LITERARY REVIEW OF THE STATE OF THE ART OF LOCAL FIELD POTENTIAL SIGNALS, ESTABLISHING THEIR HISTORY AND USE IN THE DETECTION OF SYMPTOMS OF PARKINSON'S DISEASE

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TABLE OF CONTENTS

1. ABSTRACT 6
2. INTRODUCTION 7
3. OBJECTIVES 14
   3.1. General 14
   3.2. Specific 14
4. METHODOLOGY 15
5. RESULTS 21
6. DISCUSSION 28
7. RECOMMENDATIONS AND FUTURE WORK 29
8. CONCLUSIONS 30
Bibliography 31
ANNEXES 34

LIST OF TABLES

Table 1. Summary of the included studies in this review (n = 10) 25

LIST OF FIGURES

Figure 1. Components involved in Deep Brain Stimulation Surgery [7] 11
Figure 2. Sources of neural signals. EEG is recorded from the scalp. ECoG, LFP, and action potentials are recorded through electrodes placed invasively through the skull [22]. 12
Figure 3. Example of the word cloud for article The Effect of Unilateral Subthalamic Nucleus Deep Brain Stimulation on Contralateral Subthalamic Nucleus Local Field Potentials [17]..... 15
Figure 4. Flow diagram of the literature review. 21
Figure 5. The number of studies per year. 22
Figure 6. The number of studies per authors' country of origin. 23

LIST OF ANNEXES.

ANNEX A: Access link to Annex A. Excel table classifying information for the selected articles n = 38 ……. 34

ANNEX B: Access link to Annex B. Infographic for professionals interested in how LFP signals relate to Parkinson's Disease symptoms ……... 34

1. ABSTRACT

INTRODUCTION

Local Field Potentials (LFP) are signals recorded from the subthalamic nucleus (STN) or internal globus pallidus (GPi) in patients with Parkinson's Disease (PD) and other movement disorders that have shown prominent oscillations in the beta (12-30 Hz) frequency range. Deep brain stimulation (DBS) is an effective therapy for PD when medication ceases to control the symptoms. Technology has advanced and is searching for a way to classify why LFPs are important biomarkers for PD and, through them, advance DBS technology into closed-loop interactions between the stimulation, the human brain, and the signals.

OBJECTIVES

To develop a state-of-the-art that allows health care professionals to know the current state of technology to record the signals of the local field potential in the brain and its relationship with the symptoms of Parkinson's disease.

METHODS

A database search was performed to get the literature available about LFP signals involving their correlation to PD symptoms using DBS technology. Search provided 256 articles that were analyzed and filtered to finally obtain 10 articles from which the main study would be performed. Patient characteristics, type of signal processing, type of technology, were variables studied in each paper to be able to summarize and provide a well-written review.

RESULTS

Ten articles were studied and analyzed. Spectrograms, power spectral density graphs, frequency analysis, type of therapy, patient's movements were analyzed. Through the comparison between articles, LFPs were seen to be important biomarkers, especially for tremor and rigidity when the beta band is targeted. LFP signals are also important in the definition of the type of DBS treatment for the patient.

CONCLUSIONS

Technology around LFP signals is rapidly evolving towards having automated DBS systems that help patients with PD symptoms. These signals oscillate distinctively when symptoms appear and are affected by the neurostimulation and medication.

2. INTRODUCTION

Medtronic S.A was founded in 1949 by electronic engineer Earl Bakken and his brother-in-law as a medical equipment repair shop. This store was located in Minneapolis, United States, and repaired equipment from nearby health centers. The pair was driven by passion and deep moral purpose to use their scientific knowledge to help others. In their early years, they began selling equipment and building customized requests for local hospitals including for the medical and research staff at the University of Minnesota.

Through this work, Bakken began working with cardiologist C. Walton Lillehei to make improvements to the external artificial cardiac pacemaker that at the time had to be plugged into a power outlet [1]. These pacemakers used to be large, cumbersome boxes wheeled on carts [2]. In 1957, an electrical blackout in the area caused many deaths, forcing a redesign of the pacemakers, leading to internal batteries and preventing future disasters. Bakken modified the design of a transistorized metronome and created the first battery-powered external pacemaker. From that moment, the company began to expand throughout the 1950s, selling equipment manufactured by other companies. These sales allowed the company to know the market and know the needs at the time, leading to the development of custom-made devices.

Bakken built a small pacemaker that could be attached to the body and be powered by batteries. Then, in 1960, he built an implantable pacemaker adding mechanical devices, joining electrical stimulations as a core technology, and built the headquarters for Medtronic. At this time, they produced the mission, which remains to this day, which focuses on "To contribute to human welfare by application of biomedical engineering in the research, design, manufacture, and sale of instruments or appliances that **alleviate pain, restore health, and extend life**" [3]. Through this mission, the company started expanding globally, first to Amsterdam in 1967, to Canada in 1968, and entering China, India, and other emerging markets during the early 70s.

In 1977 they introduced the first valve prosthesis. In 1983, the company expanded their designs to neurostimulation, being world pioneers in this exploration where they built off the science of using electrical stimulation to pace the heart to treat movement disorders. In 1999 they expanded into the treatment of the spine and in 2001 they began to create technologies for the care of diabetes where a team of biomedical engineers developed a continuous glucose monitor which was a key component of a closed-loop diabetes management system allowing people to better monitor their diabetes.

Over time, Medtronic began growing and buy smaller companies such as Physio-Control and Covidien, which has allowed its portfolio to grow in areas like tissue heart valves, cardiopulmonary equipment, coronary angioplasty catheters, centrifugal blood pumps, and reach ahead of competing companies such as Boston Scientific and Abbott.

Currently, Medtronic is a company that has expanded to more than 150 countries, with more than 90,000 employees, more than 49,000 patents, and more than 350 clinical trials. They have adopted an Environmental, Health, and Safety (EHS) Management System that allows the codification and practice of procedures to be safe for the workers and their surroundings also aiming to implement environmental impacts across the facilities, products, and supply chain [4]. Until January 2021, they had four main business units which were:

restorative therapies, minimally invasive therapies, diabetes, and cardiovascular where diabetes was the most prominent in Latin America. Since February 2021, a restructuring sought to give more importance to emerging therapies, so it reorganized its 4 business units into 20 operating units [5].

● **Operating units:**

Cardiac Ablation Solutions, Cardiac Rhythm Management, Cardiac Surgery, Cardiovascular Diagnostics and Services, Coronary and Renal Denervation, Cranial and Spinal Technologies, Diabetes, Ear Nose Throat, Gastrointestinal, Mechanical Circulatory Support, Neuromodulation, Neurovascular, Patient Monitoring, Pelvic Health, and Gastric Therapies, Peripheral Vascular Health, Renal Care Solutions, Respiratory Interventions, Structural Heart and Aortic, Surgical Innovations and Surgical Robotics.

- **Marketing of Deep Brain Stimulation in Latin America.**

The marketing team in the area of deep brain stimulation (DBS) focuses on ensuring that the information, both internally and to health professionals and patients, is unanimous and balanced so that the interactions and communications are aligned. Marketing in neuromodulation at Medtronic helps train health care professionals in the therapies offered, enabling therapies for people with movement disorders, such as Parkinson's disease or epilepsy, to be provided by the most specialized professionals and using the best tools and equipment. Also, the marketing area works to know the movement of the market, studies the movements of competing companies, and provides intelligent strategies to grow its market. Within the position as a neuromodulation marketing intern, there are functions such as:

- Developing and managing a monthly internal newsletter.
- Tracking product launches.
- Supervising and managing the marketing materials site.
- Working closely with the marketing team in the development of digital platform initiatives.
- Working on the development, execution, and analysis of competition information in the region.
- Working on the maintenance, analysis, and preparation of monitoring market share reports.
- Participating and working in monitoring the process of market development initiatives.

Among Medtronic's primary marketing functions are the training and education of healthcare professionals, sales representatives, and clinical specialists on neurostimulation advances and upcoming products. Deep brain stimulation (DBS) has shown dramatic clinical benefit for the treatment of different neurological and psychiatric disorders such as Parkinson's disease (PD), essential tremor (ET), dystonia, obsessive-compulsive disorder (OCD), and epilepsy. Its impact has been more notable in patients with PD and ET but studies have been increasing towards epilepsy [6].

To date, DBS therapy has been used to treat more than 160,000 people for the conditions mentioned above [7]. For dystonia, the most common symptoms are involuntary muscle contractions which worsen with stress, fatigue, or anxiety. For epilepsy, the most common symptoms are temporary confusion, loss of consciousness, uncontrollable jerking movements of arms or legs, and emotional responses like fear, anxiety, or déjà vu. For essential tremor, as its name suggests, its main symptom is tremor which occurs during day-to-day activities such as writing, drinking, brushing teeth, or walking. For Obsessive-compulsive disorder, the main symptoms vary notably from patient to patient, but the most common symptoms are the fear of germs or contamination, aggressive thoughts towards others or themselves, they need to have things in symmetrical or in perfect order, excessive cleaning or handwashing, compulsive counting, and checking things repeatedly. Finally, Parkinson's Disease's symptoms are tremor, bradykinesia (which is the slowing down of movement), stiffness, and abnormal walking. Most of the symptoms for the indications involve movement and the quality of it.

- **Parkinson's Disease**

Parkinson's disease is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination, among other symptoms that show up with time. These symptoms usually begin gradually and worsen over time. As the disease progresses, people may notice their speech and gait are affected to the point where they have to rely fully on a caretaker. Some non-motor symptoms that appear are mental and behavioral changes, sleep problems, depression, memory loss, and fatigue. This disease may affect both men and women but it has been shown that it affects men twice as much [8]. While it may not be a mortal disease, the complications it provides are severe. Epidemiological studies done in Colombia show that its prevalence is 4.7 affected every 1000 people older than 50 years [9].

The causes of Parkinson's disease are varied and it has not been specifically correlated to genetics. The main risk factor is aging as well as head injuries, insecticides, herbicides, and fungicides. This disease occurs when the nerve cells in the area of the brain that controls movement become impaired or die. Dopamine is a neurotransmitter affected by the death of the neurons in the substantia nigra (SN) in the brain [10]. The dopamine sends messages to other areas of the brain to control the human body's movements. This chemical substance helps humans have controlled and fluid muscle movements. When these cells are damaged, the lack of dopamine makes motor symptoms appear, this process of cell deterioration is called **neurodegeneration** [11]**.**

The process a person with Parkinson's Disease goes through is divided into five stages. During the first stage, tremor and other movement symptoms start appearing only showing on one side of the body. For the second stage, tremor, rigidity, and other movement symptoms affect both sides of the body even showing problems to walk and have proper posture. During the fourth stage, the symptoms are severe and limiting for the person. They can stand without help but may need assistance walking. For the final stage, the rigidity the person experiences does not allow them to stand or walk inhibiting them from having a normal life and being dependent on a caretaker [12].

Even though there is no known cure for Parkinson's Disease, there are options to treat the symptoms it generates that allow the person to regain some control. Actual

treatments include medication and deep brain stimulation (DBS) therapy. Many drugs for PD aim to reestablish dopamine temporality or mirror its function and block the action of other factors like enzymes that breaks down dopamine. In general, these drugs help to reduce muscular rigidity, increase velocity and coordination of movements, and to reduce body shaking [13]. The most common medication prescribed for Parkinson's disease is Levodopa. Levodopa acts as a dopamine agonist which activates when it reaches the brain, helping the patients with the symptoms of the disease. Still, medications may cause side effects like dizziness, loss of appetite, headaches, among other symptoms that may turn out to be worse than PD symptoms [14].

The Unified Parkinson's disease rating scale (UPDRS) is used to follow the longitudinal course of Parkinson's disease created by the Movement Disorder Society (MDS). This scale consists of four parts classifying both physical and mental symptoms of people with PD. Part I classifies non-motor experiences of daily living, Part II classifies motor experiences of daily living, Part III is a motor examination, and part IV scales motor complications. For the quantitative analysis of PD, UPDRS-III is mainly used to determine how motor symptoms change over time and according to a treatment or medication. When marked **ON** it means the typical functional state when patients are receiving medication and have a good response while **OFF** is the typical functional state when patients have a poor response despite taking medications. Concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. UPDRS-III evaluates speech, facial expressions, rigidity, finger tapping, hand movements, pronation-supination movement of hands, toe-tapping, leg agility, arising from a chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement (body bradykinesia) postural tremor of the hands, kinetic tremor of the hands, rest tremor amplitude, and constancy of rest tremor [15].

- **DBS Surgery**

DBS surgery is based on implanting high stimulating electrodes in the region of the ventral intermediate nucleus of the thalamus (VIM), the subthalamic nucleus (STN), or the internal globe pallidum (GPi). To get the best implantation place, the neurosurgeon must perform magnetic resonance imaging (MRI) and a computed tomography scan (CT scan) to be able to identify and plane the exact place in the brain in which the nervous electrical signals generate PD symptoms. The electrodes, or leads, implanted are thin isolated cables inserted through a small hole in the skull made through trepanation. An extension is connected to these leads and passed under the skin through the head, neck, and shoulder, connecting the electrodes to the neurostimulator (INS). The neurostimulator, or the battery, is the third component usually implanted under the skin near the clavicle approximately five centimeters deep.

The implantation places can be seen in figure 1, where all the components fit together to provide the patient with the best treatment. This is a minimally invasive surgery that allows the patient to return to their normal life rapidly. After performing the surgery, the doctor can program the battery in amplitude, current, bandwidth, or frequency to determine which is the best electrical therapy for each patient [6]. This program consists of electrical pulses sent to the electrodes implanted in the parts of the brain where the PD symptoms are produced and blocks them [16].

The region of the brain where the electrodes are implanted can reduce specific symptoms. For example, implanting in the VIM may reduce tremor while implanting in the STN or the GPi may not reduce tremor but may help reducing bradykinesia, rigidity, and gait impairment that affect patients with Parkinson's Disease. Increasingly, studies have noticed the potential benefit of DBS of selected brain regions for other movement disorders such as dystonia or Tourette syndrome, as well as pain and depression [16].

Advances in new DBS products include detection and analysis of local field potential (LFP) signals which help detect Parkinson's disease-related symptoms such as stiffness and dyskinesia. This detection and analysis allow the health care professional to provide a therapy more in line with the specific need of each patient [17].

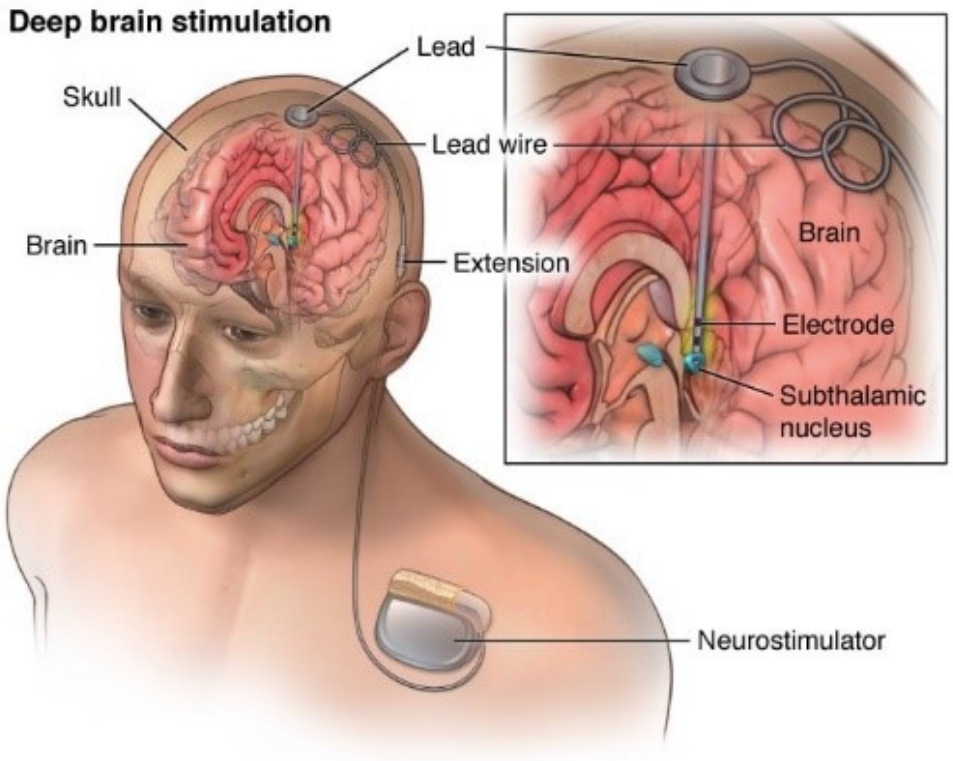

Figure 1. Components involved in Deep Brain Stimulation Surgery [7]

- **LFP SIGNALS**

While the brain is being implanted during DBS, neuroelectric field potentials are recorded to investigate brain functioning. Local field potentials (LFPs) can be recorded through the macro electrodes implanted for DBS and reflect synchronous presynaptic and postsynaptic activity from local neuronal populations and oscillate in response to the patient's clinical state [18].

LFP refers to the electric potential in the extracellular space around the neurons in the brain tissue. This signal is available in different recording configurations, ranging from single-electrode recordings to multi-electrode arrays [19]. These electrodes can be made out of metal, silicon, or glass micropipettes.

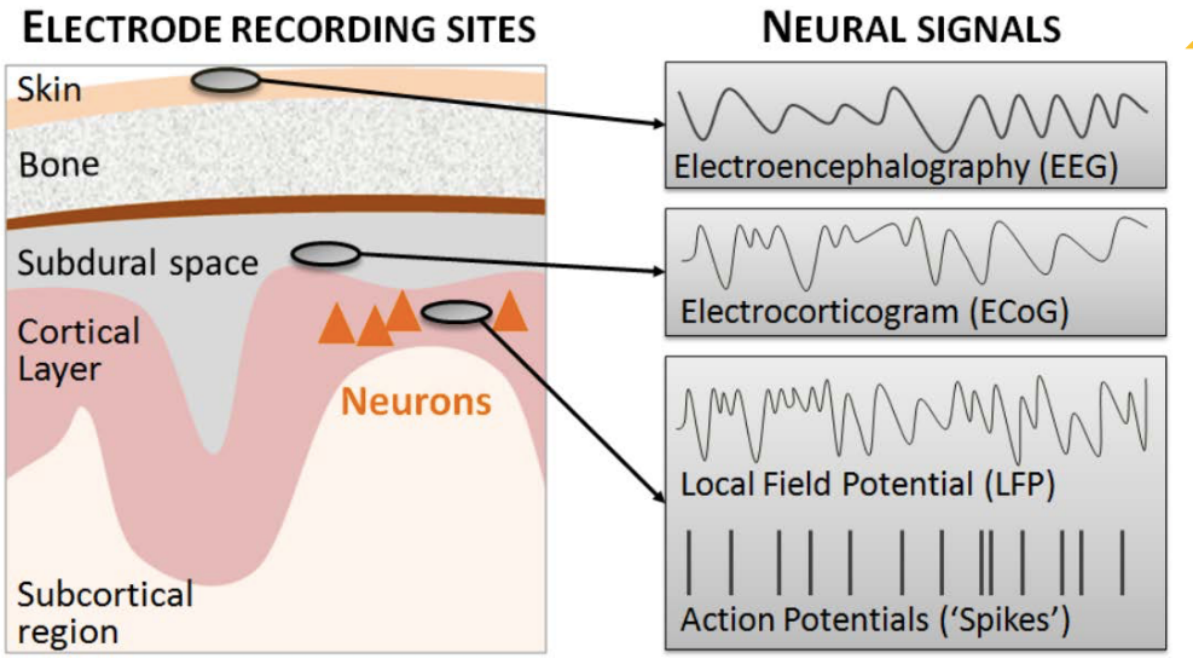

Figure 2. Sources of neural signals. EEG is recorded from the scalp. ECoG, LFP, and action potentials are recorded through electrodes placed invasively through the skull [28].

LFPs differ from electroencephalograms (EEG), which are recorded at the surface of the scalp and with macro electrodes. It is also different from electrocorticogram (ECoG) which is recorded from the surface of the brain using large subdural electrodes, while LFPs are recorded in depth from within the cortical tissue. EEG samples much larger populations of neurons because it must propagate through various media such as cerebrospinal fluid, dura matter, cranium, muscle, and skin which causes the need for filtering and diffusion [20]. In the same way, LFP signals require filtering since the recorded electrode is separated from the source's portion of the cortical tissue. In the same way, LFP and EEG signals display similar types of oscillations during wake and sleep states [21].

In 1951, it was proposed that LFP and EEG activities were generated by summated postsynaptic potentials arising from the synchronized excitation of neurons [22]. Currently, it is known that EEG and LFPs are generated by synchronized synaptic currents arising on cortical neurons, possibly through the formation of dipoles [23]. One of the characteristics of LFP signals is that its power-spectrum exhibits $1/f$ frequency scaling at low frequencies [24]–[26]. The LFPs are generated by electric currents and charges in brain cells, including neurons and glial cells. The main contribution to these signals is the synaptic currents in neurons; voltage-dependent currents and spikes can also contribute in this manner. After noise cancellation, it is considered that LFP's response on a single trial is the root mean

square (RMS) value of the filtered voltage trace. LFP tuning curves were computed from the average RMS values of all LFP traves obtained for each stimulus condition [27].

- **Technology Readiness Level**

Technology Readiness Levels are a way of estimating the maturity of technologies developed at NASA during 1974 [29]. These levels have been on different research and innovation projects like H2020, which aimed to reduce pollution in the Mediterranean by 2020. They have helped classify technology into different categories helping their research progress and eventually, their use outside of a laboratory. Also, they allow good decision-making concerning the inclusion or exclusion of new technologies and unique concepts. Technologies are assessed often as their experimentation process advances and matures before their incorporation in new system development projects. The purpose of appropriate technology is to inform organizations and support decisions as part of the implementation of advanced technology system development projects. These levels are worded differently according to their usage and region [30].

There are nine levels classifying technology which are stated below.

- Level 1 – Basic principles observed and reported
- Level 2 – Potential application validated
- Level 3 – Proof-of-Concept demonstrated analytically and/or experimentally
- Level 4 – Component and/or breadboard laboratory validated
- Level 5 – Component and/or breadboard validated in simulated or real-space environment
- Level 6 – System adequacy validated in a simulated environment
- Level 7 – System adequacy validated in a real environment [30].

TRLs are important in this study because it allows the researcher to focus on advanced technology that does not harm the patient in any way. Since DBS technology is an invasive surgery, it is important to determine if the technology has been used in real environments and record how it has affected patients and how to fix it. In any engineering environment, these levels help determine the possible areas of improvement and future research. Also, they allow the understanding of the technical maturity of technologies during their evolution regardless of their technical background.

The problem that is going to be treated focuses on conducting a search of the literature on the LFPs and identifying the advances in science concerning them. It seeks to determine the types of studies performed so that these signals will be determined as important biomarkers in the detection of symptoms of movement disorders, especially Parkinson's Disease so that sales personnel and health care professionals can have a complete view of what these signals imply in the use of new products. For this, it is expected to use a search equation both in databases of the Universidad del Rosario and Medtronic databases and provide a complete state of the art on the LFP signals and propose future studies of these. Through this search, it is expected to create an infographic that summarizes the information regarding LFPs, their history, their use as biomarkers for Parkinson's Disease, and how they are used as an advancement in DBS technology.

3. OBJECTIVES

3.1. General

To develop a state-of-the-art that allows health care professionals to understand the current state of technology used to record the local field potential signals in the brain and its relationship with Parkinson's disease symptoms.

3.2. Specific

1. Synthesize the results of existing studies in the scientific literature on local field potential signals as a biomarker in the diagnosis of symptoms in people with Parkinson's disease.
2. Design a search equation that limits and prioritizes relevant and coherent information for the study.
3. Define the types of studies performed in which the local field potential signals related to the treatment of movement disorders are analyzed.
4. Determine the current state of the study of local field potential signals focused on the place of detection in the brain and its analysis of symptoms.
5. Generate a summary of the information so that it is easily accessible and easy to understand for the health care professional.

4. METHODOLOGY

For the elaboration of this systematic review of the literature, a review protocol was performed which consisted of four main steps. First, the search strategy was determined, then the bibliographic search was carried out, followed by a selection process of relevant articles and, finally, relevant information and data were extracted to be analyzed further. For this study, any source of information on local field potential signals recorded in human patients with Parkinson's disease was included where the technology readiness level (TLR) is above 4.

- **Keyword detection**

In the first instance, an exploratory review of the literature was done to determine the main keywords that would help define and focus the global search into the topic in question. The articles selected for this global search were passed through word counts to determine the most prominent words and topics, an example for one article is shown in figure 3. The list of keywords included: Deep brain stimulation, local field potential, Parkinson's Disease, Parkinsonian disorders, dystonia, essential tremor, symptoms, beta, subthalamic, implantation, neuromodulation, neurostimulator, electrodes, microelectrodes, and stimulation. For each of these terms, a MeSH (Medical Subject Headings) term was assigned. Because of the innovation involving his study, the main keywords (Deep Brain Stimulation and Local Field Potentials) were not found in MeSH terms making a search equation based on MeSH terms not possible.

Figure 3. Example of the word cloud for article The Effect of Unilateral Subthalamic Nucleus Deep Brain Stimulation on Contralateral Subthalamic Nucleus Local Field Potentials [17]

- **Information sources**

The search was conducted during 2021 on the electronic databases PubMed and Scopus. These databases were selected because they are international sources for

healthcare articles. No articles were selected from other sources such as Google Scholar or other web browsers in an aim to maintain the search as objective as possible. The search was conducted from March 4, 2021, to April 6, 2021.

- **Search strategy**

The keywords selected previously were used to formulate different search equations used on the two electronic databases mentioned. The search terms for this review were general to avoid excluding relevant studies and included the title, abstract, and keywords of the articles. The following search queries were used and analyzed using the electronic database Scopus and next to it the number of results that each query returns from the mentioned database only:

1. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND brain AND stimulation AND (Parkinson OR Dystonia OR Essential Tremor OR Epilepsy OR OCD) AND LFP → 460 results
2. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND brain AND stimulation AND LFP → 1351 results
3. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND brain AND stimulation AND (Local Field Potential OR LFP) AND beta AND Subthalamic → 1765 results
4. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND brain AND stimulation AND (Local Field Potential OR LFP) AND beta AND Subthalamic AND human → 1717 results
5. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND brain AND stimulation AND (Local Field Potential OR LFP) AND beta AND Subthalamic AND (Parkinson OR Dystonia OR Essential Tremor OR Epilepsy OR OCD) →1140 results
6. DBS AND LFP AND Parkinson→ 418 results
7. LFP AND brain AND stimulation → 3546 results
8. LFP AND brain AND stimulation AND Parkinson → 867 results
9. LFP AND brain AND stimulation AND Parkinson AND beta → 620 results
10. ("Deep Brain Stimulation" OR Neuromodulation OR DBS) AND (Local Field Potential OR LFP) AND beta AND Subthalamic AND (Parkinson OR dystonia OR epilepsy or tremor or obsessive-compulsive disorder) → 291 results
11. (brain or subthalamic or globus) and (beta or LFP or stimulation) or adaptive or Parkinson → 385,959 results
12. brain and (subthalamic or globus) and (beta or LFP) or adaptive or (Parkinson and dystonia and epilepsy and OCD and tremor) and stimulation → 767 results
13. (brain AND (subthalamic OR globus) AND (beta or LFP) OR adaptive AND (Parkinson OR dystonia OR epilepsy OR OCD OR tremor) AND stimulation → 700 results

After analyzing each of the queries and the type of results they returned, the research equation chosen was number six (6) which includes the most general terms without limiting the search to a specific implantation place or a specific frequency band to analyze while searching for the specific effects on Parkinson's Disease. When using these in PubMed and Scopus the queries were: {(DBS[Title/Abstract]) AND (LFP[Title/Abstract]) AND (Parkinson [Title/Abstract])} and {TITLE-ABS-KEY (DBS AND LFP AND Parkinson)} respectively.

- **Inclusion criteria**

1. Any source of information about DBS, LFP signals, and Parkinson's Disease symptoms.
    a. The LFP signals mentioned should be analyzed as potential biomarkers for Parkinson's Disease.
    b. DBS technology is included if it has been implemented or deployed at least as a component or breadboard validation in a laboratory environment (TLR 4 or higher).
    c. DBS technology is included regardless of their cost.
    d. DBS technology must be used or intended to use in human adults (18 years or older).
2. Sources of information include:
    a. Studies where the applied methodologies are independent, either quantitatively, qualitatively, and technologies developed regardless of whether their results contributed negatively or positively.
3. Articles/documents published from the year 2011 to the present.
4. Articles/documents in English or Spanish.
5. Type of indexed articles, conference articles.
6. Studies published and available for full reading in scientific articles.

- **Exclusion criteria**

1. Studies that include any source of information about the existence of hardware, software, or methodologies that are focused on people under 18 years of age.
2. Animal studies.
3. Studies that are not available for a full reading.
4. Full Papers that their content does not contain sufficient information to categorize (i.e., TRL, ages, type of technology).
5. Studies published before 2011.
6. Papers that do not study humans with Parkinson's Disease.

7. Studies published in books, book chapters, Ph.D. or Master's theses, newspapers, interviews, and non-indexed journals.
8. Papers that were lecture notes at conferences, theoretical/seminar papers, and any kind of literature review.
9. Conference proceedings papers summarized and commented on several papers included in the proceedings book.
10. Studies beyond the scope of this systematic literature review.
11. Studies describing the design and composition of DBS systems (sensors, software, materials used).
12. Studies that collect LFP signals but do not analyze them.
13. Studies that exclusively focus on obtaining the signals.
14. Studies that do not use DBS therapy as a way of studying LFP signals in people with Parkinson's Disease.
15. Any study that compares LFP signals with another type of brain signals.
16. Studies that analyze the best implantation place for the DBS system.
17. Any study that does not analyze the LFP signals concerning Parkinson's disease symptoms.
18. Studies that obtain LFP signals from simulations and not from patients.
19. Studies that analyze therapies different to DBS.

- **Selection process**

For this review's selection phase, both databases were searched. The information of each article was exported to study on an Excel file where each of the found articles was assigned an ID and initial removal of duplicates was carried out. Second, the titles and abstracts of the articles were evaluated on the Mendeley Desktop application and compared with the inclusion and exclusion criteria. Two of the tutors randomly examined different articles that were accepted in the analysis of the title and abstract to validate the depuration of articles. The tutors chose IDs 1, 11, 35, 75, 122, and 139 and agreed in the acceptance of these articles and there were no discrepancies. Following this, the full text of the studies included in the first round was reviewed during the second round, the inclusion and exclusion criteria were assessed as well as the level of clinical evidence, rated the TRL scale and the scientific journal's ranking (quartile). An Excel table was completed explaining the reason for the exclusion of each of the articles that were excluded and a deeper analysis of the study for the ones included (annex 1).

- **Data collection**

For the data extraction phase, the eligibility criteria were carefully analyzed and data were extracted. An Excel spreadsheet was completed with the relevant information from

each paper and the last revision of all the included articles was made. This can be seen in detail in Annex A.

- **Data Items**

Each selected paper was carefully reviewed and the data were extracted for the following attributes: Journal/Conference Title, year of publication, country of affiliation, and type of study.

- **Participants**

The participants' ages and gender distribution, as well as the type of diagnosis of Parkinson's Disease and related movement disorders, UPDRS III on/off medication, and on/off stimulation.

- **Characteristics of the research conducted**

Sample size, length of the experiment (in years/months/weeks), number and duration of sessions, the type of topic or problem undertaken (i.e., technology-oriented studies, clinical-oriented studies, usability, or a combination of these), the design of the study for quantitative research, i.e., randomized control trial (RCT), cohort, single case design, case-control, cross-sectional and case study; for the technology-oriented studies, "technology development" was used as the study design, the setting where the DBS technology and registration of LDP signals was tested (i.e., laboratory, hospital/rehabilitation center, school, home, other), the type of outcome variables by diagnosis, a description of the main outcomes of the study, the sizes of the effects of the main outcomes variables (if reported), the type of treatment used, and the methods for reviewing and processing LFP signals.

- **Type of outcome variables**

Outcomes reported in the papers were extracted for Parkinson’s Disease and related movement disorders such as bradykinesia, dyskinesia, essential tremor.

- **Characteristics of the technologies**

The type of technology including electrodes, implantable neurostimulator, extensions, name, manufacturer of technology, whether it is available in the market, and its cost (if reported).

- **Technology readiness level (TRL) of the DBS system used in the study**

This was measured by an indicator that assesses the maturity of evolving technologies during their development and early operations. We used a technology

readiness scale from the U.S. Department of Energy [31], its scale ranges from 1 through 9, where 1 means that the technology only exists in its basic principles and 9 means that the technology is complete and can be successfully used in full operation. It can be noted that levels 1 through 3 include technology that is under investigation in a laboratory environment, levels 4 and 5 include technology under development and simulation reviews. Higher levels like 6 and 7 show technology in its validation stage and the final levels 8 and 9 include all technology that is being used in real environments in its final form.

- **Level of clinical evidence of the studies**

The level of clinical evidence was assessed for the outcomes of the clinical papers included in this review.

5. RESULTS

- **Selection process**

The database search in the identification stage resulted in 319 articles to be analyzed, where 144 were obtained through PubMed and 175 through Scopus. After adjusting the search to the years included and the languages, PubMed's search gave 115 articles while Scopus gave 141 articles. These articles summed up to 256 in total to be analyzed. Of these, 105 were duplicated and removed leaving a total of 151 articles. The titles and abstracts of the remaining articles were read and the inclusion and exclusion criteria were applied to allow the exclusion of 113 leaving a total of 38 articles. Thirty-eight full texts were read and the inclusion and exclusion criteria were applied again.

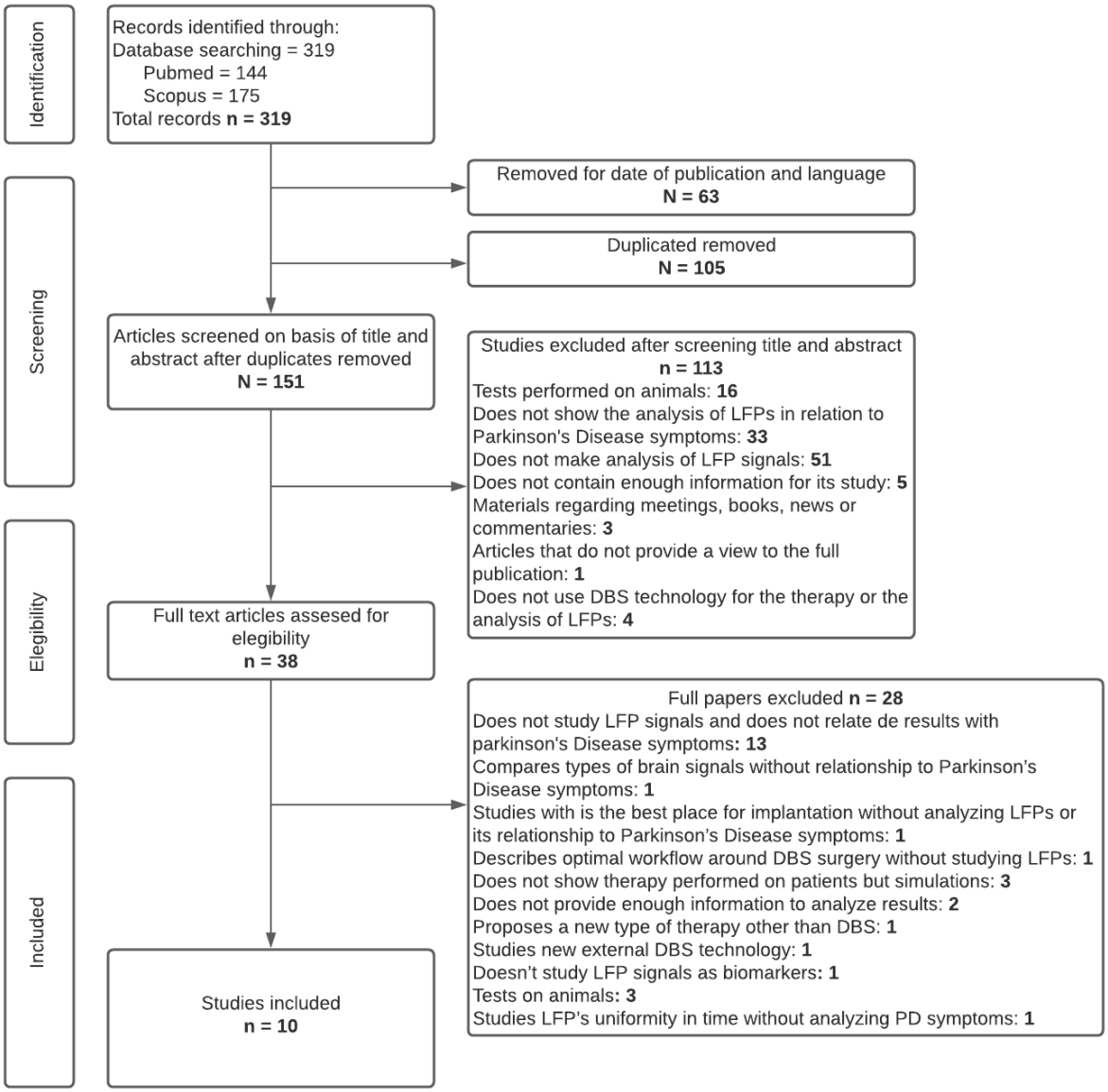

Figure 4. Flow diagram of the literature review.

As seen in figure 4, the selection progress workflow can be seen specifying each stage included in the search. As it can be seen, 113 abstracts and titles were excluded for the following reasons: performs tests on animals (16), does not show the analysis of LFPs concerning Parkinson's Disease symptoms (33), does not analyze LFP signals (51), does not contain enough information for its study (5), materials regarding meetings, books, news or commentaries (3), articles that do not provide a view to the full publication (1), does not use DBS technology for the therapy or the analysis of LFPs (4). Twenty-eight articles were excluded for the following reasons: does not study LFP signals and does not relate de results with Parkinson's Disease symptoms (13), compares types of brain signals without relationship to Parkinson's Disease symptoms (1), studies what the best place for implantation is (1), describes optimal workflow around DBS surgery without analyzing LFPs (1), does not show therapy performed on patients but simulations (3), does not provide enough information to analyze results (2), proposes new types of therapy other than DBS (2), does not study LFP signals as biomarkers (1), tests on animals (3), and studies LFP's uniformity in time without analyzing Parkinson's Disease symptoms. Finally, ten articles were included in this review, which corresponds to the last box where **n** is defined as 10.

- **Bibliometric characteristic of the journals and papers included**

The totality of articles chosen were journal papers (10/10). In figures 5 and 6, the trend for the number of studies over the years and authors' country of origin, is shown respectively. Overall, the studies were published in journals located mostly in Q1 and Q2 journal quartiles. Specifically, 5 article journals were in Q1 (50%), 4 in Q2 (40%), and 1 in Q4 (10%). The studies were conducted in four different countries; 60% of the studies were conducted in Europe and 40% in the United States.

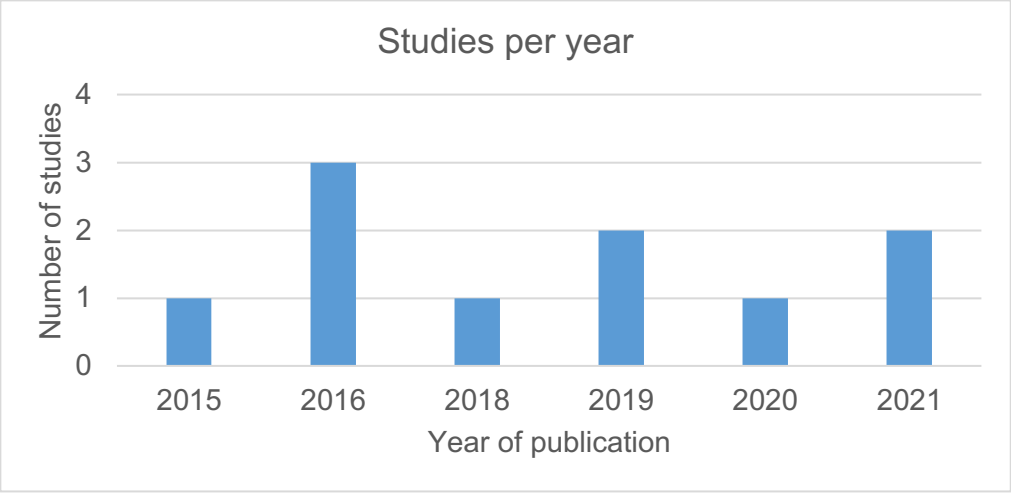

Figure 5. The number of studies per year.

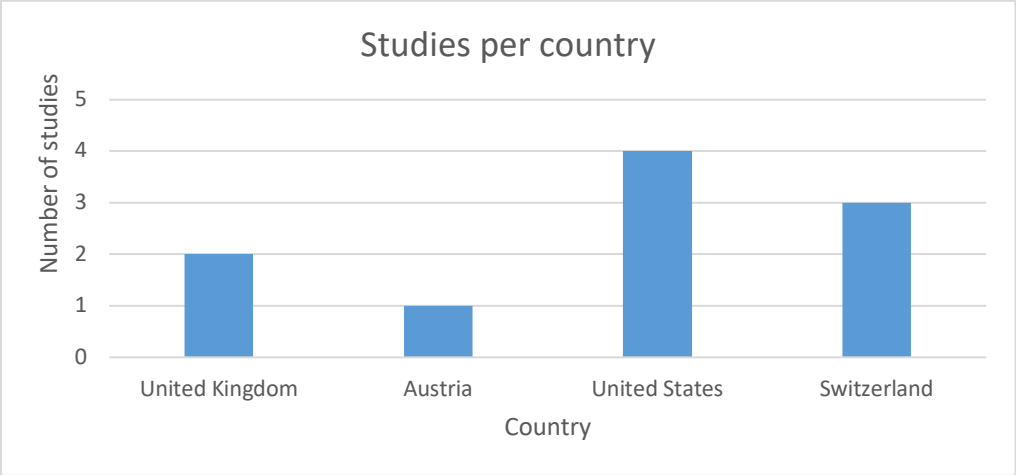

Figure 6. The number of studies per authors' country of origin.

- **Characteristics of the included studies (general)**

Table 1 shows a summary of the studies included in this review, the types of technologies, features, TRL, participants, study design, type of results obtained, and the reference of the study.

- **Studies per medical condition**

All of the studies included patients with Parkinson's disease since it was included in the inclusion and exclusion criteria. Other symptoms mentioned or specified other than PD symptoms were: tremor 50% (5/10), postural instability 10% (1/10), gait disorder 20% (2/10), rigidity 50% (5/10), bradykinesia 20% (2/10), dyskinesia 20% (2/10), and dystonia 10% (1/10). These percentages are taken independently since there might be articles that mention one or more of the mentioned symptoms. In the articles, exclusion criteria were mentioned for patients with high anxiety during surgery, major psychiatric illness, PD dementia, previous intracranial surgery, and clinical response to levodopa challenge below 30%.

- **Participants**

In total, the studies included 98 participants with a high variation in sample size (mean sample size 10.8 SD 9.04, maximum sample size 28, minimum sample size 1). Among the included studies that reported the participants' demographics, there was a gender distribution of 26% female and 74% male, the overall mean age was 58.6 with SD 9.66. The average UPDRS-III score was 44.12 with SD 4.94 and the average time (in years) since diagnosed with PD was 10.3 with SD 2.97. Two studies did not report gender, one did not show age distribution, one study did not show UPDRS-III score and two studies did not mention the length of time since patients were diagnosed.

- **Methods (study designs)**

In general, the studies used a quantitative approach 90% (9/10) with strong designs, 70% were RCT studies (7/10), 20% were single case studies (2/10) and 10% were clinical studies (1/10).

- **Settings**

Many studies consisted of two parts 90% (9/10). First, the implantation stage where the DBS electrodes are implanted either in the STN or GPi. The second stage consists of the method used to read and record LFP signals. This stage can be separated into two different settings, first, in the surgical room while the patient is implanted 60% (6/10), or post-operatively with an internal or external pulse generator 30% (3/10)

Table 1. Summary of the included studies in this review (n = 10)

		DBS System		Participants								
Medical/ occupational condition	**Total studies (%)**	**Features**	**TLR**	**N**	**Age Mean ± SD**	**Gender M/F**	**PD duration mean (years) ± SD**	**Pre-op UPDRS III (off medication)**	**DBS side**	**Design of Study**	**Types of results**	**Study**
Parkinson's Disease	9 (80%)	microelectrodes (microTargeting® electrodes, FHC), filtered microelectrodes (Lead Point - Medtronic)	9	22	54.8 ± 10.7	15/7	8 ±2.3	53 ±20	13 Bilateral, 6 R, 3L	Clinical Study/ Randomized Controlled Trial	Mixed (100%)	2
		Electrode leads (Medtronic 3389™), a pulse generator (Medtronic Percept™)	9	1	56	1/0	6	38	1 bilateral	Clinical Study/ Single Case Study	Positive (100%)	3
		Segmented electrode (Abbott St. Jude Medical model 6372), lead extension (Abbott St. Jude Medical Model 3383), neuronavigation system (Stealth, Medtronic, Inc.)	9	3	58 ± 4.6	1/2	7.6 ± 1.7	47.6 ± 3.8	2R, 1L	Clinical Study/ Randomized Controlled Trial	Mixed (33%), Positive (66%)	12
		DBS device (Activa PC+S®), quadrupolar electrodes (Medtronic 3389)	9	8	58 ± 8	7/1	13 ± 6	49 ± 12	4R, 4L	Clinical Study/ Randomized Controlled Trial	Positive (100%)	31
		DBS lead (Medtronic 3389), Neurostimulator (Activa PC + S, Medtronic, Inc.	9	7	61.7 ± 8.1	5/2	-	39.3 ± 13.38	7 Bipolar	Clinical Study/ Randomized Controlled Trial	Positive (100%)	74
		DBS lead (Medtronic 3389), Neurostimulator (Activa PC + S, Medtronic, Inc.)	9	17	61 ± 7.9	-	11 ± 3.4	43.5 ± 10.3	17 bilateral	Clinical Study/ Randomized Controlled Trial	Positive (82%), Mixed (18%)	75
		Quadripolar electrodes (Medtronic 3389), external stimulator (Medtronic DualStim)	9	11	60 ± 2.7	7/4	11.2 ± 1.3	39.9 ± 3.5	4 Bilateral, 3R, 4L	Clinical Study/ Randomized Controlled Trial	Mixed (60%), Positive (40%)	97
		DBS system (Activa PC+S™ Medtronic)	9	1	44	1/0	15	43	-	Clinical Study/Single Case Study	Positive (100%)	206
		aDBS Systems (Not specified)	-	-	-	-	-	-	-	Clinical Study/ Randomized Controlled Trial	Positive (100%)	55
Parkinson's Disease & dystonia	1 (10%)	DBS lead (Medtronic model 3389, 3387)	9	28	59.5 ± 10.1	23/5	10.7 ± 4.04	43.8 ± 18.16	16 R / 12 L	Clinical Study/ Randomized Controlled Trial	positive (100%)	86

- **Interventions/aim of studies**

All of the studies included interventions since DBS technology requires implantation and reported a duration of 3 hours when the signals were recorded in the operating room [32]–[37] and averaged 2 years when the DBS system was able to continuously record the signals [38]–[41]. The intervention aims in these studies included the determination of the effect of DBS stimulation and medication of the oscillations of LFP signals and how they are related to symptoms of Parkinson's disease.

- **Signal Processing**

Because of the atmosphere, LFPs are recorded, the recordings cannot be used without filtering and amplifying for better comprehension and analysis. The signal processing is digitally stored and analyzed in MATLAB (MathWorks, Inc.). The common sampling rate was between 250 Hz – 4.8 kHz and signals are downsampled to 1kHz. The neurostimulator computes de spectrum of the LFPs every 500 ms and evaluates peak amplitudes in a user-defined frequency band. This frequency band is usually in the beta section (12-30 Hz) but can also expand to analyze alpha (8-12 Hz) and gamma (30-140 Hz) frequencies.

The peak amplitude evaluation is performed by a fast Fourier transform. Amplitude information is reported in a center frequency defined by the user. The signal is amplified and digitized by the INS when one is part of the procedure. The signals are band-pass filtered from 2hz to 90 Hz. A notch filter is performed to filter power-line noise at 60 Hz and harmonics are removed. Spectral analysis of the signals is performed employing Welch periodogram for PSD estimation. The discrete Fourier transform magnitude is evaluated and it is averaging considering all windows. The LFP band power is obtained by evaluating the area under de PSD curve.

- **Outcomes**

In Annex A, a list of outcomes can be seen for every study reviewed. The outcomes for each study were aimed slightly different, making their analysis independent. All of the studies aimed to classify the use of LFP signals for a closed-loop version of DBS or use it as a biomarker in the detection of PD symptoms when using DBS technologies.

In the studies where the DBS technology used allowed post-op LFP recordings for longer periods, 40% (4/10) showed that LFPs recorded intraoperatively show one peak amplitude in the beta band on the left side and two distinct peak amplitudes on the right side when the patient is asked to perform stand-walk exercises and there was no stimulation active. When stimulation was turned on, an improvement of the patient's symptoms could be seen changing from UPDRS-III 38 to 6 [33], [38].

Hanrahan et Al. [39] study analyzed peaks in the beta frequency in the LFP signal six months after implantation. In this study, 52% (19/38) patients showed prominent peaks in beta frequency for the recording of six months. These peaks vary in amplitude and specific frequency range by subject. They compared LDP signals recorded over a year and compared noticing they vary across subjects but remain consistent within subjects.

Results are also portrayed in periodograms of LFPs in the logarithmic scale (dB/Hz). These graphs are developed to show how the signals vary according to the therapeutic state the patient is at. For movement and rest, the PSD coefficient changes where the patient is in movement. Raw recordings

and spectrograms help identify a pattern of high beta resynchronization 1-3,5 s after movement onset in the ON state for alternating and isometric movements [32], [33], [36].

Trager et al. identify beta band power as similar when recorded zero and 60 min off chronic neurostimulation through a time-frequency spectrogram and a PSD of resting-state LFPs from a representative subject during their set protocol. Also, the withdrawal of chronic high-frequency STN DBS reveals attenuation of pre-DBS resting-state beta band power after 6 – 12 months of continuous high-frequency DBS. Lateralized UPDRS-III scores assessed off therapy after six and twelve months of high-frequency DBS were compared to those at the initial programming [35], [41].

6. DISCUSSION

Biomarkers of PD symptoms are clinically relevant because they are aiming to be used to control adaptive DBS systems applying stimulation based on the current clinical state rather than continuously. It has been shown that LFPs are control signals that show the stability or lack thereof of brain activity regarding movement disorders depending on the place of implantation of the electrodes. Within the power spectrum, the respective performances are extremely variable. Moreover, the oscillations within different frequency bands may be significantly dissimilar, and the behavior of the energy variations between these oscillations may be opposite.

STN has been the most studied site of implantation and what to date has shown the most beneficial result for DBS therapy. Through PSDs and spectrograms, it was noted how signals change dramatically once stimulation is applied especially when it is targeted toward beta frequencies of LFP signals. Medication greatly affects the signals since it helps the patient with their symptoms. When the patients take their medications while feeling strong symptoms, the beta band of the LFP signal seems to decrease in amplitude in most of the cases.

There are few reports showing implantation in the internal globus pallidus, aiming more of the research towards STN-LFP signals. In the GPi, physiological biomarkers are subject-specific and spatially localized. Lead location is relative to anatomical structures which cause implications for lead placement and DBS programming. It was found by Aman et al. that the most beneficial effect for STN DBS came from the stimulation of the contacts with the highest magnitude of beta activity, allowing us to discuss that the higher beta activity correlates to the symptoms in PD and can be considered a viable biomarker and guide for stimulation [33]. They also studied the relationship to motor signs when there is a presence of oscillatory activity in the GPi in PD. The spectral activity was most prominent in showing tremor and bradykinesia in the GPi compared to the average power presented when the electrodes were implanted in the STN. It was noted that adaptive deep brain stimulation would not be as beneficial when implantation occurs in the GPi since the oscillatory activity dynamically changes during a peak in symptoms. It was demonstrated the utility of using patient-specific data for determining the relative location and orientation of the individual lead contacts for characterizing the relationship of LDP activity to individual motor signs and potentially determining optimal contacts for DBS [33].

In the studies, several essential factors that lead to significant difficulties in quantifying the LFP biomarkers in PD were shown to give an objective view on the topic. First, the data of LFP in PD has not been fully explored because of the innovation it involves. These signals have not been identified because of the lack of relevant databases and studies that show how they relate to PD. These records have usually been from intra-operative procedures but signals that extend for longer periods need to be studied to determine the long-term benefits of DBS. When the LFP data was able to be recorded for prolonged periods, DBS stimulation was used to show that, after long influence, the performance of abnormal oscillations did not show any significant anomalies, which confirmed that the respective oscillations could be used as a biomarker for long-term adaptive DBS control [41]. Yet, the adequate analysis of intermittent long-term LFP data is still indispensable. The quantified biomarkers are still difficult to be used as the standard because of the insufficiency of the data caused by the limited number of patients in each study trial. Having more patients to study would allow a clearer classification of the LFP signals and how it works as a biomarker for PD symptoms. Differences will greatly reduce once adaptive DBS starts earning popularity and is used in more studies.

7. RECOMMENDATIONS AND FUTURE WORK

This state-of-the-art review was aimed as a starting point for the investigation of how LFP signals may be obtained and used as a feedback signal of DBS technology. So far, no studies have been done in Latin America regarding LFPs and their relationship to PD symptoms. Given the racial difference to the current studies (North American and European), the question must be raised about how it would affect different ethnicities with different social backgrounds. One study states that alternatives that allow recordings from the same DBS electrodes used for stimulation are more ecological and available and possibly a future option [32]. In general, results must be tested in a higher number of patients in future studies since the average number of patients was very low. A study is proposed where the target patients are Latin American people who have Parkinson's disease to be able to classify LFPs as biomarkers and compare to existing studies to differentiate between constants and patterns shown and make treatment even more targeted towards all people.

As far as recommendations for future students doing their internship in Medtronic, the recommendations apply if they are involved in the neuromodulation business unit. First, this project can be continued by exploring the possibility of obtaining already recorded signals from patients. These signals can be obtained in the operating room and can be extracted to analyze in MATLAB. This would require ethics protocols and patients signing informed consent to allow their brain signals to be fully studied. By having access to these signals, even more, processing can be done where not only the LFP signals are studied, but also surrounding signals that could be deconstructed to find valuable information.

My second recommendation for future interns is to have an open mind. We often think of biomedical engineering as only being the technical work involved in running a hospital or creating new devices [42]. While this is not untrue, this profession allows branching through many different channels that allow the engineer to explore and learn about the business from other perspectives. Through marketing neuromodulation, they can learn what needs to happen to sell a medical device, what variables affect its impact in the market, and how to, through well-thought-out materials, reach their audience. It might not be the typical internship for a biomedical engineering student, but only by being one, a whole world is already available to explore a more administrative side of biomedical engineering.

8. CONCLUSIONS

Through this review of the current technology of LFP signals, it was possible to develop a state of art that allows health care professionals to know the current state of technology to record the signals of the local field potential in the brain and its relationship with the symptoms of Parkinson's disease.

The depuration of the information of the most important articles relating to this topic allowed a review to be specific and to the point, bringing forward the most important characteristics health care professionals are observing in the signals in the study.

A synthesis of the results of existing studies in the scientific literature on local field potential signals as a biomarker in the diagnosis of symptoms in people with Parkinson's disease was achieved determining how the studies correlate the two variables and how the quantifiable variables change after stimulation was performed.

It was possible to design a search equation that limits and prioritizes relevant and coherent information for the study. This was achieved to gather the most important information, with the most precise data to allow health care professionals to understand the most relevant information.

The types of studies performed in which the local field potential signals related to the treatment of movement disorders were analyzed and defined.

The current state of the study of local field potential signals focused on the place of detection in the brain and its analysis of symptoms was defined and portrayed.

A summary of the information was put together so that it is easily accessible and easy to understand for the health care professionals.

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ANNEXES

ANNEX A

Access link to Annex A. Excel table classifying information for the selected articles n=38

ANNEX B

Access link to Annex B. Infographic for professionals interested in how LFP signals relate to Parkinson's Disease symptoms.