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A Comprehensive study on the application of deep brain stimulation in PTSD

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Abstract. Nowadays, with the rapid development of society, stress from all aspects promotes increasing rates of getting mental health issues or illness. Among them, Post Traumatic Stress Disorder (PTSD) is one of the "famous" mental problems that is noticed by people heavily in recent years. At the same time, great progress in the field of medical-surgical technology has also been made. Deep Brain Stimulation (DBS), a neurosurgical process that requires implanting electrodes in specific brain regions, can be used to treat PTSD to some extent. This reviewed the previous research and study conducted using DBS targeting PTSD, synthesized results and found that DBS treatment is currently mainly at the preclinical stage; Amygdala is the most common brain region that being targeted by DBS; The combination of several treatments is more effective than only DBS treatment; and most studies about the effects of DBS on PTSD were conducted on animal models. What's more, the future study direction of this related topic including the Nonhuman Primate Research and DBS treatment with other disorders such as Parkinson's Disorder, and Obsessive-Compulsive Disorder(OCD) is also included.

Keywords: PTSD, DBS, amygdala, Parkinson's Disorder, OCD.

1. Introduction

Mental illness is always a hot issue in our life since the rapid change of society and cultures, the economic inequalities and excessive use of digital or social media platforms, lead to higher rates of sensitivity and comparison among people and thus cause mental illness. In addition to what we hear frequently daily such as depression and bipolar disorder, post-traumatic stress disorder (PTSD) gradually catches people's attention. It's a psychiatric disorder that can develop in individuals who have experienced or witnessed a traumatic event. The symptoms generally include experiencing intrusive events, and avoidance behaviors including avoiding certain places, activities, or people. Usually, the patients get negative alterations in mood, cognition and concentration difficulties, irritability, and anger outbursts. It's also crucial for us to know about the methods that can be effective for mental illness, especially PTSD in this paper. Previous papers state that generally there are three main methods including psychotherapy, medication, and neurosurgical technology in coping with PTSD. One of the technologies that can effectively help improve the situation is Deep Brian Stimulation (DBS). Through reviewing previous studies, this paper had a brief overview of DBS applications, limitations and treatment of PTSD through animal models. Thus, this paper integrates

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those study results and makes clearer conclusions about the results and research stage of this topic, which will not only allow us to have a better understanding of the conclusion and results of these related points but also get to know the limitations of some previous research so that people can clarify the directions in future and check for gaps.

2. Method

Basically, we are searching broadly for animal experiment papers and some reports of clinics on PubMed, Google Scholar, Ovid Medline, and PsycINFO, the combinations and variations of these websites help us search for keywords such as pertinent to DBS to PTSD.

2.1. Brian region

Through the results of neuroimaging of PTSD, the main focusing regions are Amygdala, prefrontal cortex, and hippocampus [1]. Among them, research conducted before mainly focused on the amygdala, the brain region that is crucial in processing emotions, specifically fear and anxiety, suggesting the amygdala is positively associated with the severity of symptoms in PTSD [2].

2.2. Animal model

Previous studies basically all chose rodents to be the experimental subjects since rodents, especially rats, share a significant amount of genetic similarity with humans and are also easier for researchers to handle in lab settings. What's more, rats have well-characterized neuroanatomy and neurophysiology (brain structures and circuits implicated in various neurological and psychiatric disorders) [3].

2.3. Settings and measures

1) Elevated plus maze: It work aiming to test the anxiety level of the research subjects, basically for rodent models. "The EPM consists of a '+' shaped maze elevated above the floor with two oppositely positioned closed arms, two oppositely positioned open arms and a center area" [4]. Researchers allow rodents to explore randomly in this maze without any aversive stimuli including electric shock, bright light, or loud sounds and use cameras or other kinds of recording devices to track the whole exploring process. This setting can be used to record rats' behaviors of anxiety because the principle behind it is that the mice have a dark-loving nature when they are born which indicates that they are willing to stay in the closed arms area of the EPM, however, they still want to explore new things since they have curiosity. Therefore, anxiety will appear due to the conflict between exploring and avoidance. The height of the maze from the ground is almost equivalent to that of humans standing on the edge of a cliff. Thus, the anxiety behavior of mice can be easily measured through the time-consuming in the open and closed arms [4].

2) Conspicuous electric balls: These balls play a role in giving rats strong external stimuli and help simulate PTSD, which cannot be escaped [5].

3) Ball burying behavior: Ball burying behaviors in rats can serve as a proxy or indicator of certain aspects of anxiety-like behavior or compulsive behavior, which are relevant to PTSD. The anxiety level can be measured by recording the times rats bury balls [5].

4) Freezing behavior test: The common method used by researchers to assess fear and anxiety-related responses in rodents, including rats. It involves the behavior in response to a potentially threatening or aversive stimulus, especially the foot electric shock we discuss here. During the test, after the rats got shocked or any other previous aversive experience, they preferred to remain stayed or less movement except breathing to cope with the stimulus. It serves the same purpose with ball-burying behavior, and they are just different responses of rodents [6].

5) Serum corticosterone level: This measure refers to the concentration of corticosterone in the blood serum, which is a steroid hormone. Serum corticosterone is secreted when dealing with pressure and regulating many physiological processes such as immune function and the stress response. The measure of serum corticosterone levels in animal models is often a helpful role in evaluating the effectiveness of the stress-reducing intervention [6].

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6) c-Fos protein: c-Fos protein is an important role in neuronal activity and stress. This molecular marker is generally used as an indicator of neuronal activation and provides insights into the brain regions and circuits responses to stimuli or pathological conditions [6].

7) Saffron: The scientific name of it is Crocus sativus, a spice derived from the dried stigmas of the saffron crocus flower. Saffron is useful for its potential medicinal properties since it includes bioactive compounds like crocin, safranal, and picrocrocin. Typically, it has positive effects on mood and can be helpful in reducing symptoms of depression and anxiety [6].

2.4. Process

Rats (220g-250g) are separated into several groups and undergo stereotactic surgery for implantation of the electrodes into specific brain regions involved in the neural circuitry of PTSD, here the brain region is BLn, the basolateral nucleus of the amygdala [4]. No matter whether to explore the differences between DBS treatment and other medications such as paroxetine [4], and saffron [5] or to investigate the effectiveness of DBS on PTSD, one extrinsic stimulus is required. Generally, researchers use conspicuous electric balls to make inescapable foot shocks, which is working as a traumatic event for rats, inducing and simulating PTSD. After a shock of one or two weeks, several groups of rats were treated by medication-paroxetine, several were treated with DBS and the others were treated by the combination of saffron (5 mg/kg) and DBS. Rats' anxiety levels were measured through the ball burying behavior times and the time they consumed when they were in the EPM close and open arms. Experimental design and time schedule were shown in Figure 1. The first phase is for habituation to help rats to live used to the lab settings and help better conduct the experiment later. Then, after the implantation of an electrode in the BLn amygdala, there is a recovery time for rats, during this period, whether rats can adapt to the electrodes is the main point of observation. A week later, the electrical foot shock is conducted on the rats, using saffron or DBS or a combination of these two methods to treat with rats' symptoms, then finish the freezing behavioral test and blood and brain sampling.

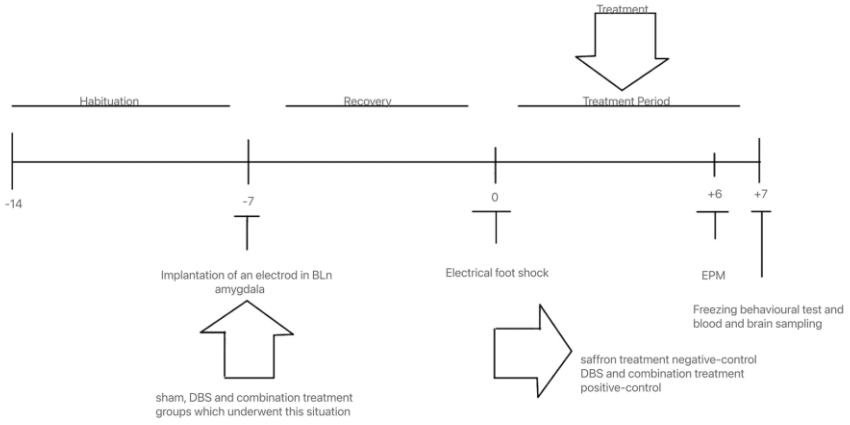

Figure 1. Experiment design and time scheduel [6].

3. Results

The results were clear and contributed to the conclusion. Firstly, researchers found that rats treated with amygdala deep brain stimulation surgery showed less ball burying behaviors compared with those treated with paroxetine, the less ball burying behaviors, the more effective DBS treated for PTSD; Second, the combination therapy of DBS treatment and saffron (5 mg/kg) increased serum corticosterone levels and reduced c-Fos protein expression and freezing behaviors time significantly ($p<0.001$). The mean corticosterone (ng/ml) of several terms that should be tested was shown in Figure 2, we can see the clear comparison among the seven columns. The single DBS treatment or the

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single saffron treatment were lower than 60 ng/ml while the combination of this two treatment reaches about 75 ng/ml, which successfully proves that any single treatment is less effective than the combination of multiple treatments. Thirdly, there's no difference in the anxiety level assessed in the EPM of rats that were treated by Amygdala DBS.

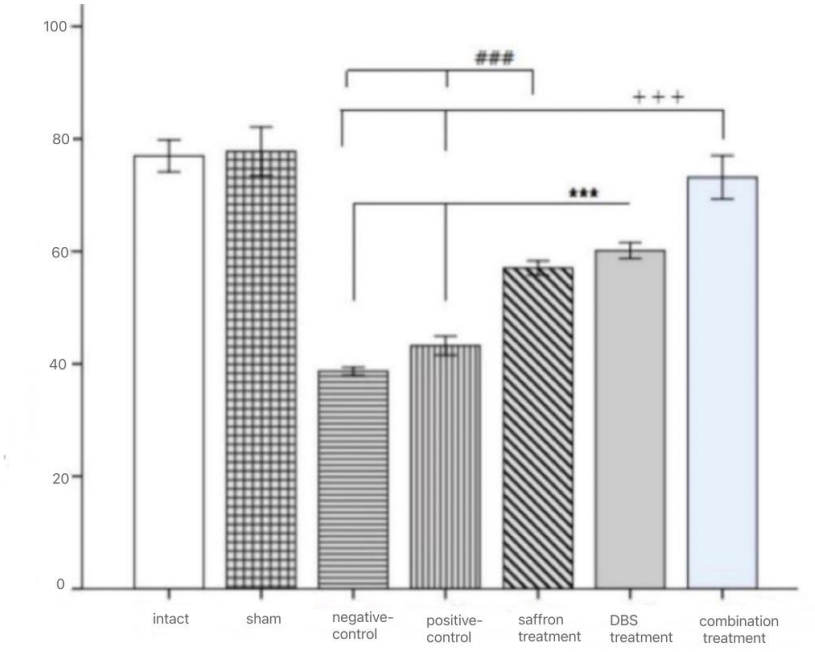

Figure 2. Change in general anxiety as measured by EPM [6].

4. Limitations and future directions

4.1. Limitations

Though the studies and achievements of DBS aiming for PTSD have been a great success for now, there are still some limitations and gaps that we should work on in the future to turn DBS into a normal medical surgery and help deal with other mental issues. Several aspects including invasiveness, surgical reliability, limited knowledge of pathways, ethical consideration, and lack of precision still need to be carefully considered. If DBS is conducted on the human brain, the most important issue that people should be aware of is the potential risks such as infection, bleeding, or damage to surrounding brain tissues [7]. What's more, the accuracy of electrodes implanted in the brain is crucial since there will be the risk of migration, and revision surgeries are complex and dangerous. Last but not least, the ethical consideration, which is the factor that should be regarded as seriously as possible when doing the surgeries or research, should be carefully addressed in both research and clinical application of DBS.

4.2. Nonhuman primate research

DBS for the current stage is only focusing on animal models, especially rodents (rats), however, the research subjects should be more and more sophisticated in the future in order to better explore the techniques that are helpful for human mental disorders. One of the research that has made a big success in treating non-human primates has set the grounds for its successful translation to Parkinsons' Disease. The most common toxin MPTP generates Parkinsonian phenotype in non-human primate (NHP) which is extremely similar to human PD with the positive response to dopaminergic drugs [8]. We can see the hope in the future that DBS working on PTSD can be successfully conducted on NHP.

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4.3. Other disorders DBS treats

4.3.1. DBS–Parkinson's disorder. Deep Brain Stimulation can help control the motor symptoms of Parkinson's disease. The symptoms of PD are tremors, slowness movement (bradykinesia), and stiffness (a measure of elasticity). PD is treated by applying high-frequency stimulation to the targeted structures (ventrolateral thalamus, internal pallidum, subthalamic nucleus–STN), generally the frequency is higher than 100Hz. The main function of DBS on PTSD is to improve the motor-related symptoms, thus, the concept of Adaptive DBS(ADBS) was developed which automatically adapts stimulation parameters to Parkinsonian symptoms [9].

4.3.2. DBS-OCD. Obsessive-Compulsive Disorder (OCD) is a more familiar mental problem that are mentioned by people during their daily life. The features of OCD are the presence of obsessions and/or compulsions. The main symptoms associated with the disorder are repeated and long-lasting thoughts, or images that are intrusive and cause distress. Patients always check things repeatedly and range things for symmetry while some of them also be disturbed by unwanted thoughts that are inconsistent with their values. Based on the studies, reduction of symptoms is achieved in the first 12-14 months after the electrode's implantation, however, whether this would be a long-term consistent reduction of symptoms and improvement of the situation is still in the debate. The current overviews confirm that DBS is potential therapy that can be developed for patients with severe symptoms of OCD [10].

5. Conclusion

Thus, through the reviews of the application of DBS in PTSD, several conclusions have already been made. For the current stage of these related topics and areas, animal models are the most common choice for researchers to conduct experiments, especially rodents since they have very similar neurological structures to human beings, also, they are easier for researchers to control and observe. Amygdala is the most common brain region that is being targeted by Deep Brian Stimulation surgery since it plays a crucial role in regulating emotions, stress, and fears, which are basically the main symptom features of PTSD. By measuring and recording different hormone levels and activities in the different parts of the amygdala, we can see and notice the effectiveness of DBS in treating PTSD. The combination of medication, DBS, and probably other treatment approaches can maximize the benefits. If any of the methods is used alone, the ideal state would not be fully achieved.

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