Electrical stimulations with fusion technologies in neuro ethics, neuromodulation, pain, psychiatry, e-Seizures and brain injuries

Venkateshwarla Rama Raju[1,2,3]

[1]Professor, [1]CMR College of Engineering & Technology, Medchal Road, Kandlakoya, Hyderabad, Telangana State, India, [2]Nizam`s Institute of Medical Sciences, Hyderabad, Telangana, India. [3]CMR Institute of Medical Sciences, Medchal Road, Kandlakoya, Hyderabad, Telangana State, India

***Corresponding Author: V Rama Raju**
Email-id: drvrr@cmrcet.org

Abstract
It is an excellent opportunity and also it is facilitating the neuroscientists neuroscience communities to acquire the data with the cutting-edge technologies. It was estimated that globally more than 2,00,000 deep brain stimulation devices both open loop and now adaptive closed loop DBS devices have been implanted for subjects with advanced idiopathic Parkinson`s disease anguishing and experiencing with neurological and also neuro psychiatric disorders. This study demonstrates the existing, ongoing, emerging and evolving the groundbreaking DBS technologies as well as the logistical and ethical issues confronting the field. The significancy of the frontiers in DBS is on cutting edge research and collaboration with the potential to advance the DBS neural stimulation field and in the following areas and field of neuromodulation in Europe and Asia – China and Indian sub-continent, Australia and other advanced countries; cutting-edgetechnologies, neuro-ethics, interventional psychiatry, adaptive DBS, neuromodulation for pain, network neuromodulation for epileptic-seizures and neuromodulation for traumatic-brain-injury.

Keywords: Deep brain stimulation (DBS), Dystonia, Epilepsy, e-Seizures, Interventional psychiatry, Interventional study (MER, STN, DBS), Movement disorders, Neuro-ethics, Open loop DBS, Pain, Parkinson`s disease (PD), Psychiatric disorders, Subthalamic nucleus (STN), Traumatic brain injury, Neuro ethics, Pain, Interventional Psychiatry, Epilepsy, and Traumatic Brain Injury.

Introduction
The cutting-edge technologies like microelectrode recordings, magnetic resonance imaging, computed axial tomography, positron emitted tomography, transcranial magnetic stimulations, deep brain stimulations, VIM and STN stimulations with DBS etc are proving the results very effectively in clinical studies and for effective medical diagnostics. This study focuses on advances in the following areas: neuromodulation in Europe, Asia and Australia; cutting-edge technologies, neuroethics, interventional psychiatry, adaptive DBS, neuromodulation for pain, network neuromodulation for epilepsy and neuromodulation for traumatic brain injury. The DBS Think Tank discussed Maslow's theories and a path to transcendence both for patients as well as for DBS practitioners. The attendees also participated in a DBS Think Tank survey, which documented the expansion of DBS into several indications such as movement disorders, psychiatric disorders, and pain and traumatic brain I juries.

Disorders. This proceeding summarizes the advances discussed atthe DBS Think Tank IX.

We presume that the reaction of a patient to levodopa (L-dopa) greatly predicts the response to induced DBS stimulus.[1] However, as we substantiate and verify this in our conglomerate-group (number of patients '*n'* = '334' subjects; *R*:0.58; R^2:0.35;$p<2.2e^{-16}$ highest significancy) the response of the individual patient can vary considerably (Figure 1). There are two ways to address the adaptability or inconsistency: Using the application of innovative statistical machine learning technique(s). Simplified and widespread linear models by applying clinical and/or diagnostic and medical data be able to be employed. Subsequently correct cross validation (CCV), estimate progresses to a highest limit mean - R^2 of 0.358. Once outcomes are dichotomized-contradicted or separated (for instance, "UPDRS" scale stage III score progress ~≥33.5%) plus superior modeling and AI-ML was utilized, the greatest discriminators estimated area under the curve (AUC) of 0.66.

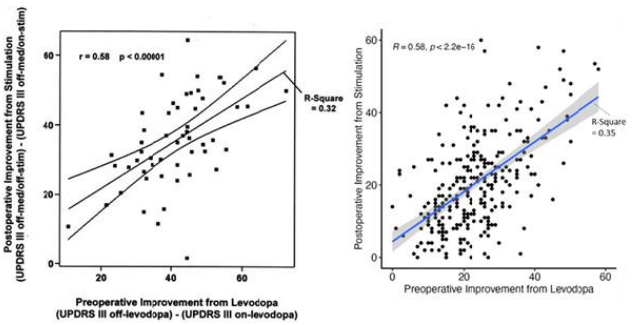

Figure 1. Correlation of UPDRS-stage III-score progress in the course of the pre op Levedopa (L-Dopa) test drive plus post op progression of UPDRS-stage III-score attributable to induced DBS stimuli just for initial description,[1] 2002; population sample n" = 56" diseased subjects) as well as existing data as of (population sample-size n"= 334"-subjects) through virtually the same statistical associations. However, the distribution or diffusion designed for specific diseased subjects are enormous.

Well- fitting curves can be achieved through limited conditions or standards. Though likely and favorable, significantly far more, collective, joint and mutual clusters of subjects, i.e., groups shall be needed and necessary too to

define the limits of this approach,[2] The next method will be to apply a new certain and contrasted consequences (for instance., tremor simplicity - difficulty of tremor DoT, QoL, FoG) to estimate likelihood. This methodology tends to progression in the area under the curve (AUC) of0.87 for freezing (axial symptoms) or offset (solidity or stability for the stabilization)plus progress to 0.76 for QoL[3-5] This second method has extra and very scope, flexibility, andleeway for the progression.

Progressing the sleep with deep brain stimulations

DBS is the best surgical and therapeutic-procedure for advanced idiopathic Parkinson`s. It is not just for Parkinson`s but then can be utilized for subjects along with more movement and control disorders involving dystonia—dystonic disorder, dystonic Writer`s cramp, essential—tremor (E.T), Musician`s cramp, followed by psychic and psychiatric-disorders. The wide range of applications indicates that the improvement of the method might be far reaching. Several indeed numerous developments use awaken physiological triangulation plus stimulus evaluations to augment the pinpointing of the effect of D B S.

Nevertheless, various diseased subjects (patients) continue to stay frightened of the awaken conscious brain surgery, i.e., locally anesthetized DBS surgery leave behind and setting down a huge disparity for the progression of DBS therapy.

To facilitate DBS in restfulness, snoozing or slumbering DBS, we considered the cortico-basal ganglia neural, i.e., neuronal network of primate animals in pro-po-fol, an anesthetic drug utilized to induce and maintaining the superior general anesthesia and to staid and dignified subjects (i.e., patients) for this medical procedure, ketamine and also interspersed pro-po-fol-ketamine (I.P.K) tranquility.[6]

Then we assessed these tranquilities in health and diseases states in Parkinson`s to that of apnea sleep controls. We discovered in poly-somno-graphy plus neural/neuronal activity microelectrode recordings in primate-animals considered together with keta-mine augments higher-frequency-power andalso synchroneity (synchronization) as pro-po-fol progresses low-down-frequency-power and also synchroneity (Figure 2). Hence, keta-mine won`t hide the lower oscillatory-frequencies which are utilized for physio-logical triangulation to BG-DBS targets. The brain spectra in ketamine state and pro-po-fol imitated or simulated rapid-eye-movement, i.e., REM and non REM (NREM) slumber activity, as well as the I.P.K-protocol looked like the fast neural-dynamics of the N-REM and REM snooze- apnea sleep-cycle.

These findings in primate-animal models could be the initial stepto napping i.e., DBS OFF in conjunction with undistorted physio logical triangulation/ or navigation. The clinical-diagnosis and the subjective evaluation of the Parkinson`sin I.P.K tranquility-protocol ought to be tested openly as well as potentially orally in groups-of-people (double-blind)studies.

Fusion of MRI and electrophysiological techniques

The detection of functional predictors by applying electro physiological techniques and MRI brain imaging is vital for enhancing the scheduling of direct DBS procedural execution further progressing the neuromodulation novelties.

One of the problem with targeting subthalamic nucleus(STN) is that due to its size is very small diameter (few millimeters) small biconvex lens structured almond shaped and not visibly discovered on the MRI (even though with good spatio temporal resolutions and dynamic ranges) as a result of lack of contrast and disparity and also dichotomy amongst the STN and the neighboring structures (in the entire STN zone).[7-9] The STN can be envisioned through the MRI but then other methods such as Lozano's technique where a position 3 millimeters lateral to the superolateral border of the red nucleus is targeted have been studied and found to be useful regions and zones (the STN zone) for induced stimuli.[10]

As the MRI techniques are not perfect absolutely, therefore, the use of electro physiological (neuro electro physiological) techniques such as microelectrode signal recording of the STN as well as intra-operative stimulus have had assisted for distinctly and unequivocally delineating the STN.[11]

Because anatomical structural concern offers some clues as to what the function of basal ganglia circuits in PD patients might be, albeit the inference of function from anatomical structure is experimental. An investigative approach for studying the function of an area of the CNS substantia-nigra (SN) is to acquire the STN neurons with extracellular micro electrode recordings in PD patients.[12-15] Other approaches involve inferences of neuronal signaling from imaging studies of blood flow and metabolism, or of variations in gene expression. By means of sampling the signal/waveform of a section of the brain during the course of the behavior and in the course of behavior, one can gain some insight into what role that part might play in actions, behavior, and performance. Neurons within different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement,[16-17] In this study, we followed the MER approach.

MER can detect subthalamic-nuclei neurons by their distinctive bursting pattern and their signals/waveforms visibly distinguish the nucleus form the surrounding structures. On stable stimulus was studied to ensure that the there is optimum use by the slightest side effects, and this is the final test to ensure the correct targeting of the STN. These techniques are generally applied in order or sequence while targeting, though the specific role of every single modality is yet not known.

However, fusion of MRI and electrophysiological – the combined techniques will give better results than individual technique. Hence, the development of the fusion of multi modal imaging plus improved and innovative-advanced data-analyses techniques fromelectro physiological pre operative and post operative and intra operative signal recordings, that support electrode placement during the stereotactic

procedure and the post operative programming.[18-19] Mainly this is pertinent while reflecting electro physiological micro electrode recording (MER) data in Parkinson`s disease symptoms of motor like tremor Parkinson`s, by means of peripheral signals/or waveforms such as electromyography (EMG) and accelerometer(ACC) are being very important techniques to evaluate the appropriateness or correctness for deep brain stimulation therapeutic-treatment.

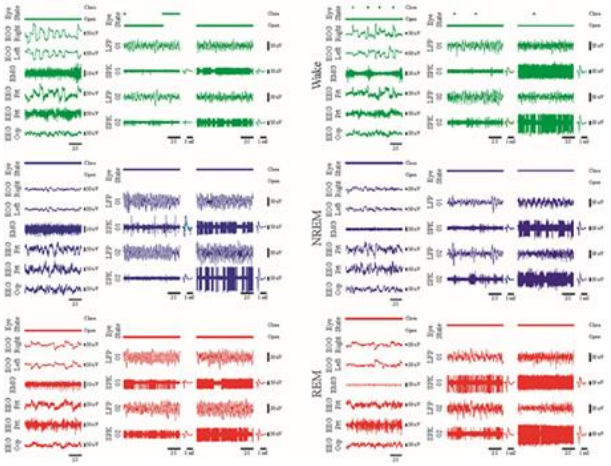

Figure 2. Samples of 10Sec duration of poly-somnography (PSG) – column 1 (eyes exposed-state and closed-state, E.O.G, E.M.G and E.E.G), local-field-potentials followed by spiking-activity (LFP - SPK) acquired with micro electrode recording (MER) system in the anterior-cortex(i.e.,frontal) and the exterior-peripheral section of the pallidal neurons, i.e.,globus-pallidus (Ctx/GPe) for the period of tranquility-periods (panel top left, middle is saline baseline - upper,olive-green;propofol—center, pink; followed by ketamine-hydrochloride - bottom, red) then throughout the awaken-apnea sleep-cycle (right, awaken - upper, olive-green; NREM is center, pink; followed by REM is at bottom/lower, and then red).[6]

We began by means of studying at the normal harmonic power of the accelerometer recordings (i.e.,mean) in Parkinson`s with tremor cardinal motor feature functioning a holding condition and were capable of differentiating amongst Parkinson disease plus essential-tremor subjects(patients) with 96% precision then suggested this magnitude as a modern symptomatic-test/diagnostic-test.[20] Lately, we established measurements as the solidity of tremor, i.e., stability-index and matched by the 'mean-harmonic-power' plus few recent other measurements such as 'cross-frequency-coupling' amongst two electromyography (EMG) followed by accelerometer (ACC) signals/waveforms as of distinct muscles.[21] To detect the electro physiological "patterns" or "signatures" directly that are concern to correlate to these findings from the edge-periphery, parallel (asynchronized) and concurrent-measure of electro-encephalo-graphy (EEG) will be needed positively.

Nevertheless, EEG-signals acquired from the seizure-epileptic subjects receiving DBS-stimulations induces unwanted noised components followed by some distortions in the frequency transform domain (*f-domain*) of the signals, specifically at the stimulus-frequency (130Hz, 160Hz or maximum 190Hz) followed by ensuing successive-harmonics. To analyze the frequency patterns/signatures, firstly, the noise and distortions must be removed. This can be done in two ways at the hardware (implementation of analog and/or digital filters) levels and at the software levels (through software programming). Rather than a simple low pass filter that's get rid of the data beyond the cut-offfrequency, we were able to build a technique that takes into account both the time and frequency (transform) domain dynamics. When the noise and distortions were removed, theoscillatory- features can be expected and projected from the encephalographic-signals, and/or local field potentials (LFPs) shown as robust predictors. We applied microelectrode recording and looked at the optimal predictor for subthalamic nucleus (STN) targeting and optimal trajectoriesand we were able to show both beta and gamma oscillatory activity as good predictors. Following the robust predictors, more process was to translate the predictors into the clinical setting as ongoing. This process was summarized in Fiureg 3. We see a clear need for the multimodal integration of distinct-features and model-types, simulation prototypes to tune plus to understand the pathophysiological mechanisms of DBS.

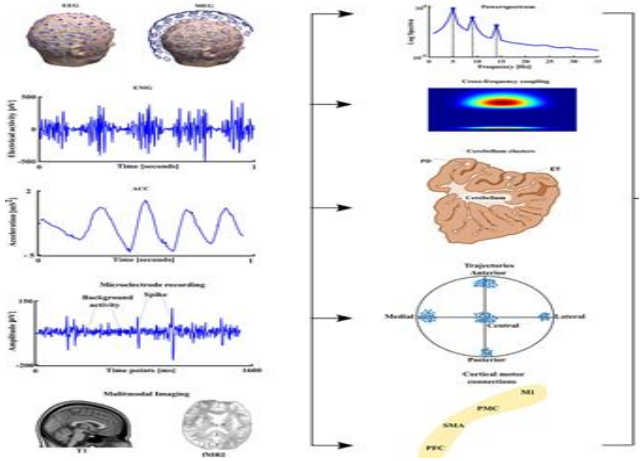

Figure 3. Diverse modern modal qualities or/modalities showed in the primary section. The panel in the top left shows wireless-EEG, MEG, second: the muscle and nerve peripheral-signals of EMG, third: accelerometer (ACC), fourth: acquisition of MER signals, followed by T1-weighted images of MRI and functional-MRI. The panel in the top right showing the extrapolated predictors. First: power-spectrum, second: power spectrum, third: cross-frequency-coupling (CFC) and source analyses-based cerebellum-clusters designed for Parkinson`s plus Parkinson`s with essential-tremors. Fourth: Path-based oscillatory-predictors and fifth,

i.e., final depicting the cortical-motor-connectivity by 4 prime regions-of-motor (RoM): primary-motor-cortex (M1), pre-motor-cortex(PMC), supplementary-motor-area(SMA) followed by pre-frontal-cortex (PFC) to subthalamic-nucleus(STN). Hence, the multi modal assimilation of all these feature-manifestations capable of leading to optimum DBS in all those Parkinson`s.

Also, model-prototypes for the long-term outcome prediction and development or real-time electro physiological monitoring shall be highly effective and more valuable. Such prototypes can be established/launched into clinical practice for effective medical diagnosis and ALSO should drive our aim of potential routes, wide-ranging of sensor-measuring engineering-device.

Australian perspective

In Queensland center of neuroscience, the pallidal (anterio medial internus, i.e., A.V-G.Pi) has demonstrated continued substantial gain for the Tourette's/syndrome (TS) movement disorder, motoric and non-motoric signs and symptoms (feature-manifestations) like obsessivecompulsivedisorder (O.C.D), cognitive-depression, cognitive-dementia(C.D) and cognitive-impairment (C I) and overall Q o L. From 2008 onwards, the team has implemented D.B.S in 28 PD subjects who were patients in conjunction withacute illness and both pathologically and therapeutically deflective or refractile T.S frequently as well as correlated developmental neuro psychiatric problems. Of these, the first two cases had leads implanted in the postero-ventral globus pallidus internus (PV-GPi) as a result of the difficulty of the motoric- tics and also self-destruction. In these two-cases, supplementary macro stimulus-leads were embedded into the Nucleus Accumbens (NA-cc) to prevent and to monitor major obsessive-compulsive-disorder signs.

Two and a half decades ago (~2008), prior to the stimulations, the other subject (patient) was committed entrenched/institutionalized in a young and teenage psychiatric ability however needed elimination of the stimulus device, i.e., D.B.S.in 2015-16, because of the implanted pulse generators (IPGs) followed by macro-lead infectious or contagious. The subject continued stimulus off, i.e., DBS OFF for six years and was significant return of the patient syndrome symptoms, i.e., Tourette syndrome symptom's and now living in the general community with a sustain.

Another subject who is a patient had obsessive-compulsive disorder-symptoms beyond the motoric-tics as well as phonic-tics, plus the m a c r o - leads were embedded into the NA-cc through the great experimental scientific-outcome of the OCD, then to a lower degree of motor-tics.

The outstanding s u b j e c t s ' patients had m a c r o - leads inserted in the am-GPI neuronsalong with substantial aid for Tourette and obsessive CD and features as well as despair and generally QoL. This gain has beencontinued over the years since many of these patients had their surgery underwent DBS. The patients have had regular continuation plus valuable to notice, minimal to no change in the DBS programming parameters were required beyond a 6–12-month time point post-operatively. One subject with am-GPi micro-leads asked for the confiscation or exclusion the device due to the no disparity during DBS ON and during DBS OFF and were capable to move here and there mingle with civic and could get the service. And hence there was no follow-up in these patients.

In our long endeavors', i t i s s h o w e d t h a t t h e considerable a n d prolonged scientific experimental clinical progress in the QoL of syndrome subjects, i.e., the Tourette syndrome subject patients in two key Tourette syndrome features also in continuous decrease in O.C.D signs and symptoms, depression, plus advanced QoL.

We believe that it is important to support pathologically and therapeutically deflective or refractile Tourette-syndrome subjects (patients) gain broader contact log on to the stimulus device, i.e., the D.B.S. device and we strongly advocate the goals of the DBS Registry and International Tourette Syndrome and corresponding data base. A huge double-blind study at a level 1 may slow down this approach because of because of lower-case rates. Hence, this interruption cane be at the expense of philanthropic advantage for the subjects with Tourette-syndrome, professions, as well as the organization.

Reviews on Tele medicine – Chinese perspectives

China was inducted into the advances of distant stimulus DBS devices and corresponding coding/programming. The authors did excellent work to build this distant-remote programming DBS device, and currently employed very largely in Chinese subcontinent. The reliable, safety and security communication via remote is the top priority. The authors utilized the coding (software S/W)) security and safeguard and alsoH / W(hardware) safety into the device. The DBS procedural process system comprises a neuro-physician (neurologist), computer-server, a terminal as well as subject (patient) terminal and presents a customized administration and a intelligible/user-friendly internet-accessible-interface, plus a real time video consulting and recording with optimal throughput that accomplishes the amount of processing and which can be achieved in the given interval of time. Apart from that DBS device,the programme too works for vagal-nerve-stimulation (VNS), a binary serial interface, sacral neuro-modulation, and a stimulus spinal-cord.

In the past, we established a collaborative video-recorder acquisition (data and information gathering) and imparting training and learning and a understanding system for the tele medicine, which was crucial and significant the remote-coding/programming. Automatically, the system can offer video-instructions, it records the data and information routinely without any human/manual intervention, and offer real-time-interactive advice, plus prevent and tame the excellence by applying the innovative and sophisticated AI-M L techniques completely. A n d i t a l s o offers a d o d g e or defaulting methodfor acquiring the data and information by the aid of others as well by the

means of an approach as a selfie-method forindividual and with unbiased-recording. More significantly, the system incorporates facial altering expertise for privacy and safety. At present, we can adjust uniqueness-of-face whilst maintaining facial scrubs and movements like blepharospasms and eyelids-blinking's. It has been also demonstrated latest innovations with Blue tooth technologies with real-time acquisition of DBS recordings and this technique apart from stimulating the brain, and it also acquires the local-field-potentials (LFPs) movement and activities, acquires the data of ECG, EMG-acceleration, and wirelessly transmits to a smart cellular mobile-phones asynchronously (parallelly) and concurrently. So, we are confident that the distant remote coding platform and the networked-system is extremely ground-breaking, inventive and pioneering and shall aid in therapeutic DBS procedure. Distinguishing.

Conclusion

We expect further tests in implementing this program, for instance the safety and privacy of subject-patient and/or acquiring sensitive symptoms/feature-manifestations as of distant detection, and sensing remotely and also distinguishing.

Source of Funding

None.

Conflict of Interest

None.

References

1. Charles P.D., Blercom V.N., Krack P., Lee S.L., Xie J., Besson G. ,et.al., Predictors of effective bilateral subthalamic nucleus stimulation for PD, *J Neurol*, Vol.59,(79),Pp:932–4.
2. Habets J.G.V., Janssen M.L.F., Duits A.A., Sijben, L. C. J., Mulders, A. E. P., De Greef, B., et al. (2020). Machine learning prediction of motor response after deep brain stimulation in Parkinson's disease-proof of principle in a retrospective cohort. *Peer J*, 2:(31), PP:8:e10317, 2020. doi:10.7717/peerj.10317
3. Gavriliuc O., Paschen S., Andrusca A., Schlenstedt C., Deuschl G., Prediction of the effect of deep brain stimulation on gait freezing of Parkinson's disease. *Parkinsonism Related Disor* 87:(121),PP:82–6, 2021. doi:10.1016/j.parkreldis.2021.
4. Jost, V.V.Vandewalle, Rizos A., Loehrer P.A., Silverdale M., Evans J.,et al.,Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease. *NPJ Parkinson's Disor.*7:(7), PP: 1–7. 2021, doi:10.1038/ s41531-021-00174-x
5. Yin Z., Bai Y., Zou L., Zhang X., Wang H., Gao D.,et.al.. Balance response to levodopa predicts balance improvement after bilateral subthalamic nucleus deep brain stimulation in Parkinson's disease. *NPJ Parkinsons Dis.* 7, 1–9. 2021.doi:10.1038/s41531-021-00192-9
6. Guang J., Baker H., Nizri O.B.Y., Firman S., Reiss U.W., Kapuller V.,et.al. Toward asleep DBS: cortico-basal ganglia spectral and coherence activity during interleaved propofol/ketamine sedation mimics NREM/REM sleep activity. NPJ Parkinson's Disorders,7:(7), PP:1–12. 2021, doi:10.1038/s41531- 021-00211-9
7. Kostoglou K., Classification and Prediction of Clinical Improvement in Deep Brain Stimulation from Intraoperative Microelectrode Recording, IEEE *Trans. BME*, 64:(5), PP: 1123-30, May 2017
8. Kim S.J., Kavirakja U., Zhen N., Elena M., Carolyn G.,et.al, Effects of Subthalamic nucleus stimulation on motor cortex plasticity in Parkinson disease, *Neurol*, 85:(1),PP: 425-32, 2015
9. Bour L.J., Contarino M.F., Foncke E.M.,.deBie R.M, Long term experience with intraoperative micro recording during DBS neurosurgery in STN and Gpi . *Acta Neuro* (Wien), 152:(12),PP:2069-77, Oct 15, 2010.
10. Zuan H., Neural Signal processing of microelectrode recordings for deep brain stimulation, Chalmers University of Technology, 2009.
11. Benabid A. L., "Deep brain stimulation for Parkinson's disease," Curr. Opin. Neurobiol., vol. 13, no. 6, pp. 696–706, 2003.
12. Benabid A. L. et al., "Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease," Stereotact. Funct. Neurosurg., vol. 62, no. 1–4, pp. 76–84, 1994.
13. Moran A. et al., "Subthalamic nucleus functional organization revealed by Parkinsonian neuronal oscillations and synchrony," Brain, vol. 131, no. 12, pp. 3395–3409, 2008.
14. Defer G. L., "Core assessment program for surgical intervention therapies in Parkinson's disease," *Mov. Disord.* 14:(4) PP. 572–84, 1999.
15. Souza Y.M.A., Schwalb J.M., Hamani C., Eltahawy H., Hoque T., Cyr J.S., Lozano A.M.. Comparison of three methods of targeting the subthalamic nucleus for chronic stimulation in Parkinson's disease. *Neurosurge*, 62:(2) PP:875-83, Feb 2008.
16. Larry S., Darwin B., Floyd E.B., Sascha L.d., Anirvan G., Nicholas C.S., Fundamental Neuroscience, 4th Edition. AP-Academic Press, 2012.
17. McClelland S., 3rd. A cost analysis of intraoperative microelectrode recording during subthalamic stimulation for Parkinson's disease. *Mov Disord*, Vol. 000, No. 000, Jun 14, 2011.
18. Escamilla G.G., Muthuraman M., Ciolac D., Coenen V.A., Schnitzler A., and Groppa S., Neuroimaging and electrophysiology meet invasive neurostimulation for causal interrogations and modulations of brain states. Neuro Image 220:(170), PP:117-44. doi: 10.1016/j.neuroimage.2020.117144
19. Muthuraman M., Bange M., Koirala N., Ciolac D., Pintea B., Glaser M., et.al., Cross-frequency coupling between gamma oscillations and deep brain stimulation frequency in Parkinson's disease. *Brain*, 143:(141), PP: 3393–3407. 2020, doi: 10. 1093/brain/awaa297
20. Muthuraman M., Hossen A., Heute U., Deuschl G., and J. Raethjen, A new diagnostic test to distinguish tremulous Parkinson's disease from advanced essential tremor. *Mov Disord.*26:(00),PP:1548–52,2011, doi: 10.1002/mds.23672
21. Biase L.d., Brittain J.S., Shah S.A., Pedrosa D.J., Cagnan H., Mathy A., et.al., Tremor stability index: a new tool for differential-diagnosis-in-tremor-syndromes. *Brain.* 140:(000),PP:1977–86,2017,doi:10.1093/brain/awx104

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