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Original Research Article

# Induced micro lesion effect on cardinal motor features of Parkinson's: A study with iMER signals of subthalamic-nuclei deep brain stimulations (Electrode-Implantation) by DBS

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ABSTRACT

Induced micro lesion effect ( **$\mu$LE)** on basic motor symptoms of Parkinson's showing good results with the intra operative micro electrode recordings (iMER) of subthalamic-nuclei (STN) signals (patterns or signatures of STN) all through deep brain stimulations (DBS). MER-induced **$\mu$LE** was computed based on the difference between tremor, rigidity, and Bradykinesia (akinesia) scores in the pre op off-state and intra op on state following MER prior to test stimulus. To study the induced micro lesion effect on cardinal motoric feature-manifestations (symptoms) of Parkinson's during the subthalamic nuclei deep brain stimulations by the intra operative microelectrode recordings. *Clinical Relevance* — stimulated intra operative microelectrode recordings micro lesion effect progressed the motor-manifestations of Parkinson's. However, uncorrelated by the electrodes employed for the period of the process. MER-induced $\mu$LE was computed based on the difference between tremor, akinesia/Bradykinesia, and rigidity scores in the pre operative OFF state and intra operative state prior to stimulus-test experiment subsequent with micro electrode recording The MLE scores were enhanced by circa ~ 22% on Brains left hemisphere (BLH) and by ~14% on Brains right hemisphere (BRH) from zero line, i.e., electrical base line ($p<0.05$). Tremor scores were progressed by ~32% (BLH) and by 14% (BRH) and ($p<0.05$), rigidity scores improved by 17.3% (BLH) and by 14.2% (BRH) ($p<0.05$) and Bradykinesia scores improved by 20.6% (BLH) and by 11.5% (BRH) and ($p<0.05$) from baseline. There was no significant difference between $\mu$LE and the number of microelectrodes used ($p>0.05$). Stimulated intra operative microelectrode recordings and $\mu$LE progressed the motor-manifestations of Parkinson's, yet, uncorrelated by the electrodes employed for the period of process.



## 1. Introduction

Deep brain stimulation or stimulator (DBS) is a surgical restorative therapy (therapeutic surgical procedure) for the patients of advanced idiopathic Parkinson disease (PD)[1–8]. Induced deep brain stimulations can be carried out by means of intra operative micro electrode signal recording (MER).[9–12] However, detection of STN neurons signatures, i.e., patterns is difficult with sole DBS. The problem with targeting STN is that, it is a undersized (few millimeters in diameter - miniature size) biconvex lens almond shaped diamond structured, not visible while tracing through magnetic resonance imaging (MRI) as a result of lack of contrast among the STN and the adjoining–neighboring

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brain sub-structures.[8,9] The STN can be visualized on the MRI but other methods such as Lozano's technic[10] somewhere a point 3 mm lateral to the superolateral border of the red-nucleus is targeted have been observed and found to be successful regions' for stimulus.[10] The diameter of STN is extremely and exceedingly unpredictable, emerging to be designate slighter and to be found located more tangential and posterior—lateral on MRI images than in atlases. Hence, researchers must be concerned in relying on coordinates virtual to the commissures for targeting of subthalamic nuclei.

As the MRI techniques are not absolutely perfect, use of electrophysiological techniques such as microelectrode recording from the subthalamic nucleus as well as intra-operative stimulations can help in clearly demarcating the STN.

Microelectrode recording can identify subthalamic neurons by their characteristic bursting pattern and their signals clearly identify the nucleus form the surrounding structures. On table stimulation is studied to ensure that the there is optimal benefit with the least side effects and this is the final test to ensure the correct targeting of the STN.

Therefore, Microrecording (the microelectrode recording "MER") is useful for identifying subthalamic-nuclei (STN) neurons patterns ("signatures"). The micro electrode signal recording can be adjunctified in the progress spontaneously of cardinal motor features of PD termed as "micro lesion effect." Though, the fact accepted its impact on Parkinson disease motor features not known objectively. This study investigated fifty two subjects with Parkinson disease, particularly, with the micro-lesion-effect on motor signs and symptoms and its correlation with the pre operative L-Dopa (a metabolic precursor of dopamine chemical messengers) in STN-DBS surgery.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment in patients with Parkinson′s disease (PD).[5,8,13] DBS can be performed with or without intraoperative microelectrode recording (MER).[9–12] MER can be accompanied by spontaneous improvement of Parkinsonian motor symptoms, referred to as the microlesion effect (MLE).[3] Although this phenomenon is widely recognized, its quantitative impact on motor symptoms is unknown. In this prospective study, the MLE on motor symptoms and its correlation with the preoperative levodopa response (LR) was investigated in 30 patients with PD who underwent DBS of the STN.

## 2. Objective

The aim is to study the effectiveness of MER and differentiate induced micro lesion result on cardinal motor feature-manifestations of Parkinson disease patients' undergone subthalamic-nuclei deep brain stimulation. MER-induced MLE was evaluated based on the difference between tremor, rigidity, and bradykinesia scores in the preoperative off-state and intraoperative state following MER and before test stimulation.

*Clinical Relevance*—MER-induced MLE improved motor symptoms and was not correlated with the number of microelectrodes used during the procedure.

## 3. Methods and Materials

Fifty two subjects by means of Parkinson disease (PD) were included in the study. Subjects with advanced idiopathic PD of six years amid good response to L-Dopa (a metabolic precursor of dopamine) and Hoehn and Yahr (H & Y ) score of less than four through normal standard cognition (eligible for surgery) were incorporated in this study. Surgery was planned using a stereotactic Cosmon-Roberts-Wells (CRW) frame that has a luminant magnetic resonance image localizer. CRW frame with an MRI protocol using Medtronic five channel Framelink programming (encoding) software. By employing the micro electrode signal recording (MER) machine for the STN signatures (i.e., patterns) was executed in all subjects extending from 10 millimeters (mm) above target to 10 mm below the STN. Closing target medley was based on the effects and dyskinesias (side-effects) of induced macro stimuli (macrostimulation) and long-established by postoperative magnetic resonance imaging.

Study period was between the period of 2011–2017. Ethical clearance was obtained following HELSINKI principles.

### *3.1. Preoperative Examination*

In all patients, tremor, rigidity, and Bradykinesia were assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) part III[6] score in the preoperative off-state.

### *3.2. Surgery and intra operative microelectrode recording*

52 subjects with PD were included in the study. Subjects with advanced PD of >5 years with good response to levodopa and H and Y score of <4 with normal cognition were eligible for surgery. Surgery was planned using a CRW frame with an MRI protocol using Framelink software with 5 channels. Microelectrode recording was performed in all subjects extending from 10 mm above target to 10 mm below STN. Final target selection was based on the effects and side effects of macrostimulation and confirmed by post op MRI.

Before the surgery (12 hours), the levodopa (antiparkinsonian-drugs) medication was off (med-off). All patients underwent preoperative magnetic resonance imaging (MRI) scanning, consisting of 1 millimeter T1 axial images, with and without gadolinium, and 2 millimeters T2-axial images (Siemens, 3–Tesla MR scanner, Erlangen,

Germany). The STN was visualized by direct targeting using T2-weighted MRI and the trajectory was planned. The number of MER electrodes used depended on the vasculature visualized using T1weighted MRI with gadolinium enhancement (Framelink 5, Medtronic Inc. Minneapolis, USA). The Leksell G frame was mounted and a stereotactic computerized tomography (CT) was performed without contrast and with a slice thickness of 1 mm (Aquillon 16 CT scanner, Toshiba, Tokyo, Japan) on the day of surgery. The MR imaging and computed axial tomography was fused—synthesized to compute the stereotactic functional frame coordinates, DBS surgery was initiated under local anesthesia for optimal MER and neurological examination. A precoronal burr hole was made on the most affected site. MER was performed using polyamide-coated tungsten microelectrodes (Medtronic; microelectrode 291; 10-$\mu$m width, impedance 1.1 $\pm$ 0.4 M$\Omega$; measured at 220 Hz) in 1-mm steps from 10 mm above the target for the first 5 and thereafter in 0.5 mm steps until the termination of STN activity and initiation of substantia nigra pars reticulata (SNpr) activity. Signals were recorded using the Lead Point System (Medtronic, Minneapolis, USA). The STN has a typical electrophysiological activity comprising high-voltage spikes, cells firing in the burst mode, and an obvious widening of the background. Before performing test stimulation using the same electrodes, patients were examined by the neurologist and baseline values for the tremor, rigidity, and bradykinesia were obtained according to the UPDRS part III scores. The microelectrode with the most typical STN pattern over the longest distance was always selected first for test stimulation. On achieving positive clinical results using lower stimulation amplitude with side effects being absent or only present at higher amplitudes, the microelectrode was withdrawn and replaced by a permanent lead (Model 3389; Medtronic, Minneapolis, USA). On achieving unsatisfying effects during test stimulation, another trajectory was chosen for clinical evaluation. The same procedure was performed on the contralateral side. MRI was performed to evaluate the position of the permanent leads and detect asymptomatic bleeding or other structural complications, following which the pulse generator (Activa PC; Medtronic, Minneapolis, USA) was placed under general anesthesia.

### *3.3. Computation of micro lesion effect*

MER-induced MLE was calculated based on the difference in tremor, rigidity, and bradykinesia scores between the preoperative off-state and the intra-operative state following MER and before test stimulation.

### *3.4. Calculation of MLE*

MER-induced MLE was calculated based on the difference in tremor, rigidity, and bradykinesia scores between the preoperative off-state and the intra-operative state following MER and before test stimulation. Statistical Analysis: Data are presented as mean $\pm$ SD. The SPSS Version 15.0 was used for statistical analysis. The data observed was abnormally distributed, and therefore, between-group differences were analyzed non-parametrically. The Wilcoxon signed ranks test was used to compare the motor scores in the preoperative off-state and the period after IM. The correlations between LR, age, and disease duration with the MLE were investigated using Spearman rho correlation test. $p<0.05$ was considered statistically significant. Micro-lesion-effect (with microrecording-induced) was assessed based on the difference between tremor, rigidity, and Bradykinesia scores in the preoperative off-state and intra operative state following MER and before test stimulation.

### *3.5. Clinico—statistical analysis*

Data are presented as mean $\pm$ SD. The SPSS Version 15.0 was used for statistical analysis. The data observed was abnormally distributed, and therefore, between-group differences were analyzed non-parametrically. The Wilcoxon signed ranks test was used to compare the motor scores in the preoperative off-state and the period after IM. The correlations between LR, age, and disease duration with the MLE were investigated using Spearman $\rho$ rho correlation test. The Pearson's $p<0.05$ was considered statistically significant.

## 4. Results and Discussion

## 5. Results

Fifty nine Parkinson's (Parkinson disease) subjects underwent the bilateral subthalamic-nuclei deep brain stimulation (STN-DBS) at our tertiary care hospital and research center in south India. Ethical clearance/approval obtained from the board following Helsinki principles. 59 needles (leads) were entrenched and 171 stimulus-electrodes applied for acquiring the signals of subthalamic nucleus (STN) neurons with microelectrode recording system (MER, 5 channels Framelink, Medtronic). In total 3 electrodes were exploited to acquire the STN neural data (MER signals of each neuron of dorsal STN). Subjects' clinical demography - gender-allocation, mean-age, mean-age at the onset/ disease duration, and focal-margin is given in Table 1 . Scores of Micro lesion were progressed by 13.6% in the right hemispheric brain (RHB) and 21.7% in the left-hemispheric brain (LHB) from (electrical) baseline and statistically significant $\chi^2$ @ 4.2857 for 1 degree of freedom, which significant at 5% with $p \leq 0.005$. Table 2 shows the pre and intra operative scores recorded with MER system. There is a significant disparity seen in all motor sub scores in focal-margins assignable to micro legion effect (significant at 5% ($p<0.005$, $\chi^2$ @9.2958 with

**Table 1:** Number of electrodes and data employed in the study (pre op)

| Parkinson Subjects | Gender | Maturity (Age) | Disease length (Yrs) | Response of Levedopa (RoL %) | Principal limit | # of electrodes |
|---|---|---|---|---|---|---|
| 30 | M:19(63%) F:11(37%) | 53±9 | 8.8±2.8 | 55±15 | R:11(37%) L:19(63%) | R: 2.9±1.2 L: 2.7±1.1 |

2 degree of freedom). Tremor scores progressed (14.3% in RHB and 31.6% ($p<0.05$), followed by Bradykinesia (11.6% and 20.7%, $p<0.05$) and rigidity (14.3% and 17.4%, $p<0.05$) from baseline. MLE was more pronounced for tremor and Bradykinesia, compared to rigidity. Comparing with rigidity, micro-lesion-effect was marked more. Scores progressed on the whole were: RHB 13.7 and LHB 21.8% and also no significant difference among the electrodes used and micro-lesion-effect. Since the micro-lesion-effect score was high in LHB and hence no correlation was found among those two ($p>0.05$).

## 6. Discussion

The present study demonstrates that substantial MLE occurs following MER. In the literature, discussions on the mechanisms of MLE are limited and include those on perifocal edema, metabolic change, and local immunological reactions within the tissue around the electrode.[7,14,15] Sitburana et al. have investigated MLE on essential tremor in patients with PD who underwent DBS of the thalamic ventral intermediate nucleus without MER.[14] They had assessed solely the tremor response of MLE preoperatively, at 24-h post-operatively, at initial activation, and at the 6-month follow-up. In their study, three quarters of patients had a moderate-to-marked MLE. They concluded that MLE had minimal long-term clinical effects, except for allowing for lower DBS settings (patients with a marked MLE had mildly lower DBS parameters). In another study, Tykocki et al. have evaluated the MLE in patients with PD who underwent DBS of the STN.[16] They used 2–5 microelectrodes for MER on each side. Authors assessed the UPDRS-III motor score preoperatively, within 48 hours of electrode implantation, and at the 6-month follow-up. They found MLE in the early postoperative period and observed a positive correlation between MLE and the degree of improvement with active stimulation. Similarly, Cersosimo et al. studied MLE in patients with PD and dystonia who underwent pallidal DBS with MER.[2] They found that MLE continued in 10 of 11 patients with PD and in 8 of 9 patients with dystonia after 6 months of Gpi-DBS. Their study concluded that the presence of MLE after electrode implantation in the Gpi may help predict motor benefit from DBS in patients with PD.

Furthermore, we also observed that MLE had the greatest effect on bradykinesia symptoms. Effects on rigidity were less than those observed for both tremor and bradykinesia. However, these findings were inconsistent with Derrey et al.'s results, which demonstrated improvement rates of 42% (tremor), 37% (rigidity), and 25% (bradykinesia) from baseline.[4] Moreover, in Derrey et al.'s study, MLE was assessed on day 3 following DBS of the STN with MER, after at least 12 h of non-dopaminergic treatment, and before pulse generator placement. They found a 27% improvement ratio in the motor score (UPDRS part III) of MLE compared with baseline (off-state) levels.

In the present study, it was hypothesized that MLE is unre-lated to the number of microelectrodes because the micro-electrodes were placed in the STN at a distance of 2 mm. The approximate STN size is as follows: AP: 5.9 mm, ML: 3.7 mm, and IS: 5 mm.[1] Therefore, the motor part of the STN has less volume than the whole and a precise MER-related MLE is not accurately observed in the motor part because the electrodes were located in the limbic or associative parts of the STN. From an electrophysiological perspective, the motor part of the STN is not different from other parts of the STN. Because the limbic and associative side effects related to MLE following DBS of the STN were not evaluated in the present study, only the relation between the number of microelectrodes used and MLE was evaluated. STN is a small but crucial junction of the basal ganglia complex that has emotional, cognitive, and motor behavioral functions. Mallet et al. have studied the emotional and motor aspects of behavior following stimulation of STN sub-regions using Atlas/MRI-based localization after DBS of the STN. They observed a hypomanic state when the stimulation was localized to the anteromedial STN; both this contact and the contact immediately dorsal to it improved the parkinsonian motor symptoms. However, the most dorsal and ventral contacts, which are located at the boundaries of the STN, neither induced the behavioral disorder nor improved motor performance. They concluded that the STN is a complex and multifunctional structure, which integrates the motor, cognitive, and emotional components of basal ganglia-controlled behaviors.[17]

## 7. Conclusion

MER-induced MLE improved motor symptoms and was not correlated with the number of microelectrodes used during

**Table 2:** Evaluation of pre op, intra post op motor scores of micro electrode recordings

| | ToRH Score | ToLH Score | A/BoRH Score | A/BoLH Score | RoRH Score | RoLH Score | Full SoRH(Totality) | Full SoLH (Totality) |
|---|---|---|---|---|---|---|---|---|
| Preoperative Scores (on off medication) | 2.1±0.8 | 1.9 ±1.3 | 2.6±0.7 | 2.9±0.8 | 2.1±0.8 | 2.3±1 | 2.2±0.2 | 2.3±0.5 |
| Intra postoperative motor scores of MER | 1.8±0.9 | 1.3±1.2 | 2.3±0.7 | 2.3±0.8 | 1.8±0.9 | 1.9±1 | 1.9±0.2 | 1.8±0.5 |
| Progress % | 14.2 | 31.5 | 11.5 | 20.6 | 14.2 | 17.3 | 13.6 | 21.7 |
| Pearson's correlation ($\sigma$) P-value | 0.004 | 0.001 | 0.02 | 0.00 | 0.002 | 0.02 | 0.002 | 0.00 |

ToRH: Tremor on Right Hemisphere, ToLH: Tremor on Left Hemisphere, A/BoRH: Akinesia/Bradykinesia on Right Hemisphere, A/BoLH: Akinesia/Bradykinesia on Left Hemisphere, SoRH: Score on Right Hemisphere, SoLH: Score on Left Hemisphere.
$\chi^2$ @ 4.2857 for 1 df, which significant at 5% with p = 0.0283
with a $\chi^2$ @ 9.2857 with 2 df, highly significant at 5% with p = 0.0045 highly significant.
with a $\chi^2$ @ 9.21 with 2 df which is significant at 5% with p =0.0015.

the procedure. The results with respect to assumptions and design variables used in this study can be enlightened. Some of these parameters can be combined for an integrated parameter approach that may provide better insights for patient management.

## 8. Authors Contribution

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

## 9. Source of Funding

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## 10. Conflicts of Interest

None.

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