REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, Volume 58, no. 3, pages: 256–273
DOI: 10.5603/pjnns.98258

ISSN: 0028-3843, e-ISSN: 1897-4260

Deep brain stimulation of anterior nucleus and centromedian nucleus of thalamus in treatment for drug-resistant epilepsy

Michał Sobstyl[1], Magdalena Konopko[2], Aleksandra Wierzbicka[3], Marek Prokopienko[1], Tadeusz Pietras[4], Kasper Sipowicz[5]

[1]Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland
[2]1st Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[3]Department of Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland
[4]2nd Department of Psychiatry, Institute of Psychiatry and Neurology, Warsaw, Poland
[5]Department of Interdisciplinary Disability Studies, The Maria Grzegorzewska University in Warsaw, Poland

ABSTRACT

Introduction. Drug-resistant epilepsy (DRE) remains poorly-controlled in c.33% of patients, and up to 50% of patients suffering from DRE are deemed not to be suitable candidates for resective surgery. For these patients, deep brain stimulation (DBS) may constitute the last resort in the treatment of DRE.

State of the art. We undertook a systematic review of the current literature on DBS efficacy and the safety of two thalamic nuclei–anterior nucleus of the thalamus (ANT) and the centromedian nucleus of the thalamus in the management of patients with DRE. A search using two electronic databases, the Medical Literature, Analysis, and Retrieval System on-line (MEDLINE) and the Cochrane Central Register of Controlled Trials (CEN-TRAL) was conducted.

Clinical implications. We found 30 articles related to ANT DBS and 13 articles related to CMN DBS which were further analysed. Based on the clinical research articles, we found a mean seizure frequency reduction for both thalamic nuclei. For ANT DBS, the mean seizure frequency reduction ranged from 48% to 75%, and for CMN DBS from 46.7% to 91%. The responder rate (defined as at least 50% reduction in seizure frequency) was reported to be 53.2–75% for patients after ANT DBS and 50–90% for patients after CMN DBS.

Future directions. ANT and CMN DBS appear to be safe and efficacious treatments, particularly in patients with refractory partial seizures and primary generalised seizures. ANT DBS reduces most effectively seizures originating in the temporal and frontal lobes. CMN DBS reduces mostly primary generalised tonic-clonic and atypical absences and atonic seizures. Seizures related to Lennox-Gastaut syndrome respond very favourably to CMN DBS.

Keywords: deep brain stimulation, thalamic stimulation, drug-resistant epilepsy, anterior nucleus of the thalamus, centromedian nucleus of the thalamus, neuromodulation

(*Neurol Neurochir Pol 2024; 58 (3): 256–273*)

Address for correspondence: Michał Sobstyl, Department of Neurosurgery, Institute of Psychiatry and Neurology, Sobieskiego 9 St., 02–957 Warsaw, Poland; e-mail: mrsob@op.pl

Received: 24.11.2023 Accepted: 2.04.2024 Early publication date: 12.06.2024

VIA MEDICA

Introduction

Despite available antiseizure medications (ASMs), drug resistant epilepsy (DRE) remains poorly controlled in approximately one-third of patients [1, 2].

The seizure-free rate after resective surgery for DRE is estimated at 59% [3]. This rate usually diminishes with a longer follow-up [3]. The seizure-free rates for temporal lobe epilepsy at 5 and 10 years after surgery are estimated at 61% and 45%, respectively [3]. However, up to 50% of patients suffering from DRE are deemed to be not suitable candidates for resective surgery [4]. For this group of patients, neuromodulation therapies may constitute the last resort in the treatment of DRE.

If resective surgery cannot be offered because of the involvement of the eloquent areas or the multifocal nature of the ictal epilepsy onset, the thalamic nuclei are an attractive region for neuromodulation. The stimulation of thalamic nuclei involves the stereotactic placement of deep brain stimulation (DBS) leads connected thereafter through connection cables to an implantable pulse generator (IPG) placed in the chest wall.

This review article will discuss the clinical application of anterior nucleus of the thalamus (ANT) and centromedian nucleus of the thalamus DBS. ANT DBS is CE marked and FDA-approved target for DBS as adjunctive therapy for patients 18 years of age or older affected by partial-onset seizures with or without secondary generalisation. The CMN DBS is not a CE marked or FDA-approved procedure. It is used for primary generalised seizures in the treatment of Lennox-Gastaut syndrome (LGS).

Another neuromodulatory technique is responsive neurostimulation (RNS). This technique has recently emerged as a safe and effective treatment for some patients with medically refractory focal epilepsy who are not candidates for surgical resection. RNS was approved in the United States in 2013 and to date c.1,800 patients have been treated worldwide [5]. RNS involves an implanted neurostimulator and intracranial leads that detect incipient seizures and respond with electrical counterstimulation [5]. Unlike thalamic DBS, which involves prespecified electrode locations within ANT or CMN, RNS involves intracranial strip and/or depth electrodes that can be flexibly configured based on knowledge of the seizure onset zone [5, 6]. Clinical studies have shown that RNS is a well-tolerated treatment option for patients especially with mesial temporal lobe epilepsy who are not candidates for a temporal lobe resection [5, 6].

ANT or CMN DBS can influence a widespread region of the cerebral cortex and limbic system. Thalamic stimulation is aimed to preserve brain tissue, and is adjustable and reversible [7, 8].

The purpose of this literature review was to present up-to-date knowledge regarding the clinical efficacy and safety of ANT and CMN DBS for DRE.

Paper selection

We conducted a systematic literature search for publications regarding DBS for DRE including the following thalamic nuclei: ANT and CMN, spanning the period from January 1980 to July 2023. The search algorithm included the following key words: deep brain stimulation, thalamic stimulation for drug-resistant epilepsy, stimulation of the anterior nucleus for epilepsy, stimulation of the centromedian nucleus for epilepsy, and thalamic stimulation. The following electronic databases were consulted: the Medical Literature, Analysis, and Retrieval System on-line (MEDLINE) and the Cochrane Central Register of Controlled Trials (CEN-TRAL). The search algorithm followed the PRISMA guidelines [9]. There were considered only research articles published in English. The research articles were restricted to the clinical studies involving only humans. No limitations were made regarding the study design. Clinical studies with at least three individuals with a minimum postoperative follow-up of 6 months DBS were included in our analysis.

The exclusion criteria included: animal studies, studies that included treatment of DRE without DBS, preclinical studies, review articles, letters to the editor, as well as clinical studies with fewer than three patients. The exclusion criteria also included articles describing patient populations other than those with DRE, and reports that mainly dealt with aspects related to surgical technique.

In relation to the fact that two thalamic nuclei constituted the separated targets, the flowchart showing the search strategy for both thalamic nuclei is presented separately in Figure 1. The search using these two databases and the above-mentioned key words yielded 43 articles presented in Figure 1. Among these, 30 articles were related to ANT DBS for DRE reporting cumulative number of approximately 635 patients. Thirteen articles were related to CMN DBS for DRE reporting cumulative number of 147 patients.

Indications and contraindications for ANT DBS

ANT is an FDA-approved and best-studied thalamic target for DBS to treat DRE [7, 8, 10, 11]. The ANT plays pivotal role in the circuit of Papez [12]. This nucleus connects to mesial, frontal and temporal regions. These brain regions are most often involved in focal epilepsy [8]. The efficacy of ANT DBS has been best documented in focal onset seizures originating from temporal or frontal lobes with or without secondary generalisation. Other predictors for ANT DBS efficacy are: age at seizure onset, normal MRI without structural abnormalities, lateralised EEG abnormality, and positive performance in executive functions [7, 9, 13–18]. Patients with DRE in whom a VNS or prior resective epilepsy surgery have failed, have also shown seizure reductions comparable to those individuals without these prior therapies [7, 19, 20].

The main contraindication for ANT DBS is a progressive neurological aetiology, usually defined as a brain tumour, Rasmussen encephalitis or dementia. Other contraindications include a history of psychogenic seizures, depression or memory deficit, suicide attempts, and psychosis unrelated to epilepsy [7, 11, 13, 16, 17]. Cognitively impaired patients who are unable to complete a neuropsychological assessment, or with an IQ of less than 70, are usually excluded from ANT DBS [7, 19].

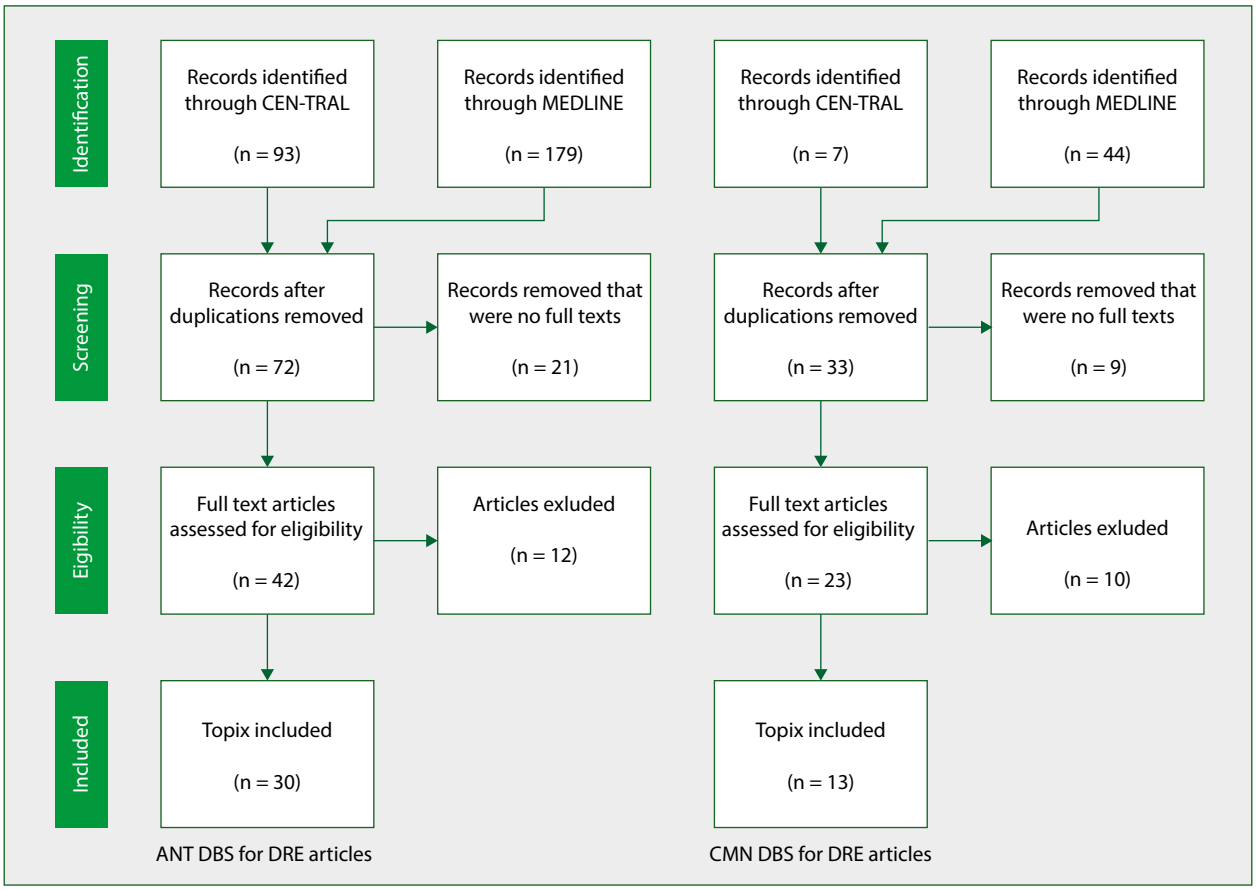

Figure 1. Chart illustrating the selection of articles for ANT DBS and CMN DBS

Clinical efficacy of ANT DBS for treatment of DRE

Upton et al. in 1985 were the first to report the outcomes of ANT DBS in 6 patients with intractable epilepsy [10]. Four of the 6 patients showed a marked seizure frequency reduction and also an improvement in psychiatric symptoms. In subsequent open-label studies, the seizure reduction ranged from 54% to 75.6% with a follow-up ranging from 10.6 to 43.8 months [11, 13, 15, 16, 22, 23]. An uncontrolled study by Andrade et al. reported a 60-month follow-up in 6 patients after ANT DBS who were all responders with at least 50% complex partial seizure reduction [17]. Based on this pilot trial, a multicentre, randomised, controlled trial was initiated [7]. The acronym of this trial was 'SANTE' (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) [7]. In this trial, over two years, there was a 56% median seizure frequency reduction, and 54% of patients were responders (defined as at least 50% seizure reduction) [7]. Five years after ANT DBS, the mean seizure frequency reduction was 69%, and the responder rate reached 68% [19]. In a 5-year follow-up, 16% of patients were seizure-free for at least 6 months [19]. Salanova et al. evaluated the efficacy and safety of ANT DBS after 7 and 10 years [20]. The most severe seizures, mainly focal to bilateral tonic clonic seizures (FBTCS), were reduced by 71% at 7 years, while focal impaired awareness seizures (FIAS) were reduced by 78%, and focal aware seizures (FAS) by 92%. At 7 years, the overall median seizure frequency reduction was 75%, with no outcome differences related to prior vagus nerve stimulation or resective surgery [20].

In the studies which followed the SANTE trial, the median seizure frequency reduction ranged from 50% to as much as 80.3%, with a responder rate exceeding 70–80% of patients [18, 21, 22, 24–42]. The outcomes of ANT DBS studies are set out in Table 1. In 2023, Peltola et al. reported the outcomes of the MORE Multicentre Patient Registry Study of ANT DBS [39]. Of the 191 patients recruited, 170 were implanted. The median monthly seizure frequency reduction at 2 years was 33.1%, and in 47 patients who completed 5 years follow-up, the median monthly seizure frequency reduction was 53.2% [39]. There were two factors which influenced strongly the outcomes: the centres recognized as high volume centres with more than 10 ANT DBS surgeries, and the presence of preoperative cognitive impairment. High-volume centres had a 42.5% monthly seizure frequency reduction, compared to 25.8% in low volume centres at 2 years. The absence of cognitive impairment resulted in a 36.1% monthly seizure reduction compared to a 26% reduction in patients with cognitive impairment [39].

Other factors (seizure origin, previous VNS therapy, resective surgery) affecting outcome of ANT DBS

Clinical long-term follow-up studies of ANT DBS have revealed that seizures originating in one or both temporal lobes, as well in frontal lobes, have a clearly better prognosis than seizures with their origin in parietal or occipital lobes [7, 19, 20].

The origin of the seizure focus may even have a stronger correlation with a long-term follow-up after ANT DBS [19, 20]. After 7 years of ANT DBS, the mean seizures frequency reductions for seizures originating in the frontal, temporal, and parietal/occipital lobes were 86%, 78% and 39% respectively [20]. Patients with multiple epileptic foci coexisted with structural brain abnormalities do not respond so favourably to ANT DBS [7, 16, 17–18]. As mentioned above, previous VNS therapy did not affect the final outcome [20]. At 7 years, patients who had previous VNS achieved a 75% mean seizure reduction compared to a 78% reduction in patients who had no prior VNS [20]. Subjects who had previous resective surgery had a median seizure frequency reduction of 69% at 7 years versus 75% without a history of resective surgery [20].

Although the evidence for the clinical effectiveness of VNS and DBS exists, the exact mechanisms of action remain unexplained [37]. PET studies during VNS have shown increased cerebral bloodflow in the thalamus [44]. This increased synaptic thalamic activity may mediate the anticonvulsant effects of VNS therapy. ANT DBS directly modulates thalamocortical activity through anterior thalamic radiation affecting the frontal lobes and limbic seizure network. Further work is needed to fully understand the effects of VNS and ANT DBS on epilepsy [20].

The predictors of clinical outcome of ANT DBS remain to be defined. A newer approach to predict the outcome to ANT DBS is the implantation of functional connectivity between the ANT and the seizure foci [45]. Xu et al. examined 18 patients with two or more seizure foci using normative human connectome data derived from 1,000 healthy participants. The authors performed functional connectivity between the seizure foci and the ANT. The degree of functional connectivity between ANT DBS and seizures foci were strongly correlated with seizure reduction [45]. The authors concluded that functional connectomic profile is a potentially reliable non-invasive biomarker to predict ANT-DBS outcomes [45]. Accordingly, the identification of ANT responders could decrease the surgical risk for patients who may not benefit and optimise the cost-effective allocation of healthcare resources.

Targeting and trajectory planning during ANT DBS surgery

One of the predictors for successful ANT DBS is the accurate placement of a DBS electrode within ANT, which ensures the optimal therapeutic effect [46, 47]. An indirect targeting method (in reference to the anterior commissure/posterior commissure line) for stereotactic determination of the ANT may not be applicable in epilepsy surgery [46, 47].

It has been shown that patients with long-standing intractable epilepsy have disturbed brain architecture, not only in the epileptic focus (foci) but also in the distinct brain areas, including the ANT. ANT atrophy is recognizable in patients with longstanding mesial temporal lobe epilepsy [48]. Most authors point out that indirect stereotactic coordinates should be used cautiously and corrections should be made following the individual patient's anatomy [46, 48]. Direct visualization of the ANT and surrounding white matter tracts such as mammillothalamic tract (MTT), external and internal medullary laminae may be accomplished by following MRI sequences such as short tau inversion recovery (STIR) or T1-weighted magnetisation prepared gradient echo (MPRAGE) [48, 49]. Fast grey matter acquisition T1 inversion recovery (FGATIR) is another 3 Tesla MRI sequence that provides thin, high-resolution images with significantly better visualisation of ANT compared to standard 3 Tesla T1 and T2-weighted images [49].

In epilepsy surgery, it is not only the ANT targeting that is challenging but also the planning of stereotactic trajectories. Most authors have used a transventricular rather than an extraventricular approach [7, 19, 20]. An alternative novel extraventricular approach with entry points (burr holes) placed in parietal regions has been recently proposed [50]. Using this parietal extraventricular approach, a successful ANT targeting rate of 90% electrode placed bilaterally within ANT was achieved. Two or more contacts within the ANT were presented in 75% of all leads [50]. In the MORE study, the success rate of placing contacts within the ANT was strictly associated with the selection of a transventricular rather than an extraventricular trajectory [51]. The transventricular approach is thus regarded as the standard and best established approach for ANT DBS [19, 20, 51].

Search for ideal target in ANT DBS for DRE

The exact best location for stimulation within ANT remains a matter of controversy. According to the experience of Lehtimäki et al., stimulation of the ANT complex has a powerful anti-seizure effect [46, 47, 51]. Stimulation at the anterior aspects of ANT reaches anteromedial (AM) and anterior principal (Apr) subnuclei [47]. AM has well established connections to the frontal cortex, anterior cingulum, retrosplenial cortex, amygdala and hippocampus [12, 14]. Guo et al. found that active contacts located more adjacent to the centre of gravity of the anterior half of the ANT volume defined as anterior centre (AC) have the best effects on seizure reduction [33].

Krishna et al. have suggested that a basolateral part of the ANT that corresponds to the anteroventral (AV) subdivision of the ANT is the most efficacious site to be stimulated [22]. This site correlates to a region posterior and superior to mtt. The search for the optimal ANT target requires further detailed studies that will correlate the exact anatomical location of active contact(s) within ANT with a clinical outcome [12, 14–18, 22, 32]. The recent study by Schaper et al. suggested that

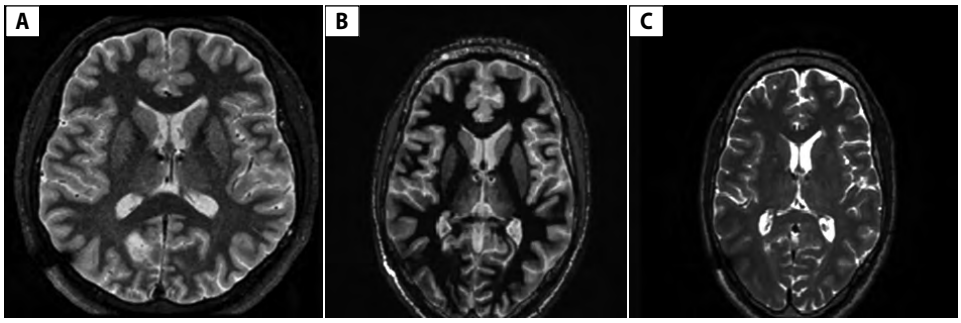

Figure 2. Postoperative ANT DBS electrodes visualization in STIR sequences (A), in 3 D T2 WMN MPRAGE sequences (B), and T2 weighted sequences (C)

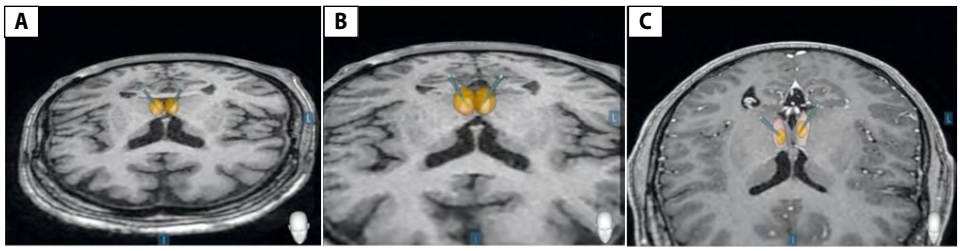

Figure 3. VTA (volume of tissue activated) of a patient with ANT DBS leads implanted in ANT bilaterally. VTA's with initial stimulation settings used in the SATNE study (5 Volts, 90 microseconds, 145 Hz) (A). VTA's of increased stimulation settings allowed to be increase at 7th and 10th months in the SANTEstudy (7.5 Volts, 90 microseconds, 185 Hz) (B). Both VTA's generated using these stimulation setting produce unspecific stimulation covering not only VTA including mamillothalamic tract and in most cases surrounding structures like dorsomedial nucleus of the thalamus. VTA affects only exclusively ANT bilaterally using the low stimulation settings (2.4 Volts, 90 microseconds, 145 Hz) (C)

stimulation of ANT-mtt junction was associated with increased seizure control, suggesting that co-stimulation of white matter of mtt may play a pivotal role in seizure control [32].

The effects of the ANT DBS on the efferents of mammillary bodies (nuclei), mainly the white matter tracts including mammillothalamic (mtt) and mammillotegmental (mtgt) tracts, may regulate the memory function. Recent studies in animals have provided evidence that mammillary body efferents are involved in regulating memory independently from the hippocampus, but the importance of these individual components in human brain functional anatomy associated with memory remains unexplained [52]. Mtgt takes part in controlling visceral functions and transforming spatial data by influencing the brainstem's autonomic nuclei. Moreover, anatomical findings suggest that tegmental afferent fibres play a crucial role in modifying transport information from hippocampal formation to the anterior thalamus [52]. Postoperative MR imaging in different sequences with implanted ANT DBS leads is set out in Figure 2.

Stimulation parameters, polarity, and mode of ANT stimulation

There are no guidelines regarding setting the initial stimulation parameters in patients undergoing ANT DBS, and various authors have used different stimulation parameters, modes, and polarities (Tab. 1). The image-verified localisation of implanted DBS leads may be of great importance for choosing appropriate contacts, stimulation polarity, and mode [7, 19, 20, 53]. It has been shown that improperly placed DBS leads have a suboptimal effect on the seizure frequency reduction, and replacements have been warranted [7, 19, 53]. Moreover, stimulation of contacts outside the ANT can elicit unwanted psychiatric adverse events or cause subjective mood and memory problems [54].

The antiepileptic effect of ANT DBS is based on animal studies and human data [7–22, 55, 56]. In animal models, thalamic stimulation at low frequencies drives synchronisation activity in distant brain regions, whereas stimulation at high frequencies desynchronises intrinsic cortical activity. High-frequency thalamic stimulation can block epileptiform activity in the cortex. A so called 'driving response' elicited by low-frequency ANT DBS is demonstrated on scalp EEG with synchronisation of brain activity. As mentioned above, high-frequency stimulation above 100–130 Hz is used to desynchronise the EEG activity. Frequencies as high as 185 Hz have also been reported, but higher frequencies can induce unwanted adverse events, and reduce battery life significantly [27].

Most older studies, including the SANTE trial, used relatively high initial voltage (around 5 Volts) [7]. An example of the volume of tissue activated (VTA) resembling the SANTE

Table 1. Clinical studies reporting outcome of ANT DBS for DRE

Authors and year of publication	Country of study's origin Time of patient recruitment	Number of patients	Follow-up, in months	Responder rate, number of patients, or percentage of responders	Seizure reduction at last follow-up	Stimulation parameters	Mode of stim	Stim. polarity
Upton et al. 1987 [10]	United States	6	42	4	NR	60–70 Hz 300 us 3.5–3.8 V	C	NA
Hodaie et al. 2002 [13]	Canada	5	15	3	54%	100 Hz 90 us 10 V	I	B/M
Kerrigan et al. 2004 [11]	United States	5	6-36	4	48%	100 Hz 90 us 1–10 V	I	B
Lee et al. 2006 [23]	South Korea	3	11.2	3	75.4%	130 Hz 90 us 10 V	I	M
Andrade et al. 2006 [17] +1 patient, 5 previously reported by Hodaie	Canada	6	60	5	more than 50%	10–185 Hz 90–120 us 1–10	I	B/M
Lim et al. 2007 [15]	Taiwan	4	43.8	1	51%	90–180 Hz 60–120 us 4–7 V	C/I	B
Osorio et al. 2007 [16]	United States March 2000 to July 2004	4	36	4	75.6%	175 Hz 90 us 4.1 V	I	M
Fisher et al. 2010 [7]	United States Trial registration 18 January, 2005	110	25	54%	56%	145 Hz 90 us 5 V	I	M
Salanova et al 2015 [19]	United States Trial registration 18 January, 2005	83	61	68%	69%	145 Hz 90 us 5 V	I	M
Lee et al. 2012 [18]	South Korea From 2005	15	27	12	70.4%	100–185 Hz 90–150 us 1.5–3.1 V	C	M
Piacentino et al. 2015 [25]	Italy 2007 to 2011	6	12	2	50%	140 Hz 90 us 4 V	I	B
Krishna et al. 2016 [22] 5 pts previously published	Toronto, Canada Early cohort 5 pts + 11 new pts	16	52	11	NR	> 100 Hz 90 us 2.4–4.7 V	C	M
Kim et al. 2017 [21]	South Korea From 2005 Early cohort 15 pts	30	74.9	NR	70%	130 Hz 90 us 1.5–3.1 V	C	M
Sitnikov et al. 2018 [24]	Russia Time period NR	12	7 months to 5.2 years	NR	80.3%	130 Hz 90 us 1.5–4 V	C	M/B
Hermann et al. 2018 [26]	Norway April 2010 to March 2015	18	12	4	NR	145 90 Hz 5 V	I	NR
Park et al. 2019 [27]	South Korea 2016 to 2017	7	12–18	5	58.4%	133 Hz 184 us 1.9–2.1 V	C	M

→

Table 1 cont. Clinical studies reporting outcome of ANT DBS for DRE

Authors and year of publication	Country of study's origin Time of patient recruitment	Number of patients	Follow-up, in months	Responder rate, number of patients, or percentage of responders	Seizure reduction at last follow-up	Stimulation parameters	Mode of stim	Stim. polarity
Koeppen et al. 2019 [28]	Hamburg, Germany, August 2011 to February 2014	10	21.5	NR	70%	145 Hz 90 us up to 5 V	I	M
Herrera et al. 2020 [29]	Canada 2013 to 2020	6	4.9 years	2	NR	145 Hz 90 us up to 8.5 V	I	M/B
Jarvenpaa et al. 2020 [30]	Finland Time period NR	27	24	19	65% [FIAS]	140 Hz 90 us 5–6 V	I	M/B
Salanova et al. 2020 [20]	United States Trial registration 18 January, 2005	73 62	7 years 10 years	74%	75% [7 years]	161 Hz 103.1 us 6.6 V	I	M/B
Tassigny et al. 2020 [31]	Belgium March to October 2016	5	15	NR	24.5%	140 Hz 90 us 5 V	I	NR
Schaper et al. 2020 [32]	Netherlands Time period NR	20	12	14	46%	145 Hz 90 us 5.6 V	I	M/B
Guo et al. 2021 [33]	South Korea Between 2016 and 2018	25 studied 19	12	15	64 .3%	130 Hz 90 us 1.5–3.1 V	C	M
Kaufmann et al. 2021 [34]	Munich, Germany, August 2011 to June 2019	23 pts [unilateral DBS 2 pts]	46.6	17	NR	140–145 Hz 90 us 1.5–3.5 V	I	M/B
Tong et al. 2022 [35]	Beijing, China Between 2015 and 2019	20 studied 11	12	6	51.4%	NR	NR	NR
Miron et al. 2022 [36]	Israel January 2017 to January 2021	11	28.5	8	54.8 ± 34.2%	140–145 Hz 90 us 5 V	I	M/B
Costa--Gerdrudes et al. 2022 [37]	Lisbon, Portugal Between 2011 and 2019	16 studied 14	11	9	NR	140–145 Hz 90 us 5 V	I	M
Yan et al. 2023 [38]	Beijing, China January 2012 to December 2021	45	44.2	29	82.2%	NR	NR	NR
Peltola et al. 2023 [39]	Europe registration 31 January 2012 Patient enrollment 21 February 2012 to 19 June 2019	170	2 years 5 years	2 years 32.3% 5 years 53.2%	2 years 33.1% 5 years 55.1%	145 Hz 90 us 5 V	I	M/B
Dague et al. 2023 [40]	Bonn, Germany 2012 to 2124	11	51.5	54.5%	73.6%	NR	NR	M/B
Parisi et al. 2023 [41]	United States, January 2011 to February 2021	31	27.6	26	65%	Low/high frequency	I/C	M/B
Sobstyl et al.2023 [42]	Poland May 2020 to October 2022	10	13.6	9	73.3%	Mean 132 Hz 84 us 3.2 V	I	M

NR — not reported; I — intermittent stimulation mode; C — continuous stimulation mode; M — monopolar stimulation; B — bipolar stimulation

study voltage and presently applied voltage is depicted in Figure 3 (A, B, C). This may suggest that the initial stimulation parameters mentioned above could not only stimulate the ANT, but also the surrounding brain tissue. Moreover, in most studies, the intermittent stimulation mode consisting of 1 minute on stimulation followed by 5 minutes off stimulation was used [7, 11, 13, 19, 20, 25]. Today, the initial stimulation voltage is usually set in the range of 2 or 3 Volts [27, 34]. The pulse width in most studies is set above 90 microseconds [7, 19, 20, 22, 25]. Most studies have used an intermittent mode of stimulation, but a few have implemented a continuous stimulation mode [10, 15, 22–24, 33]. Clinical studies, where a continuous stimulation mode has been used, report higher scores for mean seizure frequency reduction [22–24, 33, 41].

Adverse events related to ANT DBS procedures

Adverse events related to the ANT DBS procedure can be divided into three categories, (i) intraoperative-related complications (bleeding, venous infarction, improper intraoperative placement of DBS lead/s); (ii) hardware-related complications (infection, erosions, fracture or migration of a DBS lead); and (iii) stimulation-induced complications (aggravation of seizure frequency or inducing *de novo* psychiatric/behavioural symptoms or aggravation of pre-existing comorbid psychiatric/behavioural symptoms).

Special attention should be paid to possible cognitive and emotional sequelae of ANT DBS as well as outcomes assessing quality of life. The ANT is a relay structure of the circuit of Papez and cognitive as well as emotional sequelae can be elicited by stimulation of a limbic system [57]. There is a possibility of *de novo* induction or aggravation of pre-existing psychiatric symptoms [58]. A relatively large number of patients with longstanding DRE are handicapped by memory and psychiatric side effects related to uncontrolled seizures before undergoing ANT DBS. Psychiatric and neuropsychological assessments play a major role in selecting patients for DBS for DRE [7, 19].

The SANTE trial has revealed gradual improvement in the cognitive domains of attention and executive functions [19]. Tröster et al. followed patients for 7 years after ANT DBS from the previously reported prospective randomised SANTE trial, and found no significant cognitive declines or worsening of depression [59].

Mood disturbances or memory problems seen only in a blinded phase of the SANTE trial may be related to the overstimulation of the ANT as well as to a lesional (microthalamotomy) effect [7]. Monopolar stimulation using relatively high stimulation parameters (especially voltage) in an early postoperative phase may explain this transient subjective mood and memory problems [7]. Nevertheless, the long-term neuropsychological outcomes have shown improvements in memory, verbal fluency, and mood in patients after ANT DBS [59]. Other authors who used ANT DBS have noticed objective improvements in alertness and communicative behaviour [60]. ANT DBS improves some cognitive domains without causing major mood and memory disturbances [59, 60]. Adverse events including procedural, hardware and stimulation-related complications, as well as cognitive/emotional outcomes following ANT DBS, are set out in Table 2.

Indications and contraindications for CMN DBS

The second most common thalamic nucleus targeted for DRE is CMN [6]. CMN represents a thalamic relay structure of a reticulocortical system that participates in wakefulness, affective processes and in widespread regulation of cortical excitability [59, 60]. It has been shown that CM DBS is an effective treatment for primary generalised tonic-clonic or multifocal (multilobar) seizures, atonic seizures, and myoclonic seizures. Good clinical results of CMN DBS have been obtained for DRE in patients with a diagnosis of LGS [63]. Intellectual disability does not constitute a contraindication for CMN DBS, because most patients with LGS exhibit intellectual disability, ranging from moderate to profound [63].

The exclusion criteria for CMN DBS constitute individuals with an increased risk of bleeding, anatomical brain abnormalities precluding safe CMN DBS surgery, focal seizure type, and previous or current psychogenic non-epileptic seizures.

Clinical efficacy of CMN DBS for treatment of DRE

The pioneers of CMN DBS were the Velasco brothers, publishing in 1987 their first study including 5 patients with DRE [65]. Stimulation was applied through percutaneous wires resulting in focal seizures reduction by 60–100%, and generalised seizure reduction by 80–100% [65]. Thereafter, Fisher published a crossover study in 7 patients [66]. The mean seizure frequency reduction was only 30% which was not statistically significant, versus 8% when stimulation was discontinued. Among Fisher's 7 patients, three had temporal lobe epilepsy, which may explain the apparent lack of efficacy [66].

Additional studies published by Velasco's group totalling nearly 100 patients pointed out that the best results were obtained in patients suffering from generalised onset seizures and multifocal seizures [64, 65, 67]. In Velasco's experience, CMN DBS for focal seizures was limited. A two-centre, single-blind, controlled trial of CMN DBS in 11 patients with generalised and frontal lobe DRE demonstrated that CMN DBS was effective in generalised epilepsy, but not in frontal lobe epilepsy [68]. In 2020, Cukiert et al. published the results of a prospective open label study including 20 patients diagnosed with LGS [69]. CMN DBS produced significant reduction of tonic seizures by 66%, atypical absence seizures by 78%, atonic seizures by 83%, and generalised tonic-clonic seizures by 89% [69].

Recently, Dalic et al. published the results of a prospective double-blind, placebo-controlled clinical trial of CMN DBS for LGS [70]. The baseline seizure frequency reduction versus

Table 2. Adverse events including procedural, hardware and stimulation-related complications as well as cognitive/emotional outcomes following ANT DBS in patients with drug resistant epilepsy

Authors and years	Procedural--related adverse events intracranial haemorrhage	Hardware-related adverse events or other complications	Stimulation--related adverse events	Behavioural/cognitive changes	Activities of daily living
Upton et al. 1987 [10]	NR	NR	Some pts experienced euphoric and ecstatic feelings	Improvement in behaviour and emotional responses	Improvement in activities of daily living
Hodaie et al. 2002 [13]	NR	1 pt had skin erosion with wound revision	NR	Subjective improvements in cognitive status noted by family members	Subjective improvements noted by family members
Kerrigan et al. 2004 [11]	NR	1 pt required replacement of leads due to incorrect placement	NR	NR	NR
Lee et al. 2006 [23]	NR	1 pt had infection around IPG, removal of DBS system in a patient implanted in STN	NR	Subjective improvement of cognitive and behavioural status noted by family members	Subjective improvements in quality of life noted by family members
Andrade et al. 2006 [17]	NR	NR	1 pt experienced lethargy due to continuous stimulation	NR	NR
Lim et al. 2007 [15]	1 pt had small frontal haemorrhage – mild hand weakness	1 pt had erosion over extension; resulted in removal of whole system	NR	Behavioural changes occurred	Subjective improvements in quality of life
Osorio et al. 2007 [16]	NR	NR	NR	Verbal fluency, mental flexibility declined significantly in some patients	Quality of life improvement in all patients – objective assessment
Combined Fisher et al. 2010 [7] Salanova et al. [19]	No symptomatic haemorrhage 5 asymptomatic haemorrhages [4.5%]	Adverse events provided for long term follow-up implant side pain 20.9% implant side paresthesias 22.7% 14 pts developed [12.7%] infection. DBS leads not in target in 8.2% Extension fracture 4.5% IPG migration 5.5%	2 pts had acute, transient stimulation-associated seizures. 7 episodes of status epilepticus, 3 pts with status epilepticus were not stimulated	Long-term objective improvements in all domains of attention, executive functions, depression, tension/ /anxiety, subjective cognitive functioning. SUDEP: 1 baseline phase, 2 definitive and 1 possible.	Objective improvements in quality of life [Quality of Life in Epilepsy-QoLI-31]
Lee et al. 2012 [18]	NR	1 pt had infection resulted in DBS explantation	NR	NR	NR
Piacentino et al. 2015 [25]	NR	NR	NR	Objective improvements in behaviour	Objective improvements in quality of life [Quality of Life in Epilepsy-QoLIE-31]
Krishna et al. 2016 [22]	NR	1 pt had a system explanted due to infection. 1 pt with infection required wound revision. 1 system explantation due to cosmetic reasons	1 pt postoperative episode of psychosis. 2 pts developed an increase in seizure frequency in early postoperative period	1 pt developed severe postoperative agitation causing switching off of stimulation	NR

→

Table 2 cont. Adverse events including procedural, hardware and stimulation-related complications as well as cognitive/emotional outcomes following ANT DBS in patients with drug resistant epilepsy

Authors and years	Procedural--related adverse events intracranial haemorrhage	Hardware-related adverse events or other complications	Stimulation--related adverse events	Behavioural/cognitive changes	Activities of daily living
Kim et al. 2017 [21]	1 symptomatic haemorrhage left hemiparesis disappeared after 3 months	1 infection with antibiotic treatment alone. 1 pt had system explantation that was not reimplanted. Lead disconnection in 2 pts [6.9%] Revision due to suboptimal lead placement in 3 pts out of 58 DBS leads [5.2%]	2 pts had DBS hardware removals due to lack of efficacy	Improvement in word fluency task. No significant changes in general abilities, information processing, and executive functions. 1 pt complained of agitation resulting in switching off of stimulation. One [3.4%] probable SUDEP occurred 5 years after implantation	NR
Sitnikov et al. 2018 [24]	1 frontal haematoma – asymptomatic 1 haematoma in anterior lesion group	1 system explantation due to ineffectiveness. 1 infection along extension cable and IPG–preservation of DBS electrodes	2 pts experienced a current leak at the IPG site	No side effects regarding mental and emotional status	NR
Hermann et al. 2018 [26]	NR	1 transient episode of dysarthria and left central facial nerve palsy 1 pt with stimulation--induced facial twitches – reimplantation of the electrode 2 pts increased of preoperative seizures	NR	Subjective reports of more energy, better sleep, shorter and less intense seizures, better cognitive functioning	NR
Park et al. 2019 [27]	NR	NR	NR	Objective behavioural improvements	Objective quality of life improvements [Quality of Life in Epilepsy-QoLIE-31]
Koeppen et al. 2019 [28]	NR	NR	NR	NR	NR
Herrera et al. 2020 [29]	NR	NR	2 pts mild and transient headaches	1 pt had SUDEP	NR
Jarvenpaa et al. 2020 [30] includes pts from 2016	NR	NR	NR	2 pts had SUDEP	NR
Salonova et al. 2020 [20]	Reported in previous studies by Fisher and Salanova	Implant site infection from implant to 10 years — 12.7% of pts [1 year rate of 7.3%] Leads not in target 8.2%	NR	At 7 years 37.3% had depression 2/3 No deterioration in psychosocial functioning	QOLIE-31 stable improved, meaningful improvement on QOLIE-31 in 43% of patients. Satisfied or greatly satisfied 84% [54/64].
Tassigny et al. 2020 [31]	NR	NR	NR	1 pt sleep disorder, 2 pts had mild memory impairment, 2 pts sleep disturbances, 2 pts had transient depression	Objective quality of life improvements [Quality of Life in Epilepsy-QOLIE-31] improved in 4 pts
Schapper et al. 2020 [32]	NR	NR	NR	2 pts irritability and sleep problems	NR
Guo at al. 2021 [33]	NR	1 pt hardware removal due to infection	NR	NR	NR

→

Table 2 cont. Adverse events including procedural, hardware and stimulation-related complications as well as cognitive/emotional outcomes following ANT DBS in patients with drug resistant epilepsy

Authors and years	Procedural--related adverse events intracranial haemorrhage	Hardware-related adverse events or other complications	Stimulation--related adverse events	Behavioural/cognitive changes	Activities of daily living
Kaufman et al. 2021 [34]	NR	2 pts had hardware removal due to bacterial meningitis and postauricular dermal defects	Mild stimulation induced side effects	NR	Assessed in 9 pts depression [BDI] and [QOLIE-31] improved
Tong et al. 2022 [35]	NA	NR	NR	NR	NR
Miron et al. 2022 [36]	NR	Trauma necessitating hardware removal and reimplantation	NR	2 pts subjective memory deterioration, 2 pts depressive symptoms	NR
Costa-Gerdrudes et al. [37]	NR	NR	NR	3 pts suffered depression, 1 pt had psychosis	NR
Yan et al. 2023 [38]	NR	NR	NR	NR	NR
Peltola et al. 2023 [39]	DBS-related AEs were connected to procedure [n = 24] no intracranial haemorrhages, and no deaths related to DBS	Total of 11 pts [6.1%] had lead modifications, of which most frequent being explant with replacement. 2 explants due to infection [1%], 1 explant due to suicidal ideation in 1 pt	Increased frequency/ /severity] of seizure [16%], memory impairment [patient-reported complaint, 15%]	1 pt had died with definite sudden unexpected death in epilepsy [SUDEP] depressive mood [patient--reported complaint, 13%], and epilepsy [12%], headache [7%], head injury [5%], irritability [5%], anxiety [5%], cognitive impairment [5%]	2-point improvement in QOLIE-31, one third of pts improved by more than 5 points in QOLIE-31 assessment available for 78 pts
Dague et al. 2023 [40]	NR	5 pts had DBS hardware removal due to psychiatric AE or insufficient seizure reduction	Psychiatric AE noted in 5 pts	Significant deterioration in executive functions reported in 1 pt. Long-term neuropsychological effects included significant intraindividual changes in verbal learning and memory. Figural memory, attention and executive functions, confrontative naming and mental rotation were mostly unchanged, and improved	NR
Parisi et al. 2023 [41]	NR	NR	NR	1 pt subjective memory impairment, 4 pts self--reported improved memory function, 4 pts major depression episodes	NR
Sobstyl et al. 2023 [42]	Pneumothorax with urgent pleural drainage	Head injury [10%] requiring surgery for chronic subdural haematoma	NR	Cognitive functioning preserved, deterioration in mental well-being [depressed mood] of operated pts	NR

NR — not reported; pt — patient; pts — patients; SUDEP — sudden unexpected death in epilepsy; QOLIE-31 — Quality of Life in Epilepsy-31 inventory; IPG — implantable pulse generator; QOLIE — Quality of Life in Epilepsy questionnaire; BDI — Beck Depression Inventory; DBS — deep brain stimulation; STN — subthalamic nucleus; AEs — adverse events

study exit was 46.7% [69]. Apart from the abovementioned clinical studies, other studies have reported mean seizure reduction for different generalised seizures ranging from 51% to 83% [71, 72–76]. The clinical outcomes of CMN DBS for DRE are set out in Table 3.

Other factors affecting outcome of CMN DBS for DRE

The most common predictor of a good clinical outcome of CMN is the recruiting response elicited by macrostimulation. Macrostimulation is carried out for proper target confirmation. Low-frequency stimulation (3–6 Hz) generates time-locked recruiting responses that are recorded bilaterally, even after unilateral CMN stimulation; the recruiting response amplitude is usually slightly smaller over the non-stimulated hemisphere. High-frequency stimulation does not generate recruiting responses, but rather a direct current shift, noted almost exclusively over the stimulated hemisphere [77]. This recruiting response correlates with a good clinical outcome [64, 67, 69]. Another possible predictor of a good clinical outcome of CMN DBS is the involvement of reticular system network by VTA generated by stimulation settings of implanted CMN DBS leads [75]. VTAs interconnected with a reticular system network encompassing sensorimotor and supplementary cortices with cerebellum and brainstem have produced significant seizure frequency reduction [75]. The clinical data demonstrate that CM DBS outcome in DRE is highly dependent on the individual connectivity profile involving the cerebello-thalamo-cortical circuits [75].

Targeting and trajectory planning during CMN DBS surgery

CMN is a difficult nucleus to target, lacking clear boundaries on the standard T1- and T2-weighted MRI, which hinder it as a direct DBS target for clinical applications [78]. This direct targeting of CMN without clear visualisation of this nucleus becomes more challenging when the structure is smaller than 10 mm in most dimensions. Even with two-dimensional high-resolution proton attenuation-weighted images at 3T, or by optimised 3D MPRAGE protocol, clear discrimination of all thalamic substructures is not achievable [78]. The direct targeting became possible with quantitative susceptibility mapping MRI which can assist localisation of CM with clear delineation from the surrounding subthalamic nuclei [79].

CMN is located at the level of the posterior commissure 10 mm away from the midline. CMN has an oval shape [78]. The trajectory to CMN is intraparenchymal without the need to transverse the ventricles as in the case of ANT targeting. In the absence of the abovementioned direct visualisation techniques, indirect targeting is usually performed [80].

Search for ideal target in CMN DBS for DRE

The CM is an intralaminar nucleus of the thalamus and is part of the reticulo-thalamo-cortical system that mediates cortical excitability and participates crucially in the modulation of conscious state [61, 62, 65, 69]. High frequency stimulation of CMN blocks diffuse cortical recruitment and augmenting responses [77]. CMN neurons project mainly to striatum and cerebral cortex, and ipsilateral central and precentral motor areas [72]. CMN neurons projecting to the cortical motor areas are located in the lateral part of CMN within the ventrolateral CM (CMpc). Consequently, CMN DBS would be expected to be most effective in generalised and frontal epilepsies and less in temporal epilepsies [72].

In Velasco's experience, the optimal target within CMN associated with the greatest seizure frequency reduction was located in the ventrolateral part of CM (CMpc) [64, 67]. DBS leads located in this position were associated with a more than 80% reduction in seizure frequency [64]. More dorsal, posterior or medial DBS lead location was related to weaker seizure suppression. The effectiveness of DBS lead placement in this target has been proven by several reports of CMN DBS [68, 71, 72].

Modern neuromodulation software with visualisation of implanted DBS leads and simultaneous estimation of VTA has enabled interesting insights into thalamic nuclei being stimulated for DRE [75]. VTA of DBS leads implanted at the ventrolateral part of CM incorporate in the stimulation field the surrounding thalamic subnuclei such as posterior ventral part of the mediodorsal nucleus (parvocellular MD, MDpc), central lateral nucleus (CL), and posterior part of the ventrolateral nucleus (VLp) [81]. Using a relatively high stimulation setting in most reported studies, the antiseizure effect is related to the summation of neuronal activation of complex areas as CMpc, MDpc, CI, and VLp, not merely to the modulatory effect of CMN alone [72]. More focused stimulation restricted to ventrolateral CM may be more effective for generalised epilepsy, and a wider field of stimulation for multifocal, multilobar epilepsies [64, 67].

Stimulation parameters, polarity, and mode of CMN stimulation

As in the case of ANT DBS, there are no guidelines related to setting the initial stimulation parameters in patients undergoing CMN DBS. Different authors have used various stimulation parameters, modes, and polarities [64, 65, 68–70, 72]. The image-verified localisation of implanted DBS leads with visualisation of VTAs may be of great value for choosing appropriate contacts, stimulation polarity and settings [75].

Most studies have used 130 Hz stimulation, although in three studies 60 Hz stimulation was used [67, 75, 76]. In the context of neurostimulation, the application of electrical stimuli at frequencies of 80–200 Hz is considered to be 'high frequency stimulation'.

The initial stimulation voltage for CM DBS is relatively high at up to 5 V, although most recent studies of CMN DBS report a range of stimulation voltage of 1–5 Volts, indicating that lower stimulation voltage may be associated with good

clinical results [70, 72–74]. The pulse width for CMN DBS shows the widest range from 60, 90 microseconds to even 300 or 450 in older publications [69, 70–74].

The intermittent mode of stimulation was used up to 2006 [65, 66]. Continuous mode of stimulation was initiated by Cukiert in 2009 and most authors upward perform continuous stimulation of CMN for DRE [68, 69, 71–73].

The continuous mode of stimulation may be related to higher scores for mean seizure frequency reduction [70–73]. The stimulation settings, polarity as well stimulation mode in historical and present clinical trials of CMN stimulation are set out in Table 3.

Adverse events related to CMN DBS procedures

Intracranial haemorrhagic complications related to CMN DBS procedures have been encountered only in three patients [66, 74, 76]. In 2 patients the intracerebral hemorrhages were clinically silent [66, 76]. The third was a haemorrhage related to the DBS procedure which resulted in transient hemiparesis that resolved within one month [74]. Another intraoperative-related event due to pneumocephalus resulted in the misplacement of both DBS electrodes [72]. During revision surgery, both DBS electrodes were correctly implanted [72]. Patients with primary generalised seizures and with a diagnosis of LGS may be more prone to the development of skin erosions and subsequent infections. The targeted population for CMN DBS includes children and young adults where skin-related complications due to the implanted hardware pose a greater challenge compared to the adult patient population. Skin-related complications in children with LGS have been the main reason for DBS hardware explantation [64, 67, 68, 70]. Mechanical damage to the DBS hardware has also been reported in patients after CMN DBS, but less frequently than erosions and infections [64, 65].

Although the patient population for CMN DBS (LGS patients) has mild to profound mental retardation, interestingly, most studies have reported improvements in behaviour and emotional responses with better psychological functioning [64, 65, 68]. These behavioural, cognitive effects are directly related to the seizure reduction after CMN DBS [64, 65, 68]. One study reported stable psychological functioning after CMN DBS [66]. Some studies have not mentioned cognitive, behavioural changes after CMN DBS [67, 72, 73]. In general, most studies have reported improvements in activities of daily living or life satisfaction using objective clinical scales [64, 65, 68, 69, 74]. The above mentioned cognitive and emotional outcomes following CMN DBS are set out in Table 4.

Conclusions and future directions

The ANT and CMN represent the most common targeted thalamic nuclei of network brain hubs involved in the widespread propagation of epileptic seizures. The clinical experience of thalamic DBS for DRE is still limited compared to the high number of patients with multifocal DRE who are not amenable to resective surgery. The ANT DBS has shown clinical efficacy for focal to secondary generalised tonic-clonic seizures when epileptic foci involved the mesial/temporal or frontal brain regions. Epileptic foci restricted to parietal or occipital lobes do not respond so favourably to ANT DBS. The CMN DBS showed good clinical efficacy for primary generalised tonic-clonic seizures with multiple epileptic foci located in precentral motor areas, and primary somatosensory cortex.

Both thalamic nuclei are relatively small targets with different subnuclei. They both represent the relay structures of the Papez circuit (ANT), and the cerebello-thalamic-cortical circuit with afferents from reticular formation (CMN). Both thalamic targets have widespread cerebral connections through the appropriate brain networks. Compared to the anecdotal historical reports in the 20th century of ANT or CM DBS for DRE, today's image-guided targeting prevails in the proper placement of DBS leads. The postoperative confirmation of implanted DBS leads by CT/MRI done after surgery, and merging with preoperative MRI, enables the selection of implanted contacts. Moreover, the visualisation of VTAs based on individual settings can avoid the overstimulation of the targeted nucleus, reducing the possible stimulation-induced adverse events.

The novel connectomic approach in selecting appropriate patients based on connectome of the targeted nucleus with epileptogenic focus/foci may have a great value in selecting patients for thalamic DBS for DRE. Functional imaging and diffusion imaging may direct stimulation settings optimisation by estimation of VTA which incorporate the brain networks involved in epilepsy propagation.

All of these factors may bring about in future better seizure frequency reduction after ANT or CMN DBS therapy for DRE.

Table 3. Clinical studies reporting outcome of CMN DBS for DRE

Authors and year of publication	Country of study's origin, Time of patient recruitment	Number of patients	Follow-up in months, mean range	Responder rate, number of patients, or percentage of responders	Seizure reduction at last follow-up	Stimulation parameters	Stimulation mode	Stimulation polarity
Velasco et al. 1987 [65]	Mexico City, Mexico	5	6 to 37 months	5	80–100% reduction in BTCS, 60–100% reduction in partial complex seizures 100% reduction of myoclonic seizures in one patient. Astatic seizures not reduced	60–100 Hz 100 us 0.8 to 2.0 mA	I	B
Fisher et al. 1992 [66]	United States	7	3 to 13 months	3 out of 6 patients in open label phase were responders	30% in placebo-controlled phase	65 Hz 90 us 0.5 to 10 V	I	B
Velasco et al. 2000 [67]	Mexico City, Mexico from 1990 to 1993	13 2 diagnosed with TSC	Mean 41.2 12–94 months	12	Significant improvement and atypical absences, better results for LGS patients	60 Hz 90 us 4 to 6 V	I.	B/M
Velasco et al. 2006 [64]	Mexico City, Mexico	13 with LGS	46 from 23 to 132 months	12	Significant reduction in severe BTCS [GTS] and atypical absence seizures [AA] 80%	130 Hz 450 400–600 uA	I	B
Cukiert et al. 2009 [71]	Sao Paulo, Brazil	4 with GTS after callosotomy	18 from 12 to 24 months	4	78%	130 Hz 300 us 2 V	C	B
Valentin et al. 2013 [68]	London, United Kingdom, Madrid, Spain	11	24	2 out of 5 pts with frontal lobe epilepsy responders, 5 out of 6 pts with generalised epilepsy responders	81% in GTS, 10% in frontal seizures	130 Hz 90 microseconds up to 5 V, in non-responders 60 Hz was used	C	M
Son et al. 2016 [72]	Seoul, South-Korea	14	Mean 18.2 ± 5.6 from 9 to 25 months	11 [78.6%]	68 ± 22.4% [25–100%]	Mean 129.3 ± 2.7 Hz 124.4 ± 23 us 2.2 ± 0.41 V	C	M
Kim et al. 2017 [73]	Seoul, South Korea	10 [3 GTS and 7 MFE]	21	9	72% LGS patients showed 52% SR, whereas frontal epilepsy pts 80.3%	130 Hz 90 us from 1.5 to 2 V	C	M
Cukiert et al. 2020 [69]	Sao Paulo, Brazil	20 LGS or LGS like	At least 12 months follow-up, mean 30 months	90%	90% of patients responders. Significant reduction of tonic seizures 66%, atypical absence 78%, atonic 83%, and generalised tonic-clonic seizures 89%	130 Hz 300 us up to 4.5 V	C	B
Dalic et al 2021 [70]	Melbourne, Australia	20 LGS randomised 19	6	Blinded phase 50% in stimulation group versus 22% of controls. [Primary outcome measure]	46.7%	145 Hz 90 us up to 2.5 V	C	M
Alcala--Zermano et al. 2021 [74]	Rochester, United States	5	Mean 80 months–6.6 years Range [37–97] months]	3 pts [60%]	56%	2–100 Hz 60–150 us 1.0 to 6.3 V	I	B
Diaz et al. 2021 [75]	Madrid, Spain	10	Mean 92.4 months [42–129 months]	8	51–%	60 Hz 90 us up to 5 V	NR	NR
Yang et al 2022 [76]	Atlanta, United States	14 including 5 with GLS	Mean 19 ± 5 months [4.1–33 months]	12 pts [68%] were responders	91%	60–130 Hz 90–300 us 1.0–5.5 V	I [4 pts] C [10 pts]	M [4 pts] B [10 pts]

NR — not reported; I — intermittent stimulation mode; C — continuous stimulation mode; M — monopolar stimulation; B — bipolar stimulation; TSC — Tuberous Sclerosis Complex; LGS — Lennox-Gastaut syndrome; MFE — Multi Focal Epilepsy; GTS — Generalised Tonic Epilepsy; pts — patients

Table 4. Adverse events including procedural, hardware and stimulation-related complications as well as cognitive/emotional outcomes following CMN DBS in patients with drug-resistant epilepsy

Authors and year published	Procedural--related adverse events intracranial haemorrhage	Hardware-related adverse events	Stimulation-related adverse events	Behavioural/cognitive changes	Activities of daily living
Velasco et al. 1987 [65]	NR	NR	NR	Improvement in behaviour and emotional responses. Better psychosocial functioning	Improvement in activities of daily living
Fisher et al. 1992 [66]	1 patient asymptomatic bleeding	1 pt revision due to breakage of connecting cable	NR	Psychosocial functioning stable	NR
Velasco et al. 2000 [67]	NR	2 pts [children aged 5 and 6] developed skin erosions. Removal of DBS systems in both children	NR	NR	NR
Velasco et al. 2006 [64]	NR	2 pts were explanted due to repeated skin erosions that could not be controlled by plastic surgery 1 pt had rupture of extracranial lead and connection cable, uncomplicated hardware replacement	NR [patients were unaware of stimulation]	Pts were in non-convulsive status, and former neuropsychological testing was difficult	Improvements in education in most patients; 2 patients lead normal lives; 8 patients are independent or partially independent
Cukiert et al. 2009 [71]	NR	NR	Short-lasting [15–20 mins] parasthesia after each voltage increase beyond 1.0 V	Improved psychosocial functioning	Clinically relevant increase in attention level [SNAP-questionnaire]. IQ slight increase
Valentin et al. 2013 [68]	NR	1 pt had infection resulted in DBS system explanation	NR	Improvements in psychosocial functioning	Improvements in quality of life performed objectively in 7 pts, 6 months after stimulation
Son et al. 2016 [72]	Misplacement of both electrodes due to pneumocephalus requiring replacement	NR	NR	NR	NR
Kim et al. 2017 [73]	NR	NR	NR	NR	NR
Cukiert et al. 2020 [69]	NR	2 pts had developed infections at IPG location. Treatment with antibiotics	Persistent paresthesia which limited 4.5 Voltage	Before surgery, patients were unable to undergo formal neuropsychological evaluation and quantitative attention protocols	Improvement in attention, no worsening related to items of SNAP-IV questionnaire
Dalic et al. 2021 [70]	NR	All adverse events included 7 pts [35%] 1 pt had infection and mega oedema requiring removal of DBS hardware, 1 patient had trauma and emergency surgery, 2 pts had mega oedema along course of electrodes in prestimulation period	2 pts prolonged seizure status epilepticus, 1 patient with facial seizure related injury, 12 pts postoperative drowsiness with 3 pts profound drowsiness	No noticeable behavioural or cognitive adverse events, no deterioration in cognitive function	Parents/carers 18 of 19 pts reported improved alertness
Alcala-Zermano et al. 2021 [74]	1 pt had experienced postprocedural hemiparesis resolved within one month	2 pts developed hardware complications; IPG rotation requiring revision DBS hardware infection resulted in removal	NR	NR	Life satisfaction improved in 56% of pts
Diaz et al. . 2021 [75]	NR	NR	NR	NR	NR
Yang et al. 2022 [76]	1 pt with clinically silent intraventricular haemorrhage	1 pt with hardware breakage, 1 pt with postoperative aspiration event	2 pts developed subjective mood changes	2 pts developed behavioural changes [behavioural outbursts], 1 patient memory difficulties	NR

NR — not reported; pt — patient; pts — patients; IPG — implantable pulse generator; SNAP questionnaire — Teacher and Parent Rating Scale

Article information

Author contributions: *M.S. conception, data collection, intelectual input to the manuscript, literature search.*
M.K. conception, data collection, intelectual input to the manuscript, literature search.
A.W. conception, intelectual input to the manuscript.
T.P. conception, intelectual input to the manuscript.
K.S. conception, intelectual input to the manuscript.
Funding: *The authors received no financial support for the research, authorship, and publication of this article.*
Conflict of interest: *No potential conflict of interest was reported by the authors of this article.*

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000; 342(5): 314–319, doi: 10.1056/NEJM200002033420503, indexed in Pubmed: 10660394.
2. Brodie MJ, Dichter MA, Brodie MJ. Established antiepileptic drugs. Seizure. 1997; 6(3): 159–174, doi: 10.1016/s1059-1311(97)80001-5, indexed in Pubmed: 9203243.
3. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005; 128(Pt 5): 1188–1198, doi: 10.1093/brain/awh449, indexed in Pubmed: 15758038.
4. Cramer SW, McGovern RA, Wang SG, et al. Resective epilepsy surgery: assessment of randomized controlled trials. Neurosurg Rev. 2021; 44(4): 2059–2067, doi: 10.1007/s10143-020-01432-x, indexed in Pubmed: 33169227.
5. Ma BB, Rao VR. Responsive neurostimulation: Candidates and considerations. Epilepsy Behav. 2018; 88: 388–395, doi: 10.1016/j.yebeh.2018.09.032, indexed in Pubmed: 30355456.
6. Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia. 2017; 58(6): 994–1004, doi: 10.1111/epi.13740, indexed in Pubmed: 28398014.
7. Fisher R, Salanova V, Witt T, et al. SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010; 51(5): 899–908, doi: 10.1111/j.1528-1167.2010.02536.x, indexed in Pubmed: 20331461.
8. Fisher RS. Deep brain stimulation of thalamus for epilepsy. Neurobiol Dis. 2023; 179: 106045, doi: 10.1016/j.nbd.2023.106045, indexed in Pubmed: 36809846.
9. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018; 319(4): 388–396, doi: 10.1001/jama.2017.19163, indexed in Pubmed: 29362800.
10. Upton AR, Cooper IS, Springman M, et al. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol. 1985; 19-20: 223–230, indexed in Pubmed: 2980675.
11. Kerrigan JF, Litt B, Fisher RS, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia. 2004; 45(4): 346–354, doi: 10.1111/j.0013-9580.2004.01304.x, indexed in Pubmed: 15030497.
12. Child ND, Benarroch EE, et al. Anterior nucleus of the thalamus: functional organization and clinical implications. Neurology. 2013; 81(21): 1869–1876, doi: 10.1212/01.wnl.0000436078.95856.56, indexed in Pubmed: 24142476.
13. Hodaie M, Wennberg RA, Dostrovsky JO, et al. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia. 2002; 43(6): 603–608, doi: 10.1046/j.1528-1157.2002.26001.x, indexed in Pubmed: 12060019.
14. Klinger NV, Mittal S, et al. Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy. Clin Neurol Neurosurg. 2016; 140: 11–25, doi: 10.1016/j.clineuro.2015.11.009, indexed in Pubmed: 26615464.
15. Lim SN, Lee ST, Tsai YT, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia. 2007; 48(2): 342–347, doi: 10.1111/j.1528-1167.2006.00898.x, indexed in Pubmed: 17295629.
16. Osorio I, Overman J, Giftakis J, et al. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia. 2007; 48(8): 1561–1571, doi: 10.1111/j.1528-1167.2007.01044.x, indexed in Pubmed: 17386053.
17. Andrade DM, Zumsteg D, Hamani C, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology. 2006; 66(10): 1571–1573, doi: 10.1212/01.wnl.0000206364.19772.39, indexed in Pubmed: 16540602.
18. Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotact Funct Neurosurg. 2012; 90(6): 379–385, doi: 10.1159/000339991, indexed in Pubmed: 22922474.
19. Salanova V, Witt T, Worth R, et al. SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015; 84(10): 1017–1025, doi: 10.1212/WNL.0000000000001334, indexed in Pubmed: 25663221.
20. Salanova V, Sperling MR, Gross RE, et al. SANTÉ Study Group. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021; 62(6): 1306–1317, doi: 10.1111/epi.16895, indexed in Pubmed: 33830503.
21. Kim SH, Lim SC, Kim J, et al. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. Seizure. 2017; 52: 154–161, doi: 10.1016/j.seizure.2017.10.009, indexed in Pubmed: 29040867.
22. Krishna V, King NK, Sammartino F, et al. Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target. Neurosurgery. 2016; 78(6): 802–811, doi: 10.1227/NEU.0000000000001197, indexed in Pubmed: 26813858.
23. Lee KJ, Jang KS, Shon YM, et al. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. Acta Neurochir Suppl. 2006; 99: 87–91, doi: 10.1007/978-3-211-35205-2_17, indexed in Pubmed: 17370771.
24. Sitnikov AR, Grigoryan YuA, Mishnyakova LP. Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy. Surg Neurol Int. 2018; 9: 137, doi: 10.4103/sni.sni_25_18, indexed in Pubmed: 30105131.
25. Piacentino M, Durisotti C, Garofalo PG, 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(9): 1525–1532, doi: 10.1007/s00701-015-2498-1, indexed in Pubmed: 26153778.
26. Herrman H, Egge A, Konglund AE, et al. Anterior thalamic deep brain stimulation in refractory epilepsy: A randomized, double-blinded study. Acta Neurol Scand. 2019; 139(3): 294–304, doi: 10.1111/ane.13047, indexed in Pubmed: 30427061.

27. Park HR, Choi SuJ, Joo EY, et al. The Role of Anterior Thalamic Deep Brain Stimulation as an Alternative Therapy in Patients with Previously Failed Vagus Nerve Stimulation for Refractory Epilepsy. Stereotact Funct Neurosurg. 2019; 97(3): 176–182, doi: 10.1159/000502344, indexed in Pubmed: 31533117.
28. Koeppen JA, Nahravani F, Kramer M, et al. Electrical Stimulation of the Anterior Thalamus for Epilepsy: Clinical Outcome and Analysis of Efficient Target. Neuromodulation. 2019; 22(4): 465–471, doi: 10.1111/ner.12865, indexed in Pubmed: 30295358.
29. Herrera ML, Suller-Marti A, Parrent A, et al. Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy: A Canadian Experience. Can J Neurol Sci. 2021; 48(4): 469–478, doi: 10.1017/cjn.2020.230, indexed in Pubmed: 33059773.
30. Järvenpää S, Lehtimäki K, Rainesalo S, et al. Improving the effectiveness of ANT DBS therapy for epilepsy with optimal current targeting. Epilepsia Open. 2020; 5(3): 406–417, doi: 10.1002/epi4.12407, indexed in Pubmed: 32913949.
31. Tassigny D, Soler-Rico M, Delavallée M, et al. Anterior thalamic nucleus deep brain stimulation for refractory epilepsy: Preliminary results in our first 5 patients. Neurochirurgie. 2020; 66(4): 252–257, doi: 10.1016/j.neuchi.2020.03.001, indexed in Pubmed: 32497543.
32. Schaper FL, Plantinga BR, Colon AJ, et al. Deep Brain Stimulation in Epilepsy: A Role for Modulation of the Mammillothalamic Tract in Seizure Control? Neurosurgery. 2020; 87(3): 602–610, doi: 10.1093/neuros/nyaa141, indexed in Pubmed: 32421806.
33. Guo W, Koo BB, Kim JH, et al. Defining the optimal target for anterior thalamic deep brain stimulation in patients with drug--refractory epilepsy. J Neurosurg. 2020; 134(3): 1054–1063, doi: 10.3171/2020.2.JNS193226, indexed in Pubmed: 32384279.
34. Kaufmann E, Bötzel K, Vollmar C, et al. What have we learned from 8 years of deep brain stimulation of the anterior thalamic nucleus? Experiences and insights of a single center. J Neurosurg. 2020 [Epub ahead of print]: 1–10, doi: 10.3171/2020.6.JNS20695, indexed in Pubmed: 33126208.
35. Tong X, Wang J, Qin L, et al. Analysis of power spectrum and phase lag index changes following deep brain stimulation of the anterior nucleus of the thalamus in patients with drug-resistant epilepsy: A retrospective study. Seizure. 2022; 96: 6–12, doi: 10.1016/j.seizure.2022.01.004, indexed in Pubmed: 35042005.
36. Miron G, Strauss I, Fried I, et al. Anterior thalamic deep brain stimulation in epilepsy patients refractory to vagus nerve stimulation: A single center observational study. Epilepsy Behav Rep. 2022; 29(20): 100563, doi: 10.1016/j.ebr.2022.100563, indexed in Pubmed: 36119948.
37. Costa-Gertrudes R, Simão D, Franco A, et al. Anterior Nucleus of Thalamus Deep Brain Stimulation: A Clinical-Based Analysis of the Ideal Target in Drug-Resistant Epilepsy. Stereotact Funct Neurosurg. 2022; 100(2): 108–120, doi: 10.1159/000519917, indexed in Pubmed: 34915532.
38. Yan H, Wang X, Zhang X, et al. Deep brain stimulation for patients with refractory epilepsy: nuclei selection and surgical outcome. Front Neurol. 2023; 12(14): 1169105, doi: 10.3389/fneur.2023.1169105, indexed in Pubmed: 37251216.
39. Peltola J, Colon AJ, Pimentel J, et al. Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Drug-Resistant Epilepsy in the MORE Multicenter Patient Registry. Neurology. 2023; 100(18): e1852–e1865, doi: 10.1212/WNL.0000000000206887, indexed in Pubmed: 36927882.
40. Dague KO, Witt JA, von Wrede R, et al. DBS of the ANT for refractory epilepsy: A single center experience of seizure reduction, side effects and neuropsychological outcomes. Front Neurol. 2023; 9(14): 1106511, doi: 10.3389/fneur.2023.1106511, indexed in Pubmed: 36970547.
41. Parisi V, Gregg NM, Lundstrom BN, et al. Temporo-Parietal Extraventricular Approach for Deep Brain Stimulation Targeting the Anterior Nucleus of the Thalamus: Institutional Experience. Neurosurgery. 2023; 93(6): 1393–1406, doi: 10.1227/neu.0000000000002600, indexed in Pubmed: 37477444.
42. Sobstyl M, Konopko M, Sienkiewicz-Jarosz H, et al. Clinical efficacy and safety of anterior thalamic deep brain stimulation for intractable drug resistant epilepsy. Epilepsy Res. 2023; 195: 107199, doi: 10.1016/j.eplepsyres.2023.107199, indexed in Pubmed: 37531721.
43. Velasco M, Velasco F, Velasco AL, et al. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res. 2000; 31(3): 304–315, doi: 10.1016/s0188-4409(00)00085-0, indexed in Pubmed: 11036182.
44. Kulju T, Haapasalo J, Lehtimäki K, et al. Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Brain Behav. 2018; 8(6): e00983, doi: 10.1002/brb3.983, indexed in Pubmed: 29740975.
45. Xu C, Qi L, Wang X, et al. Functional connectomic profile correlates with effective anterior thalamic stimulation for refractory epilepsy. Brain Stimul. 2023; 16(5): 1302–1309, doi: 10.1016/j.brs.2023.08.020, indexed in Pubmed: 37633491.
46. Möttönen T, Katisko J, Haapasalo J, et al. Defining the anterior nucleus of the thalamus (ANT) as a deep brain stimulation target in refractory epilepsy: Delineation using 3 T MRI and intraoperative microelectrode recording. Neuroimage Clin. 2015; 7: 823–829, doi: 10.1016/j.nicl.2015.03.001, indexed in Pubmed: 26082891.
47. Lehtimäki K, Möttönen T, Järventausta K, et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul. 2016; 9(2): 268–275, doi: 10.1016/j.brs.2015.09.014, indexed in Pubmed: 26680105.
48. Jiltsova E, Möttönen T, Fahlström M, et al. Imaging of Anterior Nucleus of Thalamus Using 1.5T MRI for Deep Brain Stimulation Targeting in Refractory Epilepsy. Neuromodulation. 2016; 19(8): 812–817, doi: 10.1111/ner.12468, indexed in Pubmed: 27398710.
49. Sudhyadhom A, Haq IU, Foote KD, et al. A high resolution and high contrast MRI for differentiation of subcortical structures for DBS targeting: the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR). Neuroimage. 2009; 47 Suppl 2: T44–T52, doi: 10.1016/j.neuroimage.2009.04.018, indexed in Pubmed: 19362595.
50. Wang YC, Grewal SS, Middlebrooks EH, et al. Targeting analysis of a novel parietal approach for deep brain stimulation of the anterior nucleus of the thalamus for epilepsy. Epilepsy Res. 2019; 153: 1–6, doi: 10.1016/j.eplepsyres.2019.03.010, indexed in Pubmed: 30913474.
51. Lehtimäki K, Coenen VA, Gonçalves Ferreira A, et al. MORE investigators. The Surgical Approach to the Anterior Nucleus of Thalamus in Patients With Refractory Epilepsy: Experience from the International Multicenter Registry (MORE). Neurosurgery. 2019; 84(1): 141–150, doi: 10.1093/neuros/nyy023, indexed in Pubmed: 29554309.
52. Balak N, Balkuv E, Karadag A, et al. Mammillothalamic and Mammillotegmental Tracts as New Targets for Dementia and Epilepsy Treatment. World Neurosurg. 2018; 110: 133–144, doi: 10.1016/j.wneu.2017.10.168, indexed in Pubmed: 29129763.
53. Gross RE, Fisher RS, Sperling MR, et al. Analysis of Deep Brain Stimulation Lead Targeting in the Stimulation of Anterior Nucleus of the Thalamus for Epilepsy Clinical Trial. Neurosurgery. 2021; 89(3): 406–412, doi: 10.1093/neuros/nyab186, indexed in Pubmed: 34161589.

54. Jaseja H. Deep brain stimulation in intractable epilepsy: postulated optimal stimulation parameters. Epilepsy Behav. 2013; 29(3): 597–598, doi: 10.1016/j.yebeh.2013.09.017, indexed in Pubmed: 24126029.
55. Mirski MA, Rossell LA, Terry JB, et al. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res. 1997; 28(2): 89–100, doi: 10.1016/s0920-1211(97)00034-x, indexed in Pubmed: 9267773.
56. Mirski MA, Ferrendelli JA, et al. Interruption of the connections of the mammillary bodies protects against generalized pentylenetetrazol seizures in guinea pigs. J Neurosci. 1987; 7(3): 662–670, doi: 10.1523/JNEUROSCI.07-03-00662.1987, indexed in Pubmed: 3104550.
57. Papez JW. A proposed mechanism of emotion. 1937. J Neuropsychiatry Clin Neurosci. 1995; 7(1): 103–112, doi: 10.1176/jnp.7.1.103, indexed in Pubmed: 7711480.
58. Oh YS, Kim HJ, Lee KJ, et al. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure. 2012; 21(3): 183–187, doi: 10.1016/j.seizure.2011.12.003, indexed in Pubmed: 22209542.
59. Tröster AI, Meador KJ, Irwin CP, et al. SANTE Study Group. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017; 45: 133–141, doi: 10.1016/j.seizure.2016.12.014, indexed in Pubmed: 28061418.
60. Novais F, Pestana LC, Loureiro S, et al. Predicting de novo psychopathology after epilepsy surgery: A 3-year cohort study. Epilepsy Behav. 2019; 90: 204–208, doi: 10.1016/j.yebeh.2018.11.037, indexed in Pubmed: 30573340.
61. Van der Werf YD, Witter MP, Groenewegen HJ, et al. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Brain Res Rev. 2002; 39(2-3): 107–140, doi: 10.1016/s0165-0173(02)00181-9, indexed in Pubmed: 12423763.
62. Sadikot AF, Rymar VV, et al. The primate centromedian-parafascicular complex: anatomical organization with a note on neuromodulation. Brain Res Bull. 2009; 78(2-3): 122–130, doi: 10.1016/j.brainresbull.2008.09.016, indexed in Pubmed: 18957319.
63. Zillgitt AJ, Haykal MA, Chehab A, et al. Centromedian thalamic neuromodulation for the treatment of idiopathic generalized epilepsy. Front Hum Neurosci. 2022; 16: 907716, doi: 10.3389/fnhum.2022.907716, indexed in Pubmed: 35992953.
64. Velasco AL, Velasco F, Jiménez F, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia. 2006; 47(7): 1203–1212, doi: 10.1111/j.1528-1167.2006.00593.x, indexed in Pubmed: 16886984.
65. Velasco F, Velasco M, Ogarrio C, et al. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia. 1987; 28(4): 421–430, doi: 10.1111/j.1528-1157.1987.tb03668.x, indexed in Pubmed: 3497802.
66. Fisher RS, Uematsu S, Krauss GL, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia. 1992; 33(5): 841–851, doi: 10.1111/j.1528-1157.1992.tb02192.x, indexed in Pubmed: 1396427.
67. Velasco F, Velasco M, Jiménez F, et al. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery. 2000; 47(2): 295–304; discussion 304, doi: 10.1097/00006123-200008000-00007, indexed in Pubmed: 10942002.
68. Valentín A, García Navarrete E, Chelvarajah R, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia. 2013; 54(10): 1823–1833, doi: 10.1111/epi.12352, indexed in Pubmed: 24032641.
69. Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome during bilateral, continuous, thalamic centromedian nuclei deep brain stimulation in patients with generalized epilepsy: a prospective, open-label study. Seizure. 2020; 81: 304–309, doi: 10.1016/j.seizure.2020.08.028, indexed in Pubmed: 32947179.
70. Dalic LJ, Warren AEL, Malpas CB, et al. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). Ann Neurol. 2022; 91(2): 253–267, doi: 10.1002/ana.26280, indexed in Pubmed: 34877694.
71. Cukiert A, Burattini JA, Cukiert CM, et al. Centro-median stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy. Seizure. 2009; 18(8): 588–592, doi: 10.1016/j.seizure.2009.06.002, indexed in Pubmed: 19577937.
72. Son BC, Shon YM, Choi JG, et al. Clinical Outcome of Patients with Deep Brain Stimulation of the Centromedian Thalamic Nucleus for Refractory Epilepsy and Location of the Active Contacts. Stereotact Funct Neurosurg. 2016; 94(3): 187–197, doi: 10.1159/000446611, indexed in Pubmed: 27434073.
73. Kim SH, Lim SC, Yang DW, et al. Thalamo-cortical network underlying deep brain stimulation of centromedian thalamic nuclei in intractable epilepsy: a multimodal imaging analysis. Neuropsychiatr Dis Treat. 2017; 13: 2607–2619, doi: 10.2147/NDT.S148617, indexed in Pubmed: 29089767.
74. Alcala-Zermeno JL, Gregg NM, Wirrell EC, et al. Centromedian thalamic nucleus with or without anterior thalamic nucleus deep brain stimulation for epilepsy in children and adults: A retrospective case series. Seizure. 2021; 84: 101–107, doi: 10.1016/j.seizure.2020.11.012, indexed in Pubmed: 33310676.
75. Torres Diaz CV, González-Escamilla G, Ciolac D, et al. Network Substrates of Centromedian Nucleus Deep Brain Stimulation in Generalized Pharmacoresistant Epilepsy. Neurotherapeutics. 2021; 18(3): 1665–1677, doi: 10.1007/s13311-021-01057-y, indexed in Pubmed: 33904113.
76. Yang JC, Bullinger KL, Isbaine F, et al. Centromedian thalamic deep brain stimulation for drug-resistant epilepsy: single-center experience. J Neurosurg. 2022; 137(6): 1591–1600, doi: 10.3171/2022.2.JNS212237, indexed in Pubmed: 35395630.
77. Cukiert A, Cukiert CM, Argentoni-Baldochi M, et al. Intraoperative neurophysiological responses in epileptic patients submitted to hippocampal and thalamic deep brain stimulation. Seizure. 2011; 20(10): 748–753, doi: 10.1016/j.seizure.2011.07.003, indexed in Pubmed: 21782475.
78. Warren AEL, Dalic LJ, Bulluss KJ, et al. Targeting the centromedian thalamic nucleus for deep brain stimulation. J Neurol Neurosurg Psychiatry. 2020; 91(4): 339–349, doi: 10.1136/jnnp-2019-322030, indexed in Pubmed: 31980515.
79. Li J, Li Y, Gutierrez L, et al. Imaging the Centromedian Thalamic Nucleus Using Quantitative Susceptibility Mapping. Front Hum Neurosci. 2019; 9(13): 447, doi: 10.3389/fnhum.2019.00447, indexed in Pubmed: 31998098.
80. Cukiert A, Lehtimäki K, et al. Deep brain stimulation targeting in refractory epilepsy. Epilepsia. 2017; 58 Suppl 1: 80–84, doi: 10.1111/epi.13686, indexed in Pubmed: 28386921.
81. Morel A. Stereotactic Atlas of the Human Thalamus and Basal Ganglia. New York: Informa Healthcare 2007.