Intraoperative 3D fluoroscopy accurately predicts correct electrode location in deep brain stimulation surgery

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Dedicatória

Dedico-te a ti avô Clementino, que tanto me inspiraste na escolha deste tema.

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Resumo

Introdução: A eficácia da cirurgia de estimulação cerebral profunda (ECP) depende criticamente da posição exata do elétrodo. É, assim, necessária uma confirmação anatómica da posição do elétrodo pós-implantação para excluir desvios indesejados. Este projeto visa validar a fluoroscopia 3D (F3D) intraoperatória como uma ferramenta para determinar a posição final do elétrodo. Uma vez que é um método disponível no bloco operatório (BO), mais rápido, mais barato e de mais baixa radiação, poderá substituir a TC padrão, se for verificada uma acuidade de imagem semelhante.

Métodos: Este é um estudo retrospetivo que inclui 64 doentes (124 elétrodos) submetidos a cirurgia ECP entre maio de 2019 a janeiro de 2022, no Centro Hospitalar Universitário de São João. Todos os pacientes realizaram F3D intraoperatória após a implantação dos elétrodos definitivos e TC nas primeiras 48h pós-operatórias. Para comparar a acuidade dos dois métodos, as imagens foram fundidas numa estação de planeamento esterotáxico, e foi determinada a posição da ponta dos elétrodos em cada estudo de imagem. A distância entre a posição medida nos dois métodos foi determinada, bem como a distância entre a ponta do elétrodo e o ponto medio-comissural nos dois métodos foi também avaliada. Finalmente, o volume de ar intracraniano (pneumocéfalo) foi também quantificado e o seu potencial impacto na determinação da posição do elétrodo analisado.

Resultados: A diferença entre a posição do elétrodo estimada por F3D e TC foi de 0,85 mm (±SEM 0,03), inferior à resolução do TC (1mm). A distância ao ponto medio-comissural medida pelas duas técnicas não apresentou uma diferença significativa (13,00 ± 0,16 mm no grupo F3D e 13,06 ± 0,16 no grupo TC), mas demonstrou ser fortemente correlacionada. Apesar do pneumocéfalo ser significativamente maior no grupo F3D (6,89 ± 1,76 vs 5,18 ± 1,37 cm^3 no TC), o mesmo não se correlacionou com a diferença entre a posição do elétrodo medida pelas duas técnicas.

Conclusões: A F3D prevê com precisão a posição final do elétrodo na cirurgia de ECP. Sendo um método com menos radiação, menos dispendioso e mais rápido do que o TC, e dispensando o transporte o doente para fora do BO durante a cirurgia, poderá substituir o TC como ferramenta para determinar a posição final do elétrodo.

Palavras-chave

Fluoroscopia 3D intraoperatória; Estimulação cerebral profunda; Estereotaxia; Neurocirurgia funcional; Localização do elétrodo.

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Abstract

Background: The effectiveness of deep brain stimulation (DBS) surgery critically depends on accurate electrode position. An anatomical post-implantation confirmation of the electrode position is required to exclude unwanted shifts. This project aims to validate the intraoperative 3D fluoroscopy (3DF) as a tool to determine the final electrode position. Since it is a faster, cheaper, low-radiation method, that is readily available in the OR, it may replace the standard post operative CT, if similar imaging acuity is verified.

Methods: This is a retrospective study that includes 64 patients (124 electrode) who underwent DBS surgery, from May 2019 to January 2022, at Centro Hospitalar Universitário de São João. All patients underwent intraoperative 3DF after implantation of the definitive electrodes and a CT scan within 48 hours after surgery. In order to compare the accuracy of both methods, the images were fused in a stereotaxic planning station and the electrode tip position was determined, as well as its distance to the midcommissural point in both imaging modalities. Finally, intracranial air (pneumocephalus) volume was also quantified and its potential impact in determining the electrode position analyzed.

Euclidean coordinates of the electrode tip were used to calculate the deviation of the electrodes using the Pythagorean Theorem applied to space.

Results: The difference between the electrode position estimated by 3DF and CT was 0,85 mm (± SEM 0,03), which is inferior to the CT resolution (1mm). The distance to the midcommissural point measured in both methodologies was not significantly different (13,00 ± 0,16 mm in F3D and 13,06 ± 0,16 in CT), but was, instead, highly correlated. Despite the fact that pneumocephalus was larger in the 3DF images (6,89 ± 1,76 vs 5,18 ± 1,37 cm^3 in the CT group), it was not correlated with the difference in electrode position measured by both techniques.

Conclusions: 3DF accurately predicts final lead position in DBS surgery. Being a method with fewer radiation, less expensive, faster, and that doesn't require the patient to be transported outside the OR, it could replace CT as a tool to determine final electrode position.

Keywords

Intraoperative 3D Fluoroscopy; Deep Brain Stimulation; Stereotaxy; Functional Neurosurgery; Electrode location.

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List of Acronyms

BO	Bloco operatório
CSF	Cerebrospinal fluid
CT	Computed Tomography
DP	Doença de Parkinson
ECP	Estimulação cerebral profunda
F3D	Fluoroscopia 3D
MCP	Midcommissural point
OR	Operating room
PD	Parkinson's Disease
TC	Tomografia computorizada
3DF	3D Fluoroscopy

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Introduction

Deep brain stimulation (DBS) is a well-established treatment for movement disorders such as Parkinson's disease (PD), essential tremor, dystonia, as well as refractory epilepsy and obsessive-compulsive disorder (1,2). This procedure entails the implantation of electrodes in specific brain areas, which deliver adjustable electrical impulses in order to modulate the activity of neuronal circuits and provide therapeutic benefits. While DBS does not cure the underlying condition, it can significantly improve the quality of life of patients (3). In PD, for example, it has established itself as an effective treatment to improve symptoms such as tremors, rigidity, and dystonia (4).

The efficacy of DBS critically depends on the exact electrode position. Given the small dimensions of the targeted nuclei, the therapeutic effect relies on the accurate stimulation of the intended target and avoidance of unintended co-stimulation of nearby structures, which could elicit side effects. (2) In order to fine-tune the final electrode location, multiple intraoperative techniques are employed, such as microelectrode recording of neuronal activity and microstimulation trials (5). However, anatomical confirmation of the true electrode location post-implantation is crucial to exclude unwanted displacement during implantation of the definitive electrode (6).

Multiple imaging techniques have been described for this end, namely two-dimensional fluoroscopy, a method that is easily available in the operating room (OR), but offers limited accuracy, given that it is not three-dimensional. Alternatively, three-dimensional methods such as computed tomography (CT) and magnetic resonance imaging (MRI) can be employed, but they imply either ORs with integrated CT/MRI setups (which are highly-expensive facilities, only available in a few centers worldwide) or patient transportation to the neuroradiology unit during surgery. Although the latter is the most commonly employed method, transporting the patient, often under general anaesthesia, out of the OR can pose safety issues and significantly increases operative time and associated costs (4,6,7).

In this context, intraoperative three-dimensional fluoroscopy (3DF) with a C-arm has been proposed as a fast, inexpensive alternative, readily available in the OR and requiring lower radiation exposure compared to CT (8). Recent studies, with small patient samples, suggest a possible usefulness of 3DF in estimating the final position of electrodes in stereotactic procedures such as DBS and stereo-EEG (4,6,8-13). However, the studies on DBS do not directly compare the two methods in the same patient cohort, but instead compare different cohorts of patients undergoing either CT or 3DF. In order to effectively assess the accuracy of 3DF in relation to that of CT, we believe that it is essential to determine final electrode location using both methods in the same patients.

In this context, the current work aims to evaluate the accuracy of 3DF in estimating the final position of electrodes implanted in DBS surgery, taking as a reference the location determined by CT, the standard method at our department. A large cohort of 124 electrodes from 64 patients operated at the Neurosurgery Department of the Centro Hospitalar Universitário de São João was included. Both 3DF and CT images were acquired from every patient. We believe our findings validate 3DF as an effective tool to determine the final electrode position in DBS. Given that it is faster, cheaper, readily available in the OR and poses lower radiation exposure, it may replace the currently standard intraoperative CT.

Methods and Materials

Patient Selection

This is a retrospective study that includes a cohort of patients who underwent DBS surgery at Centro Hospitalar de São João from May 2019 to January 2022. Seventy patients who received intraoperative 3DF and early-postoperative CT (within 48h of surgery) were initially selected to be included. After applying our exclusion criteria, low-resolution CT scan (> 2mm slice width), need for revision surgery between both imaging methods), 4 patients were excluded. Two additional patients were excluded as it was not technically possible to retrieve their 3DF images from the electronic records. Therefore, 64 patients and a total of 124 implanted electrodes were included in the analysis: 58 patients with Parkinson's disease who were implanted bilaterally in the subthalamic nucleus, 4 patients with chronic pain who were implanted unilaterally in the left ventral posterolateral thalamic nucleus, 1 patient with refractory epilepsy implanted bilaterally in the anterior nucleus of the thalamus, 1 patient with dystonia implanted bilaterally in the globus pallidus internus).

Surgical procedure and Imaging

All patients underwent fluoroscopic image acquisition and 3D reconstruction with the C-arm system (Ziehm®) during surgery, between implantation of the definitive electrodes and insertion of the pulse generator, and a high-resolution CT scan (1 mm slice width) within the first 48h after surgery.

In order to compare the accuracy of 3DF to that of CT in determining the final electrode position, the following methodology was employed. Intraoperative 3DF, early-post operative CT and pre-operative MRI scans (high resolution - 1 mm slice width-T1+gadolinium) were merged in a stereotaxic planning station (Medtronic StealthStation S8®). The midcommissural point (MCP) was determined in the MRI images and used as a reference for the Euclidean coordinates. Then, the spatial position of the electrode tip was manually determined in the 3DF and CT images, independently, and the respective Euclidean coordinates were extracted (Figure 1A). Assuming the position of the electrode in CT as a reference, its position in 3DF and consequent distance between both will allow us to quantify the difference between both techniques. In order to calculate this distance, we used the xyz coordinates (representing the medio-lateral, anterior-posterior, and dorso-ventral coordinates, respectively) of the electrode tip in 3DF (x1, y1 and z1) and CT (x2, y2 and z2) and employed the Pythagorean theorem applied to space (Figure 1B), as follows:

$$\text{3DF-CT distance} = \sqrt{((x1-x2)^2 + (y1-y2)^2 + (z1-z2)^2)}$$

Furthermore, in order to statistical probe the significance of the difference between the two methods, the distance of the electrode tip to MCP (whose coordinates are x=0, y=0 and z=0 by definition) in both imaging methods was determined following analogous formulas:

$$\text{3DF-MCP distance} = \sqrt{((x1)^2 + (y1)^2 + (z1)^2)}$$

$$\text{CT-MCP distance} = \sqrt{((x2)^2 + (y2)^2 + (z2)^2)}$$

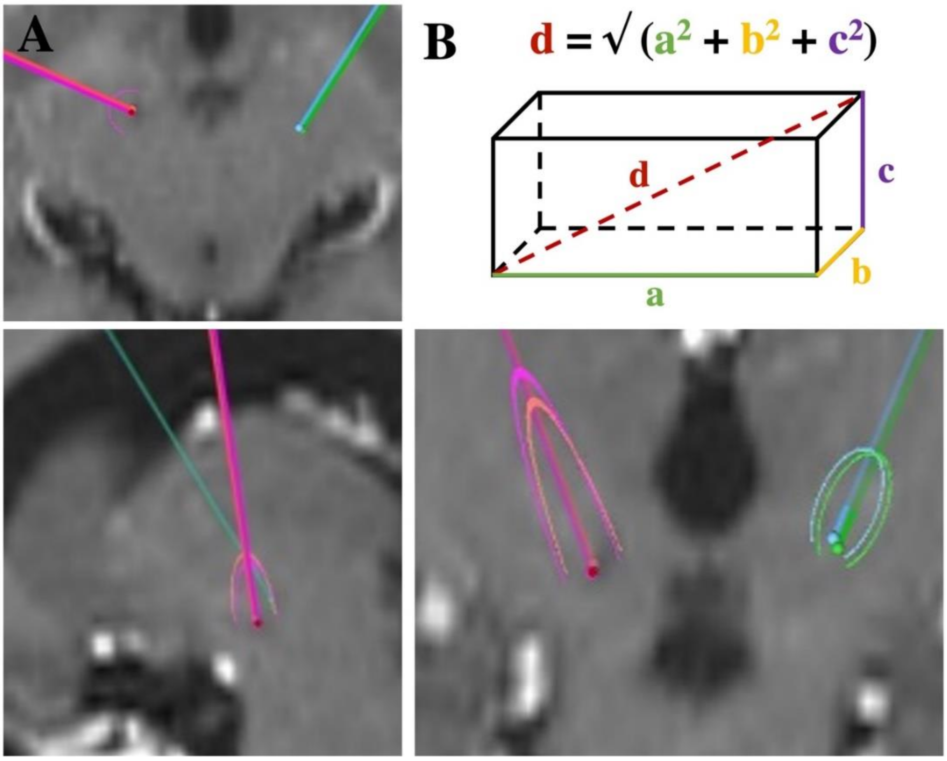

Figure 1. Methodology example. A) Locating the electrode tip in imaging scans to obtain its coordinates; B) scheme of the Pythagorean theorem applied to space, used to calculate distance between coordinates.

Pneumocephalus analysis

Given that the post-operative CT scan was acquired up to 48 hours after surgery, the time gap with the intraoperative 3DF was a concern. Furthermore, the difference in head position between modalities (head-fixed in the stereotaxic frame, in slight flexion during acquisition of intra-operative 3DF and head-free in supine position during post-operative CT acquisition) could also be a potential source of mismatch between both methods, is brain shift was a significant factor. Specifically, pneumocephalus, the presence of intracranial air, is a common DBS-related phenomenon which can lead to brain shift and targeting inaccuracy (14).

In order to control for this potential issue, we performed 3D reconstructions of pneumocephalus in our 3DF and CT images and quantified their volume. Furthermore, a correlation analysis was performed in order to assess whether the difference between 3DF and CT pneumocephalus was related to the magnitude of 3DF-CT electrode distance.

Statistical analysis

Data are displayed as mean ± standard error of mean and significance level was set to $p<0.05$. Statistical analysis and plots were performed using Graphpad Prism Version 8® software. Datasets were probed for normality using the D'Agostino-Pearson Test. As our datasets failed to pass the normality test, non-parametric Wilcoxon signed rank test was employed to compare paired samples and Spearman's correlation coefficient was calculated to assess the correlation between two variables.

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Results

3DF accurately predicts electrode tip position

A total of 124 electrodes, from 64 patients, were analyzed and their tip position assessed in 3DF and CT images. Quantification results are summarized in Table 1.

Table 1. Summary of calculated metrics

3DF-CT distance	Distance to MCP		x coordinate		y coordinate		z coordinate	
	3DF	CT	3DF	CT	3DF	CT	3DF	CT
0,85 ± 0,03	**13,00** ± 0,16	**13,06** ± 0,16	**10,91** ± 0,18	**10,91** ± 0,18	**2,95** ± 0,16	**2,87** ± 0,17	**5,78** ± 0,17	**5,94** ± 0,18
Spearman coefficient	0,91 ****		0,92 ****		0,93 ****		0,94 ****	

Data is displayed as mean ± standard error of mean. Distances and coordinates are depicted in mm. ****: p<0.0001.

The distance between electrode tip position, measured in 3DF and CT imagens was 0,85 ± 0.03 mm, which is within the resolution limit of the CT scans, which had a slice width of 1 mm. Distribution of values is displayed in Figure 2A; 65% of analyzed electrodes had 3DF-CT deviations smaller than 1mm; 94% smaller than 1,5mm and 100% below 2mm.

In order to test the statistical significance of this deviation, we compared the distance of the electrode tip to the MCP, as measured by the two methods (Figure 2B). The electrode tip distance to MCP was 13,00 ± 0,16 mm in the 3DF group and 13,06 ± 0,16 in the CT group, and were not significantly different (p=0,11). Furthermore, these variables are strongly correlated, presenting a Spearman correlation coefficient of 0,91 (p<0.0001; Figure 2C). In agreement with this, all electrode tip x, y and z coordinates are highly correlated between both methods, suggesting that there is no bias towards a specific axis in the deviation between both methods (Figure 2D, E and F). Considering these findings altogether, we conclude that the accuracy of the 3DF in estimating electrode position is comparable to that of CT.

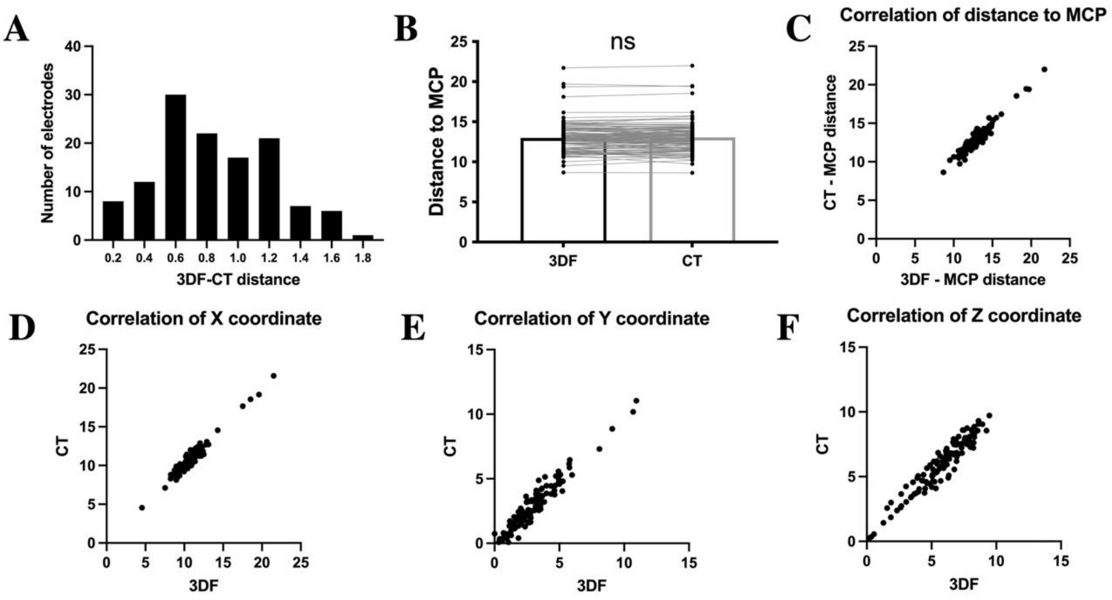

Figure 2. Electrode tip metrics. A) histogram depicting the distribution of 3DF-CT distances; B) distance to MCP in both imaging methods; each dot represents one individual electrode; horizontal lines connect the same electrode measured in 3DF and CT; C-F) Spearman's correlations across both groups of: C) distance to MCP; D) x coordinate value; E) Y coordinate value; F) Z coordinate value. Distances and coordinate values are in mm.

Brain shift did not impact the 3DF – CT comparison

As previously mentioned, potential brain shift between the timing of acquisition of both imaging methods was a concern. In order to assess whether this phenomenon was impacting our electrode tip position results, we quantified the volume of pneumocephalus in 3DF and CT images of 61 patients (three patients could not be included in this analysis because the 3DF images did not cover the most frontal part of the cranium, precluding pneumocephalus measurement). Results are summarized in Table 2.

Table 2. Summary of pneumocephalus quantification in both 3DF and CT and analysis of its impact in the electrode tip distance between imaging methods

Air volume 3DF	Air volume CT	Air volume 3DF-CT comparison	Correlation between air difference and electrode tip distance	
6,89 ± 1,76	5,18 ± 1,37	***	coefficient = 0,17	ns

Data is displayed as mean ± standard error of mean. Pneumocephalus volumes are presented in cm^3. ***: $p<0.001$; ns: $p>0.05$.

In fact, the volume of intracranial air was significantly higher in the 3DF images than the CT counterparts (6,89 ± 1,76 and 5,18 ± 1,37 cm^3, respectively; p=0.0007; Figure 3A). This difference can be explained by the fact that the 3DF is acquired shortly after dura-mater opening during surgery, while our CT data pertains to up to 48 hours after surgery, when it is expected that some of the intracranial air was already reabsorbed. However, this pneumocephalus values are rather small, when considering the total intracranial space and may not necessarily cause a relevant shift of the targeted deep nuclei and, consequently the electrode tip position across both methods.

In order to probe this, we postulated the following rational: if pneumocephalus volume difference across both methods is impacting electrode tip position, then patients with higher pneumocephalus difference between 3DF and CT would also have higher distances between electrode tip as detected in both methods. Therefore, we performed a Spearman correlation analysis and found no significant correlation between pneumocephalus difference and electrode tip distance across both methods (correlation coefficient of 0,17; p=0,0642; Figure 3B). Therefore, we conclude that the difference in intracranial air detected in both imaging methods did not impact the distance between electrode tip measured in 3DF and CT images.

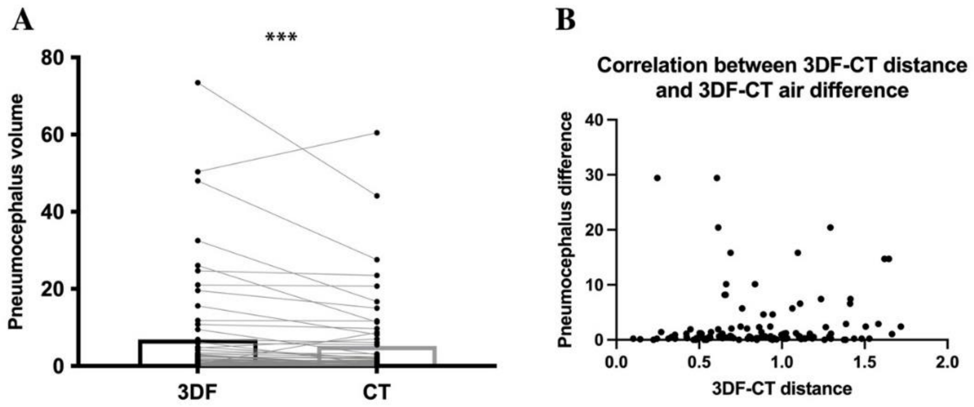

Figure 3. Pneumocephalus evaluation. A) Pneumocephalus volume was significantly higher in the 3DF images, when compared to CT images; B) however, there was no correlation between the pneumocephalus volume difference in 3DF and CT images and electrode tip 3DF-CT distance. Volumes are displayed in cm^3 and distances values in mm.

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Discussion

Correct lead position in DBS is absolutely crucial for the success of the procedure, as it has been correlated with improved clinical outcomes. For example, McClelland et al concluded that leads implanted in the subthalamic nucleus that are misplaced 2–3 mm may have an inadequate outcome (16). Therefore, imaging methods to determine the final electrode position must produce accurate anatomical information.

With this in mind, the main goal of the present study was to assess whether 3DF has comparable accuracy to CT in predicting final electrode position in DBS surgery. In order to do this, we quantified the distance between the electrode position estimated by 3DF and CT and seek to understand whether that difference was clinically meaningful. We were able to include a large number of patients and electrodes in this analysis, which, to our knowledge, makes it the largest sample size in studies addressing this research question. Another important strength is that we were able to directly compare both methods across the exact same patients, unlike other studies of comparing these imaging modalities across two separate groups of patients. We believe these facts significantly empower the magnitude of our findings.

We observed that the inter-method difference was 0,85 mm and conclude that it is not clinically relevant, for the following reasons. First and foremost, this difference is well within the limits of our methodology resolution which are mostly imposed by CT resolution (slice width of 1 mm), but also by the volume of the metallic artifact of the electrodes which can be a source of infra-millimetric variability when assigning the electrode tip. Furthermore, if a specific systematic error occurred when estimating the distance between methods, it would likely occur in a specific direction, affecting one Euclidean coordinate more than the others. Our data shows that all coordinates are highly correlated between both methods and, therefore, this small variation between 3DF- and CT-estimated electrode position is stochastic. Finally, statistical comparison between distance of electrode tip to the spatial reference – the MCP – did not show a significant difference between both methods. Taken together, these findings strongly support that 3DF is an excellent technique for predicting DBS electrode location.

Another important aspect to analyse was the possibility that the time passed between the acquisition of both imaging modalities could be influencing our conclusions. In fact, while the 3DF scans were performed intraoperatively, CT scans were conducted within 48 hours after surgery. Consequently, any potential intraoperative brain shift could have influenced the electrode position in the 3DF images but, not to the same degree in the CT scan acquired later, as intracranial air might have partially been reabsorbed 48 hours after the procedure (10).

Subdural pneumocephalus and transventricular lead passing have been postulated to cause brain shift during DBS surgery (17). Any displacement of brain structures during stereotactic procedures is predominantly caused by loss of cerebrospinal fluid (CSF), air inflow and, consequently, the modification of the physiological intracranial pressure which is usually negative. Exposure of the intracranial space to the extracranial atmospheric pressure can abolish this pressure differential resulting in brain shift. Any effects from brain shift during DBS surgery may be evident in the perioperative and immediate postoperative images (15). However, some studies suggest that brain shift might affect mostly superficial cortical targets than deep-seated brain regions such as the basal ganglia (14).

In line with the literature, we also observed that pneumocephalus volume was higher in the intra-operatively acquired 3DF than the postoperative CT scan. However, this did not impact our findings pertaining to the accuracy of estimating the electrode tip location, since there was no correlation between the degree of pneumocephalus difference across methods and the degree of distance between the electrode tip estimation by both methods. If this was the case, one would predict that patients with higher intracranial air differences between both imaging methods would also display higher degree of difference between electrode tip position across both methods. Therefore, we conclude that the time gap between the acquisition of both imaging studies is unlikely to influence our ability to compare them.

Our findings are comparable to those already published in the literature. In a 2014 study, Weise et al concluded that the accuracy of 3DF imaging in phantoms revealed a slightly lower accuracy but higher precision than the CT (10). Furthermore, in a 2020 study, Cooper et al inferred that 3DF-based frame registration showed similar implantation accuracy to CT imaging (11). Finally, a 2021 study by Restrepo et al concluded that the use of 3DF as a method for registration resulted in similar implantation accuracy compared with CT (6).

Another important point to discuss when comparing 3DF with CT methodologies is radiation exposure. This is particularly relevant in patients that require frequent imaging of the brain (6, 10, 18, 19). Although the present work did not entail an analysis on radiation dose exposure, multiple studies support a clear benefit of 3DF over CT in this regard. The above-mentioned Weise 2014 study concluded that the effective dose for 3DF was 0.65 mSv, while that for CT is almost double (10). The Cooper 2020 and Restrepo 2021 papers also calculated the average radiation exposure with 3DF and CT, concluding that 3DF dose length product was about 20% of that of CT (6).

Study limitations

There are some limitations to our study, which have already been addressed in previous sections. One important point is the difference in time and settings of acquisition of both imaging modalities. Also, the resolution limitations inherent to our methodologies, namely the metallic electrode artifact, the imaging studies resolution and the manual determination of the electrode tip. We believe that the above-mentioned strengths of our study significantly prevent these limitations from impairing our conclusions. Despite them, we still found an infra-millimetric difference between the 3DF and CT which is not clinically relevant. We believe that these limitations are likely preventing us from finding even smaller differences between methods rather than the other way around.

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Conclusion

In conclusion, we believe that our findings clearly support that intraoperative 3DF accurately predicts the final electrode position in DBS surgery. Being a faster, less expensive and less radiation exposure method that is readily available in the operation room, where it provides the opportunity to correct electrode position during the same operative period, 3DF is a powerful tool to replace CT imaging.

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Annex

Opinion of the CHUSJ Ethics Committee

SÃO JOÃO

DELIBERAÇÃO DO CONSELHO DE ADMINISTRAÇÃO

Após apreciação e pareceres favoráveis da Comissão de Ética e do Centro de Epidemiologia Hospitalar, considerando que se encontram reunidos os requisitos e demais trâmites previstos no circuito para submissão de projetos de investigação no Centro Hospitalar Universitário de S. João e em conformidade com as disposições legais em vigor, o Conselho de Administração – ao abrigo das competências previstas no Artigo 71.º dos Estatutos dos hospitais, centros hospitalares, institutos portugueses de oncologia e unidades locais de saúde, aprovados pelo Decreto-Lei n.º 52/2022, de 4 de agosto – delibera:

1. Aprovar a realização do projeto de investigação:
   - "Intraoperative 3D fluoroscopy accurately predicts correct electrode location in deep brain stimulation surgery".
   - Serviço(s) onde decorrerá o projeto de investigação: Neurocirurgia.
   - Investigador(a) principal: Patrícia Adriana Neto Fernandes.
2. Remeta-se à Comissão de Ética para os procedimentos adequados e demais trâmites convenientes.

CONSELHO DE ADMINISTRAÇÃO DO CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE • REUNIÃO DE 20 DE ABRIL DE 2023

Presidente do Conselho de Administração

Prof.ª Doutora Maria João Baptista

Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
Prof.º Doutor Roberto Roncon	Enfermeiro Paulo Emílio Mota	Dra. Sofia Leal	Dra. Fernanda Oliveira

› Comissão de Ética
› Centro de Epidemiologia Hospitalar
› Direção Clínica

CES 46/2023

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