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A Closer Look at the Psychiatric Effects of Deep Brain Stimulation to Further Guide Treatment of Refractory Epilepsy: A Focused Review

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INTRODUCTION

The effective treatment of medically-refractory epilepsy continues to be a challenge in many patients. This is especially true in those patients who do not meet criteria for resective surgery. The advent of neurostimulation for the treatment of refractory epilepsy has certainly increased the probability of gaining better control in these patients. Until more recently, vagal nerve stimulation was the only FDA approved neuromodulating treatment for the management of refractory epilepsy. In 2013 responsive neurostimulation (RNS) emerged as a promising treatment. However, it was not without limitations including the number of seizure foci that could be targeted and the inability to obtain magnetic brain imaging following placement. In 2018 deep brain stimulation (DBS) was finally approved for the treatment of medically-refractory epilepsy, though the antiepileptogenesis of deep brain stimulation has been explored for decades[1]. The results of the SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) trial led to this FDA approval and, though very promising given the efficacy in seizure reduction, concerns regarding the possible risk of adverse, psychiatric effects were raised[2,3].

The adverse, psychiatric effects reported in the SANTE trial may result in avoiding the use of DBS in epilepsy patients with history of depression, suicidality and other known psychiatric illness. While this is a reasonable caution, in many refractory epilepsy patients DBS may be the only option for improved seizure control. Thus, it is prudent to more thoroughly explore the possible, psychiatric risks associated with DBS. This review will focus on the psychiatric effects reported in various DBS targets to better determine the mental health risks and identify safer targets.

METHODS

A search of the clinical literature published between January 1, 1990 and December 31, 2019 was completed. The most relevant papers were reviewed with a focus on adverse effects, specifically adverse, psychiatric effects. The references cited in selected papers were utilized to obtain additional resources.

References listed in supplemental document

RESULTS

DBS Target	No. subjects	Indication	Stimulation parameters	Psychiatric Effects
ANT[2,3,8–21]	2-110	Epilepsy	60-185 Hz, 60-300 µs, 1-10 V	AE reported in 9 of 16 studies
CB[1,22–25]	5-17	Epilepsy	10-180 Hz, 450 µs, 2.28 V	**No AE reported**, favorable effects in 2 of 5 studies
CMN[12,26–31]	2-13	Epilepsy	60-185 Hz, 90-300 µs, 1-10 V	**No AE reported**, favorable effects in 1 of 8 studies
HIP[32–46]	2-16	Epilepsy	90-200 Hz, 60-450 µs, 1-6 V	**No AE reported**
HyTH[47–50]	3-11	CCH, Obesity, Epilepsy	180-185 Hz, 60-90 us, 1-7 V	**No AE reported**, favorable effects in 1 of 4 studies
IC[51–59]	6-30	OCD, TRD Poststroke pain	30-190 Hz, 60-330 us, 1-9 V	AE reported in all studies
NA[15,60,61]	4-10	Epilepsy, TRD	100-150 Hz, 60-210 µs, 1.5-10 V	AE only reported with combined targets (NA+caudate, NA+ANT)
SCG[62–69]	6-60	Anorexia, TRD	20-135 Hz, 90-450 µs, 2.5-8 V	AE reported in all studies
STN/GPi[7,56,70–87]	6-183	PD, OCD	125-185 Hz, 60-270 µs, 1-8 V	AE reported in 18 of 20 studies, stable effects in 1 study, favorable effects in 1 study
VIM[88–92]	10-127	ET, AT	100-185 Hz, 60-150 µs, 1-8.5V	AE reported in 3 of 5 studies

Psychiatric effects associated with each DBS target. Not all studies reported stimulation parameters. The parameters listed are a range of the parameters reported for each target.
ANT – Anterior nucleus of thalamus, CB – cerebellum, CMN – centromedian nucleus, HIP – hippocampus, HyTH – hypothalamus, IC – internal capsule (anterior limb, VC/VC – ventral capsule/ventral striatum), NA – nucleus accumbens, SCG – subcallosal cingulate gyrus, STN/GPi – subthalamic nucleus/globus pallidus internus, VIM – ventral intermediate nucleus
CCH – chronic cluster headache, OCD – obsessive compulsive disorder, TRD – treatment resistant depression, PD – Parkinson's disease, ET – essential tremor, AT – axial tremor
SI – suicidal ideation, SA – suicide attempt

DBS Target	Reported Psychiatric Effects
ANT	Anxiety, depression, paranoid ideation, "strange thoughts", SI, completed suicide
CB	None reported
CMN	None reported*
HIP	None reported
HyTH	None reported
IC	Anxiety, hypomania, transient sadness, SI, SA, worsening depression
NA	Depression, SI, SA only with combined targeting (NA+caudate, NA+ANT)
SCG	Anxiety, depression, hypomania, mania, SI, SA, completed suicide
STN/GPI	Anxiety, depression, hypomania, mania, transient mood changes, unstable mood, psychosis
VIM	Depression, transient nightmares, psychiatric disorders

*transient auditory hallucinations

DISCUSSION

By far, the DBS targets most associated with adverse, psychiatric effects include the STN and GPI as well as the SCG, IC and VIM. Mixed results were noted for the ANT as approximately half of the studies noted no adverse, psychiatric effects. For the SCG and IC, it is unclear how much the underlying, psychiatric illness of the patients contributed as for most of the studies involving these targets the indication for stimulation was treatment resistant depression. Stimulation of the SCG and IC has also shown improvement in depression[4].

The CB, CMN, HIP and HyTH are targets that may be deemed safer for further exploration. No adverse, psychiatric effects were reported and favorable effects were associated with targeting of the CB and HyTH. Hippocampal volume loss has been associated with depressive symptoms, thus hippocampal stimulation may lead to improvements in mood over time[5]. The involvement of the CMN and HyTH in mood is unclear. There is, however, some thought that the CB may have implications in modulating mood and psychiatric illness[6].

Though there are possible risks of adverse, psychiatric effects with select DBS targets, this may not have to completely preclude their use in patients with psychiatric illness. Understanding the risks and appropriately educating and counseling patients may reduce risks. The results of this review have re-demonstrated the psychiatric risks associated with STN stimulation. However, improvements in depression, anxiety and coping has been shown in STN DBS patients who received appropriate psychiatric education prior to and after implantation[7].

The limitations of this review include the lack of consistency among studies in reporting adverse, psychiatric effects as well as small sample sizes. Additionally, few studies utilized standardized methods for collecting data on psychiatric symptoms.

CONCLUSION

In conclusion the CB, CMN, HIP and HyTH are DBS targets not readily associated with adverse, psychiatric effects. These targets should be further explored to better determine their efficacy in the treatment of medically-refractory epilepsy. Additionally, more precise and standardized collection of psychiatric data in DBS epilepsy patients is needed. Pre-implantation education and close post-implantation evaluation for psychiatric effects may decrease the overall risks of psychiatric morbidity and mortality.