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Deep Brain Stimulation as a Treatment for Addictions: Could Impulsivity be the Therapeutic Target?

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Abstract

Recently there has been growing interest in Deep Brain Stimulation (DBS) for the treatment of substance use disorders. Several lines of observation currently advocate for research on this domain: Observed effects on consumption in patients treated primarily for movement disorders, preclinical data using DBS to modulate consumption behaviour, and experiences with DBS in patients treated primarily for addiction.

A further line of research, which has until now rather been neglected, is to explore its effect on specific traits of addictive behaviour, such as impulsivity. If we consider impulsivity to be an endophenotype underlying many manifestations of addiction, it would be important to know the efficacy of the different DBS-targets on impulsivity and its correlation with clinical efficacy.

Keywords: Deep brain stimulation; Impulsive behaviour; Substance related disorders

Abbreviations: DBS: Deep Brain Stimulation; ICD: Impulse Control Disorders; NAC: Nucleus Accumbens; OCD: Obsessive Compulsive Disorder; PD: Parkinson Disease; STN: Subthalamic Nucleus; SUD: Substance Use Disorders

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Summary

Recently there has been growing interest in Deep Brain Stimulation (DBS) for the treatment of Substance Use Disorders (SUD), due, among others, to observations of improved dopamine dysregulation syndrome in patients with Parkinson Disease (PD) resulting in reduced misuses and craving for dopaminergic pharmacotherapies [1,2]. DBS consists in the delivery of electrical pulses through electrodes implanted in specific brain regions aiming at neuromodulation of pathological brain circuits.

Compared to other neurosurgical interventions, it has the advantages of being reversible, minimally invasive, and adjustable, as stimulation parameters can be modified to maintain therapeutic effects. It has been used since the late 80's in the treatment of severe neurological movement disorders. Today DBS is an established treatment in Parkinson's disease, dystonia and tremor and worldwide more than 100'000 patients had surgery for DBS [3].

In the new millennium it has been progressively used in psychiatric disorders such as obsessive compulsive disorder (OCD), Tourette's syndrome and major depressive disorder [3-5]. This expansion to additional indications is also due to the relative safety of the method. Nevertheless, serious adverse events such as intracerebral hemorrhage occur in up to 2% of patients, and surgery can be fatal in up to 0.4% of cases [2]. For this reason DBS indications can only be considered in patients with severely disabling diseases resistant to conventional, on-invasive treatments.

Several lines of observation may currently advocate for further research of DBS in SUD: observed effects on consumption in patients treated primarily for PD or psychiatric disorders, preclinical data using DBS to modulate consumption behavior, and experiences with DBS in patients treated primarily for addiction. A further line of research, which has until now rather been neglected, is to explore its effect on specific traits of addictive behavior. Addiction is, among others, characterized by what has been called "a low intention–behavior correlation" [6]. This means that persons with addictions may well have the intention to behave in one way (not to consume) but eventually nevertheless

behave in another way (consuming). The psychological concept of impulsivity may be well suited to rationalize this phenomenon, as it is one individual difference variable that may influence the strength of the intention–drug use relationship [6].

Thus, the effect of DBS on addictive behavior through the modulation of impulsivity could be a promising approach to explore in future studies.

DBS in Patients Primarily Treated for Non-Addictive Disorders: Effect on Addictive Behaviours

Several publications [2,7,8] describe small series of PD patients with preoperative active pathological gambling due to dopaminergic treatment. The disabling motor fluctuations improved under sub thalamic nucleus stimulation, allowing reductions of the dopaminergic treatment and subsequent improvement of the gambling addiction.

Case reports and case series of have also been described for patients treated by DBS for anxiety disorders, OCD or Tourette's syndrome, who showed improving of alcohol misuse [9,10], heroin use [11] and cigarette addiction [12-14].

Preclinical Addiction Models and DBS

Animal studies using various models of addiction (2-bottle self-administration, reinstatement, conditioned place preference) have corroborated the interest of the DBS in the treatment of addictive disorders. While other brain regions have also been targeted with DBS, the Nucleus Accumbens (NAc) remains the most studied target region in animals.

High frequency DBS of the NAc has shown promise in animals at reducing alcohol intake in alcohol-preferring rats [15-17], cocaine self-administration and reinstatement of cocaine seeking [18-20], as well as reinstatement and preference for opiates [21-23]. On the other hand, subtalamic nucleus (STN) DBS was shown to reversibly reduce the motivation to work for cocaine-injections, and to increase motivation to work for sucrose pellets [19]. A similar effect was found for place preference.

DBS in Patients Primarily Treated for Addiction

Currently, no published randomized controlled trial on the effect of DBS in addiction is available, data being restricted to case reports or case series. In these studies NAc DBS in alcohol addicted patients has been found to decrease cravings [24-26], to promote abstinence [24-27], and to reduce tobacco consumption [25]. Similarly, in heroin addicted patients NAc, DBS induced sustained abstinence [28,29], reduced craving [28,29], and was accompanied as well by a decrease in the number of cigarettes smoked [29].

DBS and Impulsivity

Available data indicate an effect of STN-DBS (mainly studies with PD patients) as well as NAc-DBS (mainly patients treated primarily for addiction) on addictive behaviors. Thus, the ideal DBS target for the treatment of addiction begins to become a matter of debate [17]. If we consider impulsivity to be an endophenotype underlying many manifestations of addiction, it would be important to know the efficacy of the different DBS-targets on impulsivity and its correlation with clinical efficacy.

While the rational to experiment NAc modulation appears obvious in consideration of its role in addiction, the use of STN-stimulation appears less evident.

Due to its strategical position in cortico-subthalamic and cortico-striatal pathways, the STN is considered to play a crucial role not only in motor, but also in cognitive and motivational functions Also, many brain areas such as the prefrontal cortex and striatum involved in impulsivity are connected to the STN their functions may thus be influenced by STN-DBS [30-32].

The available studies investigating an effect of DBS on impulsivity used mainly STN-DBS in PD patients, and indicated that STN-DBS may induce both positive and negative outcomes regarding impulse control [32-34], for example: STN-DBS in PD patients has been found to improve performances in the stop-signal task [35-37], the go/no-go task [35,38], the Game of Dice Task [39,40] and the Simon task [41]. No effect was found regarding delay discounting [42]. On the other hand, STN-DBS in PD patients has also been found to increase risky choices in the Iowa Gambling Task [43], to increase commission errors during Go/No Go tasks [44], and to generate more errors in a 'moving dots' task under speed pressure [45], and to increase scores on the UPPS Lack of Premeditation scale [46] and on the Barratt Impulsiveness Scale [47].

Finally, PD patients under STN-DB have been found to show improvements [1,7,48] but also, in other studies, emergence or worsening of Impulse Control Disorders (ICD) [48,49]. It has been stressed out, however, that most persistent postoperative ICDs occurred in those patients who remained on high-dosage dopaminergic treatment [48], and that in the prospective studies with a marked decrease in dopaminergic treatment ICDs tended clearly to disappear [50,51].

To explain these at first glance conflicting results, STN has been proposed to modulate response thresholds and speed-accuracy trade-offs in high conflict situations providing a dynamic "hold your horses" signal to allow more time to choose the best option [33]. Conversely, speed pressure is hypothesized to dampen the activity of the STN and lower response thresholds, resulting in fast, errorful responses. Modulation of STN hyperactivity with DBS has thus been hypothesized to be able to improve impaired *proactive* inhibition in PD patients, but to possibly induce impairment of reactive inhibition leading to premature and impulsive responses. In PD patients, STN-DBS could consequently contribute to certain impulsive behavior during high-conflict decisions.

Imaging studies may support this hypothesis, identifying brain networks involved in stopping actions, including frontal regions together with subcortical areas, such as the STN or caudate [34]. They have especially revealed activation of the STN during motor inhibition and conflict resolution. The STN was also shown to be particularly engaged by late inhibition, as reflected by correlations of STN activation with longer stop signal delays [52].

Recent studies have specifically looked for changes in STN local field potential activity during stop signal tasks and suggested that beta-band subthalamic activity is involved in reactive inhibition [53-55] and in the performance of go no-go and stroop tasks [56,57]. Furthermore, analyses of STN gamma band activity

suggest that the STN implements a signal from the prefrontal cortex to switch from automatic to controlled processing, as necessitated by task demands or context [31,58,59].

What is to be Done

In order to further explore the relationship between DBS, impulsivity and addiction, several lines of research appear to be warranted.

- Most preclinical studies have used NAc-DBS. Animal studies may help to resolve the contradicting results of human STN-DBS regarding its effect on impulsivity.
- Future studies of NAc-DBS in humans could include measures on impulsivity and analyses on correlations with therapeutic efficacy.
- As modulation of STN hyperactivity with DBS has been hypothesized to be able to improve impaired proactive inhibition, it could be tested in patients treated primarily for their addiction, as addiction therapy can be conceptualized as a reinforcement of proactive inhibition of consumption behaviors. In other words, STN role in the implementation of a frontally signaled switch from automatic to controlled processing [59] could be used as support for motivational therapy, as one objective of this intervention is to reinforce conscious reasoning to counterweight automatic unreflective responding to consumption-triggering stimuli.

In conclusion, despite promising results, additional studies are required before definitive conclusions can be reached concerning the efficacy of DBS in SUDs. Almost all currently available studies on DBS in SUDs have clear limitations, and some results are contradictory. To consider impulsivity as a pivotal therapeutic target may help to clarify some of the remaining questions.

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