New targets and New indications of Neuromodulation

รศ.นพ. กฤษณพันธ์ บุณยะรัตเวช

หน่วยประสาทศัลยศาสตร์ ภาควิชาศัลยศาสตร์

คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

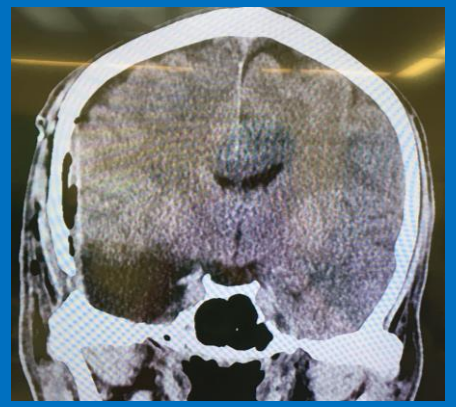
โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

EST Annual Meeting 2021 Theme: "Directions & Trends in Epilepsy Management"

Scope

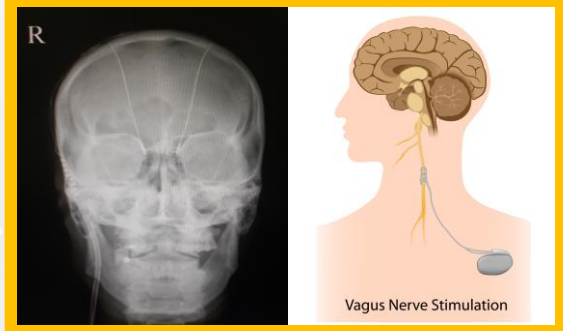
- Introduction
- Types of neuromodulation
- Common targets
- Patient selection and series
- Others

Resection



Disconnection

Modulation

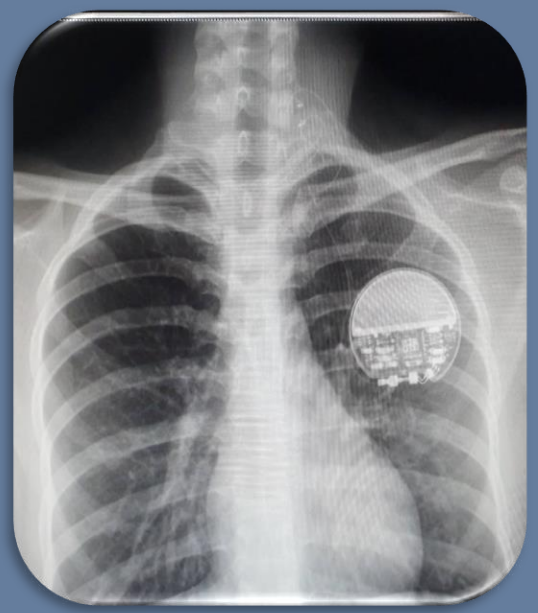


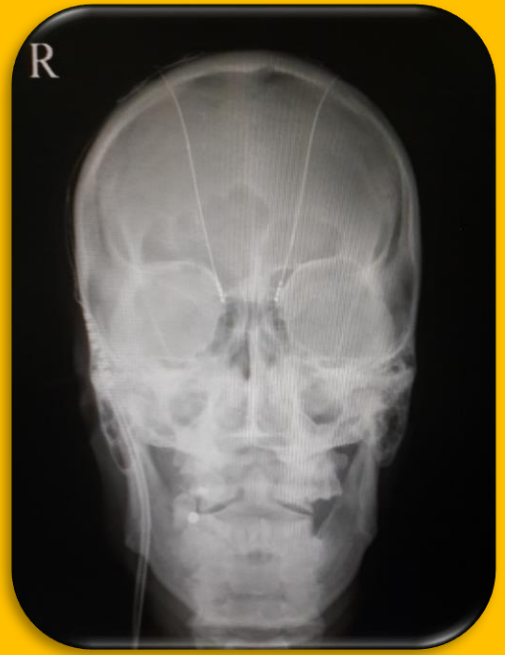
Mechanism

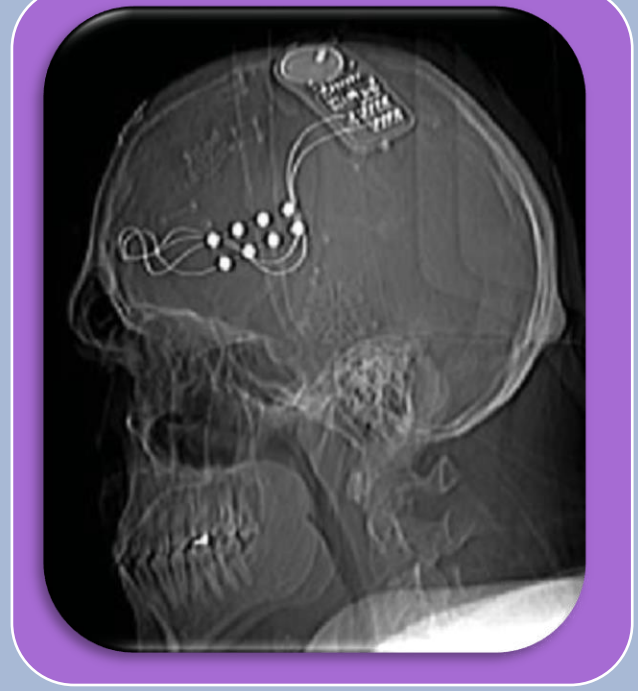
- Mostly unknown
- Reducing neuronal activity in the target
- Desynchornization (frequency dependent)
- Trial and error methods
- Lesioning effect (controversial)

Neuromodulation

Advantages	Disadvantages
• Reversible • Non destructive • Suitable for irresectable EZ • Bilateral HS	• Less effective • High cost • Device issues







VNS

Vagus Nerve Stimulation

DBS

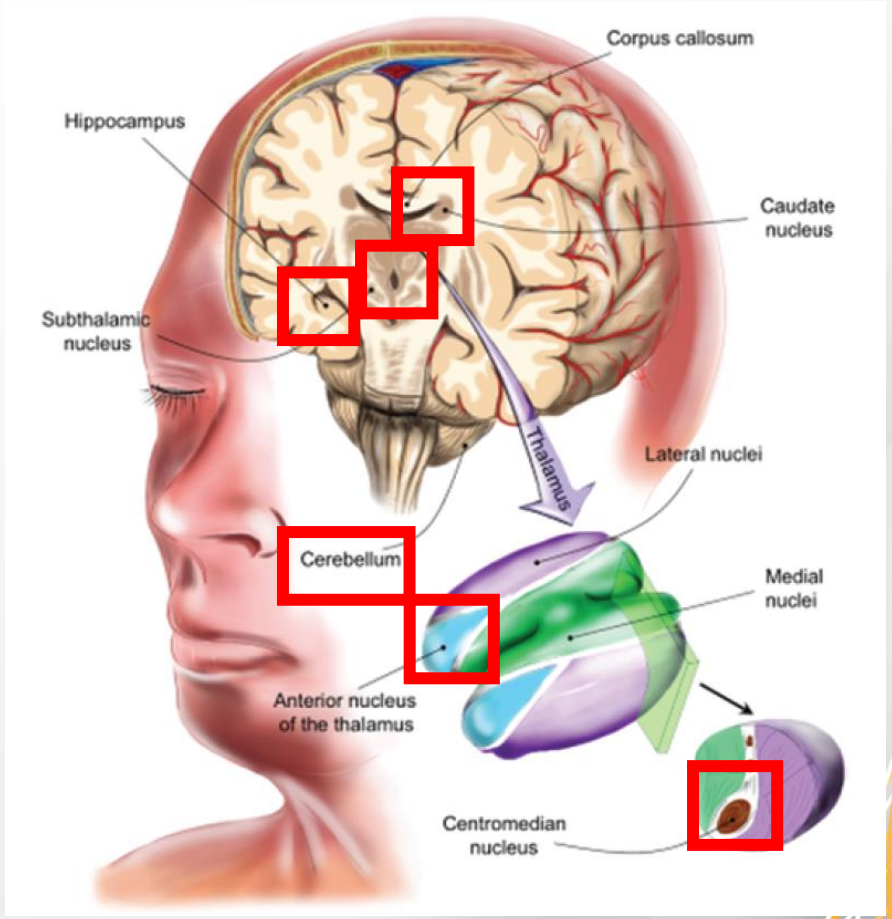
Deep Brain Stimulation

RNS

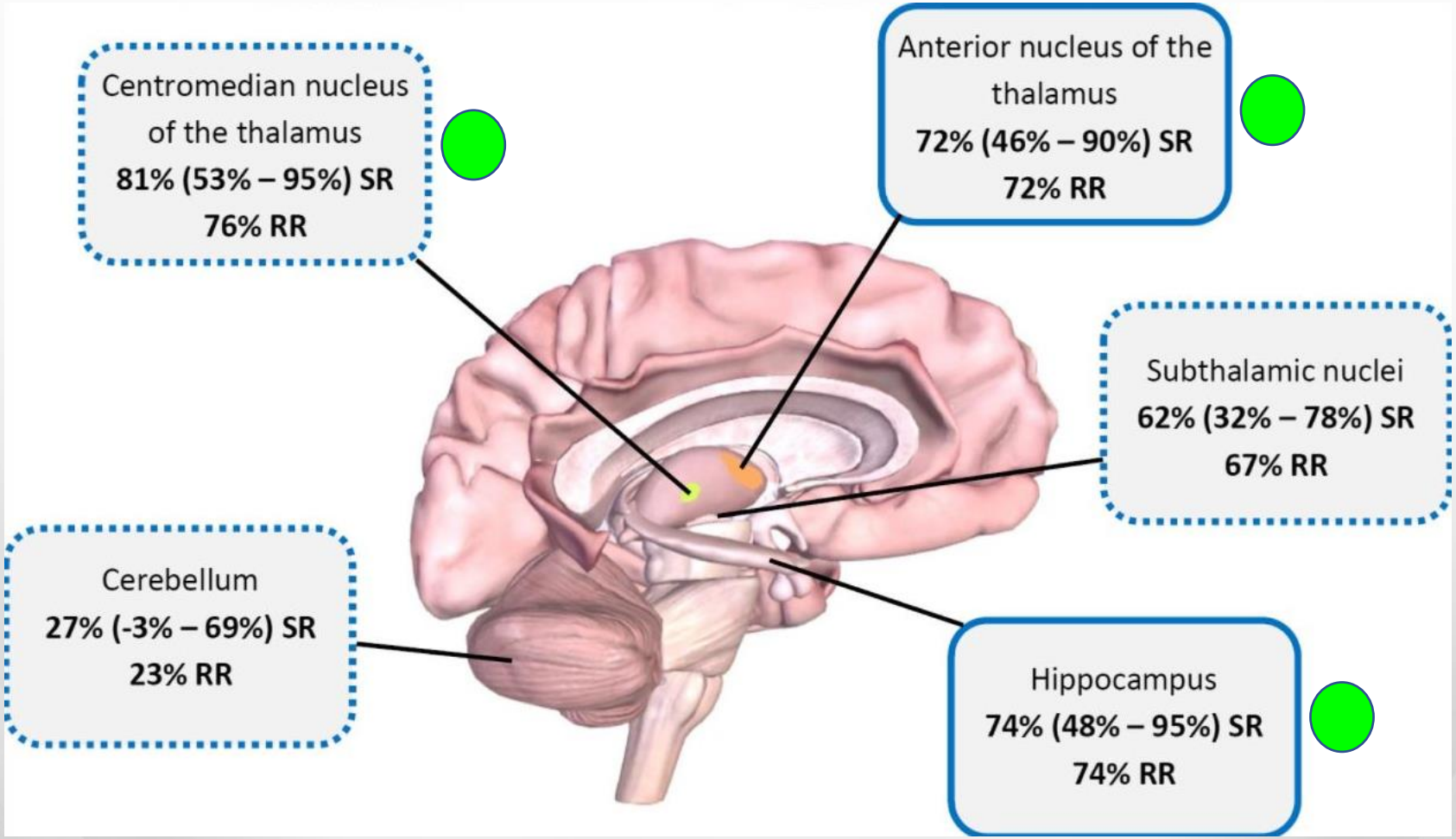
Responsive Neurostimulation

Targets

- Hippocampus
- Subthalamic nucleus
- Cerebellum
- Caudate nucleus
- CM nucleus
- Anterior Thalamic nucleus



Fridley J et al. Neurosurg Focus. 2012



Li et al. Epilepsia. 2018

TABLE 1 Summary of data from randomized controlled trials

		Outcomes during the blinded phase	
DBS target	**RCT**	**Stimulation compared with baseline**	**Sham stimulation compared with baseline**
ANT	Fisher et al. 2010[3]	40.4% median SR	14.5% median SR
HC	Tellez-Zenteno et al. 2006[34]	26% median SR	−49% median SR
	Velasco et al. 2007[35,36]	40% median SR	0% median SR
	McLachlan et al. 2010[37]	33% mean SR	4% mean SR[a]
	(Morrell et al. 2011[38])[b]	37.9% mean SR	17.3% mean SR
CMT	Fisher et al. 1992[49]	30% mean SR	8% mean SR
	Velasco et al. 2000[50]	No statistically significant SR (values not reported)	
CB	Wright et al. 1984[55]	No statistically significant SR (values not reported)	
	Velasco et al. 2005[56]	67% GTC mean SR	7% GTC mean SR
NA	Kowski et al. 2015[68]	48% mean SR[a]	14% mean SR[a]

SR, seizure reduction; ANT, anterior nucleus of the thalamus; HC, hippocampus; CMT, centromedian nucleus of the thalamus; CB, cerebellum; NA, nucleus accumbens.

[a]Values calculated from data or graphs presented in the original article.

[b]50% of participants received HC-RNS; the remainder received RNS of cortical areas.

Li et al. Epilepsia. 2018

Centromedian nucleus

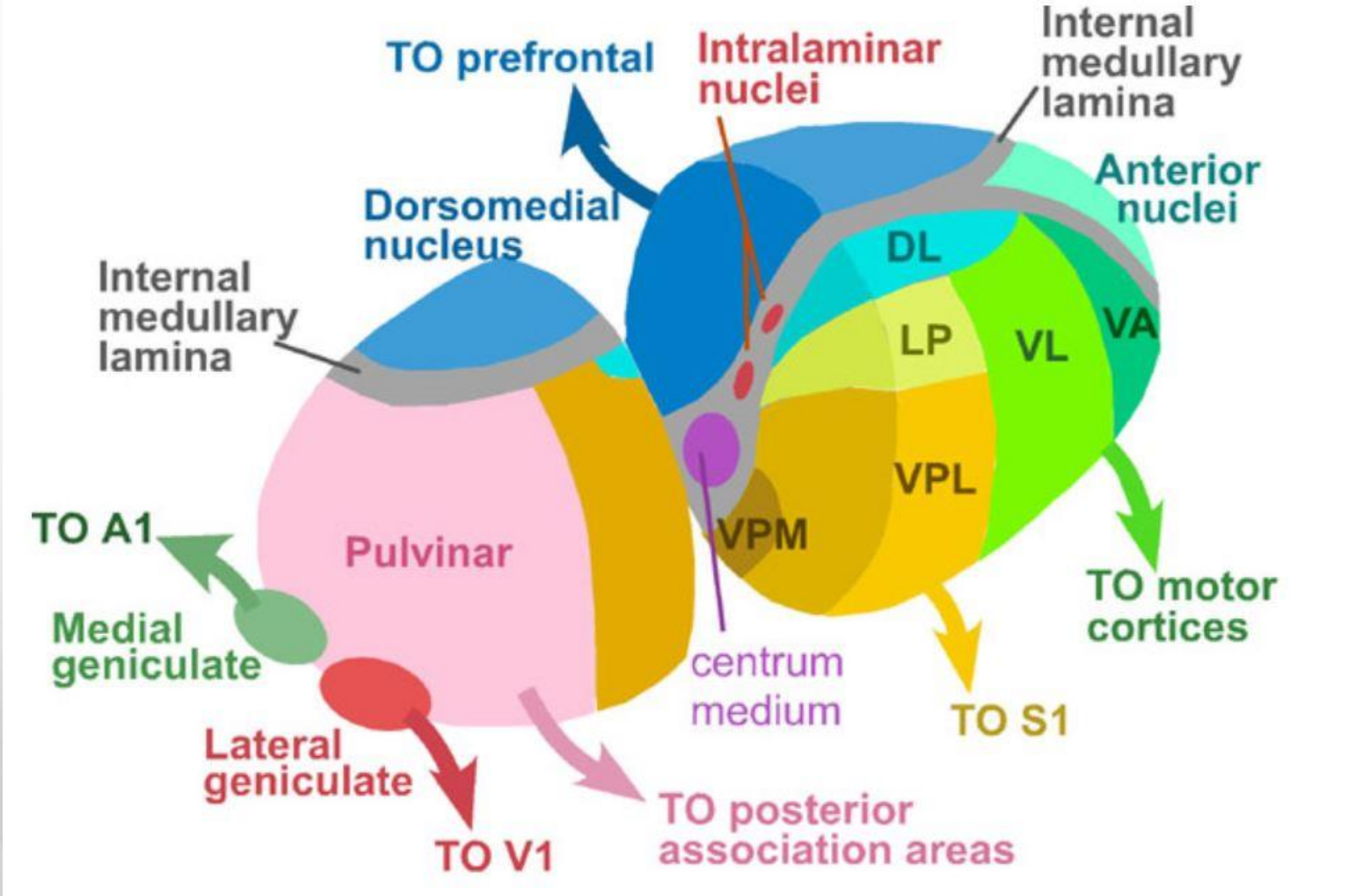


TABLE 4 Clinical data on CMT-DBS for drug-resistant epilepsy

			Seizure types & onset			DBS parameters				Results	
Study (RCTs in bold)	N	Mean age (yrs)	Focal onset seizures	Generalized onset seizures	Onset zone	Freq (Hz)	Voltage (V)	Pulse width (μs)	Timing (mins)	Mean FU (mo)	Primary outcomes (Bold if during blinded phase)
Velasco, 1987[51]	5	18	FIA	GTC, MYO, AT	NR	60-100	0.8-2.0 mA	100	1 on/4 off Alt sides	3	80%-100% GTC SR 60%-100% FIA SR
Fisher, 1992[49]	7 (2 LG)	28	FIA	GTC, TS	T, F/C, F/T, GN	65	0.5-10	90	1 on/4 off	9 blind 12-22 total	**30% (ON) vs 8% (OFF) MSR but not statistically significant.** 34% (−33% to 92%) MSR; 3/6 RR
Velasco, 2000[50]	13 (8 LG)	19	FIA, FBTC	GTC, AB	NR	60	4-6	NR	1 on/4 off Alt sides	3 blind 41 total	**No significant SR;** 82% (53%-100%) MSR for LG; 57% (13%-99%) MSR for PS
Chkenkeli, 2004[52]	5 of 54	21-40 range	FA, FIA, FBTC	GTC, TS	F, F/T, T	20-130	2-4 mA	200	Cont OR cycling	≤18	4/5 "worthwhile improvement" 1/5 "no improvement"
Velasco, 2006[12]	13 LG	13.2	—	GTC, AB	NR	130	2-3	450	1 on/4 off Alt sides	18	80% (30%-100%) MSR; 10/13 RR
Andrade, 2006[22]	2 of 8	NR	FA, FIA, FBTC	GTC	NR	100-185	1-10	90-120	Cont OR Cycling	≤7 y	0/2 RR; no long-term benefit
Cukiert, 2009[53]	4 (1 LG)	29	—	GTC, TS, AB, AT, MYO	GN	130	2	300	Cont	24	80% (65%-98%) MSR
Valentin, 2013[54]	11	37	FA, FIA	GTC, AB	F, GN	60	≤5	90	Cont	6 blind 35 total	**6/6 RR in GS group;** **1/5 RR in frontal group** 84% (49%-100%) MSR GS group; 47% (0%-95%) MSR frontal group
Valentin, 2017[32]	2 of 3	10, 8	—	GTC, TS, AB, AT, MYO	NR	NR	NR	NR	NR	48, 18	>60% SR in 10 yo No significant SR in 8 yo

Seizure types: GTC (primary generalized tonic–clonic); AB (absence); AT (atonic seizure/drop attack); TS (tonic seizure); MYO (myoclonic seizure); FA (focal aware—previously simple partial); FIA (focal impaired awareness—previously complex partial); FBTC (focal to bilateral tonic–clonic—previously secondarily generalized tonic–clonic); LG (Lennox-Gastaut syndrome).
Seizure onset: GN (generalized or not localized); F (frontal); T (temporal); C (central).
DBS parameters: Alt (alternating); Cont (continuous).
Results: FU (follow-up); mo (month); SR (seizure frequency reduction); MSR (mean seizure frequency reduction); RR (responder rate (≥50% reduction)).
Other: NR (not reported); — (seizure type not present).

Li et al. Epilepsia. 2018

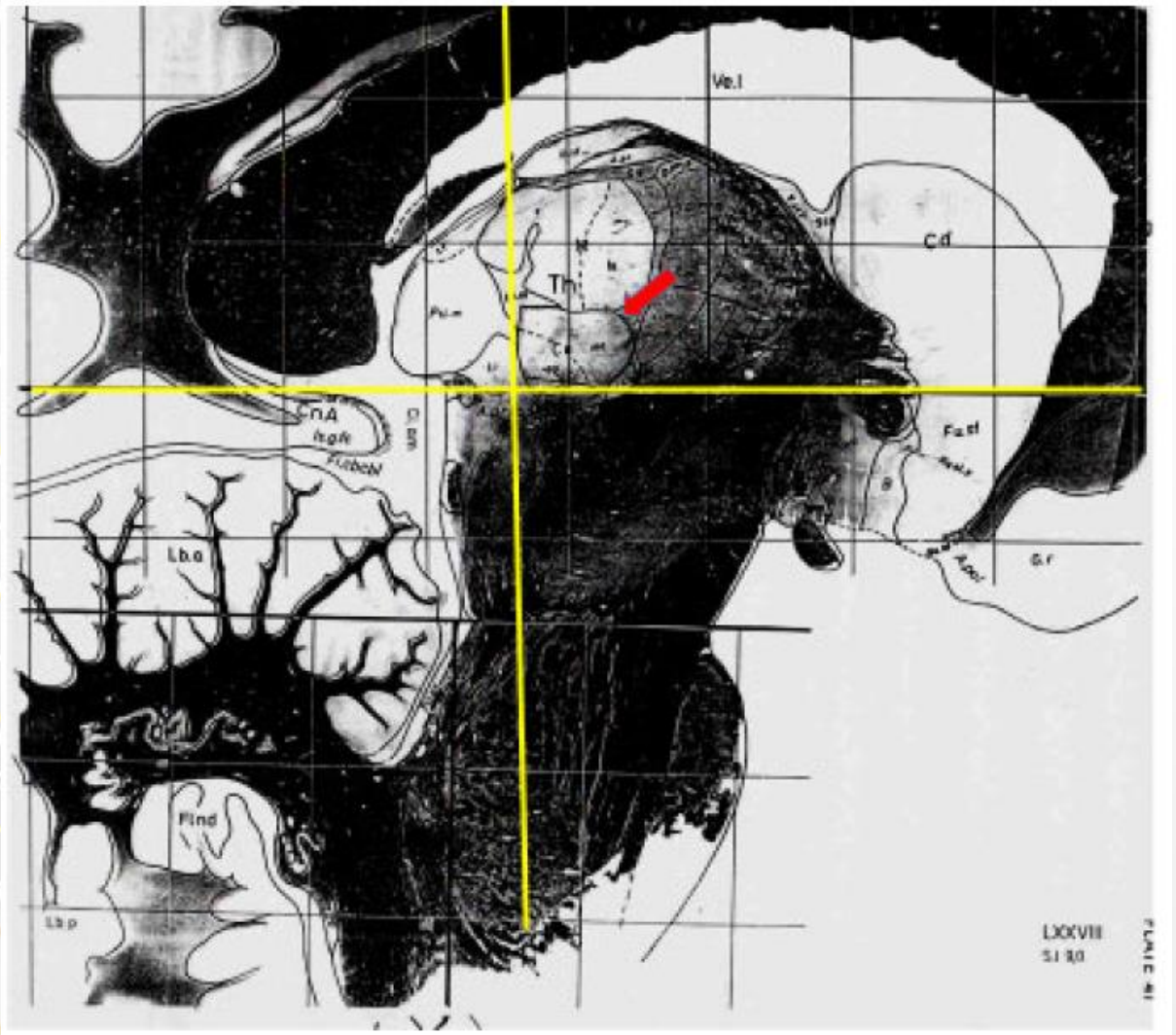
Centromedian nucleus (CM)

- LGS
- Generalized epilepsy
- Not effective for focal epilepsy (better treated with ATN, RNS, or VNS)
- Unknown foci
- RSE, SRSE (case report)

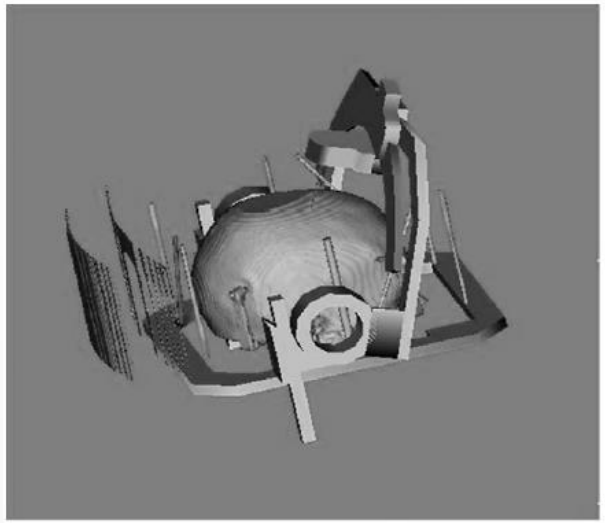
CM DBS and SE

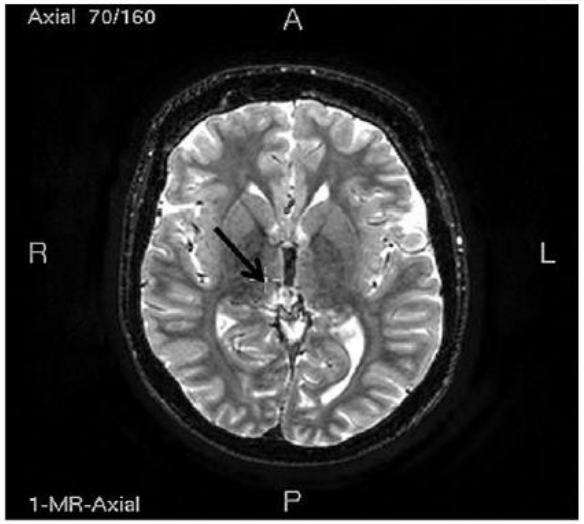
Reference	No. patients	Age (years)	Seizures' etiology	Electrodes location/ Stimulated region/Device	Treatment regime	Load (mC)	Amperage (mA)	Current drugs AEDs	Adverse effects	SE aborted and Latency from stimulation to SE abortion	Duration of SE before therapy	Setting
					30 s of intertrain interval) at 50% of the maximumo output							
Deep Brain Stimulation (DBS)												
(Franzini et al., 2008) [27]	1	22	Rasmussen encephalitis	Left caudal zona incerta	Monopolar with contacts 1 and 2 as cathodes, 90 μs, 100 Hz	?	2	BZD, AZT, IgM IV, CCS	Contralateral upper limb paresthesia	Yes, Immediately after stimulation	–	OR
(Valentín et al., 2012) [28]	1	27	Anoxic injury	Bilateral centromedian thalamic nuclei	6 Hz, 90 μs	?	5	PHT, LEV, LZP, PROP, VPA TPM, PB, MDL, sodium TP, IVIG, MP	Infection of the electrodes	Yes, Immediately after stimulation	5 weeks	OR
(Lee et al., 2017) [29]	1	17	Progressive seizure activity	Bilateral anterior thalamic nucleus	Continuous bilateral stimulation, 145 Hz, and 90 microseconds (increase to 120 microseconds after 3 days)	?	8	LTG, CLB, TPM, LEV, LZP, VPA, PER, MDL	No adverse effects	Yes, Immediately after stimulation	4 weeks	OR
(Lehtimäki et al., 2017) [30]	1	17	CVID (Common Variable Immunodeficiency) associated encephalomyelitis	Centromedian nucleus of the thalamus	180 Hz, 150μs	?	7	BZD, PHT, PROP, TP, MDL, racemic KET, S-KET, LEV, TPM, LCM, LZP, CLB, CCS, IVIG	No adverse effects	Yes, Two weeks	59 days	ICU

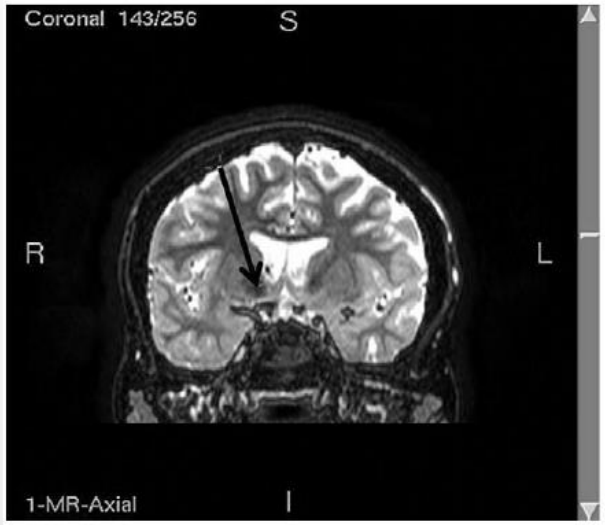
San-Juan et al. Brain Stimul. 2019

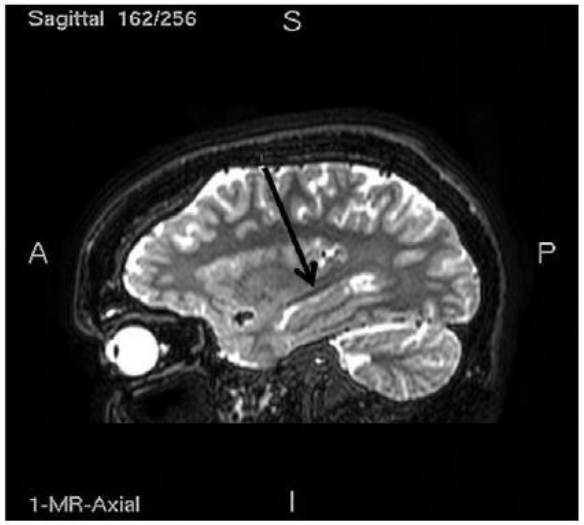


Cukiert Epilepsia. 2017









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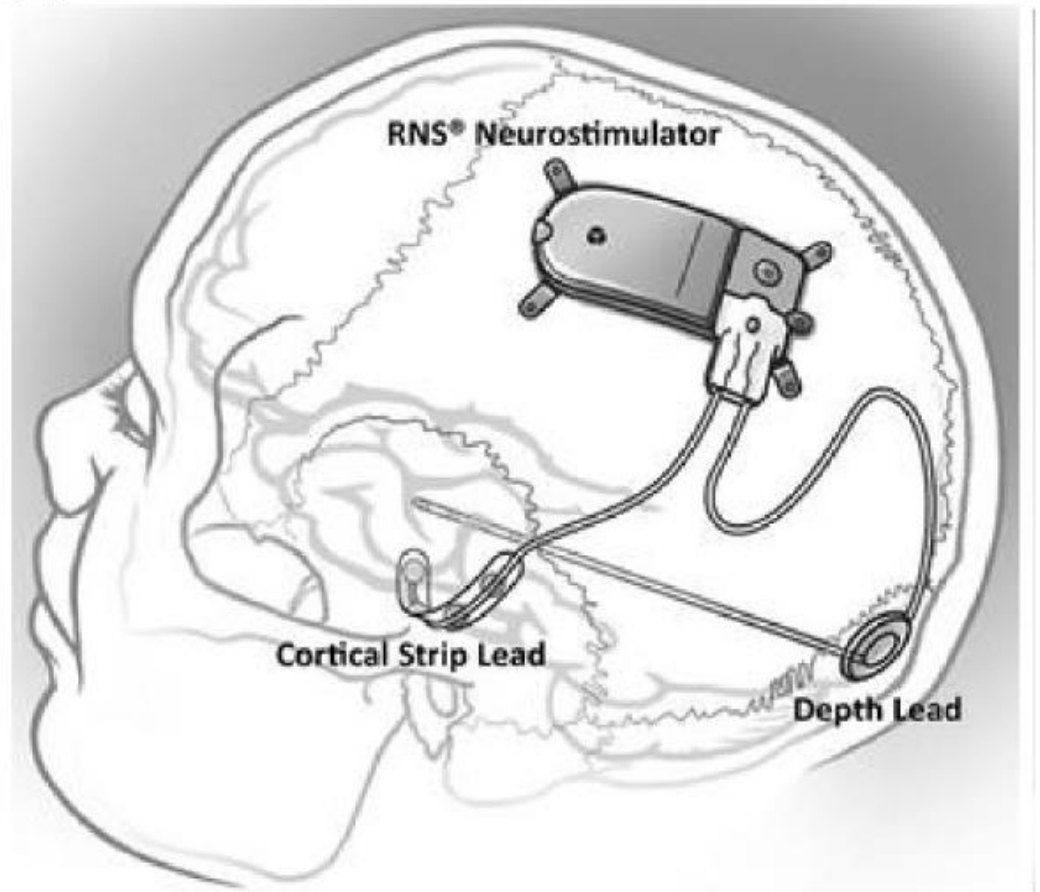

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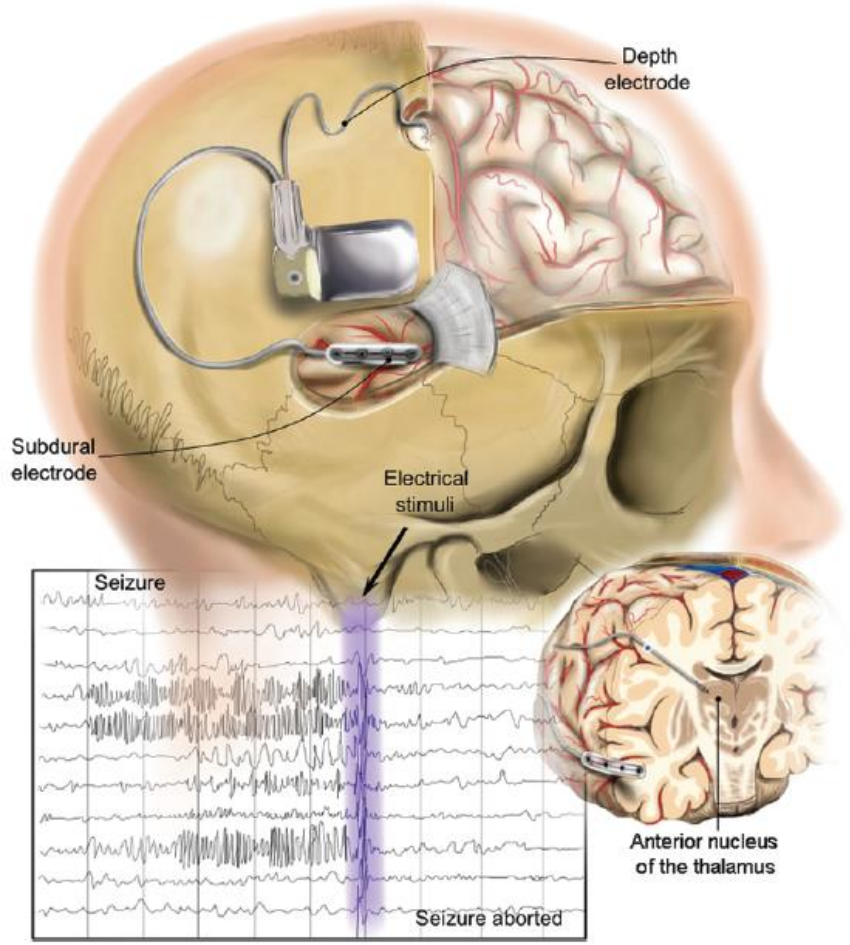

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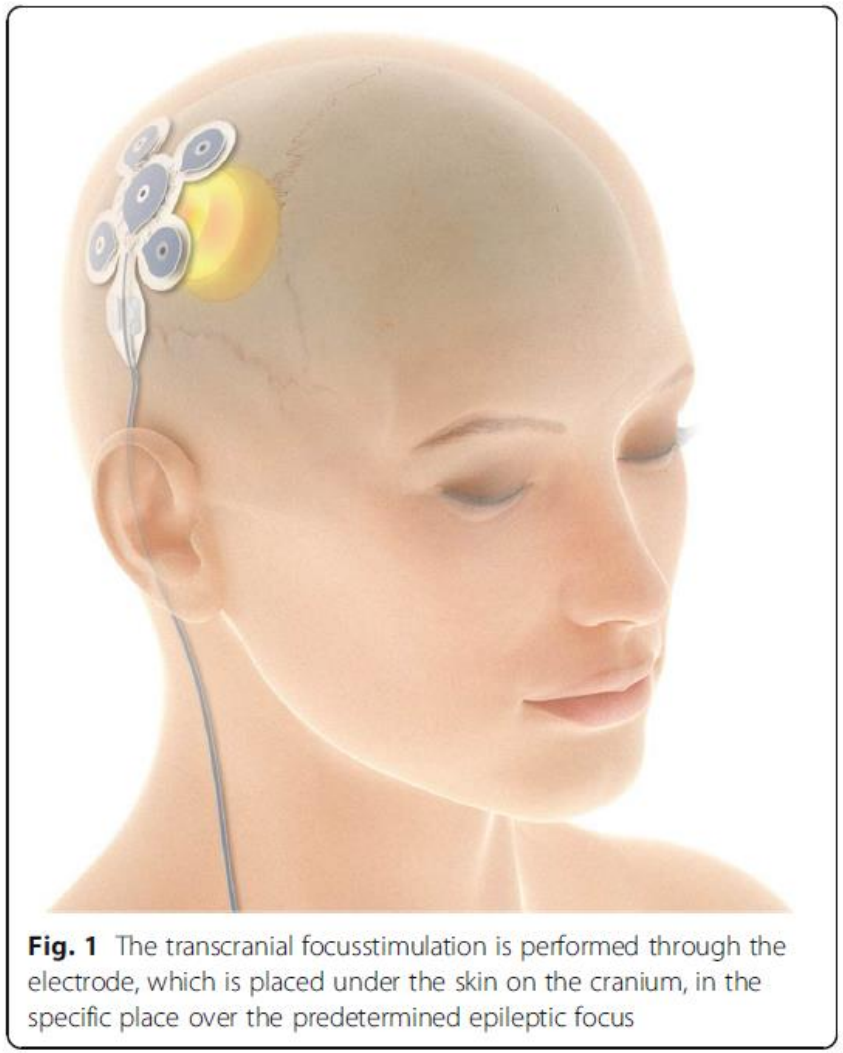
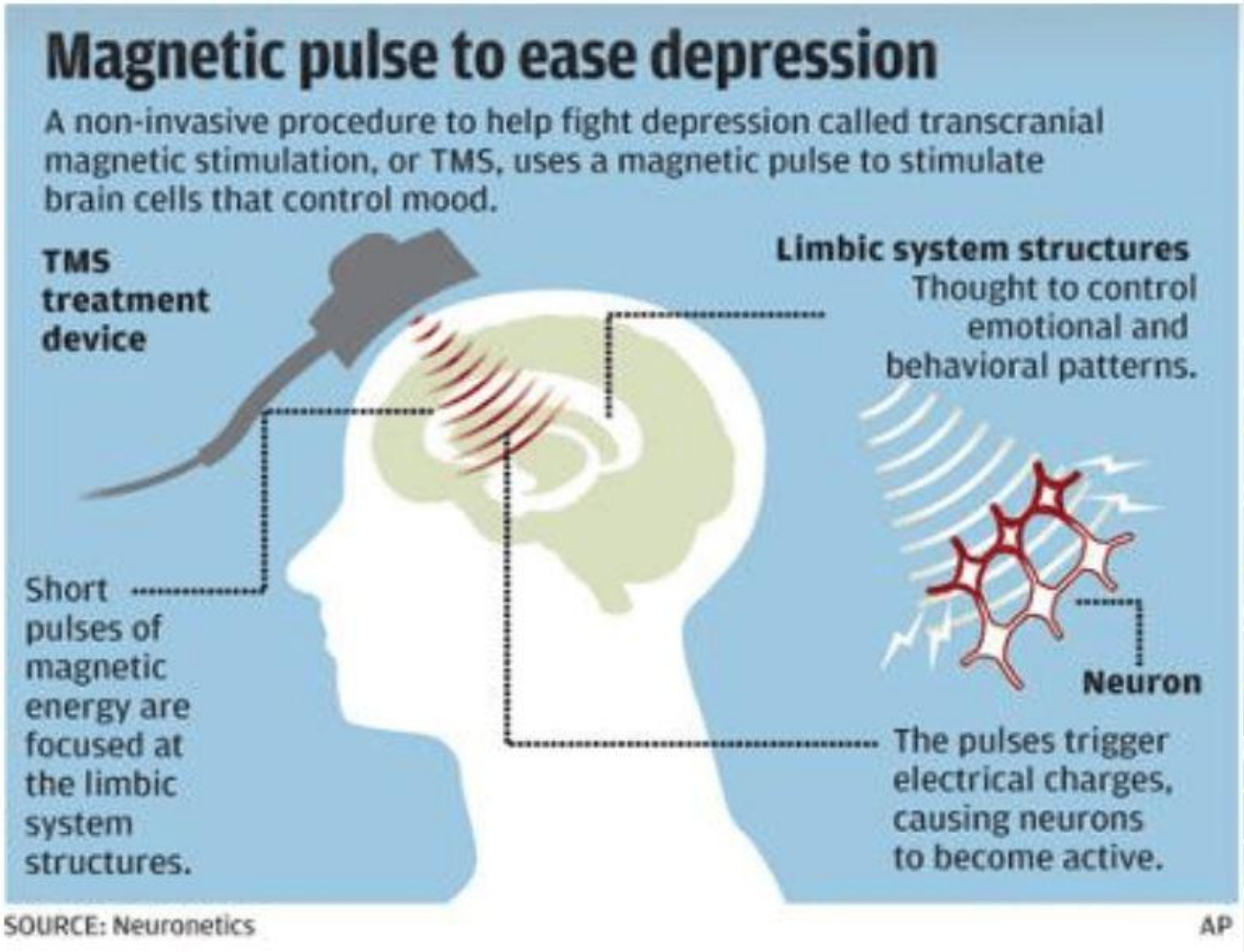


Fig. 1 The transcranial focusstimulation is performed through the electrode, which is placed under the skin on the cranium, in the specific place over the predetermined epileptic focus



Kravalis et al. Neurol Res Pract. 2020

patient-controlled neurostimulation with the EASEE®

Take home message

- Neuromodulation is a useful option in refractory epilepsy
- CM-DBS mostly effective for generalized epilepsy ie LGS
- Less invasive form of neuromodulation are being studied

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