Original Research Article

Analysis of Parkinson's disease movement disorder by M E R with S T N – Deep Brain Stimulations

Venkateshwarla Rama Raju[1,2,*]

[1]*CMR College of Engineering & Technology, Kandlakoya, Medchal Rd, Hyderabad, Telangana, India*
[2]*Fellow Neurology, Nizam's Institute of Medical Sciences (NIMS), Hyderabad, Telangana, India*

A R T I C L E   I N F O

A B S T R A C T

Brain's neuro protection is clearly the new frontier in movement disorder research and therapy. The long-term clinical studies have so far failed to prove that high-frequency stimulation has been able to slow down the evolution of the disease. So called e a r l y s t i m clinical p r o t o c o l s have only proven that it was safe to induce or stimuli sub thalamic nucleus S T N much earlier than it was so far accepted. At the experimental level, M P T P - treated monkeys, high-frequency stimuli of the S T N could protect neurons in the sub stantia nigra. To test this scientific rationale/hypothesis in humans, one would need to perform S T N induced stimuli at the very beginning of the disease, which is not easily ethically sustainable given the surgical risk, even if low, in patients who are still minimally impaired by the disease. There have been so many advancements in computing capabilities; big data management; miniaturization of electronics, devices and batteries; and new sources of energy compatible with implantation of biological devices and fuel cells. More recently, there has been an explosion of biological imaging at the nano level as well as whole-brain imaging. It is impossible to generate a reasonable picture of future technological development without being sure to be wrong. The consequence of that is that when building projects and setting new protocols as well as imagining new tools and devices, we should be confident that what has not yet been developed will eventually be created. In this article we the author explained the present past and future Parkinson's disease prediction.

1. Introduction

Experimental investigations have shown that the basal-ganglia exert an inhibitory influence on a number of motor neuron systems, and that a release of this inhibition permits a motor neuron to become active. The behavior switching that takes place surrounded by basal ganglia is prejudiced by voluminous signals of motor neurons (massive data) from many components of the substructures of the brain, including prefrontal cortex which plays a fundamental key role and thus dominant in executive functions. Its functional architectures parallel in nature, consists of sub-cortical-nuclei (SCN) in the brains of vertebrates positioned or seated at forebrain, caudate nucleus, putamen, globus pallidus (GP) and substantia-nigra (SN, Fig 3) that are complex-neural-structure correlated with motoneuron function. It receives afferents from motor cortex and drives efferent's to thalamus cortex, controls and tame the motor neuron impulses from cortex to spinal-cord. While anatomical structural organization provide some clues as to what might be the function of basal ganglia circuits in PD patients, albeit the inference of function from anatomical structure is exploratory. One investigative approach to studying-the-function of an area-of-the-CNS in particular substantia-nigra (SN) is to acquire the STN neurons with extracellular MER in locally anesthetized PD patients. [1] Other approaches involve inferences of neuronal signaling from imaging studies of blood flow and metabolism, or of changes in gene expression. By sampling the signal of a part of the brain during behavior, one can gain some insight into

* *Corresponding author.*
 E-mail address: drvenkateshwararrr@gmail.com (V. R. Raju).

what role that part might play in behavior. Neurons within different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement.[1–3] In this study, we followed the MER approach. Keeping this in mind, a retrospective study was carried out at tertiary care NIMS Hospital and research center (Hyderabad, Telangana State TS, South India) with a dedicated movement disorder unit in Neuroscience – Artificial intelligence and computer science, biomedical engineering, computational neurology, neurology and neurosurgery departments of NIMS. Twelve subjects with diagnosis of PD as per Unified Parkinson disease rating scale UPDRS (stage I-III and score 0-6) United Kingdom Parkinson disease society brain bank criteria (UK-PDSBBC) are included in the study.[4–7]

1.1. Parkinson's Disease

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-features such as symptoms akin to or reminiscent of tremor, Bradykinesia (or akinesia, i.e., slowness of movement, absence, delay in initiation), rigidity and postural instability. Though clinical-diagnosis and benefits of deep-brain-stimulation (DBS) in subthalamic-nuclei (STN) have been established, albeit, how its mechanisms augment the motoric-symptoms mainly reducing-tremors and motor-fluctuations and restoring and/or increasing motor-functioning have not been fully elucidated. Also its objective-methods for quantifying—efficacy are sparse.

We present a Principal-component (PC) feature based tracking via clustering the Parkinson's with STN-DBS by applying machine learning cluster analysis to conglomerate and construe the data based on input data and finally to quantify the efficacy of DBS predict UPDRS score objectively. Twelve (12) PD patients are included in this study. Our hypothesis is that whether DBS and innocuous microelectrodes saves STN neurons and restores motor function. In our long study, high frequency stimulation in PD brain did not dent STN neurons. Further, it is risk-free to stimulate-STN much-prior than it was accepted far so. Intra operative (or intraoperative) microelectrode-recording (MER) for targeting during deep brain stimulation (DBS) procedures has been evaluated in 46 successive patients with advanced idiopathic Parkinson's disease, who received DBS in the STN neurons. We extracted—extrapolated MER signals of STN features with PCs for computing the effects of DBS in PD. The signal parameters were transformed in to a lower-dimensional-feature space. In our computation we obtained 75% variation in scatter-plot. We find that MER gives proof of correct-positioning of microelectrode, ensures accurate-detection of STN confines and establishes its exact coordinates in a more objective

way. MER boosts safety, accuracy and efficacy of DBS-electrode implementation. Thus, MER confirms presence of abnormal STN neurons. Certainly tranquil MER can confirm clear position of electrodes and strengthen the confidence of the neurosurgeons that they are in the right-target. Availability of MER results in a vast data vis-à-vis functioning on neurons positioned-deep in the brain may further help in untying arcane—esoteric of brain.

Subthalamic nucleus deep brain stimulation (STN-DBS) alleviates the Parkinson's disease (typically called Parkinson disease designated with PD or the Parkinson's diseased population is also referred to as Parkinson's) motor/or motoric manifestations (the features or signs and symptoms or syndromes) by means of stimulating specific volumes of neural-tissue accurately. Whilst the effectiveness of point of electrode contact has been illustrated neuro electro physiological and anatomical structural correlates clinically, restorative stimuli acts liable during many discrete neural populations, imposing classification of the complete period of tissue activation. Yet, the microelectroneuro sensor (or microelectrode recording MER) acquisitions have to be planned or mapped to constructive and valuable concerned or targeting tissue movement and its volumes examined for analytical and prognostic signs.

1.1.1. Feature Manifestations - Signs and Symptoms (Syndromes and Diagnosis

Movement problems are a classic sign of Parkinson's disease and can vary among individuals in prevalence and severity. Each candidate can have one or more of these symptoms (or feature manifestations), some slightly worse than others.[1]

The four classes of cardinal motor symptoms of Parkinson's disease are[2]:

1. Tremor (quaver or quiver
2. Rigidity - Stiffness (e g , elders' limbs or bodies become more rigid
3. Bradykinesia/akinesia (e g , elders start to move more slowly
4. Postural instability (e g , impaired balance

Prime signs and symptoms of Parkinson can be so delicate that PD subjects (the Parkinson patients) often easily mistake them for facets of normal aging.[2] The features might indeed restrain at first truly. Somebody might observe and also perceive that their inscribing i.e., handwriting gets slighter, that their hand starts to shake (shaking palsy), that they possibly have supplementary complexity footing and/or standing up, or that they are a slight shaky unsteady and wobbly or sluggish. Now, the majority of those effects are rather you might think would occur as you get older and older, conversely what starts to ensue or occur is they happen to steadily and progressively inferior, shoddier and

worse, and start to distress every day activities—effects like conversation, speaking, stepping, gait walking, consuming food, drinking, or reading a newspaper, etc. At that juncture, that's when people typically ready to attend the physician.[4]

There are also regular symptoms which frequently herald and lead the motoric-signs of Parkinson's, together with hitch in apnea; transformation in sagacity of stench (sense-of-smell); fatigue – exhaustion - tiredness; restless legs; and constipation too.[5]

There is quite a bit of research at the moment going on in to what these premature and untimely signs might mean and if that may perhaps and possibly will help envisage and foresee an enhanced diagnosis and treatment of the disease.[6]

A Parkinson disease p is typically directed by presenting manifestations (called the symptoms) for the reason that there is no blood or additional examining-test to prognoses the disease. Although one might think a brain scan such as an MRI may be successful in detecting PD, "in a scan like magnetic resonance imaging, which shows structural changes in the brain, they appear normal in Parkinson's disease because these cells that die off are a very small population, yet they have a huge impact on the patient's movement.[7]

Diagnosis can also be complicated by the fact that other disorders can have similar symptoms to those exhibited with PD. After older adults are put on PD treatments for their symptoms, a more definitive diagnosis can be made. "Parkinson's disease may be difficult to diagnose initially, but the classic PD symptoms and response to medications are supportive factors.[8]

1.2. Management Then and Now

The balance of treatment for Parkinson's disease then and now is very individualized because older adults can have varying degrees of symptoms, and no two patients react in exactly the same way. The gold standard for treating PD, which has been used for many years as its primary treatment, is Levodopa (the metabolic precursor of dopamine). A type of dopamine-replacement therapy, "It's a compound that is naturally found in plants and animals, and it's a precursor to dopamine,"[9] noting that it is typically given with another compound called carbidopa to ensure its ability to cross the blood-brain barrier and get into the brain.

"When it gets into the brain, the brain cells convert L-dopa into dopamine, which reduces the tremor and some of the motor symptoms and allows the patients to lead relatively normal lives,",[10] who **note**s that L-dopa does not help with balance and other nonmotor symptoms.

However, that L-dopa can create its own problems. "One thing that happens with L-dopa is that, as patients are on it for a longer period of time, they start to have side effects called dyskinesias, which are sudden involuntary movements," Noting that they can affect older

adults' quality of life. "Imagine you're having a really hard time walking and this drug makes it better, but suddenly you get these very strange movements. One of the challenges facing therapeutic development for PD is discovering the means to improve motor function and decrease involuntary movements while maintaining quality of life for the individual and providing as full a range of motion as possible."

According to,[11] there are different categories of dopamine-replacement drugs that, by targeting different parts of the dopamine metabolic pathway as L-dopa does, increase the production of dopamine. Compounds such as Azilect, a monoamino oxidase B inhibitor, can block the degradation of dopamine, and still others enhance the activity of dopamine at its receptor (a dopamine signal). All these drugs are basically improve dopamine signaling in the brain to help the damaged circuits,".[12]

Another category of drugs is used to balance other brain chemicals that are also affected after the dopamine cells die, and there's also a third class of drugs that will affect the nonmotor symptoms patients with PD may experience, such as anxiety, depression, and orthostatic hypotension.[13]

For patients whose symptoms are minimally improved by medication, deep brain stimulation has been implemented and can be a successful treatment for some PD patients because it may reduce the need for medication and improve dyskinesias. "Recent evidence suggests that deep brain stimulation significantly improves movement and quality of life in PD patients. Consultation with a physician is necessary to determine whether this surgical procedure is the best course of action for an individual patient,"[14].

2. New Discovery and New Hopes in Neuro Protection

While quite a few and numerous cures and medications are being utilized for older adults with PD, all the current medications work on managing symptoms, but none can impede or prevent the disease's progression. Innovative and novel research discovery into neuro protection is demanding to change it. Neuro protection is where research is headed right now because levedopa (L-dopa), as far as we know, does not stop the progression of the disease. None of the drugs that are available stop the progression of the disease.[15] Hence, there is extensive effort in this area right now in both basic research and clinical trials.[16] says neuroprotection has researchers looking down new avenues for a cure, such as dietary supplements and drugs that have been used in the treatment of other disorders. For example, several ongoing clinical trials are examining the effects of creatine, which is commonly used to build muscle, and coenzyme Q10, which "works through cellular structures called mitochondria, the power plants of cells, to clear any harmful substances that are produced if the mitochondria are not working to capacity. For example, if a power plant were releasing harmful chemicals into the air, coenzyme

Q10 would serve as a filter to prevent this from happening and keep the environment clear, allowing those around to breathe better,"[17]

Both of these compounds are neuroprotective in animal models and have been well tolerated in humans, "so there is significant focus on using dietary supplements and drugs that have been utilized for other disorders that in animal models have an effect,"[18] of the potential promise of neuroprotection for stopping the progression of PD.

Mentions isradapine as an example of a compound researchers are currently studying.[19,20] on this calcium blocker typically used to treat high blood pressure. Interpreting Surmeier's results to date,[21,22] has found that isradipine makes old dopamine cells young again by changing the pattern of communication of these cells with brain circuits. Scientists are pursuing basic and clinical research to determine whether isradipine and similar compounds will improve the function of dopamine cells and provide a new therapy for PD."[23]

Other clinical trials are now examining urate's effect on PD.[24] "A large study has shown that high levels of urate may actually be protective in Parkinson's disease," Noting that there are many studies ongoing in this area right now, both at basic research and clinical trial levels.[25]

A cure for P D can be expected any day now, no one knows how close—or far away—that cure may be.[1] But according to[1–5] there is a great deal of high-quality directed, focused research that is currently being funded by the National Institutes of Health and nonprofit foundations, such as the Michael J. Fox Foundation, the Parkinson's Disease Foundation, and the National Parkinson Foundation, to bring that date closer for all those who suffer from the disease. "Researchers have made rapid progress in defining potential causes of PD." Currently, significant efforts in basic and clinical research are directed toward development of improved treatments, including the identification of neuro protective strategies that can slow disease progression. As scientists continue to discover more about the function of genes, risk factors, and brain circuits involved in PD, they work steadily toward a cure.[26]

3. Biomedical Signal Processing and Analysis

Human bodies are relentlessly communicating or corresponding the information a propos our strength and physical condition. Such information is capable of gathering throughout the bio-physio-logical instruments and devices which evaluate activity of the brain (AoB), nerve conduction velocity (NCV), stimulus intensity of deep brain stimulation, rising time of EMG and EEG gadgets, heart rate, blood pressure, oxygen saturation levels, blood glucose, and so forth. Conventionally and customarily, such dimensions are in use at precise and at particular points in temporal regions and noted-down on the subject (diseased condition) registered case sheets. The clinicians glance at these case sheets very less than two percent of those values they make during their rounds—and management or administration (means treatment medication) assessments are made based on those remote and secluded readings. Biomedical signal processing involves the analysis of those measurements to give constructive and valuable information ahead that clinicians - physicians be capable of create constructive results and assessment choices. The scientists and engineers are detecting and also detect and discover the new customs-ways to process and analyze those signals or waveforms by employing a variety of precise mathematical statistical-formulae and an array of algorithmic techniques. Functioning and running in the midst of conventionally established bio-medical measurement utilities and tools; the waveform-signals shall be quantified by the computer programmes – the software to offer clinicians amid multi-channel/real-time data and a greater imminent-insight and impending approaches to assist in clinical-diagnostic evaluations for effective prognostic diagnosis. By employing further urbane and classy refined means to examine to investigate what our body conditions are stating, the researchers can be prospectively establish the state of a candidate's physical condition and wellbeing in the course of new and less invasive frontier revolutionary cutting edge sophisticated and high rich technologies such as microelectrode recording with deep brain stimulators (MER with STN-DBS) and non invasive procedures such as functional magnetic resonance imaging (fMRI), photon imaging like positron emitted tomography (PET) and photon emission computerized tomography SPECT, computed axial tomography (CAT, transcranial magnetic stimulators (TMS) and DatScan systems at the moment.

Concurrent examination simultaneously and asynchronously shall direct to improved management of chronic neurodegenerative diseases, such as Parkinson's disease neurodegenerative movement disorder and dystonia earlier detection of adverse events such as heart attacks and brain and heart strokes and earlier diagnosis of disease. Biomedical signal processing and analysis is predominantly valuable in the critical intensive care units and in decisive settings, in which, the diseased data have to be investigated in the given interval of real time, i.e., the amount of processing that can be accomplished in the given time is accurately computed in real time. In this study we applied MER with STN DBS technologies for capturing the microelectro neuro signal recordings of subthalamic nucleus neurons and then processing those signals for effective medical diagnostics of Parkinson's (the Parkinson or Parkinson's disease).

The STN is situated at the junction of the diencephalon and midbrain, ventral to the thalamus and nostril and lateral to the nucleus. STN receives inputs from the frontal lobes. Therefore, the only cortical input to the STN is from the

frontal lobes. Damage to STN causes large scale involuntary movements.

4. Medical Imaging

In healthcare medical systems, magnetic resonance imaging (MRI) or functional magnetic resonance imaging (fMRI) help them and overcome their challenges is that of medical imaging, particularly for management and tracking of Parkinson's disease, Alzheimer's and cancer treatment. Current imaging methods for monitoring the prevalence of tumors during treatment all have their limitations. Computed Axial Tomography (CAT) scans can yield information on the silhouette – shape or form and dimensional magnitude called the size and its spatio temporal resolutions (dynamic range or resolution) is squat and stumpy, i.e., very low in contrast to supplementary techniques. Positron emission tomography (PET) scans on the other hand are able to trace the tumor by determining the metabolic activity of body tissues, but it requires injection of a radioactive tracer. Magnetic resonance imaging does boast a higher spatio temporal resolution, and it is a noninvasive technique which does not harm the brain, but often an injection of a radioactive substance is applied. While MRI is considered to be highly spatio temporal resolution, quantum computing is offering the possibility of seeing even more than we can see with this method. However, the quantum computing is in its infancy stage in North American and European countries and in India it is in fetus stage. Like in MRI magnetic fields and radio waves are used to generate images, but the difference is, with the help of quantum computing it can look at single molecules or conglomerative clusters of molecules instead of the entire tissues. With MRI the gray image will only generate light or dark, and neuroradiologists then transmutes or decodes or interprets the images and finally render the findings of the image. Another point is MRI does not confirm and does not demonstrate the tiny images in the human or animal brain such as subthalamic nucleus or nuclei (STN) in Parkinson's diseased conditions and also the image generated is not able to differentiate between tissue type and hence one cannot get a more precise interpretation of what's occurring inside the vertebra – the body. To overcome this difficulty in Parkinson's image acquisitions, a cutting edge technological machine called micro electroneurosensor recording or microelectrode recording (MER) is employed.

The predicament i.e., quandary or hitch with targeting subthalamic nuclei is that it is a small biconvex lens structure and diamond shaped component and not fully visibly detected on the MRI due to lack of contrast between the STN and the neighboring structures.[8,9] Thus other methods such as Lozano's technique where a position of 3 mm lateral to the superolateral border of the red nucleus is targeted have been studied and found to be effective areas for stimulation.[10] However, electro-neuro-physiological iMER is more effectual in pinpointing the STN than through the Lozano's physiological method. Therefore, as the MRI techniques are not absolutely ideal, use of electro-neuro-physiological signal acquisition techniques such as microelectrodes recording signals of the subthalamic nucleus over and above the intra-operative induced stimulations have facilitated visibly in differentiating the subthalamic-nuclei.

Microelectrode recording can detect and discover from the patterns or signatures of the STN neurons by their feature-characteristic bursting patterns and their giant waveforms—signals evidently categorize the nucleus neurons form the adjoining and contiguous structures. On stable stimuli is studied to guarantee and make sure that the there is most favorable and best optimal advantage and gain among the least and slightest dyskinesias i.e., side effects which is the ending test to guarantee to make sure the exact objective of the subthalamus, i.e., subthalamic nucleus..Though these techniques are employed combinedly throughout targeting more often than not, albeit, while the individual role of every modality is still anonymous and indefinite.

5. Algorithm to Improve Medical Imaging

Researchers at Microsoft have teamed up with scientists at Case Western Reserve University in Cleveland to test an algorithm that has been designed to work on quantum computers with the aim of improving medical imaging by enhancing both the speed and quality. The method is referred to as magnetic resonance fingerprinting (MRF), similar to magnetic resonance imaging (MRI). Like MRI magnetic fields and radio waves are used to generate images, however the dissimilarity and disparity is, in the midst of quantum computing it can point and look at entire (single) molecule or whole clusters of molecules in preference to the entire tissue. With MRI the image will only generate light or dark, and a radiologist then 'translates' these. The benefit with MRF is that the image generated is already able to differentiate between tissue type, giving a more accurate interpretation of what's occurring inside the body.

Quantum computing can support this more fine grained analysis due to its ability to process and analyze data in parallel, making it significantly more powerful than conventional computers. It does this through replacing the transistors we find in traditional computers with qubits, which can store data as both 0s and 1s, rather than the traditional binary method of 0s or 1s. With the power to process data in parallel the quantum computer has a far greater capacity for information transfer and manipulation, this key quality allows it to not only make processes at higher speeds, but also allows it to receive more data, which in this case results in a higher definition image.

It's not the first algorithm to have been designed in anticipation of the quantum computers that will be available

to us in the near future. Algorithms have also been created to find better ways to manage the electrical grid, improve delivery routes in urban areas, and manage risks and returns in investment portfolios.

6. Methods

6.1. Stereotactic functional neurosurgery

Surgery was done by a skilled neuro-surgeon. Stereotactic functional targets were acquired by means of a expert system amid a stereotactic functional frame (CRW) that has a luminant MR localizer. The targeting was done 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 antereo-lateral limit of red nucleus. The co-ordinates are entered into stereo-calc software which gives the co-ordinates of the STN. Another neuro navigation software –Framelink is also applied to plot the course of the electrodes and to avoid vessels. The surgery is performed with two burr holes on the two sides based on the co-ordinates. Five channels are introduced with the central channel representing the MRI target while medial (nearer the centre) and lateral (away from the centre) are placed in the x-axis while anterior (front) and posterior (back) are placed in the y-axis to swathe an area-of5mm diameter. Intra-operative microrecording (iMER) was done in all 5 channels. Five microelectrodes were passed gradually during the STN and recording is performed from 10mm over to 10mm beneath (±10mm) the STN designed on the MRI. STN was discovered by a high noise with a large baseline and an irregular discharge patterns with compound frequencies. Fig 2 shows the microelectrode recording which is obtained from the STN. By employing the iMER along 46 (bilateral) STN DBS implants in 46 PD patients 92 sides (bilateral) the MER signals of STN were gathered. However, as per the neurologists and neurosurgeons and neuroradiologists opinion 34 candidates were eliminated because of noise and distortion and blurred signatures or patterns and only 12 perfect candidates were selected from those 46 and feature extraction and associations, i.e., conglomerative clusters obtained through computation and plotted in 2D. The then features were mapped in spatio-temporal regions alongside tissue activation sizes of restorative stimuli, simulated by employing prognostically-established stimulus encoding parameters and copious custom-made, atlas sovereign anisotropic element (organ) properties derivative as of seven 7Tesla diffusion tensor MR imaging objects. Logistic least absolute shrinkage and selection operator was employed in a set-of 16 core microelectrodes beyond 19 implants to discover predictors of DBS lead points in the MER. Support vector machines by applying these predictors were exploited to predict stimulus activity. Execution was corroborated by a test set of 6 core microelectrodes.

The success of the post operative prognostic and/or clinical outcome of deep brain stimulation subthalamic nucleus (DBS-STN) surgery depends predominantly on the accurate medley of subjects (i.e., patients) and on optimal targeting, which is based on signal and neuro imaging modalities and techniques and intra operative electrophysiological recordings. Surgery is usually performed while the patient is awake, as MER is not altered by local anesthesia and clinical intra operative assessment can be carried out by evaluating possible adverse effects and improvement in Parkinsonian signs during intra operative macro and micro stimuli techniques as well.

7. Source of Funding

Conflicts of interest

The authors declare that they have no conflict of interest.

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Author biography

Venkateshwarla Rama Raju, Professor