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Intraoperative anatomical navigation in asleep deep brain stimulation as a tool for the interpretation of microelectrode recordings: a prospective study

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ABSTRACT

• **Introduction:** Microelectrode Recording (MER) is still regarded as a fundamental feature of Deep Brain Stimulation (DBS). In awake DBS, MERs are better characterized due to lack of sedation. During asleep DBS, general anesthesia interferes with MERs. Therefore, basing intraoperative lead localization in asleep DBS on extracellular recordings alone, requires huge expertise by the surgeon, who risks sub-optimal final electrode placement. This study aims to investigate whether anatomical navigation during asleep DBS surgery is a reliable and useful additional tool. The intraoperative association of anatomical (imaging studies and 3D reconstructions) and electrophysiological (microelectrode recordings) information would in fact permit a facilitated surgical procedure.

• **Methods/Materials:** Patients enrolled in this study undergo asleep DBS in the Pediatric and Functional Neurosurgery Department of Padova. During surgery, intraoperative MERs are integrated with deterministic anatomical imaging of the structures crossed by the trajectory, obtained using a dedicated software. This allows to visualize exact anatomical relationships of each point along the trajectory of the lead with the 3D reconstructed areas of interest. For Subthalamic Nucleus (STN) DBS these areas include the thalamus, the zona incerta, the STN and the substantia nigra, whereas for Globus Pallidus Internus (GPi) DBS these include the striatum, GPe, GPi, and the optic tract. To investigate whether this feature of anatomical navigation is a reliable and helpful additional factor in the decision-making for the placement of the definitive electrode, we compare the intraoperatively planned electrode placement with the postoperatively reconstructed electrode position.

• **Results**: Preliminary results show that the mean distance between the intraoperatively planned target and the postoperatively reconstructed target is <1 mm and the mean trajectory deviation <1°. There is a significant increase in target deviation between the first performed trajectory and the second one. This is coherent with the hypothesis that there's an increase of brain shift as the procedure goes on due to intraoperative liquor loss.

• **Discussion**: The study suggests that intraoperative anatomical navigation in DBS, using the dedicated software may be adequate for facilitated precise electrode placement, as there is no relevant difference between the intraoperatively planned electrode placement and the postoperatively reconstructed electrode position.

• **Conclusion**: Preliminary results suggest that the anatomical navigation is a useful and reliable tool to significantly facilitate the interpretation of intraoperative MERs.

BACKGROUND

DEEP BRAIN STIMULATION

OVERVIEW

Deep brain stimulation (DBS) is a medical treatment that involves the use of a device, called internal pulse generator (IPG), to deliver electrical impulses to specific areas deep within the brain through implanted electrodes. These electrical impulses can help regulate the abnormal activity that is causing symptoms in conditions such as movement disorders, psychiatric disorders, epilepsy and other.

During the DBS procedure, a surgeon places thin electrodes into the brain through small holes in the skull. These electrodes are connected to the IPG, which is usually implanted under the skin near the collarbone. Once the device is turned on, it sends electrical impulses to the brain through the electrodes, which can help reduce symptoms such as tremors, rigidity, and slowness of movement.

DBS is not a cure for these conditions, but it can significantly improve quality of life for people who are experiencing disabling symptoms despite optimal medical therapy. [1,2,3]

HYSTORY

The history of Deep Brain Stimulation begins with the advent of stereotactic neurosurgery. In 1873 a guided probe was used for the first time, by the neurophysiologist Dittmar, who used it to stimulate the medulla oblungata.[4]

Nevertheless, the first stereotactic instrument was developed by Horsley and Clark in 1908, used primarily for research in monkeys. The main issue of this instrument, which discouraged its use in humans, was the variability encountered between external anatomical landmarks of the skull and internal anatomy of deep brain structures.[6]

This issue was only addressed in the 1940s, when Dandy developed the now obsolete technique of pneumoencephalography, which permitted the evaluation of

the brain ventricles and cortex through the injection of air in the subarachnoid space.[7]

This allowed the development of different independently designed stereotactic atlases. In the 1940s, a French neurosurgeon named Dr. Jean Talairach developed a method based on a rectangular coordinate system for identifying and mapping the brain's functional areas. This technique, known as the Talairach atlas, was widely adopted for neurosurgical planning by clinicians around the world.[8,9]

In the meantime, Swedish neurosurgeon Dr. Lars Leksell developed the arc-centered coordinate system, which is the progenitor of the stereotactic systems still used today.[10] Its accuracy improved with the advent of CT scan in the mid 1970, which rapidly replaced pneumoencephalography.[11]

Concerning the surgical treatment of Parkinson's Disease, its history begins around the 1940s, when neurosurgeons performed resections of motor or premotor cortical areas in the hope of motor symptoms alleviation.[12]

Due to the poor outcome of these interventions, the surgical attention quickly moved more towards basal ganglia and thalamic lesioning, with a significantly better symptomatic improvement and less motor deficits.

However, in the 1970s the surgical lesioning of thalamic or basal structures largely ceased due to the drastic improvement of the medical therapy brought by Levodopa. This pause in the interest in advancement of surgical therapies for PD lasted until the 1990s, when the high prevalence of dyskinesias and motor fluctuations during chronic levodopa therapy became more evident. [13]

The first attempts to use DBS in thalamic, basal ganglia, and cerebellar regions for movement disorders were made in the early 1980s.[13] By the end of the same decade, it was already known that a high frequency stimulation of a certain target, could mimic a lesion in a controllable and reversable way.[14] The first target in which DBS was attempted in was the Ventralis Intermedius nucleus of the thalamus, which resulted in significant improvement in the pathological tremor, but leaving the rest of the parkinsonian symptoms unchanged.

Therefore, the Globus Pallidus internus gained interest, as the pallidotomies carried out in the previous decade gave some promising results. In 1994, bilateral GPi-DBS was carried out for the first time by the Swiss Department of Neurosurgery of Zürich on three patients, with excellent results in a up to 12 months follow-up.[15]

Shortly after, in 1995, Limousin et al. from the French University of Grenoble, performed the first Subthalamic Nucleus DBS, encouraged by the fact that in monkeys rendered parkinsonian, lesions and electrical stimulation of the subthalamic nucleus reduce all major motor disturbances. Their promising results paved the way most used DBS target to this day.

MECHANISM OF ACTION

Although there are many valid hypotheses about the therapeutic mechanisms underlying the clinical benefits of DBS in various pathologies, the precise way in which DBS alters the electrophysiology in the brain is still an active field of research.

It is important to note that one hypothesis does not necessarily exclude the other, and it is plausible that various different underlying mechanisms work together to produce the final clinical results.

FUNCTIONAL LESION HYPOTHESIS

Given the similar clinical results in the improvement of motor signs in Parkinson's Disease between surgical ablation and DBS of the Globus Pallidus internus and the Subthalamic Nucleus, the initial hypothesis was that applying a high frequency (>100Hz) stimulation in a given area produces a "functional lesion" that mimics a surgical lesion with the advantage of being reversible and adjustable in the intensity of stimulation, and therefore in the extension of the area of the functional lesion.[17]

Different mechanisms were proposed for the mechanism underlying this functional lesion, including depolarization block due to inactivation of sodium channels and increase in potassium flow, activation of afferent inhibitory fibers and depression of excitatory afferents.[18,19]

Nevertheless, this hypothesis alone leaves many questions unanswered. The most striking controversy arises comparing the effects of surgical ablation and DBS in the Globus Pallidus externus (GPe). Whereas the surgical lesion of the GPe is known to exacerbate motor symptoms in Parkinson's, DBS in the same region has some therapeutic effects. This is a clear indication that applying electrical stimulation does not merely cancel out the activity of the area it is applied in, but rather it changes the activity in the network.[20,21]

SOMATIC-AXONAL DECOUPLING HYPOTHESIS

The fact that the electric stimulation applies certain changes in firing rate and pattern of activity in the neuron's soma, does not necessarily translate to the same changes in the final output of the stimulated neuron. This is because axons have a lower action potential threshold which gives the possibility to the action potential to arise directly from the axon and travel both downstream, or prodromic, and upstream, or antidromic.[22,28]

This can be demonstrated by recording both the nuclei in which stimulation is applied, which may result inhibited, and nuclei that receive fibers from the stimulated nucleus, which in turn often result activated.[23]

An example of this phenomenon can be found in the study by Hashimoto et al. in which it is demonstrated that the stimulation of the Subthalamic Nucleus (STN), in monkeys rendered parkinsonian through the use of the neurotoxin methyl-phenyl-tetrahydropyridine (MPTP), resulted in increased activity in the GPi and GPe, due to the activation of glutamatergic fibers efferent from the STN.[24]

ACTIVATION HYPOTHESIS

The aforementioned findings led to the "activation hypothesis" in which the effects on the downstream nuclei naturally depend on the nature of the activated fibers (excitatory or inhibitory). This hypothesis is supported also by several studies involving imaging data. Specifically, Hershey et al. demonstrated using positron emission tomography (PET) how STN stimulation increased blood flow in midbrain (including STN), globus pallidus, and thalamus, primarily on the left side, but reduced blood flow bilaterally in frontal, parietal, and temporal cortex. [25]

In fact, there are studies suggesting the involvement of the hyperdirect corticosubthalamic pathway, one of the pathways governing motor control in basal ganglia, in the antidromic activation of cortical motor areas as a result of STN-DBS.[26]

Moreover, it is important to note that this activation hypothesis, extends not only to the stimulated neuron's efferent projection, but also to the fiber tract passing through or adjacent to the stimulated area. This is straightforward to understand if we consider the involuntary movements arising as a side effect of stimulating the STN at a high intensity, as this causes an involvement of the fibers of the capsula interna.[27]

REGULARIZATION HYPOTHESIS

More recently, a different therapeutic mechanism of DBS was proposed. It states that the high frequency stimulation applied overrides pathologic network activity imposing a more regular downstream firing pattern.[29]

Patients with Parkinson's Disease show abnormally synchronized oscillatory activity at multiple levels of the basal ganglia-cortical loop. Most of this oscillatory activity is in the beta frequency range (approximately 10-30 Hz).[30,31]

This synchronized activity in the beta range is thought to play a fundamental role in the genesis of parkinsonian symptoms, since it is shown that it is reduced during effective dopaminergic treatment and during DBS.[32,33] This is also supported by the fact that DBS stimulation at a frequency delivered to the basal ganglia at a frequency between 5-25 Hz worsened bradykinesia by inducing synchronization in the neuron's discharge pattern.[34]

It is important to note that DBS is not thought to restore physiological firing in the basal ganglia, instead it is likely that it blocks the transmission of pathological synchronized activity by overriding the firing rates of the neuron involved and stimulating a more regularized activity that enables other pathways to compensate for the loss of function in the stimulated pathway.[35]

LONG TERM EFFECTS

The time between the stimulation and the onset of therapeutic effects depends on the disorder, symptom, and chosen target.

Whereas patients with Parkinson's Disease often experience immediate cessation of tremor once the stimulation begins, axial symptoms may take hours or days to show some improvement, and in patients with Tourette syndrome tic improvement can happen after several weeks of stimulation. Similarly, the onset of tremor improvement in PD is often more rapid in stimulation of the STN than the GPi, and DBS improves symptoms in Essential Tremor within seconds, whereas dystonic movements take multiple minutes to improve in patients with primary dystonia.[36]

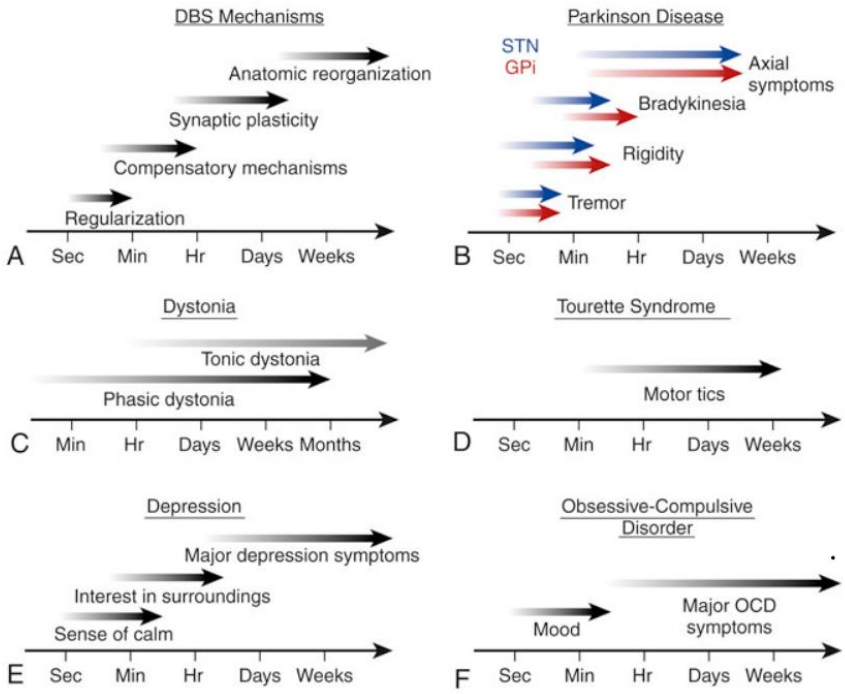

Figure 1: Deep brain stimulation effects on different pathologies and their underlying mechanisms.[35]

All these findings suggest that there are multiple mechanisms that underlie the different therapeutic effects of DBS.

DBS effects that emerge over minutes to days likely result at least in part from synaptic plasticity-related changes in the stimulated neural network. High-frequency stimulation of STN in rat brain slices induced varied forms of synaptic plasticity in different subpopulations of STN neurons including short-term potentiation (STP), long-term potentiation (LTP), and long-term depression (LTD). Even though it is reasonable to assume that similar mechanisms are at play in humans, there is scarce evidence of that to this date.[37]

NEUROPROTECTIVE EFFECTS

Although controversial, there is some evidence that DBS has some neuroprotective effects in Parkinson's Disease, slowing down the progression of symptoms. This would provide a good reason to suggest the therapy to patients with a short history of PD.

Specifically, the German trial "Early stim" compared two groups of PD patients with mean symptom onset of 7 years, and concluded that Subthalamic stimulation was superior to medical therapy after a 2-year follow-up in patients with Parkinson's disease and early motor complications.[38] One year after, an American study conducted by Schuepbach et al. did a similar study involving patients with onset of Levodopa assumption < 4 years.[39] Another study from 2018 gave class II evidence that for patients with early PD, DBS may slow the progression of rest tremor.[40]

Different mechanisms have been hypothesized to explain these apparent neuroprotective effects. One is that it might result from reduced glutamate excitotoxicity caused by limiting excitatory input to the Substantia Nigra from the STN. Another hypothesis is that there is a stimulation-induced release of neurotrophic factors or activation of GABAergic fibers, but this topic remains an active field of research to this date.[3]

RESULTS

In Parkinson's Disease, randomized controlled trials show that DBS is more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months.[41]

Therefore, it is important to highlight the fact that DBS in PD should not be considered as a last resort, but much more as validated and effective surgical therapy that can significantly improve the patient's quality of life, even though at last the disease will still progress and symptoms, especially the non-motor ones, will cause the patient's wasting.

Concerning Essential tremor, thalamic DBS has shown promising short-term results, with a reduction in tremor between 60 and 80%. However, long-term results appear to be more controversial, as literature describes a reduction in symptom improvement over a longer period.[42-44]

More detail about clinical results will be given in the sections dedicated to each specific pathology.

SURGICAL TECHNIQUE

Even though Deep Brain Stimulation surgery has now been around for many decades, there is no general consensus as to how the procedure should be carried out in a standardized way. Therefore, methods may vary greatly between different Institutions, and they constantly evolve with technological improvement and personal experience.

There are three main procedures for DBS implantation. Originally, the surgery was carried out in an awake patient, in order to be able to evaluate intraoperatively the effectiveness of the stimulation on symptom control. Since being awake during surgery is very stressful for the patient and not all of them are fit enough to withstand such a procedure, more and more Institutions have opted for an asleep intervention.

If the patient is under general anesthesia, obviously it is not possible to evaluate the symptoms directly, and two main ways have been developed in order to obviate this problem. The first one, which is adopted by our Institution, is based on the intraoperative evaluation of physiopathological electric activity in the basal ganglia through the use of Microelectrode Recording (MER) which guides the surgeon in the insertion of the final electrode.

The second one is purely based on the patient's anatomy and consists in placing directly the definitive electrode in the location chosen based on the anatomical landmarks visible in MRI studies. All three procedures will now be presented, with particular focus on the approach used at our Institution.

ASLEEP MICROELECTRODE RECORDING SURGICAL TECHNIQUE

The current approach for DBS at our Institution is here presented.

In preparation for the surgical procedure, the Brainlab Elements® software is used to determine the target on T1-contrast and FLAIR MRI imaging studies, and the trajectory is planned making sure to avoid vascular structures and ventricles.

The initial coordinates used for the most common targets (Subthalamic Nucleus and Globus Pallidus internus) go as follows:

- STN: the approximate coordinates for localization of the STN are 3 mm posterior, 4 mm inferior, and 10-12 mm lateral to the midcommissural point. The FLAIR or T1 images are then used to adjust the target with respect to the unique anatomy of each patient.

- GPi: the coordinates used for initial GPi targeting are 2 mm anterior, 5 mm inferior, and 21 mm lateral to the midcommissural point. The FLAIR or T1 images are then used to adjust the target, accounting for individual patient variability, which is high for this target.[35,150]

In regard to the trajectory planning, the approximate initial trajectory for both STN and GPi stimulation is 60 degrees from the AC-PC line in the sagittal plane and 20 degrees from the vertical in the coronal plane. Patient-specific adjustments include avoiding cortical sulci and vascular structures superficial and deep. If the lateral ventricle is crossed along the trajectory, we adjust the entry point because ventricular violation is shown to increase morbidity.

Next, the patient is placed under general anesthesia and shaved. The "Leksell Vantage CT indicator" stereotactic headframe is fixed onto the patient's head using appropriately sized screws. Next, a thin-slice CT scan of the patient's head is obtained, and it is fused with the other preoperative imaging studies, in order to obtain the precise coordinates of the chosen target relative to the patient's headframe.

After the patient is prepped and the surgical field is sterilized, the stereotactic arch is set up and a bicoronal incision is carried out. Two 14-mm diameter bur holes are performed at the electrode entry points and one side is chosen to begin the electrode implantation (usually the side contralateral to the one with more severe symptoms). The AlphaOmega micropositioner (driving unit) is set up on the stereotactic arch and three rigid cannulas (one exactly corresponding to the planned trajectory and the other 2 either anterior, posterior, lateral or medial by 1.5 mm) are advanced through brain parenchyma up to 15 mm above target, as is presented in the image. The bur hole is then filled with fibrin glue in order to decrease the chance of pneumocephalus and air emboli.

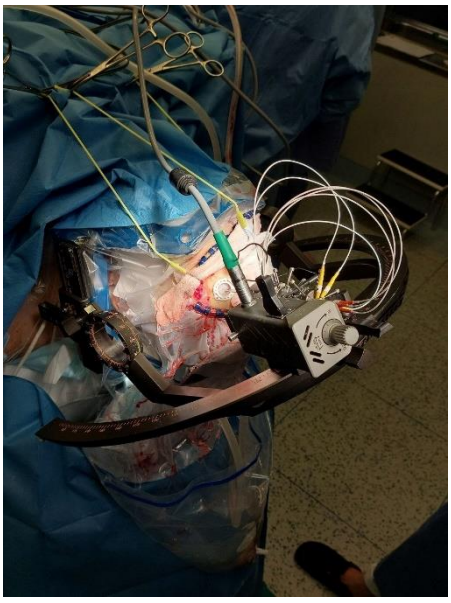

Figure 2: real Operative Room footage.

Next, the Microelectrode recording begins. One AlphaOmega "NeuroProbe STR-009080-00" (see image) is inserted in each cannula and connected to the driver. On

each probe, the yellow connector is for Macro stimulation and LFP recordings, while the red one is for Micro recordings and Micro stimulation.

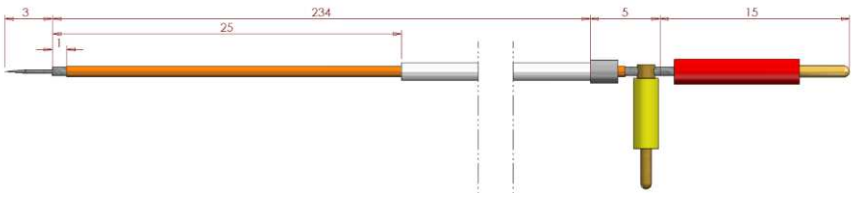

Figure 3: diagram of the AlphaOmega "NeuroProbe STR-009080-00".

The probe is then advanced using the unit driver 0.5 mm at a time, starting at least at +10mm from target until -3/4 mm after the target and recordings are visualized in real time on the AlphaOmega "Neurosmart" device.

Once all the recordings have been saved, one of the three trajectories is chosen along with the implantation depth, depending on which of the three probes showed the best electrical activity. It is mainly the surgeon's experience to guide this choice, helped by the artificial intelligence algorithm developed by AlphaOmega which gives an estimate of the location of the main structures (for example GPe, GPi and optic tract) based only on the obtained microelectrode recordings. X-ray imaging is used to document the final electrode position.

Once the decision is made, the Medtronic "B33015 SenSight™" directional lead (image below) is slowly advanced through the delivery system to the predetermined depth, and the position is confirmed through X-ray imaging.

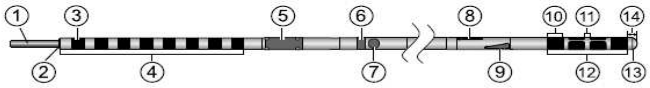

Figure 1. *Model B33005 marked directional lead.*

① Preinserted stylet	⑧ Proximal orientation marker
② Proximal end	⑨ Distal orientation marker
③ Lead contact	⑩ Electrode length–1.5 mm
④ Lead contacts total distance–17.5 mm	⑪ Electrode spacing–0.5 mm
⑤ Setscrew fixation ring	⑫ Electrodes total distance–7.5 mm
⑥ Insertion marker	⑬ Distal end
⑦ Bilateral marker (marked leads only)	⑭ Distal tip distance

Figure 4: diagram of the Medtronic "B33015 SenSight™".

Now, the insertion cannula is retracted and a support clip is positioned on the bur hole. The lead is gently held with a pincette while the cannulas are completely removed, the support clip is closed and the stylet is removed. A final X-ray is used to make sure that the electrode has not moved during this procedure.

If bilateral DBS is performed, the same procedure is repeated contralaterally.

Once both leads are fully implanted, the galea and skin are closed. A 5-cm incision is made parallel and 2 cm inferior to the left clavicle, and an Internal Pulse Generator (IPG) pocket is created over the pectoralis fascia. Using a tunnelling device, the directional leads and the IPG are connected by lead extensions which run subcutaneously on the patient's left side.

Lastly, the IPG is tested and the impedance is measured, in order to ensure that the whole system is working properly.

AWAKE SURGICAL TECHNIQUE

The awake technique requires the same preoperative planning as the asleep technique, and the patient is sedated for the placement of the stereotactic head frame. Once the thin-slice CT scan is performed and the images are fused with the preoperative MRI scans, the patient is prepped and draped and the skin incision as well as the bur holes are performed in similar fashion.

At this point, the sedation is interrupted and the patient is woken up in order to go on with the microelectrode recording. As the probes are advanced through the parenchyma, first the intrinsic electric activity is recorded, and then electric stimulation is carefully applied in order to assess the effects on the patients symptoms, as well as the side effects. The most indicative symptom is generally the tremor, since the therapeutic effect of the stimulation is visible almost instantly.

This phase is also useful to get an idea of the possible therapeutic window of the stimulation settings, as the stimulation intensity is generally increased until side effects are reported by the patient, for example involuntary muscle contractions due to stimulation of the capsula interna, or feelings of profound anxiety and fear due to stimulation of the anterior (associative) part of the STN.

Once the procedure is completed for both sides the patient is generally again sedated for the closing of the surgical site and the implantation of the internal pulse generator (IPG).

Even though the advantages of being able to assess the effects of the stimulation intraoperatively are evident, more and more Institutions are abandoning this surgical technique, since it requires a very high stress tolerance by the patient, which makes for a stringent exclusion criterion, and also because an awake procedure is very expensive, due to the abundance of different healthcare professionals necessary to make the procedure go smoothly.

ASLEEP INTERVENTIONAL MRI SURGICAL TECHNIQUE

This technique involves the sedation of the patient throughout the procedure, but does not require Microelectrode recording to examine the patient's physiology. Instead, after the opening of the dura, an intraoperative MRI scan is performed, and the target is calculated directly on the images acquired in the intraoperative setting. This method clearly has the advantage of minimizing the effect of brainshift on the anatomical localization of the target, since the typical risk factors for this phenomenon are excluded: the images are acquired when the liquor loss through the opening of the dura has already taken place and the blood pressure is (usually) kept stable throughout the procedure. This method also is more time efficient, since the most time-consuming phase of DBS (the microelectrode recording) is avoided. Nevertheless, this method also possesses some evident disadvantages. Apart from the fact that it requires the possibility of performing an intraoperative MRI, which is a diagnostic procedure that most hospitals still don't possess, it bases the whole placement of the electrode on the mere anatomy of the patient. Therefore, the surgeon doesn't have the ability to choose, or correct, the path and placement of the electrodes based on the patient's unique pathophysiologic activity.

Comparing the outcome of the different surgery methods in an objective and statistically significant way is easier said than done. For example, in 2018 Lee et al. argued that asleep iMRI DBS has a higher anatomical accuracy than MER-guided DBS, with comparable reduction in motor symptoms and medication dosage.[45]

Instead, a comprehensive literature review carried out by Wang et al. states that there are no significant differences in clinical outcomes, costs, or complications between the two techniques.[46]

However, it is important to note that there is one big bias in the definition of "stereotactic error": it is not always clearly described how it is measured in awake cases, when the surgeon intentionally places the DBS lead away from the intended target because of MER or test-stimulation findings. This decision will increase the distance from the initial target, and therefore, the "error" will be larger. In asleep cases without physiology there would have been no rationale to move away and therefore, the error would be smaller. Therefore, taken together, accuracy is an imaging outcome, not an efficacy outcome.[47]

MICROELECTRODE RECORDING

Microelectrode recording is an intraoperative technique used to examine the patient's pathophysiology with a very high spatial resolution. In fact, measuring spiking activity through the microelectrode tip we use at our Institution (the AlphaOmega Neuroprobe STR-009080-00) has a spatial resolution as low as 150 μm. This gives the operator the capability to augment preoperative imaging, which may lose accuracy due to brain shift or non-linear image distortions.

It is possible to use from 1 to 5 microelectrodes, in order to be able to explore different trajectories, which are placed in a specific manner (see image): there is one central trajectory, which is the one which is going to fall exactly on the preoperatively planned target; then there are one anterior, one lateral, one posterior and one medial trajectory which are all placed in a parallel fashion 1.5mm away from the central trajectory.

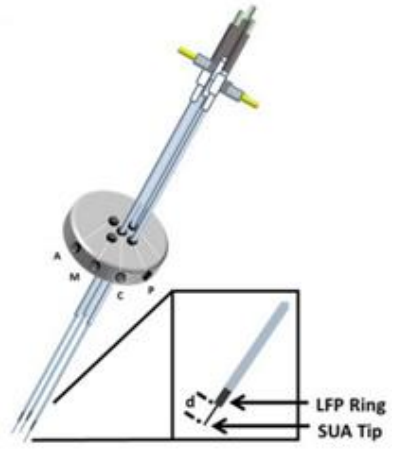

Figure 5: MER disposistion.

The neuroprobe we use is a sonus-shielded neuroprobe with iridium conductor, and proximal to the 3 mm long tip which is used to record SUA, there is a 2.34 cm long ring which is used to record Local Field Potentials (LFP).

The microelectrode is advanced slowly using a driving unit, which has a feedforward mechanism inbuilt, giving us the precise distance between the tip of the central microelectrode and the target. This allows for precise placement of the definitive directional lead in the location of interest.

The aim of MER is twofold: on one side it allows for intraoperative evaluation of the patient's electrophysiology and optimal definitive lead placement; on the other, it allows the creation of an electrophysiological dataset which can be used for post-operative analysis of spiking activity and LFP features which can lead to a better understanding of the pathophysiology of neuronal activity in the basal ganglia.

Intraoperatively, the first component of MER which is looked at are the SUA. These consist of a real-time recording of electrical activity filtered in order to show only frequencies >500 Hz, which are useful to identify spiking activity of neurons in the immediate proximity of the microelectrode tip. As the electrode approaches the target, the different brain structures it passes have a quite different spiking activity.

In general, when the electrode is located in white matter, there will be low spiking activity and low background noise, whereas if the electrode is located in grey matter background noise and spiking activity will be more prominent, and will reflect the firing characteristics of the neuronal population it is located in. For example, the Subthalamic Nucleus (STN) has an irregular firing activity with spike burst, generally easily distinguishable from the underlying Substantia Nigra pars reticulata (SNr) which in turn has a much more tonic activity with a regular inter-spike-interval (ISI).

The image below gives a representation of the ideal spiking activity which should be shown by the different structures encountered on the path to a target in the STN and in the Globus Pallidus internus (GPi).[35]

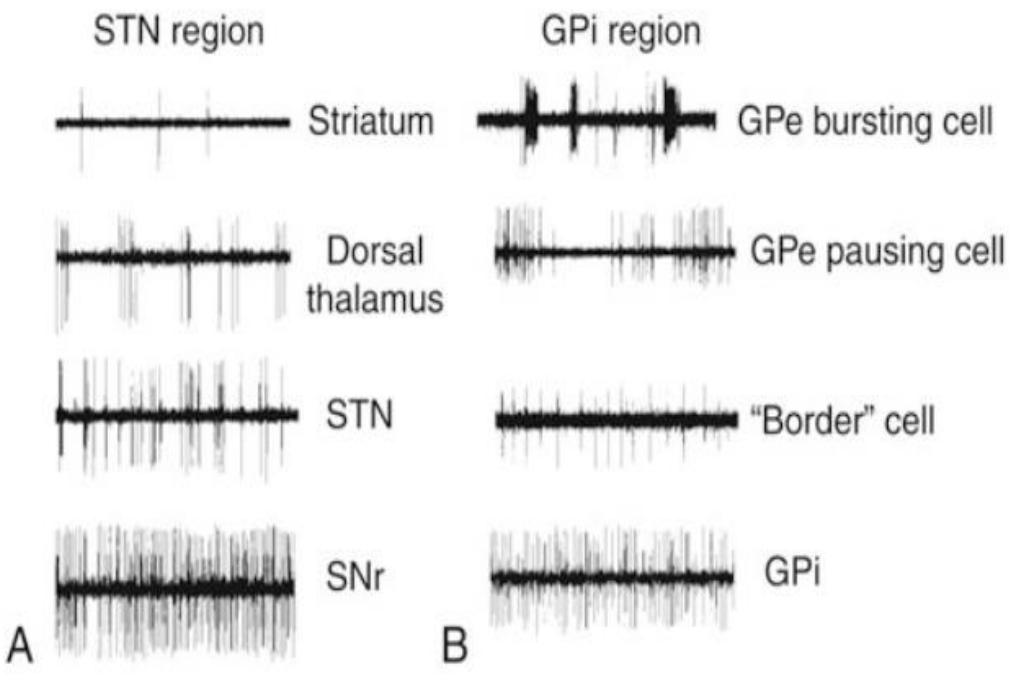

Figure 6: Expected Single Unit Activity of each different brain area passed by the electrodes.

Intraoperatively, the trajectory which shows the most characteristic electrical activity of the structures we expect to cross is usually chosen as the trajectory for the definite lead implantation.

Instead, to choose the depth of the implantation of the definitive electrode, LFP signal is taken into consideration. The AlphaOmega Neurosmart software automatically converts the recorded LFPs into a power spectral density (PSD) graph, as is displayed in the image on the side. This graph is helpful to identify the depths at which beta-range LFPs are more prominent, and since these are a marker for pathologic activity in Parkinson's Disease, it is important that the final implanted electrode covers these areas.

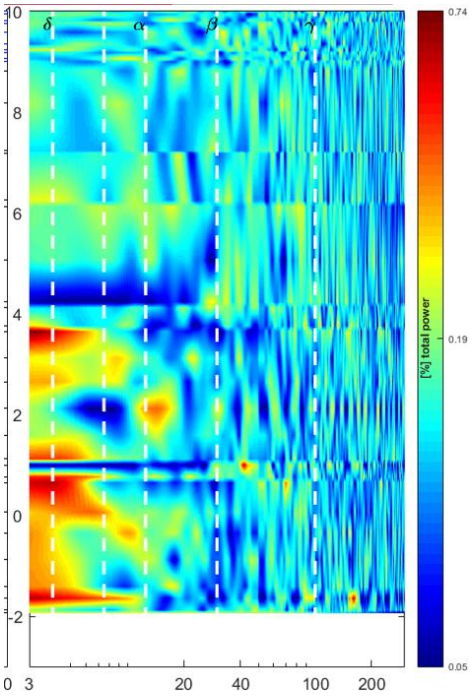

Figure 7: Power Spectral Density graph of MER signal.

On the graph we can see the LFP frequency on the x-axis, the depth of the electrode on the y-axis, and the total power as color-coded (blue means low power, and red means high power).

COMPLICATIONS OF DBS SURGERY

Even though Deep Brain Stimulation is proven to be an effective and considerably safe procedure in the treatment of several different pathologies, like all other surgical procedures it is not risk free.

The adverse events caused by Deep Brain Stimulation can be categorized into three main groups:

- **Procedure-related complications**: arise as a direct cause of the surgical intervention;
- **Hardware-related complications**: caused by the failure of the hardware to keep the intended function;
- **Stimulation-related complications**: caused by the stimulation of brain structures which are not intended to be stimulated, or by chronic stimulation of the target area.[35]

PROCEDURE-RELATED COMPLICATIONS

- **Intracranial hemorrhage**

  Although it is rare, it is certainly the most dangerous adverse effect of DBS surgery, as it can result in severe strokes or death of the patient, even though most of the time they remain asymptomatic. It is hard to give a realistic incidence of the phenomenon as the percentages reported vary greatly between different works, but in most cases literature reports an incidence of about 1%.[48]

  Some studies have investigated the correlation between MER insertion and incidence of intracranial hemorrhage and there seems to be an increased risk with the increase in number of microelectrodes used, especially in hypertensive patients.[49,50]

- **Cerebral venous infarction**

  This complication can be avoided by taking care in avoiding superficial venous structures and by not inserting the cannulas directly in the sulci. It is therefore a relatively rare complication, which presents with delayed-onset new neurologic symptoms and cerebral edema surrounding the electrodes, with or without subcortical hemorrhage.

High resolution T1 contrast MRI is advised, along with careful preoperative planning, to maximally reduce the chances of cerebral venous infarction. [51]

- **Perioperative confusion**

  Given the long operative time of DBS surgery, it is not a surprise that perioperative confusion is the most common complication, with an incidence of up to 22%. Fortunately, the confusion is usually transient, as it resolves in a period of time ranging from a couple hours to multiple days. It is important to note that this explains also the fact that preoperative dementia or cognitive impairment are an exclusion criterion for DBS surgery, as they would be exacerbated by the electrode implantation. Other risk factors include advanced age, history of hallucinations, pneumocephalus and increased operative time.[52,53]

- **Venous air embolism**

  Venous air embolism is also a rare complication, occurring mostly in awake DBS and when the patient's head is elevated more than 30 degrees. To avoid this complication, it is of vital importance to cauterize bleeding vessels and to wax the bone margins.

  The initial symptoms of a venous air embolism are persistent cough and a feeling of heaviness in the chest. From an anesthesiologic point of view, a decrease in the end-tidal CO2 is followed by a drop in saturation and blood pressure. It is important to act in the shortest time possible once clinical suspicion is high, as morbidity and mortality can be elevated: 50mL of air can lead to severe hypotension, and 300 mL to death. In this case, the surgical field should be flooded with saline solution and the patient's head should be lowered.[54,55]

- **Seizure**

  Seizures related to DBS surgery are uncommon and are mostly related to hemorrhages or consistent edema surrounding the electrodes. Most seizures occur intraoperatively or within the first 48 hours after surgery, and present in a generalized tonic-clonic fashion. Long-term anticonvulsant therapy is not likely be required.[56,57]

- **Brain edema**

  Postoperative peri-lead edema can occur in up to 15% of patients, even though many of these present as asymptomatic and therefore go undiagnosed. The onset of edema may be delayed, and no particular risk factors have been identified.[58]

HARDWARE-RELATED COMPLICATIONS

- **Extension wire fracture**

  It is thought to occur in up to 1% of patients, following abrupt cervical movements that put consistent strain on the extension wire connecting the IPG to the electrodes. This occurs more often in patients with dystonia and patients with violent tics caused by Tourette's syndrome. Wire fracture usually presents in a sudden drop in the clinical effect of DBS and can be diagnosed by an x-ray of the head and neck, as well as by checking if there is an increase in the impedance values of the system. In case of a microfracture the x-ray might not be helpful in the diagnosis.[59,60]

- **Lead tip migration**

  The incidence of lead tip migration greatly diminished with the introduction of dedicated anchoring systems of the DBS leads. Nevertheless, this complication can arise through growth of the skull after implantation (in case of DBS performed in children) or by inappropriate wire manipulation. This is this is the case in the so-called "Twiddler's syndrome", in which patients experience multiple system failures while denying any sort of voluntary manipulation.[61,62]

- **Lead tip gliosis**

  Gliosis is a normal reaction of the brain parenchyma to the surgical insertion of a foreign body. Different studies examined post-mortem histopathologic changes in the parenchyma surrounding the electrodes and concluded that modest gliotic scarring is to be expected in chronic stimulation but without any clinical consequences.[63]

- **Infection**

  Infection is the most common complication associated with DBS surgery, often resulting in complete removal of the system. The incidence of hardware-related infections greatly depends on the Institution performing the surgery, but mostly seems to range between 5% and 15%. The pathogens most frequently isolated are S. Aureus, S. epidermidis, Cutibacterium Acnes.

  When occurring, infections should be treated aggressively in order to prevent serious complications such as meningitis, cerebritis, brain abscesses and so forth. Nevertheless, more recent studies have found that most infections can be effectively managed without the removal of the complete system, which would result in prolonged interruption in the patient's care and make a subsequent reimplantation much more challenging. Wound revision without removal of the entire DBS system seems to be safe and can improve quality of life by preventing or shortening the withdrawal of DBS treatment.[64-68]

STIMULATION-RELATED COMPLICATIONS

- **Subthalamic Nucleus**

  As for the other targets of interest, stimulation-related complications can most of the times be explained by the anatomical location of the target. The corticospinal tract passes laterally to the STN and can be the cause of involuntary muscle contractions when stimulated by the DBS lead. Posterolaterally, instead, the medial lemniscus can be the cause of paresthesias, whereas the ventromedially placed cranial nerve III nucleus can be the cause of oculomotor effects.[35]

  Aside from the anatomical relationships of the STN, it is important to know that the STN itself can be divided into 3 zones: the sensorimotor (dorsolateral), the associative (dorsal mid) and the limbic (ventral anterior) zone. The DBS lead should be placed into the sensorimotor zone in order to have the most therapeutic effects. If the lead ends up too anteroventrally in the STN, the patient can experience important neuropsychologic changes, such as profound anxiety and feeling of impending doom or major depression.[69]

Another side effect to be aware of when stimulating the STN is weight gain, as almost 80% of patients increase there BMI by a mean of 1.3 kg/m^2. [70,71]

- **Internal Globus Pallidus**

  The intended target is the postero-ventral part of the GPi, and as the internal capsule lies just medial to it, it is no surprise that one of the most common stimulation-induced side effects are involuntary muscle contraction (typically of the face and hand) due to stimulation of the corticospinal tract. Inferior to the GPi, the optic tract runs its fibers from the optic chiasm to the lateral geniculate body. If the electrodes are placed to deeply in respect to the intended target, stimulation of the optic tract can induce phosphenes and, rarely, visual field cut. This is why visual evoked potentials are useful as an intraoperative monitoring system to make sure that the electrode is not placed to deep in respect to the intended target.[35]

- **Ventral Intermediate Nucleus of the Thalamus**

  An important side effect of VIM stimulation is paresthesia, due to stimulation of the ventral caudal nucleus, which lies immediately posterior to the VIM. Laterally to the thalamus the internal capsule is found, which may be cause of involuntary muscle contractions. The most common side effect, especially when stimulating the left VIM, is dysarthria, which seems to occur in 15% of patients.[72]

APPROVED INDICATIONS FOR DBS SURGERY

PARKINSONISM AND PARKINSON'S DISEASE

Giving an in-depth description of all aspects of Parkinson's Disease and Parkinsonism goes beyond the scope of this document, nevertheless it is of vital importance to master some key concepts about the diseases in which DBS can be applied in order to gain a good understanding of when and why this treatment is appropriate for the patient.

NEUROLOGY

Parkinson's Disease is a chronic and progressive neurological disorder that affects movement and is caused by the gradual degeneration of dopaminergic neurons in the brain. This results in a variety of motor symptoms, including tremors, rigidity, slowness of movement, and postural instability, as well as non-motor symptoms such as sleep disturbances, depression, and cognitive changes. While there is no cure for Parkinson's Disease, there are treatments available that can help manage symptoms and improve quality of life for those living with the condition.

- **EPIDEMIOLOGY**

  Given the lack of population screening, the incidence may be underestimated, but most incidence studies indicate it to be around 17 per 100,000 per year. The peak incidence is between 70 and 79 years of age and the mean age of onset of symptoms is 60-65 years. There is no significant difference in the pathology's incidence between genders. [73-76]

- **CLASSIFICATION**
  - **Idiopathic Parkinson's Disease (Morbus Parkinson)**

    The cause of the degeneration of dopaminergic neurons of the Substantia Nigra pars compacta (and the locus caeruleus) is poorly understood. It is thought to be multifactorial in etiology, and there seems to be also a genetic predisposition.[77]

- **Genetic Parkinson's Disease**

  Monogenetic forms of Parkinson's Disease include mutation of the Leucin Rich Repeat Kinase (LRRK2), which is the most common cause of autosomal dominant late-onset Parkinson's Disease. Mutations in the PRKN/PINK1 gene represent the second most frequent cause of autosomal-recessive inherited early-onset parkinsonism.

  Mutations in the SNCA gene encoding for α-syn represent the prototypical forms of genetic PD. These are autosomal dominant forms and include point mutations (eg, A30P, E46K, G51D, and A53T/E), as well as gene multiplications. Instead, mutations in the corresponding gene for ß-glucocerebrosidase (GBA) are considered the most common genetic risk factor in PD, meaning that not every carrier of a GBA mutation will develop PD.[78,79]

- **Atypical Parkinsonism**

  This consists of other degenerative pathologies which can mimic the symptoms of Parkinson's Disease, especially in the early stages. These include Multisystem Atrophy, Progressive Supranuclear Palsy, Lewy-Body Dementia and Corticobasal Degeneration. Typically, they do not respond as well to dopaminergic treatments and have a more rapid progression and thus a worse prognosis.[80]

- **Secondary Parkinsonism**

  In this case parkinsonian symptoms occur as a consequence of events known to cause dopaminergic neurons degeneration, such as: antidopaminergic medication (antipsychotics), trauma (the boxer's parkinsonism), toxins (methyl-phenyl-tetrahydropyridine), metabolic diseases (Morbus Wilson), infection (post-encephalitis).[80]

- **PATHOPHYSIOLOGY**

The dopaminergic neurons in the substantia nigra pars compacta undergo a degenerative process, which is in many cases caused by deposits of alpha-synuclein. The substantia nigra usually acts as an activator of the motor circuits of the basal ganglia, by promoting the direct pathway and inhibiting the indirect pathway of the basal ganglia. This explains one of the major symptoms of Parkinson's Disease: bradykinesia. The shift of the equilibrium from the direct pathway to the indirect pathway makes initiating movement more difficult.

Moreover, the relative abundancy of cholinergic neuron due to loss of dopaminergic pathways causes the tremor and the vegetative symptomatology. Other neuronal populations suffer as well in Parkinson's Disease. Degeneration of the serotoninergic neurons of Raphe Nucleus explains the depressive symptomatology that often accompanies parkinsonian patients.[81]

- **SYMPTOMS**

  The three main symptoms that define Parkinson's Disease are tremor, bradykinesia and rigidity. Before these symptoms manifest though, there often is a prodromal phase of the disease which presents with hyposmia and REM sleep behavior disorder.

  In the mid-stage of Parkinson's Disease vegetative symptoms usually start to occur, such as orthostatic hypotension and constipation.
  At a later stage, axial symptoms start to manifest, with postural instability and falls, as well as cognitive symptoms, with dementia and psychotic hallucinations. Even though this is the most typical course of the pathology, it is important to know that not all patients with Morbus Parkinson are the same. One of the first and most important distinctions made in the disease is between a tremor-dominant and an akinetic-rigid form, depending on which symptom were the most severe.[82]

  At later stages, the postural instability and gait disturbance form (PIGD) was introduced, describing patient in which axial symptoms presented early and predominantly. These patients also present more severe cognitive decline and are more likely to develop hallucinations and psychosis.[83]

- **DIAGNOSIS**

  In brief, the diagnosis of Parkinson's Disease is mostly clinical. A complete neurological examination is essential when defining the bradykinesia and the rigidity. The tremor should be a resting tremor with a frequency of 4-8 Hz, usually starts on one extremity and then spreads to both sides as the disease worsens. An important diagnostic criterion is weather the symptoms are alleviated by the intake of Levodopa. If the symptoms don't get much better, it is likely that the patient suffers from atypical parkinsonism.[81]

  As to imaging studies, the Dopamine Transporter Imaging (DaT Scan) is a helpful diagnostic tool, especially to distinguish tremor dominant Parkinson from Essential tremor, as this test is able to show the degeneration of nigro-striatal dopaminergic neurons, achieving a sensitivity and specificity over 90%.[84]

- **THERAPY**

  The medical therapy focuses on supplementing the missing dopamine through many different mechanisms, but for a complete dissertation on this topic the reader is referred to the neurology and pharmacology textbook of choice.

  The only concept worth stressing is that as the degenerative course of the disease goes on, the medical treatment has to be more and more potent, worsening therefore the dyskinesias resulting as a side effect of the medication.[81]

DEEP BRAIN STIMULATION TARGET SELECTION

The target choices for DBS for Parkinson's Disease (PD) are the Subthalamic Nucleus (STN), the Globus Pallidus internus (GPi) and the Ventral Intermediate Nucleus of the Thalamus (VIM).

While VIM-DBS may remain of some value in patients with tremor-predominant symptoms, it is largely abandoned as it alleviates other motor and non-motor symptoms less than the other two targets.[85]

In Europe, STN is considered the main target for PD patients, since it allows for a greater reduction in doses of levodopa medication. Nevertheless, mood and cognition are at higher risk for decline after STN-DBS, therefore, it is advised that

patients with cognitive impairment or slight personality disorders should undergo GPi-DBS, as this seems to be a safer option for this type of patients. Also, if the cognitive function is still good but the patient has a glucocerebrosidase gene (GBA) mutation, it is preferable to choose the GPi, as these patients are at risk for early cognitive decline.[85,35]

TIMING OF DBS SURGERY

STN-DBS is indicated for PD patients with severe resting tremor, unresponsive to conventional medical treatment or with motor complications. STN-DBS benefits are not limited to the motor aspects of the disease, but they are extended to general quality of life as well.[86]

Therefore, it is reasonable to offer this treatment at mid/early stages of the disease, to maximize the improvement of the quality of life.

The indication for surgery arises when the diagnosis of PD is certain (therefore excluding atypical and secondary forms), there is a good response to levodopa but the ON medication phase lasts less and less compared to the OFF medication phase, and the dyskinesias arising as a side effect of the medication become very evident. With that said, there is no formula that can predict the best timing for the surgery, it very much depends on factors like the patient's willingness to accept the surgery, on the course of the pathology, and on the surgeon's experience.[87]

CONTRAINDICATIONS TO DBS SURGERY

Severe cognitive impairment is a contraindication for surgery, as it may worsen significantly after surgery. In contrast to that, mild cognitive impairment can still be eligible for surgery, but most likely for GPi-DBS. Age, hypertension, diabetes all increase the surgical risk of the procedure, but don't necessarily represent an absolute contraindication.[88]

ESSENTIAL TREMOR

Essential tremor (ET) is a neurological disorder characterized by tremors typically occurring during voluntary movements. It is one of the most prevalent movement disorders, affecting millions of people worldwide. The exact cause of essential tremor is not fully understood, but it is believed to involve a combination of genetic and environmental factors.[89]

NEUROLOGY OF ESSENTIAL TREMOR

- **EPIDEMIOLOGY**

  ET is the most common movement disorder worldwide, and its prevalence increases with age, up to being prevalent in 5% of the people aged over 65 years.[90]

- **SYMPTOMS**

  The tremor is an intention tremor that arises when the patient is making a movement, which causes the rhythmic oscillation of agonist and antagonist muscles at a frequency of 8-12 Hz, so slightly faster than the parkinsonian tremor. Nevertheless, resting tremor can also occur in patients with longstanding disease. The onset and progression of the tremor is insidious, and usually starts at the limbs in an almost symmetrical fashion. Head tremor also occurs at later stages of the disease, as well as vocal tremor. Jaw tremor, instead, is relatively rare. In approximately 50% of the cases, the symptoms get better with alcohol consumption, which is why many patients with ET develop alcoholism. Other symptoms include gait impairment, hearing and smell loss, changes in oculomotor movements and even psychiatric symptoms such as depression and anxiety. [89]

- **DIAGNOSIS**

  The diagnosis of ET is essentially clinical, as it is based on a complete neurologic examination and on the patient's history.
  An MRI scan of the head can be sometimes useful to exclude a secondary source of onset of tremor, especially if other neurological findings are present. A Dopamine Transport (DAT) scan is FDA-approved for the

differentiation of tremor due to Parkinson's Disease.[89]

- **THERAPY**

  The first line of therapy is the pharmacological one, which is, however, suboptimal. Many patients do not respond, and the ones that do often do not have any perceived improvement of their quality of life. These medications include beta-blockers (propranolol), anticonvulsants (primidone, topiramate, gabapentin…) and antipsychotics (olanzapine). Another line of therapy which may be tempted before surgery is chemodenervation, which consists in the injection of botulinum toxin in medically refractory cases of ET, with controversial results.[89]

DBS FOR ESSENTIAL TREMOR

Although other targets are being considered, the VIM is by far the main target chosen to treat essential tremor. Numerous studies have shown DBS to be a safe and effective treatment for medically intractable essential tremor, even though there seems to be some decrease in efficacy over time.

The VIM is a small nucleus that lies in the ventro-lateral part of the thalamus, immediately anterior to the ventro-postero-lateral (VPL) nucleus, which receives sensory information from the whole body. One of the reasons why the VIM is chosen as the main target is that, apart from the resulting clinical outcomes, during microelectrode explorations in this area the so-called "tremor cells" can be found, which are neurons that fire at the exact same frequency of the tremor the patient is suffering of.

Concerning other possible targets, there are some promising results coming from the DBS of the caudal Zona Incerta (cZI), with some studies suggesting that it might even have a better clinical result.[91-94]

DYSTONIA

Dystonia is a heterogeneous group of movement disorders characterized by intermittent or sustained abnormal contraction of one or multiple muscle groups. These contractions can be very painful, having a profound impact on the patient's quality of life. The causes of the disease are not always known, even though in many cases they can be genetic, metabolic, post-traumatic or iatrogenic.[95]

NEUROLOGY OF DYSTONIA

- **EPIDEMIOLOGY**

  Women are affected by the disease about twice as much as men, but the exact prevalence can be hard to estimate given the profoundly heterogeneous nature of the disease. In a study of a random sample of the population over 50 years of age, the prevalence of isolated dystonia was estimated to be 732 per 100 000, suggesting that in the aging population dystonia is a common neurological disorder.[96]

- **CLASSIFICATION**

  Dystonia can be classified according to the distribution of the symptoms in:

  - Focal dystonia: affects a muscle or a group of muscles localized in one part of the body, for example torticollis or the writer's hand.
  - Generalized dystonia: affects muscles in the whole body, as in early onset torsion dystonia (Opennheim's dystonia).

  Another classification instead considers the etiology of the disease, defining:

  - Genetic/primary dystonia: it is genetically inherited and can be distinguished in isolated dystonia, where dystonia is the only manifestation, dystonia with parkinsonism, in which it is accompanied by features like tremor or bradykinesia, and dystonia with myoclonus, in which the dystonia appears in combination with episodes of true myoclonus.
  - Acquired dystonia: vascular or traumatic lesions in the basal ganglia, thalamus, corticospinal tract or cerebellum can cause dystonia.[97,98]

- **THERAPY**

  Patients with isolated dystonia are treated with anticholinergic medications. If the patient has accompanying parkinsonism than L-Dopa has proven effective as well. Focal dystonia can be treated with botulinum toxin injections, especially in patients with blepharospasm and cervical dystonia. There is also some preliminary evidence that repeated transcranial magnetic stimulation over multiple days could have a therapeutic effect.[99,100]

DBS FOR DYSTONIA

The Globus Pallidus internus has emerged as the target of choice in the treatment of primary dystonia, especially for the DYT1 dystonia, which is known not to respond to medical treatment nor to Botulinum neurotoxin injections. In general, better outcomes are associated with greater severity at baseline. There is some evidence that STN-DBS is also effective in patients with dystonia, but with no significant difference to GPi-DBS in regard to clinical outcome.[101-104]

OBSESSIVE COMPULSIVE DISORDER

Obsessive Compulsive Disorder (OCD) is a highly prevalent condition that affects people of all ages and backgrounds. It is characterized by recurring, intrusive thoughts or fears that lead to repetitive, ritualized behaviors. OCD can significantly interfere with daily life, often being the cause numerous comorbidities. Treatment consists in antidepressants (SSRIs) or surgery, in medically refractory cases.[105]

NEUROLOGY OF OCD

- **EPIDEMIOLOGY**

  The disease usually occurs in early life, mostly between 18 and 29 years of age, and has a long duration. The lifetime prevalence is about 2%, making it one of the most common psychiatric conditions worldwide.[106]

- **PATHOPHYSIOLOGY**

  OCD seems to be mediated by abnormal, partly segregated cortico-striato-thalamo-cortical pathways, as demonstrated in studies based on structural

and functional imaging. Also, the limbic system seems to play an important role in the pathophysiologic mechanisms of the disease, particularly the amygdala, which seems to be consistently hyperactivated during the expression of OCD symptoms. It is important to note that the impulsivity arising for these mechanisms is a risk factor for the development of addictive disorders, which can lead to the abuse of substance which further damage the limbic and reward circuits.[105,107-108]

- **DIAGNOSIS**

  The DSM-5 diagnostic criteria state that there has to be presence of obsessions, in the form of intrusive and repetitive thoughts or urges or the fatiguing suppression of these, and compulsions, in the form of repetitive behaviors and rituals performed in response to an obsession. These must not be the effect of any medical or recreational substance and they have to impact significantly the quality of life of the patient, in terms of being time consuming (>1 hour a day) or causing significant distress in social or occupational areas.[109]

- **THERAPY**

  The first line of therapy consists of cognitive-behavioral therapy and/or pharmacological treatment with antidepressants (SSRIs). If there is no response usually it is best to intensify or combine the therapy, switching to a second-line SSRI. If there is still no response intensive outpatient or residential therapy should be considered, along with non-invasive (transcranial magnetic stimulation and transcranial direct current stimulation) and invasive (DBS) neuromodulation.[105]

DBS FOR OBSESSIVE COMPULSIVE DISORDER

While the anterior limb of the internal capsule (ALIC) is the only FDA-approved target for intractable OCD, there are many studies concerning different targets, such as the ventral capsule and ventral striatum, the nucleus accumbens or the ventral caudate nucleus, the subthalamic nucleus, and the inferior thalamic peduncle. The treatment is reserved as a last chance for patients who have suffered from medically refractory OCD for more than 5 years, and do not have any other mental

comorbidity or substance addiction which may impair the DBS treatment. ALIC-DBS is considered to be safe, as different studies report almost no changes in the global cognitive function after surgery, while substantially alleviating symptoms.

The advantages of targeting ALIC consist of its effectiveness, as it has proven to significantly reduce symptoms in different subsets of patients, and its accessibility as a target for lead implantation. ALIC is situated within the cortico-striato-thalamo-cortical (CSTC) circuit, which is believed to be involved in the development and manifestation of OCD symptoms. By targeting ALIC, DBS aims to modulate the aberrant neural activity within this circuit and alleviate symptoms. It is generally considered a relatively safe target, even though different side effects have been reported, including mood changes, cognitive changes, or sensory disturbances.

Another common target for the disease is the ventral capsule/ventral striatum (VC/VS), which is thought to be involved in the limbic loop of the CSTC circuit, therefore associated with emotional and reward-related processes. Research suggests that both ALIC and VC/VS DBS can be effective in reducing OCD symptoms in some individuals, particularly those who have not responded to conventional treatments. However, specific response rates and outcome comparisons between the two targets may vary across studies, and individual patient characteristics can influence treatment outcomes.[110-115]

EPILEPSY

The description of the neurological bases of epilepsy goes beyond the scopes of this study, this chapter will instead focus on the relevance of DBS in the therapy for medically refractory epilepsy.

DBS FOR EPILEPSY

In context of the therapy of medically refractory epilepsy, DBS aims to modulate abnormal neural activity and to disrupt the seizure process by dampening excessive neuronal activity. It can be particularly beneficial to individuals who are not eligible of or have not responded well to surgical resection of the seizure focus.

The specific target selected depends on the individual's seizure type, seizure focus location, as well as other clinical factors. The most commonly utilized targets are:

1. Anterior Nucleus of the Thalamus (ANT): it is the only approved target for DBS in epilepsy, and the most used one. It is believed to modulate abnormal thalamocortical circuitry involved in seizure generation and propagation.
2. Centromedian Nucleus of the Thalamus (CM): while it is not yet officially approved, targeting this nucleus has shown great efficacy in reducing seizures, particularly in generalized epilepsy syndromes such as Lennox-Gastaut syndrome.
3. Hippocampus: it may be considered for DBS in case of medically refractory mesial temporal lobe epilepsy which are not indicated for surgical resection.
4. Subthalamic Nucleus (STN): it is typically considered for individuals with epilepsy and comorbid movement disorders or those with overlapping movement and seizure symptoms.

From recent meta-analyses it appears that DBS of ANT is mostly efficient for focal-onset seizures, CM for generalized syndromic seizures, and hippocampal DBS for temporal lobe seizures.[116-121]

OTHER PATHOLOGIES INVESTIGATED FOR DBS TREATMENT

TOURETTE SYNDROME

Deep brain stimulation (DBS) is considered an effective therapeutic option for individuals with severe and refractory Tourette's syndrome (TS). Commonly chosen targets for this disease include:

1. Anteromedial Globus Pallidus internus (GPi-am): GPi DBS is thought to modulate the abnormal activity within the cortico-striato-thalamo-cortical (CSTC) circuit involved in TS. It helps regulate the inhibitory output from the basal ganglia, resulting in improved motor control and reduced tics. Multiple studies have reported substantial reductions in tic frequency and severity, along with improvements in associated comorbidities such as obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD).
2. Thalamic nuclei: different thalamic nuclei have been chosen as targets for TS treatment. These include the Ventralis Oralis posterior Nucleus, the Centromedian Nucleus, the Parafascicular Nucleus and the Anterior Nucleus of the Thalamus. These all aim to modulate the abnormal thalamocortical circuitry associated with tics in TS, and while different studies have shown their potential efficacy, it remains unclear which target should be the most appropriate one.
3. Anterior Limb of Internal Capsule (ALIC): it aims to modulate the cortico-striato-thalamo-cortical circuit associated with the pathophysiologic generation of tics. Nevertheless, meta-analyses suggest that this target has an inferior efficacy in the reduction of symptoms compared to the other targets.

Based on available data, it appears that in TS, different targets are similarly effective as is the case in DBS in Parkinson’s disease. Clinical response to DBS may vary according to the clinical picture, comorbidities, and to the anatomical target. Whether the GPi really constitutes a superior target, as some recent studies are suggesting, is currently under investigation.[122-125]

DEPRESSION

Even if it remains an experimental treatment to this day, DBS has shown some promising results as a therapy of treatment-resistant depression (TRD), condition which accounts for 1-3% of all major depressions.

The brain structures that have been used as DBS targets in treating severe depression, selected based on neuroimaging and lesional studies, are the subgenual anterior cingulate cortex (sACC), the ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAcc), the lateral habenula (LHb), the inferior thalamic peduncle (ITP), the medial forebrain bundle (MFB) and the bed nucleus of the stria terminalis (BNST).

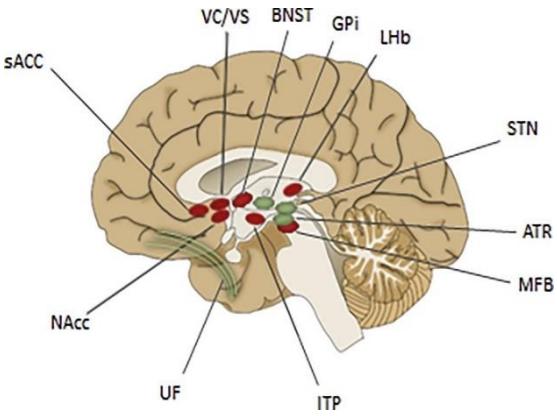

Figure 8: Possible DBS targets for treatment of major depression.

The sACC is the most used target in TRD treatment so far. Stimulation of this area modulates the activity of the limbic network, which is involved in regulating mood and emotions. The efficacy of DBS in sACC was shown to increase with individualized target identification and with the use of optimal stimulation parameters.

The NAcc, instead, is well-known for its role in the circuitry of reward and pleasure. There seems to be a direct correlation between the size and activity of the NAcc and the anhedonia perceived by the TRD patients. Stimulation in this area seems to be able to treat a disruption in the reward circuitry, which is perceived by the patient within 60 seconds of stimulation onset, with significant cognitive-behavioral improvements.[126-128]

ALZHEIMER'S DISEASE

The rationale for this still experimental treatment of Alzheimer's Disease (AD) lies in the increased release of the acetylcholine neurotransmitter, obtaining an improvement in cognitive functions. Secondly, it also increases the release of neural growth factor (NGH) and other neurotrophic factors, which have been shown to improve memory in patients with AD. The targets chosen to maximize these effects include:

1. Nucleus basalis of Meynert (NBM): this cholinergic nucleus located in the basal forebrain undergoes severe atrophy as the disease progresses. Low-frequency stimulation of this nucleus seems to be safe and free of significant adverse effects, but its efficacy is still under debate as results in different studies appear contradictory.
2. Fornix: the fornix is the predominant outflow tract of cholinergic axons from the septal area to the hippocampus, and it has been found that fornix integrity predicts memory impairment and progression to AD. While there have been cases of improvement of symptoms, there is no general consent on the efficacy of fornix-DBS, as different studies have yielded non-consistent results.
3. Ventral Capsule/Ventral Striatum (VC/VS): giving the connection of this area to the limbic circuit, the effect of the stimulation improves symptoms like apathy, lack of initiative and impaired decision making. Nevertheless, there is a scarcity of studies related to this target, therefore its effectiveness is still ongoing field of study.[129-132]

ANOREXIA NERVOSA

DBS may offer a long-term and reversible treatment option for patients with AN, but current research is not sufficient to provide evidence of a clear benefit of DBS compared to standard-of-care medical management. There is a well-established link between AN and other psychiatric conditions, particularly with major depression and obsessive-compulsive disorder. This gives reason to believe that the reward circuit has a key role in the pathologic mechanisms of the disease, and therefore neuromodulation attempts focus on areas implicated in that circuit.

The main targets for treatment of AN are the subcallosal cingulate cortex (SCC) and the nucleus Accumbens (NAcc), which give an average increase of BMI of about 24%. From the literature available to this day, it appears that SCC is the target which presents the most significant improvement in clinical outcome.

The procedure has the same possibility of adverse effects as DBS for other conditions, with one key difference being that, due to the malnourished state of the patients, the probability of poor wound healing and infection are much higher.[133-134]

OBESITY

In selected cases of morbid obesity, DBS, may be refined into a therapeutic modality for patients with failure of bariatric surgery in the future. Hypothalamic DBS for obesity has been shown to be reasonably safe in well-selected patients. The effectiveness has, however, not been shown to be robust or reproducible. Based on both biological plausibility and on observational studies, the NA has emerged as an alternative obesity DBS target.[135-136]

CHRONIC PAIN

Considering cancer-related chronic pain, oral analgesics are effective in 75–90% of patients, but only about 30% of individuals with non-cancer-related chronic pain achieve improvement from opioid treatments. Therefore, numerous other therapeutic approaches have been proposed and utilized, including non-opioid pharmacological agents, nerve blocks, acupuncture, cannabidiol, stem cells, exosomes, and neurostimulation techniques, such as DBS.

The target of DBS largely depends on the cause of the pain. For example, unilateral hypothalamic DBS seems to be very effective in treatment of chronic cluster headache, as well as stimulation of the sphenopalatine ganglion, which involves parasympathetic inhibition through high-frequency stimulation. Instead, thalamic DBS is most used for treatment of phantom limb pain.

Nevertheless, the most used target is the Periaqueductal Grey (PAG), given the hypothesis that stimulation in this area induces the secretion of endogenous opioids. Although clinical studies demonstrated favorable results of applying the DBS for chronic pain treatment, the number of patients treated by this method is declining, due to lack of approval for clinical use and development of other therapeutic approaches.[137-139]

ADDICTION

Drug addiction or substance use disorder (SUD) represents an important public health issue which constitutes a great burden to society. It is well known that this condition is pathophysiologically based on alterations of the reward circuitry in the patient's brain. Nevertheless, targeting areas involved in this circuit through DBS raises important ethical and legal questions, which need to be examined before such an experimental treatment is proposed. Given the scarcity of relevant clinical guidelines about the matter, general medico-legal principles serve as the reference. So far, the Nucleus Accumbens (NAcc) is the main target considered in the treatment of SUD. The abused substances cited in studies include tobacco, alcohol, cocaine, methamphetamines and opioids, and the results indicate a marked improvement in substance consumption and craving.

Also, other targets have been reported to have a potential benefit in treatment of SUD, such as the infralimbic cortex, the orbitofrontal cortex, the insula, and the substantia nigra pars reticulata. [140-141]

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is a chronic condition which arises after a stressor that acts as a trigger for very intense and debilitating anxiety. Almost 30% of patient affected by it remain refractory to standard therapy which involves antidepressants and psychotherapy. Extensive research has been carried out using animal models, whereas application of the treatment on humans still remains highly investigational, as only three cases have been described in literature.

The main target used for DBS is the Amygdala, which is hyperactive in patients with PTSD, causing the symptoms of hyperarousal and an exaggerated fear response. In one case, a woman was treated with DBS of the medial prefrontal cortex and the uncinate fasciculus, with astounding results, as 7 months post-operatively she didn't manifest any of the typical PTSD symptoms anymore.[142,143]

FUTURE DIRECTIONS

Anticipated advancements in deep brain stimulation technology include improvements in electrode and IPG design, like miniaturization and cranialization of the IPG. These advancements also consist in improved battery life, recharging capacity, and energy harvesting, as well as increased safety measures. Moreover, there will be improved compatibility with MRI systems of ≥3 T, antibiotic impregnation of the electrode to reduce infection risks during implantation, and protection from possible hacking of the device by third parties. Large-scale production and modernized production techniques are expected to reduce costs.

Optimized stimulation techniques will be employed, with IPGs equipped with multiple independent power sources for simultaneous control over multiple currents. There will be increased control over waveform shape, such as symmetric biphasic pulses for tremor management. Varying inter-pulse intervals or coordinated reset methods from different contacts will be used.

The stimulation will most likely not be continuous anymore, instead the so-called “adaptive” or “closed-loop” deep brain stimulation will be used, allowing for responsive stimulation. This will enhance the therapeutic window of the stimulation, as it will deliver current only when the device records a certain pathologic electrophysiologic activity. Stimulation will in fact be modulated in response to power spectra of local field potentials (e.g., beta for rigidity or gamma for dyskinesia) or seizure activity, as well as based on body position (gyroscopes) or motion (accelerometer).

To enhance the effectiveness of deep brain stimulation, electromyographic recording will provide motor feedback, and integration of multiple feedback and stimulation sites will be implemented. Artificial intelligence techniques will be utilized to fine-tune the stimulation programming. Neuroimaging advances, including enhanced anatomical resolution through specialized sequences (e.g., quantitative susceptibility mapping) or ultra-high-field (7 T) MRI, will improve targeting accuracy. Furthermore, improved automatic electrode reconstruction and segmentation will be achieved with image-processing software. By identifying 'sweet spots' through large retrospective imaging studies, deep brain stimulation programming will be enhanced. Prospective functional imaging techniques (e.g.,

functional MRI) will be utilized to identify optimal 'neural signatures' for personalized treatment.[144,145]

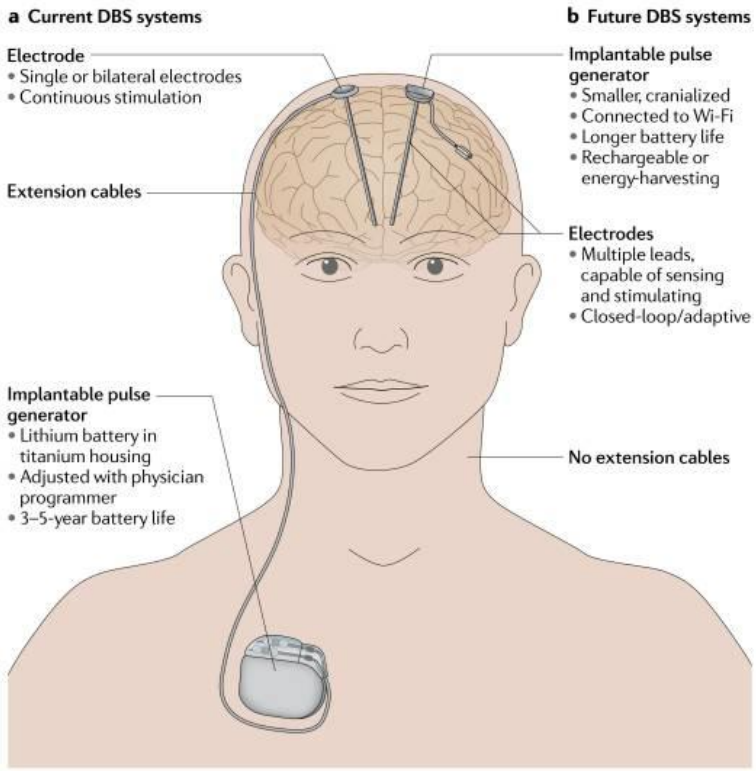

Figure 9: Current vs future features of DBS systems.

MAIN BODY

INTRODUCTION

Deep Brain Stimulation is a therapeutic procedure which has been used to treat various conditions for many decades, mainly Parkinson's Disease. To this day, it is recognized as an effective treatment for different pathologies when indications are respected. [41-44]

A fundamental characteristic needed to optimize the procedure's therapeutic effect is high precision placement of the implanted lead. To achieve this, two main methods have been described, one involving the brain's electrophysiologic features using microelectrode recording, and the other relying on the pure anatomy of the structures of interest. While both these methods taken separately have their advantages and drawbacks, in this study we present a method to combine intraoperatively both anatomical and electrophysiologic information, in order to present the surgeon all the elements necessary for the decision-making process of the optimal placement of the final lead. Moreover, no additional resources were needed to apply this method at our Institution, making it a safe and cost-effective way of improving DBS surgery. [45-47]

The primary goal of the study is, therefore, to verify the reliability of this anatomical navigation method by comparing the stereotactic coordinates of the intraoperatively planned trajectory and the post-operatively reconstructed trajectory. This aims to suggest a standardized surgical method for the implantation of a DBS lead, which permits intraoperative association of anatomical (imaging studies) and electrophysiological (microelectrode recording) information, and consequently to obtain optimal placement of the definitive electrode and better understanding of basal ganglia's functional anatomy.

MATERIALS AND METHODS

PATIENT SELECTION

Patients enrolled in this study are all patients who underwent Deep Brain Stimulation for the treatment of movement disorders at the Department of Neurosurgery of Padova from March 2023 to May 2023, for a total of n = 5 patients. The patients were enrolled prospectively following a study protocol in order to standardize the methodology used for all patients and therefore minimize potential biases. The methods described in this study protocol are summarized in the following sections of this chapter.

PREOPERATIVE IMAGING STUDIES

MAGNETIC RESONANCE IMAGING

Preoperative MRI studies are required both for target/trajectory planning and 3D reconstruction of regions of interest.
At our Institution patients undergo brain MRI following a specific protocol using a 3T scanner (Ingenia 3T, Philips Healthcare) to obtain:

- T1-weighted images (TR/repetition time = 8, TE/echo time = 3.7) with contrast;
- FLAIR/fluid attenuated inversion recovery (TR = 4800, TE = 299, TI/inversion time = 1650, flip angle = 40, matrix = 240 ×240 mm2,voxel = 1×1×1 mm3, 196 slices, 4.05 min of acquisition time)

HEADFRAME CT-SCAN

Once the stereotactic headframe is fixed on the patient's head, a thin slice CT-scan is carried out, with the following specifications: Field of View = 500; Dose Lenght Product = 2.4 mGy*cm; Computed Tomography Dose Index volume = 0.085mGy; 120 kV; 30mA.

3D RECONSTRUCTION OF AREAS OF INTEREST

3D reconstruction of areas of interest will be obtained using Brainlab Elements®[151] "Object Manipulation" version 4.0. The areas that will be reconstructed depend on the DBS target.

Concerning the Brainlab Elements® software, 3D reconstruction through object manipulation is greatly influenced by the quality of the data sets, particularly by the image resolution, slice distance, imaging contrast, field of view (FOV) and possible artifacts. Therefore, the user manual states that preoperative MRI study is required to have the following characteristics to provide optimal results:

- Different sub-modalities available (T1, T2, FLAIR)
- Less than 1 mm slice thickness
- More than 100 slices
- The FOV should be as large as possible
- High contrast-to-tissue ratio (i.e., good visualization of the different tissue classes)
- High signal-to-noise ratio

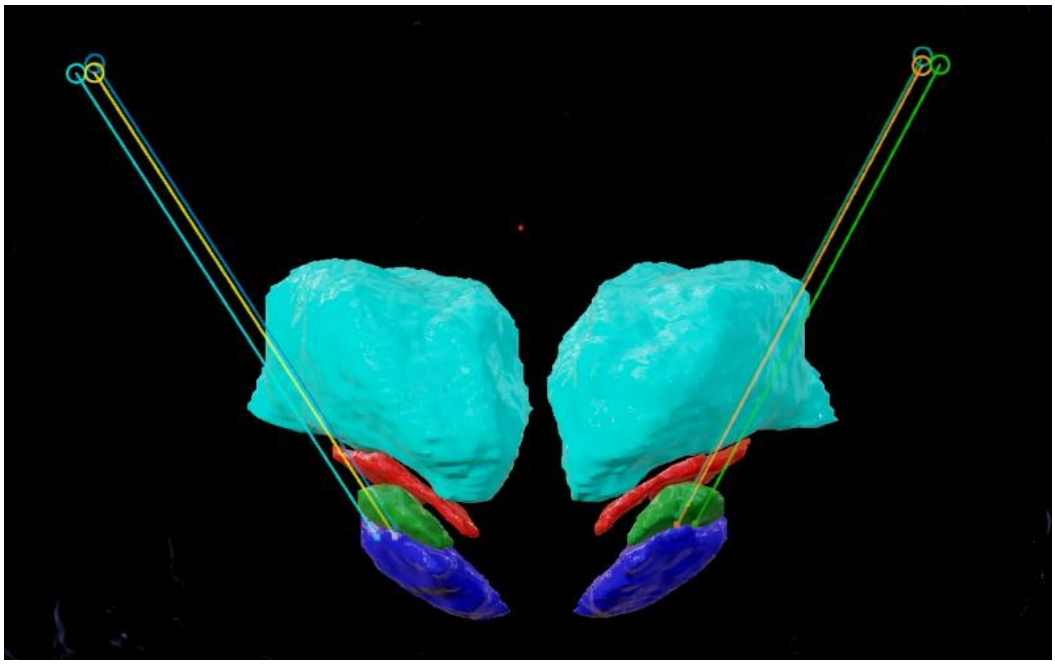

Figure 10: The 3D reconstruction of the Thalamus (light blue), the Zona Incerta (red), the STN (green) and the Substantia Nigra (dark blue) can be visualized in relationship to the planned trajectories.

Depending on the chosen DBS target we reconstructed the following areas:
For STN-DBS:

- Caudate nucleus
- Putamen
- Thalamus
- Zona Incerta
- Subthalamic Nucleus
- Substantia Nigra

For GPi-DBS:

- Caudate nucleus
- Putamen
- Globus Pallidus Externus
- Globus Pallidus Internus
- Optic tract

As to the details regarding image reconstruction, the official user manual can be found at https://userguides.brainlab.com/en/guides/object-manipulation/en/4.0/ and will be carried out first using automatic anatomy recognition and afterwards each individual structure will be revised and refined in order to obtain the most accurate result possible.

STEREOTACTIC PLANNING

Target and trajectory selection is a crucial phase for success of DBS procedures, and it is greatly influenced by the surgeon's experience. Target selection is largely based on treatment goals, since STN-DBS is associated with greater decrease in L-DOPA requirements in Parkinson's Disease, easier surgical targeting and weight gain, whereas GPi-DBS is associated with lower chance of cognitive decline, easier postoperative programming and mood stability.

The choice of the exact individual target identification goes as follows:

- STN: the approximate coordinates for localization of the STN are 3 mm posterior, 4 mm inferior, and 10-12 mm lateral to the midcommissural point. The FLAIR or T2 image set is then used to adjust the target with respect to the unique anatomy of each patient.

- GPi: the approximate coordinates used for initial GPi targeting are 2 mm anterior, 5 mm inferior, and 21 mm lateral to the midcommissural point. The FLAIR or T2 image set is then used to adjust the target, accounting for individual patient variability, which is high for this target.

- Trajectory: regarding the trajectory planning, the approximate initial trajectory for both STN and GPi stimulation is 60 degrees from the AC-PC line in the sagittal plane and 0 to 15 degrees from the vertical in the coronal plane. Patient-specific adjustments include avoiding cortical sulci and vascular structures superficial and deep. If the lateral ventricle is crossed along the trajectory, we adjust the entry point because ventricular violation is shown to increase morbidity. [35,150]

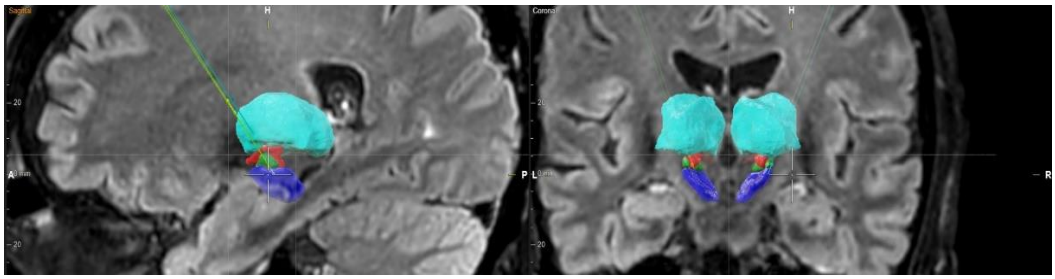

Figure 11: visualizing 3D objects and trajectories in context of the MRI study.

INTRAOPERATIVE ANATOMICAL NAVIGATION

To allow intraoperative visualization of the anatomical relationships of every point along the planned trajectory, we used Brainlab Elements® as a reference during the microelectrode recording phase. The software is equipped with a window that simultaneously shows the MRI study of choice as background, the outline of every reconstructed object and the planned trajectories. The most important feature, nevertheless, is that it visualizes the plane that is orthogonal to the trajectories at a given point, which is indicated in the axial and coronal planes in terms of distance from the chosen target and the entry point.

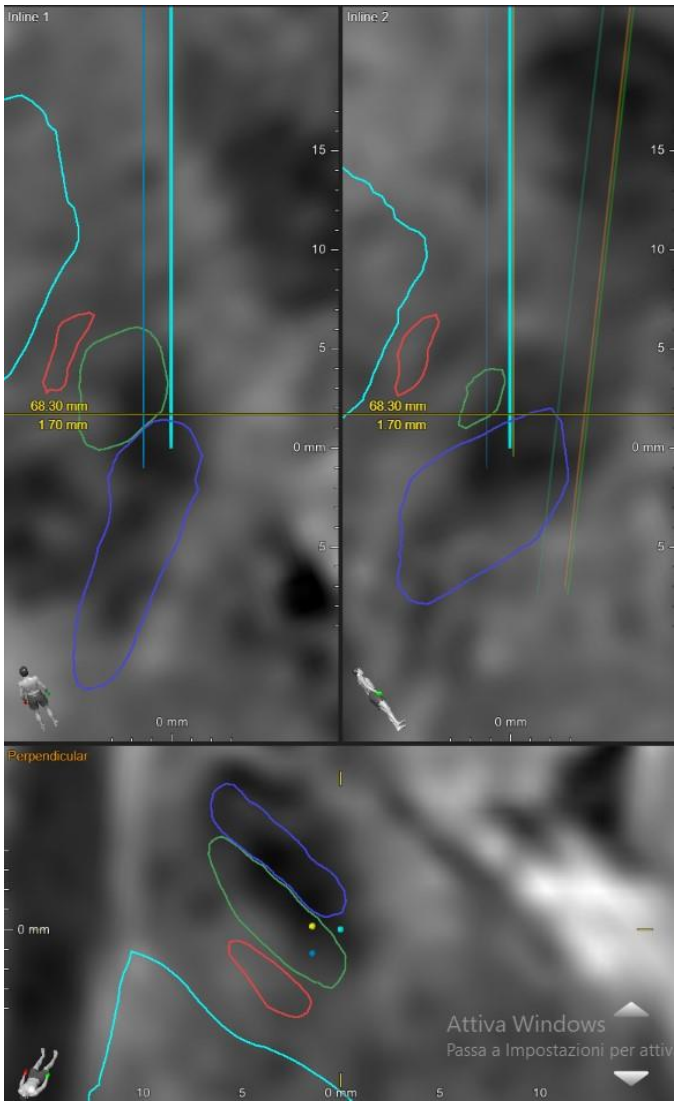

Figure 12: example view of intraoperative intraoperative stereotactic navigation.

For example, in the image above we see the axial and coronal planes superiorly, and the plane orthogonal to the trajectory inferiorly. The reconstructed objects are color-coded, the thalamus is light blue, the Zona Incerta is red, the Subthalamic Nucleus is green and the Substantia Nigra is dark blue. The trajectories are color-coded as well. For this patient, we chose to do microelectrode recording with 3 microelectrodes, one placed exactly along the planned trajectory, one posteriorly and one laterally. In the image, we can visualize the tree trajectories on the patient's right side: the yellow one is the central trajectory, the light blue one is the lateral trajectory, and the dark blue one is the posterior trajectory.

Therefore, in the above image, we can see that on the stereotacticly determined point distant 1.70 mm from the target, the tip of the microelectrodes should be located within the STN, with the lateral trajectory being the closest to the substantia nigra.

During the microelectrode recording phase of the surgery, we start recording 10 mm from the target and we advance the microelectrodes 0.5mm at a time. Each of the points in which recordings are performed are visualized on Brainlab Elements® to obtain an intraoperative anatomical navigation of the microelectrodes. This information can than be used to integrate the information provided by the spiking activity displayed by the AlphaOmega Neurosmart device.

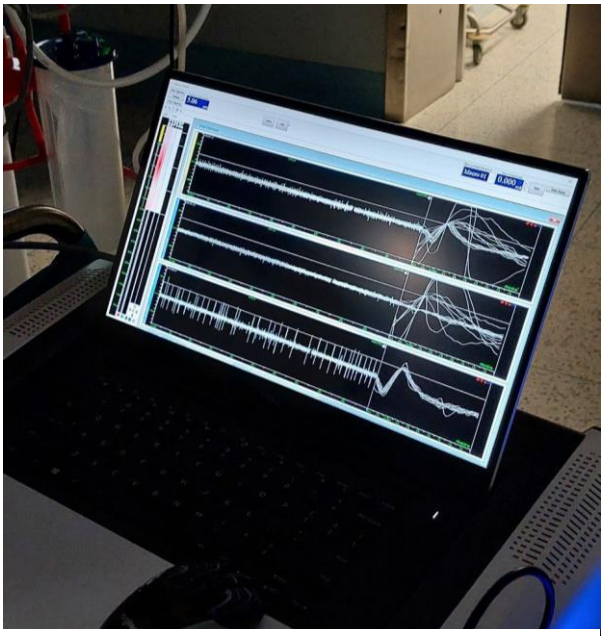

Figure 13: single unit activity as it is displayed by the AlphaOmega Neurosmart device.

INTRAOPERATIVE ASSOCIATION OF MER AND ANATOMICAL NAVIGATION

The potential of this methodology becomes clear as soon as the spiking activity is integrated with the images obtained through the software reconstruction. The image below exemplifies this concept in a GPi-DBS, showing the electrode's path in its anatomical context, and the spiking activity recorded at the corresponding depth. All data recorded by the microelectrodes are exported for further analysis in future works.

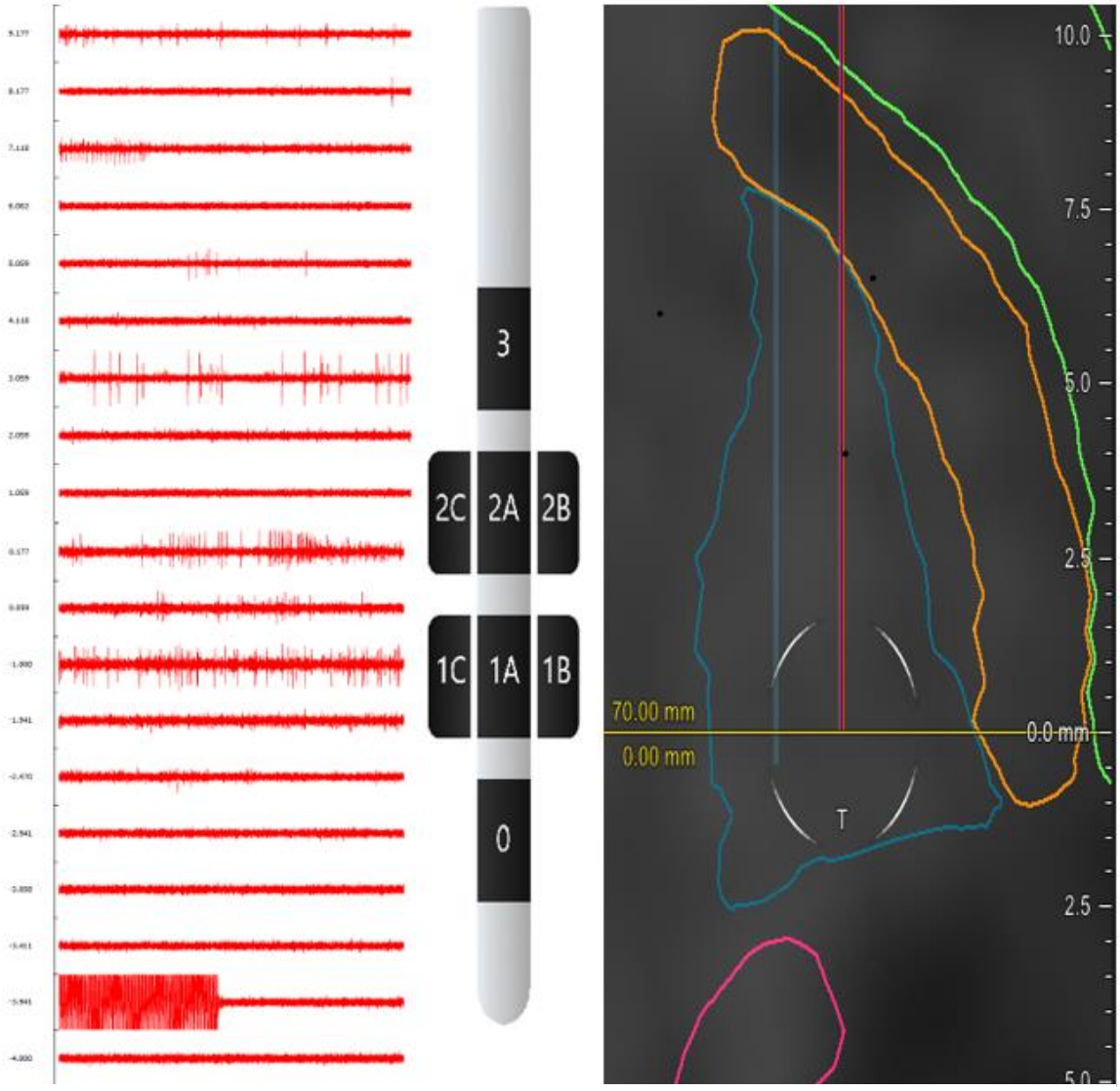

Figure 14: Association of anatomical (Brainlab image on the right) and electrophysiologic (MER on the left) information integrated to give a more complete understanding of the positioning of the electrode in GPi-DBS. We can see the outline of the Putamen (green), GPe (orange), GPi (blue), and optic tract (pink). The trajectory (pink line) is associated with the MER recorded at the corresponding depth (white numbers on the y-axis on the right)

POST-OPERATIVE LEAD RECONSTRUCTION

To assess the reliability of this method, we compare the intraoperatively visualized trajectory with the post-operatively reconstructed lead.

To obtain the post-operative reconstruction we use Brainlab Elements® "Lead Localization", which runs an automatic detection of the lead on the post-operative CT scan. The user manual for this function can be found at the link: https://userguides.brainlab.com/en/guides/lead-localization/en/1.0/?revision=1.0.

Figure 15: running automatic lead detection on the post-operative CT scan.

The reconstructed trajectory is defined, like all trajectories in Brainlab Elements®, by 5 parameters:

- X, Y, Z: these parameters define the position of the trajectory's target, as referred to the stereotactic headframe used for the operation. These values are calculated by the software in millimeters representing the distance to the midcommissural point.
- Ring angle, arch angle: these parameters define the trajectory's anteroposterior and lateral inclination respectively. They are calculated by the software in degrees referring to the vertical line.

Once these parameters are defined, we can use them to compare them with the intraoperative trajectory, corrected by the chosen depth of implantation.

This means that before we make the comparison, we have to modify the length of the trajectory by the chosen depth of implantation. For example, if, after the microelectrode recordings, the posterior trajectory is chosen and the implantation depth is set at -2,5 mm, we will modify the corresponding trajectory's length by 2.5 mm, setting it to "modify target", not "modify entry point". This enables us to eliminate an important factor of bias.

Once we can compare the parameters, it is possible to apply a simple formula to convert the difference between the stereotactic parameters X, Y and Z to a linear distance in mm between the two target points:

$$\text{Linear distance} = \sqrt{(\Delta X)^2 + (\Delta Y)^2 + (\Delta Z)^2}$$

QUALITY CONTROL

To consider this anatomical navigation reliable, we decided that the linear distance between the planned target and the post-operatively reconstructed target should be < 1 mm, and the difference between the two arch angles and the two ring angles < 3°. When this was not the case, we examined the reasons why the two trajectories were off by more than expected.

RESULTS

POPULATION

The patients who underwent DBS surgery at our Institution were n = 5. In the following table essential information for each patient is presented.

Patient	FG	MA	GM	MR	MI
Age and Gender	66, male	70, male	66, female	57, female	64, male
Pathology	Parkinson's Disease	Parkinson's Disease	Parkinson's Disease	Dystonic parkinsonism	Parkinson's Disease
Target	STN	GPi	STN	GPi	STN
First side operated on	Right	Right	Left	Left	Right

Table 1: population

Of the 5 patients, 3 were male and 2 were female, with a mean age of 64,6 years and a standard deviation of 4.8 years.

4 patients were operated for Parkinson's Disease and 1 for dystonic parkinsonism. The chosen targets were Subthalamic Nucleus (3 times) and Globus Pallidus internus (2 times). The first side operated on was chosen as the contralateral side to the one corresponding to the onset of symptoms. For example, patient FG had an onset of parkinsonian symptoms on the left side and therefore was operated on the right side first.

RAW DATA

Patient	first traje	-	RX Lead	DX traj	Δ	-	SX Lead	SX traj	Δ
FG	RX	X	86,3	86,9	-0,6	X	111,6	111,4	0,2
		Y	97,8	98	-0,2	Y	94,6	95,8	-1,2
		Z	117,8	117,8	0	Z	118,5	118,2	0,3
		ring	64,5	66,6	-2,1	ring	70,8	77,7	-6,9
		arch	72,6	73,1	-0,5	arch	108,1	108,6	-0,5
		Target dev	0,63			Target dev	1,25		
MA	RX	X	76,1	74,8	1,3	X	117,5	119	-1,5
		Y	102,5	103,8	-1,3	Y	104,6	103,8	0,8
		Z	108,2	111	-2,8	Z	112,4	110,9	1,5
		ring	82,8	83	-0,2	ring	88,4	85	3,4
		arch	82	82,5	-0,5	arch	106,4	105	1,4
		Target dev	3,35			Target dev	2,27		
GM	SX	X	84,1	84,1	0	X	106,3	107	-0,7
		Y	101,1	102	-0,9	Y	101,5	102	-0,5
		Z	118,2	118,1	0,1	Z	118,7	118,2	0,5
		ring	54,2	58	-3,8	ring	56,5	59	-2,5
		arch	72,7	72	0,7	arch	105,8	105,5	0,3
		Target dev	0,91			Target dev	0,99		
MR	SX	X	78,1	78,9	-0,8	X	117,8	117,6	0,2
		Y	104,7	105	-0,3	Y	107	106,4	0,6
		Z	111,6	110,3	1,3	Z	110,5	110,4	0,1
		ring	89,7	90	-0,3	ring	90	88,9	1,1
		arch	76,1	73,5	2,6	arch	100,4	100,7	-0,3
		Target dev	1,56			Target dev	0,64		
MI	RX	X	87,5	87,1	0,4	X	108,1	110,6	-2,5
		Y	97,1	98,2	-1,1	Y	95,3	98	-2,7
		Z	112,2	111,8	0,4	Z	115,6	112,1	3,5
		ring	66	65,9	0,1	ring	64	64,8	-0,8
		arch	75,5	73,7	1,8	arch	108,8	111,5	-2,7
		Target dev	1,24			Target dev	5,08		

Table 2: In this table all raw data are presented, organized by patient. The "RX/SX Lead" column refers to the post-operative reconstruction of the electrode, while "RX/SX traj" refers to the intraoperatively visualized trajectory. Values in X, Y, Z and target deviation are in mm, whereas ring and arch angle are in degrees.

TARGET AND TRAJECTORY DEVIATION

Considering all 5 patients together, we obtained the following results:

- Mean target deviation: 1.79 ± 1.42 mm
- Mean ring angle deviation: 2.12° ± 2.14°
- Mean arch angle deviation: 1.13° ± 0.94°

Nevertheless, during the surgery of 2 patients, a consistent amount of air entered the cranium, causing an important amount of brainshift. This was confirmed by the post-OP CT in both patients, and logically caused a great deviation between the planned and the post-operatively reconstructed target. Excluding these 2 patients, the mean target deviation is 1.00 ± 0.36 mm, which would be an acceptable result to consider this methodology as a valid anatomical navigation.

DIFFERENCE IN ERROR BETWEEN THE FIRST AND THE SECOND SIDE

We found that the error in linear distance between the planned target and the post-operatively reconstructed target is bigger in the second side operated on than in the first one, by approximately 60%.

Considering all data collected, the mean linear distance in the first side was 1.37 ± 1.14 mm and the mean linear distance in the second side was 2.21 ± 1.68 mm. If we exclude the 2 cases that presented significant pneumocephalus the mean error is 0.76 ± 0.21 mm on the first side and 1.24 ± 0.33 mm on the second side.

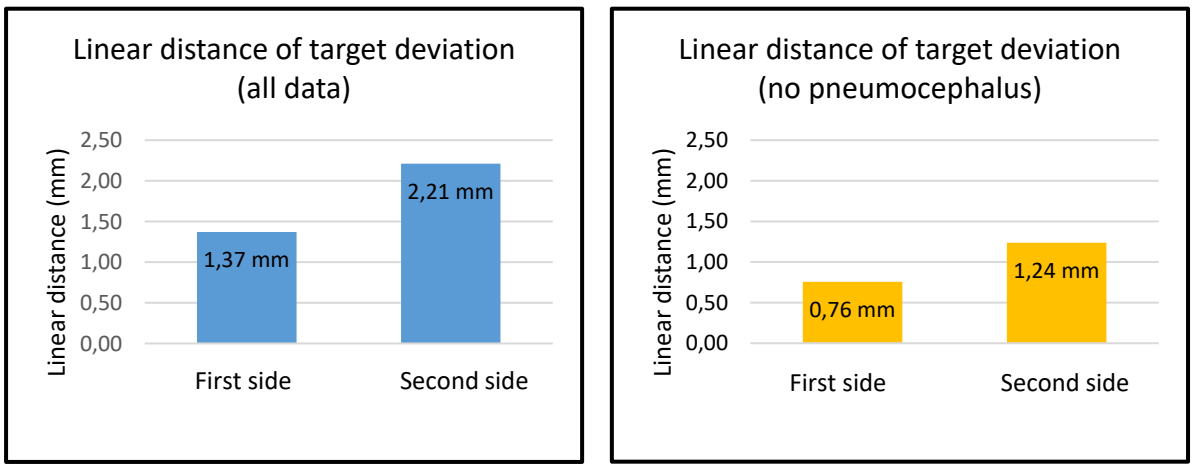

Figure 16

DISCUSSION

COMPARISON WITH LITERATURE AND CURRENT PRACTICE

To our knowledge, there is no study which describes a method to intraoperatively associate an anatomical stereotactic navigation to microelectrode recordings in Deep Brain Stimulation.

It is, however, common practice to use the Brainlab® software to identify the anatomical relationship of the final lead with post-operative reconstructions. More specifically, the "Boston Scientific" company is in a partnership with Brainlab which allows for a dedicated interface that allows the clinician to clearly visualize the patient's specific anatomy and modulate the lead's electric stimulation accordingly. This is shown to considerably reduce the DBS programming time.[146] More information on this can be found at Boston Scientific's website: https://www.bostonscientific.com/en-US/medical-specialties/neurological-surgery/image-guided-programming.html

Figure 17: Example of the clinical interface used by Boston Scientific to display the anatomical context of the DBS lead.

The “Medtronic” company also focuses on the anatomical context of the DBS lead with their product SureTune™ 4, a patient-specific visualization tool which compiles pre-, peri and intraoperative imagery with patient-specific anatomical models into a single visualization to inform programming decisions.

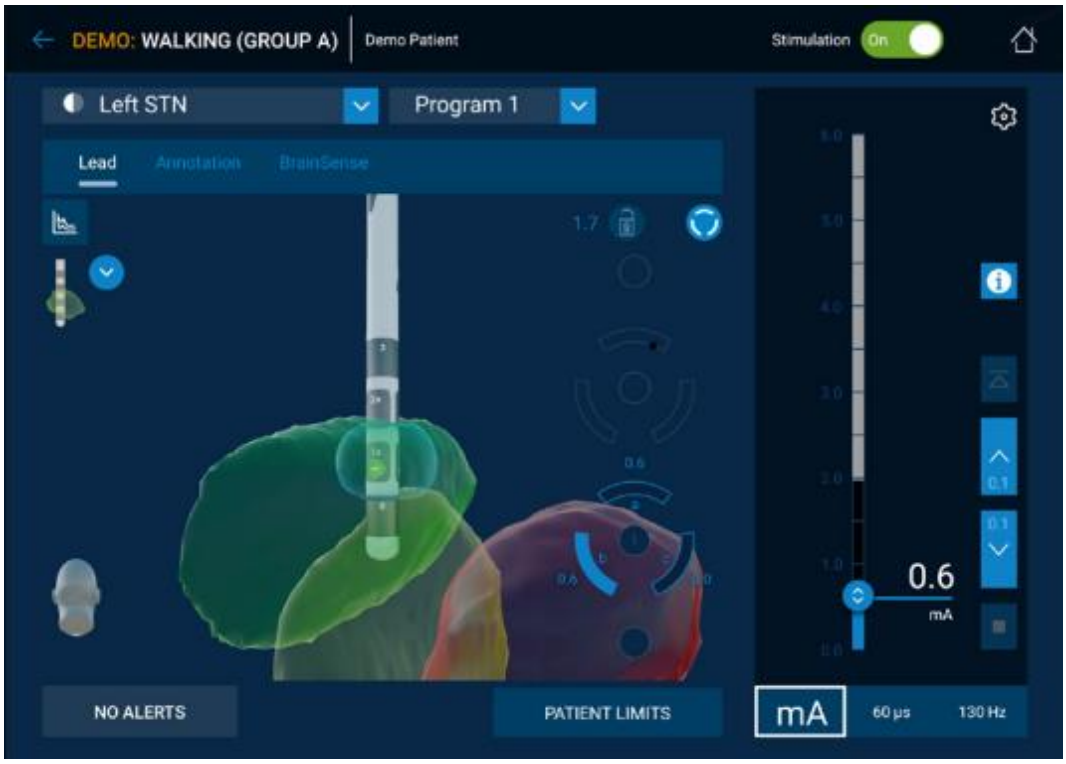

Figure 18: Example of the clinical interface used by Medtronic to display the anatomical context of the DBS lead.

Concerning an intraoperative use of anatomical information, there is another very recent study which used Random Forest modeling to statistically associate electrophysiological features on intraoperative MER and voxel intensity on preoperative T2-weighted MR imaging. This information was then used to develop an algorithm that could derive real-time positioning of the electrode just by associating MER with the preoperative imaging studies. They found that the trajectory calculated this way was significantly closer to the actual trajectory reconstructed post-operatively than the planned trajectory that is not corrected by that algorithm.[147]

While this certainly represents a further development of the work presented in this study, the significance of our results aims to provide an easy-to-use methodology to associate anatomical navigation intraoperatively, without the need for additional resources or economical investments.

SIGNIFICANCE OF INTRAOPERATIVE ANATOMO-PHYSIOLOGICAL CORRELATION

The interpretation of the signal coming from the microelectrode recording requires huge expertise by the surgeon in order to provide a correct understanding of the position of the electrode. This is also complicated by the fact that, in asleep DBS, the sedation interferes with the brain's electrical activity, blunting the signals recorded and therefore making their interpretation even more difficult.

Therefore, the anatomical reference provided by the Brainlab Elements® software gives the context necessary to interpret the recorded MER signal in a more thoughtful and complete manner. This is done by associating the features of the spiking activity recorded at each depth with the anatomical location on the planned trajectory at the corresponding distance from the target.

The image below gives an example of this association for STN-DBS: on the left the 1 second of spiking activity is displayed for each depth at which the recording took place, at the center there is an image of the electrode at the corresponding depth at which it was implanted, and on the right the anatomical location of the trajectory and its relationships to the surrounding structure are shown.

The spiking activity shown in the image is not very informative due to the short time interval that is displayed for viewing purposes, nevertheless it is possible to perceive a certain correlation with the anatomy of the patient: in the zona incerta the spikes recorded are few and the background noise is also low, in the subthalamic nucleus we can notice an irregular spiking activity and in the substantia nigra a much more tonic, regular activity is displayed.

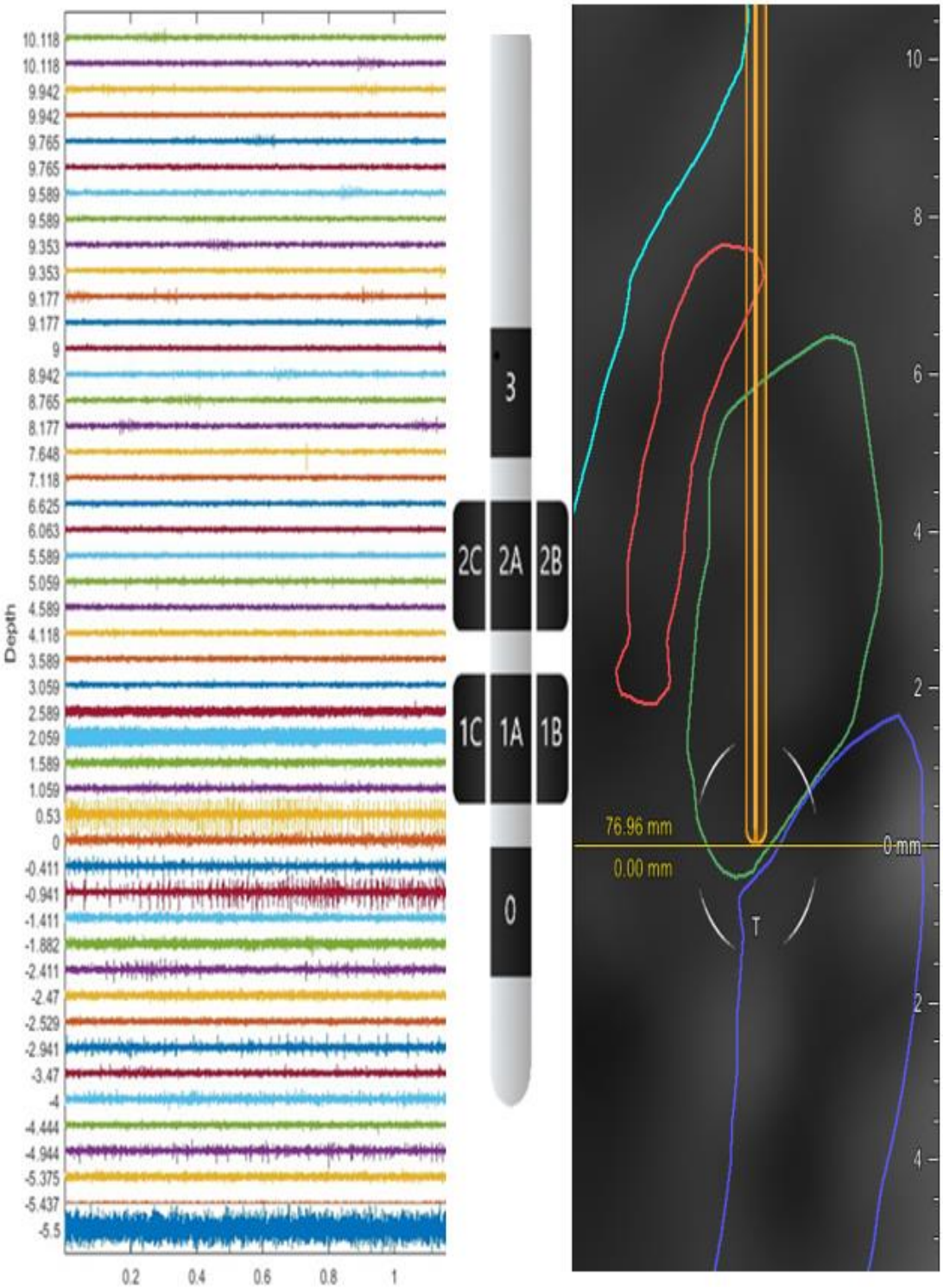

Figure 19:Association of anatomical (Brainlab image on the right) and electrophysiologic (MER on the left) information integrated during positioning of the electrode in STN-DBS. We can see the outline of the Thalamus (light blue), the Zona Incerta (red), the STN (green) and the Substantia nigra (dark blue).

TARGET DEVIATION

Given the low number of patients operated on, the results given in this study are only preliminary and not sufficient to draw any strong conclusion. Nevertheless, a total of 10 sides was examined in this study, which is sufficient to give an initial evaluation of the methodology.

Considering all data collected, the mean linear distance in the first side was 1.37 ± 1.14 mm and the mean linear distance in the second side was 2.21 ± 1.68 mm. As the data suggests, the standard deviation of these results is relatively high, and this is due to 2 patients who suffered from significant pneumocephalus after the operation. The consequent brainshift caused a significant increase in target deviation.

This was the case with patients MA and MI. Already during their surgery it was clear that a consistent amount of air penetrated their skull both from anesthesiologic parameter fluctuations and from the perceived deepening of the cerebral cortex in respect to the burr holes. Accordingly, we noticed that the spiking activity recorded by the microelectrodes presented features that did not correspond to their supposed anatomical location.

If we exclude these two patients from the calculation of the mean target deviation, we find that the value now becomes 1.00 ± 0.36 mm, which would be closer to the expected results and would prove that the methodology can be a reliable way to intraoperatively monitor the position of the electrode.

Therefore, from the experience at our Institution, we can understand that it is of fundamental importance to try to avoid the formation of pneumocephalus or at least recognize as soon as possible. When this is the case, the results of our study suggest that using the Brainlab Elements® software to intraoperatively navigate the microelectrode insertion is a useful and reliable way to facilitate the decision-making process regarding the final electrode placement.

While it is difficult to objectivate the perceived facilitation in the aforementioned decision-making process, the whole surgical team involved in DBS surgery at our Institution agreed about the usefulness of this methodology in making the interpretation of MERs easier and clearer.

COMPARISON BETWEEN THE FIRST AND SECOND SIDES

Given the low number of patients, it is premature to draw any definitive conclusions. Nevertheless, the data we collected so far seems to clearly point to a significant difference in target deviation between the first and second sides operated on, coherently with what was expected.

The literature is not unanimous on this topic as some studies report a lower accuracy in the second side operated on, whereas others suggest that the second electrode is not necessarily less accurate than the first one, even though it necessitates of more intraoperative adjustments.[148,149]

In our patients, however, the mean target deviation in the first side was 1.37 ± 1.14 mm whereas in the second side it was 2.21 ± 1.68 mm. Nevertheless, this data might not be representative of the real difference between the 2 sides because in 2 of the 5 patients a consistent amount of air entered the skull during the surgery. Since it is hard to be sure at what point exactly this happened, it is reasonable to believe that the chances that this occurred between the placement of the first and the second electrode, therefore altering the results.

If we exclude these 2 cases the mean target deviation is 0.76 ± 0.21 mm on the first side and 1.24 ± 0.33 mm on the second side. This still indicates a significant increase in target deviation as we would expect, but in a lesser amount and with a more acceptable standard deviation. This increase in deviation is most likely due to liquor loss during the procedure, as well as possible shifts in blood pressure, small entrances of air or small bleedings along the trajectory of electrode insertion.

TRAJECTORY DEVIATION

Considering the trajectory, there are two parameters that stereotacticly determine the chosen course of the electrode:

- The arch angle: it determines the latero-medial inclination of the electrode;
- The ring angle: it determines the antero-posterior inclination of the electrode.

Our results indicate that the mean angle deviation was 2.12° ± 2.14° in terms of ring angle, and 1.13° ± 0.94° in terms of arch angle.

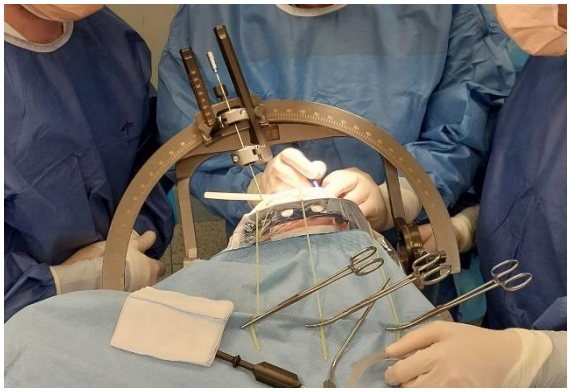

Figure 20: the arch of the stereotactic headset determines the latero-medial inclination.

As we can notice, both the mean and the standard deviation are almost double in the ring angle as compared to the arch angle. This is due to the fact that the size of the arch of the stereotactic headset is much greater than the size of the ring, as is seen from the images presented.

The greater size of the arch allows for a more precision when reporting the angle values on the headset, and this reflects on the fact that the planned trajectory is more similar to the actual trajectory in the latero-medial inclination than in the antero-posterior one.

Figure 21: the ring of the stereotactic headset determines the antero-posterior inclination.

Nevertheless, given the fact that we considered acceptable an angle deviation of less than 3°, we conclude that with a careful setting of ring and angle arch it is possible to accurately navigate the electrode's trajectory in an intraoperative setting.

CASE EXAMPLE

Given the low number of patients, the importance of singular cases is emphasized much more than statistical analysis. Therefore, the curious case of patient MR is here presented, as it is an example of how important it is to have an anatomical context.

Patient MR is a 57 year-old female affected by dystonic parkinsonism. After the multidisciplinary discussion of her case, the indication for a GPi-DBS was given.

The procedure went smoothly, and there appeared to be no significant liquor loss between the opening of the dura and the insertion of the cannulas that would guide the microelectrode.

During the MER phase of the surgery, the spiking activity recorded appeared to be clear and informative, as we recorded electrical activity that was very close to what we would expect from the Globus Pallidus internus. Nevertheless, the unexpected fact was that this activity continued way beyond the expected target and therefore the insertion of the microelectrode was continued deeper than usual until this type of activity finally ceased, at 5-6 mm deeper than the target.

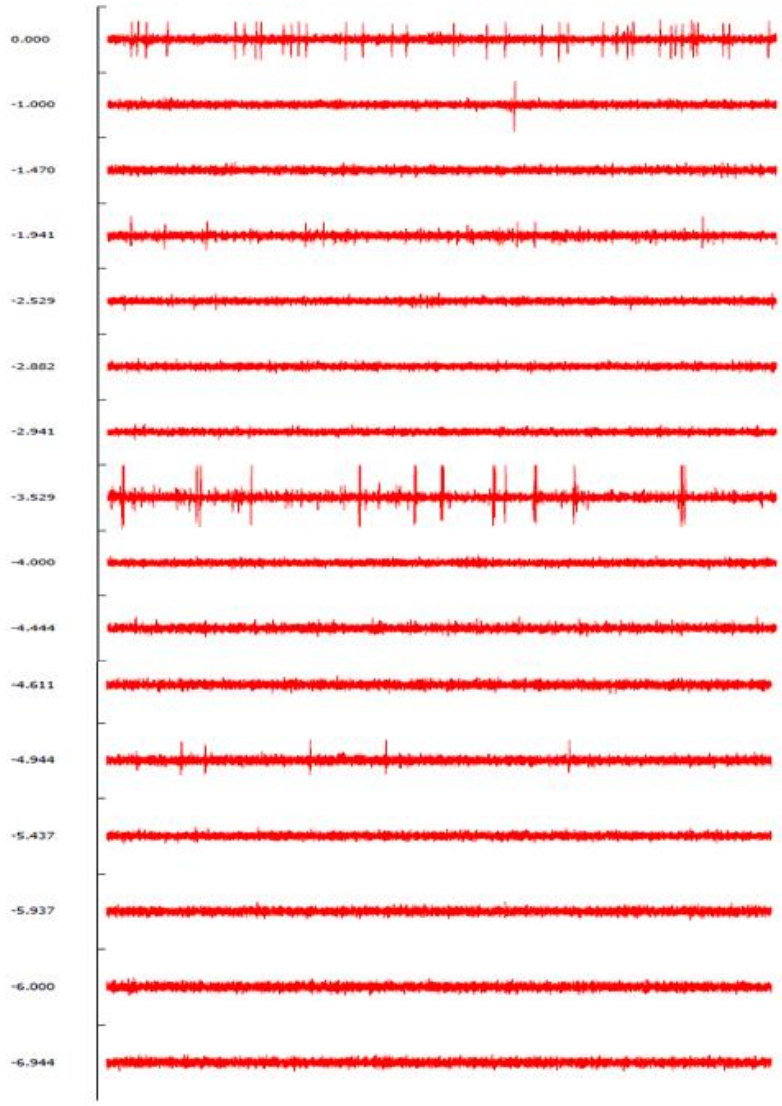

Figure 22: MER recorded during the surgery of MR.

CAVE: since only 1 second of recording is displayed per depth of recording, this image cannot allow a complete interpretation of MER signal.

Meanwhile, the anatomical reference given by the software was indicating that starting 3 mm below the target the microelectrodes were already in the optic tract, which conflicted with what we saw in the MERs because we would have expected a lot less spiking activity.

We ended up giving greater consideration to the MERs, considering that the quality of their signal was high and that we considered it possible that brainshift caused the discrepancy in the anatomical reference.

Nevertheless, after the post-OP CT it was clear that this was a mistake, as the microelectrode was inserted too deep and went in the patient's optic tract. This goes to show that the methodology can be extremely helpful when MERs show atypical features and should be taken into consideration to avoid potential surgical mistakes.

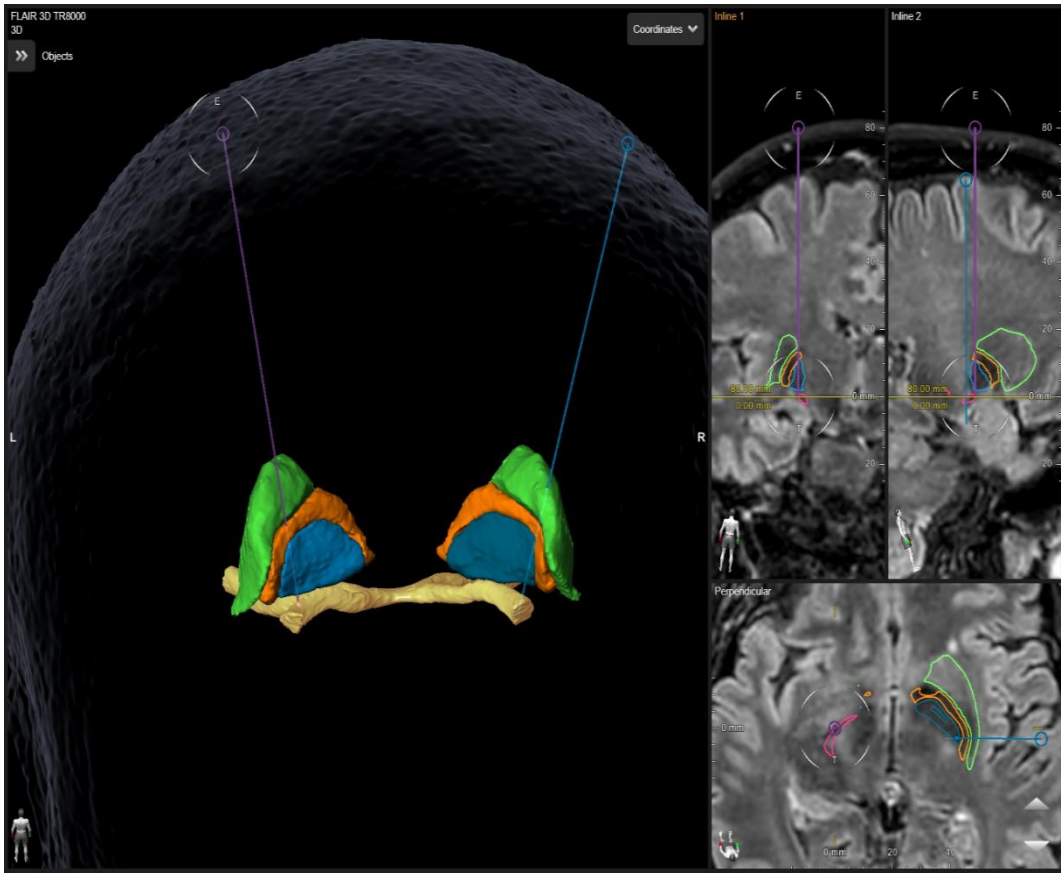

Figure 23: the reconstructed electrodes (blue and purple lines) are inserted too deep and arrive within the optic tract.

LIMITATIONS OF THE STUDY

The presented study, even if it suggests interesting results, presents several limitations that negatively impact the significance of the results.

First of all, the number of patients is not sufficient to make a meaningful statistical analysis, and the resu. All results have to be considered preliminary and cannot be considered sufficient to draw any definitive conclusion. Moreover, even if the study is carried out in a prospective fashion, there is no control group that could allow a direct comparison to better evaluate the presented methodology.

Moreover, there are some limitations due to the methodology itself. We use the Brainlab Elements® software in a way that is different from what it was designed and developed for, and this reflects in a sub-optimal interface for an intraoperative setting. This methodology also is based on preoperative imaging, which could not be always accurate in an intraoperative setting as the brainshift due to liquor loss, changes in blood pressure, entrance of air etc. are not taken into account.

Lastly, it was impossible to objectivate the perceived facilitation of MER interpretation, which is the biggest advantage of the presented methodology. The only choice was to report subjective opinions, with great consequent bias and low significance.

CONCLUSION

The comparison between the stereotactic coordinates of the preoperatively planned trajectory and the post-operatively reconstructed trajectory yielded an error below 1 mm for target deviation and below 3° for trajectory deviation. These preliminary results suggest that anatomical navigation through a dedicated software is a useful and reliable tool to significantly facilitate the interpretation of intraoperative MERs. The experience with this methodology at our Institution was very positive as it integrated the spiking activity displayed by MERs with important anatomical context, without the need for additional expenses or resources. We are confident that, if one is conscious of the possible pitfalls of the methodology, this represents an important and cost-effective way of improving the surgical procedure.

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