a). At the 9-15 months interval 11 out of 15 patients (73.3 %) showed an improvement of more than 20 % (Figure 3b).

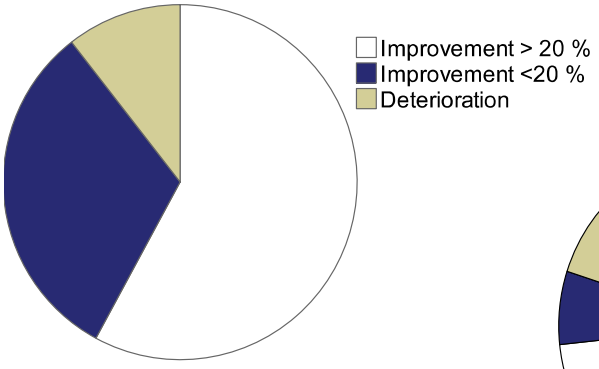

Figure 3a: Pie chart depicting severity of dystonia (BFMDRS-M) 2-6 months after DBS

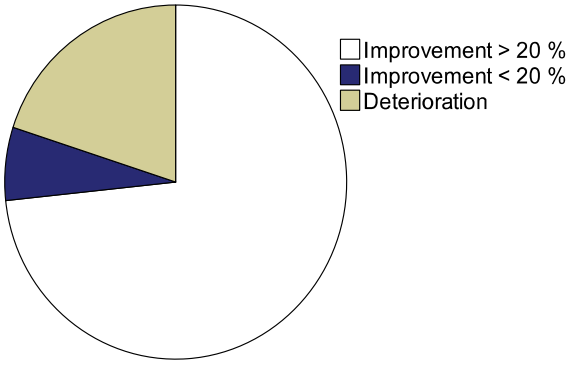

Figure 3b: Pie chart depicting severity of dystonia (BFMDRS-M) 9-15 months after DBS

Comparing absolute values, after 2-6 months 13 out of 19 patients (68.4 %) showed an improvement of at least 10 points or more according to the BFMDRS-M (Figure 4a) and at 9-15 months, 12 out of 15 patients (80 %) had improved by 10 points or more (Figure 4b).

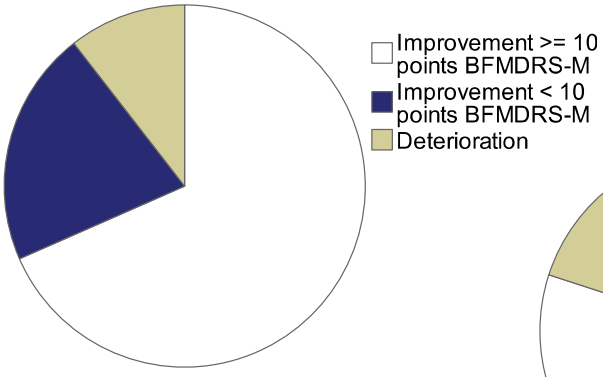

Figure 4a: Pie chart depicting severity of dystonia (BFMDRS-M) 2-6 months after DBS

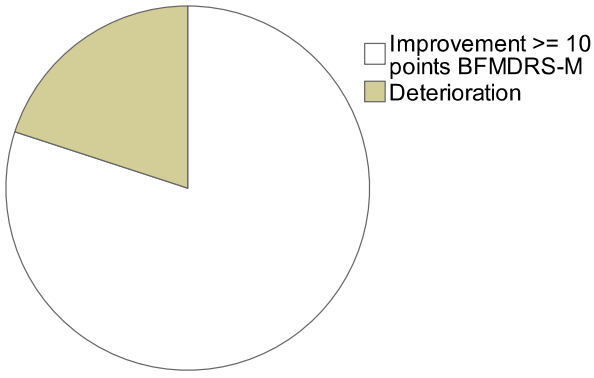

Figure 4b: Pie chart depicting severity of dystonia (BFMDRS) 9-15 months after DBS

Eight patients out of the above-mentioned 11 patients (72.7 %) who showed a clinical improvement of more than 20 % at 2-6 months after DBS, continued to show clinically relevant results 9-15 months after DBS, one of them worsened and no information was

available about the remaining two patients. Among the other eight patients who had not improved more than 20 % 2-6 months after DBS, there were two of them (25 %) who showed a clinically relevant improvement 9-15 months after DBS. However, two others out of these eight patients (25 %) remained more or less unchanged, one of them worsened (12.5 %) and no information was given about the remaining three patients at 9-15 months after DBS.

Individual absolute BFMDRS-M values are shown in Figure 5.

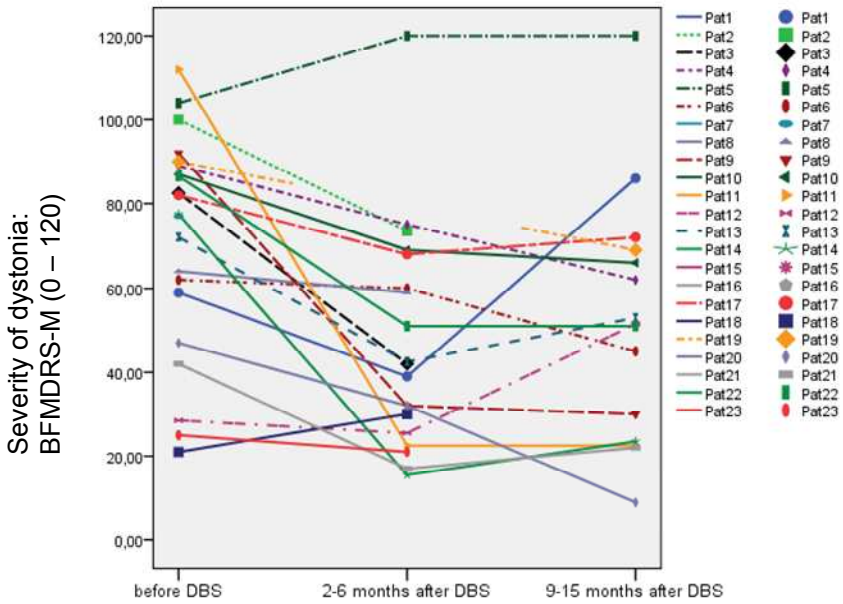

Figure 5: Line plot depicting severity of dystonia according to the BFMDRS-M for all patients individually before DBS, 2-6 months after DBS and 9-15 months after DBS

Individual percentaged change in severity of dystonia according to the BFMDRS-M at 2-6 months and at 9-15 months after DBS is shown in Figure 6. The initial point is set to 0 % in order to illustrate (positive) improvement and (negative) deterioration (Figure 6).

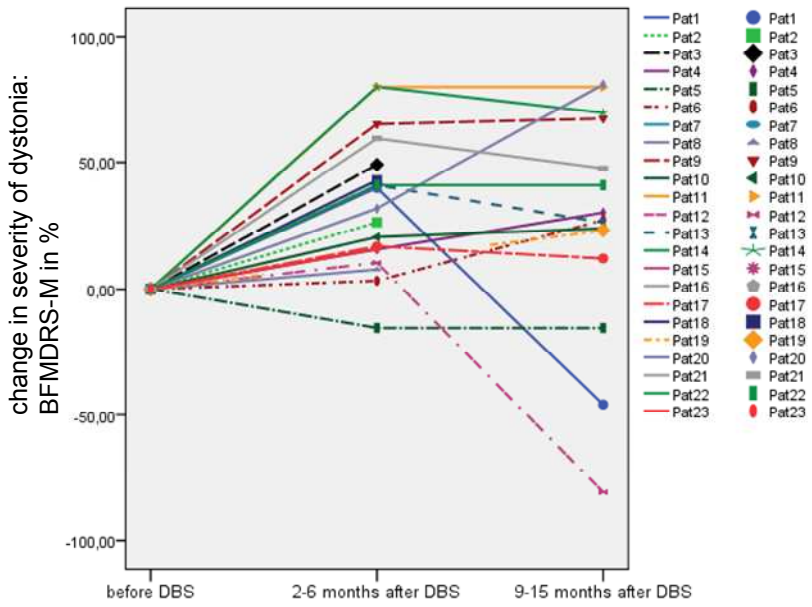

Figure 6: Line plot depicting change in severity of dystonia in percentage according to BFMDRS-M at 2-6 months and 9-15 months after DBS. Positive values illustrate improvement whereas negative values illustrate deterioration.

BFMDRS-M data from blinded video rating both before DBS and 2-6 months and 9-15 months thereafter were available only in three patients. The according preoperative result was an averaged BFMDRS-M of 65.0 ± 14.8 out of 120 (n = 3), 2-6 months after DBS of 47.5 ± 22.3 (n = 3) and of 53.7 ± 19.2 (n = 3) 9-15 months after DBS. Most probably due to the low patient number, the differences did not show any significance. The comparison of blinded video rating BFMDRS-M data between before and 2-6 months after DBS (n = 5) did not show any significance neither.

Barry-Albright Dystonia Scale (BADS)

Values of the Barry-Albright Dystonia Scale were available at all three time points in 14 patients and the trend, which emerged among BFMDRS-M assessment, could be confirmed. The mean severity of dystonia before DBS was scored 22.5 ± 5.5 out of 32 (n = 14), 2-6 months after DBS it showed a mean level of 17.4 ± 7.5 (n = 14) and 9-15 months after DBS it showed an average of 17.9 ± 8.1 (n = 14) (Figure 7). This represents a significant improvement of 5.1 points (22.7 %) at the 2-6 months interval ($T = 4.3$, $P < 0.005$), and of 4.6 points (20.4 %) 9-15 months after DBS ($T = 3.2$, $P < 0.01$). Between

the second and the third time of assessment, dystonia impaired by 0.5 points, which did not turn out to be significant.

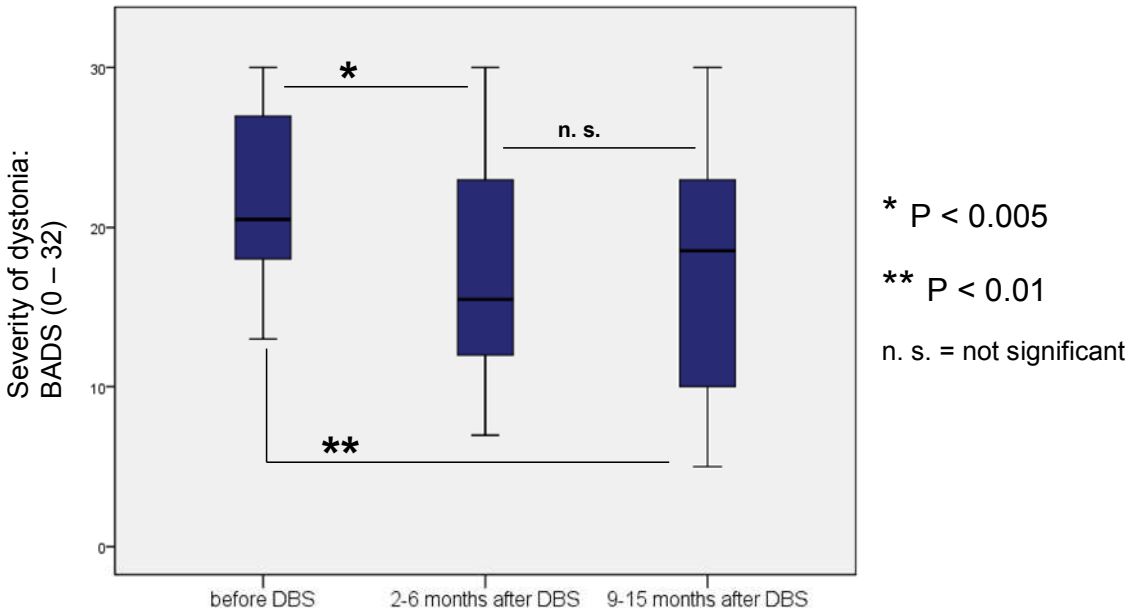

Figure 7: Box plots depicting mean scores of the Barry-Albright Dystonia Scale (0 – 32) before DBS, 2-6 months after DBS and 9-15 months after DBS.
BADS: Barry-Albright Dystonia Scale
DBS: Deep Brain Stimulation
P Values according to the unadjusted t-test for dependent samples

Global rating of dystonia (0 – 10)

Data for global dystonia rating by physicians, patients and caregivers at all three time points were available in nine patients.

Before surgery treating physicians assessed global severity of dystonia with a mean score of 7.5 ± 1.6 (n = 9) on a scale from 0-10, within the period of 2-6 months after surgery they estimated severity of dystonia with a mean score of 5.3 ± 1.9 (n = 9) and at the 9-15 months follow-up physicians scored global severity of dystonia with a mean value of 6.0 ± 2.7 (n = 9). Accordingly, they assessed a significant improvement of 2.2 points at the 2-6 months follow up (T = 5.5, P < 0.01), whereas change at 9-15 months after DBS (1.6 points) failed to reach significance.

Patients evaluated pre-operative severity of dystonia with a mean score of 7.7 ± 1.7 (n = 9), while they described severity of dystonia 2-6 months after DBS with a mean score of 4.9 ± 2.6 (n = 9) and at 9-15 months after surgery, patients rated an average score of 5.1 ± 3.0 (n = 9). Change in global severity of dystonia according to the patients was

significant both at the 2-6 months interval with 2.8 points (T = 4.5, P < 0.01) and at the 9-15 months interval with 2.6 points (T = 3.5, P < 0.01).

Caregivers estimated the preoperative level of global dystonia by 7.9 ± 1.4 points (n = 9). 2-6 months after DBS a mean score of 4.9 ± 2.6 (n = 9) was assessed and at the 9-15 months interval, caregivers graded global severity of dystonia by a mean score of 5.4 ± 2.9 (n = 9). The first difference of 3.0 points turned out to be significant (T = 5.4, P < 0.01) as did the second difference of 2.5 points (T = 3.0, P < 0.05) (Figure 8).

All results describing severity of dystonia before DBS, 2-6 months and 9-15 months after DBS are summarized in Table 3 and Table 4.

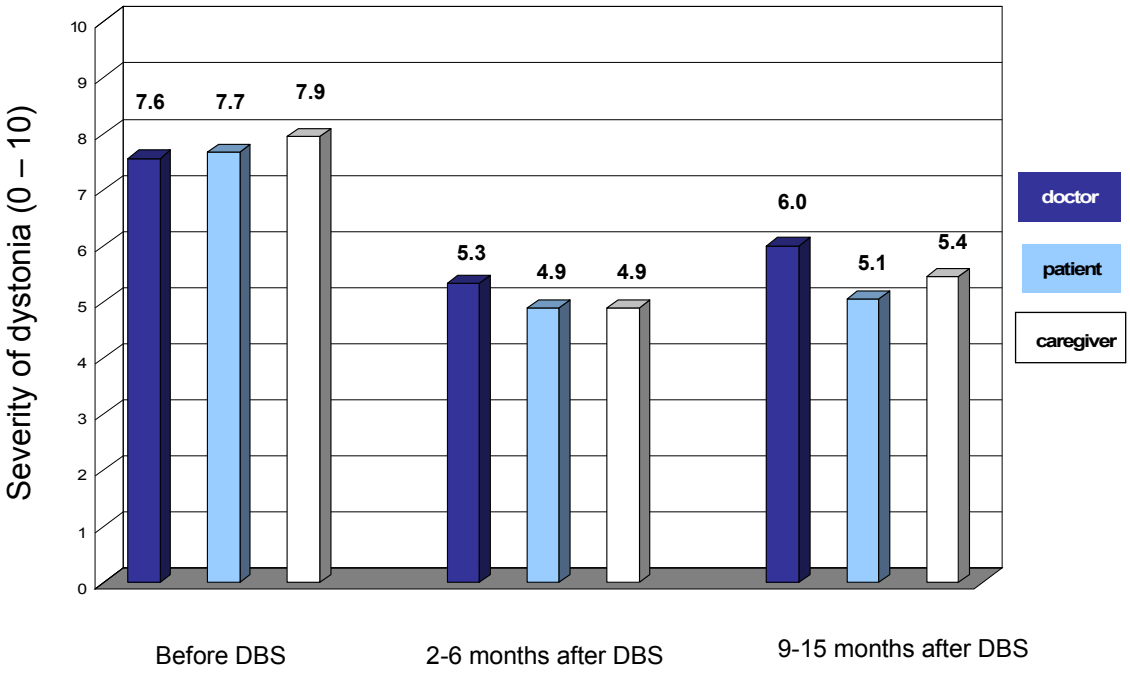

Figure 8: Bar charts comparing mean scores of global rating of dystonia (0 – 10) by doctors, by patients and by caregivers before DBS, 2-6 months and 9-15 months after DBS, 0 being no dystonia at all and 10 being the most severe generalized dystonia.
DBS: Deep Brain Stimulation
Values: Means of score

	Before DBS		2-6 months after DBS		9-15 months after DBS	
	n	score	n	score	n	score
Dystonia						
BFMDRS-M (0-120)	14	74.3 ± 24.0	14	47.8 ± 28.7	14	51.0 ± 29.7
BADS (0-32)	14	22.5 ± 5.5	14	17.4 ± 7.5	14	17.9 ± 8.1
Global rating by doctor (0-10)	9	7.5 ± 1.6	9	5.3 ± 1.9	9	6.0 ± 2.7
Global rating by patient (0-10)	9	7.7 ± 1.7	9	4.9 ± 2.6	9	5.1 ± 3.0
Global rating by caregiver (0-10)	9	7.9 ± 1.4	9	4.9 ± 2.6	9	5.4 ± 2.9

Table 3: Mean severity of dystonia according to different scores before, 2-6 months and 9-15 months after DBS
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale
BADS: Barry-Albright Dystonia Scale
DBS: Deep Brain Stimulation
n: Number of included patients
Values: Means of score ± standard deviation

	Change from baseline to 2-6 months		P Value	Change from baseline to 9-15 months		P Value	Change from 2-6 months to 9-15 months		P Value
	n	score		n	score		n	score	
Dystonia									
BFMDRS-M (0 – 120)	14	- 26.5 (-35.7 %)	< 0.01	14	- 23.3 (-31.4 %)	< 0.05	14	+ 3.2 (+ 6.6 %)	n. s.
BADS (0 – 32)	14	- 5.1 (- 22.7 %)	< 0.005	14	- 4.6 (- 20.4 %)	< 0.01	14	+ 0,5 (+ 2.9 %)	n. s.
Global rating by doctor (0 – 10)	9	- 2.2	< 0.01	9	- 1.6	n. s.	9	+ 0.7	n. s.
Global rating by patient (0 – 10)	9	- 2.8	< 0.01	9	- 2.6	< 0.01	9	+ 0.2	n. s.
Global rating by caregiver (0 – 10)	9	- 3.0	< 0.01	9	- 2.5	< 0.05	9	+ 0.5	n. s.

Table 4: Change in dystonia according to different scores
BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale
BADS: Barry-Albright Dystonia Scale
n: Number of patients
n. s.: not significant
P Values according to the unadjusted t-test for dependent samples
Values: Mean of change of score (negative values indicate improvement in dystonia whereas positive values indicate deterioration respectively)

3.3. Secondary outcome measures

Two secondary outcome measures were analyzed in this trial. The first one was disability as assessed by the Burke-Fahn-Marsden Dystonia Rating Scale - Disability scale (BFMDRS-D). The second one was Quality of life as assessed globally by caregivers on a scale from 0 – 10. As we performed multiple t-tests for dependent samples, a Bonferroni correction was applied on each variable to be tested, and the initial significance level of P = 0.05 was set to P = 0.01 (three t-tests for dependent samples for each variable). Furthermore, data for quality of life were verified by global ratings of patients and by the CCHQ; those were compared to the results obtained by the caregivers` global rating.

3.3.1. Disability

Burke-Fahn-Marsden Dystonia Rating Scale –Disability scale (BFMDRS-D)

We received BFMDRS-D data at all three time points from a total of 15 patients.
We found a mean score of 20.7 ± 5.9 out of 30 (n = 15) before DBS, a mean score of 17.5 ± 7.7 (n = 15) 2-6 months after continuous neurostimulation and a mean score of 18.5 ± 7.3 (n = 15) 9-15 months after surgery (Figure 9). Disability improved by 3.12 points (15.5 %) between baseline and 2-6 months after DBS according to the BFMDRS-D, which was not significant after Bonferroni correction (T = 2.5, P = 0.03). After 9-15 months of continuous neurostimulation, disability had improved by 2.2 points (10.6 %) and this change was not significant. Likewise, the deterioration of 1.0 point (6 %) between the 2-6 months- and 9-15 months interval was not significant (Figure 9).

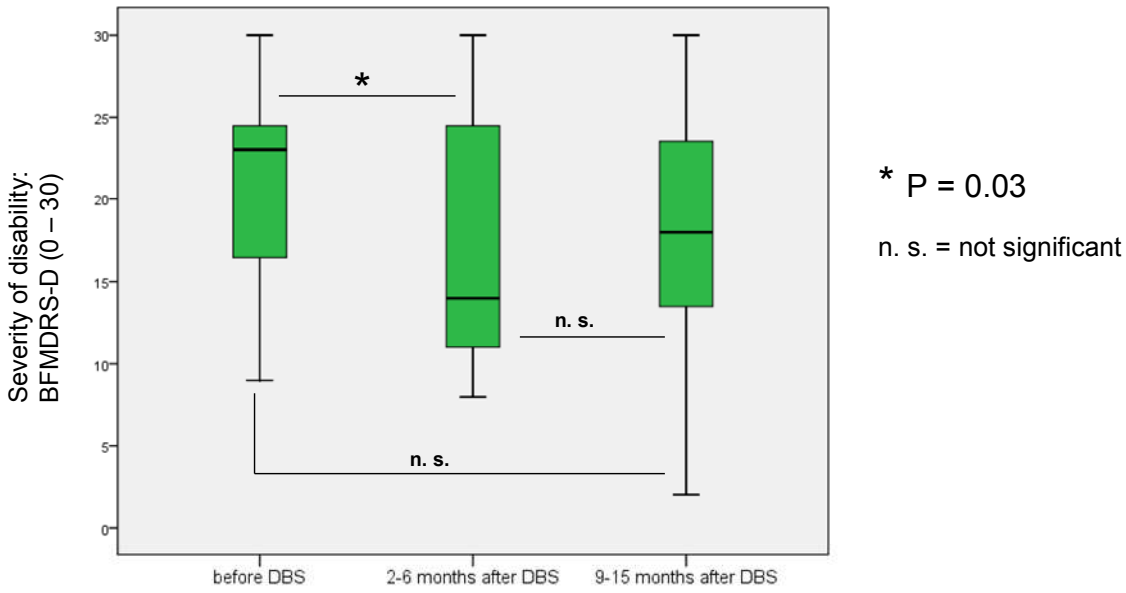

Figure 9: Box plots depicting mean scores of the BFMDRS-D (0 – 30) before DBS, 2-6 months and 9-15 months after DBS.
DBS: Deep Brain Stimulation
BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale –Disability scale
P Values according to t-tests for dependent samples after Bonferroni correction (P Value 0.03: result is not significant after Bonferroni correction)

2-6 months after DBS, we received BFMDRS-D values from 20 patients and 7 of them (35.0 %) showed a clinical improvement of more than 20 % (Figure 10a). 9-15 months after DBS, 5 out of known 16 patients (31.25 %) showed an improvement of more than 20 % (Figure 10b).

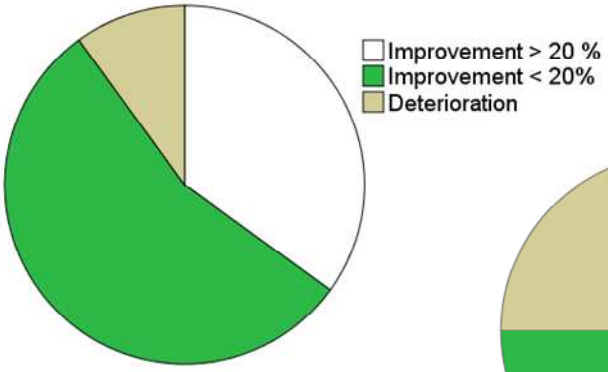

Figure 10a: Pie chart depicting severity of disability (BFMDRS-D) 2-6 months after DBS

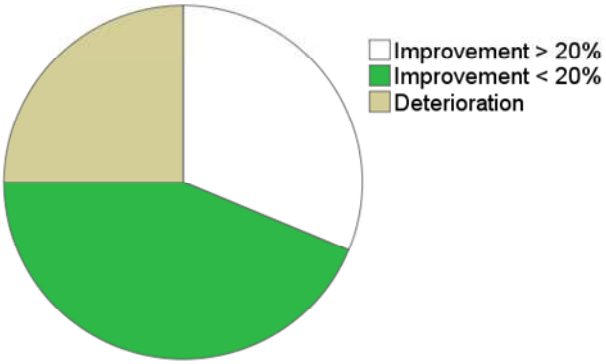

Figure 10b: Pie chart depicting severity of disability (BFMDRS-D) 9-15 months after DBS

For absolute values, at 2-6 months after DBS 8 patients out of 20 (40 %) improved by 4 points or more (Figure 11a) and at the 9-15 months-interval, 6 patients out of 16 (37.5%) showed an improvement of 4 points or more (Figure 11b).

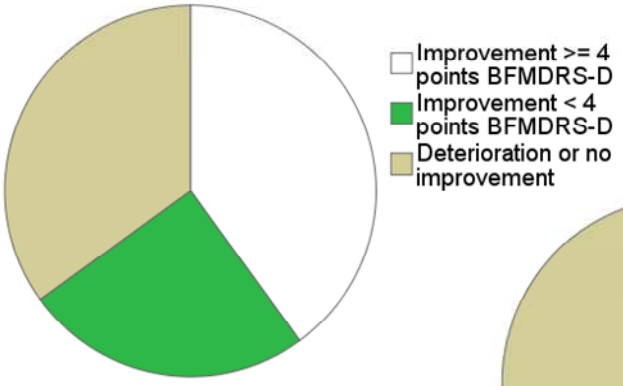

Figure 11a: Pie chart depicting disability (BFMDRS-D) 2-6 months after DBS

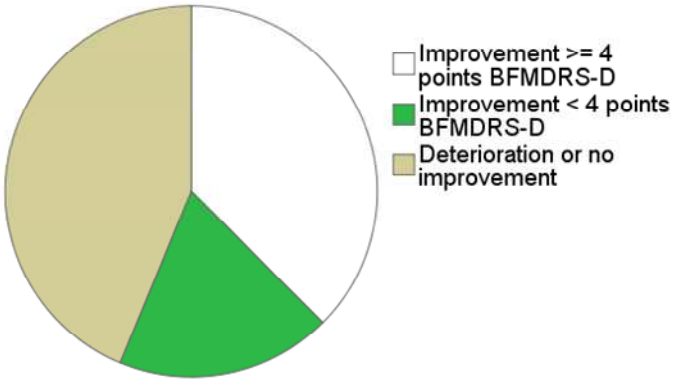

Figure 11b: Pie chart depicting disability (BFMDRS-D) 9-15 months after DBS

Individual trends in disability according to absolute values of the BFMDRS-D are shown in Figure 12.

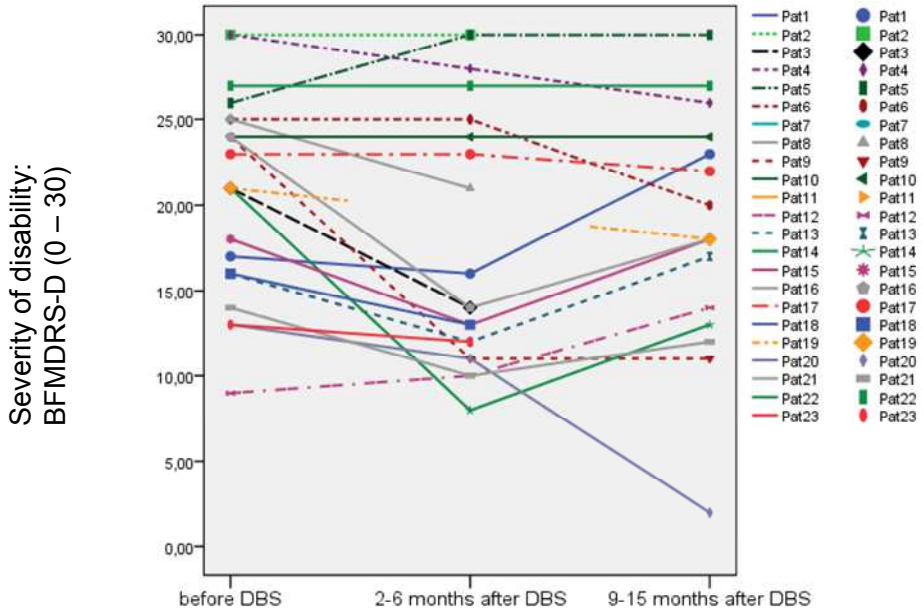

Figure 12: Line plot depicting severity of disability according to the BFMDRS-D for all patients individually before DBS, 2-6 months after DBS and 9-15 months after DBS

Individual percentaged change in severity of disability according to the BFMDRS-D at 2-6 months and 9-15 months after DBS is shown in Figure 13. The initial point is set to 0 % in order to illustrate (positive) improvement and (negative) deterioration (Figure 13).

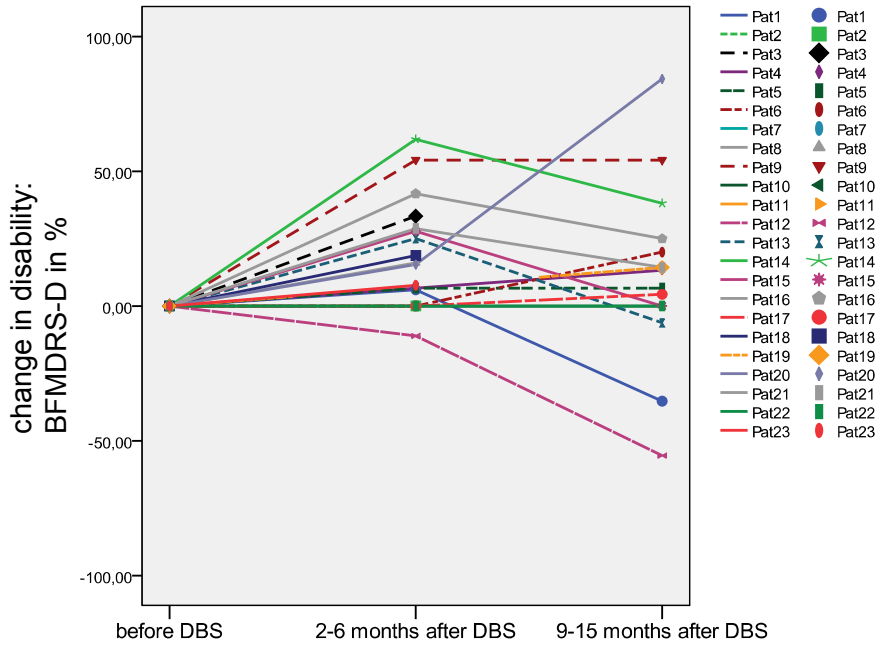

Figure 13: Line plot depicting change in disability in % according to BFMDRS-D at 2-6 months and 9-15 months after DBS. Positive values illustrate improvement whereas negative values illustrate deterioration.

Mean values of disability according to the BFMDRS-D before, 2-6 months and 9-15 months after DBS are summarized in Table 5.

	Before DBS		2-6 months after DBS		9-15 months after DBS	
	n	score	n	score	n	score
Disability						
BFMDRS-D (0-30)	15	20.7 ± 5.9	15	17.5 ± 7.7	15	18.5 ± 7.3

Table 5: Mean disability according to the BFMDRS-D before, 2-6 months and 9-15 months after DBS
BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale – Disability scale
DBS: Deep Brain Stimulation
n: Number of included patients
Values: Means of score ± standard deviation

Mean progression values for disability are listed in Table 6.

	Change from baseline to 2-6 months		P Value	Change from baseline to 9-15 months		P Value	Change from 2-6 months to 9-15 months		P Value
	n	score		n	score		n	score	
Disability									
BFMDRS-D (0-30)	15	- 3.2 (- 15.5 %)	0.03 (n.s.)	15	- 2.2 (- 10.6 %)	n.s.	15	+ 1.0 (+ 6 %)	n.s.

Table 6: Change in disability according to the BFMDRS-D
BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale – Disability scale
n: Number of patients
n. s.: not significant
P Values according to t-tests for dependent samples after Bonferroni correction
Values: Mean of change of score (negative values indicate improvement in disability whereas positive values indicate deterioration respectively)

3.3.2. Quality of life

We collected subjective evaluation data of quality of life by both patients and caregivers. Since some patients probably suffered from cognitive impairment and assessment of quality of life among very young patients applying abstract scales is difficult to conduct, data for caregivers` ratings were mainly available and we decided to take the caregivers` global ratings of quality of life as a second outcome parameter. As mentioned above, quality of life was furthermore assessed objectively by using the CCHQ. Given the higher number of available summed up CCHQ-scores (27 – 189), we used those for data analysis.

Global rating of quality of life by the caregivers (0 – 10)

A total of 17 complete caregivers` data series defining subjective quality of life was collected.

Caregivers subjectively assessed preoperative quality of life by a mean score of 2.7 ± 2.6 (n = 17), after 2-6 months, the caregivers` evaluation resulted in an average score of 5.4 ± 2.8 (n = 17) and 9-15 months after DBS caregivers estimated patients` quality of life by an average of 5.1 points ± 2.9 (n = 17). The mean difference between baseline and the 2-6 months interval of 2.7 points turned out to be significant ($T = -4.3$, $P < 0.01$). Likewise, a significant improvement of 2.4 points could be detected between baseline and the 9-15

months interval (T = -3.1, P < 0.01). The slight deterioration between the short-term (2-6 months) - and the long-term (9-15 months) result of 0.3 points did not show any significance (Figure 14).

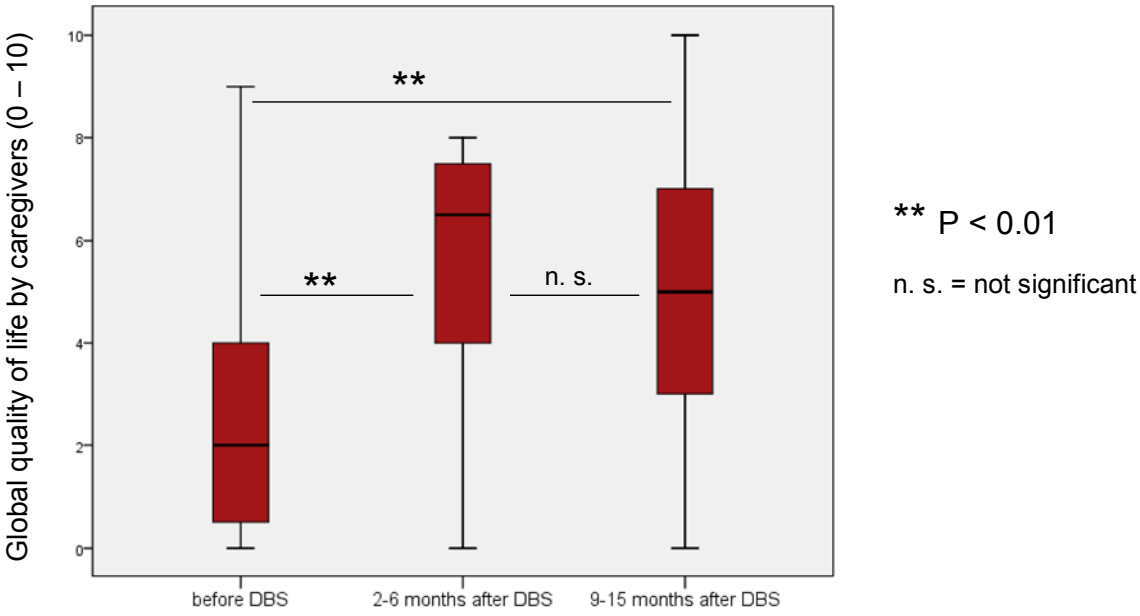

Figure 14: Box plots depicting mean scores of global rating of quality of life (0 – 10) by the caregiver before DBS, 2-6 months and 9-15 months after DBS, 10 being the best imaginable quality of life and 0 being no quality of life at all.
DBS: Deep Brain Stimulation

2-6 months after electrode implantation, quality of life data estimated by caregivers were available in 20 patients. 11 caregivers (55 %) assessed an improvement of 3 points or more. 3 of them (15 %) described an improvement of less than 3 points and 6 of them (30 %) perceived quality of life as deteriorated or unchanged (Figure 15a). At 9-15 months after surgery, 17 caregivers rated quality of life and still eight of them (47.1 %) quoted an improvement of 3 points or more. Three caregivers (17.6 %) assessed improvement by less than 3 points while six of them (35.3 %) described deterioration or no improvement (Figure 15b).

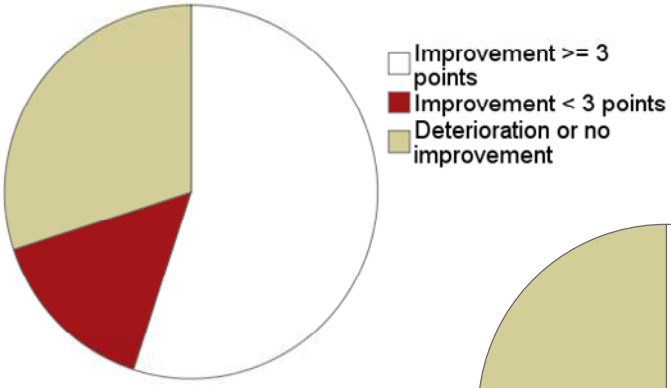

Figure 15a: Pie chart depicting Quality of life (0 – 10) as assessed by caregivers 2-6 months after DBS

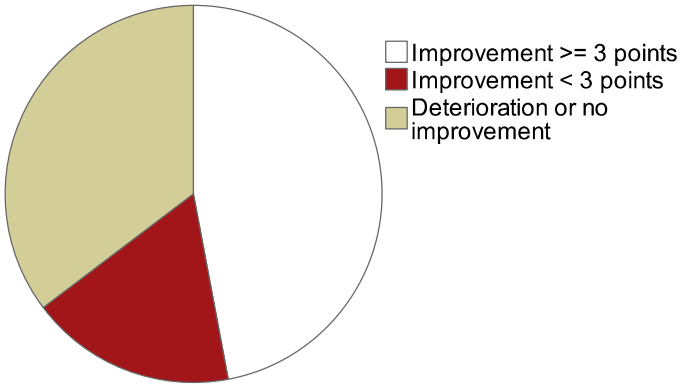

Figure 15b: Pie chart depicting Quality of life (0 – 10) as assessed by caregivers 9-15 months after DBS

Individual devolution of quality of life according to caregivers is shown in Figure 16.

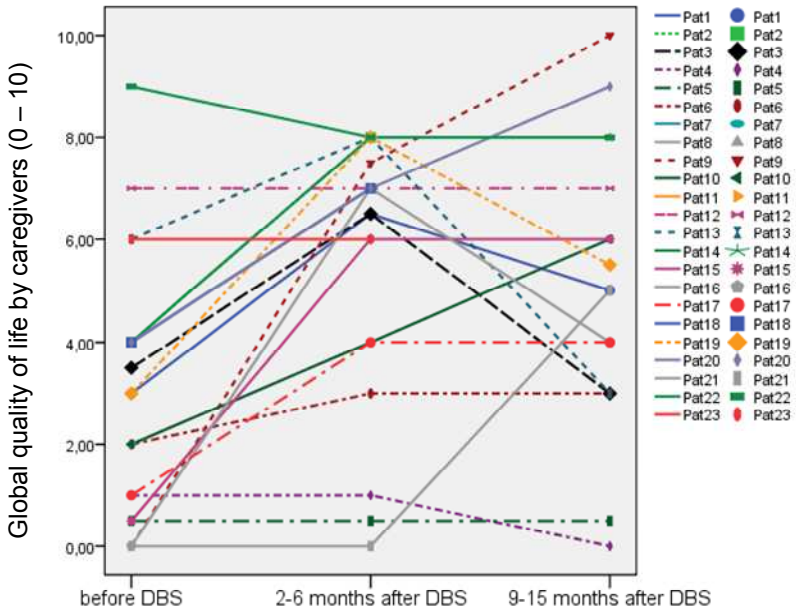

Figure 16: Line plot depicting global quality of life according to caregivers (0 – 10, 10 being the best imaginable quality of life and 0 being no quality of life at all) for each patient individually before DBS, 2-6 months after DBS and 9-15 months after DBS

Global rating of quality of life by the patients (0 – 10)

14 patients subjectively rated quality of life at all three time points. According to them, before DBS quality of life was on average 3.6 ± 2.9 points on a scale from 0-10 (n = 14) whereas after 2-6 months of continuous neurostimulation patients evaluated quality of life by a mean score of 6.3 ± 2.5 (n = 14). At the 9-15 months follow-up patients rated their subjective quality of life by a mean score of 6.1 ± 2.9 (n = 14). Consequently, global rating by the patients of quality of life significantly improved after 2-6 months by 2.7 points ($T = -3.4$, $P < 0.01$) whereas the improvement after 9-15 months of 2.5 points failed to reach significance after Bonferroni correction ($T = -2.9$, $P = 0.011$). Between the 2-6 months and the 9-15 months interval quality of life decreased by 0.2 points which was not significant (Figure 17).

The corresponding 14 caregivers estimated patients` quality of life preoperatively by an average of 3.0 points ± 2.8 (n = 14), after 2-6 months after DBS the mean score was 6.0 ± 2.6 (n = 14) and at the long-term interval the according mean result of global rating by the 14 caregivers was 5.5 ± 2.7 (n = 14). Global quality of life consequently improved by 3.0 points after 2-6 months of DBS significantly ($T = -4.3$, $P < 0.01$). At the 9-15 months follow-up, quality of life was improved by 2.5 points as compared to baseline which however was not significant after Bonferroni correction ($T = -2.8$, $P = 0.011$). Between the 2-6 months and the 9-15 months follow-up quality of life impaired by 0.5 points which was not significant (Figure 17).

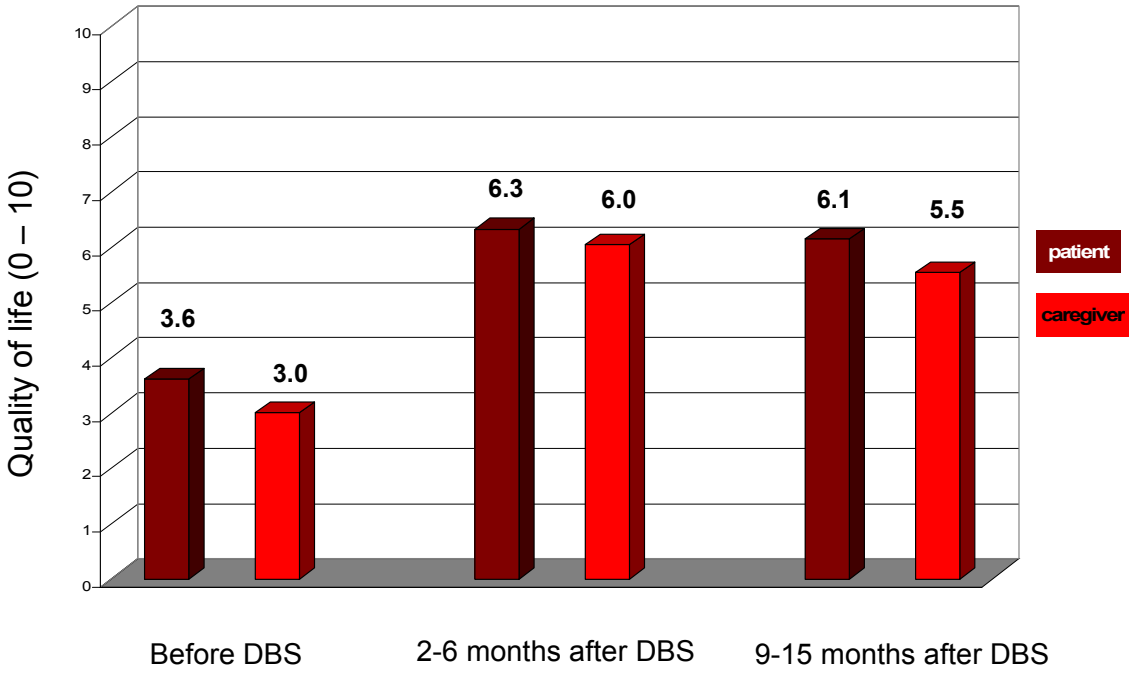

Figure 17: Bar charts comparing mean scores of global rating of quality of life (0 – 10) by 14 patients and the accordant 14 caregivers before DBS, 2-6 months and 9-15 months after DBS, 0 being no quality of life at all and 10 being the most imaginable quality of life.
DBS: Deep Brain Stimulation
Values: Means of score

Care and Comfort Hypertonicity Questionnaire (CCHQ) (27 – 189)

A total of 13 summed up CCHQ-scores was available at all three follow up – time points. Before DBS, summed up CCHQ-scores resulted in a mean score of 104.4 ± 44.1 out of 189 (n = 13), 2-6 months after DBS a mean value of 80.7 ± 49.3 (n = 13) was detected and 9-15 months after DBS the mean result of the summed up CCHQ-scores was 88.3 points ± 50.6 (n = 13). However, according to the summed up CCHQ, the positive change of 23.7 points between the time before DBS and 2-6 months after DBS failed to reach significance after Bonferroni correction (T = 3.0, P = 0.012). After 9-15 months of continuous neurostimulation, quality of life still was improved by 16.1 points, which was not significant. Likewise, the deterioration of quality of life between the 2-6 months and the 9-15 months interval of 7.6 points was not significant (Figure 18).

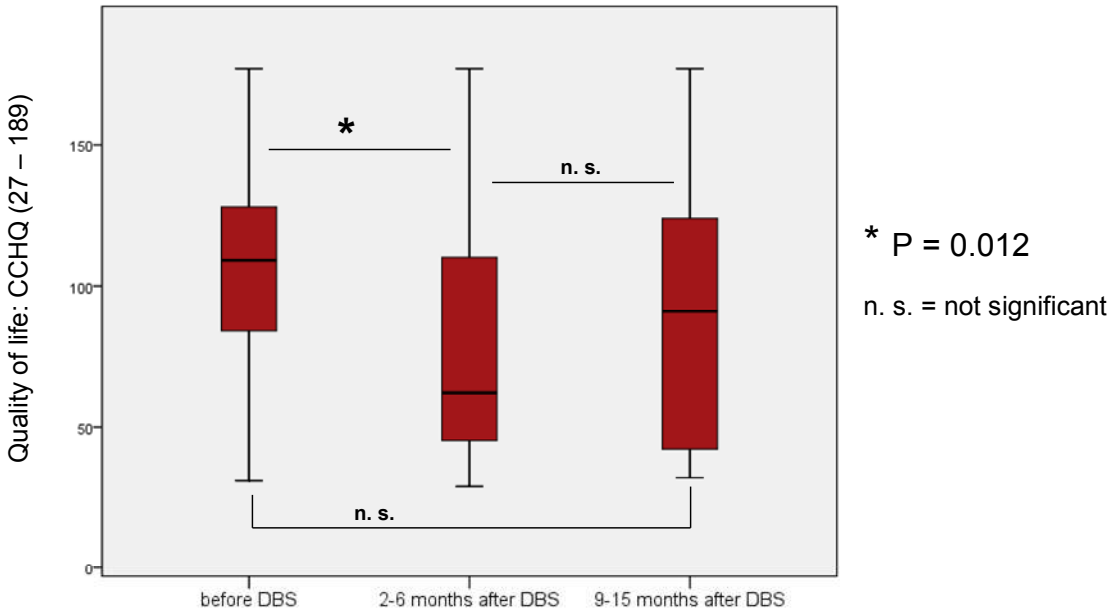

Figure 18: Mean score of the summed up CCHQ (27 – 189) before DBS, 2-6 months and 9-15 months after DBS, 27 being the best possible quality of life and 189 being no quality of life at all.
CCHQ: Care and Comfort Hypertonicity Questionnaire
DBS: Deep Brain Stimulation
P Value according to t-tests for dependent samples after Bonferroni correction (P Value 0.012: result is not significant after Bonferroni correction)

Mean scores of quality of life before DBS, 2-6 months after DBS and 9-15 months after DBS are summarized in Table 7. Change in quality of life is depicted in Table 8.

	Before DBS		2-6 months after DBS		9-15 months after DBS	
	n	score	n	score	n	score
Quality of life						
Global rating by caregiver (0 – 10)	17	2.7 ± 2.6	17	5.4 ± 2.8	17	5.1 ± 2.9
Global rating by patient (0 – 10)	14	3.6 ± 2.9	14	6.3 ± 2.5	14	6.1 ± 2.9
summed up CCHQ (27 - 189)	13	104.4 ± 44.1	13	80.7 ± 49.3	13	88.3 ± 50.6

Table 7: Quality of life before and after DBS
CCHQ: Care and Comfort Hypertonicity Questionnaire
DBS: Deep Brain Stimulation
n: number of patients
Values: Means of score ± standard deviation

	Change from baseline to 2-6 months		P Value	Change from baseline to 9-15 months		P Value	Change from 2-6 months to 9-15 months		P Value
	n	score		n	score		n	score	
Quality of life									
Global rating by caregiver (0-10)	17	+ 2.7	< 0.01	17	+ 2.4	< 0.01	17	-0.3	n. s.
Global rating by patient (0-10)	14	+ 2.7	< 0.01	14	+ 2.5	0.011 (n. s.)	14	- 0.2	n. s.
summed up CCHQ (27 - 189)	13	- 23.7 (- 22.7 %)	0.012 (n. s.)	13	- 16.1 (- 15.4 %)	n. s.	13	+ 7.6 (+ 9.4 %)	n. s.

Table 8: Change in quality of life
CCHQ: Care and Comfort Hypertonicity Questionnaire
DBS: Deep Brain Stimulation
n: number of patients
P Values according to t-tests for dependent samples after Bonferroni correction
n. s.: not significant
Values: Means of score (for the global rating, positive values indicate improvement of quality of life and negative values indicate impairment. Referring to the CCHQ, on the contrary, negative values indicate improvement of quality of life whereas positive values indicate deterioration.)

3.4. Surgical target point

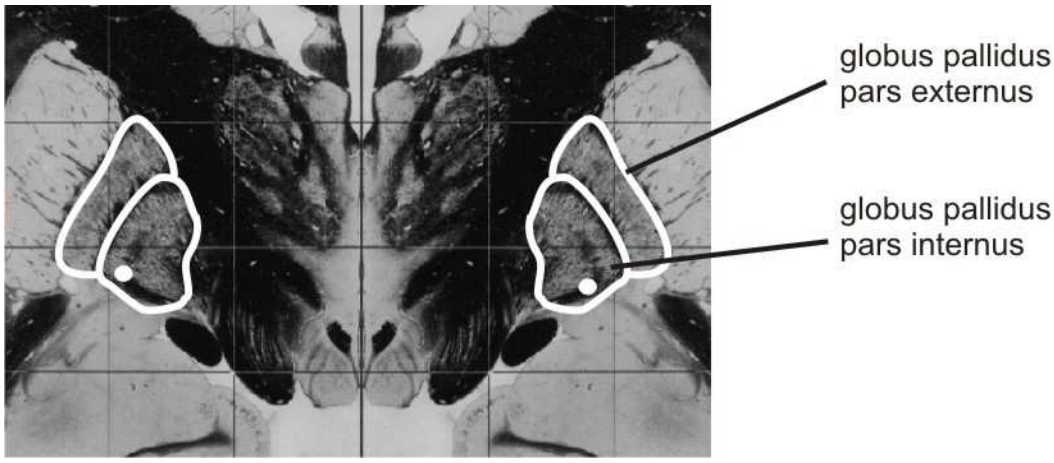

Figure 19: Coronary section plane of basal ganglia with depiction of the Globus Pallidus pars internus (GPi) and pars externus (GPe) (modified from (Nowinski and Thirunavuukarasuu, 2004)). In white line, the GPi and GPe are highlighted and the white point indicates the active electrode contact on Patient 3.

According to the Schaltenbrand-Wahren atlas (Schaltenbrand and Wahren, 1977), we recorded the surgical target point of 12 patients out of 23, which in every case was located in the GPi bilaterally. Since no exact data of target localisation techniques in different neurosurgical centres were collected, we did not calculate a standard mean target coordinate.

Individual coordinates lateral to the midsagittal plane (x-axis), anterior to the midcommissural plane (y-axis) and below the intercommissural line (z-axis) on the left as well as on the right side are registered in Table 9.

Patient number	**Left GPi**			**Right GPi**		
	x	**y**	**z**	**x**	**y**	**z**
3	18.4	3.4	-3.9	19.7	5.5	-2.3
6	20	2	-1	20	2	-1
8	20.5	1.5	-5	20.5	1.5	-3.8
9	21	3	-4	21	3	-4
11	22.6	2,9	-1.4	22.2	3.4	-0.1
12	17	1.5	-5	17	1.5	-5
13	17	1,5	0	18	2.5	0
14	15	1.5	-1	18	1	-2
19	20.6	2.3	-1.9	21.3	2.8	-2.1
20	22	2	-3	22	2	-3
21	21	2	-5	21	2	-5
23	21	2	-3	21	2	-3
Mean	19.7	2.1	-2.9	20.1	2.4	-2.3

Table 9: Surgical target point of electrode implantation
Values in millimetre
x: x-axis
y: y-axis
z: z-axis

3.5. Stimulation parameters

Mean and standard deviation of pulse frequency, of pulse width and of voltage after 2-6 and after 9-15 months of continuous DBS are listed in Table 10.
For individual parameters, please see Appendix 12 and Appendix 13.

	2-6 months after DBS (n = 19) mean (range)		9-15 months after DBS (n = 13) mean (range)	
	left	right	left	right
Pulse frequency (Hz)	133.7 (60 – 215)	140.0 (60 – 230)	128.1 (60 - 185)	128.5 (60 – 185)
Pulse width (µsec)	194.2 (60 – 450)	197.4 (60 – 450)	244.6 (60 – 450)	244.6 (60 – 450)
Voltage (V)	2.83 (1.0 – 5.0)	2.78 (1.0 – 5.0)	2.73 (1.3 – 4.6)	2.76 (1.3 – 4.6)

Table 10: Mean stimulation parameters at 2-6 and 9-15 months postoperatively
DBS: Deep Brain Stimulation
Hz: Hertz
µsec: microseconds
n: Number of patients
V: Volt
Values: Means of parameters, range in parentheses

However, no information was available about the kind of DBS-lead being implanted. Neither did we collect any data about activated lead contacts. The effective voltage being individually applied on each side was calculated for 19 patients 2-6 months after lead implantation and for 13 patients within the 9-15 months interval referring to a method by Rehncrona et al. (Rehncrona et al., 2003) (Appendix 14). We tested the correlation between effective voltage being applied and therapy outcome, but there was no amount of effective voltage being particularly effective in NBIA-dystonia.

3.6. Correlations

Since results within our first and second outcome parameters were heterogeneous, we tried to find out, if possible, correlations within those values and thus to determine dependencies and trends of predictive value.

Dystonia and disability

Change in disability according to the BFMDRS-D is shown as a function of change in dystonia according to the BFMDRS-M (Figure 20, 21). Figure 20 depicts changes from baseline to 2-6 months after DBS whereas Figure 21 shows the same correlation referring to changes from baseline to 9-15 months after electrode implantation.

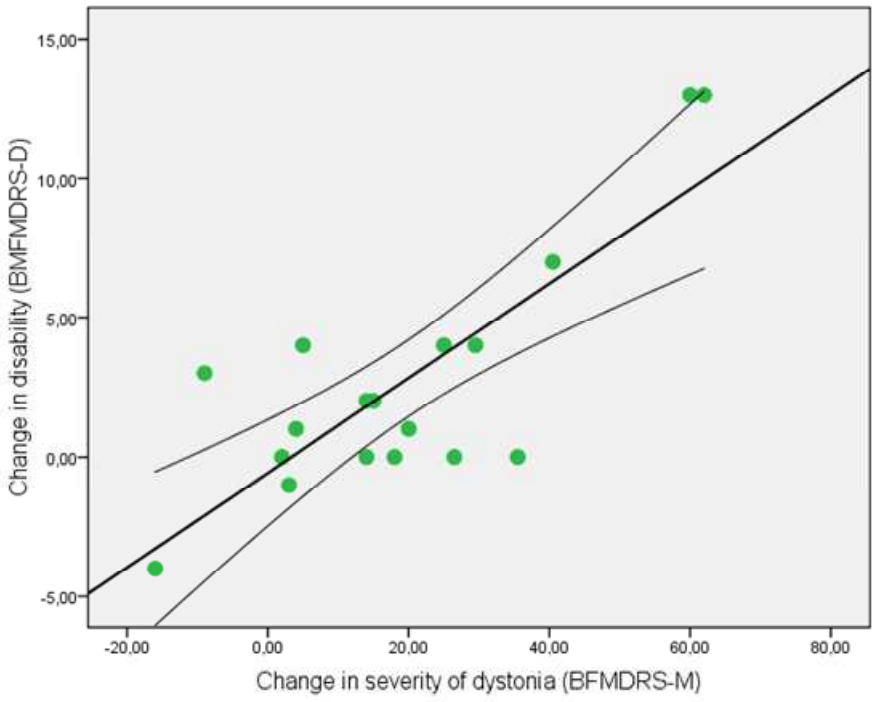

Figure 20: Change in BFMDRS-D as a function of change in BFMDRS-M (2-6 months after DBS). Positive values indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale
BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale – Disability scale

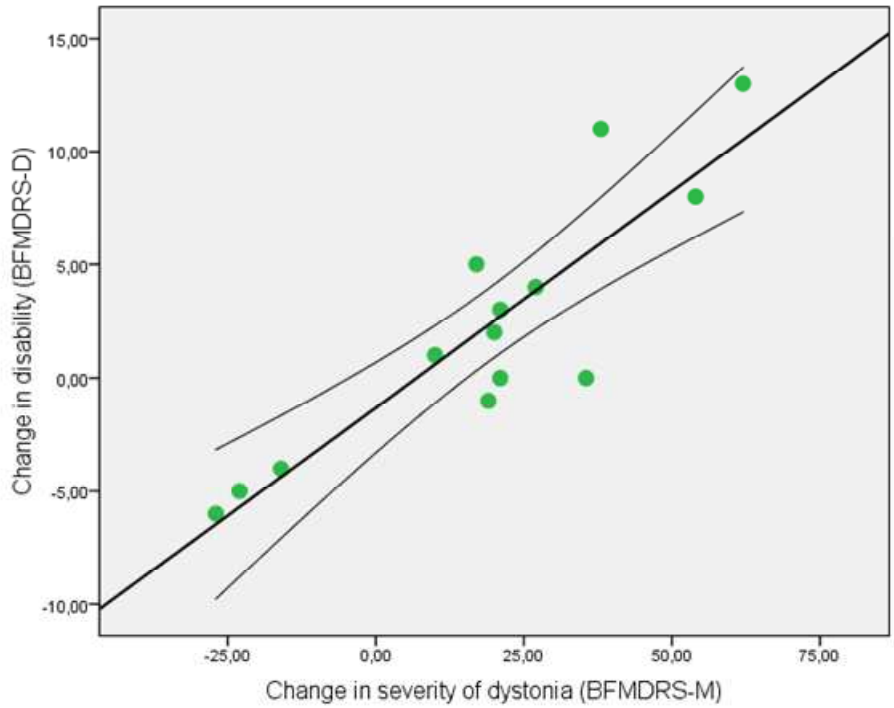

Figure 21: Change in BFMDRS-D as a function of change in BFMDRS-M (9-15 months after DBS). Positive values indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale
BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale – Disability scale

It could be demonstrated that improvement in disability at 2-6 months depends on improvement in severity of dystonia at 2-6 months after DBS and thus can be predicted by improvement in dystonia (linear regression, corr. $r^2 = 0.62$, $F = 28.4$, $P < 0.001$). Likewise it could be shown that change of disability at 9-15 months after DBS can be predicted by change of dystonia at 9-15 months after DBS (linear regression, corr. $r^2 = 0.76$, $F = 42.8$, $P < 0.001$).

Dystonia and quality of life

Change in quality of life according to the caregivers (0 – 10) as a function of change in dystonia (BFMDRS-M) is shown in Figure 22 (at 2-6 months after DBS) and Figure 23 (at 9-15 months after DBS). Quality of life was assessed by caregivers on a scale from 0-10, 0 being no quality of life at all and 10 being the best imaginable quality of life.

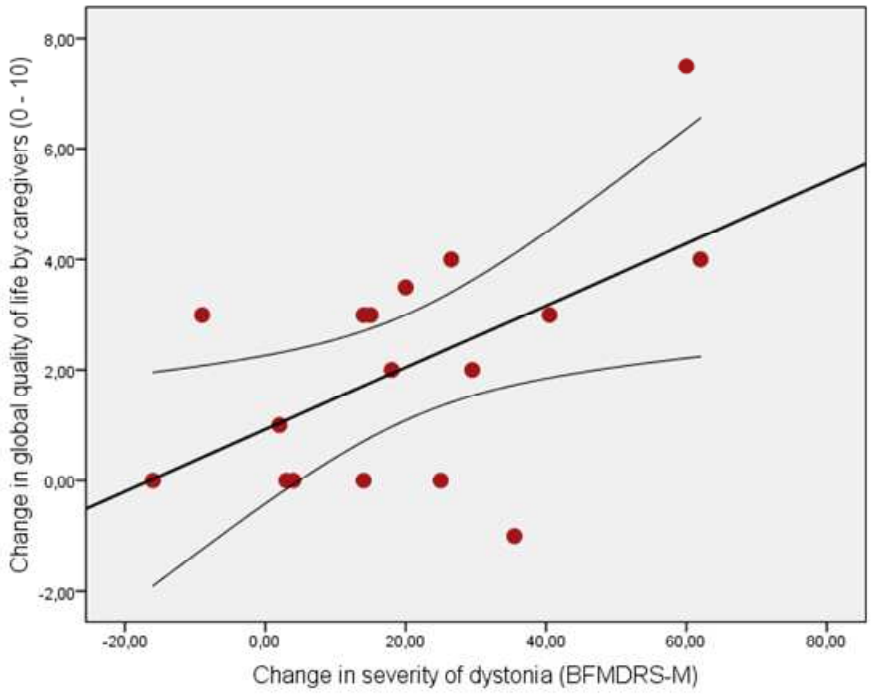

Figure 22: Global change in Quality of life according to the caregivers (0 – 10) as a function of change in BFMDRS-M (2-6 months after DBS). Positive values indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale

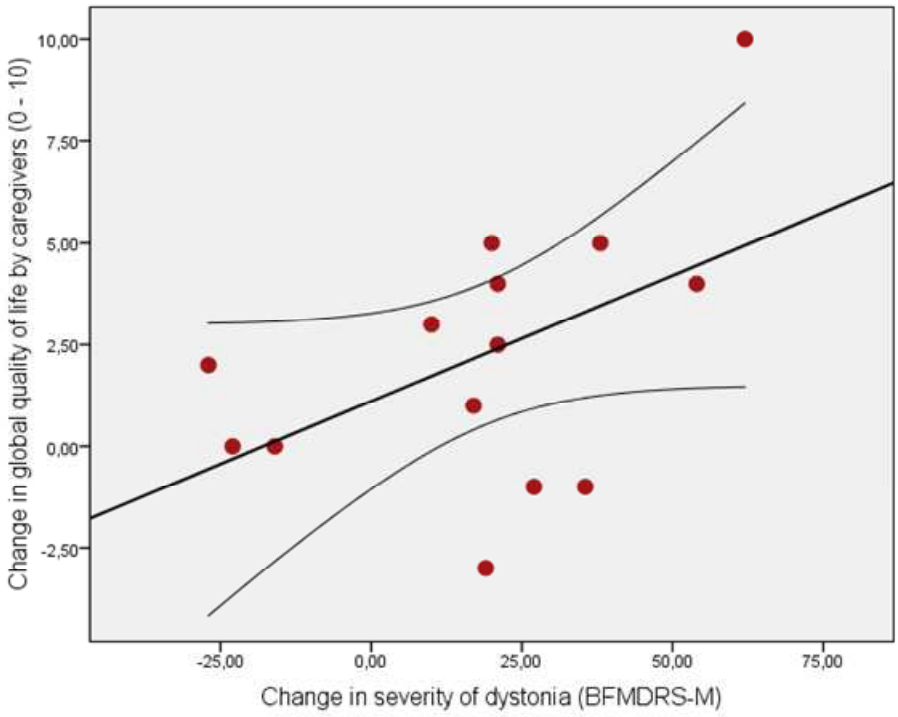

Figure 23: Global change in Quality of life according to the caregivers (0 – 10) as a function of change in BFMDRS M (9-15 months after DBS). Positive values indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale

The findings at the 2-6 months interval might indicate that improvement in dystonia is associated with an improvement in quality of life (linear regression, corr. $r^2 = 0.26$, $F = 6.7$, $P = 0.02$). However, according to the Bonferroni corrected significance level of $P = 0.01$, this issue could not be demonstrated, although there is a trend for significance. Change in severity of dystonia at 9-15 months after DBS neither is a factor of predictive value for change in global quality of life 9-15 months after operation (linear regression, corr. $r^2 = 1.8$, $F = 3.8$, $P = 0.08$).

3.7. Variables of predictive value

Furthermore, we tried to find factors of predictive value for our first outcome parameter, i. e. change in dystonia according to the BFMDRS-M both at 2-6 months after operation and 9-15 months after DBS.

Preoperative severity of dystonia

The change in dystonia according to the BFMDRS-M as a function of preoperative severity of dystonia referring to the preoperative score of the BFMDRS-M is shown in Figure 24.

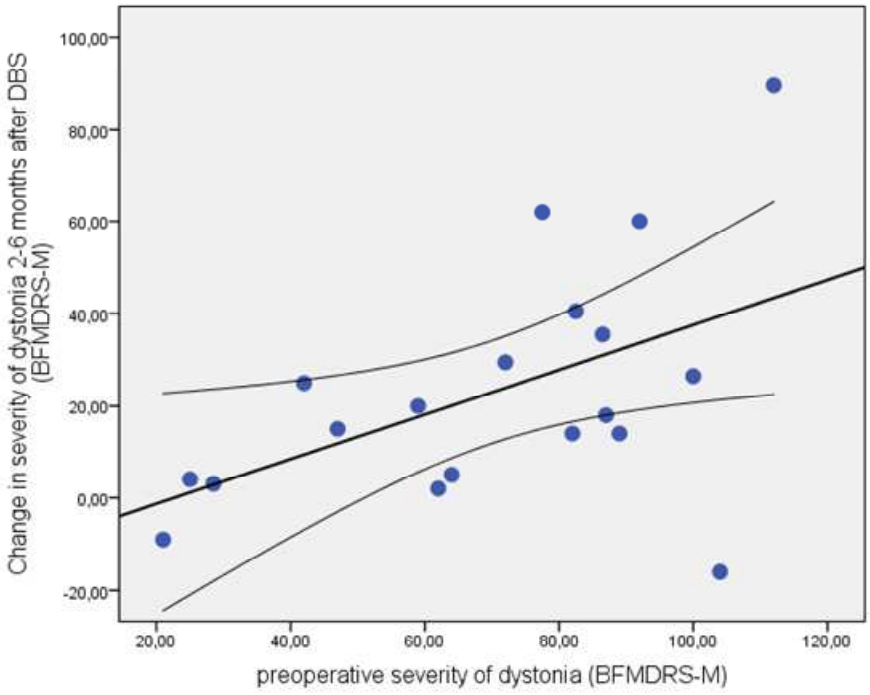

Figure 24: Change in BFMDRS-M (2-6 months after DBS) as a function of the patients` preoperative severity of dystonia according to the BFMDRS-M. Positive values on the y-axis indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale

This association shows by trend that therapy outcome is predictable by preoperative severity of dystonia (linear regression, corr. $r^2 = 0.21$, $F = 5.9$, $P = 0.03$) and consequently might point at the idea that more severely affected patients benefit more from GPi-DBS. These findings however did not show any significance after Bonferroni correction. Therapy outcome at 9-15 months was not predictable by the preoperative BFMDRS-M score neither (linear regression, corr. $r^2 = 0.16$, $F = 3.7$, $P = 0.08$).

Disease duration

Therapy outcome at 2-6 months after DBS is shown as a function of the duration of disease in Figure 25. The duration of disease is defined as the time between onset of first symptoms and electrode implantation.

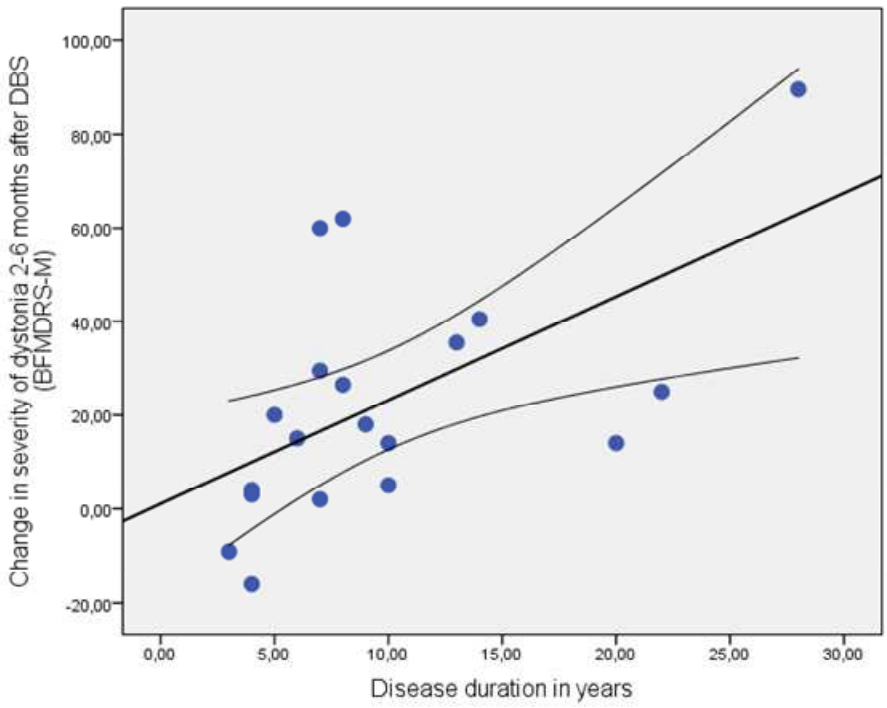

Figure 25: Change in BFMDRS-M (2-6 months after DBS) as a function of the patients` duration of disease. Positive values on the y-axis indicate improvement whereas negative values indicate deterioration.
BFMDRS-M: Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale
DBS: Deep Brain Stimulation

The extent of improvement of severity in dystonia 2-6 months after electrode implantation is predictable by the duration of disease (linear regression, corr. $r^2 = 0.29$, $F = 8.5$, $P = 0.01$). Patients with longer disease duration profit more from GPi-DBS. These patients might suffer from a subtype of NBIA being less fulminant and thus slower in progress. However, at the 9-15 months interval, therapy outcome shows a trend to be predictable by disease duration, but this correlation was not significant any more after Bonferroni correction (linear regression, corr. $r^2 = 0.21$, $F = 4.7$, $P = 0.049$).

Other factors that were available before electrode implantation, such as age at onset of disease or age at operation did not show predictive value in terms of therapy outcome.

We tested the correlation between therapy outcome and effective voltage calculated after Rehncrona et al. (Rehncrona et al., 2004), but we could not identify a certain amount of effective voltage being particularly effective in our patient sample.

3.8. Accompanying medication

We registered pharmacological anti-dystonic therapy in 21 patients out of 23 in the period of 2-6 months after DBS and in 17 patients within the time frame of 9-15 months after electrode implantation.

After 2-6 months of continuous neurostimulation 8 patients (38.1%) were able to reduce their antidystonic medication while in nine other patients (42.9%) pharmacological treatment remained unchanged and four of the patients (19%) had to increase drug therapy.

Compared to the preoperative status, eight patients (47.1%) had reduced anti-dystonic medication 9-15 months after DBS electrode implantation whereas five patients (29.4%) still were under the same treatment and four patients (23.5%) received increased medication.

3.9. Physiotherapy, occupational therapy and logopaedia

20 patients replied to the question whether they were under accompanying physiotherapy, occupational therapy and/or logopaedia.

15 of them (75%) did have perioperative supporting treatment whereas five of them (25%) did not. Due to data instability, it has not been possible to analyze the effect of these accompanying therapies on dystonia.

3.10. Adverse events

22 out of 23 patients replied to the question whether adverse events or side effects occurred in the perioperative or postoperative period. Two neurologists (L. T. and A. P.) examined according data and classified adverse events and side effects as follows:

a) Surgical adverse events, i.e. events that occurred within a period of 30 days after electrode implantation and which were due to the surgical procedure.
b) Stimulation-related adverse events, i. e. adverse events that were due to neurostimulation and that were reversible after adaptation of stimulation parameters.
c) Device-related adverse events, i.e. effects that could be referred to technical problems of the implanted stimulation system.
d) Patient-related adverse events, i.e. all other events that were correlated with the

disease itself, its progression and related complications.

Surgical adverse events

Patient 2 presented with a wound healing disorder in the abdominal field of the Internal Pulse Generator (IPG) implantation. The day after DBS surgery, patient 9 sustained a dystonic exacerbation with a following open fracture of the left femur. The initial dystonic exacerbation improved after some days of GPi-DBS and the patient presented with an excellent long-term outcome.

Stimulation-related adverse events

Patient 1 suffered from blepharospasms under monopolar stimulation but did not represent this symptom any more when consecutively bipolar stimulation was applied. In patient 8, mild worsening of gait and balance was observed after initial programming which resolved when stimulation parameters were adapted. Pat 9 initially complained about phosphenes and paresthesia due to neurostimulation, which was reversible after adjustment of stimulation parameters. Patient 10 reported hyperkinetic movements of neck and trunk when voltage of stimulation was increased too quickly. Patient 21 suffered from worsening of pre-existing gait freezing under increased applied amplitude on deeper contacts.

Device-related adverse events

Leakage of electricity occurred in one lead of patient 20, which generated symptoms such as paraesthesias around the IPG. Apart from this event, she was not able to see for half a day. After 22 months after surgery, which was outside of the formal observation period, patient 3 showed a dislocation of the IPG and cables, which had to be corrected surgically.

Patient-related adverse events

In five patients, severe adverse events were reported. Unfortunately, two of these patients succumbed to their disease.

Patient 4 developed aspiration pneumonia after two years of continuous neurostimulation. Unfortunately, she did not recover from this complication and succumbed to her disease, which was outside the observation period.

Patient 7 was referred to elective DBS but suffered a dystonic crisis with respiratory insufficiency before he could be scheduled. DBS was applied in order to relieve severe generalized muscle contractions. Regrettably, invasive therapy in combination with intrathecal baclofen did not show any effect and the patient died six weeks after the surgical intervention.

Patient 3 suffered a subluxation of the left hip. An osteotomy procedure was conducted nine months after DBS surgery with following complications such as necrosis of the head of the femur and chondrolysis. Clinical condition was persistently dominated by corresponding symptoms.

Seven months after electrode implantation patient 1 was afflicted with a severe viral infection with hospitalisation and subsequent decline of motor control and speech.

Six months after surgical electrode implantation patient 12 had a serious fall and from then on his physical condition continuously deteriorated.

4. Discussion

Our results show that GPi-DBS helps in NBIA-dystonia. We found a significant improvement in severity of dystonia and in quality of life both at the short-term- (2-6 months) and the long- term (9-15 months) assessment after surgical treatment.
According to the BFMDRS-M, dystonia significantly improved from baseline to 2-6 months after operation by 26.5 points (35.7 %). At the 9-15-months follow-up, severity of dystonia still turned out to be 23.3 points (31.4 %) less severe than before DBS. Anyhow, there was no significant change in dystonia between the 2-6 months- and the 9-15 months interval. Similarly, we could demonstrate a significant improvement in dystonia according to the Barry-Albright Dystonia Scale after 2-6 months of continuous neurostimulation and after 9-15 months after DBS. Change between the 2-6 months and the 9-15 months follow-up was not significant. According to our first outcome parameter, after 2-6 months of DBS-treatment, 57.9 % of included patients showed an improvement in severity of dystonia of more than 20 % and at the long-term interval, 73.3 % had improved by more than 20 %.
Likewise, we found a significant improvement in dystonia according to subjective ratings by doctors, patients and caregivers 2-6 months after continuous neurostimulation. Improvement of severity of dystonia between baseline and 9-15 months after DBS turned out to be significant as assessed by patients and caregivers but it did not show any significance for the physicians` ratings within the identical sample. This might be due to a recall bias caused by patients and caregivers, but at the same time might reflect subjective positive recognition of DBS-efficacy by patients and their caregivers.

Quality of life as globally assessed by caregivers significantly rose by 2.7 points from baseline to 2-6 months after surgery on a scale from 0 – 10, 0 being no quality of life at all and 10 being the best imaginable quality of life. Thereafter, quality of life declined slightly, but after 9-15 months under continuous DBS, it still showed a significant improvement of 2.4 points in comparison to the preoperative situation. Change between the 2-6 months and the 9-15 months follow-up was not significant. After 2-6 months of DBS, 55 % of the caregivers quoted an improvement of 3 points or more and at 9-15 months after surgery, 47.1 % still recognized a global improvement of 3 points or more.
According to the subjective rating of quality of life before and after DBS by patients and caregivers, the estimation of improvement in quality of life approximately seemed to correspond for both groups. Even though, change in quality of life at the 9-15 months

interval according to the patients did not show any significance after Bonferroni correction. This might be the case, because the corresponding cohort for the patient assessment was smaller, as quality-of-life estimations were less available in paediatric and sometimes psychiatrically affected patients. We collected summed-up CCHQ scores for 13 patients, and improvement of quality of life according to the CCHQ did not show significance after Bonferroni correction, although there was a trend for significance. This might also be due to few data sets, which probably were difficult to assess retrospectively for caregivers and patients. Since the CCHQ (Nemer McCoy et al., 2006) is aligned with children, its application in partially adolescent or adult NBIA-patients might meet some difficulties. Therefore, the revision of few segments might be reasonable in order to create an adolescent/adult version.

Decrease in disability was less remarkable than decrease in severity of dystonia. Disability in every-day-life ameliorated by 3.2 points (15.5 %) from baseline to 2-6 months after DBS according to the BFMDRS-D, which failed to reach significance. At the 9-15-months follow-up disability presented with a 2.2 points-improvement (10.6 %) as compared to baseline, which was not significant. Likewise, the difference between the 2-6 months and the 9-15 months interval was not significant. 2-6 months after DBS, 35.0 % out of the patient sample showed an improvement in disability of more than 20 % and 9-15 months after DBS, 31.25 % presented with a clinical improvement of more than 20 %. As the BFMDRS Disability scale has been established for primary torsion dystonia, it might be not well suited for NBIA-patients. In NBIA, there are often other kinds of movement disorders of extrapyramidal or pyramidal origin, causing further disabling features. Therefore, initial disability might persist even with reduced dystonia due to other symptoms that are part of the complex clinical picture. Moreover, the BFMDRS-D might not respect smaller ameliorations that at the same time might lead to improvement in quality of life. For example, it distinguishes between `wheelchair bound´ and `walking with assistance´, but does not take into account the autonomous transfer into and out of the wheelchair or the independent control of it.

Based on our findings we postulate that an improvement in disability in every-day-life depends on an improvement in severity of dystonia, greater improvement in dystonia being associated with a more remarkable decline in disability.

Likewise, our results imply that there is a trend for improvement in quality of life being associated with improvement in severity of dystonia, even if the appropriate correlation did not show significance after Bonferroni correction. At the same time, one should take in consideration that improvement in quality of life in dystonic patients does not exclusively depend on abatement of dystonia itself, but also reflects less pain, fewer stigmas due to reduced disability and better emotional health (Mueller et al., 2008). In our patient sample, in 47.1 % antidystonic medication could be reduced over a time of 9-15 months after DBS. In further 29.4 % out of the patient sample, antidystonic medication remained unchanged up to 9-15 months. Considering the progressive character of NBIA, we believe that this phenomenon was due to DBS-effectiveness. Since antidystonic medication often causes severe side effects such as drowsiness, this is an important aspect, which over time might allow positive change in quality of life.

Our retrospective study might possibly indicate factors of predictive value for efficacy of GPi-DBS in different NBIA-patients. Accordingly, our data might point at more severely affected patients having a more remarkable benefit from the surgical intervention. In NBIA, dystonia often develops rapidly, presenting prominent dystonic postures that however are not necessarily correlated with orthopaedic problems. This might be an explanation why GPi-DBS still helps in severely affected patients in whom fixed skeletal deformities do not play a role, yet.

Furthermore, there are hints on a better therapy outcome in patients with a longer duration of disease. Possibly, by this aspect, the situation of patients with a slower and thus less fulminant disease progression is alluded. Patients with less severe disease manifestation might still profit from GPi-DBS after longer disease duration.

Vidhailet and colleagues (Vidhailhet et al., 2005) did not find factors of predictive value testing gender, age, duration of disease and total scores or sub scores of preoperative dystonia and disability according to the BFMDRS in primary generalized dystonia under GPi-DBS-treatment. The authors argue that this effect might be ascribed to the small number of 22 patients being included in their prospective trial. Yet they found hints being suggestive for a greater benefit in dystonia patients with phasic movements than those with tonic posturing. These finding provide an eventual basis for analysis of predisposing factors for responders and non-responders in further studies.

There is a mild deterioration visible between the 2-6 months- and the 9-15 months-interval for dystonia, disability and quality of life, even if these differences are not significant. Since NBIA is a progressive disorder, we ascribe this phenomenon to disease progression while exhaustion of DBS-effectiveness seems to be less probable. Naturally, one always must take into account a strong observer bias, which is probable to occur in open studies. However, the placebo effect in DBS in dystonia has been shown to be considerably small in a double blind trial (Kupsch et al., 2006).

Since NBIA is a very rare disorder it has been necessary to put available data from all over the world together in order to coordinate a scientific study on GPi - Deep Brain Stimulation with a number of patients high enough to provide reliable information. Therefore, we tried to reach as many patients as possible to join this trial. Nevertheless, some patients might not have been included, possibly because they have not been organized within patient organisations or because they have been treated in DBS-centres that were not able or willing to participate.

Due to the many different centres, different physicians and consequently different clinical approaches that contributed to this project, data instability, heterogeneity of data and correct interpretation of data are critical aspects within this trial. Since included patients have been treated in different DBS-centres all over the world, different surgical techniques leading to target point variability might play a role. Furthermore, a probable interrater variability has to be considered. Comella and colleagues analyzed three dystonia rating scales in view of reliability, interrater correlation, and ease of use among primary dystonia patients (Comella et al., 2003). The Unified Dystonia Rating Scale (UDRS) was scored very difficult, whereas the Global Dystonia Scale (GDS) was estimated very easy by investigators. The BFMDRS was the third scale being included within the mentioned analysis, which seemed to be an expedient compromise regarding ease of use and clinical relevance. All three scales showed excellent internal consistency and good to excellent correlation among the raters.

Our intent was to have assessment of dystonia confirmed by blinded video rating, but too few videos, reflecting the clinical status at all three examination time points were available. The retrospective character of this study is one of the major causes for several participating centres not being able to provide the whole information, which has been requested, and therefore data sets of some patients, which have been included within the analysis remained incomplete. Moreover, retrospective studies often bear the risk of a

recall bias. The observer bias is another difficulty to deal with in this open trial. On the other hand, a double-blinded approach among these severely affected and often minor patients might be critical to justify from the ethical point of view. An alternative method for further studies might be the comparison between NBIA-patients who choose to be treated by DBS and those who choose not to.
Appropriate scales for NBIA-patients are not available to date and scales that have been validated for other entities of dystonia are difficult to apply in this heterogeneous patient group. Nevertheless, we used the BFMDRS to define our first outcome parameter, since there are already other publications about NBIA-dystonia (Castelnau et al., 2005) and about other forms of dystonia (Vidailhet et al., 2005; Kupsch et al., 2006) that used this scale. This approach allows the comparison with other studies and the conduction of meta analyses. NBIA-patients are often minor, but since NBIA is a rare disease, many affected patients are followed by neurologists who are not always familiar with paediatric scales.

From the mathematical point of view, percentaged change in the BFMDRS has to be seen critically because theoretically `zero´ could result as baseline. Nevertheless, percentaged results were involved, as the BFMDRS is a well-established and validated scale and therefore, the result `zero´ is not likely to appear in dystonic patients. There are other publications that depicted percentaged change in dystonia and disability according to the BFMDRS (Castelnau et al., 2005; Vidailhet et al., 2005; Kupsch et al., 2006). Since among our subjective scales from 0-10, the result `zero´ was very common, we did not reflect according percentaged change. At the same time, the informative value of total change among these subjective scales might be disputable.

The advantage of our survey is that we considered all available data sets that fulfilled our inclusion criteria. That means, that we took into account all NBIA-patients treated by GPi-DBS regardless of outcome, and consequently data sets of patients who scarcely responded or who did not respond at all to GPi-DBS were included. At the same time, data have been carefully assessed, collected and evaluated by experts in this clinical field. Thus, we believe that this study realistically reflects effectiveness of GPi-DBS in NBIA-dystonia. Although there were patients with non-favourable outcome, the mean improvement of severity of dystonia and the mean improvement of quality of life turned out to be significant according to our data. Therefore, the results of this retrospective multi-centre trial can be considered as very positive and encouraging.

Castelnau and colleagues, investigating on the benefit of GPi-DBS in six PKAN-dystonia-patients, found a mean global motor improvement of 74.6 % according to the BFMDRS and a corresponding mean disability improvement of 53 %. Both results were significant. Evaluation of therapy outcome was carried out in the first trimester after surgery when treatment benefit was detectable in all patients and results remained stable over time with a mean follow-up of 20.6 months. Furthermore they demonstrated that effectiveness of DBS does not depend on severity of preoperative dystonia and that improvement within the disability score strictly correlates with the improvement on the motor score (Castelnau et al., 2005).

We detected an improvement within the BFMDRS Dystonia movement scale which was less pronounced but still significant. In our patients, BFMDRS disability did not significantly improve. According to Castelnau and colleagues (Castelnau et al., 2005), our data indicate that improvement in disability might be correlated with improvement in dystonia.

There was no significant difference among patient characteristics between the current survey and the study by Castelnau et al., such as mean age at operation, disease duration or age at onset of disease. Since the Castelnau-group is known to have a lot of experience within DBS-treatment of secondary forms of dystonia, their patient sample might have been selected with more expertise than the patients included in our survey. Likewise, the adjustment of stimulation parameters over time might have been conducted based on greater experience. The pulse-width being applied in the Castelnau-patients was explicitly higher than in our cohort. However, in our sample, applied stimulation parameters extremely differed between various DBS-centres and therefore analysis was conducted by evaluating the applied effective voltage (Rehncrona et al., 2003) in each patient. Yet, it was not possible to identify a correlation between applied effective voltage and therapy outcome. Considering our small patient sample and heterogeneity in disease presentation, this is not surprising. Accordingly, larger studies exploring the efficacy of DBS-treatment in more homogeneous dystonia-patient groups have neither managed to determine certain stimulation settings being more or less effective (Vasques et al., 2009).

In the current study, all patients who fulfilled defined inclusion criteria were considered, regardless of outcome. In particular, we included one patient who died six weeks after surgery due to a dystonic crisis which was already observable before the operation and which did not resolve under DBS. Another patient died two years after continuous

neurostimulation due to aspiration pneumonia. In the study by Castelnau and colleagues, no lethal outcome was reported.

All patients included by Castelnau and colleagues were positive for the PANK2-mutation. In our cohort, when genetical testing was available, all patients had PKAN except for one. Thus, it was not possible to conduct a subanalysis exploring different therapy outcomes in PKAN- and non-PKAN-patients. Nevertheless, we believe that the preoperative clinical picture is a stronger predictor of DBS-efficacy than genetical status. Accordingly, we identified preoperative high severity of dystonia as being predictive for a positive therapy outcome whereas the Castelnau-group found that DBS-efficacy does not depend on preoperative severity of dystonia (Castelnau et al., 2005). Other studies about primary dystonia even demonstrated that patients with more severe preoperative dystonia had less benefit from DBS (Vasques et al., 2009). Moreover, it has been shown that in primary generalized dystonia, underlying fixed skeletal deformities, getting worse with a longer disease duration, strongly influence DBS-outcome, since at a certain point they appear to be not reversible any more (Vasques et al., 2009; Isaias et al., 2008). The frequent devolution of rapid dystonic episodes in NBIA and the associated presentation of acute severe generalized dystonia without already fixed skeletal deformities might be a reason for GPi-DBS being effective in severely affected NBIA-patients.

Additionally, we found a better therapy outcome in patients with longer disease duration. Considering the episodic disease course in many NBIA patients, we postulate that a long duration of disease is not necessarily correlated with irreversible orthopaedic problems. As already mentioned above, we believe that NBIA patients with a long aetiopathology might be affected by a subtype characterized by a slower and thus less severe course.

Umemura and colleagues reported the case of a patient who had been suffering from Hallervorden-Spatz Syndrome (patient 12) for 28 years when he underwent DBS at the age of 36 (Umemura et al., 2004). After three months of continuous DBS, the BFMDRS Dystonia movement scale had improved by 89.5 points. Yet, the authors postulate to apply surgical treatment much earlier within the course of disease because of already existing orthopaedic deformities that could not be modulated by DBS. Nevertheless, this case might underline our finding of GPi-DBS being still effective after a long duration of disease.

Krause and colleagues published a 5-year long-term follow-up of a PKAN-patient (patient 10) aged 13 at time of surgery (Krause et al., 2006). They were able to demonstrate a dramatic improvement within the BFMDRS one year after electrode implantation as compared to baseline. The motor-score decreased from 92/120 points preoperatively to 30/120 points assessed one year after the surgical intervention. After five years of continuous neurostimulation, the motor-score had regained 70/120 points, however corresponding to an over-all long-term improvement. Although Krause and colleagues observed a progressive deterioration of dystonia within the years after electrode implantation, with this case report they could demonstrate a clear long-term benefit of GPi-DBS for their NBIA-patient.
We found that DBS-efficacy in our patient population was slightly decreased at the 9-15 months follow-up as compared to 2-6 months after surgery. While at this time dystonia still was significantly improved, this did not apply to disability. Krause and colleagues gave account of an enduring improvement in both dystonia and disability over a period of five years, even though deterioration over time was obvious.

Although we found on average a significant improvement in dystonia at both the short term- and the long term- follow-up, there were patients within our cohort, who remained unchanged or who even worsened during the observation period. Other studies have already reported variable response to GPi-DBS in other forms of dystonia, although correct localisation of electrodes was assured (Vidailhet et al., 2005; Vercueil et al., 2002; Volkmann et al., 2002).

To date, a distinct explanation of dystonia patients responding variably to GPi-DBS is still missing, but in NBIA-patients who do not respond to GPi-DBS, one could think of the GPi being a critical target, since GPi-degeneration is known to be pathognomonic in NBIA. Therefore, other target points might possibly be more effective in these often severely affected patients. So far, thalamic DBS in NBIA-dystonia has been reported to be effective in some cases of NBIA- dystonia, as it has even been shown to be more efficient in some individuals with secondary forms of dystonia than the pallidal approach (Vercueil et al., 2001). We had to exclude one patient from analysis because electrode implantation was not performed targeting to the GPi but to the caudal zona incerta. This treatment appeared to be very effective since the patient improved by 74 points according to the BFMDRS-M from baseline to 2-6 months and at the 9-15 months interval, she even

presented with a positive change of 90.5 points in severity of dystonia. Despite these likewise encouraging examples, alternative target points for DBS in NBIA-dystonia are still subject to research.

The averaged extent of clinical improvement regarding dystonia was less pronounced in our patient sample than it has been reported for primary generalized dystonia, where a median improvement of 51 % has been observed as assessed by the movement score (Vidailhet et al., 2005). A larger study has been published by Cif and colleagues who documented a mean improvement of 71 % in 15 DYT1-positive patients, of 74 % in 17 subjects suffering from dystonia of unknown aetiology, and of 31 % in 21 cases of secondary dystonia due to various reasons at the 1-year- follow-up (Cif et al., 2003). Lower mean response to the surgical treatment among the secondary dystonia group is ascribed to the frequent occurrence of hypertonia of pyramidal origin, which interferes with dystonic features. This aspect might be of interest in terms of therapy prognosis. Furthermore, long-term DBS outcome highly depends on the progression of disease (Cif et al., 2003). These and other data (Tronnier and Fogel, 2000; Krause et al., 2004) might be suggestive for GPi-DBS being more effective in primary dystonia than in some forms of dystonia secondary to structural brain defects (Alkhani et al., 2000). The extent, the character and the localisation of lesions being responsible for dystonic symptoms might underlie various responsiveness to DBS treatment within secondary forms of dystonia (Vercueil et al., 2002). On the other hand, well-controlled studies about GPi-DBS in primary generalized and segmental dystonia observed non-responders in their patient samples, too and it has not been possible to identify factors that predicted response to DBS. In particular, the hypothesis that genetic status (DYT1 mutation) might influence therapeutic outcome, could not be confirmed (Vidailhet et al, 2005; Kupsch et al., 2006).

In summary, our data demonstrate the effectiveness of GPi-DBS in NBIA and in a first step, they furnish important details concerning individual indications for this promising therapy. However, considering the heterogeneous outcome in our patient sample, larger and better-controlled studies will be needed in order to find an evidence-based answer to the question which patients are going to profit from GPi-DBS and which patients potentially do not. From the present point of view, we recommend operating on patients, when available pharmacotherapy gets insufficient to control disabling dystonia or when antidystonic medication, which is needed to control severe dystonic symptoms, generates

side effects that have a considerable negative effect on quality of life. On the other hand, DBS-surgery should be conducted, as long as irreversible, severely disabling orthopaedic complications have not developed, yet. Side effects of stimulation have been shown to be reversible in most cases of our patients and no lethal outcome due to DBS-surgery has been observed. Perioperative risk in GPi-DBS is considered to be quite low when conducted within experienced centres (Vercueil et al., 2002; Joint et al., 2002) and therefore we believe, that GPi-DBS should be taken in consideration in severe NBIA-dystonia even in minor patients, when dystonic symptoms get uncontrollable by pharmacotherapy.

Currently our study group is engaged with a prospective trial investigating on the effectiveness of GPi-DBS in NBIA-dystonia. Key interests of this prospective project are to include the highest possible number of patients, to avoid data heterogeneity and data instability and to allow a long-term follow-up of NBIA-patients under DBS-treatment. We believe that a large and well-controlled study is necessary to create a database, which will enable us to better predict therapy outcome in this heterogeneous patient group.
Based on hints resulting from this first retrospective data-analysis, our future intent is to create a treatment algorithm and to offer to NBIA-patients, to their families and their treating physicians the best information we can provide.

5. Summary

NBIA, previously known as the Hallervorden-Spatz Syndrome, is a rare neurologic disorder with familial occurrence and is associated with iron accumulation particularly in the Globus Pallidus and Substantia Nigra pars reticulata (SNr) (Hallervorden and Spatz, 1922; Dooling et al., 1974). According to Gregory and Hayflick (Gregory and Hayflick, 2005) the common term NBIA delineates all progressive extrapyramidal medical conditions with brain iron accumulation within the basal ganglia and consequently includes PKAN being responsible for 50-70 % of all NBIA-cases, neuroferritinopathy, aceruloplasminemia as well as all cases with unknown cause of the disease. Depending on the NBIA-subtype, predominant features such as dystonia, spasticity, rigidity and resulting gait disorders as well as psychiatric signs and cognitive impairment occur possibly already in early childhood or later in adolescence and present with a fast or a slower progressive or episodic course (Hayflick et al., 2003).

Since pharmacotherapy in NBIA-related dystonia is considered to be limited (Justesen et al., 1999) and GPi-DBS has been successfully introduced in other forms of dystonia (Coubes et al., 1999; Kumar et al., 1999; Tronnier and Fogel, 2000; Cif et al., 2003; Krauss et al., 2003; Krause et al., 2004; Kupsch et al., 2006), the application of this modern invasive therapy in NBIA has become a matter of debate among these young and often minor patients.

So far, there are few single publications, most of them case reports (Umemura et al., 2004; Sharma et al., 2005; Krause et al., 2006; Koyama and Yagishita, 2006; Clement et al., 2007; Shields et al., 2007; Mikati et al., 2008) including a report about a series of six patients (Castelnau et al., 2005) that predominantly describe the strong benefit of GPi-DBS in NBIA.

Therefore, we considered a retrospective multi-centre analysis of all international available data of NBIA-patients treated with GPi-DBS as very important. Our intent was to summarize the worldwide experience in this field and to find out which NBIA-patients might profit to a certain extent from DBS.

Patient characteristics such as gender, age at appearance of first symptoms, age at time of operation, genetic status and MRI findings were registered. For analysis of therapy results, we used standardized tests as well as subjective scales. We asked treating physicians to quantify change in dystonia (Burke-Fahn-Marsden Dystonia Rating Scale – Dystonia movement scale) and in disability (Burke-Fahn-Marsden Dystonia Rating Scale

– Disability scale) and we asked patients and caregivers to evaluate change of quality of life (subjective evaluation of patients and caregivers on a scale from 0 to 10) due to surgical treatment. In order to quantify therapy outcome, severity of dystonia, degree of disability and quality of life were assessed before operation, 2-6 months and 9-15 months after continuous DBS. Furthermore we asked for applied stimulation settings, accompanying medical treatment, physiotherapy, complications and clinical course. Our primary outcome parameter was the difference in severity of dystonia. 2-6 months after the intervention, severity of dystonia had improved by an average of 35.7 % and at the 9-15 months interval it still showed a mean improvement of 31.4 %. After 9-15 months 73.3 % of patients showed an improvement of more than 20 %. Disability did not improve significantly. According to subjective ratings by the caregivers, quality of life had medially improved by 2.4 points on a scale from 0 to 10 at the long term interval.

As it had already been described previously (Umemura et al., 2004; Castelnau et al., 2005; Krause et al., 2006; Koyama and Yagishita, 2006; Clement et al., 2007; Shields et al., 2007; Mikati et al., 2008), we likewise were able to demonstrate a significant and long-lasting benefit of GPi-DBS in NBIA over a maximum time course of 9-15 months for our patient population.

Our data allow the assumption of a positive correlation between improvement in dystonia and positive change in disability. Moreover, our results indicate that DBS might be more effective in more severely affected patients with a longer duration of disease but larger and more precise studies will be needed in order to ascertain factors of predictive value.

Currently our study group is engaged with a prospective trial investigating on the effectiveness of GPi-DBS in NBIA-dystonia. Key interests of this prospective project are to include the highest possible number of patients, to avoid data heterogeneity and data instability and to allow a long-term follow-up of NBIA-patients under DBS-treatment.

Based on hints resulting from this first retrospective data-analysis our intent is to find an evidence-based answer to the question which patients are going to profit from GPi-DBS and which patients potentially do not. Our ultimate ambition is to create a treatment algorithm in order to offer to NBIA-patients, to their families and their treating physicians the best information we can provide.

Zusammenfassung

NBIA, vormals bekannt als Hallervorden-Spatz Syndrom, ist eine seltene neurologische Erkrankung, die familiär gehäuft auftritt und durch Eisenablagerungen, insbesondere im Globus Pallidus und in der Substantia Nigra pars reticulata, charakterisiert ist (Hallervorden und Spatz, 1922; Dooling et al., 1974). In Übereinstimmung mit Gregory und Hayflick (Gregory and Hayflick, 2005) bezeichnet der Begriff NBIA alle progressiven, extrapyramidalen Beschwerdebilder, die mit Eisenablagerungen in den Basalganglien einhergehen und schließt daher sowohl PKAN, die für etwa 50-70 % aller NBIA-Fälle verantwortlich ist, Neuroferritinopathie, Aceruloplasminämie als auch alle Fälle mit unbekannter Ursache der Erkrankung ein. Abhängig vom jeweiligen NBIA - Subtyp treten krankheitsdominierende Symptome wie Dystonie, Spastik, Rigor und daraus resultierende Gangstörungen, aber auch kognitive Einschränkungen oder psychiatrische Auffälligkeiten auf. Diese Zeichen manifestieren sich möglicherweise bereits im frühen Kindesalter oder später und unterliegen einem unterschiedlich schnellen, progressiven oder episodischen Verlauf (Hayflick et al., 2003).

Da die medikamentöse Behandlung der NBIA - assoziierten Dystonie nur eingeschränkt möglich ist (Justesen et al., 1999) und die Tiefe Hirnstimulation im Globus Pallidus internus (GPi-THS) im Rahmen der Therapie von anderen Formen der Dystonie in den letzten Jahren erfolgreich angewendet wurde (Coubes et al., 1999; Kumar et al., 1999; Tronnier and Fogel, 2000; Cif et al., 2003; Krauss et al., 2003; Krause et al., 2004; Kupsch et al., 2006), wird die Tiefe Hirnstimulation (THS) nun auch für die oft sehr jungen, mehrheitlich minderjährigen NBIA-Patienten diskutiert.

Bislang gibt es einige wenige Studien – mehrere Fallberichte (Umemura et al., 2004; Sharma et al., 2005; Krause et al., 2006; Koyama and Yagishita, 2006; Clement et al., 2007; Shields et al., 2007; Mikati et al., 2008) und einen Bericht über eine Reihe von sechs PKAN-Patienten (Castelnau et al., 2005) –, die mehrheitlich die gute Wirksamkeit der GPi-THS bei medikamentös nicht behandelbarer, generalisierter NBIA-Dystonie beschreiben.

Basierend auf dieser Datenlage wurde eine retrospektive, multizentrische Analyse aller erhältlichen Daten von NBIA-Patienten, die bislang mit GPi-THS behandelt werden, durchgeführt. Ziel war es, die weltweiten Erfahrungen in diesem Feld zusammenzufassen und möglicherweise herauszufinden, welche NBIA-Patienten in welchem Umfang von der THS profitieren.

Wir registrierten Patientencharakteristika wie das Alter zu Beginn der Symptomatik, das Alter zum Zeitpunkt der Operation, das Geschlecht der Patienten, genetische Auffälligkeiten und radiologische Merkmale. Um die Therapieergebnisse zu analysieren, benutzten wir sowohl standardisierte Tests als auch subjektive Bewertungsskalen. Dabei wurde zusätzlich die subjektive Einschätzung der behandelnden Ärzte, der Patienten und der Pfleger untersucht. Daten wurden in den Bereichen „Dystonie“, „Behinderung“ und „Lebensqualität“ vor der Operation, 2-6 Monate und 9-15 Monate danach erhoben. Außerdem fragten wir nach angewandten Stimulationsparametern, nach begleitender Pharmako- und Physiotherapie, nach Komplikationen der Behandlung und nach dem klinischen Verlauf. Als primärer Ergebnisparameter galt der Unterschied in der Ausprägung der Dystonie im Verlauf.

Wir konnten eine signifikante und anhaltende Wirksamkeit der GPi-THS im Bereich der Schwere der Dystonie und in der Lebensqualität über einen maximalen Zeitraum von 9-15 Monaten bei unserem Patientenkollektiv zeigen.

Der durchschnittliche Wert der BFMDRS Dystonia movement scale, der als wichtigster Parameter die Ausprägung der Dystonie quantifiziert, hatte sich 2-6 Monate nach dem Eingriff um durchschnittlich 26.5 Punkte (35.7 %) ($P < 0.01$) verbessert und zeigte auch noch 9-15 Monate danach eine durchschnittliche Verbesserung um 23.3 Punkte (31.4 %) ($P < 0.05$). 2-6 Monate nach dem Eingriff konnten BFMDRS-M-Daten von 19 Patienten evaluiert werden: 11 von ihnen (57.9 %) hatten sich um mehr als 20 % verbessert. Im 9-15 Monats-Intervall zeigten 11 von 15 Patienten (73.3 %) eine Verbesserung um mehr als 20 %. Dieser Trend zeigte sich ebenso am Verlauf der Schwere der Dystonie gemessen an der Barry-Albright-Scale: 2-6 Monate nach kontinuierlicher THS war die durchschnittliche Ausprägung der Dystonie signifikant um 5.1 Punkte rückläufig (22.7 %) ($P < 0.005$). 9-15 Monate nach dem Eingriff war der Wert der Dystonie im Vergleich zum Ausgangswert um 4.6 Punkte geringer ausgeprägt (20.4 %) ($P < 0.01$). Weiterhin wurde der subjektive Therapieerfolg der THS anhand einer Skala von 0-10 erfragt, wobei 10 für die ausgeprägteste, generalisierte Dystonie steht und 0 das Fehlen der Symptomatik beschreibt. Die behandelnden Ärzte schätzten den Rückgang der Dystonie zum 2-6-Monats-Intervall subjektiv als signifikant ein, wohingegen nach ihrer Beurteilung die Verbesserung der Symptomatik 9-15 Monate nach Behandlung keine Signifikanz mehr erreichte. Patienten und Pfleger hielten hingegen den Therapieerfolg gemessen an der subjektiven Einschätzung der Dystonie sowohl kurz- als auch langfristig für signifikant.

Die Behinderung, gemessen an der BFMDRS Disability scale, zeigte keine signifikante Verbesserung nach Implantation der Elektroden.

Pfleger beurteilten die Lebensqualität subjektiv auf einer Skala von 0-10, wobei 0 für keine Lebensqualität und 10 für die beste vorstellbare Lebensqualität steht. Dabei bewerteten sie die Verbesserung der Lebensqualität um durchschnittlich 2.7 Punkte ($P < 0.01$) zum 2-6 Monatsintervall ($P = 0.008$) und um durchschnittlich 2.4 Punkte ($P < 0.01$) 9-15 Monate nach dem chirurgischen Eingriff im Vergleich zum Ausgangswert. Nach 2-6 Monaten unter THS empfanden elf von 20 Pflegekräften (55 %) eine Verbesserung der Lebensqualität um 3 Punkte oder mehr. Drei Pfleger (15 %) schätzten die Verbesserung um weniger als 3 Punkte und sechs von ihnen (30 %) nahmen die Lebensqualität als unverändert oder sogar verschlechtert wahr. 9-15 Monate nach der Operation konnten 17 Einschätzungen durch die Pflegekräfte erhoben werden. Acht dieser Datensätze (47.1 %) sprachen für eine Verbesserung der Lebensqualität um mindestens 3 Punkte, drei (17.6 %) zeigten eine Verbesserung um weniger als 3 Punkte und sechs der befragten Pflegekräfte (35.3 %) beschrieben eine Verschlechterung oder keine Veränderung.

Unsere Ergebnisse deuten darauf hin, dass ein Zusammenhang zwischen dem Rückgang der Dystonie und der Abnahme des Schweregrades der Behinderung besteht, wobei die Schwere der Behinderung mit der Besserung der Dystonie abnimmt (2-6 Monate nach THS: lineare Regression, corr. $r^2 = 0.62$, $F = 28.4$, $P < 0.001$). Weiterhin fanden wir Hinweise darauf, dass ein Rückgang der dystonischen Symptomatik mit einer Verbesserung der Lebensqualität einhergeht, es zeigte sich hierfür jedoch keine Signifikanz.

Laut unseren Ergebnissen könnte die GPi-THS möglicherweise bei schwerer betroffenen Patienten und bei längerer Krankheitsdauer wirksamer sein. Es sind jedoch größere und genauere Studien nötig, um Faktoren mit prädiktivem Wert herauszufiltern.

In zukünftigen Projekten soll die Wirksamkeit von GPi-THS bei NBIA-Dystonie prospektiv erforscht werden, mit dem Ziel, eine möglichst hohe Zahl an Patienten in diese Untersuchung einzuschließen und Datenheterogenität und Dateninstabilität zu vermeiden. Außerdem soll so eine Langzeitstudie für NBIA-Patienten geschaffen werden, die innerhalb eines bestimmten Protokolls mit THS behandelt werden.

Auf Hinweisen basierend, die aus unserer ersten, retrospektiven Datenanalyse stammen, möchten wir eine evidenzbasierte Antwort auf die Frage finden, welche Patienten am meisten von der GPi-THS profitieren und welche Patienten möglicherweise keinen Nutzen daraus ziehen. Letztendlich ist es unser Ziel, einen Therapie-Algorithmus zu

entwickeln, um NBIA-Patienten, ihren Angehörigen und ihren behandelnden Ärzten die bestmögliche Beratung zukommen zu lassen, die wir mit der bisherigen Datenlage bieten können.

6. References

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Dystonia in neurodegeneration with brain iron accumulation: outcome of bilateral pallidal stimulation

Brain (2010) 133(3): 701-712 first published online March 5, 2010
doi:10.1093/brain/awq022

8. Appendix

Appendix 1: Nosology of NBIA

In the literature, it is widely referenced that in 1922 Julius Hallervorden and Hugo Spatz first described a paediatric, rather heterogeneous clinical picture characterized by a certain neurological symptomatology including movement disorders and cognitive impairment associated with iron deposit particularly within the Globus Pallidus and Substantia Nigra (Hallervorden and Spatz, 1922). This has been referred to as the Hallervorden-Spatz Syndrome for the following decades.

Wigboldus and Bruyn presented a comprehensive review about all familial and solitary cases consistent with the disease that had been documented up to the late 1960s (Wigboldus and Bruyn, 1968). They concluded a tentative classification of four categories, considering age at time of onset and clinical course.

In 1974, Dooling and colleagues established a classification of the Hallervorden-Spatz Syndrome into three main subgroups with regard to clinical as well as to pathologic criteria. They assigned all cases showing a disease pattern most similar to that reported by Hallervorden and Spatz, to group I. All these patients suffered from typical involuntary motor disorders and cognitive deterioration with onset in early childhood and progressive course. Histopathologic examination revealed most notably symmetric lesions within the GPi and SNr with spheroids and iron accumulation. Group Ia was composed of patients with familial occurrence, whereas group Ib included all sporadic cases. Group II patients showed a corresponding clinical picture but neuropathologic variations, i.e. involvement of the GPi but normal findings in the Substantia Nigra. Finally, pathologic criteria of Group III included those of group I, but their clinical presentation extremely differed (Dooling et al., 1974).

Halliday, observant of the variety of manifestations, suggested in 1995 to dedicate the term “Hallervorden-Spatz Disease” to the paediatric cases with familial cumulative appearance, and to describe the remainder as “Hallervorden-Spatz Syndrome” (Halliday, 1995).

After a first causative gene defect had been identified on chromosome 20p12.3-p13 (Taylor et al., 1996), Zhou and Gordon (Zhou et al., 2001; Gordon, 2002) postulated to implement the name “Pantothenate Kinase Associated Neurodegeneration” (PKAN), with reference to the defect on chromosome 20 encoding for pantothenate kinase 2 (PANK2).

Due to Julius Hallervorden`s and Hugo Spatz`s unethical activities during the Third Reich (Shevell, 1992) and due to new genetic findings being responsible for a great part of cases affected by this disease, effort was made to establish a more modern nomenclature of the syndrome.

In this review the name “Hallervorden-Spatz Disease” or “Hallervorden-Spatz Syndrome” is retained when necessary, e.g. to cite reports about historically diagnosed patients with the disease.

Appendix 2: PKAN

According to Hayflick and colleagues, this genetic aberration forms the basis of all classic cases of NBIA and approximately of 35 % of atypical NBIA-cases (Hayflick et al., 2003).

In PKAN the classic early onset type with beginning of symptoms before age six and/or fast episodic and progressive course has to be distinguished from the atypical form which most commonly begins at the mean age of 14 and is characterized by a slow progress in its pathology (Hayflick et al., 2003, Gregory and Hayflick, 2005).

The classic form of the disease is mainly characterized by a complex of movement disorders (Hayflick et al., 2003). Probably, these movement disorders are generated by functional interferences within the basal ganglia (Dooling et al., 1974). One of the leading symptoms is dystonia (Hayflick et al., 2003) which is defined as a "syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures" (Fahn, 1988). Generalized dystonia involves segmental crural regions and other body parts (Fahn, 1988). Further features are dysarthria and spasticity, rigidity and choreoathetosis, the latter ones resulting in gait disorders and loss of ambulation 10 to 15 years after disease onset (Gregory and Hayflick, 2005). This clinical picture may be accompanied by cognitive impairment and psychiatric signs (Dooling et al., 1974; Thomas et al., 2004).

The atypical subtype rather exhibits prominent palilalia and dysarthria (Hayflick et al., 2003) and often shows pronounced psychiatric features (Williamson et al., 1982; Morphy et al., 1989). Motor symptoms occur obligatorily, but are regarded as less severe than in classic PKAN (Gregory and Hayflick, 2005).

Corticospinal tract involvement, pigmentary retinopathy and optic atrophy are presumed to be corroborative features within PKAN (Gregory and Hayflick, 2005).

A homozygous or compound heterozygous mutation on the PANK2 gene causes a defect of Pantothenate Kinase (Zhou et al., 2001). Probably, the mitochondrial isoform is affected (Hortnagel et al., 2003). Pantothenate Kinase is a key regulatory enzyme in the synthesis of Coenzyme A (CoA) deriving from Pantothenate (Vitamin B 5) (Abiko, 1967; Rock et al., 2000). Intermediary metabolism, fatty acid synthesis and degradation, neurotransmitter and glutathione metabolism highly depend on sufficient supply of CoA (Zhou et al., 2001; Gregory and Hayflick, 2005). The type of gene mutation with corresponding consequences covering different deficits in enzyme activity up to complete

loss of Pantothenate Kinase seems to determine the phenotype's severity of clinical signs (Hayflick et al., 2003; Hartig et al., 2006; Matarin et al., 2006). Gregory and colleagues presume that energy and lipid dyshomeostasis lead to oxidative stress with subsequent membrane defects and apoptosis involving particularly the basal ganglia and retina (Gregory and Hayflick, 2005). Beside the decreased to absent level of CoA, accumulation of decomposition products within enzyme metabolism such as N-Pantothenoyl-Cysteine and Pantetheine could play a role within the pathogenesis.

Given the heterogeneity of PANK2-mutations, the clinical presentation of symptoms differs among the PKAN- group (Matarin et al., 2006; Hartig et al., 2006).

PKAN-negative cases of NBIA present with corresponding clinical features, although often different in course and severity (Hayflick et al., 2003).

Appendix 3: Diagnosis in NBIA

Iron deposits visible macroscopically as rust-brown pigmentation in the area of the Globus Pallidus and the Substantia Nigra were described as a distinctive feature for the disease (Hallervorden, 1924). Histochemical findings revealed axonal spheroids and pigmentary granules among other abnormal structures found particularly in the Globus Pallidus and the SNr (Yanagisawa et al., 1966).

Modern radiological diagnostics provide the possibility to identify NBIA-patients (Tanfani et al., 1987; Sethi et al., 1988) and even point at a distinction between PKAN and non-PKAN (Gregory and Hayflick, 2005). High iron in the basal ganglia becomes noticeable as hypointense signals on T2-weighted MRI (Drayer et al., 1987; Mutoh et al., 1988; Sethi et al., 1988; Tanfani et al., 1987). There is a helpful criterion, particularly typical of the PKAN-forms of the disease (Hayflick et al., 2003): the "eye of the tiger sign" (Sethi et al., 1988). It is characterized by a hyperintense centre within a hypointense Globus Pallidus. The hyperintensity which is consistent with increased water content seems to reflect a zone of cellular damage (Ostergaard et al., 1995) accompanied by oedema and necrosis (Gregory and Hayflick, 2005), whereas the hypointense regions represent iron accumulation (Drayer et al., 1987; Gregory and Hayflick, 2005; Sethi et al., 1988; Savoiardo et al., 1993). This radiological sign can even be observed in the pre-symptomatic phase and therefore might be of predictive quality (Hayflick et al., 2001). Hayflick and colleagues found a strict correlation between the occurrence of the "eye of the tiger sign" and the PANK2-mutation, the sign becoming more evident over time (Hayflick et al., 2003; Hayflick et al., 2006). In contrast, Hartig (Hartig et al., 2006), Kumar (Kumar et al., 2006) and Baumeister and colleagues (Baumeister et al., 2005) could not verify the correlation between the "eye of the tiger"-appearance and the PANK2-mutation.

Since the causative gene of the major form of NBIA has been identified (Taylor et al., 1996), genetical confirmation of PKAN can be obtained (Zhou et al., 2001).

Appendix 4: Pathomorphological correlates in NBIA

Abnormal neuronal signals generated within the pallido-thalamocortical pathway are supposed to play a role within the evolution of dystonia and other hyperkinetic disorders (Ford, 2004). In dystonia-patients who underwent pallidotomy, decreased – in comparison to Parkinson's Disease-patients – and irregular firing rates in the GPi and Globus Pallidus externus (GPe) were found by microelectrode recordings (Lenz et al., 1998; Vitek et al., 1999). In this context, higher severity of dystonia has been observed on the side contralateral to lower frequencies of GPi output (Lozano et al., 1997; Kumar et al., 1999). However, these results could not be confirmed by Tronnier and Fogel who did not ascertain slower firing patterns in the medial Globus Pallidus in dystonia patients (Tronnier and Fogel, 2000).

The current model of dystonia implicates the reduction and irregularity of tonic inhibitory GPi firing rates resulting in excessive excitatory output from the centromedian and the ventrolateral thalamic nuclei. The increased thalamic output leads to increased activity of the cerebral cortex and consequently to abnormal, overreaching, involuntary movements (Vitek and Giroux, 2000).
In contrast to hemiballismus- and Parkinson's Disease-patients, an augmentation in activity of pallidal sensory neurons was found in dystonia patients, which might be characteristic for dystonia (Lenz et al., 1998).

One important pathomorphological correlate, which also denominates the disease, is iron accumulation within the basal ganglia, especially in the Globus Pallidus (Dooling et al., 1974) being approximately 2.5 to three times higher as in a healthy brain (Környey, 1964; Vakili et al., 1977). Studies presume that the increased cell iron concentration in the basal ganglia originates from process modification (Swaiman et al., 1983) and correlates with increased cell iron uptake (Szanto and Gallyas, 1966; Vakili et al., 1977).

In 1985, Perry and colleagues (Perry et al., 1985) found increased levels of cysteine in the Globus Pallidus in a patient with Hallervorden-Spatz Disease and assumed that iron accumulation might be secondary to this phenomenon possibly composing cysteine-iron-chelat-complexes. From today's point of view, cystein accumulates in the affected cells as an excessive metabolite within the pathway of CoA synthesis due to metabolic

dyshomeostasis in PKAN (Zhou et al., 2001). Iron content is physiologically very high in the Globus Pallidus and the SNr, which has been discovered based on the examination of rat brains (Hill and Switzer, 1984). Cysteine leads to production of free radicals in the presence of iron and therefore causes oxidative stress and deoxyribonucleic acid (DNA) damage (Yoon et al., 2000). Similarly in aceruloplasminemia, a defect within iron homeostasis causes oxidative stress by lipid peroxidation which might play a role for basal ganglia damage (Miyajima et al., 1996).

Further pathomorphological correlates in the Hallervorden-Spatz Syndrome are spheroid bodies, neuronal loss and gliosis and are symmetrically conspicuous particularly within the Globus Pallidus and Substantia Nigra. The spheroid bodies likewise contain iron (Koeppen and Dickson, 2001). Axonal spheroids can also be identified microscopically within the cerebral cortex, the cerebellum and within the brain stem, but particularly within the basal ganglia (Halliday, 1995).
Morphologically, two distinctive features were delineated in the Globi Pallidi of two Hallervorden-Spatz Disease diagnosed patients: on the one hand, there was very dense tissue consisting of dystrophic axons, reactive astrozytes and residual neurons; on the other hand, there were areas of porous tissue characterized by vacuolization. In the context of these findings high iron deposit was mainly detected within the Globus Pallidus where increased mineralization was pronounced in central regions (Savoiardo et al., 1993).

Based on these results and on further literature, Halliday describes the pallidal triad of iron deposition, axonal spheroids and gliosis being typical of the Hallervorden-Spatz Syndrome (Halliday, 1995).

These analyses show that in NBIA pathomorphological aberrations concentrate on the Globus Pallidus and Substantia Nigra, but are not limited to those.
Accordingly, hypometabolism in striatal and pontocerebellar structures could be demonstrated in an NBIA-patient by positron emission tomography (PET) (Castelnau et al., 2001). Furthermore, NBIA was associated with excessive lipofuscin in cortical neurons and in the grey matter of the central nervous system (Defendini et al., 1973).
Moreover, an extracerebral manifestation becomes noticeable by presence of lipofuscin in bone marrow macrophages and possibly also in circulating lymphocytes (Swaiman et

al., 1983) as well as by detection of acanthocytes in the hematogram (Roth et al., 1971; Swisher et al., 1972; Higgins et al., 1992; Luckenbach et al., 1983; Tripathi et al., 1992).

Acanthocytosis (Higgins et al., 1992) and excessive lipofuscin (Luckenbach et al., 1983) might be correlated with coexisting lipid dyshomeostasis in NBIA (Tripathi et al., 1992). Therefore, it has to be added that disorders in lipid metabolism, amongst those lipid peroxidation, play an important role within the pathogenesis of the Hallervorden-Spatz Syndrome (Park et al., 1975; Tripathi et al., 1992). The enzyme Phospholipase A2 (PLA2) is also known to be critical in lipid metabolism (Balsinde and Balboa, 2005) and plays a key role in cell membrane homeostasis (Baburina and Jackowski, 1999). The most recent genetic discovery in the context of NBIA is a defect of the PLA2G6 gene, which generates a deficiency of PLA2 (Morgan et al., 2006).

Appendix 5: Deep Brain Stimulation (DBS)

Figure 26: Deep Brain Stimulation System with bilateral subcortical electrodes, connecting wires and subcutaneously implanted Internal Pulse Generator (IPG)
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Electric neuromodulation for therapeutic purpose has got a long history and, over time, it has been applied with the objective to alleviate a broad variety of pathologic neurological conditions (Gildenberg, 2005).

Beginnings of deep brain surgery for movement disorders go back to the early 1940s, when surgeons tried to relieve patients from tremor or rigidity, for instance by placing targeted lesions within the basal ganglia or ablating various parts of the basal ganglia, including Globus Pallidus, Caudate and Putamen as well as pallidofugal fibres. After having performed such a procedure, amelioration in patients with Parkinson's Disease and dystonia was obtained (Meyers, 1942; Riechert, 1962). Effort was made to improve techniques and reduce perioperative risk in the following decades (Talairach et al., 1950; Hassler et al., 1960; Markham and Rand, 1961; Riechert, 1962; Cooper, 1976b). Simultaneously, electric stimulation was widely performed for diagnostic investigations. Lack of appropriate devices prevented implementation of long-term DBS and consequently, lesion surgery dominated the therapeutic field (Gildenberg, 2005).
Finally in 1982, continuous DBS was introduced for the treatment of movement disorders (Siegfried and Lippitz, 1994b).

Although its mechanism is not clearly understood yet (Benazzouz and Hallett, 2000; Dostrovsky and Lozano, 2002), the reversibility and the adaptability of DBS and its

reduced risk as compared to the setting of bilateral ablative lesioning (Schuurman et al., 2000) are strong arguments in favour of this more modern technique (Coubes et al., 1999; Tronnier and Fogel, 2000). An assessment among tremor patients undergoing thalamotomy and/or thalamic stimulation could demonstrate a significant difference concerning the incidence of adverse events up to 6 months after surgery; thalamic stimulation was the procedure with lower perioperative risk (Schuurman et al., 2000).

With DBS, it has become possible to modulate deep brain activity in a controlled and adjustable manner (Kringelbach et al., 2007). From the current point of view, high-frequency DBS is supposed to either trigger or inhibit neuronal activity in the stimulated brain region (Vitek, 2002). Its effect is based on physiological properties of the brain tissue, which in certain diseases might be altered, and on the stimulation parameters` setting. Frequency (Hz), pulse-width (µs) and amplitude (V) differ with various therapies and involved brain structures. Moreover, DBS effects depend on the electrode position and on whose geometric relation to the surrounding tissue (Kringelbach et al., 2007).
Medtronic, Inc. (Minneapolis, MN) has developed different DBS leads equipped with four cylindrical platinum contacts. Electrodes with different contact distances are utilized for targeted brain structures of various dimensions (Alterman et al., 2004) (Figure 27).

Figure 27: Photograph showing the Medtronic, Inc., DBS leads. Each is equipped with four cylindrical contacts. Length of the electrode on the right side of the photograph, is reduced, whereas the inter-contact distances are shortened.
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Depending on the volume, which is clinically required to be stimulated, it is possible to activate one or more contacts within the electrode. Subsequent adaptation of stimulation parameters relies on the patient's symptomatic course (Coubes et al., 2002). Change of amplitude has an influence on the volume of tissue being affected by stimulation. The

modulation of pulse-width seems to result in a various number of stimulated neuronal cells and in the stimulation of different cell types (e.g. neuronal soma or axons) (Shields et al., 2007).
In movement disorders, DBS electrodes are predominantly implanted in the basal ganglia (Kringelbach et al., 2007). The Nucleus subthalamicus (STN) is considered as a safe and effective target in Parkinson's Disease (Bergman et al., 1990; Aziz et al., 1991) and high-frequency stimulation (130 - 185 Hz) of the STN has shown a marked long-term benefit in affected patients (Bittar et al., 2005a; Krack et al., 2003). In dystonia and spasmodic torticollis, neurosurgeons primarily target to the GPi (Bittar et al., 2005b) in order to apply high-frequency stimulation with broader pulse width (starting from 210 µsec) and higher voltage (2.2 – 7.0 V) in comparison to Parkinson's Disease treatment (Krauss et al., 2004). The ventral intermediate nucleus of the thalamus (Vim), however, represents an expedient target in parkinsonian tremor (Lenz et al., 1994).

The nuclear target is planned by use of standard stereotactic imaging or image fusion (Krauss et al., 2004).

Classically, coordinate calculation is performed indirectly according to standard human brain atlases (Starr et al., 1999), such as the Schaltenbrand-Wahren Atlas, which refers to the intercomissural line and to a perpendicular erected on the middle point between the anterior and posterior comissure (Schaltenbrand and Wahren, 1977).
Alternatively deep brain target localisation can be realized based on mere three-dimensional magnetic resonance imaging and visual recognition (Vayssiere et al., 2002; Coubes et al., 2002). Electrophysiological determination of the target point, which is supposed to be important for appropriate target localisation (Guridi et al., 1999; Starr et al., 1999; Tronnier and Fogel, 2000), is a matter of debate in very young patients, since it prolongs the surgical session and is not necessarily needed (Vayssiere et al., 2000; Coubes et al., 2002).
Exact electrode implantation is conducted with the aid of a stereotactic head frame. A precoronal burr hole is made, one on each side, and DBS-leads are lowered slowly and accurately to the target point (Coubes et al., 2002; Krauss et al., 2003).
The procedure is performable under local anaesthesia which allows immediate detection of macrostimulation side effects such as visual flashes or contralateral tonic muscle contractions (Krauss et al., 2004), but intraoperative immediate effects of DBS on tonus are unlikely to be observed (Tronnier and Fogel, 2000; Krauss et al., 2004).

Children most frequently are implanted under general anaesthesia, which is discussed to be utilized in all dystonia patients in order to eliminate intraoperative dystonic movements and to keep hemodynamic conditions constant (Coubes et al., 2004).

Within a second surgical procedure, an Internal Pulse Generator (IPG) is implanted subcutaneously e.g. within the abdominal area under general anaesthesia and is connected to the previously inserted DBS-electrodes (Coubes et al., 2002; Coubes et al., 2004).

Appendix 6:
Standardized scale, which was sent to all participating international centres including all parameters, which have been collected within our study. "Patient Data Part I" contains issues to be answered by the treating physicians whereas "Patient Data Part II" aims at aspects that predominantly had to be answered by patients and their caregivers.

PATIENT DATA PART I

1. Patient's date of birth (dd/mm/yy)	
2. Gender (male/female)	
3. Date of operation (dd/mm/yy)	
4. Patient's age at operation	
5. Patient's age at time of onset of symptoms	
6. Genetics (gene mutations, e.g. PANK, PLA2G6)	
7. Patient's age at time of diagnosis	
8. MRI-findings (please see 1.)	
9. Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) before operation; Disability Scale (please see 2.)	
10. BFMDRS before operation; Motor Scale (please see 2.)	
11. BFMDRS 2-6 months after operation; Disability Scale	
12. BFMDRS 2-6 months after operation; Motor Scale	
13. BFMDRS 9-15 months after operation; Disability Scale	
14. BFMDRS 9-15 months after operation; Motor Scale	
15. Global dystonia before operation according to treating physician (please see 3.)	
16. Global dystonia 2-6 months after operation according to treating physician	
17. Global dystonia 9-15 months after operation according to treating physician	
18. Mini Mental Status before operation	
19. Mini Mental Status after operation	
20. Target point of DBS (please see 4.)	
21. Stimulation setting and Stimulation parameters 2-6 months after operation (please see 5.)	
22. Stimulation parameters 9-15 months after operation	
23. Adverse events observed in the peri- and postoperative phase up to 15 months after operation	

24. Side effects of stimulation and system complications	
25. Physiotherapy, occupational therapy, logopaedia: if yes, when and how often?	
26. Accompanying medication before operation	
27. Accompanying medication 2-6 months after operation	
28. Accompanying medication 9-15 months after operation	
29. Remarks	

1. MRI-Findings: - eye of the tiger: yes/no
   - other MRI-abnormalities
2. BFMDRS (Disability Scale): **0** = normal; **30** = maximum
   BFMDRS (Motor Scale): **0** = normal; **120** = maximum
3. Global clinical rating of severity of dystonia by the treating physician:
   0 = no dystonia; **10** = most severe generalized dystonia
4. Please refer to Schaltenbrand coordinates**.**
5. Monopolar/bipolar; which pole is active? Pulse frequency in Hz; pulse width in µsec; pole amplitude in V.

PATIENT DATA PART II

1. Global dystonia before operation according to patient (please see 1.)	
2. Global dystonia 2-6 months after operation according to patient	
3. Global dystonia 9-15 months after operation according to patient	
4. Global dystonia before operation according to caregiver	
5. Global dystonia 2-6 months after operation according to caregiver	
6. Global dystonia 9-15 months after operation according to caregiver	
7. Dystonia according to "Barry-Albright Dystonia Scale" before operation (please see 2.)	
8. Dystonia according to "Barry-Albright Dystonia Scale" 2-6 months after operation	
9. Dystonia according to "Barry-Albright Dystonia Scale" 9-15 months after operation	
10. Quality of life before operation according to patient (please see 3.)	
11. Quality of life 2-6 months after operation according to patient	

12. Quality of life 9-15 months after operation according to patient	
13. Quality of life before operation according to caregiver	
14. Quality of life 2-6 months after operation according to caregiver	
15. Quality of life 9-15 months after operation according to caregiver	
16. Quality of life according to "Care and Comfort Hypertonicity Questionnaire" before operation (please see 4.)	
17. Quality of life according to "Care and Comfort Hypertonicity Questionnaire" 2-6 months after operation	
18. Quality of life according to "Care and Comfort Hypertonicity Questionnaire" 9-15 months after operation	

1. Global Dystonia: subjective rating of dystonia post hoc
   0 = no dystonia; **10** = most severe generalized dystonia

2. The "Barry-Albright Dystonia Scale" is a validated scale to assess dystonia in NBIA-patients.
   0 = absence of dystonia; **32** = maximum of dystonia

3. Quality of life: Global subjective rating of quality of life:
   0 = no quality of life; **10** = best imaginable quality of life

4. The "Care and Comfort Hypertonicity Questionnaire" is a validated scale to assess quality of life for NBIA-patients.

Appendix 7:
Burke-Fahn-Marsden Dystonia Rating Scale (Disability scale and Dystonia movement scale) (Burke et al., 1985)

BURKE-FAHN-MARSDEN DYSTONIA RATING SCALE

I. Disability scale

A. **Speech**

0- Normal
1- Slightly involved; easily understood
2- Some difficulty to understand
3- Marked difficulty to understand
4- Completely or almost completely aphonic or anarthric

B. Handwriting

0- Normal
1- Slight difficulty; legible
2- Almost illegible
3- Illegible
4- Unable to grasp, to maintain, to hold a pen

C. Feeding

0- Normal
1- Uses "ticks"; independent
2- Can feed, but not cut
3- Finger food only
4- Completely dependent

D. Eating

0- Normal
1- Occasional chocking
2- Chokes frequently; difficulty swallowing
3- Unable to swallow firm foods
4- Marked difficulty swallowing soft foods and liquids

E. Hygiene

0- Normal
1- Clumsy; independent
2- Needs help with some activities
3- Needs help with most activities
4- Needs help with all activities

Functions↓	
Speech	
Writing	
Feeding	
Eating	
Hygiene	
Dressing	
Walking	
Total Maximum = 30	

F. Dressing

0- Normal
1- Clumsy; independent
2- Needs help with some
3- Needs help with most
4- Helpless

G. Walking

0- Normal
1- Slightly abnormal; hardly noticeable
2- Moderately abnormal; obvious to naive observer
3- Considerably abnormal
4- Needs assistance to walk
6- Wheelchair bound

II. Dystonia movement scale

Segments ↓	Provoking Factor (P)	Severity Factor (S)	Weight (W)	P x S x W
Eyes	0-4	0-4	0.5	0-8
Mouth	0-4	0-4	0.5	0-8
Speech/Swallow	0-4	0-4	1	0-16
Neck	0-4	0-4	0.5	0-8
Right Arm	0-4	0-4	1	0-16
Left Arm	0-4	0-4	1	0-16
Trunk	0-4	0-4	1	0-16
Right Leg	0-4	0-4	1	0-16
Left Leg	0-4	0-4	1	0-16
			Total Maximum = 120	

1. PROVOKING FACTORS (P)

A. All regions (except speech and swallowing)

0- No dystonia at rest or action
1- Dystonia on particular action
2- Dystonia on many actions
3- Dystonia on action of distant part of body; or intermittently at rest
4- Dystonia present commonly at rest

B. Speech and Swallowing

0- No dystonia
1- Occasional either or both
2- Frequent either
3- Frequent one and occasional other
4- Frequent both

2. SEVERITY FACTORS (S)

A. Eyes

0- No dystonia
1- Slight; occasional blinking
2- Mild; frequent blinking without prolonged spasms of eyelid closure
3- Moderate; prolonged spasms of eyelid closure, but eyes open most of time
4- Severe; prolonged spasms of eyelid closure, with eyes closed at least 30 % of time.

B. Mouth

0- No dystonia
1- Slight; occasional grimacing or other mouth movements (e.g. clenched or deviated jaw, forced open mouth, forceful tongue thrusting)
2- Mild; movements in less than 50% of time
3- Almost permanent moderate dystonic movements or contractions
4- Almost permanent severe dystonic movements or contractions

C. Speech and Swallowing

0- Normal
1- Slightly involved; easily understood or occasional chocking
2- Some difficulty to understand or chokes frequently
3- Marked difficulty to understand or unable, to swallow firm foods
4- Completely or almost completely aphonic or anarthric or marked difficulty swallowing soft foods and liquids

D. Neck

0- No dystonia
1- Slightly involved; occasional twisting
2- Evident torticollis, slightly pronounced
3- Moderate twisting
4- Severe twisting

E. Arm

0- No dystonia
1- Slight; no clinical significance
2- Mild; evident dystonia, but no disability
3- Moderate; still able to grasp
4- Severe; unable to grasp

F. Trunk

0- No dystonia
1- Slightly flexed; no clinical significance
2- Evidently flexed; does not interfere with standing or walking
3- Moderately flexed; does interfere with standing or walking
4- Severely flexed; unable to stand or walk

G. Leg

0- No dystonia
1- Slight dystonia; no impairment; no clinical significance
2- Mild dystonia; brisk walking; independent
3- Moderate dystonia; interferes severely with walking; needs assistance to walk
4- Severe dystonia; unable to stand or walk with affected leg

III. Videotaped Assessment

1. Sitting in normal position; arms upon legs a) View showing the full body b) Close-up view showing different parts of body (head and neck, hands, trunk, feet)	45 sec
2. Speech – name, date, swallowing and description of actual problems a) View showing the full body b) Close-up view showing different parts of body	45 sec
3. Arm Holding Test (15 sec) Finger-Nose-Test (five times) Fast consecutive movements of both hands and feet	45 sec
4. Stand up and Stay; 90°-Rotation (four times)	30 sec
5. Walking a) View showing the full body b) Close-up view showing different parts of body	60 sec
6. Writing with each hand Name, date, complete sentence, helix View showing the full body and close-up views	30 sec
Total	4 min 15 sec

Appendix 8:
Barry-Albright Dystonia Scale (Barry et al., 1999)

Barry-Albright Dystonia Scale

Directions: Assess the patient for dystonia in each of the following regions: eyes, mouth, neck, trunk, each upper and lower extremity (8 body regions). Write the scores on the lines provided (whole numbers only). Rate severity based only on dystonia as evidenced by abnormal movements or postures.

Dystonia: sustained muscle contractions causing twisting and repetitive movements or abnormal postures.
Spasticity: velocity-dependent resistance to passive stretch.
Athetosis: distal writhing or contorting movements.
Chorea: brief, rapid, unsustained, irregular movements.
Ataxia: incoordination of movement characterized by wide-based unsteady gait, falling movements.

Eyes: Signs of dystonia of the eyes include: Prolonged eyelid spasms and/or forced eye deviations.
0_____**Absence** of eye dystonia
1_____**Slight.** Dystonia less than 10 % of the time.
2_____**Mild.** Frequent blinking without prolonged spasms of eye closure and/or eye movements less than 50 % of the time.
3_____**Moderate.** Prolonged spasms of eyelid closure, but eyes open most of time.
4_____**Severe.** Prolonged spasms of eyelid closure, with eyes closed at least 30 % of the time.
*_____Unable to assess eye movements.

Eyes:_____

Mouth: Signs of dystonia of the eyes include: Grimacing, clenched or deviated jaw, forced open mouth, and/or forceful tongue thrusting.
0_____**Absence** of dystonia
1_____**Slight.** Dystonia less than 10 % of the time and does not interfere with speech or feeding.
2_____**Mild.** Dystonia less than 50 % of the time and does not interfere with speech or feeding.
3_____**Moderate.** Dystonia more than 50 % of the time, or dystonia that interferes with speech or feeding.
4_____**Severe.** Dystonia more than 50 % of the time or dystonia that prevents speech or feeding.
*_____Unable to assess mouth movements.

Mouth:_____

Neck: Signs of dystonia of the neck include: Pulling of the neck into any plane of motion: Extension, flexion. Lateral flexion or rotation

0____**Absence** of neck dystonia.
1____**Slight.** Pulling less than 10 % of the time and does not interfere with lying, sitting, standing or walking.
2____**Mild.** Pulling less than 50 % of the time and does not interfere with lying, sitting, standing or walking.
3____**Moderate.** Pulling more than 50 % of the time or dystonia that interferes with lying, sitting, standing or walking.
4____**Severe.** Pulling more than 50 % of the time or dystonia that prevents sitting in standard wheelchair, standing or walking (i.e. requires more than standard head rest for seating)
*____Unable to assess neck movements.

Neck:_____

Trunk:

0____**Absence** of trunk dystonia.
1____**Slight.** Pulling less than 10 % of the time and does not interfere with lying, sitting, standing or walking.
2____**Mild.** Pulling less than 50 % of the time and does not interfere with lying, sitting, standing or walking.
3____**Moderate.** Pulling more than 50 % of the time or dystonia that interferes with lying, sitting, standing or walking.
4____ **Severe.** Pulling more than 50 % of the time or dystonia that prevents sitting in a standard wheelchair, standing or walking.
*____Unable to assess trunk movements.

Trunk:_____

Upper Extremities:

0____**Absence** of upper extremity dystonia.
1____**Slight.** Dystonia less than 10 % of the time and does not interfere with normal positioning or functional activities.
2____**Mild.** Dystonia less than 50 % of the time and does not interfere with normal positioning or functional activities.
3____**Moderate.** Dystonia more than 50 % of the time or dystonia that interferes with normal positioning or upper extremity function.
4____**Severe**. Dystonia more than 50 % of the time or dystonia that prevents normal positioning or upper extremity function; i.e., arms restrained in wheelchair to prevent injury.
*____Unable to assess upper extremity movements.

Left Upper Extremity:_____

Right Upper Extremity:_____

Lower Extremities:

0____**Absence** of lower extremity dystonia.

1____**Slight.** Dystonia less than 10 % of the time and does not interfere with normal positioning or functional activities.

2____**Mild.** Dystonia less than 50 % of the time and does not interfere with normal positioning or functional activities.

3____**Moderate.** Dystonia more than 50 % of the time or dystonia that interferes with normal positioning or lower extremity weight bearing or function.

4____**Severe**. Dystonia more than 50 % of the time or dystonia that prevents normal positioning or lower extremity weight bearing or function.

*____Unable to assess lower extremity movements.

Left Lower Extremity:_____

Right Lower Extremity:_____

Total Score:_____ **Rater`s initials:_____**

Appendix 9:
Care and Comfort Hypertonicity Questionnaire (Nemer McCoy et al., 2006)

CARE AND COMFORT HYPERTONICITY QUESTIONNAIRE

Role of person completing form (parent, caregiver, etc):_____
Date:_____

Please rate, how easy or difficult it is for you or your child in the last two weeks to perform the following tasks relative to a cooperative individual without a disability:

Personal Care:

1. Putting on pants?	Very easy 1 2 3 4 5 6 7 Impossible
2. Taking off pants?	Very easy 1 2 3 4 5 6 7 Impossible
3. Putting on a shirt?	Very easy 1 2 3 4 5 6 7 Impossible
4. Changing diapers?	Very easy 1 2 3 4 5 6 7 Impossible
5. Ease of sitting on a toilet seat?	Very easy 1 2 3 4 5 6 7 Impossible
6. Ease of sitting in a bathtub, with or without adaptive equipment?	Very easy 1 2 3 4 5 6 7 Impossible
7. Ease of bathing?	Very easy 1 2 3 4 5 6 7 Impossible
8. Ease of feeding?	Very easy 1 2 3 4 5 6 7 Impossible

Positioning/Transferring:

9. Ease of positioning in a wheelchair?	Very easy 1 2 3 4 5 6 7 Impossible
10. Ease of positioning in a device other than a wheelchair, such as a standing frame?	Very easy 1 2 3 4 5 6 7 Impossible
11. Ease of transferring in and out of a wheelchair?	Very easy 1 2 3 4 5 6 7 Impossible
12. Ease of putting on braces or positioning devices?	Very easy 1 2 3 4 5 6 7 Impossible
13. Ease of controlling his/ her wheelchair?	Very easy 1 2 3 4 5 6 7 Impossible
14. Ease of getting out of a car?	Very easy 1 2 3 4 5 6 7 Impossible
15. Ease of getting in a car?	Very easy 1 2 3 4 5 6 7 Impossible

Please answer the following questions using the scales provided:

Comfort:

16. Is there pain or discomfort during position changes?	Never 1 2 3 4 5 6 7 Always
17. Is there pain or discomfort during diaper changes?	Never 1 2 3 4 5 6 7 Always
18. Does the pain or discomfort prevent your child from participating in school, various programs, or other activities?	Never 1 2 3 4 5 6 7 Always
19. Is your child using pain control medicine?	Never 1 2 3 4 5 6 7 Always
20. Does your child sleep through the night?	Always 1 2 3 4 5 6 7 Never

Interaction/ Communication

21. How easy is it for your child to use communication devices? Very easy 1 2 3 4 5 6 7 Impossible
22. How easy is it for your child to play alone? Very easy 1 2 3 4 5 6 7 Impossible
23. How easy is it for your child to play with other children? Very easy 1 2 3 4 5 6 7 Impossible
24. How easy is it for your child to be completely understood by those who know your child well? Very easy 1 2 3 4 5 6 7 Impossible
25. Does your child have a problem with soaked drooling? Never 1 2 3 4 5 6 7 Continuously
26. My child's self esteem is The best I can imagine 1 2 3 4 5 6 7 The worst I can imagine
27. Describe your child! . Very happy 1 2 3 4 5 6 7 Very unhappy

Appendix 10:
Dystonia Study Group Videotape examination protocol (Comella et al., 2003)

Area assessed	Perspective	Activity
Part 1: Eyes and upper face	Close view of head and shoulders; sitting unsupported in chair without back	▪At rest (10 sec) ▪Eyes open (10 sec close view, 10 sec far view) ▪Eyes closed (10 sec close view, 10 sec far view) ▪Forced eye blinks: 10 repetitions (10 sec)
Part 2: Lower face, jaw, tongue, larynx	Patient seated	▪Close view of face at rest (10 sec) ▪Reading: standardized passage aloud (Rainbow passage). First 3 lines ▪Repeated consonants: Tee, Mee, La, Ca: 5 of each (15 sec) ▪Holding the note "eeee" for 5 sec ▪Count to 10 (5 sec) ▪Tongue protrusion: (5 sec) ▪Opening and closing mouth for 5 repetitions (10 sec)
	Swallow interview	▪Question to patient: Do you have problems with swallowing? If yes, is it occasional or frequent? Do you choke occasional or frequently? Can you swallow firm foods? Liquids?
Part 3: Neck	Seated in chair, close view head and shoulders	▪Frontal view at rest (instruct to allow head to move) (10 sec) ▪Seated with eyes closed (instruct to allow head to move) (10 sec) ▪Quiet conversation for 2 sentences (10 sec) ▪Turn head all the way to right then left ▪Tilt ear to shoulder on each side ▪Look up and look down ▪Lateral view (5 sec) ▪Walking back and forth

		twice (total 20 sec)
Part 4: Shoulders and upper arms, distal arm and hands	Far view of upper half of body	▪Arms extended supinated: 5 sec ▪ Arms extended pronated: 5 sec ▪Arms flexed at elbow in front of chest: 5 sec ▪Finger to nose: 5 repetitions ▪Finger tapping, right than left: 5 repetitions (5 sec) ▪and extend wrists with arms outstretched for 5 repetitions (5 sec) ▪Cup to lips, right than left arm (5 sec) ▪Writing: "Today is a nice day" for 3 repetitions (maximum time 15 sec) ▪Drawing spiral without hand resting on paper; right than left hand (maximum time 10 sec) ▪Hold up spiral
Part 5: Upper leg, distal leg, foot and trunk	Far view entire body, sitting Far view entire body: standing and walking	▪Sitting quietly (10 sec) ▪Heel to toe taps: 5 repetitions on each side (10 sec) ▪Standing frontal view for 10 sec ▪Standing: lateral view for 5 sec ▪Standing: back view for 5 sec ▪Walking: away and toward examiner 20 feet: 2 repetitions (maximum 20 sec)

Appendix 11:
Informed Consent Form

English Written Informed Consent Form

University Hospital Düsseldorf
Department of Neurology
Chairman: Universitätsprofessor Dr. H.-P. Hartung

Project: Treatment Results of Deep Brain Stimulation in Patients with NBIA (formerly Hallervorden-Spatz-Syndrome) und Development of a Treatment-Algorithm

Principle Investigator: Dr. Lars Timmermann, Neurology, University Hospital Düsseldorf, Germany

Name of patient: Date of birth:

DBS-center:

Written Informed Consent:

Dear patient,

you or your child is suffering from a neurological disease called NBIA (neurodegeneration with brain iron accumulation, formerly Hallervorden-Spatz-Syndrome) and was treated with bilateral Deep Brain Stimulation (DBS). We hope that the operation was successful and you benefit from this therapy.
In other diseases (e.g. Parkinson's disease) DBS is well established as a save and successful therapy. However, DBS in patients with NBIA is momentarily an experimental

approach. This means that momentarily only reports about single patients and small series of patients exists that demonstrate that this therapy is successful and save, but, taken together, our knowledge is by far incomplete. Therefore we can momentarily not answer the following questions: 1) which patients with NBIA should be treated with DBS and which patients better not, 2) which parameters of the DBS system have the best chance for improvement and 3) in which time-course can we expect an improvement.
We work in our hospital in close cooperation with the center in which you were operated on the understanding of Movement Disorders and improvements of the DBS-therapy. Therefore we want to ask you to participate in an international study: Your participation is voluntarily, your data will be carefully and anonymously handled and no disadvantages arise if you decide not to participate. The study is supported by the American NBIA Disorders Association and the German sister organization Hoffnungsbaum e.V.

In this study we want to investigate the results of DBS in patients with NBIA. We want to use professional scales of your doctor, if available your video tapes pre- and post operation, but also your own judgement of dystonia and quality of life before and after the operation. Aim of this study is to find out which NBIA patients benefit to which extend from DBS and what are the best stimulation parameters for optimum treatment results. Furthermore, the results of this study should lead to a concrete treatment plan for doctors to make DBS in NBIA patients more successful and saver.
Dr. _____ explained to me extensively the planned study and I agree that my data will be transferred in an anonymous form to the study coordination center in Düsseldorf, Germany. I had enough time to ask all questions and all my questions have been answered satisfactorily. I know that my personal anonymous data can be withdrawn without any reason at any time without any disadvantages for me.

_____ _____

Place, Date Signature Physician/Study nurse

_____ _____

Place, Date Signature Patient

Appendix 12: Individual stimulation parameters 2-6 months after DBS

Patient number	Pulse frequency (Hz)		Pulse width (µs)		Voltage (V)	
	left	right	left	right	left	right
1	145	145	210	210	3.0	3.0
2	130	130	150	150	3.5	3.5
3	130	230	210	210	2.2	2.2
5	120	120	450	450	3.5	3.5
6	60	60	90	90	1.5	1.5
8	100	100	90	150	3.5	2.6
9	130	130	210	210	2.6	2.6
10	185	185	150	150	2.8	2.8
11	185	185	120	120	5.0	5.0
12	130	150	450	450	1.3	1.3
13	130	130	450	450	1.0	1.0
14	130	130	450	450	1.5	1.5
17	215	215	90	90	3.5	3.5
18	190	190	90	90	2.5	2.5
19	130	130	120	120	4.0	4.0
20	60	60	120	120	3.6	3.6
21	130	130	60	60	3.0	3.0
22	180	180	60	60	3.2	3.2
23	60	60	120	120	2.5	2.5

Hz: Hertz; µsec: microseconds; V: Volt

Appendix 13 : Individual stimulation parameters 9-15 months after DBS

Patient number	Pulse frequency (Hz)		Pulse width (µs)		Voltage (V)	
	left	right	left	right	left	right
1	140	145	330	330	3.0	3.0
3	130	130	210	210	2.2	2.2
5	130	130	450	450	2.0	2.0
6	60	60	90	90	2.0	2.0
10	185	185	210	210	3.2	3.2
12	130	130	450	450	1.3	1.3
13	130	130	450	450	1.6	2.0
14	130	130	450	450	1.7	1.7
17	130	130	150	150	3.0	3.0
19	130	130	120	120	4.0	4.0
20	60	60	120	120	3.6	4.6
21	130	130	90	90	3.7	3.7
22	180	180	60	60	3.2	3.2

Hz: Hertz; µsec: microseconds; V: Volt

Appendix 14: effective Voltage (Volt) 2-6 months and 9-15 months after electrode implantation (Rehncrona et al., 2003)

Patient number	Effective Voltage 2-6 months after DBS (Volt)		Effective Voltage 9-15 months after DBS (Volt)	
	left	right	left	right
1	0.52	0.52	0.65	0.66
2	0.49	0.49	n. a.	n. a.
3	0.36	0.48	0.36	0.36
5	0.81	0.81	0.48	0.48
6	0.11	0.11	0.15	0.15
8	0.33	0.32	n. a.	n. a.
9	0.43	0.43	n. a.	n. a.
10	0.47	0.47	0.63	0.63
11	0.75	0.75	n. a.	n. a.
12	0.31	0.38	0.31	0.31
13	0.24	0.24	0.39	0.48
14	0.36	0.36	0.41	0.41
17	0.49	0.49	0.42	0.42
18	0.33	0.33	n. a.	n. a.
19	0.50	0.50	0.50	0.50
20	0.31	0.31	0.31	0.39
21	0.27	0.27	0.40	0.40
22	0.33	0.33	0.33	0.33
23	0.21	0.21	n. a.	n. a.
Mean	0.40	0.41	0.41	0.42

DBS : Deep Brain Stimulation

9. Curriculum vitae

Karolin Wieland

geboren am 02. Juni 1980 in Kaufbeuren
Eltern: Selma Wieland (Gymnasiallehrerin - Romanistik/Anglistik), Helmut Wieland (Studiendirektor – Physik/Mathematik)

1986-1990	Grundschule (Kaufbeuren)
1990-1999	Besuch des Jakob-Brucker-Gymnasiums in Kaufbeuren (naturwissenschaftlicher Zweig)
05/1999	Abitur
1999/2000	Freiwilliges soziales Jahr in Sant´Andrea Frius/Sardinien/Italien
2000/2001	4-monatige Arbeit in der Gastronomie
04/2001	Beginn des Medizinstudiums an der FAU Erlangen/Nürnberg
04/2003	Physikum an der FAU Erlangen/Nürnberg
2003/2004	Auslandsstudienjahr im Rahmen des Erasmus-Austauschprogramms an der Universität von Parma/ Italien
Famulaturen:	- Bezirkskrankenhaus Kaufbeuren, Neurologie, Kaufbeuren (08/2004) - Dr. med. Rainer Schwickert, niedergelassener Facharzt für Allgemeinmedizin und Tropenmedizin, Köln (03/2005) - Hospital Santo Tomas, Infektiologie, Panama City, Panama (09/2005) - St. Franziskus Hospital, Anästhesie, Köln (03/2006) - Dr. med. Th. Schmidt, Facharzt für Kardiologie, Erlangen (04/2006)
2006/2007	Medizinstudium an der Universität zu Köln - Praktisches Jahr am akademischen Lehrkrankenhaus Leverkusen, Wahltertial: Neurologie
02-03/2007	PJ-Auslandsaufenthalt am Royal Melbourne Hospital/ University of Melbourne, Thoraxchirurgie, Melbourne, Australien
seit 04/2007	Promotionsarbeit bei Prof. Dr. med. Lars Timmermann, Neurologie, Klinikum der Universität zu Köln in der AG Tiefe Hirnstimulation und Bewegungsstörungen (Vollzeit von 07/2007 bis 12/2007) Titel: „Wirksamkeit der Tiefen Hirnstimulation im Globus Pallidus internus bei NBIA – Dystonie“
06/2008	Zweiter Abschnitt der Ärztlichen Prüfung an der Universität zu Köln
02/2009-09/2010	Ärztin in Weiterbildung für Innere Medizin an der Klinik Bavaria Kreischa bei Dresden
seit 01/2011	Ärztin in Weiterbildung für Innere Medizin am Krankenhaus Dresden – Friedrichstadt, II. Medizinische Klinik