Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part II
DOI: 10.54254/2753-8818/4/20220545

Application of Non-invasive Brain-computer Interface in Neurodegenerative Disorder Diseases

Ancheng Liu[1, †], Hongyun Wang[2, a), *, †]

[1]College of Chemical Engineering and Materials Science, Tianjin University of Science and Technology, Tianjing, China, 300457
[2]School of Basic Medical Sciences, shenyang medical college, shenyang, China, 110000

[a), *] BCIgroup10@cdmc.edu.cn
[†]These authors contributed equally

Abstract. Neurodegenerative diseases (ND) are characterized by gradual loss of selectively susceptible neuron populations, usually presented by cognitive disorder and movement ability impairment, and cause great distress to patients and those close to them. The diagnosis and rehabilitation of NDs have been an unsolved challenge for many years, but brain-computer interface (BCI), a vigorously growing research area, may provide a promising tool to solve the problems. Here, we first briefly introduced the working principle of BCI, then take a few of the most common neurodegenerative diseases as an example to introduce the nowadays BCI application on NDs diagnosis and rehabilitation. This article will help researchers to gain a general understanding and appreciation of this field, and provide assistance for related studies.

Keywords: Neurodegenerative Diseases, Brain-computer Interface, Electroencephalogram, Functional Near-infrared Spectroscopy

1. Introduction

A neurodegenerative illness is a disorder in which the cells of the central nervous system stop working or die. Neurodegenerative diseases are usually incurable and worsen with time. People with neurodegenerative illnesses such as Amyotrophic Lateral Sclerosis, Parkinson's disease, and Alzheimer's disease frequently have movement and cognitive problems. The major and most difficult challenge currently is determining the etiology and mechanism of symptoms and making a diagnosis. Previously, dissecting the brains of deceased patients was a typical approach of determining the biological features and pathogenic processes of neurodegenerative disorders. This method is ineffective and one-sided. As a consequence of the advancement of brain-computer interface technology, several laboratories have begun to examine it as a novel communication alternative for patients with neuromuscular problems who are unable to use conventional improved communication approaches. Because of the brain interface, these users have a channel of communication that is not dependent on muscles or peripheral nerves. In this review, we focus on the use of non-invasive brain-computer interfaces, such as EEG and fNIRs, for investigating and treating neurodegenerative illnesses such as ALS, Parkinson's, and Alzheimer's..

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DOI: 10.54254/2753-8818/4/20220545

2. Basic working mechanism of BCI

A condition in which the central nervous system's cells stop functioning or die is referred to as a neurodegenerative disease. Usually incurable, neurodegenerative illnesses get worse over time. Movement and cognitive impairments are common in people with neurodegenerative disorders (including ALS, Parkinson's disease, and Alzheimer's disease). The main and challenging issue now is how to identify the etiology and mechanism of symptoms and make a diagnosis. In earlier research, dissecting the brains of patients after they passed away was a common method of identifying the biological traits and pathogenic mechanisms of neurodegenerative illnesses. This strategy is stagnant and one-sided. Many laboratories have started to investigate brain-computer interface (BCI) technology as a brand-new communication option for patients with neuromuscular disorders who are unable to use conventional enhanced communication techniques as a result of the development of brain-computer interface technology. These users have a channel of communication that is not dependent on muscles or peripheral nerves thanks to the brain interface. In this review, we concentrate on the use of non-invasive brain-computer interfaces for studying and treating neurodegenerative disorders like ALS, Parkinson's, and Alzheimer's, such as EEG and fNIRs.

BCI consists of both invasive and non-invasive BCI. Since invasive BCI uses surgically implanted electrodes beneath the scalp to transmit brain impulses, scar tissue may develop after surgery, weakening brain signals. The majority of published BCI research uses non-invasive, EEG-based BCL. As typical non-invasive brain computer interfaces, EEG and fNIRs are simple to wear, don't need surgery, and are reasonably priced. Applications for non-invasive EEG-based technology and interfaces are more varied.

3. EEG

Traditional scalp EEG recordings are acquired by applying conductive gel or paste to the scalp electrodes. Typically, several systems employ electrodes, each of which is connected to its own wire. Some systems employ caps or nets with embedded electrodes, particularly when high-density electrode arrays are required. The International 10-20 system outlines the placements and names of electrodes. In the majority of clinical applications, 19 recording electrodes (plus ground and system references) are employed, almost uniformly placed over the scalp (plus ground and system references). Each electrode is linked to a differential amplifier's input (one amplifier is used for every pair of electrodes), and each differential amplifier also has an extra input for the common system reference electrode. The voltage between the active electrode and the reference electrode is raised by these amplifiers. In clinical scalp EEG, analog-digital sampling typically occurs between 256 and 512 Hz; sampling rates as high as 20 kHz have been utilized in some research applications. A number of activators may be utilized when recording. These steps may lead to the detection of normal or abnormal EEG activity that would not otherwise be visible. These actions consist of hyperventilation, flashing light stimulation, eye closure, mental activity, sleep, and sleep deprivation. Digital EEG signals are electronically stored and may be filtered before to display. High-pass and low-pass filter settings are typically between 0.5-1 Hz and 35-70 Hz, respectively. In contrast to low-pass filters, which often remove high-frequency artifacts like EMG signals, high-pass filters typically remove slow artifacts like electrical signals and motion artifacts. Typically, an extra notch filter is utilized to eliminate artifacts resulting from electricity lines (60hz in the us, 50hz in many other countries). When measured from the scalp, the amplitudes of typical adult EEG signals range between 10 and 100 V.

4. FNIRs

The concentration of hemoglobin is calculated using changes in the absorption of near infrared light by near infrared spectroscopy. Light is alternatively scattered or absorbed by the tissue it passes through as it moves or travels inside the skull. Because hemoglobin is a significant NIR light absorber, variations in the amount of light absorbed can be utilized to accurately gauge variations in hemoglobin concentration. The way light travels can also be used by various NIR spectroscopy techniques to calculate blood volume and oxygenation. The method can be applied to various imaging modalities

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and is secure and non-invasive. FNIRS is a non-invasive imaging technique that measures the attenuation of near-infrared (NIR) light as well as any temporal or phase variations. Light is strongly absorbed by hemoglobin (Hb) and deoxyhemoglobin (deoxyhemoglobin). Direct transmission, diffuse reflection, specular reflection, diffuse reflection, scattering, and absorption are the six ways in which infrared light interacts with brain tissue. The absorption coefficients of deoxyhemoglobin and oxyhemoglobin were the same, therefore two or more wavelengths were selected, one above 810 nm at the iso-thickness point and the other at the iso-thickness point. Use the revised Bill - Lambert's law, where the change in the relative concentration of photons can be calculated as long as the total path length functions normally, the light emitter and detector are placed on opposite sides of the subjects' skulls (each transmitter and detector in the same side), and the tracking measurement is made possible by the elliptical path of back scattering light (reflection). Close to the light source, extra photodetectors are frequently used to handle surface artifacts since FNIRS is most sensitive to hemodynamic changes in the area closest to the scalp.

5. Application in the research and treatment of neurodegenerative diseases

5.1. BCI in Parkinson's Disease

Parkinson's disease(PD) is the second most common neurodegenerative disease after Alzheimer's disease. In 2016, about 6-1 million people worldwide were living with Parkinson's disease, compared to about 2-5 million in 1990. And age-standardized prevalence increased by 21-7% over the same period. Parkinson's disease caused 3 to 2 million disabled people and about 200,000 deaths in 2016. Age-standardized prevalence, disability and death rates increased between 1990 and 2016 in all regions with the global burden of disease, except southern Latin America, Eastern Europe and Oceania[1]. As the population ages, it will impose an increasing social and economic burden on society.

The pathological features of Parkinson's disease are the loss of nerve cells and the accumulation and spread of Lewy bodies in the substantia nigra. The disease is typically characterized by movement disorders, including resting tremor, bradykinesia, postural instability, and stiffness of the neck, trunk, and limbs. Movement disorders, such as dyskinesia (involuntary movements) and dystonia (painful involuntary muscle contractions), lead to limitations in speech, movement, and many areas of life.[2] The development of these symptoms leads to high rates of disability and care requirements. Some PD patients will also show cognitive impairment and even dementia in the course of their disease.

There is no completely rehabilitation for Parkinson's disease just like other kinds of neurodegenerative diseases, such as AD, but drugs, surgery and other therapies can treat its symptoms. Therapies such as levodopa/carbidopa or deep brain stimulation can also treat the symptoms of PD, especially tremors, as well as reducing medication intake.[3] For patients with Parkinson's disease (PD) and other movement problems, specific forms of physical therapy, such as strength training, gait analysis, and balance training, can enhance function and quality of life. PD symptoms usually occur 5 to 15 years after a patient has started to develop molecular and cellular neuropathy. One of the most pressing areas of PD research is the need for clinical biomarkers to aid in early diagnosis, as well as prognostic prediction and treatment options. In the past, due to the lack of clear biological characteristics and the inability to effectively identify the effects of drugs on Parkinson's disease, the progress of the research on Parkinson's disease pathology has been slow. With the development of electronic information technology, BCI equipment has gradually developed and matured, and has been applied to the research of Parkinson's disease.

Quantitative EEG (QEEG) is an old technique, dating back to the 1920s[4]. Data can be acquired on standard equipment, and digital EEG can be recorded and analyzed with dedicated software. QEEG provides reliable biological markers for the diagnosis of Parkinson's disease[5]. Quantitative biomarkers may be able to identify the risk of PD before disease symptoms are expressed, as achieved by directly measuring brain activity to determine cortical dysfunction. This type of population data does not yet support the use of QEEG to predict dementia in PD on an individual basis, but the work

DOI: 10.54254/2753-8818/4/20220545

presented in this study may help stratify the risk of potential study subjects before entering clinical trials aimed at preventing or delaying dementia treatments in PD. This low-cost, reliable test may complement neuropsychological testing in the future, but cannot be used as a substitute for clinical judgment, while QEEG requires that the patient be awake, non-drowsy, and free of muscle artifacts. More objective markers of disease status may reduce the variability in trials, thereby reducing the size and length (and cost) of necessary clinical trials. While biomarkers will never replace clinical examinations, objective testing may provide patients with a more reliable measure than that provided by history and physical examination.

Functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG) are often used to study the correlation between brain and body movement[6]. By comparing the oxygenated hemoglobin and deoxygenated hemoglobin indexes of patients and normal people during marching, they can also provide biological characteristics of Parkinson's disease[7]. People with Parkinson's have a hard time taking quick, accurate steps in predicting and/or responding to environmental hazards. However, The brain processes behind cognitively demanding stepping activities are still poorly understood. Fnirs can measure transient physiological changes in patients, linking increased HbO2 variability to flexible adaptation to environmental challenges[8]. Frozen gait is a common behavioral disorder in Parkinson's disease. Gait is influenced by higher-order cognitive and cortical control mechanisms. fNIRs can measure the activation pattern and activation state of prefrontal cortex when patients complete simple tasks and complex tasks[9]. To establish the theoretical framework of hemodynamic response physiology.

In the early stages of Parkinson's disease, medication is often used. The cerebral cortex information of patients during the medication period was collected by EEG and the blood oxygen concentration of patients was compared with the brain information of normal people by fNIRs so as to determine the mechanism of drug action and the side effects of drugs. Transcranial ultrasound or diffusion-weighted MRI findings of midbrain structural abnormalities or PET or SPECT findings of striatal dopaminergic terminal dysfunction support the diagnosis and rational use of dopaminergic drugs. PET and SPECT can detect changes in striatal dopamine levels after levodopa administration[10, 11] and correlate them with motor responses[12]. For example, 18F-DTBZ PET was as an Excellent Tool for the Early Diagnosis of PD[11]. Similarly, it can also be used as a tool to study the structural and metabolic pathological features of Parkinson's disease[13, 14]. Sanchez-Catasus, Bohnen[13] found that acetylcholine-dopamine imbalance exists in the striatum in the early stage of Parkinson's disease. Previous histopathological and animal studies have demonstrated axonal damage and loss of nigrostriatal pathway connectivity in patients with Parkinson's disease (PD). However, this contradicts reports from living human studies. Sanchez-Catasus, Bohnen[14] found that the impaired integrity of dopaminergic nigrostriatal nerve endings in patients with mild to moderate PD was related to the dysfunction of nigrostriatal axons.

5.2. BCI in alzheimer's disease diagnosis

Alzheimer's disease (AD) is one of the most common forms of neurodegenerative disease and the main cause of dementia. In 2018, about 50 million people have suffered from dementia, two third of them have AD, and this number is expected to triple by 2050 due to the age increasing of the global population[15]. The condition of this disease is characterized by over time impairment of memory and cognitive abilities, leading to loss of independence and, eventually, unable to live by themselves[16]. To date, AD is still irreversible as it was diagnosed, current treatments are mostly based on slowing the progression of AD rather than curing it. But thanks to the technology advancements, especially BCI devices, which provide reliable biomarkers for the diagnosis of AD in an earlier stage, offer medical care timely, thus avoiding the impairment from AD as much as possible. Here, the three most used non-invasive BCI device applications in AD will be introduced, to provide assistance for related research.

Electroencephalography (EEG) based AD study has been conducted for decades. With its excellent temporal resolution, it is widely used in the diagnosis of AD and distinguishes it from other kinds of

DOI: 10.54254/2753-8818/4/20220545

dementia. Based on whether a specific event is involved the condition of EEG recording has two main categories: resting state and a Particular Event. For AD patients, resting state EEG is more suitable because the events may make patients feel anxious and painful which causes effects on experiments[17]. During the resting state, there are four main features of EEG representations in AD patients: slowing, reduced complexity, synchronization declines, and deficiencies in neuromodulations[18]. Some studies have successfully used these characteristic changes in EEG in AD to distinguish AD patients from normal elderly control and other forms of dementia with a quite high degree of accuracy[19, 20]. But what needs to point out here is that although EEG signals can more or less diagnose AD, these EEG studies on AD do not provide reliable data with great precision, since most of them lack enough subjects. And the EEG data collection from AD patients is quite complex currently, most of them are not accessible to the public, thus making it difficult to further research[18].

AD has been widely considered as a disconnectivity disease because of its local synaptic disruptions[21]. With resting state fMRI(rs-fMRI), the functional connectivity (FC) among different regions of the brain can be quantified, and studies have identified some biomarkers for AD diagnosis and differentiate it from other dementias. FC integrity appears to decline in healthy aging, but this decline is exacerbated in AD, with certain systems, such as the default mode network (DMN), bearing the brunt of the damage[22]. The DMN has been demonstrated to be impacted in all kinds of AD variations and hence has been the most researched network as a possible biomarker to discriminate between AD and non-AD dementia in the early disease stages. In some DMN study, both AD and mild cognitive impairment (MCI) was observed with a greater drop in FC between the anterior and posterior regions of the DMN, as well as a decrease in within-network connectivity in the posterior DMN, which is similar to healthy elderly people, but more robust, related to the diminished DMN connectivity[23]. Further studies detected a biphasic FC pattern in AD frontal connectivity, which expressed increased activity in the early phase and diminished in the more serve phase[24]. Other FC networks, like the salience network and central executive network (CEN), also showed somewhat changes between AD and health control[23]11. Thus, AD can be diagnosed and differentiated with these FC network alterations.

Histologically, AD is characterized by abnormal Aβ accumulation which occurs decades before the start of clinical symptoms[25], therefore AD can be diagnosed at an early stage if we target these Aβ deposits as a tool, and that is what we use positron emission tomography (PET) to do. [11C]PiB was the first probe put in use with specific binding to Abeta, to date, numerous studies have been conducted and applied clinically about this radiotracer, making us successfully apply it in PET imaging to assist in the diagnosis of AD with pretty high sensitivity and specificity[26]. Other tracers, mostly are those labeled with fluorine-18, such as [18F]flutemetamol, [18F]florbetaben, and [18F]Florbetapir also have good sensitivity and specificity when clinical studies[27]. But some problems still exist when applying these tracers, like [11C]PiB, its uptake was found in normal healthy elderly control and other forms of dementia, and fluorinated tracers showed less specificity than [11C]PiB, causing more background noise[28]. So recently, a cut-off line was conducted with the centiloid method, to process data in a more comprehensive way, and assist with relevant clinical work and research[29]. Each of these three methods has its own advantages when applied, and it is necessary to select or combine multiple devices according to the situation when conducting AD-related research and practical applications.

5.3. BCI for the communication and movement assisting of ALS patients

Amyotrophic Lateral Sclerosis (ALS) is a fatal multisystem neurodegenerative disease in which motor system impairment is considered its predominant manifestation. Patients with ALS have to endure the pain caused by progressive physical immobility, and most of them also with somewhat cognitive impairment[30]. Over the past decades, several devices with different systems were put used for motor disabled people, like eye trackers, speech-based interface, and robotic assistive devices[31]. The contribution of these devices to patients is undeniable, but they are still unsatisfactory and have more

DOI: 10.54254/2753-8818/4/20220545

or less defects in practical applications, especially for those in extreme pathological conditions. Based on this, with BCI, ALS patients can control extra devices by signals generated from their brain, therefore assisting their mobility and communication. Here, since it is the most often used and investigated component, the EEG-based devices will be the major discussed here.

The use of EEG-based BCI devices is now very common in people with paralysis, such as wheelchairs, prostheses and robots, especially during the time of the COVID-19 pandemic. EEG-based non-invasive BCI mainly includes three modalities with different brain signals: slow cortical potentials, sensorimotor rhythms, and P300 potentials, and each of them has provided a promising solution for motor-impairment people. For ALS patients, the studies are mainly focused on P300, a kind of late positive potential elucidated 300ms in response to a task-relevant stimulus, and compared to other modalities, it requires less training for people[32]. Based on P300, a kind of speller system was created for assisting the communication and interaction with environments of ALS patients[33]. In this old study, 26 alphabet and several symbols were exhibited on a screen and flashed repeatedly, then people need to focus on the character they want when it flashed, P300 will be triggered and uploaded to the computer and that letter will be output. After several continuous operations, people can create a completed word or a sentence. Although there are some deficits in accuracy and application, there is no doubt that this pioneering study paved the way for this area, and make a great contribution to paralyzed people regaining communication ability. To date, numerous P300-based speller systems were conducted, with more accuracy and more diversity, making it easier to use and apply in other areas[31].

Sensorimotor Rhythms (SMRs) are rhythms that can be derived from EEG data that is only collected in sensorimotor regions and allow physically specific voluntary modulation. Studies about it mainly focus on its motor modulation character, to control a cursor or external devices. With SMRs, one of the first non-invasive movement control devices was conducted in 2004[34]. In this study, signals over the right and left sensorimotor cortices were recorded, after processing, the movement of a cursor can be controllable. Well-trained people showed a good performance using it and getting better over the training sessions. Another study[35], firstly demonstrated motor impairment people can use EEG-based devices to control the cursor in multidimensions. Furthermore[36], they also demonstrated that mobility-limited people can use EEG to control an external device by signals from their brain when they imagine the movement of their limbs. provide a novel and promising tool to regain the quality of life for ALS patients.

Slow cortical potentials (SCPs) are the result of intracortical or thalamocortical inputs to certain cortical layers, with positive and negative forms, people can learn the control of these potentials to complete a task. The most well-known SCPs system is the thought translation device (TTD) system. Participants in the TTD program need to learn how to control their SCPs on their own so they may choose letters, words, or pictograms in a computerized language assistance software. With the change between positive and negative SCPs, patients can choose different letters, and thus communicate verbally[37]. Improved solutions to the TTD system proposed by some other studies have also been shown somewhat successful[38]. However, SCP-based BCI is difficult to implement extensively since it requires extensive training, specialized care, and ongoing technological support, while not every patient can gain full control of their SCPs, thus its application in some clinical research and other aspects is still indispensable.

6. Conclusion

The development of BCI has been going on for decades, this powerful and promising tool has provided numerous solutions to those unresolved challenges. Most studies are based on medical research and clinical applications, especially in neurodegenerative diseases. Among these, research in non-invasive devices has received the most attention because of their good patient acceptance and nowadays data analysis advancements. The use of NDs may be classified into two categories: dementia diagnosis and motor impairment rehabilitation. For dementia patients, BCI can record brain activity to distinguish between different types of dementia and normal elderly people, or it can target

DOI: 10.54254/2753-8818/4/20220545

specific pathological alterations for imaging-based diagnosis. For individuals with motor limitations, brain signals will be input into outside devices and then driven to aid communication and interact with the environment. We are unable to thoroughly discuss the current state of research in this area in a single manuscript, but some general ideas were provided here for assistance. Currently, these technologies have achieved some success and are widely used, especially affected by COVID-19, but there are still some shortcomings that exist, like long period training requirement and the accuracy rate needs to be improved. We believe that with further optimization of algorithms, improved temporal resolution and better understanding of brainwaves will make these techniques more accurate and easier to use.

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