Deep Brain Stimulation In The Treatment Of Cocaine Addiction

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Abstract. The history of cocaine addiction as a considerable public health issue has remained more than a century. In recent decades, as the population of cocaine addicts has risen again, more external interventions, such as neurotechnology, medication, and psychological therapy, are being considered and discovered as tools to address the effectiveness of the issue. Deep Brain Stimulation (DBS) has emerged as a potential intervention as existing treatments are limited to managing and healing cocaine addiction effectively. This paper delves into the multifaceted relationship between cocaine addiction and DBS, drawing insights based on neurobiological functions and existing experiments in rodent models. While DBS has been given expectation in targeting addiction-related neural circuits such as rewarding systems, its effectiveness and safety in decreasing cocaine craving remains a critical topic. This paper also emphasizes the caution of translating the results of preclinical experiments into clinical applications. In an era when innovative therapeutic strategies are urgently needed, this article explores the intricate promise of DBS in the treatment of cocaine addiction, providing a balanced perspective on its potential and challenges in reshaping addiction therapies. The purpose of the paper is to make the process of overcoming cocaine addiction easier using neurotechnology, specifically deep brain stimulation, and furthermore, to reduce the population of cocaine users in the United States.

Keywords: cocaine addiction, deep brain stimulation, nucleus accumbens, neurotechnology.

1. Introduction

Cocaine, the second most commonly used drug in the United States, has a long history within the country, dating back to the early 20th century when the Harrison Narcotics Tax Act brought federal attention and regulation to narcotic drugs, including cocaine [1]. Despite early regulations, cocaine's use persisted, becoming a popular recreational drug globally [2]. The hippie movement of the 1960s and early 1970s popularized the use of psychoactive substances and contributed to a wider permissiveness of drug experimentation. About a decade later, the 1980s cocaine epidemic, marked by the rise of crack cocaine, brought widespread addiction and social unrest to urban communities.

In recent years, the United States has witnessed a resurgence in cocaine's popularity, reversing previous declining trends. In 2021, approximately 1.7% of the U.S. population aged 12 or older, equivalent to around 4.8 million people, reported using cocaine within the past year [3]. Yet, cocaine addiction carries consequences beyond the sheer number of users, as addiction is a neurological condition characterized by the compulsive use of substances despite harmful consequences. This issue poses a substantial public health challenge, including the alarming rise in drug overdose fatalities linked to cocaine, which surged from 6,784 deaths in 2015 to 15,883 in 2019. Moreover, between 2019 and 2021, there was a notable 54% increase, resulting in 24,486 deaths attributed to cocaine use [4].

The escalating addiction rates underscore the global imperative for safer and more effective treatment options. Presently, available treatments encompass medication and behavioral therapies, each with its own set of limitations. Medications may introduce side effects and the risk of substituting one addiction for another, while Cognitive-Behavioral Therapy predominantly addresses psychological aspects, leaving physical cravings unaddressed. Research by Professor Magill at Brown University revealed that the efficacy of CBT alone is modest, with an effect size of only 0.144 [5]. Combining CBT with pharmacotherapy increases the effect size to 0.18 - 0.28, highlighting CBT's potential as a complementary therapy [6].

In the realm of neuroscience, Deep Brain Stimulation (DBS) has emerged as a rapidly advancing technique in recent decades. Since gaining approval from the U.S. Food and Drug Administration for Parkinson's disease treatment in 1997 [7] , DBS has found widespread recognition for its clinical efficacy. During DBS, an interface with a brain patch delivers electrical signals or electrodes to specific areas, influencing the brain's responses and bodily commands to achieve desired effects. Given that addiction largely stems from the brain's reward system, DBS is now being explored as a potential treatment for drug addiction by disrupting addictive processes. This essay aims to explore the pharmacology of cocaine addiction, existing DBS experiments for cocaine addiction treatment, and potential future developments. It serves to consolidate existing knowledge on the potential of DBS in treating cocaine addiction while providing insights into future trends. The objective of the article is to improve cocaine addiction in the community with the most updated biotechnology approach and to help more people who can't kick the habit to escape their misery.

2. Neurobiology on Cocaine and Addiction

Cocaine is commonly used with the goal of inducing intense feelings of euphoria, pleasure, and increasing energy. When cocaine is ingested, whether by snorting, smoking, or injecting, it quickly crosses the blood-brain barrier and interferes with normal functions of neurons. The most rapid change being caused is the amount of dopamine built up in the brain, which leads to the excited and well-being feeling experienced by the drug user [8].

2.1. How Does Cocaine Function

Many drugs of abuse increase dopamine release, while cocaine functions to stop them from being recycled. Under a normal condition, after the release of neurotransmitters that contain dopamine from the presynaptic neuron, the postsynaptic neuron nearby will have proteins called dopamine receptors to pick up the neurotransmitters and store them for the next use. However, when cocaine is introduced, it binds to dopamine transporters and impedes their function. This blockade prevents the reuptake of dopamine, allowing it to accumulate in the synaptic cleft. Consequently, an excess of dopamine accumulates between neurons, leading to prolonged and intensified stimulation of dopamine receptors on the receiving neuron.

In response to the excessive dopamine levels, the brain adapts by reducing the number of dopamine receptors, attempting to counteract this abnormal influx. This adaptation results in reduced neurotransmitter absorption when normal dopamine levels are released, culminating in feelings of depression and heightened cravings for further drug use. According to the American Addiction Center, up to a third of clinically depressed people engage in drug or alcohol abuse in 2023 [9].

2.2. Relation Between Reward System And Addiction

The brain's reward system plays the majority and essential role in the addiction process. This innate mechanism allows the brain to associate with diverse stimuli, substances, situations, events, or actions, with favorable outcomes [10]. Typically, during activities vital for survival, neurons in the ventral tegmental area will trigger release of neurotransmitters containing dopamine and send them to the nucleus accumbens. Upon dopamine reception, the brain registers the behavior as positive and reinforces the desire to repeat it. While the use of cocaine also triggers a large amount of dopamine floating around, the brain will recognize “having cocaine” as a positive behavior and form the desire for more.

Addiction can be conceptualized as a cyclic process comprising three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving) [11]. This cycle tends to worsen over time and entails neuroplastic changes affecting the brain's reward, stress, and executive function systems. To date, researchers have primarily explored the application of Deep Brain Stimulation (DBS) during the latter two stages, aiming to restore the disrupted reward system and alleviate withdrawal-related distress.

3. DBS In Animal Model Treatments

Since 2003, numerous clinical trials have been conducted to explore the potential of deep brain stimulation (DBS) as a treatment for addiction of a variety of substances such as tobacco, alcohol, opioids, and methamphetamine/amphetamine [12]. However, while these studies have yielded valuable results, DBS as treatment of addiction has not yet received clinical approval. Majority of the studies have used animals as models to reveal potential consequences and elucidate underlying mechanisms.

3.1. Cue-Induced Reinstatement of Cocaine Seeking in Rats

In a study involving prediction and reward conducted with monkeys, scientists established associations between the delivery of apples and the appearance of light cues [13]. As the study concluded, it was observed that, following repeated pairings of visual and auditory cues with rewards, dopamine neurons adjusted the timing of their phasic activation. This shift occurred from happening just after reward delivery to taking place at the onset of the cue. When the reward was not promptly delivered following the initiation of the light cue, dopamine neurons exhibited a significant reduction in activity, falling below their normal baseline firing rate precisely when the reward was anticipated. This experiment highlights the strong connection between addictive behaviors and the brain's rewarding system, and the fact that environmental cues are associated with craving.

Given the pivotal role of the reward system in the preoccupation and anticipation stages of drug addiction, Deep Brain Stimulation (DBS) emerges as a potential strategy for intervention. In a 2014 study involving mice with drug addiction, DBS was applied to investigate its capacity to disrupt the link between environmental cues and cocaine-seeking behavior [14]. Initially, two groups of mice self-administered cocaine for 21 days in the presence of a light cue. After the cue-reward association was established, bilateral DBS was administered to the nucleus accumbens shell using bipolar stainless steel electrodes in one of the mouse groups. Subsequently, when both groups were exposed to the same light cue as before, a significant reduction in active lever responses and a decreased desire for cocaine were observed in the group that had undergone DBS treatment. This result suggests that DBS has the potential to disrupt the connection formed by the reward system between environmental cues and the craving for cocaine. Such disruption could empower drug users to regain control over their desires instead of succumbing to the influence of addiction.

3.2. Locomotor Activity And Irritability-like Behavior In Rats After DBS

However, a contrasting study conducted in January 2023 yielded different results [15]. Male rats were rendered cocaine-dependent after days of self-administered cocaine, after which they were divided into two groups: a control group and a DBS group. The DBS group received 150μA of monophasic bilateral high-frequency DBS targeted at their NAcc shell, while the sham group (control group) was connected to the cables but did not receive any stimulation. Subsequent brain activity measurements revealed an unexpected increase in GluR1 levels in the DBS group. GluR1 was strongly and positively associated with responsiveness to cocaine-related cues and the potential for cocaine craving. As a result of GluR1 level elevation, the data showed a significant increase in locomotor activity and cocaine self-administration after the DBS treatment. However, a decrease in irritability-like behaviors in the DBS group is also shown by an irritability score of approximately 18, which was 8 points lower than the sham group. It was also reflected in the reduction of defensive and aggressive behaviors in the DBS group.

Contrary to previous expectations, DBS therapy appeared to reinforce cocaine cravings rather than reducing addiction. However, it did demonstrate efficacy in mood regulation by reducing mood-related irritability during cocaine withdrawal. This study challenges the feasibility and reliability of DBS in the treatment of cocaine addiction while confirming its effectiveness in reducing irritable behavior.

Both preclinical and clinical studies suggest that accumbens Deep Brain Stimulation has prospect for future development as a therapy for addiction. However, it is imperative to acknowledge the distinctions between human and rodent brains, emphasizing the need for caution in conducting clinical trials.

4. Future Experiment Assumption

Considering the primary goal of this study, which is to contribute to the reduction of cocaine use within the population, and the mechanisms of Deep Brain Stimulation (DBS), the majority of studies have focused on investigating DBS during the withdrawal and craving stages, rather than the intoxication stage. Much of the existing research has primarily targeted Deep Brain Stimulation of the accumbens shell, recognized for its significant potential in influencing the craving phase during the third stage of drug addiction. However, dopamine, a key player in the reward system, is associated with various regions in the human brain.

In a 2021 study, the infralimbic cortex emerged as a promising target for DBS to prevent cocaine relapse effectively. Furthermore, it has demonstrated that applying DBS to the basolateral amygdala (BLA) and ventral hippocampus (vHipp) is successful in reducing the resurgence of both cocaine and sucrose-seeking behaviors [16]. Subsequent paragraphs will explore multiple potential DBS targets, each selected based on its distinct neurobiological functions within the brain.

4.1. Anterior Cingulate Cortex

As an important component of the reward system, the anterior cingulate cortex (ACC) plays a central role in cognitive decision-making and emotion regulation. One of its main functions is conflict monitoring, which involves detecting differences between conflicting options and further influencing decision-making processes. This was demonstrated in a 1998 study that observed ACC activity while participants performed letter-distinguishing tasks [17]. In addition, the anterior cingulate cortex facilitates emotional processing by connecting reward and punishment information to stimulate emotional responses associated with individual behavior. More specifically, the sub-cingulate cortex (often referred to as area 25) may be an important link between reward and punishment and bodily autonomic responses [18].

Based on ACC's primary functions of decision making and emotional regulation, DBS of the ACC may offer a means to regulate these processes, potentially reducing cocaine craving and preventing relapse. While further research is needed to elucidate the specific mechanisms involved, the ACC's multifaceted role within the reward system suggests it could be a valuable target for innovative therapeutic approaches in addressing cocaine addiction.

4.2. Glutamatergic System

During the cocaine withdrawal phase, the glutamatergic system of the brain undergoes some significant shifts [19]. As the primary excitatory neurotransmitter in the brain, glutamate plays a key role in all aspects of neural function such as learning, memory, and synaptic plasticity. Medications that are currently used for other addictions such as acamprosate appear to work by creating a balance between stimulatory glutamate and inhibitory γ-aminobutyric acid. Thus potentially decreasing the suffering of alcohol-dependent individuals during withdrawal stage [20]. Analogously, cocaine usage disrupts the delicate balance within the glutamatergic system, culminating in escalated extracellular glutamate levels, which can lead to euphoria and, in extreme cases, excitotoxicity.

In an effort to regulate the glutamatergic system, DBS can potentially reduce the activation of glutamate-releasing neurons in key brain regions including the cerebral cortex, hippocampus, basal ganglia and cerebellum [21]. This reduction aims to mitigate the excessive glutamate signaling associated with cocaine addiction. Notably, DBS has demonstrated its ability to decrease the firing rate of neurons in the subthalamic nucleus when used for Parkinson's disease [22], offering potential

prospects for the adjustment of glutamate-related processes in addiction therapy. Further research is essential to fully explore the therapeutic potential of DBS in restoring glutamate balance.

5. Discussion

DBS is by far the most promising and researched treatment for cocaine addiction, one reason being its contribution to other diseases. One of the reasons for this is because of the contributions it has made to other disorders to date; DBS has been approved for use in Parkinson's disease, essential tremor, and dystonia, and has proven its effectiveness. It is also being studied as an intervention for psychological disorders, and has been shown to be effective for the time being [23]. The advantage of the use of DBS includes adjustability, physical safety, and reduced medication reliance. As DBS programming is controlled and change can be made anytime, it is easy to adjust the amount of electrodes passed or even reversing to remove electrodes. This provides a higher safety and fit for the patient based on their own situation [24]. DBS requires only a very small incision compared to other procedures. According to the Michigan Medical Society, the scar after healing is only 3-5 inches [25]. At the same time, since DBS can significantly alleviate symptoms in conditions like Parkinson's disease, it allows patients to reduce their reliance on high doses of medications. This reduction in medication dosage can lead to a decrease in medication-related side effects and fluctuations in symptom control.

However, DBS still contains some controversies and shortages. Whether implanted hardware remains safe as the time passes is an unsolved concern due to the weakness of the brain and the uncontrollable side of technology. While DBS is intended to improve symptoms, it can also lead to side effects such as mood changes, cognitive changes, speech disorders, and motor problems. Finding the right stimulation parameters may require adjustments and time. For instance, patients undergoing Medtronic DBS Therapy for Movement Disorders have reported instances of depression, suicidal thoughts, and suicide [26]. It's important to note that DBS is an invasive surgical procedure with associated potential risks, such as hemorrhage and infection [27]. These findings emphasize the need for caution in translating preclinical successes of DBS into clinical applications, given the intricate nuances of human neurobiology.

6. Conclusion

Among evolving addiction therapies, deep brain stimulation (DBS) is a promising but intricate approach to treating cocaine addiction. Although preclinical studies have demonstrated the potential of deep brain stimulation therapy to disrupt addiction-related neural pathways and reduce irritability during withdrawal, recent experimental results have unexpectedly exacerbated cocaine cravings, casting a shadow of skepticism. At the same time, the ethical issues and the potential risk of damaging the brain should be considered seriously.

Despite DBS, many other neurotechnologies have been considered as the future solution of drug addiction. Over the past twenty years, a growing interest is also presented in another neurotechnology called repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive method of stimulating cortical regions and aiming to trigger changes in neuronal activity. Therefore it is considered a safer treatment compared to DBS. Within the approval by the Food and Drug Administration as treatment for depression, scientists are also performing experiments with the purpose of using rTMS as treatment for addictions.

In conclusion, DBS is a promising treatment for cocaine addiction. Based on the available research, DBS has a visible potential to block cocaine cravings during drug withdrawal and to help stabilize mood control. In the meantime, more in-depth research and trials are needed to fully understand the effects of DBS on the brain and the benefits and drawbacks of this therapy to be used to refine the potential for more of what it can bring.

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