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Abstract. Deep brain stimulation of the medial globus pallidus (GPM) is a surgical procedure for treating patients suffering from Parkinson's disease. Its therapeutic effect may be limited by the presence of pyramidal tract side effect (PTSE). PTSE is a contraction time-locked to the stimulation when the current spreading reaches the motor fibers of the pyramidal tract within the internal capsule. The objective of the study was to propose a preoperative predictive model of PTSE. A machine learning-based method called PyMAN (PTSE model based on artificial neural network) accounting for the current used in stimulation, the three-dimensional electrode coordinates and the angle of the trajectory, was designed to predict the occurrence of PTSE. Ten patients implanted in the GPM have been tested by a clinician to create a labeled dataset of the stimulation parameters that trigger PTSE. The kappa index value between the data predicted by PyMAN and the labeled data was 0.78. Further evaluation studies are desirable to confirm whether PyMAN could be a reliable tool for assisting the surgeon to prevent PTSE during the preoperative planning. © 2016 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.3.2.025001](https://doi.org/10.1117/1.JMI.3.2.025001)]

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1 Introduction

Deep brain stimulation (DBS) of the medial globus pallidus (GPM) is a surgical procedure for treating patients suffering from Parkinson's disease, experiencing medically refractory symptoms,¹ and contraindicated at our center for the subthalamic nucleus targeting. The procedure consists in implanting deep brain electrodes with an optimal placement and optimal electrical stimulation parameters that alleviate the symptoms while avoiding structures that trigger side effects.² To improve targeting, preoperative patient-specific models are built from multimodal medical images^{3,4} such as preoperative magnetic resonance images (MRI) registered with an anatomical^{5–7} or histological atlas.^{8,9} A patient-specific model allows neurosurgeons to visualize on a three-dimensional (3-D) virtual representation of the cerebral structures of interest such as basal ganglia. Additionally, postoperative CT scan or MRI can be registered to the preoperative patient-specific model to define the final location of the electrode contacts inside the patient-specific model as well as inside the atlas.

Our team has carried out an intensive modeling study to design a patient-specific model based on the ParkMedAtlas template,⁵ an anatomical atlas specifically designed to fit the anatomy of patients with Parkinson's disease. This common anatomical space has been used to correlate the electrode

locations with clinical data.¹⁰ The software suite using the atlas was PyDBS:⁶ a software that assists the surgeon from the preplanning step to the postoperative analysis of the electrode location. In DBS, the therapeutic window¹¹ is a concept defined by a lower limit, the minimum current required to alleviate the symptoms. The upper limit is the threshold, which triggers a side-effect time-locked to the stimulation. Most of the time, this limit is reached by the appearance of pyramidal tract side effect (PTSE).¹² Clinically, PTSE are muscle contractions time-locked to the stimulation, induced by the current spreading to the pyramidal tract. An electrode triggering PTSE at a low threshold has to be shifted to ensure a wider therapeutic window.

In this prospective study, 10 patients implanted in the GPM were postoperatively tested by a clinician to determine the electrical parameters that trigger PTSE. From these data, we proposed a method for predicting the PTSE based on artificial neural network and introduced PyMAN (PTSE model based on artificial neural network).

2 Material and Methods

2.1 Clinical Data

We enrolled in our study 10 patients having had electrodes implanted in the GPM for at least 3 months to avoid microlesion

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effect¹³ (Table 1). Ten bilaterally implanted patients were hospitalized in our department for their standard postoperative follow-up examinations from January 2014 to June 2015. The mean [standard deviation (SD)] time between surgery and the study was 32 (25.88) months. All met the criteria of the United Kingdom Parkinson's Disease Society Brain bank for idiopathic Parkinson's disease.¹⁴ The female-to-male ratio was 4 to 6, with a mean (SD) age of 57.5 (9.4) years and mean (SD) disease duration of 13.3 (4.5) years at the study. Patients were evaluated 3 months before and 3 months after surgery using the Unified Parkinson's Disease Rating Scale (UPDRS).¹⁵ The mean (SD) preoperative motor score (UPDRS part III) was 45.1 (12.2) in the medication-off condition, and 27 (0.6) in the medication-off, stimulation-on condition 3 months after surgery, corresponding to a 40.1% improvement.

First, the surgical procedure involved¹⁶ attachment to the patient's head of a stereotactic Leksell frame, then the implantation of bilateral quadripolar DBS electrodes (3387 Medtronic, Minneapolis, Minnesota) in the postero-ventral part of two GPM in a single operating session, under local or general anesthesia. Anti-Parkinsonian treatment was stopped the evening before surgery. The therapeutic and side effects of the stimulation were assessed throughout the procedure by a neurologist. Programmable pulse generators (Activa PC, Medtronic, Minneapolis, Minnesota) were implanted in the subclavicular region and connected to the electrodes.

The mean (SD) coordinates of the left active contacts were at 3 months postoperatively: 25.23 mm (2.89) for the lateral direction, 9 mm (2.14) posterior to the anterior commissure, and 1.07 mm (4.2) under the AC–PC line for the dorso-caudal direction. The mean (SD) coordinates of the right active contact were: 23.43 mm (2.96) for the lateral direction, 8.84 mm (3.23)

posterior to the anterior commissure, and 0.56 mm (2.03) under the AC–PC line for the dorso-caudal direction. The average stimulation parameters (SD) for the left side were a voltage of 2.93 V (0.35), a pulse width of 100 μ s (31.62), and a frequency of 115 Hz (46). For the right side they were a voltage of 2.85 V (0.39), a pulse width of 86 μ s (30.62), and a frequency of 124 Hz (30.98).

The 10 patients were assessed by two clinicians to determine the electrical parameters, which trigger PTSE at an average (SD) of 32 months (25.88) postoperatively. First, the implantable pulse generator was stopped by clinicians. Impedances were checked and each of the four electrode contacts was reviewed bilaterally (except for the patient 7) using monopolar stimulation. The stimulation voltage was increased from 0 to 6 V, using a 0.5-V step, which appears in our experience more sensitive than a progressive rise. We applied a simple Ohm's law using the recorded impedances to convert the voltage into current, making the electrical parameters comparable. Pulse width and frequency were set, respectively, at 60 μ s and 130 Hz for all the patients. We chose a qualitative assessment: for each electro-clinical test, PTSE was present or absent. A testing session consisted of a systematic review of an electrode. An electrode has four contacts. The voltage was increased from 0 to 6 V using a 0.5-V step. Thus, a bilateral review consisted of $2 \times 4 \times 13 = 104$ clinical tests. Particular attention was paid to PTSE definition.¹⁷ Clinically, PTSE is a muscle contraction occurring on the face and upper limbs, rarely on lower limbs. It is reproducible and time-locked to the stimulation. We evaluated the subjectivity of the clinical diagnosis process by running an interrater study. Four patients were assessed during the same week of hospitalization by the two different clinical experts. The kappa index value¹⁸ was used to compare the clinicians' results. The protocol

Table 1 Demographic and clinical data of 10 patients with bilateral medial pallidal DBS.

Patient	Sex	Age at the surgery (years)	Disease duration before the surgery (years)	Preoperative UPDRS Dopa OFF	Postoperative UPDRS Dopa OFF–Stim ON	Time between the surgery and the study (months)	Disease form	More affected side in the beginning	Right voltage	Left voltage
1	M	60	23	40	27	60	A-T	L	3.2	3.2
2	M	67	10	65.5	37	12	A-T	R	3	2.8
3	F	52	11	38.5	23	24	A-T	L	2.7	2.7
4	M	54	14	58	45	18	Mixed	G	3.5	3.5
5	F	40	15	32.5	16	24	A-T	R	2.5	2.5
6	F	70	16	21	13.5	72	Mixed	R	2.6	2.9
7	M	64	12	31.5	12	72	A-T	L	3.3	3.3
8	M	48	12	63.5	42	6	Mixed	R	3.5	3.5
9	F	55	14	30.5	14	12	Mixed	R	2.3	2.5
10	M	54	6	52.5	37	12	Mixed	R	2.9	2.7
Mean (SD)		57.5 (9.4)	13.3 (4.5)	45.1 (12.2)	27 (0.6)	32 (25.88)			2.95 (0.42)	2.96 (0.39)

Note: A-T, akinetic-hypertonic; B, bilateral; F, female; U, unilateral; L, left; M, male; R, right; SD, standard deviation; Left voltage, chronic voltage on the left electrode at the clinical review; Postop UPDRS III Dopa OFF - Stim ON, postoperative unified Parkinson's disease rating scale part III assessed 3 months after the surgery in the medication off, stimulation-on condition; Preop UPDRS III Dopa OFF, preoperative unified Parkinson's disease rating scale part III assessed 3 months prior to surgery in the medication off-condition; Right voltage, chronic voltage on the right electrode at the clinical review.

was approved by the institutional review board of Rennes University Hospital. After a complete description of the study, written informed consent was obtained from each participant and the study was conducted in accordance with the Declaration of Helsinki.

2.2 Pyramidal Tract Side Effect Model Based on Artificial Neural Network Design

PyMAN was implemented in a software environment (called PyDBS⁶) allowing fully automatic computation of a preoperative patient-specific model from his/her multimodal medical images and from anatomical atlases (allowing segmentation of anatomical targets not visible in the medical images). PyDBS segments patient's brain structures by registering ParkMedAtlas anatomical atlas to patient's MRI image. After surgery, PyDBS segments the implanted electrodes from a postoperative CT scan image. For each patient, the patient-specific model was computed from a preoperative 3T T1-weighted MRI with gadolinium injection (1 mm × 1 mm × 1 mm, Philips Medical system), a 3T T2-weighted MRI (1 mm × 1 mm × 1 mm, Philips Medical system), and a postoperative CT scan (0.44 mm × 0.44 mm × 0.6 mm, GE Health care VCT 64). The patient's images were registered with the ParkMedAtlas anatomical atlas.⁵ After a preliminary step of automatic electrode contact segmentation based on image processing, combinations of linear and nonlinear registrations allowed each stimulated contact to be warped into the ParkMedAtlas template. Both the contact segmentation and the registration algorithms had already been validated.^{5,19} The registration workflow was composed of a linear CT to MRI registration, a global affine MR-to-template transformation, a local affine MR-to-template transformation with a mask on deep structures, and a final non-linear local registration. Using this procedure, the contact positions could be precisely warped into the ParkMedAtlas template. This common anatomical space allowed comparison of electrode locations among the patients (Fig. 1).

PyMAN was designed in RapidMiner (version 6.4), a software platform that provides an integrated environment, which develops and evaluates machine learning techniques. It is well suited for research prototyping and implementation. We

Fig. 1 Example of 14 chronically used contacts registered in the ParkMedAtlas atlas. Medial left view of the right internal capsule (gray), the GPm (orange), and the electrode contacts (red dots). A: anterior; I: inferior; P: posterior; S: superior.

studied three models, with increasingly complex attributes, which could explain the occurrence of PTSE. The first model was a single-rule induction model, which only accounted for the amount of current delivered from the electrode contact. We determined, for any given electrode location, the current threshold that maximized the prediction accuracy of PTSE. The second model was an artificial neural network. This model represented the nonlinear relation between the current delivered from the electrode contact and the 3-D electrode coordinates (x, y, z). The purpose was to distinguish the motor fibers of the pyramidal tract within the internal capsule. An essential challenge when using clinical compatible imaging is to differentiate the functional fibers (e.g., the motor fibers when studying PTSE) within the internal capsule.⁴ The third model (Fig. 2) extended the second one, with the angle of the trajectory, i.e., the coronal, sagittal, and frontal angles. Indeed, axonal activation is facilitated by a parallel current to the myelinated fibers.²⁰

Architecturally, the neural network received four inputs for model 2 and seven for model 3: the amount of current delivered by the electrode contact, the location of the contacts in three dimensions within the atlas (X, Y, Z) for model 2, and the angle of the electrode trajectory in the three planes (i.e., coronal, sagittal, and axial) for model 3. After performing a sensitivity analysis on its architecture, we found that a single hidden layer with 10 nodes using a sigmoid transfer function produced accurate results. The inputs were used to train the model to predict the occurrence of PTSE using the labeled electro-clinical dataset obtained from the testing sessions of the 10 patients. Finally, the output layer delivered the occurrence or not of PTSE. Hence, the PTSE current threshold can be indirectly predicted by the computer.

Fig. 2 PyMAN architecture. The input nodes represent the electrode location, the current delivered and the angle of the surgical trajectory. The hidden layer converts the weighted attributes to the output layer via a sigmoid function that predicts the occurrence of pyramidal tract side effect. A(a): axial angle; A(c): coronal angle; A(s): sagittal angle; current: current delivered from the electrode contact; PTSE: pyramidal tract side effect; X: latero-medial coordinates; Y: antero-posterior coordinates; Z: rostro-caudal coordinates.

2.3 Pyramidal Tract Side Effect Model Based on Artificial Neural Network Validation

For validation, we used a ten-fold k cross-validation strategy on the collected data, i.e., 988 electro-clinical tests. The training and test sets were divided up using a stratified sampling (i.e., each subset had the same ratio of positive and negative cases). The quantitative validation was computed by a confusion matrix, comparing the clinically observed effects with the predicted ones. Performance evaluation was done using sensitivity (Se), specificity (Spe), positive predicted value (PPV), negative predicted value (NPV), and kappa index value.¹⁸ The kappa was obtained by confronting the labeled data and the predicted value.

The neural network was trained with the $k - 1$ subsets and tested on the remaining one. This process enabled the calculation of the validation error (i.e., error rate from the testing set) and the training error (i.e., error rate from the training set). Overtraining the neural network could lead to overfitting the training set and inaccurate predictions of the PTSE of the testing set. To prevent PyMAN from overtraining, we used an evolutionary algorithm that terminated the training, when the validation error became larger than the training error.

The results of the predictive performance were compared between models 1 and 2. The predictive performance was also compared between models 2 and 3. We used a Mann–Whitney U nonparametric test in SPSS version 22 (IBM, Armonk, New York). A P -value of less than 0.05 was deemed significant.

3 Results

An amount of 988 electro-clinical tests were used for the validation (i.e., the clinical tests from the 19 electrodes studied). Over the whole group of patients, the prevalence of PTSE was 6.51%. The kappa index value of the interrater study was 0.905.

Table 2 displays the results of the clinical testing sessions. The mean (SD) impedance of the chronically used contacts was 1422.67 Ω (548.82), whereas the impedance of the other contacts was 1719.22 Ω (894.02). The mean (SD) current threshold that triggered PTSE was 3.89 mA (2.04) for all the contacts. The median (SD) voltage threshold that triggered PTSE was 5.00 V (1) for all the contacts. The mean (SD) PTSE current thresholds were 3.50 mA (2.08) for contact 0

Table 2 Stimulation parameters and PTSE data of 10 patients with bilateral medial pallidal DBS.

Patient	Side	Plot 0		Plot 1		Plot 2		Plot 3	
		I	V	I	V	I	V	I	V
1	L	653	5.5	841	ND	700	ND	871	ND
	R	675	4	788	6	763	ND	815	ND
2	L	1920	ND	1532	ND	796	ND	1779	ND
	R	1532	3.5	894	5.5	902	ND	1498	ND
3	L	1826	2	1293	4	1280	5.5	1280	ND
	R	2667	5	1535	4.5	1786	ND	3217	ND
4	L	1076	ND	1085	ND	2541	ND	2800	ND
	R	1244	ND	1015	ND	2654	ND	3480	ND
5	L	2592	5.5	2496	ND	3356	ND	3003	ND
	R	2224	4.5	2006	ND	2383	ND	2301	ND
6	L	663	ND	757	ND	658	ND	830	ND
	R	1122	ND	793	ND	828	ND	891	ND
7	L	1188	ND	733	ND	1838	ND	740	ND
8	L	1184	5	1060	ND	1734	ND	1898	ND
	R	1303	5.5	1192	5	1847	ND	2192	ND
9	L	2108	4	1289	ND	1224	ND	2325	ND
	R	2451	5.5	1557	ND	1561	ND	2267	ND
10	L	1249	6	1388	ND	2569	ND	3415	ND
	R	1249	5.5	1341	ND	2773	ND	3338	ND

Note: I , impedance (Ω) measured from the electrode contact (impedances in bold are the impedances of the chronically used contacts); L, left electrode; ND, not determined (i.e., the PTSE threshold was beyond 6 V); R, right electrode; V , voltage (V) threshold triggering PTSE.

Table 3 PTSE predictive performance and comparison of models 1 and 2 obtained during the evaluation procedure.

	Se		Spe		PPV		NPV		Kappa	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Model 1	7.62	(7.66)	95.93	(1.98)	10.94	(12.09)	93.72	(0.66)	0.04	(0.09)
Model 2	66.53	(28.93)	98.76	(1.78)	86.96	(23.59)	97.37	(2.34)	0.68	(0.26)
P	<0.001		<0.001		<0.001		<0.001		<0.001	

Note: Model 1, current-based; Model 2, current and electrode-coordinate-based; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Spe, specificity.

Table 4 PTSE predictive performance and comparison of models 2 and 3 obtained during the evaluation procedure.

	Se		Spe		PPV		NPV		Kappa	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Model 2	66.53	(28.93)	98.76	(1.78)	86.96	(23.59)	97.37	(2.34)	0.68	(0.26)
Model 3	83.92	(14.10)	97.88	(2.22)	80.3	(17.59)	98.73	(1.09)	0.78	(0.11)
P	0.09		0.39		0.29		0.25		0.09	

Note: Model 2, current and electrode-coordinate-based; Model 3, current, electrode-coordinate and trajectory-based; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Spe, specificity.

and 4.80 mA (2.03) for contact 1. One PTSE was triggered at 4.30 mA for contact 2. The stimulation of the contact 3 did not trigger a PTSE. The results obtained from the validation procedure are presented in Tables 3 and 4.

The kappa index value between the predicted PTSE and the clinically observed effects was 0.04 for the single-rule induction modeling (model 1). The graphic representation of the model 1 is displayed in Fig. 3. The representation of the volume of tissue activated by the DBS is based on the work of Butson et al.²¹

Figure 4 displays the clinical implementation of the second model of PyMAN modeling. The model was executed for each voxel of the patient's MRI. The amount of current needed to

trigger a PTSE (i.e., the upper limit of the therapeutic window) is displayed for the electrode trajectory chosen by the neurosurgeon. The kappa index value of the second model was 0.68. All the model 2 diagnostic parameters were significantly higher than model 1. A visual analysis of Fig. 4 by an anatomist showed that the overall location associated with a lower PTSE threshold was the posterior limb of the internal capsule. Increasing risk is also present when the fibers go down to the internal capsule. Finally, when the angles of the electrode trajectory were added (i.e., model 3), the kappa index value reached 0.78. There were no significant differences between the models 2 and 3 diagnostic parameters.

Fig. 3 Graphic illustration of the first model (i.e., single-rule induction) with lateral view of a right electrode example. For any electrode location, a splitting term is determined to predict the occurrence of a PTSE. The volume of tissue activated by the DBS is displayed in green (left view) when the model does not predict PTSE. The volume of tissue activated is displayed in red (right view) when the model predicts a PTSE. Electrode contacts (dark red); Internal capsule (gray); GPm (orange); Volume of tissue activated (green and red) A: anterior; I: inferior; P: posterior; S: superior.

We have proposed an approach for preoperative predictive modeling of PTSE. For its validation, 10 patients implanted in the GPm were tested for PTSE. The overall results showed a high degree of agreement between the prediction of PyMAN and the labeled data. These results are sufficient to submit this tool to an evaluation study on migrating PyMAN from the laboratory to the preplanning station of the neurosurgeon.

Journal of Medical Imaging

Apr–Jun 2016 • Vol. 3(2)

0.78. Although model 3 tended to perform better, there were no significant differences with model 2. The tests might have lacked the power to show a difference. This tendency needs to be confirmed on a larger cohort to confirm whether the myelinated fibers of the pyramidal tract might be activated differently depending on the angle of the trajectory.

Butson et al.⁴ modeled the volume of tissue activated by the electrode stimulation. They proposed to use this technique to avoid PTSE. The idea was to avoid the overlapping between the volume of tissue activated and a segmented internal capsule that contains the motor fibers responsible for PTSE. Hence, they calibrated their model on a single patient²³ to propose an optimal accuracy, which might avoid the PTSE. They recorded PTSE with an electromyogram on the patient. Their most advanced model predicted PTSE starting the activations from 0% to 30% of the internal capsule fibers. Similarly, Madler and Coenen²⁴ assessed a simplified volume of tissue activated model using clinical measurement of PTSE. They reported their results on two patients showing a PTSE threshold starting from 0% to 5% of activated fibers. However, the models were not evaluated on a testing dataset due to the limited number of patients included in the studies. The next logical step will be to compare the volume of tissue activated method with the one we proposed on the same testing dataset.

Despite the high level of accuracy of data-driven machine learning algorithms such as the PyMAN, the method provides little insight into the wide range of effects of the electrical stimulation around the target area. Further works may enhance the model to cover other electrical parameters. In our case, we only investigated a pulse width of 60 μ s and 130 Hz, which are the most common electrical settings.²⁵ It would have been too tiring for patients to undergo additional testing (e.g., a testing session of a bilateral implanted patient lasted approximately 1 h). Therefore, the models studied did not integrate other pulse widths and frequencies.

The patients were tested at least 3 months after surgery. The patients tested during the postoperative programming may have their trajectories already optimized to avoid pyramidal stimulation. Here, the objective of the study was to validate the accuracy of the method. Further work will establish whether this technique may actually reduce the incidence of PTSE compared to the current approach.

5 Conclusion

We designed and validated PyMAN, a model for predicting PTSE induced by GPM stimulation. We used the complex non-linear relations between the 3-D electrode locations, the current delivered by the electrode contact, and the angle of the trajectory. We proposed a graphic version of the model to help the neurosurgeon select the optimal target. PyMAN should be considered as an additional tool for computer-assisted DBS surgery. The model was validated on a prospective cohort of 10 patients. An additional prospective evaluation study should also be conducted to compare the predictive performance of PyMAN with the method based on the estimation of the volume of tissue activated by DBS. However, the overall results already showed a high degree of agreement between the prediction of PyMAN and the labeled data. They are sufficient to justify migrating PyMAN from the laboratory to the preplanning workstation used by the neurosurgeon and to start evaluating its impact on surgery duration and clinical scores.

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