HHS Public Access

Author manuscript

Psychiatr Clin North Am. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Psychiatr Clin North Am. 2018 September ; 41(3): 479–483. doi:10.1016/j.psc.2018.04.008.

Therapeutic Applications of Invasive Neuromodulation in Children and Adolescents

Deniz Doruk Camsari, MD[1], **Melissa Kirkovski, PhD**[2], and **Paul E. Croarkin, DO**[1,*]

[1]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, USA

[2]Deakin Child Study Centre, School of Psychology, Deakin University, Geelong, Australia

SUMMARY

While the application of non-invasive brain stimulation methods to children and adolescents has been frequently studied in depression, autism spectrum disorder, attention-deficit hyperactivity disorder, and other neuropsychiatric disorders, invasive methods such as deep brain stimulation (DBS) and vagal nerve stimulation (VNS) have received less attention. At present, DBS and VNS have demonstrated utility in young patients especially for dystonia and epilepsy in children. Notably, VNS has FDA clearance for intractable epilepsy in patients aged 4 years and older. Further measured work with invasive neuromodulation for children and adolescents with debilitating neuropsychiatric disorders could provide new treatment options and expand current knowledge base of neurocircuitry across development.

Keywords

neuromodulation; invasive brain stimulation; deep brain stimulation; DBS; vagal nerve stimulation; VNS; children; adolescents

INVASIVE NEUROMODULATION

Neuromodulation is a rapidly growing field that includes a variety of stimulation modalities. While neuromodulation techniques have been used to treat medical conditions for thousands of years, contemporary neuromodulation began in the 1960s with the advent of deep brain stimulation (DBS). In adults, advances and growing evidence in the efficacy and safety of invasive neuromodulation techniques have already led to the study and in some cased FDA clearance for a number of indications. Parkinson's disease, essential tremor, and epilepsy are

*Corresponding Author: Paul Croarkin, DO, 200 First Street SW, Rochester, MN 55905, telephone: (507) 239-2557, croarkin.paul@mayo.edu.

FINANCIAL DISCLOSURES

Dr. Croarkin has received research grant support from Pfizer, Inc., National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Mayo Clinic Foundation. He has received equipment support from Neuronetics, Inc. and receives supplies and genotyping services from Assurex Health, Inc. for investigator-initiated studies. He is the primary investigator for a multicenter study of adolescent TMS funded by Neuronetics, Inc. Drs. Doruk Camsari and Kirkovski have no financial disclosures

the most widely studies conditions in adults.[1] As of 2017, FDA clearance in children are limited to use of vagal nerve stimulation (VNS) in drug resistant epilepsy, and DBS in dystonia.

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) is an invasive neuromodulatory technique that involves electrical stimulation of the 10th cranial nerve, the vagus nerve, via an implanted electrical stimulator. Vagal nerve stimulation (VNS) is most commonly used to treat intractable epilepsy and treatment resistant depression.[2] Common stimulation settings are 1–3 mA, 20–30Hz, 130–500 μs.[2] In 1997 the FDA approved the use of VNS in treatment of intractable epilepsy in adults and children ages 12 and older.[3] In 2017 another device was approved for partial-onset medication refractory epilepsy in patients as young as 4. A systematic review and meta-analysis of the efficacy of VNS in 326 children described a response rate of 38% (more than 50% reduction in seizure frequency). The study did note high variability and limited evidence.[4] In order to assess tolerability and side effect profile the authors included additional case reports and retrospective studies, with a total of 1249 children included. Despite the high percentage of side effects (70–80%), the majority of the patients tolerated these side effects well and continued treatment. Common side effects included procedure-related complications including hoarseness (1%), dyspnea (<1%), fluid collection around the stimulator, infection (3%). Other side effects were device-related complications such as hardware failure (3%) and stimulus-related complications such as aspiration (%5) due to vocal cord dysfunction during stimulation period including. Arrhythmias were noted as delayed complications. There were 5 sudden unexplained death in epilepsy patients (SUDEP) and 4 unrelated deaths. The authors also maintained that that VNS may improve sleep quality, behavior, mood and reduce treatment expense.[4]

Deep Brain Stimulation

Deep brain stimulation (DBS) is one of the early brain stimulation techniques that emerged in 1960s and has since been used to treat multiple different neurological and psychiatric conditions. DBS is an invasive procedure where the lead is placed in the targeted areas of the brain and is connected to the implanted pulse generator which is extracranially placed. DBS is considered favorable as compared to surgical ablation procedures with regard to reversibility of the procedure and lower risk of complications.[5] The FDA cleared DBS for Parkinson's Disease tremor in 2001 and essential tremor in 1997. Other indications under FDA humanitarian device exemptions include dystonia in 2007, obsessive compulsive disorder in 2009 and closed loop stimulation for epilepsy.[6] Other areas of interest include major depressive disorder, Tourette's Syndrome, addictions, and obesity. In children, DBS use has been primarily limited to dystonia, but epilepsy, TD and OCD have also been considered as potential targets.

Dystonia

When pharmacological interventions fail to provide improvement, more invasive interventions such as pallidotomy and DBS are considered to treat symptoms and decrease disease burden in dsytonia.[7,8] The Globus Pallidus interna (GPi) has been the main target of DBS in treating dystonia in both adults [6] and children,[9,10] however other regions, including

the STN and thalamic ventralis intermedius have also been targeted. Bilateral stimulation of GPi with higher frequencies (100 Hz) has been reported to be the most common application of DBS in dystonia, yet lower frequencies have also been used.[8] Wider pulses were found to be poorly tolerated.[10] DBS has been shown to have superior efficacy especially in primary generalized dystonia.[11] Haridas and colleagues demonstrated that in primary generalized dystonia patients (n=22) under the age of 21, DBS is a safe method of treatment leading up to 94% improvement in Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) motor scores at 3 years follow-up.[9] Several factors have been identified as good prognostic factors[8] including early intervention,[12,13] certain gene mutations,[12] and absence of other clinical features such as contractures.[14] Other subgroups of dystonia were also explored in terms of DBS responsiveness including dyskinetic cerebral palsy (DCP),[15] and pantothenate kinase associated neuro- degeneration (PKAN),[16] as well as other acquired dystonia due to prematurity and kern icterus, and neurodevelopmental and degenerative dystonia, but the evidence is limited.[8]

Tourette's Disorder

In refractory cases of TD, DBS has been shown to be an effective treatment to reduce symptoms but there are few studies in children and adolescents. An important limitation to use of DBS in children is the temporal decline in symptom severity by adulthood with almost 30% of the patients becoming symptom free, and 75% experiencing significant improvement in their symptoms over time.[17] Among the few case reports, Shaded and colleagues showed that bilateral GPi-DBS in a 16-year-old patient with intractable Tourette's Syndrome was effective to reduce tic severity by 76% for motor and 68% for vocal tics leading to significant improvement in impairment, neurocognitive functions and comorbid OCD symptoms.[18] Similar improvements were reported in another study that include two patients under 18 with the stimulation of centro-median parafascicular (CM-POF) nucleus of thalamus.[19] Conversely, Dueck and colleagues reported no improvement of symptoms with bilateral GPi-DB in 16-year-old patient with TS and intellectual disability.[20]

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) characterized by obsessions and compulsions and its prevalence in children and adolescents is estimated to be 3%.[21] Neuroimaging studies have demonstrated disturbance of cortico-striato-thalamo-cortical circuits in OCD.[22,23] Initial treatment options include CBT with exposure response prevention and pharmacotherapy, yet approximately 50% of pediatric patients fail to respond initial therapeutic approaches.[24] In certain circumstances stereotactic ablation has been shown to be effective.[25] In adults DBS was approved under humanitarian device exemption by the FDA in 2009 for the treatment of OCD. Common target of DBS include the anterior capsule and the nucleus accumbens, leading up to 38% improvements and even remission. In children and adolescents given the possibility of spontaneous remission into adulthood, invasive techniques remain a last resort. However, a 16 year-old patient with bilateral GPi-DBS had improvements in OCD symptoms.[26]

SUMMARY

Invasive brain stimulation techniques such as DBS and VNS have emerged as important therapeutic modalities for adults with Parkinson's disease, essential tremor, treatment resistant depression, obsessive-compulsive disorder, and epilepsy. At present, systematic studies of DBS and VNS in children are lacking. As with noninvasive neuromodulation, future research and clinical practice with children receiving invasive forms of brain stimulation must involve careful consideration of ethical and neurodevelopmental concerns. In the future, noninvasive neuromodulation will likely present options for young patients with severe neuropsychiatric disorders and could inform developmental understandings of neurocircuitry.

References

1. Youngerman BE, Chan AK, Mikell CB, McKhann GM, Sheth SA. A decade of emerging indications: deep brain stimulation in the United States. Journal of neurosurgery. 2016; 125(2):461–471. [PubMed: 26722851]
2. Edwards CA, Kouzani A, Lee KH, Ross EK. Neurostimulation Devices for the Treatment of Neurologic Disorders. Paper presented at: Mayo Clinic Proceedings; 2017.
3. Schachter SC. Vagus nerve stimulation therapy summary Five years after FDA approval. Neurology. 2002; 59(6 suppl 4):S15–S29.
4. Klinkenberg S, Majoie H, Aalbers M, et al. Vagus nerve stimulation in children with epilepsy a review of literature on efficacy, secondary effects, and side-effects. VNS in children. 2015:17.
5. Pahwa R, Lyons KE, Wilkinson SB, et al. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. Movement disorders. 2001; 16(1):140–143. [PubMed: 11215575]
6. Tekriwal A, Baltuch G. Deep Brain Stimulation: Expanding Applications. Neurologia Medico-Chirurgica. 2015; 55(12):861–877. [PubMed: 26466888]
7. Mink JW. Special concerns in defining, studying, and treating dystonia in children. Mov Disord. 2013; 28(7):921–925. [PubMed: 23893449]
8. Cif L, Coubes P. Historical developments in children's deep brain stimulation. Eur J Paediatr Neurol. 2017; 21(1):109–117. [PubMed: 27693334]
9. Haridas A, Tagliati M, Osborn I, et al. Pallidal Deep Brain Stimulation for Primary Dystonia in Children. 682011
10. Marks WA, Honeycutt J, Acosta F, Reed M. Deep Brain Stimulation for Pediatric Movement Disorders. Seminars in Pediatric Neurology. 2009; 16(2):90–98. [PubMed: 19501337]
11. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. The Lancet. 355(9222):2220–2221.
12. Vasques X, Cif L, Gonzalez V, Nicholson C, Coubes P. Factors predicting improvement in primary generalized dystonia treated by pallidal deep brain stimulation. Movement Disorders. 2009; 24(6): 846–853. [PubMed: 19199337]
13. Isaias IU, Alterman RL, Tagliati M. Outcome predictors of pallidal stimulation in patients with primary dystonia: the role of disease duration. Brain. 2008; 131(7):1895–1902. [PubMed: 18567622]
14. Marks WA, Honeycutt J, Acosta F, Reed M. Deep brain stimulation for pediatric movement disorders. Paper presented at: Seminars in pediatric neurology; 2009.
15. Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: challenges and opportunities. European Journal of Paediatric Neurology. 2017; 21(1):118–121. [PubMed: 27289260]
16. Timmermann L, Pauls KAM, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: outcome of bilateral pallidal stimulation. Brain. 2010; 133(3):701–712. [PubMed: 20207700]

17. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. Journal of psychosomatic research. 2009; 67(6):497–501. [PubMed: 19913654]
18. Shahed J, Poysky J, Kenney C, Simpson R, Jankovic J. GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. Neurology. 2007; 68(2):159–160. [PubMed: 17210901]
19. Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. Journal of Neurology, Neurosurgery & Psychiatry. 2008; 79(2):136–142.
20. Dueck A, Wolters A, Wunsch K, et al. Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe Tourette syndrome and mental retardation. Neuropediatrics. 2009; 40(05):239–242. [PubMed: 20221961]
21. Stewart S, Geller D, Jenike M, et al. Long-term outcome of pediatric obsessive–compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatrica Scandinavica. 2004; 110(1):4–13. [PubMed: 15180774]
22. Chiu C-H, Lo Y-C, Tang H-S, et al. White matter abnormalities of fronto-striato-thalamic circuitry in obsessive–compulsive disorder: a study using diffusion spectrum imaging tractography. Psychiatry Research: Neuroimaging. 2011; 192(3):176–182.
23. Sakai Y, Narumoto J, Nishida S, et al. Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder. European Psychiatry. 2011; 26(7):463–469. [PubMed: 21067900]
24. Pediatric O. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. Jama. 2004; 292(16):1969. [PubMed: 15507582]
25. Liu K, Zhang H, Liu C, et al. Stereotactic treatment of refractory obsessive compulsive disorder by bilateral capsulotomy with 3 years follow-up. Journal of Clinical Neuroscience. 2008; 15(6):622–629. [PubMed: 18406144]
26. Sheppard DM, Bradshaw JL, Purcell R, Pantelis C. Tourette's and comorbid syndromes: obsessive compulsive and attention deficit hyperactivity disorder. A common etiology? Clinical Psychology Review. 1999; 19(5):531–552. [PubMed: 10467490]

KEY POINTS

- Vagal nerve stimulation has FDA approval for intractable epilepsy in patients ages 4 and older.
- Deep brain stimulation has been used on a limited basis in youth with dystonia and intractable tic disorders.
- Further measured work with invasive neuromodulation for children and adolescents with debilitating neuropsychiatric disorders could provide new treatment options and expand current knowledge base of neurocircuitry across development.