

Observations on Unaided Smoking Cessation after Deep Brain Stimulation of the Nucleus Accumbens

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Key Words

Cigarette smoking · Deep brain stimulation · Nicotine dependence · Nucleus accumbens · Smoking cessation

Abstract

Aims: We explore whether clinical research on deep brain stimulation (DBS) of the nucleus accumbens (NAc) to treat addiction is justified besides theoretical speculation. **Methods:** Since 2004, 10 patients who were also smokers were treated at the University of Cologne for Tourette's syndrome (TS), obsessive-compulsive disorders (OCD) or anxiety disorders (AD) by DBS of the NAc. We assessed their smoking behavior after DBS and (in retrospection) before by the Fagerström Test for Nicotine Dependence (FTND) and additional items. **Results:** Three male patients were able to quit smoking after DBS. They were less dependent and higher motivated compared to the rest of the sample. They are stimulated with a higher voltage. During 1-year, 2-year, and 30-month follow-ups, we found a higher rate of successful smoking cessation (20, 30 and 30%) compared to unaided smoking cessation in the general population (13, 19 and 8.7%). **Conclusions:** Albeit the results of the study are severely limited by the method of retrospective self-assessment of psychiatric patients, further research of DBS of the

NAc to treat addiction seems justified. In addition to biological mediators, psychosocial factors should be assessed in further prospective studies. Copyright © 2009 S. Karger AG, Basel

Introduction

The mesocorticolimbic system is of importance in obsessive-compulsive disorders (OCD), Tourette's syndrome (TS) and anxiety disorders (AD) [1, 2]. Therefore, experimental treatments of those disorders by deep brain stimulation (DBS) of the NAc have been performed [3–5]. Only recently we observed in this context the unintended alleviation of alcohol dependence in a patient with an anxiety disorder who was treated by DBS of the NAc [6]. Another report indicates that stereotactic ablative procedures in the NAc can alleviate opioid dependence [7]. Actually a relative general consensus prevails that the mesocorticolimbic pathway, which includes the nucleus accumbens (NAc), plays a major role in substance dependence. For example, nicotine reaches the CNS within seconds after inhalation and docks to several subtypes of nicotinic acetylcholine receptors (nAChR) which are detectable mainly in the ventral tegmental area and the NAc [8, 9].

Aims of the Study

Taking into account the theoretical knowledge, it is very conceivable that the short-term functional lesioning or long-term modulation of the NAc by DBS might have an effect on the neurobiological circuits relevant for addiction to cigarette smoking. In this article we will describe our retrospective findings on changes in smoking behavior after and before DBS of patients who were treated for other psychiatric disorders by DBS of the NAc. The main question addressed in this article is whether prospective studies on DBS of the NAc to treat addiction are justifiable beside theoretical argumentations. The secondary aim was to describe results helpful for further research that could be obtained without the need for surgery.

Methods

Since 2004, 20 patients with severe and standard treatment refractory AD, OCD and TS have been treated by DBS of the NAc at the University of Cologne. The majority of patients stay in regular contact to the clinic. Therefore, we knew that out of the 20 patients treated, 10 patients were daily smokers at any time before or after DBS. These patients were integrated in our study. After a qualitative interview of the patients about their smoking behavior, we developed, following peer suggestion, a more extensive questionnaire for quantitative assessment of possible mediators like severity of addiction and motivation to quit and put it into use. The patients were interviewed directly or by phone. Changes in medication and primary psychiatric disorder were collected.

Questionnaire

We measured the patients retrospective and current nicotine dependence by the Fagerström Test for Nicotine Dependence (FTND) [10] and added questions about their past and present motivation to cut down on smoking (ranging from 1 not existing to 5 very strong), the number of attempts to quit smoking (none/one/two to three/four or more) and the longest period without smoking before DBS. In addition, we asked how long they have been smoking and whether they regularly consume or consumed any other drug of abuse.

Successful cessation of smoking was defined as a clear statement by the patient that he or she stopped smoking for at least 4 months and that he or she scored zero points on the FTND. If cessation was successful after DBS, we asked how many attempts were undertaken and how many months passed until the first attempt. If the first attempt after DBS was successful, this was seen as an argument for an effect of DBS. We included data on whether the primary mental disorder improved or worsened after DBS, as such a change in stressors might also explain a change in smoking behavior.

Surgical Procedure

The detailed stereotactic procedure was similar for all patients and has already been described elsewhere [3, 4, 6]. In accordance with the computer-supported determination of access and elec-

trode trajectories one (unilateral) or two (bipolar) quadripolar electrodes (Medtronic 3387) were implanted stereotactically in the NAc and the neighboring anterior limb of the internal capsule (fig. 1). The tips of the electrodes were directed into the fundus subventricularis medialis of the NAc. The selected target points were chosen in accordance with the atlas of Mai et al. [11] and transformed to the corresponding position of the patient's brain with regard to AC-PC coordinates. The correct positioning of the electrodes was postoperatively confirmed by means of CT and conventional X-ray procedures. As the majority of patients were included in ongoing studies, postoperatively they were all seen regularly every 3 months. Across these assessment times the modifications of stimulation parameters varied. It should be noted that the aim of changing these parameters was the alleviation of the primary mental disorder. No nicotine addiction counseling or treatment was intended or undertaken by the medical personnel. The treatment results of some patients have already been published [3, 4, 6].

Results

The sample consists of 7 male and 3 female smokers, with an average age of 43.5 (SD 8.48) years. Except for patient 3 (8 years) all patients had smoked for longer than 10 years. Only 9 of the 10 patients could be reached for detailed questioning. We knew from regular medical consultations that this currently unreachable patient did not change her daily consumption rate of cigarettes before or after DBS and that she had not made any attempts to quit smoking. The limited data about her are tabulated together with the detailed data of the other cases in table 1. Stimulation parameters and changes in medication before and after surgery are collected in table 2.

Concomitant Consumption

Only patient 1 fulfilled the diagnostic criteria for alcohol dependence. As reported elsewhere, patient 1 reduced his alcohol consumption after DBS of the NAc without further explicit motivation [6]. No patient reported the consumption of other drugs of abuse.

Abstinence Motivation

The mean abstinence motivation before DBS was 2.89 (SD = 1.05) and after DBS 2.75 (SD = 0.89). For 7 of the 9 patients, their motivation score did not change in the course of the DBS. Patient 4 was unsure about his motivation after DBS and chose not to rate himself.

FTND Score

The mean score on the FTND before DBS was 4.44 (SD = 2.07) and after DBS 3.33 (SD = 3.16). For 6 of the 9 patients their FTND score did not change in the course of

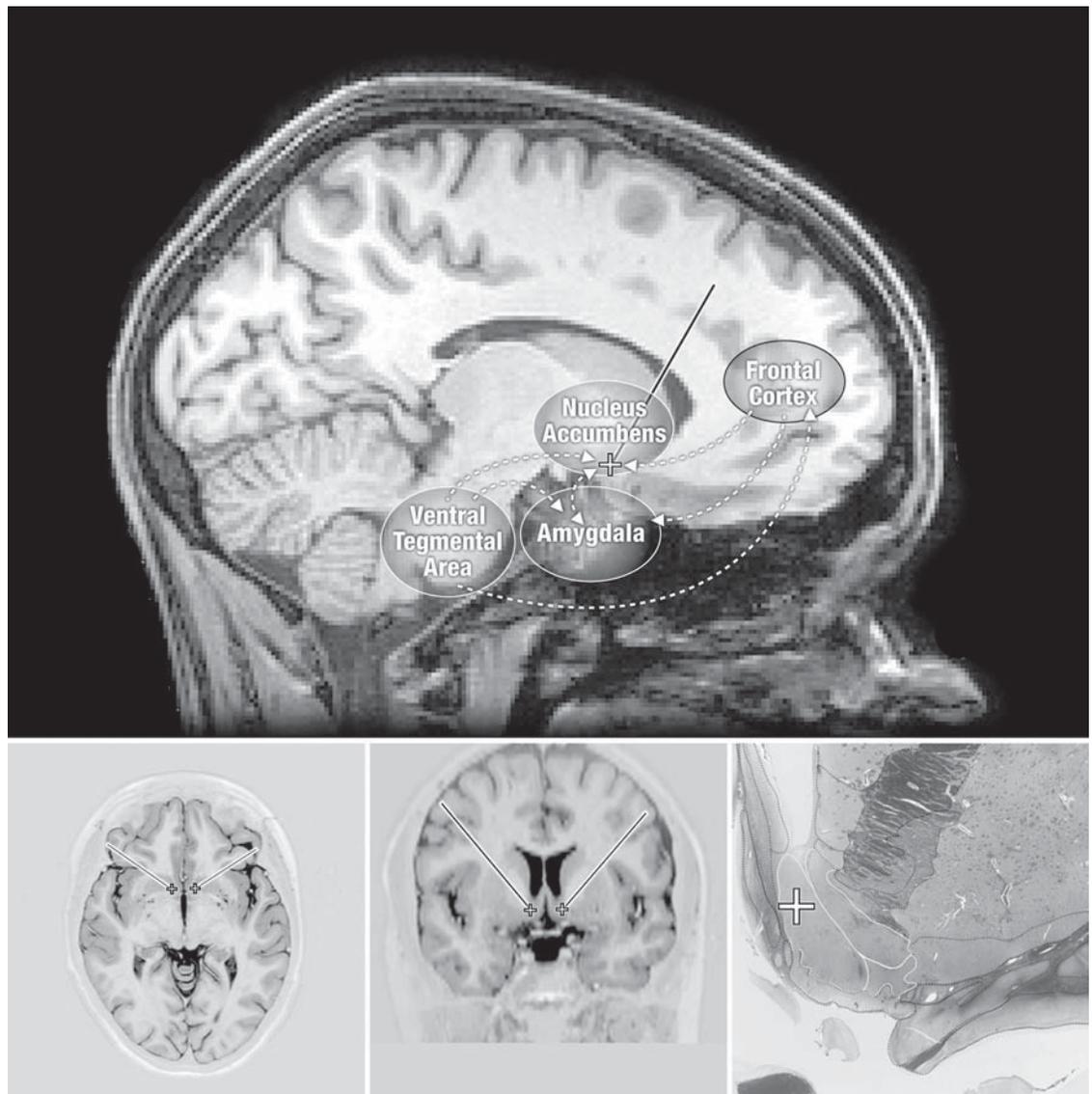


Fig. 1. Reconstructed electrode trajectory superimposed on preoperative MRI. Graphic and anatomical presentation of the nucleus accumbens (cross) in different plains, extracted with permission from Mai et al. [11]. In addition the figure shows the main areas and pathways of the mesocorticolimbic circuit that are seen to be involved in chemical dependence.

the DBS. Patient 5 increased his FTND score by one point because his frequency of daily smoking raised from 11–20 to 21–30 cigarettes. He explained this raise as a shift in his obsessive-compulsive behavior, as he feels compelled to put out his cigarettes soon after lighting them.

Attempts to Quit Smoking

No patient successfully stopped smoking before DBS. Three patients attempted to quit after DBS and were successful with their first attempt. They did not relapse for a

mean of 28.0 (SD = 5.57) months and until present. This attempt took place on average 13.5 (SD = 14.85) months after the implantation.

Differences between Successful Quitters and Non-Attempters

Successful quitters mean FTND score before DBS is lower: 3.66 (SD = 1.15) compared to the rest of the samples 4.83 (SD = 2.40). No patient with a FTND score higher than six attempted to quit after DBS. Successful quitters' mean

Table 1. Clinical data and smoking behavior

Patient No.	Stimulation	Motivation before DBS	FTND before DBS	Attempts before DBS	Duration before DBS	Motivation after DBS	FTND after DBS	Attempts after DBS	Time till first attempt	Duration after DBS	Primary disorder	Amelioration by DBS	Age	Sex
1	bilateral	2	3	2-3	some days	2	3	0	-	-	AD	no	54	m
2	bilateral	5	3	2-3	3 months	4	cessation	1	8 months	29 months	TS	yes	42	m
3	unilateral	3	5	2-3	some days	4	cessation	1	3 months	33 months	OCD	no	40	m
4	unilateral	4	3	0	-	n.a.	cessation	1	24 months	22 months	OCD	yes	47	m
5	unilateral	2	5	0	-	2	6	0	-	-	OCD	no	45	m
6	unilateral	2	3	0	-	2	3	0	-	-	OCD	yes	58	f
7	bilateral	2	6	0	-	2	6	0	-	-	TS	no	40	m
8	bilateral	3	9	2-3	6 days	3	9	0	-	-	TS	yes	28	m
9	bilateral	3	3	0	-	3	3	0	-	-	TS	yes	40	f
10	unilateral	?	?	0	-	?	?	0	-	-	OCD	yes	40	f

Duration of longest abstinence is given either in months or days. Degree of amelioration of the primary mental disorder is derived from already published studies [3, 4, 6]. 'No' means improvement is $\leq 25\%$; 'yes' means it is $> 25\%$ on corresponding measurements. Data from case 10 is only from early stage of questioning. AD = Anxiety disorder; TS = Tourette's syndrome; OCD = obsessive-compulsive disorder.

Table 2. Stimulation parameters and change in medication

Patient No.	Preoperatively	Postoperatively	Stimulation parameter
1	SSRI, NL, MS	no relevant changes	0: off, 1: -, 2: -, 3: off, case: +; 130 Hz, 90 μ s, 3 V
2	BZ	no medication	0: -, 1: -, 2: off, 3: off, case: +; 130 Hz, 90 μ s, 6 V
3	SSRI, NL, BZ	no relevant changes	0: -, 1: -, 2: off, 3: off, case: +; 140 Hz, 90 μ s, 4.5 V
4	CLM, SSRI, BUS	SSRI, SNRI	0: -, 1: -, 2: -, 3: off, case: +; 145 Hz, 90 μ s, 6.5 V
5	BZ	no relevant changes	0: -, 1: -, 2: off, 3: off, case: +; 140 Hz, 90 μ s, 4.5 V
6	SSRI	no relevant changes	0: -, 1: -, 2: off, 3: off, case: +; 140 Hz, 90 μ s, 4.5 V
7	MS, B, NL	no relevant changes	0: -, 1: -, 2: off, 3: off, case: +; 145 Hz, 90 μ s, 4.5 V
8	N, SSNRI	NL, SSNRI, SSRI	0: -, 1: -, 2: -, 3: off, case: +; 130 Hz, 90 μ s, 5.5 V
9	CLM, MS, NL	SSRI, MS	0: -, 1: -, 2: off, 3: off, case: +; 130 Hz, 180 μ s, 4.5 V
10	SSRI, NL, BZ	no relevant changes	0: -, 1: -, 2: off, 3: off, case: +; 140 Hz, 90 μ s, 4.5 V

SSRI = Selective serotonin reuptake inhibitor; NL = neuroleptics; BZ = benzodiazepine; CLM = clomipramine; BUS = buspirone; SNRI = selective norepinephrine reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; MS = mood stabilizer.

motivation score before DBS is higher: 4.00 (SD = 1.00) compared to the rest of the samples 2.33 (SD = 0.52). In addition, every patient who at some point rated a motivation of four or higher attempted to quit after DBS and was successful. Patients who successfully quit smoking were stimulated at a higher voltage (mean 5.67, SD = 1.04) compared to the rest of the samples (mean 4.43, SD = 0.73).

Other Circumstances

It should be noted that we did not observe any relevant somatic conditions or incisive biographic events which could be responsible for the change in nicotine consumption of the successful quitters.

Discussion

Less-dependent and higher-motivated male smokers were able to quit smoking in the course of DBS of the NAc. This might not be surprising. Some authors report that a strong motivation to quit is important for initial success and long-term maintenance [12]. Yet, other authors report that those who relapse during unaided smoking cessation experience inter alia more withdrawal symptoms and are more likely to be tempted by the presence of others smoking [13]. This latter point might suggest that neurobiological circuits for withdrawal or cue reactivity might have been influenced by DBS of the NAc.

On the one hand, studying the effect of DBS on already treated patients offers the opportunity of first findings without the need for possibly unjustified new surgeries. On the other hand, the study thus becomes limited by the method of a retrospective self-assessment of psychiatric patients. Besides arguing that there might exist a direct effect of the psychiatric disorder on answering the questionnaire, it might be proposed that the successful smoking cessations were caused by the amelioration of the primary mental disorder, especially of OCD-like symptoms [14, 15]. But there seems to be no consistent association between the degree of amelioration, the type of disorder, the medication and smoking outcome. When compared with unaided smoking cessation in the general population (we could find no reports on unaided cessation in groups with psychiatric disorders), cessation after DBS was higher. The rate of abstinence in our sample was 20% after 1 year and 30% after 2 years, while the rate of abstinence in the general population of 13% after 1 year and 19% after 2 years [12] or 8.7% after 30 months [16].

We did find a difference in mean voltage and that the patient that worsened in his consumption was stimulated with the lowest voltage. A common interpretation of voltage increase is that the electrical field becomes larger, thus affecting a greater portion of the target area. This might be taken as hint for prospective studies that there might be cumulative effects for stimulating different areas of the Nac, probably the core and shell. In addition, we find it is very remarkable that every attempt to quit after DBS was successful. But as this is a retrospective and non-blind study, influence by medical personal and retrospective bias cannot totally be ruled out. Please note that due to the heterogeneity of the sample, our results should be interpreted with caution and only offer a rough

and preliminary guideline on what to expect from further research. Nevertheless our results speak in favor of a prominent role of the nucleus accumbens in the pathogenesis of addiction.

Conclusion

Less-dependent and higher-motivated male smokers which were stimulated at a higher voltage successfully stopped smoking more often and following their first attempt after DBS of the NAc compared with the rest of the sample and the general population. The results of the study are severely limited by the method of retrospective self-assessment of psychiatric patients. At the current time, we do not advise DBS as a possible standard treatment for any addiction. But we think the results can be used to justify clinical research on treatment of addiction by DBS of the NAc due to two reasons: successful smokers quit following their first attempt after DBS and the rate of smoking cessation seems to be higher than in the general public. The results can also offer a rough sketch for expectations from prospective studies, but we suggest that besides biological factors like stimulation parameters especially psychological and social factors like abstinence motivation or employment situation should be meticulously investigated and controlled in upcoming prospective studies. Especially abstinence motivation is probably high in patients which consent to experimental treatment, which could bias results. In addition, we stress the importance to develop ethical consensus guidelines for neurosurgical research in this vulnerable population.

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