Chapter 1

Deep Brain Stimulation in Treatment-Refractory Addiction

Angelo Lavano, Giusy Guzzi, Attilio Della Torre, Donatella Gabriele, Domenico Chirchiglia, Carmelino Angelo Stroscio and Giorgio Volpentesta

Additional information is available at the end of the chapter

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Abstract

Surgical treatment for addiction has been proposed after the successful efficacy of deep brain stimulation (DBS) for the treatment of neurological movement disorders such as Parkinson's disease (PD). In the field of psychiatric diseases, DBS has been used firstly for obsessive compulsive disorder (OCD) and treatment-resistant depression. The role in addiction has been proposed only recently. The target areas for DBS in treatment-refractory addiction are nucleus accumbens (NAcc), lateral hypothalamus (LH), amigdala, lateral habenula (LHb), dorsal striatum, prefrontal cortex (PFC) and subthalamic nucleus (STN). A well-documented rationale for the choice of the target is required in order to investigate the effectiveness, safety and feasibility. NAcc appears to be the most effective and safe target for DBS followed by STN; PFC is another promising target but needs further exploration to establish its suitability for clinical purposes. DBS is not free of risks, so every patient has to be carefully evaluated and precise ethical standards must be defined in the form of inclusion and exclusion criteria.

Keywords: deep brain stimulation, psychosurgery, addiction, nucleus accumbens, nucleus subthalamicus

1. Introduction

The term "psychosurgery" was coined by Egas Moniz in 1935 to indicate the set of surgical procedures performed on the brain to treat diseases and psychiatric symptoms. The goal is to change the behavioral—obviously pathological—aspects, placing not only clinically but also

ethically complex problems. The entry into the neurosurgical practice of neuromodulation methods has opened up a new scenario due to their flexibility and reversibility in their possible application to the treatment of addiction, such as substance abuse, gambling and internet gaming. The term "addiction" generally indicates a model of persistent redundant behaviors despite adverse medical or psychological results. The common element is recurrent problematic behavior accompanied by a preoccupation with the behavior [1, 2]. It is attested that the development of addiction is not simply the effect of the acute impact of the substance or behavior [3–5] but instead represents a state of imbalance in the reward system [6]. Alterations in prefrontal, limbic and cortical areas seem to be involved in addiction and maladaptive behavior not only in animal models but also in human neuroimaging studies [7–9]. The areas most involved in the manifestations of addiction are represented by the dopaminergic connections between ventral tegmental area (VTA) and nucleus accumbens (NAcc), which modulates learning, memory and repetitive behaviors. Stimulation of NACC in animals has proven to control acquired behaviors as a result of alcohol and cocaine consumption [10–12].

2. Neurobiological mechanism

The development of addiction finds its anatomical and neurobiological bases in the so-called neurocircuitry of reward, and it is important to better understand when and how the reward system is activated [13]. The term "reward" is defined as any event that increases the probability of a response with a positive hedonic component. The ascending meso-cortico-striatal dopamine systems seem to have a key role in the rewarding properties of nearly all drugs of abuse [14]. In humans, positron emission tomography studies have shown that intoxicating doses of alcohol and drugs release dopamine and opioid peptides into the ventral striatum [15, 16], activating low-affinity dopamine D1 receptors, which are necessary for the rewarding effects of drugs [17]. This specific circuitry includes not only dopamine and opioid peptides but also γ-aminobutyric acid (GABA), glutamate, serotonin, acetylcholine and endocannabinoid systems that act at the level of either the ventral tegmental area or nucleus accumbens. Balanced circuits result in proper inhibitory control and decision-making and normal functioning of reward, motivation, stress and memory circuits. These circuits also interact with circuits that are involved in mood regulation, including stress reactivity (which involves the amygdala, hypothalamus and habenula) and interception (which involves the insula and anterior cingulate cortex and contributes to the awareness of negative emotional states). Drugs of abuse usurp executive function circuits, motivational circuits and stress circuits via multiple neurotransmitter-specific neuroplasticity circuits. Key neurotransmitters that are implicated in these neuroadaptations include dopamine, enkephalins, glutamate, γ-aminobutyric acid, norepinephrine, corticotropin-releasing factor (CRF), dynorphin, neuropeptide Y and endocannabinoids.

3. DBS for the treatment of addiction

The use of deep brain stimulation (DBS) for the treatment of addiction was fortuitous, starting from observation in some PD patients the escalation of their intake of dopamine replacement

therapeutics in a manner similar in some ways to addiction, a phenomenon known as dopamine dysregulation syndrome (DDS) [18]. Witjas et al. in 2005 described a reduction of the behavioral disorders as well as addiction to dopaminergic treatment in two PD patients who underwent subthalamic nucleus (STN)-DBS [19]. Subsequently, other studies confirmed the resolution of dopamine dysregulation syndrome following STN-DBS for PD [20–22]. In rat models it was demonstrated that lesions of the STN decrease motivation to take cocaine suggesting that STN-DBS might be a therapeutic option for addiction [23]. In 2007, during a DBS procedure of the nucleus accumbens (NAcc) in a heavy drinker patient with agoraphobia and panic attacks, a rapid reduction of the alcohol intake of the patient was observed [24]. Similarly, three additional patients receiving accumbens DBS for other indications were reported to have spontaneously quit smoking [25].

4. Mechanism of action

The mechanism of action of DBS remains unclear. As to the anatomical organization of the nucleus accumbens, it is divided into two major subregions, the core and shell, which differ from each other both functionally and anatomically. The core receives projections from the anterior cingulate and dorsal prelimbic, while the shell receives projections from the infralimbic and ventral prelimbic cortices [26, 27]. DBS of the accumbens shell or core increased c-Fos immunoreactivity, a measure of neuronal activation in these nuclei. c-Fos study indicates that DBS of the accumbens shell activates the infralimbic cortex, which could have contributed to the DBS-induced activation of the shell [12]. DBS applied to either the accumbens core or shell reduced alcohol consumption [11]. In contrast, DBS of the medial accumbens shell, but not the accumbens core, attenuated cocaine priming-induced reinstatement of drug seeking [12]. Moreover, since enhancing neuronal activity in the nucleus accumbens actually promotes the reinstatement of cocaine seeking [28, 29], DBS-induced inactivation of the nucleus accumbens via depolarization inactivation and/or activation of inhibitory neurons may be responsible for the attenuation of cocaine reinstatement [30–32]. Electrophysiological studies showed that accumbens DBS attenuated the spontaneous activity of cortico-accumbal glutamatergic neurons but also stimulated cortical interneurons, apparently via recurrent inhibition [33]. However, GABA agonist-induced inactivation of the infralimbic cortex attenuated the reinstatement of cocaine seeking induced by a priming injection of cocaine [12], which is consistent with accumbens DBS indirectly activating GABAergic interneurons. These results suggested that DBS of the accumbens shell produced complex effects throughout the circuit in which the shell is embedded. It is generally agreed that cocaine self-administration results in aberrant activity in the cortico-accumbal system and it appears that normalization of this system is one of the main effects of accumbens DBS [34, 35].

5. Targets

The proposed target areas for DBS in treatment-refractory addiction are several but well-documented rationale for the choice of the target is required in order to investigate the effectiveness, safety and feasibility.

5.1. Nucleus accumbens (Nacc)

There is considerable preclinical evidence to support a role for the nucleus accumbens in mediating the motivational effects of conditioned stimuli associated with the drug leading to its anticipation. DBS in the NAcc has been successful in treating the behavioral component in addiction disorders and substance abuse [36, 37]. Ablative surgeries targeted at the NAcc have been used for several years (between 2000 and 2004) in China with mixed results, but a relapse rate of 50% and ethical concerns now limit the use of destructive procedures in the treatment of addiction [38–40]. The limited outcome and the consecutive side effects (poor concentration, poor short-term memory, aconuresis, changes in sexual desire and decreased interest to various degrees) are nevertheless expected considering the preclinical data investigating the role of the nucleus accumbens. However, there is no clear evidence for a specific alteration of the nucleus accumbens in addicted individuals. Despite the reserves considered earlier, few clinical studies are considering application of DBS in the accumbens of addicts and therefore as first indication with successful results as for example on one case of heroin addiction [41, 42]. Clinical data about the efficacy of NAcc stimulation exist in the literature in small case series. In two single case studies, two patients who underwent bilateral NAcc stimulation for heroin addiction experienced abstinence from opioids to the last follow-up, respectively, at 6 years and 6 months [42, 43]. A similar outcome was observed in other two separate cases of patients with chronic, severe alcoholism who were treated with DBS in the NAcc reporting abstinence at 1 year [24, 25, 44]. In a single case of NAcc DBS for obsessive compulsive disorder (OCD), quit smoking was reported [45], but a subsequent analysis of 10 patients who received DBS of the NAcc for OCD, TS, or anxiety found that only three patients achieved nicotine abstinence within 30 months [46]. These case reports show the potential for treatment of substance abuse disorders with DBS of the NAcc, but randomized and blinded studies are lacking. However, DBS of NAcc, as any other basal ganglia targets, can be associated with unpredictable limbic symptoms such as mania and depression [47]. A recent study showed that the DBS of different NAcc subregions had different effects on a natural reward such as the motivation for food intake. Specifically, the stimulation of the lateral shell decreased the motivation to food while the stimulation of the core was without effects [48]. According to some authors, there would be a different response of NAcc neurons to natural rewards with respect to secondary rewards to drug intake even if it was not possible to demonstrate a preferential localization of such neurons in the core or in the shell [49]. The NAcc shell is unlikely to be a good candidate for DBS, considering the empirical evidence for its detrimental effect on general motivation and impulse control [50]. In conclusion, the NAcc DBS seems to be able to exercise a significant control over drug abuse and behavioral components mostly in alcohol and oppiate addictions; therefore, alternative structures have been considered for DBS with limited preclinical empirical or theoretical support.

5.2. Lateral hypothalamus (LH)

The hypothalamic drive control of food-motivated behavior has been extended to drug reward [51]. The lateral portion of the hypothalamus (LH) may be a possible target in the treatment of addiction as it has been demonstrated at this level of important transcriptional modifications in subjects with compulsive drug intake and significant control of alcohol intake following radiofrequency stereotactic lesions of the ventromedial nucleus [52].

The side effects of hypothalamotomy consist of amnesia, vegetative crisis and reduction of libido and sexual desire [41]. The unconventional electrical stimulation of LH in rats while reducing the stimuli that induce the use of cocaine does not change the motivation for its intake [53]. Therefore, electrical stimulation of the posterior hypothalamus seems to have similar effects to the lesion producing a reduction of cocaine intake but preserving the processes of motivation [54]. The lack of effectiveness on motivation and possible severe adverse effects make lateral hypothalamus a target that cannot be used in addiction at the moment.

5.3. Amygdala

Amygdala is involved in the process of evaluating the positivity or negativity of experience and in the formation of connections between experience and other signals becoming the center of emotional memory and learning [55]. In humans, the reduction of amygdala volume has been related to increase in desire for alcohol and cocaine intake and greater tendency to relapse [56], while in rats its functional block leads to increase in compulsivity of cocaine intake and seeking and reduction of its anxiety-producing effect [57, 58]. However, DBS of the amygdala does not find a clinical application in the treatment of addiction at present, even if it has been proposed by some authors [59].

5.4. Lateral habenula (LHb)

The lateral habenula (LHb) is a critical brain structure modulating aversive and rewarding behaviors through the GABAergic and glutaminergic efferent projections to the ventral tegmental area (VTA) by means of the fasciculus retroflexus (FR). The selective degeneration of this bundle in drug abuse led to a possible use of deep brain stimulation for the treatment of this condition. In rats, deep brain stimulation of LHb with low-frequency (10 Hz)-high-frequency alternate stimulation (100 Hz) attenuates cocaine self-administration, extinction training and reinstatement of cocaine seeking while conventional high-frequency stimulation did not have any effect and low-frequency stimulation increases cocaine self-administration [60]. The effect of unconventional LHb DBS on cocaine reinforcement may be due to reduction of the cocaine-induced increase in glutaminergic input to the VTA.

5.5. Dorsal striatum

Recent studies documented that deep brain stimulation of the dorsolateral caudate/putamen significantly attenuates cocaine seeking following chronic cocaine self-administration and withdrawal in rats [61] and also an increase of gray matter in both the ventral and the dorsal striatum in human addicts [62]. The application of DBS in the dorsal striatum may induce undesirable hypokinetic symptoms similar to Parkinson's disease symptoms due to the spread of current to the close motor regions.

5.6. Prefrontal cortex (PFC)

Cingulotomies have been performed for the drug-dependence treatment in order to interrupt obsessional thoughts about drug use. Significant complications have progressively been

documented like impaired motivation, attention and executive functions [55, 56], in addition to very low effectiveness over addictive behaviors. Recent data showed decreased prefrontal activity on fRMN in drug-abuse patients and increased compulsive behavior after DBS of the lateral orbital cortex. The latter effect makes this procedure counterproductive [63].

5.7. Nucleus subthalamicus (STN)

High-frequency stimulation of the subthalamic nucleus (STN) in Parkinsonian patients is reported to induce primarily motor effects but also psychiatric effects. The likely explanation for these effects is the partitioning of the STN into sensorimotor, associative and limbic anatomo-functional territories. The sensorimotor territory (posterolateral) is the target for PD, while the associative-limbic territory (anteromedial) is the target for OCD. STN-DBS has not yet been tested in addicts, but there are clinical observations in PD patients after STN-DBS, reporting craving for sweet food in some cases or decreased addictive behavior toward DAergic treatment [19–22]. To date, there is no report of STN-DBS effects on any form of addiction in OCD patients, but in these patients, the compulsive component of the disease is reduced by the stimulation [64]. STN-DBS may play a role in preventing the loss of control of drug intake in addicts. The interest on STN-DBS in the treatment of addiction is based on clinical reports and preclinical data obtained in rats subjected to either lesion or DBS of STN. The stimulation of this target is able to dissociate various rewards, decreasing the motivation for the drug without diminishing other forms of motivated behaviors. This ability is demonstrated in two original studies. The first study documented the opposite effect of STN-DBS on the motivation for cocaine and for the natural reward; the other study proved that the stimulation of this target reduces motivation for cocaine while increasing motivation for sucrose, emphasizing the potential beneficial effects of STN-DBS for the treatment of cocaine addiction [23, 65]. Moreover, it was demonstrated that lesions of STN decreased incentive motivation (seeking behavior) for cocaine while inducing the opposite effect (facilitating incentive motivation) for food [23, 65–68]. This result suggests that STN-DBS may not be appropriate for all forms of addiction, but this remains to be investigated in other models of alcohol addiction. Therefore, STN represents a potentially effective target for the treatment of addiction that can decrease the desire for some drugs without influencing other motivated behaviors.

6. Conclusion

Ethics in the history of psychosurgery has played a secondary role in experimentation due to the lack of effective medical therapy for mental disorders. The highest ethical standards for the use of DBS should be applied. The great suffering of patients and their poor quality of life, as well as the high social costs, are in favor of the use of this method in patients resistant to pharmacological therapy. Some fundamental ethical problems are mostly extendable to all clinical interventions as well as to neurostimulation procedures in neurological and psychiatric disorders. The reversibility of the method and the potential benefits are important ethical arguments for the use of DBS in addiction. On the other hand, DBS is not free of

risks (hemorrhages, infections, battery life), so every patient has to be carefully evaluated, and precise ethical standards must be defined in the form of inclusion and exclusion criteria. Beyond the negative parabola of psychosurgery, a rational scientific solid, a precise experimental protocol and adherence to a rigid ethical code are key factors to ensure the success of these researches. As to the target, the nucleus accumbens is very promising. We must keep in mind when choosing new optimal neural targets that likely the local and surrounding DBS influences might depend on the stimulated structure and its specific afferents, efferents, cell types, ratio of projection neurons to interneurons and transmitter systems.

Declaration of interests

We declare no competing interests.

Contributors

The authors contributed equally to writing the manuscript.

Author details

Angelo Lavano*, Giusy Guzzi, Attilio Della Torre, Donatella Gabriele, Domenico Chirchiglia, Carmelino Angelo Stroscio and Giorgio Volpentesta

*Address all correspondence to: lavano@unicz.it

Unit of Stereotactic and Functional Neurosurgery, Department of Medical and Surgical Sciences, University "Magna Graecia", Catanzaro, Italy

References

[1] Cleary DR, Ozpinar A, Raslan AM, Ko AL. Deep brain stimulation for psychiatric disorders: Where we are now. Neurosurgical Focus. Jun 2015;**38**(6):E2

[2] Bradizza CM, Stasiewicz PR, Paas ND. Relapse to alcohol and drug use among individuals diagnosed with co-occuring mental health and substance use disorders: A review. Clinical Psychology Review. 2006;**26**:162-178

[3] Feltenstein MV, See RE. The neurocircuitry of addiction: An overview. British Journal of Pharmacology. 2008;**154**:261-274

[4] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; **35**:217-238

[5] Koob GF, Volkow ND: Neurobiology of addiction: A neurocircuitry analysis. Lancet Psychiatry. 2016;**8**:760-73

[6] Robinson TE, Berridge KC. Review the incentive sensitization theory of addiction: Some current issues. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2008;**363**:3137-3146

[7] Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, et al. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biological Psychiatry. 2002;**51**:134-142

[8] Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. The American Journal of Psychiatry. 2002;**159**:1642-1652

[9] Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. Psychopharmacology. 1999;**146**:373-390

[10] Goto Y, Grace AA. Limbic and cortical information processing in the nucleus accumbens. Trends in Neurosciences. 2008;**31**:552-558

[11] Knapp CM, Tozier L, Pak A, Ciraulo DA, Kornetsky C. Deep brain stimulation of the nucleus accumbens reduces ethanol consumption in rats. Pharmacology, Biochemistry, and Behavior. 2009;**92**:474-479

[12] Vassoler FM, Schmidt HD, Gerard ME, Famous KR, Ciraulo DA, Kornetsky C, et al. Deep brain stimulation of the nucleus accumbens shell attenuates cocaine priming induced reinstatement of drug seeking in rats. The Journal of Neuroscience. 2008;**28**:8735-8739

[13] Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science. 1997; **278**:52-58

[14] Wise RA. Roles for nigrostriatal—Not just mesocorticolimbic—Dopamine in reward and addiction. Trends in Neurosciences. 2009;**32**:517-524

[15] Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. Science Translational Medicine. 2012;**4**:116ra6

[16] Volkow ND, Wang GJ, Telang F, et al. Profound decreases in dopamine release in striatum in detoxified alcoholics: Possible orbitofrontal involvement. The Journal of Neuroscience. 2007;**27**:12700-12706

[17] Caine SB, Thomsen M, Gabriel KI, et al. Lack of self-administration of cocaine in dopamine D1 receptor knock-out mice. The Journal of Neuroscience. 2007;**27**:13140-13150

[18] Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: Reward systems gone awry? Lancet Neurology. 2003;**2**:595-604

[19] Witjas T, Baunez C, Henry JM, Delfini M, Regis J, Cherif AA, Peragut JC, Azulay JP. Addiction in Parkinson's disease: Impact of subthalamic nucleus deep brain stimulation. Movement Disorders. 2005;**20**:1052-1055

[20] Knobel D, Aybek S, Pollo C, Vingerhoets FJ, Berney A. Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): A case report. Cognitive and Behavioral Neurology. 2008;**21**:187-189

[21] Lhommee E, Klinger H, Thobois S, Schmitt E, Ardouin C, Bichon A, Kistner A, Fraix V, Xie J, Aya Kombo M, Chabardes S, Seigneuret E, Benabid AL, Mertens P, Polo G, Carnicella S, Quesada JL, Bosson JL, Broussolle E, Pollak P, Krack P. Subthalamic stimulation in Parkinson's disease: Restoring the balance of motivated behaviours. Brain. 2012;**135**:1463-1477

[22] Eusebio A, Witjas T, Cohen J, Fluchere F, Jouve E, Regis J, Azulay JP. Subthalamic nucleus stimulation and compulsive use of dopaminergic medication in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 2013

[23] Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. Nature Neuroscience. 2005;**8**:484-489

[24] Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: Valuable therapeutic implications? Journal of Neurology, Neurosurgery, and Psychiatry. 2007;**78**:1152-1153

[25] Kuhn J, Lenartz D, Huff W, Lee SH, Koulousakis A, Klosterkoetter J, Sturm V. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: Valuable therapeutic implications? J Neurol Neurosurg Psychiatry. 2007;**78**:1152-1153

[26] Heimer L, Alheid GF, de Olmos JS, Groenewegen HJ, Haber SN, Harlan RE, Zahm DS. The accumbens: Beyond the core-shell dichotomy. The Journal of Neuropsychiatry and Clinical Neurosciences. 1997;**9**:354-381

[27] Zahm DS. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. Neuroscience and Biobehavioral Reviews. 2000;**24**:85-105

[28] Ping A, Xi J, Prasad BM, Wang MH, Kruzich PJ. Contributions of nucleus accumbens core and shell GluR1 containing AMPA receptors in AMPA- and cocaine-primed reinstatement of cocaine seeking behavior. Brain Research. 2008;**1215**:173-182

[29] Cornish JL, Duffy P, Kalivas PW. A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. Neuroscience. 1999;**93**:1359-1367

[30] Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. Neurology. 2000;**55**:S13-S16

[31] Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neuroscience Letters. 1996;**215**:17-20

[32] Kiss ZH, Mooney DM, Renaud L, Hu B. Neuronal response to local electrical stimulation in rat thalamus: Physiological implications for mechanisms of deep brain stimulation. Neuroscience. 2002;**113**:137-143

[33] McCracken CB, Grace AA. Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. The Journal of Neuroscience. 2009;**29**:5354-5363

[34] Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: A pathology in prefrontal accumbens glutamate transmission. Neuron. 2005;**45**:647-650

[35] Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission: Potential therapeutic targets for craving and addiction. Annals of the New York Academy of Sciences. 2010;**1187**:35-75

[36] Blomstedt P, Sjöberg RL, Hansson M, Bodlund O, Hariz MI. Deep brain stimulation in the treatment of obsessive compulsive disorder. World Neurosurgery. 2013;**80**:e245-e253

[37] Wu H, Van Dyck-Lippens PJ, Santegoeds R, van Kuyck K, Gabriels L, Lin G, et al. Deep-brain stimulation for anorexia nervosa. World Neurosurgery. 2013;**80**:S29.e1-S29.e10

[38] Li N, Wang J, Wang XL, Chang CW, Ge SN, Gao L, et al. Nucleus accumbens surgery for addiction. World Neurosurgery. 2013;**80**:S28.e9-S28.e19

[39] Wu HM, Wang XL, Chang CW, Li N, Gao L, Geng N, et al. Preliminary findings in ablating the nucleus accumbens using stereotactic surgery for alleviating psychological dependence on alcohol. Neuroscience Letters. 2010;**473**:77-81

[40] Xu J, Wang G, Zhou H, Tian Z, Luo Q, Jiang J. Neurosurgical treatment on alleviating heroin psychological dependence. Chinese Journal of Neurosurgery. 2005;**10**:590-593

[41] Stelten BM, Noblesse LH, Ackermans L, Temel Y, Visser-Vandewalle V. The neurosurgical treatment of addiction. Neurosurgical Focus. 2008;**25**:E5

[42] Valencia-Alfonso CE, Luigjes J, Smolders R, Cohen MX, Levar N, Mazaheri A, van den MP, Schuurman PR, van den BW, Denys D. Effective deep brain stimulation in heroin addiction: A case report with complementary intracranial electroencephalogram. Biological Psychiatry. 2012;**71**:e35-e37

[43] Zhou H, Xu J, Jiang J. Deep brain stimulation of nucleus accumbens on heroin-seeking behaviors: A case report. Biological Psychiatry. 2011;**69**:e41-e42

[44] Kuhn J, Gründler TO, Bauer R, Huff W, Fischer AG, Lenartz D, et al. Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring. Addiction Biology. 2011;**16**:620-623

[45] Mantione M, van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: Therapeutic and research implications: Case report. Neurosurgery. 2010;**66**:E218

[46] Kuhn J, Bauer R, Pohl S, Lenartz D, Huff W, Kim EH, et al. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. European Addiction Research. 2009;**15**:196-201

[47] Saleh C, Okun MS. Clinical review of deep brain stimulation and its effects on limbic basal ganglia circuitry. Frontiers in Bioscience. 2008;**13**:5708-5731

[48] van der Plasse G, Schrama R, van Seters SP, Vanderschuren LJ, Westenberg HG. Deep brain stimulation reveals a dissociation of consummatory and motivated behaviour in the medial and lateral nucleus accumbens shell of the rat. PLoS One. 2012;**7**:e33455

[49] Carelli RM, Ijames SG, Crumling AJ. Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus "natural" (water and food) reward. The Journal of Neuroscience. 2000;**20**:4255-4266

[50] Sesia T, Temel Y, Lim LW, Blokland A, Steinbusch HW, Visser-Vandewalle V. Deep brain stimulation of the nucleus accumbens core and shell: Opposite effects on impulsive action. Experimental Neurology. 2008;**214**:135-139

[51] Marchant NJ, Hamlin AS, McNally GP. Lateral hypothalamus is required for context-induced reinstatement of extinguished reward seeking. The Journal of Neuroscience. 2009;**29**:1331-1342

[52] Ahmed SH, Lutjens R, van der Stap LD, Lekic D, Romano-Spica V, Morales M, Koob GF, Repunte-Canonigo V, Sanna PP. Gene expression evidence for remodeling of lateral hypothalamic circuitry in cocaine addiction. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**:11533-11538

[53] Levy D, Shabat-Simon M, Shalev U, Barnea-Ygael N, Cooper A, Zangen A. Repeated electrical stimulation of reward-related brain regions affects cocaine but not "natural" reinforcement. The Journal of Neuroscience. 2007;**27**:14179-14189

[54] Everitt BJ, Stacey P. Studies of instrumental behavior with sexual reinforcement in male rats (*Rattus norvegicus*): II. Effects of preoptic area lesions, castration, and testosterone. Journal of Comparative Psychology. 1987;**101**:407-419

[55] Muller UJ, Voges J, Steiner J, Galazky I, Heinze HJ, Moller M, Pisapia J, Halpern C, Caplan A, Bogerts B, Kuhn J. Deep brain stimulation of the nucleus accumbens for the treatment of addiction. Annals New York Academy of Sciences. 2013;**1282**:119-128

[56] Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, Jenike MA, Rauch SL. Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive–compulsive disorder. The American Journal of Psychiatry. 2002;**159**:269-275

[57] Wenzel JM, Waldroup SA, Haber ZM, Su ZI, Ben-Shahar O, Ettenberg A. Effects of lidocaine-induced inactivation of the bed nucleus of the stria terminalis, the central or the basolateral nucleus of the amygdala on the opponent-process actions of self-administered cocaine in rats. Psychopharmacology. 2011;**217**:221-230

[58] Xue Y, Steketee JD, Sun W. Inactivation of the central nucleus of the amygdala reduces the effect of punishment on cocaine self-administration in rats. The European Journal of Neuroscience. 2012;**35**:775-783

[59] Langevin JP. The amygdala as a target for behavior surgery. Surgical Neurology International. 2012;**3**:S40-S46

[60] Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E, Ben-Tzion M, mi-Ad L, Yaka R, Yadid G. Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behavior. Neuropharmacology. 2010;**59**:452-459

[61] Hollander JA, Im HI, Amelio AL, Kocerha J, Bali P, Lu Q, Willoughby D, Wahlestedt C, Conkright MD, Kenny PJ. Striatal microRNA controls cocaine intake through CREB signalling. Nature. 2010;**466**:197-202

[62] Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain. 2011;**134**:2013-2024

[63] Klanker M, Post G, Joosten R, Feenstra M, Denys D. Deep brain stimulation in the lateral orbitofrontal cortex impairs spatial reversal learning. Behavioural Brain Research. 2013;**245C**:7-12

[64] Lim SY, O'Sullivan SS, Kotschet K, Gallagher DA, Lacey C, Lawrence AD, Lees AJ, O'Sullivan DJ, Peppard RF, Rodrigues JP, Schrag A, Silberstein P, Tisch S, Evans AH. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. Journal of Clinical Neuroscience. 2009;**16**:1148-1152

[65] Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chereau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardes S, Czernecki V, Ardouin C, Krebs MO, Bardinet E, Chaynes P, Burbaud P, Cornu P, Derost P, Bougerol T, Bataille B, Mattei V, Dormont D, Devaux B, Verin M, Houeto JL, Pollak P, Benabid AL, Agid Y, Krack P, Millet B, Pelissolo A. Subthalamic nucleus stimulation in severe obsessive–compulsive disorder. The New England Journal of Medicine. 2008;**359**:2121-2134

[66] Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C. Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**:1196-1200

[67] Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. The Journal of Neuroscience. 2002;**22**:562-568

[68] Uslaner JM, Dell'Orco JM, Pevzner A, Robinson TE. The influence of subthalamic nucleus lesions on sign-tracking to stimuli paired with food and drug rewards: Facilitation of incentive salience attribution? Neuropsychopharmacology. 2008;**33**:2352-2361