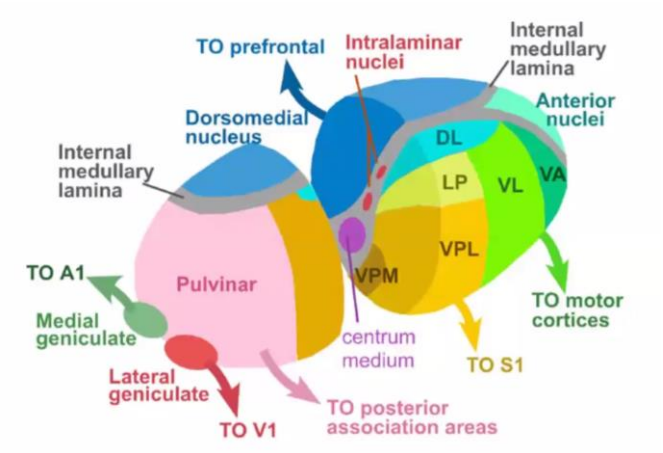
DBS in Epilepsy

Last updated: April 27, 2024

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

N.B. there are epilepsies that do NOT involve thalamus!

Mechanism of Action – see p. E11 >>
Comparison of Neuromodulations (RNS, DBS, VNS) – see p. E11 >>
Thalamic SEEG – see p. E13 >>
Thalamic FUS – see p. Rx15 >>



HISTORY

- Hunter and Jasper showed that seizures could be induced by electrical stimulation of the thalamus.
  Hunter J, Jasper HH. Effects of thalamic stimulation in unanaesthetised animals; the arrest reaction and petit mal-like seizures, activation patterns and generalized convulsions. Electroen Clin Neuro 1949;1(3):305–24.
- Monnier and colleagues showed that medial thalamic stimulation could desynchronize ECoG.
  Monnier M, Kalberer M, Krupp P. Functional antagonism between diffuse reticular and intralaminary recruiting projections in the medial thalamus. Exp Neurol 1960; 2(3):271–89.

ANT

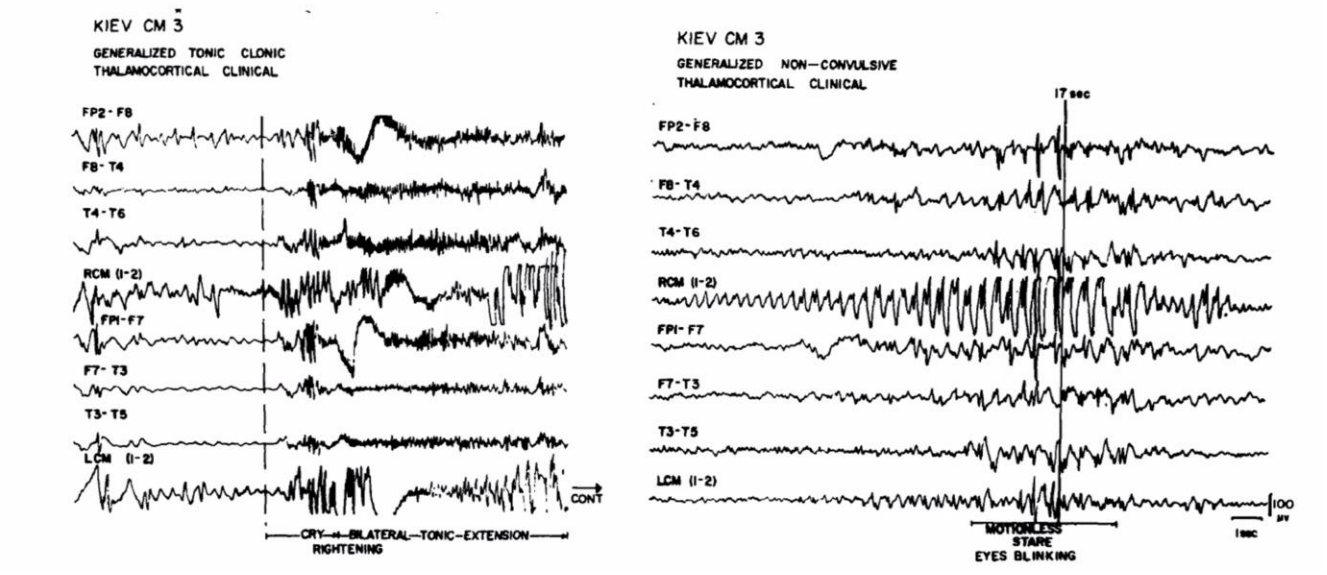
- proposed by Upton and colleagues for suppression of epileptiform discharges within the limbic system; in 1987, they reported significant seizure control in 4 of 6 patients.
  Upton AR, Cooper IS, Springman M, et al. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol 1985;19-20:223–30.

CM

- in the 1980s, Velasco and colleagues explored the CM as a DBS target for idiopathic generalized epilepsy (IGE), reporting excellent results.
  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):421–30.

CMT participates early in generalized seizures

Epileptiform EEG Activities of the Centromedian Thalamic Nuclei in Patients with Intractable Partial Motor, Complex Partial, and Generalized Seizures.
Velasco et al, 1989.



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).

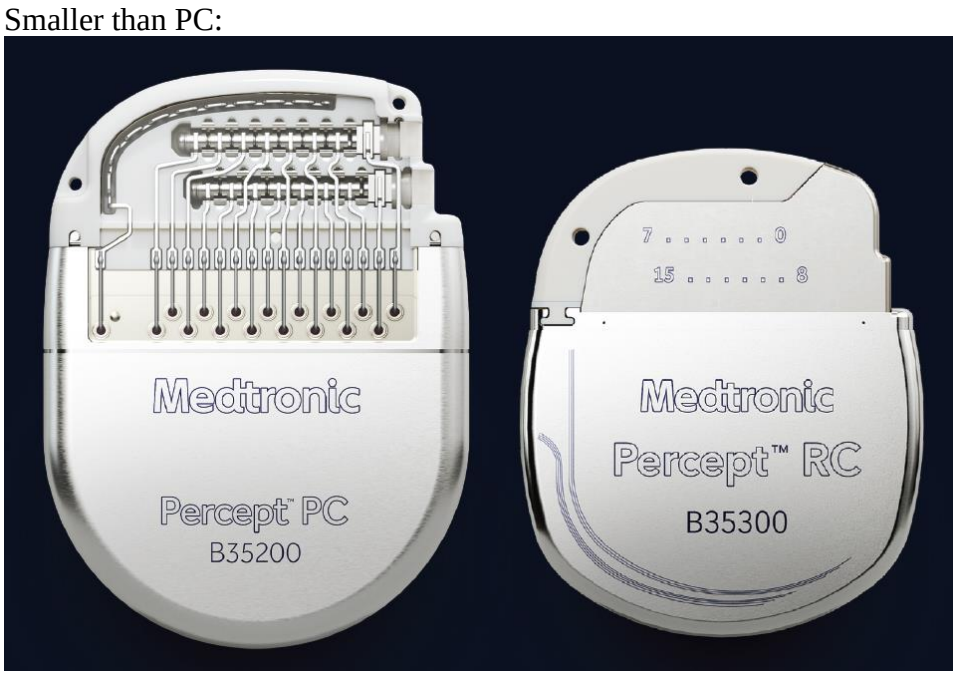
BATTERY

ACTIVA PC

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

PERCEPT RC (B35300)

Smaller than PC:



PERCEPT PC (B35200)

Medtronic.com/Percept >>

Weight	61g
Height	68mm
Length	51mm
Channels	2

- BrainSense™ technology - captures **local field potentials (LFP)** using the implanted DBS lead simultaneously while delivering therapeutic stimulation. see below >>
  N.B. right subclavicular position gives less cardiac artefacts (cf. left position)
- 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.

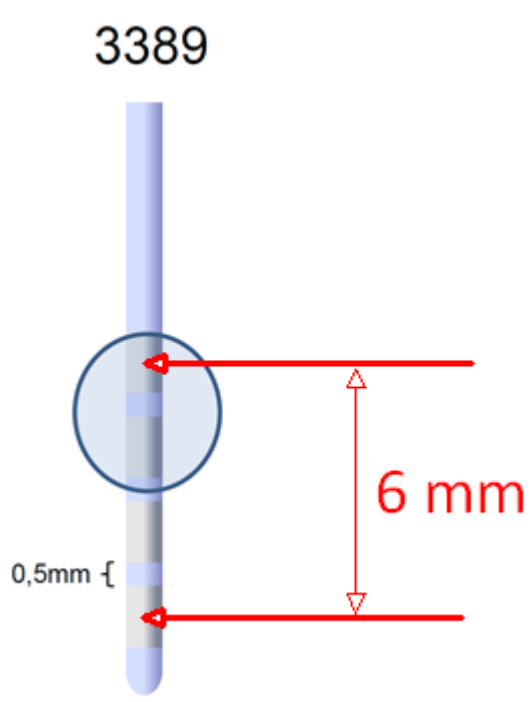
PLUGS

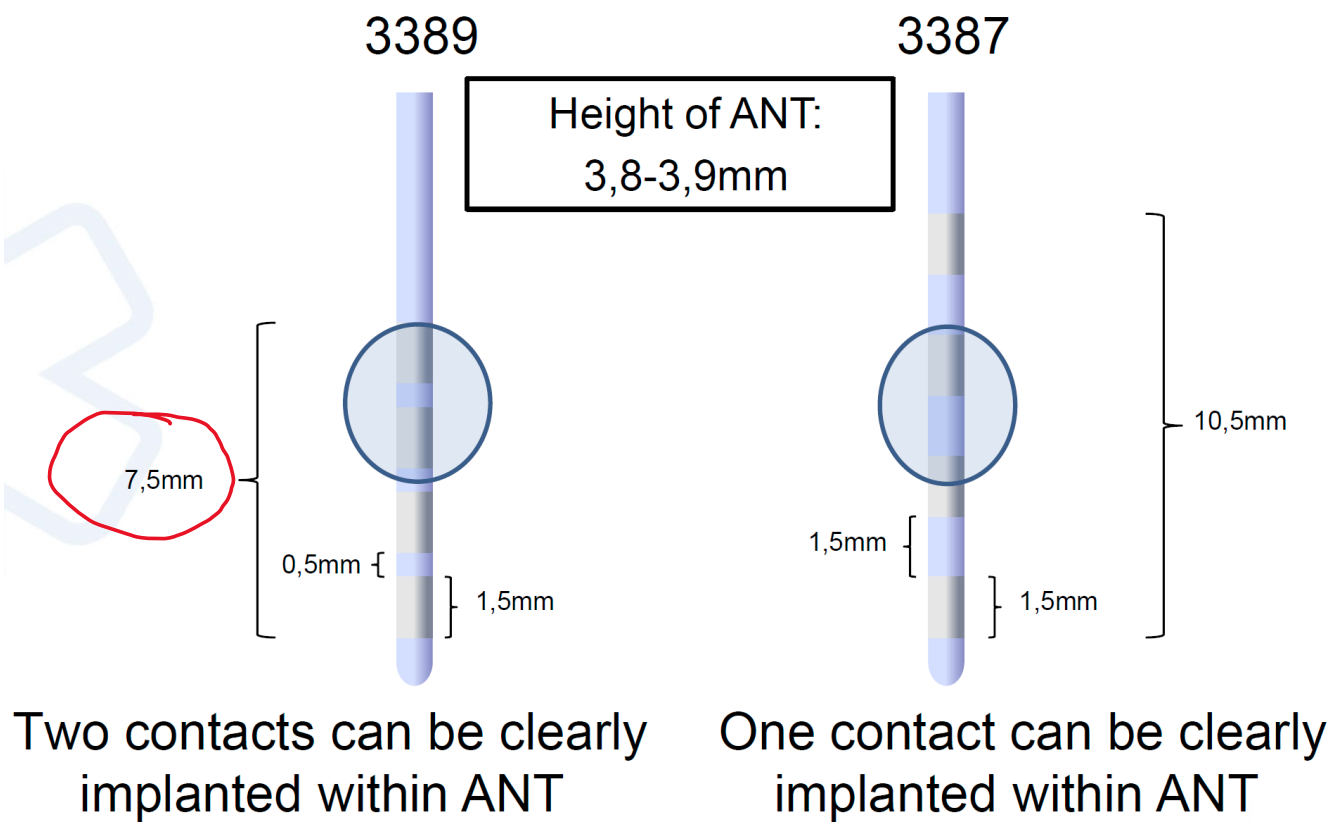
LEADS

FDA approved:
3387 (used in SANTE trial)
3389 - preferred

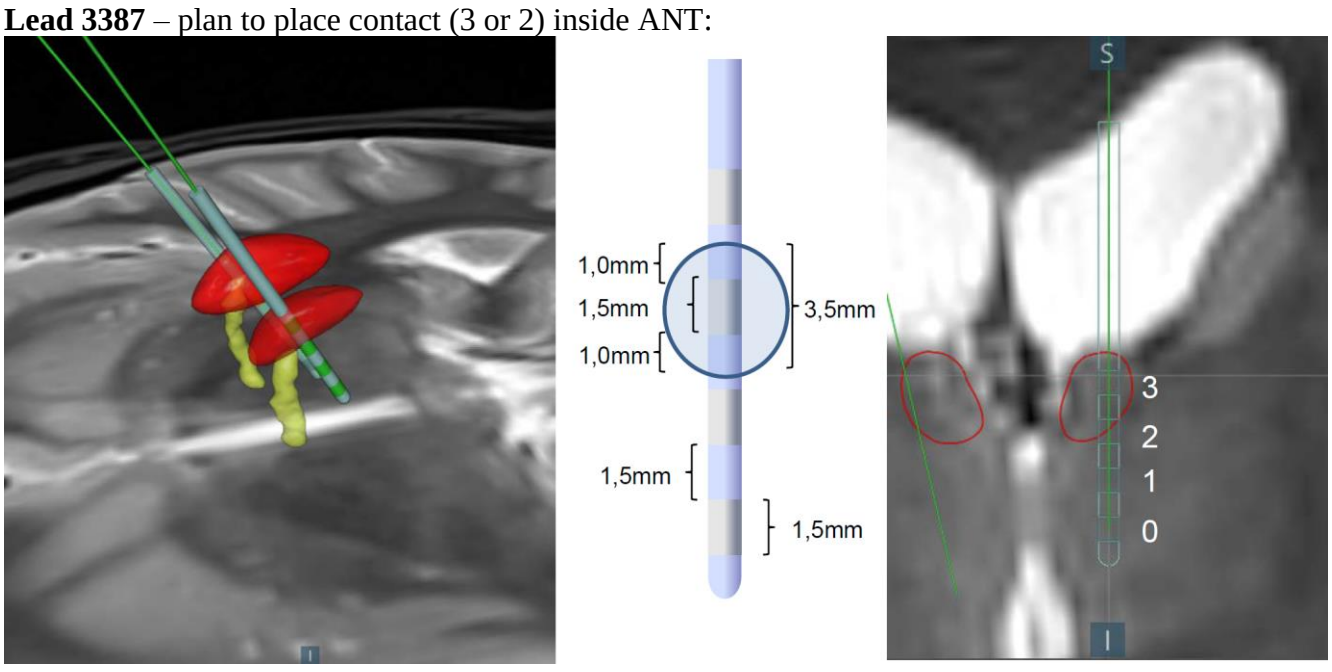
- use "at target" cannula; "10 mm above" cannula may cause DBS lead to deviate (some experts set target 8 mm deeper so that "10 mm above" cannula enters the parenchyma).

N.B. with lead 3389, the distance between the centers of first and last contact is **6 mm** – when planing trajectory and target, plan that 6 mm segment to incorporate into ANT (if want all contacts be in ANT, target must be 7.5* mm deep in ANT)
*AlphaOmega DBS lead holding device and ruler are set to exclude the distal plastic lead tip





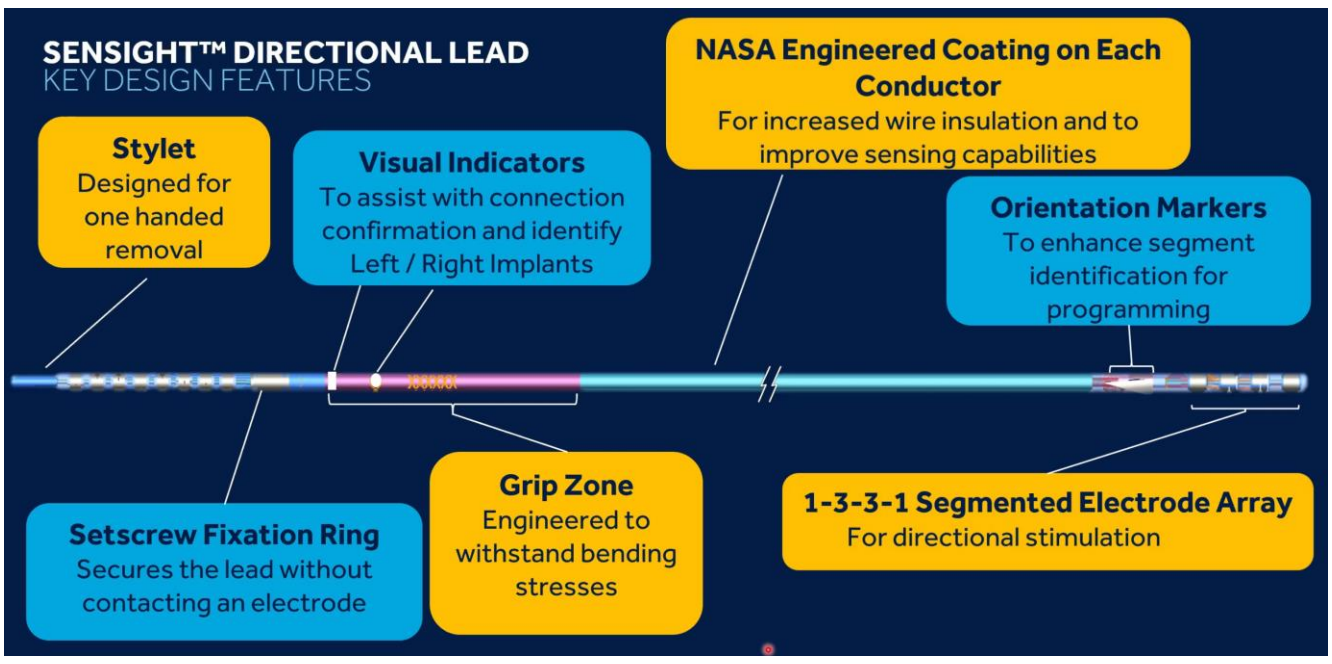
Lead 3387 – plan to place contact (3 or 2) inside ANT:

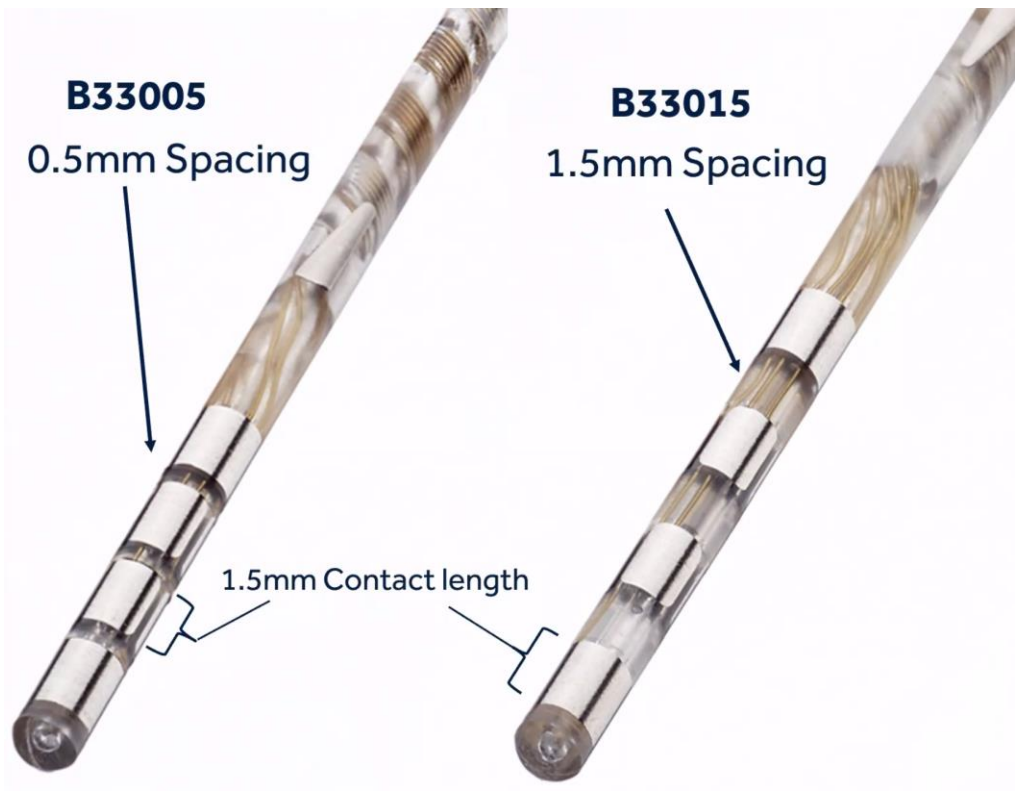


SENSIGHT (MEDTRONIC) – DIRECTIONAL 1-3-3-1 LEAD

- lead tip is 1 mm from bottom of distal (0) contact.
- 33 cm and 42 cm lengths.
- 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.

*old leads (3389, 3387) - 1.27 mm





From **tip** to **the proximal end of the most proximal contact** – 8.5 mm (B33005) or 11.5 mm (B33015) but for surgical target, subtract 1 mm as measurement rulers take this into account (i.e. 1 mm tip is excluded when measuring DBS lead on ruler for DBS lead holder):

B33005 lead: when planning trajectory, plan 7.5 mm segment to straddle the stimulation target.
B33015 lead: when planning trajectory, plan 10.5 mm segment to straddle the stimulation target.

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
LEAD PLACEMENT

Stylet

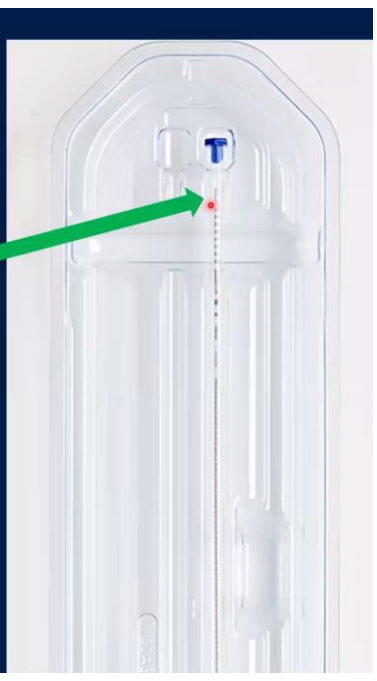
- Ensure stylet is fully seated in the lead before attaching depth stop
- Best to do this right out of the packaging, as it may move during shipping

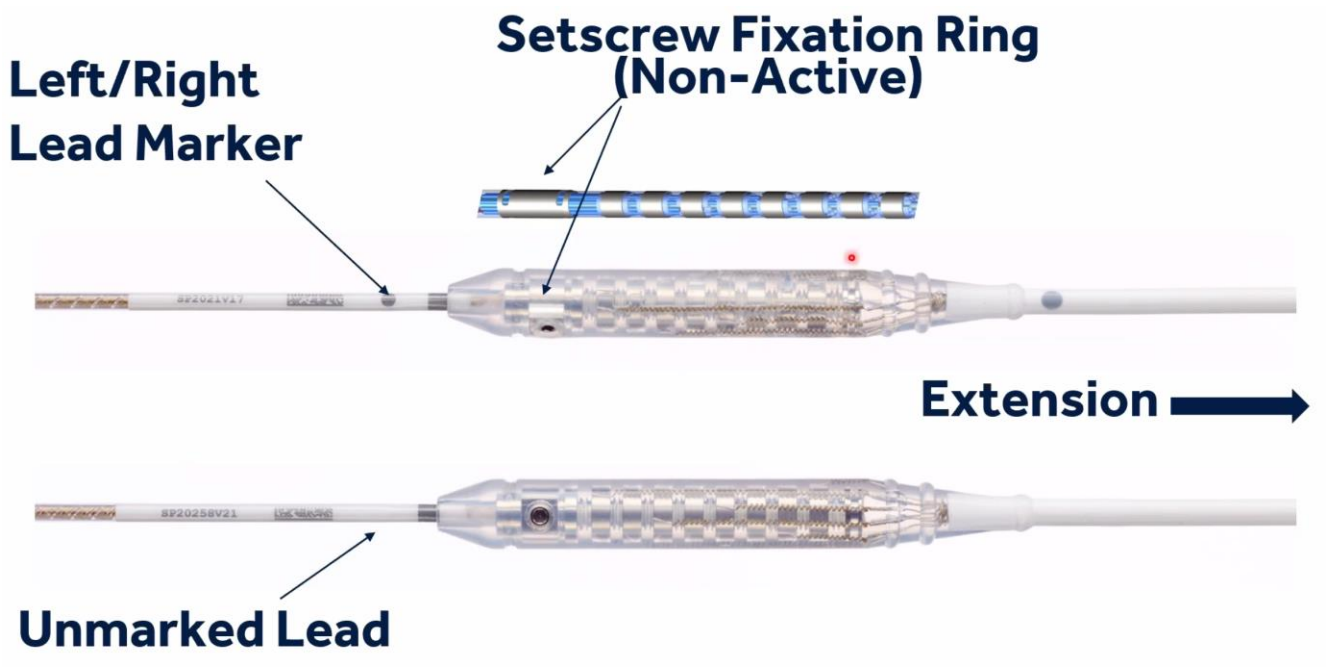
Left/Right lead markers

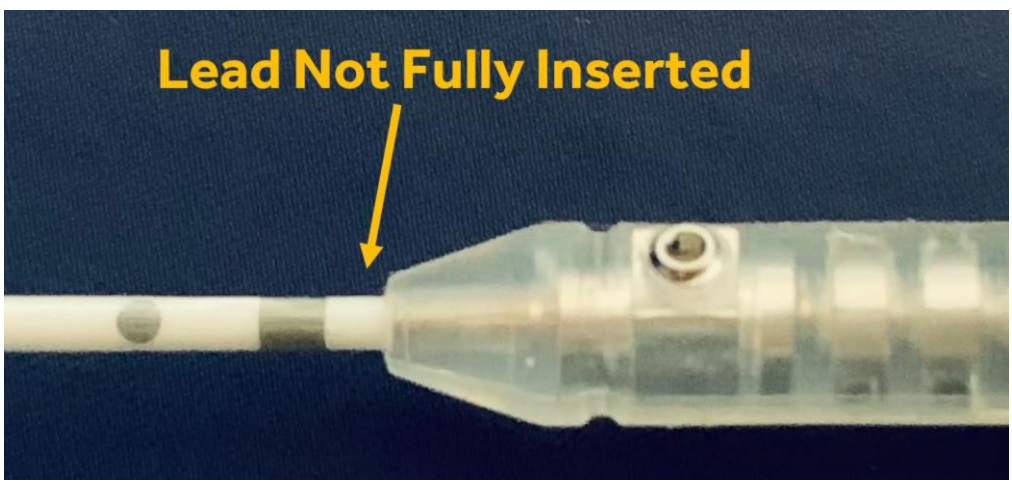
- No recommended convention, clinician preference

Alignment of segments

- Can be entered into the clinician programmer post operatively

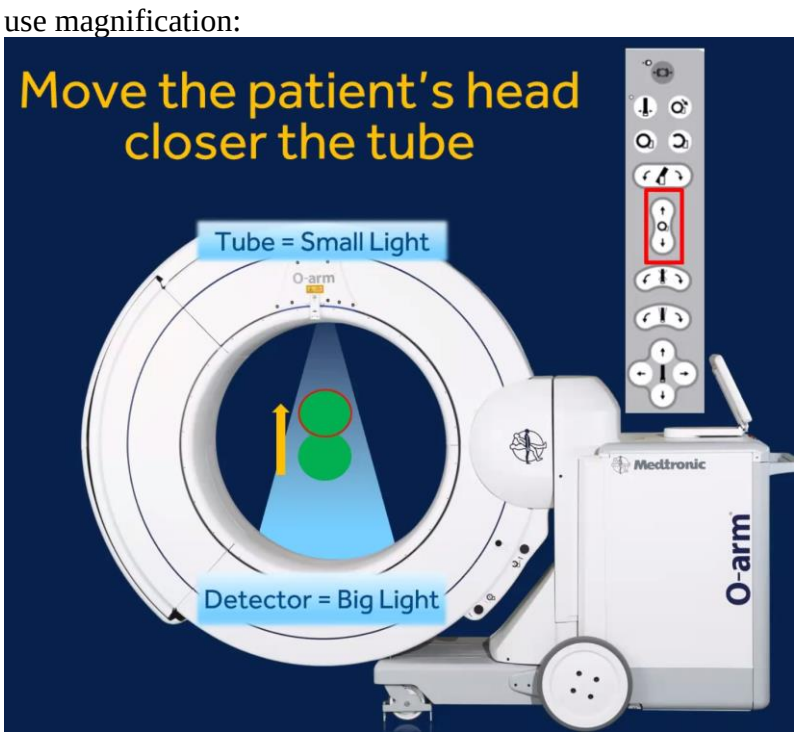




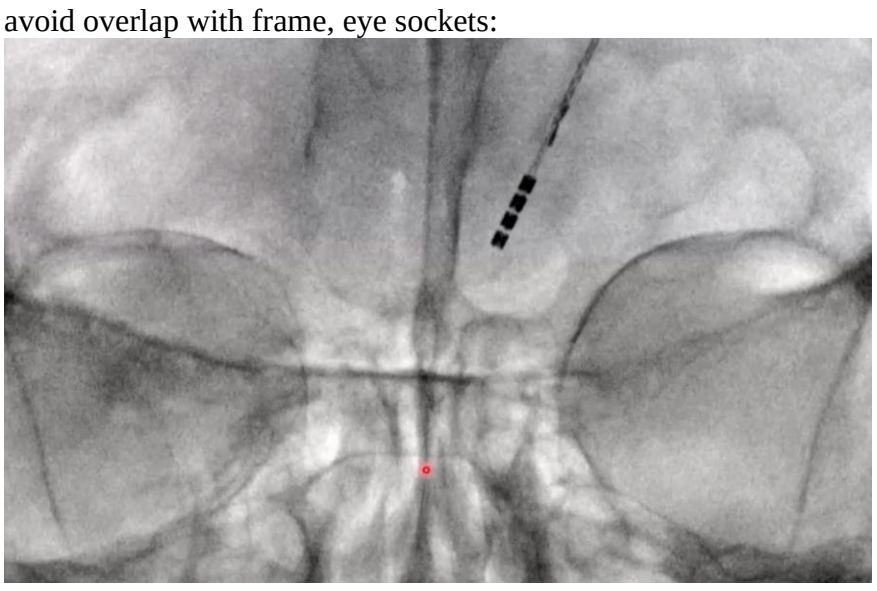


ORIENTATION MARKERS

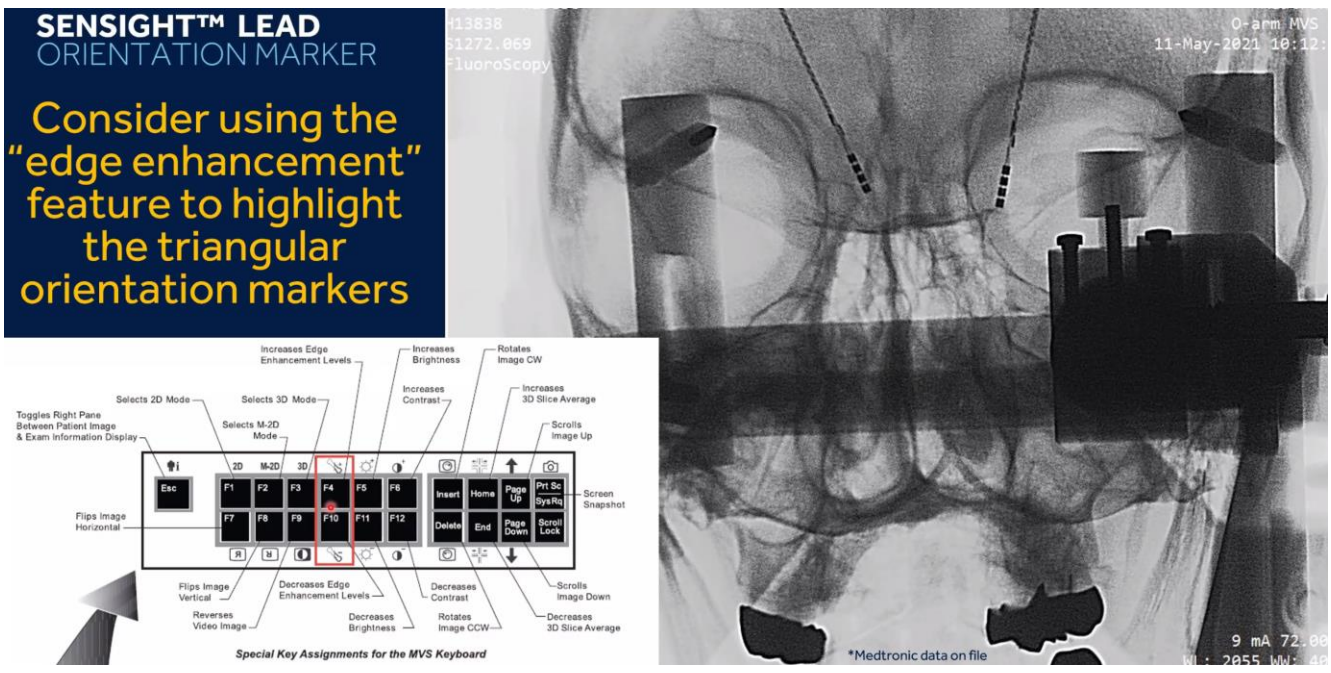
- best to image 1 month postop (brain settles); but can be done intraop:
  - either fluoro or O-arm (MRI does not show markers)
  - remove stylet
- use magnification:



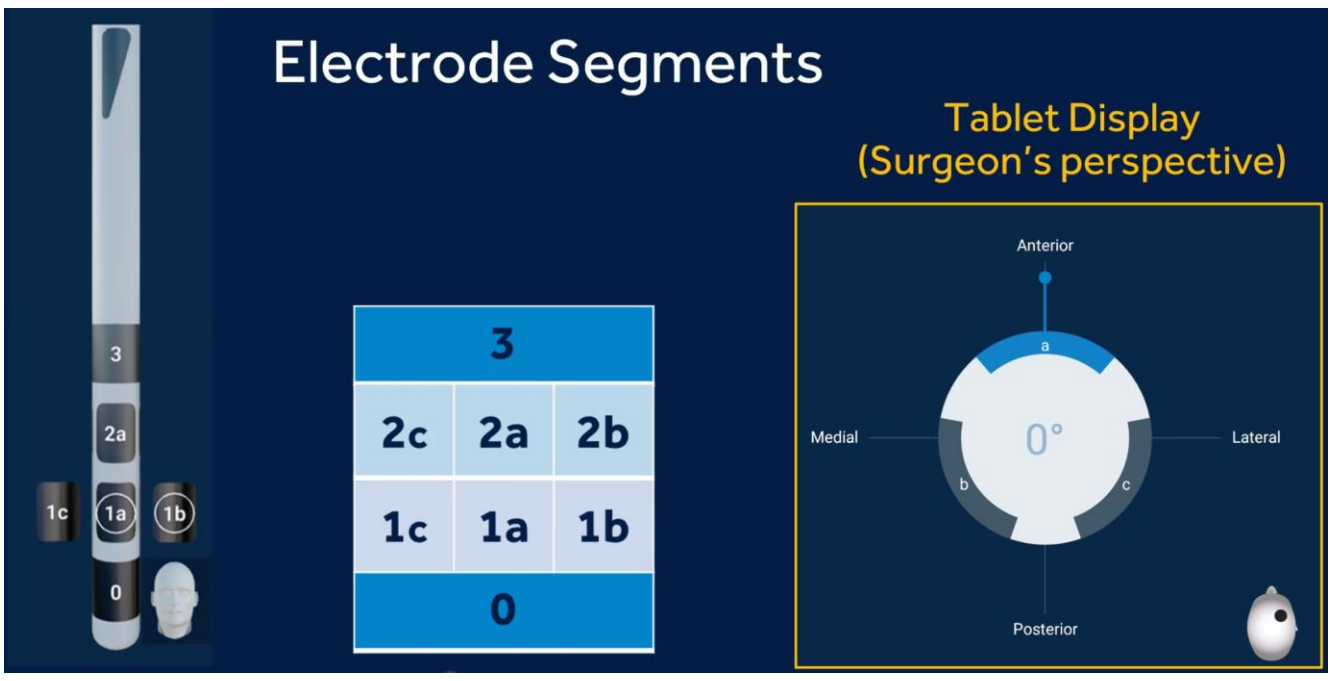
- avoid overlap with frame, eye sockets:

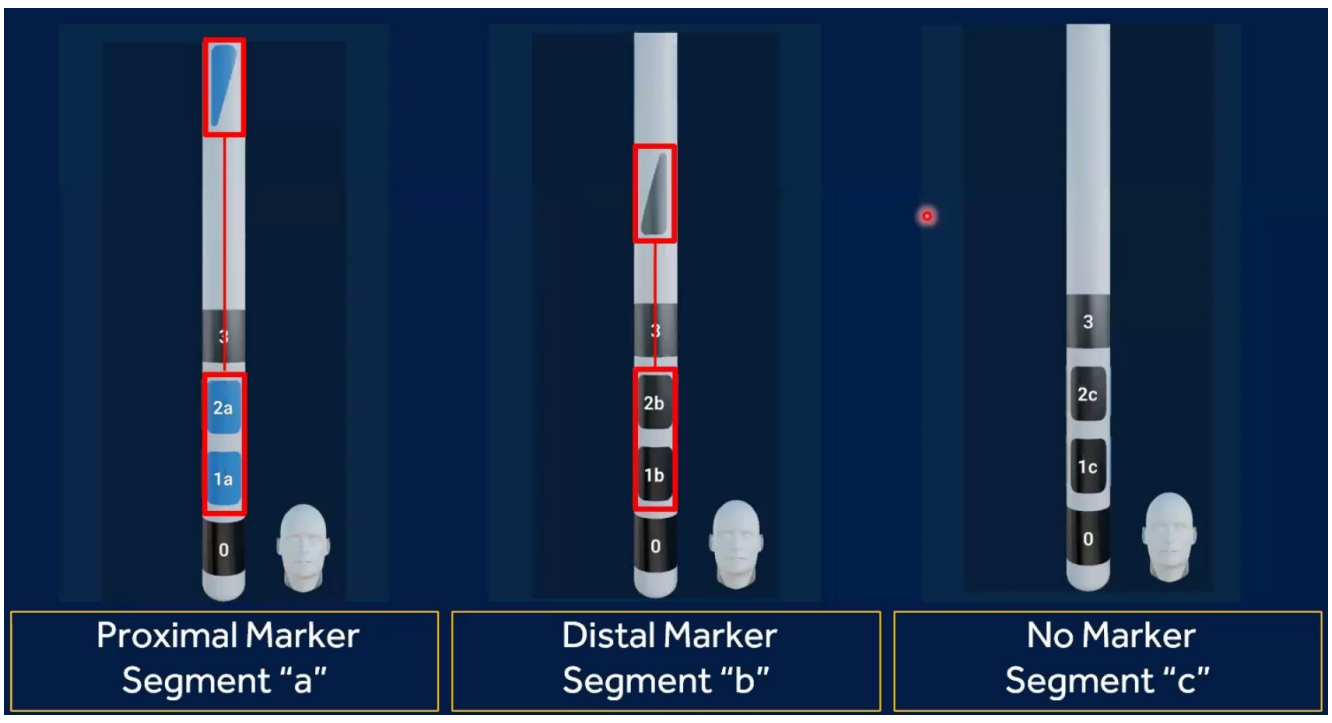


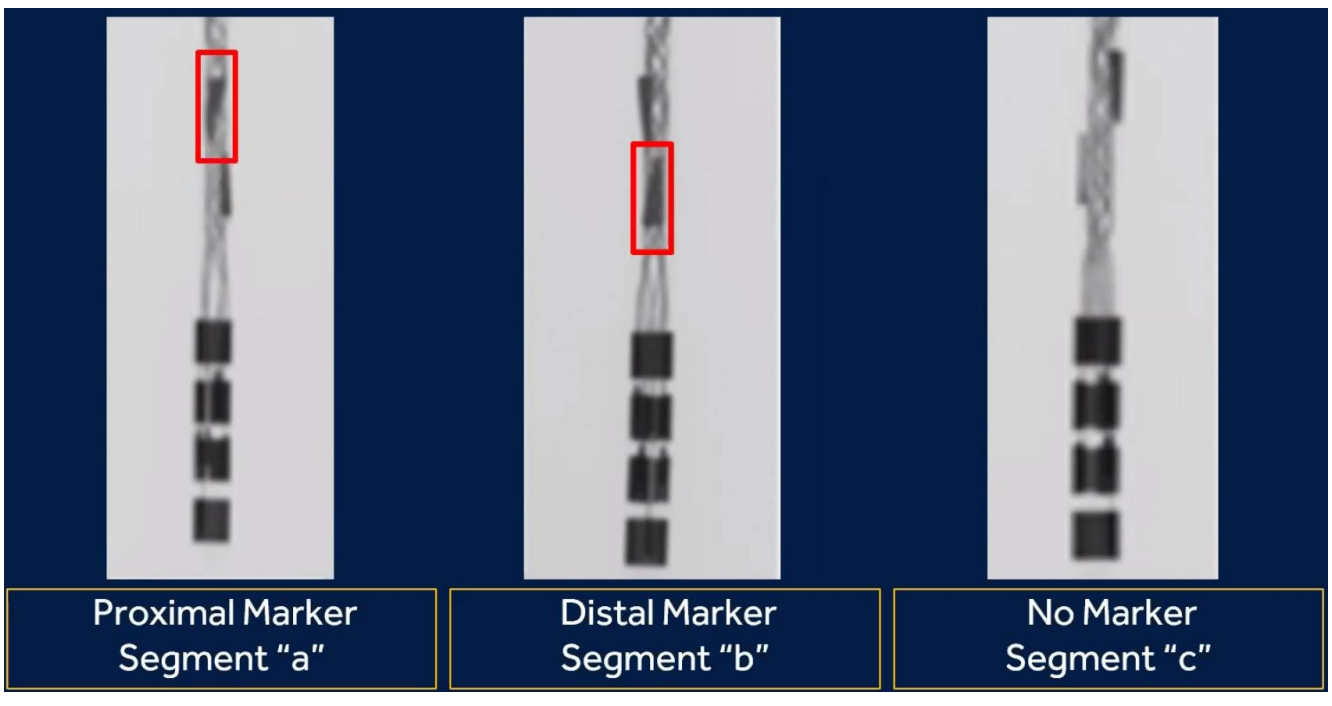
- use "edge enhancement" feature in O-arm:



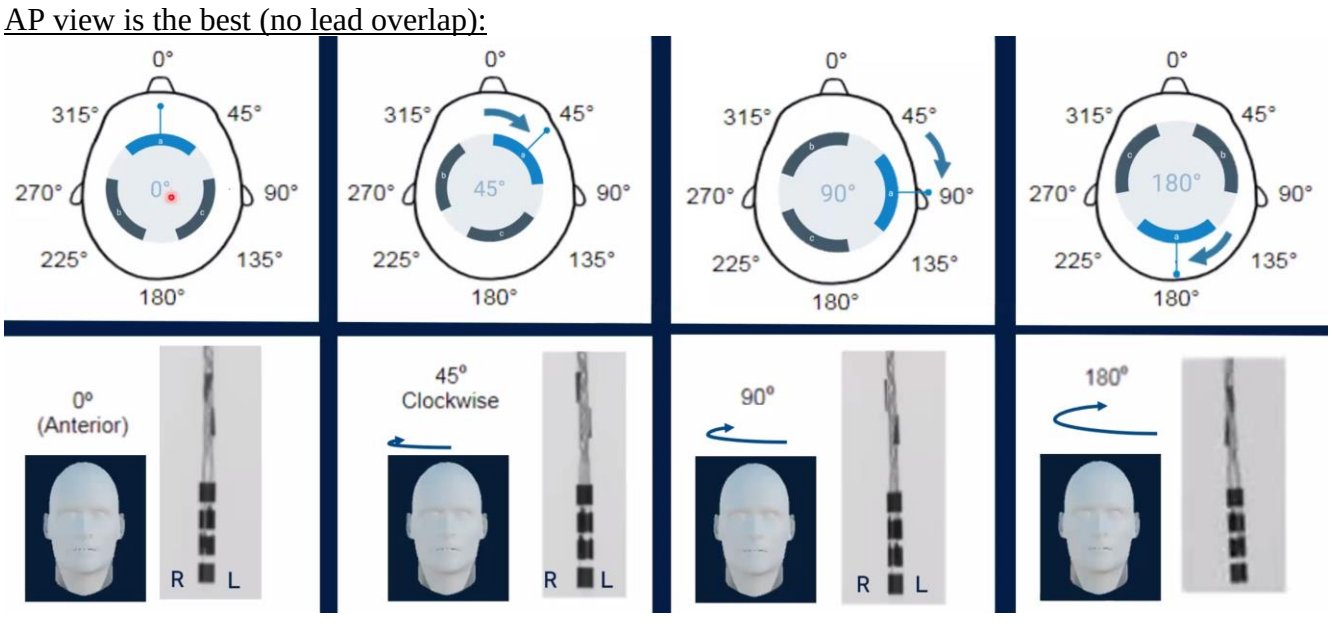
- proximal marker aligns with 1a and 2a segments
- distal marker aligns with 1b and 2b segments



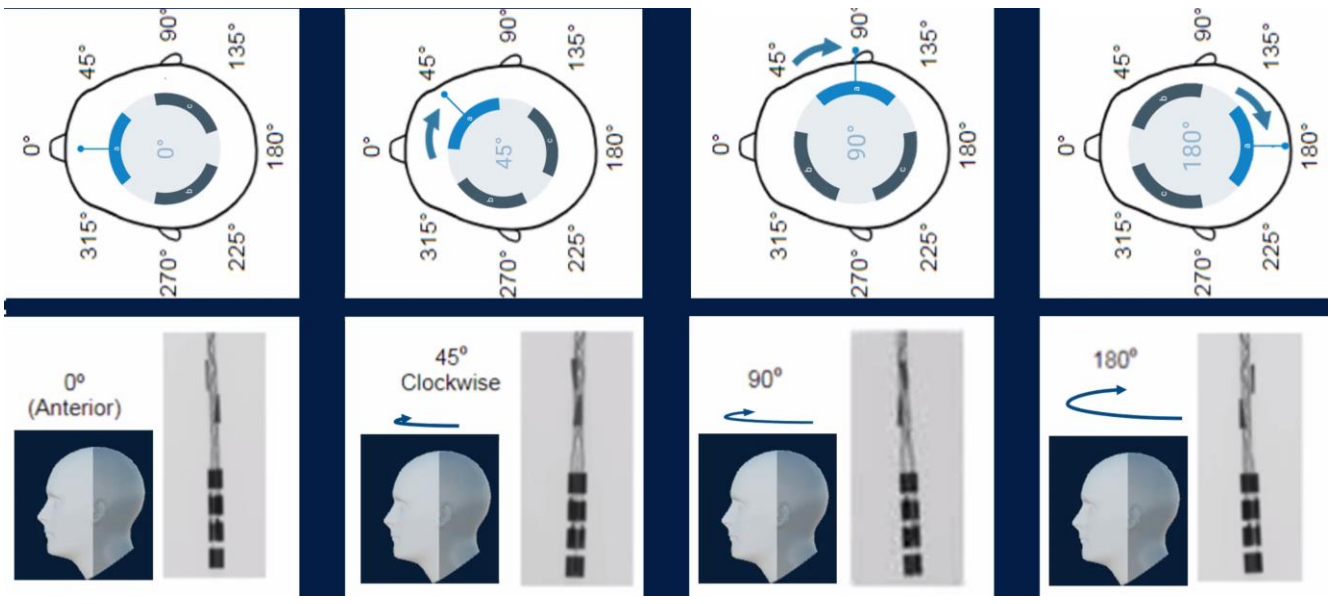




<u>AP view is the best (no lead overlap):</u>



<u>Lateral view:</u>



IMPEDANCES

- due to smaller segmental contacts, normal impedances have higher upper limit:
  monopolar: 350-8000 Ohm
  bipolar 350-10000 Ohm

BURHOLE COVER

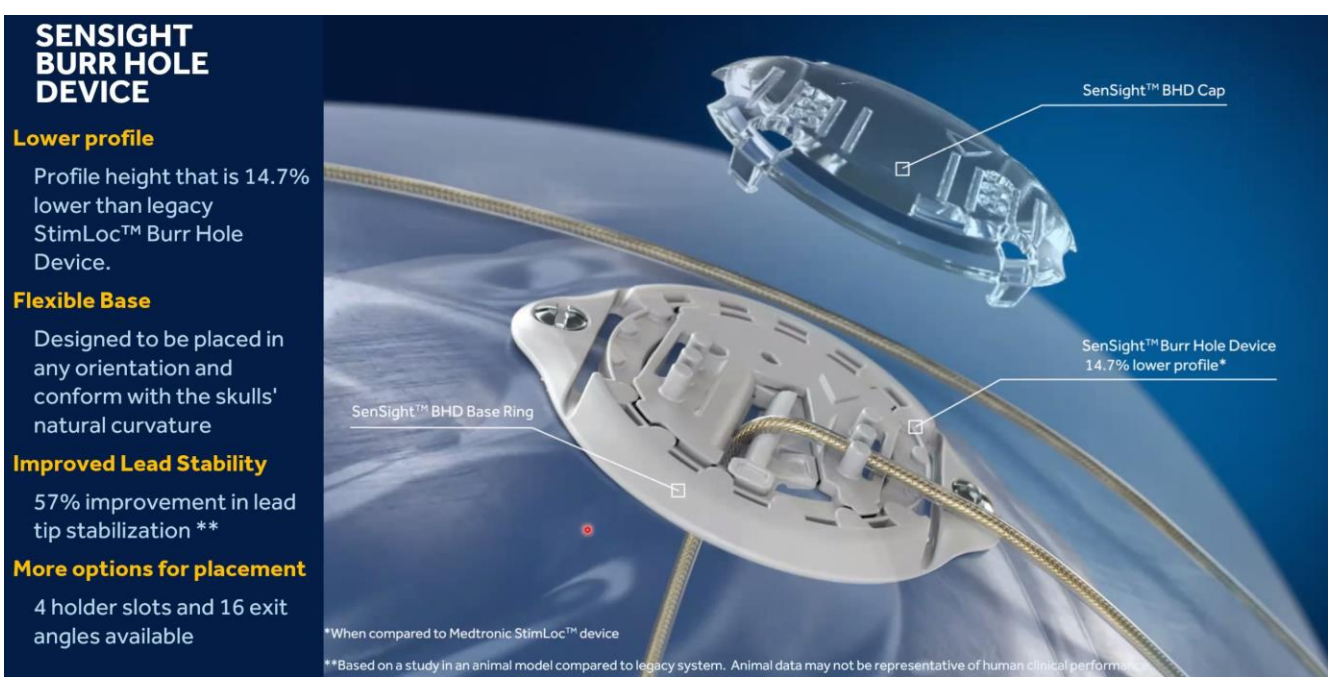
SENSIGHT (B32000)

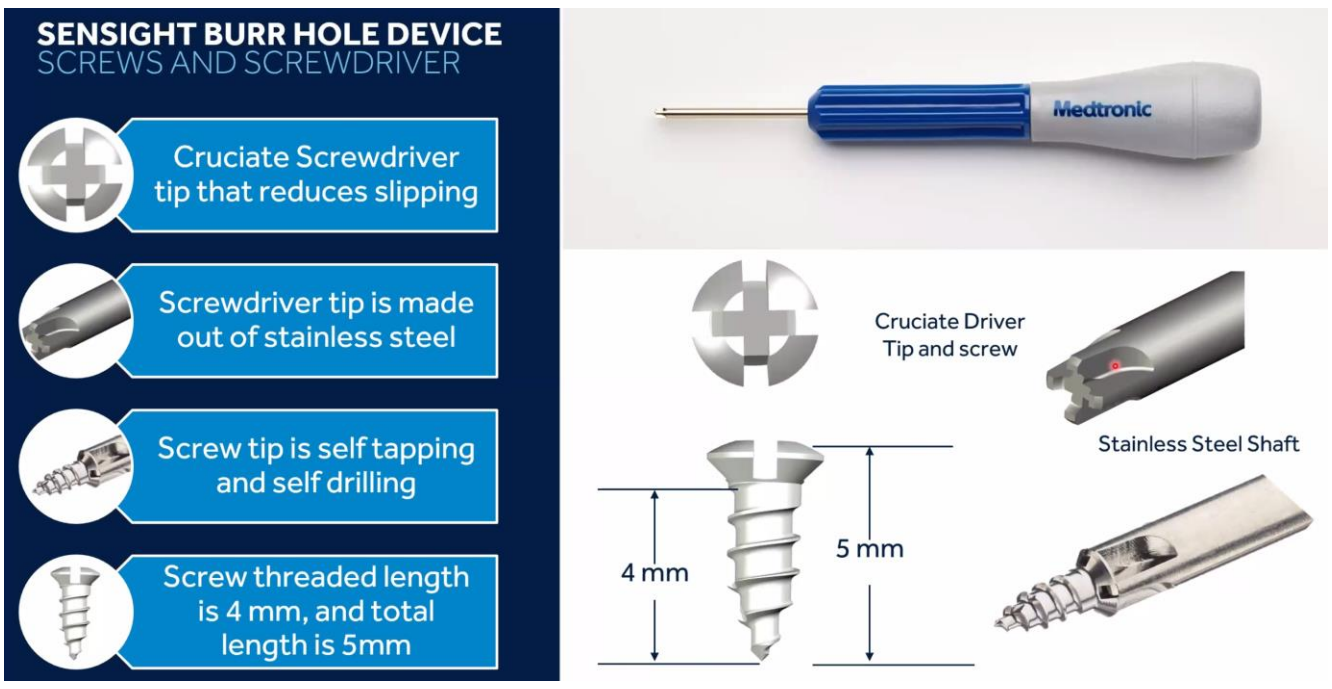
- only for SenSight leads (for old leads need to use Stimloc)

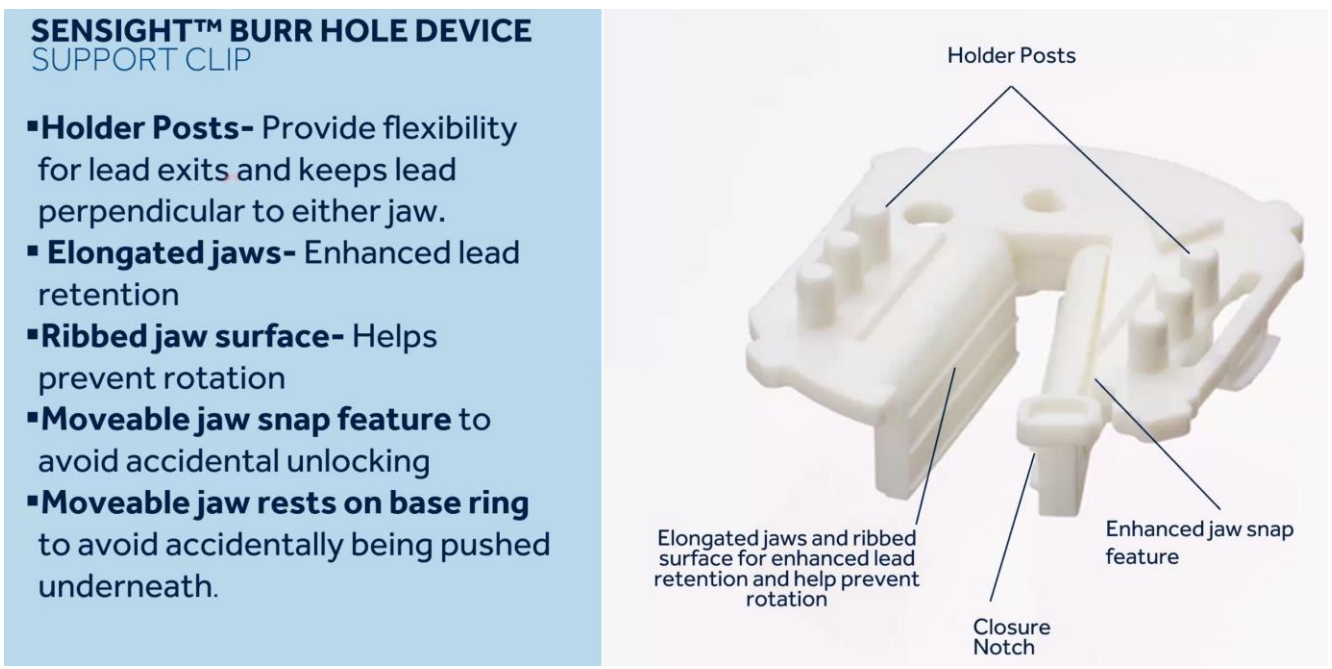
- improved visual contrast – cap is clear plastic, ring is white plastic (line up triangles when applying cap).

N.B. if outer table skull bone is drilled off to allow hardware countersink (e.g. for occipital entry sites), makes sure to drill off deep bone shelf* around before placing base ring (otherwise drill will damage plastic and will prevent clip fixation).

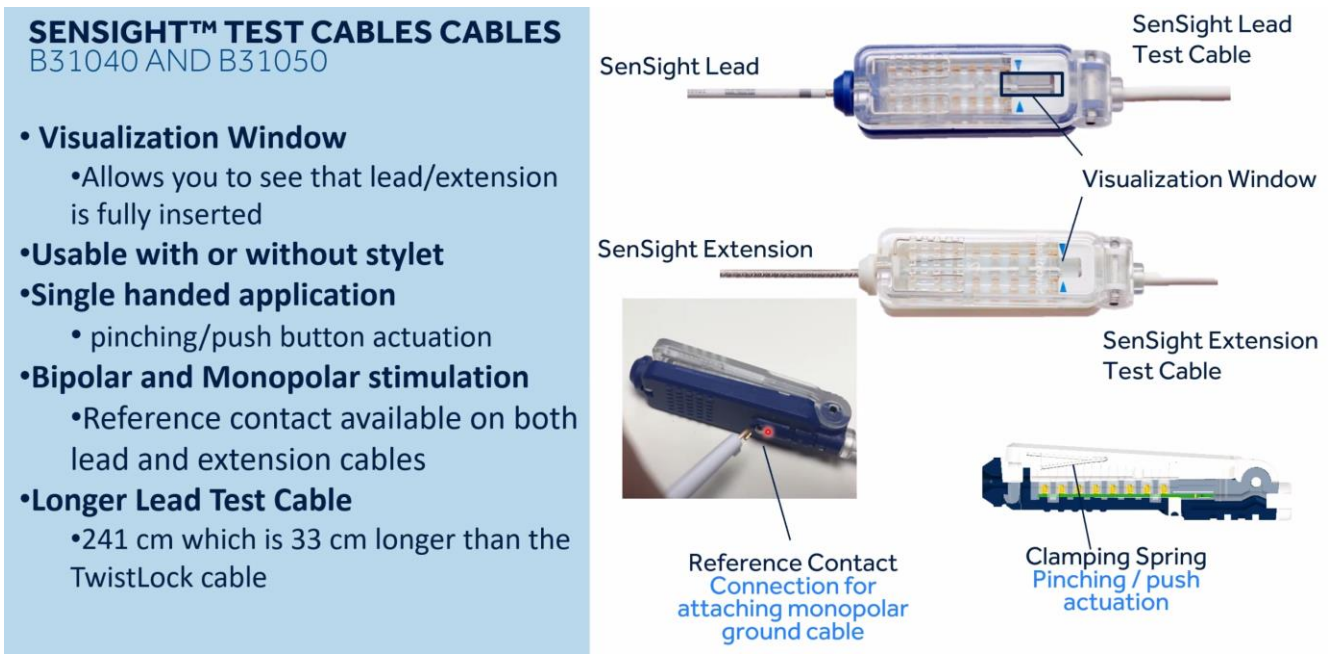
*otherwise, there will be clip collision!

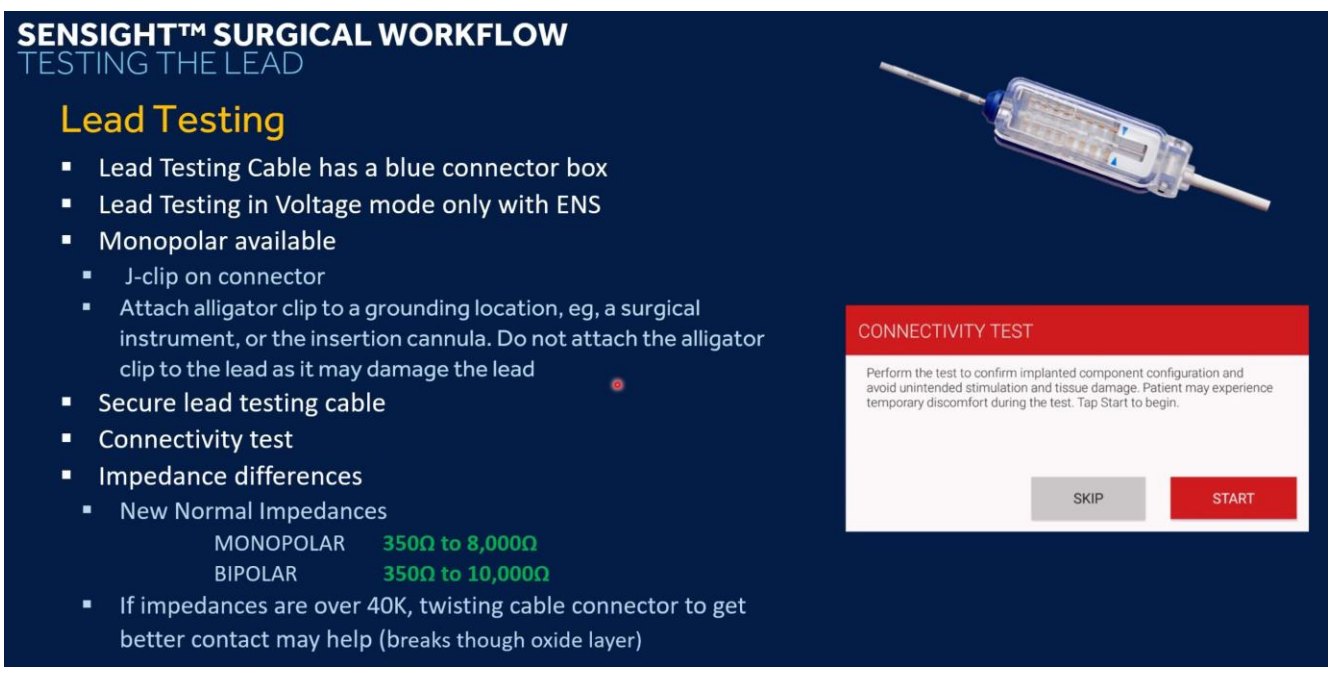






TESTING CABLES

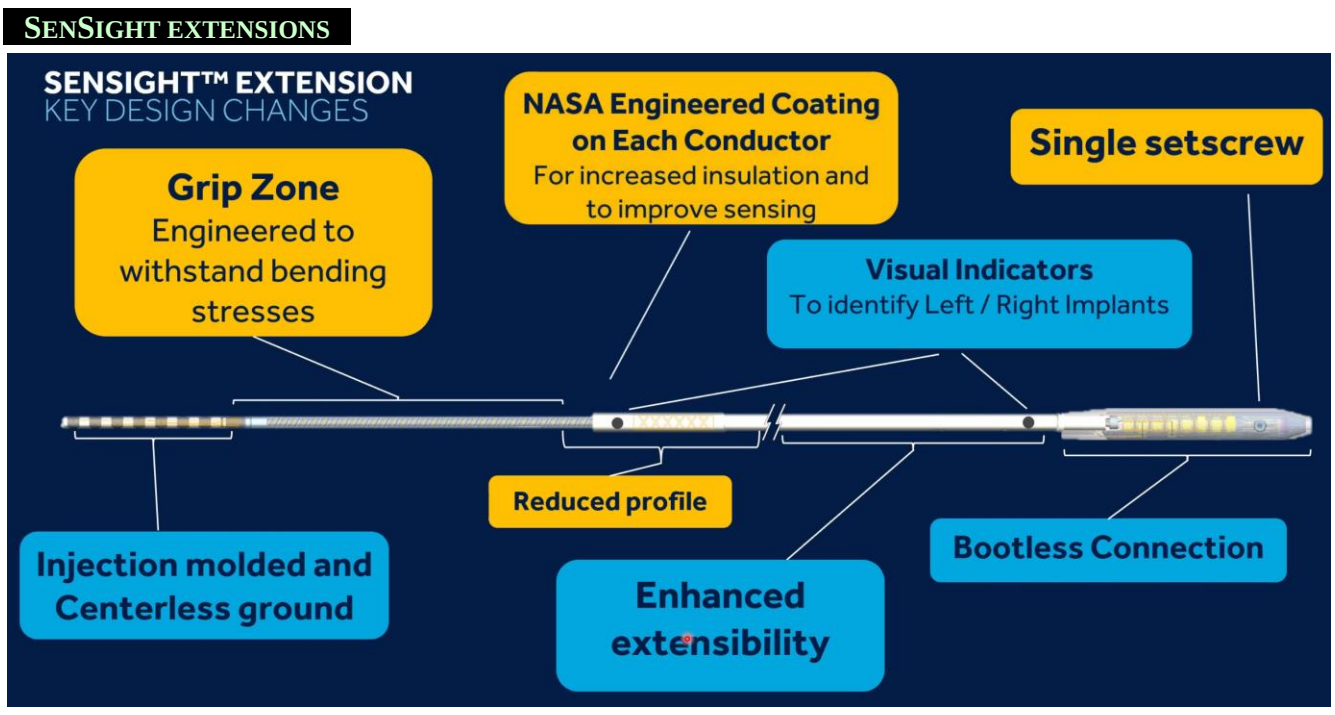


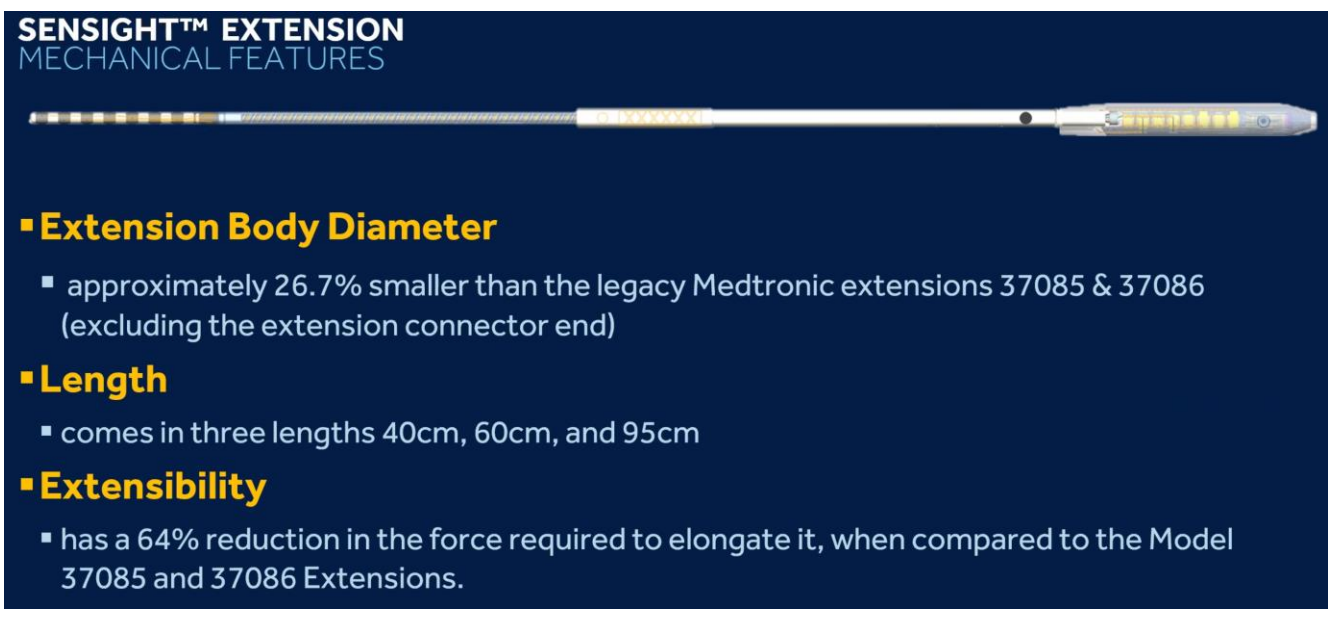


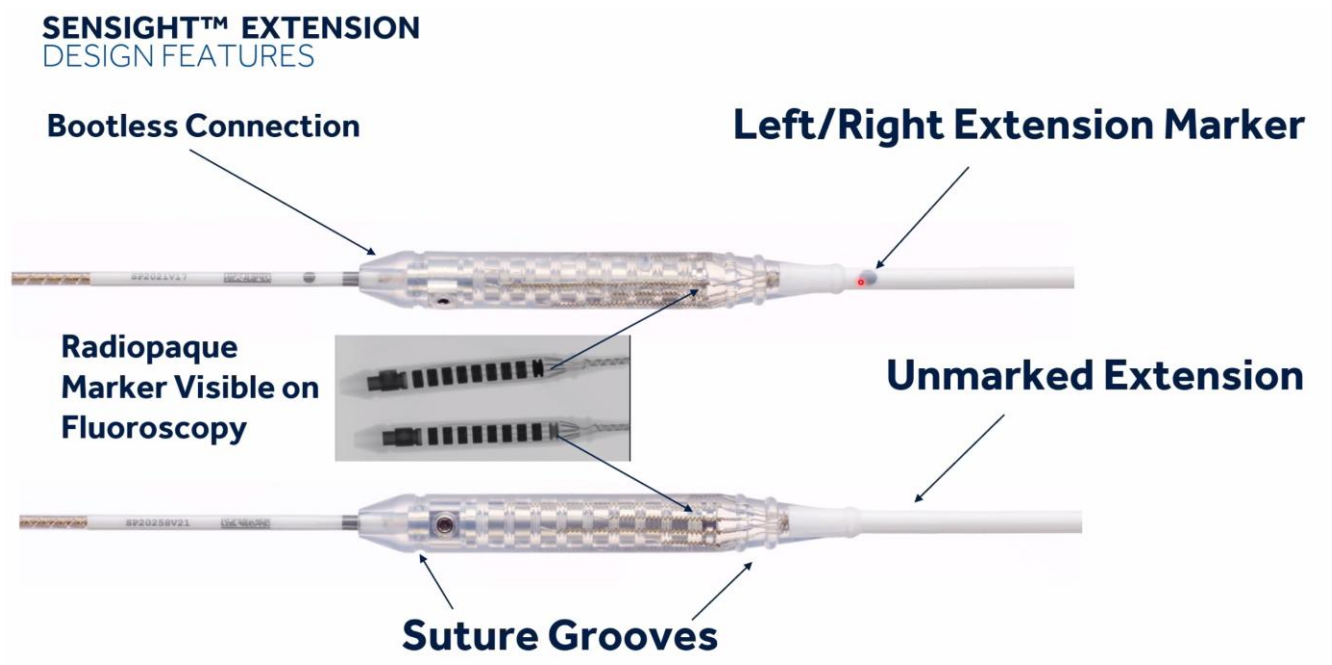
EXTENSIONS

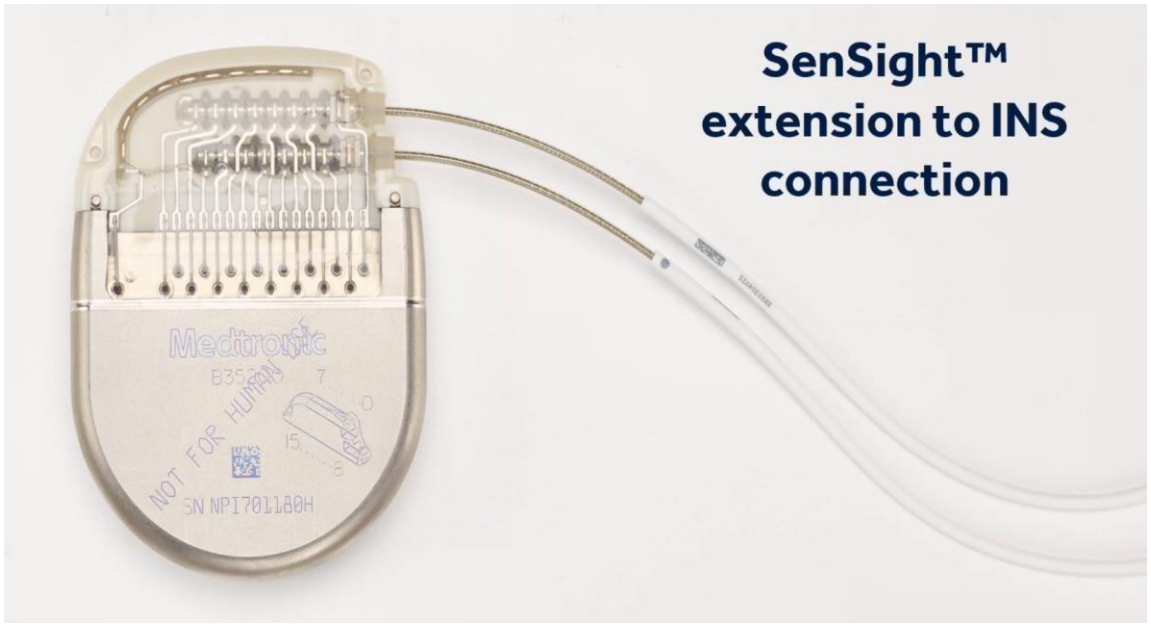
- allow 15% length stretch.
- tunneler (passer) is inserted from cranium towards thorax – as then to pull extension hubs up (towards cranium).

SENSIGHT EXTENSIONS









White 5 in.-oz torque wrench used for connections to Percept™ PC INS

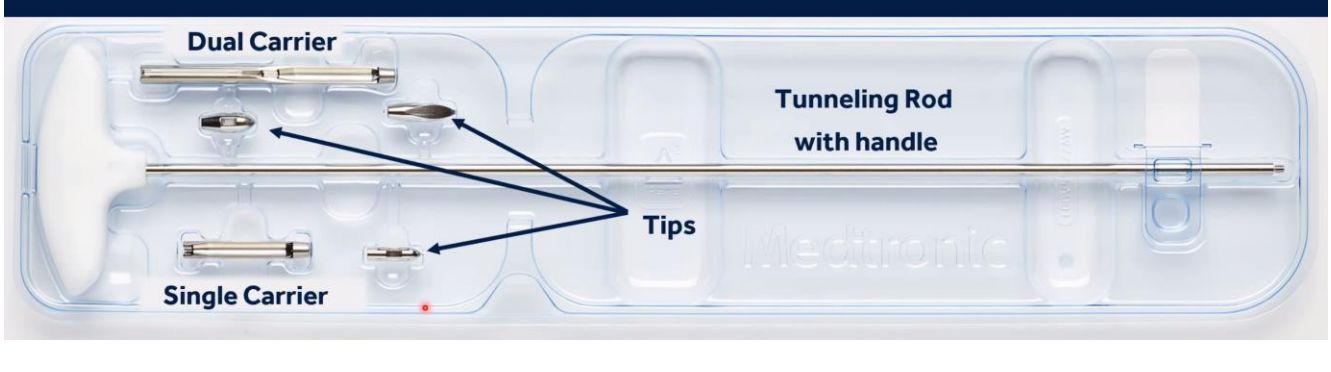
NOTE: The blue 4 in.-oz wrench should still be used for connection to Activa™ Devices

SENSIGHT™ EXTENSION TUNNELER KIT
B31030

Each tunneling tool kit includes:

- One Tunneling rod with handle
- Three Tips (Single, Dual and Wedge)
- Two Carriers (single and dual)

The SenSight™ Extension Tunneler Kit has specifically designed dual & single extension carriers for the SenSight™ Extensions.
It is not compatible with Legacy Extensions



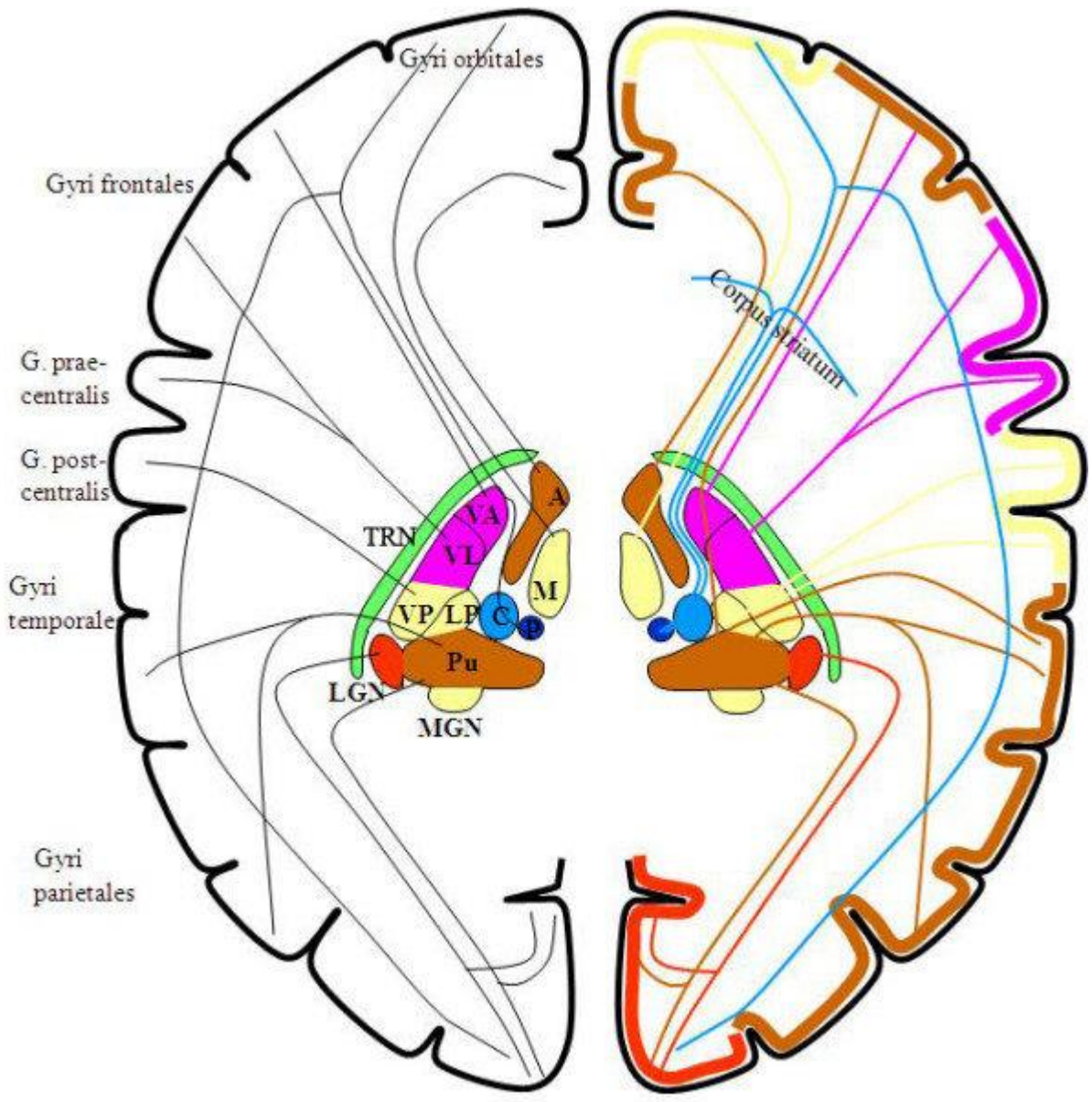
NEUROBIOLOGY

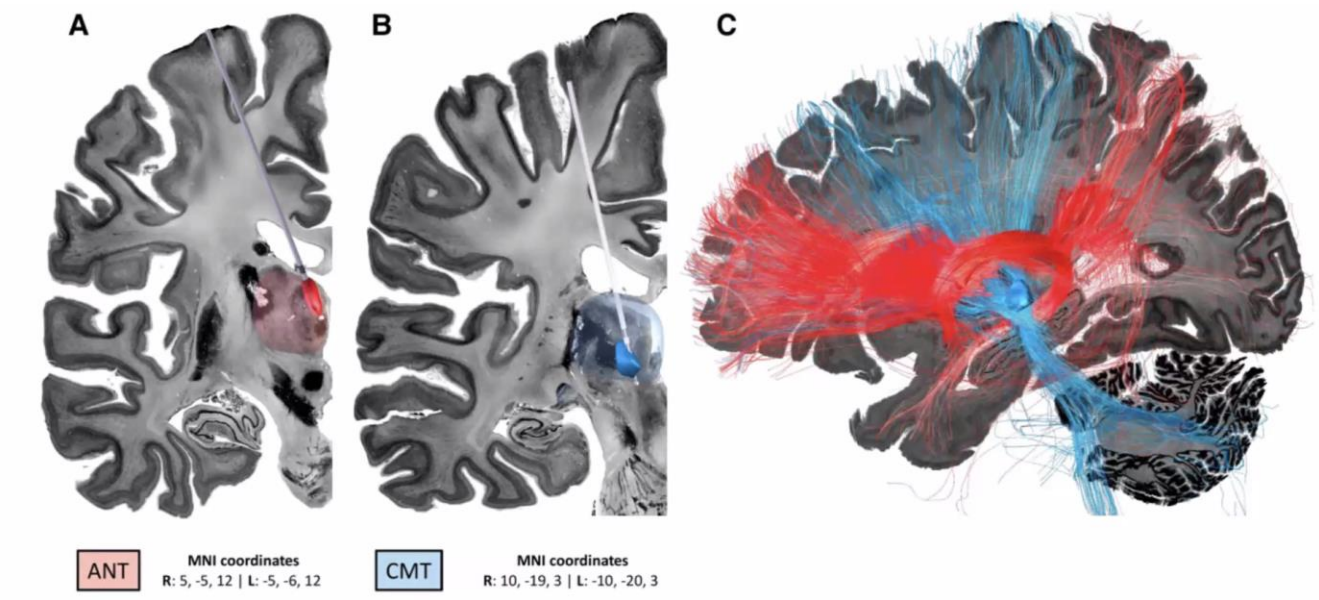
- DBS activates both inhibitory and excitatory pathways; net result depends on target nuclei.

TARGET SELECTION

	ANT	CM	Pulvinar
Frontal		+	
motor cortex		+	
Temporal, lateral			+
Temporal, mesial	+		
Limbic system	+		
Occipital			+

- for ***unilateral epilepsies*** (ideally, verify with SEEG) – implant ANT and CM on the same side.
- if **early thalamic involvement** is demonstrated by SEEG, then choose RNS (otherwise, use DBS or RNS with cortical lead for detections ["corticothalamic" strategy]).





Piper et al. BRAIN 2022

THALAMIC ATLASES

THOMAS

Jason H Su et al. Thalamus Optimized Multi Atlas Segmentation (THOMAS): fast, fully automated segmentation of thalamic nuclei from structural MRI. Neuroimage . 2019 Jul 1:194:272-282. doi: 10.1016/j.neuroimage.

- https://github.com/thalamicseg/thomas_new
- segments thalamus into 12 nuclei.
- THOMAS was rigorously evaluated on 7T MRI data - accuracy was very high, with uniformly high Dice indices: at least 0.85 for large nuclei like the pulvinar and mediodorsal nuclei and at least 0.7 even for small structures such as the habenular, centromedian, and lateral and medial geniculate nuclei. Volume similarity indices ranged from 0.82 for the smaller nuclei to 0.97 for the larger nuclei.
- THOMAS works well for distorted anatomies (such as LGS).
- segmentation technique based on **white-matter-nulled MP-RAGE (WMn MP-RAGE)** imaging:

White-matter-nulled MP-RAGE sequence parameters

	1.5T (GE)	3T (GE)	3T (Siemens)	7T (GE)
TR/TS (ms)	10.4/3000	10/4500	10/4000	10/6000
TI (ms)	350	500	500	680
Flip (deg)	10	9	7	4
Matrix	224×224×124	180×180×200	256×256×160	180×180×200
Slice thickness (mm)	1.2	1	1.1	1
Parallel imaging	None	None	2×1	1.5×1.5
Scan time (min)	7.5	10		5.5
Coil	8-channel GE	8-channel GE	24-channel Nova	32-channel Nova

Tourdias T et al. Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. Neuroimage 84, 534–545. 10.1016/j.neuroimage.2013.08.069

MOREL

ANTERIOR NUCLEI OF THALAMUS (ANT)

History – see above >>

Pending read

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.

V. Salanova. Deep brain stimulation for epilepsy. Epilepsy Behav, 88 (2018), pp. 21-24

Bouwens van der Vlis TAM, Schijns O, Schaper F, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurg Rev. 2018.

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

M.C.H. Li, M.J. Cook. Deep brain stimulation for drug-resistant epilepsy. Epilepsia (2017), pp. 1-18

Lehtimäki K, Möttönen T, Järventausta K, Katisko J, Tähtinen T, Haapasalo J, et al: Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul 9:268–275, 2016

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.

Kamali A, Zhang CC, Riascos RF, Tandon N, Bonafante-Mejia EE, Patel R, et al: Diffusion tensor tractography of the mammillothalamic tract in the human brain using a high spatial resolution DTI technique. Sci Rep 8:5229, 2018

Received: February 22, 2016 Revised: May 3, 2016 Accepted: May 11, 2016

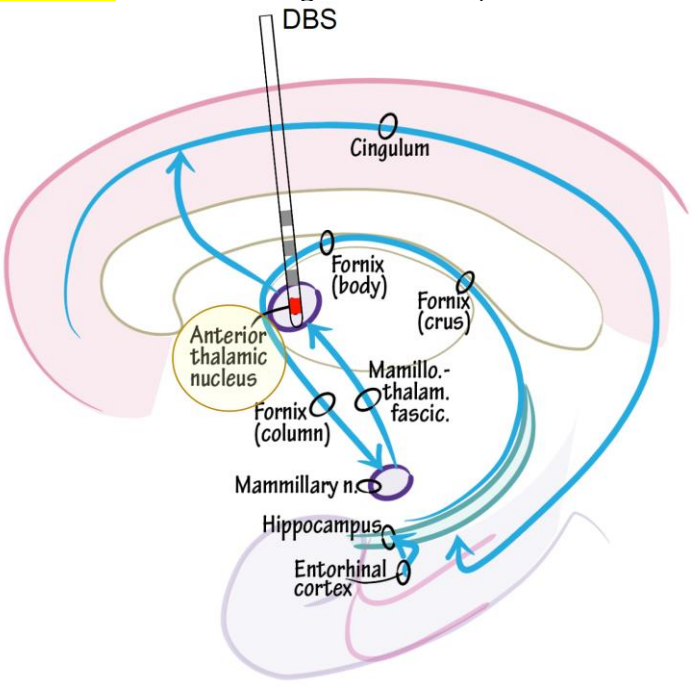
(onlinelibrary.wiley.com) DOI: 10.1111/ner.12468

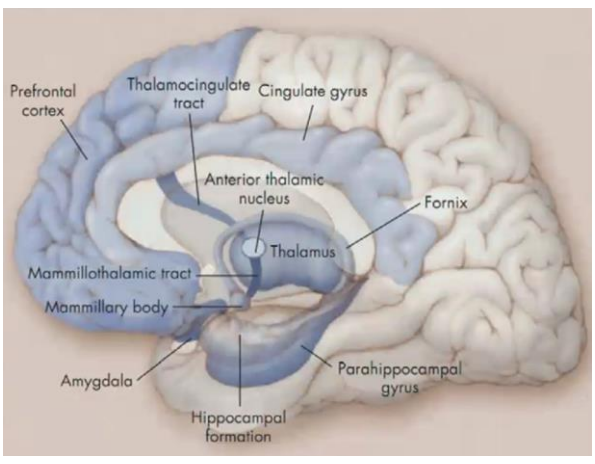
Imaging of Anterior Nucleus of Thalamus Using 1.5T MRI for Deep Brain Stimulation Targeting in Refractory Epilepsy

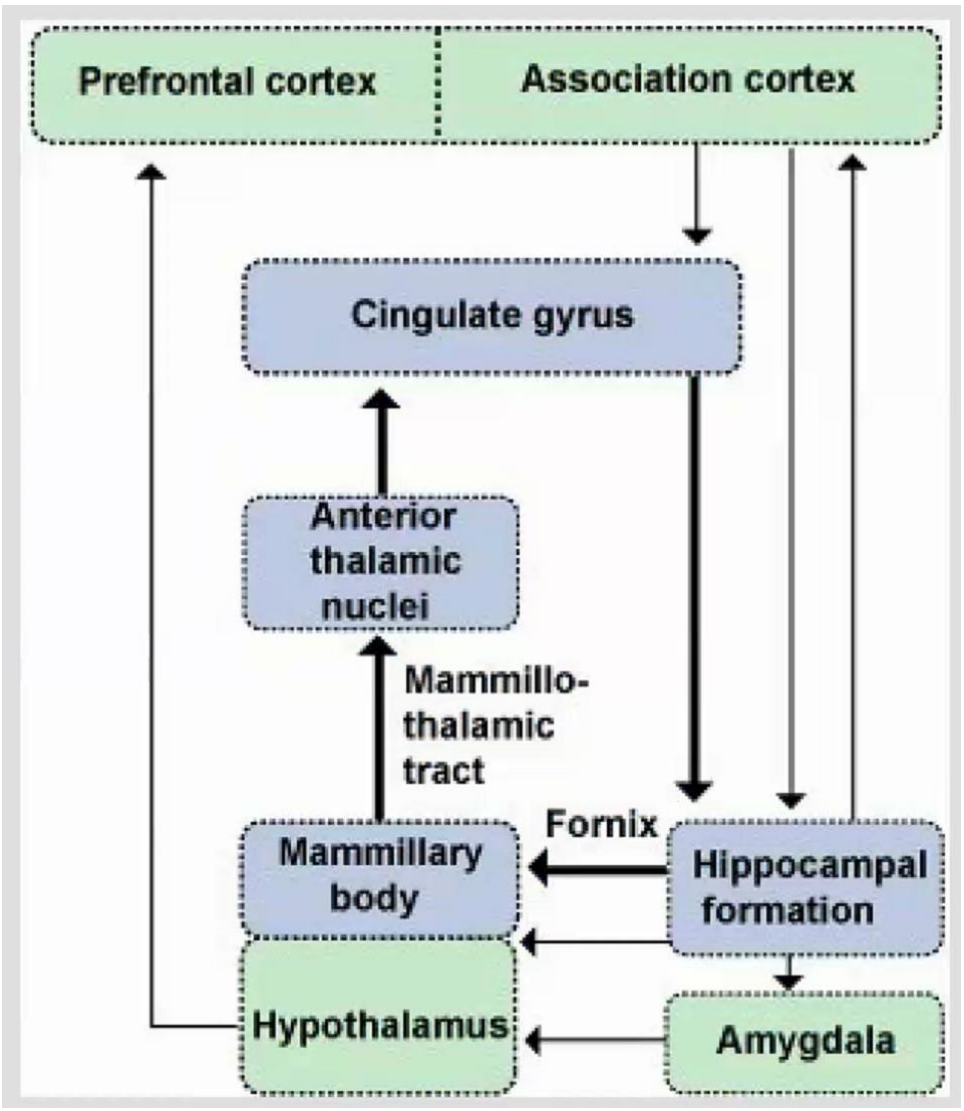
Elena Jiltsova, MD*; Timo Möttönen, MD†; Markus Fahlström, MSc‡; Joonas Haapasalo, MD, PhD†; Timo Tähtinen, MD†; Jukka Peltola, MD, PhD†; Juha Öhman, MD, PhD†; Elna-Marie Larsson, MD, PhD‡; Tommi Kiekara, MD, PhD§; Kai Lehtimäki, MD, PhD*†

ANATOMY

Central node of **Papez circuit** (close anatomical connectivity between the ANT and mesial limbic structures - desirable target for MTLE)

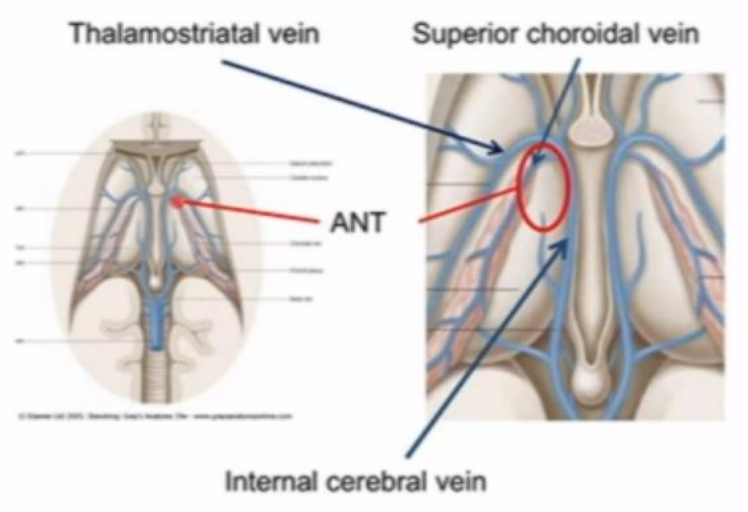




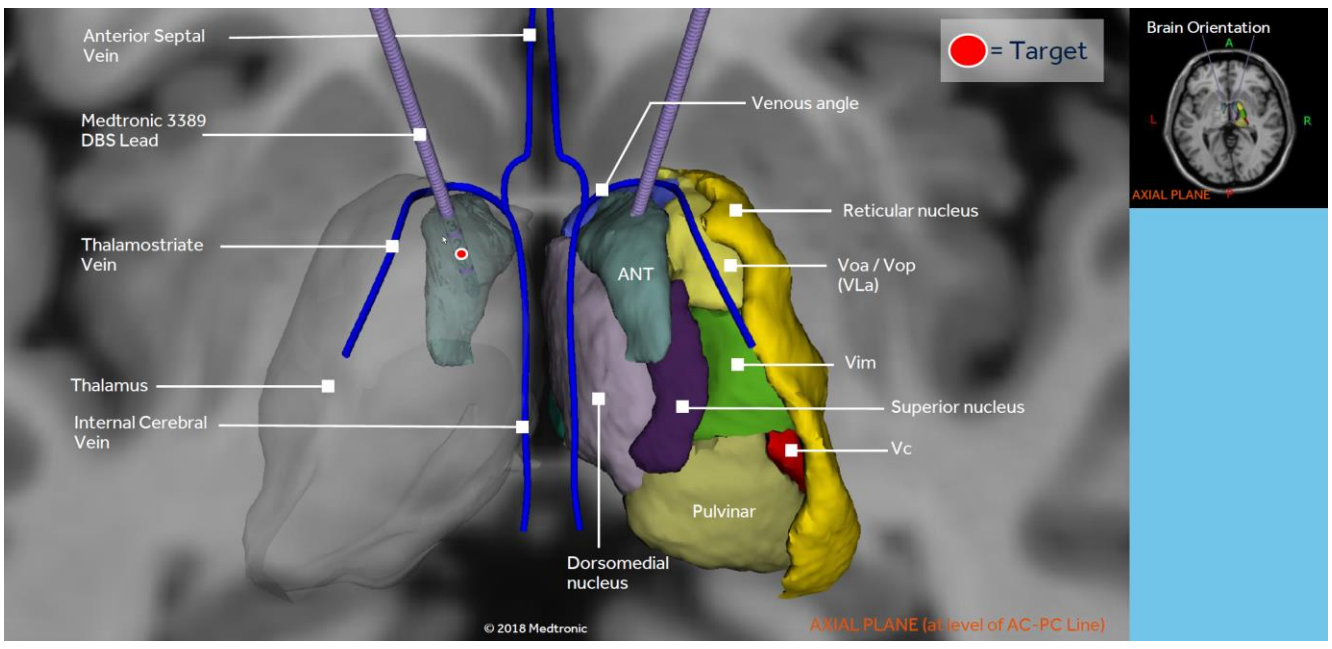


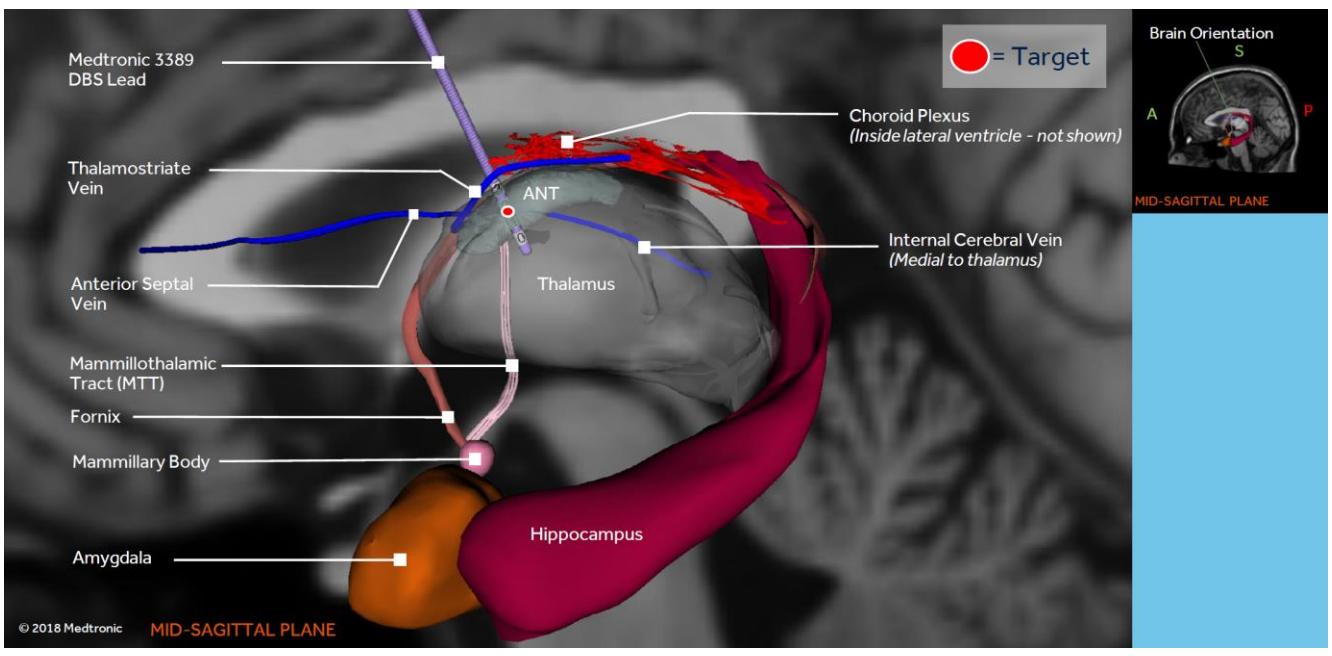
Fronto-temporal / limbic epilepsies may respond best (as opposed to parieto-occipital epilepsies).
vs. CM nucleus – whole cortex; pulvinar – visual cortex
Irving Cooper reasoned that due to its location in Papez circuit, ANT could serve as a key location to disrupt limbic seizures.

- dimensions 4 x 10 x 5.5 mm
- located at the floor of the lateral ventricle
- surrounded by plexus choroideus, thalamostriatal vein, and 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, mammillary bodies via mammillothalamic tract, and 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.
        ANT works well for limbic epilepsies (CM – frontal).
    - DBS is least effective for FAS (focal aware seizures); however, maybe DBS converts FUAS (focal unaware seizures) to FAS and gives such false impression?

Approved in Europe since 2010.

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!

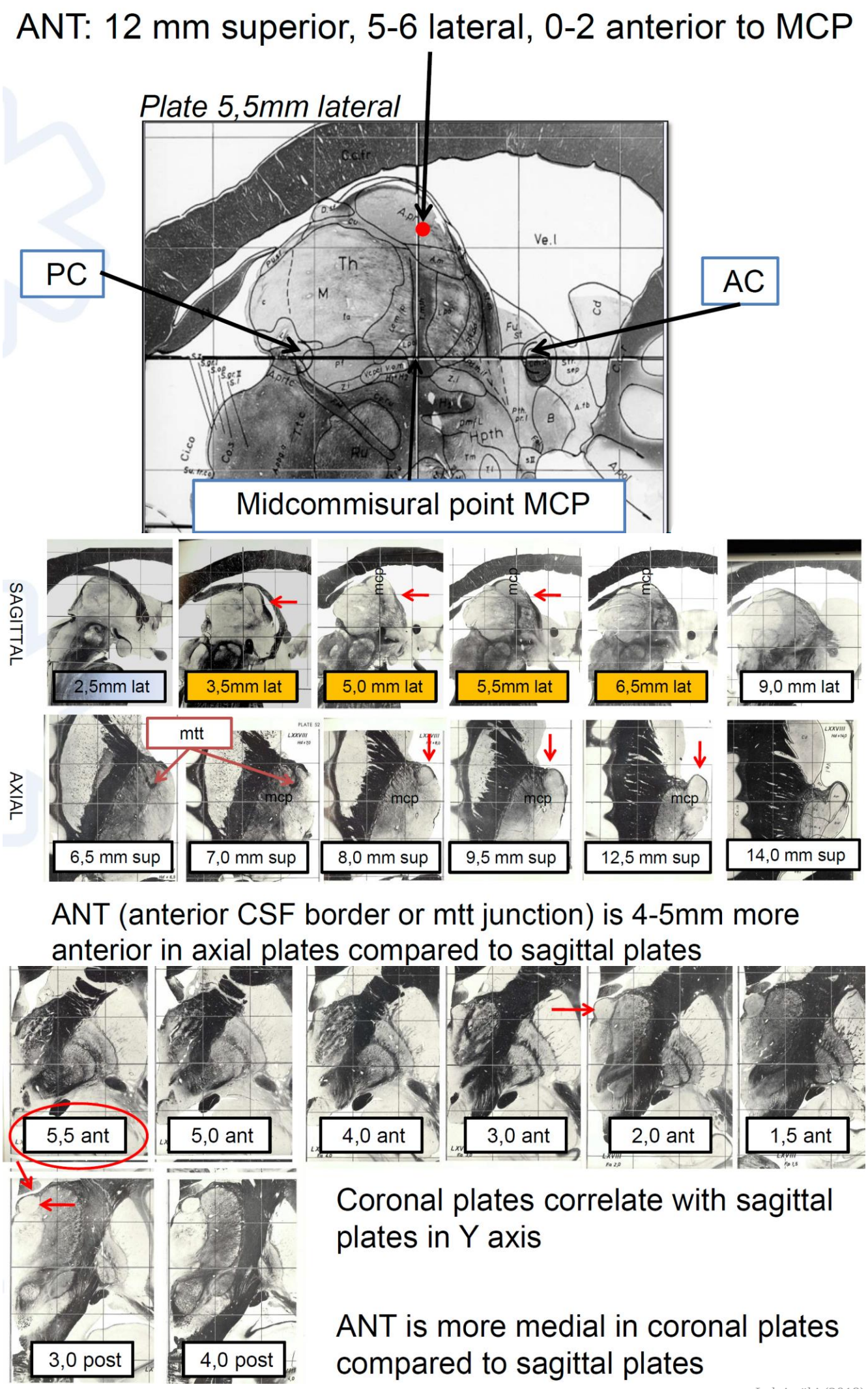
MNI coordinates:

Right: 5, -5, 12
Left: -5, -6, 12

- 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

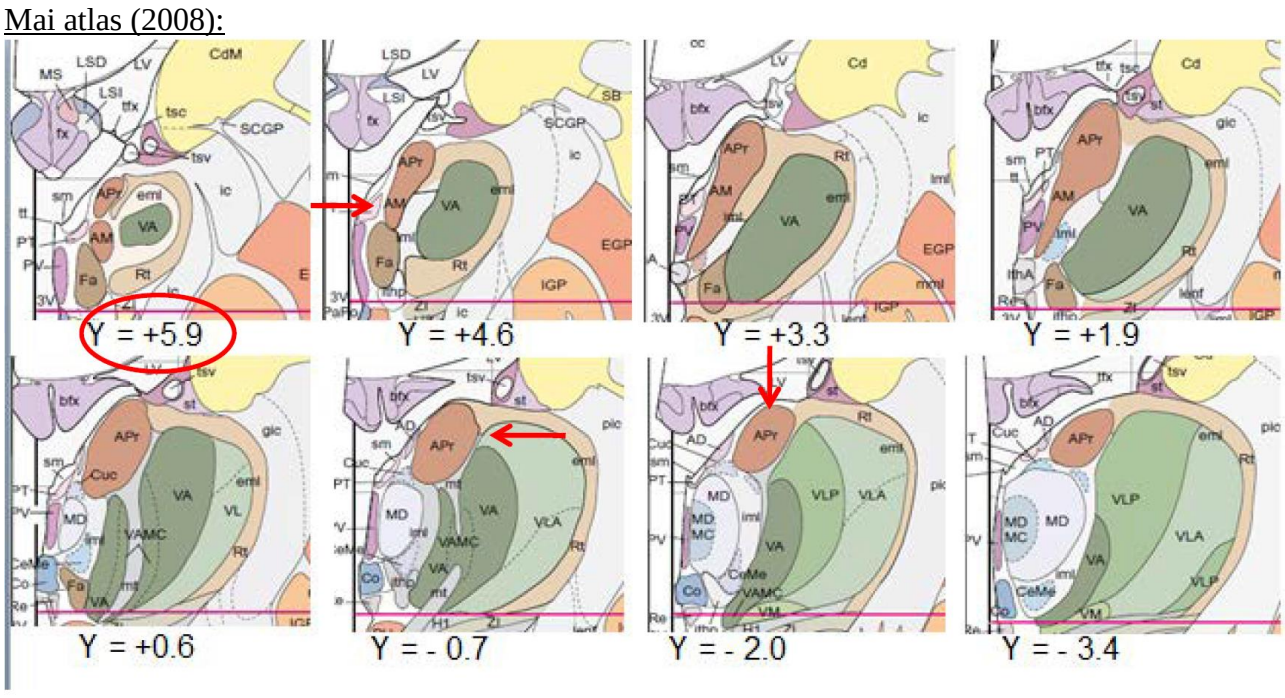
posterior aspects of the ANT prevented the spread of stimulation current into the ANT, which limited the utility of electrodes placed in that region.
Krishna et al. found similar results, noting that patients with the most long-term stimulation benefit had electrodes placed in the anteroventral ANT in close proximity to the ***mammillothalamic tract***.

Schaltenbrand-Warren atlas:



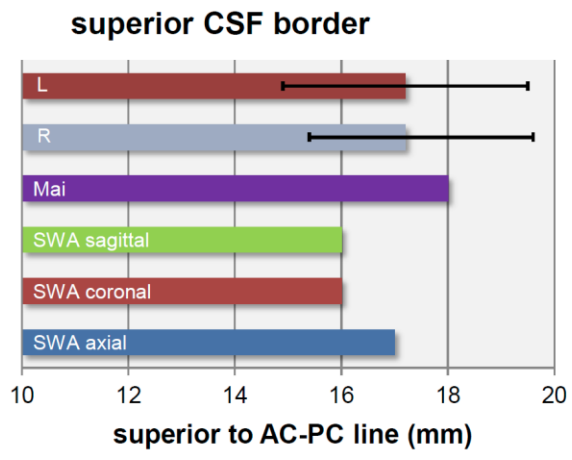
Lehtimäki (2018)

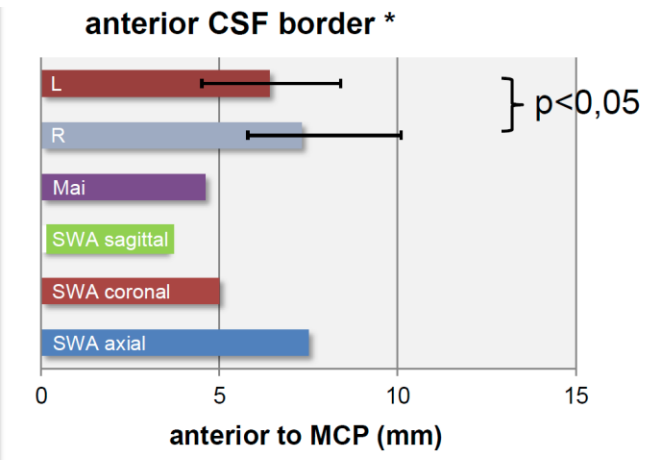
Mai atlas (2008):

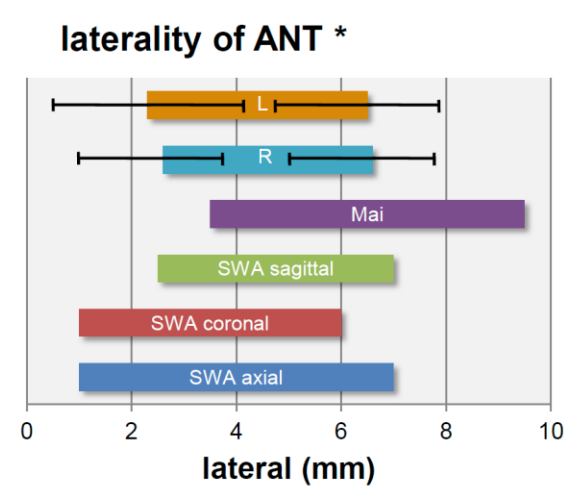


Correlates relatively well with schaltenbrandt atlas sagittal plates (anterior border ≈ 5mm anterior to MCP, mamillothalamic tract at midcommisural plane)

Lehtimäki (2018)





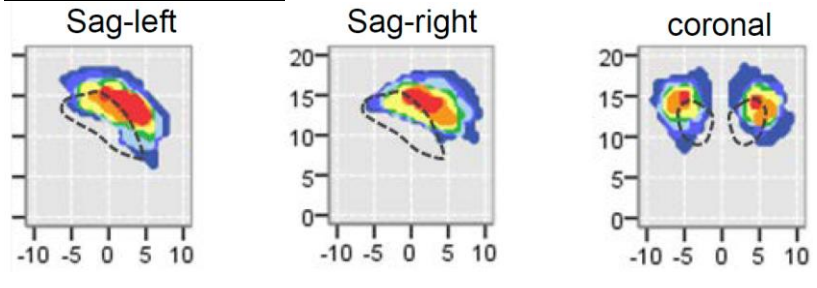


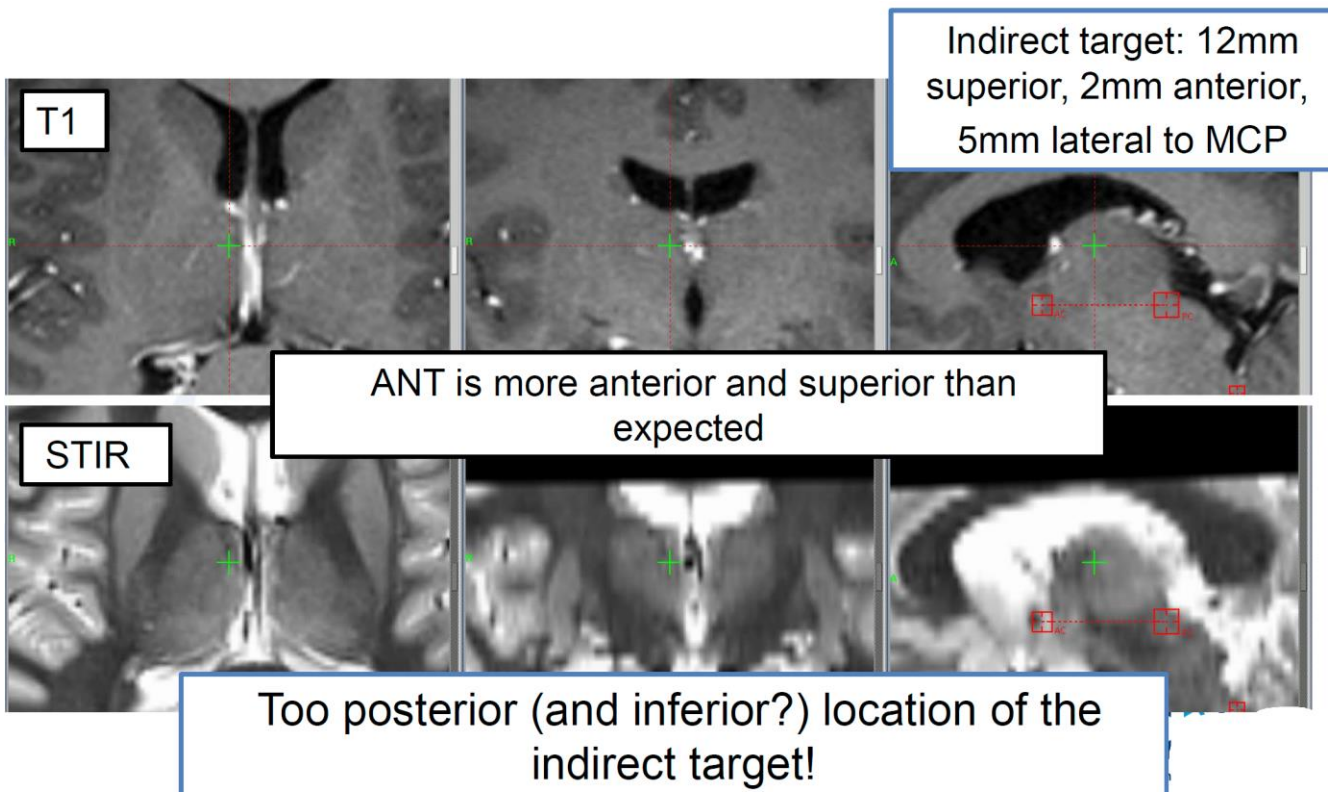
measured 5mm below the superior border

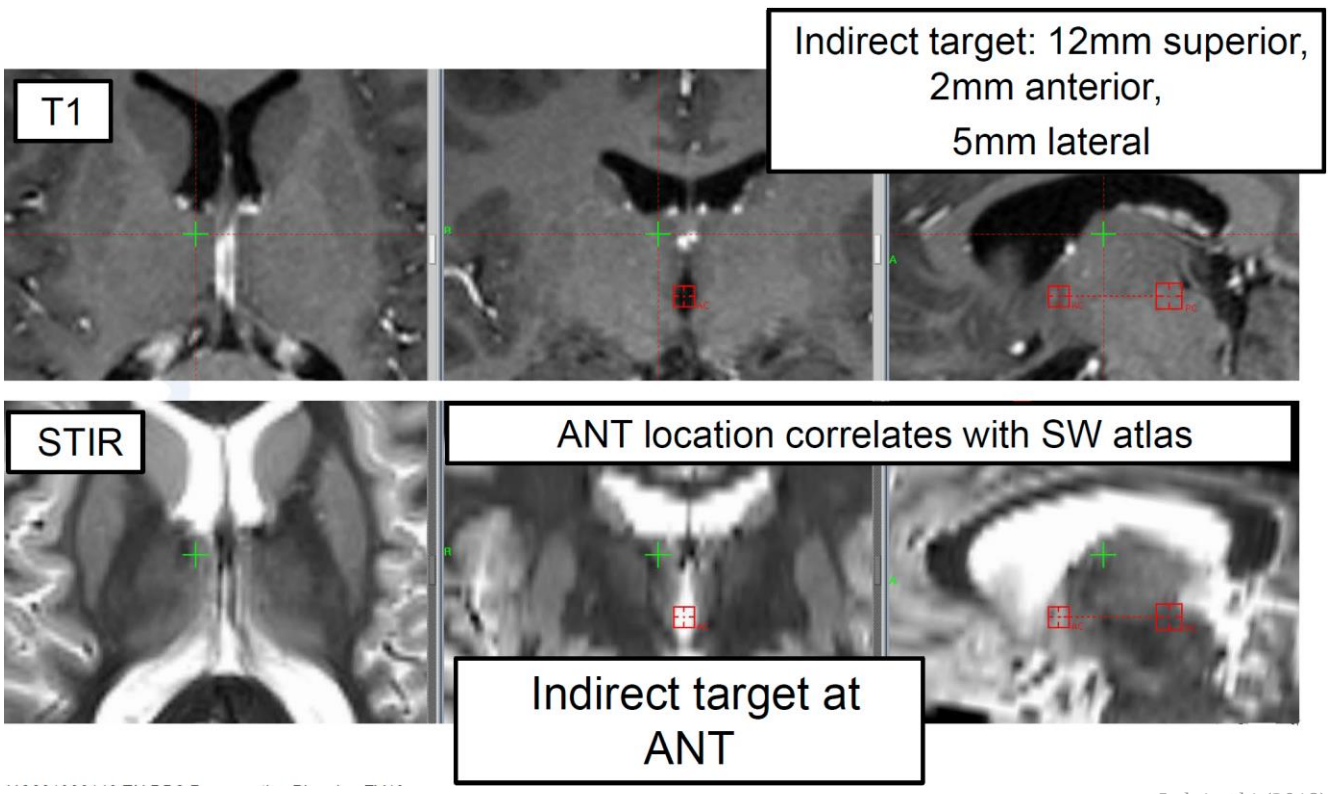
Axial plates of SWA seems to be the most realistic approximation of ANT location compared to patient data!

Lehtimäki K, unpublished

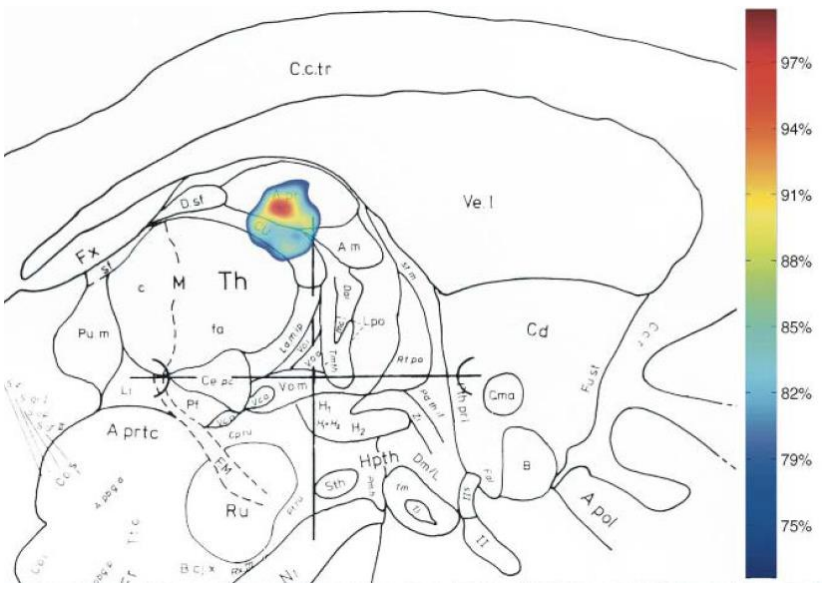
Anatomical variation:







Lehtimäki (2018)



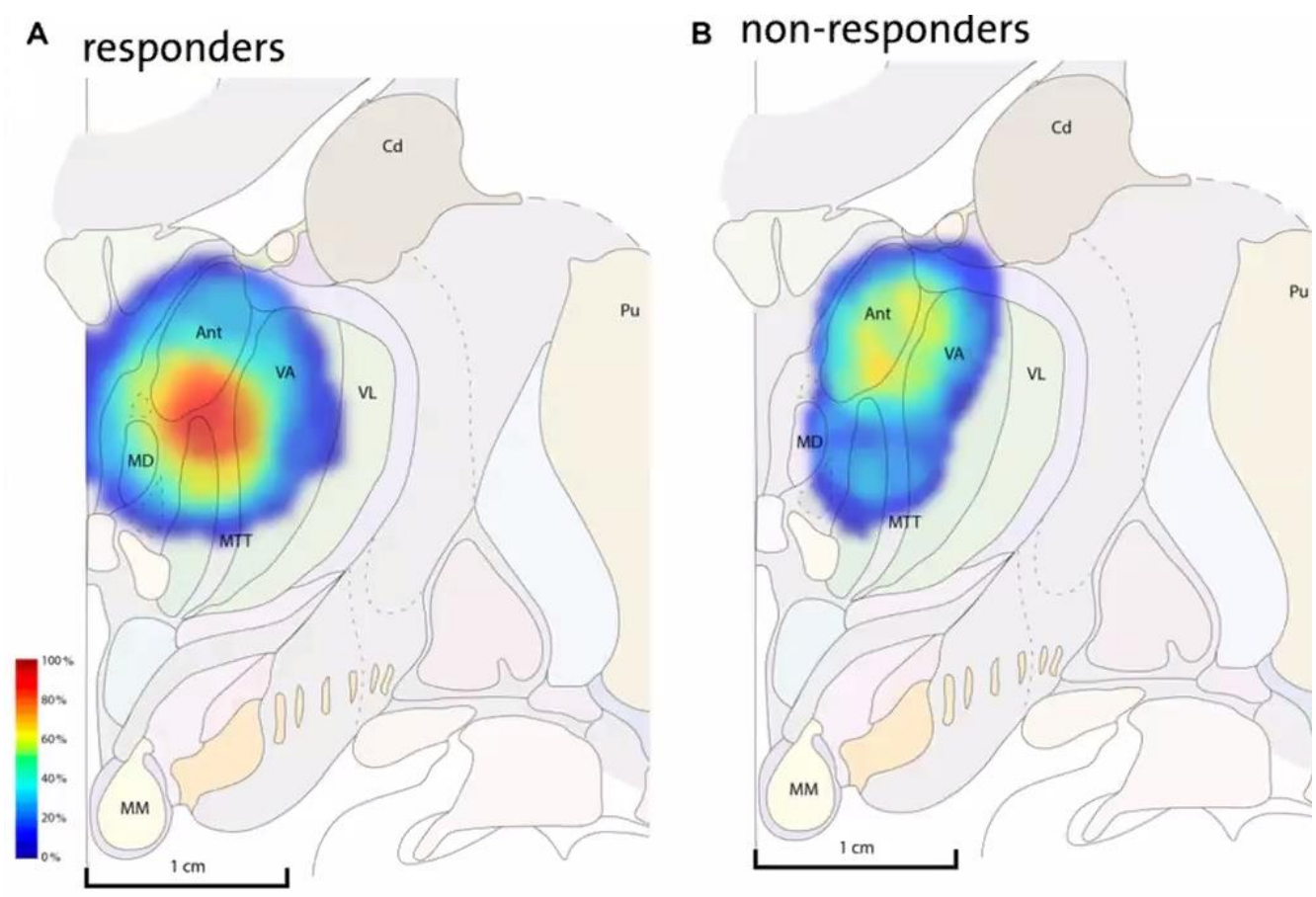


FIGURE 5. *Stimulation heat maps superimposed on an adaptation of the Mai atlas 3rd edition (12,0 mm - coronal plate 31) to visualize the activation scores (range of 0%-100%) in anatomic space. The hot-spot (intersection of VTAs with the highest activation score) of responders* **A** *is located at the medio-ventral ANT in close vicinity to the ANT-MTT junction in contrast to no evident hot-spot in non-responders* **B**.

Schaper et al. Neurosurgery (2020) epub

DIRECT TARGETING

UCSF MRI protocol for CM imaging >>

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

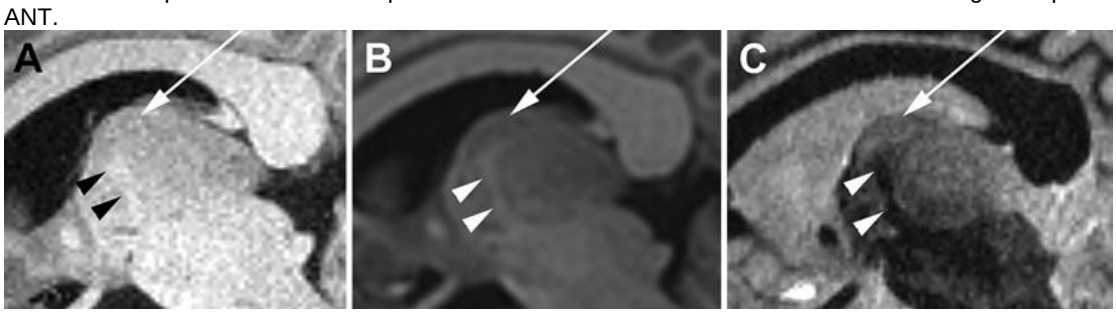
Target - within the anteroventral subdivision of the ANT, superior and slightly posterior to the entry of the MTT into the ANT.

- 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–Wahren atlas.

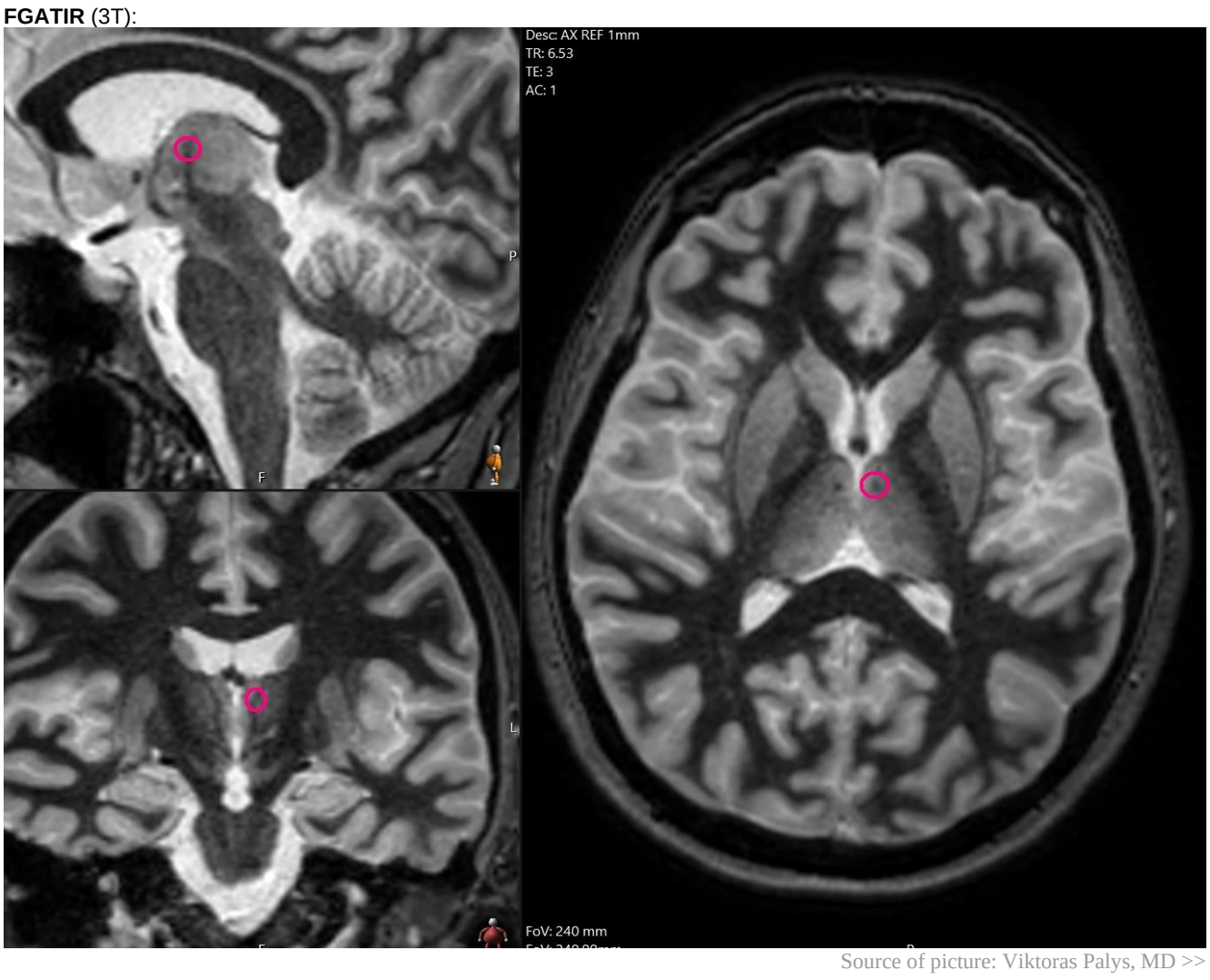
3T MRI with transmit-receive coil:

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_3 - poor delineation of the mammillothalamic tract and ANT.
B. **MP-RAGE** acquired at 1.2 mm_3 - better illustrates the mammillothalamic tract and ANT.
C. **FGATIR** acquired at 0.8 mm_3 - superior delineation of the mammillothalamic tract allowing more precise definition of the ANT.

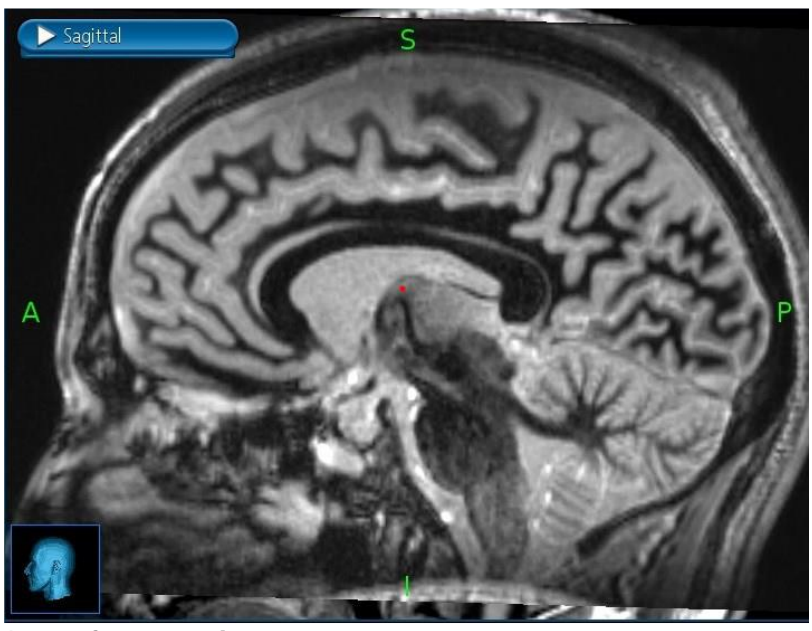


FGATIR (3T):



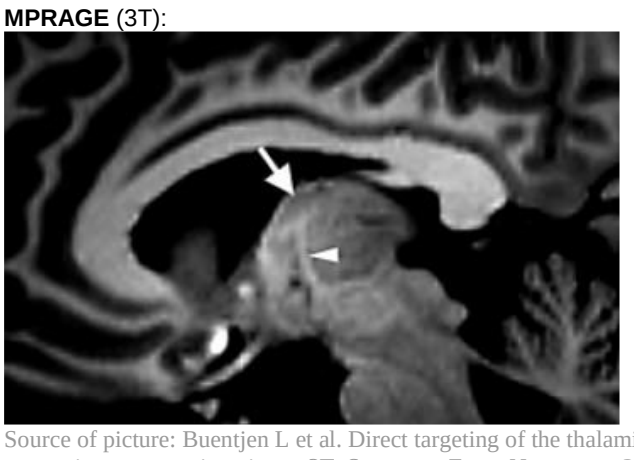
Source of picture: Viktoras Palys, MD >>

FGATIR (3T):



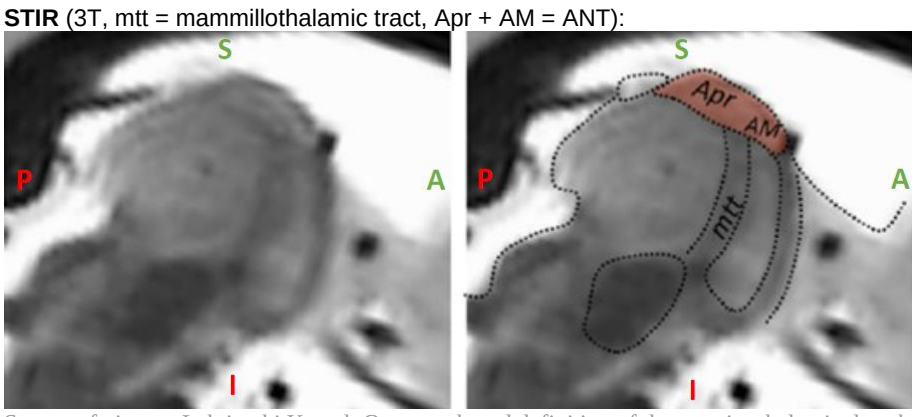
Source of picture: Medtronic

MPRAGE (3T):



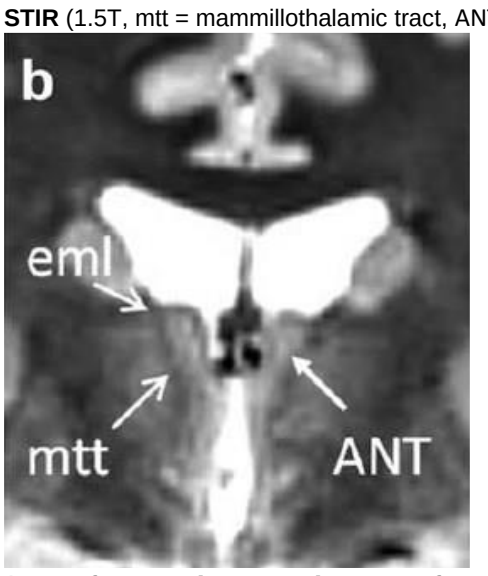
Source of picture: Buentjen L et al. Direct targeting of the thalamic anteroventral nucleus for deep brain stimulation by T1-weighted magnetic resonance imaging at 3T. Stereotact Funct Neurosurg. 2014; 92:25-30

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



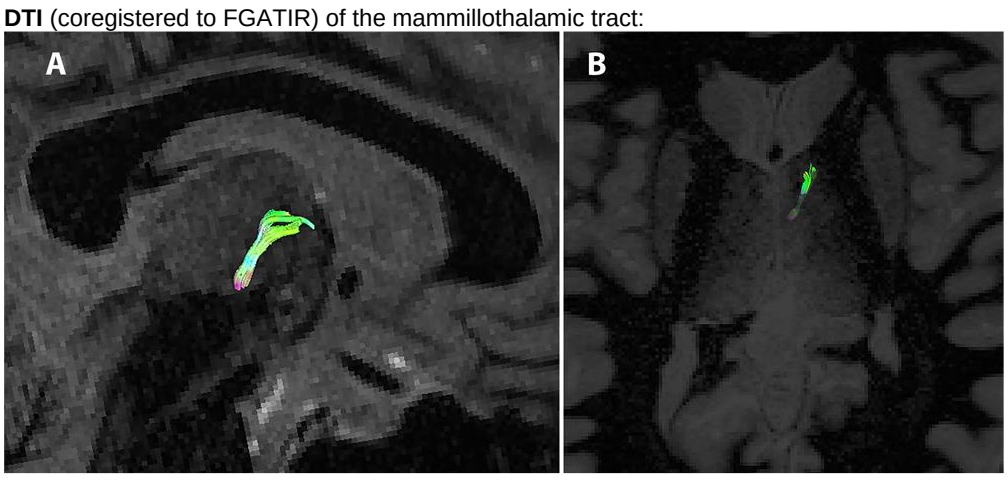
Source of picture: Lehtimaki K et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. *Brain stim*. 2016; 9: 268-275

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

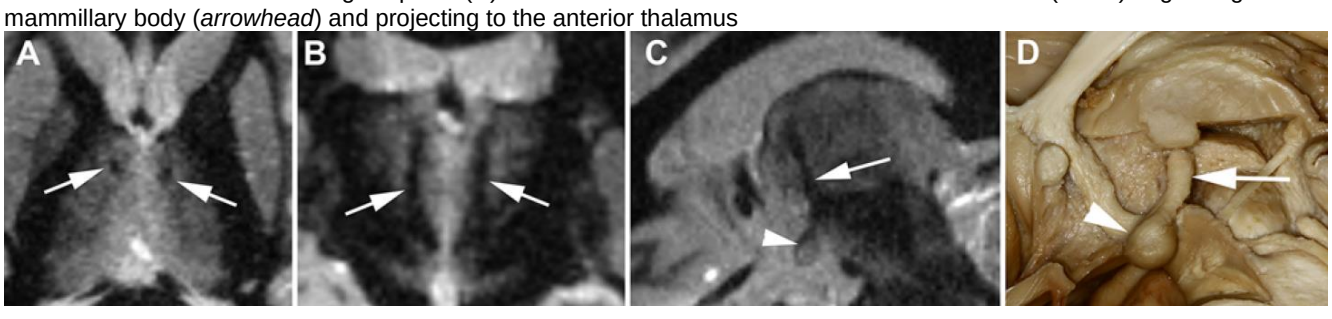


Source of picture: Jiltsova E et al. Imaging of anterior nucleus of the thalamus using 1.5 T MRI for deep brain stimulation targeting in refractory epilepsy. Neuromodulation. 2016; 19(8):812-817

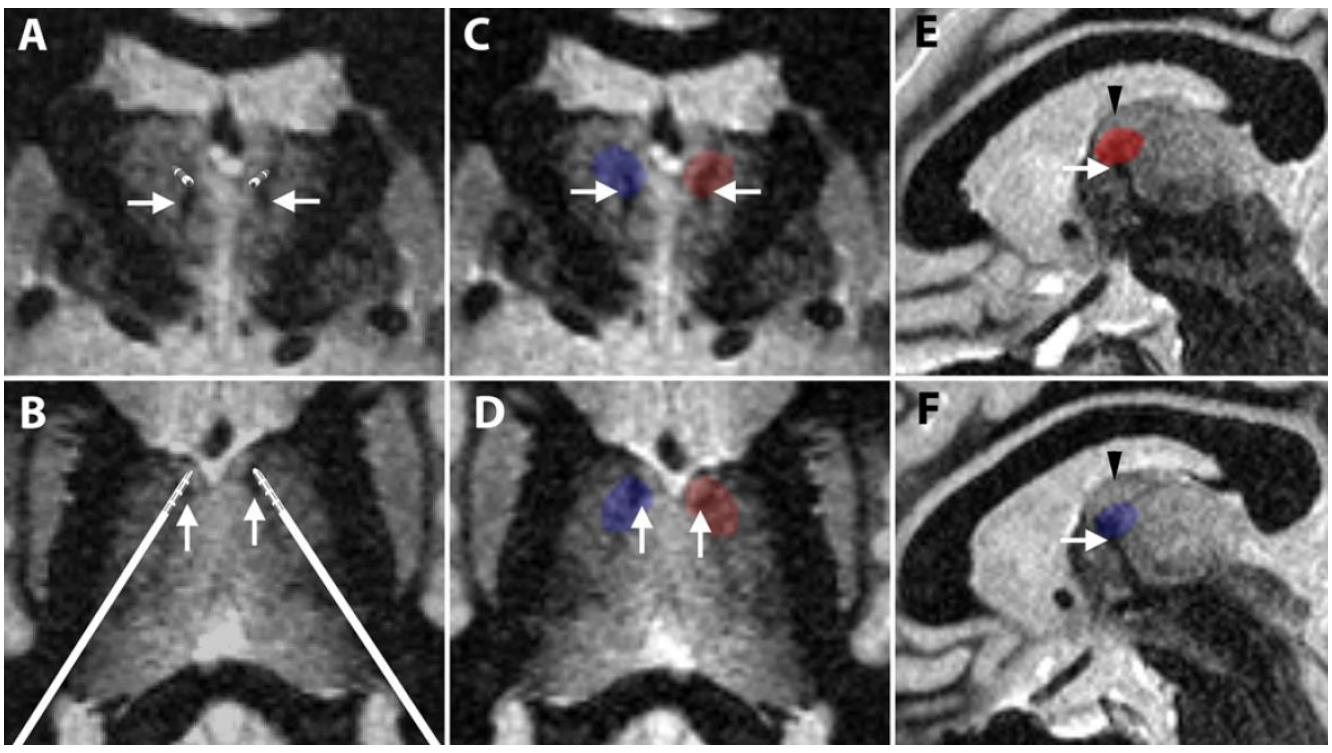
DTI (coregistered to FGATIR) of the mammillothalamic tract:

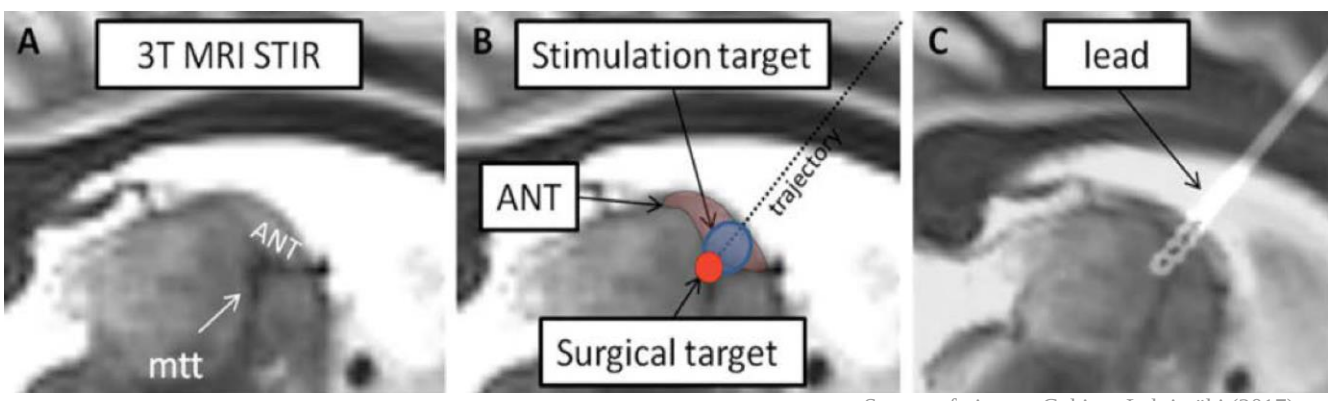


FGATIR MR images in the axial (**A**), coronal (**B**), and sagittal (**C**) planes. The mammillothalamic tract (*arrows*) is clearly visualized as a linear hypointensity extending dorsally from the mammillary body (*arrowhead*) to the anterior thalamus.
Cadaveric dissection in the sagittal plane (**D**) illustrates the course of the mammillothalamic tract (*arrow*) originating in the mammillary body (*arrowhead*) and projecting to the anterior thalamus

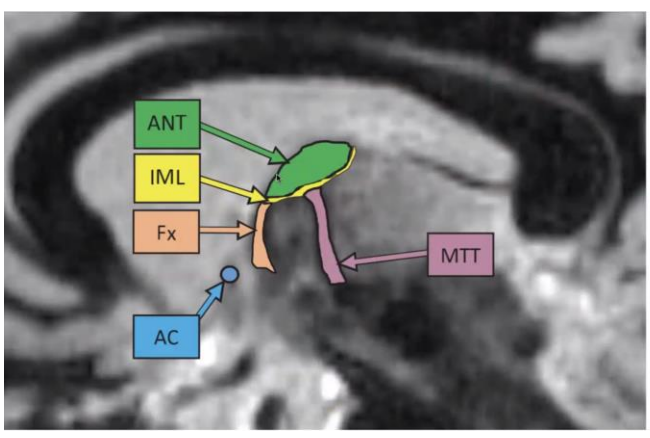


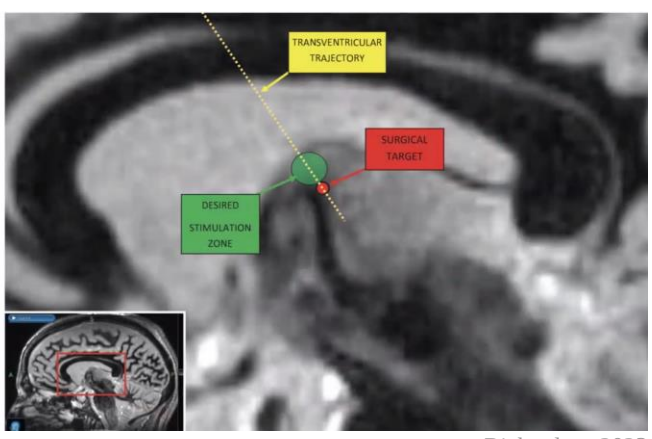
ANT DBS electrode (Medtronic 3389) localization coregistered to the preoperative FGATIR MR image.
Final electrode localization is shown relative to the mammillothalamic tract (*arrows*) in the coronal (**A**) and axial (**B**) planes. Coronal (**C**), axial (**D**), left parasagittal (**E**), and right parasagittal (**F**) images show VTAs for the right (*blue*) and left (*red*) ANT electrodes relative to the mammillothalamic tract (*arrows*) and ANT (*arrowheads*). The VTAs are closely localized to the junction of the mammillothalamic tract and ANT on both sides.



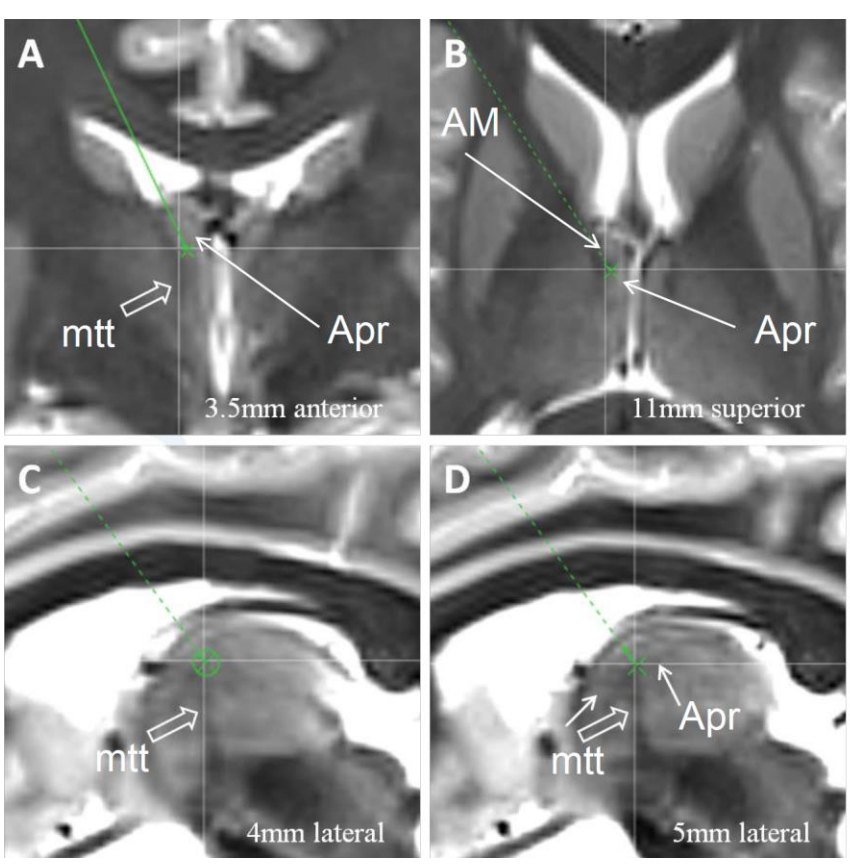


Source of picture: Cukiert, Lehtimäki (2017) >>





Richardson 2023

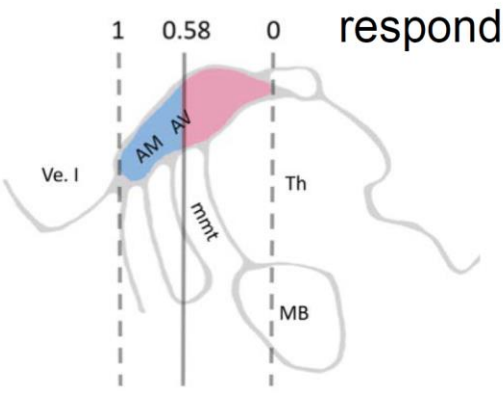


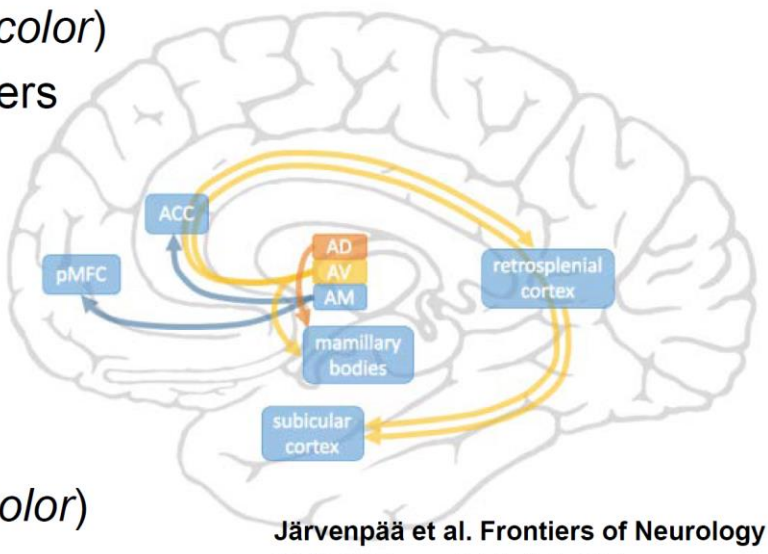
Surgical target 3,5mm from CSF surface

The centre of 3389 (interspace 1&2) to target point

Two uppermost contacts (3&2) in ANT

74% of the contacts (*blue color*) responders

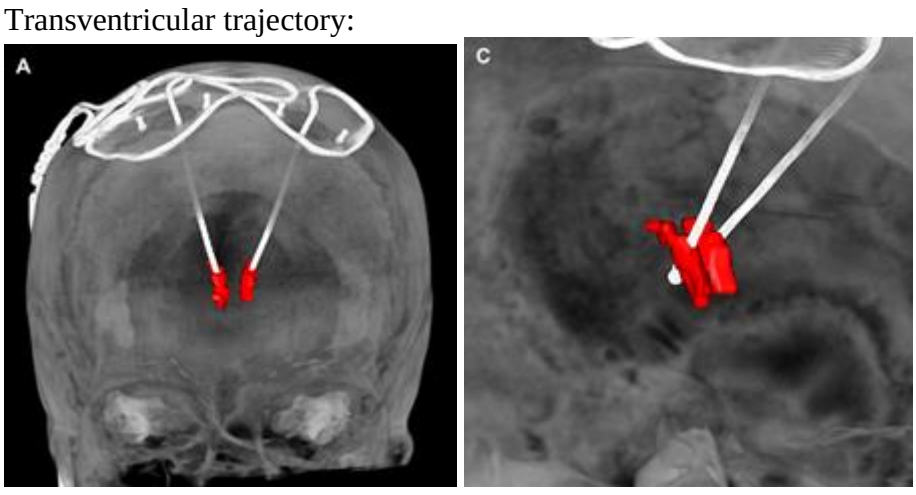




83% of the contacts (*red color*) non-responders.

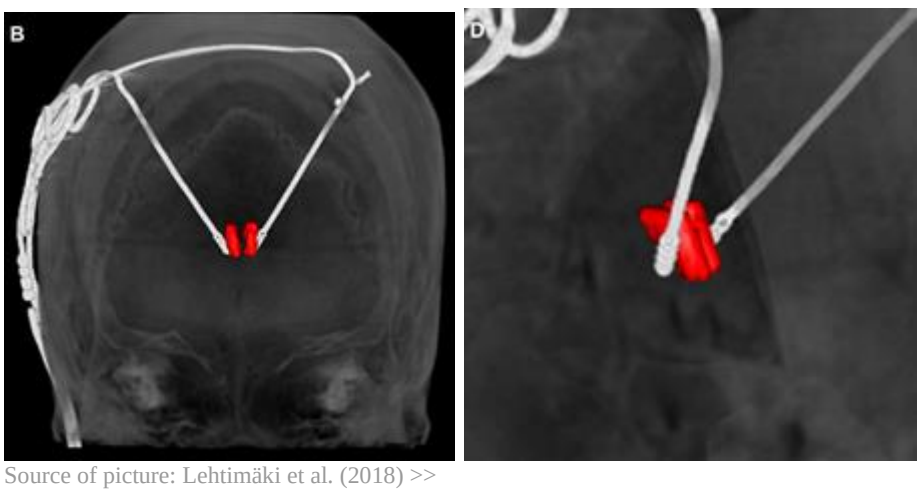
Järvenpää et al. Frontiers of Neurology 2018 | Volume 9 | Article 324

Transventricular trajectory:

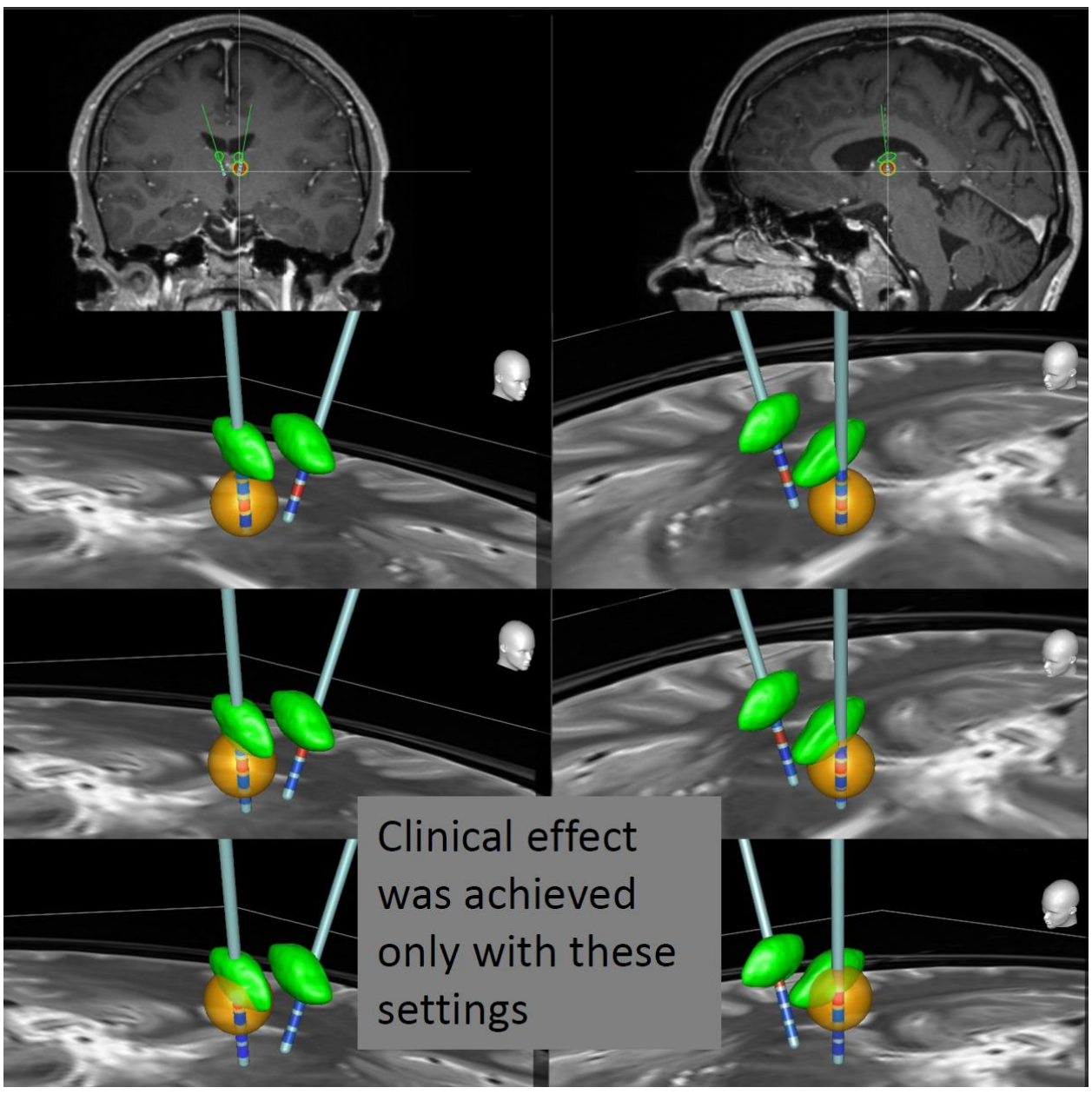


Source of picture: Lehtimäki et al. (2018) >>

Extraventricular trajectory (missed ANT):



Source of picture: Lehtimäki et al. (2018) >>



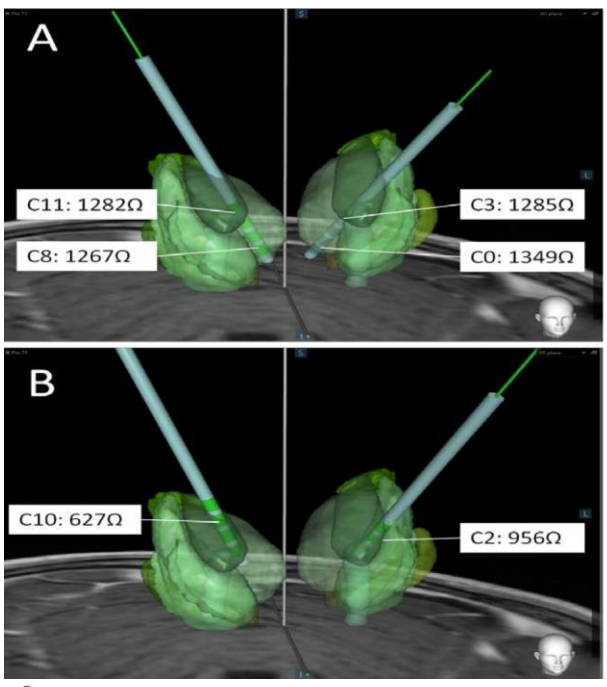
ELECTRODE VERIFICATION – HIPPOCAMPAL ELECTRODES

- 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.

Van Gompel JJ, Klassen BT, Worrell GA, Lee KH, Shin C, Zhao CZ, et al: Anterior nuclear deep brain stimulation guided by concordant hippocampal recording. Neurosurg Focus 38(6):E9, 2015

ELECTRODE VERIFICATION – IMPEDANCES

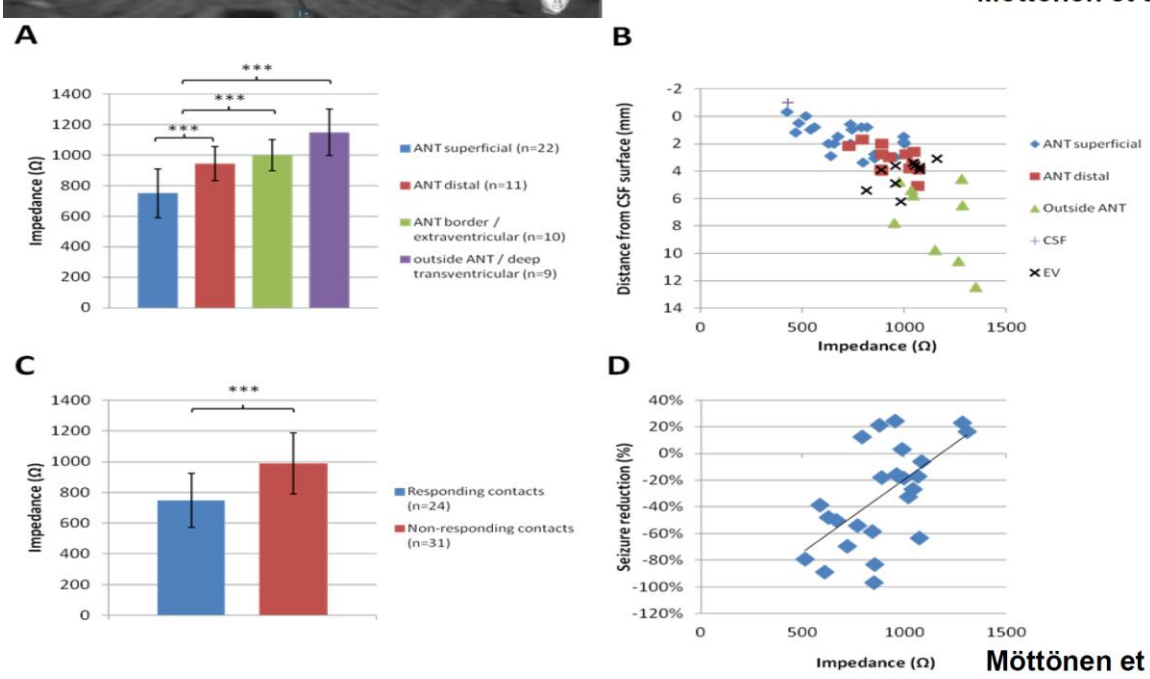
- impedances in CSF are lower than in parenchyma ("CSF wicking" effect – CSF tracks along DBS lead into brain parenchyma and impedances drop).
- impedance in CSF is 200-300 Ohm.



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



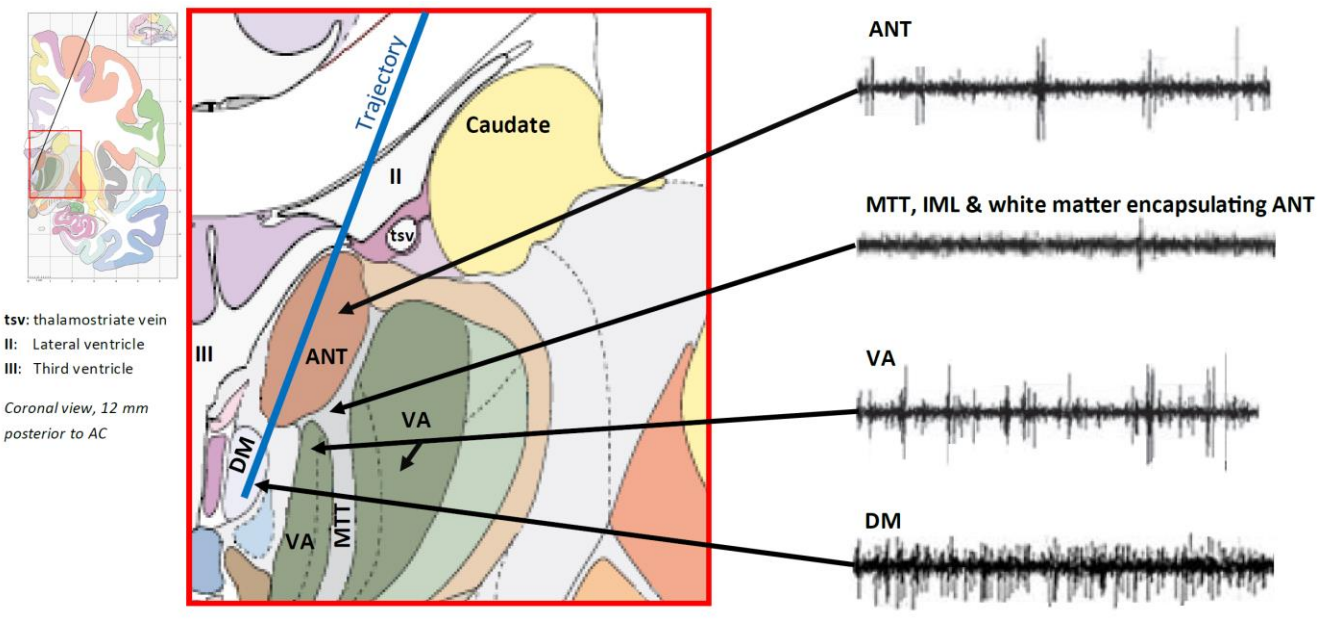
Möttönen et al, submitted

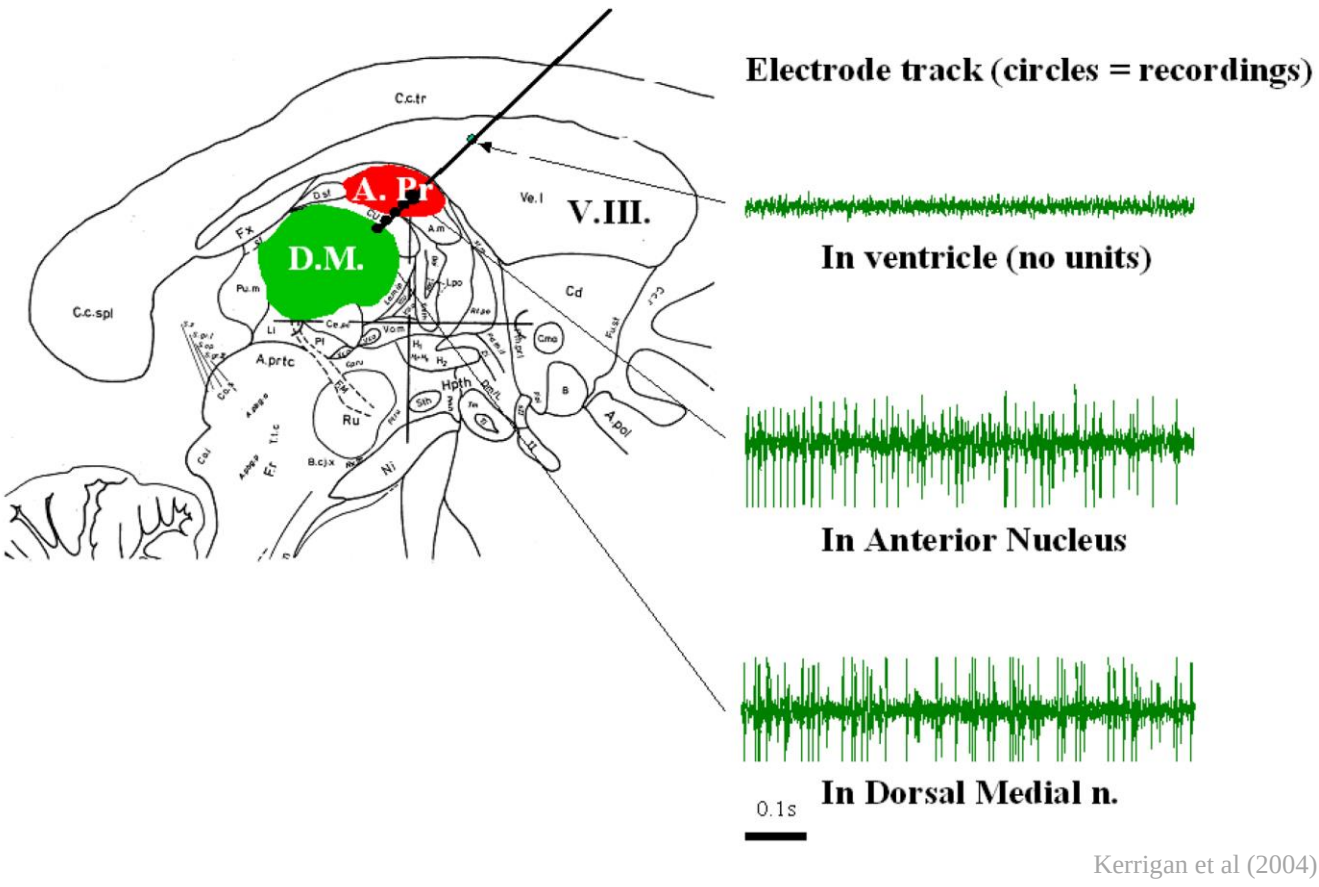
ELECTRODE VERIFICATION – MER

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

Descending along the trajectory...

Lateral Ventricle	Quiet
ANT	Low frequency spikes with low background activity and bursting cells present
Internal Medullary Lamina	Spiking activity attenuates at the inferior aspect of the ANT when electrode passes into the IML (white matter)
Dorsomedial (DM) Nucleus of the Thalamus	A slightly more **medial** trajectory may encounter the DM nucleus The DM exhibits more regular firing patterns than the ANT and with a lower spike amplitude
OR	
Ventral Anterior (VA) Nucleus of the Thalamus	A slightly more **lateral** trajectory may encounter the VA nucleus The VA exhibits higher frequency spiking activity than that observed in the ANT





Kerrigan et al (2004)

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 - inferomedial) - Spiking activity with higher frequency than ANT (VA nucleus - inferolateral)

TRAJECTORIES

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

Lehtimäki K, Coenen VA, Gonçalves Ferreira A, Boon P, Elger C, Taylor RS, et al: The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the international multicenter registry (MORE). Neurosurgery [epub ahead of print], 2018

- 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, esp. if TV route is used.

	TV	EV
at least 1 contact at ANT	90%	71%
at least 1 contact at ANT bilaterally	84%	58%
leads missing the ANT	10%	30%
mean number of contacts at ANT	1.63	1.40

TRANSVENTRICULAR FRONTAL (PRECORONAL)

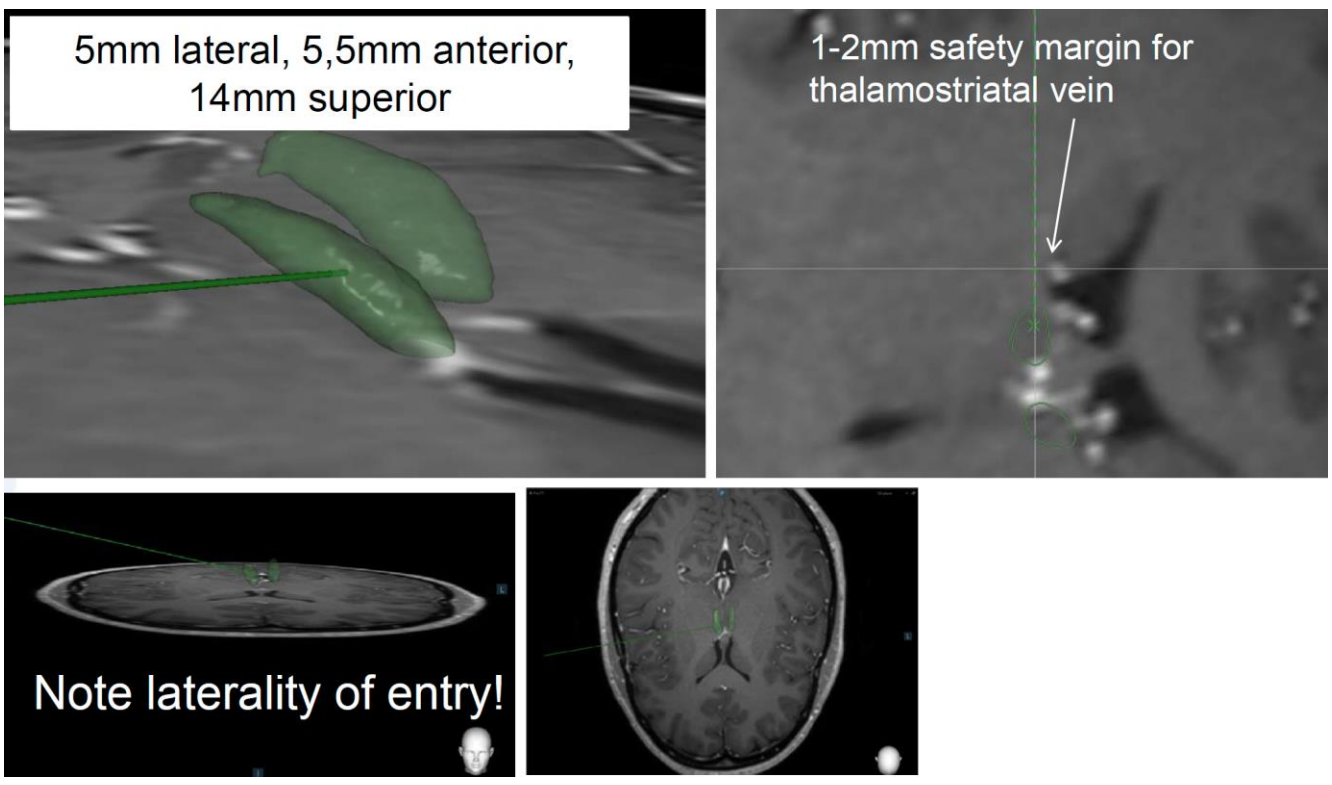
- ~ 60° posterior from an axial plane parallel to AC-PC plane, i.e. ~ 30° anterior from a coronal plane perpendicular to AC-PC plane.
- trajectory typically runs through the narrow vascular window between superior choroidal vein (medially) and thalamostriate vein (laterally, between caudate and ANT); blunt stylet advanced 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 - 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 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%

LATERAL EXTRAVENTRICULAR (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 MTT-ANT junction rather than ANT nucleus per se.



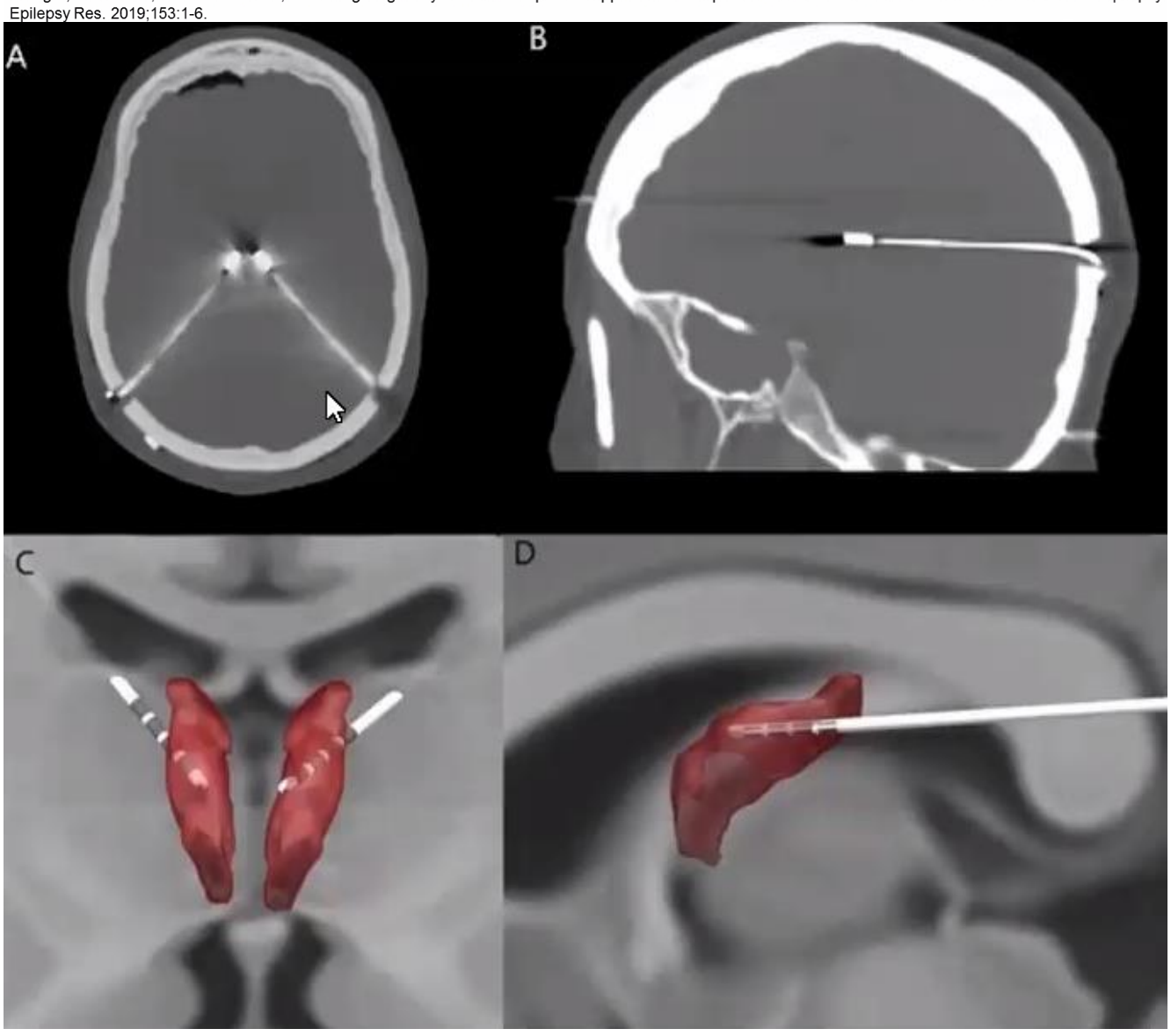
- ANT-miss lead trajectories, the leads were systematically more inferior and had their courses directed more posteriorly compared to ANT-hit trajectories
- with respect to MTT/ANT junction, ANT-hit lead trajectories were clearly located superior to the MTT/ANT junction and at the level or slightly posterior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

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.

Wang Y, Grewal SS, Middlebrooks EH, et al. Targeting analysis of a novel parietal approach for deep stimulation of the anterior nucleus of the thalamus for epilepsy. Epilepsy Res. 2019;153:1-6.



POSTOP

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

Tröster AI et al. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017 Feb; 45:133-141.

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 < 2.4% (95% CI 1.7%–3.3%) risk of seizures and that 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.
- if *pre-existing depression*, consider RNS instead.

Prior suicide attempt - contraindication for DBS!

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!

There are case series that have suggested neuropsychological and cognitive effects with chronic ANT stimulation:

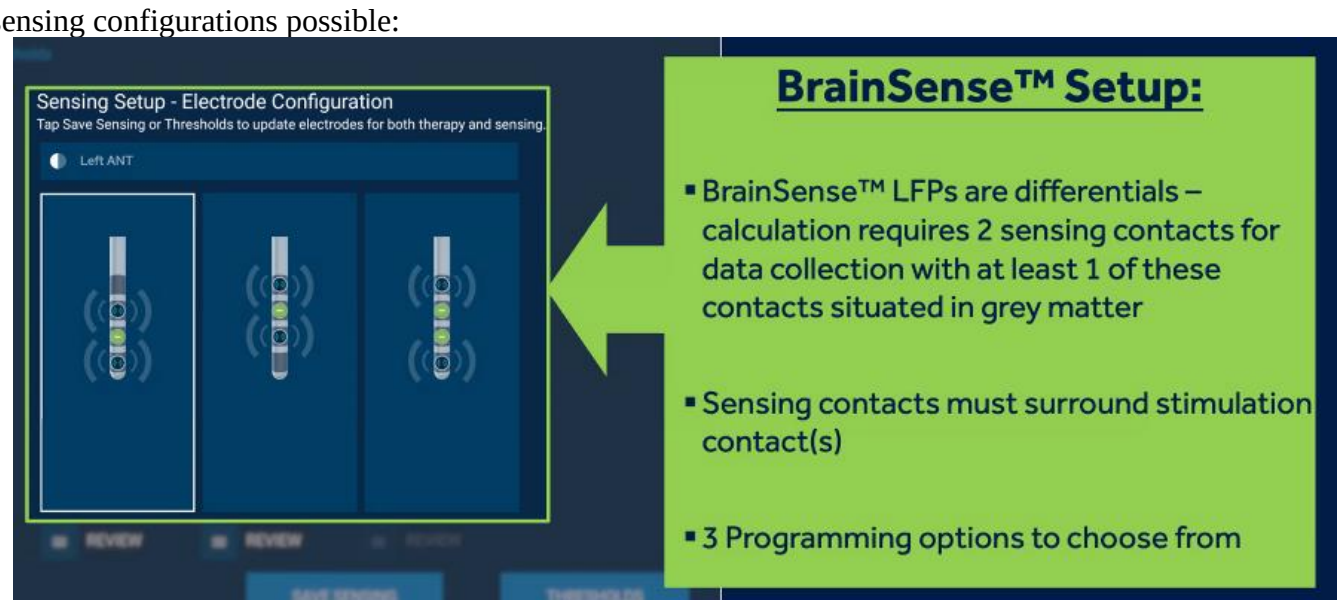
1) decreased response inhibition
   Hartikainen KM et al. Immediate effects of deep brain stimulation of anterior thalamic nuclei on executive functions and emotion-attention interaction in humans. J Clin Exp Neuropsychol. 2014;36(5):540-550
2) sleep disruption
   Voges BR, Schmitt FC, Hamel W, et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. Epilepsia. 2015;56(8):e99-e103.
3) psychiatric adverse effects
   Jarvenpaa S, Peltola J, Rainesalo S, Leinonen E, Lehtimaki K. Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy. Epilepsy Behav. 2018;88: 373-379

PROGRAMMING

Feature	Description	Percept™ PC + SenSight™ Lead	Percept™ PC + 1x4 Lead	Activa™ PC/RC + SenSight™ Lead	Activa™ PC/RC + 1x4 Lead
Segment Mode (Monopolar Only)	Enable and disable directional lead segments	✓		✓	
OptiStim™ Control	Adjust the amplitude of a single electrode without impacting the amplitude of other electrodes in the configuration	✓	✓		
ShapeLock™ Control	Create a unique field shape, including relatively dissimilar amplitude contributions from various electrodes, then grow and shrink that shape	✓	✓		
Multiple Rates	Program multiple rates within a group or lead	✓	✓		
CC / CV Capabilities	Amplitude Mode: Constant Current (CC) or Constant Voltage (CV)	CC	CC	CV	Either

BRAINSENSE

3 sensing configurations possible:



- epilepsy signature LFP peaks are typically located in 8-12 Hz range (Percept PC can records 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

Parameter	Typical Starting Value
Amplitude	5 V *In clinical practice clinicians may start at a lower amplitude and titrate up slower as they access patient response and tolerability.
Pulse Width	90 μs
Rate	145 Hz
Electrode Configuration	Unipolar Mode: Single electrode or two adjacent electrodes negative, case positive (all patients in the SANTE clinical trial were in unipolar mode)
Cycle of Therapy	Cycling mode ON: 1 minute on, 5 minutes off
SoftStart™Stop	programmed to 8 seconds

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*)
*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).
- contacts in thalamus but outside ANT cannot stimulate ANT as white matter capsule creates barrier.
- 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.

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

OUTCOMES

QUALITY OF LIFE

- improvements in quality of life at 5 years remained stable at 7 years, whereby 43% of subjects experienced a clinically meaningful improvement.
  Salanova V, Sperling MR, Gross RE, et al. The SANTE´ study at 10 years of followup: effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia 2021;62(6):1306–17.

SEIZURES

- 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).
  Toni Kulju et al. Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Brain Behav . 2018 Jun;8(6):e00983. doi: 10.1002/brb3.983. Epub 2018 May 8.

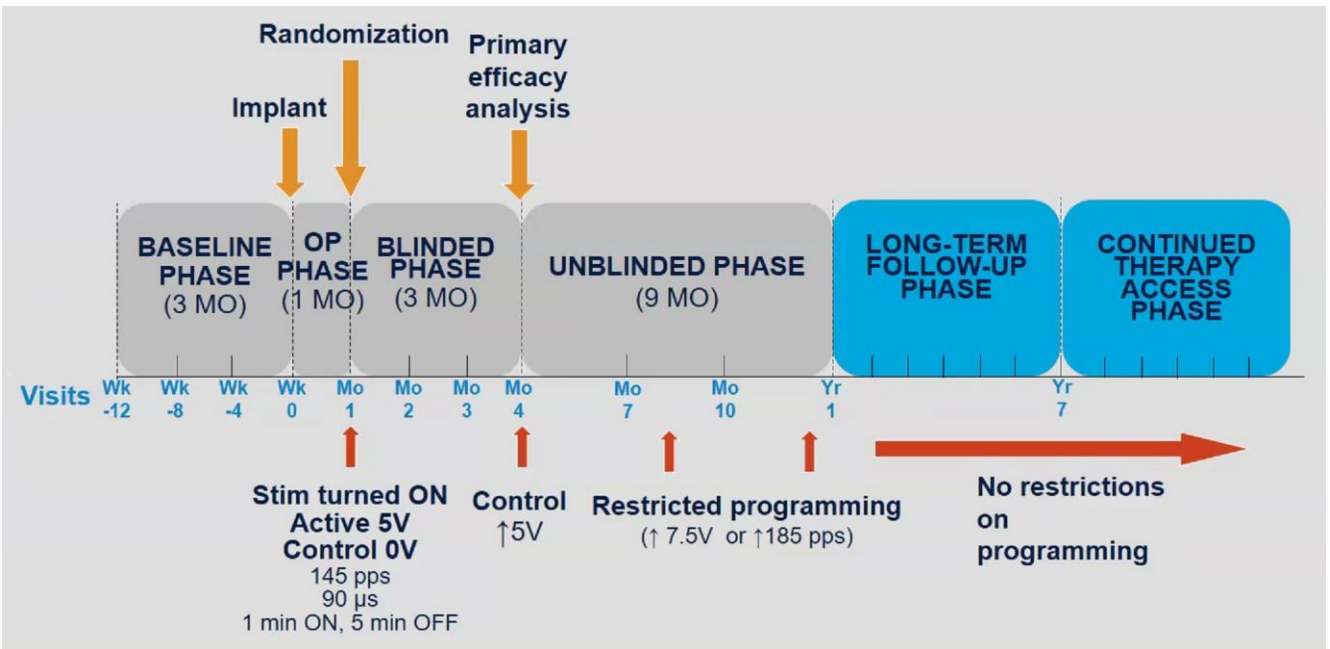
STIMULATION OF THE ANTERIOR NUCLEUS OF THALAMUS FOR EPILEPSY (SANTE) TRIAL

Complete set of trial data >>
Fisher RS, Salanova V, Witt T et al. and the SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010 May; 51(5):899-908

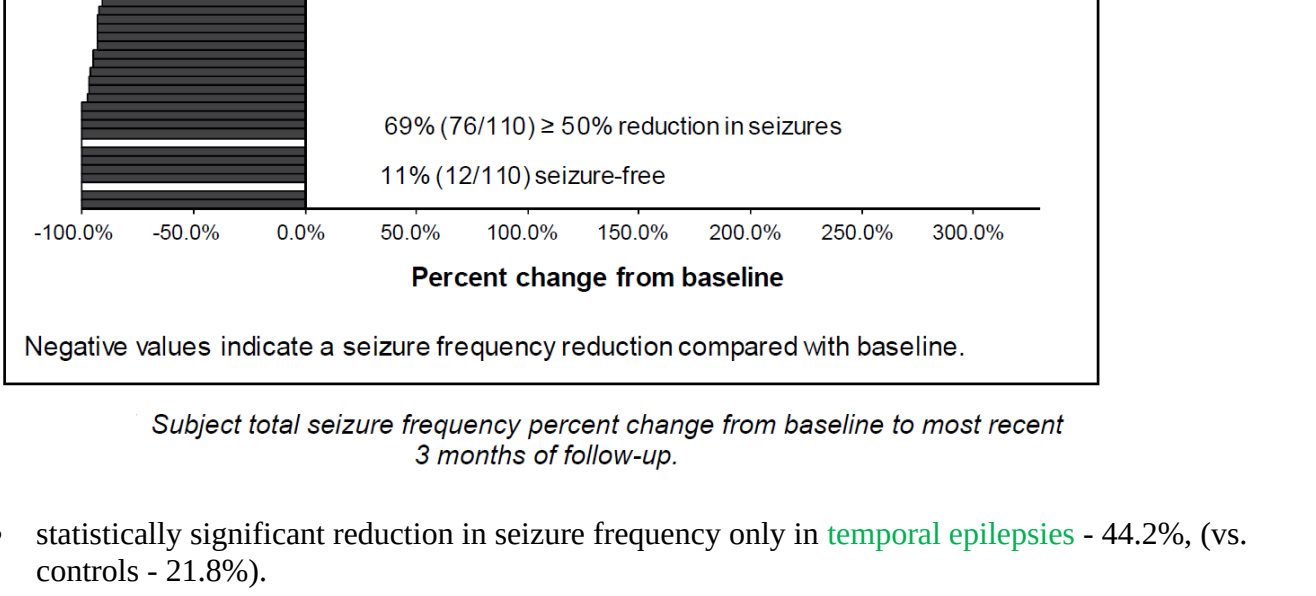
5-year outcome:
Salanova V et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015 Mar10; 84(10):1017-25.

7-year outcome:
Sandok E et al. Long term outcomes of the SANTE Trial: 7-Year Follow-Up. American Epilepsy Society Annual Meeting. 2016 Abst. 1.298.

- 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.



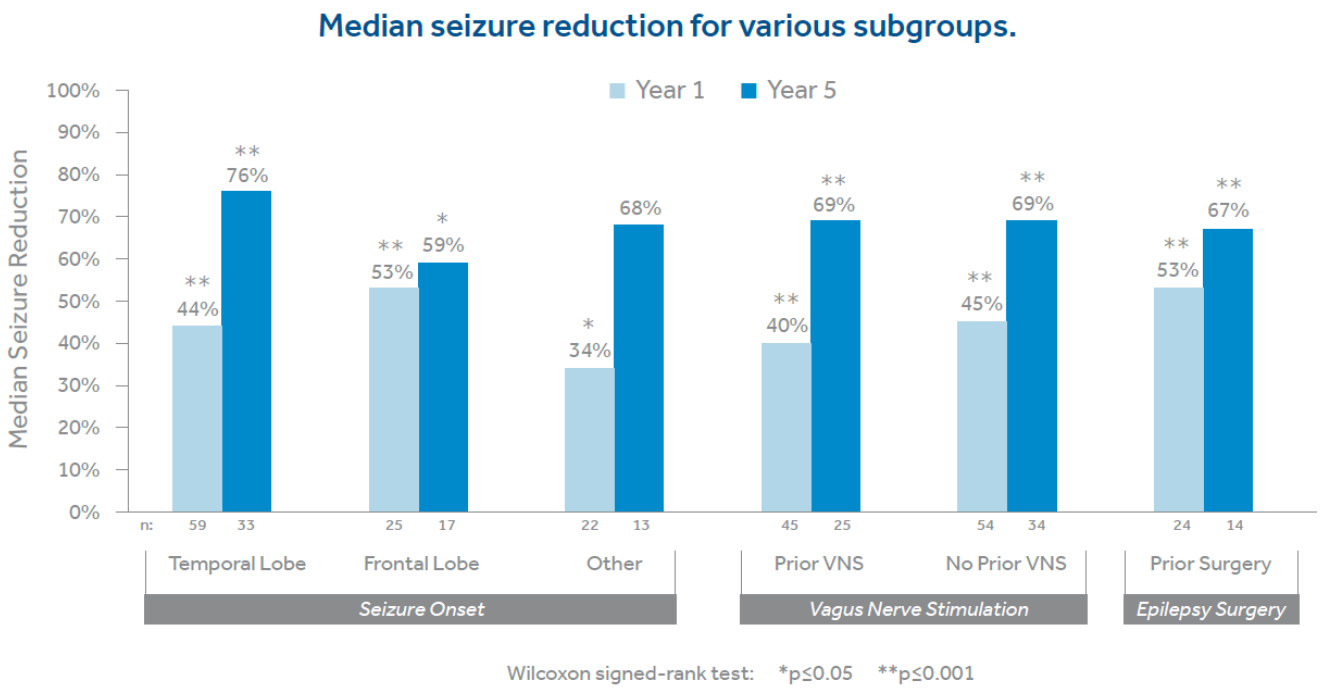
Seizure reduction for those subjects who had at least 70 days of diary in the 3 months before each annual visit.

1 year n=99 | 2 years n=82 | 3 years n=75 | 4 years n=76 | 5 years n=59

Subject total seizure frequency percent change from baseline to most recent 3 months of follow-up.

- 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

EPAS Study Overview: Study Design, Geography, Enrollment, Duration

Global, interventional, prospective, multicenter open-label, post-market study

- 25 investigational centers in the US and Europe (sites currently selected)
- Enrollment of 216 patients to implant 140 subjects to obtain 112 subjects with follow-up data at 3 years
- Inclusion and exclusion criteria similar to SANTE
- 3-Month prospective baseline for CMM Phase
- Neuroimaging collected pre/post implant
- Setting DBS programming parameters based on standard of care
- AEDs tracked and can be changed anytime during the study
- The follow-up for subjects who meet implant criteria for the DBS for Epilepsy System is 3 years and 4 months
- For subjects who do not meet the implant criteria is 3 months, or less in the case of subjects who enroll with pre-existing diary data
- Total study duration for each subject is 3 years and 4 months (39 months)
- Overall duration for the study is approximately 10 years

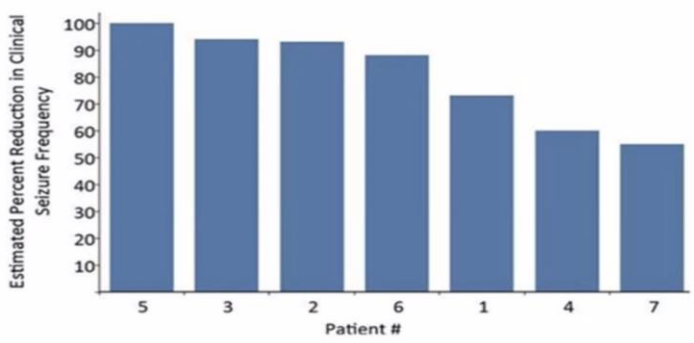
CENTROMEDIAN NUCLEUS OF THALAMUS (CM)

History – see above >>

Read:

Brain-responsive corticothalamic stimulation in the centromedian nucleus for the treatment of regional neocortical epilepsy

David E. Burdette [a], M. Ayman Haykal [a], Beata Jarosiewicz [b], Rachel R. Fabris [a], Gabe Heredia [a], Kost Elisevich [a], Sanjay E. Patra [a]



Follow up: Avg of 17 months (range: 8-28 months)

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-327512).

[1]Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts, USA
[2]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[3]Department of Neurology, Charite Universitatsmedizin Berlin, Berlin, Germany
[4]Department of Neurosurgery, Harvard Medical School, Boston, Massachusetts, USA

Epilepsy

OPEN ACCESS

Original research

Responsive neurostimulation of the thalamus improves seizure control in idiopathic generalised epilepsy: initial case series

Nathaniel D Sisterson,[1] Vasileios Kokkinos,[1] Alexandra Urban,[2] Ningfei Li,[3] R Mark Richardson [1,4]

Patient	Years since diagnosis	Months implanted	Sex	Seizure type	AEDs (n) Trialled	AEDs (n) At RNS implant	AEDs (n) At MRFU	Seizure frequency Pre-RNS	Seizure frequency Post-RNS	Engel score	Seizure severity Pre-RNS	Seizure severity Post-RNS
1	8	33	F	Absence with eyelid myoclonia	6	2	0	60/day	6/day	IB	4	2
2	11	27	M	Absence, GTC	9	4	2	3/week, 1/month	<1/month, <1/year	IIA	5	2
3	5	25	F	Absence, GTC	3	1	1	3/week, 2–4s/month	<1/month, <1/year	IIIA	5	2
4	14	24	F	Myoclonic, absence, GTC	5	2	2	1/day, 1 /week, 1 /year	<1/day, <1/week, <1/year	IC	4	1

Key messages

What is already known on this topic
► Responsive neurostimulation is an effective treatment for drug-resistant focal epilepsy and may be equally or more effective for drug-resistant idiopathic generalised epilepsy (IGE). The thalamus is an important node in IGE seizure networks and a potential target for responsive neurostimulation.

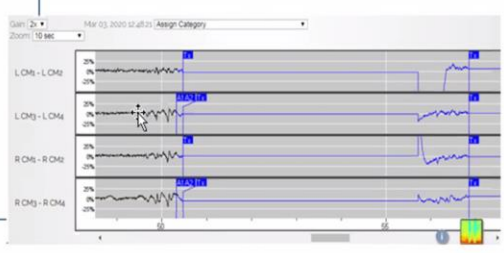
What this study adds
► In this retrospective study of four patients with drug-resistant IGE, seizures were readily detected in the centromedian region of the thalamus and used to trigger closed-loop thalamic stimulation that dramatically reduced seizure frequency and severity.

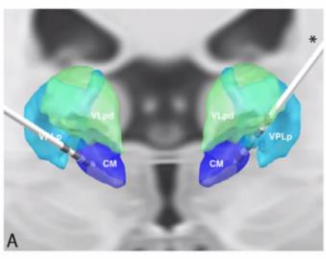
How this study might affect research, practice or policy
► A phase 3 clinical trial to study thalamic RNS for drug-resistant IGE is planned to begin enrolling in 2022.

Original research

Responsive neurostimulation of the thalamus improves seizure control in idiopathic generalised epilepsy: initial case series

Nathaniel D Sisterson,[1] Vasileios Kokkinos ,[1] Alexandra Urban,[2] Ningfei Li,[3] R Mark Richardson [1,4]





All 4 patients had detectable ictal signatures with RNS System implanted in CM thalamic nucleus

- 75%–99% seizure reduction in all patients
  - Decreased seizure duration and severity (4/4)
  - Significant improvements in quality of life.

Sisterson ND, et al. J Neurol Neurosurg Psychiatry 2022;**93**:491–498

*RNS System is not FDA approved for the treatment of IGE.

DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial)

ANN NEUROL 2022;91:253–267

Linda J. Dalic, MBBS ,[1,2] Aaron E. L. Warren, PhD,[1,3,4] Kristian J. Bulluss, PhD,[5,6,7] Wesley Thevathasan, DPhil,[1,5,8] Annie Roten, BAppSci,[2] Leonid Churilov, PhD,[1] and John S. Archer, PhD[1,2,3,4]

Seizure outcome during bilateral, continuous, thalamic centromedian nuclei deep brain stimulation in patients with generalized epilepsy: a prospective, open-label study

Arthur Cukiert *, Cristine Mella Cukiert, Jose Augusto Burattini, Pedro Paulo Mariani

- Cukiert et al. Seizure 18 (2009) 588–592
- Son et al. 2016

ELSEVIER

Archives of Medical Research 31 (2000) 304–315

REVIEW ARTICLE

Acute and Chronic Electrical Stimulation of the Centromedian Thalamic Nucleus: Modulation of Reticulo-Cortical Systems and Predictor Factors for Generalized Seizure Control

Marcos Velasco, Francisco Velasco, Ana Luisa Velasco, Fiacro Jiménez, Francisco Brito and Irma Márquez

frontiers in Neurology

CASE REPORT
published: 28 April 2021
doi: 10.3389/fneur.2021.656585

Case Report: Responsive Neurostimulation of the Centromedian Thalamic Nucleus for the Detection and Treatment of Seizures in Pediatric Primary Generalized Epilepsy

*William P. Welch[1], Jasmine L. Hect[2] and Taylor J. Abel[2,3]**

[1] Division of Pediatric Neurology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2] Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [3] Department of Bioengineering, University of Pittsburgh Swanson School of Engineering, Pittsburgh, PA, United States

Responsive Neurostimulation of the Thalamus Improves Seizure Control in Idiopathic Generalized Epilepsy: A Case Report

Vasileios Kokkinos, PhD [•‡]
Alexandra Urban, MD[§¶]
Nathaniel D. Sisterson, BA[‖]
Ningfei Li, PhD [#]
Danielle Corson, BS[§‖]
R. Mark Richardson, MD, PhD [•‡]

*Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts; ‡Harvard Medical School, Boston, Massachusetts; §University of Pittsburgh Comprehensive Epilepsy Center, Pittsburgh, Pennsylvania; ¶Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ‖Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; #Department for Neurology, Charité – University Medicine Berlin, Berlin, Germany

BACKGROUND AND IMPORTANCE: At least 25% of patients with idiopathic generalized epilepsy do not obtain adequate seizure control with medication. This report describes the first use of responsive neurostimulation (RNS), bilaterally targeting the centromedian/ventrolateral (CM/VL) region in a patient with drug-refractory Jeavons syndrome (eyelid myoclonia with absences).

CLINICAL PRESENTATION: A patient, diagnosed with eyelid myoclonia with absences (EMA) and refractory to medication, was offered RNS treatment in the CM/VL region of the thalamus. Stimulation was triggered by thalamic neural activity having morphological, spectral, and synchronous features that corresponded to 3- to 5-Hz spike-wave discharges recorded on prior scalp electroencephalography.

CONCLUSION: RNS decreased daily absence seizures from a mean of 60 to ≤10 and maintained the patient's level of consciousness during the occurring episodes. This therapy should be evaluated further for its potential to treat patients with pharmaco-refractory generalized epilepsy.

KEY WORDS: Generalized epilepsy, Responsive neurostimulation, Centromedian nucleus, Thalamus

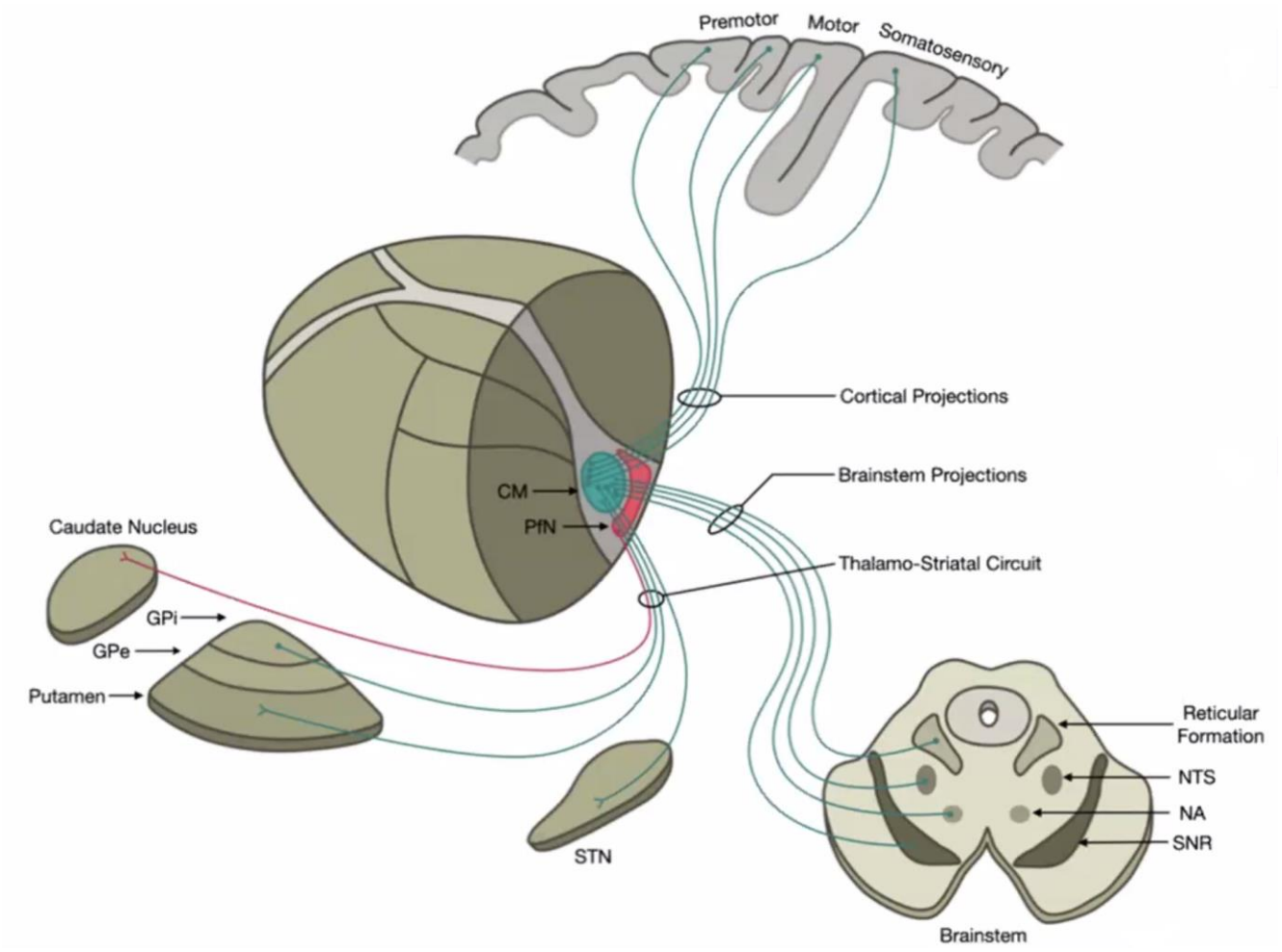
Neurosurgery 0:1–6, 2020 DOI:10.1093/neuros/nyaa001 www.neurosurgery-online.com

ANATOMY

- CMN is largest of the intralaminar nuclei - spheroid-shaped nucleus approximately 10 mm in diameter.
- CMN is in **posterior group of the intralaminar nuclei** of the thalamus (together with parafascicular (PF) and central lateral (CL) nuclei).
- CM has sparse neuronal cell density of ~ 2200/mm^3 (vs. mediodorsal, PF and pulvinar nuclei ~ 3200–5000/mm^3)

CONNECTIONS

N.B. CMT has much more widespread connections than ANT (vs. ANT - "only" Papez - fronto-temporal / limbic epilepsies; pulvinar – visual cortex)



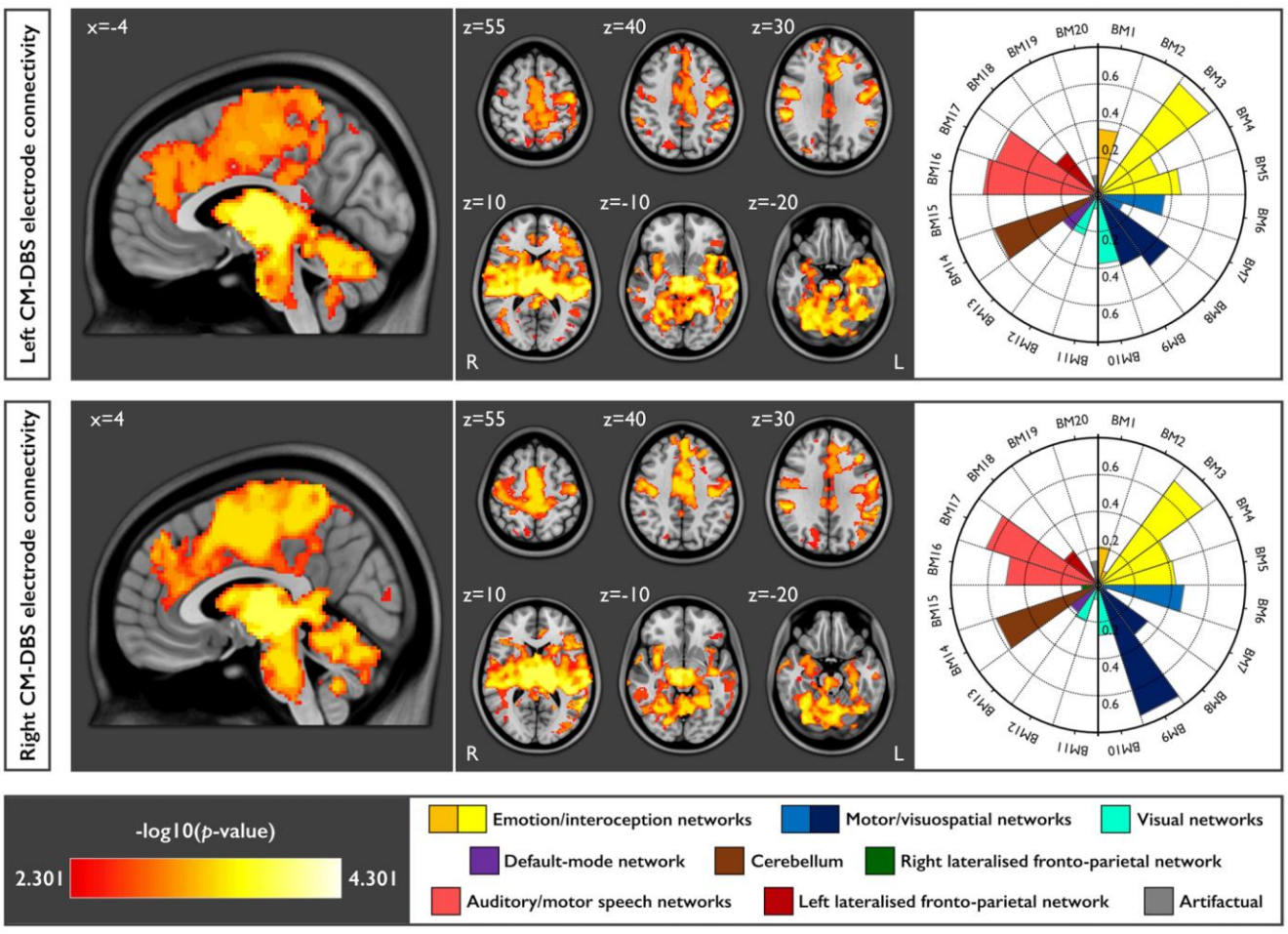
- motor cortex provides input to the CMT, as do the globus pallidus interna (GPi).
- CMT projects back to the motor cortex as well as the striatum with particular preference for the putamen and the head of the caudate nucleus proximal to the internal capsule.
- CM's connectivity is theorized to play a key role in a range of arousal, cognitive and sensorimotor processes.

fMRI resting-state - functional connectivity calculated from positions of implanted DBS electrode contacts within the centromedian nucleus (CM):

(A) Sagittal and axial brain maps showing areas of significant positive mean functional connectivity strength ($p < 0.005$, corrected for family-wise error after threshold-free cluster enhancement) 19 calculated separately for the left (upper row) and right (lower row) DBS electrode contacts within the CM from 16 patients. Connectivity maps are colored using a -log10 transformation of voxel-wise p values. The x and z coordinates indicate axial and sagittal voxel positions (mm) in Montreal Neurological Institute 152 2009b template space, respectively.

(B) Polar plots quantifying spatial similarity between the connectivity maps in (A) and each of 20 intrinsic connectivity networks (ICNs) derived from the 'BrainMap' (BM) meta-analytic database of >1800 prior task-related neuroimaging studies. Spatial similarity is expressed as a value ranging from 0 to 1 (larger wedges in the plot indicate high similarity with the BM ICN; smaller wedges indicate low similarity). Each wedge is colored according to the hypothesized functional role(s) of the BM ICN, as indicated by the figure legend in the lower right.

Interpretation: connectivity from CM-DBS electrode positions is maximal with BM ICNs that normally support emotional/interoceptive, motor/visuospatial, cerebellar and auditory/motor speech processing; in contrast, connectivity is less apparent with frontoparietal, default mode and visual BM ICNs.



Source of pictures: Aaron E L Warren et al. 2020 >>

FUNCTIONS

- 'gate control' function by propagating only salient stimuli during attention-demanding tasks.

INDICATIONS

- majority of available data support the use of CM DBS for generalized epilepsies, including Lennox-Gastaut syndrome.
    - current data is only from level III-IV studies.
- CM works well for frontal epilepsies (ANT – limbic).

- CM has literature regarding also neuromodulation therapies for:
    1. Tourette syndrome
    2. Parkinson's disease
    3. Generalized epilepsy
    4. Intractable neuropathic pain
    5. Restoring consciousness in PVS

TARGETING

- stimulation was most effective when focused on the anterior and inferolateral "parvocellular" CMN border, extending into the ventral lateral nucleus.

Warren AE et al. The optimal target and connectivity for deep brain stimulation in Lennox–Gastaut syndrome. Ann Neurol. 2022;92(1):61-74.

INDIRECT TARGETING

MNI coordinates:

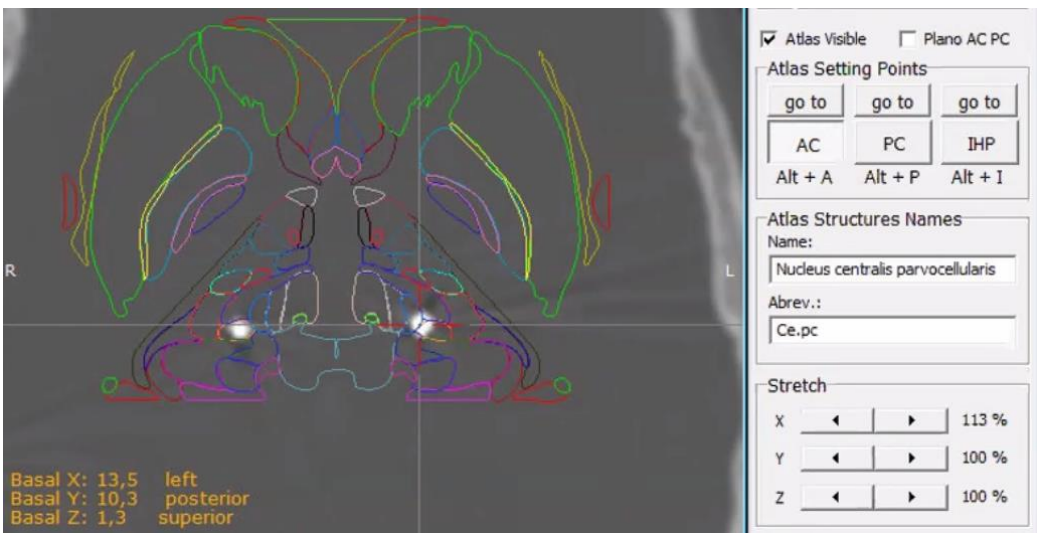
Right: 10, -19, 3
Left: -10, -20, 3

AC-PC coordinates:

10 mm lateral to **PC**
0-3 mm superior to **PC**
~ 6 mm anterior to **PC**

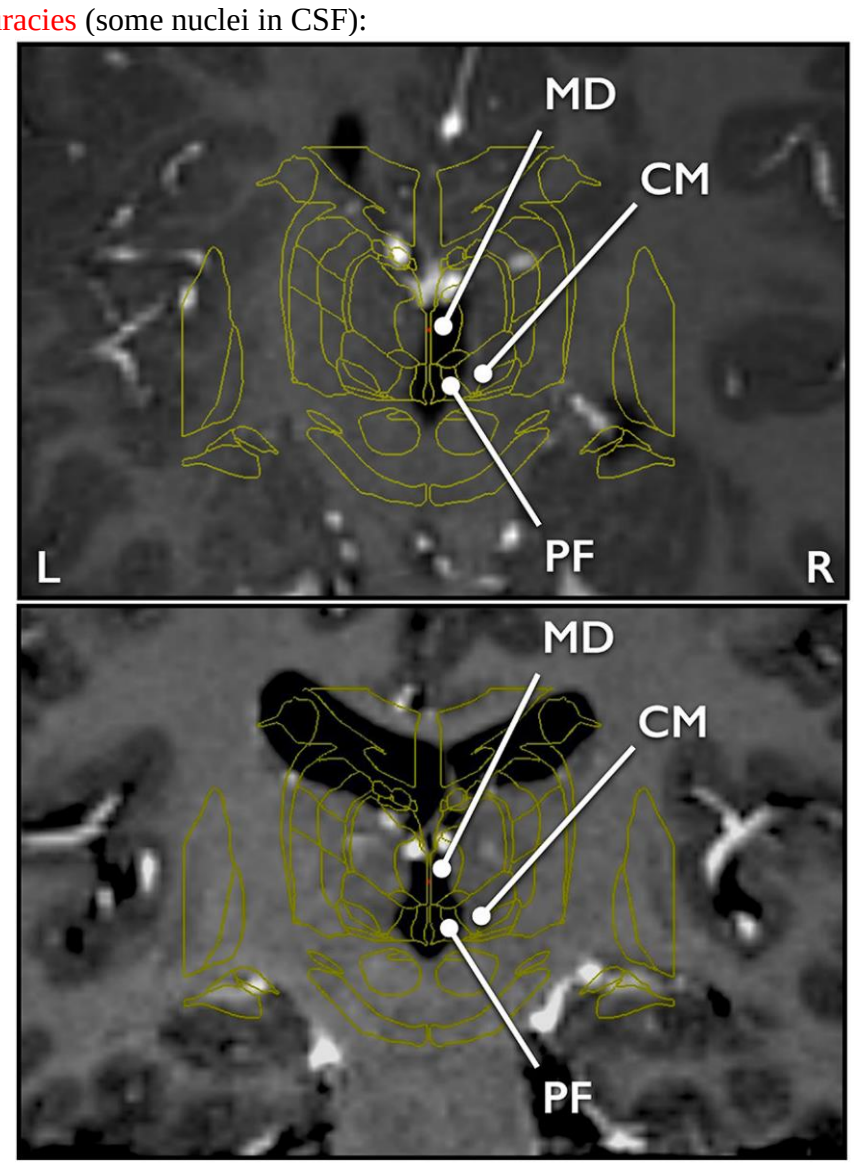
Warren et al 2020 case series:

8.1 mm lateral (range 6.7–10.6) to **midcommissural point**
9.8 mm posterior (range 2.4–12.6) to **midcommissural point**
1.1 mm superior (range -4–2.9) to **midcommissural point**



- risk is that indirect targeting will place contacts too lateral → sensory side effect.

Examples of coronal images and **Schaltenbrand and Wahren atlas** – 2 different patients with structural brain abnormalities due to malformations of cortical development – shows potential inaccuracies (some nuclei in CSF):

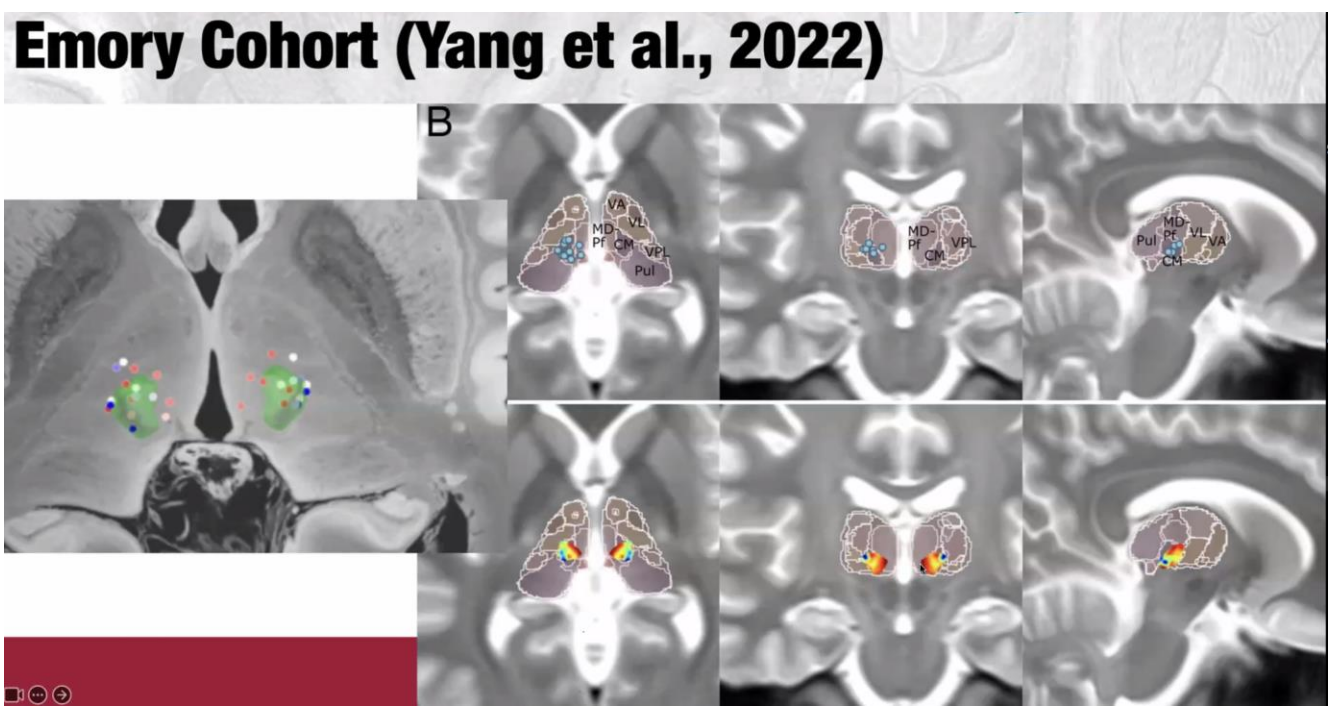


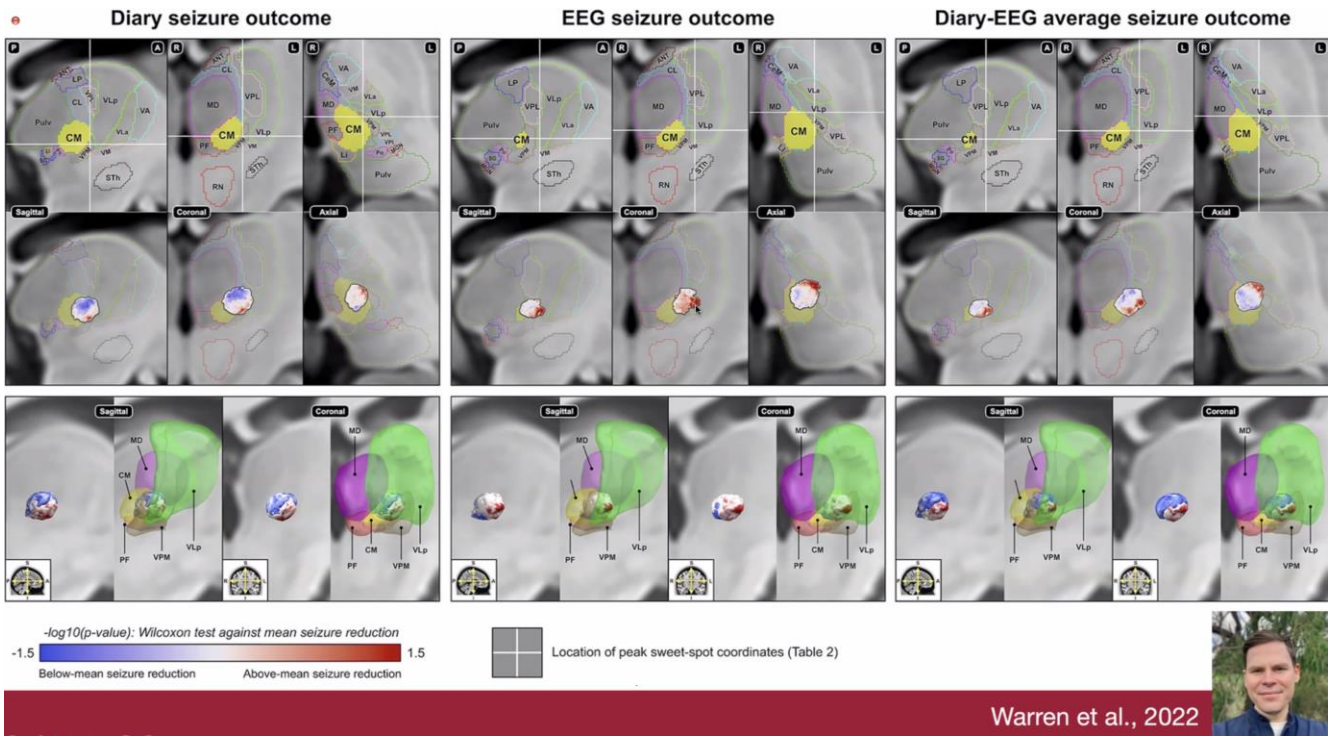
Source of pictures: Aaron E L Warren et al. 2020 >>

DIRECT TARGETING

BEST TARGET

- traverse **center** of CM (Dr. Richardson).
- best CM part is **antero-medial** (Emory).
- for LGS – best CM part is **antero-lateral-inferior** (Dr. Rolston).





IMAGING

- CM cannot be seen even on 7T MRI (vs. ANT).

A. **Magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE)** sequence; MP2RAGE differs from MPRAGE by acquiring two volumes with different inversion times that are combined into a unified volume that shows improved grey/white matter image contrast.

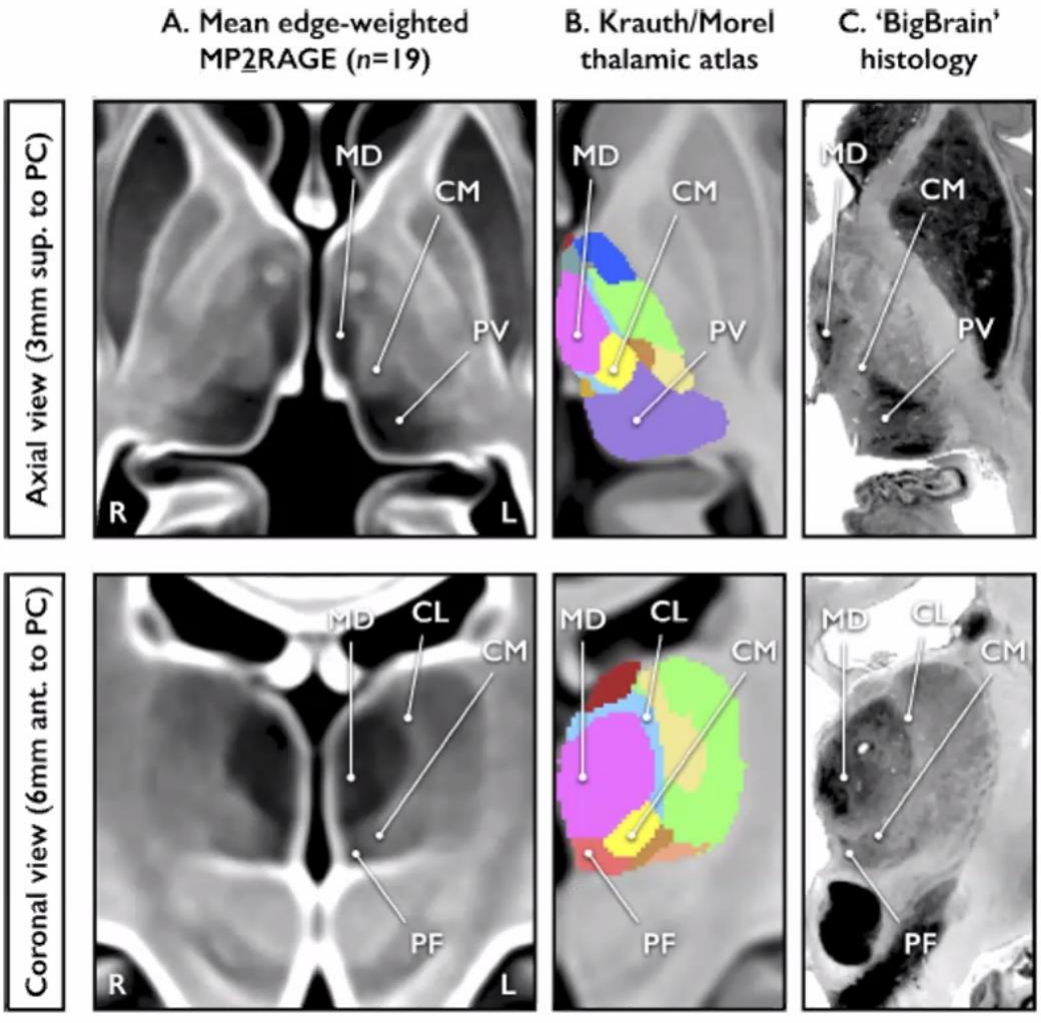
- edge-detection method (Sobel operator) can highlight intrathalamic borders visible on MP2RAGE.
  - Sobel operator computes the gradient magnitude at each image point (ie, change in signal intensity from one voxel to the next), where areas of high gradient indicate likely 'edges'.
  - voxel intensities within each of the MP2RAGE and Sobel-processed images are converted to *z*-scores, and then a novel 'edge-weighted MP2RAGE' image is calculated by summing together the two *z*-score images: this weighted each MP2RAGE voxel by its likelihood of indicating a border between areas of differing signal intensity (ie, border voxels became 'brighter' in the summed image, whereas non-border voxels became 'darker').
- Warren et al. 2020 found that SWI has worse visualization than MP2RAGE.

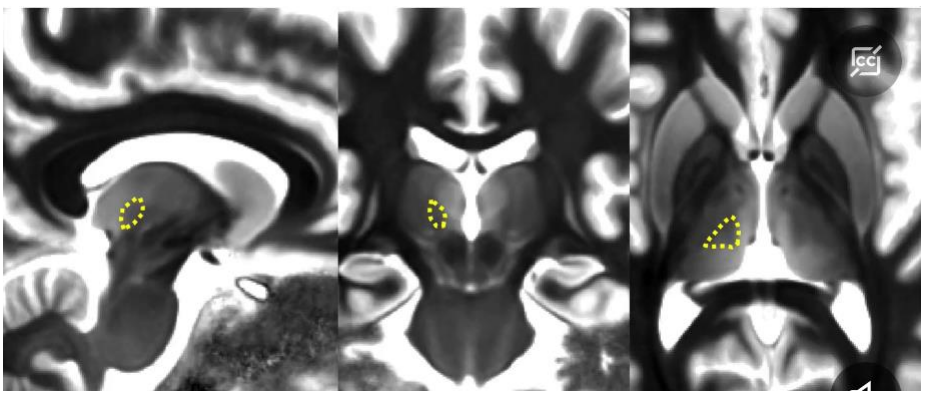
Edge-weighted MP2RAGE following spatial warping to Montreal Neurological Institute (MNI) 152 2009b template space.

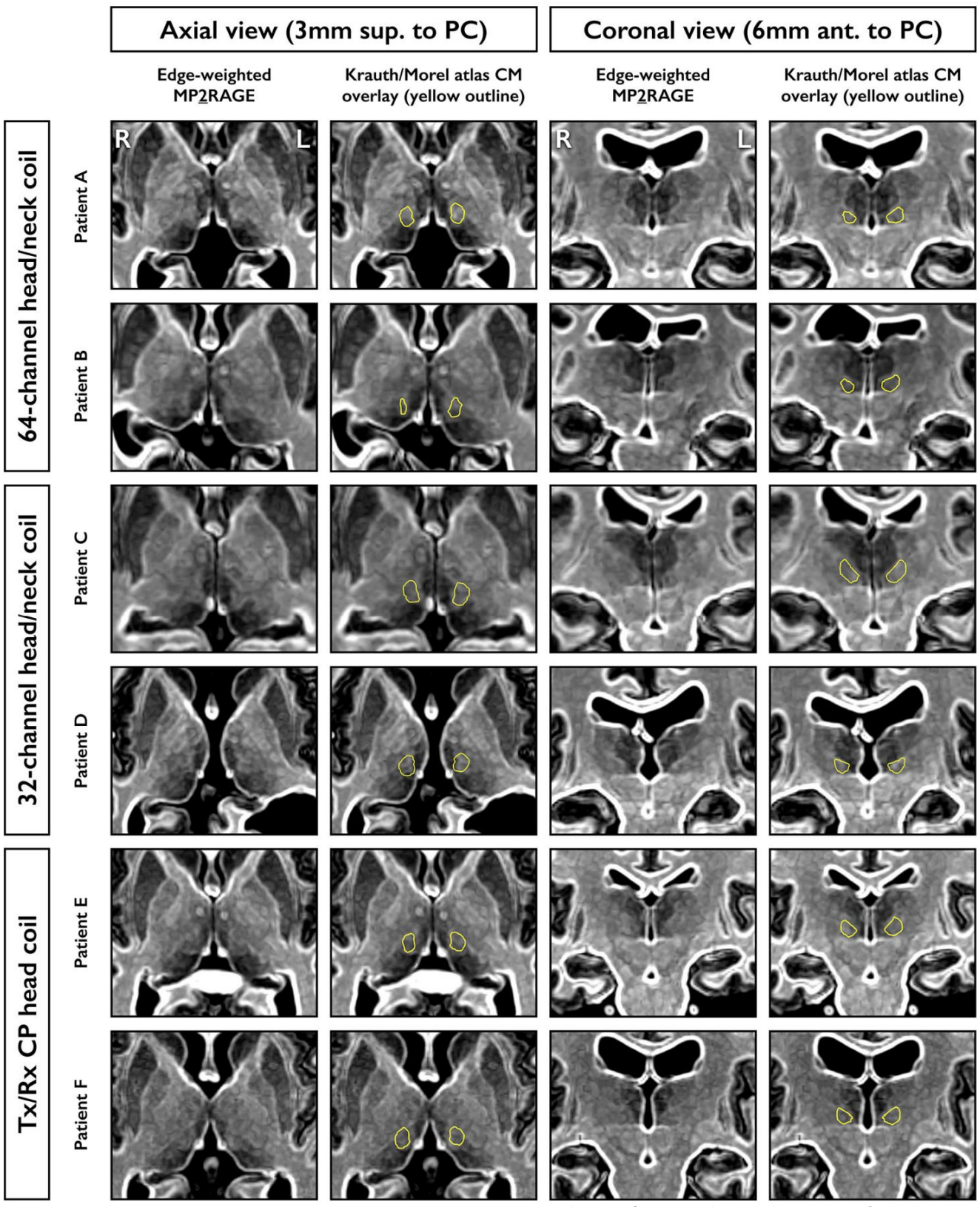
Axial (upper row), CM appears as a hyperintense region bordered medially by hypointense mediodorsal nucleus (MD) and posteriorly by hypointense pulvinar nucleus (PV).

Coronal (lower row), CM is bordered superiorly by MD and medially by hypointense parafascicular (PF) nucleus, while CM's approximate lateral extent is suggested by thin line of relative hyperintensity consistent with centrolateral nucleus (CL). It is best appreciated ~3 mm superior and ~6 mm anterior to the posterior commissure (PC)

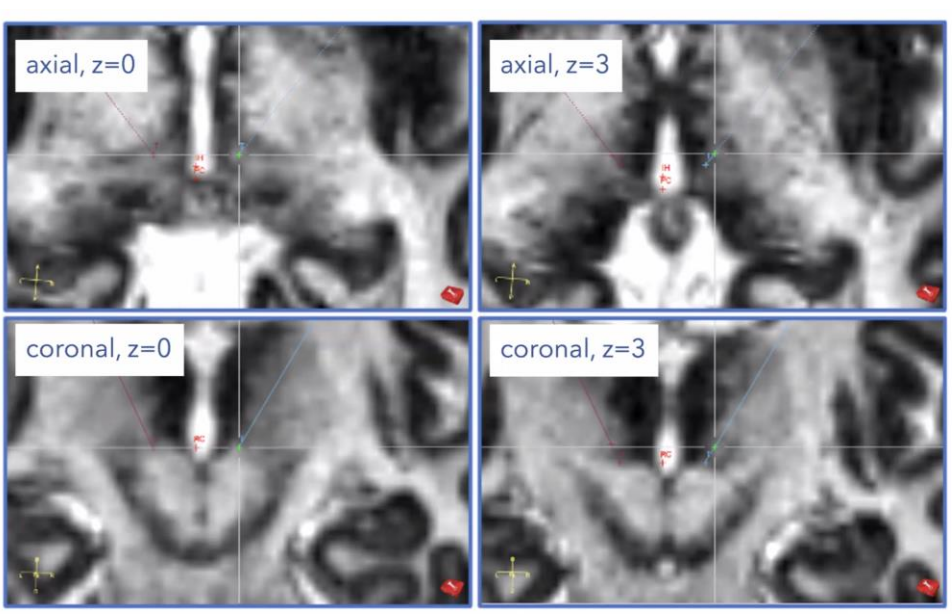
(B and C) Atlas comparisons - location of the CM on edge-weighted MP2RAGE shows good correspondence with the CM's position determined by the Krauth/Morel and BigBrain thalamic atlases:







Source of pictures: Aaron E L Warren et al. 2020 >>



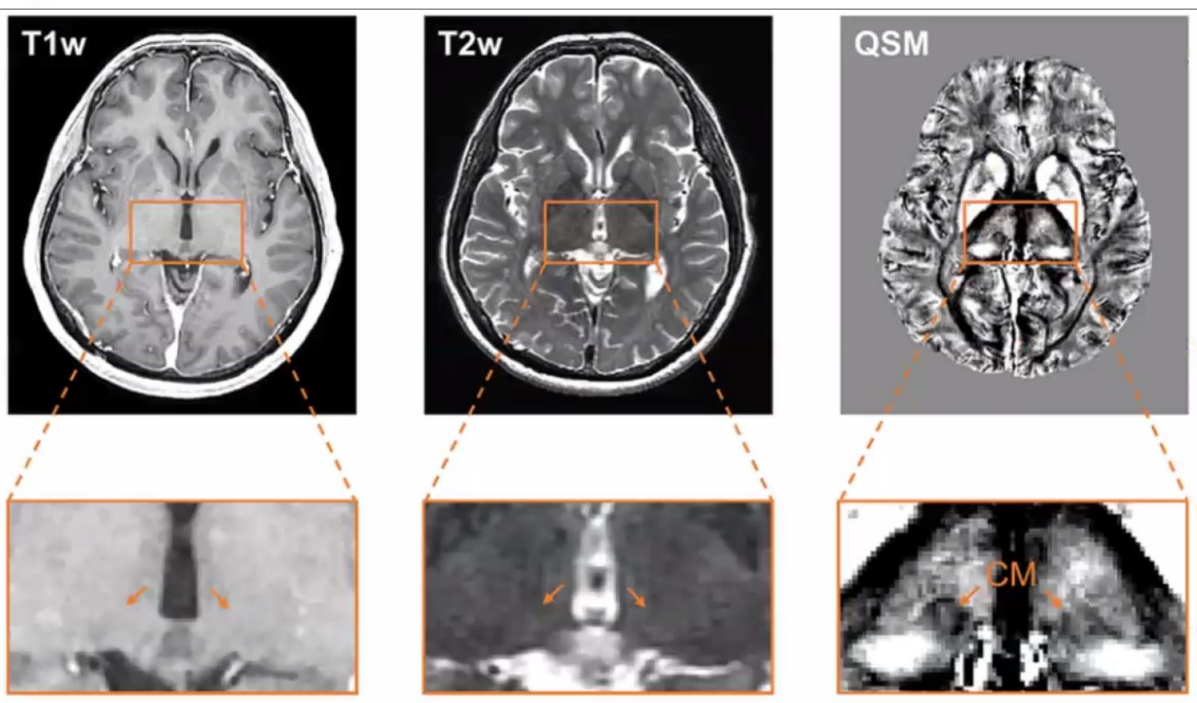
- Indirect targeting w/AC-PC coordinates (+/-8, -10, 0)
- Entry point near coronal suture
- Advance view along this trajectory to the imaging planes 3mm above PC
- Direct targeting = adjust target point until trajectory traverses center of CM

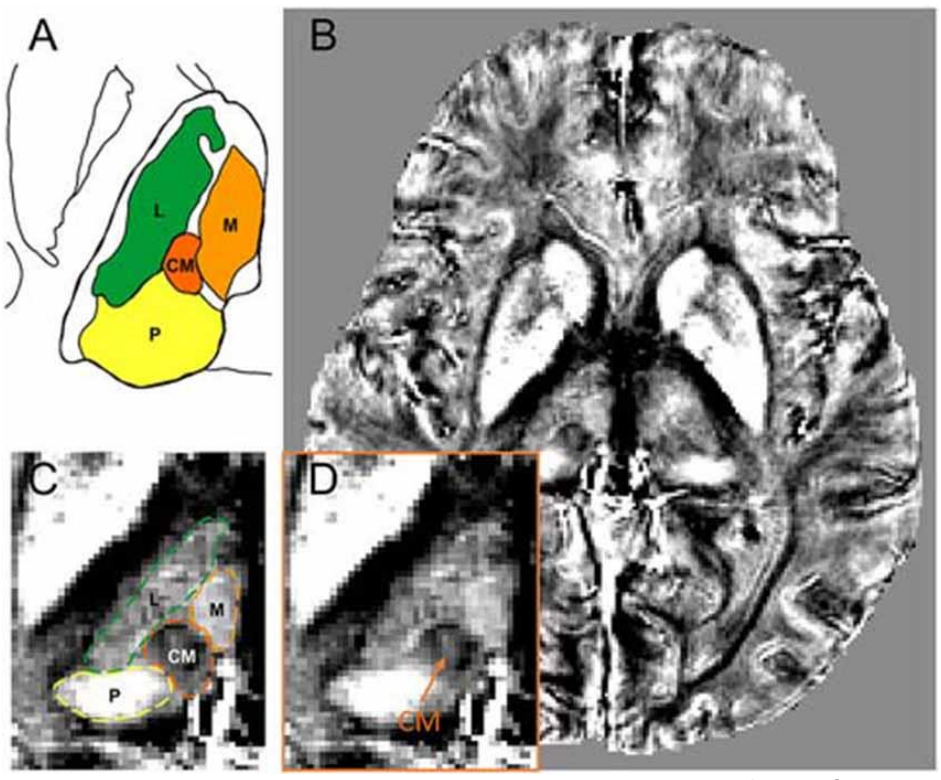
Richardson 2023

B. Quantitative susceptibility mapping (QSM)

- QSM is reconstructed from 3D gradient recalled echo (GRE)

Parameter	3D T1w	2D T2w	3D GRE
Imaging plane	Axial	Axial	Axial
Field of vision (mm)	240 × 240	240 × 240	240 × 240
Matrix	320 × 320	320 × 320	320 × 320
Resolution (mm)	0.75 × 0.75 × 1.5	0.75 × 0.75 × 1.5	0.75 × 0.75 × 1.5
Time of repetition (ms)	7.04	3,000/4,000	32.80
Time of echo (ms)	3.47	128.60/106.03	11.00
Scan time (s)	172	346	528

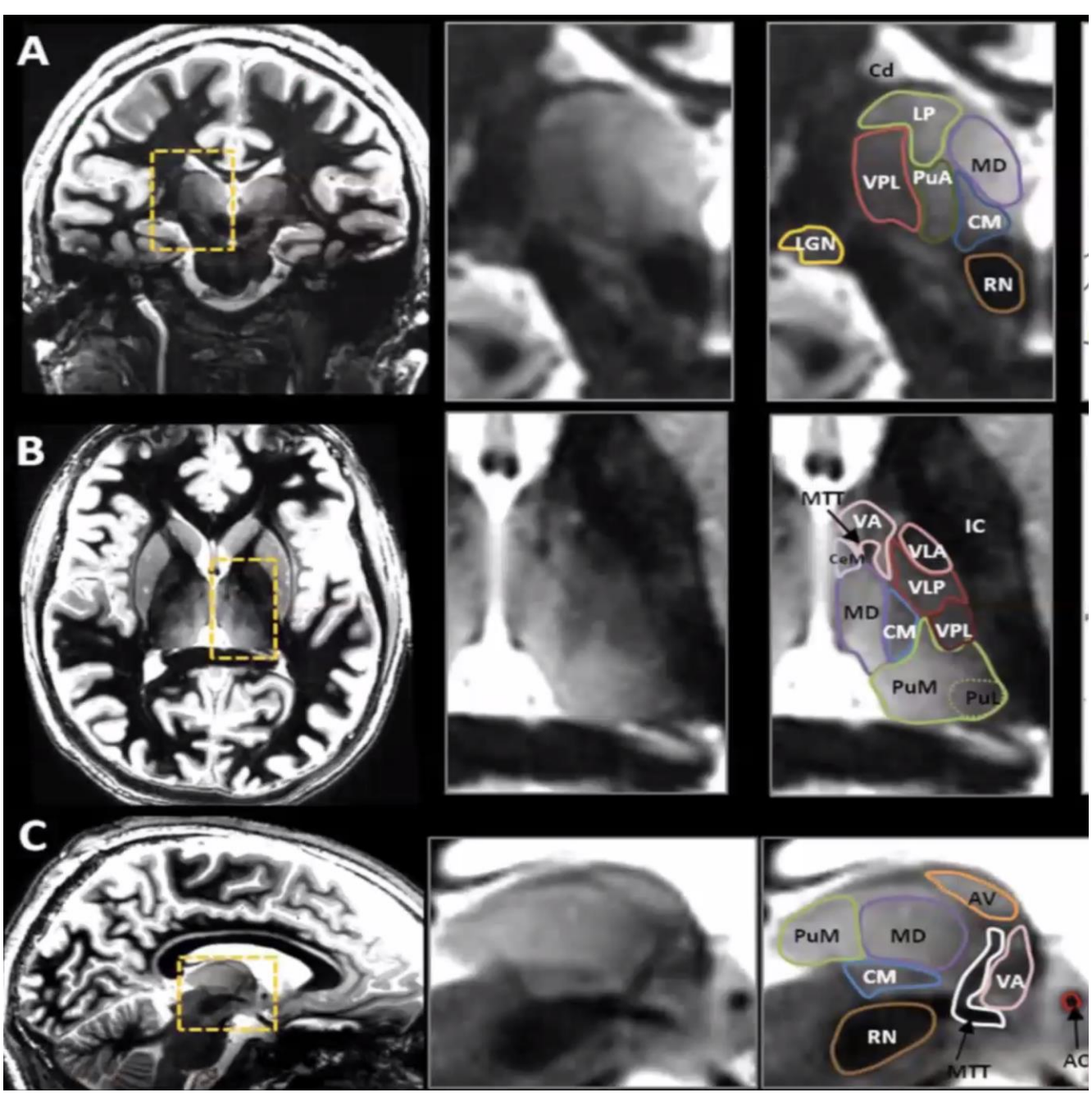




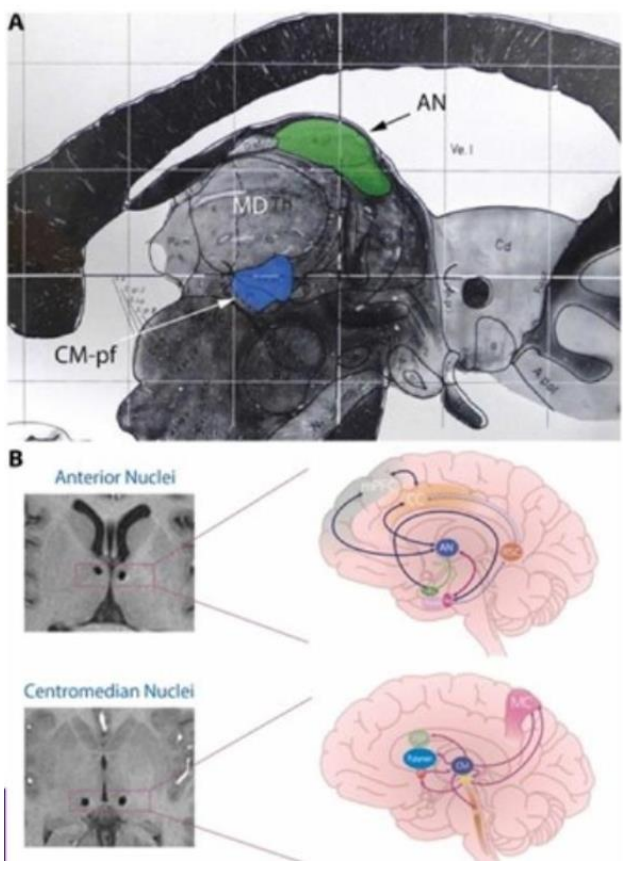
Source of pictures: Jun Li et al. 2020 >>

C. FGATIR

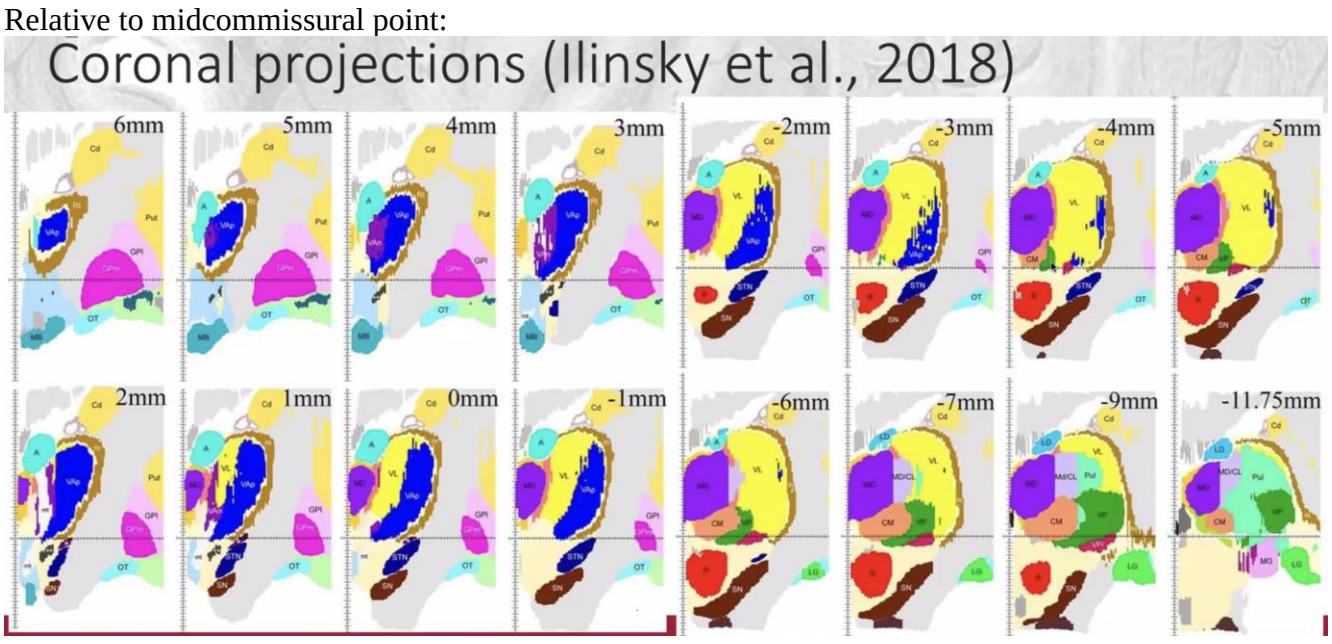
- some merge **FGATIR** and **regular MPRAGE** – "the drop-shaped CM" is opposite intensity than neighboring pulvinar and medial group and also opposite intensities on FGATIR and regular MPRAGE.



ATLAS



Relative to midcommissural point:



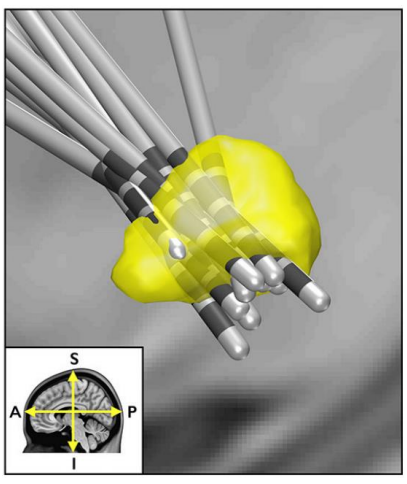
MER, STIMULATION

- **MER** cannot guide reliably;
    - Waren et al. 2020: ***reduced spike firing rate and background noise*** in CM (posterior intralaminar nuclei are neurophysiologically 'quieter' than adjacent structures during spontaneous recordings while under general anesthesia).
- Waren et al. 2020 performed **microelectrode stimulation** at target depth (130 Hz, 60 μsec) - to determine the stimulation threshold for clinical motor effects (clinically detectable movement or change in muscle tone) – internal capsule effects:

  < 4 mA – no motor response.
  4–6 mA – motor response in 9.4% patients
  9–10 mA – motor response in 58% patients

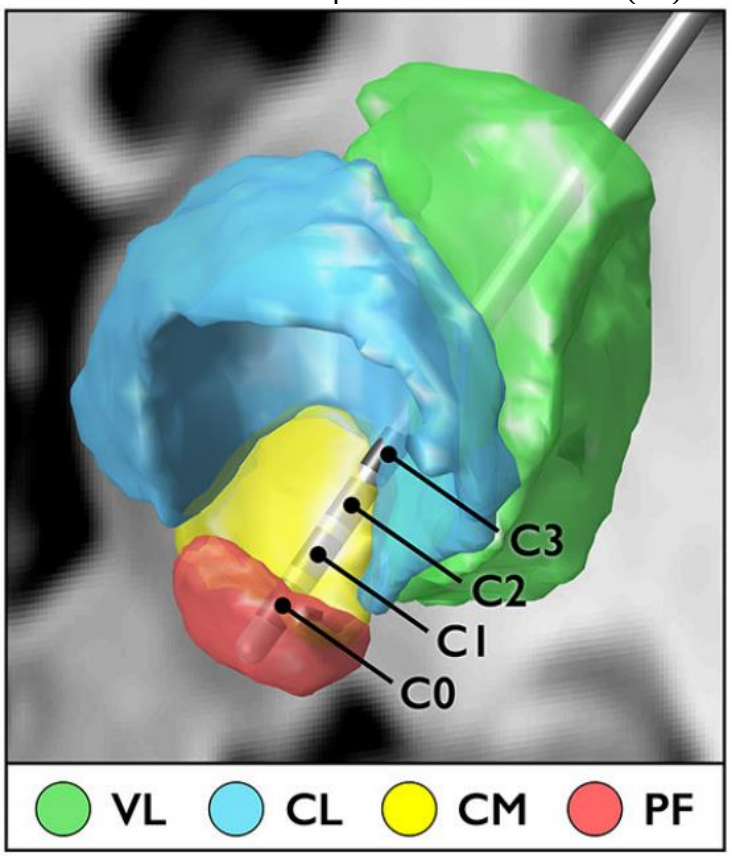
  N.B. no target positions were adjusted as a result of these test stimulations!

TRAJECTORY

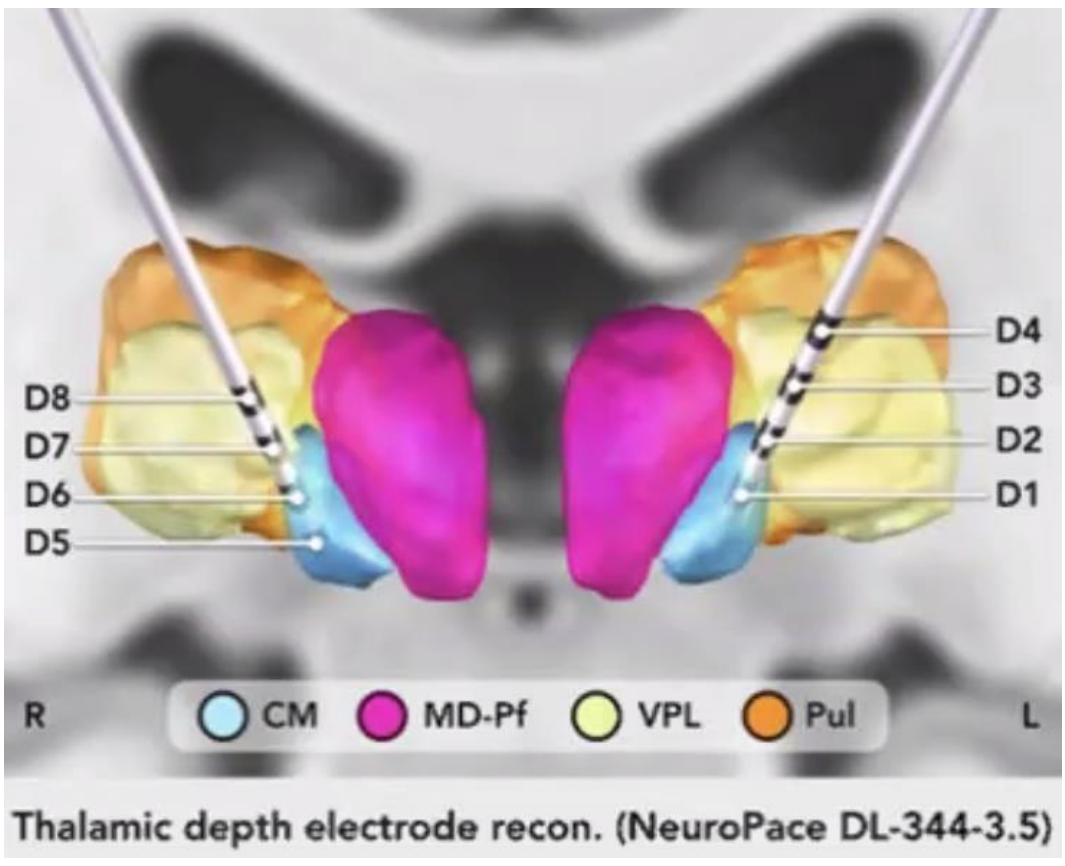


Options

A. Entry at **coronal suture**
- trajectory enters thalamus at the level of ventrolateral nucleus (VL) and passes through centrolateral nucleus (CL).
- plan trajectories to avoid VPL.
- at least 2–3 stimulation contacts within the CM, with the most inferior contact (C0) positioned near the border between CM and parafascicular nucleus (PF).



Source of pictures: Aaron E L Warren et al. 2020 >>



B. **Parietal** approach – also spears **pulvinar**.

MALPOSITIONED ELECTRODE

- **too lateral** → sensory side effects (paresthesias)
- **too deep** (pretectal area) → upward gaze deviation.

PROGRAMMING

Dr. A. Cukiert:

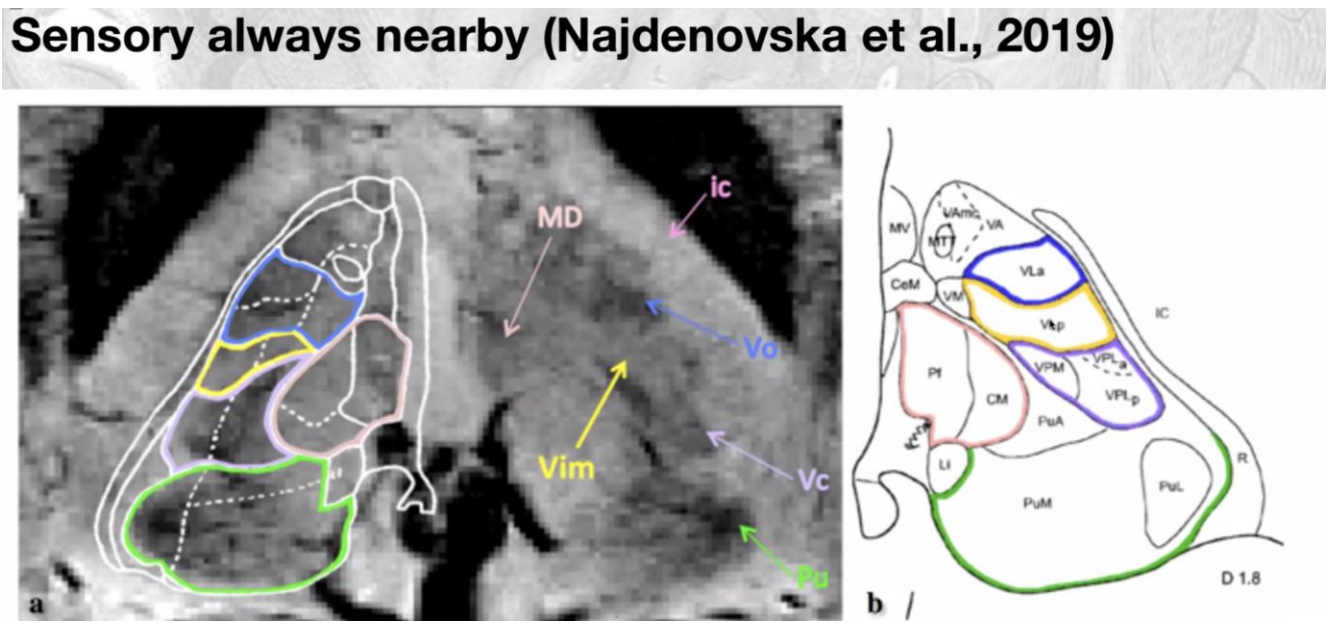
- 130 Hz, 300μsec, bipolar (0-3 & 4-7).
- Upper limit: ~ 5V
- 0.5V increment every week.
- Common complain at higher intensity: paresthesias (last minutes-hours).

Different studies of LGS patients

1-10 V
5-145 Hz
60-300 µs
Continuous or cycling

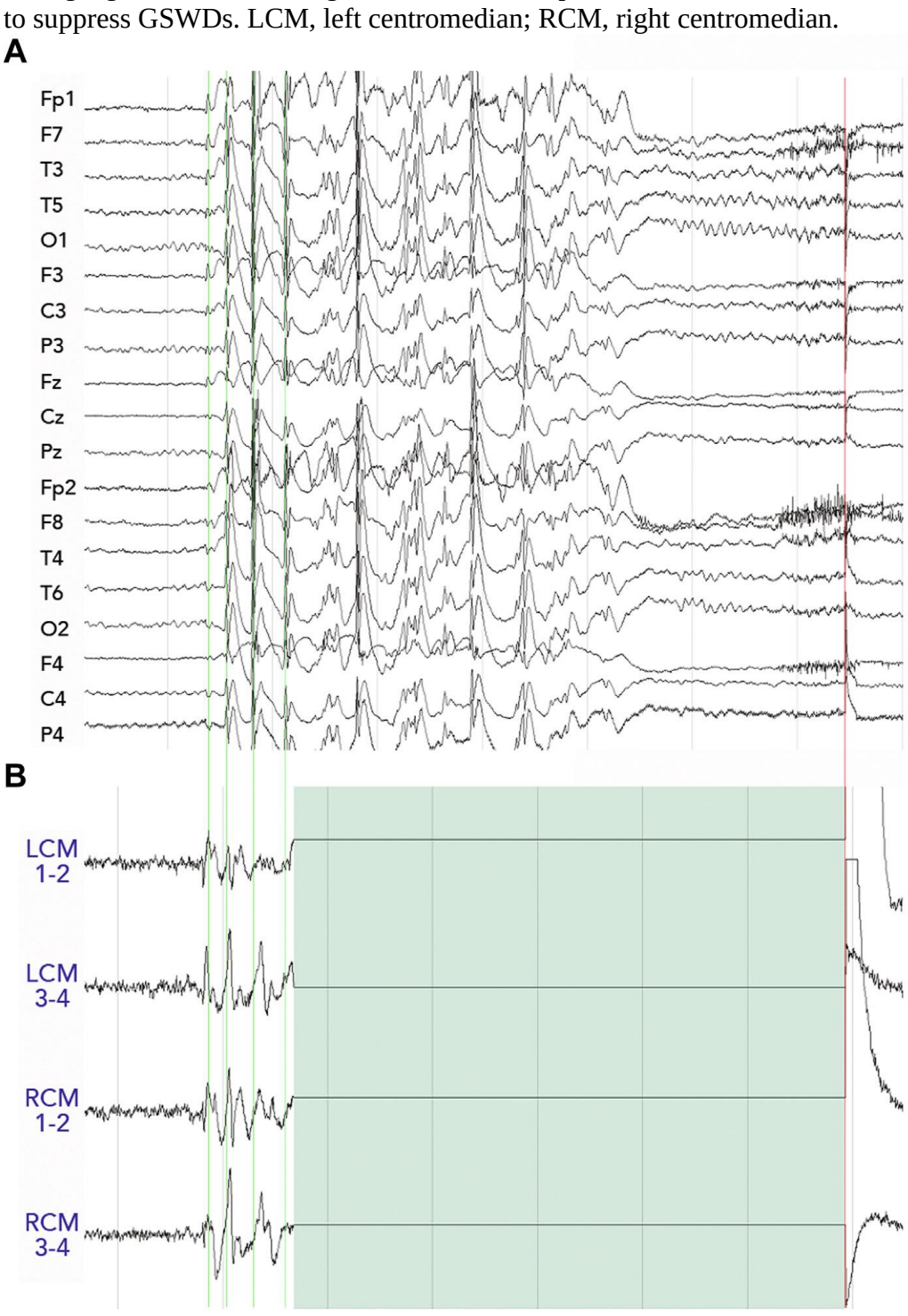
SIDE EFFECTS

- most common side effect – sensory (contacts too lateral – avoid VPM/L nuclei).



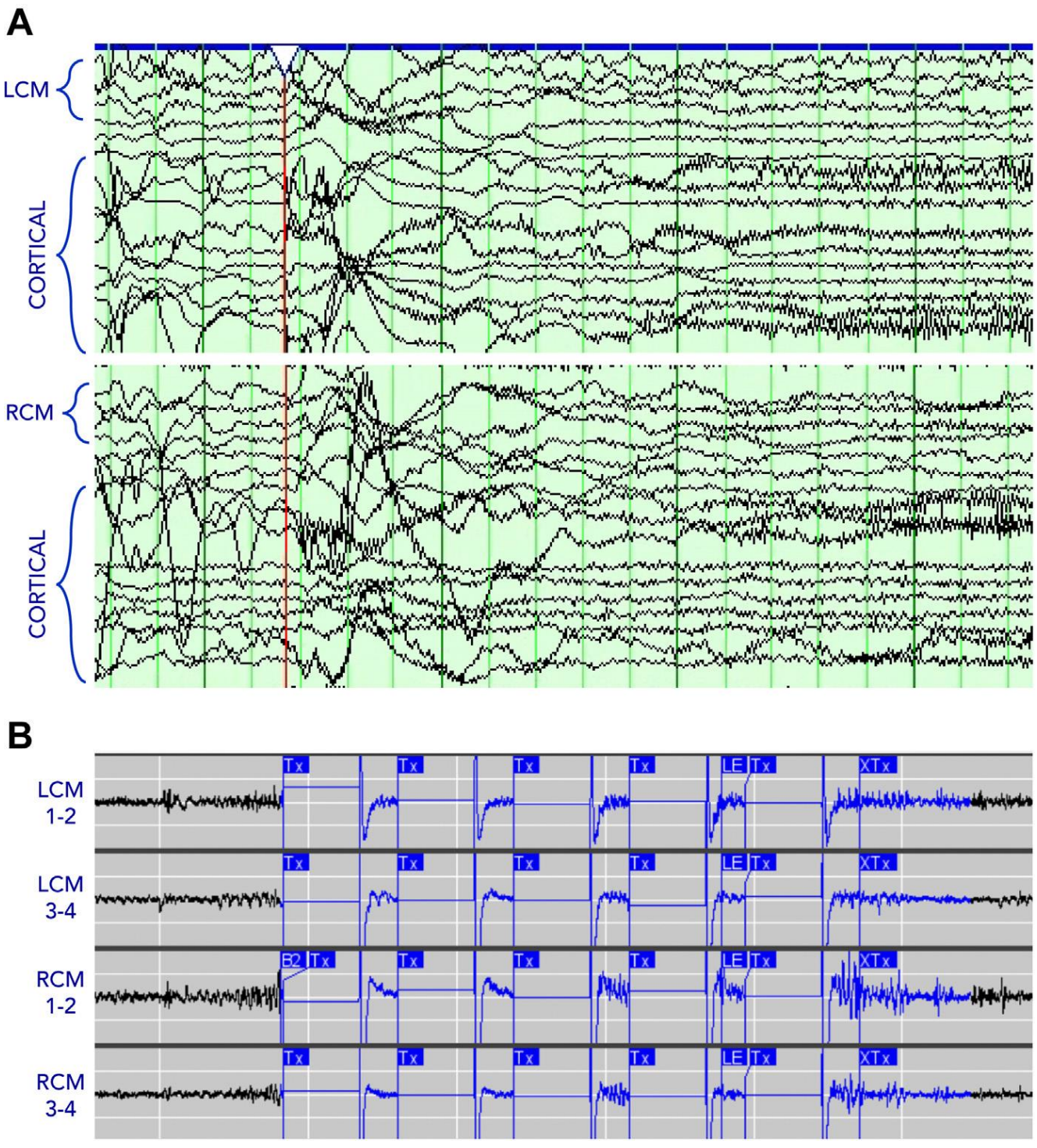
RECORDINGS

Patient with IGE. Simultaneous scalp EEG (A) and thalamic EEG recordings on RNS device (B), during a generalized discharge, exhibit a similar pattern of GSWDs. Stimulation (green block) is seen to suppress GSWDs. LCM, left centromedian; RCM, right centromedian.



Richardson et al 2022

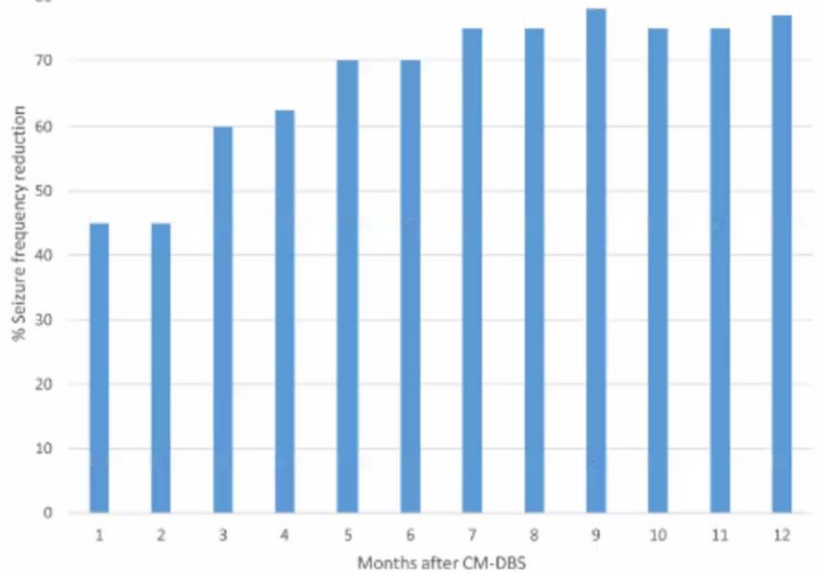
Thalamic CM recordings during SEEG. (A) CM contacts are active simultaneous with the cortical contacts at seizure onset. (B) Similar low-voltage fast activity subsequently was detected on the device and programmed to trigger stimulation.



Richardson et al 2022

OUTCOMES

- response rates from 0% (Andrade et al. Neurology 2006;66:1571–1573) to 100% (Cukiert et al. Seizure 18 (2009) 588–592)
- Son et al. 2016: 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:



- 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	ESTEL trial (Dalic et al)
N	13	4 pts s/p CC	2	20
Pathology	LGS	IGE 2 LGS 2	SGE 1 Multifocal 1	LGS
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	Sz free 2 87-95% 6 50-80% 3 < 50% 1	100% RR Av 78%	Initially worsened, no clear diff in on and off	Median seizure reduction 46.7% (interquartile range [IQR] = 28-67%) for diary-recorded seizures and 53.8% (IQR = 27-73%) for electrographic seizures
Neuropsych outcome	Improvement related to Sz Outcome	Improved alertness (SNAP IV)	N/A	
Comments	Anterolateral nucleus in parvocellular best response	Improvement in alertness at 0.5 V, sz control at 1.5 V		

TRIALS

IDIOPATHIC GENERALIZED EPILEPSIES

NAUTILUS study – **RNS** for centromedian nucleus of thalamus.

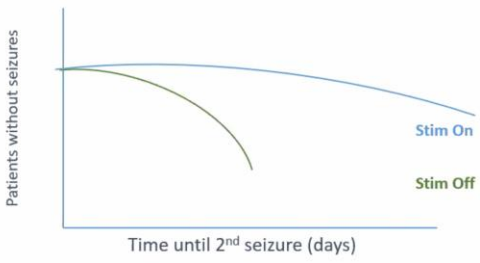
- Randomized single blinded "time-to-event" design
- Patients exit blinded portion after 2nd generalized tonic clonic seizure or 1 year after implant, whichever is first

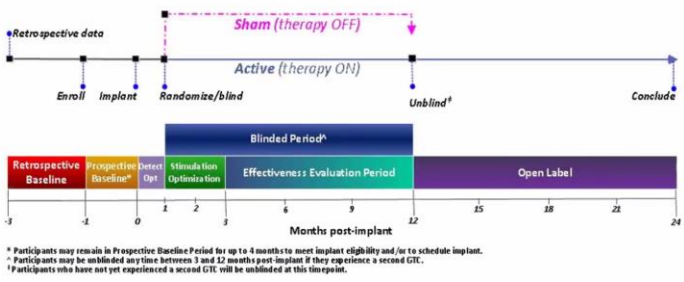
Ethical design

- Enhances patient acceptability and safety,
- Avoids potential confound of acute implant effect on seizure frequency

Efficient design

- Primary safety and effectiveness endpoints at 1 year
- Continued follow-up to 2 years





LENNOX-GASTAUT

Review of CM DBS for LGS

Shlobin, Nathan A. et al. Deep Brain Stimulation of the Centromedian Nucleus of the Thalamus for Lennox-Gastaut Syndrome: A Systematic Review and Individual Patient Data Analysis. Neurosurgery, December 30, 2022.

- **DBS**
- ≥ 50% seizure reduction in 80.9% of patients (better than VNS or callosotomy)
- seizure freedom rate < 10%.
- overall mean seizure reduction of 62.9%.
- Quality of Life improved in 30/34 (88.2%) patients.

LGS Feasibility Study (RNS) – **RNS** for centromedian nucleus of thalamus.

RNS® System Feasibility Study of Thalamocortical Responsive Neurostimulation for Treatment of Lennox-Gastaut Syndrome

Safety and provide preliminary evidence for efficacy of bilateral corticothalamic responsive stimulation

- Prospective two-stage single-blind cross-over
  - 2 neurostimulators; 4 leads
  - 20 patients: 3 stimulation conditions

Scientific Goals

- Define the best location for leads and stimulation settings in individual patients
- Optimize each patient's outcome by using RNS® System data to guide detection and stimulation programming

NEUROPACE
EMORY HEALTHCARE
MASSACHUSETTS GENERAL HOSPITAL
Mount Sinai Hospital
NYU Langone MEDICAL CENTER
LIKE MEDICINE
UCSF Health
UF College of Medicine
HEALTH UNIVERSITY OF UTAH
NIH

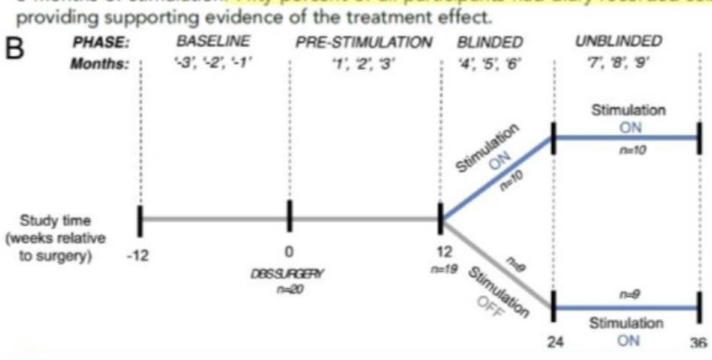
ESTEL trial (DBS) – **DBS** for centromedian nucleus of thalamus in LGS.

- ESTEL trial found reduction in electrographic, but not diary-recorded, seizures.
  - 50% were responder (vs. 22% in control group).
  - 59% electrographic reduction of seizures (vs. 0% in control group).

DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial)

Linda J. Dalic, MBBS,[1,2] Aaron E. L. Warren, PhD,[1,3,4] Kristian J. Bulluss, PhD,[5,6,7] Wesley Thevathasan, DPhil,[1,5,8] Annie Roten, BAppSci,[2] Leonid Churilov, PhD,[1] and John S. Archer, PhD[1,2,3,4]

Results: Between November 2017 and December 2019, 20 young adults with LGS (17–37 years; 13 women) underwent bilateral CM-DBS at a single center in Australia, with 19 randomized (treatment, n = 10 and control, n = 9). Fifty percent of the stimulation group achieved ≥50% seizure reduction, compared with 22% of controls (odds ratio [OR] = 3.1, 95% confidence interval [CI] = 0.44–21.45, $p = 0.25$). For electrographic seizures, 59% of the stimulation group had ≥50% reduction at the end of the blinded phase, compared with none of the controls (OR = 23.25, 95% CI = 1.0–538.4, $p = 0.05$). Across all patients, median seizure reduction (baseline vs study exit) was 46.7% (interquartile range [IQR] = 28–67%) for diary-recorded seizures and 53.8% (IQR = 27–73%) for electrographic seizures.
Interpretation: CM-DBS in patients with LGS reduced electrographic rather than diary-recorded seizures, after 3 months of stimulation. Fifty percent of all participants had diary-recorded seizures reduced by half at the study exit, providing supporting evidence of the treatment effect.



ANN NEUROL 2022;91:253–267

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial)

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ANN NEUROL 2022;91:253–267

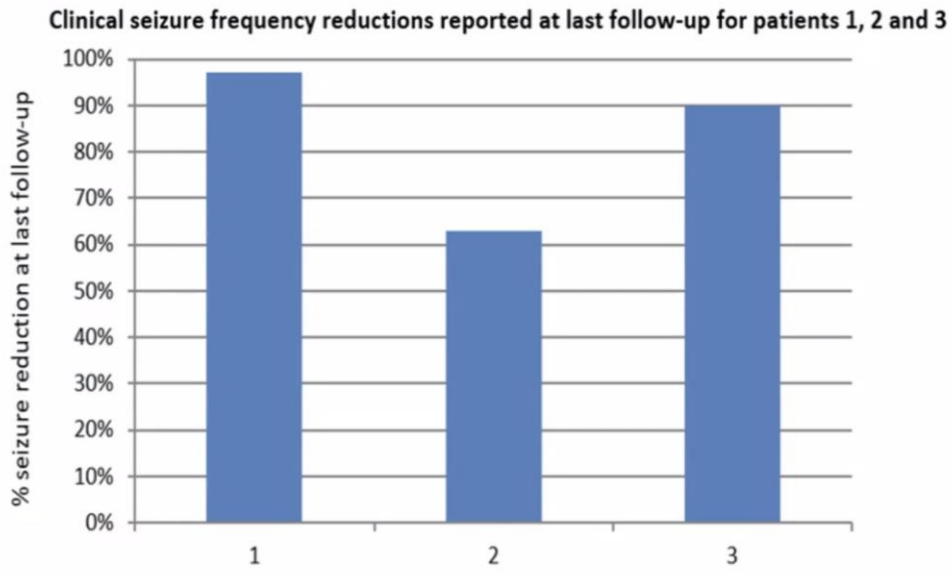
- Prospective, double-blind, randomized study of non-responsive CM-DBS in patients with Lennox-Gastaut Syndrome (LGS)
- 19 patients randomized to 3 months active or sham stimulation
- ≥ 50% reduction in patient reported seizures in 50% of stimulation group, compared to 22% of sham

PULVINAR

Read:

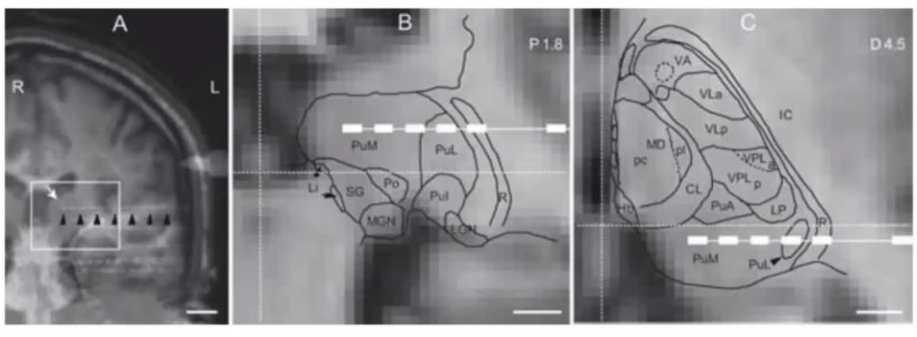
Brain-responsive corticothalamic stimulation in the pulvinar nucleus for the treatment of regional neocortical epilepsy: A case series

David Burdette[1] | Emily A. Mirro[2] | Michael Lawrence[1] | Sanjay E. Patra[1]

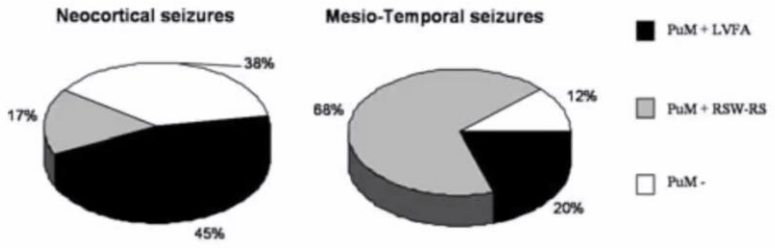


Pulvinar participates in temporal lobe seizure propagation

Involvement of Medial Pulvinar Thalamic Nucleus in Human Temporal Lobe Seizures
Rosenberg et al., *Epilepsia* 2006

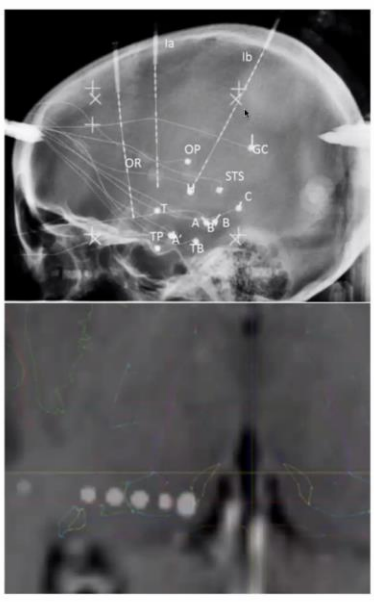


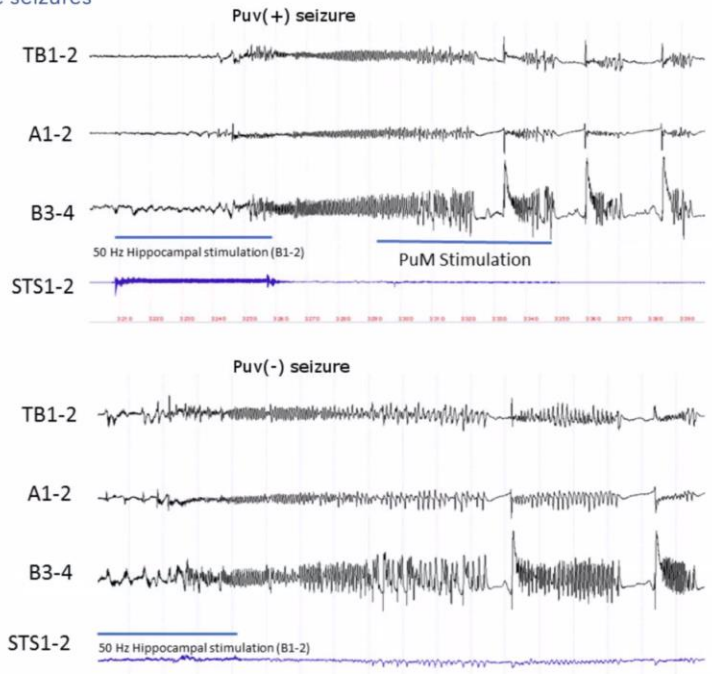
Pulvinar ictal activity was present in all seizures that spread mesial ←→ neocortical



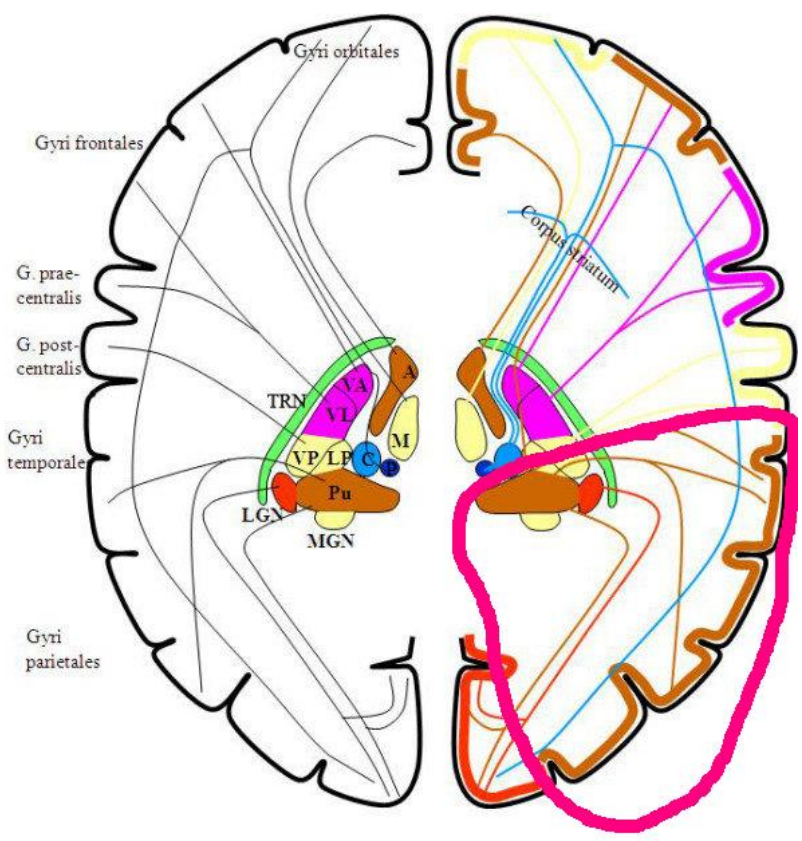
Pulvinar participates in temporal lobe seizure propagation

The effect of medial pulvinar stimulation on temporal lobe seizures
Filipescu et al., *Epilepsia* 2018





CONNECTIONS

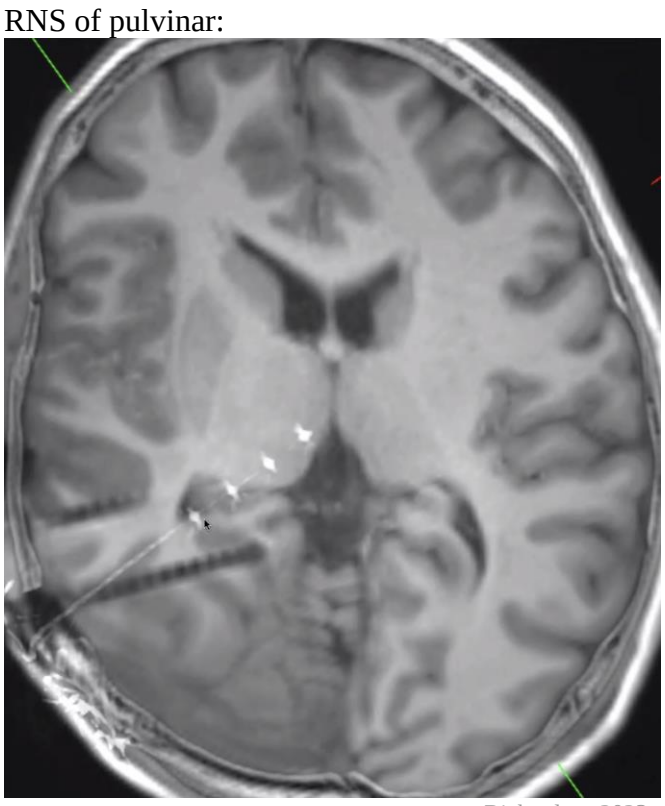


- pulvinar is the most posterior nucleus of the thalamus.
- evidence of pulvinar stimulation for:
    1. **Posterior quadrant epilepsy** - lateral pulvinar relates mainly to the visual system and dorsomedial to parietal regions (visual-processing parietal regions).
    2. **Mesial temporal epilepsy** (less than ANT) - medial pulvinar links to amygdala, hippocampus, temporal neocortex, cingulate and orbitofrontal cortex.
        - some studies have suggested that seizures arising from the lateral temporal lobe more rarely interact with PuM directly; rather, PuM may be involved in the propagation of seizures between mesial and lateral temporal cortices. vs. others have suggested that preferential pathways interconnect PuM with various cortices including the temporal neocortex, TP junction, and insulo-opercular region.

TARGETING

DIRECT

RNS of pulvinar:



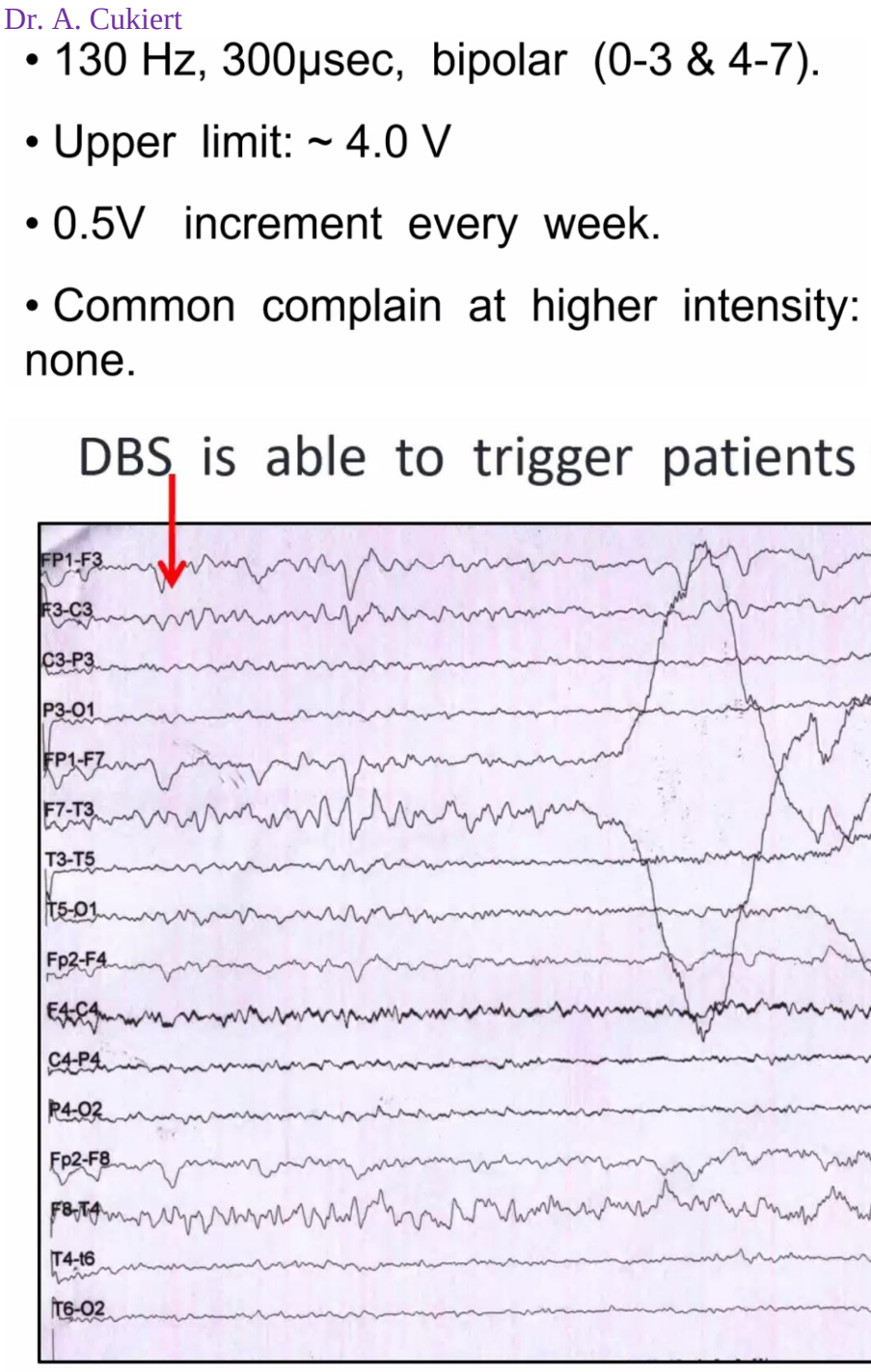
Richardson 2023

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



Outcomes

Study	n	Randomization	Stim Param	Seizure Outcome	Neuro-psych	Comment
Velasco et al Epilepsia '07	9	Immediate on vs 1 mo delay	130 Hz 450 us cyclic	100% RR 4/9 sz free	No decline	Absence of MS on MRI predicts success
Boon et al Epilepsia '07	10	no	130 Hz 450 us cont	70% RR 1/10 sz free (+MS)	No decline	Pts selected based on dec in spikes with stim
Telez-Zellento et al Neurol '06	4	Alternating 1 mo blocks over 6 mo	190 Hz 90 us cont	25% RR ¼ sz free	No decline	Design of randomiz not optimal

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, 6 patients achieved ≥ 90% seizure reduction, 3 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

Author	N	Localization of epilepsy	Outcome
Benabid/Chabardes *2002*	3	sensory motor cortex	67-87%
	2		< 50%
	1		0
Shon (Seoul) *Stereotact Funct Neurosurg 2005;83:84–90*	2	FLE s/p failed resection	87-89%
Handforth (UCLA) *Epilepsia 47(7):1239–1241, 2006*	1	Bitemporal epilepsy	50%
	1	Frontal encephalomalacia	33%
Neme (Santiago)	1		> 50%
	3		< 50%

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

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this LINK