Neurostimulation in Epilepsy (DBS+Vagus)

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성균관의대

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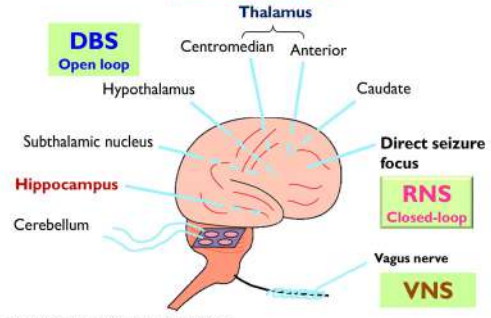
Background for neurostimulation Tx for DRE

- **Not all DRE patients** can be **candidates** for resective surgery
  - Ictal foci – not localized, bilateral or multifocal
  - Seizures may originate from functionally eloquent areas (ex. Motor cortex or language area) → result in **irreversible neurological deficit**
- Unavoidable **loss of normally functioning brain tissues** by surgical resection
- Inevitable **perioperative surgical risks**: ex. bleeding, infection, pain ....

→ Need for less invasive & much simpler methods

Neurostimulation (palliative) therapy
- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS)
- *Responsive neurostimulation (RNS)*

Electrical Brain Stimulation
Invasive Methods



Theodore WH and Fisher RS, Lancet Neurol 2004;3:111-8.

보험급여 기준

- 두개강내 신경자극기 설치술 (DBS)의 보험급여 인정기준
  나. 뇌전증
  – 2년 이상 항경련제 치료에 불응하는 난치성 뇌전증으로 기존의 수술적 치료가 불가능하거나 실패한 경우
- 미주신경자극기 설치술 (VNS)의 보험급여 인정기준
  – 2년 이상 항경련제 치료에 불응하는 난치성 부분발작 간질
  – Lennox-Gastaut syndrome으로 수술적 치료가 불가능하거나 실패한 경우에 인정함.

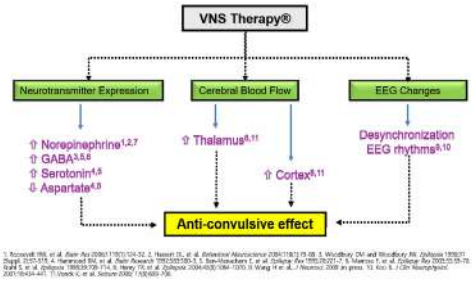
※주: 작용기전이 서로 다른 2가지 이상의 약물을 2년 이상 사용하여도 발작 조절이 힘든 경우

Vagus Nerve Stimulation (VNS) for intractable Epilepsy

Vagus Nerve Stimulation (VNS)

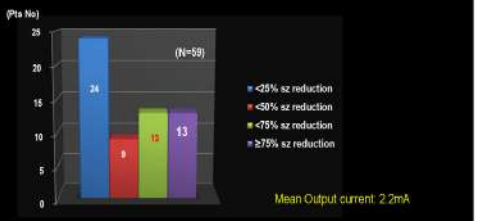
- Intermittent programmed electrical stimulation of left vagus nerve that sends signals to the brain
- Option of magnet activated stimulation
- Adverse effects local, related to stimulation of vagus nerve (hoarseness, throat discomfort, dyspnea)
- Mechanism of action - unknown
- Early clinical trials show that **35%** of patients have a 50% reduction in seizure frequency and 20% experience a 75% reduction after 18 months of therapy.
- May improve mood and allow AEDs reduction
- FDA approved for refractory partial onset seizures(1997) and refractory depression(2005)
- Available in Korea since 2010

VNS: Mechanisms of action



Long-term efficacy & tolerability in SMC data

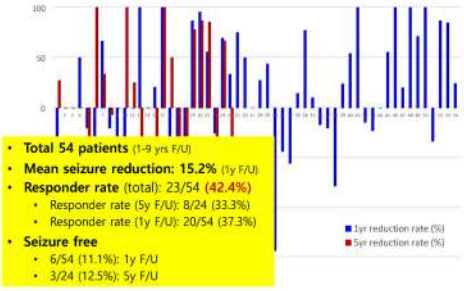
2013 ANA presented



- Mean seizure frequency was decreased (28.9→ 16.0/mo, $p < 0.001$)
- Overall responder rate was **44.1%** (26/59)
- Seven pts (**11.9%**) became **seizure free** after VNS stimulation

Recent long-term data of VNS in adult PWE in SMC

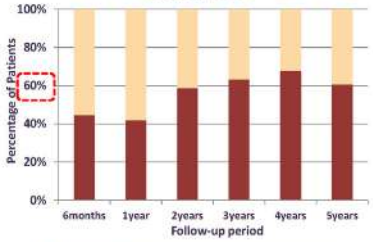
2011 ~ 2019



- **Total 54 patients** (1-9 yrs F/U)
- **Mean seizure reduction: 15.2%** (1y F/U)
- **Responder rate** (total): 23/54 **(42.4%)**
  - Responder rate (5y F/U): 8/24 (33.3%)
  - Responder rate (1y F/U): 20/54 (37.3%)
- **Seizure free**
  - 6/54 (11.1%): 1y F/U
  - 3/24 (12.5%): 5y F/U

Evolving pattern of seizure frequency reduction during the follow-up period (N = 38) (childhood & adolscents)

Presented at KEC 2017

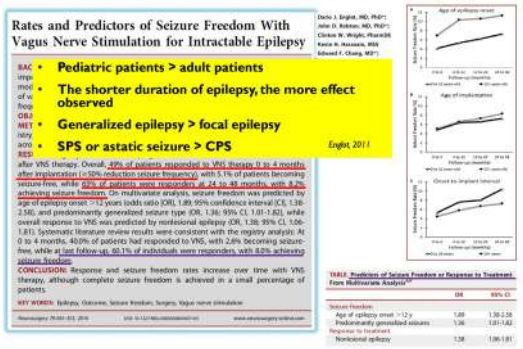


Non-responder : seizure frequency reduction < 50%

Responder : seizure frequency reduction ≥ 50%

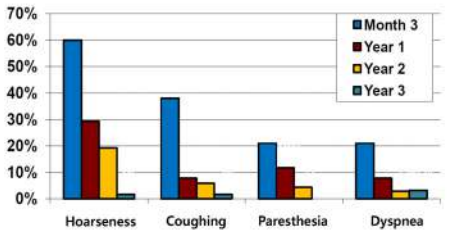
Asan Medical Center Children's Hospital

Meta-analysis of long-term VNS prognosis



Side effects from VNS

Morris, 1999



Most side effects occur only during stimulation, and usually decrease over time

Unmet issues in VNS

- What causes the difference between treatment effects in children and adults?
- What's the optimal stimulation modality in the individual patient? VNS vs. DBS
- What's the optimal stimulation parameter?
  - Frequency / pulse width / intensity
  - On/off duration

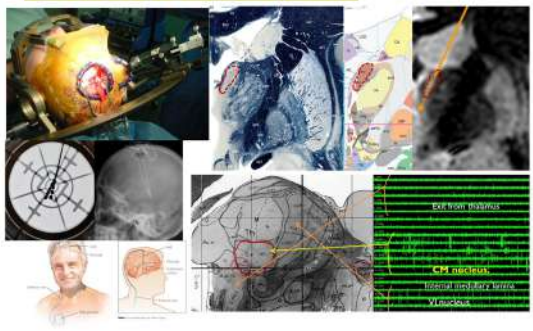
Table 1: Specifications and Product Information

Stimulation Parameters	Available Parameter Settings
Output current	0-6.0 mA in 0.25-mA steps ±0.25 (1 mA, ±10%, ±1 mA
Signal frequency	1, 2, 5, 10, 20, 30, 50 Hz ±5%
Pulse width	130, 250, 500, 750, 1000 μsec ±10%
Signal ON time	7, 14, 21, 30, 60 sec, ±10% or +7 sec, whichever is greater (–10% or –7 sec in Magnet Mode)
Signal OFF time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min, and 5 to 180 min (5 to 60 in 5-min steps, 90 to 180 in 30-min steps) +0.1 / -0.4 sec or +1%, whichever is greater
Magnet activation	Provided by Magnet application (output current, pulse width, and signal ON time may be independently programmed for this purpose)
Reset parameters	Settings are unchanged. An output is disabled (0.0mA).

국내 VNS 시술 총 건수

Year	New	Reimplant	Total
1999	18	0	18
2000	2	0	2
2001	5	0	5
2002	8	0	8
2003	8	0	8
2004	13	0	13
2005	88	1	89
2006	58	0	58
2007	37	0	37
2008	29	1	30
2009	35	1	36
2010	23	0	23
2011	30	0	30
2012	29	5	34
2013	50	14	64
2014	58	11	69
2015	90	14	104
2016	76	6	82
2017	73	15	88
2018	127	11	138
2019	68	7	75
	923	86	1009

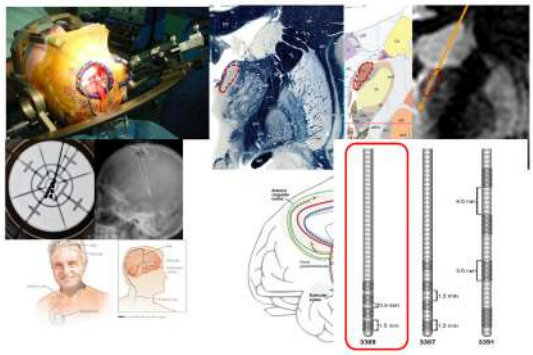
DBS (Deep Brain Stimulation)



DBS on anterior thalamic nucleus (ATN) for Intractable Epilepsy

손1

DBS on ant. Thalamic nucleus (ATN DBS)



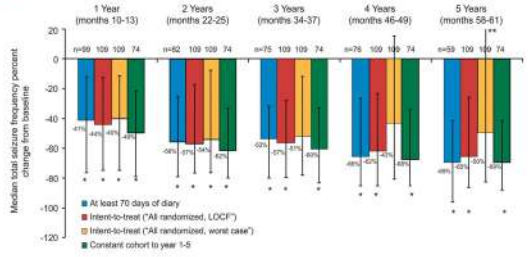
SANTE trial (*the 1st DBRCT*)

Results during Double-Blind Phase

Fisher, 2010

Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy

Neurology® 2015;84:1-9



Lessions from SANTE trial (ATN DBS)

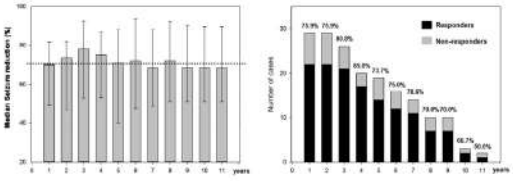
- Median sz reduction in **TLE:** significantly better than that of neocortical epilepsy
- **Complex partial seizure, severe (disabling) seizure: most effective**
- **Recently, ATN DBS was approved by FDA.** (May, 2018)

Seizures from Fronto-Temporal Origin (e.g. bilateral hippocampal sclerosis), not suitable for resective surgery → *Good Candidate for ATN DBS*

Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience

Seong Hoon Kim[a,1], Sung Chul Lim[a,c,1], Jiyeon Kim[b], Byung-Chul Son[c], Kyung Jin Lee[c], Young-Min Shon[d,e]

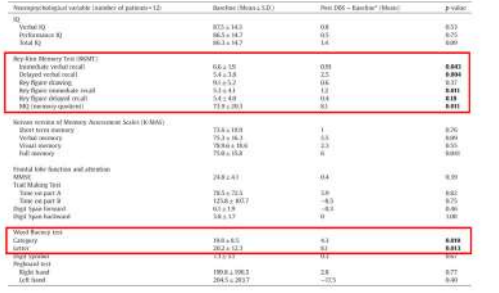
- 11-year median seizure reduction was 70%: 13.8% seizure-free for at least 1 year.
- Temporal onset (9), frontal onset (8), & multifocal or generalized onset (12 pts).
- No difference of clinical outcome among their epilepsy syndromes



Results from CMC data: 2005 ~ 2016

Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience

Seong Hoon Kim[a,1], Sung Chul Lim[a,1], Jiyeon Kim[b], Byung-Chul Son[c], Kyung Jin Lee[c], Young-Min Shon[d,e]



Interim Results at SMC (*since 2016. 04*) : *ATN DBS*

- 31 cases (**28** cases; F/U > 1 yr)
  - Dx: B TLE 12 / F-TLE 9 / MFE 11
  - Responder rate (>50% sz reduction): 18 /27 **(66.7%)**
  - Sz free for more than 1 year: 2 patients **(7.4%)**
  - Median sz reduction: **66.7%** (at least >3M F/U only, the last 3 Mon)
  - Complication:
    - Wound infection: 1 (3.2%)
    - Lack of efficacy: 2 (6.4%)
    - Removal of devices: 3 (9.6%)
    - Minor complaints:
      - Chronic pain 3
      - depression 2 (transient),
      - psychosis 2 (improved by antipsychotic medication)

The effects ATN stimulation in epileptic brain

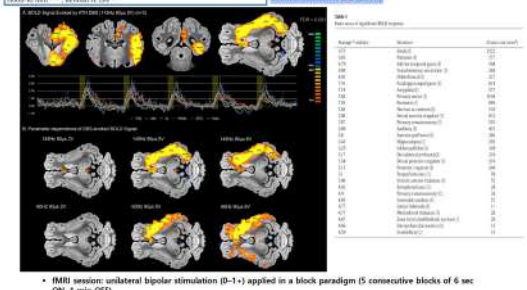
: How does it work? Still unknown, but some hypotheses

1. Changes in neuronal excitability
2. **Alteration of network architecture** (McIntyre, 2010)
3. **Increase of neurotransmitter or substance release**
4. Changes in Neurogenesis

Clues from fMRI studies

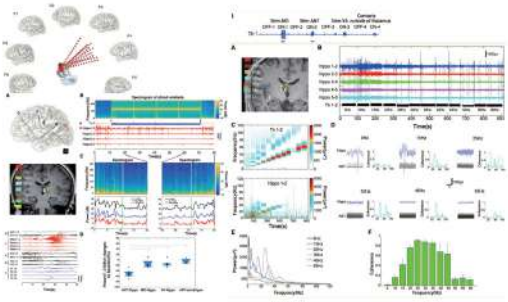
Anterior Thalamic Deep Brain Stimulation: Functional Activation Patterns in a Large Animal Model

Brain Stimulation ■■ (2016)



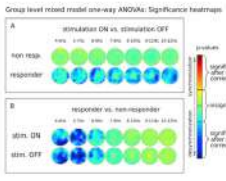
- fMRI session: unilateral bipolar stimulation (0–1+) applied in a block paradigm (5 consecutive blocks of 6 sec ON, 1 min OFF)
- ATN DBS resulted in activation within temporal, prefrontal, and sensorimotor cortex. An amplitude dependent increase in cluster volume was observed at 60 Hz and 145 Hz stimulation

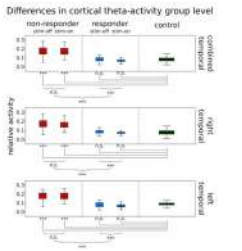
High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans



Desynchronization of temporal lobe theta-band activity during effective anterior thalamus deep brain stimulation in epilepsy

Neuroimage 218 (2020) 116967





- Significant main effects of stimulation-condition were found for the responder sub-group only & present in both the theta and alpha frequency bands
- Both ON & off, the main effect was localized to the theta-frequency band.

- Group level differences in temporal theta activity between non-responders, responders, and healthy control subjects
  - significantly greater levels of theta-band activity in non-responders (during stimulation ON and OFF) compared to both responders and healthy controls

Desynchronization of temporal lobe theta-band activity during effective anterior thalamus deep brain stimulation in epilepsy

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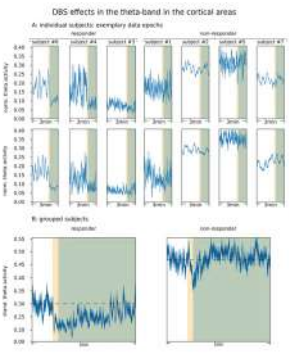
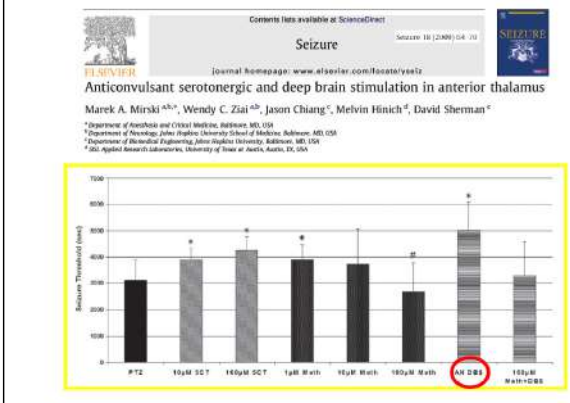


- **Time-domain analysis of theta desynchronization effects**
  - Non-responders did not show a sustained ANT-DBS related reduction in cortical theta-activity.
  - Responders had an overall lower level of theta activity.
  - → *Those with TLE may be preferred candidates for ANT-DBS procedures*
  - Theta desynchronization may be a potential predictor of therapeutic responsiveness.
    - Reducing burden or resources during long-term F/U for measuring their outcome after ATN DBS



Contents lists available at ScienceDirect

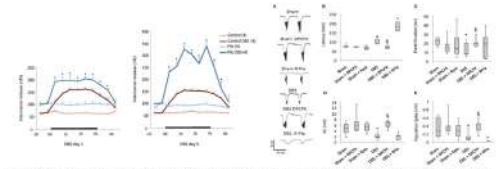
Seizure

journal homepage: www.elsevier.com/locate/yseiz

Anticonvulsant serotonergic and deep brain stimulation in anterior thalamus

Marek A. Mirski [a,b,*], Wendy C. Ziai [a,b], Jason Chiang [c], Melvin Hinich [d], David Sherman [e]

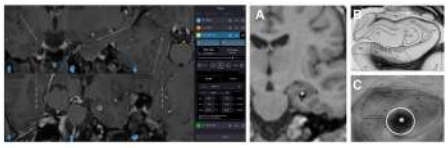
Role of adenosine in the antiepileptic effects of deep brain stimulation



- Hypothesis: ATN DBS increased ATP release & induced accumulation in adenosine (ADO) (Boison, 2008)
- ATN DBS significantly increased **Hippocampal ADO release**
  - By microdialysis, 5th day ADO release was found to be remarkably increased at Pilo + DBS session (more than that of 1st D)
- Hippocampal ADO release after ATN DBS may activate A1 receptor
  - (1) Hippocampal excitability↓ observed after ATN DBS & was reversed in slices given A1 antagonists (DPCPX)
  - (2) A1agonists (R-Pia) to animals receiving DBS potentiated the antiepileptic effects of stimulation.

→ **An evidence of the antiepileptic effects of DBS may be mediated by ADO.**

Hippocampal DBS for Intractable Epilepsy

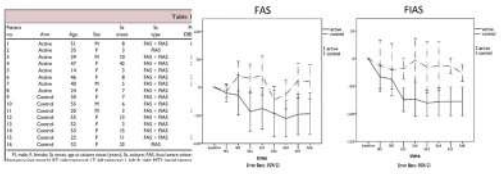


Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study

*†Arthur Cukiert, †Cristine Mella Cukiert, ‡Jose Augusto Burattini, §Pedro Paulo Mariani, and *Daniela Fontes Bezerra

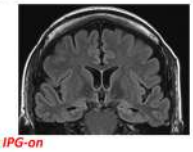
Epilepsia. 2017

- Stimulation: 2V, 130Hz, 300 us / cathode – anterior two, anode – far posterior one, electrode 3391)
- Hip-DBS was effective in reducing FAS and FIAS frequency in patients with refractory TLE (**87% sz reduction** after 6M)
- There was no short-term major morbidity or mortality



Hippocampal DBS cases in Korea

- **1st Case:** 52/F, sz onset: 36 Y.O.
- Sz Type
  1) dialeptic sz only or 2) dialeptic + automotor sz (2-3 /wk)
  3) rare GTCs (< 1/yr)
- Brain MRI: definite B HS
- Associated memory impairment/depression



HP-DBS (2015.12.28) → Sz free for 60days *without IPG-on*

→ Turn on IPG postop. 3M & sz disappeared again

- **Long-term outcome**
  - **Sz frequency during last 6M : 0.5 /month (95% sz reduction)**
  - **Improved mood & resumption of social activities** (that have not been possible)
  - **Last visit (2020.09):** R 1.8V/L 1.5V, 300usec, 130Hz (0/-1/-2 on), continuous
- **Subsequent 2 cases** (F/U > 1yr)
  - Male 50yo/ female 29yo: **75% sz reduction, respectively**
  - **No disabling seizures detected**

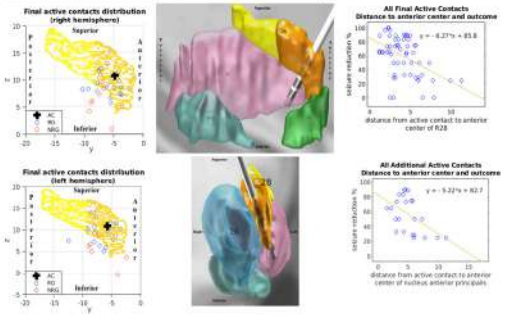
Unresolved queries

- **Are there clinical or anatomical biomarkers for predicting the outcome of DBS therapy?**
- **What can we target more accurately? What is the best method for targeting?**
- **What is the optimal therapeutic parameters**
  - High frequency vs. low frequency
  - Continuous stimulation vs. cyclic stimulation
- **For whom does it work?**
  - Focal vs. Generalized epilepsy
  - Temporal vs. Frontal or posterior epilepsy
- **When can we detect the optimal therapeutic effect after DBS?**

Defining the optimal target for anterior thalamic deep brain stimulation in patients with drug-refractory epilepsy

Wendy Guo,† Bang-Bon Koo, PhD,‡ Jae-Hun Kim, PhD,‡ Rafeeque A. Bhadelia, MD,§ Doe-Won Seo, MD, Seung Bong Hong, MD,* Eun Yeon Joo, MD,* Seunghoon Lee, MD,† Jung-Il Lee, MD,† Kyung Rae Cho, MD,† and Young-Min Shon, MD*†

J Neurosurg. 2020



Factors ensuring successful DBS for DRE in the future

Optimization of patient-specific therapy

- Tx intervention should be correlated with **patient-specific EEG pattern**
- Need to **find better biomarkers of ictogenesis** & epileptogenesis

Treating large & chronic electrophysiological data

- Make a **centralized** and **long-term storage** solution for the deposit & management of **large physiologic signal database**
- Use powerful **machine learning** tools designed for processing **huge raw EEG data (big data**; e.g. 'Neural dust')

Delivering innovative, less invasive electronics

- **Smaller, soft & safe materials should be preferred.**
- **Conventional electrodes - more rigid with a large mismatch in bending stiffness & resulting in relative sheer motion, glial scarring and neuron depletion at the probe & aggravation of immune response to a foreign body**


Take home message
Future of therapy in drug-refractory epilepsy
• More precise, evidence-based methods are mandatory
• VNS & DBS: promising tool for treat DRE
– Closed-loop system will overcome the position of open loop system in medical market soon.
• Need for robust & accurate sz detection & prediction devices
– Self reporting by patients: usually incorrect
– Innovative devices & algorithms will be introduced & translated into clinical use with enormous speed globally