DBS is indicated for poorly localized or multiple regions of seizure origin. Comparison of Neurostimulations (RNS, DBS, VNS) – see p. E11 >.

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Cerebral cortex, hippocampal electrodes, direct targeting, deep brain stimulation, electrode verification, intraoperative microelectrode recording, MEG, microcircuit, MRI, Papez circuit, PTA, RNS, DBS, VNS.

Last updated: August 8, 2020


Cukiert, Lehtimäki et al. Deep brain stimulation targeting for refractory epilepsy. Epilepsia 2017


Elena Jiltsova, MD; Timo Möttönen, MD; Markus Hahlström, MSc; Joonas Haapasalo, MD, PhD; Timo Talithinen, MD; Jukka Peltola, MD, PhD; Juha Öhman, MD, PhD; Elna-Marie Larsson, MD, PhD; Tommi Kiekara. MD, PhD; Kai Lehtimäki, MD, PhD

Imaging of Anterior Nucleus of Thalamus Using 1.5T MRI for Deep Brain Stimulation Targeting in Refractory Epilepsy

DBS in Epilepsy

ANATOMY

Central node of Papez circuit

Central node

spatial resolution

Diffusion tensor imaging, tractography, thalamus, THA, GABAergic, habenula, subthalamus, hippocampus, fornix, mamillary bodies, mammillothalamic tract.
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 choroida, 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**
- **refractory to ≥3 antiepileptic medications.**
- ≥ 6 seizures per month over the 3 most recent months (with no more than 30 days between seizures).

**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):
- 10-16 (12) mm superior
- 0-5 (2) mm anterior to MCP or 8 mm anterior to PC
- 4-7 (5) mm lateral

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:

Lehtimäki (2018)

Mai atlas (2008)
Correlates relatively well with schaltenbrandt atlas sagittal plates (anterior border = 5mm anterior to MCP, mamillothalamic tract at midcommissural plane)

Lehtimäki (2018)

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

Lehtimäki K, unpublished

Indirect target: 12mm superior, 2mm anterior, 5mm lateral to MCP

ANT is more anterior and superior than expected

Too posterior (and inferior?) location of the indirect target!

Indirect target at ANT
**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 anterointerior subdivision of the ANT, superior and slightly posterior to the entry of the MTT into the ANT.

**3T MRI**

a) STIR
b) FGATIR (better and faster than STIR)
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 mm3 - poor delineation of the mammillothalamic tract and ANT.
B. MP-RAGE acquired at 1.2 mm3 - better illustrates the mammillothalamic tract and ANT.
C. FGATIR acquired at 0.8 mm3 - superior delineation of the mammillothalamic tract allowing more precise definition of the ANT.

**FGATIR (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

**MP-RAGE (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):**


**DTI (coregistered to FGATIR) of the mammillothalamic tract:**

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. Control (C), axial (D), left parasagittal (E), and right parasagittal (F) images show VTAs for the right (blue) and left (red) ANT electrodes relative to the mammillothalamic tract (arrow) and ANT (arrowhead). The VTAs are closely localized to the junction of the mammillothalamic tract and ANT on both sides.

Coronal (C), axial (D), left parasagittal (E), and right parasagittal (F) images show VTAs for the right (blue) and left (red) ANT electrodes relative to the mammillothalamic tract (arrow) and ANT (arrowhead). The VTAs are closely localized to the junction of the mammillothalamic tract and ANT on both sides.

74% of the contacts (blue color) responders
83% of the contacts (red color) non-responders.

Surgical target 3.5mm from CSF surface
The centre of 3389 (interspace 1&2) to target point
Two uppermost contacts (3&2) in ANT

Source of picture: Cukiert, Lehtimäki (2017)
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.


Electrode Verification - Impedances

- Impedances in CSF are lower than in parenchyma.

A. Transventricular leads implanted deeper than anticipated

B. Revision of the leads aiming most cranial contacts at the superior border of ANT

Möttönen et al, submitted
Electrode Verification - MER

Location too MER observations

Posterior
Thinner MER cross-section if posterior to target region of ANT - Posterior to ANT = No neuronal activity (IML)

Anterior
Anterior to ANT = No neuronal activity (lateral ventricle) - Cells representative of ANT if within the nucleus but anterior to target region

Lateral
No neuronal activity (IML) - Spiking activity with higher frequency than ANT (VA nucleus)

Medial
No neuronal activity (IML) - Spiking activity with lower spike amplitude and more regular firing patterns than ANT (DM nucleus)

Inferior (along electrode trajectory)
No neuronal activity (IML) - Spiking activity with lower spike amplitude and more regular firing patterns than ANT (DM nucleus - infro-medial) - Spiking activity with higher frequency than ANT (VA nucleus - inferolateral)

TRAJECTORIES

SANTE trial – transventricular frontal (recommended for best accuracy)
MORE registry – lateral extraventricular (fails to enter ANT most often of all approaches).
Mayo Clinic – posterior extraventricular.

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

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.
- MER appears not to be a crucial factor in successful lead placement in the ANT.

E27 (8) DBS in Epilepsy

Möttönen et al, submitted

**DBS IN EPILEPSY**

---

**TRANSEXTREME FRONTAL (PROXIMAL)**
- 60° posterior from an axial plane parallel to AC-PC plane, i.e. 30° anterior from a coronal plane perpendicular to AC-PC plane.
- trajectory typically runs through the narrow vascular window between the superior choroidal vein and thalamostriate vein (between caudate and ANT); blunt stylet advances slowly pushes veins away.
- sometimes choroid plexus is on top of ANT (but it is a mobile structure so hemorrhage is rare – Dr. Lehtimäki goes through it).
- MORE study - we distinct types of misplacements were observed:
  a) too deep position of the lead in a trajectory through the ANT
  b) deviation of the lead from the trajectory through the ANT - 1 lead deviated medially and 2 leads were positioned in CSF spaces - related to the penetration of the lateral ventricle.

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

**LATERAL EXTREMEVENTRICULAR (TRANSCORTICAL)**
- passes through eloquent cortex, such as the operculum.
- provides improved mediolateral 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; compromise between these anatomical limits is most likely achieved by adjusting the target inferiorly, laterally, and posteriorly, probably aiming to stimulate the MTI-ANT junction rather than ANT nucleus per se.

**POSTERIOR INFERIOR PARIETAL**
- 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.

**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 – 17,680 USD (2019 October)
  - Percept PC: Medtronic.com/Percept
  - Weight: 61g
  - Height: 68mm
  - Length: 51mm
  - Channels: 2

**LEADS**
FDA approved: 3387 (used in SANTE trial) - 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).

Lead 3387 – plan to place contact (3 or 2) inside ANT:

- allow 15% length stretch.

COMPLICATIONS, SIDE EFFECTS


1. **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 hemorrhages.

- 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.

2. **Psychiatric side effects**

- SANTE: depression 37.3% (vs 1.8% in controls) – patients need to be watched closely!

- changing stim contacts almost always helps.

3. **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.

4. **Sleep disruptions with vivid dreams.**

Neuropsychological monitoring of memory and mood is recommended in ANT DBS!

PROGRAMMING

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 1.5-2.0 V and increase monthly (or even longer intervals – analogy with adjusting AEDs) by 0.5 V to target 4.5-5.0 V (up to 7.5 V)

- gradual amplitude increase helps to minimize occurrence of side effects

- keep symmetrical between sides.

- corresponds to 4-7 mA.

**Pulse width** 90 usec (this is invariable*)

**Frequency** 145 Hz (this is invariable*)

*hardware allows to change it but in studies it did not make any difference
Duty cycle: 1 min on, 5 mins off.

Monopolar
- typically not the deepest contact
- usually most centrally located contact
- do not use contacts with low impedances – electrical current will shunt into CSF (not into parenchyma).
- alternative – wide bipolar stim (anode most distal).
N.B. bipolar stimulation is used to limit current spread into surrounding structures.

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

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.

STIMULATION OF THE ANTERIOR NUCLEUS OF THALAMUS FOR EPILEPSY (SANTE) TRIAL
Complete set of trial data:
5-year outcome:
7-year outcome:

• 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): 13 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.

Seizure reduction for those subjects who had at least 70 days of diary in the
3 months before each annual visit.

end of blinded segment
Unblended segment

-41% -30% -53% -65% -69%
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.

CENTROMEDIAN NUCLEUS OF THALAMUS (CMT)

CMT, together with the parafascicular nuclei, form the posterior group of the intralaminar nuclei of the thalamus. The 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).

majority of available data support the use of CMT DBS for the treatment of generalized epilepsies, including patients suffering from Lennox-Gastaut syndrome.

current data is only from level III-IV studies.

imaging – CMT cannot be seen even on 7T MRI (vs. ANT).

placed under general anesthesia with recruiting response.

Outcomes


the largest series, published by Son et al. in 2016 reported a 99% 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.

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.
patients selected from population undergoing invasive electrodes: diagnostic electrodes replaced with stimulation electrodes at site of seizure focus.

- 60-100% response rates (some become seizure free).

-causes no change in neuropsychological tests.

<table>
<thead>
<tr>
<th>Study</th>
<th>Velasco et al</th>
<th>Cuikert et al</th>
<th>Andrade et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>4 pts w/CC</td>
<td>2</td>
</tr>
</tbody>
</table>

Pathology

- LGS
- IGE 2
- LG 2
- SGE 1 Multifocal 1

Targeting

- Recruiting response
- Recruiting response

Stim parameters

- 130 Hz, 450 µs, 2.3 v
- 130 Hz, 300µs, 2v
- 100-185 Hz, 90-120 µs, 1-10v

Outcome

- Seizure control
- No changes in neuropsychological outcomes

Neuropsych outcome

- Improvement related to Seizure Outcome
- Improved alertness (SNAP IV)
- N/A

Comments

- Anterolateral nucleus in parvocellular best response
- Improvement in alertness at 0.5v and sz control at 1.5 v

HIPPOCAMPUS

Cukiert et al (2017) - the results of a prospective, double-blinded, 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. reported on 11 patients who underwent bilateral HCP DBS electrode implantation, with the efficacy of unilateral and bilateral HCP DBS in 16 patients with refractory TLE:

- 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.
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Study

<table>
<thead>
<tr>
<th>Study</th>
<th>n Randomization</th>
<th>Stim Param</th>
<th>Seizure Outcome</th>
<th>Neuropsych</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velasco et al Epilepsia ‘07</td>
<td>9 Immediate on vs 1 mo delay</td>
<td>130 Hz 450 µs cycle</td>
<td>100% RR 49/sz free</td>
<td>No decline</td>
<td>Absence of MS on MRI predicts success</td>
</tr>
<tr>
<td>Boon et al Epilepsia ‘07</td>
<td>10 no</td>
<td>130 Hz 450 µs cont</td>
<td>70% RR 1/10 sz free (AMS)</td>
<td>No decline</td>
<td>No decline</td>
</tr>
<tr>
<td>Tézé-Zellent et al Neurol ‘06</td>
<td>4 Alternating 1 mo blocks over 6 mo</td>
<td>190 Hz 90 µs &amp; 25% RR 9/sz free</td>
<td>No decline</td>
<td>Design of random not optimal</td>
<td></td>
</tr>
</tbody>
</table>

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STN

<table>
<thead>
<tr>
<th>Author</th>
<th>N Localization of epilepsy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benabid/Chabardes 2002</td>
<td>3 sensory motor cortex</td>
<td>67.87% &lt; 50%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Shon (Seoul) Stereotact Funct Neurosurg 2005;83:84–90</td>
<td>2 FLE s/p failed resection</td>
<td>87.89%</td>
</tr>
<tr>
<td>Handforth (UCLA) Epilepsia 47(7):1239–1241, 2006</td>
<td>1 Bitemporal epilepsy</td>
<td>50%</td>
</tr>
<tr>
<td>Neme (Santiago)</td>
<td>1 Frontal encephalomalacia</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

CEREBELLUM

- 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