




# Parkinson's Disease Database Analysis of Stereotactic Coordinates Related to Clinical Outcomes

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**Abstract.** Parkinson's Disease is one of the leading movement disorder diseases. It is the fourth most common neurological disease, after migraine, stroke and epilepsy. The motor symptoms of the disease significantly impair daily living and quality of life and exact a high burden on both patients and their caregivers. Deep Brain Stimulation is a proven therapy for this disease, getting positive outcomes while reducing medication. In this paper, stereotactic system used for Deep Brain Stimulation (DBS) procedures will be described. Different planning methods will be observed and compared to the gold standard normally used, neurophysiological coordinates recorded intra-operatively. MRI, CT scan and direct calculation of stereotactic coordinates will be compared and group in three different groups, according to DBS therapy outcomes: "very good DBS therapy", "good DBS therapy" and "not major improvement".

Database of 72 DBS electrodes implanted in Parkinson's Disease patients will be studied. Most potentially beneficial ranges of deviation within planning and neurophysiological coordinates from the operating room will be assessed, in order to provide neurosurgeons with more landmarks in order to achieve the best outcomes within a millimetric technique.

We could confirm three main highlights out of this study: the neurophysiological length of the Subthalamic Nucleus does not play a major role in outcomes while being within normal range; CT scan calculations were the most accurate; direct calculations should not be used as major deviations were observed.

**Keywords:** Parkinson's disease · Deep brain stimulation  
Movement disorders · Decision tree · Stereotactic coordinates

## 1 Introduction

Parkinson's disease is a chronic, neurodegenerative disease whose chief symptoms are motor difficulties such as tremor, rigidity, bradykinesia and postural instability.

It is the fourth most common neurological disease, after migraine, stroke and epilepsy.

The motor symptoms of the disease significantly impair daily living and quality of life and exact a high burden on both patients and their caregivers.

About 0.3% of the population, or 1.2 million Europeans, are currently suffering from Parkinson's disease.

As the population ages, the prevalence of Parkinson's disease will increase [1, 2].

Demographic studies show that elderly individuals' proportion will increase rapidly in the following years. The general evolution of medicine, together with a much better quality of life, will be translated in an increase of population age. Also the decrease in birth rates and child mortality, lead us also to an unavoidable increase in the average age of world population [3].

In Spain, according the National Institute of Statistics, in 2020 19.7% of population will be more than 65 year-old, and in 2050 this percentage will get to 31.2%, being the group older than 75 year-old the one increasing the most, from 7.6% in 2002 to 16.8% in 2050. In 2050 Spain will also be the European country with the highest rate of people older than 65 year-old; and also in that year it will be the third one with the highest percentage of people older than 80 year-old (12.8% of the population). Only Italy (14.1%) and Germany (13.6%), will have higher rates.

Even more interesting is the aging of population in developing countries, which would go from a poverty to an elderly population stage, without going through an stable and wealthy state.

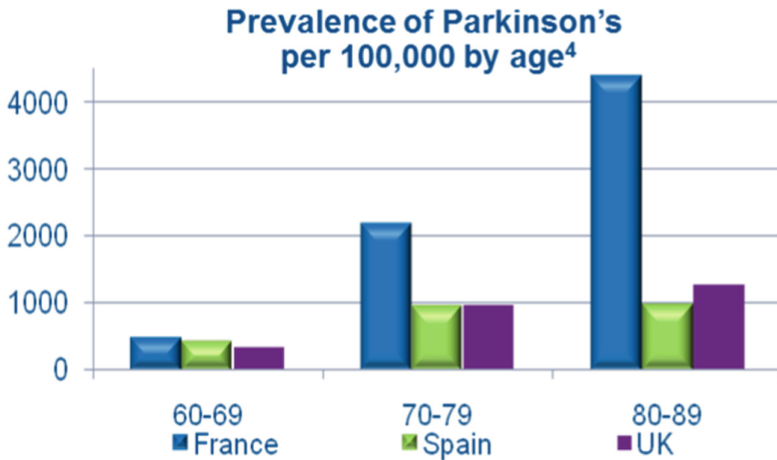
This increase in age for the population will be associated to an increase of chronic diseases and disabilities, both in the physical and also the psychiatric and social areas. As discussed, diseases as Parkinson's Disease will increase their prevalence.

Nowadays 1.2 million Europeans are affected by Parkinson's Disease, with main countries being observed in the following figure (see Figs. 1 and 2):



**Fig. 1.** PD prevalence per country in Europe

Deep brain stimulation (DBS) is a surgical procedure used to treat the motor symptoms of Parkinson's disease.



**Fig. 2.** Prevalence of PD per 100,000 by age

DBS uses a surgically implanted pulse generator to deliver electrical stimulation to the brain through leads with contact electrodes in their distal end. This is performed using Stereotactic techniques.

The electrode leads are implanted in the brain using MRI or CT scan to identify the correct area of the brain (thus defining coordinates), to target with stimulation, usually the subthalamic nucleus, thalamus or globus pallidus.

Once implanted, the leads are connected to the implantable pulse generator (IPG), generally implanted beneath the clavicle, with an extension wire which runs under the skin [5, 6].

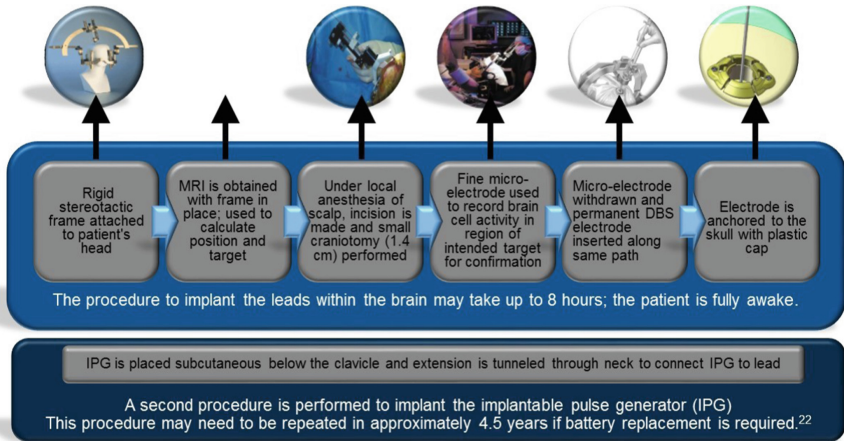
Main study objectives are:

- Analyze a database of 72 implanted electrodes for Deep Brain Stimulation using stereotactic systems, to treat Parkinson's Disease. Define if a surgery of this kind would be successful in advanced through different patterns of coordinates deviation within CT scans or MRI, in relation to the "Gold Standard" from the operating room: neurophysiological coordinates.
- Specify a maximum deviation range calculated during the planning stage of the surgery, to assure a successful therapy after implantation.

## 2 Materials and Methods

Parkinson's Disease patients implanted with Deep Brain Stimulation systems (electrodes and implantable pulse generator, IPG) following standard DBS surgical procedure for planning and implantation (see Fig. 3).

Food and Drug Administration (FDA), approved DBS as a treatment for Essential Tremor in 1997, for Parkinson's Disease in 2002 and for Dystonia in 2003. DBS is also used for chronic pain and has been used to treat or psychiatric disorders, such as depression or OCD.

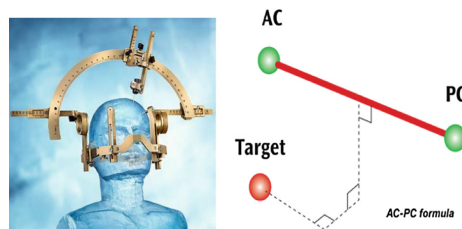


**Fig. 3.** DBS surgical procedure

The most common brain area used nowadays for Parkinson's Disease treatment with DBS is subthalamic nucleus, which is a brain nucleus of tiny size (3–4 mm high  $\times$  2–3 mm width).

Neighbor structures stimulation could lead to undesired side effects when stimulating, thus bad clinical results. Precision in electrodes location is critical during the surgical procedure. This is why stereotactic coordinates system is used, in order to place the target structure and place the electrode in the right spot. These coordinates are applied using a stereotactic frame located in patient's head (see image).

Medical images acquisition is then performed (CT scan and MRI), so anterior and posterior commissures could be identified. Afterwards the target is identified using them, and this "target coordinates" (see Fig. 4) are then translated and placed in the frame to perform the external adjustment in the frame, in order to be able to place the electrodes deep in the brain correctly.

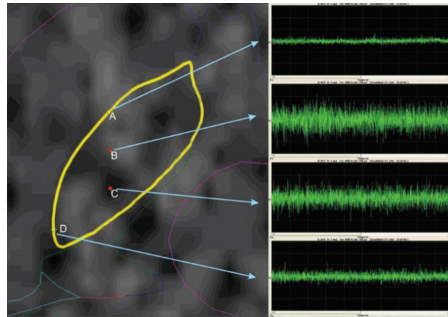


**Fig. 4.** Stereotactic frame system and AC-PC coordinates to target

Seventy-two electrodes implanted in Hospital Central de Asturias (HUCA); by Dr. Fernando Seijo's team using planning through CT and MRI scans taken pre-operatively.

Stereotactic coordinates are calculated by direct targeting of the subthalamic nucleus and by manual calculation from Anterior and Posterior Commissures (AC-PC), landmarks.

Neurophysiological coordinates and target length (subthalamic nucleus length) calculated intraoperatively with a Micro Electrode Recording (MER) system, targeting first theoretical coordinates (calculated during planning phase); and then shifting accordingly to neurophysiological and clinical response (Fig. 5).



**Fig. 5.** Subthalamic nucleus MER recording

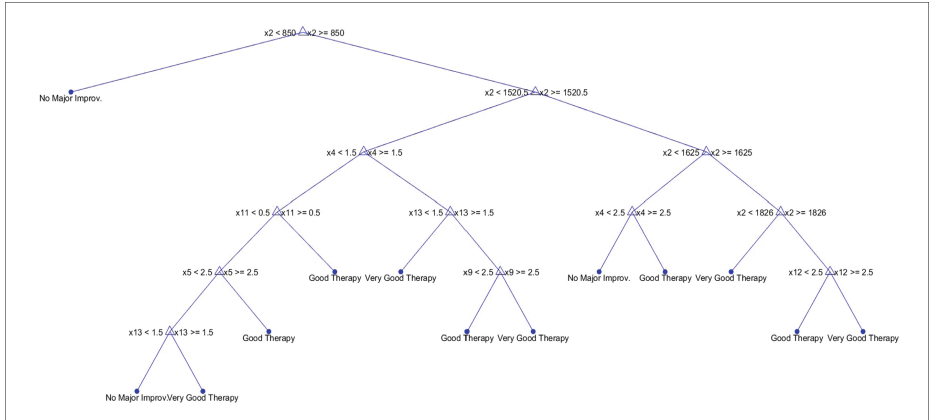
Patients were then treated with the stable combination within Deep Brain Stimulation and adjusted (and minimized) medication, Levodopa.

UPDRS III scale, which assess motor symptoms and it's the most widely performed to validate DBS results, was used to assess the outcome for the therapy and baseline level of disease.

33% of patients were classified as very successful treatment; 37% as successful treatment and 14% as not successful treatment. This range was assessed though a meta-analysis of different publications up to date (see Fig. 6) (Table 1).

As we could observe, maximum improvement average was around 55% in UPDRS III; however as recent studies are already showing around 60% improvement due to new technologies [16], including a trial performed in the center of reference studied in this article. Thus, the ranges were defined as a very successful therapy (as significantly better than previous studies), for patients treated with DBS with more than 60% improvement in UPDRS III scale.

Other scales such as UPDRS II or medication reduction were also studied, however as UPDRS III scales measuring motor symptoms is the most widely used, the results of this paper are focused on those three sub-group based on UPDRS III percentage of improvement (Table 2).



**Fig. 6.** Decision tree classification including medication as variable of study

**Table 1.** Comparison groups depending on clinical outcomes due to DBS

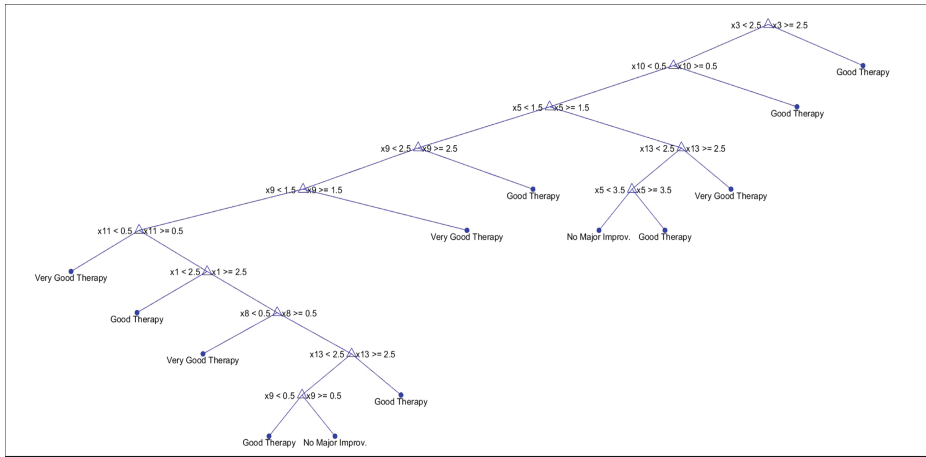
Very successful treatment	Successful treatment	Not successful treatment
>60% UPDRS III improvement (vs. pre-op)	[35,60]% UPDRS III improvement (vs. pre-op)	<35% UPDRS III improvement (vs. pre-op)

**Table 2.** Meta-analysis of previous clinical trial of DBS treatment for PD patients

Primary author	No. of subjects implanted	Study Design	Follow up	Claim
Deuschl 2006 <sup>7</sup>	78	Randomized pairs trial	6 mos.	• 41% improvement in UPDRS III scores
Follett 2010 <sup>8</sup>	299	Multi-center, randomized, blinded	24 mos.	• 25.3% improvement in UPDRS III scores
Fraix 2006 <sup>9</sup>	95	Prospective, multi-center	12 mos.	• 57% improvement in UPDRS III scores
Rodriguez-Oroz 2005 <sup>10</sup>	69	Blinded, multi-center study	3-4 yrs.	• 50% improvement in UPDRS III with STN and 39% improvement with Gpi at 3-4 yrs.
Gervais-Bernard 2009 <sup>11</sup>	42	Prospective, single-center	5 yrs.	• 55% improvement in UPDRS III scores
Lefaucheur 2008 <sup>12</sup>	54	Single-center study	12 mos.	• 56% improvement in UPDRS III scores without medication, 73% improvement with medication
Moro 2010 <sup>13</sup>	51	Non-randomized, prospect, blinded, multi-center study	5-6 yrs.	• 20% (GPI) to 45% (STN) improvement in UPDRS III scores
Tir 2007 <sup>14</sup>	103	Prospective, single-center study	12 mos.	• 43% improvement in UPDRS III scores
Zangaglia 2009 <sup>15</sup>	32	Prospective, naturalistic controlled study	3 yrs.	• 26% improvement in UPDRS III scores, compared with 15% decline in non-DBS cohort

### 3 Results

Subthalamic nucleus length recorded through MER system was not of significant value to define better clinical outcomes. Length was within similar range in all three controlled groups ([4.36, 4.50] mm). (see Figs. 6 and 7).



**Fig. 7.** Decision tree classification without including medication as variable of study

Direct target coordinates calculation shows the highest difference with Gold Standard, getting to major deviation in the Z-Axis (dev > 2.3 mm).

CT-Scan and MRI-scan calculated coordinates show similar behavior in terms of comparison with Gold Standard group for X and Y-axis. However, MRI-scan coordinates differ significantly more than CT-scan coordinates when comparing Z-axis. (see Figs. 6 and 7).

Deviation average compared to “gold standard” neurophysiological coordinates showed no significant value to determine better outcomes, as the three control groups showed similar results for deviations in each coordinate and modality. (see Figs. 6 and 7).

Variables studied and their corresponding classification variable assigned (from X1 to X15), were as followed (Table 3):

Decision tree classification analysis was performed using these 15 clinical variables as input. Classification output was obtained after training the classification method with the different subject’s sub-groups (and 15 clinical variables per subject).

Results were studied following two different methodologies, taking into account initial medication or without taking it into account, getting to the main highlights below:

**Table 3.** Clinical variables studied with their corresponding classification variable assigned for the study.

Variable X1	Variable X2	Variable X3	Variable X4	Variable X5	Variable X6	Variable X7	
Neurophysiological STN length	Ldopa medication (pre-op) (mg)	Dev. Coordinates Xct-Xnph	Dev. Coordinates Xmri-Xnph	Dev. Coordinates Xdir-Xnph	Dev. Coordinates Xcontrol-Xnph	Dev. Coordinates Yct-Ynph	
Variable X8	Variable X9	Variable X10	Variable X11	Variable X12	Variable X13	Variable X14	Variable X15
Dev. Coordinates Ymri-Ynph	Dev. Coordinates Ydir-Ynph	Dev. Coordinates Ycontrol-Ynph	Dev. Coordinates Zct-Znph	Dev. Coordinates Zmri-Znph	Dev. Coordinates Zdir-Znph	Dev. Coordinates Zcontrol-Znph	L-dopa medication (post-op)(mg) stim ON
		* Variable "ct" * Variable "mri" * Variable "dir" * Variable "control" * Variable "nph"		CT scan image based coordinate mri scan image based coordinate CT scan image based coordinate post-op CT scan image based coordinate "gold standard", neurophysiological recording intra-op based coordinate			

### 3.1 Variables Classification Accounting Medication

Medication level is a key indicator for DBS therapy success (“not major improvement” for patients with meds (Ldopa) pre-op < 850 mg.

This makes sense initially as most of the eligible patients for DBS therapy are usually pretty advanced PD patients with already high dose of medication. However, with this study we could observe that in cases when anyways DBS is performed, and in which patients are not yet taking high doses of medication, DBS is not providing major improvement in the therapy. We could also observe that the higher the pre-op medication level was, the better results in percentage of improvement in UPDRS III were observed.

We could also observe that the deviation within MRI coordinates and Neurophysiological coordinates when comparing X-axis was providing better outcomes when deviation was higher. This means that when trying to find the subthalamic nucleus intra-operatively, neurosurgeons should take into account that correct deviation should be taken in that X-axis instead of Y-axis.

### 3.2 Variables Classification Without Medication

As we defined previously, direct coordinates are the ones adding higher deviation compared to “gold standard” neurophysiological coordinates, so we could assess these should not be taking into account primarily when compared to MRI and CT scan coordinates when analysis results.

This leads us, when observing the decision tree classification performed for this chapter, extracting pre-op medication from the variables studied, to define that “very good outcomes” are observed when X-axis CT scan deviation from neurophysiological coordinates is minor to 2.5 mm and also Z-axis deviation with CT scan compared to intra-operative Z-axis is almost zero (<0.5 mm).



Together with the previous analysis using also the pre-op medication indicator, we could observe that potentially, a deviation of  $>1.5$  mm from the MRI coordinates calculated should be taken into account when trying to find the target intra-operatively; but also that neurosurgeons should not deviate further to 2.5 mm from the CT scan X-axis coordinates calculated during planning step.

## 4 Discussion

Important to note that neurophysiological length of the subthalamic nucleus recorded, does not affect clinical outcomes while being within range ( $>4$  mm).

After analyzing the results, we can confirm CT-scan calculations as the most accurate ones when planning for Deep Brain Stimulation.

Direct calculation should be voided as major deviation in Z-axis was observed, which could be even dangerous during surgical procedure, leading to hemorrhages or undesired stimulation.

Further analysis is needed to assess a specific landmark as key indicator for successful therapy. This is already in progress as Decision Trees and other classification methods are being used to define the key differentiator for a very successful Deep Brain Stimulation Therapy.

## 5 Conclusion

It seems clear that as technology advances, the need of algorithms to optimize the time of the clinical team is becoming more important. Pre-operative algorithms will lead to optimization for operating room timings, and will allow functional units using Deep Brain Stimulation for a better understanding and estimation of potential positive outcomes for many patients.

On the other hand, we cannot forget the variability within patients; thus being impossible to assess a general and standard methodology for all treated cases.

This study shows promising results in classification for Deep Brain Stimulation cases; allowing physicians to choose CT scan images as initial method when planning coordinates manually for Deep Brain Stimulation. This is increasingly changing as automatic fusion and planning algorithms are being introduced to calculate planning using fewer calculations.

Subthalamic nucleus length recorded was usually believed as an indicator for a better trajectory; however, the opposite has been proven with these results, showing less weight from that variable when getting better clinical outcomes.

More research and development on pre-operative algorithms to potentially assess Deep Brain Stimulation outcomes are needed, but in any case, this study demonstrates that CT scan images are the most accurate ones.

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