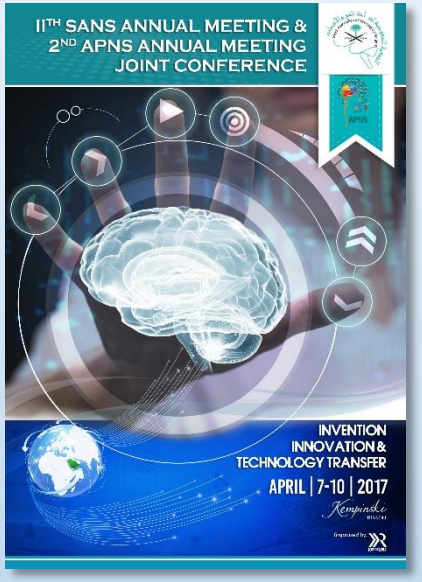
Modulation of Epileptic Network by Responsive Technology



Dr Faisal T. Sayer, B.Med.Sc, M.D., M.Sc., SBNS

Consultant and Chairman, Department of Neurosurgery, Ibn Sina Hospital.
Residency program Director, Kuwait Institute for Medical Specialization.
Vice-chairman, The Kuwait Society of Neurological Surgeons

email: faisal.sayer.t@gmail.com

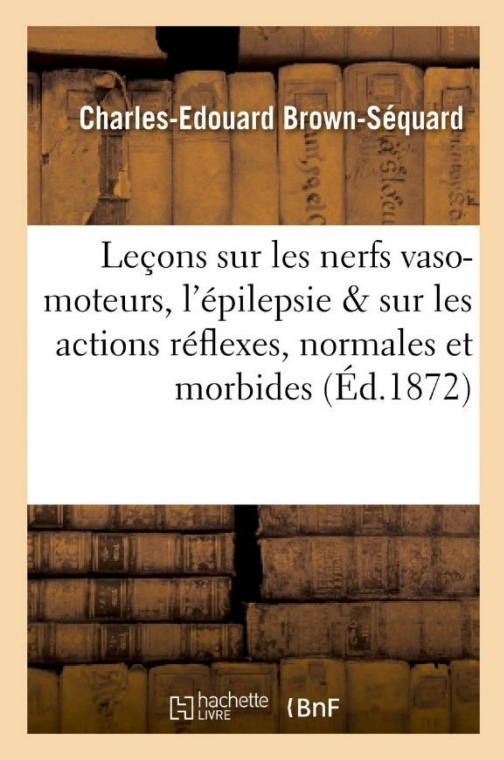
Patients with refractory epilepsy may not be amenable to resective surgery due to:

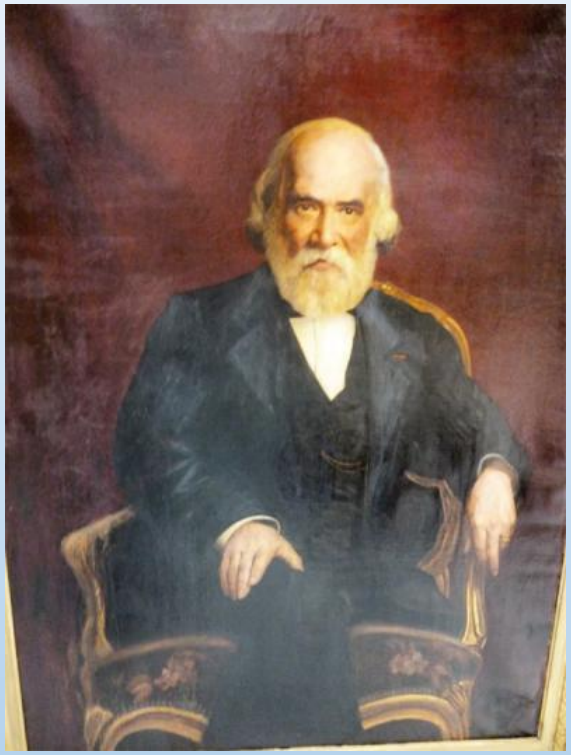
1. Multifocality of the epilepsy.
2. Localization of the epileptic focus within functional cortex.
3. Failed prior resective surgery.

Neurostimulation techniques granted FDA approval for the treatment of such cases:

1. Vagus nerve stimulation (VNS).
2. Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS).
3. Responsive neurostimulation (RNS).

Already in the nineteenth century ‘counter-irritation’ was suggested as a potential strategy to abate epileptic activity.

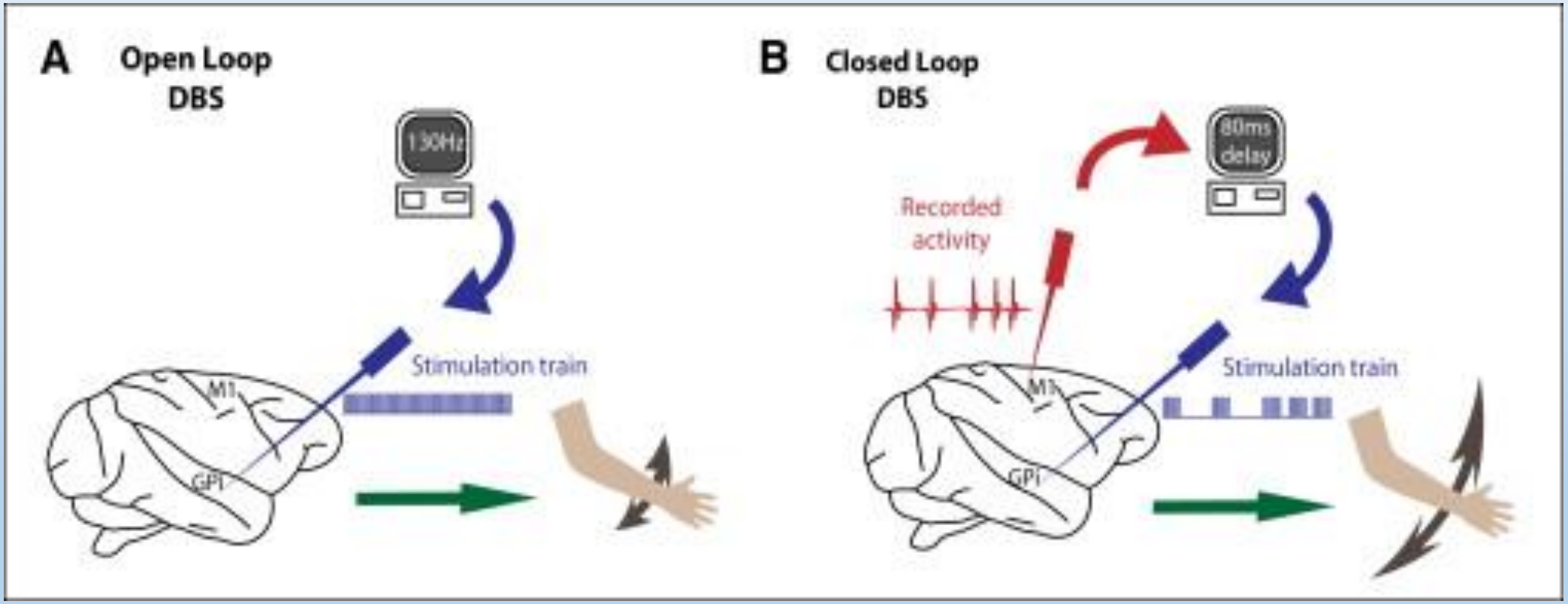




Brown-Séquard CE. Researc Boston Med Surg J. 1856–1857;55–57; Jackson H. Lancet. 1868;91(2333):618–619.

***Open-loop* stimulation:** Stimulation of nerve tissue in a fixed, scheduled manner and independent of ongoing and variable neuronal activity.

***Closed-loop* (responsive) neurostimulation:** electrical pulses are delivered upon detection of seizure activity.



Closed-loop (responsive) neurostimulation

1. Delivering electrical current only when ‘necessary’ lowers the total daily dose of delivered current, prolonging battery life and reducing adverse effects.

2. Absence of stimulation during normal brain activity prevents disruption of normal brain function in eloquent areas.

The algorithm should be highly sensitive, specific and fast.

Closed-loop (responsive) neurostimulation

In an optimal scenario ‘sensing and pacing’: clinically seizures are not only aborted, but even prevented..

Early detection of ictal EEG activity requires intracranial electrodes exactly at the site of seizure onset.

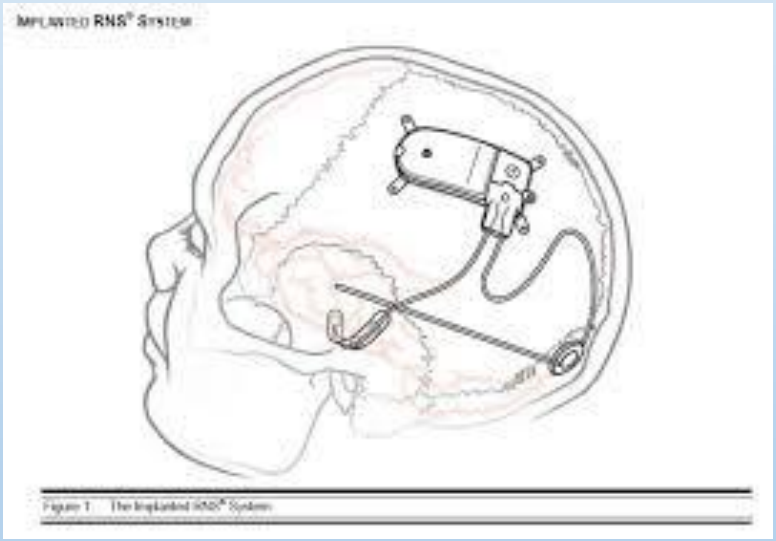
Seizure activity may also be recorded outside the brain, which allows a more accessible read-out:

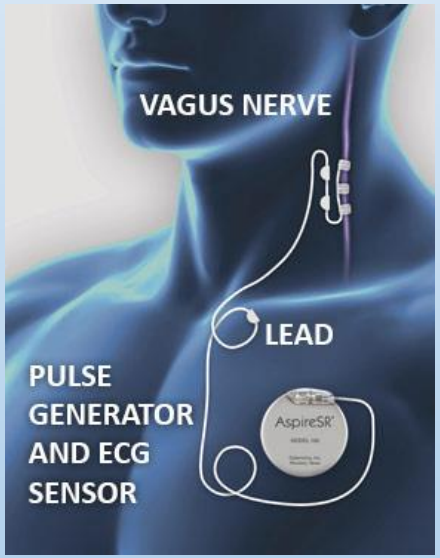
1. Abnormal behavior.
2. Seizure-related muscle activity (EMG).
3. Seizure-related cardiac changes (ECG).

Closed-loop (responsive) neurostimulation

1. The RNS system (Neuropace, Inc.) FDA approval (November 2013).

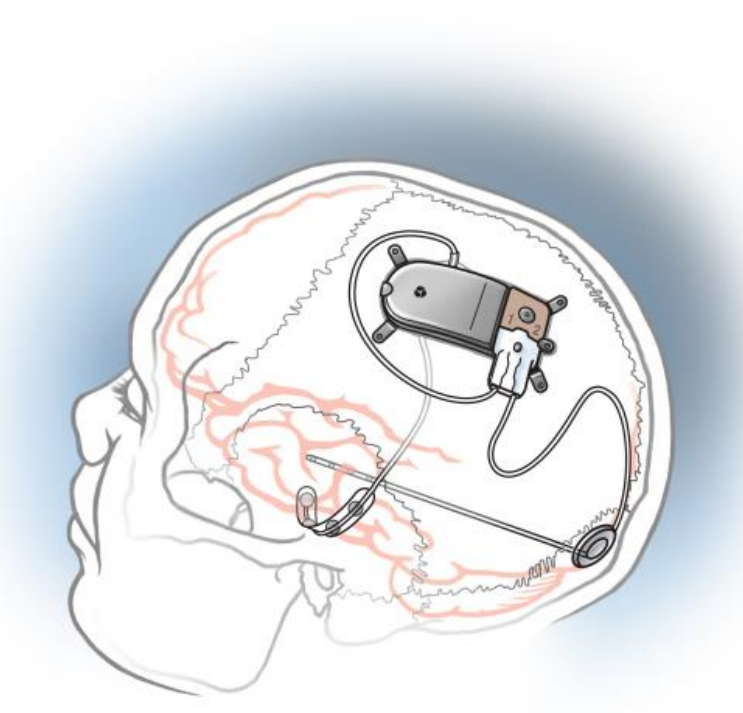
2. The AspireSR VNS system in which a cardiac-based seizure-detection (CBSD) algorithm was incorporated for additional on-demand stimulation (FDA approval May 2015).





The time window between ictal EEG and clinical seizure onset may favor intracranial closed-loop stimulation systems compared with closed-loop treatments that measure ictal activity outside the brain.

The RNS system



Connected to one or two electrodes:

- 4-contact depth lead.
- 4-contact cortical strip.

The contacts serve a dual function:

- Continuous monitoring of electrophysiological activity.
- Delivery of electrical pulses.

It is not a detection system for clinical seizures.

As soon as relevant EEG changes are identified stimulation is initiated

Closed-loop stimulation occurred 600–2000 times a day

cumulative total of <5 min of stimulation over 24 h (battery longevity).

Sun FT, Morrell MJ. Neurotherapeutics.2014;11 (3):553–563; Morrell MJ, Group RNSSiES. Neurology. 2011;77(13):1295–1304..

The RNS system

2-year randomized blinded controlled safety and efficacy study.

191 patients	
Age	18–66 years
Epilepsy duration	2–57 years
Had refractory epilepsy with ≥3 disabling seizures per month	
Had been localized to one (45%) or two (55%) seizure foci.	
had invasive EEG monitoring	59%
prior epilepsy surgery (and/or VNS)	32% (34%).

The RNS system

12-week blinded evaluation period	
Stimulation group	−37.9%
Control group	−17.3%

implantation effect

Fisher R, Salanova V, Witt T, et al. Epilepsia. 2010;51(5):899–908.

Trend towards increased efficacy over time		
	Stimulation group	Control group
after 1 month	34.2%	25.2%
2 months	38.1%	17.2%
3 months	41.5%	9.4%

Morrell MJ, Group RNSSiES. Neurology. 2011;77(13):1295–1304.

Heck CN, King-Stephens D, Massey AD, et al. Epilepsia. 2014;55 (3):432–441.

The RNS system

Long-term open-label extension study providing an additional 7 years of efficacy and safety data.

Bergey GK, Morrell MJ, Mizrahi EM, et al. Neurology. 2015;84 (8):810–817.

open-label follow-up period	
1 year	44%
2 years	53%
year 3	60%
year 6	66%

Heck CN, King-Stephens D, Massey AD, et al. Epilepsia. 2014;55 (3):432–441.
Bergey GK, Morrell MJ, Mizrahi EM, et al. Neurology. 2015;84 (8):810–817.

some improvement	84%
≥50% reduction in seizure frequency	60%
seizure-free	16%

The RNS system

Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas.

Jobst BC, Kapur R et al., Epilepsia. 2017 Apr 7.

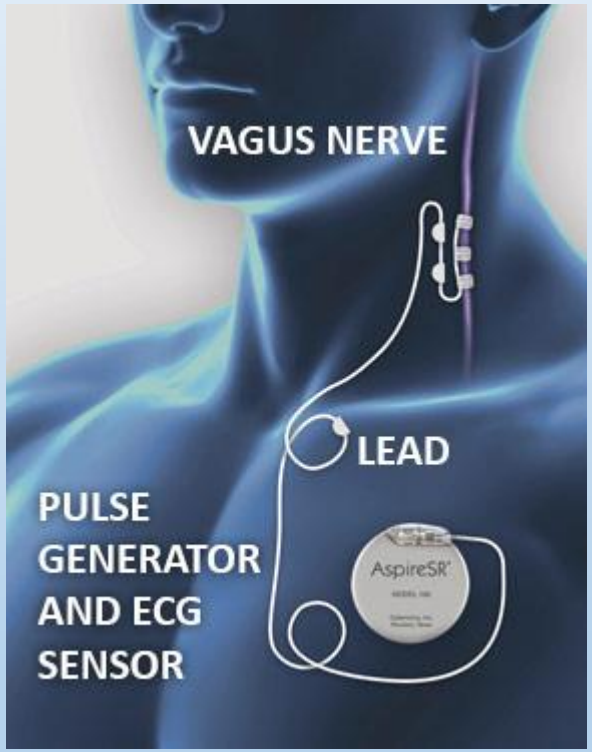
Median percent seizure reduction

Frontal and parietal seizure onsets	70%
Temporal neocortical onsets	58%
Multilobar onsets	51%

Patients with lesions on MRI	77%
Patients with normal MRI findings	45%

Closed-loop VNS

Recently a new VNS device has been developed (AspireSR) allowing automated on-demand VNS triggered by CBSD. The closed-loop algorithm functions in addition to conventional duty cycle VNS in one device



Ictal tachycardia occur in >80% of adult epilepsy patients.

Cardiac changes may precede electrical/clinical onset with several seconds, resulting in a considerable amount of seizures that may be detected and prematurely aborted.

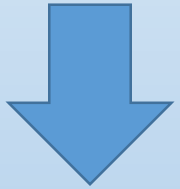
Modulation of Epileptic Network by Responsive Technology

Epileptogenesis

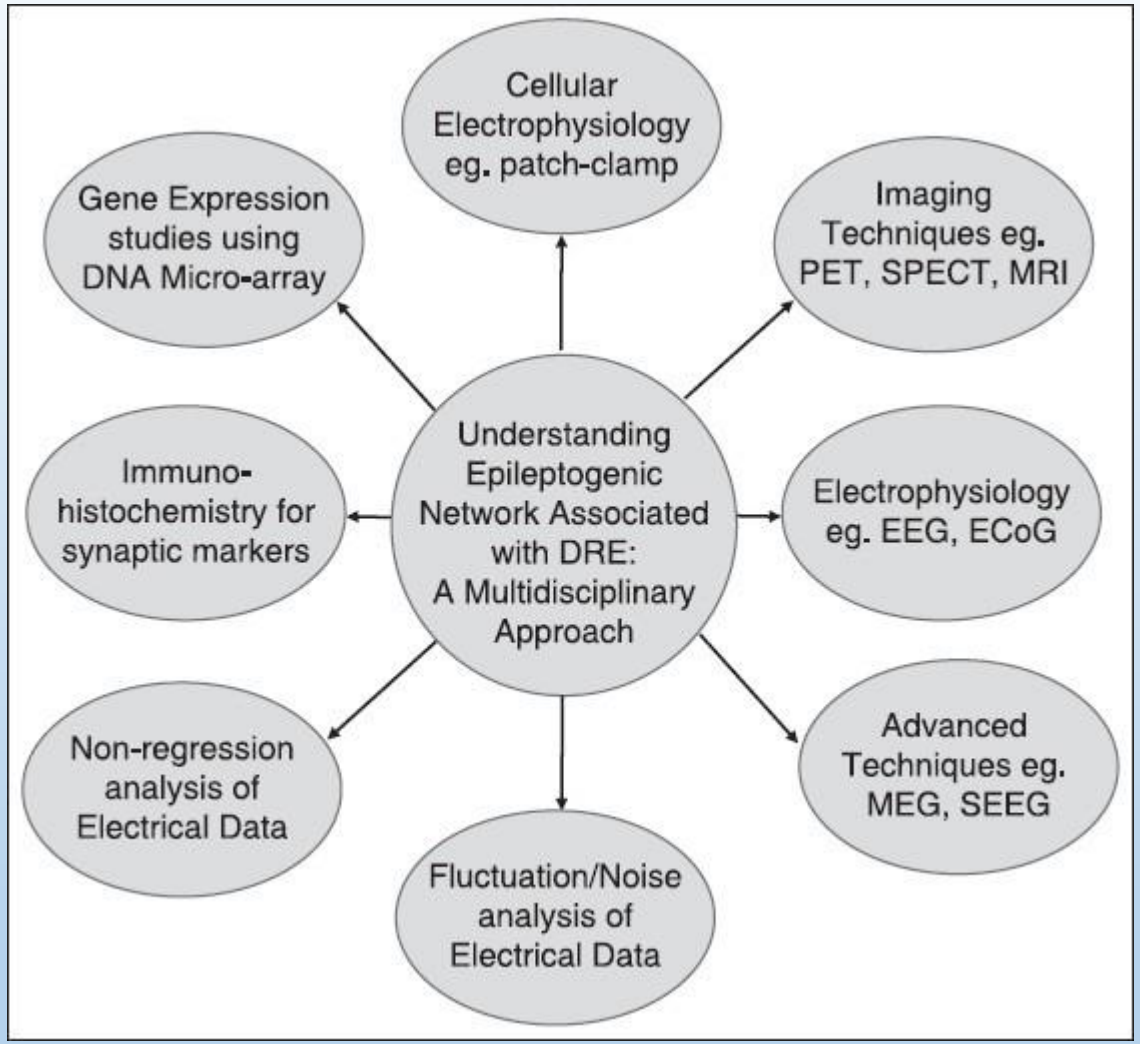
Disruption of these mechanisms create a imbalance between excitation and inhibition.

Neural network hypothesis: Epilepsy become refractory due to seizure-induced alterations of brain plasticity:

Axonal sprouting	**Synaptic reorganization**	**Neurogenesis**	**Gliosis**



Formation of abnormal neural network	
Loss of the inhibitory effect of endogenous AE system	Prevent the AEDs from entering their targets
DRE	



No single investigation delineate the epileptgenic zone.

Current investigations, have different levels of spatial and temporal resolutions.

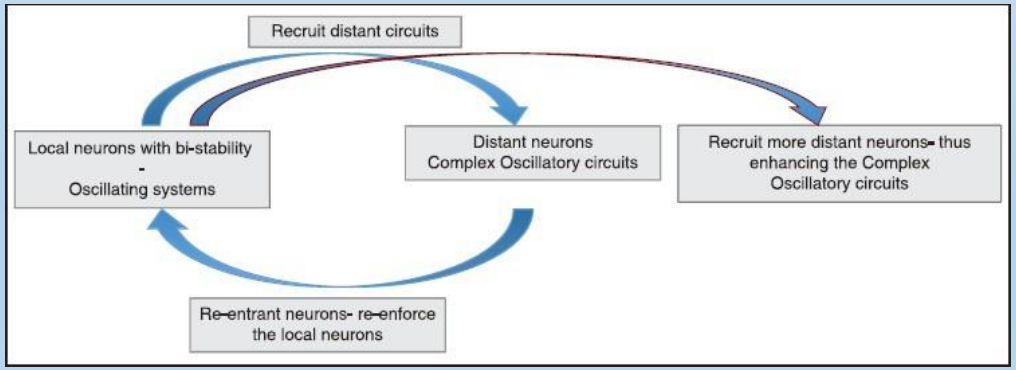
Different modalities of investigations provide different snapshots of the epileptogenesis at different time periods and at variable magnifications.

The epileptogenic focus is not a “fixed” zone but a dynamic, constantly changing group of networks.

Janszky *et al.*, demonstrated that the seizure freedom was inversely proportional to the duration of epilepsy:

Duration of epilepsy between 1 and 10	90% Class I Engel
Duration of epilepsy being >30 years	30% Class I Engel

The “network” hypothesis can explain this by the fact that more neurons become recruited into the “epileptogenic network” over a period of time if epilepsy is not controlled.



Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, et al. Brain. 2005;128:395–404.

The idea of directly stimulating the cortex is appealing, as seizures are thought to arise from cortical grey matter.

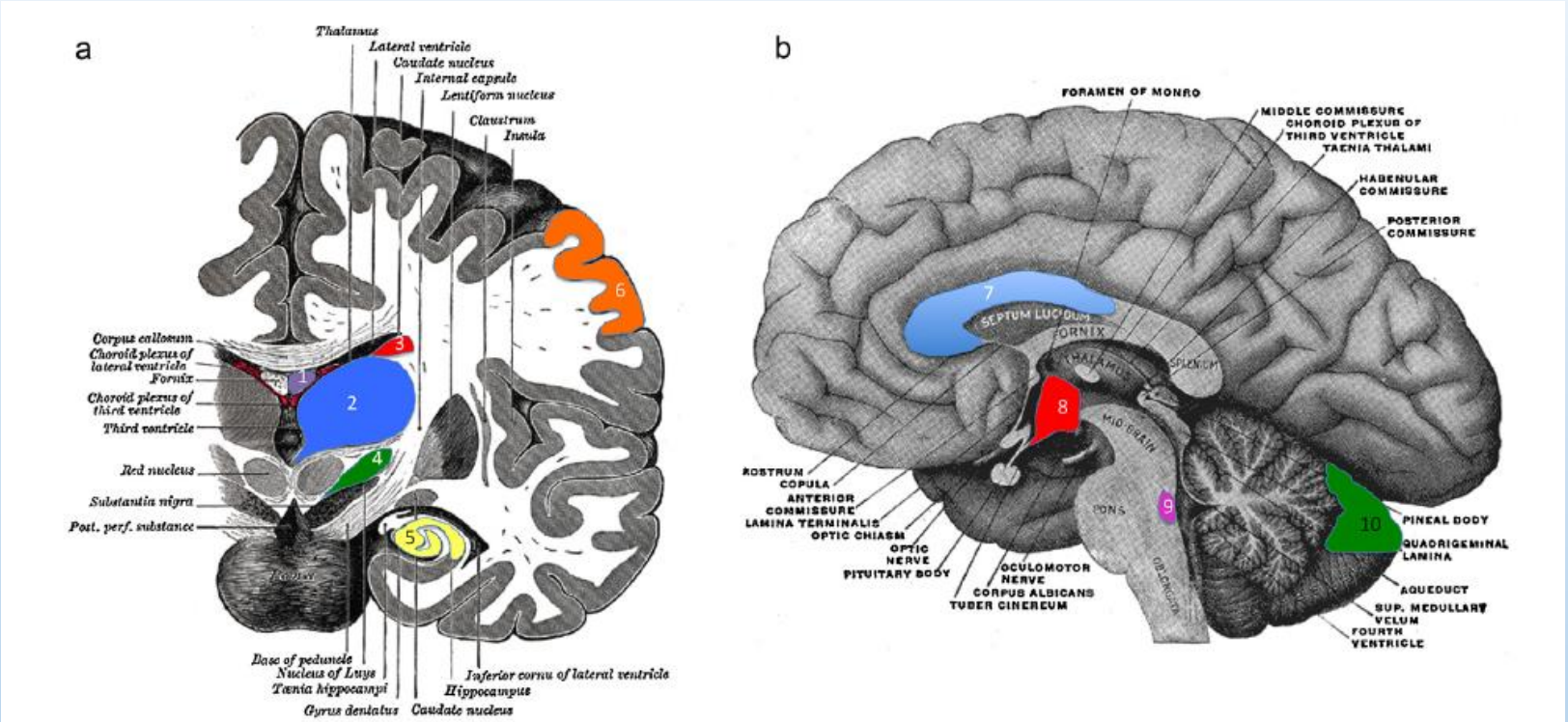


Fig. 1. Neural stimulation sites used in the treatment of epilepsy. 1. Fornix; 2. Thalamus; 3. Caudate; 4. Subthalamic nucleus; 5. Hippocampus; 6. Cortex; 7. Corpus callosum; 8. Hypothalamus; 9. Locus coeruleus; 10. Cerebellum. Adapted from Ref. [57], Fig. 717 (A) and Fig. 715 (B).

Different deep grey matter nuclei have been targeted based on experience with basal ganglia stimulation in movement disorders.

However, targeting white matter fibers may represent an alternative to stimulation of neural cell bodies.

Why white matter stimulation?

1. Lower current is required to modulate neural activity.

2. Its stimulation paradigm is more efficient, where stimulating a small number of axons in white matter allow the current to propagate to the neuronal cell bodies, either ortho- or antidromically, to impact large cortical areas.

3. White matter tracts stimulation is thought to synchronize its electrical output, and subsequently ‘overdrive’ the electrical activity of the downstream cortical epileptogenic zone, effectively reducing seizures.

Effects of white matter stimulation

Although the short-term physiological effects of white matter stimulation seem to be restricted to grey matter structures that share a synapse, long-term effects are assumed to have a more extensive modulatory influence throughout the brain.

A recent study comparing diffusion tensor imaging and PET in an epileptic patient before and after implantation of a vagal nerve stimulator demonstrated:

- improved diffusion in the right fimbria and fornix after six months of stimulation.
- increased ratio of fractional anisotropy in those white matter tracts.
- globally improved cerebral glucose metabolism.

DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Neurology 2013 Feb 26;80(9):786–91.

The observations of an acute and delayed therapeutic effect of RNS suggest multiple mechanisms of action.

Acute effects	Changes in cellular inhibition or excitation changes in cerebral blood flow axonal and glial release of neurotransmitters
Long-term effects	Synaptic plasticity. Neurogenesis. Cortical reorganization.

The progressive reduction in seizure frequency over time suggests that electrical stimulation might have effects beyond those on ion channels.

These findings support the hypothesis that long-term white matter stimulation can induce neural network transformations distant to the site of stimulation.

Conclusion

The RNS technology reflects the culmination of decades of research in electrical stimulation for seizures and offers an alternative to traditional epilepsy surgery for patients with drug-resistant partial-onset seizures.

There are multiple mechanisms mediating the effects of electrical brain stimulation on seizures.

The decrease in seizure frequency over time suggests that electrical stimulation might alter gene expression or perhaps brain network architecture and connectivity.

The RNS represents a milestone in the treatment of medically resistant epilepsy, providing an alternative to surgery that is both adjustable and reversible.

Further research and clinical experience will provide a more clear understanding of the mechanisms underlying its effect on seizures, as well as further refinement of indications and applications.