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Lead-DBS: an additional tool for stereotactic surgery

Renato Barradas Rodrigues[1]*, Victor Lima Araujo[2], Pamella Yoko Omori[1], Nicolle dos Santos Moraes Nunes[3], Marco Antônio Orsini Neves[3], Renata Rodrigues Teixeira Castro[3], Bruno Lima Pessoa[1]

SUMMARY

OBJECTIVE: Use Lead-DBS software to analyze stereotactical surgical outcome of an operated population and demonstrate that small target deviations do not compromise the stimulation of desired structures, even with small amperages.

METHODS: Image exams of patients submitted to deep brain stimulation for movement disorders treatment were processed in Lead-DBS software. Electrode stereotactic coordinates were subtracted from the planned target and those deviations, compared among different anatomical targets and sides operated firstly and secondly. We also quantified the frequency of relation between the activated tissue volume and the planned target through computer simulations.

RESULTS: None of the 16 electrodes were exactly implanted at the planned coordinates. A stimulation of 3 mA reached 62.5% of the times the planned coordinates, rising to 68.75% with a 3,5 mA. No statistical significance was demonstrated in any comparison of laterality and anatomical sites.

CONCLUSIONS: The simulation of small amperage fields could reach the intended target even when electrode placement is suboptimal. Furthermore, such a goal can be achieved without overlapping the volume of activated tissue with undesired structures. Software Lead-DBS proved to be a valuable complementary asset for surgical stereotactical result assessment.

KEYWORDS: Deep brain stimulation. Software. Neurosurgery. Movement disorders. Parkinson disease.

INTRODUCTION

Movement disorders refer to a group of neurological conditions that cause abnormal voluntary or involuntary movements. This spectrum of disorders includes Parkinson's disease (PD), dystonia, tremor, ataxia, as well as other less prevalent diseases[1-3]. Even though the clinical presentation of these disorders varies, they share similarities, such as a rising prevalence and incidence over the years[4]. Taking into account the aging of populations and the increase in life expectancy, the World Health Organization (WHO) estimates that 1% of the global population over 65 years old is affected by PD and predicts that the number of individuals affected in 2030 will be of 8 million[4]. To improve the management of motor symptoms, surgical treatment with deep brain stimulation (DBS) is a longing alternative that can be associated with classical pharmacological treatment, thus reducing the dosage and side effects of dopaminergic drugs and improving motor clinical outcome and life quality[5,6].

[1]Universidade Federal Fluminense, Department of General and Specialized Surgery – Niterói (RJ), Brazil.
[2]Centro Federal de Educação Tecnológica Celso Suckow da Fonseca, School of Mechanical Engineering – Nova Iguaçu (RJ), Brazil.
[3]Universidade Iguaçu, Department of Neuroscience and Neurology – Nova Iguaçu (RJ), Brazil.
*Corresponding author: renato_barradas@hotmail.com
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The correct electrode positioning has been deemed of crucial importance because accurate electrode placement ensures stimulation of desired structures (such as subthalamic nucleus and internal globus pallidus), at the same time preventing excitation of areas whose stimulation could cause adverse motor and behavioral effects (red nucleus, internal capsule, substantia nigra, and medial lemniscus)[7,8]. Precise implantation of the electrodes by the surgeon is a challenging task, and it is exemplified by the fact that large trials showed a substantial variation of final electrode position in patients[7,8].

Those variations and errors can be due to technical or anatomy-related factors. Technical factors can be the precise determination of the stereotactic coordinates because of image distortions, pixels size, and the thickness of image slices. Brain-related factors involve the human heterogeneity of brain tissue and the intracranial relocation of the brain as a result of dura mater perforation with the subsequent inflow of air in the subdural space, which occurs during the surgical procedure[9].

However, misplacement of the electrode often does not affect clinical outcomes[10,11]. As previously mentioned, the further away the electrode is from its intended trajectory, the higher are the chances of poor clinical outcome and emergence of side effects[7,8]. Even so, the setup of the device remains a crucial step in these patients' follow-up. Performed by a specialist, selection of poles, amplitude, frequency, and pulse width can be optimized for better clinical outcomes[12]. The volume of activated tissue (VAT) can attenuate motor and non-motor (such as verbal fluency) symptoms and minimize the risk of collateral effects[13,14].

Lead-DBS (lead-dbs.org; Horn & Kühn.; RRID:SCR_002915)[15] is a free online software based on MATLAB language and functions, used to process, and combine different image modalities. It can also remove artifacts and enhance image quality[16]. Importantly, it also allows to localize (either automatically or manually) the placement of intracerebral electrodes and recreate them on 3D interactive atlases.

Despite not being a licensed software for clinical use (therefore, not licensed for intraoperative use) it can recreate electromagnetic activity, revealing the overlap between electrodes activity and cerebral parenchyma[15]. Our experience with this software seems to confirm medical literature on the aspect of the positive contribution of the VAT set up for DBS outcome[13,14,17].

We aimed with this study, firstly, to demonstrate the valuable use of technology (specifically, Lead-DBS) as a complementary tool for surgical outcome evaluation. Secondly, we intended to show that electromagnetic activity can relate to the desired cerebral areas, even when electrode placement is suboptimal.

METHODS

Study participants

Eight patients with movement disorders, previously evaluated by the Federal Fluminense University hospital (University Hospital Antonio Pedro, HUAP) neurosurgery team, were submitted to DBS surgery for treatment of motor symptoms between the years 2017–2020. Their surgeries were prescribed following National Health Surveillance Agency (ANVISA) recommendations, and the procedure was always performed by the same team of surgeons. Five of the patients had idiopathic PD, two had primary dystonia, and one had rubral tremor secondary to multiple sclerosis exacerbation. There were four male and four female patients, and their ages varied between 10–79 years (48.6±18.7).

Imaging exams

All patients were submitted to a pre-operatory 3T cranial magnetic resonance imaging (MRI) six months before the procedure. Those exams had at least 60 coronal slices, starting at the upper point of the skull, with a slice thickness of 1.4 mm, and no inter-slice gaps. The sequences acquired on this protocol were T1, T2, and flair. A post-operative high-resolution CT scan with at least the same number and thickness of slices was performed 30 days after the surgery. Only one patient had a post-operative MRI. Those exams were already part of the routine medical evaluation followed by the neurosurgery team. One of the neurosurgeons responsible for this trial evaluated image quality and the absence of artifacts before image processing. Exams were also approved by an image quality filter function on Lead-DBS.

Surgical procedure

Surgeries were performed following national regulatory agency and medical literature recommendations[18]. The patients were subjected to a pre-operatory CT with an isocentric system linked to their skull. This image was used to plan surgical trajectory and target, using intra-operative computer software recommended by the electrode manufacturer. The obtained stereotactic coordinates were plotted at the isocentric system to guide the trajectory and final target.

After bone exposure, a 15 mm opening was made using a surgical drill, followed by the opening of the dura mater. A micro-electrode system was placed to verify localization during the surgery. After reaching the desired target, electrode (Medtronic model 3397) macrostimulations with the patient awake were performed. If a significant improvement of motor function was observed with no side effects, the surgery was deemed complete. If not, a trajectory or target correction was performed.

Software acquirement and utilization

Lead-DBS (version 2.3) and SPM12 were used within the Matlab 2018a platform[14,19].

Data generation

All image inputs on Digital Imaging and Communications in Medicine (DICOM, a standard format for radiological images visualization in medicine) format were converted to Neuroimaging Informatics Technology Initiative (NIfTI, an open file format usually used for neuroimaging manipulation) files using SPM 12 software conversive function. The electrode model implanted for each patient was obtained by consulting patient medical records and was introduced at the program. The protocols used for co-registration and normalization of images were the ones recommended at the Lead-DBS official walkthrough for each imaging modality. Next, a brain-shift function was also performed[20], followed by electrode trajectory automatic pre-reconstruction[21]. Manual electrode trajectory correction was the last step before tridimensional reconstruction.

Montreal Neurological Institute (MNI) coordinates were obtained for electrode limits, and each pole was converted to Anterior commissure/Posterior commissure related coordinates (AC/PC) using Lead-DBS[22]. Optimal target coordinates were the same as standard coordinates defined by Schrader (2002) and were marked on the 3D reconstruction image[8]. We subtracted the coordinates from the centroid of the contact visually closest to the optimal target to obtain optimal target distancing (Table 1). On pre-operative planning, stereotactic optimal coordinates are defined not only by standard coordinates but also with an individual MRI evaluation and stereotactic atlases observation. Even though, we chose to use the above-mentioned standard coordinates because of their closeness to our patients' planned targets (all patients had no difference of planned targets larger than 1 mm on each axis from such coordinates) and, therefore, a way to promptly mark an optimal target on each reconstruction and facilitate our data analysis.

The volume of activated tissue (VATs) was then simulated using 2–3,5 mA monopolar settings[23], at the pole visually closest to the optimal target. These simulations were always conducted by the same researcher and were raised until the minimum voltage that led to an overlap of VAT, and the optimal target was reached. Screenshots were archived for each patient.

Statistical analysis

All data were processed using IBM SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A Kruskal-Wallis test was used to identify statistical significance between two comparisons:

Table 1. Optimal target stereotactic coordinates considered for this respective study.

	Right			Left[a]		
	x	y	z	x	y	z
Gpi	20	3	5	-20	3	5
STN	13	-3	5	-13	-3	5

[a]The difference between laterality in the same anatomical targets is only the module of the x-axis. Gpi: Internal globus pallidus; STN: Subthalamic nucleus.

1) Distance from an ideal target between firstly operated side and secondly operated side;
2) Distance from an ideal target between GPi and STN.

The significance threshold used was $p<0.05$.

RESULTS

Electrode localization

The average values of:

1) electrode inferior limit and
2) deviation from the optimal target, together with standard deviation, are listed in Table 2.

The x and y axes had smaller deviations compared to the z-axis. The differences of electrode localization between different anatomical sites were not significant with a threshold of $p<0.05$ (p-values of 0.67, 0.75, 0.9, respectively for each axis). Similarly, differences of electrode placement between sides operated firstly and secondly (the left side and the right side were operated first on four times each) showed no statistical significance with a threshold of $p<0.05$ (Figure 1).

VATs simulations

We found an overlap of the VAT and the optimal target in 10 electrodes placed (62.5%), using a limit of 3 mA for amperage. This overlap was observed in 11 (68.75%) electrodes when the limit for amperage was raised to 3.5 mA.

Clinical outcome

This study did not evaluate clinical improvement from surgeries or conducted a clinical follow-up. However, the medical records of patients undergoing surgery in the period from June 2017 to June 2020 indicate that no secondary surgery was performed because of post-surgical complications or for the purposes of electrode placement correction.

Table 2. Stereotactic surgical outcomes by subgroups.

Anatomical Target	Stereotactic surgical outcome						Optimal target deviations[a]					
	Left			Right			Left			Right		
	x	Y	z	x	y	z	x	y	z	x	y	z
Gpi	-20.91 ±0.5	2.5 ±1.52	7.92 ±1.68	19.53 ±2.68	3.06 ±1.44	6.58 ±3.12	-0.91	-0.49	2.92	-0.47	0.06	1.58
STN	-13.07 ±1.44	-3.41 ±2.21	6.22 ±0.67	8.74 ±2.11	-3 ±1.07	7.36 ±1.81	-0.075	-0.41	1.22	-4.26	-0.0075	2.36

The values anticipated by a plus or minus sign are standard deviation while the others refer to average. Gpi: Internal globus pallidus; STN: Subthalamic nucleus. [a]The values of standard deviation plotted on the surgical outcome group are the same for their respective correspondent on optimal target deviations group, since those values were obtained by a subtraction from a fixed optimal value for each anatomical target.

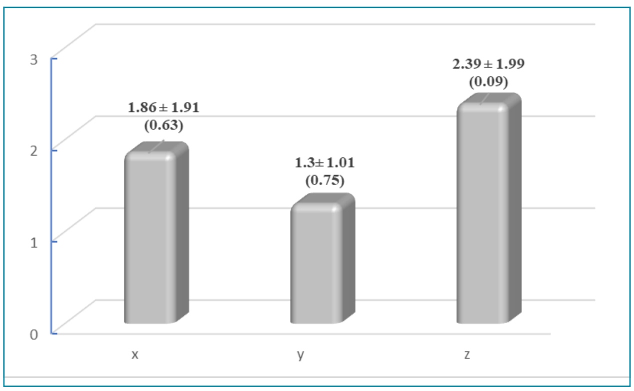

Figure 1. Differences between axes of sides operated firstly and secondly in millimeters. On top of each bar mean and standard deviation values were placed for each axe. p-values placed between parenthesis were obtained by a Kruskal-Wallis test between the two groups.

DISCUSSION

Despite conducting a study with a limited number of heterogeneous patients, we had consistent observations regarding the stereotactic localization of the electrodes. When observing the x and y axes, it was notable the closeness of electrode placement values (no more than 2–2.5 mm) with the established optimal targets. The z-axis had larger deviations, but this fact is already expected because of brain shift influence (brain shift effect is larger on cranial-caudal axis because intracranial air entry has a larger effect on this same axis)[7,8]. As previously mentioned, small deviations are acceptable in clinical practice and do not usually compromise the clinical outcome of DBS surgery[24,25].

Even though this study could not quantify if there was a statistical difference in clinical outcome between different anatomical targets or sides operated consecutively (larger influence from brain shift on the second side), we can affirm that we do not consistently make deviations due to those variables (no statistical significance found).

We aimed to reaffirm (with the use of Lead-DBS software), as previously reported, the capacity of the VAT to reach the desired structures, even when small deviations occur during electrode placement[13,14,17]. The scientific consensus is that stronger stimulations bring higher risks of side effects such as sexual perversion, language impairment, emotional disturbances, extrapyramidal symptoms, and others[13,14,17]. Even so, VATs generated with 2–3.5 mA (the initial voltage utilized when DBS is activated) showed a satisfactory area of stimulation, which overlapped with the optimal targets in 68,75% of electrodes implanted. Yet, despite such reach, the VATs did not stimulate areas that could generate adverse effects (substantia nigra, rubral nucleus, or internal capsule). Other parameters, such as pulse amplitude and frequency, which were not considered in this study, could modify the area of stimulation.

Another important point is the complementary use of Lead-DBS. Although manufacturers of DBS platforms provide a demonstration of the magnetic field on their software, none of them can show the nuclei stimulated according to the values set on the DBS itself (amperage, voltage, and others). Having a multimodal imaging software, such as Lead-DBS, that provides such information accompanied by the stereotactic surgical outcome, may provide surgeons a more accurate analysis of their work.

Lastly, it is important to mention that Lead-DBS use is widely accepted as a complementary tool. Its role for research and other goals are already validated and reviewed in the medical literature[15]. The impact of the VAT role on therapeutic effects for many disorders is also another issue substantially addressed and consolidated on medical literature[13,14,17].

Therefore, this study corroborates the fact that Lead-DBS is a valuable complementary tool for surgical stereotactical outcome evaluation and that VAT amperage can optimize the area of stimulation without co-stimulate unwanted structures.

CONCLUSIONS

This study corroborated Lead-DBS quality as a complementary tool for surgical stereotactical outcome assessment. Simulations showed that small amperage VATs can stimulate the desired structures without reaching potentially originators of adverse effects.

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AUTHORS' CONTRIBUTIONS

RBR: Conceptualization, Formal analysis, Software, Investigation, Writing – original draft. **VLA:** Software, Investigation, Writing – original draft. PYO: Formal analysis, Investigation, Writing – original draft. **NSMN:** Formal analysis, Investigation, Writing – original draft. **MAON:** Investigation, Supervision, Validation. **RRTC:** Investigation, Supervision, Validation. **BLP:** Conceptualization, Investigation, Supervision, Validation, Writing – original draft.

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