DBS in Epilepsy

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

ANTERIOR NUCLEI OF THALAMUS (ANT)

Fisher RS et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010 May; 51(5):899-908

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

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

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

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

ANATOMY

Part of **Papez circuit**

- isolated from the rest of thalamus by internal laminae.
- subnuclei (all have distinct patterns of connectivity): anterodorsal, anteroventral, and anteromedial.
- projects to superior frontal and temporal lobe structures commonly involved in seizures.
- inputs from the subiculum, the mammillary bodies via the mammillothalamic tract, and the retrosplenial cortex.

INDICATIONS

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

Available in Europe since 2011.

FDA APPROVAL

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

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

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

TARGET

Nucleus (antero)principalis

AC-PC coordinates (golden coordinates in parentheses):
10-16 (12) mm superior
0-5 (2) mm anterior to MCP
4-7 (5) mm lateral
N.B. individual variations up to 5 mm (even between sides) – need direct targeting!

- best stim contacts – 2-3 mm above where mammillothalamic tract terminates.
- 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***.

IMAGING

3T MRI: STIR or FGATIR

TRAJECTORIES

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

TRANSVENTRICULAR FRONTAL

- watch for thalamostriate vein (between caudate and ANT).
- sometimes choroid plexus is on top of ANT (but it is a mobile structure so hemorrhage is rare – Dr. Lehtimäki goes through it).

LATERAL EXTRAVENTRICULAR

POSTERIOR INFERIOR PARIETAL

Van Gompel et al.: First, electrodes were placed along a posterior inferior parietal route, to avoid intraventricular hemorrhage and lead misplacement associated with transventricular and lateral transcortical approaches. Second, they used recordings from concomitantly placed hippocampal electrodes to verify accurate lead placement.

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.

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).

EXTENSIONS

- allow 15% length stretch.

COMPLICATIONS, SIDE EFFECTS

1. **Exacerbating seizures / inducing new seizures**.

- review of 2101 electrode placements across 16 reports revealed an incidence of new onset seizures in up to 13% of patients.12 At least 74% of seizures occurred around the time of electrode placement, with many patients experiencing intracranial hemorrhage. In this analysis, the authors estimated that DBS is associated with a < 2.4% (95% CI 1.7%–3.3%) risk of seizures and that the postprocedural risk of seizures from chronic DBS was approximately 0.5% (95% CI 0.02%–1.0%).
- separate report examined 161 patients who had 288 leads placed. Among these patients, 4.3% experienced seizures. The vast majority (86%) of seizures occurred within 48 hours after lead implantation.

2. **Psychiatric** side effects

- changing stim contacts may help

3. **Sleep** disruptions

PROGRAMMING

Starting parameters (3 weeks postop):
Amplitude 5 V
Pulse width 90 msec
Rate 145 Hz (this is invariable)
Duty cycle: 1 min on, 5 mins off.
Unipolar

- seizures may occur at initiation of stimulation.

Further adjustments (begin > 3 mos postop):

- keep symmetrical between sides.

Differences from DBS for movement disorders

1) intermittent (vs. continuous) stimulation
2) contact is programmed to be a cathode (negatively charged electrode) and case as anode – to cause depolarization block

OUTCOMES, SANTE TRIAL

- prior VNS or epilepsy surgery do not affect DBS results.

Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial (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

- prospective, randomized, double-blind pivotal study.

- 110 patients who were implanted with a Medtronic DBS system at 17 centers located in the U.S.
- patients with ≥ 50% reduction in seizures:
  3 months 40.4% vs. 14.5% in placebo
  13 months 43% (n=99)
  25 months 54% (n=81)
  37 months 67% (n=42)
  7 years 75% (18% experienced at least one 6-month seizure-free period, 7% were seizure-free for the preceding 2 years)
- statistically significant reduction in seizure frequency only in temporal epilepsies - 44.2%, (vs. controls - 21.8%)
- 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.
- side effects:
  1. Depression 14.8% (vs 1.8% in controls)
  2. Memory impairment 13% (vs 1.8% in controls); all resolved with no group differences in 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.

Medtronic Registry for Epilepsy (MORE) >>
- Product Surveillance Registry.

CENTROMEDIAN NUCLEUS OF THALAMUS (CMT)

- CMT, together with the parafascicular nuclei, form the posterior group of the intralaminar nuclei of the thalamus. The motor cortex provides input to the CMT, as do the globus pallidus interna (GPi). The 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.
- majority of available data support the use of CMT DBS for the treatment of generalized epilepsy, including patients suffering from Lennox-Gastaut syndrome.
- current data is only from level III-IV studies.
- placed under general anesthesia with recruiting response
- response rates from 0% (Andrade et al. Neurology 2006;66:1571–1573) to 100% (Cuikert et al. Seizure 18 (2009) 588–592)
  - the largest series, published by Son et al. in 2016 reported a 79% response rate (11 of 14 patients), with a mean seizure frequency reduction of 68%; they did not find any correlation between lead positioning and the magnitude of seizure reduction on regression analysis.
- 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**	**Cuikert et al**	**Andrade et al**
N	13	4 pts s/p CC	2
Pathology	LGS	IGE 2 LGS 2	SGE 1 Multifocal 1
Targeting	Recruiting response	Recruiting response	
Stim parameters	130 Hz, **450 µs**, 2-3 v	130 Hz, **300µs,** 2v	100-185 Hz, **90-120 µs**, 1-10v
Outcome	Sz free 2 87-95% 6 50-80% 3 <50% 1	100 % RR Av 78%	Initially worsened, no clear diff in on and off
Neuropsych outcome	Improvement related to Sz Outcome	Improved alertness (SNAP IV)	N/A
Comments	Anterolateral nucleus in parvocellular best response	Improvement in alertness at 0.5v and sz control at 1.5 v	

HIPPOCAMPUS

- patients selected from population undergoing invasive electrodes: diagnostic electrodes replaced with stimulation electrodes at site of seizure focus.
- 60-100% response rates (some become seizure free).
- causes no change in neuropsychological tests.

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. reported on 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.

Importantly, the authors found that 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, and 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