Neuromodulation: Current Trends in Interfering with Epileptic Seizure

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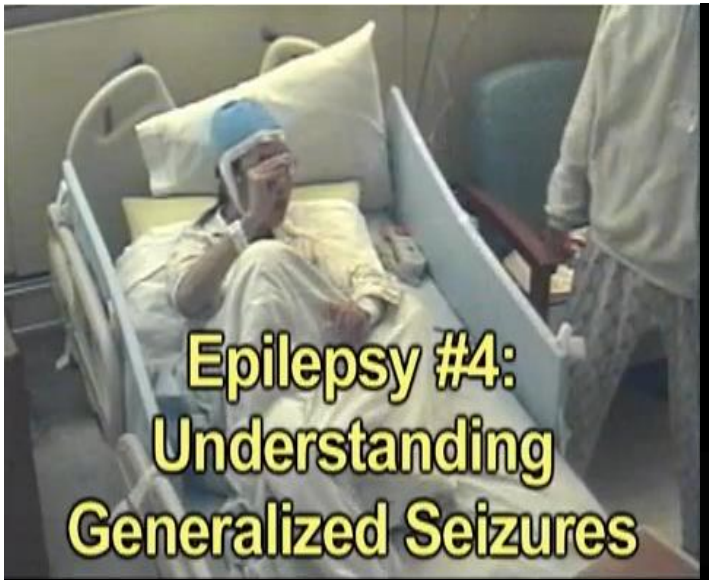
Understand Epilepsy(뇌전증;간질)

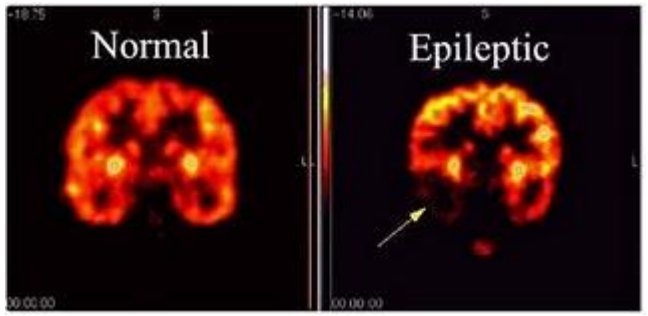
- Seizure - a medical condition in which too many brain cells become excited at the same time
- Epilepsy - the condition of having spontaneously recurrent seizures



Epilepsy (뇌전증;간질)

- 50 million people worldwide
  – Mostly in developing countries
  – More likely in young age, or over 65

- Usually controlled, but cannot be cured with medication
  – Surgery may be considered in difficult cases.



http://jessicaksmith.blogspot.com/2010/07/45000-sudden-unexplained-deaths-in.html

The cause of Epilepsy

- **Two groups : Brain injuries and chemical imbalances in the brain**
- **Brain injuries** : Anything that injures the brain can lead to seizures, but in over half the cases no cause can be identified.
  - The type of injury : age-dependent.

  → In children : birth traumas, infections like meningitis, congenital abnormalities, or high fevers

  → In the middle years : head injuries, infections, alcohol, stimulant drugs, or medication side effects

  → In the elderly : brain tumors and strokes

- **Chemical imbalances** : Drugs like alcohol, cocaine,

  low blood sugar, low oxygen, low blood sodium, or low blood calcium, Kidney failure, liver failure, or other conditions.

Control method

- 70% of patient : antiepileptic mediation
- 30% of patient : surgical intervention

- Control of epileptic seizures

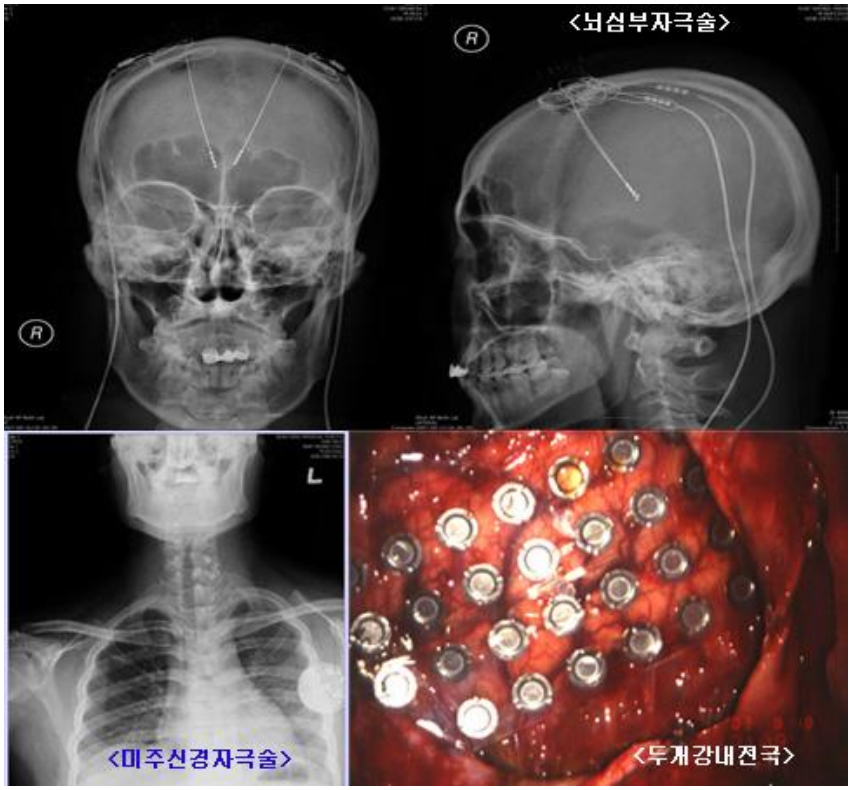
→ Neuromodulation: the use of chronic stimulation of the brain

→ In 1970, 1st implantable stimulating systems:

used cerebellar stimulation to control different varieties of epileptic seizure

Stimulation for Epilepsy

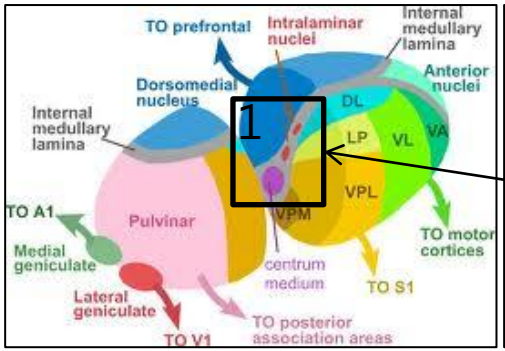
Vagal afferent nerve stimulation(VNS)

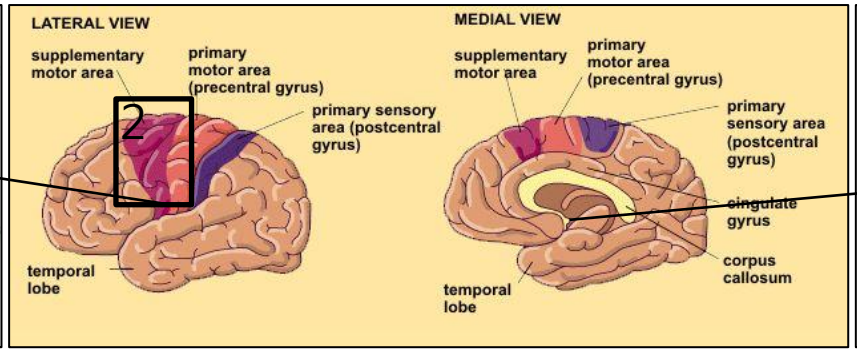


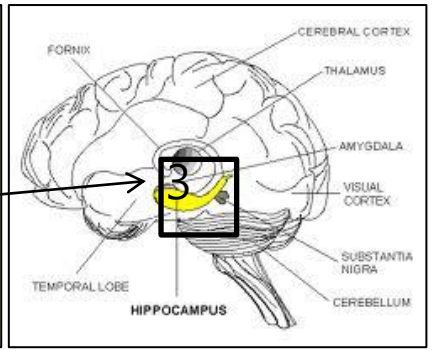
http://well.knn.co.kr/03_health/health_view.asp?seq=239

Three deep brain stimulation

	Stimulation position	Type of epileptic seizure
1	The centromedian nucleus of the thalamus (→ ESCM)	Intractable generalized seizures and atypical absences of the Lennox-Gastaut syndrome
2	The hippocampus (→ ESHC)	Mesial temporal lobe seizures
3	The supplementary motor area (→ SMA)	Motor seizures initiated in this zone (unpublished data)







Electrical Stimulation of the Centromedian Thalamic Nuclei (ESCM) (1 of 5)

- Used in cases of difficult to control seizures with multifocal onset in the frontal and temporal lobes

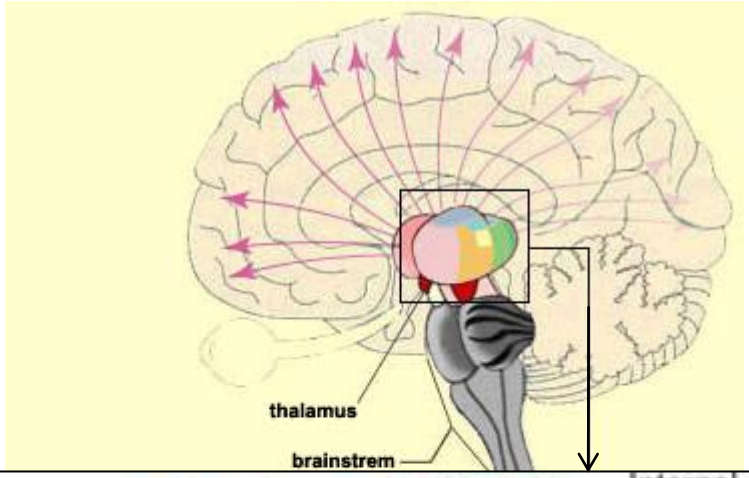
  ex. Best result - Lennox-Gastaut syndrome,

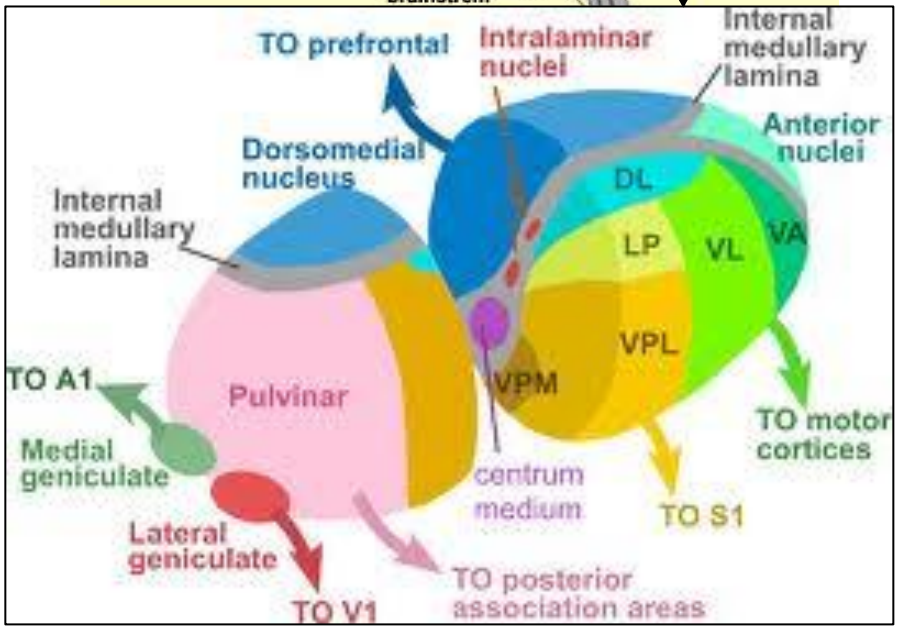
  Secondary tonic clonic generalization

  (not focal origins as in temporal lobe seizures)

Electrical Stimulation of the Centromedian Thalamic Nuclei (ESCM) (2 of 5)

- The role of midline and intralaminar thalamic nuclei in the genesis and propagation of epileptic attack
- From 1963, thalamorcortical interactions are essential in the development of them





http://www.edoctoronline.com/medical-atlas.asp?c=4&id=21820&m=1&p=1&cid=1055&s=

Electrical Stimulation of the Centromedian Thalamic Nuclei (ESCM) (3 of 5)

- Stimulate the Centromedian thalamus (CM) : interfere with the thalamocortical interactions and thus stop either the genesis or propagation of the seizures
- The cause of Target: relatively large size, close relationship to the conventional stereotaxic(입체정위) landmarks

Electrical Stimulation of the Centromedian Thalamic Nuclei (ESCM) (4 of 5)

- CM : the cause of stereotaxic landmarks

  → an intralaminar nucleus: the nonspecific reticular-thalamo-cortical system that transmits and integrates the cerebral inputs of the generalized seizures

Electrical Stimulation of the Centromedian Thalamic Nuclei (ESCM) (5 of 5)

- Procedure of ESCM

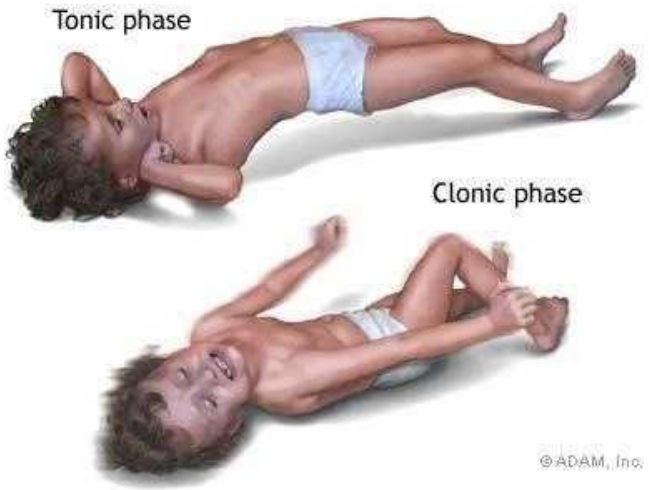
  1. Selection of responding patients
  2. Verifying correct DBS implantation based on definition of CM optimal area
  3. Performing periodic monitoring of the reliability of ESCM on a long term follow up

Procedure of ESCM
1. Patient selection

- Analyze 13 patients with Lennox Gastaut Syndrome(LGS)
- LGS → severest forms of childhood epilepsy, 90% of patients: mentally retareded, 80% of patients: continue through adulthood
- Selected patients – secondary LGS with stable/nonprogressive diseases, primary LGS with no demonstrable lesion in the MRI

Lennox-Gastaut syndrome

http://professionals.epilepsy.com/wi/print_section.php?section=devdis_lgsynd



- The variety of fit types that occur, often starting with drop attacks
- An EEG showing diffuse slow spike waves (<2.5 cps)
- Burst of rapid (10Hz) during slow sleep
- Mental deterioration
- peak onset : 1~7 years of age

Characteristics of LGS

1) drug-resistant generalized seizures
2) the tonic and atonic seizures (경직/무긴장 발작)
3) atypical absences
4) myoclonic attacks(간대성 근경련)
5) episodes of nonconvulsive and tonic *status epilepticus*(간질지속상태)

Procedure of ESCM
2. Correct targeting

- CM – Large nulceus with several subdivisions
- For the optimal result with ESCM
- With adequate target localization

→ Streotaxic (defined ventriculography and MRI)

→ Neurophysiologic Definition

Procedure of ESCM
2.1. Streotaxic

- Defined ventriculographic & MRI confirmation of the CM target
- Ventriculogrphic - placed in both CM nuclei through a coronal incision and bifortal burr holes
- MRI – confirm electrode position

Procedure of ESCM
2.1. Streotaxic

- CM localization by air ventriculography
- The anterior(AC) & The posterior(PC) & ventricle with remarkable precision
- Two lines – the AC-PC line & ventricle line perpendicular to the PC
- Electrodes – fixed to burr holes
- Using a plastic ring and silastic ring caps
- Position along the trajectory of the electrode plotted on sagittal(시상봉합의, 화살모양의) and frontal sections

Procedure of ESCM
2.1. Streotaxic

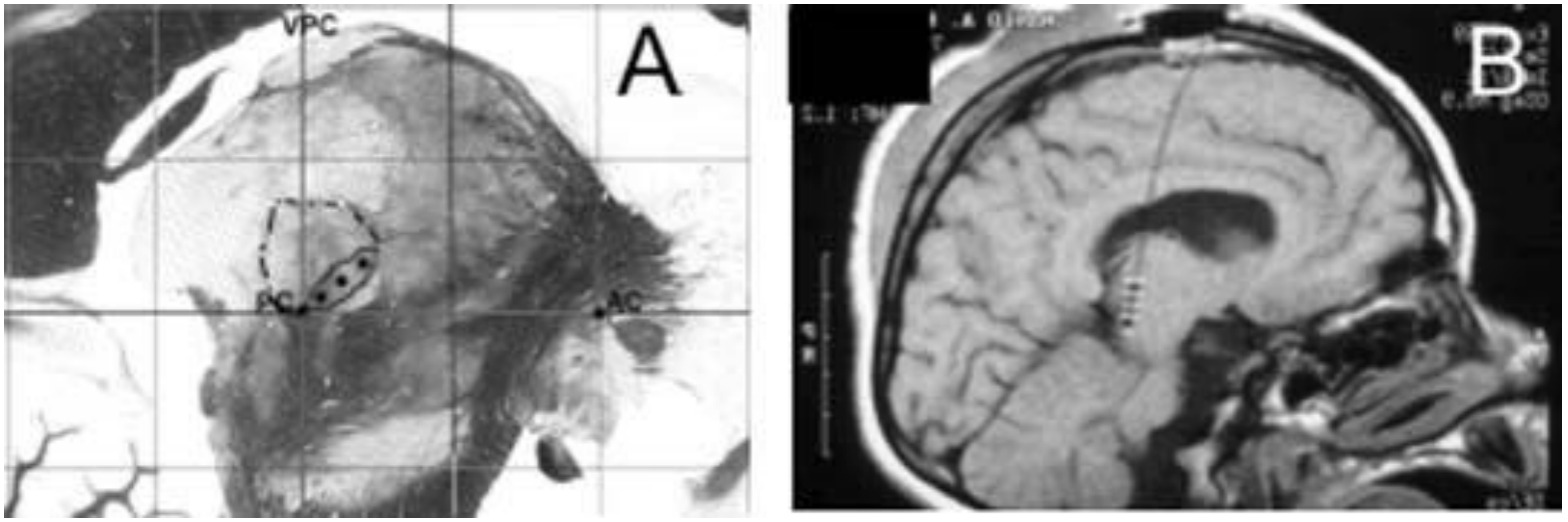


FIG. 1. Stereotaxic placing of the centromedian (CM) electrodes.
A: Stereotaxic diagrammodified from Schaltenbrand and Bailey showing the optimal stereotaxic target. CM localization is accomplished by air ventriculography. This method demonstrates anterior (AC) and posterior (PC) commissures of the third ventricle. Two lines are drawn, the AC-PC line and the vertical line perpendicular to the PC (VPC). The target point for the electrode tip was a distance 10mmfrom midline and the intersection of the AC-PC line with the VPC. Cmdelineated by *discontinuous line, optimal target delineated by the continuous line.*
B: Sagittal MRI showing right CM electrode implanted in patient
KCMM12. The electrode has four contacts, two of which are chosen for ESCM.

Procedure of ESCM
2.1. Ventriculograpic Definition

- optimal targets – located in the basolateral(기저측면의) portion of the CM (parvocellular(소세포의) portion-maximal neuronal population)

Procedure of ESCM
2.2. Neurophysiologic definition

- Electrical incremental and desynchronzing – elicited by unilateral electrical stimulation (low/high frequency)
- Low-frequency(6/s) - elicit incremental response with typical waxing and waning profile
- High-frequency(60/s) – elicit desynchronzation; superimposed on a slow negative shift

Procedure of ESCM
3. periodic monitoring of the reliability of ESCM on a long term follow-up

- Useful for monitoring the efficiency of ESCM - Incremental responses, EEG desynchronization, and slow negative shift (not - electrical stimuli)
- Questionable reliability - patient's lack of subjective sensation, the long latency
- using 10 or 60/s and 6V transcutaneous (경피성의) activation of CM

Procedure of ESCM
4. Chronic Stimulation

- The parameter

- 2h of daily stimulation sessions
- 1-min trains of Lilly pulse (;*balanced biphasic*) with and interstimulus interval of 4 min, alternating right and left CM
- 130Hz frequency
- 450 *μs* in duration
- amplitude of 400-600*μ*A

Result of ESCM

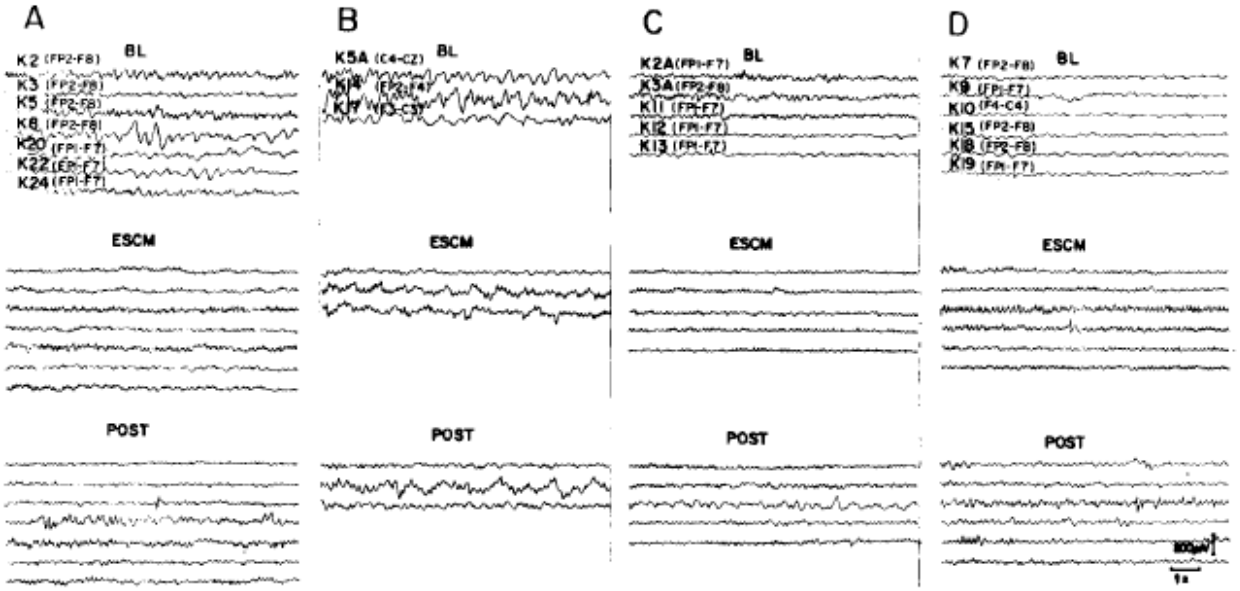


FIG. 2. Effect of electrical stimulation of the centromedian thalamic nuclei (ESCM) on background EEG activity (individual patients): 10-s samples of background EEG activity from three consecutive records obtained at the end of the baseline (BL), ESCM, and poststimulation (Post) periods in all patients of different groups: groups A (n = 7), B (n = 3), C (n = 5), and D (n = 6). Scalp regions where samples were obtained during BL period in different patients are indicated at top of each sample.

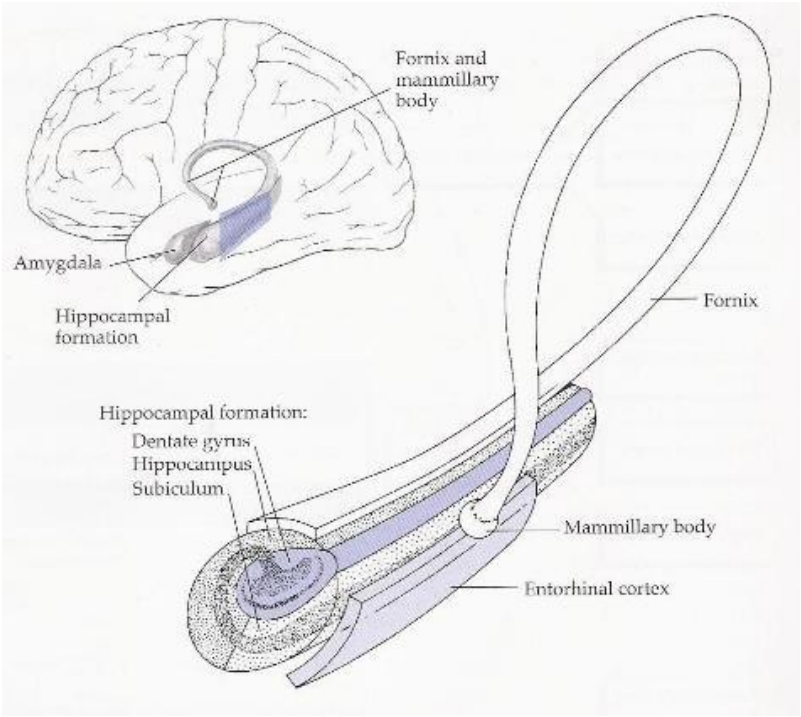
- all patients with excellent result (100% improvement)
  - generalized seizures
  - correct stereotaxic placement
  - electrophysiological responses

Velasco. et al , Effect of Chronic Electrical Stimulation of the Centromedian Thalamic Nuclei on Various Intractable Seizure Patterns: 11. Psychological Performance and Background EEG Activity *Epilepsia, Vol. 34, No. 6, 1993*

Electrical Stimulation of the Hippocampus (ESHC)

- Complex partial seizures arising from the hippocampus
- Low surgical possibility
  - bilateral hippocampal foci
  - epileptic focus located areas for speech and memory

→ Neuromodulation



http://ahsmail.uwaterloo.ca/~amarlin/neuroanatomy.html

Electrical Stimulation of the Hippocampus (ESHC)

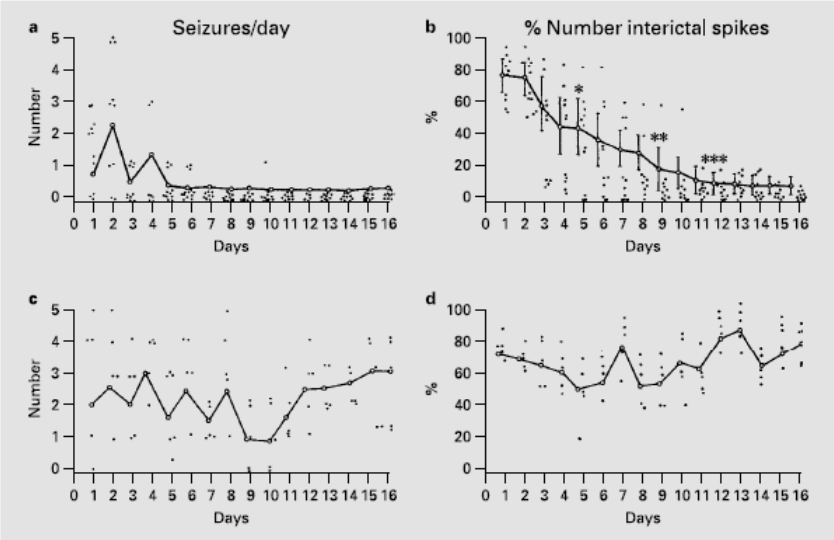
- ESCM → not for complex partial seizures originating in the temporal lobe
- ESHC → significant and long-lasting effect on seizures
- Subacute(아급성의;급성과만성의중간) hippocampal stimulation(SAHCS): preliminary study
- SAHCS – bipolar, between continuous electrode contacts, and continuous stimulation with biphasic Lilly pulses, 130Hz frequency, 450 *μs* in duration, amplitude of 200-400*μ*A, 2~3weeks' duration

Patients of SAHCS

- 10 Patients with nonlesional temporal lobe epilepsy in whom intracranial electrodes
  - 2 Patients: bilateral hippocampal depth electrodes
  - 8 patients: unilateral subdural electrode grids on the pial(; the delicate innermost layer of the meninges, the membranes surrounding the brain and spinal cord) surface of the basotemporal cortex
  - all patients: non antiepileptic drugs(AEDs) for 72hr prior to SAHCS
- SAHCS for a minimum of sixteen days

Results of SAHCS

- 7 of 10 patients: an evident antiepileptic response – abolished complex partial and secondary generalized tonic-clonic seizures
- 3 of 10 patients: not respond
- Abnormalities- depth of electrode penetration, lesion due the foreign body electrodes
- depend on a lesional process & a <u>functional blockage of the hippocampus</u>



Velasco, "Electrical Stimulation for Epilepsy: Stimulation of Hippocampal Foci" Stereotact Funct Neurosurg 2001;77:223–227

Electrical Stimulation of the Hippocampus (ESHC)- CHCS

- Chronic HippoCampal Stimulation(CHCS)

- produce a sustained antiepileptic effect without undesirable effects on language and memory

- consider 6 patients, follow-up 1~4 years

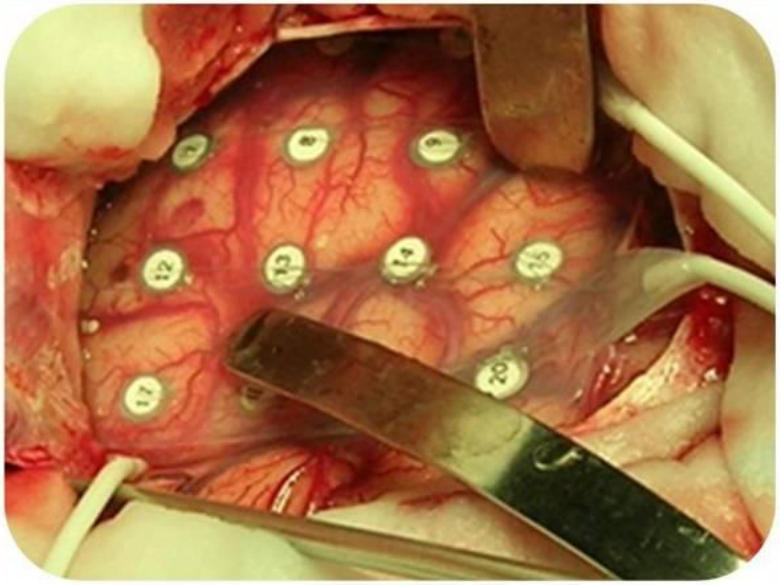
- bilateral hippocampal transitory 8 contact depth electrodes

- 2 patients: bilateral independent hippocampal foci

- 4 patients: hippocampal focus on dominant hemisphere with evidence of memory situated here

Chronic Stimulation (CHCS)

- The parameter
- 1-min trains of Lilly pulse with and interstimulus interval of 4 min
- bilateral electrode : same but alternate right and left hippocampus
- 130Hz frequency
- 450 *μs* in duration
- amplitude of 400-600*μ*A



http://www.ehow.co.uk/about_4696990_causes-temporal-lobe-epilepsy.html

The results of ESHCS

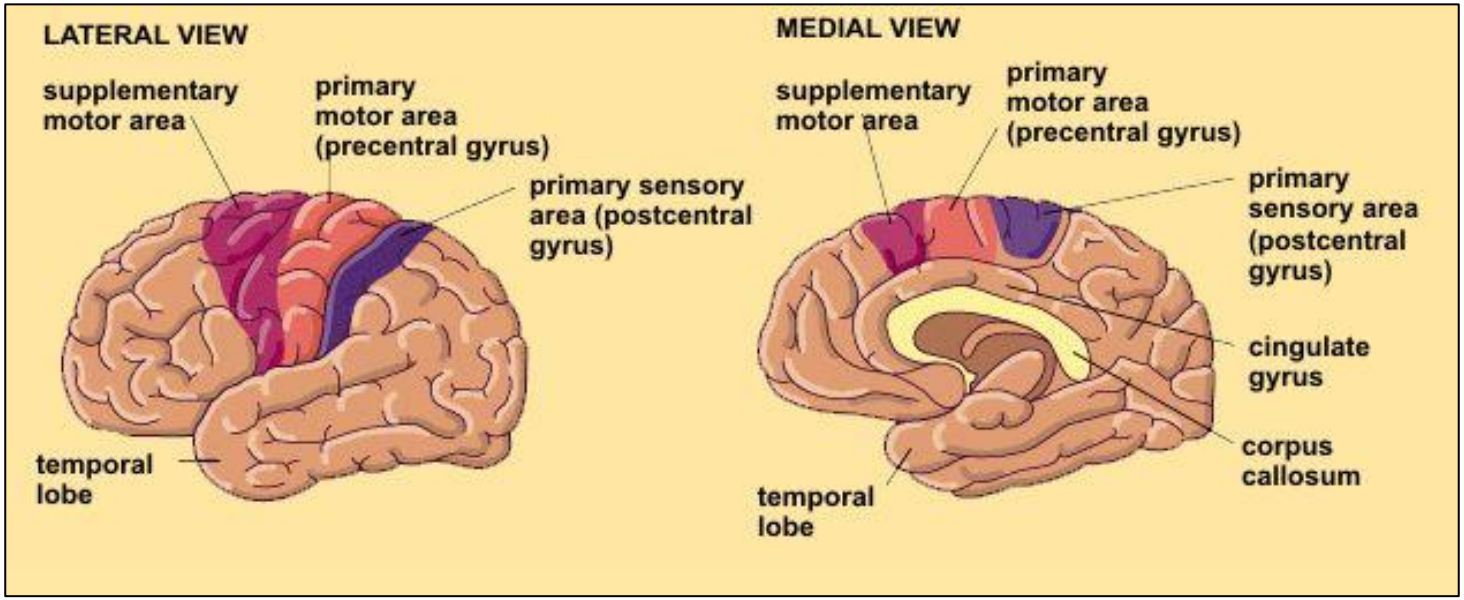
- Divided two groups

  → normal MRIs (3 patients) → best results

  → ipsilateral(신체의 같은 쪽(좌 또는 우)) hippocampal sclerosis(경화증) (3 patients) → slight improvement
- ESHC effective in the control of mesial temporal lobe seizures(해마경화증)

Neuromodulation of the Supplementary Motor Area (SMA)

- SMA : crucial role in movement organization – sequential timing and planning of motor tasks
- Located in the mesial surface of the superior frontal gyrus



Neuromodulation of the Supplementary Motor Area (SMA)

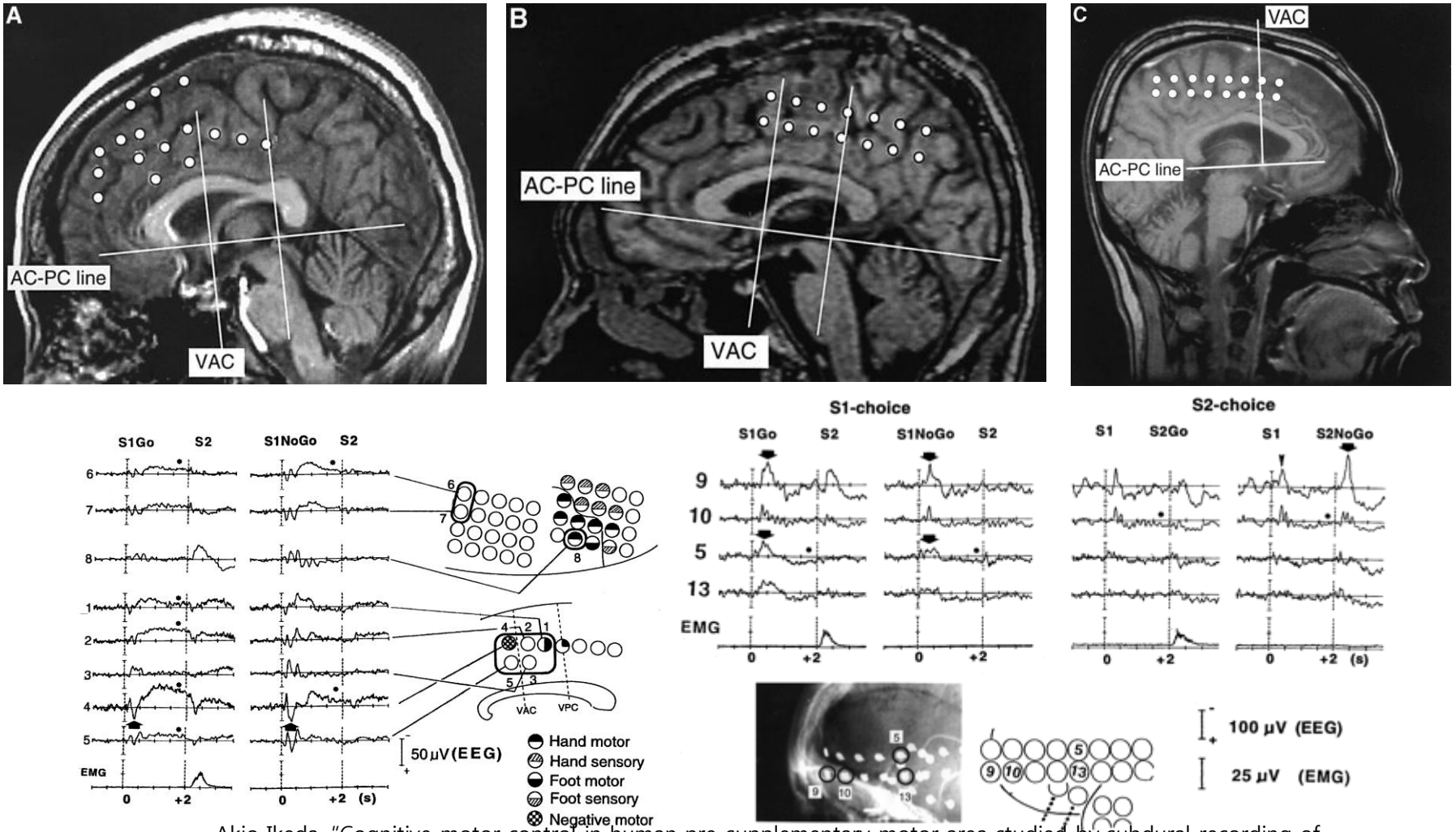
- Ablation of the SMA - limited results, a high incidence of neurological deficit
- 17-years-old male with normal MRI

- start seizing 14 years old
- With abrupt posturing of left arm
- Sudden version of the head to the left
- With preserved consciousness
- Occasional secondary tonic-clonic seizures
- EEG of frontal parasagittal epileptic activity
- Conduct abnormalities with perseverance
- Verbal aggressiveness

Neuromodulation of the Supplementary Motor Area (SMA)

- Implanted Bilateral 20 contact grids in SMA
- AEDs tapered(점점 줄이다) and daily depth recording
- Ictal EEG → a mesial focus located in right SMA
- Reinitianted AEDs
- Grids were explanted and replaced by a four contact electrode for CS
- The parameter – bipolar continuous stimulation, 130 Hz, 3.0V
- RESULT → immediate decrease in seizure occurance , maintained for nine months

Neuromodulation of the Supplementary Motor Area (SMA)



Akio Ikeda, "Cognitive motor control in human pre-supplementary motor area studied by subdural recording of discrimination/selection-related potentials", *Brain (1999) 122 (5): 915-931. doi: 10.1093/brain/122.5.915*

Conclusions of Neuromodulation

- Several advantages
  - nonlesional
  - not interfere with the functioning eluquent areas
  - improve neuropsychological performance
- several disadvantages
- Expensive
- need periodic follow-up
- Must be exchanged (battery wear down)
- The skin erosion(짓무름)

Conclusions of Neuromodulation

- Need to improve neromodulation
  - less invasive
  - include rechargeable batteries
  - remote controlled (remove extension cables)
  - be low cost
  - more reliable and user friendly software