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Implantation of microchips into the subthalamic nucleus neurons of Parkinson‘s disease and movement disorders

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ABSTRACT

D B S is a typical interventional procedure performed for Parkinson patients both by giving local anesthesia and also and global anesthesia mainly to reduce the cardinal motor symptoms. However, it is not giving the results for the non motor symptoms. Some groups of subjects are not eligible for neurosurgical DBS operation in local anesthesia because of medical causes, for instance enormous fright and panic, concentrated co-operativity, or coughing-attacks. Microrecording (MER) has been shown to be helpful in DBS surgery. The goal of this study was to estimate the likelihood probability, i.e., practicability of M E R for S T N D B S neurosurgery under general anesthesia plus to compare the data of intra operative M E R also the prognosis data by that of the contemporary-literature of PD-subjects enduring or experiencing the surgery under local anesthesia. The data of 12subjects by advanced PD, mean4.2 as per Hoehn and Yahr status, were operated by S T N D B S, due to certain medical conditions decreeing not in DBS under local anesthesia, were on second thoughts investigated. Every procedure was accomplished under analgosedation by propofol or remifentanil and intra operative M E R with induced STN DBS. In support of M E R, remifentanil was ended wholly and propofol was reduced to the degree to the extent in so far as much as that achievable. The S T N can be detected intra operatively in every subject by M E R. A characteristic satiated stuffed pattern/signature was detected, while a broadening of the electrical-baseline-noise nd distortion could not be as satisfactorily and sufficiently detected as in subjects in local-anesthesia. The daily off-phases of subjects were decreased from 50% to17%, while UPDRS Scale stage III+ score was concentrated condensed as of42, pre-operative, prescription “OFF” to22, induced stimuli was “ON”, medication OFF and 11, stimuli and “O N”, medication O N. 2subjects proved a transient neuro psycho logical deteriorating following neurosurgery, however together had pre accessible occurrences incidents of discourse not in direction.

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 combination of cardinal motoric-symptoms: tremor, Bradykinesia/akinesia, 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 motoric-symptoms principally reducing-tremors and motor-fluctuations and restoring and/or increasing motor-functioning have not been fully elucidated. 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

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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.

Parkinson's disease (PD) is the second most common neurodegenerative disease which is characterised by the convolution of tremor, rigidity, Bradykinesia (akinesia) and postural instability. The search for optimal cure is on for the past 2 centuries since the time it was first described by James Parkinson.[1] The main pathology of Parkinson's disease is present in the nigrostriatal system which is characterised by the degeneration of the dopaminergic neurons in the substantia-nigra pars compacta/reticulata (S N p c/p r).

S N p c is a part of the basal-ganglia (BG) which modulates the cortex and helps in fine tuning motor-activities. There are two dopaminergic pathways involved form the striatum to the thalamus and the cortex- direct pathway which leads to stimulation of the cortex and the indirect pathway which inhibits the cortex. The dopaminergic supply from the SNpc acts by D1 receptors which activate the direct pathway and the D2 receptors which inhibit the indirect pathway. Absence of these neurons leads to an increased firing from the subthalamic-nuclei (STN) and globus pallidal interna (GPi) neurons which lead to increased inhibition of the thalamic neurons and cortex and overall reduced movement.[2] The advent of treatment with initial tuned regimen of oral Levodopa (L-dopa, the metabolic precursor of dopamine) followed by the armamentarium of various drugs but the medical treatment is fraught with appearance of various side effects such as dyskinesias and on-off phenomenon.

The dopaminergic drive in normal patients is a continuous one and oral medications however cannot completely mimic the normal state with drug concentrations changing from trough to peak levels based on the time of consumption. Initial ablative surgeries performed during the 1950s targeting the globus pallidus interna and thalamus improved with the onset of stereotactic surgery and deep brain stimulation techniques. This involves inhibition of the brain structures with high frequency oscillations usually of the frequencies ranging from 130 to 190 Hz. This high frequency inhibition of neurons in two structures –subthalamic nucleus and GPi has improved symptoms in patients with Parkinson's disease and has become the standard of care in advanced disease.[3,4] Further, on head to head comparison of the therapeutic options, a recent study has shown that DBS is more effective than the best medical therapy in improving "on" time without troubling dyskinesias by 4.6h/day, motor function in 71% versus 36% on medical therapy, and in quality of life, 6 months after surgery.[5,6]

Of the two, subthalamic nucleus (STN) stimulation is associated with more drug reduction compared to globus pallidal stimulation. Subthalamic nuclei deep brain stimulation (STN DBS) involves placing two leads, one in each subthalamic nucleus with a pulse generator placed under the skin on the chest. The surgery is performed under stereotactic guidance –i.e., a stereotactic frame is placed on the head and the nucleus is identified on the magnetic resonance imaging (MRI) of the brain and the co-ordinates are obtained in the vertical and the horizontal planes, then with the help of these co-ordinates the leads are placed through a small hole on the scalp.

For optimal therapeutic efficacy of DBS, it is imperative to have accurate electrode lead placement.[7] A small deviation in the electrode positioning may cause it to be misplaced in the surrounding structures such as the corticospinal tract, red nucleus, oculomotor nerve and other structures. Improper targeting may lead to various side effects such as speech disorders, visual deficits with diplopia, ocular deviations or motor stiffness.[7]

2. Medical Imaging

Hospital based MRI machine works by placing a subject (patient) inside a magnetic field, such that protons in the body's atoms align with the machine's magnet. The machine then sends radio waves through the body area being imaged, which knocks the protons out of alignment. When these pulses are switched off, the protons realign and emit electromagnetic (EM) waves at a particular frequency. If the frequency emitted by the body's tissues matches that of sensors in the machine, the two frequencies will resonate like guitar strings tuned to the same note. The machine uses this resonance to reconstruct an image of the body. 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.

3. Algorithm to Improve Medical Imaging

An algorithm can be built in such a way that to work on quantum computers in the midst of the objective of progressing medical imaging by means of advancing both the acceleration - speed and eminence quality and class, i.e., excellence superiority (worth very much—value). The method is referred to as magnetic resonance fingerprinting (M R F), similar to magnetic resonance imaging (M R I). Like M R I 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—shadowy and gloomy, and a radiologist then 'translates' these. The benefit with M R F 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. On the other hand, Quantum computing can support this more fine grained analysis due to its ability to process and analyze data in parallel in concurrent, making it significantly more powerful than conventional computers. It does this through replacing the transistors we find in traditional computers by means of qubits, which can store data as 0‘s and 1‘s, rather more willing than the usual conventional 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.

4. Aiming the Subthalamic nucleus (S T N) Neurons with M R I

The difficulty or predicament by way of aiming S T N is that it is very small factor in an important area of the brain plus cannot be clearly visible or cannot be detected on raw MR images of T1 weighted due to lack of contrast between the STN and the surrounding structures.[8,9] So other modus operandi is employed. It can be seen on MRI but the acquired T1 weighted image has to be transformed. However, other methods for instance, Lozano's technique where a position of 3mm on the side of the brain which is imaginative which is tangential(lateral) to supraolateral—superolateral boundary-perimeter of the red nucleus is aimed contain been examined and found to be effectual regions for induced stimuli.[10]

As the MRI techniques are not absolutely perfect, use of electrophysiological techniques such as microelectrode recording from the subthalamic nucleus as well as intra-operative stimulation have helped in clearly demarcating the STN. Microelectrode recording can identify subthalamic neurons by their characteristic bursting pattern and their signals clearly identify the nucleus form the surrounding structures. On table stimulation is studied to ensure that the there is optimal benefit with the least side effects and this is the final test to ensure the correct targeting of the STN.

Though, the above methods are usually employed in aiming the STN for the successful detection and implantation of the D B S electrode with deep brain stimulations, but the individual function of every modality is still not known yet. The goal of the this research was to study the associative relationship or parallel connection or link (i.e., correlation) of microrecording by the absolute region or territory preferred for the period of bi lateral ST N D B S performed at our research centre.

5. Methods

A retrospective study was carried out at a tertiary care hospital with a dedicated movement disorder unit from South India. 46 patients with diagnosis of PD as per United Kingdom Parkinson disease society brain bank criteria were included. All the patients were willing to undergo the procedure and fulfilled the following criteria to be eligible for STN-DBS i.e., they had disease duration of 6 years or more, good response to tuned regimen of oral Levodopa (L-dopa, the metabolic precursor of dopamine), able to walk independently in drug "ON" state and had normal cognition. All PD patients who were wheelchair or bed bound, had dementia or severe psychiatric disturbances were excluded.

Surgery was performed in all by a qualified neurosurgeon. Stereotactic targets were acquired using a specialised system with a stereotactic frame (CRW) which has a luminant MR localiser. 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 antereolateral border 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 used 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. 5 channels are introduced with the central channel (as channel 1) representing the MRI target while medial (nearer the centre) representing as channel 2 and lateral (away from the centre) representing as channel 3 are placed in the x axis while anterior (front) representing as channel 4 and posterior (back) representing as channel 5 are placed in the y axis to cover an area of 5 mm diameter. Intra-operative recording was performed in all 5 channels. All five microelectrodes are slowly passed through the STN and recording is performed from 10mm above to 10mm below the STN calculated on the MRI. STN IS identified by a high noise with a large baseline and an irregular discharge with multiple frequencies. Figure 1 shows the microelectrode recording which is obtained from the STN. The channel with maximum recording and the earliest recording were recorded on both sides.

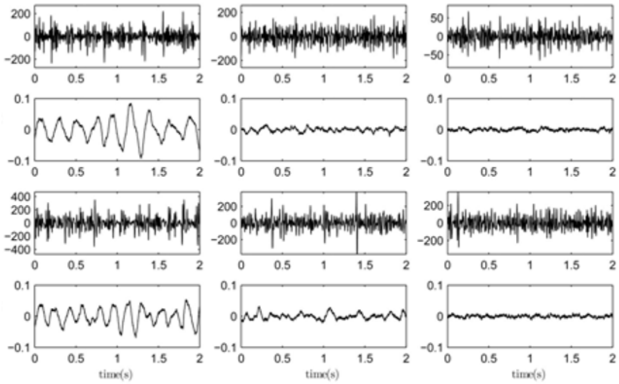

Fig. 1: Microrecordings (MER) of sub thalamic nucleus neuronsthrough the deep brain stimulations of a Parkinson subject with DBS off (left)and on (middle) and one healthy control (right) during the isometriccontraction of BB muscles.

Intra operative test stimulation was performed in all channels from the level at the onset of MER recording. Stimulation was done at 1mv, 3mv to assess the improvement in Bradykinesia (akinesia), rigidity and tremor. Appearance of dyskinesias (side-effects) was considered to be associated with accurate targeting. Side effects were assessed at 5mv and 7mv to ensure that the final channel chosen had maximum improvement with least side effects.

Correlation was assessed between the aspects of MER and the final channel chosen in 46 patients (92 sides).Figure 2

6. Results

Forty six Parkinson's diseased subjects were included with mean age of 58.1 + 9.1 years with a mean disease duration of 8.8 + 3.64 years. Out of 5 channels, STN microelectrode recordings were detected in 3.5 +1.1 on right side and 3.6 +1.04 on left side. Final tract selected were most commonly central seen in 42.3% followed by anterior in 33.7%. Concordance of final tract with the channel having the highest recording was 58.7%, with channel showing maximum width of recording was 48% and with either was 64%. Absence of any recording in the final tract chosen was seen in 6.52%. Out of 6 subjects, one had no recording and lead was placed in central channel. Two patients had medial, 2 anterior and 2central channels as their final tract. This was selected based on induced macro stimulus.

7. Discussion

We assessed the role of microelectrode stimulation in selection of the final channel. Compared to the anatomical

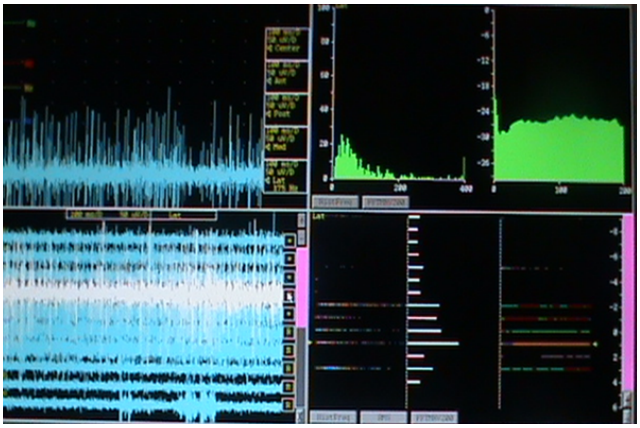

Fig. 2: Microrecording – thesegment within the image zenith left depicts MER-signal-recording in asingle-level in a single-channel; the panel (bottom-left) illustrates themicrorecording in central-channel above 11millimetres depicts typicalfiring-pattern by means of asymmetrical-firing plus broad-baseline noted(from-1.00level; the top right illustrates typical histogram-frequency also FastFourier Transform (F F T) waveforms of a characteristic S T N neuron; underneath(base) right depicts equivalent in a radial or lineal manner.

localisation based on MRI where the final tract was seen only in 42.3% the microlectrode recording was associated with final channel in 64 %. This is similar to a previous study wherein by using MER, an average pass through the STN of 5.6 mm was achieved compared to 4.6 mm if central tract was selected as per imaging.[11–18]

MER by itself is not a complete tool to clearly distinguish—discriminate the optimal target as the line of the DBS lead may not correspond to the axis of the STN. Further the impedance of the microelectrode may vary as they may be influenced by the brain tissue and may not show a clear recording. Still MER definitely confirms the clear position of the electrodes and bolsters the confidence of the neurosurgeons that they are in the target. Further the availability of microelectrode recording results in a vast data regarding the functioning on the neurons situated deep in the brain and may help in further untying mysteries of the brain.

8. Conclusion

S T N operation for idiopathic P D via M E R direction is potential through high-quality diagnostic findings by usual anesthesia. Intra operative M E R of S T N area can be done in normal anesthesia by a singular anesthesiao logical p r o t o c o l. In this setting, usual S T N characteristic-pattern can be detected, while normal broadening of the milieu-noise baseline despite the fact that toward the inside the S T N area is visibly not present. Thus the method might broaden the clusters-of-subjects qualified for S T N-neuro-operation. Even though the medical-clinical progressions and parameter-settings in this study were in the range of the existing theory, auxiliary randomized proscribed studies are fundamental to contrast and measure up the findings of S T N D B S in usual-anesthesia and local-anesthesia. Micro electrode recording is functional to corroborate the right path but has to be taken in thought by means of effects on induced macro stimuli.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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