



## Original Research Article

## Circuitous Goal of bSTN deep brain stimulator in parkinson disease: A study with fusion MRI guided by Computed Axial tomography and microneurosensory recording MER techniques

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## ABSTRACT

In advanced idiopathic Parkinson disease (PD), for targeting the subthalamic-nuclei deep brain stimulation (STN-DBS), the fusion MR and functional magnetic resonance imaging (MRI, fMRI) guided by computed axial tomography (CAT), positron emitted tomography (PET) functional imaging systems and recently DatScan are extensively applied, albeit, the MRI is continually unreachable for entity. The goal of this study was to detect whether the circuitous targeting of STN for DBS employing geometrical stereotactic functional frame based MRI, CAT and microneurosensory recording or microelectrode recording (MER) guidance which are effective and safe methods to establish the factors and parameters that offered and built to effectual outcome. The results showed that the circuitous targeting of STN-DBS employing stereotactic functional neurosurgical frame based CAT and MER in PD subjects were effectual and confined which is consistent with our hypothesis. Better symmetry of the fixation of frame resulted in better outcomes of the STN-DBS particularly when horizontal-deviation was  $\leq 2$ mm and perpendicular-deviation was  $\leq 1$ mm. If the subjects cannot go through the direct imaging modality due to physical problems then circuitous method can be followed. Clinical relevance—in clinical settings fusion techniques is causal and causative and safe treatment to corroborate the factors and parameters that sets outcome. Using quantum computing, the cell imaging can be improved.

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## 1. Introduction

Parkinson disease (PD) is a chronic neurodegenerative disease. Being a multi-component- systemic neurological-disorder, PD presents by fundamental motor and frequently hindering non motoric feature-manifestations.<sup>1,2</sup> Deep brain stimulation of subthalamic nucleus (STN-DBS) is a well distinctive surgical technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease (PD).<sup>1,2</sup> However, the clinical efficacy of DBS depends on accurate targeting of STN via singular plans indeed quite a few (numerous) techniques are applied

and suitable technique is chosen. So far scientists reached the STN through CAT and MRI for the implantation of the electrode with DBS surgery for reducing tremors. However, in the beginning (1993) due to lack of technology scientists implanted the electrodes on trial error based heuristics mechanism. Positron emitted tomography (PET) functional imaging of STN DBS through MRI, STN DBS through CAT; through PET have been applied.<sup>3</sup> Techniques like circuitous targeting through MRI, fusion MRI which involves computed axial tomography (CAT) and magnetic resonance imaging; circuitous targeting of STN through intra operative microelectrode recording had been employed to pinpoint the deep brain stimulus targets.<sup>4</sup> But conducting PD research on human patients particularly on

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idiopathic Parkinson's disease subjects may be due to their cardinal motor features (the signs and symptoms), which includes few problems to patients such as palpable-tremor, rigorous dystonia, claustrophobia, asymmetric tremors like stooped forward with gradient trunk and presumably having complexity and impenetrability in gait.<sup>4–6</sup> Hence, for targeting the STN, the fused techniques such as fusion MRI guided by computed axial tomography (CAT), and PET are largely applied, albeit, MRI is continually unreachable. So, the purpose of this study is to detect whether the circuitous targeting of STN for deep brain stimulus (DBS) employing stereotactic functional frame based MRI, CAT and microelectrode recording (MER).<sup>7</sup> guidance which are effective and safe methods to establish the parameters for effectual results. The circuitous computed axial tomography is employed to spot the subthalamic, whereas microrecording (the micro electrode recording) is applied to verify the best trajectory for exact implantation of microelectrodes based on MER signal patterns (or signatures) of STNs.<sup>2,7</sup>

## 2. Hypothesis/Rationale

### 2.1. Hypothesis

Even though the technique of intra operative ventriculography incorporates in the elimination of cerebrospinal fluid from ventricles<sup>6</sup> which gives dependable detection and discovery of the posterior commissure and anterior-commissure that are historic pointers and sign-posts for circuitous targeting methods.<sup>4</sup> On the contrary to ventriculography, MRI and CAT CT are least insidious—invasive, simplicity, alleviates and done with ease. Since, the hitch with targeting STN is that, it is a small biconvex lens and almond shaped diamond structure and markedly not perceptible on the MRI attributable to need of distinction or contrast and disparity amid STN and the neighboring structures.<sup>8,9</sup> The STN can be visualized on the MRI but other methods such as Lozano's technique where a position 3 mm lateral to the superolateral border of the red nucleus is targeted have been studied and found to be effective areas for stimulation.<sup>10</sup>

Owing to noise and distortion (poor temporal resolutions of MRI), the visibility of STN on MR imaging and also inadequate clarity of the anterior-commissure and posterior-Cummins and subthalamic-nuclei by CT, the amalgamation of stereotactic frame based CAT and magnetic resonance techniques are contemplated to fuse the progress and gaining of the two techniques, augment the spatio-temporal resolutions and precision of the confinement. Plus targeting of the STN and electrophysiological micro-recordings are employed through deep brain stimulus to guarantee the better implantation of microelectrodes along the subthalamic-homunculus<sup>4,11</sup> and to identify MER signatures (or patterns) that correlate with improved motor

symptoms.<sup>2</sup>

But, magnetic resonance neuroimaging on idiopathic Parkinson disease subjects (patients) may be intricate due to their cardinal motoric-feature manifestations that includes few problems to patients such as palpable-tremor, rigorous dystonia asymmetric tremors like stooped forward with gradient trunk and presumably having complexity and impenetrability in gait<sup>4–6</sup>. Therefore, to overcome this limitation in reaching and targeting the STN, it can be hypothesized with fused techniques such as fusion MRI guided by computed axial tomography and electrophysiological micro recordings.

## 3. Aims and Objectives

Fusion MRI methods guided by stereotactic frame based functional computed axial tomography and microelectrode signal recordings are largely applied to target the subthalamic nucleus (i.e., signal patterns or signatures of STN). Yet, MRI is all the way cannot point for an attribute or entity. Hence, the objective of this study was to find out in case if the circuitous targeting of the STN for DBS, via by means of stereotactic geometrical frame-based CAT and electrophysiological techniques of the same kind, analogous, and parallel micro recording from the subthalamic nucleus as well as intra operative stimulus for demarcating the STN, legibly, and perceptibly decipherable.

## 4. Endpoints

Circuitous targeting of STN DBS in Parkinson's disease with fusion MRI guided by CAT and MER will be accomplished examined in this study. The CAT is employed to find the STN, whilst physiological micro electrode recordings of STN signal acquisitions are employed to verify the best path for perfect position of the microelectrodes down the subthalamic-homunculus. This study was performed to investigate whether the use of frame-based stereotactic functional CAT and MERs was accurate for guiding the targeting of STN in DBS and the factors that supported to significant outcome. Due to the circuitous targeting, we paid attention on whether the symmetry of the fixation-of the head-frame straightly exaggerated the subjects' motor progressions.

MRI guidance through CAT and MER in Parkinson's was effectual and protected management for decisive parameters and factors that confer to better result.

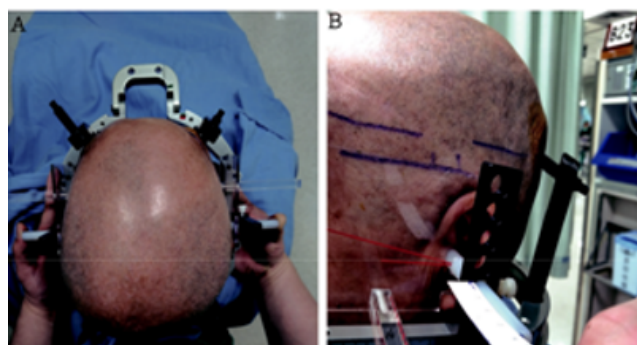
## 5. Materials and Methods

Study Design: A retrospective study was carried out at a medical sciences university tertiary care hospital research centre with a dedicated biomedical and movement disorder unit from South India. 34 patients with diagnosis of PD assessed with Unified Parkinson Disease Rating Scale (UPDRS) stage-III score of Hoehn and Yahr (H&Y)<sup>2</sup> as

per United Kingdom Parkinson Disease Society Brain Bank Criteria (UKPDS-BBC) were included.<sup>2</sup> All 34 subjects were willing to undergo the procedure and fulfilled the following criteria to be eligible for STN-DBS i.e., they had disease duration of 6 years or more, good response to tuned regimen of oral Levodopa (L-dopa, the metabolic precursor of dopamine), able to walk independently in drug “ON” state and had normal cognition. The subjects’ clinical details are recapitulated in the Table. The subjects demonstrated is mean standard error (MSE) or mean standard of the mean (MSEM) for chronic—capricious(variables) or frequency (in %) for categorical—capricious(variables).

### 5.1. Surgery

3.1 All PD patients who were wheelchair or bed bound, had dementia or severe psychiatric disturbances were excluded. The perpendicular and perpendicular distances between the midpoint of the head frame and the brain midline at the septum pellucidum intensity and the greater perimeter of the two-sided lens on a skeletal and undernourished part brain scan by CAT were distinguished as the perpendicular-deviation and perpendicular-variation. Following the anesthesia, a CRW-frame was applied such that the frame was centered on the midline to allow for the maximum symmetry between the right and left hemispheres of the brain such that it was as analogous as probable to the anterior-commissure(AC) to the posterior-Cummins(PC) and right-hemisphere of the brain to the left-hemisphere brain symmetrical-planes (see Figure 1).



**Fig. 1:** (A). Ear strip-chart depicting the equilibrium and perfect arrangement of the CRW-frame. CRW-frame and pinning helped for fixing the frame, and reduce the perpendicular and horizontal-variations between RH-side and LH side.<sup>4</sup>, (B). The head frame was fixed which was medial on the midline, hence setting for symmetry maximally between RH and LH of the brain such that it was concurrent as possible to the AC and PC RH-plane - left HS-plane.<sup>4</sup>

A stereotactic 1 millimeter thickness, section-angle analogous to CRW-frame, and CAT image was acquired with the geometrical frame-based stereotactic computed axial functional tomography (the CAT).

Based on usual geometrical co – ordinates of the target structure of the geometry of the brain-atlas, a circuitous target was chosen for CAT. The projected co – ordinates for the goal position was 12 millimeters cross starting the peduncle, 3 millimeter following the mid-commissural-point, and few-millimeters (4mm to 5mm) under the anterior-commissure and posterior-Cummins-line. The protected Trans frontal lobe trajectory to the object was positioned circa  $\sim 15^\circ$  from the sagittal-plane and  $60^\circ$  to  $70^\circ$  in the frontal and lateral path while avoiding cortical and peri—ventricular—veins. Roughly, touching (more-or-less) the subthalamus, the microrecording signal dynamics and motion movement portrayed augmented amplitudes correlated to the subthalamic-nuclei. Once lead gone on to the STN, the settings of neighboring commotion amplified stridently, and giant-amplitudes (due to stimulus intensity) asymmetrical and uneven lop-sided and spikes through firing-rates by means of frequencies (30Hertz and 70Hertz) depicted. The exit of the tip and tilt of the microelectrode beyond the nucleus subthalamic was signified with a shrink in adjacent-noise and the occurrence of spontaneous impulsive—neuronal-activity (spur of the movement) contrasted along whilst the lead was in the subthalamic-nucleus.

As soon as the neuronal-activity runs into and which was distinctive of the SNpc that was differentiated by the expected dis—charges at 75Hertz to 110Hertz, and then the signal recording was stopped. The inferior circumference of zero (0) contact was embedded in to SNpr. Hence, this zero contact touches contacts 2 or 3 probably positioned behind the retral i.e., dorsal sensorimotor area of nuclei (subthalamic). The length of the unilateral nuclei (dogged by microrecording) was the space linking the microrecording ingress in to nuclei and egress out of nuclei. When it is  $\leq 4$ mm, we impeded the signal-recording following 2-trajectories on both-sides. Since, electrode (3389 consists of 4iridium-platinum cylindrical surfaces with 1.27mm diameter were implanted and hence testing has to done. Therefore, by employing stimulator (externus) intra operative bipolar test stimulus’s for checking the dyskinesia’s were accomplished. The stimulus voltage was steadily augmented from 3volts to 3.5volts. For corroborating the lead contact, subjects undergone for T2-weighted imaging. Following a week of the first implantation, the electrodes were connected to a hypodermic (situated subcutaneously in the epidermis) programmable pulse generator (PPG). Every subject was clinically and technically administered mono polar stimulus and impulses by means of setting the factors—parameters disjointly in the range of 2.5 volts to 4.3volts, with 60mSeconds pulse-width, and 90Hertz to 190Hertz frequency ranges.

To identify MER signatures (or patterns) that correlate with improved motor-symptoms, the electro-

physiological confirmation and fine-tuning of the target region was confirmed by invoking the smart programme—software (Medtronic). The uses of electrophysiological microrecording technique as of the STN and intra-operative stimulus have helped in clearly demarcating the nuclei (subthalamic).<sup>2,4</sup> The following 2Figure 2 and 2 depict the signal acquisition of STN recording.

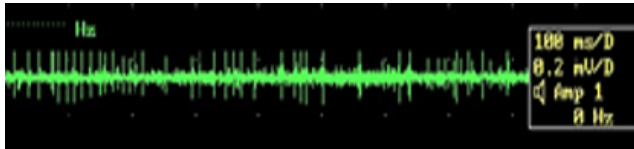


Fig. 2: Microrecording in a discrete-level in a discrete-channel

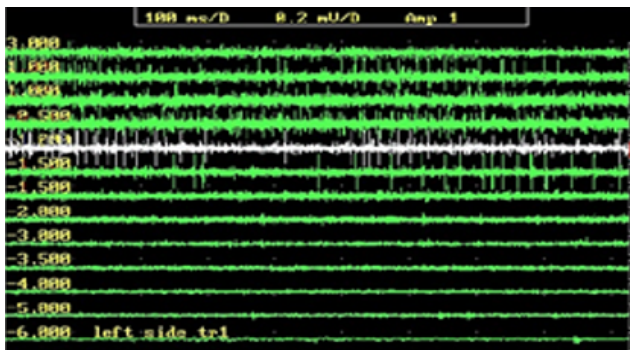


Fig. 3: Microrecording in the central channel over 11mm and showing the typical firing pattern with irregular firing and broad baseline noted from -1.00 onwards. . .

Recording in the mid channel over 11mm and shows the typical firing pattern with asymmetrical and lopsided firing and broad baseline noted from -1.00 levels (Figure 3),<sup>2</sup>

## 5.2. Evaluation

The subjects were evaluated by the Unified Parkinson Disease Rating Scale stage-III-scores. The difference in the post op UPDRS-stage-III scores of the subjects between the DBS “OFF” and “ON” in the “OFF- medication-state” was distinct as depicted in A. The pre op baseline score in med OFF state was distinct as depicted in B and the pace and the progression of UPDRS-stage-III score was distinct as given by  $\frac{A}{B} (100)$ .<sup>12</sup> For the perpendicular-deviation, the CAT picture of septum pellucidum which was very near to anterior-commissure and posterior-Cummins perpendicular line was selected.

The perpendicular distance between the mid-point of the head-frame and the mid-line of brain on a fine tomography scan-part, thickness-of-slice is 1mm; at the septum-pellucidum level was evaluated preoperatively and distinct at the perpendicular deviation showed in (Figure 5) and the



Fig. 4: Computed axial tomography (CAT) image. The perpendicular dashed-line (C to L) pointing towards septum-pellucidum. C is the mid-point of the horizontal line (i.e., on the axis-X).

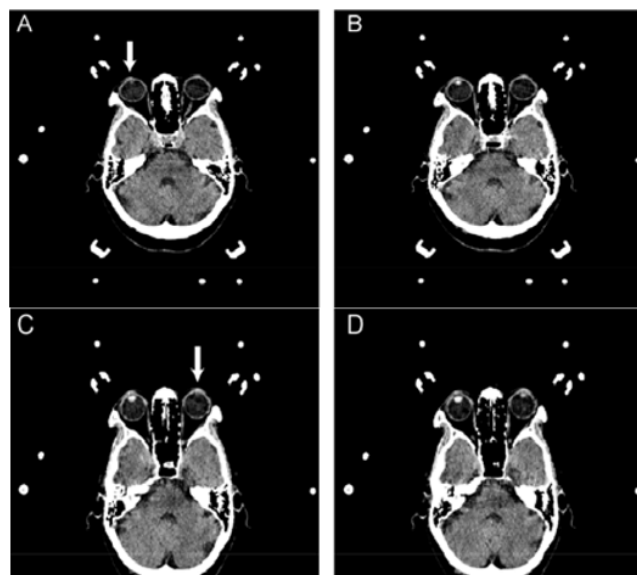
distance of the superior border of the bilateral lens on a skeletal CAT image part is 1mm, i.e., the thickness of slices (ToS) was pre operatively assessed which is distinctive as depicted in Figure 5 as perpendicular deviation.

By applying the microrecording system, the duration (distance end to end –length) of the nuclei (subthalamic) was distinguished as an average of the space between the star-point (SP) and the end-points (EP) of the bSTN. The dimension—magnitude—of-STN was 5.9mm (by the antero-posterior AP), 3.7mm (by means of medio-lateral ML), and 5mm (via d dorso-ventral DL).<sup>13</sup> Hence, the entry paths of the micro-recordings in to sub-thalamic-nuclei in the AL direction were verified that the proper measuring distance of the STN was between 4 and 6 mm.

## 5.3. Clinico—statistical analysis

Constant—capricious (variables) are demonstrated in Table 1 .

As the mean-standard-error (MSE) or mean standard-error-of-mean (SEM), whilst categorical-variables are demonstrated via frequencies/percentages (%). The dissimilarities of positive-effects versus adverse-effects were computed by sample t-tests for constant capricious (variables) and/or  $\chi^2$  test for categorical variables. The chi-square  $\chi^2 @ 4.2866$  for 1 degree of freedom, which is significant at 5%, with  $p \leq 0.05$ , with  $\chi^2 @ 9.2857$ , with 2 degree of freedom which is highly significant at 5% with  $p \leq 0.0089$ . A series of uni-variate



**Fig. 5:** A—B. CAT images for DBS operation with an interval distance of each 1mm (serially). Image A shows the better boarder of the right-lens indicated with down-arrow; left-lens was unavailable in this picture. C— D. Superior boarder of the left-lens (showed with down arrow. The perpendicular-deviation was calculated from image (serial) as 2mm.

linear-regression was done for making out factors which were potentially connected by the progressions in the UPDRS-scores. The p-values  $\leq 0.03$  considered in this study for the variables.

#### 5.4. Findings

The clinical details of all the subjects recapitulated in the Table 1. Following the therapeutic DBS surgical-operation, subject UPDRS-stage-III-scores progressed by  $48 \pm 2.8\%$  in the range of 20 to 81 measured up to subject's baseline OFF-levedopa (medication OFF) scores. Mean recorded length difference of the STN among the first and last single recording trajectories was  $5.37 \pm 0.16$  millimeters in the range of 3.99 to 7.50. The UPDRS-stage-III score progress was 48 and 2.8%. As per the micro signal recording (MER), the MSE length of the nuclei (subthalamic) was 5.37mm and 0.16mm in the range of 3.99 to 7.50. The mean of standard error mean or mean standard error (MSE) of bSTN stimulus factors of pulse-width, current-voltage, and frequency was  $60 \pm 0$ ,  $3.3 \pm 0.06$ , and  $135.48 \pm 4.93$ . The magnitude of the MSE, i.e., volume of the pneumo-cephali in the post op MRI was  $5.29 \pm 2.02$  Cubic-centimeters (CC) in the range of 0 to 59. The MSE horizontal-deviation was  $1.7 \text{mm} \pm 1.2 \text{mm}$  in the range of 0mm to 5mm, and the perpendicular MSE deviation was  $1.2 \text{mm} \pm 0.7 \text{mm}$  in the range of 0mm to 2mm.

Multiple linear-regression-analysis (LRA) disclosed the augmented lengths of perpendicular-regression-coefficients (PRC) B:-0.0626; with high degree 95% of confidence interval (CI):-0.113 to -0.013, and perpendicular deviations B:-0.0497, 95%CI:-0.083 to -0.017 were coupled with less progression in the subjects on the UPD rating scale. Even though, the lead insertions can be executed by means of higher frequencies eventually, the lead insertion errors can takes place in all the modalities, such as imaging modalities, planning, frame, in opening of the burr hole, frame application fiducially, imaging and planning, burr hole opening, electrode insertion, and lead-fixation. As the targeting precision is distressed in various operational-steps, each pace desires to be meticulously and methodically observed to reduce potential errors if any.

#### 6. Conclusion

The results showed that the circuitous targeting of STN-DBS employing stereotactic functional neurosurgical frame based CAT and MER in PD subjects were effectual and confined which is consistent with our hypothesis. Better symmetry of the fixation of frame resulted in better outcomes of the STN-DBS particularly when horizontal-deviation was  $\leq 2 \text{mm}$  and perpendicular-deviation was  $\leq 1 \text{mm}$ . If the subjects cannot go through the direct imaging modality due to physical problems then circuitous method can be followed. In this study, microrecording (MER) yielded the proof of correct-positioning of microelectrodes,

**Table 1:** Clinical details of Parkinson disease subjects (patients)

Capricious(variables)	Mean standard error (MSE)
Number of subjects (PD patients)	36
Age of the patients	$58.9 \pm 1.6$
Gender (male, female)	
male%	23 (67.6470 ~ 68%)
Duration of disease (yrs)	$14.6 \pm 0.9$
UPDRS-Stage-III, "Med OFF" (Pre op)	$48.9 \pm 1.7$
UPDRS-Stage-II, "Med OFF" (Pre op)	$20.28 \pm 0.38$
UPDRS-Stage-I, "Med OFF" (Pre op)	$2.94 \pm 0.8$
Clinical rating of dementia (pre op)	$0.29 \pm 0.05$
MMSE (pre op)	$26.48 \pm 0.47$
Response of L-Dopa	$46 \pm 3$
ADL pre op, "Med OFF"	$50.76 \pm 4.41$
Rating scale of depression	$2.06 \pm 0.56$
H&F stage, "Med OFF" (pre op)	$3.36 \pm 0.12$
Progress	$48 \pm 2.8$

ensured accurate-detection of STN and detected its exact coordinates in a more objective way.<sup>2</sup> MER boosts safety, accuracy and efficacy of DBS-electrode execution. The availability of MER results in a vast data vis-à-vis functioning on neurons positioned-deep in the brain may further help in untangling esoteric of brain.<sup>2</sup>

## 7. Authors contribution

This study designed and developed by the first author and computational work was done by the rest of the authors.

## 8. Source of Funding

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## 9. Conflicts of Interest

None.

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