Aus dem Institut für klinische Neurowissenschaften und medizinische Psychologie

der Heinrich-Heine-Universität Düsseldorf

Direktor Univ.- Prof. Dr. Alfons Schnitzler

Einfluss der Stimulationsrichtung auf die therapeutische Breite der tiefen Hirnstimulation bei Patienten mit essentiellem Tremor

Dissertation

zur Erlangung des Grades eines Doktors der Medizin

Der medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Petyo Nikolov

2020

Als Inauguraldissertation gedruckt mit Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachter: Prof. Dr. med. Alfons Schnitzler

Zweitgutachterin: PD Dr. med. Marion Rapp

Teile dieser Arbeit wurden als Manuskipt veröffentlicht:

Bruno, S., Nikolov, P., Hartmann, C.J., Trenado, C., Slotty, P.J., Vesper, J., Schnitzler, A., Groiss, S.J. (2020), „Directional deep brain stimulation of the ventral intermediate thalamic area for essential tremor increases therapeutic window“ Submitted to Neuromodulation: Technology at the Neural Interface

Weitere eigene Publikationen:

Nikolov, P. *et al.* Cerebellar Involvement in DYT-THAP1 Dystonia. *Cerebellum Lond. Engl.* **18**, 969–971 (2019)

Zusammenfassung

Der essentielle Tremor (ET) ist eine der häufigsten neurologischen Bewegungsstörungen. Für einen Teil der ET Patienten ist die tiefe Hirnstimulation (THS) eine etablierte Behandlungsmöglichkeit. Limitiert wird der tremorsupprimierende Effekt der THS insbesondere, wenn höhere Stimulationsintensitäten für eine suffiziente Tremorsuppression benötigt werden, weil es hierdurch zu Induktion von Nebenwirkungen kommen kann. Da die Fasersysteme in sehr enger topographischer Beziehung zueinanderstehen, sind stimulationsinduzierte Nebenwirkungen durch die Modulation des Stimulationsfeldes nicht immer zufriedenstellend beherrschbar. Vielversprechend erscheinen dabei neuere Stimulationssysteme, weil sie die Anpassung der Stimulationsrichtung durch speziell dafür konfigurierte segmentierte Stimulationselektroden ermöglichen.

Ziel der aktuellen Studie war es deshalb, in einem doppelblinden Design zu untersuchen, ob bei Patienten mit ET und einer THS, die therapeutische Breite durch eine Anpassung der Stimulationsrichtung vergrößert und die klinische Effektivität der THS verbessert wird.

Dabei war die therapeutische Breite primärer Outcome Parameter, während die klinische Effektivität, das Stimulationsvolumen und der Energieverbrauch als sekundäre Outcome Parameter fungierten. In die Studie wurden 10 Patienten eingeschlossen. Es wurden die therapeutischen Breiten der ungerichteten sowie aller drei gerichteten Stimulationen auf der klinisch besten Kontakthöhe bestimmt, wobei die Stimulationsrichtung mit der größten therapeutischen Breite als die beste Stimulationsrichtung eingestuft wurde. Als nächster Schritt wurden klinische Scores sowie kinematische Messungen des Tremors und der Ataxie in drei Konditionen (Stimulation-OFF, ungerichtete Stimulation, beste gerichtete Stimulation) durchgeführt.

Die therapeutische Breite der besten gerichteten Stimulation war signifikant größer als die der ungerichteten Stimulation. Das Stimulationsvolumen bei vergleichbarer Intensität an der Nebenwirkungsschwelle war ebenso größer bei der gerichteten Stimulation. Es gab keine Unterschiede bezüglich klinischer Effektivität und Energieverbrauch zwischen den beiden Konditionen.

Zusammenfassend war die gerichtete Stimulation der ungerichteten Stimulation aufgrund der größeren therapeutischen Breite überlegen. Bezüglich klinischer Effekte und Energieverbrauch war die gerichtete Stimulation genau so effektiv wie die ungerichtete Stimulation. Deshalb sollte primär eine gerichtete THS bei Tremor Patienten vorgezogen werden.

Summary

Essential tremor (ET) is one of the most common movement disorders. Deep brain stimulation (DBS) provides therapeutic opportunity for some ET patients, as it is known to significantly reduce tremor. Nevertheless, tremor suppression effect of DBS is largely limited when higher stimulation intensities are needed. Larger electrical fields, resulting from higher intensities, can spread to neighbouring structures, causing side effects. Because the neuronal pathways are densely arranged, stimulation side effects are not always easy to manage. In this context, modern stimulation devices seem promising because they are equipped with segmented electrodes, permitting an adjustment of the direction of stimulation. It is believed that this so called directional stimulation could reduce side effects.

Hence, the goal of the current study is to investigate if directional stimulation increases therapeutic window and clinical efficacy, compared to conventional omnidirectional stimulation in patients with ET using a double-blind design.

We defined therapeutic window as primary outcome parameter, while clinical efficacy, volume of neuronal activation and energy consumption were secondary outcome paramters. Ten patients were enrolled in the study. Therapeutical windows of omnidirectional stimulation and directional stimulation in three directions at the clinically best level of contacts were compared. The stimulation direction with the largest therapeutic window was defined as best directional stimulation. Next, clinical scores, as well as digital measueremts for tremor and ataxia were obtained in three conditions (Stimulation-OFF, omnidirectional and best directional stimulation).

Therapeutic window was signficantly larger in directional stimulation, compared to omnidirectional. Volume of neuronal activation at similar intensities was also larger in directional stimulation. There were no difference regarding clinical efficacy and energy consumption between the two conditions.

Taken together, directional stimulation was superior to omnidirectional one because of the larger therapeutic window. Regarding clinical efficacy and energy consumption, directional stimulation was as good as omnidirectional. For this reasons, directional DBS should be considered first line for tremor patients.

Abkürzungen

DBS	Deep brain stimulation
dDBS	Directional deep brain stimulation
ET	Essential tremor
GABA	Gamma-amminobutyric acid
HFS	High frequency stimulation
Hz	Herz
ICARS	International Cooperative Ataxia Rating Scale
IPG	Implantable pulse generator
LFS	Low frequency stimulation
mA	Miliamper
MER	Microelectrode recordings
mICARS	Modified International Cooperative Ataxia Rating Scale
mV	Millivolt
oDBS	Omnidirectional deep brain stimulation
PD	Parkinson’s disease
PSA	Posterior subthalamic area
SARA	Scale for the Assessment and Rating of Ataxia
SET	Side effect threshold
SPECT	Single photon emission tomography
STN	Subthalamic nucleus
TEED	Total electrical energy delivered
TETRAS	The Essential Tremor Rating Scale
TT	Therapeutic threshold
TRS	The Tremor Rating Scale
TW	Therapeutic window
V	Volt
VIM	Nucleus ventralis intermedius
VNA	Volume of neuronal activation

Abbildungsverzeichnis

Inhalt

1 Introduction

1.1 Historical underpinnings

Records of tremor in humans date back thousands of years in Egypt, India, Israel, Greece and Rome. The writings of Galen of Pergamon (130–200 AD) and much later reports from the 17th and 18th centuries show that the physicians of those times distinguished between kinetic and rest tremor in their patients (1). Although ancient sources mention different kinds of tremor in the course of history (2), the term essential tremor (ET) was first coined by the Italian physician Pietro Burresi in 1874 (3). During one of his conferences, he described a case of an 18-year-old male with severe action tremor as a single symptom for which another differential diagnosis was not probable. Burresi called it simply essential tremor, the word “essential” placing emphasis on the inert nature of the ailment, which belongs to the body itself and does not come from the outside. Nevertheless, the word “essential” could be misleading, according to some contemporary experts, because it implies a certain sense of desirability or naturalness in the syndrome.

At the end of the 19th century, the term, “essential tremor”, was already in frequent use by neurologists to describe cases of kinetic tremor with hereditary links and to delineate it from other tremor forms (3). One of the first attempts to classify the disease was made in 1983 by Marsden and coworkers, who differentiated four kinds of ET and posed the question of whether the disorder is a single entity or rather a family of diseases with different variations of symptoms (4). In their model they defined four types of ET. Type one was considered to be a form of mild tremor of the hands, which was viewed as an enhanced form of physiological tremor. Type two was seen as more severe, could affect multiple body regions and was caused by dysfunctional central oscillations. Type three was classified as an extremely severe tremor, which often led to a stereotactic operation. And finally, type four was considered to be a non-specific trait of other neurological conditions (e.g., demyelinating neuropathy, dystonia, Parkinson’s disease) (5–7).

Although these classifications for ET are now rejected, the idea of considering ET as a group of movement disorders rather than a single entity is of great

importance and a current subject of debate (8). The classical view of ET as a single monosymptomatic condition has been undermined to make place for a broader view, considering the possibility of ET as a family of diseases, each of them having different etiological, genetic, pathophysiological and clinical aspects (2,9,10). The debate raises new questions concerning this enigmatic condition and is the subject of a significant amount of both clinical and basic scientific research.

1.2 Epidemiology of essential tremor

Essential tremor belongs to the most common neurological conditions. The prevalence information differs considerably in the literature. A study in urban Lagos, Nigeria has shown age-adjusted prevalence of approximately 0.2% for subjects ≥ 40 years (11), whereas researchers from Finland have estimated the prevalence to be 5.5% for the same age group (12). However, the differing design and screening tools should be taken into consideration, as well as the fact that the disorder is more often found in the Caucasian population than in the African population (13).

A study in Istanbul, Turkey from 2009 estimated the prevalence of ET in the population aged over 40 years to be 4%, with no prevalence difference between genders (14). The incidence is reported to be 23.7 per 100,000 patient years, according to a study in Rochester, Minnesota (15). Although there has been little evidenced research on the mortality rate in ET, a study from 2007 in Spain estimated that it had increased (16).

Despite the high occurrence of ET, especially in the elderly population, it seems that a considerable number of cases remain hidden or misdiagnosed (17). This phenomenon could be attributed to the fact that the main clinical feature of the condition, namely the action tremor, overlaps to a great extent with symptoms of other movement disorders such as Parkinson's disease (PD) and dystonia (18). Furthermore, there is growing epidemiological evidence, that ET could be associated with PD (10,19,20), so that the borders between the different clinical pictures could be blurred. Hence, in a clinical setting, such coexistence between several movement disorders, in one patient, would be difficult to discover.

1.3 Clinical features of essential tremor

A tremor is defined as "*A rhythmic and oscillatory movement of a body part with a relatively constant frequency and variable amplitude. It is caused by either alternating or synchronous contractions of antagonistic muscles*" (Jankovic et al. (21)). As the central pacemaker communicates with the motion apparatus through oscillations, a tremor is actually a part of the movement process itself and a requirement for the performance of fast alternating motions (22). Although tremor motions are to some extent physiological, they can be enhanced by certain states of the organism such as hypoglycemia, hypothermia, hyperthyroidism, physical exhaustion and alcohol withdrawal. Psychological factors like stress could also serve as triggers. In this case, the enhanced tremor is considered pathological. In general, tremor becomes pathological when its properties (frequency, amplitude and rhythmization pattern) change (22). Pathological tremor exists also in a number of neurological disorders, including ET.

The different forms of pathological tremor are classified, according to the body posture in which they mainly occur, into two main groups: rest and action tremor. Rest tremor occurs when the musculature is in a relaxed state. It is a typical symptom of Parkinson's disease. Action tremor, on the other hand, presents itself during voluntary movement. Furthermore, action tremor is divided into several subtypes, which overlap significantly. The subtypes are called postural, orthostatic, kinetic, isometric, in addition to the position-specific postural and task-specific kinetic tremor forms (23). Postural tremor presents itself when the affected limb maintains a steady position against gravity, for example, with outstretched arms to the front (24). Orthostatic tremor occurs usually in the lower limbs and trunk during standing. Kinetic tremor is a rather broad definition and describes any tremor that occurs during continuous voluntary movement, for example, writing, eating, pouring a glass of water and so on (2). Kinetic tremor is further divided into simple kinetic (the tremor amplitude remains the same during the whole movement) and intention tremor (where the tremor amplitude increases as the affected limb approaches the visual target). Intention tremor is related to a cerebellar dysfunction. Isometric tremor emerges during rigid muscle contraction (e.g., making a fist). Position-specific postural tremor occurs only while maintaining one certain position. Task-specific kinetic tremor occurs when

performing one certain task (e.g., writing). A mixture of kinetic and postural tremor is typical for ET, which can express itself in separate body regions.

The hallmark of ET is an action tremor of the arms (22). It usually has a frequency of 6–12/sec, which decreases with age (25) and affects both arms. Nevertheless, it can also take place in other body parts such as the neck, jaw, tongue and facial muscles (12), and in the legs (26). Typical for the arm tremor are fast stretching and bending movements of the fingers in contrast to PD, where pronation and supination movements occur (22). It responds favorably to ethanol and has a progressive nature, with the clinical manifestations expanding over time and the tremor becoming more severe (2).

Another feature of ET is that the action tremor can spread from the arms to the head (27). According to a study, published by Hubble et al. (28), head tremor, in combination with arm tremor, affected up to 50% of the ET patients. An isolated head tremor, however, is rather rare and affects 1–10% of ET patients (29). Its directionality appears to change over time (30). In addition, head tremor is observed to be more common in female ET patients, who also had a worse outcome (28). These findings suggest that gender plays a role in the phenotypic expression of ET.

In general, some of the ET symptoms underline a possible cerebellar involvement. Deuschl et al. have observed, with the means of kinematic measurements of the limbs, that the severity of intention tremor among patients with ET is compatible with those patients having known cerebellar damage (31). A way to detect mild cerebellar dysfunction in its early stages is tandem gait testing (32). It has been reported that up to 50% of ET patients in a study group show tandem gait abnormalities in comparison to healthy controls. The tandem gait difficulties were more frequent in older patients and in those ones with longer disease duration, which suggests an age related progression of ET (33). An interesting observation is that despite the tandem gait abnormalities, ET seems to leave the normal gait unaffected (34).

Although the predominant sign of ET is the action tremor, there have also been reports of ET patients with rest tremor. These findings reveal that correctly diagnosing ET can sometimes be difficult. In comparison to PD, where the rest

tremor can affect the legs, in ET patients it was only observed in the arms. With varying prevalence among the different clinical sample groups (1–50%), rest tremor is a sign of an advancing disease (35).

Despite the fact that ET is mainly viewed as a movement disorder, there is growing evidence of further, non-motor features associated with the disease. Reports of olfactory deficit (36) and even abnormalities outside the central nervous system, such as hearing impairment, have been published (37). Moreover, the Body Mass Index of ET patients is known to be lower, probably because of greater energy expenditure due to the tremor (38). Cases with ET have been described as having poorer global cognitive performance and frontal executive function than controls without ET. Forgetfulness among the cases was reported, (39) in addition to higher levels of depression (40). Thus, the neuropsychological findings in ET cases suggest a possible involvement of frontocerebellar circuits. To sum up, the clinical features of ET give the impression that it is expanding in anatomical space and over time. It appears that ET starts to develop in the cerebellum but, in its course, can spread and damage multiple pathways in the brain, causing further abnormalities. Such phenotypic behaviour is well known in other neurodegenerative conditions such as Alzheimer's disease, Huntington's disease and Parkinson's disease. The assumption that ET might be a condition of similar nature raises further questions regarding the etiology and pathophysiology behind it.

1.4 Diagnosis of essential tremor

Since there is no accurate biological or imaging marker for ET (10) the main part of ET diagnosis remains clinical. Patient history and physical examination are important milestones. A typical patient history includes familial predisposition and positive response to ethanol. A significant number of patients also report an early onset age for the tremor. According to the onset time of the tremor, there are juvenile (age of onset ≤ 40 years), presenile and senile (age of onset 75–80 years) variations (41).

It is essential for ET to be clearly defined to reduce confusion and increase diagnostic consistency. The International Parkinson and Movement Disorder Society published a consensus statement in 2018, regarding the classification of ET among other tremor syndromes (23). The classification rests on two main

axes: *First:* clinical features, which describe a syndrome and *Second:* etiology. The advantage of this approach is that it allows a more consistent and detailed description of tremor syndromes. For instance, one tremor syndrome might be caused by multiple etiologies, but multiple etiologies might also flow into one syndrome.

In this relation, ET is defined as an isolated tremor syndrome of bilateral upper limb action tremor, with at least three years' duration, with or without tremor in other locations, as well as absence of dystonia, ataxia or parkinsonism (23). Additional "soft signs" might reflect phenotypic variability and are thus labeled in the diagnostic criteria as "essential tremor plus". They include impaired tandem gait, questionable dystonic posturing, memory impairment, tremor at rest, in addition to further mild neurological signs that are not typical for other diagnoses (23).

A correct diagnosis of ET is a challenging task since experts estimate that 30–50% of the cases first diagnosed with ET, later on prove to be other conditions with similar symptoms. The two main conditions of ET that might exhibit a similar array of clinical features are PD and dystonia.

Other differentiation tools in addition to clinical exploration are still in development. Neurophysiological quantitative analysis methods for the tremor properties, such as accelerometry and surface electromyography (EMG), have been proposed to compare ET and PD. While accelerometry measures the tremor frequency and amplitude, surface EMG can identify synchronous or reciprocal activity of antagonistic muscles (42). However, the comparative studies using those neurophysiological tools show no significant differences between PD and ET (43).

Neuroimaging techniques using single-photon emission tomography demonstrate promising results in distinguishing between the two conditions. The technique uses specially developed tracers that bind to the dopamine transporter in the central nervous system. Being a presynaptic protein, dopamine transporter is less abundant in PD cases, when compared to ET or healthy subjects (44). Thus, neuroimaging might provide a useful supplement to clinical examination.

Finally, the clinician might examine the patient's response to treatment to establish the correct diagnosis (*diagnosis ex juvantubis*). Pharmacological agents that are known to lessen the tremor in PD patients are anticholinergic drugs, dopamine agonists, in addition to direct dopamine substitutes such as levodopa. On the other hand, the therapy of choice for ET includes several β-adrenergic antagonists. Nevertheless, caution is required when using the treatment-diagnostic principle because in both PD and ET groups of patients there are a certain number of responders and nonresponders to the pharmacological therapy (42). Moreover, it has been shown that the effect of the β-adrenergic blocker nadolol is beneficial in both PD and ET patients, so that no differentiation between the conditions based on the therapy is possible (45). Hence, knowledge of the pattern of clinical features in ET is a required skill to establish the right diagnosis.

1.5 Etiology of essential tremor

In the 19th century, disease origins were allotted in three groups according to their heritability: nonheritable (e.g., small pox), partly heritable (e.g., heart disease, cancer) and absolutely heritable conditions (e.g., hemophilia, Friedreich's ataxia, Huntington's disease) (3). Essential tremor appears to follow the principles of the second group, as the disease propagation cannot be fully explained by its heritability links. There is, however, a chance of developing ET when a familial accumulation occurs. In the etiology of ET, a possible gene-environmental interaction could be thinkable, meaning that additional factors besides the genes themselves could influence and trigger the disorder development.

Some genes have a linkage tendency, which means they are very likely to be inherited together because of their topographical location on the chromosome. Such genes may serve as genetic markers for linkage analysis of family members and be associated with conditions that run in the family, when compared to the genetic material of healthy subjects of a control group. Indeed, a linkage analysis of a large American family with Czech origins and known ET distribution among its members showed a possible candidate for an ET-related gene between the gene loci D2S168 and D2S224 on the chromosome 2p22-p25. Furthermore, expanded CAG trinucleotide frequencies were identified and associated with ET in the same study (46). Thus, a parallel could be drawn between the etiologies of

ET and Huntington's disease, where a CAG trinucleotide extension is a known cause of the disorder.

Moreover, there are further complex gene modification processes in addition to the copy number variants that could contribute to the development of ET. Some of them processes could include rare and uncommon effect alleles and *de novo* and gonadal mosaicism or epigenetic changes (47). In this relation, mosaicism describes the formation of cells with different genetic material in one organism, due to mutations. Then, the so-called chimeric organism could present certain abnormalities in comparison to the normal population.

Further, the field of epigenetics studies elucidates the process of turning on and off diverse genes. This process is physiological because it regulates the molecular dynamics of a biological system. In some cases, however, it could be damaged and, thus, causes the development of disorders. Finally, non-coding variations of the genome could also be responsible for ET.

Because of the above-mentioned complexity of the genetic mechanisms of ET, its inheritable patterns are still not fully understood. Furthermore, the research field offers challenges because of the large genotypic and phenotypic heterogeneity of the condition. Essential tremor can currently only be phenotyped through clinical history and examination, which also differ. Consequently, the related genes in the process remain elusive (47).

The disease tends to aggregate in families and first-degree relatives of ET cases are known to have five times higher risk of developing the disorder themselves, compared to controls (48). On the other hand, 30–70% of the diagnosed ET cases tend to have a family history and more than 80% of the patients with the juvenile variation of the disorder report having at least one first-degree relative with ET (49). A study of twins showed a concordance of 60% for monozygotic and up to 27% for dizygotic kinship, which supports a genetic involvement but also implies some additional environmental influence (50).

Thus, several modes of inheritance and transmission are proposed, including both Mendelian and complex disease patterns. Potential genes for ET that follow a Mendelian pattern of inheritance could be *Epithelial-Mesenchymal Transition* genes (EMT1, EMT2, EMT3), as well as the *mitochondrial serine protease gene*

HTRA2 (46,51–53). An example of a complex disease inheritance pattern is the autosomal dominant mode of inheritance with reduced penetrance (47). Possible genes related to ET that follow such an inheritance mode could be *Leucine rich repeat and Ig domain containing 1* (LINGO1) (54) and the *solute carrier family* gene (SLC1A2) (55).

According to some experts, the nature-nurture principle could well apply for the development of ET. Indeed, the environment could play a modifying role with certain susceptible genotypes (2). A number of environmental toxins associated with ET have been identified, including harmane, lead and some agricultural pesticides. Nevertheless, additional studies are needed to evaluate the etiological importance of particular environmental toxins (56).

1.6 Pathophysiology of essential tremor

Essential tremor is often described as a neurodegenerative process, which has its origins in the cerebellum (57). Indeed, a vast number of degenerative changes in the cerebellum have been examined: both in post-mortem tissue and with the help of imaging techniques.

The cerebellum is a highly complex biological structure involved in action planning, correct movement execution, stance and gait, as well as oculomotor control. Found in its cortex, the Purkinje cells are GABAergic neurons. They build large dendritic arbors and receive excitatory (Glutamate) input from the climbing and parallel cell fibres, which come from other brain regions. The basket and stellate cells, on the other hand, provide inhibitory (GABA) input (58), (59). Studies with post-mortem brain samples showed Purkinje cell dendritic swellings (60), reduction in the Purkinje cell counts (61), heterotopic placement of Purkinje cell soma (62) and changes in their axonal morphology. Furthermore, there are reports of increased basket cell axonal connections (63) and decreased climbing fibres Purkinje cells synaptic density (64), which all indicate damage within the cerebellar cortex. These findings are supported by a series of imaging studies, which show functional and metabolic abnormalities inside the cerebellum (57). Furthermore, electrophysiological studies based on transcranial magnetic stimulation protocols over the cerebellum found reduced cerebellar inhibition over the motor cortex in patients with ET (65,66).

Thus, the cerebellar structures in ET appear to be the basis of a pathological tremorgenic network (67). Because of the rich cerebellar connections to other brain regions, including the thalamus, the mesencephalon and medulla oblongata, as well as the frontal cortex, the disrupted network might have a significant influence over the whole central nervous system. These speculations could bring a possible explanation of the broad palette of clinical features seen in ET. Patients with ET often have a deteriorated quality of life; some of them have difficulties doing simple household activities or suffer social withdrawal. Appropriate therapy for the condition is of great importance.

1.7 Drug therapy for essential tremor and its limitations

Generally, the choice of the proper therapy depends on the severity of the tremor. There are cases with mild, moderate, persistent and heavily persistent ET (68). While mild and moderate tremor occur only in stressful situations and might not require continuous therapy, the persistent forms can cause disability and should be treated over the long term. It is important that the treatment decision is taken individually and adjusted to the special needs of the patient. Consumption of nicotine and caffeine could exacerbate ET, so that the patient should be advised against them. Furthermore, medications that might worsen the tremor are β-agonists and corticosteroids, which are commonly used in the therapy of chronic obstructive pulmonary disease (COPD) (2). Therefore, special attention should be paid to patients with multimorbidity.

Propranolol (non-selective β-blocker in doses of 60–320 mg/d) and primidone (barbiturate derivate in doses of 250–1000 mg/d), which are viewed as first-line drugs for ET, prove to be effective in long-term treatment, improving clinical scores and tremor amplitude (69–71). The first-line therapy agents exhibit up to 70% response rate and a dropout rate of approximately 30% (72). Hence, these drugs have no therapeutic effect or benefit in nearly 30% of the patients and another 12% develop tolerance against them (70). Moreover, side effects of the pharmacotherapy should be taken into account. On the one hand, hypotension, depression and asthma failure are known side effects of treatment with β-blockers. Common side effects of primidone, on the other hand, are nausea, malaise and fatigue. Acute side effects are known to occur in 8% of patients with propranolol and in 32% of patients with primidone (70). Furthermore, chronic side

effects of propranolol were described in 17% of the patients, while primidone showed no chronic sides effects whatsoever. In addition, primidone, in its function as a depressant of the central nervous system, should not be combined with alcohol. A combination therapy with both propranolol and primidone could be possible and should be considered because in this way their effects enhance each other, which leads to smaller doses and diminished side effects.

The second-line therapy of ET includes topiramate (100–200mg twice daily) and gabapentin (400–600mg three times a day). Since these are anticonvulsive drugs, their dose should be slowly increased to the desired level. Topiramate, when used as a monotherapy, results in a significant decrease in tremor severity. Its main side effects include weight loss and paresthesia (73). Gabapentin, on the other hand, is associated with nausea, ataxia and weight gain in more than 30% of the patients. The second-line agents show a 30–50% response rate and a dropout rate of up to 30% (72). Furthermore, the third-line therapy of ET includes nimodipine (calcium channel blocker in doses up to 120mg/d) and clozapine (D4 receptor blocker in doses of 25–75mg/d). Although the response rate for the third-line therapy, at 50%, is relatively high, the dropout rate for ET remains unknown (72). While common side effects of nimodipine are edema, hypotension and headaches, clozapine might cause nausea, orthostatic hypotension, syncope, bone marrow depletion, and agranulocytosis.

In conclusion, it is clear that each third patient with severe persistent ET does not receive sufficient benefit from pharmacotherapy. Pharmacological agents often do not suppress the tremor completely, although in many cases 70–80% tremor suppression is considered an excellent result.

Nevertheless, most of the patients who come to seek medical attention due to the tremor, report disability, which not only causes deterioration in the activities of daily living but also causes social withdrawal. Essential tremor patients feel often embarrassed when involved in public and outdoor activities. This often leads to early retirement and reduces the circle of acquaintances. As a consequence, social withdrawal may cause or worsen an already existing depression. The patients with persistent ET and severe symptoms are, however, exactly those who require adequate therapy the most. In such cases, where the

drug treatment is not efficacious, there is the possibility of electrical stimulation of distinct regions inside of the brain.

1.8 Deep brain stimulation as a therapy for essential tremor

The stimulation of subcortical structures, also known as deep brain stimulation (DBS), has its origins in lesional neurosurgery. Such a surgery describes an interventional method, where a lesion in a defined target is deliberately made to reduce otherwise untreatable symptoms. In the case of drug-resistant tremor, the classical target for a lesion is the thalamus. As the procedure developed in time, intraoperative test stimulation for precisely detecting the target was used. Furthermore, the possibility of intraoperative recordings of electrophysiological potentials opened up. Thus, in addition to its application as a therapy for movement disorders, the approach enabled a more extensive exploration of the subcortical structures in humans, which laid the foundation of modern anatomic nomenclature of structures such as the basal ganglia and the thalamus (74). Over time, the ablative procedure was replaced by continuous DBS, which had fewer side effects and resulted in a better improvement of function (75). For DBS, in contrast to thalamotomy, the stimulating electrodes are left inside the brain and are connected to a subcutaneously implanted pulse generator (IPG) via extension cable.

First introduced in 1987 for ET (76), DBS is recommended for patients younger than 75 years with severe drug-resistant postural and kinetic tremor. Comorbidities such as dementia and depression should be taken into consideration, as well as the overall functional benefit for the ET patient due to the procedure (74). The operation has 1–4% risk of cerebral hemorrhage and 1–2% additional risk of infection (77). Nevertheless, the therapeutic value of DBS for ET is undisputable. Studies show long-lasting efficacy of DBS in tremor suppression (78) and relevant improvement of the ability to perform the activities of daily life (75). Bilateral stimulation is significantly more effective than unilateral stimulation (79). In addition to the outcome of no increase in mortality, compared to the normal population, DBS for ET shows a high long-term satisfaction among patients (80,81). There are even reports of increased mortality if a severe ET is not properly treated with DBS (82). Thus, DBS proves to be an effective

symptomatic long-term treatment for ET, which boosts the quality of life for patients.

1.9 Underlying mechanisms of deep brain stimulation for essential tremor

Despite the effective tremor suppression through DBS, the anatomical and neurophysiological mechanisms behind it are poorly understood. According to the Cerefy brain atlas (83), the motoric thalamus is divided into Nuclei ventrooralis anterior (VOA) and posterior (VOP), Nucleus ventrointermedius (VIM), as well as Nucleus ventrocaudalis (VC). These regions are all richly connected with other centres of the brain, with VIM receiving mainly input from the cerebellum (74). The ventral edge of VIM and the posterior subthalamic area (PSA) have been identified as the targets of choice for DBS when treating ET. While the stimulation of PSA might provide lower energy consumption, compared to that of VIM, the clinical effectiveness of both approaches remains the same (84). The working mechanism behind the tremor suppression is explained as a modulating activating stimulation, which exercises its influence on the pathological oscillations of affected thalamo-cortical and cerebello-thalamic networks (74). The assumption is based on imaging techniques of blood flow (85,86). Moreover, electrophysiological recordings from the brain and muscles demonstrate a disrupted tremorgenic network, which supports oscillations within the tremor range. When applied, DBS switches the oscillations to a lower amplitude and higher frequency. Subsequently, the tremor ceases (87). On a biochemical level, an upregulation of GABAergic and dopamine neurotransmitter systems are believed to be involved in the process (88). A possible model for such a disrupted tremorgenic network includes sensorimotor cortical, thalamic, cerebellar and brainstem sites, forming the anatomic basis for remote effects of VIM/PSA stimulation (89). It is also believed that the dento-thalamo-cortical-tract could play a major role in the anatomic model because successful electrode placement within its vicinity results in good tremor control (90).

1.10 Side effects of deep brain stimulation

With the thalamus being a main transitional zone of connections, it is not surprising that in addition to tremor suppression, the VIM/PSA stimulation can also influence other features. The modulation effect on the cerebellar and

thalamic function can exhibit itself in side effects such as paresthesia, muscle contraction, ataxia and dysarthria. Higher cognitive functions do not appear to be affected (91). The side effects are reversible because they disappear once the IPG is switched off and they are dose dependent. They emerge, probably, as a result of an expanding electrical field, which consequently affects neighbouring fibre tracts (74). Furthermore, VIM/PSA stimulation has a dichotomy impact on gait ataxia. While overstimulation exacerbates gait ataxia, a proper adjustment of stimulation parameters improves it, (92) with the ET-related ataxia being kinematically distinct from the stimulation-induced type (93). Therefore, optimization and proper setting of stimulation parameters can, on the one hand, reduce tremor and improve gait ataxia and, on the other hand, reduce side effects.

1.11 Ways to reduce the side effects of deep brain stimulation

The adjustable stimulation parameters include polarity, stimulation intensity, pulse frequency and width. Moreover, novel stimulation devices with segmented electrode contacts allow for directional stimulation. In VIM/PSA DBS, intensity is usually adjusted between 1–4 mA. Further increase of the intensity, which is sometimes needed for efficient tremor suppression, is limited because of the side effects.

1.12 Goal of the study

The goal of the current study is to compare directional DBS (dDBS) versus conventional omnidirectional DBS (oDBS) of the PSA for ET. The study is to provide answers to the following question:

Is dDBS superior to oDBS regarding therapeutic window (TW) as primary outcome parameter, and volume of neuronal activation (VNA), clinical efficacy and total electrical energy delivered (TEED) as secondary outcome parameters?

2 Materials and Methods

2.1 Study design

The “Materials and Methods”, and “Results” sections were adapted from Bruno and Nikolov et al. (94).

In the current study, therapeutic window (TW) was the primary outcome parameter, while clinical efficacy, volume of neuronal activation (VNA) and total electrical energy delivered (TEED) were considered secondary outcome parameters. Each study session lasted two hours. While the DBS programmer was unblinded regarding the stimulation condition, the rater and the patient were blinded.

First, the stimulation was switched off to accomplish a baseline evaluation of the scores TETRAS, TRS, mICARS, SARA as well as kinematic measurements with Kinesia™ and Zebris™.

Second, thresholds for therapeutic and side effects were double-blinded estimated in three segments (dDBS), as well as omnidirectionally (oDBS), on the best clinically reported contact level. The definition for TW was the difference between therapeutic and side effect threshold. Best dDBS was observed in the segment with the widest TW. Impedance was also measured.

Third, the first step was double-blind repeated two times with each patient in randomized order (one time with oDBS and one time with best dDBS). The study protocol is illustrated in **Figure 1** below.

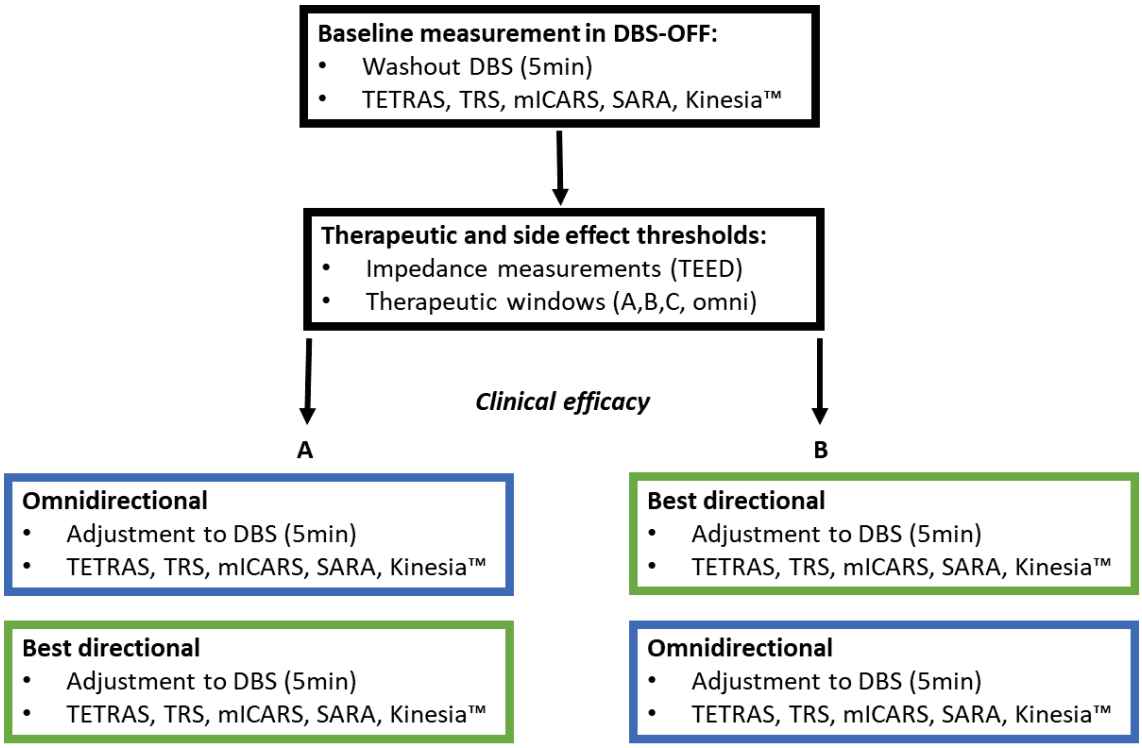

Figure 1: Schematic of the study protocol. Determination of therapeutic windows and comparison of the clinical efficacy occurred randomized and double blind (The figure belongs to a manuscript (94)).

2.2 Patient collective and operation technique

A total of ten patients affected by ET and treated with DBS of the PSA were enrolled, with biometric and demographic features randomly selected. The entire group fulfilled the criteria for DBS treatment and all of them received leads implantation at least three months before participating in the study, in order to avoid any lesion effects.

The electrodes implantation was executed in cooperation with the Department of Neurosurgery and Stereotaxy at the University Hospital in Düsseldorf. First, structural MRI was obtained several days prior to operation to localize the target. To determine the proper coordinates of the target, the patient's head was inserted into a stereotactic frame (Leksell Sterotactic System™, Elektra, Sweden). All patients were operated on under general anesthesia. A CT scan with contrast agent was obtained. Next, the MRI and CT scan images were fused to plan the trajectory from the skull towards the target (Elements software™, Brainlab). After the determination of the appropriate trajectories for the left and right hemisphere,

lateral right mounting was set to determine the degrees of x, y, z, arc and ring angles of the coordinate system for electrode implantation. To measure EEG-signals during the operation, corkscrew electrodes were positioned at Fz, Cz, Oz, and also on the left and right temporal bone (Spec medica GmbH, Italy). After the burr hole procedure on each side, up to five electrodes with micro-macro components were inserted along the trajectories (one central and four additional electrodes anterior, medial, lateral and posterior within 2mm distance from the central one, respectively). In some cases, certain trajectories were omitted because of blood vessels or other anatomical obstacles in the vicinity. Microelectrode recordings (MERs) were obtained in steps of 1mm, starting above and continuing beyond the target point, to ensure target localization (ISIS MER System, Inomed Medical GmbH, Emmendigen, Germany). The micro-component of the electrodes recorded single cell signals, while the macro-component was used for test stimulation. Next, the trajectory with the most prominent MER activity and least side effects during test stimulation was chosen for the final placement of the DBS leads. The leads of the Abbott Infinity system provide the possibility for directional stimulation in three horizontal planes (A, B and C) at the second and third contact levels **(Figure 2)**. A DBS lead model with 1.5mm contact spacing was applied. The impulse generator was connected to the leads and implanted subcutaneously on the abdomen.

The preferable level for chronic stimulation in the clinical routine was assessed at least one month postoperatively by clinical cathodal monopolar review (60µs pulse width, 130 Hz stimulation frequency). The electrode orientation in the PSA was determined for each patient postoperatively, based on three independent x-ray images (sagittal plane, coronal plane, and a 45° projection). **Figure 3** shows the postoperative electrode localization in nine of the patients.

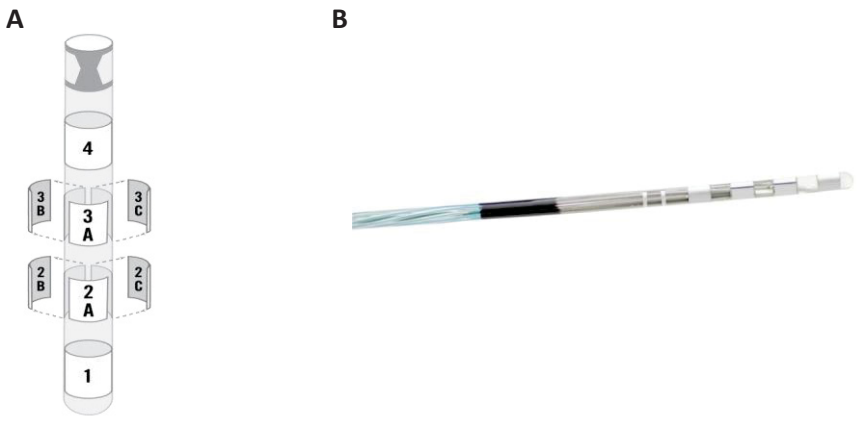

Figure 2 : A: Schematic depiction of an Abbott Medical™ stimulation electrode with four levels of contacts. Levels two and three consist of three directional segments (A, B and C). The figure was created by Abbott Medical™ and is presented here after an explicit permission.

B: Real image of an Abbott Medical™ stimulation electrode. The figure was created by Abbott Medical™ and is presented here after an explicit permission.

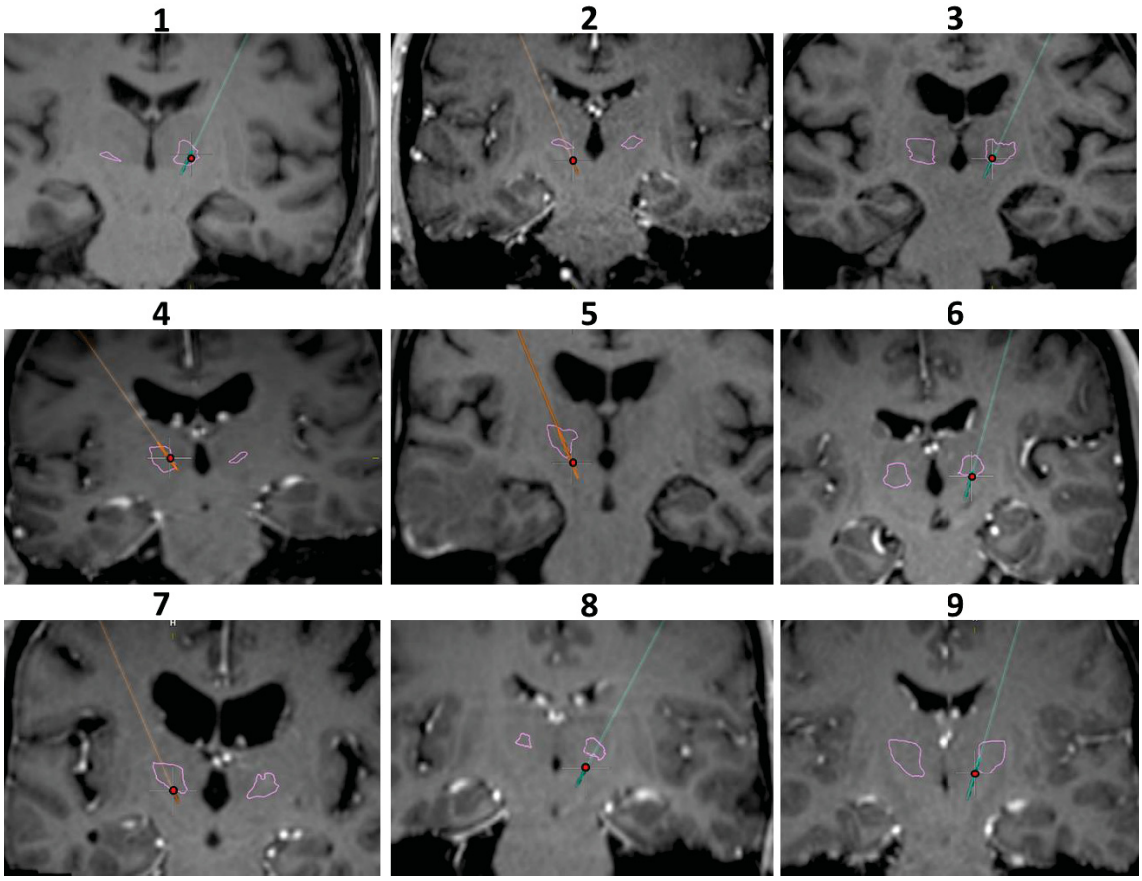

Figure 3: Postoperative MRI/CT fusion images corresponding to nine patients. (The figure belongs to a manuscript (94)).

Enrolment criteria were sufficient medical and mental fitness, comprehension of the study conditions and a subscribed informed consent sheet. Exclusion criteria

were coexistence of further neurological conditions, poor clinical response of tremor to DBS treatment or poor general health, which would possibly reduce the patient's understanding of the study protocol. Cancellation criteria included both the above-mentioned exclusion criteria, as well as taking back the consent declaration. Individual information regarding gender, age, height, body weight, first diagnosis of ET, disease duration, familial predisposition, symptom palette and severity, ethanol response of tremor, short- and long-term side effects of DBS, as well as current medication for each patient were also documented.

2.3 Baseline measurement

Unblinded baseline measurements were carried out. Here, assessments of the hemi-body scores of Fahn-Tolossa-Marin Tremor Rating Scale (TRS) (95) and The Essential Tremor Rating Assessment Scale (TETRAS) (96) comprising items from the worse affected side were conducted. In addition, whole-body ataxia scores (modified International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome (mICARS)) (97), Scale for the assessment and rating of ataxia (SARA)) (98) and digital hemi-body accelerometry with Kinesia™ motion sensor (Great Lakes NeuroTechnologies Inc., Cleveland, US) on the index finger, as well as gait analysis with the Zebris™ system were obtained.

2.4 Therapeutic windows

Therapeutic threshold (TT) was defined at the stimulation intensity where visible tremor reduction occurred. Side effect threshold (SET) was defined as stimulation intensity where sustained side effects first appeared. Both TT and SET were measured in four conditions (segments A, B, C and omnidirectional) in nine patients. In one of the patients TT and SET were determined only in two conditions (segment A and oDBS). Therapeutic window (TW) was defined as the difference between TT and SET. The contact level for the stimulation protocol was taken, based on the clinical monopolar review. Only the contact level, which exhibited the largest TW, was examined in the study. The directionality of the contralateral electrode was adjusted to match the setting of the investigated side.

The stimulation intensity was increased in steps of 0.5mA (on segments A, B, C for dDBS and for oDBS) until persistent side effects occurred. Afterwards, finer

tuning in steps of 0.1mA was performed to determine SET. Next, we decreased the stimulation intensity in 0.5mA steps for oDBS and 0.1mA steps for dDBS until the tremor reappeared, to establish TT. Here we used 0.1mA steps for dDBS because of the higher energy density and larger VNA (99). We then defined absolute TW, as SET minus TT, and relative TW as TW/TT in percent for all four conditions (segments A, B, C and oDBS). The segmented contact (A, B or C) with the widest relative TW was defined as best dDBS contact. **Figure 4** depicts the programming unit (IPad); the subcutaneously placed pulse generator (Infinity™) and the DBS leads.

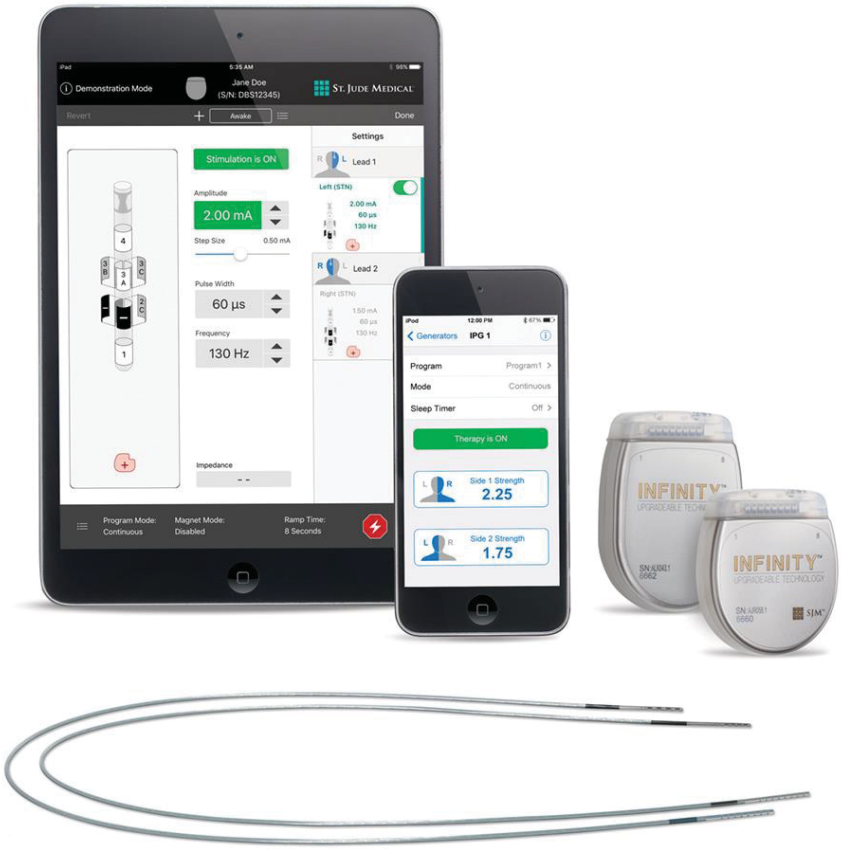

Figure 4: Remote programming device, subcutaneously implantable pulse generator, and electrode wires. The figure was created by Abbott Medical™ and is presented here after an explicit permission.

2.5 Volume of neuronal activation and total electrical energy delivered

In all conditions, VNA at TT and SET was calculated as a function of stimulation intensity, using polynomial regression.

Furthermore, impedances at TT and SET for oDBS and dDBS in seven patients were measured. On this basis, we could calculate TEED, using the formula suggested by Koss et al. (100) for constant current stimulation: TEED = (current² × pulse width × frequency × impedance x 1s).

2.6 Clinical efficacy

Clinical efficacy was compared in a double-blind trial between best dDBS and oDBS. The electrode not tested was programmed either directionally or omnidirectionally by matching the stimulation mode of the investigated electrode. Stimulation intensity was set 0.1 mA below SET. When changing conditions, we applied a wash-out period of five minutes. Then, clinical assessment of the hemi-body scores for tremor (TRS, TETRAS), whole-body scores for ataxia (mICARS, SARA), hemi-body accelerometry with the Kinesia™ device and Zebris™ gait analysis were made for both conditions.

2.7 The Tremor Rating Scale

The Tremor Rating Scale (TRS) is a widely used clinical scale, which is divided into three parts (A, B and C). Each part has a subtotal score that could be added up or used separately for independent analysis. While parts A and B represent task-specific quantitative scores, part C provides global assessment, where both patient and examiner participate in completing the evaluation.

In part A the tremor is assessed in nine different body regions (face, tongue, voice, head, right and left arm, right and left leg, trunk). Furthermore, the score quantifies the tremor at rest, in posture and during action. Obviously, not all of the above-mentioned body regions would exhibit all three kinds of tremor. For example, voice tremor is seen only during action and head tremor usually emerges at rest. Therefore, some of the body regions were accordingly adjusted to the type of scoring. The severity of the tremor was evaluated in line with the tremor amplitude from 0 (no tremor), 1 (light tremor, barely recognizable, could be intermittent), 2 (moderate tremor with amplitude <1cm, could be intermittent), 3 (distinct tremor with amplitude 1–2cm), to 4 (severe tremor with amplitude >4cm). In the end, the scores of all the body regions and the different kinds of tremor that were observed in those body regions were totalled. For example, the right arm of a patient trembles at rest with light tremor (1), in posture with

moderate tremor (2) and during action also with moderate tremor (2). The left arm of the patient, in contrast, trembles distinctly only during action (3). Therefore, the score for the performance of both arms will be: 1+2+2 (right arm) + 0+0+3 (left arm) =8. The worst possible outcome in part A was 80 points.

Part B of the TRS determines the manual functions of the patient, based on their handwriting, drawing an Archimedes spiral and pouring a glass of water. The scoring form provides space for spiral drawing and handwriting. The performance is evaluated, similarly to part A, with notes from 0 to 4. Handwriting was examined only on the dominant hand and the same sentence was written in the different DBS conditions for better comparison. The evaluation of the handwriting was as follows: 0 (no tremor during writing), 1 (light tremor, barely recognizable, could be intermittent), 2 (moderate tremor with amplitude <1cm, could be intermittent), 3 (distinct tremor with amplitude 1–2cm) and 4 (severe tremor with amplitude >2cm). The drawing part was subdivided into parts a, b and c. It was estimated on both arms. In part a, the patient was asked to draw a big spiral, in part b, a smaller one and in part c, the ability to connect dots while drawing parallel lines was examined. Each of these items was performed once with the left hand and once with the right hand. The results were evaluated with notes from 0 to 4: 0 (normal drawing ability), 1 (light tremor, the drawing lines cross sometimes), 2 (moderate tremor, the drawing lines cross often), 3 (performing the task is very difficult with a lot of crossings) and 4 (performing the task is not possible). In the end, all of the points from the subitems a, b and c were added up. In addition, water pouring was quantitatively assessed by the examiner, according to how much of the fluid was spilled: 0 (normal), 1 (cautious and slow, but nothing gets spilled), 2 (a small amount is spilled <10%), 3 (a substantial amount is spilled 10–50%), 4 (most of the fluid is spilled). Finally, all of the points of the items of part B were added up. The worst possible outcome in part B was 32 points.

Part C determines the functional disability due to the tremor. It consists of the following items: speech, eating, drinking, dressing, hygiene and writing. The items in part C are also rated with notes from 0–4. In contrast to parts A and B, part C does not examine the tremor severity directly but relies on the patient's own assessment. Because part C is more subjective and cannot be tested in the three conditions of the study, it was waived and not used during it.

The overall interrater reliability of TRS was reported to be approximately 0.9 (constructed with Spearman's correlation) (95). The interrater reliability regarding only spirals drawings and handwriting, however, was, with 0.5, rather poor. Moreover, the tremor amplitude in ET seldom reached 4 cm, as the assessment system suggests (96). In order to avoid those limitations, the tremor in the current study was also assessed with TETRAS.

2.8 The Essential Tremor Rating Assessment Scale

In contrast to TRS, The Essential Tremor Rating Assessment Scale (TETRAS) was specially developed for examining the severity of ET. It is a scale developed by the Tremor Research Group. It consists of 12-item activities in the daily living subscale, and a 10-item performance subscale, assessing tremor in the head, face, tongue, speech, arms, legs, during spiral drawing, handwriting, point approaching and standing.

The evaluations in the 10-item performance subscale occur in 0 to 4 point intervals, defined in terms of tremor amplitude ranges. Head tremor is assessed as follows: 0 (no tremor),1 (tremor with an amplitude <0.5cm), 2 (tremor with an amplitude from 0.5 to <2.5cm), 3 (tremor with an amplitude from 2.5 to 5cm) and 4 (tremor with an amplitude >5cm). Rating of face and tongue tremor is: 0 (no tremor), 1 (barely visible), 2 (noticeable), 3 (obvious and present in most facial contractions) and 4 (gross, disfiguring tremor). Voice is assessed with 0 (no tremor), 1 (slight, during "*aaah*" and "*eee*" only), 2 (during "*aaah*" and "*eee*" and minimal in speech), 3 (obvious tremor in speech), 4 (some words difficult to understand). Tremor of the upper limb is assessed during three manoeuvres: foreword horizontal reach posture, lateral "*wing beating posture*" and finger-nose-finger testing. The average value of the three is then calculated and taken as a final score, representing the upper limb performance. The scoring system for the upper limb is as follows: 0 (no tremor), 1 (<0.5cm), 2 (tremor with amplitude 1 to <2.5cm), 3 (tremor with amplitude 2.5 to ≤5cm), 4 (tremor with an amplitude >5cm). The lower limb is assessed when extended parallel to the ground for 5s and during heel-shin maneuver. The average of the two is taken for the final estimation of lower limb tremor. The scoring system for the lower limb is: 0 (no tremor), 1 (barely visible), 2 (obvious but mild), 3 (tremor with amplitude ≤5cm), 4 (tremor with amplitude >5cm).

Handwriting is scored as follows: 0 (no tremor), 1 (barely visible), 2 (obvious tremor but legible), 3 (some words illegible) and 4 (completely illegible). Drawing of two Archimedes spirals with each hand is scored with 0 (no tremor), 1 (barely visible), 2 (obvious tremor), 3 (portions of figure not recognizable), 4 (figure not recognizable).

During the dot approximation task, the subject is asked to hold their index finger to a dot on a piece of paper as close as possible without touching it. The assessment is as follows: 0 (no tremor), 1 (<0.5cm), 2 (tremor with amplitude 1 to <2.5cm), 3 (tremor with amplitude 2.5 to ≤5cm) and 4 (tremor with amplitude >5cm). Finally, the last item of the direct tremor assessing part of TETRAS is standing. Standing is examined with knees 10–20cm apart from one another and flexed at 10–20°. Arms are down at the subject's side. Scoring for standing tremor is: 0 (no tremor), 1 (barely visible), 2 (obvious but mild), 3 (moderate) and 4 (severe). Finally, all the scores for the different tremor items were totalled. The worst possible outcome was 40 points. The 10-items performance subscale of TETRAS showed interrater reliability ranging up to 0.96 for upper limbs and head, while the reliability for voice, face, trunk and lower limbs was lower (96).

2.9 The Modified International Cooperative Ataxia Rating Scale

Ataxia was examined with the modified International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome (mICARS)(101) and the Scale for the assessment and rating of ataxia (SARA)(98), whereas both of the scales possess similar items. Nevertheless, ICARS yields more items than SARA and contains four parts. Both scoring systems follow the rule that the worse the clinical outcome is the higher the scoring. While the interrater reliability for mICARS is estimated to be 0.92, those for SARA amounts to 0.93, which proves the tests to be equally robust (97).
The first part of mICARS deals with gait and stance. The following items are included in it: gait (from 0 to 8); gait velocity (from 0 to 4); stance stability with the eyes opened (from 0 to 6); ankle distance in normal stance (from 0 to 4); balance with unified feet and opened eyes (from 0 to 4); balance with unified feet and closed eyes (from 0 to 4); sitting (from 0 to 4). The second part of mICARS rates movement and coordination. It contains the following items: heel-shin slide test

for intention tremor (0 to 4); heel-shin slide test for action tremor (0 to 4); finger-nose test for fluency and dysmetria (0 to 4); finger-nose test for intention tremor (0 to 4); finger-chase test (0 to 4); fast alternating hand movements (0 to 4) and drawing a spiral (0 to 4).

Part three quantifies speech fluency (0 to 4) and speech comprehensibility (0 to 4). Part four deals with oculomotor deficits such as nystagmus (0 to 3); saccades (0 to 2) and saccades dysmetria (0 to 1), while performing eye movements. Finally, the points are added up. The worst possible outcome was 72 points.

2.10 Scale for the Assessment and Rating of Ataxia

The Scale for the assessment and rating of ataxia demonstrates good interrater and retest reliability (98). It consists of eight items, which are scored similarly to mICARS: gait, stance, sitting, speech fluency, finger-chase test, nose-finger test, fast alternating movements and heel-shin slide. The executions of the items are, however, more precisely defined than those in mICARS.

Gait (0 to 8) is first observed while walking parallel to a wall and then during tandem walking (heels to toes). Stance is estimated (0 to 6) first in natural position, second with feet together in parallel (big toes touching each other) and third, in tandem (both feet on one line with no space between heel and toe). Sitting (0 to 4) is examined without the support of the feet, with opened eyes and with arms stretched to the front. Speech (0 to 6) is assessed during normal conversation. During a finger-chase test (0 to 4), the patient is asked to perform five sudden, consecutive and fast pointing movements in unpredictable directions on a frontal plane. The movements should have amplitude of 30cm and a frequency of 2s. The patient is instructed to follow the movements with his index finger as fast and as precisely as possible. Nose-finger test (0 to 4) is evaluated according to the average patient performance. With fast alternating movements (0 to 4) the patient is asked to perform ten cycles of repetitive pro- and supination movements of the hand. The heel-shin manoeuvre (0 to 4) is to be repeated three times on each side. The best of the three trials is then taken for scoring. The last four items of SARA are to be performed and scored on both sides. The average value of both sides for each item is taken for the final score. The worst possible outcome in SARA was 40 points.

2.11 Kinematic measurements

To objectify the effect of DBS, examination of tremor and ataxia was also performed digitally. Tremor was evaluated with the help of a motion sensor device called Kinesia™. Gait/stance ataxia was estimated with the help of both Kinesia™ and a weight distribution analysis system called Zerbis™.

About Kinesia™

Kinesia™ (CleveMed) system proved to be a suitable tool for tremor evaluation. Its measurements show good correlation with clinical assessment tremor scores for ET (102). The device consists of a motor sensor unit, which is remotely connected via Bluetooth to an iPad. The iPad serves as a command surface unit. The technical details of the device have already been described (103). The sensor unit

> *integrates a flex circuit with three orthogonal accelerometers and three orthogonal gyroscopes to capture motion with six degrees of freedom…. The interface software includes a patient database, real time data displays and integrated videos to guide subjects through clinical exams, (Guiffrida et al.* (103))

The movement recordings were band-pass filtered between 3.5 and 11 Hz in order to avoid any background noise from voluntary movements (102). For the purposes of the study, the sensor was attached to the middle phalanx of the index finger on the more affected site and the tremor was assessed both in action and in repose. Furthermore, gait and stance were estimated with the sensor attached to the belt. The motion recordings were then processed and transformed into scores (from 0 to 5 in increasing decrements), which reflect tremor severity. The scores were anonymously transferred to an external server, where they could be downloaded and evaluated by the clinician.

For the digital accelerometry, patients had to hold their arms outstretched in front of their body for 15s and touch the tip of their nose with their index finger repeatedly for another 15s. Accelerometry and gait analysis were performed on eight patients. **Figure 5** shows the Kinesia™ sensor unit, attached to the index finger.

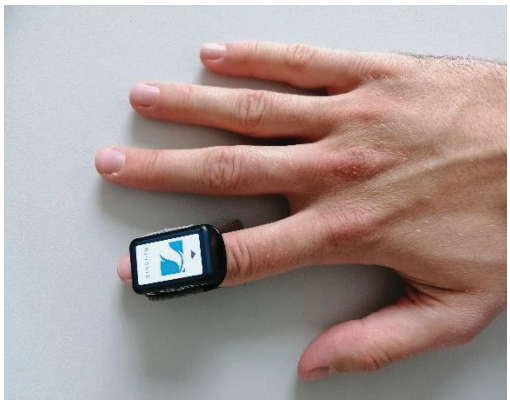

Figure 5: Kinesia™ sensor on the index finger, viewed from above (CleveMed technology, USA).

About Zebris™

The Zebris™ walking pad consists of two gait platforms, which are positioned next to each other on the floor and in this way build a walking path for the patient across the gait laboratory. The platforms are equipped with weight distribution sensors, which feed data recordings continuously to a software program connected to them. The device has a high temporal resolution, so that fluctuations of the patient's gait and posture can be detected.

In all three conditions (DBS-OFF, oDBS and dDBS) patients had to stand normally (30s); stand with closed eyes (30s); stand with feet together, so that the toes touch each other (30s); stand on one foot (15s); stand in tandem position (15s); walk normally and walk in tandem line. For the stance/gait analysis we calculated the average step length and step time, in addition to the average variance of pressure distribution of the feet, and compared these between conditions.

2.12 Lead localization and statistical analysis

To ensure reliable target localization, coordinates of the active contacts in the x, y and z-axes were determined to calculate the distance to the mid-commissural point (MCP). The statistical analysis was executed with Graphpad Prism™. The Shapiro-Wilk test was used to test for normality. Friedman test for independent analysis and Dunn's multiple comparison test as post-hoc analysis were conducted for the comparative analysis between conditions.

2.13 Legal issues

The study was in compliance with the Helsinki Declaration and approved by the Ethics Committee of Heinrich Heine University (Study number: **5384R**). The subjects were informed both orally and in writing on the purpose of the study, its procedure and risks. Furthermore, it was explicitly pointed out to the subjects that participation in the study was absolutely voluntary and could be revoked at any time without any negative consequences for further treatment. The pseudonymization of personal data was executed by a responsible physician. In this connection, no data with names and initials was used, but a study specific number code was generated, so the individual disclosures about personal and factual background could not be attributed to the single subjects without knowledge of the code. Thus, the personal data were protected from unauthorized access.

2.14 Occurrence of side effects and safety

All investigations took place in the Centre for Movement Disorders and Neuromodulation at the Department of Neurology, which is part of the University Clinic in Düsseldorf. They were executed in the presence of experienced physicians, so that potential side effects could be treated immediately. Reversible stimulation side effects could indeed appear during the programming session. For the VIM/PSA DBS they mostly included paresthesia, dysarthria, ataxia, muscle contractions and oculomotor symptoms. Such side effects are also common during the clinical parameter adjustment and unavoidable during clinical system programming. Therefore, the patients were already familiar with them. The side effects were transient and could be immediately eliminated through reprogramming. The patients were informed in detail regarding them and were enrolled in the study only after their explicit consent was given.

3 Results

During the study process, no severe relevant side effects occurred. Mean electrode location was 11.37±0.636mm lateral; 4.71±0.465mm posterior and 1.81±0.262mm inferior with respect to the mid-commissural point, which was in line with earlier reports on successful PSA DBS (104,105). **Table 1** illustrates the orientation of the segments for each condition in each patient.

Patient-ID	oDBS	Best dDBS		Second-best dDBS		Worst dDBS	
	rTW	Direction	rTW	Direction	rTW	Direction	rTW
001	0	P	61.1	AL	40.9	AM	0
002	25	A	25	PM	11.1	PL	0
003	16.6	PM	45	L	32.1	AL	3.3
004	33.3	M	50	PL	34.8	AL	15.6
005	0	AL	72.2	P	41.6	AM	16.6
006	300	AL	330	PL	213	M	127
007	40	P	135.3	AM	40	AL	13.3
008	133.3	PL	700	AL	150	M	175
009	200	AL	1.1	AM	300	P	140

Table 1: Active segment orientation: A=anterior; P=posterior; M=medial; L=lateral; AL=anterolateral; AM=anteromedial; PL=posterolateral; PM=posteromedial. The rTW for oDBS, best, second-best and worst dDBS are shown as percentages from the corresponding TT. The data, presented here was obtained by Bruno and Nikolov et al. (94)

3.1 Therapeutic window

There was a significant difference in TW between conditions (X^2=19.72, p=0.0002). The best directional DBS (dDBS) TW (213.2 ± 80.99 %) was significantly larger, compared to both omnidirectional DBS (oDBS) (83.1 ± 35.19%; p<0.05) and worst dDBS (54.6 ± 23.69 %; p<0.001; **Figure 6**). There was also significant difference in TT between conditions (X^2=14.18; p=0.0027). Best dDBS TT (1.6 ± 0.22 mA) was significantly lower, compared to both oDBS

(2.3 ± 0.21 mA; p<0.05) and worst dDBS (2.4 ± 0.25 mA, p<0.001; **Figure 7A**). Post-hoc analysis did not reveal significant difference between SET (p>0.05; **Figure 7B**).

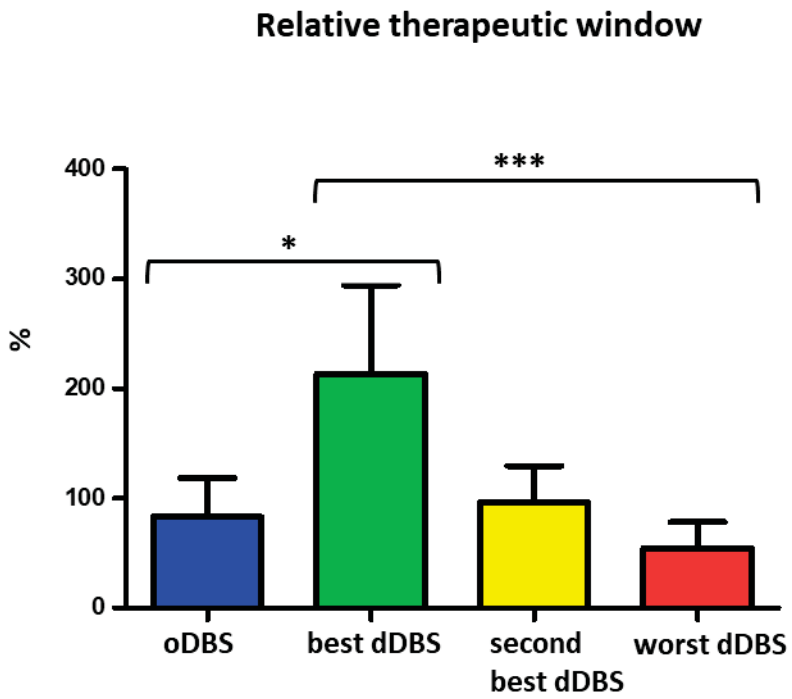

Figure 6: Relative TW. Error bars represent SEM; (*)p<0.05; (**)p<0.01; (***)p<0.001. (The figure belongs to a manuscript (94)).

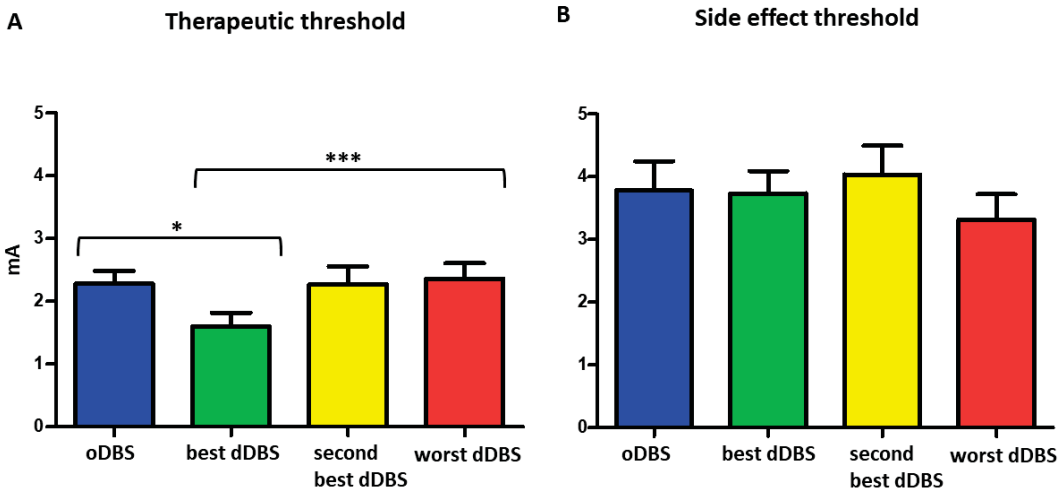

Figure 7 : TT and SET. Error bars represent SEM; (*)p<0.05; (**)p<0.01; (***)p<0.001. (The figure belongs to a manuscript (94)).

3.2 Volume of neuronal activation

With growing intensity, VNA for dDBS became larger than VNA for oDBS (**Figure 8**). VNA at TT (X^2=14.56, p=0.0022) and SET (X^2=18.74, p=0.0003) were significantly different between conditions. While VNA at TT was smaller for oDBS (30.19±4.032mm³) compared to worst dDBS (62.81±8.238mm³; p<0.01, **Figure 9A**), VNA at SET for best (130.4±19.47 mm³) and second-best dDBS (117.7±16.52mm³) were significantly larger than for oDBS (65.43±11mm³; p<0.01, **Figure 9B**).

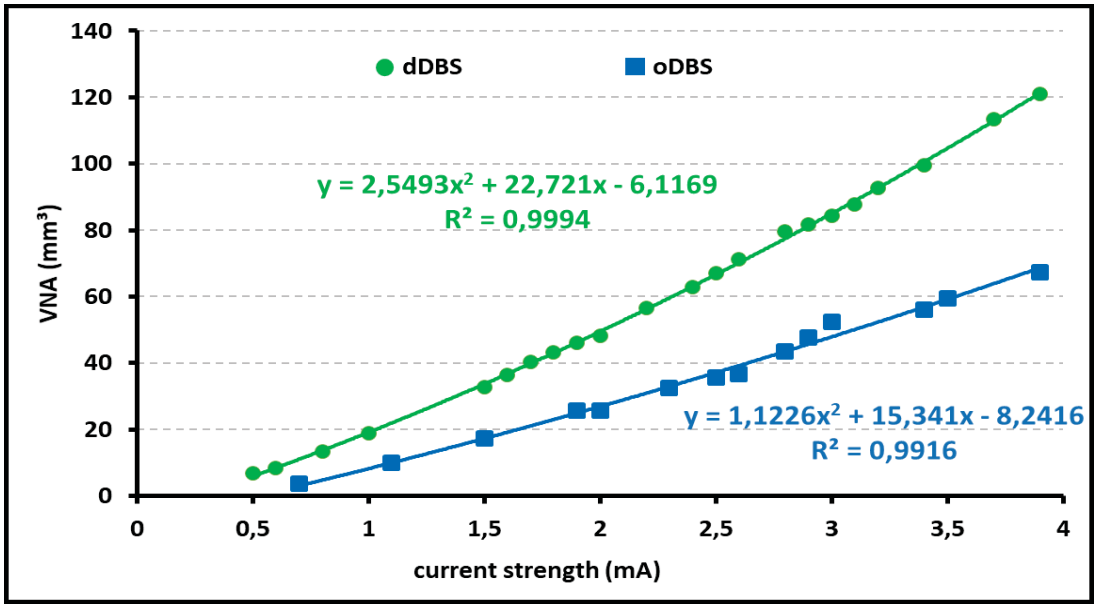

Figure 8: Relation between VNA and stimulation intensity for dDBS and oDBS. (The figure belongs to a manuscript (94)).

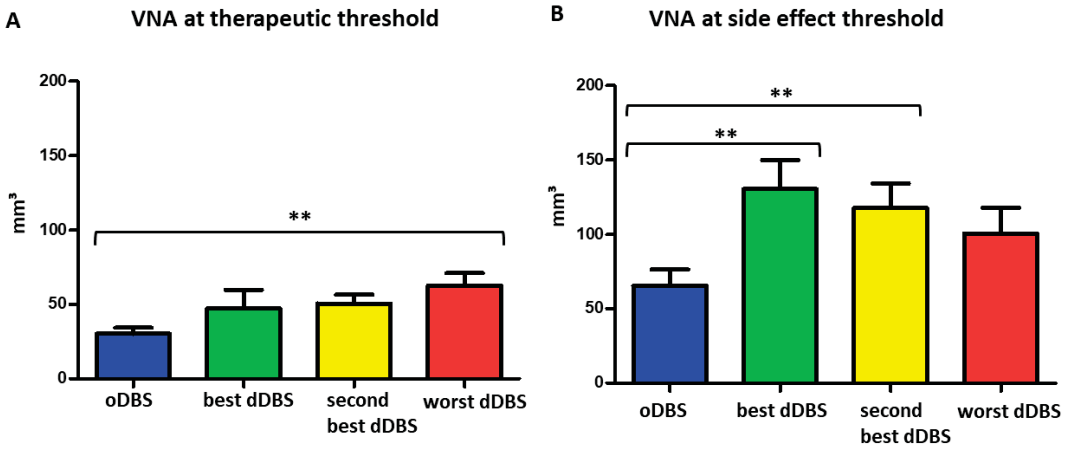

Figure 9: VNA at TT and SET. Error bars represent SEM; (*)p<0.05; (**)p<0.01; (***)p<0.001. (The figure belongs to a manuscript (94)).

3.3 Clinical scores

Severity of tremor was significantly different between conditions (TRS: X^2=15.44, p<0.0001; TETRAS: X^2=16.7, p<0.0001). The TRS in DBS-OFF (42.7±2.211) was significantly higher than in oDBS (10.7±5.315, p<0.01) and best dDBS (10.9±1,929, p<0.01; **Figure 10A**). Moreover, TETRAS in DBS-OFF (15.4±1.176) was also significantly higher than in both oDBS (6.4±1.127, p<0.01) and best dDBS (5.9±1.038, p<0.001; **Figure 10B**). There were no differences between best dDBS and oDBS in the tremor scores.

Severity of ataxia was significantly different between conditions (mICARS: X^2=14, p<0.0001, SARA: X^2=11.14, p=0.0001). Post-hoc analysis showed significantly higher mICARS for DBS-OFF (17.4±1.392) vs. oDBS (10.4±1.137; p<0.05) and best dDBS (9.6±1.275; p<0.001, **Figure 11A**). Further, SARA was also significantly higher for DBS-OFF (8±1.043) compared to oDBS (5.7±1; p<0.05) and best dDBS (5.2±0.813; p<0.01, **Figure 11B**). There were no differences between oDBS and best dDBS in the ataxia scores.

Postural and kinetic tremor severity according to the accelerometry measurements was also significantly different between conditions (X^2=11.76, p=0.0011; X^2=13.71, p<0.0001, respectively). Tremor amplitude in the DBS-OFF condition was significantly higher compared to oDBS or best dDBS, (p<0.05; p<0.01, respectively). There were no differences oDBS and best dDBS (**Figure 12A and B**).

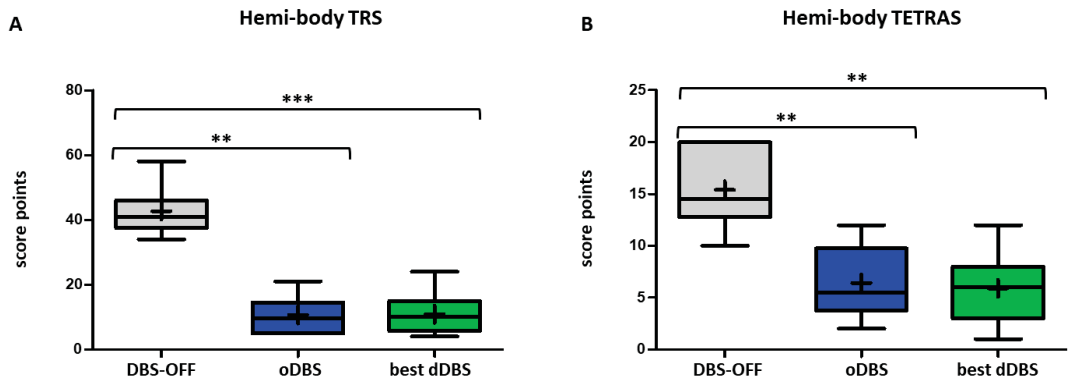

Figure 10: A: TRS; B: TETRAS. Error bars represent SD; (*) p<0.05; (**) p<0.01; (***) p<0.001. (The figure belongs to a manuscript (94)).

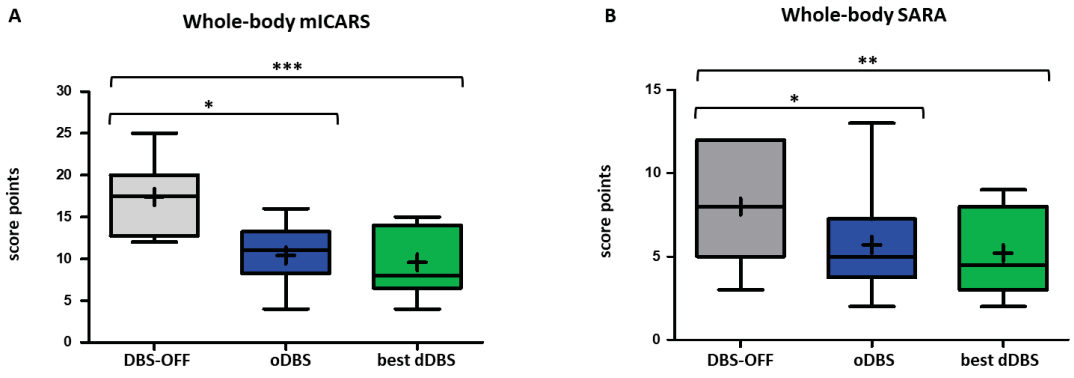

Figure 11: A: mICARS; B: SARA. Error bars represent SD; (*) p<0.05; (**) p<0.01; (***) p<0.001. (The figure belongs to a manuscript (94)).

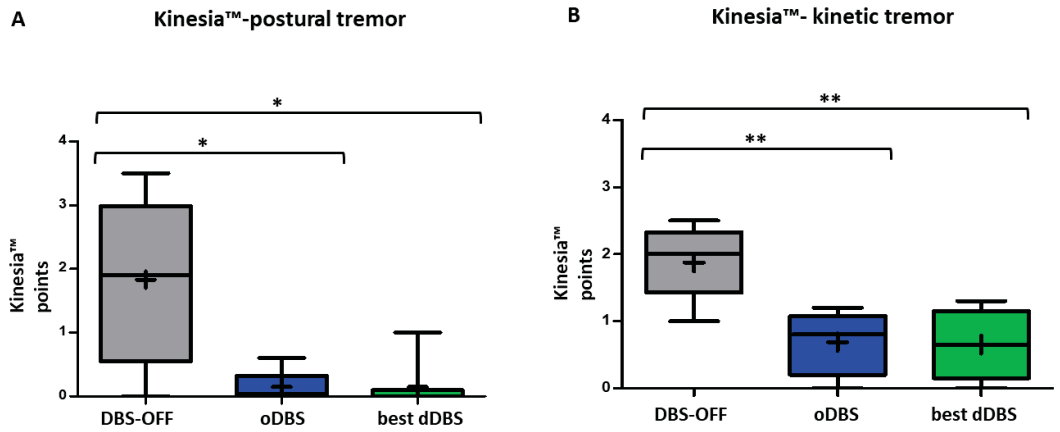

Figure 12: Accelerometry for postural and kinetic tremor. Error bars represent SD; (*) p<0.05; (**) p<0.01; (***) p<0.001. (The figure belongs to a manuscript (94)).

3.4 Total electrical energy delivered

There was a significant difference between conditions in TEED at TT (X^2=16.03; p=0.0011) and SET (X^2=12.77; p=0.0052). While TEED at TT for best dDBS (31.13±11 µW) was significantly lower compared to second-best (80.28±28.26 µW; p<0.01) and worst dDBS (87.54±19.6 µW; p<0.01, **Figure 13A**). Furthermore, TEED at SET was significantly higher for second-best dDBS (295.7±78.44 µW) compared to oDBS (127.7±35.97 µW; p<0.01, **Figure 13B**).

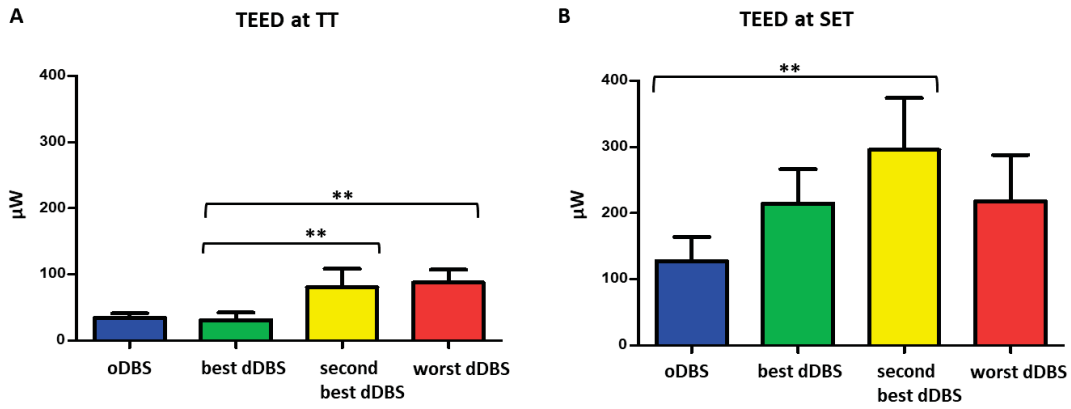

Figure 13: A: TEED at TT; B: TEED at SET. Error bars represent SEM; (*)p<0.05; (**)p<0.01; (***)p<0.001. (The figure belongs to a manuscript (94)).

3.5 Gait and stance analysis

We found no significant differences regarding the variance of pressure distribution of the feet during stance and gait between the three conditions (DBS-off, oDBS, best dDBS; $p>0.05$). No significant differences between the three conditions were found also when comparing average step length and average step time ($p>0.05$).

4 Discussion

Our study had three main results: first, dDBS widens the therapeutic window, while maintaining clinical efficacy; second, the wider TW in dDBS is due to smaller TT, compared to oDBS; and, third, directionality persists even at higher stimulation intensities.

Essential tremor belongs to the most common neurological disorders and tends to advance with the onset of age, thus, causing substantial deterioration in the quality of life. Although pharmacological therapy significantly improves the clinical outcome for ET patients, one third of them experience no sufficient beneficial effect from drug treatment and are in need of further solutions. In fact, up to 53% of the patients suffering from tremor, in general, might stop taking their medication because of insufficient symptom control and side effects (106).

The results of the current study give answers regarding the improvement of DBS quality for ET patients. Indeed, properly treating severe forms of ET is often a challenge for the clinician. Often, the optimal DBS setting is a compromise between tremor suppression and side effects. Finding the balance between them for the patient requires regular visits and considerable patience. Although DBS has an undisputed value in reducing tremor severity and improving quality of life, in some cases a discrepancy may occur between patient's expectations and the objective beneficial effect. In such cases, finding the best DBS programming setting that responds to the individual needs is of great importance.

4.1 Electrical stimulation of neuronal tissue

To understand why stimulation at the same spot in the brain is capable of producing multiple effects, we have to know (1) which anatomical elements are stimulated; (2) how do their response to the stimulation differ and (3) how the DBS programming interacts with the anatomical elements.

DBS modulates multiple cellular elements via an electric field around an electrode. Neuronal tissue is highly inhomogeneous and consists of different cellular populations, each of them having separate electrophysiological properties. Not only the different neuronal populations, but also the different cellular segments, possess distinct properties. For example, the cellular bodies

have significantly higher resistance and capacitance compared to the axons (107). Therefore, gray matter, white matter and cerebrospinal fluid would exhibit different resistance and would not react to stimulation in the same way. In fact, some electrical stimuli are selective to certain types of cellular components. Such selective stimulation of distinct structures in the brain is the key to the therapeutic value of DBS. The goal in the context of ET would be, on the one hand, to suppress the pathological oscillations of the tremorgenic network, while, on the other hand, not affecting other fibre tracts or nuclei in the anatomical vicinity. While the operation technique allows a precise targeting of the ventral part of VIM/PSA as the target of choice for DBS, it is up to the DBS programming to further specify in the stimulated structures. When the electrode is already placed, its position cannot be adjusted and deviations as small as 2–3 mm could completely abolish the beneficial effect (108). In conclusion, the more selective the stimulation is, the less the impact on additional structures and the fewer the side effects. To achieve such selective stimulation for ET, one should consider (1) which is the best target of choice and (2) how to program DBS in such a way as to selectively stimulate only that target of choice.

4.2 Targets of choice for deep brain stimulation in essential tremor

Although the traditional target of choice for chronic ET-DBS is VIM, the PSA just beneath it has proven itself to be equally effective in alleviating tremor severity (109). Addressing this issue, Hamel et al. have found that the more distant electrodes inside VIM have even better therapeutic effect than the proximal ones. The white matter area, PSA, is positioned inferior to the thalamus, which contains the prelemniscal radiation as well as zona incerta. It functions as a transitional zone for fibre tracts involved in motor functions. Stimulation of PSA often ensures better tremor control, while overstimulation is burdened with side effects. The side effects reported from patients in the current study overlapped largely with those described in previous observations. The most common among them were dysarthria, gait ataxia and nausea. An explanation of the functioning mechanism behind VIM/PSA DBS has already been proposed (93,110). Groppa et al. have suggested that the beneficial effect of DBS on VIM/PSA is due to inhibition of the

dentato-thalamo-cortical loop, which anatomical vicinity significantly correlates with the positions of the best leads (93).

The dentato-thalamo-cortical loop is the main fibre tract that connects the cerebellum with the motor cortex. It is involved in movement planning and execution and has its origins in the cerebellar dentate nucleus. From there, it makes its way to the ventrolateral thalamus, crossing the PSA. After the changeover of the fibres inside the thalamus, the next transitional zone is the motor cortex. The motor cortex is then connected with the pons and from there, the information flows back into the cerebellum. Thus, the dentato-thalamo-cortical loop is closed (111). Neuropathological findings suggest cerebellar involvement in ET and stimulation of the dentato-thalamo-cortical loop effectively alleviates tremor in ET patients. The loop appears to be the primal target of choice. High frequency stimulation (HFS) probably plays a role as an inhibitory filter, which switches the pathological oscillations of the tract back to normal (74).

Nevertheless, the dentato-thalamo-cortical loop is not the only pathway that goes through the PSA and selectively stimulating it poses a challenge. Another pathway that is found in the region is the rubro-olivo-cerebellar loop (93). It has its origins in the red nucleus, which lies within the anatomical vicinity of PSA. The red nucleus is divided into two parts containing distinct neuronal populations: the parvocellular and the magnocellular part. The rubro-olivo-cerebellar tract connects the parvocellular part of the red nucleus with the inferior olive. From there, the signals flow to the cerebellar cortex and afterwards to the dentate nucleus. Finally, the dentate nucleus is connected with the parvocellular part of the red nucleus and the loop is closed. The rubro-olivo-cerebellar loop is known to be responsible for motion precision and fineness, which are needed in target motor skills and during speaking (111). As six of our patients developed dysarthria as an immediate sign of overstimulation, it could be suggested, that DBS in those cases affected the rubro-olivo-cerebellar loop. Moreover, a meta-analysis study showed that up to 41% of the ET patients who undergo bilateral DBS develop some form of speech impairment (112). Furthermore, the same study reported the risk of dysarthria to be higher under bilateral stimulation when compared to unilateral one.

Another tract, that runs through the PSA is the cerebello-rubro-spinal loop (93). It has its origins in the cerebellar interposed nucleus and from there it is connected to the magnocellular part of the red nucleus. From the red nucleus, it forms the rubro-spinal tract, gathering sensory information from the motion receptors in the muscle spindles. From the spinal cord the fibres go back to the cerebellar interposed nucleus. The cerebello-rubro-spinal loop is held responsible for regulating the muscle tone of the body and changes in its signals might lead to the appearance of ataxic symptoms (93,111). As all of the patients in the current study reported gait ataxia as a long-lasting side effect, the cerebello-rubro-spinal loop might also pose an unwanted DBS-target.

Furthermore, two patients in the study reported nausea and headache as lasting immediate side effect of overstimulation. As the vestibular nuclei are to be found in the brain stem, not far away from PSA, and taking under consideration the nausea as a side effect, there would also be a possibility of their unwanted co-stimulation.

All of the patients, when increasing the stimulation intensity, reported paresthesia in the upper limb, correspondent to the stimulation site. Despite the unpleasantness of this side effect, it was only transient and was observed just for a few seconds. It could be attributed to a temporary stimulation of the ventralis caudalis nucleus, which has a somatosensory function and is positioned posterior to VIM (113).

In short, it becomes clear that the anatomical structures around the ventrolateral thalamus belong to multiple systems and are involved in multiple functions.

4.3 Deep brain stimulation programming

4.3.1 Stimulation intensity

Deep brain stimulation could be programmed individually with proper adjustment of parameter settings. To begin with, there is a relation between stimulation intensity and stimulation radius. With higher intensity, the stimulation radius grows. The intensity, on the other hand, decreases with growing distance from the source (107). Furthermore, highly myelinated axons with higher velocity need less intensity to be excited, compared to those with lower velocity. The axon

segment, which is mainly activated by DBS is the Ranvier node, because it possesses the smallest resistance (107). In addition, the three-dimensional orientation of an axon plays a role for its excitation pattern, as axons, which run parallel to the voltage gradient, are most likely to be excited. In contrast, axons that are perpendicular to the voltage gradient are not affected by the current (114). To sum up, whether a certain axon is excited or not depends on its distance from the electrode, its diameter and its spatial orientation.

4.3.2 Pulse width

In principle, the longer the pulse width is, the smaller the intensity needed to activate an axon. The minimal amount of current, which is needed to excite an axon with infinite stimulus duration, is termed rheobasis. The time needed to excite an axon, with the amount of current double the rheobasis, is called chronaxie. The chronaxie of single myelinated fibres in the CNS varies from 40 to 100 µs (107).

The relationship between pulse width and intensity has been described with the following empirical equation: $I = I_r(l + \frac{C}{t})$. I signifies intensity, I_r stands for the rheobasis, l describes the membrane constant, C is chronaxie and t is time. The equation can be used to calculate different chronaxies when changing the current intensity and, in this way, define different neuronal populations within a volume of tissue (115). Defining different neuronal populations on the basis of chronaxie has already been applied in ET patients with subthalamic stimulation. Under supra-therapeutic PSA DBS, different chronaxies have been observed, which means that different loops are probably selectively stimulated (93).

In the context of STN-DBS, reducing the pulse duration to <60µs widened the therapeutic window by 182%. The maximal beneficial effect was reached at 30µs (116). Chronaxie measurements of STN suggest that decreasing the pulse width selectively excites axons of smaller size and at shorter distance from the electrode. In this way a more selective DBS is achieved. Within the context of ET, shorter pulse width up to 40µs proves to be a promising programming option, as it increases SET, while maintaining TT (117).

4.3.3 Stimulation polarity

Electrode polarity plays an important role in designing DBS. As used in the current study, cathodal monopolar stimulation creates a stream of positive particles towards the negative polarized cathode. In contrast, anodal stimulation creates a particle stream away from the electrode (107). During anodal stimulation, up to four times higher intensities are needed to achieve the same effects as with cathodal stimulation (118).

4.3.4 Stimulation frequency

Another way to program DBS is to change frequency. When using higher frequencies, smaller intensities are needed to reach TT in ET (119). Very high frequencies might interfere with the refractory period of the axons and, consequently, inhibit it. Nevertheless, when the stimulation frequency is long enough to give the axon time to recover it can sustain a certain oscillation pace within the axon. The frequencies used for DBS are usually >100 Hz. While low frequencies (<10Hz) could worsen tremor in STN-DBS, higher frequencies have been demonstrated to improve it, with a saturation of the beneficial effect at approximately 200 Hz (120). Although the cellular mechanisms behind this beneficial effect are poorly understood, such higher frequencies might play a filtering role (121).

In the context of ET-DBS, HFS improves tremor. Low frequency stimulation (LFS) with <10Hz causes global tremor increase (122). Tremor in ET is suppressed more effectively with HSF in PSA than in VIM (110). Nonetheless, lowering the stimulation frequency in 20Hz intervals until TT was reached, significantly improved gait and ataxia in ET (123).

4.3.5 Directional deep brain stimulation

Although novel devices allow directional DBS, there is little clinical evidence regarding this new approach in ET. In order to understand why dDBS could play a role in achieving better outcome, first we have to view its biophysical properties and compare them with the conventional oDBS. While oDBS creates a spherical field around the axis of the lead, the biophysical model of dDBS would have an ellipsoid shape, pointing in certain direction (124).

Furthermore, the same intensity increment in both stimulation settings increases the volume of neuronal activation of dDBS more significantly compared to oDBS (124, 125). The notion that dDBS might yield higher beneficial effects is already supported by several studies, mostly in PD. An intraoperative double-blind comparison of dDBS versus oDBS in 11 PD and two ET patients showed significantly wider TW and lower TT for best dDBS compared to oDBS (127). In the same study, TW for best dDBS was 41% wider; TT with 43% lower and the VNA with 6mm³ smaller than for oDBS. Another intraoperative comparison, performed by a separate research group reported up to 1.5mA higher SETs for dDBS in a group of eight PD patients (128).

Moreover, similar results have been reported by Steigerwald et al. in a study exploring the beneficial effects of chronic dDBS in PD (129). The beneficial effect of dDBS was also reported by Timmermann et al. who estimated significant SET increase for dDBS with sustained clinical efficacy (130).
While these findings support the idea that dDBS provides larger programming flexibility for PD, little is known concerning the effect of dDBS for ET. Although the two conditions exhibit different pathological mechanisms and targets of choice inside the brain, the principle of dDBS could have a universal value in both clinical conditions. Theoretically, it could also be applied in the setting of ET. In the context of ET, dDBS could not only widen TWs but also help in defining the best target of choice for DBS. Thus, it could broaden our understanding of the mechanisms behind DBS in ET and define smaller targets of choice.

4.3.6 Effects of directional deep brain stimulation in the posterior subthalamic area on therapeutic window and volume of neuronal activation

According to our findings, TW in dDBS for ET is wider than in the conventional oDBS, which results from smaller TT. Our results are in line with earlier reports on the topic. For example, Rebelo et al. have shown TT in dDBS to be 31% lower than in oDBS (99). This probably resulted from greater VNA increase within the same intensity increments when stimulating directionally.

All in all, we could observe a larger VNA at dDBS than in oDBS at similar SET. This finding argues for a certain level of field restriction retention, also with higher stimulation intensities.

4.4 Deep brain stimulation and clinical scores

In this study, for the first time, the immediate effects of dDBS and oDBS in PSA on clinical tremor and ataxia scores have been studied systematically and prospectively. All clinical scores, as well as accelerometry indicated better tremor control and smaller tremor amplitude when the stimulation was switched on. No significant difference was observed between dDBS and oDBS regarding clinical effectiveness, which implies that dDBS is as effective as oDBS. It is important to mention, that our study explored only immediate stimulation effects. Hence, it cannot be excluded that beneficial and side effects might change under chronic stimulation. Regarding the underlying mechanisms of VIM/PSA DBS it is believed that the modulation of dentate-thalamic fibres is responsible for immediate therapeutic effects serving for both suppression of tremor and reduction of ataxia (93, 130). There are reports of a gradual decrease of VIM/PSA stimulation efficacy over time, following excellent initial tremor suppression (132). Likewise, stimulation-induced progressive gait ataxia is a known phenomenon emerging under chronic VIM/PSA DBS and causing a relevant decline in quality of life (92, 93, 130).

4.5 Inter-individual variability of directional deep brain stimulation for essential tremor

In our study, we observed substantial inter-individual variability among the patients' satisfaction with DBS. There are several factors that might contribute to these differences: (1) different anatomical and functional properties of PSA DBS, compared to the better established STN-DBS; (2) individual features of the patient such as ET-phenotype, onset age and patient expectations; (3) habituation effects towards DBS.

(1) dDBS has already proven superior to oDBS in PD patients. In the context of PD, the target of choice is the STN and the side effects are believed to be caused by, among others, an unwanted stimulation of the internal capsule (127). As the anatomical surroundings of VIM/PSA and STN differ, it could be possible that the structures causing side effects are more densely positioned around VIM than

around STN. Hence, to perform field restriction upon VIM structures, as well as on the dentato-thalamo-cortical loop might be more difficult than on STN. This suggestion is supported by the fact that the ET exhibits a narrower frequency-intensity tolerance than PD (133). Moreover, Dembek et al. and Sreigerwald et al. have used the same increments of stimulation intensity (step sizes of 0.5–1mA) for both dDBS and oDBS. Nevertheless, VNA expands more with growing intensity in dDBS. Therefore, smaller increment size might be more appropriate for dDBS, as an increment of 0.5mA, when stimulating directionally, could blur out a potential difference with oDBS. In our study, VNA at SET in dDBS was significantly larger than in oDBS, before the occurrence of side effects. Yet, further studies are needed to accomplish a comparative anatomical exploration of STN and VIM/PSA responses to dDBS.

(2) Furthermore, ET is not a static condition. As the condition may have a neurodegenerative component and worsen over time, it probably affects additional structures in the process. This means that not every patient would respond equally to DBS. Factors, such as patient age and disease duration would play a possible role in the effectiveness of DBS. Moreover, there are different phenotypic variations of ET, which might also respond differently to the therapy. In this relation, further studies are needed to analyze if the age of the patient, the onset of the disease and the disease duration have an impact on the effectiveness of DBS. Another major factor includes the patient expectations from DBS. Unrealistic expectations might decrease levels of satisfaction, even at the presence of beneficial effects.

(3) In the context of chronic stimulation there might be habituation factors which have an impact on the effectiveness of DBS. A habituation effect was reported by Barbe et al. who have proven that the beneficial clinical effect on tremor after a systemic parameter optimization faded in the 10 weeks-follow up (84). Moreover, reports from older studies have suggested that the stimulation intensities need to be gradually increased over time, in order to achieve the same clinical benefit as in the beginning (132).

4.6 Conclusion

We found dDBS to be superior to conventional oDBS regarding therapeutic window and as equally effective as oDBS regarding clinical effect and energy consumption. Furthermore, in dDBS higher stimulation volumes were realizable

at similar side effect thresholds, which argues for some persistence of directionality. Therefore, dDBS could compensate for suboptimally placed leads and should be considered first line for tremor patients.

4.7 Alternative therapeutic strategies

Novel devices provide other DBS programming opportunities besides directional stimulation. For example, minimizing the electrode diameter would be a good step towards a more selective stimulation technique (124). Moreover, novel techniques provide the opportunity for interleaving stimulation and closed loop stimulation. The interleaving stimulation makes it possible to switch on multiple directions of stimulation at the same time. Thus, DBS can be programmed in numerous ways to fit individual needs. In fact, interleaving stimulation has already been demonstrated as significantly improving verbal fluency under DBS when compared to a conventional mode of stimulation for ET (134). Closed loop stimulation, on the other hand, could interact with the neuronal environment. The electrodes receive input information from the brain tissue or the limbs and consequently send impulses only when needed. Such an interactive pacemaker could not only prolong IPG-life span but also reduce the habituation effect. The technology continues to be in development for chronic stimulation.

5 Literature:

1. Louis ED. Essential tremor.Arch Neurol 2000;57:1522–24.

2. Louis ED. Essential tremor. Lancet Neurol [Internet]. 2005 Feb [cited 2017 May 16];4(2):100–10. Available from: http://www.sciencedirect.com/science/article/pii/S1474442205009919

3. Louis ED, Broussolle E, Goetz CG, Krack P, Kaufmann P, Mazzoni P. Historical underpinnings of the term essential tremor in the late 19th century. Neurology [Internet]. 2008 Sep 9 [cited 2017 May 18];71(11):856–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461999/

4. Marsden, CD.; Obeso, JA.; Rothwell, JC. Benign essential tremor is not a single entity. In: Yahr, MD., editor. Current Concepts of Parkinson's Disease and Related Disorders. Amsterdam: Excerpta Medica; 1983. p. 31-46.

5. Lee MS, Kim YD, Im JH, Kim HJ, Rinne JO, Bhatia KP. 123I-IPT brain SPECT study in essential tremor and Parkinson's disease. Neurology. 1999 Apr 22;52(7):1422–6.

6. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor--some controversial aspects. Mov Disord Off J Mov Disord Soc. 2011 Jan;26(1):18–23.

7. Elble, RJ.; Deuschl, G. Tremor. In: Brown, WF.; Bolton, CF.; Aminoff, M., editors.Neuromuscular Function and Disease: Basic,Clinical and Electrodiagnostic Aspects. Philadelphia: W. B. Saunders Co; 2002. p. 1759-1779.This is a review of the clinical neurophysiology of tremor.

8. Louis ED. "Essential Tremor" or "the Essential Tremors": Is This One Disease or a Family of Diseases? Neuroepidemiology [Internet]. 2014 [cited 2017 May 15];42(2):81–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945103/

9. Benito-León J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol [Internet]. 2006 [cited 2017 May 17];2(12):666–78. Available from: https://www.nature.com/nrneurol/journal/v2/n12/full/ncpneuro0347.html

10. Jankovic J. Essential tremor: A heterogenous disorder. Mov Disord [Internet]. 2002 Jul 1 [cited 2017 May 17];17(4):638–44. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.10221/abstract

11. Okubadejo NU, Bankole IA, Ojo OO, Ojini FI, Danesi MA. Prevalence of essential tremor in urban Lagos, Nigeria: a door-to-door community-based study. BMC Neurol [Internet]. 2012 Sep 27 [cited 2017 May 15];12:110. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488469/

12. Rautakorpi I, Takala J, Marttila RJ, Sievers K, Rinne UK. Essential tremor in a Finnish population. Acta Neurol Scand [Internet]. 1982 Jul 1 [cited 2017 May

16];66(1):58–67. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0404.1982.tb03129.x/abstract

13. Louis ED, Marder K, Cote L, Pullman S, Ford B, Wilder D, et al. Differences in the Prevalence of Essential Tremor Among Elderly African Americans, Whites, and Hispanics in Northern Manhattan, NY. Arch Neurol [Internet]. 1995 Dec 1 [cited 2017 May 16];52(12):1201–5. Available from: http://jamanetwork.com/journals/jamaneurology/fullarticle/593768

14. Sur H, İlhan S, Erdoğan H, Öztürk E, Taşdemir M, Börü ÜT. Prevalence of essential tremor: A door-to-door survey in Şile, Istanbul, Turkey. Parkinsonism Relat Disord [Internet]. 2009 Feb [cited 2017 May 16];15(2):101–4. Available from: http://www.sciencedirect.com/science/article/pii/S1353802008001077

15. Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: a 45-year study. J Neurol Neurosurg Psychiatry [Internet]. 1984 May [cited 2017 May 16];47(5):466–70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1027820/

16. Louis ED, Benito-León J, Ottman R, Bermejo-Pareja F; Neurological Disorders in Central Spain (NEDICES) Study Group: A population- based study of mortality in essential tremor. Neurology 2007; 69: 1982– 1989.

17. Benito-León J, Bermejo-Pareja F, Louis ED, Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of essential tremor in three elderly populations of central Spain. Neurology. 2005 May 24;64(10):1721–5.

18. Louis ED, Ford B, Frucht S, Barnes LF, X-Tang M, Ottman R. Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. Ann Neu- rol 2001;49:761 – 769b.

19. LaRoia H, Louis ED. Association between Essential Tremor and Other Neurodegenerative Diseases: What Is the Epidemiological Evidence? Neuroepidemiology [Internet]. 2011 Sep [cited 2017 May 15];37(1):1–10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142098/

20. Louis ED, Clark L, Ottman R. Familial Aggregation and Co-Aggregation of Essential Tremor and Parkinson's Disease. Neuroepidemiology [Internet]. 2016 [cited 2017 May 17];46(1):31–6. Available from: http://www.karger.com/Article/Abstract/442021

21. Jankovic J, Fahn S. Physiologic and pathologic tremors. Diagnosis, mechanism, and management. Ann Intern Med. 1980 Sep;93(3):460–5.

22. Poeck K, Hacke W. Neurologie. 12th ed. Springer; 2006. 815 p.

23. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the Classification of Tremors. From the Task Force on Tremor of the International Parkinson and Movement Disorder Society. Mov Disord Off J Mov Disord Soc [Internet]. 2018 Jan [cited 2020 Feb 6];33(1):75–87. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6530552/

24. Larsen TA, Calne DB. Essential tremor. Clin Neuropharmacol. 1983;6(3):185–206.

25. Elble RJ. Essential tremor frequency decreases with time. Neurology. 2000 Nov 28;55(10):1547–51.

26. Poston KL, Rios E, Louis ED. Action Tremor of the Legs in Essential Tremor. Parkinsonism Relat Disord [Internet]. 2009 Sep [cited 2017 May 15];15(8):602–5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2728140/

27. Critchley M. Observations on essential (heredofamial) tremor. Brain J Neurol. 1949 Jun;72(Pt. 2):113–39.

28. Hubble JP, Busenbark KL, Pahwa R, Lyons K, Koller WC. Clinical expression of essential tremor: Effects of gender and age. Mov Disord [Internet]. 1997 Nov 1 [cited 2017 May 20];12(6):969–72. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.870120620/abstract

29. Louis ED, Ford B, Frucht S. Factors associated with increased risk of head tremor in essential tremor: A community-based study in northern Manhattan. Mov Disord [Internet]. 2003 Apr 1 [cited 2017 May 20];18(4):432–6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.10395/abstract

30. Robakis D, Louis ED. Head Tremor in Essential Tremor: “Yes-Yes”, “No-No”, or “Round and Round”? Parkinsonism Relat Disord [Internet]. 2016 Jan [cited 2017 May 15];22:98–101. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4695227/

31. Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain J Neurol. 2000 Aug;123 (Pt 8):1568–80.

32. De Jong RN. The neurologic examination. Hagerstown Maryland: Harper & Row, 1979:422.

33. Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. Mov Disord [Internet]. 1994 Jan 1 [cited 2017 May 20];9(2):193–6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.870090212/abstract

34. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. Brain J Neurol. 2001 Nov;124(Pt 11):2278–86.

35. Louis ED, Hernandez N, Michalec M. Prevalence and Correlates of Rest Tremor in Essential Tremor: Cross-Sectional Survey of 831 Patients Across Four Distinct Cohorts. Eur J Neurol Off J Eur Fed Neurol Soc [Internet]. 2015 Jun [cited 2017 May 15];22(6):927–32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4414706/

36. Louis ED, Bromley SM, Jurewicz EC, Watner D. Olfactory dysfunction in essential tremor: a deficit unrelated to disease duration or severity. Neurology. 2002 Nov 26;59(10):1631–3.

37. Benito-León J, Louis ED, Bermejo-Pareja F. Reported Hearing Impairment in Essential Tremor: A Population-Based Case-Control Study. Neuroepidemiology [Internet]. 2008 Feb [cited 2017 May 21];29(3–4):213–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2824584/

38. Louis ED, Marder K, Jurewicz EC, Watner D, Levy G, Mejia-Santana H. Body Mass Index in Essential Tremor. Arch Neurol [Internet]. 2002 Aug 1 [cited 2017 May 21];59(8):1273–7. Available from: http://jamanetwork.com/journals/jamaneurology/fullarticle/782583

39. Benito-León J, Louis ED, Bermejo-Pareja F, Neurological Disorders in Central Spain (NEDICES) Study Group. Population-based case-control study of cognitive function in essential tremor. Neurology. 2006 Jan 10;66(1):69–74.

40. Lombardi WJ, Woolston DJ, Roberts JW, Gross RE. Cognitive deficits in patients with essential tremor. Neurology. 2001 Sep 11;57(5):785–90.

41. Murray TJ. Essential tremor. Can Med Assoc J [Internet]. 1981 Jun 15 [cited 2017 Jul 5];124(12):1559–70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1862527/

42. Thenganatt MA, Louis ED. Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations. Expert Rev Neurother [Internet]. 2012 Jun [cited 2017 May 15];12(6):687–96. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475963/

43. Burne JA, Hayes MW, Fung VSC, Yiannikas C, Boljevac D. The contribution of tremor studies to diagnosis of parkinsonian and essential tremor: a statistical evaluation. J Clin Neurosci Off J Neurosurg Soc Australas. 2002 May;9(3):237–42.

44. Benamer HTS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: The [123I]-FP-CIT study group. Mov Disord [Internet]. 2000 May 1 [cited 2017 May 16];15(3):503–10. Available from: http://onlinelibrary.wiley.com/doi/10.1002/1531-8257(200005)15:3<503::AID-MDS1013>3.0.CO;2-V/abstract

45. Foster NL, Newman RP, LeWitt PA, Gillespie MM, Chase TN. Treatment of resting tremor by beta-adrenergic blockade. Am Heart J. 1984 Oct;108(4 Pt 2):1173–7.

46. Higgins JJ, Pho LT, Nee LE. A gene (ETM) for essential tremor maps to chromosome 2p22-p25. Mov Disord [Internet]. 1997 Nov 1 [cited 2017 May 16];12(6):859–64. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.870120605/abstract

47. Clark LN, Louis ED. Challenges in Essential Tremor Genetics. Rev Neurol (Paris) [Internet]. 2015 [cited 2017 May 15];171(6–7):466–74. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4863985/

48. Louis ED, Ford B, Frucht S, Barnes LF, X-Tang M, Ottman R. Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. Ann Neurol. 2001 Jun;49(6):761–9.

49. Louis ED, Dogu O. Does Age of Onset in Essential Tremor Have a Bimodal Distribution? Data from a Tertiary Referral Setting and a Population-Based Study. Neuroepidemiology [Internet]. 2007 [cited 2017 Jul 22];29(3–4):208–12. Available from: http://www.karger.com/Article/Abstract/111584

50. Tanner CM, Goldman SM, Lyons KE, Aston DA, Tetrud JW, Welsh MD, et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. Neurology. 2001 Oct 23;57(8):1389–91.

51. Gulcher JR, Jónsson Þ, Kong A, Kristjánsson K, Frigge ML, Kárason A, et al. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. Nat Genet [Internet]. 1997 Sep [cited 2017 May 16];17(1):84–7. Available from: https://www.nature.com/ng/journal/v17/n1/abs/ng0997-84.html

52. Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB, et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. Brain J Neurol. 2006 Sep;129(Pt 9):2318–31.

53. Unal Gulsuner H, Gulsuner S, Mercan FN, Onat OE, Walsh T, Shahin H, et al. Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease. Proc Natl Acad Sci U S A. 2014 Dec 23;111(51):18285–90.

54. Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, Jonsdottir GA, et al. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet. 2009 Mar;41(3):277–9.

55. Thier S, Lorenz D, Nothnagel M, Poremba C, Papengut F, Appenzeller S, et al. Polymorphisms in the glial glutamate transporter SLC1A2 are associated with essential tremor. Neurology. 2012 Jul 17;79(3):243–8.

56. Louis ED. Environmental Epidemiology of Essential Tremor. Neuroepidemiology [Internet]. 2008 [cited 2017 May 22];31(3):139–49. Available from: http://www.karger.com/Article/Abstract/151523

57. Louis ED. Essential Tremor: From Bedside to Bench and Back to Bedside. Curr Opin Neurol [Internet]. 2014 Aug [cited 2017 May 15];27(4):461–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4122986/

58. Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A, McNamara JO, and White LE (2008). Neuroscience. 4th ed. Sinauer Associates. pp. 432–4.

59. Production bücher de I and. Kurzlehrbuch Neuroanatomie [Internet]. [cited 2017 May 22]. Available from: http://www.buecher.de/shop/anatomie-biologie-physiologie/kurzlehrbuch-neuroanatomie/ulfig-norbert/products_products/detail/prod_id/22914316/

60. Yu M, Ma K, Faust PL, Honig LS, Cortés E, Vonsattel J-PG, et al. Increased Number of Purkinje Cell Dendritic Swellings in Essential Tremor. Eur J Neurol [Internet]. 2012 Apr [cited 2017 May 22];19(4):625–30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3297734/

61. Axelrad JE, Louis ED, Honig LS, Flores I, Ross GW, Pahwa R, et al. Reduced Purkinje Cell Number in Essential Tremor. Arch Neurol [Internet]. 2008 Jan [cited 2017 May 22];65(1):101–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847418/

62. Kuo SH, Erickson-Davis C, Gillman A, Faust PL, Vonsattel JP, Louis ED. Increased number of heterotopic Purkinje cells in essential tremor. J Neurol Neurosurg Psychiatry. 2011; 82(9):1038– 40.

63. Erickson-Davis C, Faust PL, Vonsattel J-PG, Gupta S, Honig LS, Louis ED. "Hairy Baskets" Associated with Degenerative Purkinje Cell Changes in Essential Tremor. J Neuropathol Exp Neurol [Internet]. 2010 Mar [cited 2017 May 15];69(3):262–71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2865233/

64. Lin C-Y, Louis ED, Faust PL, Koeppen AH, Vonsattel J-PG, Kuo S-H. Abnormal climbing fibre-Purkinje cell synaptic connections in the essential tremor cerebellum. Brain [Internet]. 2014 Dec [cited 2017 May 15];137(12):3149–59. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4240294/

65. Hanajima R, Tsutsumi R, Shirota Y, Shimizu T, Tanaka N, Ugawa Y. Cerebellar dysfunction in essential tremor. Mov Disord [Internet]. 2016 [cited 2019 Sep 18];31(8):1230–4. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/mds.26629

66. Bologna M, Rocchi L, Leodori G, Paparella G, Conte A, Kahn N, et al. Cerebellar Continuous Theta Burst Stimulation in Essential Tremor. The Cerebellum [Internet]. 2015 Apr 1 [cited 2020 Feb 7];14(2):133–41. Available from: https://doi.org/10.1007/s12311-014-0621-0

67. Schnitzler A, Münks C, Butz M, Timmermann L, Gross J. Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. Mov Disord Off J Mov Disord Soc. 2009 Aug 15;24(11):1629–35.

68. Rajput AH, Rajput A. Medical Treatment of Essential Tremor. J Cent Nerv Syst Dis [Internet]. 2014 Apr 21 [cited 2017 May 15];6:29–39. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999812/

69. Zesiewicz TA, Kuo S-H. Essential tremor. BMJ Clin Evid [Internet]. 2015 Dec 15 [cited 2017 May 15];2015. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4681313/

70. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology. 1989 Dec;39(12):1587–8.

71. Lees M, Regier L, Jensen B. Pharmacologic management of essential tremor. Can Fam Physician [Internet]. 2010 Mar [cited 2017 May 16];56(3):250–2. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2837692/

72. Hedera P, Cibulčík F, Davis TL. Pharmacotherapy of Essential Tremor. J Cent Nerv Syst Dis [Internet]. 2013 Dec 22 [cited 2017 May 15];5:43–55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3873223/

73. Connor GS. A double-blind placebo-controlled trial of topiramate treatment for essential tremor. Neurology. 2002 Jul 9;59(1):132–4.

74. Claßen J, Schnitzler A, Appenrodt P, Bauer S, Behr R. Interventionelle Neurophysiologie: Grundlagen und therapeutische Anwendungen. 1st ed. Stuttgart: Thieme; 2012. 352 p.

75. Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, et al. A Comparison of Continuous Thalamic Stimulation and Thalamotomy for Suppression of Severe Tremor. N Engl J Med [Internet]. 2000 Feb 17 [cited 2017 May 22];342(7):461–8. Available from: http://dx.doi.org/10.1056/NEJM200002173420703

76. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J:Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus.Lancet1991,337:403–406.

77. Bosch DA. Stereotactic techniques in clinical neurosurgery. Wien, Germany: Springer-Verlag, 1986.

78. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor | Journal of Neurology, Neurosurgery & Psychiatry [Internet]. [cited 2017 May 16]. Available from: http://jnnp.bmj.com/content/66/3/289.long

79. Pahwa R, Lyons KL, Wilkinson SB, Carpenter MA, Tröster AI, Searl JP, et al. Bilateral thalamic stimulation for the treatment of essential tremor. Neurology. 1999 Oct 22;53(7):1447–50.

80. Børretzen MN, Bjerknes S, Sæhle T, Skjelland M, Skogseid IM, Toft M, et al. Long-term follow-up of thalamic deep brain stimulation for essential tremor – patient satisfaction and mortality. BMC Neurol [Internet]. 2014 Jun 5 [cited 2017 May 20];14:120. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052337/

81. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord Off J Mov Disord Soc. 2001 May;16(3):464–8.

82. Louis ED, Benito-León J, Ottman R, Bermejo-Pareja F:A population based study of mortality in essential tremor.Neurology 2007,96:1982–1989.

83. Nowinski WL. The cerefy brain atlases. Neuroinformatics [Internet]. 2005 Dec 1 [cited 2017 May 26];3(4):293–300. Available from: https://link.springer.com/article/10.1385/NI:3:4:293

84. Barbe MT, Liebhart L, Runge M, Deyng J, Florin E, Wojtecki L, et al. Deep brain stimulation of the ventral intermediate nucleus in patients with essential tremor: Stimulation below intercommissural line is more efficient but equally effective as stimulation above. Exp Neurol [Internet]. 2011 Jul [cited 2017 May 26];230(1):131–7. Available from: http://www.sciencedirect.com/science/article/pii/S0014488611001191

85. Ceballos-Baumann AO, Boecker H, Fogel W, Alesch F, Bartenstein P, Conrad B, et al. Thalamic stimulation for essential tremor activates motor and deactivates vestibular cortex. Neurology. 2001 May 22;56(10):1347–54.

86. Perlmutter JS, Mink JW, Bastian AJ, Zackowski K, Hershey T, Miyawaki E, et al. Blood flow responses to deep brain stimulation of thalamus. Neurology. 2002 May 14;58(9):1388–94.

87. Yousif N, Mace M, Pavese N, Borisyuk R, Nandi D, Bain P. A Network Model of Local Field Potential Activity in Essential Tremor and the Impact of Deep Brain Stimulation. PLoS Comput Biol [Internet]. 2017 Jan 9 [cited 2017 May 15];13(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5261813/

88. Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol [Internet]. 2015 Oct 1 [cited 2017 Sep 14];133(Supplement C):27–49. Available from: http://www.sciencedirect.com/science/article/pii/S030100821500088X

89. Klein JC, Barbe MT, Seifried C, Baudrexel S, Runge M, Maarouf M, et al. The tremor network targeted by successful VIM deep brain stimulation in humans. Neurology. 2012 Mar 13;78(11):787–95.

90. Fenoy AJ, Schiess MC. Deep Brain Stimulation of the Dentato-Rubro-Thalamic Tract: Outcomes of Direct Targeting for Tremor. Neuromodulation Technol Neural Interface [Internet]. 2017 Mar 1 [cited 2017 May 27];n/a-n/a. Available from: http://onlinelibrary.wiley.com/doi/10.1111/ner.12585/abstract

91. Heber IA, Coenen VA, Reetz K, Schulz JB, Hoellig A, Fimm B, et al. Cognitive effects of deep brain stimulation for essential tremor: evaluation at 1 and 6 years. J Neural Transm [Internet]. 2013 Nov 1 [cited 2017 May 27];120(11):1569–77. Available from: https://link.springer.com/article/10.1007/s00702-013-1030-0

92. Fasano A, Herzog J, Raethjen J, Rose FEM, Muthuraman M, Volkmann J, et al. Gait ataxia in essential tremor is differentially modulated by thalamic stimulation. Brain [Internet]. 2010 Dec 1 [cited 2017 May 27];133(12):3635–48. Available from: https://academic.oup.com/brain/article/133/12/3635/306759/Gait-ataxia-in-essential-tremor-is-differentially

93. Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J. Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. Brain [Internet]. 2014 Jan 1 [cited 2017 May 11];137(1):109–21. Available from: https://academic.oup.com/brain/article/137/1/109/360972/Physiological-and-anatomical-decomposition-of

94. Bruno S, Nikolov P, Hartmann CJ, Trenado C, Slotty PJ, Vesper J, et al. Directional deep brain stimulation of the ventral intermediate thalamic area for essential tremor increases therapeutic window. Neuromodulation Technol Neural Interface. 2020;

95. Stacy MA, Elble RJ, Ondo WG, Wu S-C, Hulihan J. Assessment of interrater and intrarater reliability of the Fahn–Tolosa–Marin Tremor Rating Scale in essential tremor. Mov Disord [Internet]. 2007 Apr 30 [cited 2017 May 29];22(6):833–8. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.21412/abstract

96. Elble R, Comella C, Fahn S, Hallett M, Jankovic J, Juncos JL, et al. Reliability of a new scale for essential tremor. Mov Disord Off J Mov Disord Soc [Internet]. 2012 Oct [cited 2017 May 30];27(12):1567–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157921/

97. Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a Brief Ataxia Rating Scale (BARS) Based on a Modified Form of the ICARS. Mov Disord Off J Mov Disord Soc [Internet]. 2009 Sep 15 [cited 2017 Aug 28];24(12):1820–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3800087/

98. Schmitz-Hübsch T, Montcel ST du, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia Development of a new clinical scale. Neurology [Internet]. 2006 Jun 13 [cited 2017 May 30];66(11):1717–20. Available from: http://www.neurology.org/content/66/11/1717

99. Rebelo P, Green AL, Aziz TZ, Kent A, Schafer D, Venkatesan L, et al. Thalamic Directional Deep Brain Stimulation for tremor: Spend less, get more. Brain Stimulat [Internet]. 2018 May 1 [cited 2018 May 20];11(3):600–6. Available from: http://www.sciencedirect.com/science/article/pii/S1935861X17310318

100. Koss AM, Alterman RL, Tagliati M, Shils JL. Calculating total electrical energy delivered by deep brain stimulation systems. Ann Neurol [Internet]. 2005 Jul 1 [cited 2018 May 20];58(1):168–168. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.20525

101. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci. 1997 Feb 12;145(2):205–11.

102. Mostile G, Giuffrida JP, Adam OR, Davidson A, Jankovic J. Correlation between Kinesia system assessments and clinical tremor scores in patients with essential tremor. Mov Disord [Internet]. 2010 Sep 15 [cited 2017 May 11];25(12):1938–43. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.23201/abstract

103. Giuffrida JP, Riley DE, Maddux BN, Heldman DA. Clinically deployable Kinesia™ technology for automated tremor assessment. Mov Disord [Internet]. 2009 Apr 15 [cited 2017 May 31];24(5):723–30. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.22445/abstract

104. Blomstedt P, Sandvik U, Fytagoridis A, Tisch S. THE POSTERIOR SUBTHALAMIC AREA IN THE TREATMENT OF MOVEMENT DISORDERSPAST, PRESENT, AND FUTURE. Neurosurgery [Internet]. 2009 Jun 1 [cited 2019 Apr 23];64(6):1029–42. Available from: https://academic.oup.com/neurosurgery/article/64/6/1029/2581166

105. Velasco FC, Molina-Negro P, Bertrand C, Hardy J. Further definition of the subthalamic target for arrest of tremor. J Neurosurg [Internet]. 1972 Feb 1 [cited 2019 Apr 23];36(2):184–91. Available from: https://thejns.org/view/journals/j-neurosurg/36/2/article-p184.xml

106. Louis ED, Rios E, Henchcliffe C. How are We Doing With the Treatment of Essential Tremor (ET)? Persistence of ET Patients on Medication: Data from 528 Patients in Three Settings. Eur J Neurol Off J Eur Fed Neurol Soc [Internet]. 2010 Jun 1 [cited 2017 Sep 1];17(6):882–4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2889923/

107. Ranck JB. Which elements are excited in electrical stimulation of mammalian central nervous system: A review. Brain Res [Internet]. 1975 Nov 21 [cited 2017 Aug 25];98(3):417–40. Available from: http://www.sciencedirect.com/science/article/pii/0006899375903649

108. Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011 Feb;68(2):165.

109. Hamel W, Herzog J, Kopper F, Pinsker M, Weinert D, Müller D, et al. Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor. Acta Neurochir (Wien). 2007 Aug;149(8):749–58; discussion 758.

110. Herzog J, Hamel W, Wenzelburger R, Pötter M, Pinsker MO, Bartussek J, et al. Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. Brain J Neurol. 2007 Jun;130(Pt 6):1608–25.

111. Kurzlehrbuch Neuroanatomie: Norbert Ulfig: Bücher [Internet]. [cited 2017 Sep 9]. Available from: https://www.amazon.de/Kurzlehrbuch-Neuroanatomie-Norbert-Ulfig/dp/3131429518/ref=sr_1_fkmr0_1?ie=UTF8&qid=1504957251&sr=8-1-fkmr0&keywords=kurze+lehrbuch+der+neuroanatomie%2C+ulfig

112. Alomar S, King NKK, Tam J, Bari AA, Hamani C, Lozano AM. Speech and language adverse effects after thalamotomy and deep brain stimulation in patients with movement disorders: A meta-analysis. Mov Disord [Internet]. 2017 Jan 1 [cited 2017 May 27];32(1):53–63. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.26924/abstract

113. Gibson WS, Jo HJ, Testini P, Cho S, Felmlee JP, Welker KM, et al. Functional correlates of the therapeutic and adverse effects evoked by thalamic stimulation for essential tremor. Brain [Internet]. 2016 Aug [cited 2017 May 15];139(8):2198–210. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4958905/

114. Rushton W a. H. The effect upon the threshold for nervous excitation of the length of nerve exposed, and the angle between current and nerve. J Physiol [Internet]. 1927 Sep 9 [cited 2017 Sep 5];63(4):357–77. Available from: http://onlinelibrary.wiley.com/doi/10.1113/jphysiol.1927.sp002409/abstract

115. Holsheimer J, Dijkstra EA, Demeulemeester H, Nuttin B. Chronaxie calculated from current-duration and voltage-duration data. J Neurosci Methods. 2000 Apr 1;97(1):45–50.

116. Reich MM, Steigerwald F, Sawalhe AD, Reese R, Gunalan K, Johannes S, et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. Ann Clin Transl Neurol [Internet]. 2015 Apr [cited 2017 May 28];2(4):427–32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4402087/

117. Moldovan A-S, Hartmann CJ, Trenado C, Meumertzheim N, Slotty PJ, Vesper J, et al. Less is more – Pulse width dependent therapeutic window in deep brain stimulation for essential tremor. Brain Stimul Basic Transl Clin Res Neuromodulation [Internet]. 2018 Apr 26 [cited 2018 May 20];0(0). Available from: https://www.brainstimjrnl.com/article/S1935-861X(18)30141-4/fulltext

118. BeMent SL, Ranck JB. A model for electrical stimulation of central myelinated fibers with monopolar electrodes. Exp Neurol. 1969 Jun;24(2):171–86.

119. Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien). 1993;58:39–44.

120. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. Mov Disord [Internet]. 2006 Jun 1 [cited 2017 May 29];21(S14):S284–9. Available from: http://onlinelibrary.wiley.com/doi/10.1002/mds.20961/abstract

121. Zheng F, Lammert K, Nixdorf-Bergweiler BE, Steigerwald F, Volkmann J, Alzheimer C. Axonal failure during high frequency stimulation of rat subthalamic nucleus. J Physiol. 2011 Jun 1;589(Pt 11):2781–93.

122. Pedrosa DJ, Auth M, Eggers C, Timmermann L. Effects of low-frequency thalamic deep brain stimulation in essential tremor patients. Exp Neurol [Internet]. 2013 Oct [cited 2017 May 27];248:205–12. Available from: http://www.sciencedirect.com/science/article/pii/S0014488613001829

123. Ramirez-Zamora A, Boggs H, Pilitsis JG. Reduction in DBS frequency improves balance difficulties after thalamic DBS for essential tremor. J Neurol Sci [Internet]. 2016 Aug 15 [cited 2017 May 27];367:122–7. Available from: http://www.sciencedirect.com/science/article/pii/S0022510X1630332X

124. Schüpbach WMM, Chabardes S, Matthies C, Pollo C, Steigerwald F, Timmermann L, et al. Directional leads for deep brain stimulation: Opportunities and challenges. Mov Disord Off J Mov Disord Soc. 2017 Aug 26;

125. Krishnan T, Mustakos R, Steinke GK. 374 Modeling the Effects of Current Steering With Directional Leads. Neurosurgery. 2016 Aug;63 Suppl 1:211.

126. Volkmann J, Chabardes S, Steinke GK, Carcieri S. 375 DIRECT DBS: A Prospective, Multicenter Clinical Trial With Blinding for a Directional Deep Brain Stimulation Lead. Neurosurgery. 2016 Aug;63 Suppl 1:211–2.

127. Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain J Neurol. 2014 Jul;137(Pt 7):2015–26.

128. Contarino MF, Bour LJ, Verhagen R, Lourens MAJ, de Bie RMA, van den Munckhof P, et al. Directional steering: A novel approach to deep brain stimulation. Neurology. 2014 Sep 23;83(13):1163–9.

129. Steigerwald F, Müller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. Mov Disord [Internet]. 2016 Aug [cited 2017 May 11];31(8):1240–3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089579/

130. Dembek TA, Reker P, Visser-Vandewalle V, Wirths J, Treuer H, Klehr M, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. Mov Disord Off J Mov Disord Soc. 2017 Aug 26;

131. Reich MM, Brumberg J, Pozzi NG, Marotta G, Roothans J, Åström M, et al. Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy? Brain [Internet]. 2016 Nov 1 [cited 2017 May 27];139(11):2948–56. Available from: https://academic.oup.com/brain/article/139/11/2948/2422128/Progressive-gait-ataxia-following-deep-brain

132. Hariz MI, Shamsgovara P, Johansson F, Hariz G-M, Fodstad H. Tolerance and Tremor Rebound following Long-Term Chronic Thalamic Stimulation for Parkinsonian and Essential Tremor. Stereotact Funct Neurosurg [Internet]. 1999 [cited 2017 May 17];72(2–4):208–18. Available from: http://www.karger.com/Article/Abstract/29728

133. Cagnan H, Little S, Foltynie T, Limousin P, Zrinzo L, Hariz M, et al. The nature of tremor circuits in parkinsonian and essential tremor. Brain J Neurol. 2014 Dec;137(Pt 12):3223–34.

134. Barbe MT, Dembek TA, Becker J, Raethjen J, Hartinger M, Meister IG, et al. Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor. Neurology [Internet]. 2014 Feb 18 [cited 2017 May 27];82(7):614–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3963416/

6 Anhang

Modified International Cooperative Ataxia Rating Scale (mICARS):

I. Gang und Stand

1. **Gang**
   0. **normal**
   1. **Fast normal, aber breitbasig**
   2. **Klar abnorm, aber ohne Hilfsmittel**
   3. **Schwankender Gang, Schwierigkeiten beim Wenden, aber ohne Hilfsmittel**
   4. **Freies Laufen nicht möglich, Patient stützt sich gelegentlich an der Wand ab**
   5. **Pat. kann nur mit einem Stock laufen**
   6. **Pat. kann nur mit zwei Stöcken oder am Rollator laufen**
   7. **Pat. kann nur mit Hilfsperson laufen**
   8. **Pat. nicht gehfähig**

2. **Ganggeschwindigkeit**
   0. **normal**
   1. **gering vermindert**
   2. **deutlich vermidnert**
   3. **extrem langsam**
   4. **freies Gehen nicht möglich**

3. **Standfestigkeit mit offenen Augen**
   0. **normal, kann >10Sek. auf einem Bein stehen**
   1. **kann mit geschlossenen Beinen stehen und in Tandem-Position, jedoch nicht >10 Sek. auf einem Bein**
   2. **kann mit geschlossenen Beinen stehen, aber nicht in Tandem-Position**
   3. **kann nicht mit geschlossenen Beinen stehen, aber in normaler Position mit nur leichtem Schwanken**
   4. **Kann ohne Hilfe stehen mit beträchtlichem Schwanken**
   5. **Kann nur mit Halten an einem Arm stehen**
   6. **Kann nur mit Halten an beiden Armen stehen**

4. **Knöchelabstand bei normalem Stehen**
   0. **Normal (<10cm)**
   1. **>10cm**
   2. **25-35cm**
   3. **>35cm**
   4. **normales Stehen nicht möglich**

5. **Schwanken bei geschlossenen Beinen mit offenen Augen**
   0. **Normal**
   1. **Leiches Schwanken**
   2. **Moderates Schwanken (<10cm am Kopf)**
   3. **Schweres Schwanken (>10cm am Kopf), Sturz zu befürchten**
   4. **Sofortiges Umfallen**

6. **Schwanken bei geschlossenen Beinen mit geschlossenen Augen**
   0. **Normal**
   1. **Leichtes Schwanken**
   2. **Moderates Schwanken (<10cm am Kopf)**
   3. **Schweres Schwanken (>10cm am Kopf), Sturz zu befürchten**
   4. **Sofortiges Umfallen**

7. **Sitzen**
   0. **Normal**
   1. **Leichtes Schwanken des Rumpfes**
   2. **Moderates Schwanken des Rumpfes**
   3. **Schweres Schwanken**
   4. **Unmöglich**

II. Bewegung und Koordination

8. **Knie-Hacke-Versuch: Intentionstremor**
   0. **Normal**
   1. **Herunterfahren nicht flüssig oder verlangsamt, aber ohne Wackeln**
   2. **Herunterfahren am Schienbein mit Wackeln**
   3. **Herunterfahren am Schienbein mit lateralen Bewegungen**
   4. **Herunterfahren am Schienbein mit extremen lateralen Bewegungen oder Test unmöglich**

9. **Knie-Hacke-Versuch: Aktionstremor**
   0. **normal**
   1. **Tremor hört sofort auf, wenn die Hacke das Knie erreicht**
   2. **Tremor hört nach max. 10 Sek. auf, wenn die Hacke das Knie erreicht**
   3. **Tremor hält mehr als 10 Sek. an, wenn die Hacke das Knie erreicht**
   4. **Anhaltender Tremor oder Test nicht durchführbar**

10. **Finger-Nase-Versuch: Flüssigkeit und Dysmetrie**
    0. **normal**
    1. **Bewegung nicht ganz flüssig**
    2. **Bewegung in 2 Phasen abgehackt und/oder moderate Dysmetrie**
    3. **Bewegung in 2 Phasen abgehackt und/oder deutliche Dysmetrie**
    4. **Pat. erreicht die Nase nicht**

11. **Finger-Nase-Versuch: Intentionstremor**
    0. **Normal**
    1. **leichte Abweichungen, Amplitude <10cm**
    2. **Moderater Tremor mit Amplitude >10cm**
    3. **Tremor-Amplitude 10-40cm**
    4. **Schwerer Tremor mit Amplitude >40cm**

12. **Finger-Finger-Test**
    0. **Normal**
    1. **Leicht instabil**
    2. **Amplitude >10cm**
    3. **Amplitude 10-40cm**
    4. **Ruckartige Bewegungen >40cm**

13. **Diadochokinese**
    0. **Normal**
    1. **Leicht Dys- oder Bradydiadochokinese**
    2. **Klare Dys- oder Bradydiadochokinese aber ohne schwankenden Ellenbogen**

3. **Stark irreguläre und langsame Diadochokinese mit schwankendem Ellenbogen**
4. **Nicht möglich bei starker Diadochokinese**

14. **Archimedes-Spirale zeichnen**
    0. **Normal**
    1. **Leichte Abweichungen von der vorgegebenen Linie**
    2. **Starke Abweichungen mit Rückführung auf die vorgegebene Linie**
    3. **Stärkste Beeinträchtigung mit Hypermetrie**
    4. **Nicht möglich**

III. Sprache

15. **Dysarthrie: Sprechflüssigkeit**
    0. **Normal**
    1. **Leicht verlangsamt**
    2. **Moderat verlangsamt**
    3. **Beträchtlich verlangsamt**
    4. **Sprechen nicht möglich**
16. **Dysarthrie: Verständlichkeit**
    0. **Normal**
    1. **Etwas undeutliches Sprechen**
    2. **Undeutlich, die meisten Wörter sind zu verstehen**
    3. **Sehr undeutlich, überwiegend unverständlich**
    4. **Sprechen nicht möglich**

IV. Okulomotorikstörungen

17. **Blickrichtungsnystagmus**
    0. **Normal**
    1. **Persistent**
    2. **Persistent, jedoch moderat ausgeprägt**
    3. **Persistent und beträchtlich ausgeprägt**

18. **Blickfolge**
    0. **Normal**
    1. **Leicht sakkadiert**
    2. **Deutlich sakkadiert**

19. **Dysmetrie der Sakkaden**
    0. **Nicht vorhanden**
    1. **Deutliches Über- oder Unterschreiten der Sakkaden**

Punktsumme Teil I (max. 34): _____

Punktsumme Teil II (max. 52): _____

Punktsumme Teil III (max. 8): _____

Punktsumme Teil IV (max. 6): _____

Gesamtscore (max. 100): _____

Scale for the assessment and rating of ataxia (SARA)

Rater: Datum: Patient: Programmierer:

1) Gang	2) Haltung
Der/Die ProbandIn wird gebeten (1), in einem sicheren Abstand parallel zu einer Wand zu gehen, inklusiv eine halbe Umdrehung (eine Umdrehung um die entgegengesetzte Richtung des Ganges) und (2) in Tandem (Fersen zu Zehen) ohne Unterstützung zu gehen.	Der/Die ProbandIn wird gebeten zu stehen (1) in neutraler Position, (2) mit den Füßen parallel zusammen (Große Zehen in Berührung miteinander) und (3) in Tandem (beide Füße in einer Linie, keinen Abstand zwischen Ferse und Zehen). Der/Die ProbandIn ist Barfuß, die Augen sind geöffnet. Für jede Untersuchung sind drei Versuche erlaubt. Der beste Versucht wird evaluiert.
0. Normal, keine Schwierigkeiten beim Gehen, Umdrehen und Tandemgehen (bis zu einem Falschen Schritt erlaubt) 1. Leichte Schwierigkeiten, nur sichtbar bei 10 konsekutiven Schritte in Tandem 2. Deutlich abnormal, Tandemgehen >10 Schritte nicht möglich 3. Beträchtliche Schwankung, Schwierigkeiten bei der Halbumdrehung, aber ohne Unterstützung 4. Markante Schwankung, intermittierende Unterstützung auf der Wand erforderlich 5. Schwere Schwankung, ständige Unterstützung auf einem Stock oder leichte Unterstützung durch einen Arm erforderlich 6. Gehen >10m nur mit starker Unterstützung (zwei spezielle Stöcke oder Rollator oder begleitende Person) 7. Gehen <10m nur mit starker Unterstützung (zwei spezielle Stöcke oder Rollator oder begleitende Person) 8. Gehen unmöglich, sogar mit Unterstützung	0. Normal, Stand in Tandem für >10s möglich 1. Stand mit den Füßen zusammen ohne Schwankung möglich aber nicht für >10s in Tandem 2. Stand mit den Füßen zusammen für >10s möglich, aber mit Schwankungen 3. Stand für >10s ohne Unterstützung in neutraler Position, aber nicht mit den Füßen zusammen 4. Stand für >10s in neutraler Position möglich nur unter intermittierender Unterstützung 5. Stand für >10s in neutraler Position möglich nur unter dauernder Unterstützung durch einen Arm 6. Stand für >10s in neutraler Position unmöglich, sogar unter dauernder Unterstützung durch einen Arm

Score		Score	

3) Sitzen

Der/Die ProbandIn wird gebeten, im Bett ohne Beinunterstützung zu sitzen, die Augen sind geöffnet, die Arme sind nach vorne gestreckt.

0. Normal, keine Schwierigkeiten beim Sitzen >10s
1. Kleine Schwierigkeiten, intermittierende Schwankungen
2. Dauernde Schwankungen, aber Sitzen für >10s ohne Unterstützung möglich
3. Sitzen für >10s nur mit intermittierender Unterstützung möglich
4. Sitzen für >10s ohne dauernder Unterstützung nicht möglich

4) Sprechen

Das Sprechen wird im Rahmen der normalen Konversation evaluiert.

0. Normal
1. Vermutliche Sprachstörung
2. Beeinträchtigtes Sprechen aber leicht zu verstehen
3. Manche Wörter sind schwer zu verstehen
4. Viele Wörter sind schwer zu verstehen
5. Nur einzige Wörter sind zu verstehen
6. Sprechen komplett unverständlich

Score		Score	

5) Finger-Folgen-Versuch

Es wird für jede Seite getrennt evaluiert. Der / Die ProbandIn sitzt bequem. Falls nötig, Unterstützung des Körpers und Hilfe mit den Beinen ist dabei erlaubt. Der/Die UntersucherIn sitzt vor dem ProbandIn und führt 5 plötzliche und schnelle zeigende Fingerbewegungen in unberechenbaren Richtungen auf einer frontalen Ebene und in 50% der Reichweite der ProbandIn durch. Die Bewegungen haben eine Amplitude von 30 cm und eine Frequenz von 2s. Der/Die ProbandIn wird gebeten die Bewegungen mit seinem/ihrem Zeigefinger zu folgen, so schnell und exakt wie möglich. Die mittlere Leistung von den letzten 3 Bewegungen wird evaluiert.

0. Keine Dysmetrie
1. Dysmetrie unter Zielüberschreitung <5cm

6) Finger-Nase-Versuch

Es wird für jede Seite getrennt evaluiert. Der/Die ProbandIn sitzt bequem. Falls nötig, Unterstützung des Körpers und Hilfe mit den Beinen ist dabei erlaubt. Der/Die ProbandIn wird gebeten kontinuierlich mit seinem/ihrem Zeigefinger von seiner/ihrer Nase bis zum Finger der UntersucherIn zu zeigen. Der Finger der UntersucherIn befindet sich in 90% der Reichweite der ProbandIn. Die Bewegungen werden mit mittlerer Geschwindigkeit durchgeführt. Die durchschnittliche Leistung wird nach der Amplitude des Tremors evaluiert.

0. Keiner Tremor
1. Tremor mit Amplitude <2cm
2. Tremor mit Amplitude <5cm

2. Dysmetrie unter Zielüberschreitung <15cm 3. Dysmetrie unter Zielüberschreitung >15cm 4. Die Durchführung von 5 zeigender Bewegungen nicht möglich			3. Tremor mit Amplitude >5cm 4. Die Durchführung von 5 zeigender Bewegungen unmöglich	
Score	Rechts	Links	**Score**	Rechts/Links
Mittelwert von beiden Seiten (R+L)/2			Mittelwert von beiden Seiten (R+L)/2	

7) Schnell wechselnde Handbewegungen	**8)Knie-Hacken-Versuch**
Es wird für jede Seite getrennt evaluiert. Der/Die ProbandIn sitzt bequem. Falls nötig, Unterstützung des Körpers und Hilfe mit den Beinen ist dabei erlaubt. Der/Die ProbandIn wird gebeten 10 Zyklen von repetitiv-wechselnde Pro- und Supinationsbewegungen seiner/ihrer Hand so schnell und exakt wie möglich durchzuführen. Die Hand liegt auf dem Oberschenkel. Die Bewegungen werden von der UntersucherIn in einer Geschwindigkeit von ca. 10 Zyklen in 7s demonstriert. Die genauen Zeiten für die Durchführung der Bewegungen sind zu messen.	Es wird für jede Seite getrennt evaluiert. Der/Die ProbandIn liegt auf dem Bett, ohne die Beine zu flektieren und wird gebeten, das Bein zu heben und somit mit der Ferse auf dem Knie des kontralateralen Beins zu zeigen. Nachher wird er/sie gebeten mit der Ferse entlang des Schienbeins bis zum Knöchel herunterzurutschen. Schließlich wird das Bein auf dem Bett zurückgelegt. Die Aufgabe wird 3 Mal durchgeführt. Das Herunterrutschen sollte innerhalb 1s erfolgen. Falls der/die ProbandIn bei allen 3 Versuchen, ohne Kontakt zum Schienbein herunterrutscht, wird 4 evaluiert.
0. Normal, keine Unregelmäßigkeiten (Durchführung<10s) 1. Leicht unregelmäßig (Durchführung<10s) 2. Offensichtlich unregelmäßig, einzige Bewegungen schwer zu unterscheiden oder relevante Unterbrechungen vorhanden, Durchführung jedoch <10s	0. Normal 1. Leicht abnormal, Kontakt zum Schienbein erhalten 2. Offensichtlich abnormal, verliert Kontakt zum Schienbein zu drei Mal währen der drei Zyklen. 3. Schwer abnormal, verliert Kontakt ≥4 mal, während der drei Zyklen.

3. Sehr unregelmäßig, einzige Bewegungen schwer zu unterscheiden oder relevante Unterbrechungen vorhanden, Durchführung >10s 4. 10 Zyklen sind nicht durchzuführen			4. Die Aufgabe ist nicht durchzuführen.		
Score	Rechts	Links	**Score**	Rechts	Links
Mittelwert von beiden Seiten (R+L)/2			Mittelwert von beiden Seiten (R+L)/2		

Essential Tremor Rating Assessement Scale (TETRAS)

Rater: Datum: Patient: Programmierer:

	Bewertung			
Testgegenstand	**1**	**2**	**3**	**4**

Kopf	0,5 cm	0,5 bis < 2,5cm	2,5 bis 5cm	>5cm
Gesicht	Kaum sichtbar	Bemerkbar	Offensichtlich, in den meisten facialen Kontraktionen vorhanden	Grobes, entstelltes Zittern
Zunge				
Sprache	Leicht, nur bei „aaah“ oder „eeeh“	Bei „aaah“ und „eeeh“ und minimal beim Reden	Offensichtliches Zittern beim Reden	Manche Wörter schwer zu verstehen
Obere Extremität	Kaum sichtbar	1 bis < 3cm	5 bis < 10cm	≥20cm
Untere Extremität	Kaum sichtbar	Offensichtlich aber mild	< 5 cm	> 5cm
Spiralen	Kaum sichtbar	Offensichtliches Zittern	Teile der Figur nicht erkennbar	Ganze Figur nicht erkennbar
Handschrift	Kaum sichtbar	Offensichtliches Zittern aber lesbar	Manche Wörter nicht lesbar	Komplett unlesbar
Punktnäherung	Kaum sichtbar	1 bis < 3cm	5 bis < 10cm	>20cm
Stehen	Kaum sichtbar	Offensichtlich aber mild	Mittel	Schwer

*Bei keinem Tremor sind die Gegenstände mit **0** zu evaluieren.

Tremor-Beurteilungsskala (TRS)

A. Tremor

0 nicht vorhanden
1 gering ausgeprägt, kaum wahrnehmbar, kann intermittierend auftreten
2 mäßig ausgeprägt, Amplitude < 1 cm, kann intermittierend auftreten
3 deutlich ausgeprägt, Amplitude 1 – 2 cm
4 stark ausgeprägt, Amplitude > 2 cm

	Ruhe	Haltung	Aktion/Intention	Punkte
1. Gesicht				
2. Zunge				
3. Stimme				
4. Kopf				
5. Rechter Arm				
6. Linker Arm				
7. Rumpf				
8. Rechtes Bein				
9. Linkes Bein				
Punktsumme Teil A (max. 80)				

B. Handfunktionstestung

11. Handschrift (nur dominante Hand)

0 nicht vorhanden
1 gering ausgeprägt, kaum wahrnehmbar, kann intermittierend auftreten
2 mäßig ausgeprägt, Amplitude < 1 cm, kann intermittierend auftreten
3 deutlich ausgeprägt, Amplitude 1 – 2 cm
4 stark ausgeprägt, Amplitude > 2 cm

12. – 14. Zeichnen

0 normal
1 leichtes Zittern, Linien kreuzen sich gelegentlich
2 mäßiges Zittern, Linien kreuzen sich häufig
3 große Schwierigkeiten beim Lösen der Aufgabe, viele Fehler
4 kann die Zeichnung nicht ergänzen

	Rechte Hand	Linke Hand	Punktsumme
12. Zeichnung a			
13. Zeichnung b			
14. Zeichnung c			

a) Rechts

b) Rechts

c) Rechts

a) Links

b) Links

c) Links

15. Getränk eingießen

0 normal
1 vorsichtiger als Person ohne Tremor, verschüttet nichts
2 verschüttet wenig (bis 10%)
3 verschüttet eine beträchtliche Menge (10 – 50%)
4 verschüttet das meiste

C. Funktionelle Behinderung durch den Tremor

16. Sprache

0. normal
1. leichtes Zittern der Stimme bei Nervosität
2. ständiges leichtes Zittern der Stimme

3. **mäßiges Zittern der Stimme**
4. **starkes Zittern der Stimme, teilweise unverständlich**

17. Essen (nur feste Nahrung)

0. **Normal**
1. **leichte Beeinträchtigung, Essen fällt selten von der Gabel**
2. **mäßige Beeinträchtigung, Erbsen u.ä. fallen häufig herunter, muss den Kopf weit über den Teller beugen**
3. **deutliche Beeinträchtigung, kann nicht selbst schneiden und benutzt beide Hände zum Essen**
4. **starke Beeinträchtigung, braucht Hilfe beim Essen**

18. Aufnahme flüssiger Nahrung

0. **normal**
1. **leichte Beeinträchtigung, kann noch einen Löffel benutzen, aber nicht wenn dieser voll ist**
2. **mäßige Beeinträchtigung, kann Löffel nicht benutzen, benutzt Tasse oder Glas**
3. **deutliche Beeinträchtigung, muss Tasse oder Glas mit beiden Händen halten**
4. **starke Beeinträchtigung, muss Strohhalm benutzen**

19. Hygiene

0. **normal**
1. **leichte Beeinträchtigung, ist selbstständig aber etwas vorsichtiger**
2. **mäßige Beeinträchtigung, ist jedoch noch selbstständig**
3. **deutliche Beeinträchtigung, feinmotorische Tätigkeiten wie schminken oder rasieren nur mit beiden Händen möglich**
4. **starke Beeinträchtigung, unfähig feinmotorische Tätigkeiten auszuüben**

20. Ankleiden

0. **normal**
1. **leichte Beeinträchtigung, ist selbstständig aber etwas vorsichtiger**
2. **mäßige Beeinträchtigung, ist jedoch noch selbstständig**
3. **deutliche Beeinträchtigung, braucht z.B. Hilfe beim Zuknöpfen**
4. **starke Beeinträchtigung, braucht auch bei einfachen motorischen Tätigkeiten Hilfe**

21. Schreiben

0. **normal**
1. **geringe Beeinträchtigung, leserlich, kann noch Briefe schreiben**
2. **geringe Beeinträchtigung, leserlich, kann keine Briefe schreiben**
3. **deutliche Beeinträchtigung, unleserlich**
4. **starke Beeinträchtigung, kann keine Schecks o.ä. mehr unterschreiben**

Danksagung

Diese Arbeit ist als ein Kooperationsprojekt zwischen dem Bereich Bewegungsstörungen und Neuromodulation der Klinik für Neurologie und der Sektion Funktionelle Neurochirurgie und Stereotaxie der Klinik für Neurochirurgie am Universitätsklinikum Düsseldorf entstanden.

Ich möchte hiermit herzlich Herrn Professor Dr. Alfons Schnitzler, sowie Herrn Dr. Stefan J. Groiss und Frau Dr. Sabine Bruno für die exzellente Betreuung bedanken.

Dazu möchte ich mich herzlich bei Herrn Professor Dr. Jan Vesper, sowie Herrn PD Dr. Phlipp Slotty bedanken, da ohne deren Unterstützung dieses Projekt nicht realisierbar gewesen wäre.