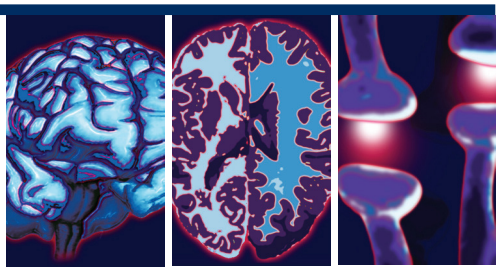
Review



Mechanisms of Deep Brain Stimulation for Epilepsy and Associated Comorbidities

Jiahui Deng[1], Guoming Luan[1,2,3,†]

Abstract

Deep brain stimulation (DBS) is an important effective treatment for pharmacoresistant epilepsy, but its mechanism is still not clear. In clinical application, the possible effects and mechanisms DBS in treatment of epilepsy are different according to different stimulation parameters. We reviewed the mechanisms of DBS in different frequencies including high frequency and low frequency in the treatment of epilepsy, covering the inhibition or excitation of synaptic, pathological neuronal and network activity, pathological rhythms or oscillation and neurotransmitter systems. As the onset and progression of seizure, it's more frequent accompanied with cognitive and psychiatric comorbidities in patients with epilepsy. We review the possible mechanism of DBS in treating epilepsy associated comorbidities including cognitive and memory disorders. With the further development of clinical application and basic research of DBS, the processing of clinical individualized therapy of DBS in epilepsy and evaluation of effects of DBS in associated comorbidities may contribute to extend the understanding of the mechanisms of DBS for epilepsy and associated comorbidities.

Keywords:

Epilepsy, Comorbidity, Deep brain stimulation, Neuromodulation

Introduction

Epilepsy is a common neurological disorder characterized by repeated spontaneous neurological or behavioral changes, often associated with cognitive impairment, psychiatric symptoms, and social function deficit. Worldwide prevalence of epilepsy is estimated by approximately 1% in the population [1-4]. In fact, more than 30 percent of patients with epilepsy are still unable to get adequate control of their seizures although with medicine therapy [5,6]. And surgical methods are only suitable for epilepsy patients with focal lesions clear, if the lesion is not clear or bilateral cerebral hemisphere involvement, as well as patients with higher risk of cognitive impairment, surgical methods can't be conducted. Therefore, electrical stimulation is very important means to suppress seizures.

In fact, the use of brain electrical stimulation is not a new treatment method, but it has gained much attention in the recent more than 20 years [7]. One of the most commonly used method is the deep brain stimulation (DBS), namely through stimulating electrode implanted and

[1]Department of Neurosurgery, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing, China

[2]Beijing Key Laboratory of Epilepsy, Beijing, China

[3]Center of Epilepsy, Beijing Institute for Brain Disorders, Beijing, China

[†]Author for correspondence: Guoming Luan, M.D., Ph D., Professor and Chief Physician in Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Xiangshan Yikesong 50, Haidian district, Beijing, 100093, China. Tel: +86 1062856718, Fax: +86-10-62856902, email: luangm3@163.com

connected with subcutaneous pulse generator to implement the electrical stimulation, and activation of specific brain areas and control the related brain network to achieve the therapeutic effect [8,9].

DBS was first used in the treatment of motor disorders, such as Parkinson's disease (PD), tremor and dystonia. The good effect of DBS in treatment of motor system diseases leads to widely extended study of the basal ganglia circuits [10-14]. At the same time, it makes people to expand its scope to the treatment of other neurological diseases such as epilepsy and mental diseases such as depression, which makes a deeper understanding of the neurobiological mechanisms and brain networks of the nervous system diseases [15-19]. What's more, DBS is a kind of controllable treatment, which has obvious individuation and reversibility. These features make DBS significantly superior to surgical resection. Moreover, in the past more than 20 years, DBS has been shown to be safer and with less complications and mortality.

■ Applications of DBS for epilepsy

Early scientific evidences have shown potentially beneficial effects of DBS on epileptiform activity in cat models [20-22]. And then electrical stimulation in patients has also been examined in a number of relatively small human trials targeted in the cerebellum [23-25]. Along with the development of research about DBS, the targets of DBS are more diverse and abundant. In addition to the cerebellum, effective sites include hippocampus, subthalamus, hypothalamus, anterior thalamus; caudate, brainstem and seizure focus [26-28].

Among them, the anterior thalamic nucleus (ANT) is the most widely used stimulation targets. Because of the physiological replacing role of electrodes, ANT-DBS has better therapeutic effect than ANT damage [29-31]. ANT DBS has considerable protection effect in 1985 first reported by Cooper and Upton [32]. They reported a seizure reduction in the frequency of 4 in 6 patients. Furthermore, many clinical researches including multicenter, double-blind, randomized bilateral SANTE experiment of ANT-DBS in epilepsy also verify the effectiveness [33-35].

They reported in 110 patient's 40.4% seizure decline in treatment group compared with 14.5% in the control group. After 2 years it is 56% median reduction in seizure frequency, and onset of 54% patients was reduced by 50%. 14 patients were seizure free for at least 6 months. Another including 191 subjects randomized multicenter double-blinded controlled trial of responsive focal cortical stimulation (RNS System) [36,37]. They reported a progressive and significant improvement with time as the median percent reduction in seizures was 44% at 1 year and 53% at 2 years. These clinical studies, most patients can tolerate DBS stimulation, and with no side effects of related exercise and low or no adverse effects neuropsychological function or mood.

■ The mechanism of DBS for epilepsy

Although the clinical use of DBS has emerged for several decades, understanding of the mechanisms for the therapeutic action of DBS remains poorly defined. The therapeutic mechanism(s) of DBS may complicate. The authors reported it may involve inhibition or excitation of synaptic, pathological neuronal and network activity, pathological rhythms or oscillation and neurotransmitter systems [38-42].

However, the optimal "antiepileptic parameters" including frequency, duration, and mode of delivery (pulses vs continuous stimulation) of DBS for reducing the frequency of seizures are much variable among patients. Moreover, the suitable stimulation parameters in a patient-specific manner could lead to indispensable for antiepileptic effects. In fact, interpretation of laboratory and clinical data is challenging because of a lot of stimulation protocols used, as the different stimulation frequencies and target locations. The frequencies of stimulation display different strategies to intervene with epileptiform. We will review the mechanisms based on the frequencies. A wide range of stimulation frequencies have been used between 0.1 and 400 Hz. Studies have shown that high frequency stimulation (HFS; usually >70 Hz) and low frequency stimulation (LFS; usually <12 Hz) are beneficial for suppressing epileptic seizures. While intermediate frequencies (IFS, around 50 Hz) trigger epileptic afterdischarges, favor thalamic oscillations and entrain epileptic dynamics, and was actually used as damage method in the kindling model of epilepsy [43-48], not involved in this review.

■ Mechanism of high frequency DBS

Applied a high-frequency stimulation produces a direct and indirect influence on the cell

bodies, dendrites or axons. HFS could produce a transient blockade of intrinsic voltage-gated currents in subthalamic nucleus, indicating single-spike and bursting modes of discharge for interrupting ongoing activities of STN neurons [49]. These effects closely related to the synaptic transmission, underlying HFS may induce the synaptic plasticity [50]. Moreover in rat hippocampal brain slices, depressed excitatory postsynaptic potentials by HFS maybe on account of the decreased presynaptic axon excitability at synapses between CA1 pyramidal neurons and Schaffer collaterals [51]. Synaptic depression induced by HFS may be due to neurotransmitter depletion, reported as decreasing in concentrations of excitatory amino acids such as glutamate and aspartate, while the enhancing of inhibitory synaptic transmission by HFS such as γ-aminobutyric acid releasing from afferent fibers and thereby [52,53]. Similarly, it's been reported local HFS inhibits neurons of human subthalamic nucleus, which may inhibit intrinsic synaptically mediated responses as neuronal firing [54].

Modulation of the network is proposed based on the concept that disease treated with DBS are fundamentally disease of a specific brain network, rather than a specific neuron type, ion channel, or molecule [55]. In order to establish a framework related to network effects of DBS, measurements involved in cerebral blood flow and metabolic imaging, functional imaging, and electrophysiology (including scalp and intracranial electroencephalography and magnetoencephalography). Thalamocortical network is an important structure in epilepsy treat with DBS. In fact, HFS given to any location within the thalamocortical network is likely to affect the whole network. When adding glutamate release and glutamate-dependent activation of I_h, HFS may abolish thalamic network oscillations [56]. Further, HFS conducts the disruption of the thalamocortical network's dysrhythmia by an initial excitatory mechanism and subsequently develops inhibitory processes depending on neurotransmitter release. Regarding this, HFS maybe neither only inhibitory nor excitatory, but rather perform the disruption of network oscillations and rhythmic activity [56-58]. In addition to neurons in the network, astrocytic activity has been effected by HFS, which implicating an important role of astroglia in this modality [59,60]. As astrocytes could be directly depolarized by HFS [61], regulate the inhibitory synapses in activity-dependent modulation and have the potential to modulate distant/local neural networks through the release of adenosine and gliotransmitters including glutamate and ATP [62,63]. In the brain, adenosine is regarded as endogenous anticonvulsant and seizure terminator [64-66]. Furthermore, the upregulation of adenosine and its kinase during the astrogliosis as a crucial link between astrocyte and neuron dysfunction may provide a pivotal role in the abnormal network of neuron and glia in epilepsy [67-69]. Considering of possible action of adenosine in prediction and prevention of epileptogenesis [70], it will be an alternative target in mechanism of DBS in treatment of epilepsy.

■ Mechanism of low frequency DBS

From 1980's, electrical low-frequency stimulation (LFS) has been reported effectively treating kindled seizures [71]. With animal models and clinical applications, it has shown LFS could inhibit seizure activities and reduce frequency of seizures [72-75]. Although numerous researches have displayed the potential therapeutic effect of LFS on epileptic seizures, the underlying mechanisms are still unknown.

LFS induced long-lasting hyperpolarization underlies seizure reduction [76]. And it could decrease the discharges of interictal spiking [72]. LFS showed blockade of in vitro ictogenesis coincides with increased epileptiform response frequency-dependent increase latency in rodent brain slices, which may contribute to decrease epileptiform synchronization [77]. In bilateral hippocampal slice, LFS decreased 4-AP–induced epileptiform activity [76]. Some studies described LFS induces a transient synaptic depression that alters synaptic transmission [45]. Further, LFS in the GPe exerts therapeutic effect on seizures due to interference with delta rhythms [78]. LFS could modulate cortical oscillations with state-dependent [79].

In hippocampal CA1 pyramidal cells of kindled rats, LFS application may have effects on spontaneous inhibitory and excitatory post-synaptic currents preventing seizure-induced raise in the occurrence of sEPSCs and seizure-induced decrease in occurrence and activity duration of sIPSCs [80]. Moreover, LFS could enhance the effectiveness of phenobarbital on GABAergic currents, implicating a positive interaction between phenobarbital and LFS through GABAA currents, which indicated a well effective combined therapy [81]. LFS either immediately or in close interval rapid kindling

stimulation may inhibit the kindling-induced epileptogenesis [82]. It indicates LFS as an efficient technique can be used in closed loop seizure system to predict and prevent epileptic discharges.

Mechanism of DBS for epilepsy and associated comorbidities

Epilepsy patients common happen with other diseases, including nervous system disease, mental illness and physical diseases. The incidences of migraine, tic disorder, autism, attention-deficit/ hyperactivity disorder, depression, anxiety disorders, bipolar disorder and psychotic disorder are much higher than general population [83-89].

Seizures patients are often accompanied with cognitive disorders, particularly in learning and memory related functions, which often regarded as secondary to epilepsy or caused by epilepsy [90-94]. A small sample in patients with refractory temporal lobe epilepsy with amygdalohippocampal DBS showed improvement in emotional wellbeing [95]. Another research with nine patients with intractable epilepsy underwent by bilateral ANT- DBS suggested significant improvements in both verbal recall fluency tasks and oral information processing [30]. Application of LFS in kindling-induced seizure animal models improved cognitive impairment associated spontaneous alternation behavior in Y-maze test, concerning of the upregulation in calcineurin gene expression in the hippocampal area [96]. Further, application of LFS in kindle rats for a long-term could improve effect on spatial learning and memory, which show a dependence of the number of applied LFS [97]. In fact, dysfunction of epilepsy and cognition may even be bidirectional affected with each other, which in some extent share common pathological process following dysfunction of Papez circuit and limbic system including the hippocampus, which induced abnormal hippocampal-dependent behaviors, including spatial learning and memory [94,98-100]. Of interest, Helmstaedter and Witt highlighted the relevance limbic encephalitis to temporal lobe epilepsy with hippocampal atrophy and sclerosis as with successful immunomodulatory therapy, the seizures disappear as well as cognition and mood improving [94], which may provide a new cue to explore the mechanism and application of DBS.

Conclusion

Although there has been a lot of research on the mechanisms of DBS in treating epilepsy, it is still not clear. In fact, because the organism is a complex system, the mechanisms of DBS is complex and different. In this paper, we distinguish the mechanism of different frequencies of epilepsy, but the clinical application of high-frequency stimulation to treat epilepsy, while obviously the role of low frequency stimulation cannot be ignored. It has been reported the latest neuromodulator have been able to carry out high - low frequency conversion therapy, providing an important area of our individual treatment in clinic. We summary the mechanism of DBS for comorbidity of epilepsy, however unabundant, mainly because many diseases accompany epilepsy in the pathological process, they may be transformed into side effects during or after the treatment of DBS epilepsy,, such as depression. This suggests that we should be more delicate and careful in the design of clinical stimulus protocols, to ensure that the benefits of the stimulation process are maximized.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81671285), the Capital Health Research and Development of Special (2016-1-8012), Beijing Municipal Science & Technology Commission (Z161100000516230, Z161100002616016), National Key Research and Development Program (2016YFC0105902), Project supported by Beijing Postdoctoral Research Foundation (2016 ZZ-42).

Reference

1. Neligan A, Hauser WA, Sander JW. The epidemiology of the epilepsies. *Handb. Clin. Neurol* 107(1), 113-133 (2012).
2. Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J. Neurol. Neurosurg. Psychiatry* 61(5), 433-443 (1996).
3. Beghi E, Hesdorffer, D. Prevalence of epilepsy--an unknown quantity. *Epilepsia* 55(7), 963-967 (2014).
4. Fiest KM, Sauro, KM, Wiebe, S, *et al.* Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology* 88(3), 296-303 (2017).
5. Asadi-Pooya AA, Stewart GR, Abrams DJ, *et al.* Prevalence and Incidence of Drug-Resistant Mesial Temporal Lobe Epilepsy in the United States. *World. Neurosurg* 99(1), 662-666 (2017).
6. Golyala A & Kwan P. Drug development for refractory epilepsy: The past 25 years and beyond. *Seizure* 44(1), 147-156 (2017).

7. Hariz MI, Blomstedt P, Zrinzo L. Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg. Focus* 29(2), E1 (2010).
8. Lozano AM, Dostrovsky J, Chen R, *et al.* Deep brain stimulation for Parkinson's disease: disrupting the disruption. *Lancet. Neurol* 1(4), 225-231 (2002).
9. Deniau JM, Degos B, Bosch C, *et al.* Deep brain stimulation mechanisms: beyond the concept of local functional inhibition. *Eur. J. Neurosci* 32(7), 1080-1091 (2010).
10. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends. Neurosci* 12(10), 366-375 (1989).
11. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends. Neurosci* 13(7), 266-271 (1990).
12. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain. Res. Rev* 20(1), 91-127 (1995).
13. Smith Y, Bevan MD, Shink E, *et al.* Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86(2), 353-387 (1998).
14. Temel Y, Blokland A, Steinbusch HW, *et al.* The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Prog. Neurobiol* 76(6), 393-413 (2005).
15. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. *J. Clin. Invest* 119(4), 717-725 (2009).
16. Nestler EJ, Barrot M, DiLeone RJ, *et al.* Neurobiology of depression. *Neuron* 34(1), 13-25 (2002).
17. Pauls DL, Abramovitch A, Rauch SL, *et al.* Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nat. Rev. Neurosci* 15(6), 410-424 (2014).
18. Schulze-Bonhage A. Brain stimulation as a neuromodulatory epilepsy therapy. *Seizure* 44(1), 169-175 (2017).
19. Boccard SG, Pereira EA, Aziz TZ. Deep brain stimulation for chronic pain. *J. Clin. Neurosci* 22(10), 1537-1543 (2015).
20. Mutani R. Cobalt experimental hippocampal epilepsy in the cat. *Epilepsia* 8(4), 223-240 (1967).
21. Reimer GR, Grimm RJ, Dow RS. Effects of cerebellar stimulation on cobalt-induced epilepsy in the cat. *Electroencephalogr. Clin. Neurophysiol* 23(5), 456-462 (1967).
22. Hablitz JJ. Intramuscular penicillin epilepsy in the cat: effects of chronic cerebellar stimulation. *Exp. Neurol* 50(2), 505-514 (1976).
23. Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans. Am. Neurol. Assoc* 98(), 192-196 (1973).
24. Wright GD, Weller RO. Biopsy and post-mortem findings in a patient receiving cerebellar stimulation for epilepsy. *J. Neurol. Neurosurg. Psychiatry* 46(3), 266-273 (1983).
25. Cooper IS, Amin I, Riklan M, *et al.* Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. *Arch. Neurol* 33(8), 559-570 (1976).
26. Lockman J, Fisher RS. Therapeutic brain stimulation for epilepsy. *Neurol. Clin* 27(4), 1031-1040 (2009).
27. Graber KD, Fisher RS. in Jasper's Basic Mechanisms of the Epilepsies, Bethesda MD: Michael A Rogawski, Antonio V Delgado-Escueta, Jeffrey L Noebels, Massimo Avoli and Richard W Olsen., (2012).
28. Cukiert A, Lehtimaki K. Deep brain stimulation targeting in refractory epilepsy. *Epilepsia* 58(1), 80-84 (2017).
29. Kerrigan JF, Litt, B, Fisher, RS, *et al.* Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia* 45(4), 346-354 (2004).
30. Oh YS, Kim, HJ, Lee, KJ, *et al.* Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. *Seizure* 21(3), 183-187 (2012).
31. Gibson WS, Ross, EK, Han, SR, *et al.* Anterior Thalamic Deep Brain Stimulation: Functional Activation Patterns in a Large Animal Model. *Brain. Stimul* 9(5), 770-773 (2016).
32. Cooper IS, Upton AR. Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. *Biol. Psychiatry* 20(7), 811-813 (1985).
33. Fisher R, Salanova V, Witt T, *et al.* Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51(5), 899-908 (2010).
34. Bergey GK, Morrell MJ, Mizrahi EM, *et al.* Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 84(8), 810-817 (2015).
35. Salanova V, Witt T, Worth R, *et al.* Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 84(10), 1017-1025 (2015).
36. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 77(13), 1295-1304 (2011).
37. Heck CN, King-Stephens, D, Massey, AD, *et al.* Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 55(3), 432-441 (2014).
38. Boison D. Deep brain stimulation in the dish: focus on mechanisms. *Epilepsy. Curr* 14(4), 201-202 (2014).
39. McIntyre CC, Savasta M, Kerkerian-Le Goff L, *et al.* Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin. Neurophysiol* 115(6), 1239-1248 (2004).
40. Montgomery EB Jr., Gale JT. Mechanisms of action of deep brain stimulation (DBS). *Neurosci. Biobehav. Rev* 32(3), 388-407 (2008).
41. Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. *Prog. Neurobiol* 133(1), 27-49 (2015).
42. Cagnan H, Pedrosa D, Little S, *et al.* Stimulating at the right time: phase-specific deep brain stimulation. *Brain* 140(Pt 1), 132-145 (2017).
43. Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. *Nature* 214(5092), 1020-1021 (1967).
44. Jayakar P, Alvarez LA, Duchowny MS, *et al.* A safe and effective paradigm to functionally map the cortex in childhood. *J. Clin. Neurophysiol* 9(2), 288-293 (1992).
45. Mina F, Benquet P, Pasnicu A, *et al.* Modulation of epileptic activity by deep brain stimulation: a model-based study of frequency-dependent effects. *Front. Comput. Neurosci* 7(1), 94 (2013).
46. Talairach J, Bancaud J, Szikla G, *et al.* New approach to the neurosurgery of epilepsy. Stereotaxic methodology and therapeutic results. 1. Introduction and history. *Neurochirurgie* 20(Suppl1), 01-240 (1974).
47. Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalogr. Clin. Neurophysiol* 32(3), 281-294 (1972).
48. Pinotsis D, Robinson P, Beim Graben P, *et al.* Neural masses and fields: modeling the dynamics of brain activity. *Front. Comput. Neurosci* 8(1), 149 (2014).
49. Beurrier C, Bioulac B, Audin J, *et al.* High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J. Neurophysiol* 85(4), 1351-1356 (2001).
50. Shen KZ, Zhu ZT, Munhall A, *et al.* Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. *Synapse* 50(4), 314-319 (2003).
51. Kim E, Owen B, Holmes WR, *et al.* Decreased afferent excitability contributes to synaptic depression during high-frequency stimulation in hippocampal area CA1. *J. Neurophysiol* 108(7), 1965-1976 (2012).
52. Liu HG, Yang AC, Meng DW, *et al.* Stimulation of the anterior nucleus of the thalamus induces changes in amino acids in the hippocampi of epileptic rats. *Brain. Res* 1477(1), 37-44 (2012).
53. Liu LD, Prescott IA, Dostrovsky JO, *et al.* Frequency-dependent effects of electrical stimulation in the globus pallidus of dystonia patients. *J. Neurophysiol* 108(1), 5-17 (2012).

54. Filali M, Hutchison WD, Palter VN, *et al.* Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Exp. Brain. Res* 156(3), 274-281 (2004).

55. Llinas RR, Ribary U, Jeanmonod D, *et al.* Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl. Acad. Sci. U S A* 96(26), 15222-15227 (1999).

56. Lee KH, Hitti FL, Chang SY, *et al.* High frequency stimulation abolishes thalamic network oscillations: an electrophysiological and computational analysis. *J. Neural. Eng* 8(4), 046001 (2011).

57. McIntyre CC, Hahn PJ. Network Perspectives on the Mechanisms of Deep Brain Stimulation. *Neurobiol. Dis* 38(3), 329-337 (2010).

58. Alhourani A, McDowell MM, Randazzo MJ, *et al.* Network effects of deep brain stimulation. *J. Neurophysiol* 114(4), 2105-2117 (2015).

59. Witcher MR, Ellis TL. Astroglial Networks and Implications for Therapeutic Neuromodulation of Epilepsy. *Front. Comput. Neurosci* 6(1), 61 (2012).

60. Vedam-Mai V, van Battum EY, Kamphuis W, *et al.* Deep brain stimulation and the role of astrocytes. *Mol. Psychiatry* 17(2), 124-131, 115 (2012).

61. Kang J, Jiang L, Goldman SA, *et al.*. Astrocyte-mediated potentiation of inhibitory synaptic transmission. *Nat. Neurosci* 1(8), 683-692 (1998).

62. Tawfik VL, Chang, SY, Hitti, FL, *et al.* Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. *Neurosurgery* 67(2), 367-375 (2010).

63. Bekar L, Libionka, W, Tian, GF, *et al.* Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nat. Med* 14(1), 75-80 (2008).

64. Boison D. Adenosinergic signaling in epilepsy. *Neuropharmacology* 104(1), 131-139 (2016).

65. Li T, Quan Lan J, Fredholm BB, *et al.* Adenosine dysfunction in astrogliosis: cause for seizure generation? *Neuron. Glia. Biol* 3(4), 353-366 (2007).

66. Luan G, Gao Q, Zhai F, *et al.* Adenosine kinase expression in cortical dysplasia with balloon cells: analysis of developmental lineage of cell types. *J. Neuropathol. Exp. Neurol* 74(2), 132-147 (2015).

67. Li T, Lytle N, Lan JQ, *et al.* Local disruption of glial adenosine homeostasis in mice associates with focal electrographic seizures: a first step in epileptogenesis? *Glia* 60(1), 83-95 (2012).

68. Luan G, Gao Q, Guan Y, *et al.* Upregulation of adenosine kinase in Rasmussen encephalitis. *J. Neuropathol. Exp. Neurol* 72(11), 1000-1008 (2013).

69. Li T, Steinbeck JA, Lusardi T, *et al.* Suppression of kindling epileptogenesis by adenosine releasing stem cell-derived brain implants. *Brain* 130(Pt 5), 1276-1288 (2007).

70. Li T, Ren G, Lusardi T, *et al.* Adenosine kinase is a target for the prediction and prevention of epileptogenesis in mice. *J. Clin. Invest* 118(2), 571-582 (2008).

71. Gaito J, Nobrega JN, Gaito ST. Interference effect of 3 Hz brain stimulation on kindling behavior induced by 60 Hz stimulation. *Epilepsia* 21(1), 73-84 (1980).

72. Yamamoto J, Ikeda A, Satow T, *et al.* Low-frequency electric cortical stimulation has an inhibitory effect on epileptic focus in mesial temporal lobe epilepsy. *Epilepsia* 43(5), 491-495 (2002).

73. Goodman JH, Berger RE & Tcheng TK. Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. *Epilepsia* 46(1), 1-7 (2005).

74. Lim SN, Lee CY, Lee ST, *et al.* Low and High Frequency Hippocampal Stimulation for Drug-Resistant Mesial Temporal Lobe Epilepsy. *Neuromodulation* 19(4), 365-372 (2016).

75. Ghotbeddin Z, Janahmadi M, Yadollahpour A. Study of the anti-seizure effects of low-frequency stimulation following kindling (a review of the cellular mechanism related to the anti-seizure effects of low-frequency electrical stimulation). *Neurol. Sci* 38(1), 19-26 (2017).

76. Toprani S, Durand DM. Long-lasting hyperpolarization underlies seizure reduction by low frequency deep brain electrical stimulation. *J. Physiol* 591(22), 5765-5790 (2013).

77. Kano T, Inaba Y, D'Antuono M, *et al.* Blockade of in vitro ictogenesis by low-frequency stimulation coincides with increased epileptiform response latency. *J. Neurophysiol* 114(1), 21-28 (2015).

78. Cheng H, Kuang YF, Liu Y, *et al.* Low-frequency stimulation of the external globus palladium produces anti-epileptogenic and anti-ictogenic actions in rats. *Acta. Pharmacol. Sin* 36(8), 957-965 (2015).

79. Alagapan S, Schmidt SL, Lefebvre J, *et al.* Modulation of Cortical Oscillations by Low-Frequency Direct Cortical Stimulation Is State-Dependent. *PLoS. Biol* 14(3) (2016).

80. Ghafouri S, Fathollahi Y, Semnanian S, *et al.* Effects of Low Frequency Stimulation on Spontaneous Inhibitory and Excitatory Post-Synaptic Currents in Hippocampal CA1 Pyramidal Cells of Kindled Rats. *Cell. J* 18(4), 547-555 (2017).

81. Asgari A, Semnanian S, Atapour N, *et al.* Low-frequency electrical stimulation enhances the effectiveness of phenobarbital on GABAergic currents in hippocampal slices of kindled rats. *Neuroscience* 330(1), 26-38 (2016).

82. Jalilifar M, Yadollahpour A, Moazedi AA, *et al.* Low Frequency Electrical Stimulation Either Prior to or after Rapid Kindling Stimulation Inhibits the Kindling-Induced Epileptogenesis. *Biomed. Res. Int* 2017(1), 8623743 (2017).

83. Kanner AM. Depression in Epilepsy: A Neurobiologic Perspective. *Epilepsy. Curr* 5(1), 21-27 (2005).

84. Kanner AM. Mood disorder and epilepsy: a neurobiologic perspective of their relationship. *Dialogues. Clin. Neurosci* 10(1), 39-45 (2008).

85. Toldo I, Perissinotto, E, Menegazzo, F, *et al.* Comorbidity between headache and epilepsy in a pediatric headache center. *J. Headache. Pain* 11(3), 235-240 (2010).

86. Brooks-Kayal AR, Bath, KG, Berg, AT, *et al.* Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia* 54(04), 44-60 (2013).

87. Cardamone L, Salzberg M, O'Brien T, *et al.* Antidepressant therapy in epilepsy: can treating the comorbidities affect the underlying disorder? *Br. J. Pharmacol* 168(7), 1531-1554 (2013).

88. Reilly C, Atkinson P, Das KB, *et al.* Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics* 133(6), e1586-1593 (2014).

89. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. *Handb. Clin. Neurol* 134(1), 267-285 (2016).

90. Holmes GL. The long-term effects of seizures on the developing brain: clinical and laboratory issues. *Brain. Dev* 13(6), 393-409 (1991).

91. Helmstaedter C, Kurthen M, Lux S, *et al.* Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann. Neurol* 54(4), 425-432 (2003).

92. Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet. Neurol* 3(11), 663-672 (2004).

93. Jambaque I, Pinabiaux C, Lassonde M. Cognitive disorders in pediatric epilepsy. *Handb. Clin. Neurol* 111(1), 691-695 (2013).

94. Helmstaedter C, Witt JA. Epilepsy and cognition - A bidirectional relationship? *Seizure* S1059-1311(17), 30154-30161 (2017).

95. Miatton M, Van Roost D, Thiery E, *et al.* The cognitive effects of amygdalohippocampal deep brain stimulation in patients with

temporal lobe epilepsy. *Epilepsy. Behav* 22(4), 759-764 (2011).

96. Ghafouri S, Fathollahi Y, Javan M, *et al.* Effect of low frequency stimulation on impaired spontaneous alternation behavior of kindled rats in Y-maze test. *Epilepsy. Res* 126(1), 37-44 (2016).

97. Esmaeilpour K, Sheibani V, Shabani M, *et al.* Effect of low frequency electrical stimulation on seizure-induced short- and long-term impairments in learning and memory in rats. *Physiol. Behav* 168(1), 112-121 (2017).

98. Beldhuis HJ, Everts HG, Van der Zee EA, *et al.* Amygdala kindling-induced seizures selectively impair spatial memory. 1. Behavioral characteristics and effects on hippocampal neuronal protein kinase C isoforms. *Hippocampus* 2(4), 397-409 (1992).

99. Cammisuli S, Murphy MP, Ikeda-Douglas CJ, *et al.* Effects of extended electrical kindling on exploratory behavior and spatial learning. *Behav. Brain. Res* 89(1-2), 179-190 (1997).

100. Laxpati NG, Kasoff WS, Gross RE. Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials. *Neurotherapeutics* 11(3), 508-526 (2014).