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Original Article

Factors affecting targeting accuracy in minimally invasive twist drill deep brain stimulation

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ABSTRACT

Background: The efficacy of deep brain stimulation (DBS) relies on accurate stereotactic electrode placement. Post-implantation imaging enables assessment of electrode positioning and quantification of targeting accuracy. While DBS is typically performed through burr hole, this study examines targeting accuracy factors using a minimally invasive twist drill technique.

Methods: We retrospectively analyzed 86 patients (171 electrodes) who underwent DBS at our institution. Different measures of targeting error were defined and compared. Analysis focused on trajectory error (TE), the closest perpendicular distance between the electrode's center and target locus. Seventeen demographic, clinical, and procedural variables were assessed for potential impact on accuracy. Multivariate mixed effects models were applied to identify significant associations.

Results: Mean (±standard deviation) TE was 1.4 (0.7) mm. Electrodes tended to lie medial (0.3 ± 0.1 mm; mean ± 95% confidence interval), posterior (0.6 ± 0.1 mm), and superior (0.5 ± 0.1 mm) to targets. Three variables were independently and significantly associated with greater TE: use of one of two stereotactic frames (effect size 0.4 ± 0.2 mm), second-side implantation in bilateral surgery (0.3 ± 0.2 mm), and decreasing coronal approach angle (0.04 ± 0.03 mm/°). All three factors were associated with significantly more posterior implantation, while second-side and decreasing coronal angle also yielded a more superiorly located point of closest approach of the electrode.

Conclusion: We present a thorough multivariate analysis of targeting accuracy in DBS, identifying significant factors associated with accuracy within our workflow. We suggest that such targeting error analysis should be performed routinely by neurosurgeons undertaking DBS to audit targeting accuracy and identify error sources within their workflows.

Keywords: Accuracy, Deep brain stimulation, Electrode, Stereotactic surgery, Targeting error

INTRODUCTION

Deep brain stimulation (DBS) is now an established therapy for several neurological disorders. More than 160,000 patients have implanted DBS systems globally, with approximately 12,000 new implants performed annually.[31] This is expected to increase as the population ages and new indications emerge.[33] Successful DBS depends in part on the accurate placement of electrodes into specific subcortical brain structures using stereotactic methods and suboptimal

electrode placement risks treatment failure.[13,41,45] Targeting errors describe discrepancies between intended and actual electrode placement, have multiple potential sources, and are potentially cumulative. Possible contributing factors include magnetic resonance imaging (MRI) distortion, registration errors, variance in stereotactic space definition, procedural influences, mechanical properties of the brain, and frame-based errors.[20,32] Placement of an electrode within 2 mm of a target has often been quoted as an approximate tolerance limit in stereotactic implantation.[20,30,44] For some indications such as Parkinson's disease and tremor, intraoperative adjuncts such microelectrode recording (MER) and/or test stimulation with awake clinical assessment have been used to verify implantation accuracy or guide adjustment of electrode placement.[34] Increasingly, with the advent of advanced high-field MRI, more DBS implantations are being performed "asleep" and guided by targets visualized directly on imaging.[53] This has reported benefit of greater patient comfort, less procedural anxiety, potentially fewer hemorrhagic complications from micro-electrode penetrations, shorter procedure duration, and lower cost.[5,14,25,26,52] Primary stereotactic targeting accuracy is perhaps even more important in asleep DBS where confirmatory intraoperative measures are not performed. However, even with the prevalent use of MER, suboptimal lead placement can account for almost half of cases of revisional DBS surgery.[46]

Few studies have analyzed factors associated with targeting accuracy in DBS, and none have analyzed DBS inserted by minimally invasive twist drill craniostomy, which has been shown to be safe and effective with minimal hemorrhage rates.[4] Here, we report a retrospective analysis of DBS targeting errors in a large single-center case series under the care of the same surgeon using the same stereotactic system. We describe and compare methods for the quantification of targeting error. We sought to determine how procedural variations in our practice, as well as basic clinical and demographic differences, might influence these errors to identify specific factors that are associated with increased error.

MATERIALS AND METHODS

Patients

We retrospectively evaluated the first 90 patients to undergo DBS implantation at our center from 2016 to 2020, under the care of a single neurosurgeon (E.A.C.P.). Targeting data were unavailable for four patients and, therefore, these were excluded from further analysis. All but one patient underwent bilateral electrode implantation. Final analyses were therefore performed for 171 brain leads in 86 patients. All patients were assessed and deemed suitable candidates for surgery by a multidisciplinary team and provided written informed consent to the surgical procedure. The study had local institutional approval under clinical governance provisions (registration number AUDI003419, St George's University Hospitals NHS Foundation Trust, London, U.K.).

Surgical technique

Our DBS implantation procedure has been described previously.[38] Patients all underwent planning 1.5 T or 3 T MRI (approximately 1 mm isotropic voxels, awake or under general anesthesia [GA] if required) in the months before surgery, based on which frontal trajectories to the target (subthalamic nucleus [STN] for Parkinson's disease, ventral intermediate thalamus and caudal zona incerta for tremor [Vim/ZI], ventral intermediate thalamus, and STN [Vim/STN] for dystonia) were planned on dedicated software (Neuroinspire™, Renishaw, Gloucestershire, UK), avoiding sulci, vessels, and ventricles. Trajectory plans typically incorporated an offset, placing the tip of the lead a specified distance beyond the target locus and placing the target within the lead's "active zone" or contact span [Figure 1]. The planning software yielded the frame coordinates of the planned lead tip, and ring and arc angles for the trajectory. Electrodes were implanted either awake under local anesthesia with intraoperative neurologist-led macrostimulation and assessment, or "asleep" under GA, using one of two identical Cosman-Roberts-Wells (CRW) stereotactic frames (Integra LifeSciences, Burlington, MA, USA) with the intubation head ring fixed to the head parallel to the infraorbitomeatal line. A stereotactic high-resolution computed tomography (CT) scan was performed with the Brown-Roberts-Wells localizer frame (BRW-LF) (reconstructed slice thickness 0.625 mm). This was registered with the preoperative MRI on the planning software and the planned trajectories expressed in stereotactic space to yield the required frame parameters. Implantation trajectories were checked by passing a blunt rigid probe (closed Nashold side-cutting biopsy needle, 2.0 mm external diameter; Integra LifeSciences, Burlington, MA, USA) to target in the stereotactic frame seated on a phantom base. Leads were implanted using the frame through 2–3 cm linear frontal scalp incisions. The skull entry point was marked with a 2.7 mm diameter stereotactic twist drill (CRW, Integra) dipped in methylene blue dye, and a small pilot divot was made with a hand drill. A craniostomy and durotomy were made by hand with the frame-mounted stereotactic twist drill, taking care to avoid cerebrospinal fluid egress and pneumocephalus with continuous irrigation. The same blunt rigid probe was passed down the trajectory to the intended lead tip location to make a tract and was then removed before insertion of the lead with its internal stylet *in situ*. Care was taken to avoid deviation off the bone edges on entry. The stylet was removed and the lead secured adjacent to the craniostomy with a straight 12 mm titanium

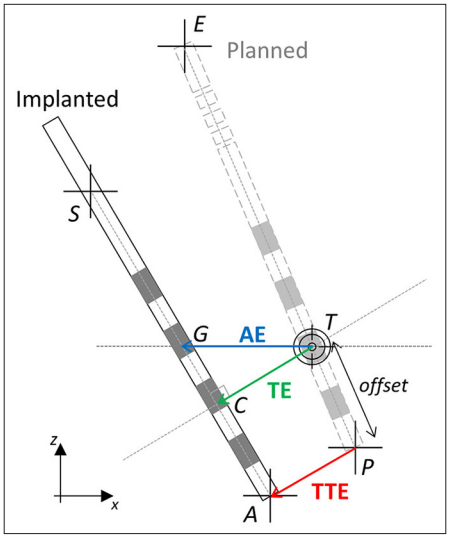

Figure 1: Illustration of the definition of trajectory points and determination of targeting errors, viewed in the coronal plane (X and Z axes shown). The preoperative electrode trajectory plan (grey dashed outline) consists of a target (T) and entry point (E) and planned tip (P) placed beyond the target by the offset distance. The actual implanted electrode (solid black outline) can be defined by the coordinates of the tip (A) and a point on the center of the shaft 2–2.5 cm proximally (S). Trajectory error (TE) is the perpendicular distance between the target and the closest point on the lead (C). Axial error (AE) is the distance between the target and center of the implanted electrode in the same axial plane (G). Tip-to-tip error (TTE) is the distance between planned and actual electrode tips (P and A, respectively). Further details can be found in the Supplementary Material.

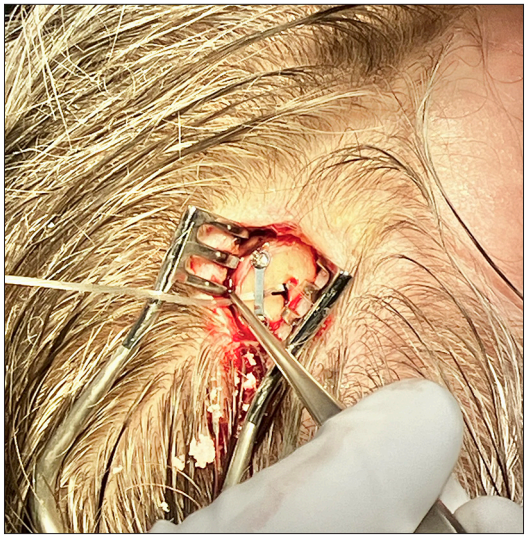

Figure 2: 2.7 mm twist drill craniostomy adjacent to a deep brain stimulation lead with a silk suture tie, secured with a straight 12 mm titanium two-hole plate and screws (MatrixNEURO, DePuy Synthes, Raynham, MA, USA).

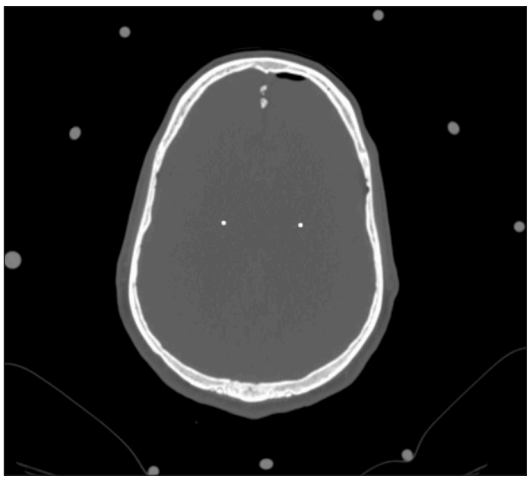

Figure 3: Immediate postoperative high-resolution axial computed tomography of subject with twist drill deep brain stimulation with minimal intracranial air.

two-hole plate and screws (MatrixNEURO, DePuy Synthes, Raynham, MA, USA) [Figure 2], and the craniostomy sealed with bone wax. In bilateral procedures, the second lead was subsequently implanted using the same technique. After implantation of both leads, a further high-resolution CT was performed [Figure 3] and co-registered with the preoperative imaging to verify lead position and electrode contact direction. Patients underwent implantable pulse generator (IPG) implantation either immediately (unstaged surgery) or in a second operation, typically 6 days later (staged surgery for research).[19,38]

Implanted hardware included Medtronic (Minneapolis, MN, USA) 3389 leads with Activa posterior commissures (PC) or Activa rechargeable (RC) IPG, Boston Scientific (Marlborough, MA, USA) Vercise (DB-2201) and Vercise Cartesia (DB-2202) leads with Gevia RC or Vercise PC IPG, and the St Jude Medical (Abbott Laboratories, Lake Bluff, IL, USA) Infinity System with either 0.5 or 1.5 mm spaced directional leads and Infinity 7 IPG. Choice of hardware depended on indication, surgical target(s), and clinician and patient preference, all determined by a multidisciplinary team comprising neurosurgeons, neurologists, and a neuropsychologist.

Quantification of targeting accuracy

Pre- and post-operative imaging was assessed retrospectively on the planning software. Anterior (AC) and PC, and a mid-sagittal point were identified on preoperative volumetric

T1-weighted MRI. Points of interest were expressed in *X* (mediolateral), *Y* (anteroposterior), and *Z* (supero-inferior) coordinates relative to the midcommissural point (MCP). For each lead, the co-ordinates of the planned target and entry point, as well as the planned offset distance, were noted. Planned tip coordinates were derived by geometric extrapolation of the trajectory by the offset distance [Figure 1].

Postoperative CT was used to obtain coordinates of the actual implanted lead tip as well as a point at the center of the shaft 2–2.5 cm proximal to the tip used to define the implanted lead trajectory [Figure 1]. This was performed by two surgeons together for the first 20 patients in order to cross-check designated points and refine the workflow, and once, it was clear that there was very little disparity between the surgeons, by one of them for the remaining patients. The coordinates of the center of the stereotactic frame relative to MCP were also noted.

Three measures of accuracy were considered and determined as per the mathematical workflows below using custom-written scripts in MATLAB (R2021b, The MathWorks, Natick, MA, USA) [Figure 1]:

(1) The tip-to-tip error (TTE), that is, the discrepancy between the planned and actual lead tips, which can be expressed as a scalar Euclidean distance as well as a vector with components in X, Y, and Z dimensions
(2) The trajectory error (TE), that is, the closest perpendicular distance between the center of the implanted lead and the target, which can be expressed as a scalar Euclidean distance as well as a vector with components in X, Y, and Z dimensions. For the rare occasions on which there was no perpendicular from the target to the lead, the closest point on the lead was taken as the tip
(3) The axial error (AE), that is, the distance between the center of the lead and the target in the axial (Z) plane of the target, which can be expressed as a scalar, as well as its vector components in the X and Y dimensions.

A mathematical description of how these measures are derived is provided in the Supplementary Material [Supplementary Figure 1 and Supplementary Methods]. The MATLAB code used can be accessed in a public repository (https://github.com/AMostofi7/DBS_acc).

Procedural, clinical, and demographic variables

For each implanted lead, we collected data on a total of seventeen procedural, clinical, and demographic variables that we thought might conceivably contribute to measurements of implantation accuracy:

- Age – age in years at time of surgery (continuous)
- Sex (categorical)
- Order – the temporal order in which the 90 considered operations occurred, with 1 being the first and 90 the most recent (ordinal)
- Staging – whether surgery performed staged or unstaged (categorical)
- GA – electrode implantation performed "asleep" under GA or awake under local anesthesia (categorical)
- MRI – 1.5 T or 3 T MRI field strength (categorical)
- GA_MRI – MRI performed under GA or awake (categorical)
- Electrode – model of implanted brain lead (categorical)
- Target – target brain structure (categorical)
- Indication – clinical indication for DBS (categorical)
- Side_order – in bilateral surgery, first or second implanted side (categorical)
- Frame – which of two identical CRW stereotactic arcs (labeled A and B) was used (categorical)
- Surgeon – whether implantation was performed by a consultant surgeon or by fellow/resident while supervised by a consultant (categorical)
- Coronal_angle – calculated coronal approach angle from vertical of planned trajectory in AC-PC space [continuous; Supplementary Figure 2 and Supplementary Methods]
- Sagittal_angle – calculated sagittal approach angle from horizontal of planned trajectory in AC-PC space [continuous; Supplementary Figure 2 and Supplementary Methods].
- Pneumocephalus – total volume of pneumocephalus estimated on postoperative CT using abc/2 method for volume of an ellipsoid (continuous).[29,36]
- Frame-MCP – distance from mid-commissural point to stereotactic frame center as a measure of base ring placement (continuous).

Data pertaining to the distribution of these variables is summarized in Table 1.

Statistical analysis

Quantification and basic statistical description of the different measures of targeting error was performed in Microsoft Excel (version 2019) and MATLAB (R2021b, The MathWorks, Natick, MA, USA). An exploratory analysis of predictors of targeting error was performed on IBM Statistical Package for the Social Sciences Statistics (version 28) using linear mixed model analyses. All measurements of errors are in millimeters. An initial exploration for multicollinearity revealed only a strong correlation between the variables target and indication ($r = 0.756$, $P < 0.001$); therefore, *indication* was removed from the list of variables in further analysis. Measures of targeting error were set as the dependent variable, while the remaining sixteen independent variables were set as fixed factors. Independent variables predictive of targeting error were further investigated *post hoc* with mixed effects models incorporating only these independent variables and targeting error in each of the X, Y, and Z dimensions as dependent

variables in three separate models. The magnitude of X dimensions for the left-sided leads was taken to allow leads from the left and right sides to be compared on equivalent axes, positive X indicating more lateral placement regardless of side. Participant was set as a random factor in all models to account for the repeated measure from the first and second sides of electrode implantation in bilateral surgery. A threshold significance level of 0.05 was applied for the initial analysis of targeting error magnitude. For the *post hoc* direction-specific error analysis, a significance level of 0.05 with a Bonferroni correction factor of 3 (i.e., 0.017) was applied for the three separate models for X, Y, and Z errors. Where mean error values are quoted, subsequent values report standard deviation (SD) in parentheses or ±95% confidence interval based on the t-distribution.

RESULTS

Comparison of measures of targeting error

We sought to compare the three different measures of targeting error to determine the pros, cons, and utility of each. Linear regression revealed significant correlations between all measures [Figure 4]. However, there was a much stronger linear association between AE and TE [Figure 4c; $R^2 = 0.95$] than between TTE and TE [Figure 4a; $R^2 = 0.41$] and TTE and AE [Figure 4b; $R^2 = 0.32$]. We noted a number of instances in which the TTE was noted to be high, yet the TE was comparatively low. Four such leads are highlighted in Figure 4 (triangular markers) for which TTEs were >4 mm, yet TEs were ≤2 mm. On review of these leads, this was because the lead had been placed on an accurate trajectory yet anchored at a position more advanced along the trajectory than intended with proximal contacts still in close proximity to the target. In such cases with sizable TTE and low TE, reflective of "advancement error," the presence of multiple contacts affords some redundancy and does not necessarily risk an adverse clinical outcome.

When examining measures of AE, we observed the limitation that for seven leads, the lead did not cross the axial plane of the target and the tips were 0.5–1.7 mm (median 0.7 mm) superior to the target plane. In these cases, AE is undeterminable. Given these observations, we decided that the most appropriate measure of targeting error to analyze further would be TE.

Overall measures of targeting accuracy

The mean scalar TE for all 171 implanted leads was 1.4 (0.7) mm. In each dimension, the point of closest approach of the lead to the target was a mean of 0.3 ± 0.1 mm medial, 0.6 ± 0.1 mm posterior, and 0.5 ± 0.1 mm superior to the target. This reveals significant but sub-millimeter systematic mean targeting error tending to a closest point to target, that is medial, posterior, and superior to that intended. This is well visualized when plotting the point of penetration of the lead in the axial plane of the target [Figure 5].

We performed a correlation analysis to see if there was any association between TE in the first versus the second implanted side in patients implanted bilaterally in the same operative session [Figure 6]. This showed a weak but significant

Table 1: Data on patients and distributions of variables studied.

	No. of patients	86
	Bilateral/unilateral	85/1
	No. of electrodes	171
Independent variable		
Age	Years	60 (9) [24, 81]
Sex	M/F	58/28
Order	1-90	-
Staged	Staged/unstaged	50/36
GA	GA/awake	62/24
MRI	1.5 T/3 T	45/41
GA_MRI	GA/awake	8/78
Electrode	Medtronic 3389	36
	Boston Scientific DB-2202	66
	Boston Scientific DB-2201	34
	St Jude Medical 1.5	27
	Other	8
Target (electrodes/patients)	STN	112/56
	Vim/STN	32/16
	Vim/ZI	27/14
Indication (electrodes/patients)	Parkinson's disease	124/62
	Tremor	27/14
	Dystonia	20/10
Side_order	First side, left/right	53/32
Frame	A/B	70/101
Surgeon	Consultant/Fellow	126/45
Coronal_angle	°	22.6 (4.1) [11.4, 34.1]
Sagittal_angle	°	24.1 (8.2) [0.5, 40.3]
Pneumocephalus	ml	1.0 (2.7) [0, 18.7]
Frame-MCP	mm	22.0 (10.5) [1.3, 55.0]

Values for continuous variables are reported as mean (SD) [Range].
SD: Standard deviation, GA: General anesthesia, MRI: Magnetic resonance imaging, STN: Subthalamic nucleus, MCP: Midcommissural point, Vim/ZI: Ventral intermediate thalamus and caudal zona incerta for tremor, Vim: Ventral intermediate thalamus.

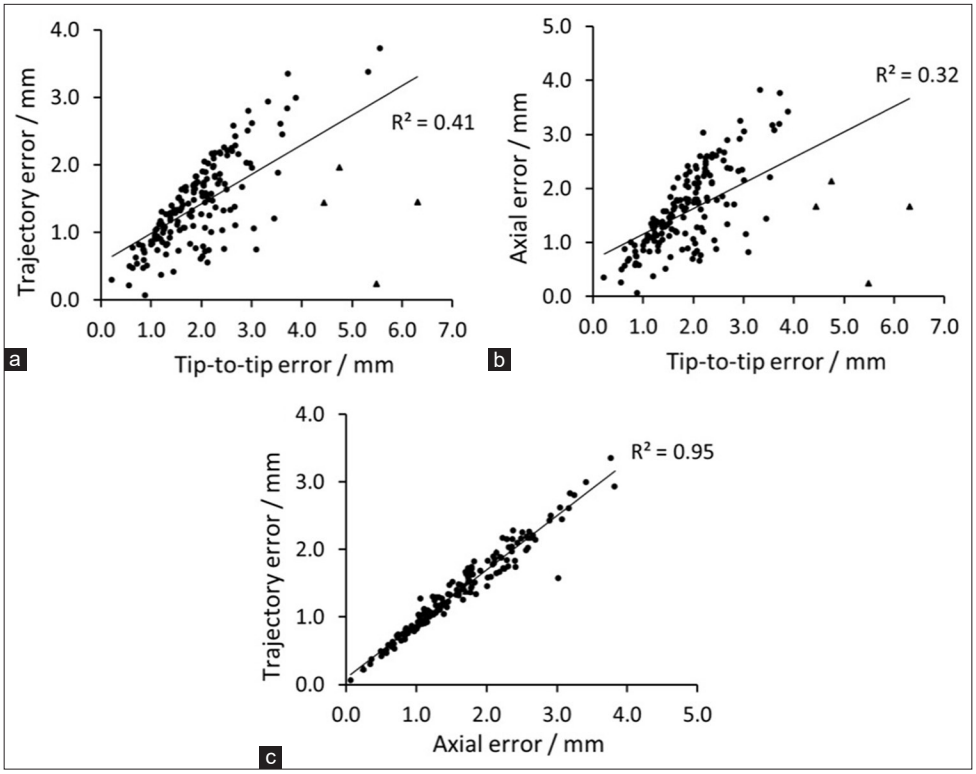

Figure 4: Linear regression plots examining relationships between different targeting error measures: (a) TE versus TTE, (b) AE versus TTE, and (c) TE versus AE. All measures are positively correlated with one another ($P < 0.05$, Pearson correlation) but coefficients of determination, R^2, show that the strongest linear relationship exists between TE and AE. Electrodes which show high TTE (>4 mm) but low TE (≤2 mm) are denoted by triangular markers. TTE: Tip-to-tip error, TE: Trajectory error, AE: Axial error.

correlation ($r = 0.253$, $P = 0.020$) with a low coefficient of determination ($R^2 = 0.06$), suggesting that error in one side accounts for a low proportion of error variance in the other.

Multivariate analysis of factors related to targeting error

An exploratory mixed effects model incorporating our 16 independent variables identified three significantly and independently predictive of TE as a dependent variable [Table 2]. The first is side_order with fixed-effect estimate 0.3 ± 0.2 mm greater TE for the second implanted side. Next is frame, with stereotactic arc B resulting in greater TE by an estimated 0.4 ± 0.2 mm. Finally, coronal_angle was a significant variable with TE decreasing as coronal approach angle increased by an estimate of 0.04 ± 0.03 mm per degree.

We next examined *post hoc* the relationship of the identified predictive variables to the vector components of TE [TE_x, TE_y, and TE_z; see Supplementary Material] to determine the dimension and direction of effects on TE. In further mixed effects models with TE_x, TE_y, and TE_z as dependent variables, only the identified predictive factors side_order, frame, and coronal_angle were included as independent variables [Table 3]. The variables frame and side_order had significant effects on error in the Y and Z dimensions. Specifically, stereotactic arc B was associated with TE that was more posteriorly (0.7 ± 0.2 mm) and superiorly (0.4 ± 0.2 mm) directed. The same was true for second side implantation, which was also associated with greater TE in the posterior (0.3 ± 0.2 mm) and superior (0.2 ± 0.2 mm) directions [Table 3]. There was also a small but significant effect of coronal_angle in the Y dimension only, with less posteriorly directed error as coronal approach angle increases by an estimate of 0.05 ± 0.03 mm per degree.

DISCUSSION

Here, we report an analysis of targeting errors in DBS surgery from a large single-center, single-surgeon case series using a minimally invasive twist drill approach. Targeting error can be defined in a number of ways, and we have explored three possible definitions (TE, AE, and TTE) in our analysis. Based on our planning workflow and software, which outputs stereotactic coordinates for the brain lead tip, TTE should provide the "purest" measure of procedural error. However, we demonstrate that while TTE can be high due to inadvertent advancement of the lead along its trajectory,[50]

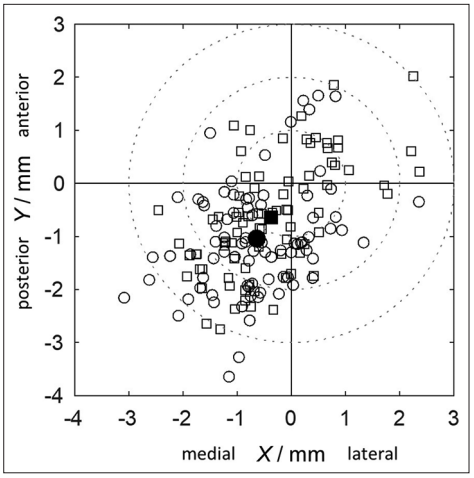

Figure 5: Points of penetration of all brain leads in the axial plane of the target relative to the target point at the origin. This is effectively a graphical representation of AE magnitude and direction. First side implantations are represented by open squares and second side implantations by open circles. The corresponding mean AE for first and second side implantations are denoted by the solid square and circle, respectively. Dotted circles represent radii of 1 mm, 2 mm, and 3 mm from the target. The sign of the X-coordinate for the left-sided electrodes has been reversed to allow right- and left-sided implantations to be visualized on common axes. Second side implantation is associated independently with significantly more posterior implantation error. AE: Axial error.

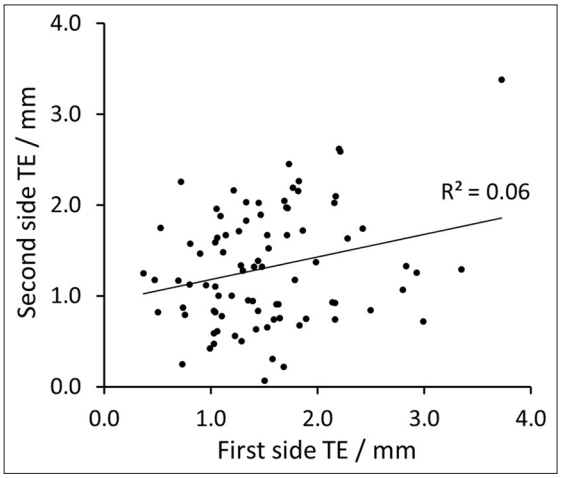

Figure 6: Linear regression plot of TE for electrodes implanted second during bilateral surgery versus those implanted first. TE between the two sides is significantly correlated (r = 0.252, P < 0.05) but the low coefficient of determination means that error on one side does not predict well that on the other side. TE: Trajectory error.

Table 2: Estimate of fixed effects on dependent variable TE for the independent variables studied.

Variable	Estimate (95% CI)	Sig.
Age	−0.005 (−0.017, 0.008)	0.449
Sex	0.160 (−0.082, 0.402)	0.193
Order	−0.000 (−0.007, 0.007)	0.982
Staged	−0.098 (−0.373, 0.177)	0.481
GA	0.002 (−0.395, 0.399)	0.982
MRI	0.044 (−0.203, 0.290)	0.481
GA_MRI	0.239 (−0.194, 0.672)	0.992
Electrode	−0.032 (−0.167, 0.104)	0.727
Target	0.019 (−0.184, 0.222)	0.277
Side_order	0.260 (0.064, 0.456)	**0.010***
Frame	−0.362 (−0.583, −0.142)	**0.001***
Surgeon	0.163 (−0.115, 0.441)	0.249
Coronal_angle (per °)	−0.037 (−0.066, −0.008)	**0.013***
Sagittal_angle (per °)	0.001 (−0.015, 0.017)	0.875
pneumocephalus (per mL)	−0.000 (−0.000, 0.000)	0.506
Frame-MCP (per mm)	0.010 (−0.000, 0.021)	0.058

Sig.: Significance. *P<0.05, GA: General anaesthesia, MRI: Magnetic resonance imaging, MCP: Midcommissural point, TE: Trajectory error, CI: Confidence interval. Significant results highlighted in bold

Table 3: Estimates of fixed effects in each dimension. Includes only the three independent variables significantly associated with TE applied to three models examining errors in X, Y, and Z dimensions with TE_x, TE_y, and TE_z as dependent variables, respectively.

Dimension	Variable	Estimate (95% CI)	Sig.
X	Side_order	−0.138 (−0.380, 0.104)	0.262
	Frame	0.015 (−0.239, 0.269)	0.909
	Coronal_angle	0.011 (−0.020, 0.041)	0.502
Y	Side_order	−0.284 (−0.484, −0.083)	**0.006***
	Frame	−0.657 (−0.875, (−0.438)	**<0.001***
	Coronal_angle	0.049 (0.022, 0.075)	**<0.001***
Z	Side_order	0.210 (0.056, 0.364)	**0.008***
	Frame	0.364 (0.142, 0.586)	**0.001***
	Coronal_angle	−0.024 (−0.049, 0.001)	0.058

Sig.: Significance, *P<0.05, CI: Confidence interval, TE: Trajectory error. Significant results highlighted in bold

the target locus usually still remains within an acceptable distance of a contact within the electrode's active zone unless the advancement error is very large, which is rare in our experience. While it appears to result in a smaller volume of intracranial air than surgery through burr hole [Figure 3],[2] we acknowledge that our technique of twist drill craniostomy and lead anchoring with a small plate is potentially vulnerable

to small advancement errors compared to other methods, such as the use of intraoperative image intensifiers or burr-hole anchoring devices.[17,51] Furthermore, advancement error is relatively simple to address by withdrawal or advancement of the lead along the existing trajectory *in situ,* whereas correction of a large TE requires repeat implantation. Therefore, we focused the analysis on errors relating to the trajectory, which can cause contacts to be placed away from the target. We appreciate that in other settings and workflows, examination of TTE may be of greater interest.

Other measures of error often described are the 3D error and Euclidean error, which variably denote either TTE or the discrepancy between intended and actual positions of a pre-specified electrode contact,[6,7,11,28,32] which we did not examine here but could potentially be susceptible to the same advancement-related drawback. This justifies examination of other measures such as TE and AE (often referred to as radial error), both of which have been used previously in the literature.[7,9,20,30,32,39,45,50] We demonstrate that TE and AE are closely and linearly related, though AE has the disadvantage of losing information in the superoinferior (Z) dimension and being strictly undefined in a small number of cases in which an electrode fails to intercept the axial plane of the target. However, AE has utility for error visualization when AE as a vector is plotted in two dimensions, it provides a way of appraising the magnitude and direction of targeting error that is intuitive to most practitioners in mirroring cross-sectional imaging in the axial plane [Figure 5]. We show further that errors on both sides in bilateral surgery are weakly correlated, suggesting either that erroneous first side implantation is to a small extent causative of error in the second side or that there are error-causing factors in the procedure which are common to both sides.

Targeting accuracy comprises three main concepts.[35] The first is accuracy which is a measure of average closeness to the target such that an accurate process yields low average error. The second is unbiasedness which is a measure of central tendency, such that an unbiased process results in errors that are spatially evenly distributed around the target with a zero average. The third is precision which is a measure of dispersion or variability in placement. In terms of accuracy, our mean scalar TE of 1.4 mm compares favorably with that quoted by other centers in the published literature,[32] while analysis of vector components revealed a small but significant sub-millimeter bias toward a closest point that is medial, posterior, and superior to the target. This posteromedial tendency has also been observed by others who have suggested applying correction factors to compensate for it.[10,20,21,36] It is worth noting that with frontolateral entry points, posterior implantation will necessarily place the perpendicular point of closest approach of the electrode superior to the target locus. The TE SD of 0.7 mm, which relates to precision, also compares well against measures reported in the literature.[32] In practice, we have not had to resite any implanted electrodes on suspicion of inadequate therapeutic effect from suboptimal placement. We speculate that the posteromedial implantation tendency, which is exhibited by most cases with the largest magnitude TE, may be pragmatically well-tolerated in the majority of our implanted patients in whom the STN is targeted for Parkinson's disease, as displacement in this direction encroaches on the caudal zona incerta in the posterior subthalamic area, which can be another effective target in this condition.[3,20,39,43] It is also in a direction away from internal capsular fibers and would, therefore, increase the threshold for stimulation-related motor and speech side-effects.

Targeting error in DBS surgery is cumulative, and many elements are potential contributors. We sought to identify factors within our daily practice that might influence targeting error. Our surgical method, while relatively consistent in its broad approach – for example, in the use of a single type of planning software and stereotactic apparatus, twist drill craniostomy, absence of micro-electrode recording, and metal plate lead anchoring mechanism – still contains a number of procedural variations. We sought to determine what influence these variations within the scope of a single surgeon's practice, as well as differences in basic clinical and demographic parameters may have on measures of targeting error. When assessing the contribution of these factors, it is important to examine the independent impact of the variables to avoid potential confound from covariates, hence the use of multivariate mixed-effect models in this study.

We demonstrate that three procedural factors are independently and significantly associated with sub-millimeter increases in targeting error: (1) second side implantation; (2) one of two specific stereotactic arcs used; and (3) decreasing the coronal approach angle on the implantation trajectory. We further show that second side implantation and the less accurate arc are both associated with significantly posterior and superior implantation to that intended, while the effect of decreasing coronal approach angle was to increase error in the posterior direction.

Second side implantation has previously been considered as a potential source of error, with brain shift and pneumocephalus from first side implantation as potential substrates.[1,18,23,37] Two recent reports highlight this effect, while only one of these reported greater Euclidean error magnitude on the second side compared to the first, both described significantly more AC placement of the second lead, in contrast to our findings.[6,11] One further study similarly showed greater second side error related to volume of pneumocephalus,[1] whereas we found no specific effect of pneumocephalus volume on error.[28] However, many other studies have also shown no difference between the

first and second sides.[2,12,42,47,49] This observed variability in presence or absence and direction of a second side effect suggests that either it is a product of the specific implantation technique used rather than a universal phenomenon, or that, unlike ours, other studies have not looked at the effect independently of other error-related factors.

The effect of coronal approach angle has also been demonstrated previously. Holl *et al*. demonstrated that, in their workflow, an angle of <10° (defined in stereotactic frame space) was associated with less targeting error than angles of 10° or greater.[20] Likewise, Starr *et al*. found that the lateral component of their measured TTE increased with increasing coronal approach angle, although this was explained effectively as an artifact of lead anchoring error, which is more likely to yield error in a horizontal direction as the angle increases.[50] In contrast, we demonstrate that increasing coronal approach angle is independently associated with decreased TE magnitude. This was also observed in another study but associated with error in the medial direction and only when targeting the Vim thalamic nucleus.[27] This was speculated by the authors to be a consequence of greater proximity to the ventricle with "steeper" trajectories. This discrepancy again may reflect the specifics of apparatus and/or technique.

Others have attempted to identify significant influences of stereotactic equipment on targeting errors. In a comprehensive review, Li *et al*. focused part of their investigation on methodological variation between different published series to examine differences between stereotactic systems.[32] With the caveat that publication bias may affect the conclusions drawn from meta-analysis of published accuracy data,[30,40] they demonstrated that average reported targeting errors had generally decreased over time and that newer robotic and intraoperative MRI-based systems appeared to yield less error than conventional frame-based methods. While they sought to establish the effect on targeting error of different stereotactic systems, our observed effect of the stereotactic arc shows that even within a single system, the specific apparatus used has a significant influence. This highlights the importance of regular servicing and calibration of stereotactic equipment, on which the basis of the stereotactic method lies.[35]

Previous studies have taken a similar approach to ours by analyzing procedural factors related to targeting accuracy.[27,36] Among the variables they studied, Mirzadeh *et al*. identified that shorter procedure time, asleep surgery, and frame-based stereotaxy with flat supine positioning versus frameless stereotaxy with 30° head elevation were all associated with increased accuracy.[36] They also noted that error tendencies were target-specific, with a posteromedial tendency, like that observed in our data, seen in STN-targeted implantations which make up the majority of our procedures. Ko *et al*. examined some of the variables studied here, such as target nucleus, implant side, and coronal and sagittal approach angles, and revealed that targeting Vim was more error-prone than targeting STN or globus pallidus pars interna, with a further effect of coronal approach angle, but only on the accuracy of implantations targeting Vim.[27] These analyses reinforce the principle that procedural factors can and do influence targeting errors in DBS.

This study has some limitations. First is the retrospective observational design and the potential associated sources of bias. Second is the contribution of potential discrepancies in CT-MRI registration to the measured targeting error, which is not accounted for in the methodology. A previous study using the same stereotactic planning software determined that this was <0.5 mm in each dimension with the imaging protocols used in the authors' center.[16] Unless there is a confounding relationship between this uncalculated error and variables in our study, which does not appear apparent, then this is unlikely to have an impact on our reported results. Third, while the study includes a large number of implantations, the large number of variables, some with few data points, potentially reduces the power of the statistical analysis to identify significant factors. Fourth, our targeting error measures were made using a single lead localization method, namely, manual reconstruction from immediate post-implantation CT studies, on a single planning software platform, as this pragmatic approach replicates what would commonly be performed as part of a routine clinical workflow. It is possible that delayed imaging after resolution of any pneumocephalus or brain shift gives a more accurate representation of the final lead position.[48] Furthermore, we acknowledge that there are a number of other ways in which DBS leads can be localized, each with relative pros and cons. These include different post-implantation imaging modalities such as standard or intraoperative MRI and intraoperative CT or 3D fluoroscopy,[8,15,24,50] as well as automated lead detection algorithms available in both commercial and open-source software packages such as BrainLAB Elements (BrainLAB AG, Munich, Germany) and Lead-DBS.[18,22] These differences, as well as variations in image fusion algorithms employed by different planning software, are also potential sources of discrepancies in the measurement of errors. The influence of the specific software and lead localization method used on the findings of implantation accuracy analysis, such as that presented here, is not something we set out to address in this work and is a pertinent question for future investigation. Fifth, the factors that we have identified as significantly associated with targeting error still represent only a fraction of the overall error, the remainder of which is stochastic and/or potentially accounted for by variables not considered in this analysis.

CONCLUSION

The extent of systematic DBS targeting accuracy analysis in daily practice is not known, with existing literature indicating

limited and potentially biased reporting. We demonstrate here that TE is a useful method for quantification of DBS implantation accuracy and is closely correlated with AE which is a convenient measure for graphical visualization of the magnitude and spatial distribution of errors. Multivariate analysis of independent procedural and clinical variables can reveal factors independently predictive of magnitude and direction of targeting error, which may be unique to the equipment and technique employed. It is important to acknowledge that most functional neurosurgeons have individual preferences regarding which specific region within a so-called "defined target," they select as the optimal target locus, such as targeting the absolute center of the STN versus its posterior superior part. Nevertheless, we advocate that such systematic error analysis should be routinely performed as part of surgical workflows, regular clinical audit, and registry practices in functional neurosurgery. This is essential in order to benchmark accuracy against real-world data, to highlight relevant associated factors within the scope of each surgeon's practice, and to understand better the relationship between targeting accuracy, electrode location, and risk of suboptimal clinical outcome. Mitigating measures can then be applied if deemed necessary, which might include the application of compensatory correction factors or changes in workflow.

Half a decade on from the data collected here, the senior author continues to use twist drill craniostomy to minimize air ingress and brain shift, but has transitioned to a newer and more frequently maintained stereotactic frame and all DBS operations asleep and only radiofrequency ablation operations awake.

Ethical approval: Institutitional Ethics Committee (IEC)permission obtained for the study under clinical governance provisions (registration number AUDI003419, St George's University Hospitals NHS Foundation Trust, London, U.K.). All procedures performed in studies involving human participants were in accordance with the ethical standards of the UK National Health Service and St George's University Hospitals NHS Foundation Trust and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study had local institutional approval under clinical governance provisions (registration number AUDI003419, St George's University Hospitals NHS Foundation Trust, London, U.K.). Approval granted on 30 January 2023.

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