Review

Deep brain stimulation in the treatment of tardive dyskinesia

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Abstract: Tardive dyskinesia (TD) is a phenomenon observed in psychiatry following the predominantly long-term use of dopamine receptor blockers (antipsychotics) widely used in psychiatry. TD is a group of involuntary, irregular hyperkinetic movements, mainly in the muscles of the face, eyelid muscles, lips, tongue, and cheeks, and less frequently in the limbs, neck, pelvis, and trunk. In some patients, TD takes on an extremely severe form, massively disrupting functioning, moreover, causing stigmatization and suffering. Deep brain stimulation (DBS), a method used, among others, in Parkinson's disease, is also an effective treatment for TD and often becomes a method of last resort, especially in severe, drug-resistant forms. The group of TD patients who underwent DBS is still very limited. The procedure is relatively new in TD, so the available reliable clinical studies are few and consist mainly of case reports. Unilateral and bilateral stimulation of two sites has proven efficacy in TD treatment. Most authors describe stimulation of the globus pallidus internus (GPi); less frequent descriptions involve the hypothalamic nucleus (STN). In the present paper, we provide up-to-date information on the stimulation of both mentioned brain areas. We also compare the efficacy of the two methods by comparing the two available studies, which included the largest groups of patients. Although GPi stimulation is more frequently used clinically, our analysis indicates comparable results (reduction of involuntary movements) with STN DBS.

Keywords: tardive dyskinesia; schizophrenia; antipsychotics; deep brain stimulation

1. Introduction

Tardive dyskinesia (TD) is a group of symptoms characterized by irregular and involuntary movements that most commonly affect the tongue, lips, jaw, face, and sometimes the peri-orbital areas. In some cases, patients also have irregular movement of the trunk and limbs [1,2]. TD is a specific type of secondary dystonia, mainly caused by chronic use of dopamine receptor antagonists. The onset of TD usually occurs after years of taking neuroleptics but may also appear earlier, even after several months. The risk is related, among others, to the strength of the drug binding to the dopaminergic D2 receptor. In the elderly, symptoms may become apparent after a shorter period of use of the drug, the early onset of these symptoms and their intensity may indicate features of organic brain damage [3]. Due to the need for long-term treatment, neuroleptics are the main reason for TD's appearance in clinical practice. Yet, when using other antidopaminergic drugs such as antiemetics (domperidone, bromopride, and metoclopramide), antidepressants such as trazodone, amitriptyline, clomipramine, fluoxetine, and sertraline or calcium channel blockers the risk of TD appearance, while significantly lower, should be highlighted [4].

Interestingly, tardive dyskinesia can appear both during the use and after the discontinuation of neuroleptics. The prevalence of tardive dyskinesia is estimated at 0.4-9% in patients receiving antipsychotics, while some studies indicate a more frequent

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occurrence of TD (20%-50%) [5,6]. According to the DSM-5, TD can be diagnosed when antipsychotic-induced tardive dyskinesia follows exposure to neuroleptics for at least three months (one month in individuals aged ≥60 years) and persist for at least one month after the last dose of the drug [7]. This iatrogenic complication may persist long after drug discontinuation and might become permanent [1,5]. TD often results in disability, with mild to severe functional impairment (significantly impaired gait, speech, and swallowing) in about 10% of cases, causing a heavy burden on both patients and their caregivers [5]. In addition to physical burden and pain, tardive dyskinesia leads to social exclusion and ostracism in patients with these symptoms. The patient with TD looks bizarre and disturbing to the observer, immediately drawing attention to the psychic problems of the patient, somehow corresponding to one of the archetypal images of mental illness.

2. Etiology and risk factors

Key importance in the etiology of TD has genetic predisposition, which mediates the risk for TD development [4,8]. Yet, the usage of dopamine receptor antagonists is responsible for the exposure of this predisposition [9,10]. Table 1 shows the factors associated with an increased risk of TD [11–18]. Table 2 summarizes the genetic factors that modulate the risk of TD [19–22].

Table 1. Nonmodifiable and modifiable risk factors of TD

Nonmodifiable factors	Modifiable factors
advanced age	type of dopamine receptor blocking agents
female sex	duration of illness
Caucasian or African ethnicity	dosage and length of exposure to a dopamine receptor blocker
intellectual disability	intermittent antipsychotic treatment,
brain damage	anticholinergic treatment
negative symptoms in schizophrenia	smoking
	alcohol and cocaine abuse/dependence
	akathisia

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Table 2. Genetic factors influencing the manifestation of TD

DRD2 & DRD3
HTR2A (5-HT2A receptors)
COMT
MnSOD
cytochrome P450 (CYP2D6)
GSK-3ß
3'- regulatory region of *Nurr77* mRNA
SLC6A11, GABRB2 and GABRC3 related to GABAergic transmission
GRIN2A related to NMDA receptor and glutamatergic transmission
GSTM1, GSTP1, NOS3 and NQO1 involved in oxidative stress reactions
BDNF
GLI2 - GLI family zinc finger 2
HSPG2

Genes DRD2 & DRD3 – D2 & D3 receptor, D - dopamine, HTR2A - 5-hydroxytryptamine receptor 2A, 5-HT – serotonin, COMT - catechol-O-methyl-transferase, MnSOD - manganese superdismutase, CYP2D6 – cytochrome P450 2D6, GSK2ß - Glycogen synthase kinase 2 beta, mRNA - messenger RNA, SLC6A11 - solute carrier family 6 member 11, GABRB2 - gamma-aminobutyric acid type A receptor subunit beta 2, GABRC3 - gamma-aminobutyric acid type A-rho receptor subunit beta 2, GABA - γ-Aminobutyric acid, GRIN2A - glutamate ionotropic receptor NMDA type subunit 2A, NMDA - N-methyl-D-aspartate, GSTM1 - Glutathione S-transferase Mu 1, GSTP1 - glutathione S-transferases P1, NOS3 - nitric oxide synthase 3, NQO1 - NAD(P)H quinone dehydrogenase 1, BDNF – Brain Derived Neurotrophic Factor, GLI2 - GLI family zinc finger 2, HSPG2 - heparan sulphate proteo-glycan 2

The main pathogenetic mechanisms associated with the development of TD are the hypersensitivity of postsynaptic D2 receptors and their upregulation associated with their long-term blockade. This leads to changes in cortico-striatal transmission and motor symptoms [23]. The abnormalities also concern the increase in blood flow in the prefrontal cortex, the anterior cingulate gyrus, and the cerebellum, which accompany the increase in the activity of the prefrontal and premotor cortex during the appearance of involuntary movements, which may indicate a decrease in impulse selection and lead to the appearance of involuntary movements [24]. The constant blocking of D2 receptors along with D1 activation may also be important to explain the appearance of symptoms over a longer period of time and their irreversibility [25]. However, it seems that not only disorders of dopaminergic transmission are involved in the development of TD, but changes in serotonin (5-HT), glutamate, cholinergic and opioid transmission may play a supportive role [26,27]. The involvement of the serotonin system in TD is indicated by studies on animal models. It was found that inhibition of serotonergic neurons with 8-OH-DPAT (8-hydroxy-2-(dipropylamino)tetralin significantly reduces TD severity. 8-OH-DPAT is one of the first discovered agonists of the serotonergic 5-HT1A receptors. It mediates hyperpolarization and reduction of the firing rate of the postsynaptic neuron).

 doi:10.20944/preprints202211.0258.v1

Conversely, administration with fenfluramine or fluoxetine (both increasing the level of serotonin) suppressed the previously obtained improvement. Preclinical studies indicate that deep brain stimulation of subthalamic nucleus (STN DBS), a technique described in latter article parts, reduced the release of 5-HT in the hippocampus and prefrontal cortex, while EPN DBS (entopeduncular nucleus, internal globus pallidus (GPi) equivalent in rodents) did not affect 5-HT release. Despite the above, both STN and EPN DBS attenuate TD with equal effectiveness, despite their different effects on the 5-HT system, leading to the conclusion that the mechanism of 5-HT reduction does not determine the effectiveness of DBS in rats. However, due to the difficulty in assessing the severity of TD in rats, it is worth exploring this mechanism precisely in people suffering from TD. This is all the more noteworthy as when comparing STN and GPi stimulation, the former is considered at least as effective in reducing TD in humans [1].

Oxidative stress and related neuronal damage both take an important place in research on the etiology of TD. Antipsychotics, especially classic drugs, may be toxic by direct inhibiting complex I of the mitochondrial electron transport chain. Toxicity may also result from the increased production of free radicals and hydrogen peroxide, which are a consequence of the blockade of the D2 receptor and an increase in dopamine turnover [19,28,29]. The weakening of the antioxidant mechanisms may explain the progressive nature of the changes and their irreversibility [30–32]. In neuroimaging studies, a decrease in the caudate nucleus volume was observed in the group of patients diagnosed with schizophrenia with TD compared to those with this psychosis without dyskinesia [9,33,34].

3. Assessment tools

The most widely used instrument to assess TD is the Abnormal Involuntary Movement Scale (AIMS). The patient performs several tasks described in the instructions. On that basis, the severity of facial and oral movements, extremity movements, trunk movements, and global judgments is scored on a 0-4 scale (up to 40 points in total) [35]. A separate evaluation concerns dental status (with an annotation yes/no). Another scale is The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which consists of movement and disability subscales. Tool measures dystonia in nine body regions (incl. the eyes, mouth/speech and swallowing, neck, trunk, arms, and legs; each extremity is assessed individually) with scores ranging from 0 (lack of symptoms) to 120 [36].

4. Pharmacological treatment

TD treatment is difficult and often leads to disappointing results, so the best method is to prevent their onset [37]. Atypical antipsychotics have a lower potential to cause TD. The drugs should be used in the lowest effective doses, particularly if TD appeared earlier or the current treatment induced its onset. When TD appears, initially, it is necessary to reduce the drug dose or, if this does not eliminate TD, switch to a drug with a lower potential for inducing TD, such as clozapine or quetiapine.

The pharmacological treatment of TD is challenging; the conventionally administered pharmacotherapies are only beneficial at the initial stage; available data points to a lack of satisfactory outcomes in long-term use [5].

 doi:10.20944/preprints202211.0258.v1

VMAT2 (vesicular monoamine transporter 2) inhibitors: tetrabenazine, valbenazine, and deutetrabenazine are the first drugs group recommended for TD treatment [2]. In randomized controlled trials, valbenazine, and deutetrabenazine demonstrated efficacy in ameliorating TD symptoms with a favorable benefit-risk ratio. For this reason, valbenazine and deutetrabenazine should be considered a first-line treatment for TD. While the currently available evidence suggests that tetrabenazine is another good option for TD, it is not considered a first-line drug due to more side effects than other VMAT2 inhibitors and very few studies. Amantadine (300 mg per day) may be used when these treatments are ineffective or contraindicated. However, evidence to support the use of amantadine for TD is scarce and limited to short observations [2]. Another discussed treatment option is the short-term administration of clonazepam, but the effectiveness of this method is also limited. Furthermore, considering the acute and long-term consequences (sedation, cognitive decline, tolerance, addiction, and risk of falls, especially in the elderly), routine use of benzodiazepines is not recommended [2,5]. The use of Vitamin E does not improve TD symptoms but may prevent their worsening. When other options fail, some authors recommend pyridoxine (vitamin B6) use, but the optimal dose and treatment duration has not been established yet [2]. In focal dystonia, such as cervical dystonia, botulinum toxin injection may be applied. It is a highly effective approach, but the level of satisfaction with this treatment is low in part of the patients, and they fail to follow up for repeated injections. Therefore, the pharmacotherapeutic method should be regarded as adjuvant therapy instead of a priority choice (the doses of the TD-inducing drug should be reduced or changed) as the disease progresses to the advanced stage [5]. Recommendations of the American Academy of Neurology for TD treatment indicate (level B of recommendations) clonazepam, Ginkgo Biloba extract (EGb-761), and diltiazem, when amantadine, tetrabenazine, galantamine, and eicosapentaenoic acid have level C. Other test substances, incl. reserpine, bromocriptine, biperiden, selegiline, vitamin E, vitamin B6, baclofen, and levetiracetam, have not received a recommendation from the Academy at this stage [38]. Newer recommendations position new-generation VMAT2 inhibitors (deutetrabenazine and valbenazine) at level A recommendation, clonazepam and Ginkgo biloba at level B, while amantadine, tetrabenazine, and GPi DBS (globus pallidus internus deep brain stimulation) are at level C [39].

5. Deep brain stimulation

A promising method that may offer new opportunities for this group of patients is deep brain stimulation (DBS). DBS is a clinical procedure in which a precisely controlled electric current is passed through electrodes surgically implanted in the brain. This method enables rapid and, more importantly, long-term improvement in motor function and quality of life (QoL) in patients with TD [1,5]. In recent decades, DBS has been successfully used to treat several movement disorders, including Parkinson's disease and dystonia. More recently, DBS has also been used to treat patients with tardive dyskinesia and OCD, especially in drug-resistant forms [5,6]. Monopolar (unilateral) stimulation modes are the most commonly used, although we also have descriptions of bipolar modes [40–44]. In addition to the potential for rapid and long-term improvement, the advantages of DBS

 doi:10.20944/preprints202211.0258.v1

include its relatively nondestructive nature, adjustability, reversibility, and the ability to perform DBS bilaterally in a single surgical session [5,45].

The disadvantages of the DBS technique are the requirement for continuous follow-up visits with repeated optimization of pacing parameters (it can also offer potential parameter adjustments) and the risk of hardware complications (incl. electrode displacement, battery depletion, inflammation around parts of the device) [45]. When the effectiveness of pharmacotherapeutic methods is unsatisfactory, and symptoms are chronic and very severe, DBS becomes the treatment of last resort [46]. According to available studies, this method is safe and minimally invasive, with no severe complications during the follow-up periods [5].

The primary criterion for inclusion in DBS is the high severity of symptoms that significantly impede function and have lasted for more than a year, with no satisfactory response to pharmacological treatment with clozapine or tetrabenazine for at least four weeks at the highest doses tolerated by the patient. Exclusion criteria are similar to those for patients with other dystonias - significant cognitive impairment, unstable mental status, severe depressive symptoms, and comorbid medical problems that may increase surgical risk; an initial brain scan is recommended [43].

In addition to correct patient selection and electrode placement, proper and time-coordinated programming of the equipment is crucial. This is important because we already have multi-segment electrodes (from Abbott, Boston Scientific), and each segment's current characteristics can be programmed separately. This complicates programming (current of different amplitude, voltage, amperage, and pulse width can be used) but certainly expands the possibilities for stimulation. Once the electrode has been placed, the direction of the electrode can be changed, optimizing the clinical outcome. This allows continuous monitoring of the effectiveness of the stimulation and provides an opportunity to implement modifications but it becomes vital when the initially planned electrode placement has failed (in about 40%). The typical inaccuracy of surgical robots or stereotaxic methods is 1-2 mm, in addition, during surgery, the brain can change position by 2-4 mm [47–56]. A similar problem arises when the electrode is displaced. Reprogramming often avoids reoperation and allows optimization of parameters if the dislocation is not critical [57,58]. It is worth adding that no clear guidelines have been developed so far, although there are recommendations regarding the programming of stimulators [59–61]. In programming, it is important to be aware of the temporal sequence of observed changes - not all symptoms respond to stimulation simultaneously. For example, during stimulation of the hypothalamic nucleus in Parkinson's disease, the earliest (seconds) tremor subsides, followed by rigidity (seconds-minutes), bradykinesia (minutes-hours), and axial symptoms (hours-days). These symptoms appear after the stimulation is turned off in the same order [62,63].

Previous research in TD patients has focused on the stimulation of two areas in the brain: the inner globus pallidus (GPi) and the hypothalamic nucleus (STN) belonging to the basal ganglia. These nuclei belong to motor circuits, including cortico-thalamo-basal ganglia junctions, which are believed to be the morphological substrate of TD. Most projects focused on the stimulation of GPi, the preferred target, while less is known about

 doi:10.20944/preprints202211.0258.v1

STN stimulation [3,5]. Nevertheless, both STN and GPi stimulation were shown to be beneficial in reducing TD [37].

5.1. Internal globus pallidus (GPi)

The primary target of GPi DBS is the posteroventrolateral part [44,45,64–67]. Several descriptions concern the stimulation of the posteroventromedial area [68,69]. Ventral parts of the posterior globus pallidus have a somatotopic organization associated with the motor cortex, which determines the goals of stimulation, while the median part is related to the limbic cortex and the dorsal part is associated with the prefrontal cortex [70].

Stereotactic techniques based on MRI (magnetic resonance imaging) or CT-MRI (a combination of CT and MRI techniques) help correct electrode placement [71]. Usually, The optimal electrode placement is within 19-22 mm lateral to the line between anterior and posterior commissure, 4-6 mm inferior to that line, and 2-4 mm anterior to the mid-commissural point [43,44,65,69,72–77]. In one description, the electrode position corresponded to the somatotopic face area [78]. The most common practice uses microelectrode recordings (MERs) to detect discharges of neurons in the GPi and to order "noisy signals" with DBS. The most common stimulation parameters used were the voltage (amplitude) of the current (1.0-7.0 V) [41,65], frequency (60-185 Hz) [40,67,76,79], and pulse width (60-450 μs) [40,43,76,79–81]. A detailed list of electrodes used, voltages, location, and effectiveness of the treatments can be found in the study by Morigaki et al. [82]. With several exceptions of bipolar modes [40–44] other reports concern monopolar stimulations.

Much of the literature was single patient reports [41,45,66,68,71–73,75,76,78,80,83–85], small groups of 2-4 people [44,65,67,69,77,86,87] or slightly larger groups [40,43,74,79,81,88,89] when 19 patients were the largest cohort [37].

5.1.1. Motor Effects

The reported efficacy (reduction in dystonia scores) ranges from 28% to 100%, with most reports showing ≧60% improvement, with a follow-up period of up to 11 years [37]. Improvement is described as stable even after 4-year follow-up. In addition to improvement in symptoms, most investigators consistently report a significantly favorable change in the quality of life and daily functioning. Nevertheless, there are also descriptions of no overall change in this area [43,90].

Clinical responses appear either during the surgical procedure and the first activation of stimulation or in the first days after turning on the equipment [43,44,65,66,68,74,84,87]. If clinical responses are observed shortly after switching on the device, we can precisely program the equipment at the outset; in other cases, patient adjustments are made at follow-up visits or via the Internet more recently [91]. The manufacturer recommends the lowest sufficient stimulator settings, combining optimal performance with less load and longer battery life.

Changes in the treatment of choreiform dyskinesia are noted earlier, tonic postural dystonia responds later, symptoms improve gradually, and changes are observed after weeks or even months of stimulation [42,44,73,84,87–89]. In fixed dystonias, the efficacy of GPi-DBS is lower [40,43,65,79].

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5.1.2. Non-motor effects & side effects

Despite its invasiveness, DBS is characterized by a low number of complications and is considered a safe, effective, and well-tolerated method [3]. The frequency of all side effects reaches 9%. Observations of non-motor effects are very scarce. DBS may induce transient affective states (mild to moderate depressive syndrome in most cases); authors also emphasized some increase in suicidal risk [71,92]. However, at longer follow-up, there was an improvement in mood, which could also be explained by relief from the burden of motor symptoms, disability, or social impact [37,43,74,78]. In one study, six months after treatment, one patient had a brief psychotic episode, and another patient had symptomatic improvement allowing the discontinuation of antipsychotic drugs [74]. Contrary to the first reports, the negative influence of continuous pallidal (GPi) DBS on cognitive functions has not been confirmed [37,43,69].

The procedure of implanting the electrode itself was associated with the possibility of incorrect placement or electrode displacement, infections, and pain associated with the connection cable. Gait and balance disturbances contributing to falls have also been observed. These disturbances were transient and resolved after optimization of DBS parameters [37]. GPi is involved in speech fluency, and stuttering is then a common symptom during DBS in this area. A higher risk of speech disorders appears if the stimulation penetrates the internal capsule medial and posterior to the GPi. Dysarthria occurs in almost 30% of patients; severe cases may require speech therapy [37]. Despite the complications being infrequent, the risk-benefit ratio always needs to be weighed, keeping in mind that DBS becomes the last resort in patients with severe TD when symptoms are severe, functioning is significantly impaired, and other treatment options are insufficient.

5.2. The subthalamic nucleus (STN)

The subthalamic nucleus (STN), belonging to the basal ganglia, is a less commonly studied DBS target in TD treatment. Less frequent use is, among others, related to psychiatric complications (depression, suicidality, mania, and impulse-control problems) observed during DBS of this brain structure in patients with Parkinson's Disease.

5.2.1. Motor symptom

So far, only several cases of STN DBS for TD have been reported. In addition to the Deng study, which we will discuss later [5], Zhang et al. published a description of a series of nine patients treated with STN DBS for secondary dystonia (2 with tardive dystonia) [93]. In one case, the dystonia followed neuroleptic treatment and improved by 92% in the BFMDRS 3 months after stimulator implementation. Other description (12 patients with primary dystonia and 2 with TD) using STN DBS showed improvement ranging from 76 to 100% in the BFMDRS [94]. In one case of severe TD dystonic symptoms almost disappeared after STN DBS, only slight tremor of hands an minimal elevation of right shoulder were noted in following period. Six and twelve years after the operation BFMDRS total score was 0 [3]. One patient underwent DBS placement in the left and right STN with near-complete resolution of tremors [95].

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5.2.2. Non-motor effects & side effects

The anatomical location of STN is very close to several functionally significant areas. Therefore, induced side effects are also associated with stimulating adjacent nuclei and nerve tracts. Table 3 presents the most common side effects with postulated structures responsible for their appearance. Due to the lack of detailed descriptions regarding TD, the table lists observations during STN DBS in Parkinson's disease.

Table 3. Side effects and the brain area surrounding STN, which stimulation may be responsible for the appearance of symptoms

Side effect	Brain area
spastic muscle contraction	internal capsule
uni- or bilateral gaze deviation	fibers stemming from the frontal eye field running in the internal capsule, fibers of the third nerve (inferomedial to the STN and within the red nucleus), sympathetic fibers within the zona incerta or STN
autonomic symptoms	hypothalamus and red nucleus
paresthesia	medial lemniscus
speech impairment	internal capsule, the pallidal and cerebello-thalamic fiber tracts medial and dorsal of the STN, medial left-sided STN stimulation in right-handed patients, higher left STN voltage
depression	substantia nigra
mania	medial and ventral areas of STN
impulse control disorder	ventromedial and limbic areas of STN, SNr, medial forebrain bundle
cognitive problems	ventral and medial parts of STN, perforation of the caudate nucleus during surgery (?)

STN - subthalamic nucleus, SNr - substantia nigra pars reticulata

5.3. Internal globus pallidus (GPi) and subthalamic nucleus (STN) DBS comparison

Authors suggest better results with STN-DBS using lower stimulation parameters (and longer battery life) compared to GPi-DBS, while there is no study directly comparing the effects of stimulation of both areas; later in this article, we will compare the outcomes of two GPi and STN studies with the largest patient groups.

The largest study assessing the DBS effectiveness of GPi was performed by Pouclet-Courtemanche et al., it included originally 19 patients with 18 reaching 6-month follow-up, while 14 participants were evaluated in the long-term observation (6-11 years) [37]. On the other hand, Deng et al. analyzed the results of STN-DBS in a group of 10 individuals, with all included at the 6-month and the long-term (12-105 months) follow-up [5]. The aforementioned time points were common for both studies among other follow-up lengths. Furthermore, the mutual form of assessment of motor symptoms was only AIMS. We compared the effectiveness of DBS at the different sites using a 2-sample z-test for proportions. In the case of the study by Pouclet-Courtemanche et al., no median/mean data

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for the AIMS score was available at all time points. Regardless the calculation of proportions was possible based on the graph analysis presenting a change in the AIMS score at the different follow-ups. For the 6-month follow-up time point, the proposition was 0.49 (n=18) and 0.15 (n=10) for the GPi-DBS and the STN-DBS respectively. In the comparison, the difference did not reach statistical significance with p=0.079 which is most likely due to the small sample sizes in both studies, as the trend is clearly visible (Figure 1). Statistical analysis of a long-term follow-up was not performed due to a great disparity in the observation period, which could affect the result.

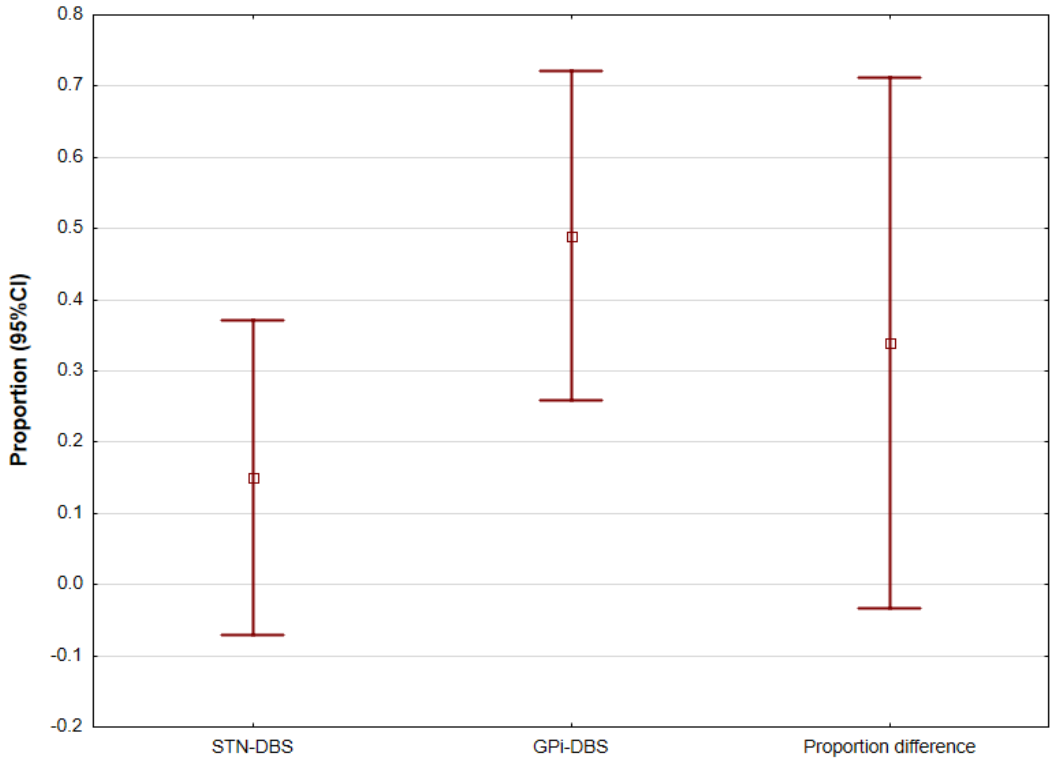

Figure 1. Proportion comparison of AIMS score (initial evaluation to 6-moths follow-up) between STN-DBS and GPi-DBS.

AIMS - Abnormal Involuntary Movement Scale, DBS -deep brain stimulation, GPi - internal globus pallidus, STN - subthalamic nucleus.

6. Discussion

Deep brain stimulation (DBS) is an established treatment for patients with tardive dyskinesia when pharmacological therapy alone does not provide sufficient relief or is associated with disabling side effects. With this method, patients achieve satisfactory results in both the short and long term, with a relatively small number of complications. As we previously mentioned, the main sites with proven efficacy of its stimulation are the subthalamic nucleus (STN) and internal globus pallidus (GPi). Although GPi remains the standard stimulation target, our comparison in small groups shows at least comparable efficacy of STN- and GPi- DBS, including 6-month follow-up. Similar conclusions come from comparisons of the two methods in PD [96]. However, further research is needed to confirm this conclusion, also because the trend may nevertheless indicate an advantage for STN-DBS.

 doi:10.20944/preprints202211.0258.v1

To broaden knowledge and outline research plans that should be performed in the first place, it is worth looking at solutions employed in DBS procedures in patients with other health problems. DBS is a method that has been implemented for years in various conditions such as dystonia, Parkinson's disease, and obsessive-compulsive disorder. This method is also recommended for patients with severe and treatment-resistant forms of the disease. It is noteworthy that STN is the standard site of stimulation in PD [97]. According to the symptomatic profile of PD, preferences include alternative targets, e.g., the thalamic ventral intermediate nucleus (VIM) or GPi. Recent research in this area has focused on the search for other sites of stimulation as the posterior subthalamic area (PSA) or caudal zona incerta (cZi). The PSA is located ventrally to the VIM, between the red nucleus and the STN. PSA-DBS is not significantly different from VIM-DBS in suppressing tremor, but clinical benefit from PSA-DBS is attained at lower stimulation amplitudes [98]. Also, several open-label studies have shown a good effect in the reduction of PD symptoms with DBS in the caudal zona incerta (cZi) [99].

While both TD and PD treatment have the same standard stimulation sites, it is worth investigating other experimental stimulation sites in TD treatment, such as PSA, cZi, or finding new targets. Treatment of refractory TDs with DBS is not a low-cost method, requiring an experienced neurosurgical team and precise instrumentation. It is also not a life-saving method, but if we want to have a full range of possible medical procedures that may expand our understanding of the brain (we consider it crucial), this research must be continued and intensified. The latest technical achievements in the field of construction of stimulators and electrodes, e.g., modeling the shape of the impact field, as well as the results of new studies, focused on the paths connecting the gray matter of various brain regions, allow us to expect discoveries in research using DBS, hopefully also in TD.

Author Contributions: Conceptualization, D.S.; methodology, D.S.; validation, D.S.; formal analysis, A.S., A.G. and D.S.; investigation, A.G. and D.S.; resources, D.S.; data curation, A.G. and D.S.; writing—original draft preparation, A.S., A.G. and D.S.; writing—review and editing, A.G. and D.S.; visualization, A.G. and D.S.; supervision, D.S.; project administration, D.S.; funding acquisition, D.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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