Safety and feasibility of nucleus accumbens stimulation in five patients with epilepsy

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Abstract In five adult patients with intractable partial epilepsy, safety and feasibility of chronic bilateral electrical stimulation of the nucleus accumbens (NAC) were assessed, also providing initial indications of therapeutic efficacy. Concurrent medication remained unchanged. In this phase 1 trial, clinical outcome parameters of interest were Quality of Life in Epilepsy questionnaire (QOLIE-31-P), Beck Depression Inventory, Mini International Neuropsychiatric Interview, neuropsychological testing, and Liverpool Seizure Severity Scale. Those data were obtained after 6 months of NAC stimulation and compared to the equivalent assessments made directly before implantation of electrodes. Additionally, monthly frequencies of simple partial seizures, complex partial seizures (CPS), and generalised tonic–clonic seizures (GTCS) were assessed during 3 months before electrode implantation and at the end of 6-month NAC stimulation. Proportion of responders, i.e. ≥50 % reduction in frequency of disabling seizures (sum of CPS and GTCS), was calculated. Main findings were unchanged psychiatric and neuropsychological assessment and a significant decrease in seizure severity (p = 0.043). QOLIE-31-P total score trended towards improvement (p = 0.068). Two out of five participants were responders. The median reduction in frequency of disabling seizures was 37.5 %. In summary, we provide initial evidence for safety and feasibility of chronic electrical stimulation of the NAC in patients with intractable partial epilepsy, as indicated by largely unchanged neurocognitive function and psychiatric comorbidity. Even though our data are under-powered to reliably assess efficacy, the significant decrease in seizure severity provides an initial indication of antiepileptic efficacy of NAC stimulation. This calls for larger and at best randomised trials to further elucidate efficacy of NAC stimulation in patients with pharmacologically intractable epilepsy.

Keywords Deep brain stimulation · Neuropsychology · Psychiatry · Quality of life · Seizure frequency · Seizure severity

Introduction

In patients with intractable partial epilepsies, optimal adjustment of antiepileptic drugs (AED) fails to improve seizure frequency in at least 65 % of patients [1]. Presurgical evaluation of these patients leaves a substantial proportion of an estimated 40 % unreaesected [2], either due to ineligibility for surgery or because patients decide against this non-reversible but potentially curative procedure [3]. This difficult-to-treat patient group needs alternative treatment options. In the last decade, deep brain stimulation (DBS) has received increasing interest as a therapeutic option for these patients [4, 5]. Even though DBS is reversible and verifiably safe [6], so far this procedure has not been broadly used for intractable epilepsy. This may be partly due to the fact that—in contrast to most
resective treatment strategies—DBS is not a causative treatment approach and rarely results in seizure freedom [7]. Also, in patients treated with DBS for indications other than epilepsy, cognitive [8, 9], psychiatric [8, 10, 11], or behavioural side effects [12, 13] have been known for decades and might overshadow a differential view on this new treatment strategy for particular epilepsy patients.

Recently, a randomised controlled clinical trial demonstrated efficacy of electrical stimulation of the anterior nucleus of the thalamus (ANT) in terms of seizure frequency reduction [14]. In particular, patients with temporal lobe epilepsy appear to benefit from ANT stimulation [14, 15]. However, depression and memory impairments were significantly increased in patients with ANT stimulation [14]. Another single-blind trial evaluated the antictal efficacy of centromedian thalamic (CMT) nucleus DBS [16]. The authors found no relevant effect in terms of seizure frequency reduction in patients with frontal lobe epilepsy, whereas in patients with generalised epilepsy, mean reduction in seizure frequency was 77 %. Other targets, such as the Ncl. subthalamicus have been discussed as possibly effective in small uncontrolled trials [17–19]. Recently, this target has been chosen for distinct epilepsy syndromes, such as progressive myoclonus epilepsy [18] and epilepsy due to ring chromosome 20 [20].

To identify and characterise new DBS targets for patients with difficult-to-treat epilepsy, we assessed safety and indications of chronic bilateral stimulation of the nucleus accumbens (NAC).

This structure plays a decisive role in both functional and anatomical connectivity between frontal and temporal lobes [21, 22]. In rodent models of generalised [23, 24] and both temporal [25–28] and frontal lobe seizures [29], the NAC has been shown to be involved in propagation of epileptic activity. Furthermore, NAC stimulation has been demonstrated to elicit euphoria in psychiatrically unaffected patients [30] and to ameliorate symptoms in patients with major depression [31]. Patients with epilepsy are at high risk for comorbid depression [32] and common network characteristics for both disorders have been proposed [32, 33].

In the following, we report clinical outcome of NAC stimulation in five patients with intractable partial epilepsy following an in-house protocol. We assessed the effect of electrical stimulation on quality of life, psychiatric and neuropsychological parameters, and additionally on severity and frequency of disabling seizures.

Methods

In-house protocol for deep brain stimulation

Five patients with medically intractable partial epilepsy (defined as failure of at least two AEDs in adequate doses to produce seizure freedom for at least 12 months [34]) became part of our in-house protocol for bilateral DBS of the NAC between January 2010 and December 2012. All patients first underwent comprehensive assessment for potential resective epilepsy surgery. Resection or advised invasive EEG monitoring was refused by the patients, or resection was not advisable at all or had been ineffective. Subsequently, patients were only offered DBS surgery if they had an average frequency of at least one disabling seizure per month (complex partial seizure [CPS], and/or generalised tonic–clonic seizure [GTCS]). Patients were not offered DBS if they suffered from progressive neurodegenerative disorders or had additional non-epileptic seizures, if IQ was lower than 70, if they were pregnant, or if they were currently treated with vagus nerve stimulation.

As chronic stimulation of the vagus nerve and of the ANT has been shown to be efficacious in large-scale controlled trials [14, 35], all patients with intractable and non-resectable partial epilepsy were subsequently offered these widely accepted minimally invasive surgery options and our in-house protocol for NAC stimulation (details see below). The five patients reported here took part in pre-operation interviews, in which all eligible patients were informed about different levels of evidence concerning safety and efficacy, current legal status of approval, and the extent of invasiveness of each surgical procedure. The possible risk of any surgical intervention led ten eligible patients to decide against any optional minimally invasive procedure. Two patients opted for VNS because the surgical intervention does not involve the brain, and another two patients decided for DBS of the ANT because of the greater evidence for efficacy. According to our pre-interventional discussions with patients, those who elected to undergo DBS felt that the risk of invasive surgery was outweighed by the possible benefit of direct effects on deep brain structures, as opposed to an indirect influence via a cranial nerve.

Outcome parameters of interest were mean change in patient-reported outcome questionnaires including Liverpool Seizure Severity Scale (LSSS) [36], Beck Depression Inventory (BDI-IA) [37], Quality of Life in Epilepsy Questionnaire (QOLIE-31-P) [38], and a standardised psychiatric interview employing Mini International Neuropsychiatric Interview (MINI) [39], as well as a neuropsychological test battery. The latter covered in detail the areas of attentional performance [test of attentional performance (TAP 2.2)], cognitive speed [trail making test (TMT)], performance evaluation system subtest 7 (LPS, i.e. Leistungsprüfungs-system, subtest 7), d2–attention stress test], executive function [“Regensburger” word fluency test (RWT), Hamasch 5-point test (HSPT)], memory and learning functions [verbal learn and memory test (VLMT), Wechsler Memory Scale-Revised (WMS-R)], and word...
retrieval (Boston naming test). All parameters were pre-
operatively assessed and compared to the results at the end
of 6-month NAC stimulation. We also assessed the pro-
portion of responders (\( \geq 50\% \) seizure frequency reduction)
comparing the mean frequency of disabling seizures sur-
veyed in the 3 months prior to electrode implantation to the
data after 6 months of NAC stimulation. AEDs remained
unchanged 3 months before electrode implantation and
during 6 months of follow-up.

Surgery

Implantation of DBS systems was performed under general
anaesthesia. Using standardised stereotactic technique, four
Medtronic Model 3387 DBS leads (Medtronic\textsuperscript{\textregistered}, Minne-
apolis, MN, USA) were implanted bilaterally into the NAC
and ANT and subsequently connected to a single impulse
generator (IPG; Activa-PC, Medtronic\textsuperscript{\textregistered}, MA, USA). We
defined the NAC 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 mid-sagittal plane,
3–4 mm ventral and 6–8 mm lateral of the midline [40]. In
addition, we modified the atlas coordinates according to the
individual treatment planning-MRI displaying on coronal
reconstructions of a 3D-MPRAGE series (3 T scanner,
0.8 mm\(^3\) resolution) the medial border (vertical limb of
Broca’s diagonal band) and the ventral border (olfactory
tubercle/horizontal limb of Broca’s diagonal band) of the
NAC region (Fig. 1). The angulation of the trajectory rel-
ative to the intercommissural line was chosen to cover with
two electrode contacts the central/lateral part (NAC core)
and the medial part (NAC shell) [40, 41]. ANT targeting
was also guided by atlas-based coordinates (Schaltenbrand
and Wahren, 6 mm lateral to, 8 mm anterior to and 12 mm
above the midcommisural point) and direct visualisation of
this nucleus on 3D-MPRAGE images [42]. The electrode
localisation was documented intraoperatively by stereo-
tactic X-ray imaging using X-ray tubes installed in the OR
and by postoperative CT examinations. CT as well as X-ray
images were fused with the planning-MRI (Fig. 1).

Following surgery, NAC stimulation was initiated after
mean 20.4 days (\( \pm 10.5 \)) and continued for 6 months
(125 Hz, 5 V, 90 \( \mu \)s, 1 min on, 5 min off). Voltage
reduction in 2 V steps was allowed in case of unexpected
events such as pending series of disabling seizures, status
epilepticus, or severe cognitive or psychiatric impairments.
Additional ANT electrode implantation was chosen to
allow for alternative chronic stimulation of the ANT in
case of ineffective NAC stimulation (but in all five
patients, ANT stimulation has not been used). Chronic
stimulation of the ANT has been shown to be effective
regarding frequency of CPS and severely impairing sei-
zures [14]. The Institutional Review Board of the Univer-
sity of Magdeburg approved the surgical procedure
(registration number 03/08). All patients granted written
informed consent for implantation of the neurostimulation
system.

Statistics

Due to interindividual heterogeneity, scores of neurocog-
nitive testing at the end of the NAC stimulation period
were related to values collected prior to electrode
implantation and expressed as fractions of one. After
testing for Gaussian distribution (Kolmogorov–Smirnov test), which was negative for all parameters, the Wilcoxon rank sum test was used for comparison of ordinal data. Categorial data were tested with Fisher’s exact test. \( P \lt 0.05 \) (two-sided) were considered statistically significant.

**Results**

Five patients (2 females), 30–53 years old (mean, 41.6 ± 10.6 years), were diagnosed with epilepsy 17–32 years (mean 23.6 ± 7.3 years) prior to DBS surgery. Clinical details are summarised in Table 1. Presurgical video-EEG evaluation revealed seizure onset zones in left mesio-temporal (2 patients), bilateral mesio-temporal, left fronto-temporal or bilateral frontal (each 1 patient) structures. Only one patient with left mesio-temporal epilepsy had undergone prior resective surgery (anterior temporal lobectomy due to hippocampal sclerosis, no seizure freedom), all other patients had non-lesional 1.5 or 3.0 T MRI. At time of electrode implantation, patients were administered 2–4 (mean 2.6) AEDs.

Regarding seizure severity, the LSSS was significantly reduced after 6 months of NAC stimulation as compared to scores prior to implantation of electrodes \( (p = 0.043) \). The QOLIE-31-P total score as well as its subscales “seizure worry” and “overall” improved only by trend (both \( p = 0.068 \)). Neuropsychological testing, the MINI and the BDI-IA did not show significant differences after NAC stimulation in comparison to examinations before electrode implantation (Table 2). Two out of five patients were responders with \( \geq 50\% \) frequency reduction of disabling seizures (patient #3, 50 %, and patient #4, 85.4 % reduction). Both responders’ and non-responders’ distal contacts were inside the target zone, as postoperative CT as well as X-ray images fused with the planning-MRI have revealed.

Overall, we found a median reduction of disabling seizure frequency of 37.5 %, but no significant changes in the mean frequencies of simple partial seizures (SPS), CPS and GTCS (Table 2). The time course of mean frequency of SPS, CPS and GTCS is depicted in Fig. 2.

BDI-IA and/or MINI revealed depressive symptoms in three patients (#3, #4, #5) prior to electrode implantation. Following NAC stimulation, depressive symptoms resolved in one of them (patient #4). Patients #1 and #2 did not have depressive symptoms before surgery and at the end of NAC stimulation. With regard to other psychiatric entities assessed by MINI, patients #3 and #5 had new onset generalised anxiety disorder after 6-month NAC stimulation. However, only patient #5 had an increase in the total number of psychiatric conditions (from 0 to 2 [generalised anxiety and major depression]). In this patient, stimulation voltage had to be reduced as a precaution from 5 to 3 V in accordance with our in-house protocol due to abrupt increase in seizure frequency.

**Discussion**

In five patients with intractable partial epilepsy, clinical consequences of 6-month NAC stimulation were comprehensively assessed including quality of life, and psychiatric and neuropsychological signs or symptoms, and seizure severity. The main finding was a lack of deterioration of neuropsychological parameters or psychiatric conditions, and overall reduction in subjectively perceived seizure severity. Concerning seizure frequency, our small cohort revealed a median frequency reduction of disabling seizures of 37.5 %, two out of five patients experienced a
seizure reduction of at least 50%. Looking at the time course of seizure frequency postsurgically, there was a decrease before stimulation was initiated (Fig. 2). This is similar to the observation by Fisher et al. [14] and Hodaie et al. [42] after insertion of electrodes for ANT stimulation, and has also been reported by Valentin et al. [16] after electrode implantation into CMT. Whether this pre-stimulation decrease in seizure frequency suggests a short-term placebo effect or a microlesional effect by electrode implantation is still a matter of discussion.

The SANTE (stimulation of the anterior nuclei of thalamus for epilepsy) trial, so far the only large-scale randomised controlled DBS study in epilepsy, showed that ANT stimulation results in significant seizure frequency reduction after 3 months [14]. Complementary to the 110 patients reported in SANTE, our five patients showed significantly reduced seizure severity after 6 months of NAC stimulation in spite of an overall unchanged mean seizure frequency. The non-significant decrease in frequency of GTCS and increase of CPS might be an explanation for this significant reduction in

| Table 2 Clinical outcome after six months of NAC stimulation |
|-------------------------------------------------------------|
| Prior to electrode implantation | After NAC stimulation | Wilcoxon test | Fisher’s exact test |
|-------------------------|-----------------|---------------|------------------|
| Patients reported outcome questionnaires (mean ± SD) |
| LSSS | 59.00 ± 3.67 | 49.60 ± 8.41 | **0.043** |
| BDI-1A | 10.80 ± 7.46 | 6.60 ± 6.07 | 0.104 |
| QOLIE-31-P-total score | 45.87 ± 09.82 | 50.72 ± 08.32 | 0.068 |
| Subscale “energy” | 23.75 ± 20.67 | 14.69 ± 03.87 | 0.581 |
| Subscale “mood” | 25.25 ± 12.02 | 31.90 ± 31.05 | 1.000 |
| Subscale “daily activities” | 13.60 ± 15.16 | 30.00 ± 31.74 | 0.144 |
| Subscale “cognition” | 16.38 ± 13.88 | 26.71 ± 23.14 | 0.465 |
| Subscale “medication effects” | 34.17 ± 36.27 | 38.17 ± 16.30 | 0.465 |
| Subscale “seizure worry” | 04.85 ± 03.52 | 19.30 ± 14.60 | 0.068 |
| Subscale “overall” | 20.00 ± 17.80 | 30.06 ± 14.27 | 0.068 |

Neuropsychiatric interview—MINI (number of participants)

| Major depression | 2/5 | 1/5 | 1.000 |
| Suicidal tendency | 1/5 | 1/5 | 1.000 |
| Mania | 0/5 | 0/5 | n.c. |
| Panic disturbance | 1/5 | 0/5 | 1.000 |
| Agoraphobia | 0/5 | 0/5 | n.c. |
| Social phobia | 0/5 | 0/5 | n.c. |
| Obsessive–compulsive disorder | 0/5 | 0/5 | n.c. |
| Substance addiction | 0/5 | 0/5 | n.c. |
| Psychosis | 0/5 | 0/5 | n.c. |
| Generalised anxiety disorder | 0/5 | 2/5 | 0.444 |

Neurocognitiond | 1 | 1.06 ± 0.18 | 0.225 |
| Attentional performance | 1 | 1.08 ± 0.18 | 0.465 |
| Cognitive speed | 1 | 0.97 ± 0.05 | 0.225 |
| Executive functions | 1 | 1.29 ± 0.47 | 0.255 |
| Memory and learning function | 1 | 0.95 ± 0.30 | 0.500 |
| Word retrieval | 1 | 1.03 ± 0.04 | 0.258 |

Frequency of seizure types in 28-day periods (mean ± SD)

| SPS | 0.27 ± 0.37 | 0.50 ± 0.87 | 0.593 |
| CPSb | 1.27 ± 1.64 | 2.20 ± 4.01 | 1.000 |
| GTCS | 2.27 ± 3.23 | 1.40 ± 1.04 | 0.893 |
| Disabling seizures | 3.53 ± 2.79 | 3.60 ± 4.93 | 0.893 |

*SD standard deviation, n.c not calculated, NAC nucleus accumbens, SPS simple partial seizure, CPS complex partial seizure, GTCS generalised tonic–clonic seizure, LSSS Liverpool Seizure Severity Score, BDI-1A Beck Depression Inventory, version IA, QOLIE-31-P Quality of Life in Epilepsy, M.I.N.I Mini International Neuropsychiatric Interview
*3 out of 5 patients with SPS
*b3/7 CPS
*c All experienced GTCS
*d Due to interindividual heterogeneity, results of neurocognitive testing after NAC stimulation were related to the individual values prior to electrode implantation and expressed as fractions of 1 (±SD)
seizure severity. The trend to less GTCS may also be reflected by the decrease in “seizure worry” score in the quality-of-life assessment. Also, the item “seizure worry” correlated with seizure severity, as found in other studies [43]. Thus, we tend to interpret the non-significant trend to reduction in “seizure severity” as plausible. The lack of statistical significance with regard to improvement of this item and the summarised quality-of-life score is likely due to the small number of patients. Similar to our study, Valentin et al. comprehensively assessed the effect of DBS of the CMT nucleus in a small number of patients (n = 11; frontal lobe and generalised epilepsies) [16]. In seven of their patients, seizure severity score and quality of life assessments were available. Compared to the results before implantation, a significant improvement both in seizure severity and QOLIE-32-P total score was noted after 3 months of CM stimulation. Thus, they found that quality-of-life score improves parallel to reduction of seizure severity score. This correlation has already been validated in large cohorts and seems to be independent from seizure frequency [43–45].

NAC stimulation has been shown to ameliorate symptoms in patients with major depression [31, 46]. Our standardised psychiatric evaluation by MINI revealed no significant change in our cohort. However, one patient benefited from NAC stimulation concerning depressive symptoms. It cannot be determined whether this observation is seizure- or target-dependent, because this patient (#4) was a responder with an 85.4 % reduction in seizure frequency. Worsening of cognition and depressive symptoms as reported due to ANT stimulation in the SANTE trial, however, are probably target-dependent. Even though seizure frequency declined after ANT stimulation, patients complained significantly more often of depressive symptoms and memory deficits than unstimulated control subjects. In one of our patients (#4), depressive symptoms resolved with decreased seizure frequency, and patient #5 experienced an increase both in seizure frequency and in numbers of psychiatric symptoms. Both observations may suggest a seizure-dependent effect on psychiatric symptoms. We therefore cannot report an independent antidepressant effect of NAC stimulation in our cohort.

Interestingly, our overall cohort did not show changes in neuropsychological subscores (Table 2), indicating that NAC stimulation seems to be inert concerning cognitive function. An open observational study on ANT stimulation, which allowed for AED changes, reported amelioration in verbal memory during 12 months of stimulation [47]. In the controlled SANTE trial, however, significantly more patients complained of memory deficits and similarly of depressive symptoms [14]. A plausible explanation for the observed neurocognitive side effects is the well-known involvement of the ANT in memory processing [48, 49].

The major methodological limitation of this case series is the small number of patients, which renders our findings primarily anecdotal. Also, a placebo effect of high expectation due to an invasive intervention cannot be excluded due to the uncontrolled and unblinded protocol. This, however, included a long time period of 6 months, which
in our view makes a pure placebo effect rather unlikely. Furthermore, placebo studies found that a positive response due to elevated post-interventional expectancy is negligible for a long-term placebo effect [50]. Lastly, due to the unblinded in-house protocol we cannot exclude that microlesional effects of the NAC or the ancillary implanted ANT electrodes are in part responsible for the significantly reduced seizure severity score. However, the SANTE trial showed normalisation of seizure frequency within 3 months in the cohort of unstimulated patients [14]. In our cohort, there was a marked postsurgical seizure frequency reduction before NAC stimulation onset, which was not sustained for more than a month (Fig. 2). These two observations suggest a subsidence of a putative microlesional effect at the latest within 3 months.

To reliably assess efficacy of NAC stimulation, the cohort is underpowered compared to well-established minimally invasive procedures such VNS and DBS for ANT. However, initial evidence for safety and feasibility of NAC stimulation in patients with intractable partial epilepsy is presented, and the findings may point to some preliminary evidence for antictical efficacy. The lack of neurocognitive and psychiatric side effects merits possible advantages for the target NAC, so we conclude that further exploration of this target would be worthwhile. To assess for placebo or microlesional effects, a randomised controlled trial would be required. Furthermore, a larger number of patients would be necessary to confirm antictical effects of NAC stimulation and to discriminate putative responders and non-responders according to their electroclinical features.

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Ethical standard The authors complied to the specific ethical standards of Springer concerning the statements of potential conflict of interests, of Informed Consent and of Human and Animal Rights (including the Helsinki Declaration of 1975, as revised in 2000 and 2008).

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