Effects of Deep Brain Stimulation on Neurotransmitter Systems in Rodent Models of Epilepsy
A Systematic Review

Rafi Matin[1,2], Kristina K. Zhang[1,2], Flavia Venetucci Gouveia[1], George M. Ibrahim[1,2,3]

[1]Neuroscience and Mental Health, The Hospital for Sick Children. [2]Institute of Medical Science, University of Toronto, [3]Division of Neurosurgery, Hospital for Sick Children, Toronto, Ontario, Canada

Introduction

- One-third of patients with epilepsy continue to experience debilitating seizures despite receiving the best available medical treatments[1].
- Deep brain stimulation (DBS) is a neuromodulation technique that involves surgically implanting electrodes to electrically stimulate specific brain regions and is a promising treatment for patients with refractory epilepsy[2].
- However, the specific mechanisms by which DBS reduces seizures are not well understood, hindering the development of more personalized treatments for optimal seizure reduction [3].
- The effects of DBS on neurotransmitter systems have been characterized in other disorders, but this has been less thoroughly investigated in the context of epilepsy [4].
- Here, we present findings from a systematic review on studies in rodent models of epilepsy that have explored the effects of DBS on neurotransmitters.

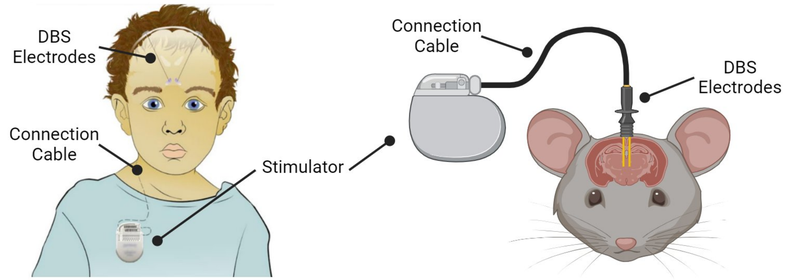

Figure 1. DBS in clinical and preclinical settings. DBS electrodes are surgically implanted in precise brain regions, delivering controlled electrical currents generated by a stimulator.

Objectives

1. Review the preclinical literature investigating DBS effects on neurotransmitters in rodent models of epilepsy.
2. Summarize the targeted brain regions, neurotransmitters studied, and employed methods.
3. Highlight the major effects of DBS on neurotransmitter systems associated with therapeutic effects.

Methods

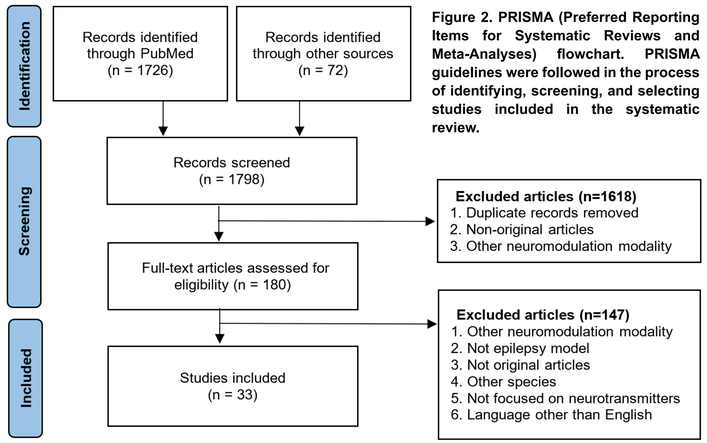

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. PRISMA guidelines were followed in the process of identifying, screening, and selecting studies included in the systematic review.

Results

Brain regions targeted

A variety of brain regions were targeted with DBS across the included articles. The most frequently targeted brain regions includes the anterior thalamic nuclei (ANT) (n=6, 22.2%), hippocampus (n=5, 18.5%), amygdala (n=5, 18.5%), and perforant path (n=5, 18.5%) (Fig 3).

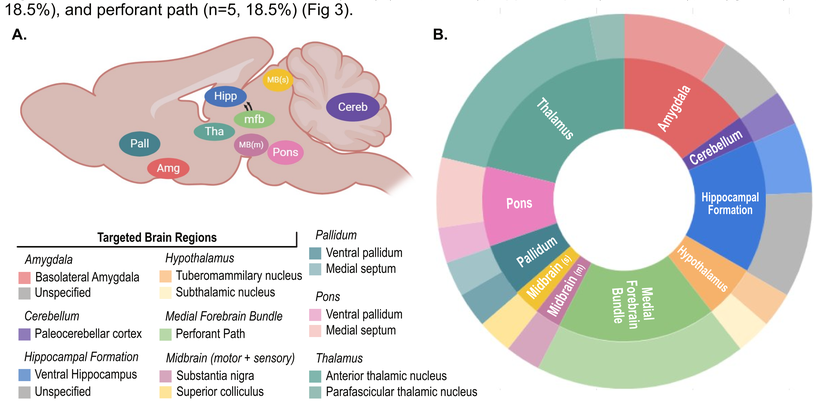

Figure 3. Brain regions targeted by DBS. A) Scheme of a sagittal view on a rodent brain illustrating the brain regions targeted by DBS. B) Overview of the targeted brain regions across included articles.

Neurotransmitters studied & methods employed

The effects of DBS were most frequently studied in relation to GABA (47.2% of studies), serotonin (5-HT) (13.9%), and adenosine (11.1%) (Fig 4A). Various methods were used to asses neurotransmitter effects at different durations of DBS (Fig 4B).

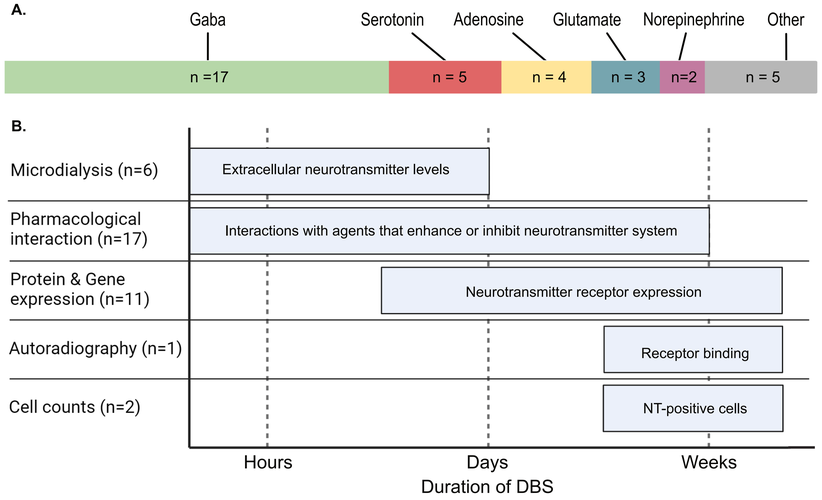

Figure 4. Overview of neurotransmitters studied and methods employed. (A) Breakdown of neurotransmitters studied across included articles. "Other" neurotransmitters included opioids, endocannabinoids, galanin, and histamine. (B) Overview of methods used to assess neurotransmitter effects, including the duration of DBS studied for each method, and the primary outcomes obtained. Abbreviations: NT, neurotransmitter.

Effects of DBS on neurotransmitters

Table 1. Effects of DBS on neurotransmitter systems.

DBS Target	Neurotransmitter	Primary Findings
Anterior nucleus of the thalamus	Adenosine	↑ Adenosine levels in the hippocampus ↓ Adenosine-kinase levels in the hippocampus
	GABA	↑ GABA levels in the hippocampus ↑ Hippocampal GABAergic interneurons
	Glutamate	↓ Glutamate levels in the hippocampus
	Serotonin	↑ local 5HT metabolite levels Antiseizure effects were blocked with 5-HT1A receptor antagonist
Basolateral amygdala	GABA	Antiseizure effects were augmented with GABAergic ASMs ↑ GABAa receptor binding as measured by autoradiography
	Serotonin	Antiseizure effects were blocked with 5-HT1A receptor antagonist
Basal ganglia	GABA	↑ GABA levels in the SNr (STN-DBS) Antiseizure effects were blocked with GABAa receptor antagonist (SNr-DBS)
	Glutamate	↑ glutamate levels in the SNr & GP (STN-DBS)
Cerebellum	GABA	Antiseizure effects were augmented with GABAergic ASMs
Hippocampal formation	GABA	↑ local GABA levels & GABAa receptor expression Antiseizure effects were augmented with GABAergic ASMs
Locus Coeruleus	Norepinephrine	Antiseizure effects were blocked with β-adrenoceptor antagonists
Perforant path	Adenosine	↑ Adenosine A1 receptor expression in the dentate gyrus
	Galanin	↑ GalR1, GalR2 receptor expression in the dentate gyrus
	Endocannabinoids	↑ CB1 receptor expression in the dentate gyrus

Abbreviations: ASM, anti-seizure medication; CB, cannabinoid; DBS, deep brain stimulation; GABA, gamma-aminobutyric acid; GalR, galanin receptor; GP, globus pallidus; SNr, substantia nigra; STN, subthalamic nucleus; 5HT, 5-hydroxytryptamine.

Conclusions

- Various brain regions and neurotransmitters have been studied, indicating that DBS has duration-dependent effects, influencing neurotransmitter systems both locally at the target site and in remote regions.
- Studies have primarily focused on the effects of DBS on inhibitory neurotransmitters, such as GABA, often exploring effects within a specific region.
- Future research should consider exploring changes in both excitatory and inhibitory neurotransmitters across broader neural networks.

References & Acknowledgements

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