DBS in Epilepsy

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DBS is indicated for poorly localized or multiple regions of seizure origin.

Comparison of Neuromodulations (RNS, DBS, VNS) – see p. E11

ANTERIOR NUCLEI OF THALAMUS (ANT) ................................................................. 1


Cakiroglu, Lehtimaki et al. Deep brain stimulation targeting for refractory epilepsy. Epilepsia 2017


ANATOMY

Central node of Papez circuit
Fronto-temporal epilepsies may respond best (as opposed to parieto-occipital epilepsies). Irving Cooper reasoned that due to its location in Papez circuit, ANT could serve as a key location to disrupt limbic seizures.

- dimensions 4 x 10 x 5.5 mm
- located at the floor of the lateral ventricle
- surrounded by plexus choroides, the thalamostriatal vein, and the internal cerebral vein:
  - located at the anterior-superior-medial aspect of the thalamus and constitutes its anterodorsal border.
  - partially enveloped (isolated from the rest of thalamus) by a myelin-rich sheath belonging to the mammillothalamic tract (MTT) and the internal medullary lamina
  - subnuclei (all have distinct patterns of connectivity): anterodorsal, anteroventral, and anteromedial.
  - projects to superior frontal and temporal lobe structures commonly involved in seizures.
  - inputs from the subiculum, the mammillary bodies via the mammillothalamic tract, and the retrosplenial cortex.
  - MTT joins ANT at its inferior border slightly anterior to the midpoint of ANT in the anterior–posterior axis (this junction is close to the border between anterior principal and anteromedial subnucleus according to the Schaltenbrand–Wahren atlas).
INDICATIONS

- most useful in partial epilepsy (with/without secondary generalization).
- there is no seizure type that would predict response to DBS.
  - according to study by Piacentino et al. (6 patients) ANT DBS was most effective in patients with epileptic origins strictly in the limbic system who had no discrete anatomical lesions.
  - DBS is least effective for FAS (focal aware seizures); however, maybe DBS converts FUAS (focal unaware seizures) to FAS and gives such false impression?

Available in Europe since 2011.

FDA APPROVAL

May 1, 2018 FDA has granted premarket approval for Medtronic’s DBS therapy:

- adjunctive therapy for reducing the frequency of seizures
- bilateral anterior thalamic nucleus stimulation
- 18 years of age or older
- partial-onset seizures, with or without secondary generalization
- refractory to ≥ 3 antiepileptic medications.
  - ≥ 6 seizures per month over the 3 most recent months (with no more than 30 days between seizures).

Medtronic has preauthorization request guides and also letter samples for appeals in denial cases.

TARGET

Nucleus (antero)principalis
- superior, anterior part of ANT
- best stim contacts – 2–3 mm above where mammillothalamic tract terminates.

High anatomical variability (more variable coordinates than any other stereotactic target) – direct targeting is preferable!

INDIRECT TARGETING

AC–PC coordinates (golden coordinates in parentheses): 12-5-2
10-16 (12) mm superior
4-7 (5) mm lateral
0-5 (2) mm anterior to MCP or 8 mm anterior to PC

N.B. individual variations up to 5 mm (even between sides) – need direct targeting!

- indirect targeting is particularly challenging in epilepsy as the thalamus is known to atrophy in the setting of chronic epilepsy.
- no characteristic MER signatures.
- no side effect profile to guide targeting.

Dr. Lehtimäki targets slightly lateral to prevent lead slipping medially into 3rd ventricle.

Lehtimäki et al. analyzed the placement of 62 contacts in 15 patients, 10 of whom were responders. Using an ANT-normalized coordinate system, they found that contacts in responders were placed significantly more anteriorly and superiorly than they were in nonresponders. They hypothesized that the white matter structures at the inferior and posterior aspects of the ANT prevented the spread of stimulation current into the ANT, which limited the utility of electrodes placed in that region.

Krishna et al. found similar results, noting that patients with the most long-term stimulation benefit had electrodes placed in the anteroventral ANT in close proximity to the mammillothalamic tract.

Schaltenbrand-Warren atlas:

ANT: 12 mm superior, 5-6 lateral, 0-2 anterior to MCP
ANT (anterior CSF border or mtt junction) is 4-5mm more anterior in axial plates compared to sagittal plates.

Coronal plates correlate with sagittal plates in Y axis.

ANT is more medial in coronal plates compared to sagittal plates.

Correlates relatively well with schaltenbrandt atlas sagittal plates (anterior border = 5mm anterior to MCP, mamillothalamic tract at midcommissural plane).

Axial plates of SWA seems to be the most realistic approximation of ANT location compared to patient data.

Anatomical variation:
DIRECT TARGETING:

ANT is commonly located more anterior and superior in 3T MRI compared to the target based on SW atlas sagittal data!

**Target** - within the anteroventral subdivision of the ANT, superior and slightly posterior to the entry of the MTT into the ANT.

- MTT/ANT junction is slightly anterior to the midpoint of ANT in the anterior–posterior axis;
- MTT/ANT junction is close to the border between anterior principal and anteromedial subnucleus according to the Schaltenbrand–Wahr atlas.

3T MRI with transmit-receive coil:

- a) **STIR**
- b) **FGATIR** (better and faster than STIR) – needs at least on 3T scanner
- c) **DTI** – some experts say it does not add extra value to FGATIR

Comparison of three imaging protocols in delineating the mammillothalamic tract (arrowheads) and ANT (arrow):

A. **MP-RAGE** acquired at 0.8 mm – poor delineation of the mammillothalamic tract and ANT.
B. **MP-RAGE** acquired at 1.2 mm – better illustrates the mammillothalamic tract and ANT.
C. **FGATIR** acquired at 0.8 mm – superior delineation of the mammillothalamic tract allowing more precise definition of the ANT.

**Source of picture:** Medtronic
MPRAGE (3T):

Source of picture: Buentjen L et al. Direct targeting of the thalamic anteroventral nucleus for deep brain stimulation by T1-weighted magnetic resonance imaging at 3T. Stereotact Funct Neurosurg. 2014; 92:25-30

STIR (3T, mtt = mammillothalamic tract, Apr + AM = ANT):


STIR (1.5T, mtt = mammillothalamic tract, ANT = Anterior nucleus of the thalamus, eml = external medullary lamina):


DTI (coregistered to FGATIR) of the mammillothalamic tract:

Source of picture: Cukiert, Lehtimäki (2017)

FGATIR MR images in the axial (A), coronal (B), and sagittal (C) planes. The mammillothalamic tract (arrow) is clearly visualized as a linear hypointensity extending dorsally from the mammillary body (arrowhead) to the anterior thalamus.

Cadaveric dissection in the sagittal plane (D) illustrates the course of the mammillothalamic tract (arrow) originating in the mammillary body (arrowhead) and projecting to the anterior thalamus.

ANT DBS electrode (Medtronic 3389) localization coregistered to the preoperative FGATIR MR image. Final electrode localization is shown relative to the mammillothalamic tract (arrow) in the coronal (A) and axial (B) planes. Coronal (C, dorsal), left parasagittal (D), and right parasagittal (F) images show VTA’s for the right (blue) and left (red) ANT electrodes relative to the mammillothalamic tract (arrow) and ANT (arrowhead). The VTA’s are closely localized to the juncture of the mammillothalamic tract and ANT on both sides.
Transventricular trajectory:

Extraventricular trajectory (missed ANT):

Clinical effect was achieved only with these settings
**Electrode Verification – Hippocampal Electrodes**

- Hippocampal electrodes are placed, and the Medtronic Activa PC+S system used to record ANT stimulation-induced hippocampal evoked potentials as electrophysiological confirmation of appropriate placement of the ANT leads.
- Impedances in CSF are lower than in parenchyma (“CSF wicking” effect – CSF tracks along DBS lead into brain parenchyma and impedances drop).
- Impedance in CSF is 200-300 Ohm.

**Electrode Verification – Impedances**


**Electrode Verification – MER**

Unnecessary and dangerous (narrow vascular window) in transventricular trajectory.

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Trajectory angle should be adapted to align with the individual shape of the ANT.

**SANC trial** – transventricular frontal (recommended for best accuracy without safety issues)

**Morriz registry** – lateral extraventricular (fails to enter ANT most often of all approaches).

**Moye Clinic** – posterior extraventricular.

Trajectory angle should be adapted to align with the individual shape of the ANT!

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**Data from MORE**


- 73 ANT-DBS implants (146 leads) in 17 European centers participating in the MORE registry. 53.4% used an extraventricular (EV) trajectory and 46.6% used a transventricular (TV) trajectory.

**TV**

- 60° posterior from an axial plane parallel to AC-PC plane, i.e. ~ 30° anterior from a coronal plane perpendicular to AC-PC plane.

**TV**

- trajectory typically runs through the narrow vascular window between superior choroidal vein (medially) and thalamostriate vein (laterally), between caudate and ANT; blunt stylet advanced slowly pushes veins away.

- sometimes choroidal plexus is on top of ANT (but it is a mobile structure so hemorrhage is rare – Dr. Lehtimäki goes through it).

**TV**

- MORE study - two distinct types of misplacements were observed:
  a) too deep position of the lead in a trajectory through the ANT (placing of most superior contacts at MD or internal medullary lamina)
  b) medial deviation of the lead - 1 lead situated in structures bordering the third ventricle and 2 leads were positioned in CSF spaces - related to the penetration of the lateral ventricle.

**TV**

- TV trajectory traverses ANT with at least 95% probability, the main surgical challenge being the correct depth of the lead!

The rate of ANT-miss using transventricular trajectory with 3389 lead is 17.2%.

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**LATERAL EXTRAVENTRICULAR (TRANSCORtical)**

- passes through eloquent cortex, such as the operculum.
- provides improved mediatoolateral coverage.
- thalamostriate vein runs at the anterior and lateral aspect of ANT - in order to reach ANT from frontal EV approach, a very lateral and posterior entry point is needed to pass the thalamostriate vein, which is in contrast limited by frontal eloquent cortex. Between these anatomical limits is most likely achieved by adjusting the target inferiorly, laterally, and posteriorly, probably aiming to stimulate the MTT-ANT junction rather than ANT nucleus per se.

**Note laterality of entry**

- 5mm lateral, 5.5mm anterior, 14mm superior - thalamostriate vein
- 1.2mm safety margin for thalamostriate vein

**ANT-miss lead trajectories**

- the leads were systematically more inferior and had their courses directed more posteriorly compared to ANT-hit trajectories

- with respect to MTT/ANT junction, ANT-hit lead trajectories were clearly located superior to the MTT/ANT junction at a slightly lower level or slightly posterior to the MTT/ANT junction, whereas ANT-miss lead trajectories had their courses systematically below and grossly posterior to the MTT/ANT junction.

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**Posterior Inferior Parsital**

- greatest anteroposterior coverage
- Van Gompel et al. - electrodes are placed along a posterior inferior parietal route, to avoid intraventricular hemorrhage and lead misplacement associated with transventricular and lateral transcortical approaches.

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**TRAJECTORIES**

**SANC trial** – transventricular frontal (recommended for best accuracy without safety issues)

**Morriz registry** – lateral extraventricular (fails to enter ANT most often of all approaches).

**Moye Clinic** – posterior extraventricular.
HARDWARE (MEDTRONIC)

PATIENT REMOTE

- same as for movement disorders but has blue button “Seizure” – it is programmable (e.g. logging the event, restarting stim cycle).

BATTERY

ACTIVA PC
- same as for movement disorders.  see p. Op360 >
- List price – 17,000 USD (2019 October)

PERCEPT PC (B35200)
- see p. Op360 >
- List price – 17,000 USD (2019 October)

- BrainSense™ technology - captures local field potentials (LFP) using the implanted DBS lead simultaneously while delivering therapeutic stimulation.  see below >
- full-body 3T MRI eligibility (1.5T with Activa PC)
- > 15% longer battery life than Activa PC (smart battery technology provides real-time prediction of remaining battery life based on usage history).
- 20% smaller than Activa PC.

PLUGS

- Connector Plug works with SenSight™ Extension as well as Activa™ RC/PC and Percept™ PC Devices
- Note the change in model number from 831060 to 831061, but there is no change to the plug itself

LEADS

- FDA approved:
  - 3387 (used in SANTE trial)
  - 3389 - preferred
use “at target” cannula; “10 mm above” cannula may cause DBS lead to deviate (some experts set target 8 mm deeper so that “10 mm above” cannula enters the parenchyma).

N.B. with lead 3389, the distance between the centers of first and last contact is 6 mm – when planning trajectory and target, plan that 6 mm segment to incorporate into ANT.

SENNSIGHT™ (MEDTRONIC) – DIRECTIONAL 1-3-3-1 LEAD

- lead tip is 1 mm from bottom of distal (0) contact.
- lead diameter 1.36 mm – inner diameter of cannula must be at least 1.57 mm
- aim to place contacts 1 and 2 at target – greatest programming and sensing flexibility.
DBS IN EPILEPSY

SENSIGHT™ LEAD DESIGN

1-3-3-1 electrode design
• Electrode levels 0 and 3 are full rings
• Electrode levels 1 and 2 are split into 3 isolated electrodes to enable directional stimulation

Orientation markers
• 2 inverted and independently isolated triangles
• Produce two distinguishably visible artifacts on Fluoroscopy and X-Ray to guide directional programming post-operatively

SENSIGHT™ SURGICAL WORKFLOW

Styllet
• Ensure styllet is fully seated in the lead before attaching depth stop
• Best to do this right out of the packaging, as it may move during shipping

Left/Right lead markers
• No recommended convention, clinician preference

Alignment of segments
• Can be entered into the clinician programmer post-operatively

Left/Right Lead Marker

Setscrew Fixation Ring (Non-Active)

Extension

Unmarked Lead

Lead Not Fully Inserted

Styllet + Handle can be removed with one hand once the SenSight™ Burr Hole Device clip is closed

Proximal End

33 cm and 42 cm lengths.
ORIENTATION MARKERS:

- best to image 1 month postop (brain settles); but can be done intraop:
  - either fluoro or O-arm (MRI does not show markers)
  - remove stylet
- use magnification:
  - avoid overlap with frame, eye sockets:
  - use “edge enhancement” feature in O-arm:
  - proximal marker aligns with 1a and 2a segments
  - distal marker aligns with 1b and 2b segments
**AP view is the best (no lead overlap):**

- **Lateral view:**

  - **Impedances:**
    - Due to smaller segmental contacts, normal impedances have higher upper limit:
      - Monopolar: 350-8000 Ohm
      - Bipolar: 350-10000 Ohm

  - **Burhole Cover SENSIGHT (B32000):**
    - Only for SensiSight leads (for old leads need to use Stimloc)
    - Improved visual contrast - cap is clear plastic, ring is white plastic (line up triangles when applying cap)

**Bursight Burr Hole Device**

- Profile height is 14 ± 2% lower than legacy
- Stimloc™ Burr Hole Device
- Improved Lead Stability
- 17% improvements in lead tip stabilization
- More options for placement
- 4 hole sets and 18 entry angles available
DBS in Epilepsy

SENSIGHT™ BURR HOLE DEVICE
SUPPORT CLIP

- Holder Posts: Provide flexibility for lead exits and keeps lead perpendicular to either jaw.
- Elongated jaws: Enhanced lead retention
- Ribbed jaw surface: Helps prevent rotation
- Moveable jaw snap feature to avoid accidental unlocking
- Moveable jaw rests on base ring to avoid accidentally being pushed underneath.

SENSIGHT™ TEST CABLES CABLES
B31000 and B31005

- Visualization Window
  * Allows you to see that lead/extension is fully inserted
- Usable with or without stylet
- Single handed application
  * pinching/push button actuation
- Bipolar and Monopolar stimulation
  * Reference contact available on both lead and extension cables
- Longer Lead Test Cable
  * 241 cm which is 33 cm longer than the Twistlock cable

SENSIGHT™ SURGICAL WORKFLOW
TESTING THE LEAD

- Lead Testing
  * Lead Testing Cable has a blue connector box
  * Lead testing in voltage mode only with ENS
  * Monopolar available
  * J-clip on connector
  * Attach alligator clip to grounding location, e.g., a surgical instrument, or the bar of metal. Do not attach the alligator clip to the lead tip as this may damage the lead.
  * Secure lead testing cable
  * Connectivity test
  * Impedance differences
    * Normal Impedance
      * MONOPOLAR: 1000 to 8000
      * BIPHASIC: 6000 to 10,000
    * If impedances are over 40K, testing cable connector to get better contact may help break through inside layer.

SENSIGHT™ EXTENSION CHANGES

- Grip Zone: Engineered to withstand bending stresses
- Injection molded and Centerless ground
- Reduced profile
- Enhanced extensibility
- Single setscrew
- Visual indicators: To identify Left / Right implants
- Bootless Connection
- NASA Engineered Coating on Each Conductor
  * For increased insulation and to improve sensing

TESTING CABLES

- 15% length stretch.

EXTENSIONS

- 15% length stretch.
Wound care, MRI, electrosurgery, follow ups. see p. Op360 >>

- regular room 1 night postop after 1st stage; one day surgery for 2nd stage.

### COMPLICATIONS, SIDE EFFECTS

1. 4.5% of the patients had asymptomatic intracranial hemorrhage (ICH) in SANTE ← more frequent than in DBS surgery for movement disorders specifically (2.16% of ICH)
2. **Exacerbating seizures / inducing new seizures** (0.5-13% with 74-86% of those occurring around the time of electrode placement or initiation of stimulation)
   - review of 2101 electrode placements across 16 reports revealed an incidence of new onset seizures in up to 13% of patients. At least 74% of seizures occurred around the time of electrode placement, with many patients experiencing intracranial hemorrhage.
   - others estimated that DBS is associated with a <2.4% (95% CI 1.7%–3.3%) risk of seizures and that the postprocedural risk of seizures from chronic DBS was approximately 0.5% (95% CI 0.02%–1.0%).
   - separate report examined 161 patients (288 leads) - 4.3% experienced seizures - the vast majority (86%) of seizures occurred within 48 hours after lead implantation.

3. **Psychiatric side effects**
   - **SANTE:** depression 37.3% (vs 1.8% in controls) – patients need to be watched closely!
   - changing stim contacts almost always helps.

4. **Cognitive side effects**
   - **SANTE:** subjective memory impairment 27.3% (vs 1.8% in controls); all resolved with no group differences on objective neuropsychological testing.
   - at 7 years: no significant cognitive declines or worsening of depression scores were observed through the blinded phase or at year 7.
   - Improved scores were observed at 7-years on measures of executive functions and attention.

5. **SLEEP**
   - disruptions with vivid dreams.

Neuropsychological monitoring of memory and mood + slow titration are recommended in ANT DBS!

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**PROGRAMMING**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>Percept™ PC + SetSight™</th>
<th>Percept™ PC + 1st Lead</th>
<th>Active™ PC/RC + SetSight™ Lead</th>
<th>Active™ PC/RC + 1st Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Segment Mode</strong></td>
<td>Enable and disable directionality of lead segments:</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td><strong>OptiStim™ Control</strong></td>
<td>Adjust the amplitude of a single electrode without impacting the amplitude of other electrodes in the configuration</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td><strong>SnapLock™ Control</strong></td>
<td>Create a unique field shape, including relatively dense amplitude contributions from various electrodes, other field shapes, or a combination of those</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Multiple-Rites</strong></td>
<td>Program multiple rates within a single or multiple leads</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td><strong>CC / CV Capacities</strong></td>
<td>Amplitude Mode: Constant Current (CC) or Constant Voltage (CV)</td>
<td>CC</td>
<td>CC</td>
<td>CV</td>
<td>Either</td>
</tr>
</tbody>
</table>

**3 sensing configurations possible:**

- epileptic signature LFP peaks are typically located in 8-12 Hz range (Percept PC can record only in 5 Hz wide band) – look for those recorded (upon patient triggered events) and also during programming session.
- turn LFP detection right after battery implantation (POD 0) – will obtain baseline LFP peaks while still off stim.

**Stimulation**

Differences from DBS for movement disorders
1. intermittent vs. continuous stimulation – “cycling”.
2. contact is programmed to be a cathode (negatively charged electrode) and case as anode* – to cause depolarization block.

*patients may feel tingling at battery site
Phase I (start 2-3 weeks postop) – increasing output

Amplitude – start at 0.5 mA (old way - 1.5-2.0 V) and increase q2-4 weeks by 0.5 mA (0.5 V) (or even longer intervals – analogy with adjusting AEDs) up to 4 mA (4.5-5.0 V, up to 9.0 V); most patients need 2-3 mA.
- gradual amplitude increase helps to minimize occurrence of psychiatric side effects
- keep symmetrical between sides.
- corresponds to 4.7 mA (some experts recommend current-based programming to mitigate impedance effects that maybe very asymmetric)

Pulse width 90 msec (this is invariable*)
Frequency 145 Hz (this is invariable*)
*Duty cycle: 1 min on, 5 mins off.

Phase II – changing cycling
Decreasing off time from 5 to 3 min.

N.B. directional stim is available only in monopolar mode.

OUTCOMES

- best effects are on disabling, multifocal epilepsy as well as temporal lobe epilepsy (involvement of Papez circuit).
- it takes time for efficacy to build up (vs. DBS in movement disorders).
- seizures may intensify upon initiation of stimulation.

ROLE OF PREVIOUS VNS
SANTE data – see below >>

There is a putative association between VNS and DBS responses
- in 10/11 patients, the response to VNS seemed to be similar to the response to DBS; progressive response to VNS was likely to correlate with a progressive response to DBS in 3/3 patients; partial response to VNS was associated with a fluctuating response pattern to DBS in 2 patients; 5/6 nonresponders to VNS were also nonresponders to DBS (one of the VNS nonresponders obtained progressive response to DBS).

STIMULATION OF THE ANTERIOR NUCLEUS OF THALAMUS FOR EPILEPSY (SANTE) TRIAL
Complete set of trial data >>


- level I evidence for medically refractory partial seizures with or without secondary generalization - positive effects of bilateral stimulation appear to be long-lasting + patients had improved quality of life.
- multicenter, prospective, randomized, double-blind, parallel groups pivotal study – high quality data.
- 110 patients who were implanted with a Medtronic DBS system at 17 centers located in the U.S.
- blinded phase – 3 months.
patients with ≥ 50% reduction in seizures (median seizure reduction numbers are very close): 3 months 40.4% vs. 14.5% in placebo 13 months 43% (n=99) 25 months 54% (n=81) 37 months 67% (n=42) 5 years 68% 7 years 74% (18% experienced at least one 6-month seizure-free period, 7% were seizure-free for the preceding 2 years) in real life may expect better results than in SANTE, as SANTE investigators did not know the exact target location.

- statistically significant reduction in seizure frequency only in temporal epilepsies - 44.2%, (vs. controls - 21.8%).
- complex partial seizures were significantly reduced compared to simple partial and partial to generalized seizures.
- patients previously implanted with a VNS device* or who underwent resective surgery prior to DBS had outcomes that were not different from previously nonoperated patients.
  *for SANTE trial, patients had VNS explanted because VNS was ineffective
- side effects – see above 
- analysis revealed placement outside the ANT in 8.2% of electrodes (vs. 3.6% in DBS for movement disorders).
- of note, one outlier subject in the trial whose seizures dramatically worsened (210 seizures in 3 days compared to their baseline seizure rate of 19 seizures per month) necessitated outlier analysis to satisfy primary endpoints and played a role in delaying FDA approval for years, until long-term data demonstrated clearer benefit.

**MEDTRONIC REGISTRY FOR EPILEPSY (MORE)**
- multicenter international registry conducted since October 2011 in 13 countries and using an open label observational study design to evaluate the long-term effectiveness, safety, and performance of ANT-DBS.

**EPAS**
- FDA-mandated postapproval DBS trial

**CENTROMEDIAN NUCLEUS OF THALAMUS (CMT)**

**Read:**
- Outcome during bilateral, continuous, thalamic centromedian nucleus deep brain stimulation in patients with generalized epilepsy: a prospective, open-label study
- Aaron Colton, - Grünthal Mela Colton, - Joe Jayson Deidre, - Pedro Fons Navarrete

**Targeting the centromedian thalamic nucleus for deep brain stimulation**
- Aaron E. L. Warren, - Veronika Remond, - Anne Rotten, - Kristian J Bulluss, - John Archer

**Imaging the Centromedian Nucleus Using Quantitative Susceptibility Mapping**
- Jan Li, - Yifei Liu, - Lorenzo Guadagno, - Wenping Xu, - Fei Wu, - Chukwunke U, - Deepak S, - Brian Song, - Chongxiang Zhang, - and Xiaoguang Yue

**Anatomy**
- CMT, together with the parafascicular nuclei, form the posterior group of the intralaminar nuclei of the thalamus.
- Motor cortex provides input to the CMT, as do the globus pallidus interna (GPi).
- CMT projects back to the motor cortex as well as the striatum with particular preference for the putamen and the head of the caudate nucleus proximal to the internal capsule.

**N.B. CMT has much more widespread connections than ANT (“only” Papez).**

**Indications**
- majority of available data support the use of CMT DBS for the treatment of generalized epilepsy, including from Lennox-Gastaut syndrome.
- current data is only from level III-IV studies.

**Targeting**
- CMT cannot be seen even on 7T MRI (vs. ANT); QSM+FGATIR sequence is promising.
• MIR cannot guide reliably.
• indirect targeting – 10 mm lateral to PC

**Procedure**
- placed under general anesthesia with recruiting response.
- if electrode is too lateral → sensory side effects (paresthesias)
- if electrode is too deep (pretectal area) → upward gaze deviation.

**Programming**
Dr. A. Cukiert:
- 130 Hz, 300µsec, bipolar (0-3 & 4-7).
- Upper limit: ~5V
- 0.5V increment every week.
- Common complain at higher intensity: paresthesias (last minutes-hours).

**Outcomes**
- response rates from 0% (Andrade et al. Neurology 2006;66:1571–1573) to 100% (Cukiert et al. Seizure 18 (2009) 986-992)
  - the largest series, published by Son et al. in 2016 reported a 79% response rate (11 of 14 patients), with a mean seizure frequency reduction of 68%; they did not find any correlation between lead positioning and the magnitude of seizure reduction on regression analysis.
  - Cukiert et al. 2020:
HIPPOCAMPUS

- patients selected from population undergoing invasive electrodes: diagnostic electrodes replaced with stimulation electrodes at site of seizure focus.
- need Medtronic 3391 lead with longer distance between contacts (approved for OCD indication) or Boston Scientific DBS lead.
- 60-100% response rates (some become seizure free!); – some experts believe that DBS is better than RNS (so far DBS is not FDA approved for hippo).
- causes no change in neuropsychological tests.

Programming

Dr. A. Cukiert

- 130 Hz, 300µsec, bipolar (0.3 & 4-7).
- Upper limit: ~ 4.0 V
- 0.5V increment every week.
- Common complain at higher intensity: none.

DBS is able to trigger patients typical seizures

Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Randomization</th>
<th>Stim Param</th>
<th>Seizure Outcome</th>
<th>Neurropsych</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velasco et al</td>
<td>9</td>
<td>Immediate on vs 1 mo delay</td>
<td>130 Hz 450 µs cyclic</td>
<td>100% RR 4/9 sz free</td>
<td>No decline</td>
<td>Absence of MS on MRI predicts success</td>
</tr>
</tbody>
</table>

DBS in Epilepsy

best responders more anterior and lateral in CM, concentrated in parvocellular portion
less effective in focal epilepsies although it did help with secondary generalization.
causes no change in neuropsychological tests; benefit - improved attention.

Study | Velasco et al | Cukiert et al | Andrade et al |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>4 pts 4p CC</td>
<td>2</td>
</tr>
<tr>
<td>Pathology</td>
<td>LGS</td>
<td>IGE 2, LOS 2</td>
<td>SGE 1, Multifocal 1</td>
</tr>
<tr>
<td>Targeting</td>
<td>Recruiting response</td>
<td>Recruiting response</td>
<td>100-185 Hz, 90-120 µs, 1-30v</td>
</tr>
<tr>
<td>Stim parameters</td>
<td>130 Hz, 450 µs, 2.3 v</td>
<td>130 Hz, 300µs, 2v</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>97.95% 2</td>
<td>50-80% 3</td>
<td>&lt;50% 1</td>
</tr>
<tr>
<td>100% RR  Ax 78%</td>
<td>Initially worsened, no clear diff in on and off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurpsych outcome</td>
<td>Improvement related to Sx Outcome</td>
<td>Improved alertness (SNAP IV)</td>
<td>N/A</td>
</tr>
<tr>
<td>Comments</td>
<td>Anterolateral nucleus in parvocellular best response</td>
<td>Improvement in alertness at 0.5v and sz control at 1.5 v</td>
<td></td>
</tr>
</tbody>
</table>
Cukiert et al (2017) - the results of a prospective, double-blind, randomized controlled trial evaluating the efficacy of unilateral and bilateral HCP DBS in 16 patients with refractory TLE:
- 2 months after surgery, all patients were randomized to stimulation on or off for a 6-month blinded period.
- of the 8 patients randomized to the on-stimulation group, 4 became seizure free and 7 were defined as responders, whereas 1 patient did not respond to DBS therapy.
- the experimental group experienced significantly fewer simple partial and complex partial seizures than the control group throughout the blinded period.

Vonck et al. - 11 patients who underwent bilateral HCP DBS electrode implantation, with stimulation laterality applied based on seizure localization:
- after 2.5–3 years of follow-up, patients who were initially started on unilateral stimulation were converted to bilateral stimulation if seizure reduction of > 90% had not been achieved.
- at final follow-up, and after switching to bilateral stimulation as necessary, patients achieved seizure reduction rates ranging from 40% to 70%, and 2 patients achieved < 30% seizure reduction.
- switching from unilateral to bilateral stimulation further improved seizure outcomes in 3 of 5 patients with unilateral ictal onset.
- implementing day-night cycling after attaining treatment stability did not affect seizure control.
- no changes in neuropsychological testing were noted after DBS therapy.

### STN

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Localization of epilepsy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benabid/Chabardes 2002</td>
<td>3</td>
<td>sensory motor cortex</td>
<td>67.87%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>&lt; 50%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Shon (Seoul) Stereoelectrofunc 384-90</td>
<td>2</td>
<td>FLE s/p failed resection</td>
<td>87.89%</td>
</tr>
<tr>
<td>Handforth (UCLA) Epilepsia 47(7):1239–1241, 2006</td>
<td>1</td>
<td>Bitemporal epilepsy</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Frontal encephalomalacia</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>Neme (Santiago)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

while the cerebellum (hemispheres) has the longest history in DBS for the treatment of epilepsy, results have been mixed. Therefore, stimulation of the cerebellum has fallen out of favor.

### NUCL. ACCUMBENS

### POSTERIOR HYPOTHALAMUS

BIBLIOGRAPHY for ch. “Epilepsy and Seizures” → follow this LINK