Deep Brain Stimulation Surgery for Alcohol Addiction

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Key words
- Addiction
- Craving
- Deep brain stimulation
- Nucleus accumbens
- Reward system
- Stereotaxy

Abbreviations and Acronyms
CT: Computed tomography
DBS: Deep brain stimulation
DS: Dorsal striatum
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
HF: High frequency
IPG: Impulse generator
LFP: Local field potential
MRI: Magnetic resonance imaging
NAc: Nucleus accumbens
PCL-R: Hare’s Psychopathy Check List–Revised
PFC: Prefrontal cortex
VS: Ventral striatum
VTA: Ventral tegmental area

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INTRODUCTION

Disease
Alcohol dependence or alcoholism constitutes one of the most serious public health problems worldwide with a comparably high prevalence of 4.5% related to 1 year (2001–2002) for the population of the United States of America (49). In the Global Status Report from 2004, the World Health Organization estimated that about 2 billion people worldwide consume alcoholic beverages (64). Among those are 76.3 million with diagnosable alcohol use disorders. Moreover, the global burden related to alcohol consumption expressed in terms of morbidity or mortality is high. Alcohol is estimated, for instance, to cause worldwide about 20%–30% of esophageal cancer, liver cancer, cirrhosis of the liver, homicide, epileptic seizures, and motor vehicle accidents (61). In essence, alcohol causes 1.8 million deaths (3.2% of total) and a loss of 58.3 million (4% of total) of disability-adjusted life years (63).

According to the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) of the American Psychiatric Association (1), the most common and global standard in psychiatry and psychology, alcohol dependence, or other drug addiction is characterized as the repeated use of a drug despite recurrent adverse consequences. Alcohol dependence is a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the seven criteria listed in Table 1, occurring at any time in the same 12-month period. Characteristic hallmarks of drug addiction in essence are compulsion to seek and take the drug, loss of control to limit intake, and emergence of a negative emotional state reflecting a motivational with-
 них. It has complex effects on glutamate-
N-methyl-d-aspartate activity and is a y-
amino-butyric acid agonist. Its mode of
action can simply be described as repair of
the balance between these two transmitter
systems, which is disturbed by alcohol (26).

Both naltrexone and acamprosate have been
tested in a high number of random-
ized controlled trials worldwide. With re-
spect to the percentage of patients con-
tinuing abstinence under medication compared
to placebo, the results display a great vari-
ability, with relapse rates ranging from 30%
to 80%. Cochrane reviews revealed a rather
low effect size with Cohen’s d around 0.25
and odds ratios in most of the meta-
analyses in the order of 1.25 (41).

Also great efforts have been made to pre-
vent relapses by application of different psy-
chotherapeutic modalities such as brief in-
tervention (31 studies), social skills training
(25 studies), motivational enhancement (17
studies), cognitive therapy (10 studies), and
others (24). After a thorough review of the
literature, the Institute of Medicine, United
States, could not identify a modality being
superior to others tested and recommended
consecutively the combination of the vari-
ous approaches together with individual-
ized treatment strategies (2-4).

Deep Brain Stimulation for Alcohol
Addiction—Motivation

Both high relapse rates after conservative
treatment and the adverse effects of chronic
alcohol abuse on the physical, mental, and
social performance of these patients are the
main reasons to search for alternative ther-
apies. Since the pioneering work of Benabid
et al. in the 1980s (6), deep brain stimula-
tion (DBS) became an established method
for the treatment of Parkinson disease (10,
60), tremor (38), and generalized or seg-
mental dystonia (37, 56). Meanwhile, DBS,
which is an attractive method because of its
potential reversibility when the stimulator
is switched off, has been extended for the
Treatment of patients with neuropsychiatric
diseases during the last years.

The motivation for our group to treat al-
cohol-addicted patients with nucleus accu-
bens (NAc) high-frequency (HF) DBS
in an open-label study is based principally
on an accidental observation published by
Kuhn et al. in 2007 (36). These authors re-
ported a case treated for severe anxiety dis-
order and secondary depressive disorder
with bilateral NAc DBS. Although the in-
tended treatment failed, the patient re-
ported that with initiation of stimulation,
his alcohol dependence had improved sub-
stantially. Here we summarize our prelimi-
nary results of a small case series, in which
we treated five patients with severe alcohol
addiction refractory to standard therapy by
applying off-label HF DBS in the NAc. All
patients gave their informed consent to
both treatment and examination according
to our study protocol, which we performed
with permission of the ethic commission of
our hospital. Results of treatment for three
of these five patients were already published
(23, 47).

PATIENTS AND METHODS

Surgical Candidates

Inclusion criteria were as follows: age rang-
ing from 25 to 60 years, alcohol dependence
according to ICD-10 (international classifi-
cation of diseases) and DSM-IV, history of
alcoholism of at least 10 years, inpatient
detoxification following abstinence of at least
2 weeks, a minimum of two long-term inpa-
tient therapies of at least 6 months, and
unsuccessful therapy with acamprosate or
naltrexone or disulfiram. Exclusion criteria
were as follows: history of seizures, antisoc-
ial personality (score of >20 on Hare’s
Psychopathy Check List–Revised), brain
damage visible on CT and MRI scans, alco-
hol-related personality deprivation, past
history of addiction to another substance or
currently using another substances of
abuse, or additional psychiatric disorders
(DSM-IV axis I or II) unrelated to alcohol
dependence. Furthermore, we performed
neuropsychological tests (listed below in
“clinical assessments”) before surgery to
ensure—in addition to the clinical evalua-
tion—that patients are able to give in-
formed consent and in order to exclude pa-
 tients with mild mental retardation.
Patients were excluded if the IQ was below
80 or a score was below 80% of the average
score.

Persons primarily responsible for indi-
cating DBS were the psychiatrist of our
group (B.B.) and the neurosurgeon (J.V.).
When both persons had agreed to NAc
stimulation, a third, independent psychia-
trist controlled the first decision and gave a
final statement. If the latter was negative,
patients were not treated with DBS.
The off-label use of a technical device, which means the use other than the one indicated for a medicinal product with marketing authorization depending on an individual case-by-case decision, does not require a vote from an ethic commission. Regardless, we treated the patients in accordance with a positive vote from the ethic commission of the medical faculty of the University of Magdeburg.

**Surgical Procedure**

Treatment planning standards and the surgical procedure are, in general, described elsewhere in detail (57). Briefly, a few days prior to surgery, patients underwent non-stereotactic MRI examination. Treatment planning was performed using special software (Precisys AG, Heidelberg, Germany). Sturm et al. originally worked out targeting of the NAc in 2003 (54). We defined the target referred to the most distal contact of the quadripolar electrode to a point 2 mm rostral to the anterior commissure at the level of the midsagittal plane, 3–4 mm ventral and 6–8 mm lateral of the midline. Coordinates were taken from a microscopic atlas of the human brain (40). If necessary, we modified the atlas standard coordinates according to landmarks displayed in the individual treatment planning MRI, and indicated the border of the NAc region. Important landmarks, which can be clearly visualized on coronal MRI scans (T1-weighted sequences, 1.5 T; Intera, Philips, Best, The Netherlands), are the vertical limb of Broca’s diagonal band, which is located medially to the NAc, and the olfactory tubercle as the ventral border of the target region. The target was finally defined in projection onto the caudo-media1, subventricular part of the NAc, which according to histochromical criteria represents the remnant of the shell area in the primate (54).

For stereotactic implantation of the brain electrodes (model 3387; Medtronic, Minnesota, MN, USA) with the patient in general anesthesia, we used a modified Riechert-Mundinger stereotactic frame. Intraoperatively we performed a stereotactic CT examination integrating the preoperative treatment planning MRI images via image fusion. The electrode localization was documented by stereotactic x-ray imaging using x-ray tubes installed in the operating room. In addition, we performed postoperative CT examination. CT as well as x-ray images were fused with the planning MRI in each case, displaying that the distal contacts of the DBS electrode were placed in the caudo-media1, subventricular part of the NAc as intended, the third contact within the transition area to the medial, and the highest, or the fourth, contact at a point in the most medial part of the capsule or in the transition area to the caudate. CT images also excluded any intracranial hemorrhage. Figure 1 displays the final electrode position of case 6.

In cases 1 and 2, the electrode leads were externalized, allowing electrical test stimulation and recording of local field potentials (LFPs) from the depth contacts in different psychopathological tasks during five postoperative days. In all patients, electrode leads were connected to an impulse generator (IPG; Medtronic, Minneapolis, Minnesota, MN, USA) with the patient in general anesthesia, we used a modified Riechert-Mundinger stereotactic frame. Intraoperatively we performed a stereotactic CT examination integrating the preoperative treatment planning MRI images via image fusion. The electrode localization was documented by stereotactic x-ray imaging using x-ray tubes installed in the operating room. In addition, we performed postoperative CT examination. CT as well as x-ray images were fused with the planning MRI in each case, displaying that the distal contacts of the DBS electrode were placed in the caudo-media1, subventricular part of the NAc as intended, the third contact within the transition area to the medial, and the highest, or the fourth, contact at a point in the most medial part of the capsule or in the transition area to the caudate. CT images also excluded any intracranial hemorrhage. Figure 1 displays the final electrode position of case 6.

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Clinical Assessments

The Alcohol Dependence Scale was applied for preoperative testing only. Preoperatively and at 6 and 12 months after initiation of DBS, we used the following tests: Obsessive-Compulsive Drinking Scale, Alcohol Urge Questionnaire, Rey Auditory Verbal Learning Test (using a German translation), Hamburg Wechsler Intelligence Test for adults, Subtest 3 of the “Leistungsprüfsystem,” Multiple Choice F& Word Test-B, as well as Trail Making Test A und B.

Pre- and postsurgical assessment also included the Symptom Check List–90 as well as clinical interviews to follow up on possible changes in psychopathology. In addition, we took routine blood samples and documented the number and duration of relapses and abstinence intervals. Before surgery, the patients underwent inpatient detoxification followed by an abstinence phase of at least 2 weeks. After surgery and start of NAc DBS, the patients did not receive additional psychotherapy or anti-craving medication; however, attending support groups was recommended.
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Table 2. Characteristics of Five Patients Treated with Bilateral High-Frequency NAc-DBS for Severe Alcohol Addiction

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age (years)</th>
<th>Follow-up Time (months)*</th>
<th>Time of Alcohol Intake (years)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>36</td>
<td>48</td>
<td>24</td>
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</tr>
<tr>
<td>5</td>
<td>56</td>
<td>32</td>
<td>18</td>
</tr>
</tbody>
</table>

*Follow-up time is defined as the time from date of surgery until September 31, 2011.

Neuropsychological Tests and Electrophysiology

For a detailed description of the methodology, and of the neurophysiological technique in particular, we refer to a previous publication by our group (23). Summarized, immediately after operation but prior to connection of the stimulation electrodes to the IPG, we registered LFPs from the externalized brain electrodes in patients 1 and 2 while they performed cognitive tasks addressing action monitoring and incentive salience of drug-related cues. In addition, we also obtained surface electroencephalographic activity (Fz, F3, F4, Cz, Pz, P3, and P4 referenced to the right mastoid process).

The action monitoring study was performed in case 1 using a typical flanker task. During rapid presentation of letter strings (HHHHH, SSSSS, HHHHH, SHHSH, SHHSS), the patient had to react by button press on the displayed center letter with either the left hand (for letter S) or the right hand (for letter H). We presented a total of 880 stimuli (350 congruent, duration 100 ms, stimulus onset asynchrony 900–1100 ms) over a period of 20 minutes. Registered were errors for correct trials and the overall error rate; both conditions were differentiated into correct compatible and correct incompatible trials. In addition, we computed posterior slow activity as an index of behavioral adaptation after a performance error (42).

For the incentive salience test, we used a task developed to address visual selection processes in a modified version (25). In one series the patient was presented two colored pictures (targets), which had to be attended by the patient and required a decision ("living" or "non-living" object), and two gray pictures (distracters), and in 50% a contrary condition (e.g., target: "living", distractor: "non-living") was displayed contralateral to the attended target picture, whereas in the other 50% alcohol-related cues were presented (e.g., a bottle of beer, a bar). Importantly, because of special arrangement of the visual stimuli, the task per se made alcohol-related cues irrelevant. In addition, alcohol-related cues were presented outside the patient's attentional focus.

RESULTS

From October 2007 through February 2009, we treated five male patients with NAc-HF DBS for severe alcohol addiction. The median age of the five patients was 44 years (range: 35–65 years). Four of the five patients started drinking at teenage, one subject at the age of 38. Alcohol Dependence Scale scores ranged from 24 to 41. On average, the total time since drinking was 26 years, ranging from 18 to 41 years. The actual follow-up ranges from 31 to 47 months (average: 38 months) if referred to September 30, 2011.

Case Reports

Three of these patients were published in detail by one of the coauthors (U.M.) (47). The two patients (cases 1 and 2) mentioned in this report who have remained abstinent still remain so after more than 4 years and report an ongoing absence of craving for alcohol. Both patients were unemployed before DBS therapy and went back into full-time employment. The follow-up of the third patient is almost identical. Even though he had some episodes of drinking, the overall frequency of relapses and the amount of drinks have reduced on treatment with NAc-DBS. Currently, this patient is serving a jail sentence due to a revoked suspended sentence related to a crime committed before DBS therapy was started. Whereas he did not manage to remain abstinent serving a forensic therapy a couple of years prior to NAc-DBS, now he reports no craving or interest in drinking, although there would have been numerous possibilities to drink in jail.

The scores for Alcohol Dependence Scale, Global Severity Index of the Symptom Check List–90 summary score, Alcohol Urge Questionnaire and the OCDC-G (separated for alcohol-related thoughts and compulsion) of these three patients measured preoperatively and during a 12-month observation period after initiation of NAc-DBS are summarized in Table 3. Unsurprisingly, in case 3, Obsessive-Compulsive Drinking Scale scores did not constantly drop down to zero but increased repeatedly to values ranging from 5 to 10 (drinking thoughts) and from 9 to 15 (drinking behavior) in the context of relapses.

The fourth patient was 51 years old when he underwent surgery for NAc-DBS in December 2008 and had been addicted to alcohol for almost 20 years. Initially, he consumed alcohol on a steady basis (delta alcoholic). However, over time this drinking pattern changed and he increasingly drank heavy amounts at once with loss of control. He underwent numerous detoxification treatments, two long-term inpatient therapies, and one long-term outpatient rehabilitation treatment without permanent success. Reasons for relapses before NAc-DBS were craving for alcohol or personal stress. After initiation of DBS therapy, this patient reported immediate and ongoing absence of craving. After staying abstinent for more than 16 months, he had a few very short relapses over the next 12 months because of personal stress. Approximately 2.5 years after DBS surgery, the patient was suddenly almost lost to follow-up and experienced a prolonged relapse. Fourteen months later, he was referred to our hospital because of generalized seizure. At admission, surgical dressing for several scalp lacerations was necessary. At that time the patient reported that compared to the previous year, the stimulation never reached the effect he had experienced at the beginning of DBS therapy. We, therefore, performed a CT examination with 2-mm slices. Transformation of these images with the treatment planning MRI series showed caudal ventral dislocation of both brain electrodes (10-mm difference compared with postoperative control images). Surgery for replacement of the electrodes was performed. Intraoperatively, we found both brain electrodes tightly fixed in scar tissue, indicating that electrode displacement most probably had occurred quite some time ago. Since this replacement, the patient reports an effect comparable to what he had already experi-
enced during the time of clinically effective NAc-DBS.

The fifth patient was 55 years old when he started his DBS therapy in February 2009. He had been addicted to alcohol for about 20 years. Similar to the fourth patient, he first started drinking on a steady basis; in the years before DBS, he experienced very heavy relapses with loss of control. Withdrawal treatments were sometimes complicated by delirium that required treatment with haloperidol in addition to diazepam. On occasion of the last relapse before we started with NAc-DBS, the patient had to be admitted to the intensive care unit because of coma due to a blood alcohol level of 0.34%. Reasons for relapse before DBS were craving for alcohol or personal stress. Again, following DBS, this patient reported an immediate and ongoing absence of craving. Since initiation of DBS, the patient has had four short relapses of 1–3 days each due to personal stress but remains abstinent otherwise.

Summing up, to our knowledge, the present clinical study is the first attempt to treat alcohol addictive patients with NAc-DBS. All patients included were severely affected. They had taken large amounts of alcohol for a long time and all of them had experienced multiple unsuccessful treatment cycles combining standard medication therapy with psychotherapy prior to DBS treatment. The most significant positive effect of NAc stimulation was complete disappearance of craving, which we collectively observed in the entire cohort. In addition, two of five patients remained completely abstinent for more than 4 years. In the three cases with stress-related relapses, both frequency of the events and the intensity of the relapses were considerably reduced compared with the time before NAc-DBS. Prior to study inclusion, all patients were unemployed or had part-time jobs only, whereas under NAc stimulation, four of the five patients are fully employed now. The fifth patient (case 3) has to serve a sentence for a crime committed before we started DBS therapy.

**Side Effects, IPG Replacement**

In the present small case series, no adverse events related to surgery occurred. High-frequency stimulation of the NAc was tolerated without permanent side effects. Only one patient (case 2) had a transient episode with hypomania when bipolar stimulation was initialized according to the protocol. After readjustment of IPG settings, choosing the most distal contact for monopolar stimulation and concomitantly reducing the stimulation energy (130 Hz, 3.5 V, 90 μs), the symptoms disappeared. Impulse generators were replaced in all four patients, stimulating in the bipolar mode 22–26 months after first surgery, when on occasion of scheduled visits the external control device indicated remaining battery capacity of approximately 10%. Three patients did not notice low battery capacity. One patient reported “inner restlessness” at that time.

**Neuropsychological Tests**

The following summarizes the results of the neuropsychological tests and electrophysiological data obtained from the externalized brain electrodes and surface electroencephalography registration when the patients performed the tests. For details, we refer the reader to our previous publication (23).

**Action Monitoring Study.** Registration of average surface event-related potentials (electrode Cz referenced against mastoid process) and bipolar averaged LFPs obtained time-locked to the erroneous motor response displayed a typical error-related negativity followed by the so-called error-related positivity in the event-related potentials (significant differences, P < 0.005). In the NAc on both sides, similar error-related modulations were seen, which were much more pronounced in the bipolar recordings between the two most distant electrode contacts 0 and 3 than in the recordings between contacts 2 and 3. Activity from both sides was very similar. Cross-correlation analysis comparing depth and surface electrode activity showed that in both hemispheres, error-related negativity obtained from the NAc preceded the surface error-related activity by 39 ms.

**Incentive Salience Task.** When patients 1 and 2 performed the visual selection test, we compared trials with an alcohol-related or neutral distracter stimulus on the side contralateral to the target stimulus. In LFPs recorded from the left NAc (bipolar recording between electrode contacts 0 and 3), we registered a rather early difference between waveforms obtained to stimulus arrays with a neutral distracter and those with an alcohol-related distracter. The emergence of the registered waves was statistically signifi-

**Table 3. Patient Scores of the Alcohol Dependence Scale, Global Severity Index of the Symptom-Checklist-90, Alcohol Urge Questionnaire, and Obsessive-Compulsive Drinking Scale–German version Separated for Alcohol-Related Thoughts and Drinking Behavior**

<table>
<thead>
<tr>
<th>Case Number</th>
<th>ADS Preoperation</th>
<th>ADS Preoperation 6-month</th>
<th>ADS Preoperation 12-month</th>
<th>AUQ Preoperation</th>
<th>AUQ Preoperation 6-month</th>
<th>AUQ Preoperation 12-month</th>
<th>OCDS-G Preoperation</th>
<th>OCDS-G Preoperation 6-month</th>
<th>OCDS-G Preoperation 12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>68</td>
<td>52</td>
<td>56</td>
<td>29</td>
<td>8</td>
<td>6</td>
<td>11/18</td>
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<td>62</td>
<td>33</td>
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<td>18/19</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37</td>
<td>10</td>
<td>8</td>
<td>11/20</td>
<td>(0)*</td>
</tr>
</tbody>
</table>

Values were obtained preoperatively and 6 and 12 months after initiation of NAc-DBS.

ADS, Alcohol Dependence Scale; GSI, Global Severity Index; SCL-90, Symptom-Checklist-90; AUQ, Alcohol Urge Questionnaire; OCDS-G, Obsessive-Compulsive Drinking Scale–German version; NA, not assessed.

*OCDS scores dropped down to zero but periodically increased to values ranging from 5 to 10 (drinking thoughts) and from 9 to 15 (drinking behavior) in context of relapses.
cant. LFPs obtained from the right NAc, however, did not show reliable differences between the two conditions in this task.

**DISCUSSION**

**Development of Alcohol Addiction**

Addiction is the continued use of a mood-altering substance or behavior despite adverse consequences, or a neurologic impairment leading to such behaviors (5). Older theories explaining the development of addiction, however, focused only on mechanisms related to the acute impact of a drug on neural networks. Pleasurable effects after drug consumption are considered to drive mainly the desire for repeated reward. Furthermore, frequent drug consumption stimulates tolerance development, which decreases the reinforcing properties of a substance and bears the risk for increases in dosage. Besides positive reinforcement, negative reinforcement mechanisms also are involved. In negative reinforcement, acute or prolonged withdrawal symptoms, such as the emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when intake of a drug is prevented, result in continued use as a means to avoid the aversive consequences of drug withdrawal (13, 35).

Reinforcement or conditioning theories are considered to provide explanations for the initiation and maintenance of compulsive drug use but are insufficient to fully explain relapses. Relapses, the most problematic aspect of drug addiction, can occur even after long periods of abstinence or even if the individual has the strong will to abstain. More recently presented theories proposed a concept of disequilibrium in the brain’s reward system in consequence of several neuroadaptation steps initiated by prolonged drug use. One conceptualization of motivational changes associated with addiction is the “incentive sensitization” theory brought forward by Robinson and Berridge (51). They hypothesized that drugs utilize systems in the brain that are normally involved with incentive motivation and reward for natural appetitive reinforcers, directing individuals or animals to stimuli with salience for preservation of the species. Enduring hypersensitivity not only to the drug itself but also to drug-associated stimuli (cues) leads to a shift from “drug liking” (the hedonic aspect of drug consumption) to “drug wanting,” with prolonged compulsive drug-seeking patterns (51).

Other theories focusing on particular aspects of drug-induced neuroadaptations with less or more overlap between the different perspectives address primarily the following: (a) formation of ingrained drug habits as a consequence of aberrant stimulus response learning (12, 59, 61); (b) alterations in prefrontal cortical (PFC) activity, leading to reduction in behavioral control and decision-making skills (15, 16, 29); and (c) overlaps between limbic and cortical areas involved in addiction and memory (27), which cause maladaptive associative learning (11).

Emanating from a conceptualization that drug addiction has aspects of both (a) impulse control disorders, which are largely associated with positive reinforcement, and (b) compulsive disorders, which can be related to negative reinforcement mechanisms and automaticity, Koob proposed an addiction cycle composed of three stages: the “binge/intoxication stage,” the “withdrawal/negative affect stage,” and the “preoccupation/anticipation stage.” These three stages interact with each other, become more intense, and finally lead to the pathological state known as addiction (32, 33). In a comprehensive review, Koob and Volkow (35) focused on the brain neurocircuitry engaged at each of the above-mentioned states, as well as on changes within and on interactions among their single parts as a consequence of drug abuse. The most vulnerable structure in the “binge/intoxication state” is the ventral tegmental area (VTA) and the mesolimbic dopaminergic system. The authors stated that most dopamine-mediated reinforcement occurs at the level of the NAc because this brain region has multiple inputs from other brain structures, which are also critically involved in reinforcement such as the central nucleus of the amygdala (CeA) and the ventral pallidum. With some delay, the interaction between ventral striatum (VS), dorsal striatum (DS), and the thalamus will lead to the development of compulsive drug-seeking behavior (35).

**Mechanisms**

The NAc has two morphologically distinct subunits, shell and core, which are distinguished by differential expression of neuroptides and synaptic afferent inputs (45).

In rodents, these anatomical subunits display functional differences also. The core is suggested to be involved in guiding behavior toward a specific goal based on learning; the shell seems to be crucial for unconditioned reward-seeking behaviors (68). Stimulation of either the NAc shell or core region in the normal brain of rodents can elicit different effects. In Wistar rats, for instance, high-frequency NAc-DBS of the accumbens core prevented the induction of long-term potentiation in the dentate gyrus of the hippocampus, and stimulation of the accumbens shell increased the magnitude of long-term potentiation induction—demonstrating opposing effects on this plastic phenomenon (39).

In contrast with rodents, the shell area has regressed in the primate and is no longer clearly distinguishable, except for the fact that it carries the typical receptors (D1–D3 dopamine receptors, opiate receptors, receptors for a multitude of bioactive proteins and peptides). It is supposed that in the primate and the human brain, the shell and core function together in a kind of concerted action rather than independently from each other, as elaborated in Sturm et al. (54).

Analysis of NAc function, which together with the olfactory tubercle and the islands of Calleja represents the ventral subregion of the striatum, revealed that this region is a pivotal center within brain systems regulating motivation and reward. Reward is suggested to be an important mechanism for the development of addictive behavior (34). Substances of abuse such as alcohol occupy the brain networks belonging to the brain reward system represented by two main neuro-chemical pathways, the mesocortical and the mesolimbic pathway, the latter extending from the ventral tegmental area of the midbrain via the medial forebrain bundle to the NAc. Natural rewards, but also most drugs with addiction potential including alcohol, lead to increased extracellular dopamine concentration in the NAc. In contrast to natural rewards, however, dopamine activity does not adapt or habituate to repeated drug exposure (62). Moreover, repeated drug exposure induces sensitization of dopamine transmission in the NAc (50). By these mechanisms, substances with addictive potential can become a powerful rewarding, discriminative, and reinforcing stimulus (35). Because of its functional and anatomical position, the NAc has a central
position within the brain areas and neurocircuits involved in the development of addiction such as VTA, lateral hypothalamus, VS and DS, amygdala, hippocampus, and prefrontal/cingular cortex. Thus, electrical stimulation of this target may give the opportunity to modulate or correct neuroadaptive changes caused by substance abuse.

McCracken and Grace investigating the effect of electrical stimulation of the NAc in the normal rat brain demonstrated that HF NAc-DBS suppressed pyramidal cell firing and enhanced slow LFP oscillations in the orbitofrontal cortex via antidromic activation of corticostriatal recurrent inhibition (43). Data from another study of these authors recording simultaneously LFPs from multiple sites in the rat brain, suggesting that HF NAc-DBS, which is considered to be therapeutically active, and low-frequency NAc-DBS, which is regarded as a possible delterious stimulation pattern, produce distinct region-specific and frequency band-specific changes in LFP oscillations. High-frequency NAc-DBS, for instance, selectively affected spontaneous and evoked LFP oscillatory power and coherence within and between the medial PFC (mpFC), lateral orbitofrontal cortex, mediodorsal thalamus, and NAc. The authors concluded that NAc-DBS might achieve therapeutic effects by enhancing rhythmicity and synchronous inhibition within and between afferent structures, thereby normalizing the function of a neural circuit that has aberrant disease-specific activity (44).

Two animal studies provided evidence that electrical manipulation of the NAc can specifically improve behavior associated with addiction, such as uncontrolled drug intake, craving, and relapse. Knapp et al. (31) used an in vivo self-administration model for their investigation. Rats with free access to either water or a 10% ethanol-water solution that developed stable alcohol consumption within 5 to 7 weeks were then treated with daily HE DBS applied either in the NAc shell or the NAc core for 5 minutes reduced alcohol intake significantly. This stimulation effect was independent of the stimulation site, shell or core, and did not impair the consumption of water (31). Vassoler et al. (55) demonstrated in rats that electrical stimulation with 160 Hz in the NAc shell attenuated significantly the reinstatement of drug seeking precipitated by higher cocaine doses but did not affect the reinstatement of food seeking. However, stimulation of the DS did not change cocaine reinstatement. Thus, the authors concluded that the observed NAC-DBS effect was both anatomically and reinforcer specific.

**Clinical Data**

One disadvantage of the present pilot study is that the patients were treated with a nonblinded stimulation protocol. The reason for this practice was the off-label use of DBS basing on individual case-by-case decisions. However, the long follow-up of the patients treated so far with ongoing complete response referred to craving can be seen as one argument against a significant placebo effect. In addition, the postoperative course of case 4 who experienced deterioration of a previously good treatment effect in context with displacement of the brain electrodes can be interpreted as an involuntary treatment-free interval and as another argument against a bias due to placebo effects.

By contrast, Zhou et al. (66) reported a patient treated successfully with bilateral NAC-DBS for heroin addiction, who remained abstinent for another 3.5 years even when the stimulator was removed at the request of the patient and his family after 2.5 years of continuous stimulation (145 Hz, 90 μA, 2.5 V). The brain electrodes were stereotactically placed using coordinates comparable to the presented alcohol study, except for the anterior distance to the AC (7.5 mm instead of 2.5 mm) (66).

In addition, bilateral ablation of the NAc performed by Wu et al. in an uncontrolled, prospective open-label study in 12 patients was effective to treat alcohol addiction. These patients had consumed alcohol for a mean time of 15 years (6–27 years) and were dependent of alcohol for a mean time of >6 years (range: 3–10 years). Nine of 12 patients (75%) with a follow-up of >6 months did not relapse and did not consume alcohol at all. In the remaining three cases, relapses occurred. Bilateral ablation of the NAc caused only transient side effects (hypomia) in one case (65). Taking into consideration the central position of the NAc in a network integrating contextual information from the hippocampus, emotional information from the amygdala, with cognitive information from the PFC in selection of goal-directed behaviors (19), this low number of side effects after destruction of both nuclei is surprising.

In two patients treated in the present study, we registered simultaneously LFPs from the target area and surface electroencephalography while they performed neuropsychological tasks. The flanker task chosen for the action-monitoring study presents incongruent flanker letters, which give rise for a high number of performance errors. In these experiments, erroneous but not correct button presses lead to a characteristic negativity of event-related potentials, the so-called error-related negativity generated in the anterior cingulated cortex.

The comparison of signals recorded from depth and surface electrode activity showed that in both hemispheres, error-related negativity obtained from the NAc preceded the surface error-related activity. Same results were already registered by one coauthor (T.M.) in a patient treated with unilateral NAC-DBS for obsessive-compulsive disorder (48). Taken together, we interpreted these data as confirmation of the hypothesis that the NAc is involved in the generation of a signal triggered by error-mediated dopamine release from midbrain dopaminergic neurons projecting to the NAc and being part of a human action monitoring system. Given that the NAc may weight information coming from limbic and prefrontal regions in order to shape goal-directed behaviors and taking into consideration that action motoring has conceptually been linked to reinforcement learning, malfunction of this nucleus can significantly drive the development of compulsive drug seeking, which is a hallmark of addictive behavior (13). On the other side, it is comprehensible that electrical stimulation of this brain area can substantially counterbalance neuroadaptations caused by long-lasting drug abuse.

One motivation for the incentive salience study in the present patients was the incentive sensitization theory of addiction formulated by Berridge and Robinson (7, 51). In essence, following alcohol or drug intake, the mesolimbic reward system is activated leading to dopamine release in the VS and NAc. Comparable to the mechanisms involved in reward prediction in animals, NAc dopamine release attributes “incentive salience” to drug-associated cues. This cue-induced dopamine release then can mediate “wanting” of substances with addictive po-

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tential. Drug-related stimuli might also induce craving in addicted patients, triggering drug-seeking behavior.

In the past years, several investigators used positron emission tomography or functional MRI (fMRI) to study noninvasively specific cue-related activation of brain areas, in particular, of those structures belonging to the brain’s reward system such as VTA or NAc and of anatomical units connected with the reward system (e.g., DS, thalamus, PFC) (17, 58).

Kareken et al. used blood oxygen level–dependent fMRI to display the response to alcohol-related olfactory stimuli (odors of beer and whiskey) and non-alcohol-related olfactory stimuli (odors of grass and leather) in 10 high-risk drinkers and five low-risk (control group) drinkers. In the high-risk group, the difference between the blood oxygen level–dependent signal in response to alcohol-related olfactory stimuli compared to that obtained for non-alcohol-related olfactory stimuli was significantly greater in the NAc but also in some voxels registered from the VTA. The authors concluded that alcohol-related olfactory stimuli might activate the dopamine mesocorticolimbic system to a greater degree than non-alcohol-related olfactory stimuli (30). Also active cocaine abusers responded to conditioned, cocaine-related cues. When exposed to videos depicting cocaine scenes of individuals procuring and administering cocaine, test subjects exhibited significant dopamine increases in the DS but not in the VS where the NAc is located (59). The discrepancy in the expected response of the VS and the activation instead of the DS can be interpreted as reflecting the intensification of habits with increasing chronicity of addiction.

Interestingly, positron emission tomographic imaging studies indicated that after detoxification, overall dopaminergic neurotransmission in the VS of alcohol-dependent patients is reduced. In particular, reduction of availability and sensitivity of central dopamine D2 receptors was associated with the subsequent relapse risk in these patients. Also alcohol craving correlated specifically with both low dopamine synthesis capacity and reduced dopamine D2-receptor availability in the VS including the NAc (21, 22). Even though speculative, it can be assumed that in an advanced stage of addiction, the presentation of drug-associated cues can still cause dopamine release that triggers reward craving or relapse, but that, however, other brain areas are more activated than the NAc itself. Animal studies, for instance, demonstrated that the presentation of alcohol and drug-associated cues can lead to relapse even if no dopamine is released in the VS (52).

Besides the reward system, the PFC also is activated in response to the presentation of drug-related cues (see overview in Goldstein und Volkow [16]). Comparable to the blood oxygen level–dependent effect registered for the NAc, the pure taste of alcohol (vs. litchi juice) increased activity in the PFC of young drinkers also. This result can be considered a specific response because it correlated with alcohol craving (14). By contrast, in non-dependent alcohol drinkers, alcohol administration reduced cue-related activity in the orbitofrontal cortex. In addition, dopamine dysfunction was correlated not only with the severity of alcohol craving but also with increased processing of alcohol-associated cues in the anterior cingulate and medial PFC (22)—brain areas in which an increased processing of alcohol cues has been associated with an increased relapse risk (20).

In the actual study, we presented neutral and alcohol-related images or cues outside the visual field attended by the patients. In LFPs recorded from the left NAc (bipolar recording between electrode contact o–3) we found a difference between waveforms obtained to stimulus arrays with a neutral distracter and those with an alcohol-related distracter. In the right NAc, however, we did not observe reliable differences between the two conditions. Seen in the context of the relationship between dopamine release in the NAc and increased attribution of “incentive salience” to drug-associated stimuli, increasing motivational value and attentional processing of drug-related cues on the one side and dopamine-mediated shift from drug “liking” to drug “wanting” on the other side, we interpreted these unilateral LFP changes in our two patients as surrogate for cue-induced dopamine-dependent NAc activity. The alcohol-related cues were able to drive NAc activity even when presented outside the attentional focus, which suggests that these cues are processed in a highly automatic fashion, thus being uncontrollable for the affected person. Given the long-range influence of DBS on neural networks and its ability to significantly modify signal transmission, it seems feasible that high-frequency DBS has the ability to improve dysfunction not only at the stimulation site but also in projection areas of the NAc such as the PFC.

Future Directions

Data from in vivo investigations, single case reports, as well as from small case series studies provide evidence that modification of the NAc function can remarkably improve addiction behavior. However, to date the results from clinical application of DBS are very preliminary. Therefore, the first goal of future studies should be to corroborate the observed improvement also in prospective studies using randomized, double-blind, and crossover stimulation protocols for DBS. This point is considered in two projects, conceptualized and actually started by members of our group. The German Research Foundation funds both research projects aimed at treating patients with NAc-DBS for alcohol addiction.

Although one project (principal investigator: B.B.) is a multicentric clinical study, the other combines clinical and complementary in vivo investigations (principal investigators: H.-J.H., J. V.). In addition to the outcome measures of relapse and abstinence, the second project in its clinical part will concentrate primarily on the detailed assessment of possible cognitive impairments caused by NAc-DBS, in particular in the long term.

The central anatomical position of the NAc, which is located close to several other functionally relevant structures such as the bed nucleus of the stria terminalis, the medial forebrain bundle, or the vertical limb of Broca’s diagonal band (40), and the pivotal functional role of the NAc as a motor limbic interface (46) does not only give rise to concerns related to possible cognitive impairment caused by DBS but also raises the question as to which anatomical units in the surrounding of the stimulation site have to be electrically affected in addition to the NAc to achieve maximum clinical improvement in addictive patients.

The stimulation pattern required to achieve clinical improvement, in particular, with reference to the stimulation frequency, is not adequately defined to date. Patients treated for primary generalized dystonia...
with pallidal DBS, for instance, are routinely stimulated with 130 Hz or higher frequencies, which is comparable to the IPG adjustment used in alcohol-addicted patients. However, there are a few reports from patients with dystonia indicating that probably frequencies around 60 Hz are quite sufficient to gain the same clinical benefit as achieved with higher stimulation frequencies (28), which may also be valid for DBS in addiction treatment.

Another central question that should be addressed in the future is whether the NAc represents a universal site for DBS treatment of addiction or if different types of substance dependence require different stimulation targets. Besides clinical observations, the results from positron emission tomographic imaging recording activation patterns in response to the substance of abuse or drug-related stimuli with the patient’s on and off stimulation could be an important source for information to further clarify this point. Table 2.

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