Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/64/20241574

Compare the open-looped DBS and closed-looped DBS on treatment on tourette syndrome

Manqi Wang

International Department, Chengdu Foreign Language School, No.33 Baicao Road, Cooperation Street, Chengdu, China

200190@yzpc.edu.cn

Abstract. Tourette Syndrome (TS), a complex neurodevelopmental disorder featured by persistent motor and vocal tics, has seen Deep Brain Stimulation (DBS) emerge as an efficacious treatment option for refractory cases. This study aims to systematically review and compare the roles of open-loop and closed-loop DBS modalities in treating TS, to elucidate their respective strengths, priorities, and clinical outcomes. Through a comprehensive literature review and data analysis, this paper delves into the mechanisms, technical advantages, and effectiveness of both DBS paradigms in managing TS symptoms, mitigating comorbidities, and enhancing quality of life. Furthermore, the disparities in safety, tolerability, long-term efficacy, and the influence of patient-specific requirements on therapeutic strategy selection are evaluated. Besides, this paper also culminates with a summary and outlook, advocating for ongoing exploration to refine closed-loop DBS pathways and concurrent appraisal of open-loop DBS within specific patient cohorts, thereby advancing the precision and personalization of TS therapy.

Keywords: Tourette syndrome, deep brain stimulation, open-loop DBS, closed-loop DBS, neurodevelopmental disorders.

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disease, featuring at least one-year lasting multiple motor and vocal tics that onset in childhood [1]. Compared to the children without TS, the child patients with TS are more likely to be the targets of bullying [2]. They have lower levels of social skills as well, which directly weaken their social competence [3]. To conclude, TS brings not only the physical suffer such as the injury caused by sudden tics but also the social disability. Moreover, with the worldwide data, the researchers find that there was rapid growth in 2017–2020 in TS population [4]. More diagnosis increases the demands for more effective treatment to deal with the growing TS population.

Fortunately, Deep Brain Stimulation (DBS), an expected treatment for motor disorders, is a potential treatment to TS. According to NIH, DBS is a surgical procedure, using a battery-charged medical device that is implanted into the certain spots in brain through surgery to conduct electrical stimulation that reaches different effect such as reduce the symptoms. One of the typical implications of DBS on motor disorders is on Pakinson Disease (PD). Research has shown that DBS improved dynamic postural stability [5] and release the symptoms such as bradykinesia, rigidity and tremor control in patients with PD [6]. However, as another motor disorder that begin in childhood, TS has less systematic organization of research on the impact and potential of DBS.

DOI: 10.54254/2753-8818/64/20241574

To make this article of systematic review more organized and efficient, two main perspectives will be shown with attention: open-looped DBS and closed-looped DBS, which are differentiated by their mechanisms. Therefore, this study will mainly focus on the impact of DBS on TS from the perspectives of different types, which are respectively closed-loop and open-looped DBS, to figure out their specialization, priority, and outcomes under different conditions.

2. Overview of DBS in TS

The first stereotactic surgery to treat TS can be dated back to 1970. Later, diverse research is done to study the relationship between DBS and TS from the perspectives of different simulation places and pattern. For example, Lauren and his crew study the DBS on TS patients, and they provided several suggestions such as age limits and corresponding policy insight [7]. However, with different study emerging, the debate becoming more intense. More ideas influx with their reasons and conclusions.

However, the precondition of joining this debate is being the appropriate and capable TS patients for DBS treatment. It can not only make sure the study results more valid, but also prevent some potential injury to the participants. The criteria of using DBS to treat TS is determined in 2015 by the team mentioned previously. There are six pillars: (1) it should receive a professional diagnosis of TS through DSM-5; (2) tics are a prominent feature and cause of disability; (3) tics are refractory to conservative therapies; (4) persistent and optimized treatment of medical, cognitive,and psychiatric comorbidities for 6 months have been implemented; (5) expected compliance during monitoring in stable psychosocial environment; (6) neuropsychological profile compatible with surgeryand postoperative follow-up. More importantly, if the patient is younger than 18 years old or the conditions need to be treated urgently, the local official institutions will interfere [7]. Through these criteria based on duration of symptoms, impact, and previous therapies, more suitable patients can be selected to be treated with DBS, and then guarantee the safety.

After selection, the types of DBS need determining. With two main categories, open-looped and closed-looped DBS, the mechanisms behind them are distinct. The right choice can't be made before specifically understanding of their working mechanisms. DBS uses a network to incorporate several and nonexclusive mechanisms and organize the treatments. These different mechanisms vary based on specific conditions [8]. For open-looped DBS as known as conventional DBS (cDBS), the simulation is adjucted in fixed trial period determined by doctors, but not by real-time feedback, which might induces overstimulation and understimulation [9]. On the other hand, closed-lopped DBS as known as adaptive DBS (aDBS) make adjustments based on the detection of sensors and the feedback of designed algorithms [10].

3. Open-looped DBS in TS

Open-looped DBS has fixed and regular pattern that is designed in advance, such as the artificial manipulation of frequency, amplitude and duty cycle [9]. It mainly focuses on several spots in the brain: Globus Pallidus internus (GPi), Subthalamic Nucleus (STN) , and Ventral Intermedius Nucleus (VIM). Although there might be some preference differences between open-looped DBS and closed-looped DBS, the essential differences exist in mechanisms.

The mechanisms of open-loop DBS can be concluded into key words: latency, subjectivity. In the first place, open-loop DBS is consisting of different treatment periods. Within each interval, the artificial manipulation mentioned above is fixed based on the previous diagnosis. Thus, when patients's conditions change, the implantation will still function at the same value throughout one treatment period. Only when the next course of treatment begins, the adjustment will be made to fit patients' changes in conditions. However, the treatment interval is long, usually every 3-12 months after DBS implantation [10]. Secondly, the set value for every interval and the variation between different intervals are mostly determined by the specialists or physicians. It leads to the subjectivity of open-loop DBS.

Targetting TS, the criterion of choosing conventional DBS is important since it's the precondition of implementing the treatment and exploring its efficacy. The first important standard for TS patients is treatment-resistant. For those patients that is not sensitive or responded well to traditional coginitive

DOI: 10.54254/2753-8818/64/20241574

therapy or drug treatment, open-loop DBS is a good choice. Next, high severity shoud be taken into consideration as well, specifically referring to a score >35/50 on the Yale Global Tic Severity Scale (YGTSS) as a threshold [11]. The last major standard is age. Interestingly, age is not mandatorily fixed, while it's related to the ethical problems. For the patients under 18 years old who are potential receiver of cDBS, the local offcial institutions should enter the process and fully inform related people [12].

The clinical outcome of cDBS is significant. The researchers conducted a study that last for six months, and found that cDBS generated a 33.3% improvement on the YGTSS and 52.8% on the Modified Rush Videotaping Scale for Tic (MRVRST) and two patients had more than 40% improvement at six months [13]. Through the evaluation of multiple scales, the results of improvement on TS patients are more convincing in this study. Nevertheless, the results can't be fully understood without knowing the pathology of TS. The dysfunction of cortico-striato-pallido-thalamo-cortical networksand is interrelated to TS. Specifically, compared to controls, neural pathways connecting the cerebral cortex, the basal ganglia and the thalamus are the place where white matter abnormalities exist. In this pathway, the structural connectivity of two brain parts striatum and thalamus with primary motor, sensory cortices, paracentral lobule, supplementary motor area and parietal corticeshad abnormally improved. The improvement positively associated with severity of tics measured by the YGTSS no matter what medication status, age or gender of patients currently are [14]. Therefore, the improvement on TGTSS mentioned in the six-month study above is related to the DBS stimultion on the network that is closely related to TS.

The functions of cDBS is further confirmed by its impact on another type of motor disorder as TS, PD. Researchers conducted long-term experiment, and gathered the evidence that shows the improvement in motor movements and tremor. Although both motor features and tremor improve, there's still existing difference: the stimulation of STN and GPi contributes to the enhancement of motor movement, and the stimulation of thalamic ventralis intermedius contributes to the tremor [15]. This phenomenon not only indicates the functions of open-loop DBS on PD, but also effectively shows the distinct roles of different brain parts, which turns to be the disadvantages of open-loop DBS that will be discussed later. On the other hand, cDBS also plays a role in a common type of mood disorder, depression. In the research that includes six respondent patients with treatment-resistent major depression, researchers found that severity of depression decreases fast, which is reflected by the observation that the mean of Montgomery-Åsberg Depression Rating Scale of the whole sample was reduced by>50% at day 7 after start of stimulation. Longitudally, 12 to 33 weeks after DBS, social functioning improved in the entire sample from serious to mild impairment, and four of them became remitters [16]. The first-handed data of this experiments confirms the positive effect of open-loop DBS on depression.

The advantages of open-loop DBS are not only the positive effect on patients with depression and Pakinson Diseases, but also the relatively low requirement for complicated algorithms. Nonetheless, the drawbacks such as the side effects of DBS cause quite a few challenges. One of the most typical side effect of cDBS is speaking side effect. Reseachers found that in a significant percentage of patients, speech deterioration is found to be the side effect after cDBS [17]. Moreover, from the perspective of cost, energy consumption is also a serious problem for cDBS since the whole system of implantation is powered by electricity from batteries. The batteries need charging after a certain period after surgery. The solution includes placing batteries that store the enery to support DBS under the skin of patients, but it inflict movement difficulty upon the patients.

4. Close-looped DBS in TS

Although open-loop DBS has great achievements, scientists are interested in a more recent type of DBS is closed-loop DBS, which is known for its real-time adjustment through specific feedback mechanisms. It's mainly divided into two kinds: responsive DBS (rDBS) and aDBS [18]. For responsive DBS, it delivers stimulation for a constant duration after event detection [19]. The other category, adaptive DBS, adjusts the stimulation parameters according to biomarkers which reflect the patient's clinical state [20].

DOI: 10.54254/2753-8818/64/20241574

The significance of close-loop DBS is reflected by its real-time circle, which represents of brain stimulation evolution.

Although both aDBS and rDBS belongs to close-loop DBS and share something similar in mechnisms, they show differences in many perspectives. Thus, full understanding can't be gained without specifically discussing the mechansims of both, targetting TS. Primarily, rDBS delivering stimulation periodically and only in response to symptom-relevant situations. It conveys the stimulation constantly in a certain period, the changes in different periods respond to the real-time detection of clinical status of patients. Based on the patient-initiated annotations, this system is able to time-lock them to relevant behaviors or symptoms experienced by the patient [21]. On the other hand, aDBS is also one of the most promising method to treat TS. Compared to the fixed stimulation during certain period based on the real-time adjustment, aDBS has greater flexibility. It focuses on the real-time adjustment according to clinical status at any time. The detailed description of the mechansims of aDBS is that the control system available in closed-loop DBS equipments in different usages is a type of state feedback control. The inputs of it to the Linear Discriminant are a function containing neural features and biomarkers, and the output is the feedback based on different levels of stimulation, including amplitude and frequency [18].

Researchers that are interested in rDBS conducted series of identical experiments and collected data of different groups to compare. In earlier time, clinical data collected during a 12-month period of responsive therapy brings to the light the improvements from baseline scores in both Modified Rush Tic Rating Scale (MRTRS) and YGTSS scores. The MRTRS score improved by 64%, while the latter showed a 48% enhancement. This study also highlights that responsive stimulation led to a 63.3% increase in the anticipated mean battery life of the neurostimulator [22]. Recent research published in 2024 divided participants into three groups: without stimulation, with conventional open-loop stimulation, and with embedded responsive stimulation. After six months, 50% of subjects in the responsive group exhibited a greater than 30% reduction in the YGTSS while using responsive DBS settings. Critically, all three groups demonstrated that the responsive approach was both safe and well-tolerated [23]. Safety and patient acceptance are pivotal considerations for future clinical practice as this treatment becomes commercially available. A notable neural disorder associated with TS is obsessive-compulsive disorder (OCD), which frequently co-occurs in TS patients. rDBS may also benefit OCD patients. The first human application of rDBS in the ventral striatum for treatment-refractory OCD indicated significant improvements in obsession and compulsion, characterized as rapid, robust, and durable. While the generalizability of this study is limited due to the singularity of the patient, the comorbid engagement, and the extra active electrodes outside the NAc-VeP zone, it nonetheless underscores the positive and comprehensive clinical outcomes associated with rDBS [21].

For the other type aDBS, it offers significant advantages over conventional drug treatments for motor disorders by enabling highly customized treatment regimens based on individual characteristics and symptoms [24]. The primary source of feedback in aDBS is derived from local field potentials (LFPs), which aggregate pre-synaptic and post-synaptic activities from large neural populations, providing real-time insights into a patient's condition. Findings indicate that oscillatory patterns in TS are regulated by DBS treatment, leading to symptom improvement, suggesting that recorded LFPs could enhance the management of TS [25]. The study indicates that changes in LFPs could potentially serve as signatures for controlling aDBS devices.

The advantages of close-loop DBS include longer life of implamentations and timeliness. Especially for rDBS, the responsive stimulation leads to a 63.3% enhancement in the neurostimulator's anticipated average battery life [22]. The battery in implantation resembles the engine of the entire system so longer battery life will not only extend the life of the implantation, but also reduce the cost of maintenance by recharging less frequently. Additionally, aDBS is able to conduct stimulation based on the current status by detecting biomarkers. Without obvious delay, aDBS can go through the complete feedback control system to apply the real-time change on the patients so that the treatment on patients is more suitable to the current state of patients.

DOI: 10.54254/2753-8818/64/20241574

However, although close-loop DBS has significant outcomes in TS treatment, there are still challenges that limit its advance. Firstly, it's difficult for researchers to figure out the most effective brain targets to implant stimulation electrodes [23]. For DBS, several targets such as STN and GPi are all commonly used. Even if the biomarkers are chosen, their effectiveness need careful and long-time examinations. Thus, the right choice that maximizes the efficacy and minimizes the side effect is the challenge in front of the current applications. Moreover, software is the other barrier. In order to satisfy the real-time adjustment, the detection of the biomarker requires to be highly sensitive and precise. A program for a successful close-loop DBS need highlt personalized design, which greatly increase the difficulty of close-loop DBS [10]. For the function of the close-loop DBS, the research mainly concentrates on the short-term effects, but the long-term efficacy of close-loop DBS still needs further experiments and exploration [18].

5. Comparative analysis: Open-looped and closed looped

Together with analysis of both open-loop DBS and close-loop DBS from different aspects, the comparison can be made to evaluate two kinds of DBS. From multiple dimensions, the comparison is summarized in the table 1.

Table 1. The comparison summary of open-loop DBS and close-loop DBS

	Open-loop DBS	Close-loop DBS
Tic reduction efficacy	33.3% improvement on the YGTSS 52.8% improvement on the MRVRST	48%/ 30% improvement on the YGTSS 64% improvement on the MRTRS
Effects on comorbid conditions	Positive effect on depression	rDBS benefits OCD patients
Long-term function	Shorter battery life	Longer battery life
Side effect profiles	Speech deterioration	Safe and well-tolerated
Technical requirement	Artificial diagnosis	Algorithmic advance

In the first comparison standard, tic reduction efficacy, both of them show obvious improvement in different scales. Close-loop DBS has greater improvement in YGTSS. Also, it contributes to the 64% improvement of patients' conditions in MRTRS. Close-loop DBS not only shows a greater efficacy in tic reduction, but also has more extended battery life. More importantly, in the cases, close-loop DBS is safe and well-tolerated, without apparent side-effect such as speech deterioration in open-loop DBS. Nevertheless, both of them shares the similarity that they affect the comorbid conditions of TS. For open-loop DBS, it tends to have positive effect on depression, and for close-loop DBS, OCD patients are benefited.

6. Emerging research and future directions

In light of the findings presented in this study, several promising and potential avenues for future research of TS emerge. Two future directions are worthy of discussing: other potential targets and other advanced techniques to treat TS.

There are several spots in brain that are not studied extensively but being found to have potential functions as the targets of DBS. Anterior limb of internal capsule (ALIC) is a typical example. In the earlier time, the findings of several study published suggest that stimulation of the anterior internal capsule may be a safe and effective procedure for the treatment of TS [26]. However, in the conversation of this field, another study indicates the results that anterior internal capsule site produced side effects including altered mood and impulse control. Later one, this potential target haven't been studied extensively despite the debate, which leaves the space to dive deep into [27]. The other potential single target is Forel's field H1, which is found to work safely and effectively [12]. However, the clinical outcomes of it are not sufficiently studies to determine whether it's a feasible target that can be used in

DOI: 10.54254/2753-8818/64/20241574

a wider range. Moreover, compared to the single target of DBS mentioned above, the combinations of the targets of DBS can't be overlooked as well. In addition to DBS, other methods are studied for the treatment of TS. In the first place, Theta Burst Stimulation (TBS) is studied to better understand the pathophysiology of TS. The research indicates the differences between healthy people and the TS patients: after intermittent TBS, motor-evoked potential amplitude changes were greater in 11 healthy controls compared to 10 adult patients with TS [28]. Although the functions of TBS is not extensively studied, its function is expected to induce faster and long-term effects on synaptic plasticity than conventional approaches [29].

7. Conclusion

TS is a neurodevelopmental disorder featured by lasting motor or verbal tics. As an important potential treatment, DBS can be mainly divided into two categories, open-loop and close-loop. Though both of them show significant improvement in patients' conditions, close-loop DBS shows a greater improvement in tics through the evaluation of YGTSS, and it has a more extended battery life which leads to the longevity of implantation. Moreover, in side effect profiles, close-loop DBS also shows a safer and more tolerated characteristic, compared to the speech deterioration of open-loop DBS. With those advantages compared to open-loop DBS, close-loop still face great limitation: the complicated computer programming for its real-time adjustment. Depite the comparisons, both of them show the effectiveness on reducing the comorbid including depression OCD; they both have great potential in the future research from perspectives including other possible targets such as ALIC and Forel's field H1.

References

[1] Bloch M., Leckman J.. Clinical course of Tourette syndrome. J Psychosom Res. 2009; 67 (6) :497-501.
[2] Bitsko R., Claussen A., Lichstein J, et al. Mental health surveillance among children -United States, 2013–2019. MMWR Suppl. 2022;71(2):1-42.
[3] Robinson L.R, Bitsko R.H, Schieve LA, Visser SN. Tourette syndrome, parenting aggravation, and the contribution of co-occurring conditions among a nationally representative sample. Disabil Health J. 2013;6(1):26-35.
[4] Yang C, Zhang J, Zhao Q, Zhang J, Zhou J, Wang L. Trends of Tourette syndrome in children from 2011 to 2021: A bibliometric analysis. Front Behav Neurosci. 2022;16.
[5] Conway Z.J, Silburn P.A, Perera T, O'Maley K, Cole M.H. Low-frequency STN-DBS provides acute gait improvements in Parkinson's disease: a double-blinded randomized crossover feasibility trial. J Neuroengineering Rehabil. 2021;18(1):125.
[6] Au K., Wong J., Tsuboi T, et al. Globus pallidus internus (GPi) deep brain stimulation for Parkinson's disease: Expert review and commentary. Neurol Ther. 2020;10(1):7-30.
[7] Schrock L.E, Mink J.W, Woods D.W, et al. Tourette syndrome deep brain stimulation: A review and updated recommendations. Mov Disord. 2014;30(4):448-471.
[8] Herrington T.M, Cheng J.J, Eskandar E.N. Mechanisms of deep brain stimulation. J Neurophysiol. 2016;115(1):19-38.
[9] Ghasemi P, Sahraee T, Mohammadi A. Closed- and open-loop deep brain stimulation: Methods, challenges, current and future aspects. J Biomed Phys Eng. 2018;8(2):209-216.
[10] Parastarfeizabadi M, Kouzani AZ. Advances in closed-loop deep brain stimulation devices. J Neuroeng Rehabil. 2017;14(1).
[11] Casagrande S., Cury R.G, Alho E.J.L, Fonoff ET. Deep brain stimulation in Tourette's syndrome: Evidence to date. Neuropsychiatr Dis Treat. 2019;15:1061-1075.
[12] Xu W, Zhang C, Deeb W, et al. Deep brain stimulation for Tourette's syndrome. Transl Neurodegener. 2020;9(1).
[13] Robertson N.P. Advances in Tourette's syndrome. J Neurol. 2023;270(3):1808-1810.
[14] Worbe Y, Marrakchi-Kacem L, Lecomte S, et al. Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome. Brain. 2015;138(Pt 2):472-482.

[15] Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet Neurol. 2012;11(5):429-442.
[16] Schlaepfer T.E, Bewernick BH, Kayser S, Mädler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biolo.Psy. 2013;73(12):1204-1212.
[17] Little S, Tripoliti E, Beudel M, et al. Adaptive Deep Brain Stimulation Parkinson's Disease: Reduced Speech Side Effects Compared to Conventional Stimulation Acute Setting. J Neurol Neurosurg Psychiatry. 2016;87(12):1388-1389.
[18] Prosky J, Cagle J, Sellers KK, et al. Practical Closed-Loop Strategies Deep Brain Stimulation: Lessons From Chronic Pain. Front Neurosci. 2021;15.
[19] Sun F.T, Morrell M.J. The RNS System: Responsive Cortical Stimulation Treatment Refractory Partial Epilepsy. Expert Rev Med Devices. 2014;11(6):563-572.
[20] Priori A, Maiorana N, Dini M, Guidetti M, Marceglia S, Ferrucci R. Adaptive Deep Brain Stimulation (aDBS). Int Rev Neurobiol. 2021:111-127.
[21] Nho Y.H, Rolle CE, Topalovic U, et al. Responsive Deep Brain Stimulation Guided by Ventral Striatal Electrophysiology Obsession Durably Ameliorates Compulsion. Neuron. 2023.
[22] Molina R, Okun M.S, Shute JB, et al. Report Patient Undergoing Chronic Responsive Deep Brain Stimulation Tourette Syndrome: Proof of Concept. J Neurosurg. 2018;129(2):308-314.
[23] Okun M.S, Cagle J, Gomez J, et al. Responsive Deep Brain Stimulation Treatment Tourette Syndrome. Sci Rep. 2024;14(1):6467.
[24] Neumann W.J, Turner R.S, Blankertz B, Mitchell T, Kühn A.A, Richardson RM. Toward Electrophysiology-Based Intelligent Adaptive Deep Brain Stimulation Movement Disorders. Neurotherapeutics. 2019;16(1):105-118.
[25] Marceglia S, Rosa M, Servello D, et al. Adaptive Deep Brain Stimulation (aDBS) for Tourette Syndrome. Brain Sci. 2017;8(1):4.
[26] Flaherty A.W, Williams Z.M, Amirnovin R, et al. Deep Brain Stimulation Anterior Internal Capsule Treatment Tourette Syndrome: Technical Case Report. Oper Neurosurg. 2005;57(suppl_4):ONS-E403-ONS-E403.
[27] Shields D.C, Cheng M, Flaherty AW, Gale J, Eskandar EN. Microelectrode-Guided Deep Brain Stimulation Tourette Syndrome: Within-Subject Comparison Different Stimulation Sites. 2008;86(2):87-91.
[28] Wu S.W, Gilbert D.L. Altered Neurophysiologic Response Intermittent Theta Burst Stimulation Tourette Syndrome. Brain Stimul. 2012;5(3):315-319.
[29] Rachid F. Safety Efficacy Theta-Burst Stimulation Treatment Psychiatric Disorders: Review Literature. J Nerv Ment Dis. 2017;205(11):823-839.