



## Review

# Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy

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## ABSTRACT

Epilepsy affects 50 million people worldwide and about 30% of these patients will not be adequately controlled with antiepileptic drugs (AEDs) alone. For patients where resective surgery is not indicated, deep brain stimulation (DBS) may be an effective alternative. The majority of available literature targets the thalamic nuclei (anterior; centromedian), subthalamic nucleus, hippocampus, and cerebellum. Here, we review patient outcomes and adverse events related to DBS to these various targets. Data show DBS may be a safe and effective treatment option for refractory epilepsy.

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## 1. Introduction

Epilepsy is a very common neurological disorder occurring in approximately 50 million people worldwide [1]. Of these patients, approximately 15 million (30%) experience inadequate control of their seizures with medications alone [2]. Meta-analysis of available data suggests that modern anti-epileptic drugs (AEDs) will only benefit about 6% of these patients over placebo [3]. Drug resistant epilepsy has been suggested to occur as a result of two major mechanisms. The first is decreased net entry of the drug through the blood–brain barrier due to P-glycoprotein, a natural cellular defense that extrudes xenobiotics [4]. In refractory epilepsy, it has been suggested that P-glycoprotein is overexpressed leading to decrease drug transport through the blood–brain barrier and thus sub-therapeutic levels [5]. The second mechanism of drug resistance is reduced sensitivity to the drug at a cell-receptor level or by altering sensitivity of ion channels [6–8]. Standard of care for drug-refractory epilepsy is resective epilepsy surgery. For example, surgery is reported to lead to long-term seizure freedom in about 58% of medial temporal lobe epilepsy (MTLE) patients eligible for surgery [9]. When surgical intervention is not indicated or where surgery did not provide relief, deep brain stimulation (DBS) is one alternative treatment for refractory epilepsy. Other well studied interventions include ketogenic diet [10–14], vagal nerve stimulation [15–17], and perhaps trigeminal nerve stimulation [18–21].

In this review, we focus on available clinical data for the use of DBS in the treatment of refractory epilepsy in studies with well-defined anatomic targets. The mechanisms by which DBS improves seizure outcomes and preclinical data will also be discussed. Table 1 summarizes findings, stimulation parameters, and patient data from each study. Current clinical trials for DBS in epilepsy are presented in Table 2.

## 2. Mechanism

A detailed mechanism of action of DBS has yet to be established, though several mechanisms of action have been proposed. Stimulation of brain structures with electrodes may lead to inhibition of those structures [22]. Stimulation could therefore be applied directly to a seizure focus or along a conducting pathway to exert its effects. The obvious benefit of using neuromodulation to inhibit seizure activity versus a more invasive surgical procedure is that stimulation is reversible and modifiable. The exact mechanism of inhibition very likely depends on which brain structure is being stimulated [22]. Functional MR imaging (fMRI) has been performed during stimulation studies, and has shown that it activates cortical and subcortical neuronal pathways [23]. Specifically, stimulation of thalamic ventralis caudalis led to activation of the primary somatosensory cortex, secondary somatosensory cortex, other parts of the thalamus and insula, while stimulation of the

periventricular gray matter led to activation of the cingulate cortex and the medial wall of the third ventricle [23]. The thalamus and basal ganglia were activated when stimulation was applied to the ventral intermediate nucleus (VIM) of the thalamus [23]. This sort of network mapping makes fMRI an ideal imaging tool to help appreciate the connections and possibly mechanisms involved in DBS therapy.

In 2002, a study of 14 patients ( $n = 10$  with Parkinson's disease (PD);  $n = 4$  with epilepsy) were examined with EEG following DBS implantations to the subthalamic nucleus (STN) in an effort to better understand the mechanism underlying its clinical effects [24]. Single, paired, and burst pulses were tested. They found that burst pulses at therapeutic frequency augmented rather than diminishing the EEG response, suggesting STN DBS does not exert effects by a simple inhibitory function [24]. It has been reported that the suppressive effects may be due to an increase in extracellular potassium and neural depolarization blockade [25]. Further, they report that direct current (DC) stimulation was able to suppress activity due to membrane hyperpolarization [25]. Other studies have found that the hyperpolarizing effects were mediated by GABA<sub>B</sub> inhibitory post-synaptic potentials and a slow after-hyperpolarization, not depolarizing blockade [26]. It has also been suggested that highly plastic neural networks change with DBS in a protective manner to prevent seizures [27]. Frequency of stimulation is well documented to affect outcomes. For example, animal models show high-frequency stimulation in temporal lobe epilepsy (TLE) is superior to low-frequency stimulation [28–30].

More recent data suggest that DBS can reduce phase-amplitude interactions in synchronized neuronal network seen in Parkinson's disease (PD) [31]. Phase-amplitude coupling between low-frequency rhythms and amplitude of broadband activity may allow for communication between regions of the brain [32]. To determine the effect of DBS on phase-amplitude coupling, 23 PD patients underwent STN stimulation with simultaneous electrocorticography potential recording. STN stimulation led to decreased phase-amplitude coupling that was reversed upon cessation of stimulation. Specifically, decreases in interactions between the phase of beta rhythm (13–30 Hz) and broadband (50–200 Hz) amplitude were seen along with improvements in measures of clinical function [31]. This suggests that correction of over-active phase-amplitude coupling may underlie the mechanism of DBS in PD and could be examined in epileptic circuits as well.

Some concerns exist in the literature about the efficacy of DBS with and without a reported micro-lesional effect caused by electrode placement, especially within the thalamus ('microthalamotomy'). This is suggested to account for at least part of the seizure reduction effect in some of the studies reviewed [33–40], but debated or specifically controlled for by others [41–45]. A number of targets have been utilized in an attempt to control seizures,

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