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Intelligent Deep Brain Stimulation Systems: A General Review

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ABSTRACT Brain Stimulation is now becoming the preferred approach where pharmacological treatment is ineffective in neurological conditions such as Parkinson's Disease (PD), Tourette Syndrome, Addiction disorder, Depression, and Anxiety. The brain can be stimulated by electrical current, light, and sound energy, invasively or non-invasively. The article comprises of pathophysiology in Parkinson's, current pharmacological modalities used for the treatment (along with limitations), and deep brain stimulation as the last resort. The article also provides a comprehensive analysis of intelligent Deep Brain Stimulation methods (procedure, architecture, and type) from the studies and research conducted in the last five years. In the end, research gaps and associated challenges are discussed.

INDEX TERMS Brain stimulation, deep brain stimulation, intelligent equipment, medical expert systems.

I. INTRODUCTION

Parkinson's Disease is the most common chronic neuronal degenerative disorder [1], [2]. Including Parkinson, other neurological conditions such as depression [3], anxiety [4], loss of memory [5], Epilepsy [6], [7] and Drug addiction [8] are also being treated with brain stimulation technique since multiple side effects are seen with long-term use of oral medication [9]. So, medical practitioners are in search of non-pharmacological treatment (such as Deep Brain Stimulation) which has a similar therapeutic effect but with lesser side effects either in the short-term or in the long-term specifically in Parkinson's [10]. The objective of this research (in long-term) is to provide a feasible way of applying neuromodulation with a novel, knowledge-based, informed computer-aided through a system in the future.

From the review of literature, it is been found that the neural biomarkers or signals are of significant importance to automate any Brain Stimulation process along with volumetric tissue activation [11] and functional connectivity. However, in upcoming sections, the studies will be discussed in detail.

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The other important issues related to the application of neuromodulation are listed as:

1. The calculation of Effective dose [11], [12].
2. Reducing the Side Effects [13], [14].
3. Mechanism of action.
4. Potential sites for stimulations [15].
5. The open-loop mechanism in current therapies [16].
6. Potential Neural Bio-Markers [17].
7. Making the process less time-consuming, efficient, and error-proof [12].

So, the following research objectives can be drawn from the previous studies that there is a need for an effective and better deep brain stimulation system for maximizing therapeutic benefit in terms of:

1. Intensity.
2. Amount of time the neuromodulation is applied.
3. Regions or areas targeted for stimulation.
4. The volume of activation (brain tissues) during stimulation.

In the current setup of DBS (deep brain stimulation), the electrodes used for neuromodulation in the deep brain stimulation technique are placed invasively inside the brain [18]. The problem arises when there is a need for stimulation of two different areas of the brain which requires

multiple electrodes to be placed. To, overcome this problem, novel stimulation devices should be used to apply neuromodulation, eliminating the need for surgery or any operative procedure. From the review of literature, some of the key findings are observed and are listed as:

1. Deep Brain Stimulation requires the implantation of intracortical electrodes. Therefore, surgery is required to perform implantation [18] and complications occur [19]. Sometimes revisions are faced as well [20].
2. The electrodes are implanted in a single area (this means that stimulation for multiple regions cannot be done with this setting or they require multiple electrodes to be implanted) [15], [18].
3. Implanted Pulse Generator (IPG) is required for this purpose. This pulse generator is implanted in the cervical region through a surgical process.
4. The pulse generator is powered by a battery. The battery provides sufficient energy for the production of current and should last for a long time [13].
5. The current architecture of deep brain stimulation is open-loop [16], [17], [21]. This means that the process flow is unidirectional, the applied stimulation has constant parameters and remains unchanged during the stimulation period. This imposes a challenge that the ongoing dynamics or the discomfort faced by the patient is not noticed by the system (feedback) but only by the neuro-physician.
6. The initial dose of current for the stimulation or programming is manipulated by the patient's response [21].
7. The effective dose is a matter of debate. For example, for some people, lesser side effects may be called effective and for some higher improvement is considered effective [22], [23].
8. The removal of electrodes surgically is required when the patient is feeling too much discomfort or if the neuro-physician decides that no more neuromodulation is required. So, removal of electrodes as associated with complications [24]–[27]

One study reported that up to 48.5% cases were of reimplantation due to lack of benefit from therapy or improper targeting. North American dataset highlighted cases of removal and revision up to 34.0% from 15.0% [28]. There are multiple issues of which only a few are mentioned above, there is a need for a better neuromodulation device or a neurostimulator. Multiple companies tried to design better neurostimulators (e.g., Medtronics, a bio-engineering company, designed a device that is connected with the mobile phone of the patient). Scientists are looking forward to a technique that will be cost-effective, non-invasive, and feasible.

However, the other intents of this article are described as:

1. Enlighten the reader about the pathophysiology of disease as compared to normal brain function.
2. Explore the application of electrical stimulation and non-pharmacological, FDA-approved Deep brain stimulation for the treatment of Parkinson's.
3. Review and analyse advance DBS techniques (proposed in recent years).
4. Identify the shortfalls and discuss improvement of models (from recent studies).

The rest of the article is organized as follows:

Introduction: explains the problem, and the intent of literature review.

Normal Brain Function & Disorder: the section describes the normal brain function, pathophysiology and treatment modalities.

Neuromodulation: describes the therapeutic use of neuromodulation.

Biomarkers: highlights potential neural biomarkers in DBS systems.

Advance DBS Systems: discusses the recently proposed models, biomarkers and results

Discussion: highlights the valuable aspects of each study/model.

Challenges: provides an overview of research gaps.

Verdict: Concludes this article.

II. NORMAL BRAIN FUNCTION & DISORDER

Cells in the brain are called neurons. A neuron is an **excitable cell** (for example electrically) which transmits signals (bits of information) throughout the body. Neurons are classified in different types but commonly all neurons possess a cell body (or soma), an axon and set of dendrites. The axon is considered as the signal transmitter while the dendrites are considered as receivers as they receive signals from the surroundings (that is sensory inputs and other neurons) (FIGURE 1). Neurons are connected to each other via synapses. Neurons secretes certain chemical components known as neurotransmitters. By release of these chemicals, electrical potential is generated inside the nerve body and axon. The end of the axon is called axon terminal where the release of neurotransmitter (or neuromodulators) and neurohormones occur in exchange of the electrical signals. Neurons channel their potentials by movement of ion through voltage-gated ion paths across the membranes (sodium, potassium and chloride ions are the greatest contributor to the common neuron in terms of membrane potential). The resting membrane voltage of common neuron is -70mV. So, it is now clear that electrical stimulation is helpful in activating neuron. A special feature of most synapses is that signals normally pass only in forward direction [29], [30].

Parkinson was first described as Shaking Palsy by Dr. James Parkinson in 1817. The progressive, neurodegenerative disease is characterized by **motor** and nonmotor functions [31]. Motor functions include muscle rigidity (stiffness of the muscles), bradykinesia (slow movements), and resting tremor (involuntary tremors when the person is at rest). The pathophysiology identifies the PD as the disorder of extrapyramidal system (part of motor cortex which is responsible for involuntary movements). The extrapyramidal system involves **motor region,** an area of the brain which

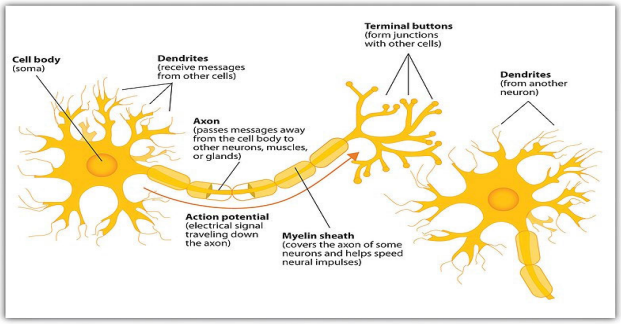

FIGURE 1. **Neuron and its components (courtesy of wikipedia).**

is responsible for producing, controlling, modifying body movements in an appropriate fashion. Due to loss of neurotransmitter (dopamine) in this region (basal ganglia), clinical features of Parkinson appear such as weak muscular activity, slower movement and tremors. **Basal Ganglia** involves internal **globus pallidal** segment of the ventral striatum and the pars reticulata portion of substantia nigra (FIGURE 2). These areas are viable for stimulation as suggested by many studies [11], [12], [15]–[17], [32].

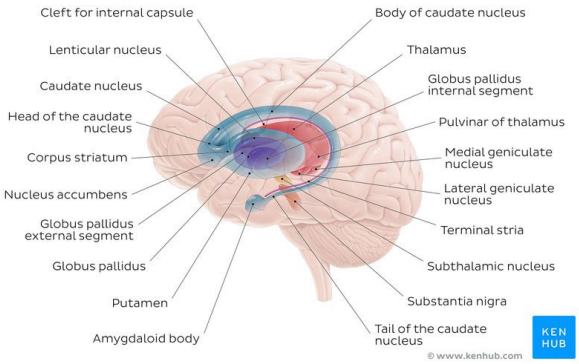

FIGURE 2. **Various nuclei in deeper regions of brain (image borrowed from kenhubu).**

The question arises what if the medicine fails, or doesn't work either or is **ineffective**. Parkinson Disease has been known for its drug resistance [33], if the dopamine is used for a longer time. Levodopa is the most efficacious drug [33] but the its use is not effective in sleep problems, autonomic dysfunction, posture and gait problems, freezing, speech problems, affective and cognitive disorders [33].

For such reasons, alternative strategies are adopted of which electrical stimulation is one. Other strategies may include drug repurposing and gene therapy (ProSavin, to restore the dopaminergic activity in the brain by the gene carrier lentivirus vector encoding DOPA, decarboxylase, TH and GTPCH1) [31] and drug repurposing [34].

III. NEUROMODULATION & DEEP BRAIN STIMULATION

Neuromodulation, is one of the alternative treatment techniques for Parkinson other than pharmacological. The application of neuromodulation requires the understanding of brain, underlying mechanics and dynamics. The matter is still in debate that the underlying mechanism of action of neuromodulation is not fully understood yet ([17], [35]–[39]). However, the treatment is approved by regulatory bodies (FDA approvements) for treatment of PD, ET Dystonia, OCD and Epilepsy [40] and being tested for over a variety of diseases such as depression [22], anxiety [4], Tourette Syndrome [41] etc. It is common that Electrical stimulation is used for the treatment of various physical ailments for a long time such as Functional Nerve Stimulation [42].

The term neuromodulation is itself defined as the technique of altering neuronal activity by means of stimulus either from chemical or from electrical or any other form (e.g., optic, acoustic or ultrasonic) [43]. However, being limited to Electrical stimulation which is common, consists of variety of applications methods, techniques, and sites (for stimulation). For example, the electrical stimulation can be transcranial (non-invasive) or it can be intracortical (invasive) [44]. Recently, a new technique called cranial nerve stimulation has developed allowing the axonal pathways to be stimulated. These axonal pathways are responsible for carrying information to the brain giving rise to the higher cognition. Most of the types are either invasive (deep brain stimulation) or non-invasive (transcranial electrical stimulation) or both (cranial nerve stimulation) [45]. The other non-invasive established techniques are listed below:

A. ***Transcranial Magnetic Stimulation (TMS):*** Associated with the high frequency impulses (electrical) to generate action potentials. This technique is focused on providing the threshold current to neurons. This technique is characterized in terms of providing single pulses as well as in repetitive patterns, with the chances of interference in current ongoing brain oscillations [46].
B. ***Transcranial Electrical Stimulation (TES):*** Involves low potentials acceleration for neurons. It increases the *chances of getting action potential* in any neuron lying in specific brain area [33].
C. ***Transcranial Direct Current Stimulation (tDCS):*** Preferred to produce excitatory effects in brain by producing potentials between two electrodes. Alternating current can also be given with some parameters kept in mind like frequency, position and strength of the current applied [48], [49].
D. ***Transcranial Random Noise Stimulation (tRNS):*** It is neither used to produce excitatory effects, nor the underlying mechanism is completely known as compared to other techniques. It can interfere with ongoing brain processes. The magnetic effects (due to changing magnetic field) are passed through scalp and reach towards brain [50].

Other than electrical, there are stimulation methods which includes neuromodulation by light [51] and ultrasound [52], [53].

The current **deep brain stimulation** (DBS) setup for the neuromodulation is characterized as: an **implantation**

of electrodes into deep regions of the brain for modulating neural function in order to ameliorate neurological or psychiatric condition [18]. Further, an IPG (implantable pulse generator) is placed below the clavicle (sub dermally) (FIGURE 3). The IPG contains battery and wire leading to the connected electrodes inside the skull for the delivery of electrical pulses. The stimulation **parameters** can be controlled externally by clinicians or by patients. The parameters include pulse width, frequency, and voltage, which are altered according to the need of patient and to achieve optimum efficacy. However, the mechanism of modulation is generally believed that low-frequency pulses excite the neurons whereas high-frequency stimulation appears to inhibit or reduce the local activity. The knowledge and the selection of specific areas for stimulation is important. For example, it has been observed that STN-DBS (deep brain stimulation over sub thalamic nuclei) is effective in medication reduction while GPi-DBS (stimulation over globus pallidus internal) has been effective to ameliorate psychiatric illnesses in patients [18]. So, the selection of appropriate area for stimulation is also a matter of concern.

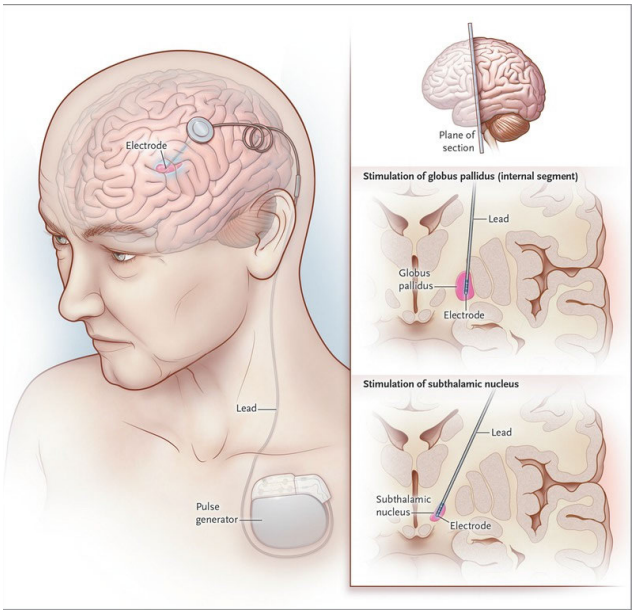

FIGURE 3. DBS setup [10], A complete picture (at left), brain section utilized for neuromodulation (top right), electrode placement in globus pallidus (middle right), and in subthalamic nucleus (bottom right).

Since, the precise physiology of stimulation is unknown, this poses few challenges as mentioned previously. First, the parameters of stimulation (frequency, pulse width, and potential) need to be optimized to achieve maximum benefit from the therapy [54]. Second, the improvement from the treatment is dependent on selecting the right brain area or target stimulation site. However, there is a possibility of more than one target stimulation site for single disease [15], [16], [55]. For instance, it can be noticed in the (TABLE 2) there are multiple sites or target areas for the brain stimulation in Parkinson. Third, the depletion of the battery is highly dependent on the parameters of stimulation such as amount of charge needed, frequency, etc. [56]. Battery replacement surgery is more common for the patients of dystonia as compared to patients of other diseases.

IV. BIOMARKERS

Classification of brain activity is important for understanding the ongoing dynamics during neuromodulation. For example, epileptic seizure patterns or ESP are used for the detection of Seizures during its presence. ESP can be detected through the electrodes placed over the scalp in EEGs [57]–[59] Similarly, EEG is well-known for the classification of brain activities such awake, sleeping, though processing. Similarly, abnormal brain function can be detected by means of electrical recordings [58], [60], and neuroimaging [61].

To record ongoing brain activity by electrical means, multiple modalities have been proposed such as EEG, ECoG, LFPs and Spikes. EEG is the method to record cerebral activity from the **outside of brain** by placing electrodes **over the scalp**. Richard Caton, in 1875 recorded the neuro-electrical activity (of animals) for the first time. However, the major work was done by a German psychiatrist named Hans Berger in 1924. The EEG represents neuronal activity (FIGURE 4).

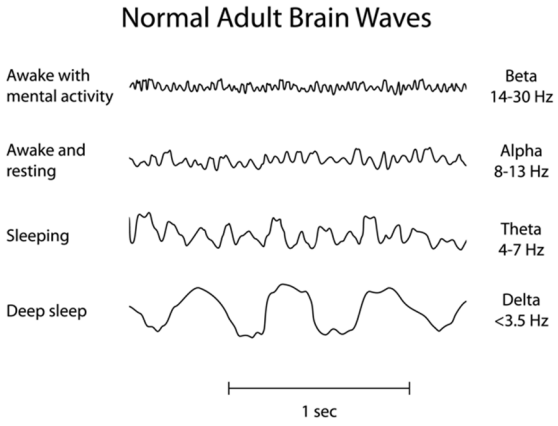

FIGURE 4. EEG-based oscillations and respective activities (courtesy of medcampus.io).

For example, EEG waveform pattern is **altered** during seizures (FIGURE 5). The EEG waveforms contains information like evoked potential (EP) and event-related potential (ERP) which are associated with neural activity due to specific stimulus. EEG has higher temporal resolution but limit its accurate interpretation due to various signals coming from other parts of the body. The original cerebral signal is attenuated with such signals coming from scalp, eyes, tongue and even heart. Hence EEG signals are susceptible to noise while interpreting waveforms [51]. The signal classification [63]–[65] is given as (FIGURE 5):

Despite these challenges, the waveforms have shown significant changes which are noticeable in EEG. For example, in patients of PD, there is an increase in delta activity [66],

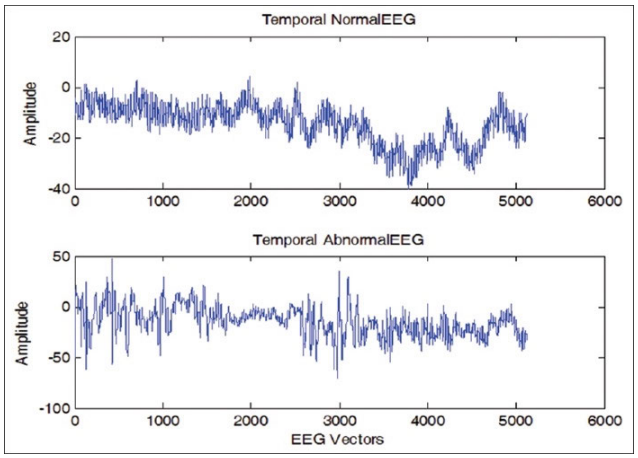

FIGURE 5. Sample electroencephalogram signal from normal and seizure subjects from [63].

PD patients with dementia have **slower EEGs** than patients of PD without dementia, and presence of **beta oscillations** in PD [66], [67]. The EEG waveforms in Parkinson disease can be seen (FIGURE 6 and FIGURE 7) as:

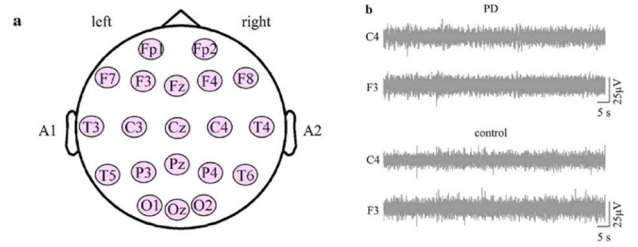

FIGURE 6. (A) Placement of electrodes in clinical experiment. (B) Difference in oscillations from electrode C4 AND F3 of controlled and PD patients [64].

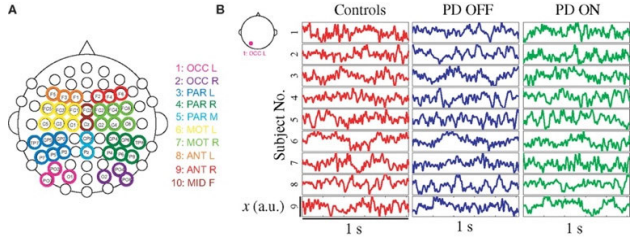

FIGURE 7. EEG waveforms of PD states [60].

The recording of intracerebral electric potential by means of electrodes invasively is known as Local Field Potential [68]. The electrical synchrony is produced by the population of neurons (each contributing to form larger, noticeable potential) [69]. Local Field Potentials (LFP) are considered as potential Biomarkers in Parkinson Disease [70]. LFPs have similar waveforms like EEG. Studies are being conducted to correlate brain activity and cognitive function [71]. Local field potential is collected from **deep layers** than from the surface. When the recording of sample electrical activity is from superficial layers of the brain (invasively), it is called Electrocorticography or ECoG [72].

It is seen that ECoG have spatial (mm scale) and temporal (ms scales) resolution than other techniques. Further, it is less susceptible to signal contamination than EEG and MEG. Recording of electrical activity from different levels of the brain are described in FIGURE 8 and FIGURE 9.

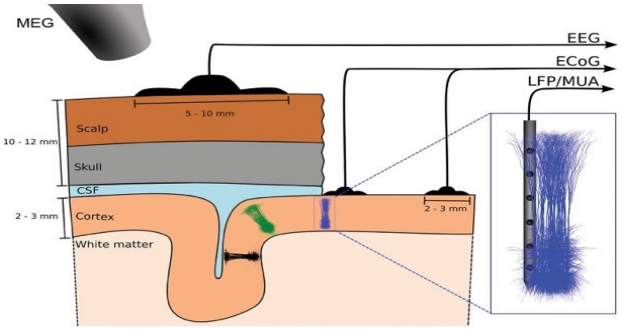

FIGURE 8. Levels of recording [73].

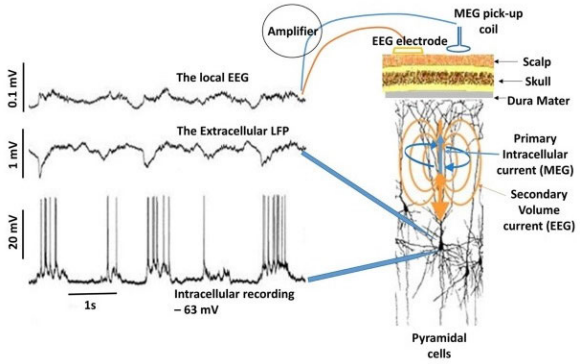

FIGURE 9. Patterns on each different level of recording [74].

It is now clear that EEG is non-invasive as compared to the other two (LFP & ECoG).

Multiple modalities have been suggested to diagnose the disease (e.g., Parkinson, Epilepsy, Seizures). These modalities are helpful in Computer-based assessment of diseases when the expert is unavailable. The patterns identified in MRI are helpful to be used in computer-based diagnosis and patient profiling where the specific anatomy of the brain must be known before treatment [61]. Other than imaging technologies, many researchers have used beta-band frequencies by means of ECoG for the determination of Tremor [21], [54], [56].

V. INTELLIGENT DEEP BRAIN STIMULATION SYSTEMS

The term intelligent used in this article refers to the system being able to carry out neuromodulation in an effective way. For example, saving battery drains, having better frequency to reduce side effects, making the modulation whenever required, and so on. So, the discussion is now focused on advance system the application of neuromodulation for the purpose of treatment and getting maximum benefit from the therapy.

The proposed system by [13] is effective for **axial** as well as **appendicular** symptoms. Axial symptoms are gait and posture instability while appendicular symptoms feature loss of appetite etc. Traditional DBS (generates High-Frequency pulses) is effective for appendicular symptoms more than for axial symptoms in Parkinson patients. The stimulation on sub thalamic nuclei (in Basal Ganglia region) by low-frequencies may reduce the speech issue and gait/balance but it is ineffective for appendicular symptoms and may have negative effects (may worsen the symptoms). So, a **Dual-Frequency (IL-IL or interleave-interlink)** based stimulation technique is applied to overcome the issue (of Low and High frequency associated after effects). In between the high and low frequencies, there is interleaving (infusing) frequency. It was originally designed to reduce the side effects of stimulation. Aconstant-frequency pulse with differing amplitude and width is generated by rapid and altering activation of two independent programs (Interleave and Interlink). The authors have combined interleaving with Low-Frequency DBS for sustaining appendicular symptoms (not worsening) and improving the axial symptoms in Parkinson patients.

This method works by two low frequencies, positioned through the DBS lead. The overlapping area receives the high-frequency stimulation whereas the non-overlapping areas are stimulated by low frequencies (FIGURE 10). The stimulation over these areas, in return controls the appendicular and axial symptoms of patient. It is achieved by an optimal electrode. In case the optimal electrode is missing, a survey is conducted to find the best contact of two electrode.

The improvement was measured using the CGI-C scale or Clinical Global Impression of Change (an easily applicable tool to scale the improvement over time [75]). The results were promising (despite the 9 out of 67 had incomplete control of appendicular symptoms with the patients average age of 65.9 years). It can be seen in FIGURE 11 that improvement is by 42.9% (or in simple terms patients stated that they improved much or very much). Few of the interesting matters from the study are also discussed. The one is the long-term effect, which is substantial in the following study reporting that the benefits were maintained to a long time period of an average of 22 months. The second one is the

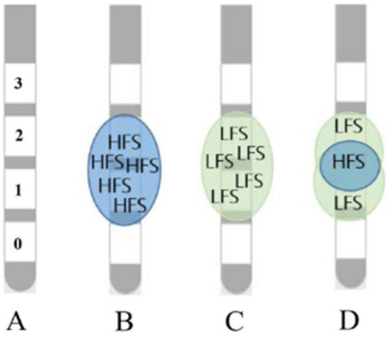

FIGURE 10. DBS lead (A), Conventional HFS (B), LFS (C), and IL–IL (D) [13].

usual battery drain in High-frequency DBS over sub thalamic nuclei. However, in this case, the battery drain was lower than HFS because IL-IL utilizes LFS which causes battery to last longer than conventional HF DBS. The third one is the premature return, which in this case was the early withdrawal of patients due to incomplete appendicular symptom control. The study had its own limitations including the quantitative measure of severity of disease. The one most important is the underlying mechanism of action of the treatment dynamics, which are still unknown. The suggested technique may have been specific to patients not improving with HFS (in appendicular symptoms) until the mechanism of action is certain.

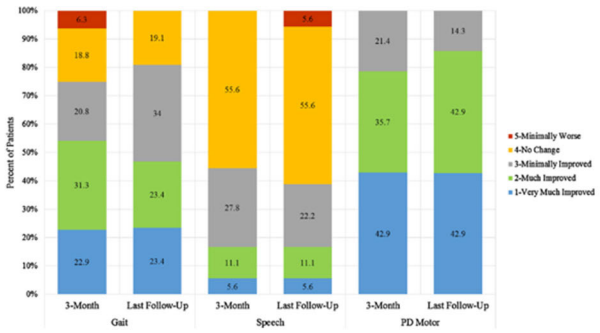

FIGURE 11. Improvement scale placement [13].

A model proposed by [36] is an **energy-efficient closed-loop DBS system** based on **Reinforcement Learning** algorithm. Reinforcement Learning is a simple umbrella term used to segregate learning strategies based on trial and error, reward and punishment, action and feedback [76]. The parameters during neuromodulation, are regulated by Reinforcement learning algorithm tested by computer-based brain model or simulation [77]. The model was found to be energy-efficient than conventional DBS. The use of computational model of Parkinsonism, where the network model consisted of interlinked biophysically-based spiking neurons, the PD state was defined by distorted relay reliability of the thalamus.

A system proposed by [78] stimulated two areas of Basal Ganglia in order to reduce intensity of electric field, the side effects, and the hand tremor. This system is called Active Disturbance Rejection Control (ADRC) which is based on a Deep Deterministic Policy Gradient (DDPG). A conventional feedback controller is used to stimulate STN and GPi simultaneously. The system was effective over the other state-of-the-art strategies.

[12] has presented the technique to **automate** the error-prone and hectic process of manually **programming** the electrode of DBS. The system consumed the **imagery data** of cerebellar area of motor thalamus into grid points for approximate afferent and efferent axonal pathway orientations. By this way, the Finite-Element Model simulated the volumetric tissue voltage getting through the DBS. This approach could reach to global optima within seconds and

promise the optimal DBS arrays automated configuration based on density.

[14] has presented effective technique to automate the stimulation process for the suppression of tremors. Commonly, DBS-leads are connected to a (surgically implanted) battery which delivers power. The idea is to use a BCI computer, which performs the process of DBS **stimulation automatically** (without intervention of human) as shown in FIGURE 12. This process of enabling and disabling stimulation is carried out through **neural sensing** of **movement** (via surgically implanted electrodes) which is further regulated on the basis of use of the effected limb. It means, the more the patient's effected limb is used for the movements and coordination, the more stimulation is applied. Thus, the **required amount** of **stimulation** is delivered is **controlled manner**.

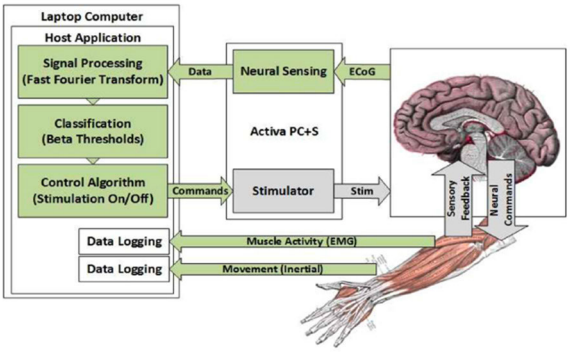

FIGURE 12. System developed by [21].

This also manages the misuse of stimulation when effected limb or any movement is not sensed via the electrodes. By this way, the effective and energy-efficient stimulation is applied chronically. Therefore, reducing the time of depletion of surgically implanted batteries as well as reducing total number of stimulations applied. Improvements are also shown as the patient is able to draw spirals in the test (FIGURE 13).

Similarly, one effective (or as good as clinician) DBS programming system is proposed by [54]. This system performs at least as good as the clinician in terms of selecting the optimal parameters of DBS programming to maximize the therapeutic effects of stimulation to reduce the essential tremor and tremor in PD. The architecture is similar (in most parts)

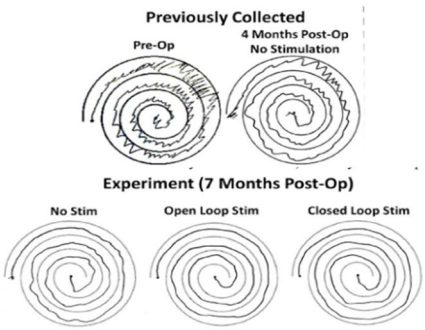

FIGURE 13. Improvement in spiral hand drawings [21].

to the one proposed by [14]. The wearable sensors for tremor tranfer the data towards an external computer which is further classified and used to direct the stimulation towards the brain in a closed, circular manner (FIGURE 14). The parameters are applied on the neurostimulators (MD Activa system). The array of optimal settings is ranked according to the **maximum benefit** or therapeutic effect on the patient. These ongoing dynamics are reported by the patient via user control panel or interface were fed back towards the computer to optimize the next electrical stimulation sequence. A smartwatch with inertial measurement unit is used to track the tremors which is sent to the computer via wireless medium. The **optimum settings** are considered to be the one with least volume of tremor (IMU data). The figure (FIGURE 14) explains well about the flow of the process and the modules of the system.

The system proposed by [21] not only performs the online tuning of the parameters but also learns the Neural Markers specific to one patient. The improved control strategies are better with non-stationary dynamics due to the data-driven and patient-specific identification of neural markers. These neural markers are also session-specific. It is based on **machine learning algorithm** to learn **patient-specific neural markers**.

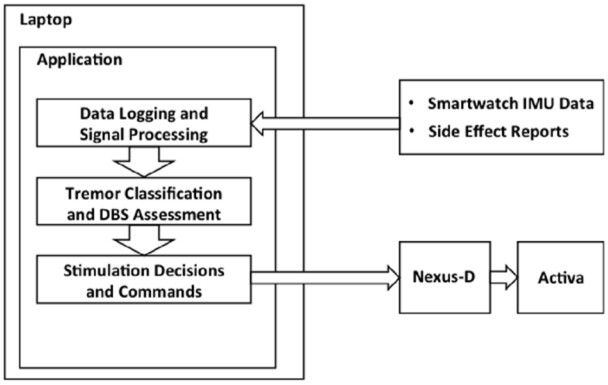

FIGURE 14. System developed by [54].

The system proposed by [79], the patient's ECoG patterns are collected to match with existing patterns present into computer. The system performs identification of specific ECoG patterns (classification) with the help of machine learning (ML) algorithm. Later, when the pattern is identified correctly (as the volitional movement of hand or feet), the Closed-Loop DBS system delivers the stimulation (HFS). Thus, the stimulation is only **delivered** when the patient is **experiencing symptoms** or the patient is near to experience tremor. The essential element in this study is the use of beta-band frequencies (same Neural Markers which were used in the studies of [14], [39]). Additionally, a similar (compared with [54]) peripheral G-Watch with 3-axis Gyro was also included for the detection of tremor. The process flow of the data collection, filtering, analysis and command execution is similar (FIGURE 15). Separate classifiers were trained for On and Off states of stimulation by means of

the data collected in prompt task given to each subject. This study identifies itself as the first-of-its-kind ML-based DBS (closed-loop and adaptive). This could yield new expectations in the future of Neuro-engineering. It simply works as a BCI-based CL DBS (intelligent, as the word would be) where stimulation is applied whenever it is required. The **beta-band** (12-30 Hz) contributed to the favored selected features of the classifier. Similarly, in the this, transmission delays were encountered due to a long-loop of communicating devices.

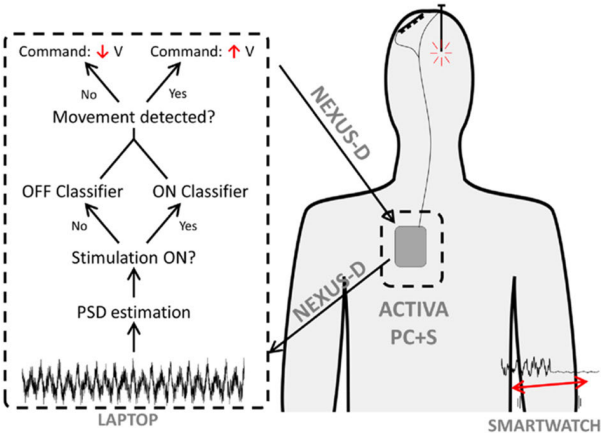

FIGURE 15. System developed by [79].

The system proposed by [73] **modifies parameters** such as **amplitude** and **frequency** of the applied stimulation by non-linear predictive control function. It was found to be less energy-consuming than conventional DBS. The Local field potentials were taken as bio feedback signals due to their relation with **beta band** of ∼20 Hz frequency which is correlated with PD symptoms. The identification of LFP output based on particular stimulation was the main focus. A computer-based brain model called BG Model is used based on physiological data in the study. This function was effective on relay reliability of the thalamus neurons when contrasted with the PD state. The BG model was based on Neuron created from HH-equation [77].

The study proposed by [80] is an adaptive Neural-Network based scheme DBS system. The Neural-Network modifies the parameters during electrical neuromodulation. The adaptive controller based on Neural Networks called BPNN is the simple yet efficient than PID. The strategy achieves better control performance without changing parameters of the controller in contrast with PID algorithm. The **energy expenditure** is proven to be **reduced** by 58.26%.

[80] not only present a Neural-Network based scheme for the control of stimulation in DBS but also verifies the scheme on a Basal Ganglia Thalamic Cortical Computational Model for Parkinson Disease. The need for such an adaptive and **personalized stimulation framework** is based on few issues. The first one is the constant and consistent stimulation. By the means of constant, the stimulation is applied with a constant high frequency (greater than 100 Hz). By the means of consistent, the simulation is applied continuously to the patients regardless it is required at the moment or not. This prolong (consistent) stimulation is increases the side effects like speech impairment and muscular tension/contraction. In order to make the process efficient, these parameters must be considered.

A novel approach towards understanding the LFP-based detection of tremor on-set is discussed by [56]. The onset of tremor may be the key of demand-driven deep brain stimulation scheme when the **neuromodulation** is **applied** only it is **required**. Thus, analyzing the **Local field patterns** for the detection of tremor onset is suitable. The tremor onset (TO) is recognized by the transition between non-tremorous resting state (NT) and tremor state (T). These dynamics classify such diseases as dynamical diseases. By applying Recurrence Networks and time-series analysis in the phase space, the approach seems suitable for the categorization of different LFPs. However, the number of patients is limited to four (4).

The system proposed by [17] is an **adaptive** brain stimulation system. The stimulated regions were **two areas** of the basal ganglia (**sub thalamic nuclei** and **globus pallidus internal**) simultaneously. STN (subthalamic nuclei) is controlled by adaptive one controller based on feedback error learning. The GP (globus pallidus) is stimulated by another controller based on partial state feedback. Both controllers were robust in terms of handling system parameter variability. The objective of the proposed design was to answer three situations. First is the reduction in the hand tremor. The second one is the degree of stimulation delivered during the period. The third one is the ratio of delivered stimulation in health condition to unhealthy condition. In terms of evaluation of the system, BG model is used with a customized scheme to update the control parameters in real-time. The stimulation of either STN or GP (alone) have shown to reduce the hand tremor but showing side effects are present. The stimulation delivered to STN and GP simultaneously to both areas have shown to decrease in hand tremor with lesser energy being delivered to brain and lesser number of side effects appeared on the patient.

All these studies are discussed thoroughly on the basis of their architecture, process and outcome. The TABLE 1 consists all the discussed studies on the improvements in DBS. Other than making the stimulation better over a single area, many studies have applied stimulation to multiple areas. These areas multiple be linked functionally or anatomically. The human connectome is considered as **Human Brain Connection Matrix**. The network of anatomical connections interlinking various neural elements is long study. The Human Connectome Project is a combined effort of various researchers from different countries to highlight functionally and anatomically connected areas [81]. The use of connectome is important in neurological conditions as the treatment is better due to stimulation over more than one area of the brain [17].

Researchers have selected multiple regions for the neuromodulation in Parkinson Disease [17], Depression [32],

TABLE 1. Details of proposed models.

Ref.	Type	Bio mark.	Para. Regulation	Outcome/Findings
[36]	DBS (Adaptive)	-	Use of Reinforcement Learning	• Energy-efficient DBS • Use of Reinforcement learning for Optimizing parameters
[78]	DBS (Demand-driven and Adaptive)	ECoG	Adaptive Controller for multi-region Simultaneous stimulation	• Energy-efficient DBS • Effective strategy
[12]	DBS	MRI Scans	Automated DBS programming through MRI scans	• Automated programming of DBS electrodes
[14]	Closed-Loop	ECoG	An autonomous BCI computer to control on-demand stimulation	• Process Automation • Energy-Efficient • Demand-driven
[54]	Closed-Loop	ECoG	Closed-loop based parameter optimization	• Process automation • Best stimulation ranking
[21]	Closed-Loop	ECoG	Optimizing parameters based on Neural Markers (session-specific)	• Automated Programming • Personalized medicine
[16]	DBS	-	Multi-region stimulation for PD (STN and GPi)	• Use of simultaneous stimulation based for PD
[17]	DBS (Adaptive)	-	Multi-region stimulation for PD (STN and GPi)	• Effective system
[82]	DBS	-	Multi-region for OCD	• ALIC-DBS and STN-DBS for stimulation
[39]	DBS	-	Multi-region for MDD and OCD	• PFC-DBS • Theta oscillations

and in others. Stimulation over multiple areas have shown to get better results as compared individual stimulation of any of the area or both [16]. So, the understanding of human connectome either functionally or anatomically supports its significance in neuroscience. The statement that areas of the brain are connected functionally and anatomically can also be supported by the applying stimulation on different sites of the brain. The potential DBS targets for various diseases are shown (TABLE 2) [18]:

It seems obvious that multiple areas vouch for same disease. For example, Internal globus pallidus is common in Dystonia and Parkinson (TABLE 2). That's why the understanding of human connectome is important for

TABLE 2. Stimulation areas for various diseases.

#	Indication	Target(s)	Status
1	Parkinson's	Subthalamic nucleus	Well-established
		Internal globus pallidus	
2	Essential tremor	Ventral intermediate thalamus	
3	Dystonia	Internal globus pallidus	
4	Parkinson's	Pedunculopontine nucleus	Not widely implemented, still under investigation
		Zona incerta	
5	Essential tremor	Zona incerta	
6	Pain	Periaqueductal and periventricular grey matter	
		Ventral posterolateral and posteromedial thalamus	
		Anterior cingulate cortex	
7	OCD	Anterior limb of internal capsule	
		Medial thalamus	
8	Tourette's	Internal globus pallidus	
9	Epilepsy	Hippocampus	
10	Depression	Subgenual cingulated	
		Nucleus accumbens	
11	Cluster headache	Posterior hypothalamus	
12	Addiction	Nucleus accumbens	Very limited investigation, largely hypothetical
13	Anorexia	Nucleus accumbens	
14	Obesity	Nucleus accumbens	
15	Alzheimer's	Fornix	
		Ventromedial prefrontal cortex	
16	Huntington's	Internal globus pallidus	

neuromodulation of various diseases. Recently, [55] have predicted the outcomes of therapy (% change in UPDRS-III Score) using a **connectome-based** approach. A machine learning algorithm was used to extract the features from Fifty (50) patients (using Gradient Boost Regression Trees algorithm) as shown in FIGURE 16 and FIGURE 17. The MRI scans with BOLD response are used to reconstruct the brain network with functional connectivity links. The identified connectomes (FIGURE 18) were top eleven (11) predictive connections among others, which are helpful in surgical outcomes of DBS before the operation.

Similar study conducted [32], have identified the various targets for stimulation. **Two distinct circuit targets** for two isolated clusters of depressive symptoms. One cluster of symptoms was related to sadness and anhedonia while the other cluster encompasses anxiety and somatic symptoms. The different neuromodulations were applied to these circuits and results were correlated. Each circuit responded for a

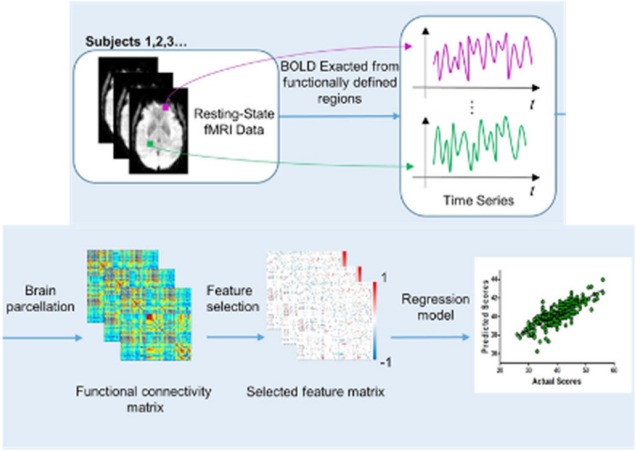

FIGURE 16. Process of work [68].

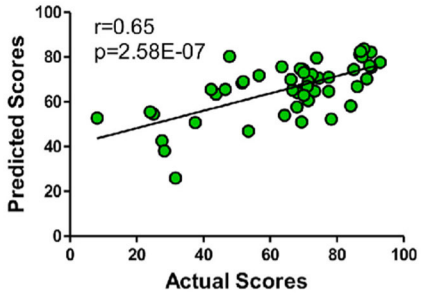

FIGURE 17. Regression scores [68].

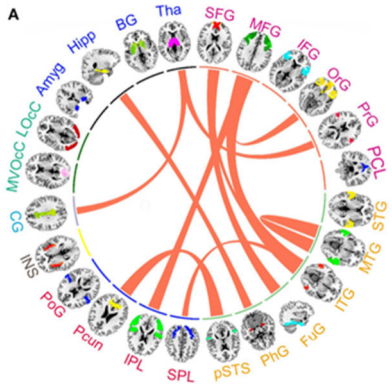

FIGURE 18. Identified connectomes [68].

different set of symptoms. The symptomatic improvement was drawn from 14 clinical TMS trials in an investigative analysis. The regions were identified from the large connectome database and assisted by fMRI for the mapping of brain circuits.

The condition associated with the disorder in auditory system (peripheral, but rarely it can be central). The patient starts to listen sound without any external factor (apparent sound) is called Tinnitus. Tinnitus is not a serious disease (neither it should be called disease) but when the ringing in the ears (sounds) are too loud or don't go away, this can cause serious issues like anxiety, depression, memory and concentration problems besides mental and emotional distress. A meta-analysis conducted by [15], revealed that stimulation to **Left Dorsolateral Prefrontal Cortex** (with cathodal transcranial direct current) with **bilateral auditory cortex** (with transcranial random noise) has shown greatest improvement in the quality of life and severity of the tinnitus. With the help of functional imaging studies, researchers are able to identify the areas of hyperactivity, which are anterior cingulate cortex, insula and both auditory cortices. Thus, leading towards a treatment strategy by suppressing the areas of hyperactivity by tRNS. tRNS has been found to be effective in suppressing hyperactivity in cerebral cortex by low-frequency. Whereas, high-frequency induces higher brain activity in tinnitus patients using tRNS (transcranial Random Noise Stimulation). tDCS (transcranial Direct Current Stimulation) has the same effect but it is applied with weak current. tDCS has the potential to enhance or suppress activity on the stimulated brain area. Therefore, the two stimulation methods are taken as useful as Non-invasive brain stimulation treatments for tinnitus. Though, many studies are available on topic (104), the selected studies were 32. The rest of the studies were found to have issues as non-random clinical trials, no clinical trials, lack of adequate control, duplicated sample sources, protocol but not trials results, and un-related to outcome of interest. So, this study titles the most comprehensive meta-analysis performed to prove the efficacy and acceptability of NIBS in the treatment and management of tinnitus. Multiple studies revealed that the combination of BS like high and low frequency, TBS and TMS were effective than individual application. The main finding is the cathodal TDCS plus anodal TDCS combined with rTNS associated with the most contributed in improvement in quality of life as well as severity of the disease (Figure 19). One important procedure called priming procedure which is additive stimulation over dorsolateral prefrontal cortex, with RNS is associated with improving severity of Tinnitus. Furthermore, tRNS was found to be superior in suppressing intensity of tinnitus and decrement in distress than the tDCS.

Obsessive Compulsive Disorder (OCD) is considered as the presence of obsessions and/or compulsions. Obsessions

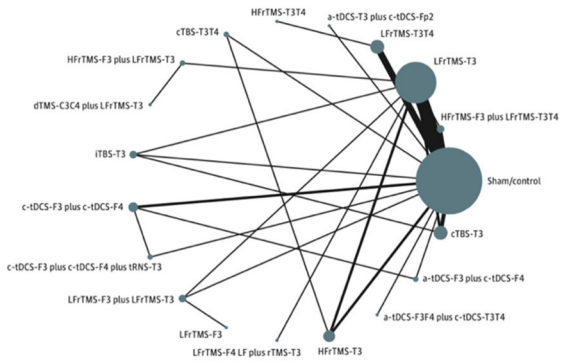

FIGURE 19. The Network Structure of Changes of severity of Tinnitus [15].

are impulses or urges, thoughts, images which are persistent and repetitive. These impulses are interrupting and unwanted, commonly associated with anxiety. Compulsions are the acts performed on the obsession in order to feel or the reach a sense of completeness. Mostly, the completeness or fullness is achieved by following strict and rigid rules. The obsessions create anxiety and a sense of discomfort intrinsically which is resolved by compulsion as a response [83]. The following study is related to the treatment of OCD. A **unified connectome** for the treatment of OCD using DBS is presented in the study done by [82] which is available in atlas form as well. A four-cohort study comprising of fifty (50) number of participants underwent stimulation (deep brain) to the anterior limb of the internal capsule, subthalamic nucleus or nucleus accumbens. By the approved treatment of OCD through neuromodulation on ALIC, various other locations/sites are suggested by different researchers for the treatment. These sites include ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAcc), inferior thalamic peduncle (ITP), anteromedial globus pallidus interna (amGPi), medial dorsal and ventral anterior nuclei of the thalamus (MD/vANT), superolateral branch of the medial forebrain bundle (slMFB), bed nucleus of the stria terminalis (BNST), and the common Subthalamic Nucleus. This paradigm-shift is also noticed in the treatment of Parkinson. For example, motor basal-ganglia cortical cerebellar loop (distributed brain network) instead the conventional focal stimulation of specific nuclei of globus pallidus or subthalamic nuclei. Further, one study was able to identify area or specific subsection of anterior limb of internal capsule which was associated with the higher symptom alleviation in OCD.

It is commonly observed that OCD and MDD show lack in cognitive control. A study led by [39] shows that enhancement of PFC-driven cognitive control can be achieved by the stimulation in VCVS DBS (ventral capsule/ventral striatum (VC/VS) area where **theta** oscillations increase in medial and lateral prefrontal cortex as a result. Reference [39] has identified a connectome.

It is now common multiple areas vouch for the stimulation of similar problem (e.g., Parkinson, Depression [32]). For example, two identified regions in Basal Ganglia are potential targets for stimulation for Parkinson Disease such as subthalamic nucleus and globus pallidus internal. High electrical frequency (130-185 Hz) to different regions with constant intensity. This study [16] suggests **stimulation of two different regions** simultaneously like STN and Globus Pallidus internal for the treatment of Parkinson. This strategy is effective to reduce the side effects which include the speech disorder and muscular contraction. The controller is also controlled by FOSMC and IJAYA algorithm as shown below.

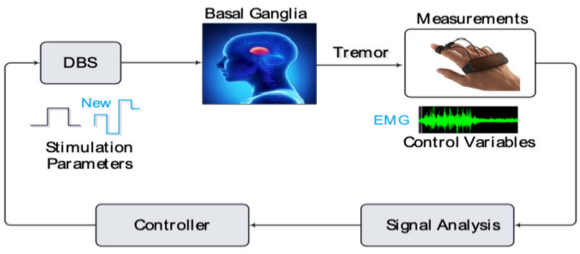

FIGURE 20. System designed by [16].

The reviewed studies related to connectome-based stimulation have shown another direction for the improvement of DBS system.

VI. DISCUSSION

Many researchers are trying to make the process of stimulation more and more effective. The reviewed studies are discussed in the following points:

i. [13], The improvement in the trials have shown that the technique of IL-IL (Interleave-interlink) frequency should be considered in the future for application of neuromodulation.

ii. [36], first, despite the simplified brain-like computational model, it is far away from a real brain with variables. Secondly, the application of Reinforcement Learning is considerable within contemporary systems of such nature.

iii. [12], although the system is innovative in its use of imagery data to program DBS electrodes; the use of simulation is not so typical means of testing the neuromodulation dynamics.

iv. [14], the proposed system is effective in terms of energy-saving and reducing the number of stimulations (and associated side effects). The system is viable to be used in consumer-level personalized DBS systems

v. [54], the proposed system is effective and consumes tremor data from IMU sensor instead of Beta-band classification. The use of ranking for each stimulation parameters and results is a good way of assessment. The proposed system is viable to be used in Personalized DBS systems.

vi. [21], the proposed system is an adaptive DBS system which applies Machine Learning algorithm to learn patient-specific neural markers (from ECoG). This process modifies the parameters as the stimulation is applied. This system is viable to be used in Personalized DBS systems.

vii. [79], the proposed system is effective to be used in neuromodulation application for the treatment of Parkinson. However, the use of two classifiers (ON and OFF) is new. The system is via to be used as an adaptive personalized stimulation tool.

viii. [84], The idea appears to be notable among the alternative methods used by other authors as this study has consumed the nonlinear predictive control function for the modulation of parameters. However, the beta-band frequencies from ECoG patterns were taken as Neural Marker in this study as well. (2) The use of computational model is an unfair means of evaluating the process as the computational model is a simulation.

ix. [80], it must be noted for the BGTC model (computational), striatum is missing which should include in future iterations. The states of PD are not discussed at the ionic-level as well. Computational models are useful for testing and validating the stimulation before going towards the patients. However, computational models for disease should mimic the exact the same dynamics, properties and response to one in real-life.

x. [56], the proposed system is adaptive DBS based on LFP patterns. However, the study is unique from other when compared with the application or use of Recurrence Networks and time-series analysis.

xi. [17], the proposed is helpful to reduce side effects and to maximize therapeutic benefit from stimulation over two regions. However, the study is deficit in the real-world results and found to be tested on a computational mode. The novelty lies in the proposed models of AFEL and PSF as a controller scheme of STN and GPi regions being stimulated through neuromodulation in DBS.

To get maximum benefit from therapy sessions, researchers have applied stimulation over various areas. Such **multi-region stimulation** studies are discussed in the following points:

i. [12], the use of imagery data to reconstruct brain network in assistance to stimulation. However, the use of connectome, defining connections based on anatomically connected areas is significant in the study.

ii. [32], the application of connectome-based neuromodulation has shown effective results.

iii. [15], The reasonable areas to stimulate are found to be anterior cingulate, insula and auditory cortices. A significant finding suggests that stimulation over frontal lobe and then over auditory cortices weas found to be superior than rTMS (random Transcranial Magnetic Stimulation) on auditory cortices only (either by low or high frequency).

iv. [82], this leads to the idea that there are two potential regions for the stimulation or neuromodulation for OCD. One is the ALIC-DBS and other one is the STN-DBS. The study showed that the connectivity-driven stimulation may be helpful in the treatment.

v. [39], the study has identified an important connectome for the treatment of OCD and MDD.

vi. [16], the study is found to lack in real-world stimulation results. However, the novelty of the study is focused towards the FOSMC controller and IJAYA algorithm for the closed-loop DBS architecture. The study also presents the Basal Ganglia Thalamic Cortical Model for testing and evaluation purpose of the study and similar.

VII. CHALLENGES & RESEARCH AREAS

It is now conclusive that connectome plays an important role in the maximization and optimization of therapeutic outcome [16], [17]. This increases the gained benefit from optimal stimulation site as compared to conventional way of stimulation over a single area [15]. However, more challenges other than connectome are discussed in detail as:

A. The current setup of DBS involves human effort. Thus, automation of the system is required to make the system efficient and better. However, the automation of the Neuromodulation system requires that device must be **aware** (in terms of knowledge) of:
   a. **Safety-charge Limit**in neuromodulation [37].
   b. **Neuronal synchronisation**, **plasticity** and mechanism of **neo-synapses** [37] [6].
   c. **Parameters** (frequency, pulse width, and amplitude) which can be **optimized** to get maximum benefit [22].
   d. **Electrical conductivity** of the **tissues** [11] and Optimal coil placement in case of non-invasive treatment [85].
   e. **Inhibitory effects** stimulation can cause [13], [86]. So, must compensate for changes.
   f. **Side effects**of specific regions [14].
   g. Connectome plays an important role therapy. So, **optimal site** for stimulation can be found with the help of connectomes [87].
   h. **Connectomes** vary from patient to patient [35].
   i. Stimulation over **multiple areas** is more effective than single area. So, it should be applied whenever and wherever possible [16].
   j. **Low** and **high frequencies** applied to an area have distinct results or effects(for example appendicular and axial symptoms) [13].

B. The computer program for the **monitoring**, **control** and **application** of neuromodulation must:
   a. Gain **experience** and learn through trial-and-error (as any clinician would).
   b. Learn from apparent or unnoticeable **feedback** of **discomfort** (or reactions) as well as feedback of **comfort** and improvement.
   c. **Increase** its **knowledge** as the number of patients increase.

C. The Patient's Neural Markers are helpful in **assessment of condition** (during neuromodulation). Some of the neural markers are:
   a. **Gamma** [88], **theta** [39], and **beta** oscillations [66] which can be detected from ECoG and EEG waveforms.
   b. MRI scans are found to be helpful in constructing **patient-specific brain model**. These scans are useful for understanding and identifying disease or neurological condition. These MRI scans can be used to identify connectomes as well.

There are computational models to test and evaluate the neuromodulation system. However, a mathematical brain construct cannot replace patient-varying natural biological neural network.

VIII. VERDICT

The literature review of past studies has unveiled many issues to which many researchers have tried to solve such as energy expenditure, demand-based stimulation, more effective frequency and so on. Application of stimulation over **multiple areas** (simultaneously or sequentially) have greater results than stimulation over single area. The use of computational models to test and evaluate proposed stimulation systems is not as good as **real-world** clinical trial. The system must be intelligent in ways of applying stimulation such as the **how much** and **when** it is required. For that, beta and gamma oscillations play an important role. There must be an intrinsic **knowledge** to the system about the **disease**, **consequence** of the stimulation and **dynamics** related to neurons and electricity. The overall system must be at least invasive as it can be. Such findings are important to design new stimulation system.

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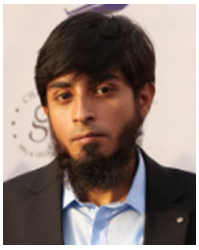

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