European Expert Opinion on ANT-DBS therapy for patients with drug-resistant epilepsy (a Delphi consensus)

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ABSTRACT

Introduction: Although deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) represents an established third-line therapy for patients with drug-resistant focal epilepsy, guiding reports on practical treatment principles remain scarce.

Methods: An Expert Panel (EP) of 10 European neurologists and 4 neurosurgeons was assembled to share their experience with ANT-DBS therapy. The process included a review of the current literature, which served as a basis for an online survey completed by the EP prior to and following a face-to-face meeting (Delphi method). An agreement level of ≥71 % was considered as consensus.

Results: Out of 86 reviewed studies, 46 (53 %) were selected to extract information on the most reported criteria for patient selection, management, and outcome. The Delphi process yielded EP consensus on 4 parameters for selection of good candidates and patient management as well as 7 reasons of concern for this therapy. Since it was not possible to give strict device programming advice due to low levels of evidence, the experts shared their clinical practice: all of them start with monopolar stimulation, 79 % using the cycling mode. Most (93 %) EP members set the initial stimulation frequency and pulse width according to the SANTE parameters, while there is more variability in the amplitudes used. Further agreement was achieved on a list of 7 patient outcome parameters to be monitored during the follow-up.

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Conclusions: Although current evidence is too low for definite practical guidelines, this EP report could support the selection and management of patients with ANT-DBS.

1. Introduction

There are about 50 million people in the world suffering from epilepsy, and more than 30 % experience continuing seizures despite the administration of appropriately dosed antiepileptic drugs, a condition named drug-resistant epilepsy (DRE) [1]. For selected patients, a chance of controlling DRE seizures lies in resecting the epileptogenic region of the brain [2]. Unfortunately, 30–57 % of patients will not be seizure-free after surgery [3–9] and many patients cannot undergo resective surgery due to poorly localized or multifocal onsets, which complicates localization and surgical strategies greatly. For those patients, viable treatment options are provided by vagus nerve stimulation [10,11], deep brain stimulation (DBS) [12], and responsive neurostimulation (only approved in the U.S.) [13].

The concept of DBS targeting the anterior thalamic nuclei (ANT-DBS) as a treatment of DRE has been examined with positive results in the studies of Cooper et al. [14,15] and Upton et al. [16], the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized controlled trial [17,18] and a series of open-label clinical studies [19–31]. With the SANTE study, ANT-DBS has obtained Class I evidence and a CE mark as adjunctive treatment for reducing the frequency of focal onset seizures of adults with DRE in Europe [32] and FDA approval in the United States since April 2018 [33].

Despite the increasing interest in ANT-DBS for epilepsy, some questions remain challenging, including the physiological mechanism, optimal programming, best targeting as well as lead placement techniques [34–36]. Optimization of target points for ANT-DBS in epilepsy remains a challenge [31] and a potential cause for outcome variation [37–39]. The choice of the active contact and parameter setting are key factors for the clinical response and the occurrence of side effects, but approaches vary greatly from report to report. A guiding report, though, is still not available.

Consensus group methodologies, such as the Delphi method [40], are used to synthesize expert opinions in a systematic way when evidence is lacking or questions are not manageable with experimental and epidemiological methods. An Expert Panel (EP), made up of 10 European neurologists and 4 neurosurgeons with multi-annual experience on ANT-DBS therapy was assembled to evaluate current knowledge and to share experience on patient selection and management, as well as on therapy outcome evaluation.

2. Methods

2.1. EP board composition

The 14 EP members were selected according to the following criteria:

1) Panellists are recognized as experts in implanting and/or managing ANT-DBS epilepsy patients. This criterion translates into the category of expert-neurosurgeon for DBS implantation and expert-epileptologist for managing DRE patients implanted with ANT-DBS. European centres performing DBS for epilepsy were ranked according to the total number of procedures performed from high to low volume. Enrolment rates from the observational, "real world" Medtronic Registry for Epilepsy (MORE; NCT01521754 [37]) were used for benchmarking purposes. Following this process, it was concluded that centres with at least 9 implanted patients could provide the highest expertise on DBS for epilepsy and shall have been preferably involved in the Delphi panel. The experts shall have

implanted and/or followed up at least nine ANT-DBS patients at the time of selection [the mean number of ANT-DBS patients per centre was 20.86, with a range of 10–43].
2) Efforts were made to be as inclusive as possible to represent geographical variety [eight EU countries were represented in the EP: Belgium, France, Finland, Germany, Hungary, Netherlands, Portugal, Switzerland]. Thereby, each country was represented by a maximum of two experts.
3) The number of neurologists was meant to be higher than the neurosurgeons', as the majority of questions are related to dimensions in line with the neurologist's expertise.

2.2. Delphi approach

A four-step Delphi approach was implemented including a nominal group process:

Step 1: A literature review on ANT-DBS was conducted. MEDLINE and EMBASE databases were searched from January 2000 until January 2019 using the following search strategies: ((*dbs OR deep brain OR brain depth OR (anterior NEAR/2 nucle*) OR ('brain depth stimulation'/exp)) and (stimulat* OR electrode* OR neuromodulat* OR neurostimulat* OR electrostimulat* OR electroneurostim*) and (epilep* OR 'epilepsy'/exp)*). The database search yielded a total of 323 publications. Based on the abstract review, the EP members selected 86 publications for in-depth review. All ANT-DBS related studies were included, apart from case reports with less than three patients. A final number of 46 papers reporting information on criteria for patient selection, patient management and patient outcomes were selected and summarized as pre-reading material for all EP members.

Step 2: A web-based Delphi panel process, a method used in the literature to determine and integrate expert opinions on a particular topic and to attempt to reach a consensus by using consecutive rounds of survey questions, was conducted to develop consensus recommendations [40]. The Delphi panel comprised of two blind questionnaire rounds via Qualtrics electronic survey platform. In line with previous consensus reports [41], the EP members defined that consensus was reached when there was an agreement of ≥71 % of respondents (at least 10 out of 14 EP members). For most of the questions, EP members could give multiple answers and add comments.

The first round of the online survey was developed based on the outcome of the literature review results and sent to all members before the face-to-face meeting to establish the initial level of agreement.

Step 3: The results of the literature review and the first survey round were analysed and debated by the EP members in a face-to-face meeting. The meeting was held in November 2019 in the European Medtronic Headquarter in Tolochenaz, Switzerland, and sponsored by Metronic. During the meeting, the results of the first survey round were shared and the following topics were discussed in detail by the EP members:

- Patient selection criteria and reasons for concern
- Patient management strategy, including lead targeting, initial stimulation settings, and stimulation optimization strategies in case of insufficient therapeutic benefit
- Patient outcomes evaluation during follow-up, including seizure frequency and severity, side effects, quality of life, as well as patient´s overall satisfaction

The EP members decided to slightly modify the formulation of some questions to better clarify their meaning and to add more questions in

the second survey round to address additional topics.

Step 4: In a second round and in line with the Delphi method, all EP members were invited to complete the modified online survey in order to analyse the new level of agreement achieved by the EP members after the face-to-face meeting.

Aspects with relevance for ANT-DBS patient selection and management that were additionally discussed during the face-to-face meeting, but were not addressed in the survey, were also included in the manuscript and marked as discussion results.

3. Results

3.1. Literature review

Thus far, the SANTE trial is the only available randomized study, focussing on safety and efficacy parameters [17,18]. Information on which patients could benefit from the therapy is still limited. Potential predictors of ANT-DBS efficacy reported in the literature are summarized in Table 1.

Besides the SANTE trial, only 13 studies – evaluating small cohorts of 4–22 patients - reported data on stimulation settings used in ANT-DBS patients: starting frequency was set between 90 and 185 Hz, pulse width between 60 and 150 μs, and amplitude between 1 and 10 V. Cycling was alternate in 8 studies [17,25,28,29,44,45] (57 %), continuous in 2 studies [26,46] (14 %), mixed in 1 study [47] (7%) and not reported in the remaining 2 studies [27,48] (14 %). Only 2 studies (14 %) reported a pre-defined strategy to adjust stimulation parameters [19,20], while all the others reported that the adjustments were done "at physician discretion".

Patient-reported outcomes were evaluated in 5 studies. The most frequently collected epilepsy-specific questionnaires were QoLIE-31 (Quality of Life in Epilepsy Patients) and LSSS (Liverpool Seizure Severity Scale) [17,18,25,29,49], objectifying a significant improvement in quality of life as well as a significant reduction in seizure severity under ANT-DBS treatment. Affective symptoms were most frequently assessed using the Beck Depression Inventory (BDI) [17,18,25,49].

3.2. Survey results and face-to-face meeting

The first survey question addressed the EP opinion on the current level of evidence for ANT-DBS therapy. All EP members agreed on the fact that, even though ANT-DBS is as established effective third-line

therapy option for DRE patients, more evidence is needed on its efficacy in specific patient populations as well as stimulation strategies in order to improve therapy outcome. Four (29 %) members stated that further evidence is needed on safety aspects.

3.2.1. Patient selection criteria

When asked for parameters taken into consideration when selecting a candidate for ANT-DBS, the EP members only achieved a consensus (defined as level of agreement ≥ 71 %) on the parameter "patient preference" (79 %) during the first survey round. A subsequent discussion during the face to face meeting revealed that the question needed further specification, as ANT-DBS candidates usually undergo a pre-surgical evaluation upfront during which clinical and demographic parameters such as age, seizure aetiology and semiology are already evaluated. In the second survey round, 93 % of the EP members agreed to the need for a multidisciplinary pre-surgical evaluation including video-EEG recording of habitual seizures, magnetic resonance imaging (MRI), neuropsychological evaluation, and an interdisciplinary case conference. One expert (7%) deemed only the interdisciplinary case conference necessary to assess an ANT-DBS candidate. Given these preconditions, an expert agreement was reached on 4 of the parameters that should be critically evaluated before ANT-DBS candidate selection (Table 2), i.e. "patient preference" (86 %), "operability (including coagulation/platelet function)" (86 %), "history and prevalence of psychogenic seizures" (86 %) and "psychiatric history (e.g. history of depression or memory deficit)" (79 %). According to the experts` evaluation, "patients with refractory temporal lobe epilepsy (TLE)" (86 %) who are not candidates for resective surgery and "patients who failed resection or VNS treatment" (71 %) can be considered good candidates for ANT-DBS (Table 2).

A "progressive aetiology (e.g. tumor, dementia, Rasmussen encephalitis)" was regarded as a contraindication for ANT-DBS treatment by 11/14 (79 %) experts during the first survey round. After the face-to-face discussion and rephrasing of the question to relative reasons of concern instead of contraindications, consensus was achieved on 7 parameters: progressive aetiology (86 %), history of suicidal attempts (93 %), depression (86 %), psychogenic seizures (71 %) or psychosis (unrelated to seizure) (86 %), general MRI contraindications (71 %), and unreliable seizure diary (71 %) (Table 2).

3.2.2. Patient management

During the first survey round, no consensus was achieved on the parameters that could improve ANT-DBS therapy outcome, including

Table 1
Potential predictors of ANT-DBS efficacy identified in literature.

Predictors of DBS efficacy	
Possibly associated	Possibly unrelated
TARGET PREDICTORS	
Anterior electrode location:	
- Distance of the active contact to the lateral wall of the third ventricle [31]	
- Mammillothalamic tract and the ventrodorsal distance to midcommissural plane [31]	
Ictal side treated (unilateral seizure onset patients) [42]	
PATIENTS PREDICTORS	
Age at seizure onset [42]	Age at seizure onset [26]
	- Age at the time of ANT-DBS implantation [26,42]
	- Disease duration from the age of seizure onset to age at the time of ANT-DBS [26,42]
Temporal lobe epilepsy [17,18,43]	Seizure aetiology [26]
	Sex [42]
Normal MRI without structural abnormality [43]	Normal MRI without structural abnormality [42]
	Partial seizures or secondarily generalized seizures [42]
Less impaired patients [21]	
Lateralized EEG abnormalities (TLE) [42]	
	Prior surgery / VNS treatment [17,18]

Note: studies listed in Table 1 included different numbers of patients, thus a direct comparison might be inaccurate.

Table 2
Results of the first and second survey round on patient selection criteria.

Survey questions*	Agreement level during 1st survey round (%)	Agreement level during 2nd survey round (%)
Important parameters for (de-)selection and management of ANT-DBS candidates		
Important parameters for selection and management of ANT-DBS candidates are:		
- **Operability (including coagulation/platelet function)**	7	100
- **Patient´s preference**	79	86
- **History and prevalence of psychogenic seizures**	64	86
- **Psychiatric history (e.g. history of depression or memory deficit)**	64	79
- Onset zone	7	64
- Presence of structural abnormality	43	43
- Sleep disturbances	7	36
- Epilepsy duration from the age of seizure onset to the age at the time of consideration for ANT-DBS	7	14
Best (1st survey round)/good (2nd survey round) candidates for ANT-DBS are:		
- **Patients with refractory TLE**	79	86
- **Patients who failed resection or VNS treatment**	57	71
- Patients with secondarily generalized seizures	57	64
- Patients with partial-onset (focal) seizures	43	64
- Patients with normal MRI	14	57
- Patients with positive performance in executive functions tests	21	50
- Patients with lateralized EEG abnormalities	7	29
- Patients with inherent epilepsy aetiologies (e.g. focal cortical dysplasia, double cortex, …)	21	21
- Patients younger than your average refractory population	14	14
Contraindications (1st survey round)/relative reasons for concern (2nd survey round) for ANT-DBS are:		
- **History of suicidal attempts**	57	93
- **History of depression**	29	86
- **History of psychosis (unrelated to seizure)**	57	86
- **Progressive aetiology (e.g. tumor, dementia, Rasmussen encephalitis, …)**	79	86
- **General MRI contraindications (e.g. older implants)**	57	71
- **Unreliable seizure diary**	50	71
- **History of psychogenic seizures**	43	71
- Implantation preconditions only being able to implant one hemisphere	29	64
- Significant mental disability/having legal guardian	29	29
- Mild cognitive impairment	14	21
- No secondary generalized seizures	7	7
- Unknown seizure origin	0	7

* The wording and precision of the survey questions was modified between the first and second survey round according to the results of the face-to-face meeting, resulting in the differences in the level of agreement on the listed parameters between both time points.

different electrode target positions, micro-electrode guided implantation, awake implantation, and ictal side treatment. The EP board discussion revealed that the experts rate some of the parameters differently, depending on the implantation approach used. For example, they aim at different thalamic targets using the transventricular or the extraventricular approach. They thus decided to duplicate this question for the intra- and extraventricular implantation approach to better assess the approach specific characteristics. Eight panellists declared to have experience with the extraventricular approach and agreed that an "anterior electrode location within ANT/Y coordinate" (7/8; 88 %) and an "electrode in proximity to the mammillothalamic tract (MTT)" (6/8; 75 %) may improve the outcome of ANT-DBS. All but one panellist (13/ 14) were experienced with the transventricular approach and 12 of them (92 %) agreed that ANT-DBS treatment´s outcome might be improved by an anterior electrode location within ANT/Y coordinate.

A question concerning the timepoint of ANT-DBS stimulation activation was additionally added in the second survey round as it was considered clinically relevant. It revealed that the majority of EP members (9/14; 64 %) start stimulation immediately after implantation, while the remaining 5 (36 %) wait for one to two months, one of them (1/14; 7%) activating the stimulation only after the first seizure occurred. However, none of the EP members experienced excessive changes in impedance measurements with early DBS activation, in line with DBS for movement disorders where DBS can also be activated in the early postoperative phase.

According to both survey rounds, the expert choice of the active electrode contacts for stimulation initiation is usually based on the electrode localization, which is determined by electrode reconstruction using the pre-operative MRI and post-operative CT scan (86 % agreement). During the face-to-face meeting, the experts added that
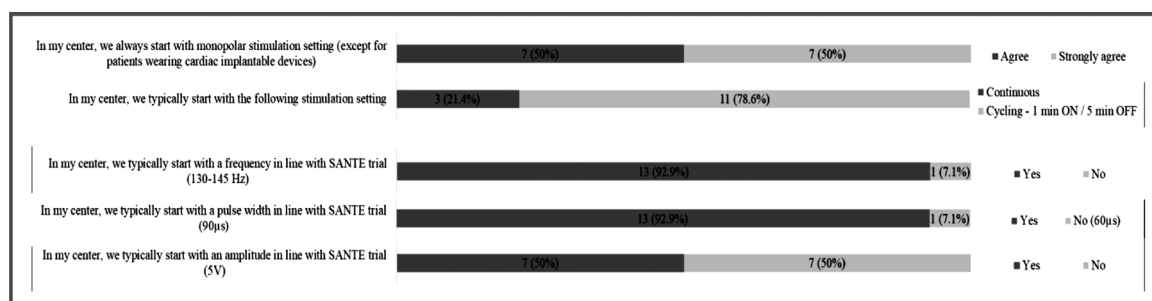

Fig. 1. EP members' clinical practice in device programming.

polysomnography based analysis of the stimulation associated arousal frequency could potentially serve as a biomarker to identify the most effective electrode contact [50].

Fig. 1 shows the results of five questions on device programming which were modified and added in the second survey round to describe the EP members clinical practice on this topic. All EP members stated to start with monopolar stimulation, except in patients wearing other implanted devices such as a cardiac pacemaker. Also, the majority (79 %) starts the initial stimulation in the cycling mode (1 min ON and 5 OFF). For stimulation frequency and pulse width, 13/14 (93 %) EP members agreed on using parameters in line with the SANTE trial ($130 - 145$ Hz and 90 μs respectively). In contrast, only 50 % of EP members set the first stimulation amplitude according to the SANTE trial (5 V), the other half of the experts prefer to start with lower values ($2 - 4$ V).

In case therapeutic benefits, which include a decrease in seizure frequency and severity and an improvement in life quality, are not obtained, the most common strategy (79 %) used by the EP members was changing the active contact within the ANT. Alternative strategies used by single centres did not achieve EP consensus (Table 3).

If stimulation-related side effects occur, the majority of the EP members (79 %) first gradually decrease the stimulation voltage to reach a satisfactory clinical response. In specific cases, a temporary stimulation arrest, lowering the stimulation amplitude at night, or re-evaluating the best coverage of the ANT based on volume of activated tissue (VAT) modelling are proposed strategies (Fig. 2).

3.2.3. Patient outcome

In the first survey round, the EP members were provided with a list of generic and epilepsy-specific questionnaires based on the results of the literature review and asked which of them they use to monitor the patient reported outcomes after ANT-DBS therapy. A majority was only achieved for the BDI (71 %). Congruently, 86 % of the EP members stated that they monitor aspects of depression and anxiety during the follow-up, together with aspects of seizure symptom reduction (100 %). During the face-to-face meeting, the EP members agreed that using established questionnaires like the BDI or PROMs can provide valuable information, but clinical implementation is rare since questionnaire completion and data analysis are time consuming, biased and might not capture all relevant outcome aspects. Further, outcome assessment tools are not uniformly available across languages. A questionnaire with manageable extent that specifically addresses only the most relevant aspects of ANT-DBS therapy would be desirable but is still unavailable. EP members stated that they thus typically use well structured interviews to assess aspects of ANT-DBS outcome instead of questionnaires whose completion and analysis can be time consuming. In the second survey round, the experts agreed that the following parameters should be monitored on a regular basis, irrespective of which tool is used (questionnaire, clinical interview, seizure diary etc): incidence of depression and anxiety (100 %), seizure frequency (100 %) and severity (93 %), memory and cognitive performance (100 %), quality of life (93

%), sleep quality (79 %) and incidence of infections (79 %) (Fig. 3).

The EP members stressed that according to long-term evaluations, reported depression and memory impairment are typically not objectifiable and might be the result of improved awareness due to fewer and milder seizures under ANT-DBS treatment [49]. A series of studies even claimed that ANT DBS may have positive effects on mood [17,18], verbal fluency, and delayed verbal memory [24].

4. Discussion

It still remains a challenging issue to identify the best candidates and device programming parameters for ANT-DBS therapy. Considering the low level of evidence in the literature, expert consensus using a systematic methodology could represent a useful tool to support clinicians in the selection and management of ANT-DBS patients. To our knowledge, this is the first publication that summarizes the consensus beliefs of experienced clinicians in patient selection for and optimization of ANT-DBS. To reach consensus on the above parameters, EP members decided to use the Delphi method, a flexible and adaptable but systematic tool to gather and analyse the needed data about a specific topic. Delphi survey consisted of two rounds. After the first round, the consensus was low to moderate on almost all the items. This was mainly due to the fact that clinical evidence on these topics is low. A face-to-face meeting helped to better clarify the meaning of some questions and to identify additional topics for discussion. For these reasons some questions were modified or newly added. Where it was not possible to reach consensus or to give strong advices, EP members decided to share their experience to support the choice of other clinicians.

4.1. Patient selection

Patients receiving DBS treatment for DRE are a very heterogeneous group in regard to age at seizure onset, DRE aetiology, seizure burden, medication and level of cognitive abilities. Although ANT-DBS treatment is a safe and effective treatment for DRE patients, predictors for positive outcome are still scarce. Previous reports suggested that defined electrode location within the ANT [28,31], temporal epilepsy syndromes [17,18,29,42,43] especially with later age at disease onset, lateralized EEG abnormalities, and ictal side treatment [42], patients with limited impairment [21], as well as positive performance in executive function tests [45] might be associated with a favourable outcome. Accordingly, the EP members approved ANT-DBS treatment in DRE patients with TLE who are no candidates for resective surgery and those who did not sufficiently benefit from resection/VNS therapy. Selection of specific patient subgroups based on clinical or demographic factors, though, remains inconclusive due to lack of evidence. Gooneratne et al. [51] proposed a pathway for patients with focal DRE based on currently available data on efficacy, safety, costs and invasiveness of the therapy. The experts' discussion revealed that a full presurgical evaluation is typically performed before assigning a DRE

Table 3
Strategies to follow when therapeutic benefits are not immediately obtained.

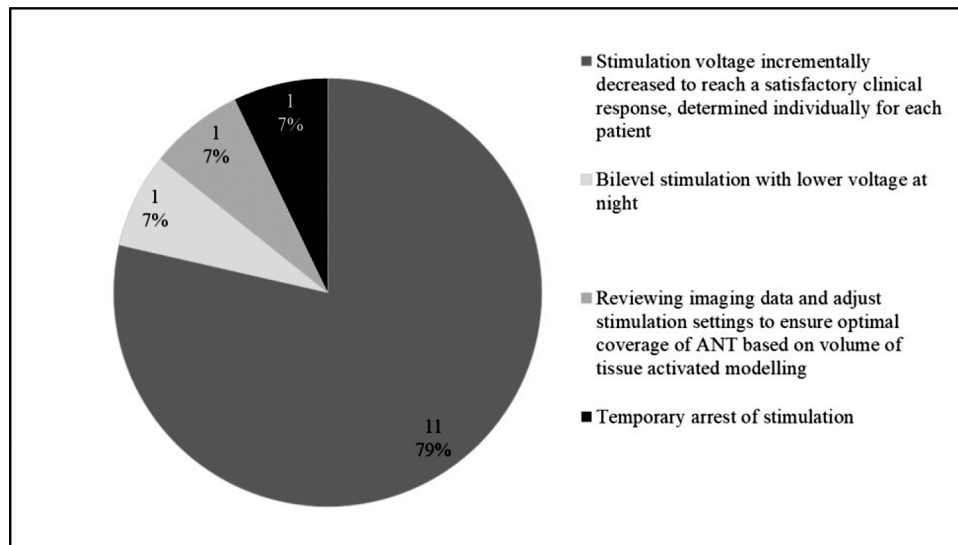| Strategies during the first year (1ˢᵗ survey round)/ first strategy (2ⁿᵈ survey round) chosen when therapeutic benefits are not obtained:	Agreement during 1ˢᵗ survey round (%)	Agreement during 2ⁿᵈ survey round (%)
- **Change contact within ANT**	7	**79**
- Reviewing imaging data and adjust stimulation settings to ensure optimal coverage of ANT based on volume of tissue activated modelling	64	57
- Stimulation voltage incrementally increased to reach a satisfactory clinical response	**79**	43
- Change cyclic mode to a faster cycle rate or continuous stimulation	29	43
- Re-evaluate therapeutic impedance	7	36
- Change to bipolar stimulation setting	43	21
- Switch frequency to 40 Hz	7	21
- Increase pulse width	14	14

Fig. 2. Strategy chosen by EP members when putative stimulation-related side effects appear during the follow-up.

patient candidate to ANT-DBS. Further, patient's preference, operability, psychiatric history and history of psychogenic seizures were rated relevant for patient selection and management. No contra-indications were seen for ANT-DBS treatment besides progressive epilepsy aetiologies, but history of psychiatric symptoms, frequent psychogenic seizures, MRI contraindications and unreliable seizure documentation should raise concern. It is thus all the more important to conduct interdisciplinary case discussions to individually weigh the expected value against the potential risks of ANT-DBS treatment and to define realistic expectations.

4.2. Patient management

The mechanism underlying the effects of ANT-DBS for DRE is not completely understood [34,35]. As a result, optimal postoperative patient management strategies require complex decision making and are largely based on trial-and-error methodologies, particularly when it comes to select the ANT-DBS stimulation parameters. As thousands of individual stimulation parameter combinations are possible, it appears evident that a proper clinical evaluation of each one is unfeasible. Defining the optimal programming for an ANT-DBS device to maximize therapeutic benefit thus may become a difficult and time-consuming process [52]. Overall, it has been estimated that the DBS programming process in movement disorder can require up to 20 h per patient [53] and even more in epilepsy where stimulation has to be adjusted over several months. Against this background, the stimulation parameters of the only randomized-controlled trial, the SANTE study, prevailed in clinical practice. However, half of the EP members prefer to start with lower stimulation amplitudes (2 − 4 V) compared to the SANTE trial, adjusting the amplitude during the follow-up visits if clinically required. This strategy might reduce the risk of stimulation related side effects and save battery power. During the initial programming, deviation form monopolar stimulation is only made in the presence of other implanted stimulation devices like cardiac pacemakers. The majority of EP members further agreed on using cycling mode upon stimulation activation, although evidence is still limited for both
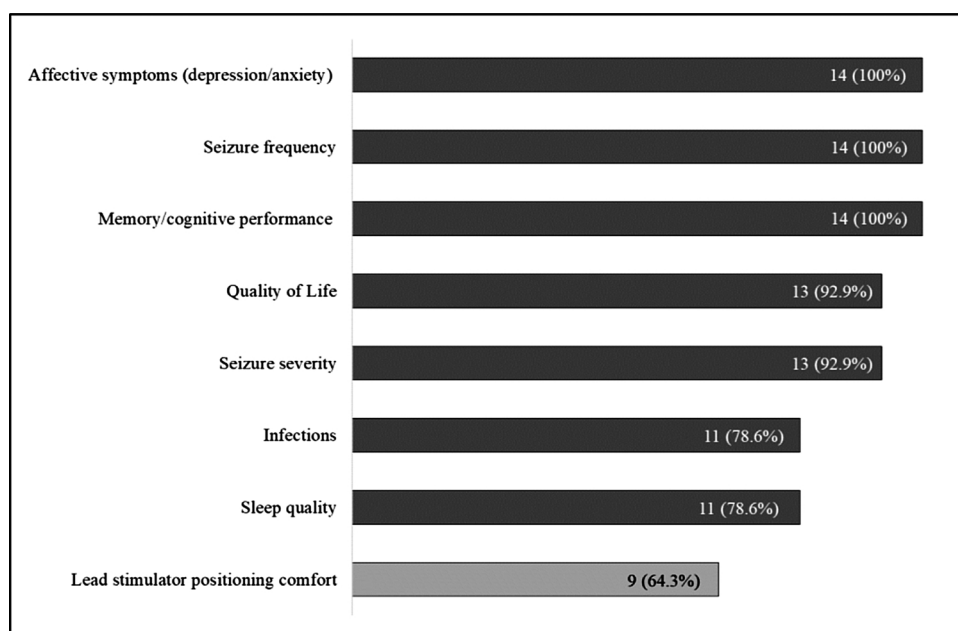

Fig. 3. Agreement on patient outcomes to be collected during the follow-up.

approaches revealing no clear outcome differences between cycling and continuous stimulation [26,46,47].

The therapeutic benefit of ANT-DBS is strongly dependent on the accurate surgical placement of the DBS electrode [28,31,54]. To date, the ideal coordinates for ANT-DBS lead positioning have not been unanimously defined [38]. Based on the published data and their own experience, the EP members proposed that efforts should be made to place the electrode in the anterior and superior portion of the ANT. Thereby, similar clinical effects can be achieved with the trans- and extraventricular implantation approach, but in case of the extra-ventricular approach it might be more difficult to successfully place the lead within the target location [37]. Direct stereotactic targeting of the MTT might be an effective alternate approach [31]. The electrode contacts for stimulation initiation are thus mainly selected depending on their position within the ANT, usually determined visually based on the fusion of the postop CT and preop MRI scan. However, about 10 % of electrodes end up outside the ANT [37,38]. In these cases, the use of monopolar stimulation mode might be beneficial, because it creates a broader electric field than bipolar stimulation, and thus might still re-sult in some stimulation of the ANT and a clinical response. High vol-tage monopolar stimulation, though, might cause side effects [50], in particular if the electrode is positioned too lateral, and thus re-im-plantation should be considered in individual cases.

Although it is common sense that the initiation of deep brain sti-mulation should follow a period of recovery from postoperative changes at the electrode-tissue interface, there is no clear guideline concerning the optimal timepoint of stimulation initiation for ANT-DBS. However, the majority of EP members still activate the DBS system within the first week after surgery. Only every third expert adheres to a postoperative interval of about one month.

In case of an insufficient clinical response, the experts prefer to change the active contact within the ANT to assure optimal coverage of the VAT and ANT. In individual cases, an increase of the stimulation amplitude or modifications of stimulation cycle, frequency or stimula-tion mode might be beneficial.

Although relevant ANT-DBS related psychiatric side effects are modest in number and clinically manageable by reprogramming the stimulation parameters, they could well jeopardize the overall success of ANT-DBS treatment if left untreated. Putative stimulation related side-effects should thus be addressed by gradually decreasing the sti-mulation amplitude or temporarily pausing the stimulation. Tailored strategies such as changing the active electrodes, modifying the sti-mulation parameters, or programming bilevel stimulation with lower amplitudes during night in case of disrupted sleep might be im-plemented in individual patients [50]. In order to promptly detect sti-mulation related side effects, the EP panel recommended to regularly monitor the neurocognitive function and psychiatric symptoms during the follow-up visits.

4.3. Patient outcome

The panellists agreed that ANT-DBS therapy has the potential to significantly reduce the seizure frequency and severity in patients with drug resistant epilepsy - typically achieving similar success rates like in the SANTE trial [17,18]. They emphasized that - besides seizure fre-quency and severity - outcome evaluation should also encompass neu-rocognitive function, mood, and aspects of quality of life. Of note, op-timal outcome is only achieved if patient expectations are met besides significant improvement in clinical parameters. There is growing re-cognition of the value of assessing wider impacts of treatments by the means of health status reports that come directly from the patient. Such reports are named "*patient reported outcomes measures*" (PROMs) and are questionnaires that capture and quantify treatment impacts from the patient's perspective [55]. PROMs are well established methods of capturing what actually matters to patients [56]. A structured review rated the SF-36 as the preferred generic measure of health status and the QoLIE-31 for the measurement of epilepsy-specific quality of life, to be used in combination as complementary evidence [57]. Nevertheless, only a subset of ANT-DBS studies collected PROMs and standardized questionnaires to measure ANT-DBS outcomes [17,18,25,29,49]. The most frequently collected standardized questionnaires and epilepsy-specific PROMs were QoLIE-31, LSSS, and BDI [17,18,25,29,49]. Al-though not commonly used in clinical routine for reasons of practic-ability and availability, the application of defined sets of ques-tionnaires/PROMs might still be essential in clinical trials or when specifically requested by Compentent Authorities. In daily clinical routine, the experts recommend to regularly monitor a defined set of parameters – no matter which available tool is used in the end, i.e. PROMs, clinical interview, seizure diary or similar.

4.4. Limitations

The outcome of this panel review is not a substitute for clinical judgment and is not intended to define a standard of practice or re-quirement for ANT-DBS treatment. Further, the content of this report and EP members' opinions may not be suitable for all patients. It is expected that physicians will appropriately individualise their judg-ment in unique clinical circumstances. No single document can rigidly categorise appropriate practice in this setting; therefore, EP members offer this as a clinical opinion combined with practical suggestions. In the absence of evidence on this topic, deriving expert opinion in a systematic manner like in this Delphi panel, can be a meaningful tool to guide clinicians in their practice.

5. Conclusions

Currently, there is limited clinical evidence on how to better select patients for ANT-DBS therapy and manage them post-operatively. After an analysis of the current literature and opinion sharing, EP members agreed on the definition of 4 parameters for patient selection and 7 reasons for concern, reported their practised way of DBS programming and defined a list of important outcome parameters to be monitored during follow-up. This report could support clinicians in the selection and management of candidates for ANT-DBS therapy. Further agree-ment will be needed when additional evidence becomes available. Further, this expert opinion report may serve as an impetus for a set of international guidelines for evaluating selection and optimization of neurostimulation for epilepsy.

References

[1] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9. https://doi.org/10.1056/NEJM200002033420503.

[2] Miller JW, Hakimian S. Surgical treatment of epilepsy. Continuum (Minneap Minn) 2013;19:730–42. https://doi.org/10.1212/01.CON.0000431398.69594.97.

[3] Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89:310–8. https://doi.org/10.1016/j.eplepsyres.2010.02.007.

[4] Althausen A, Gleissner U, Hoppe C, Sassen R, Buddewig S, Von Lehe M, et al. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. J Neurol Neurosurg Psychiatry 2013;84:529–36. https://doi.org/10.1136/jnnp-2012-303811.

[5] Elsharkawy AE, Behne F, Oppel F, Pannek H, Schulz R, Hoppe M, et al. Long-term outcome of extratemporal epilepsy surgery among 154 adult patients. J Neurosurg 2008;108:676–86. https://doi.org/10.3171/JNS/2008/108/4/0676.

[6] Lee JJ, Lee SK, young Lee S, Park K-Il, Kim DW, Lee DS, et al. Frontal lobe epilepsy: clinical characteristics, surgical outcomes and diagnostic modalities. Seizure 2008;17:514–23. https://doi.org/10.1016/j.seizure.2008.01.007.

[7] Dorward IG, Titus JB, Limbrick DD, Johnston JM, Bertrand ME, Smyth MD. Extratemporal, nonlesional epilepsy in children: postsurgical clinical and neurocognitive outcomes. J Neurosurg Pediatr 2011;7:179–88. https://doi.org/10.3171/2010.11.PEDS10265.

[8] Liava A, Francione S, Tassi L, Lo Russo G, Cossu M, Mai R, et al. Individually tailored extratemporal epilepsy surgery in children: anatomo-electro-clinical features and outcome predictors in a population of 53 cases. Epilepsy Behav 2012;25:68–80. https://doi.org/10.1016/j.yebeh.2012.05.008.

[9] Pinheiro-Martins AP, Bianchin MM, Velasco TR, Terra VC, Araújo D, Wichert-Ana L, et al. Independent predictors and a prognostic model for surgical outcome in refractory frontal lobe epilepsy. Epilepsy Res 2012;99:55–63. https://doi.org/10.1016/j.eplepsyres.2011.10.008.

[10] Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 2011;20:57–63. https://doi.org/10.1016/j.yebeh.2010.10.017.

[11] Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr 2016;18:97–104. https://doi.org/10.3171/2016.1.PEDS15534.

[12] Morace R, DI Gennaro G, Quarato P, D'Aniello A, Amascia A, Grammaldo L, et al. Deep brain stimulation for intractabile epilepsy. J Neurosurg Sci 2016;60:189–98.

[13] Skarpaas TL, Jarosiewicz B, Morrell MJ. Brain-responsive neurostimulation for epilepsy (RNS ® System). Epilepsy Res 2019;153:68–70. https://doi.org/10.1016/j.eplepsyres.2019.02.003.

[14] Cooper IS, Upton AR, Amin I. Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol 1980;43:244–58.

[15] Cooper IS, Upton AR, Amin I, Garnett S, Brown GM, Springman M. Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Int J Neurol 1984;18:179–87.

[16] Upton AR, Amin I, Garnett S, Springman M, Nahmias C, Cooper IS. Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Pacing Clin Electrophysiol 1987;10:217–25.

[17] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x.

[18] Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84:1017–25. https://doi.org/10.1212/WNL.0000000000001334.

[19] Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 2004;45:346–54. https://doi.org/10.1111/j.0013-9580.2004.01304.x.

[20] Lim S-N, Lee S-T, Tsai Y-T, Chen I-A, Tu P-H, Chen J-L, et al. Long-term anterior thalamus stimulation for intractable epilepsy. Chang Gung Med J 2008;31:287–96.

[21] Järvenpää S, Rosti-Otajärvi E, Rainesalo S, Laukkanen L, Lehtimäki K, Peltola J. Executive functions may predict outcome in deep brain stimulation of anterior nucleus of thalamus for treatment of refractory epilepsy. Front Neurol 2018;9:1–8. https://doi.org/10.3389/fneur.2018.00324.

[22] Middlebrooks EH, Grewal SS, Stead M, Lundstrom BN, Worrell GA, Van Gompel JJ. Differences in functional connectivity profiles as a predictor of response to anterior thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes. Neurosurg Focus 2018;45:E7. https://doi.org/10.3171/2018.5.FOCUS18151.

[23] Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66:1571–3. https://doi.org/10.1212/01.wnl.0000206364.19772.39.

[24] Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure 2012;21:183–7. https://doi.org/10.1016/j.seizure.2011.12.003.

[25] Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 2007;48:1561–71. https://doi.org/10.1111/j.1528-1167.2007.01044.x.

[26] Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotact Funct Neurosurg 2012;90:379–85. https://doi.org/10.1159/000339991.

[27] Hartikainen KM, Sun L, Polvivaara M, Brause M, Lehtimäki K, Haapasalo J, et al. Immediate effects of deep brain stimulation of anterior thalamic nuclei on executive functions and emotion-attention interaction in humans. J Clin Exp Neuropsychol 2014;36:540–50. https://doi.org/10.1080/13803395.2014.913554.

[28] Lehtimäki K, Möttönen T, Järventausta K, Katisko J, Tähtinen T, Haapasalo J, et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul 2016;9:268–75. https://doi.org/10.1016/j.brs.2015.09.014.

[29] Piacentino M, Durisotti C, Garofalo PG, Bonanni P, Volzone A, Ranzato F, et al. Anterior thalamic nucleus deep brain Stimulation (DBS) for drug-resistant complex partial seizures (CPS) with or without generalization: long-term evaluation and predictive outcome. Acta Neurochir (Wien) 2015;157:1525–32. https://doi.org/10.1007/s00701-015-2498-1.

[30] Krishna V, King NKK, Sammartino F, Strauss I, Andrade DM, Wennberg RA, et al. Anterior nucleus deep brain stimulation for refractory epilepsy. Neurosurgery 2016;78:802–11. https://doi.org/10.1227/NEU.0000000000001197.

[31] Koeppen JA, Nahravani F, Kramer M, Voges B, House PM, Gulberti A, et al. Electrical stimulation of the anterior thalamus for epilepsy: clinical outcome and analysis of efficient target. Neuromodulation 2019;22:465–71. https://doi.org/10.1111/ner.12865.

[32] Medtronic Newsroom. Medtronic receives European CE mark approval for deep brain stimulation therapy for refractory epilepsy. Medtronic Press Release; 2017.

[33] FDA. Medtronic DBS system for epilepsy PMA supplement approval. 2018.

[34] Ineichen C, Glannon W, Temel Y, Baumann CR, Sürücü O. A critical reflection on the technological development of deep brain stimulation (DBS). Front Hum Neurosci 2014;8:1–7. https://doi.org/10.3389/fnhum.2014.00730.

[35] Montgomery EB. The epistemology of Deep Brain Stimulation and neuronal pathophysiology. Front Integr Neurosci 2012;6:1–8. https://doi.org/10.3389/fnint.2012.00078.

[36] Chiken S, Nambu A. Mechanism of deep brain stimulation. Neurosci 2016;22:313–22. https://doi.org/10.1177/1073858415581986.

[37] Lehtimäki K, Coenen VA, Gonçalves Ferreira A, Boon P, Elger C, Taylor RS, et al. The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the international multicenter registry (MORE). Neurosurgery 2019;84:141–50. https://doi.org/10.1093/neuros/nyy023.

[38] Wu C, D'Haese P-F, Pallavaram S, Dawant BM, Konrad P, Sharan AD. Variations in thalamic anatomy affect targeting in deep brain stimulation for epilepsy. Stereotact Funct Neurosurg 2016;94:387–96. https://doi.org/10.1159/000449009.

[39] Imbach LL, Baumann CR, Poryazova R, Geissler O, Brugger P, Sarnthein J, et al. Anticonvulsive effect of anterior thalamic deep brain stimulation in super-refractory status epilepticus crucially depends on active stimulation zone—a single case observation. Seizure 2019;71:286–8. https://doi.org/10.1016/j.seizure.2019.08.015.

[40] Hsu C, Sandford BA. The Delphi technique: making sense of consensus. Pract Assessment, Res Eval 2007;12:1–8.

[41] Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401–9. https://doi.org/10.1016/j.jclinepi.2013.12.002.

[42] Chang B, Xu J. Deep brain stimulation for refractory temporal lobe epilepsy: a systematic review and meta-analysis with an emphasis on alleviation of seizure frequency outcome. Childs Nerv Syst 2018;34:321–7. https://doi.org/10.1007/s00381-017-3596-6.

[43] Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia 2018;59:273–90. https://doi.org/10.1111/epi.13964.

[44] Koeppen JA, Nahravani F, Kramer M, Voges B, House PM, Gulberti A, et al. Electrical stimulation of the anterior thalamus for epilepsy: clinical outcome and analysis of efficient target 2018. 2018. https://doi.org/10.1111/ner.12865.

[45] Järvenpää S, Peltola J, Rainesalo S, Leinonen E, Lehtimäki K, Järventausta K. Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy. Epilepsy Behav 2018;88:373–9. https://doi.org/10.1016/j.yebeh.2018.09.006.

[46] Oh Y, Jin H, Jin K, In Y, Lim S, Shon Y. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure Eur J Epilepsy 2012;21:183–7. https://doi.org/10.1016/j.seizure.2011.12.003.

[47] Lim S, Lee S, Tsai Y, Chen I, Tu P, Chen J, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 2007;48:342–7. https://doi.org/10.1111/j.1528-1167.2006.00898.x.

[48] Krishna V, Kon N, King K, Andrade DM, Wennberg RM. Anterior nucleus deep brain stimulation for refractory epilepsy: insights into patterns of seizure control and efficacious target. Neurosurgery 2016;0:1–10. https://doi.org/10.1227/NEU.0000000000001197.

[49] Tröster AI, Meador KJ, Irwin CP, Fisher RS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure 2017;45:133–41. https://doi.org/10.1016/j.seizure.2016.12.014.

[50] Voges BR, Schmitt FC, Hamel W, House PM, Kluge C, Moll CKE, et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. Epilepsia 2015;56:e99–103. https://doi.org/10.1111/epi.13045.

[51] Gooneratne IK, Green AL, Dugan P, Sen A, Franzini A, Aziz T, et al. Comparing neurostimulation technologies in refractory focal-onset epilepsy. 2016. p. 1174–82. https://doi.org/10.1136/jnnp-2016-313297.

[52] McIntyre CC, Chaturvedi A, Shamir RR, Lempka SF. Engineering the next

generation of clinical deep brain stimulation technology. Brain Stimul 2015;8:21–6. https://doi.org/10.1016/j.brs.2014.07.039.

[53] Hunka K, Suchowersky O, Wood S, Derwent L, Kiss ZHT. Nursing time to program and assess deep brain stimulators in movement disorder patients. J Neurosci Nurs 2005;37:204–10.

[54] Moro E, Poon Y-YW, Lozano AM, Saint-Cyr JA, Lang AE. Subthalamic nucleus stimulation: improvements in outcome with reprogramming. Arch Neurol 2006;63:1266–72. https://doi.org/10.1001/archneur.63.9.1266.

[55] U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics

Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006;4:79. https://doi.org/10.1186/1477-7525-4-79.

[56] Peters M, Crocker H, Dummett S, Jenkinson C, Doll H, Gibbons E, et al. Pilot study of patient reported outcome measures (PROMs) in primary care. Oxford; 2013.

[57] Davies N, Gibbons E, Fitzpatrick R, Mackintosh A. A structured review of patient-reported outcome measures (PROMs) for epilepsy. 2009.