IP Indian Journal of Neurosciences 2020;6(4):317–326

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

IP Indian Journal of Neurosciences

Journal homepage: https://www.ipinnovative.com/journals/IJN

Original Research Article

Statistical analysis of MER data of STN Neurons with DBS in Parkinson‘s movement disorders

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ARTICLE INFO

Article history:
Received 20-10-2020
Accepted 19-11-2020
Available online 30-11-2020

Keywords:
Variance
Root Mean Square (RMS)
Implanted Pulse Generator (IPG)
Local Field Potentials (LFPs)
Deep Brain Stimulation (DBS)
Microelectrode Recording (MER)
Parkinson‘s disease (PD)
Power Spectral Density (PSD)
Root Mean Square (RMS)
Stimulus (or Stimulation) Paradigm (or Model) (SP)
Standard Deviation (SD)
SubthalamicNucleus (STN)
Unified Parkinson‘s Disease Rating Scale (UPDRS)

ABSTRACT

The goal of this study is to acquire and analyze LFP recordings within the map of Parkinson‘s environment of clinical-applications for significant-prognostics and this goal is achieved with frequency-analysis ranging the band from 1Hertz-250Hertz and coherence band between 0 and 1 level followed by entropy. The results of the study suggest that the spatial reach of the LFP can extend quite a few millimeters. The study presents a broad research into the existing research which gives insights into the origin of LFP-signals and discovers the variables that need to be considered when analyzing LFP signals in clinical settings principally DBS-applications. Dependable correlations between motoric-features and the mechanisms of the LFP power spectra (the power spectral density-PSD) imply that LFPs can serve as bio markers, i.e., bio signals for Parkinson‘s and movement-disorders (MDs). Specifically, the cardinal motoric feature has been shown to correlate by tremor and β-oscillations and cohered amid 8 Hertz to 28 Hertz. Thus, the local field-potential connotations are for improved microelectrode targeting and for the development of a multichannel/ real time and thus online, personalized adaptive/closed-loop-systems. Variables like geometry of the electrode recording arrangement can have a significant effect on LFP amplitude, pulse width, stimulus intensity and spatial reach, whilst the effects of other variables, like impedance of electrode are frequently frivolous. Entropy was measured in all 12 patients (right hemisphere brain with DBS-ON = 1.4 ± 0.1; DBS-OFF: 1.4 ± 1.9; and left hemisphere brain ON: 1.5 ± 0.1 and OFF: 2.3 ± 1.2 for tremor complexity while root mean square (RMS) computed for amplitude. For the data consistency, coherence was applied to see the variation (inconsistency) and irrationality (if any) which was a normalized measure of linear association in frequency domain where in the bounded-measure was between 0 and 1. If it is ≥ 0.75 but ≤ 1 (i.e., $\geq 0.75 \leq 1$) there is linear association and hence coherent, else no coherence. We obtained coherence-diagnostic-value ≥ 0.75.

1. Introduction

Parkinson‘s disease (PD) is a continual progressive neurodegenerative disorder which is distinguished by the convolution of a broad spectrum of elements called “cardinal-motoric-symptoms”. Based on clinical and predictive prognostic estimation, the cardinal-motor-features were classified into four classes of symptoms, namely, rigidity, akinesia(Bradykinesia), postural-instability and tremor by means of the score of the Unified Parkinson‘s Disease Rating Scale (UPDRS) stage III.[1–7]

Louis and Mahlon[7] have provided insights into well-established observation that cognitive and emotional problems accompany many motor-disorders originating from failure of BG circuit. Furthermore, their findings provided a new framework for exploring how BG elements malfunction in various illnesses, including PD. Although dopamine loss-clearly causes the disease‘s motor perturbations, the allied changes in BG activities

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https://doi.org/10.18231/j.ijn.2020.058

were ambiguous and thus motor disturbances feature predominantly. De Long's model which included detailed road maps of stimulatory and inhibitory signals through the basal-ganglia offered concepts, ideas, notions and perceptions. With the introduction of STN-DBS,[6–8] the experimental investigations are conducted in two ways.

Deep brain stimulator (DBS) is an innovative frontier surgical therapeutic technological method for reducing the symptoms of Parkinson's disease (PD) and other movement disorders (MDs) as well, such as Tics, Tourette syndromes and Huntington disease. Apart from these, it is also giving food results on epileptic seizures in patients with epilepsy. It gives a unique opportunity to examine the electrical oscillations (harmonic-ripples) neural-activity of various sub-cortical (deep) brain structures in PD-MDs subjects.[9–20] However, the electrically induced stimulus local field potentials are a great concern in subthalamic-nuclei(STN) recording. LFP's are oscillations, gauged to determine and connote the collective neuronal-discharge from neurons neighboring the electrode. The acquisition of extracellular activity of irregular patterns of STN activity typically acquired from a population of neurons discovered as local field potentials (LFPs) has cast off brilliance on the pathophysiology and confiscate and clutch the underlying clinical prognostic information to direct in modern medical administration.[15]

DBS is a stereotactic functional neurosurgical procedure principally entrenched by a neurologist and surgery by a qualified and suitable surgeon for functionally implanting electrodes into a predetermined target region based on the signs and symptoms being treated by surgery. The target coordinates are derived, confirmed based on pre operative magnetic resonance imaging (MRI), and customized through electrophysiological microelectrode-recording (MER) technique while stimulating electrode deeply into the important part of the brain, intraoperatively (intra op).[15] The technique allocates the detection of neurons which are characteristic-features of the concern target during firing-rate, voltage-amplitude and signature-patterns. For instance, through MER, the subthalamic-nuclei (STN) is usually detected with setting-noise, increased firing-rate and frequency of bursting-neural-cells. Consequent upon, the DBS electrode is implanted based on the patterns (or signatures) found by MER. Both the MER and DBS electrode leads are capable of recording LFPs. The acquired signal is referred to as a 'biomarker' which can vary in accordance with the nature, for instance, biomedical, bioelectrical, biochemical, neurological, physiological, and biological.

Local field potentials are widely employed feed-back responsive signals/waveforms in adaptive closed loop DBS systems[21–23] that are also referred to as 'intracranial electroencephalograph-waveforms' computed-generated from the extracellular-space by transmitting electrical-potentials (the action potentials) in the course of axons. These field-potentials are often replicate neuronal procedures happening within the local-region around the electrode in the neuronal-extracellular-space. Priori et al[24] established the suitability of LFPs as the feedback signal in the adaptive DBS systems for Parkinson disease subjects. A key advantage is that LFPs can be directly acquired from the stimulating electrodes. The other advantage is the long term constancy attained at the electrode-tissue-interface.[25] Typically LFPs have amplitudes of up to 200 micro-volts (μV) with energies less-than 500Hz.[23] In contrast to electrical-potentials (the action-potentials), local-field-potentials have a reasonable spatio-temporal resolutions, classically around 1millimeter.[26]

Microelectrode recording (MER) or microelectrode signals recording of local field potentials with subthalamic-nuclei deep brain stimulation is most useful for interpreting Parkinson diseases (PD) signal analysis acquiescent to elucidation are fetching ever more germane or pertinent. These signals are supposed to emulate STN neurons and action potential movement and, these potential frequency modulations are coupled to spiking-events.

Also, the existing microelectrode-recording (MER) data vis-à-vis the neuro-electro-physiological (NEP) irregularities (of uncharacteristic) in the subthalamic-nuclei which probably lead acuteness of the PD features (i.e., the non-genetic phenotype PD symptoms) are very scanty. In this study, we[9–12] state that activity in associated-bands of local field potentials (LFPs) gathered with multi-channel subcutaneous micro electrode recording system and DBS leads from sub-territories of STN give characteristic neurophysiological information about the PD symptoms-indications.

Subthalamic-nucleus deep brain stimulation (STN-DBS) is an effective treatment for advanced Parkinson's disease (PD). In this, there are two electrophysiological techniques sustain detection of the optimal target. One is to record neuronal activity with microelectrodes (MER). The other is to record the local field potential (LFP) from the DBS electrode used for chronic stimulation. The relative predictive value of the two techniques is to be established. We explore whether there is any advantage in combining intra op LFP techniques with MER. High frequency deep brain stimulation (DBS) in the STN area has proven to be an effective treatment for patients with advanced PD. Surgical targeting of the area is by and large facilitated by MER of single units and milieu neuronal activity. An auxiliary technique has been promoted as a candidate intra op aid for targeting the optimal stimulation site along the planned DBS electrode trajectory and selecting the best contacts for chronic stimulation.

This study discusses the how beta-oscillations in the STN-DBS enhance our understanding clinically in prognostic diagnosis of recordings of local field potentials.

Following the Helsinki principles, the study was approved by the institute ethical committee following Helsinki principles.

2. Goal

To implant the pulse generators and acquire the local field potentials during subthalamic-nuclei (STN) recording and to analyze these potentials using coherence and entropy techniques, to find out if an adaptive closed loop DBS system responding to patient specific, clinically relevant brain or movement signal feedback is highly effective than the currently available, open loop DBS therapy in Parkinson's disease (PD) as précised by the motor score on the Unified Parkinson's Disease Rating UPDRS stage III Scale, and also, as per United Kingdom Parkinson disease society brain bank (UKPDS BB) criteria and specific phenotypic quantifications.

Implanted pulse-generators by contacting biological-amplifiers circuitry was employed to acquire local field potentials. In every subject, the contacting/sensing electrodes resoluted to be in or in front of the sensorimotor area of the target nuclei STN were exploited for LFP signal-recording.

2.1. Scientific-rationale

Parkinson's disease is a foremost movement disorder and the prime root cause is damage to the central-nervous –system (CNS). In spite of every study on this malady, the formation-mechanism of its manifestations remained mysterious. But it is quiet obscure why damage to substantia nigra only which is, a tiny element of the brain (few millimeters), causes a wide-range of motor-symptoms? Still, the basic reasons of brain damages and injuries prolong to be wholly expounded and also understanding the brain function is very complex. Some cutting edge frontline engineering and technological tools and utilities are un-soothing to comprehend the behavioral actions and activities and performance of complex-systems.[27] In this connection, mathematical frameworks and statistical signal modeling and then simulation modeling's through computer (i.e., computer simulated prototypes through computational simulation techniques) is one of the most significant tools. Computational simulation models for the progression of this malady have begun in 1999 and today it is expanded profoundly. These engineering developmental tools are very helpful not only in improved perceptive and thoughtful of the PD, but also presenting innovative therapeutic-methods, and it's envisage prediction and impediment, and in its early diagnosis. At present DBS is constrained to non-adaptive open loop stimulus method, without automatic adjustments or settings to the subject's activity status, oscillations plus kinds of motoric-features, drug-medication (i.e., dosages) or neural markers of the disease. Adjustments of stimulation parameters are not conducted during real-time in real-time based on the ongoing neurophysiological variations in the brain. Hence, adverse effects on patient may be induced due to overstimulation of the brain. Whilst subject at home, every adjustment to DBS settings occur or during visits. Such constraints sometimes may lead to further health hazards and cross dyskinesias - side-effects like, cognitive dementia(CD) and cognitive impairment (CI), feelings, the doldrums, hallucinations, and both upper body symptoms (such as, dysarthria, deglutition, and respiratory-function) and lower body symptoms (like gait disorders, freezing of gait (FoG) and including symptoms associated groups like tremor-dominant (TD) and postural-instability gait difficulty (PIGD)) and axial symptoms (slurred inaudible speech). These features have a key impact on disease progression, and thus, the subjects' quality of life (QoL) and the encumbrance of caregiver.

2.2. Significancy of the study and its importance to Biomedical engineering and Neuroscience

Subthalamic nucleus deep brain stimulation is a momentous therapeutic stereotactic neurosurgical operational technique which reduces tremors and restores motor function in subjects (patients) with advanced idiopathic Parkinson's disease both unilateral and bilateral STN-DBS, and for many disorders. The advances in stereotactic functional neurosurgical automatic operational techniques have fundamentally replaced ablative methods. Mahlon[5] formulated a new model for the brain's circuitry and exposed a fresh target for this illness. Alim Louis Benabid[6] devised an effective and reversible intervention that remedies neuronal misfiring in Parkinson's disease. However, a well designed neuro bio marker perfectly giving vital information on the PD motoric and non motoric features in subthalamic-nucleus and also globus pallidus interna is not yet developed. In this study, we account the results of neural correlates of PD motor symptoms in the territory of subthalamic nucleus. Despite advances in magnetic resonance MRI particularly in connections with better spatio-temporal resolutions in latest 10 Tesla, the electrophysiological microrecording (MER) technique continues to be well applied for pinpointing on STN detection and discovery based on signatures (or MER signal patterns of STN neurons) with deep brain stimulating procedure.[3,4,28–30] Hence, our results will give potentials for the construal explication of oscillatory-dynamics of STN and that these signatures or patterns which are confined very well by the intra op MER can be used as objective tools for future technologies of neuromodulation. The study also highlights the variability in spontaneous LFPs amongst the subjects and the neuronal data. Although the work deals with the signal processing Applications to the human motor sensory nervous system it deals with application of electro neuro physiological evaluation of dystonic

and dexterous and movement disorders, in particular neuromuscular, writer's cramp with and without mirror movement (i.e., dystonic mirror movenets) it has broad implication in the development and innovation of newer signal processing and electrophysiological techniques and Improving the currently available EMG machines for Evaluating all types of neuromuscular diseases and disorders in Particular dystonias. It will be of great interest to the Scientists/engineers involved in biomedical research in the fields of biomedical instrumentation and signal processing applications to neuro electro physiology.

MER has been the gold standard for lead targeting in DBS, however patients must be awake during this surgery, it requires more instrumented passes into the brain, and operative time is longer. Targeting can be performed using intra operative MRI or intra operative computed axial tomography (iCT) to place electrodes with equal accuracy, which is appealing to patients since it is performed under general anesthesia and may result in lower morbidity and cost.

2.3. Provocative pathways

Whilst Mahlon began his experimental investigations in his research work (1960s), the basal-ganglia which is meant for body movement and control had been implicated in movement, principally for the reason that flaws there were connected amid infirmity such as PD in which motor turbulences feature notably. Little was known; yet, vis-à-vis how closely the basal ganglia contribute to movement. To find out, Mahlon embedded microelectrodes into rhesus-macaque-monkeys' brains and evaluated the activity of explicit neurons in the BG whilst the rhesus carried out imparted training exercises, actions and/or events. He thus matched neurons by tasks; some influenced and prejudiced, for instance, the direction, magnitude/size, or the pace or tempo of arm, leg, or facial movements. Thus, he mapped out the association of the motoric-circuit. Derived from his own research-work and that of other researchers plus existing anatomical-structural information, Mahlon proposed a model wherein BG neurons operate in separate circuits. Numerous pathways originate from distinct centers in the cerebral-cortex, run through BG, and end back at terminus point where they started; the circuits work alongside one another and allow concurrent operations that parallel processing the emotions, thoughts, and motor functions. This experimental work provided insights into the entrenched, ingrained, and deep rooted observation that cognitive and emotional problems accompany many motor disorders that stem from BG failings. Also, the findings provided a new framework for exploring how BG elements and mechanisms malfunction in a variety of illnesses, including PD. Although dopamine loss obviously causes the disease's motor perturbations, the associated changes in BG activities were unclear. Mahlon's model that included detailed maps-of-stimulatory, and inhibitory-signals through the BG given the ideas. For instance, the final-stop in the motor-circuit of the BG is a anatomical-structure that sends restraining and preventive and limiting instructions forward, thereby suppressing other components of the motor system. Anything that causes superfluous activity at that site might generate the symptoms that characterize-PD.

2.4. From aficionados to imminent and impendings

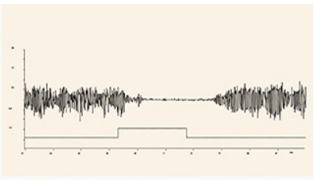
In the early 1980s, sporadic outbreaks of a syndrome that mimics Parkinson's disease started occurring among drug addicts and scientists traced it to a chemical, MPTP, that was contaminating some batches of synthetic heroin. Medical management of the compound to monkeys reproduced the key clinical and pathological features of PD, and thus offered a powerful new tool for studying the illness. Mahlon seized upon the opportunity. A part of the basal ganglia called the subthalamic nucleus drives the inhibitory output signal, and in 1987, Mahlon reported that MPTP triggers neurons in the subthalamic nucleus of monkeys to fire excessively. Perhaps, Mahlon reasoned, the over exuberant signals quash motor activity in PD. If so, inactivating the subthalamic nucleus might ameliorate some of the illness's worst symptoms. Next, he did an experiment that would transform PD treatment. He administered MPTP to two monkeys; as usual, they gradually slowed down until they sat motionless, their muscles stiffened, and they developed tremors. Mahlon then injected a second toxic chemical that inactivated the subthalamic nucleus. Within one minute, the animals began to move. Gradually, their muscles loosened and the tremors ceased. These findings strongly supported the hypothesis that hyperactivity in the subthalamic nucleus underlies PD symptoms.

2.5. Higher frequencies and greater confidences

Louis has been attempting the Parkinson's neurodegenerative disease in America. In a throwback to the pre Levodopa era, the trickiest PD-patients those who did poorly with long term pharma ceutical treatment would wind up in the operating room. Louis craved a new tool—something safer that would quiet the most disabling symptoms of PD. In the year 1987, while operating in a PD subject he was about to create a lesion with essential tremor, a condition that causes tremulous in different parts of the subject. He was targeting an element of the thalamus that leads to tremor. Characteristically, the subject was awake so Louis could test whether he had positioned the right tissue; he placed a probe into the stain that he planned to lesion and sent an electrical-pulse to guarantee that distressing perturbing and tormenting this site did not cause or produce endangered and undesired-effects. As a rule he used γ-waves with $\leq$50Hertz frequency,

although he determined to find out what would happen if he increased the frequency. Just below 100 Hertz (γ-waves range: 31Hertz –200Hertz), and that went unexpectedly occurred impressive and the tremor clogged. The Parkinson subject became so still, Louis thinking that he had caused an unintended unintentional muscle retrenchment. He switched off the stimulus and he contrite for his lapse or elapse. The subject told Louis not to express regret, as it was happened the first time in many years that his hand had not shaken. Louis continued the procedure, amid the similar result. Also, when he withdrew the current, the tremor recurred. Thus, the cause was reversible. So, Louis realized he was onto something exciting. (Figure 1)

The hand of an individual with essential tremor before (left) and during (right) high-frequency stimulation. Fuzziness connotes shaking in these two-second exposures.



Black lines measure amplitude of tremor before (left), during (middle), and after (right) high-frequency stimulation.

Fig. 1:

The DBS had been inducing used for more than twenty years to treat ache and twinge, but no one had dialed up the frequency. Following the year, he attempted and also aimed the same approach for Parkinson subjects. In addition, he implanted a device which was on the market for pain relief and delivers constant stimuli. Some of the individuals benefited from the procedure, and no complications occurred. Louis in the early 1991 reported that high-frequency stimulus could be deployed bilaterally (in left and right brain) in people with essential tremor and PD; this strategy reduced tremor on two sides of the body. The gains were long lasting, and adverse effects were placid; also, any undesired outcomes could be reversed by reducing the stimuli.

Louis knew (although the technique quelled tremors) that this motoric-symptom was not the one that most debilitated people with PD. Perhaps high-frequency stimulus of brain regions and sub-structures other than the thalamus (i.e., the subthalamic nucleus) would alleviate the more troublesome aspects of the illness such as slowness of movement, postural instability and rigidity, he reasoned. In this state of mind, Louis read Mahlon's report that damage to the STN wipes out many symptoms of PD in primates and in non primate animals. This site was not an attractive target: Lesioning procedures and spontaneous lesions had established decades earlier that, when things went wrong, violent flailing could result. By that time, however, Louis had performed high-frequency stimulation of the thalamus and other brain regions' in $\geq$150PD patients. He was confident that he would cause no harm in the subthalamic nucleus; if necessary, he could remove the electrode.

In the year 1995, Louis reported his results in 1995 from the first humans who underwent bilateral, high frequency stimuli of the STN 3 subjects with severe PD. The treatment suppressed slowness of movement and muscle rigidity. 8 years later, he confirmed and extended these results in a study of individuals who had undergone the procedure 5 years earlier. The surgical-operation restored motor skills, suppressed tremor, and improved the ability to conduct normal activities of daily living. Furthermore, people were able to slash their dosage of L-dopa and related medications, which reduced associated complications. In the year 2002, the US Food and Drug Administration (FDA) approved high-frequency stimulation of the subthalamic nucleus for treating advanced idiopathic Parkinson's disease. The method is not a cure, and it does not reverse all aspects of the malady. In particular, the non motoric and axial feature symptoms such as speech, cognition and dementia continue to decline. Many questions remain about the mechanism of this intervention. It might jam or replace inappropriate circuit activity. Regardless how it works, functional neurosurgeons are using high-frequency deep brain stimulation to combat an ever-growing number of sites and diseases: essential tremor, dystonia—a condition of involuntary muscle contractions—and even psychiatric illnesses. The FDA approved its use for obsessive-compulsive disorder in 2009, and scientists are investigating applications for drug-resistant depression and Tourette Syndrome. Through their open-minded explorations and willingness to challenge dogma, Louis and Mahlon have delivered extraordinary medical innovations to humankind. By reaching deep into the brain sub structures, they have soothed some of the most troubling conditions that corrupt it.

3. Materials and Methods

The DBS surgery was performed with two burr holes on the two sides (left and right hemisphere) based on the co-ordinates. Five channels that are introduced with the central-channel representing the MRI target while medial and lateral are placed in the x-axis coordinates while anterior and posterior are placed in the y-axis coordinates to envelop or to swathe an area of 5 mm diameter. DBS leads consisting annular-contacts were implanted in the STN area. LFP signal acquisitions were done in all PD-patients bilaterally. Electrodes are gradually conceded during subthalamic-nuclei and signal acquisition was performed. STNs are detected with larger-noises and distortions with a larger-baseline and an asymmetrical-discharge by means of multiple-frequencies.

Surgery was planned using a CRW frame with a diagnostic magnetic resonance imaging (MRI) protocol using Framelink software with 5 channels. Surgery was

performed in all by a qualified neurosurgeon. Stereotactic targets were acquired using a specialized system with a stereotactic Cosmon-Roberts-Wells (CRW) frame which has a luminant MR (MRI) localizer. The targeting was performed according to Lozano's technique – 2mm sections are taken parallel to the plane of anterior comissure-posterior commissure line and at the level with maximum volume of red nucleus, STN is targeted at 3 mm lateral to the anterolateral border of red nucleus. 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 operative MRI.

For carrying the microelectrode signal recording of subthalamic-nucleus with deep brain stimulator, we passed five innocuous microelectrodes in an array with a central, lateral, medial, posterior, and an anterior point location positioned at a 2mm distance to describe the limits of the subthalamic-nuclei. Single neuron and multi-unit-neural microrecording has done by means of 10μ micron-width tiny microelectrodes having an input impedance of 1.1 ± 0.4megOhms and was précised at 220Hz maximum-frequency as per the technical specifications or configuration (Medtronic). The MER signals of STN neurons were acquired with biomedical biosignal-amplifiers (10,000 times amplification and ample variable gain) of the Medtronic 5 channel Lead Point machine, by applying with a bootstrapping-method was filtered with analog band passed between 0.5kH-5kHz, with gain-of -3dB and 12dB/Oct(Medtronic-specifications or configurations). All the signals were sampled at 12kilo-Hertz using a $2^{N=12}$ bit (4096 sample amplitude digital values) analog to digital converter (ADC) of Dynalogue (maker). Later, the signals were sampled up to 24kilo-Hertz off-line by using a language for technical computing called "Mat-Lab" software. Following by a two seconds signal-stabilization duration following the close-up of electrode movement, multi neural unit segments were acquired for a period of five seconds to twenty seconds (each trial) duration. The microelectrodes were sophisticated in the steps of 500 micron-m in the direction of the target by a hardware tool called microdrive, initially with 8mm subthalamic-nuclei over the target based upon resonance imaging i.e., magnetic resonance imaging.

Point of contacts of DBS targets with Microelectrodes Recordings: The subthalamic-nuclei was perceptibly differentiated from the dorsally located zona-incerta and lenticular fasciculus, i.e. the H_2 field mounting abruptly in milieu noise level and amplify in liberation-rate normally differentiated by metrical-periodic explode of movement with a explode-frequency amid 5Hz to 20Hz. Profound into the STN periodic explode-movement right and left shifted to higher frequencies lying between 15Hz to 40Hz. There was no frequency shifting after 40Hz frequency and all the signal components are vertical (Fig's 2,3) with no right and left shit (note: there is frequency shift in our recording). There were more asymmetrical firing-units experimented. The ventral-border of the STN was recognized shrink and background-noise abruptly and a decrease of multi-unit activity (MUA) across a distance of 0.5mm to 2 mm, and, passing the ventral border of the STN, a sharp diminish in background-firing was found, with more regular firing-units, μfire frequency from 20Hz to 80Hz, of the substantia-nigra.

3.1. *Clinico statistical analysis*

3.1.1. *Coherence estimation*

Coherence is a statistical evaluation term (for consistency) which is a measure of the liner association between two subthalamic nucleus neuronal signals (STN – STN) to see the featuristic resemblances or characteristics for logistic reasoning (the rationale behind coherence is consistency, logical reasoning, and rationality and to see if there is any variance (inconsistency)). It is a normalized measure of the linear association between two signals in the frequency domain, where It is a bounded measure taking values ($0 \geq 0.75 \leq 1$), where 0 indicates that there is no linear association or relationship (that is process 'y' is of no use in linearly predicting process 'x'), and 0.75 indicates a better linear association but 1 indicates a perfect linear association or relationship at that frequency.

Coherence between the tremor-dominant and oscillations of field-potentials at twice the frequency of tremor possibly will signify a real neuro-electro physiological-correlation, ripples-noise and distortion or a combination of both.[31] However, when comparing tremor-related EMG-LFP coherence between tremor dominant and Bradykinetic PD symptoms, the disparities in coherence in the single tremor frequency range between PD subtypes appeared to be independent of disparities in the binary-frequency-tremor range.[15] This supports the hypothesis that field potentials binary-frequency-tremor is significant neuro-electro-physiologically.

The variance of coherence was normalized by transforming the square root of the coherence (or complex valued function referred to or termed 'coherency') at each frequency using the Fisher's transform, this results in variance ($P < 0.05$) which is statistically significant standard value.

This results in values of constant variance for each record given by 1/2L. Where, L is the number of segment lengths used to compute the coherence. Here one may note that, the transformed coherence may be > 0.75 and/or >1.

3.2. *Variance* (σ)

Variance is the average of the squared deviations of each data point from the μ-value. For a population of size N, the

variance sigma square, is computed as,[5,32]

$$\sigma^2 = \left[\frac{1}{N}\left[\sum_{i=1}^{N}\left(x_i - \bar{\mu}\right)^2\right]\right] \text{..... (1)}$$

Similarly for a sample size it is denoted by s square and is evaluated as,

$$S^2 \left[\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}\right] \text{.....(2)}$$

The $\bar{\mu}\,[\sigma^2]$ and the variance Var $[\sigma^2]$ of σ^2 are computed as,

$$\text{Var}\,[\,\sigma^2] = \bar{\mu}\,[(\,\sigma^2 - \sigma^{-2})^2] = \text{Var}\,[\varepsilon] \text{.....(3)}$$

Because x is written as the convolution of σ and white Gaussian-noise W passed through H, the conditional distribution of x given σ^2 is Gaussian distribution with a μ of zero and a variance of σ^2:

$$p(x/\sigma^2) = \left[\frac{1}{\sqrt{2\pi\sigma^2 exp}} \;-\; -\frac{x^2}{2\sigma^2}\right] \text{.....(4)}$$

3.3. Standard deviation

The standard-deviation (or SD) of a sample is the square root of the variance which is measured as[5,32],

$$s = \sqrt{s^2} = \left[\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}\right] \text{.....(5)}$$

as a result,

$$\text{`}\sigma\text{'} = \sqrt{\sigma^2} \text{.....(6)}$$

is standard deviation of the given population.

3.4. Root Mean Square (R M S)

The root-mean square (RMS) or root mean square deviation (RMSD) or root-mean-square error (RMSE) (or sometimes root-mean-squared error) factor mostly used in engineering and medicine for a statistical significance. It is often used for computing the disparities among the values (sample or population values) predicted by a model or an estimator and the values observed. In our computation the sample size is N (= 12).

To compute the R M S of a given population N, in our case it is (N = 12), one has to square the given population in the N and then determine the arithmetic-$\mu$of the squares. Finally, take the square root of the findings and computed by using the following equation

$$R\,M\,S = \left[\sqrt{\left[\frac{(a_1^2 + a_2^2 + \ldots a_n^2)}{n}\right]}\right] \text{.....(7)}$$

$$= \left[\sqrt{\frac{\sum_{i=1}^{n} a_i^2}{n}}\right] \text{.....(8)}$$

In our 12 population computation, the RMS for the *Left Hemisphere Brain* during DBS "ON" is 1.1 ± 0.8 and during "OFF" it is 5.9 ± 11.9. Similarly, R M S for the *Right Hemisphere Brain* during DBS "ON" is 0.9±0.3 and during "OFF" it is 2.6 ± 4.7.

3.5. Normalizing Impedance and RMS

The estimation of the root mean square of unprocessed multi unit S T N - M E R local field potentials activity acquired by the micro electrodes at apiece and at every microelectrode-depth or intensity is defined as in the following equation

$$\text{Root Mean Square} = \bar{X} = \left[\sqrt{\frac{\sum_{i=1}^{n}(X_i - \mu)^2}{(n-1)}}\right] \text{...(9)}$$

In this equation, X - vector-quantity of sampled analog M E R – L F P signal with μ, and X_i is every sample, and n is the total number of samples in the sub division. The root mean square values are prone to microelectrode properties, for instance, the impedance of microelectrode; thus the necessity of R M S normalization in order to be an absolute quantity or gauge. In the earlier investigations the normalization of R M S with the white - matter of the of pre S T N zero-line, i.e., base line R M S producing what the investigators defined as the "N R M S". The technique is highly pragmatic for detecting S T N borders and for exhibiting the micro electrode signal recording of S T N trajectory graphically/ or diagrammatically.

In this study, we intend to contrast the μ mean - R M S in the S T N to clinical/diagnostic diagnosis and/or clinic prognostic parameters, such as feature-symptom rigorousness and progression of the post operation which is impelled or driven and provoked our re-evaluation of the normalization technique. It is observed that in spite of zero line/base line normalization, the S T N – N R M S still demonstrated significant correlation to the impedance of the microelectrode which was gauged#1kilo-Hertz at the start of every trajectory; R=00.3291, P=49.60001. The ρ coefficient point to 10% (R^2) of μ of N R M S inconsistency in the S T N might be elucidated by the impedance of the microelectrode. This confounding result might masquerade basic medical correlation's. We therefore employed an different technique for normalizing R M S in the S T N: impedance normalized R M S (I N R M S). The I N R M S in the S T N was computed with the below expression

$$R\,M\,S_i = I\,N\,R\,M\,S_i = -\,a \times [I_i - Mean\,(\mu)\,I] \text{.....(10)}$$

Here, R M S_i is the mean-μ of RMS in fastidious nuclei in μ micro volts and 'I_i' is the equivalent impedance of microelectrode in megΩs which was gauged@1kilo-Hertz, the vector-quantity of all impedances are 'I', and 'a' is the 'linear' which is a μ of I, that guarantees following the normalization of the impedance. Here, μ is not changed which is relative to the unprocessed, and not normalized the *R M S*. Here, *N R M S* has a singular-μ. We have initiated that the normalized mean of RMS (NRMS), i.e., normalized by pre-STN baseline activity did not correlate significantly with Parkinson's disease symptoms or postoperative improvement. Normalizing the RMS by impedance removed the confounding impedance correlation and revealed a significant correlation with both preoperative rigidity and postoperative reduction in Unified Parkinson's Disease Rating Scale (UPDRS) and F, respectively). It is this impedance normalizes the technique that employs to compute the PSD in order to normalize.

3.6. Computing the PSD spectrum

To compute the spectrum, i.e., power-sepctral-density (PSD) spectrum, the unprocessed analogue signal was rectified by the absolute operator and the μ was subtracted (Moran et al., 2008; Moran and Bar-Gad, 2010). Using the rectified signal, which follows the envelope of multi-unit activity, we were therefore able to detect burst frequencies below the range of the operating room band-pass filter (250–6000 Hz). Since the local field potential frequency domain was filtered out by the recording apparatus, our resulting power spectral density represents only spiking activity. The average power spectral density was calculated in each trace using Welch's method, with a 1s Hamming window (50% over-lap) and spectral resolution of 1/3 Hz. Values within 2 Hz of the 50 Hz power supply artifacts' and their harmonics were removed and interpolated from the surrounding values. Two different methods were used to normalize the power spectral density: Dividing the power spectral density by the total power of the signal between 3 and 200 Hz (excluding power spectral density values within 2 Hz of the 50 Hz power supply artifacts' and their harmonics) creating a relative power spectral density. This method exposed the 'relative' power across frequencies. For ex-ample two pure sine waves with the same frequency but of dif-ferent amplitudes would have identical relative power spectral densities. This method is particularly useful in identifying the dorsolateral oscillatory region of the STN (Zaidel et al., 2009). The relative spectrum i.e., power spectral density computing diagram be viewed in the following graphs/images.

Normalizing the power spectral density by electrode impedance in the identical manner as the described above for the RMS (i.e. by offsetting its correlation with the measured electrode impedance). This method retained the 'absolute' level of power, exposing the magnitude for each frequency in the signal. In the above example of two sine waves with the same frequency but of different amp-litudes (measured by equal impedance electrodes), the impedance normalized power spectral densities would be different. Since the dependence of power on electrode impedance could be different for specific power spectral density frequencies, the normalization was performed separately for each frequency band in question. In order to qualify this, we computed the correlations for 1–100 Hz power spectral density individually (in steps of 1 Hz)—all correlations were significant (P50.01; median P50.0001). Furthermore, re-analysis using a single value for normalization across all frequencies (the μ linear coefficient of the regression line) did not change our results presented below. This method was used for the regression analysis presented in Fig. 7. For all power spectral density normalization, correlation analyses and plotting in this manuscript, the logarithm of the power spectral density was used.

3.7. Entropy

To compute the local field potentials, the thermodynamic entropy is used. It is a measure of the fraction of the internal energy of a neuron which is not available to function. In neurons impulse progression, such as the flow of neuron from one state to another state, i.e., neuron sending impulses from one state to another state typically referred to as "divergency" and similarly receiving impulses from other state neurons is usually referred to as "convergency". It is said that entropy is increases at all times.[9]

To establish the functional nonlinear multivariate (Taylor's series) local field potentials, i.e., LFP signals, say F, in a deep brain stimulator 'correlation' or 'relation' r (t), then, we can establish the relation r (t) as,

r (t) = F[s(t)], ...(11)

to discretize prior times:

s(t)=(s(t-Δt), …, s(t-LΔt))= (s_1, s_2, s_3…, s_L) .....(12)

Consider the only current-response (r) then, we can write (r) as

(r) = r (0), ...(13)

and F is a multivariate LFP signals for r in terms of s_1, s_2, s_3…, s_L.

So, to compute lower-order coefficients, we surmise that the others are as zero (0). Hence, the maximum-entropy is computed distributed as

$K - exp^{\left(-c(r-F(s_{1,\ldots,}\, s_L)\,)2\right)}$ .....(14)

In multivariate analysis, the μ and covariance's controlled or conditioned as:

$K - exp^{((x-m)TC(x-m)\}}$ .....(15)

and, in independent variable or analysis, with marginal's P (x), Q(y): P(x) × Q(y) or P(x)Q(y) .....(16)

In this study, the entropy method is of non-linear-dynamics (signals with different phase amplitudes and with different frequencies) which computes negative (-Ve) natural-logarithm of the conditional-probability that two-sequences in a time series/time-domain which are analogous for 'm' number of points are analogous for m+1 points.[33] In our computation, we obtained the entropy value which showed the tremor-complexity during DBS "ON" for the brain right-hemisphere (left side: 1.4±0.7) and "OFF" states (2.3±1.6), and for the right hemisphere the tremor complexity during DBS "ON" is (1.3±0.7) and during "OFF" state in left-hemisphere it is 1.5±1.6. So, if we observe, in our computation, carefully, as we already mentioned that entropy is increases at all times,[9] and so the entropy is increased in either case. This also (the results) indicating that the PD-patients cardinal motor-symptoms were effectively reduced with DBS.

4. Results

The results of the study suggest that the spatial reach of the LFP can extend quite a few millimeters. The study presented

a broad research into the existing research which has given the insights into the origin of LFP-signals and identified the variables that need to be considered when analyzing LFP signals in clinical settings principally DBS-applications. Dependable correlations between motoric-features and the mechanisms of the LFP power spectra - the power spectral density:PSD implied that LFPs can serve as bio markers (bio signals) for PD and movement-disorders (MDs) as a clinical relevance. In particular, the cardinal motoric feature has been shown to correlate by tremor and β-oscillations and cohered amid 8 Hertz to 28 Hertz. Thus, the local field-potential connotations are for improved microelectrode targeting and for the development of a multichannel/ real time and thus online, personalized adaptive/closed-loop-systems. Variables like geometry of the electrode recording arrangement can have a significant effect on LFP amplitude, pulse width, stimulus intensity and spatial reach, whilst the effects of other variables, like impedance of electrode are frequently frivolous. Entropy was measured in all 12 patients (right hemisphere brain with DBS "ON" = 1.4 $\pm$ 0.1; DBS OFF: 1.4 $\pm$ 1.9; and left hemisphere brain ON: 1.5 $\pm$ 0.1 and OFF: 2.3 $\pm$ 1.2 for tremor complexity while root mean square (RMS) computed for amplitude. For the data consistency, coherence was applied to see the variation (inconsistency) and irrationality (if any) which was a normalized measure of linear association in frequency domain where in the bounded-measure was between 0 and 1. If it is $\geq$ 0.75 but $\leq$ 1 (i.e., $\geq$ 0.75 $\leq$ 1) there is linear association and hence coherent, else no coherence. We achieved the $\geq$ 0.75 as a coherence diagnostic-value.

5. Conclusions

This study highlights that the continuous stimulation re activates the neural-cells and prevents the apoptosis. Thus, stimulation through DBS has prospective-benefits of varying the disease-process. This has been observed experimentally and clinically in our patient population, and patients those underwent stimulus through deep brain stimulator had a longer endurance plus improved quality-of-life contrasted to their accomplices who had remedial medical drug treatment in only. The field potentials gathered from deep brain stimulating electrodes in PD patients have given neuroscientists with a novel method for understanding, and potentially refining treatments for movement disorders. Correlating aspects of the LFP frequency spectrum with clinical symptoms has provided new insights into the pathophysiology of these disorders, and mounting evidence suggests that LFPs will be useful in improving current therapies in this arena. In particular, LFP oscillations have proven to be useful in localizing DBS surgical targets. LFPs may ultimately be able to inform a closed-loop DBS device that is responsive to individual patient symptoms in real time.

6. Source of Funding

DST funded CSRI under the Ministry of Science & Technology (MST), Govt of India, New Delhi.

7. Conflict of Interest

None.

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Cite this article: Raju VR. Statistical analysis of MER data of STN Neurons with DBS in Parkinson's movement disorders. *IP Indian J Neurosci* 2020;6(4):317-326.