IP Indian Journal of Neurosciences 2022;8(1):57–63

Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Original Research Article

Subthalamic nucleus projection by SVM based MER Data via deep brain stimulation: A study of spike uncovering

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ARTICLE INFO

Article history:
Received 16-01-2022
Accepted 21-02-2022
Available online 05-03-2022

Keywords:
Deep brain stimulation
Local field potentials
Microelectrode recording Parkinson's disease
Microelectrodes
Singleunit recording
Sub thalamic (or Subthalamic)
Nucleus

ABSTRACT

This study was conducted at a medical university tertiary care hospital and research center of dedicated Parkinson and movement disorders unit in Hyderabad (South India) with a purpose to optimize projection of STN by applying M.E.R patterns analytically. 52 locally anesthetized Parkinson's (diseased subjects/patients) underwent bilateral S.T.N-D.B.S. Concurrent M.E.R signal recording was done in a Ben's-gun pattern setup with a 5core-pentode (5microelectrodes were set in an array scenario). Using spikes and circumstantial (or contextual) background-activity dissimilar parameters plus their phantom estimates in various-frequency-bands which include low-frequency(θ :2Hz–7Hz), α:Hz–12Hz, β : $13Hz$–$20Hz$ (sub-divided as low-β) and superior β:21Hz–30Hz and γ:31Hz-49Hz were computed. The ideal electrode implantation through better clinical-effect/dyskinesia ratio given to the peak spike-rate(S.R) in 86% of the implant. The amplitude mean-background activity in low-chucked βfrequency-range(FR) was analogous to right depth in 86% and right-hemisphere position in 95% of the implantation.

1. Introduction

Parkinson's disease (PD) is a brain disorder with distinct molecular, functional, and structural features. It is the complex neurodegenerative disease of the brain that causes tremors, particularly in the elderly–matured, which is, differentiated by the convolution of cardinal motoric-symptoms or feature manifestations, namely, tremor, Bradykinesia/akinesia (slowness of movement, i.e., absence, delay in initiation), rigidity and postural instability. Though clinical-diagnosis and benefits of deep-brain-stimulation (DBS) in subthalamic-nuclei (STN, or s-nuclei) have been established, albeit, how its mechanisms augment motoric-symptoms principally reducing-tremors and motor-fluctuations and restoring and/or increasing motor-functioning have not been fully elucidated.

The STN-DBS was developed as a basic corrective option, is an active therapy for patients with Parkinson's disease (PD)[1] when PD motor symptoms such as tremor, rigidity, and Bradykinesia, and postural instability are not preventive by the medication.[2] However, its success is impeded by limited and some degree of knowledge of restorative mechanisms and the lack of a robust feedback signal for tailoring induced stimulations. The fundamental outcomes of the induced stimuli are for the progress of these key objective motor symptoms. Parkinson disease and the impact of DBS for ideal prognostic response have been shown to be a complex-system (network) level-impact.[3,4] But prognostics and computational observations have shown that the success of STN-DBS varies profoundly in setting the DBS electrodes through superior accuracy obsessed by the sensori-motor

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https://doi.org/10.18231/j.ijn.2022.011

zone of s-nuclei corresponding to the dorso lateral base portion-of-nucleus.[5–9] The somatotopic scenario of sensori-motor zone in STN plus it is relative to movement and tremor in Parkinson subjects has been highly instituted.[10,11] MER gives the correction position of the STN and based on MER signal patterns (signatures), the STN is identified and implanted DBS electrodes.

2. Materials and Methods

52 prospective subjects with Parkinson's Disease (PD) were incorporated in the study. Subjects with advanced idiopathic PD of ≥5 years (>=)and Hoehn and Yahr (H and Y) score of ≤4(<=) with normal cognition were eligible for surgery. Probable subjects who were wheelchair or bed bound, had cognitive impairment/dementia (IC/CD) or severe psychiatric disturbances were excluded. Surgery was planned by applying a Cosman–Roberts–Wells (CRW) (Integra, Burlington, MA, USA) fixed stereotactic frame was set over the subjects head devoid of the transdermic transcutaneous screw obsession which would be necessary in the physical-setting. CRW head frame applied for inflexible fixation (obsession to head-skull(cranium)) for stereo tactic functional-neurosurgery. The frame was fixed to cranium via 4 screws positioned across graphite-posts. Exterior crate, i.e., cage was served as a MR localizer for image registration. The subjects were then positioned in a horizontal (i.e.,-supine) point, including the C.R.W frame firmly fixed to the couch.

The following Figure 1 showing the various stages of the DBS surgical procedure right from the MRI image transformations onto computer operating room via wireless internet, STN-DBS electrode implantation and MER signals recording.

A 7 Tesla MRI protocol using Frame link software with multi channels (a core pentode electrode consists of 5 electrodes arranged in an array) maximum 5 channel electrode. Microelectrode recording was performed in all subjects extending from 10 mm above target to 10 mm below STN ($maximum\ positive + Ve\ to\ maximum\ negative - Ve\ peak, i.e.,\ going\ upto \pm 10mm$). Final target selection was based on the effects and side effects of macro stimulation and confirmed by post-operative MRI.

The subjects mean age was 58.1±9.1 years, mean disease duration was 8.8±3.64 years. Prior to implantation of the DBS electrodes, the mean UPDRS scale stage III+ score in 'off' state was 52.7±10.6 and in 'on' state was 13.4 ± 5.0. Sub thalamic nuclei (STN) microelectrode recordings (MER) were detected in a mean of 3.5±1.1 channels on the right hemisphere side and 3.6 ±1.04 on the left hemisphere side. Final channel selected were most commonly central seen in 42.3% followed by anterior in 33.7%. Concordance of final track with the channel having the highest recording was 58.7%, with the channel showing maximum depth of recording was 48% and with either was 64%. Absence of any recording in the final tract chosen was seen in 6.52%, in these subjects, the tract was preferred based on stimulus results. The intensity of the electrodes were detected through the microelectrode (MER) recordings in 75.6%.

3. DBS Surgery

Based on the CRW frame, the skull was drilled, and 5 microelectrodes were introduced into the brain over five channels -central anterior (front), posterior (back), medial (near midline) and lateral (away from midline). Recording was started from 10 mm above the target determined by the MRI and is extended 10 mm below.

Then stimulation was done with 130Hz, 70 microsecond pulse width and response were seen with increasing amplitude. Whichever channel shows the best response, that is chosen. The first level of MER recording was used to determine the depth of DBS electrode placement - that is if recording starts at -5 level, the lead was placed from that level.

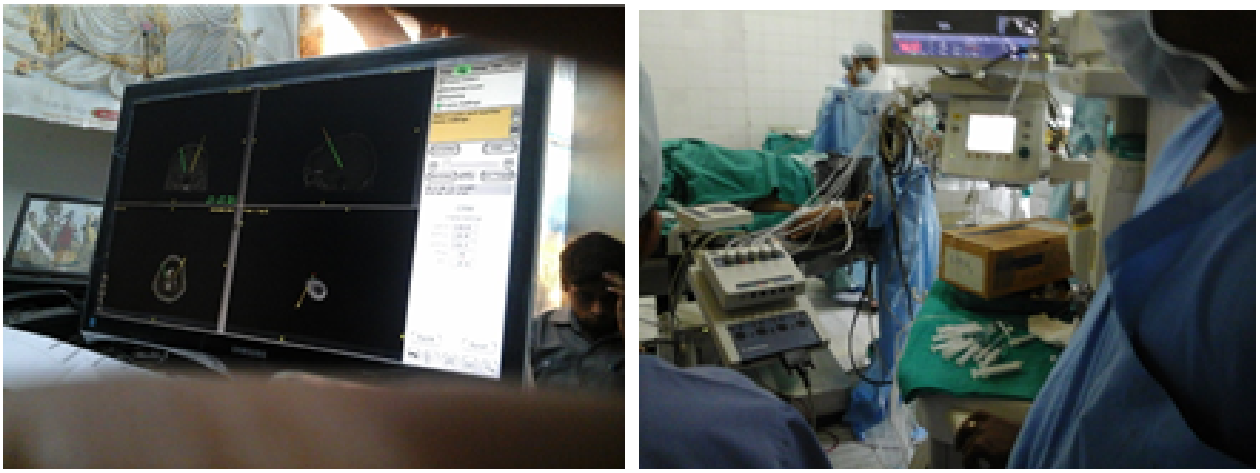
Intra-operative recording was accomplished in all 5 channels. All the five microelectrodes were gradually passed through the STN, and recording was performed from 10mm above to 10mm below (maximum positive +Ve to maximum negative -Ve peak, i.e., going up to ±10mm) the STN was computed on the 7 Tesla functional-MRI.

The channel with maximum recording and the earliest recording was acquired on two sides. Intra operative test stimuli was achieved in all channels from the level at the onset of MER recording. Stimulation was done at 1mv, 3mv to assess the progress in the motoric symptoms, tremor, bradykinesia, and in rigidity. Occurrence of dyskinesias were correlated with precise targeting. Dyskinesias were evaluated at 5mv and 7mv to guarantee that the final channel selected had highest progress in conjunction with least side effects. Correlation was measured amongst the characteristics of MER and the final channel selected in 52 PD subjects (104 sides). The pulse-width was set for 60μSeconds for the duration at 130Hz, and the current-voltage was accustomed to the singular subject. Institute ethical approval was done following the Helsinki affirmation and principles(1975) and the subjects were informed their consent and written permission obtained for their anonymized data to deduce the inferences and for conclusions drawn for the analysis purpose.

A support vector machine (SVM)-based microelectrode recording (MER) system (Medtronic) for acquiring the signals of S.T.N neurons (MER signals with bilateral STN-DBS) was applied.

A sequence of steps during the DBS electrode implantation in a PD subject and simultaneous microelectrode signal recording (MER)

A. Identification of the STN nearby red nucleus B. Instrumentation Setup



C.DBS Surgery D. Making bur hole

E.MER with STN-DBS F. MER signals of STN Neural recording

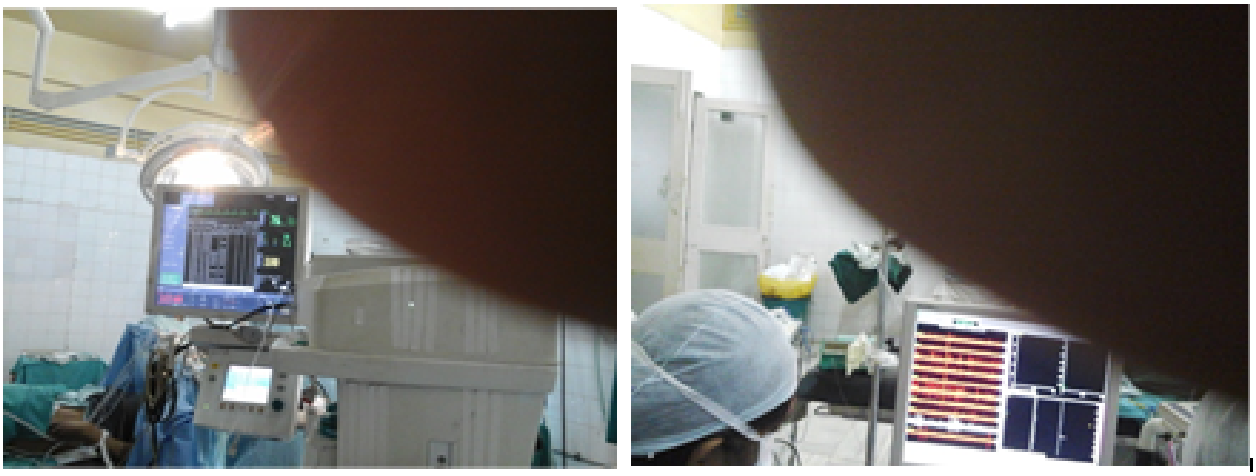


Fig. 1: Implantation of electrode: A complete MER with STN-DBS approach

4. Microeelctrode Recording

The microelectrode signals of sub thalamic nucleus neurons of Parkinson's were recorded from every electrode of pentode microelectrode set which consists of 5 micro electrodes in an array and for two sides separately, implanted in either side (bilateral: right and left hemispheres) of PD brain. MER signals digital data was acquired concurrently from all electrodes arranged in standard Ben's Gun pattern in every hemi sphere (HS) for approximately and virtually 30seconds (mean recording time for the entire cohort was 42.20 ±7.43seconds) with a sampling rate of 24kiloHz. Due to aliasing and heavy ripples, i.e., oscillations, 24kHz sampling rate was used. Contemplating the object site (target-location) at 0mm, MER recordings were acquired from every point at 1mm microrecording movement-steps (i.e.,depths) signal intensities, 10mm directly above the abaxial (dorsal)border plus 4mm further down the target s-nuclei. A micro electrode can detect the variations in the extra cellular field triggered by the electric-current-flows from the neighboring neuron and from other adjacent neural-cells[. For extra cellular intra operative MER acquisition recordings, spikes are usually detected as digital signals (current-voltage) which surpass a limit, the features and specifics of distinct varieties of spikes and their instigation has been explored.[12,13]

The segmentation (separation was performed as follows in an algorithmic step-wise procedure

Step#1: The examined data was partitioned into just as long non-overlapping sections of length 0.5seconds (Table 1).

We achieved a vector s = (s[1],s[2]…s[l]) of non-overlapping segments.

5. MER Data analysis

The microrecording (MER) signal spikes were detected by applying the "script" and "wave clue" inbuilt in functions from Mat-Lab tools and micro electrode recording data was investigated by applying the customized MATLAB offline programming tools. The MER data followed by the analysis were ghettoized into the three components to excerpt dissimilar parameters of interest.[14–27]

6. Noise removal

The unwanted signals are usually referred to as the "artefacts" (noise components from various sources such as user, instrument, external power lines/mains lines frequencies, etc.). A C components (and D C components as well), user equipment's/various surgical-components pertaining to DBS surgery, instrument noise, patient movement and other exogenous noises as well. The acquired micro recording signals of STN data was lowered to 30seconds measurement for every subject participated in this study and was subjected to separation for eliminating exogenous unwanted noised components. Data separation is a procedure of splitting the data into 'n' number of epochs—which is a process of extracting explicit and precise (unambiguous) time-windows from the continuous real signal. Discrete and distinct epochs were then examined scrutinized for the occurrence of existence of noisy data and the same was removed. To prevent the noise due to concatenation of non-adjacent epochs we interjected the epochs with Piecewise Cubic Hermit Interpolating Polynomial ("PC-CHIP") process/technique.[16,28] Through separation, the micro recording signals of STN data was splitted into non-overlapping epochs of 0.5Seconds and was arranged in an array of vector: $S = [s_{(1)}, s_{(2)}, s_{(3)},\ldots, s_{(l)}]$, $[s_{(1)}, s_{(2)}, s_{(3)},\ldots, s_{(l)}]$, are non-overlapping epochs of micro recording data-vector-"S".

The observed data was segmented into equally long non-overlapping segments of distance 0.5 seconds (Table 1).

Table 1: serdefined variables: Separation of the data into non-overlapping segments

User-identified variables	Variable quantity chosen
region measurement (s)	0.5
key-level (threshold) value	1.8

7. Identification of the spike

The technique applied for spike detection could be divided into three main steps—spike-sorting and spike-detection, choice of spike-features followed by the clustering of certain spike features. The details of this method have been explained in detail previously by Falkenberg et.al.,[29] and Quiroga et.al.,[30] however, we state here very concisely. Initially, a band pass digital filter with 0.5kHz and 5kHz (utilizing fourth order Butterworth filter) was applied to filter the higher-signal strength, low frequency activity envisaging the spikes.[31]

The MER signals of STN spike detections and the separation modules are schematically shown inFigures 2 and 3.

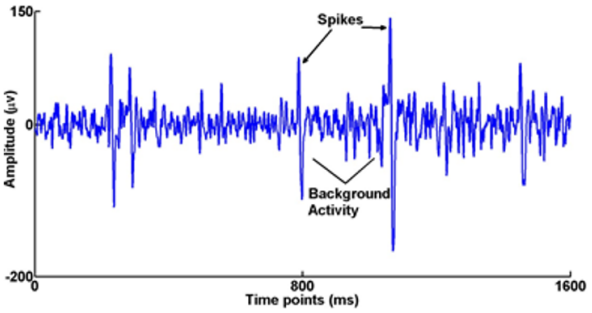


Fig. 2: 2: Raw MER signal

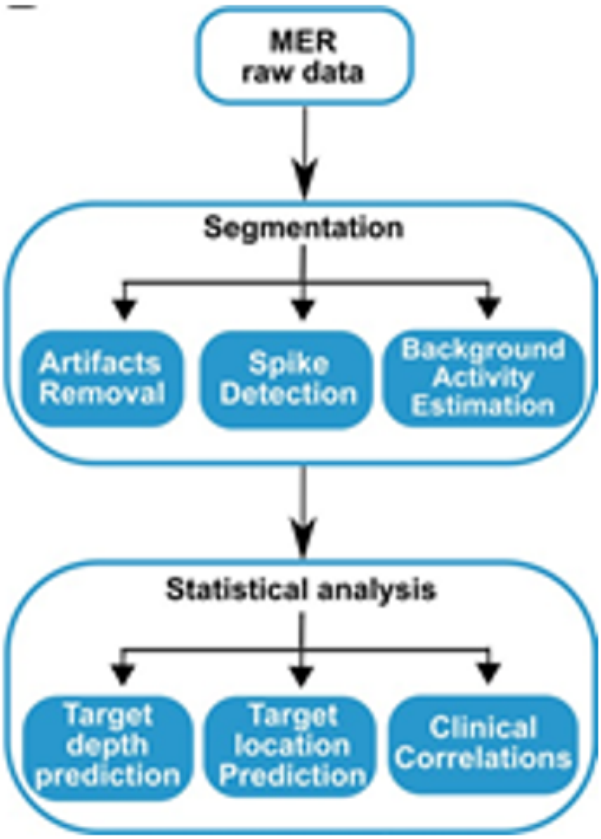


Fig. 3: Modules

Through the circumstantial-background activity, we have processed the parameters to examine the oscillating/fluctuatery-features of the acquired signal-waveform. Preceding investigations have shown that basal-ganglia-circuit activity in Parkinson's disease and movement disorders entails improve in FR, a propensity in the direction of exploding plus irregular synchronization in the STN neurons. These irregularities and also correlation to the effect of stimuli has been detected in several bands-frequencies. Thus, we have computed the spectral-estimations, namely, amplitude-mean (AM), maximum-peak of the signal (MPoS), i.e., power of the signal root mean square (RMS), in the following bands-frequencies range: typical-low-frequency from 2Hz to 7Hz, α from 8Hz to 12Hz, $\beta - band$ (sub divided as low-point short_ β, i.e., from 13Hz to 20Hz, high-level superior-β from 21Hz to 30Hz and $\gamma - band$ from 31Hz to 49 Hz by applying the power-spectral-density (PDF) through the technique of Welch.

The Focal (locus) point of the Foci (or Nuclei) and its estimation: Throughout the DBS functional- neurosurgery, the coordinates for anterior commissure (AC) and posterior commissure (PC) were defined and modified to the coordinates of sub thalamic nuclei neurons through straight conception, which is in general 11.5mm lateral, 3mm posterior and 3mm caudal in relation to Middle of AC - PC. Thus, defined and the customized intensity is deemed or judged to be the accurate target intensity in our—study. Moreover, dorso-lateral territory of the nuclei which was exclusively defined for every PD-subject by applying experimental and DBS surgical-procedure, is the object, i.e., the target point and hence is judged as the acceptable implant spot. The best possible object place and intensity for the pentode-electrodes were validated more by estimating the Unified Parkinson's disease rating scale (UPDRS) stage III score pre-operative (pre-op) prior to seven days and post operative (post-op) following ninety (90) days. Just those individual PD subjects were deemed in the study who were considerably advanced UPDRS-stage-III progress of more than 75%, through the prescription following the DBS surgical-operation.

The parameters were computed in support of the aimed at MER signals of STN data acquired at various complexities from 10mm above and 4mm below the target nucleus. The computed parameters were then utilized for the estimate of implant spot plus appropriate intensity then for the contrast through the findings from eye-visual-examination. Therefore, the underlying hypothesis being, intensities at which these parameters are examined to have relatively superior-amplitudes assessed to more stimulus-intensities, reminiscent of the eye-visual-examination and is the object-stimulus-point in nuclei, i.e.,STN. Therefore, the finding precision is computed based on the number of times achieved parameters determined-value and quantifiable-object target corresponds or matches. At this juncture, an intelligent neuro-electro-physiologist skilled in Parkinson's disease and movement disorders examined the spike-rate(SR) attentively and visually (SRV/VSR) for the intent of contrast or evaluation. Furthermore, the parameters achieved within the object site were associated additionally through scientific-experimental (clinical) parameters utilizing the Pearson's correlation-coefficient (p-value typically≤ 0.05, $\leq = 0.05\ is\ significant\ statistically$) for defining the sensori-motor dissection of the sub thalamic nuclei. The manifold evaluation improvement was achieved for all the correlation outcomes for every Parkinson patient of individual and/or separate (separable) variables by employing the Bonferroni-rectification.

8. Results

52 subjects recruited in this study, the computation was done on sixteen subjects only and the remaining subjects were eliminated by the neurologists as per the objective criteria. Thirty-two sites from sixteen-subjects with bilateral STN-DBS microelectrodes were detected. The mean of the fast Fourier transformation (FFT) Mean Fourier transformed β-band amplitude from the background signal activity in sub thalamic nuclei tallied to the object-target intensity in

82.01% of the Parkinson diseased subjects. While dividing β in at a low level and at greater frequency-bands, shorter β, i.e.,13Hz to 20Hz was confer to the object intensity through yet better precision in 85.02% of the PD patients. The mean of the γ-band amplitude computed by using the related background-signal activity in substantia nigra pars reticulata paralleled to the object-target intensity (depth) in 86.03%. Likewise, the spikes-rate in nuclei was in correspond to the target-depth in 85.01% plus the number of spikes in substantia-nigra (reticulata) is 99.8% in all Parkinson's. Amongst other parameters, L.v.R was in consensus to object (target) intensity accurately is 78.11% in all the Parkinson subjects. The following Table 2 gives the computations of 21 parameters values (in %) via background-activity, spikes, inter spike interval and burst index followed by the accuracy of the likelihood estimation (the prediction).

9. Conclusions

The intra operative microrecording, i.e., MER and computational analysis (computerized assessment) of spiking and contextual-activity in the β-band frequency ranges may possibly advance to appropriate encouraging sign along with a translational-value for the clinical-diagnostic-practice. This study findings demonstrated that spiking-rate was reliable for discovering the object-intensity plus increased β-activity allowed differentiating the STN limits and also distinguish it from adjacent structures especially the most significant substantia nigra pars reticulata. Similarly, the object choice and ultimate (anode cathode) electrode-positioning in the interior s-nuclei based on greater β-band frequency-ranges activity correlates by an enhanced clinical and/or diagnostic result and specifically an enhancement of motoric akinesia symptoms.

10. Conflict of Interest

The authors declare that there is no conflict of interest.

11. Source of Funding

None.

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Author biography

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Cite this article: Raju VR. Subthalamic nucleus projection by SVM based MER Data via deep brain stimulation: A study of spike uncovering. *IP Indian J Neurosci* 2022;8(1):57-63.