REVIEW ARTICLE

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Is deep brain stimulation effective in Huntington's disease? — a systematic literature review

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ABSTRACT

Introduction. Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. Substantial for a diagnosis of the disease are motor disorders, with chorea as a hallmark symptom. Other disease manifestations include cognitive dysfunction and psychiatric disorders. Currently, pharmacological treatment plays the most important role in the therapy of HD patients. However, deep brain stimulation (DBS) is considered a potential therapeutic option.

Aim of the study. Systematic review of current literature on DBS efficacy and safety in the management of motor, behavioural and cognitive functions in patients with HD.

Material and methods. A systematic review was conducted with the use of the Scopus database and the following search criteria: TITLE (huntington*) AND TITLE-ABS-KEY ('deep brain stimulation' OR 'neuromodulation'). Our search criteria included original studies with at least five patients, reporting any motor, cognitive and/or behavioural, and functional assessment data with at least a 6-month follow-up. Finally, four selected publications were analysed.

Results. In all analysed publications, we found a statistically significant improvement of Unified Huntington's disease Rating Scale (UHDRS) chorea subscore by an average of 40, to over 60% after DBS implantation. Heterogeneous results were obtained for UHDRS total motor score. DBS did not improve functional capacity of HD patients in the analysed studies. We found no systematic assessment concerning the effect of DBS in HD on behaviour, cognition or speech.

Conclusions. DBS implantation could be considered as a therapeutic option for patients with severe, drug-resistant chorea. However, the evidence for this is limited. To date, no high-quality data based on randomised controlled trials supports the long-term safety and efficacy of DBS in HD. This treatment option should therefore currently be considered as investigational.

Key words: deep brain stimulation, Huntington's disease, chorea, globus pallidus

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Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. It is caused by CAG trinucleotide repeat expansion in the gene *HTT*, which results in encoding an expanded polyglutamine stretch in the huntingtin protein. Substantial for the diagnosis are motor symptoms, namely chorea, dystonia, tics and parkinsonism in young-onset disease. In the natural course of the disease, chorea progresses from sporadic, low-amplitude facial and extremity twitches to regular, large-amplitude motions of the entire body. Although chorea is a hallmark HD symptom, it becomes less significant in the late stages of the disease [1]. Initially mild cognitive dysfunction gradually progresses to full-blown dementia [2, 3]. Depression with an increased risk of suicide attempts and apathy are common in HD patients.

Pharmacological treatment with neuroleptic medications and tetrabenazine plays the most important role in the therapy of chorea in HD patients [4]. However, their use is limited due to side effects and incomplete effectiveness.

Deep brain stimulation (DBS) has been used in evidence-based indications for the therapy of Parkinson's disease (PD), tremor and dystonia, using established protocols for qualification and treatment. There are also reports of potential DBS effectiveness in other indications, for example Gilles de la Tourette syndrome (GTS) [5] and treatment-resistant addictions to alcohol and psychoactive substances, although clinical data on this topic is limited [6]. The mechanism of action of DBS is still not fully understood. In HD patients, DBS of the globus pallidus internus (GPi) has been of growing interest as an alternative to the pallidotomy method of treatment, potentially alleviating major symptoms [7].

The aim of this study was a systematic review of the current literature on DBS efficacy and safety in the management of motor, behavioural and cognitive functions in patients with HD.

Paper selection

The method of systematic review was based on PRISMA guidelines [8]. An initial search was conducted with the use of the Scopus database and the following search criteria: TITLE (huntington*) AND TITLE-ABS-KEY ('deep brain stimulation' OR 'neuromodulation') in June 2021. The identification of relevant studies including 103 papers was performed using the following steps. Firstly, on the basis of the initial search, we aimed to identify randomised controlled trials (RCTs) reporting data on motor symptoms, functional status, speech, comprehensive behavioural and cognitive functioning pre-surgery and at least 12 months post-surgery. Unfortunately, we found no such study. Secondly, we broadened our search criteria to capture not only RCTs, but all original studies with at least five patients, while keeping the other criteria unchanged. Of four original studies with ≥ 5 cases, only one fulfilled all those pre-established inclusion criteria [9], see Suppl. Fig. 1. In one of the studies [10], only a 6-month follow-up was available, and in two others no standardised behavioural assessment was reported [11, 12]. Finally, we decided to include and analyse one RCT and three open trials reporting any motor, functional, cognitive and behavioural data with at least a 6-month follow-up [9–12] (Fig. 1), even if this data was limited in terms of follow-up length, and not as extensive as expected.

Results

Patient qualification

Patients undergoing DBS implantation in the analysed studies were in different disease stages, and disease stage was assessed differently in the reviewed studies. Sanrey et al. [12] included in their study patients with early-to-moderate HD according to the disease stages defined by Shoulson and Fahn, which corresponds to grades I–III in this classification. In the study by Gonzalez et al. [11], one inclusion criterion was a Total Functional Capacity (TFC) score ≤ 8, which corresponds to stage II or higher according to Shoulson and Fahn. One study [10] enrolled patients with at least moderate-stage motor symptoms as measured by ≥ 30 Unified Huntington's disease Rating Scale total motor score (UHDRS TMS), but there was no information on the disease stage. Zittel et al. [9] reported that patients were in the advanced stage of the disease, but the authors did not define their specific criteria.

There were no cut-offs in terms of patient age, which differs from the usual standards used in the qualification of PD patients to DBS. One study only [10] reported the number of pre-surgery pharmacotherapy trials and reported severe brain atrophy as one of the exclusion criteria to DBS.

In only two studies was the presence of a reliable caregiver among the inclusion criteria [11, 12]. Only one study reported the use of psychometric scales assessing some of the psychiatric symptoms [10], and no cut-offs were provided. In only one study was a history of suicidal ideation explicitly addressed [11], and in none of them was a history of substance abuse discussed. Patient qualification criteria are set out in Table 1.

DBS target and stimulation settings

In three studies, patients underwent bilateral GPi implantation. In one study [10], electrodes were implanted in such a way that the lowermost contact was located in the upper part of the GPi, and the higher contacts were located in the globus pallidus externus (GPe). In the first phase of this study, controlled and double-blind, patients were randomly assigned to either GPi stimulation for six weeks followed by GPe stimulation for six weeks, or vice versa. Then, in the uncontrolled follow-up phase, chronic pallidal stimulation at the target with the best effect and least side effects was used to assess chronic treatment effects. This study showed that GPi and GPe stimulation are equally effective. We did not analyse the stimulation settings in the discussed publications, as they were adjusted individually depending on clinical response and adverse effects.

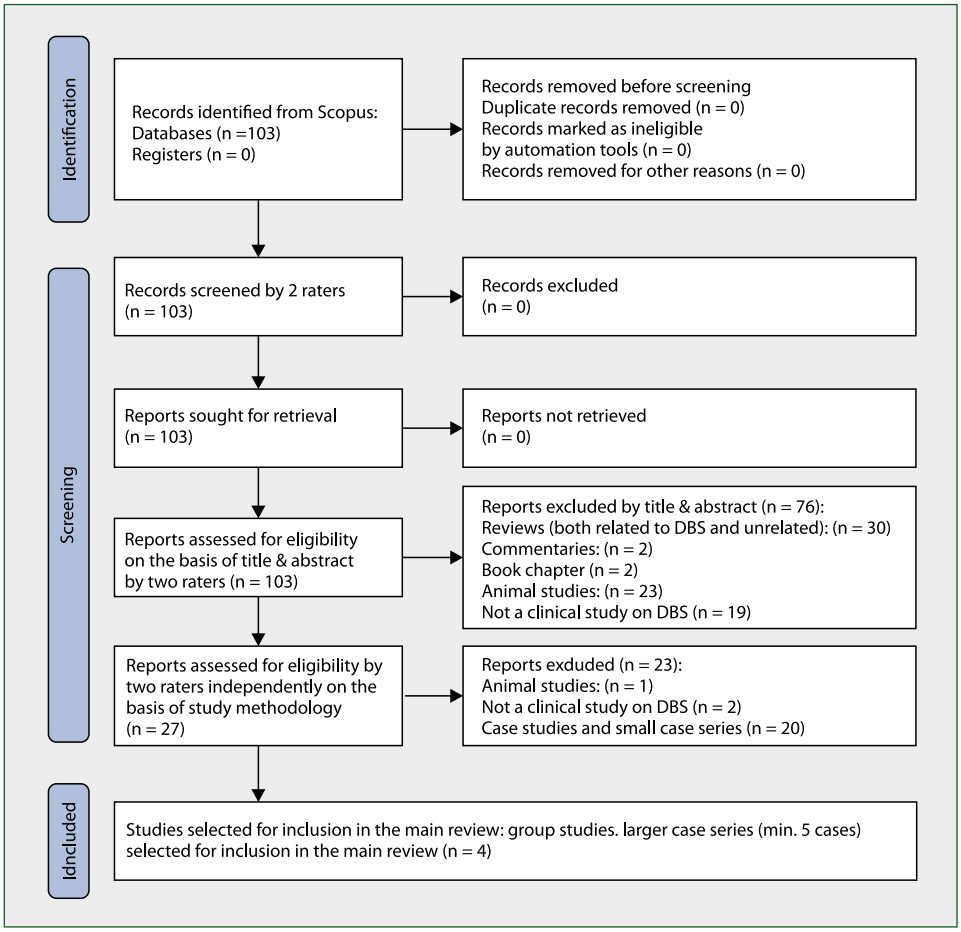

Figure 1. Identification of studies via databases and registers

Long-term motor and functional outcomes of DBS

Motor function and functional status after DBS in HD patients are set out in Table 2, which contains results obtained after six months follow-up, because this was the common evaluation time point in 3/4 studies. Table 2 also shows the results obtained at the final follow-up visit. In the four discussed publications, motor outcome of all patients was assessed using UHDRS, where both TMS and chorea subscores were analysed. Functional outcome was assessed using UHDRS TFC in all four studies, UHDRS Functional Assessment was used in three, and UHDRS Independence Scale in one. We did not include the motor and functional outcomes measured in other scales in our table, because they were assessed in single studies only. If obtained results were important for drawing conclusions, we discuss them in the core text.

Heterogeneous results were obtained for UHDRS TMS: in one study, a statistically significant deterioration of UHDRS TMS was shown six months after DBS, but not at the final follow-up (median 3 years after DBS) [11]. In another study, statistically significant deterioration of UHDRS TMS was shown at the final follow-up (median 4 years after DBS) [12]. One study [9] showed a statistically significant improvement of UHDRS TMS six months after DBS implantation, which was no longer present at the final follow-up (12 months after DBS). In the fourth study [10], UHDRS TMS did not significantly change after DBS compared to pre-DBS. Nevertheless, in all analysed publications, a statistically significant improvement of UHDRS chorea subscore was found, both at six months follow-up and at the final follow-up visit (six months, one year, median 3 years and median 4 years after DBS, depending on publication). In the discussed studies, UHDRS chorea subscore at the final follow-up visit improved by an average of 40, to over 60% compared to baseline.

Two studies [9, 11] assessed the effect of DBS during off-stimulation, on-medication tests. In the study by Gonzalez et al. [11], regular off-stimulation tests showed that there was a persistent improvement of chorea after DBS implantation. The authors proved that there was a statistically significant difference, ranging from 30-77.3%, in UHDRS chorea subscore during off- and on-stimulation conditions at the final follow-up visit (median 3 years after DBS), with no significant difference in dystonia scores. The duration of the off-stimulation period was not reported, although the authors noted that

Table 1. Patient selection

Patients' demographic and clinical characteristics					Patient qualification criteria					
Author, publication year	n	Age at DBS surgery, mean ± SD; min–max	Disease duration at DBS surgery, mean ± SD; min–max	Number of pharmacotherapy trials; criteria of pharmacotherapy unresponsiveness	Functional impairment	Behavioural		Cognitive		Stable psychosocial environment/caregiver availability
						Self-report	Clinician's ratings	Dementia screening	Neuropsychological assessment	
Gonzalez et al., 2014	7	49.71 ± 19.41 years; 30–78 years	4.86 ± 2.27 years; 3–8 years	NR; chorea unresponsive or poorly responsive to medical treatment (including tetrabenazine or a combination of at least one neuroleptic and another drug)	UHDRS IS ≤ 70; UHDRS TFC ≤ 8	Scores NR; patients with unstable psychiatric comorbidities excluded		MDRS — no cut-offs	Scores NR; no severe cognitive impairment as demonstrated by preserved language skills	Yes; support of a reliable caregiver
Wojtecki et al., 2015	6	39.67 ± 18.67 years; 23–71 years	9.5 ± 6.47 years; 3–21 years	≥ 2 (lack of effect or side effects at maximal tolerable dose); tiapride and tetrabenazine mandatory for chorea patients	UHDRS TMS ≥ 30	BDI HADS Major depression or dominant psychiatric symptoms as exclusion criteria	MADRS BPRS	MDRS < 120	NR	NR
Zittel et al., 2018	6[1]	45 ± 2.28 years; 42–49 years	10.3 ± 3.1 years; 7–14 years	NR; chorea not sufficiently controlled by oral medication or treatment limited by side effects	Severe chorea leading to impairment in activities of daily living or recurrent injuries	Standardised psychiatric interview — unspecified		MDRS, MMSE	BNT, verbal fluency	NR
Sanrey et al., 2021	13	45.70 ± 14.88 years; 30–78 years	4.38 ± 1.61 years; 3–8 years	NR; chorea unresponsive or poorly responsive to medication	Disabling chorea; early to moderate disease stage[2]	Psychiatric comorbidities under control		One third of patients presented with normative cognitive status (MDRS total score ≥ 123/144) at baseline on MDRS; no-cut-offs	Neuropsychological assessment with no cut-offs	Yes; support of at least one reliable caregiver

BDI — Beck Depression Inventory; BNT — Boston Naming Test; BPRS — Brief Psychiatric Rating Scale; HADS — Hospital Anxiety and Depression Scale; MADRS — Montgomery-Åsberg Depression Rating Scale; MDRS — Mattis Dementia Rating Scale; NR — not reported; UHDRS IS — Unified Huntington's Disease Rating Scale Independence Scale; UHDRS TFC — Unified Huntington's Disease Rating Scale Total Functional Capacity; UHDRS TMS — Unified Huntington's Disease Rating Scale Total Motor Score; [1]cognitive data available for five cases; [2]according to disease stages defined by Shoulson and Fahn

Table 2. Short-term and long-term motor and functional outcomes of deep brain stimulation in Huntington's disease

Author, publication year	n	Medication pre-DBS	Medication at final follow-up post-DBS	Final follow-up assessment	Motor function			Functional status		
					Pre-DBS	6 months after DBS	At final follow-up	Pre-DBS	6 months after DBS	At final follow-up
Gonzalez et al., 2014	7	7 patients treated with tetrabenazine and/or neuroleptic	5 patients treated with tetrabenazine and/or neuroleptic	3 years after DBS (median)	UHDRS TMS 48.7 ± 18.35 UHDRS chorea subscore 17.0 ± 4.65	UHDRS TMS 49.4 ± 7.09* UHDRS chorea subscore 9.6 ± 3.71*	UHDRS TMS 58.8 ± 12.93 UHDRS chorea subscore 7.0 ± 3.39* improvement by 59.8 ± 22.9% *compared to baseline	UHDRS IS 62.9 ± 12.54 UHDRS FA 13.3 ± 3.95 UHDRS TFC 5.14 ± 2.34	UHDRS IS 64.3 ± 9.76 UHDRS FA 13.0 ± 5.23 UHDRS TFC 5.14 ± 2.34	UHDRS IS 50.0 ± 18.71 UHDRS FA 7.0 ± 4.36 UHDRS TFC 3.0 ± 2.23
Wojtecki et al., 2015	6	4 patients treated with tetrabenazine and/or neuroleptic	3 patients treated with tetrabenazine and/or neuroleptic: in one patient dose reduction	6 months after DBS	UHDRS TMS 54.3 ± 17.6 UHDRS chorea subscore 8.8 ± 7.5	UHDRS TMS 48.2 ± 24.4 UHDRS chorea subscore 3.5 ± 3.2 * improvement by 60.2% * compared to baseline	UHDRS TMS 48.2 ± 24.4 UHDRS chorea subscore 3.5 ± 3.2 * improvement by 60.2% * compared to baseline	UHDRS IS NR UHDRS FA 5.2 ± 3.9 UHDRS TFC 12.0 ± 8.7	UHDRS IS NR UHDRS FA 6.7 ± 5.5 UHDRS TFC 12.7 ± 9.7	UHDRS IS NR UHDRS FA 6.7 ± 5.5 UHDRS TFC 12.7 ± 9.7
Zittel et al., 2018	6	6 patients treated with tetrabenazine and/or neuroleptic	6 patients treated with tetrabenazine and/or neuroleptic: in two patients dose reductions, in four patients dose reductions and withdrawal of certain drugs	1 year after DBS	UHDRS TMS 71.8 ± 10.8 UHDRS chorea subscore NR	UHDRS TMS improvement by 17% * compared to baseline UHDRS chorea subscore improvement by 47 ± 23% * compared to baseline	UHDRS TMS deterioration by 5% compared to baseline UHDRS chorea subscore improvement by 40 ± 15% * compared to baseline	UHDRS IS NR UHDRS FA 8 ± 5.33 UHDRS TFC 2.17 ± 2.14	UHDRS IS NR UHDRS FA 7 ± 4.82 UHDRS TFC 2.33 ± 1.75	UHDRS IS NR UHDRS FA 5.5 ± 4.76 UHDRS TFC 2 ± 1.67
Sanrey et al., 2021	13	12 patients treated with tetrabenazine and/or neuroleptic	11 patients treated with tetrabenazine and/or neuroleptic	4 years after DBS (median)	UHDRS TMS 42.5 ± 16 UHDRS chorea subscore 16.75 ± 4	NR	UHDRS TMS 55.75 ± 13 * UHDRS chorea subscore 7.41 ± 4 * improvement by 56% * compared to baseline	UHDRS IS NR UHDRS FA NR UHDRS TFC 7.69 ± 3.12	NR	UHDRS IS NR UHDRS FA NR UHDRS TFC 2.30 ± 1.75 *

*statistically significant; NR — not reported; UHDRS chorea subscore (maximum 28, higher score corresponds to more severe chorea); UHDRS FA — Unified Huntington's Disease Rating Scale Functional Assessment (maximum 25, higher score corresponds to better functional status); UHDRS IS — Unified Huntington's Disease Rating Scale Independence Scale (maximum 100, higher score corresponds to higher independence level); UHDRS TFC — Unified Huntington's Disease Rating Scale Total Functional Capacity (maximum 13, higher score corresponds to higher functional capacity); UHDRS TMS — Unified Huntington's Disease Rating Scale Total Motor Score (maximum 124, higher score corresponds to more severe symptoms)

some patients presented with clinical worsening immediately after turning the stimulation off, while in others deterioration occurred as much as 24 hours later.

Zittel et al. [9] also showed a statistically significant difference in chorea comparing off- and on-stimulation conditions at both follow-up time points (by 39% and by 37% six months and one year after DBS, respectively). Patients were assessed six hours after stimulation had been turned off. However, the accuracy of these results may be limited because the clinical assessment was not blinded.

The study reports on the effects of DBS on dystonia and bradykinesia are heterogenous. In the study by Gonzalez et al. [11], bradykinesia and dystonia insignificantly gradually worsened after DBS implantation, partly due to disease progression and partly to DBS. In the study by Wojtecki et al. [10], the effects on dystonia were heterogenous and statistically non-significant. Although half of the patients showed a marked improvement of dystonia of more than 50% as assessed using the Burke-Fahn-Marsden Dystonia Rating Scale, hypokinetic-rigid symptoms did not improve. Zittel et al. [9] also obtained non-conclusive results in terms of dystonia and bradykinesia: improvement of dystonia in three patients, worsening in two, and no change in one; improvement of bradykinesia in three patients, worsening in two, and no change in one.

The four studies under discussion did not precisely analyse the influence of DBS implantation on gait and postural stability in HD patients. Only one study [11] assessed UHDRS gait/steadiness subscore, and no statistically significant difference was observed either at six months or at the final follow-up visit (median 3 years after DBS implantation) compared to baseline. The influence of DBS implantation on gait is discussed in the analysed publications mainly in the context of adverse events. Gonzalez et al. [11] found that two patients experienced freezing of gait in the first weeks after DBS implantation, which was partially controlled by modification of the stimulation parameters and levodopa treatment. In the study by Wojtecki et al. [10], among the adverse events of DBS, gait impairment after reprogramming was reported in one patient, and gait impairment and fall in one patient. Three patients in the study by Zittel et al. [9] experienced gait impairment after DBS implantation. Two of them presented with stimulation-dependent spasticity.

Patient functional status was analysed in the discussed publications with the use of three scales. UHDRS Functional Capacity deteriorated significantly at the final follow-up in the study by Sanrey et al. [12], and did not change significantly in the other analysed studies. UHDRS Functional Assessment did not significantly change after DBS in three studies [9–11]. UHDRS Independence Scale assessed by Gonzalez et al. [11] had insignificantly changed at six months and at the final follow-up.

Long-term behavioural outcomes of DBS

None of the four selected studies used the clinician-rated psychiatric assessment based on both patient and caregiver reports, Problem Behaviour Assessment-short (PBA-short), which is universally used at HD clinics [13].

Changes in psychiatric symptoms were only vaguely described. In 3/4 studies, details of psychiatric assessment were not reported [9, 11, 12]. In the fourth study [10], the clinician-rated assessment was global (Brief Psychiatric Rating Scale, BPRS) and only mood was assessed in detail. Gonzalez et al. [11] reported unspecified post-surgical behavioural problems in one case. Sanrey et al. [12] stated that behavioural changes resulted in increased neuroleptic dose in two cases. Wojtecki et al. [10] reported no deterioration on BPRS, while Zittel et al. [9] stated no psychiatric side-effects. None of the studies explicitly addressed such major neuropsychiatric issues as apathy or irritability. Thus, the effect of DBS on behaviour in HD remains unclear. Behavioural outcomes of DBS in HD patients from the reviewed publications are summarised in Suppl. Table 1.

Long-term speech and cognitive outcomes of DBS

Objective speech parameters were not monitored in detail in any of the reviewed studies on DBS in HD. In only one study [11] was UHDRS speech/orolingual subscore assessed, and no statistically significant difference was observed either at six months or at the final follow-up visit (median 3 years after DBS implantation) compared to baseline. None of the four studies reported the use of a UHDRS cognitive test battery or addressed the six cognitive domains as specified in DSM-5. Cognitive screening only was performed in three studies [9–11]. In the fourth study [12], a more extensive but incomplete neuropsychological assessment was performed. The paucity of speech and cognitive data does not allow us to draw any firm conclusions. Cognitive and language outcomes of DBS in HD patients from the reviewed publications are set out in Suppl. Table 2.

Discussion

This systematic review shows that there have been no long-term RCTs on DBS in HD addressing not only motor and daily function but also behaviour, speech and cognition. We were able to find only four original studies including at least five patients that fulfilled our criteria for assessment of DBS in the treatment of HD patients. The qualification criteria used in the selected studies differ from published recommendations on DBS in other disorders, e.g. PD and GTS. Standardised inclusion criteria for DBS in HD are not yet established.

Based on the analysed publications, it is difficult to draw conclusions regarding the long-term impact of DBS implantation on patients' motor and functional status. The assessment is hampered by the small size of the groups (four studies with a total of 32 patients) and their heterogeneity. The age of the patients, the duration of disease, and the stage of disease all differed. The inclusion criteria for the studies also varied. Although all four studies included patients with drug-resistant chorea, the criteria for drug resistance were for

the most part not defined. Another limitation is that in only one study [10] was the clinical evaluation blinded. The other three were open-label. This might bias the assessments due to the placebo effect and to high expectations of improvement by both patients and physicians.

Despite the numerous differences between the discussed studies, all of them have clearly shown a statistically significant improvement of chorea despite no long-term overall motor function improvement (see UHDRS chorea subscore and UHDRS TMS in Tab. 2). The effect of DBS on chorea was also proved by an increase of chorea severity during off-stimulation.

It can be concluded that the alleviation of chorea after DBS may persist for up to four years, as this was the longest follow-up period among the analysed publications. There are no homogeneous and statistically confirmed conclusions regarding the impact of DBS on dystonia, bradykinesia, gait, speech or functional status.

In a review article by Bonomo et al. [14], 20 studies describing the effect of DBS in HD patients (n = 42) were analysed. Apart from the three articles that we included in our analysis, the authors also provided results for 12 case reports and five case series. In the analysed studies, the pharmacotherapy preceding DBS differed, and no common criteria for drug resistance of chorea were defined. Among all the publications analysed, ten studies showed an improvement in UHDRS total score (range: 5.4–34.5%) and four studies revealed a deterioration in UHDRS total score (range: 3.8–97.8%) after GPi-DBS implantation. All studies showed improvement in UHDRS chorea subscore after bilateral GPi-DBS (range: 21.4–73.6%). Thus, the results obtained by the authors were also inconclusive in terms of DBS implantation's impact on the overall motor outcome, although they confirmed the positive impact of DBS on chorea.

In the recently published *MDS Evidence-Based Review on Treatments for Huntington's Disease* [15], an expert group reviewed 22 selected studies and evaluated the evidence of therapeutic options for HD patients. Among the 33 clinical questions formulated by the authors, three were related to DBS. These questions concerned whether DBS combined with best medical treatment improves motor function, functional capacity and quality of life of HD patients compared to best medical treatment alone or compared to sham stimulation combined with best medical treatment. For any of the questions regarding DBS, no eligible trials were found and the expert group was unable to reach a conclusion on this topic.

None of the four reviewed studies on DBS in HD addressed cognition in a comprehensible way. Data on DBS sequelae in other movement disorders suggests that cognitive function needs to be monitored in detail. In PD, in most cases DBS is associated with a slight albeit not clinically meaningful deterioration in some cognitive domains [16]. Nevertheless, patients are psychologically examined before surgery to exclude dementia as the main contraindication for DBS surgery. As HD is associated with early, prominent and rapidly progressing cerebral atrophy, affecting also posterior brain areas [17], particular care should be taken to analyse the cognitive safety of DBS in HD. As shown in one post-mortem study, electrodes can even become displaced due to cerebral atrophy in HD [18].

Despite the fact that HD patients can suffer from severe and heterogeneous dysarthria and dysphagia [19], speech was not monitored in detail in any of the reviewed studies on DBS in HD. This is surprising, because the appearance or worsening of dysarthria, dysphagia and stuttering are known complications of DBS treatment in other indications [20–22].

Monitoring of neuropsychiatric symptoms in HD patients both pre- and post-DBS has been insufficient in the reviewed studies. PD literature reports behavioural side-effects of DBS including increased suicide risk [23], psychotic symptoms, depression, hypomania, anxiety [24], impulsivity [25], irritability, emotional lability and pseudo-bulbar effect [24]. Thus, in PD, DBS is not recommended in cases with prominent and poorly controlled psychiatric symptoms [26]. However, the described side effects were proven for the implantation of DBS into the subthalamic nucleus, not to the GPi as in the HD patients in the discussed publications. In HD, a variety of behavioural symptoms is present in 73-100% of patients [27–29]. Neuropsychiatric symptoms (depression and apathy) are associated with disability in HD [30], and so the monitoring of such symptoms seems to be crucial when assessing the efficacy of HD treatment procedures on functional status.

Therefore, as none of the reviewed studies reported comprehensive neuropsychiatric data pre- and post-DBS surgery in HD, there is insufficient data to claim that DBS is useful or safe in terms of neuropsychiatric status.

An important argument when considering the method is that DBS implantation is an invasive neurosurgical procedure with the risk of side effects and complications. Possible operation-related complications include among others intracranial haematoma, epileptic seizure, respiratory distress, and hydrocephalus, whereas hardware-related complications include for example electrode migration or extension wire fracture [31]. Other adverse events after DBS include neuropsychiatric complications [32]. There are also infectious complications e.g. incomplete stitch removal can result in superficial wound infection and consequently even the formation of a brain abscess and the necessity of hardware removal [33]. One dangerous complication, although not one directly related to the DBS implantation procedure, is battery depletion. Such an event, so far reported in PD and dystonia patients, can be life-threatening due to a sudden recurrence of disease symptoms [34]. In the reviewed publications, apart from minor complications, severe adverse events of DBS were reported, such as postoperative malignant hyperthermia, gait impairment and hyperkinesia after reprograming, and suicide attempts. All the side effects of DBS which occurred in HD patients in the analysed publications are set out in Suppl. Table 3.

In many patients in the discussed publications, treatment after DBS implantation was modified several times, so we

decided to compare treatment before DBS to that at the final follow-up (Tab. 2). In all studies, at the final follow-up the number of patients treated with tetrabenazine and/or a neuroleptic decreased, or the medication doses were reduced, compared to baseline.

Currently, there are two active DBS trials with pallidal stimulation in HD with estimated completion in 2022: one is a Chinese trial with sham stimulation (www.clinicaltrials.gov) and the other is a European trial comparing a stimulation-on group to a stimulation-off group. Neither of these trials is comparing DBS to best medical treatment.

Summary of results

- Chorea severity improves after DBS in HD by c.50%;
- DBS does not improve functional capacity of HD patients;
- There is insufficient data on impact of DBS on dystonia and bradykinesia in HD patients;
- There have been no systematic assessments concerning effect of DBS in HD on behaviour, cognition or speech;
- Overall quality of analysed and other available studies is poor. Specifically, there are many unanswered questions regarding the safety of such procedures, and no established protocol for patient recruitment.

Conclusions

Based on the current evidence, DBS surgery may be considered only in patients with severe, troublesome and drug-resistant chorea and should not be offered to all patients with HD. This conclusion will be verified in two ongoing, randomised and controlled trials.

At present, GPi DBS can be offered to HD patients only as an experimental (investigational) treatment which requires Ethical Committee consent and financial support.

We recommend that randomised, controlled studies be performed to show the real efficacy and safety of DBS in a population of HD patients.

Conflicts of interest: *GW: Study Site's Principal Investigator in Wave and Roche HD studies. MR-B: Study Site's Principal Investigator in Prilenia Neurotherapeutics and Roche HD studies. JS: Study Site's Principal Investigator in Wave and Roche HD studies. Other authors: no conflict to declare.*
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References

1. Mahant N, McCusker EA, Byth K, et al. Huntington Study Group. Huntington's disease: clinical correlates of disability and progression. Neurology. 2003; 61(8): 1085–1092, doi: 10.1212/01.wnl.0000086373.32347.16, indexed in Pubmed: 14581669.
2. Paulsen JS, Long JD. Onset of Huntington's disease: can it be purely cognitive? Mov Disord. 2014; 29(11): 1342–1350, doi: 10.1002/mds.25997, indexed in Pubmed: 25142616.
3. Paulsen JS, Langbehn DR, Stout JC, et al. Predict-HD Investigators and Coordinators of the Huntington Study Group. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry. 2008; 79(8): 874–880, doi: 10.1136/jnnp.2007.128728, indexed in Pubmed: 18096682.
4. Bachoud-Lévi AC, Ferreira J, Massart R, et al. International guidelines for the treatment of Huntington's disease. Front Neurol. 2019; 10: 710, doi: 10.3389/fneur.2019.00710, indexed in Pubmed: 31333565.
5. Billnitzer A, Jankovic J. Current management of tics and Tourette syndrome: behavioral, pharmacologic, and surgical treatments. Neurotherapeutics. 2020; 17(4): 1681–1693, doi: 10.1007/s13311-020-00914-6, indexed in Pubmed: 32856174.
6. Sobstyl M, Kupryjaniuk A, Mierzejewski P. Nucleus accumbens as a stereotactic target for the treatment of addictions in humans: a literature review. Neurol Neurochir Pol. 2021; 55(5): 440–449, doi: 10.5603/PJNNS.a2021.0065, indexed in Pubmed: 34633060.
7. Cubo E, Shannon KM, Penn RD, et al. Internal globus pallidotomy in dystonia secondary to Huntington's disease. Mov Disord. 2000; 15(6): 1248–1251, doi: 10.1002/1531-8257(200011)15:6<1248::aid-mds1029>3.0.co;2-q, indexed in Pubmed: 11104214.
8. Page M, Moher D, McKenzie J. Introduction to PRISMA 2020 and implications for research synthesis methodologists. Research Synthesis Methods. 2021; 13(2): 156–163, doi: 10.1002/jrsm.1535.
9. Zittel S, Tadic V, Moll CKE, et al. Prospective evaluation of Globus pallidus internus deep brain stimulation in Huntington's disease. Parkinsonism Relat Disord. 2018; 51: 96–100, doi: 10.1016/j.parkreldis.2018.02.030, indexed in Pubmed: 29486999.
10. Wojtecki L, Groiss SJ, Ferrea S, et al. Surgical Approaches Working Group of the European Huntington's Disease Network (EHDN). A prospective pilot trial for pallidal deep brain stimulation in Huntington's disease. Front Neurol. 2015; 6: 177, doi: 10.3389/fneur.2015.00177, indexed in Pubmed: 26347707.
11. Gonzalez V, Cif L, Biolsi B, et al. Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study. J Neurosurg. 2014; 121(1): 114–122, doi: 10.3171/2014.2.JNS131722, indexed in Pubmed: 24702329.
12. Sanrey E, Macioce V, Gonzalez V, et al. Does pallidal neuromodulation influence cognitive decline in Huntington's disease? J Neurol. 2021; 268(2): 613–622, doi: 10.1007/s00415-020-10206-w, indexed in Pubmed: 32886253.
13. McNally G, Rickards H, Horton M, et al. Exploring the validity of the short version of the problem behaviours assessment (pba-s) for huntington's disease: a rasch analysis. J Huntingtons Dis. 2015; 4(4): 347–369, doi: 10.3233/JHD-150164, indexed in Pubmed: 26756591.
14. Bonomo R, Elia AE, Bonomo G, et al. Deep brain stimulation in Huntington's disease: a literature review. Neurol Sci. 2021; 42(11): 4447–4457, doi: 10.1007/s10072-021-05527-1, indexed in Pubmed: 34471947.
15. Ferreira JJ, Rodrigues FB, Duarte GS, et al. An MDS evidence-based review on treatments for Huntington's disease. Mov Disord. 2022; 37(1): 25–35, doi: 10.1002/mds.28855, indexed in Pubmed: 34842303.
16. Rothlind JC, York MK, Carlson K, et al. CSP-468 Study Group. Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy. J Neurol Neurosurg Psychiatry. 2015; 86(6): 622–629, doi: 10.1136/jnnp-2014-308119, indexed in Pubmed: 25185211.

17. Johnson EB, Ziegler G, Penny W, et al. Dynamics of cortical degeneration over a decade in Huntington's disease. Biol Psychiatry. 2021; 89(8): 807–816, doi: 10.1016/j.biopsych.2020.11.009, indexed in Pubmed: 33500176.
18. Vedam-Mai V, Martinez-Ramirez D, Hilliard JD, et al. Post-mortem findings in Huntington's deep brain stimulation: a moving target due to atrophy. Tremor Other Hyperkinet Mov (N Y). 2016; 6: 372, doi: 10.7916/D8ZP462H, indexed in Pubmed: 27127722.
19. Diehl SK, Mefferd AS, de Riesthal M, et al. Motor speech patterns in Huntington disease. Neurology. 2019; 93(22): e2042–e2052, doi: 10.1212/WNL.0000000000008541, indexed in Pubmed: 31662494.
20. Koeglsperger T, Palleis C, Hell F, et al. Deep brain stimulation programming for movement disorders: current concepts and evidence-based strategies. Front Neurol. 2019; 10: 410, doi: 10.3389/fneur.2019.00410, indexed in Pubmed: 31231293.
21. Macerollo A, Sajin V, Bonello M, et al. Deep brain stimulation in dystonia: State of art and future directions. J Neurosci Methods. 2020; 340: 108750, doi: 10.1016/j.jneumeth.2020.108750, indexed in Pubmed: 32344043.
22. Yin Z, Cao Y, Zheng S, et al. Persistent adverse effects following different targets and periods after bilateral deep brain stimulation in patients with Parkinson's disease. J Neurol Sci. 2018; 393: 116–127, doi: 10.1016/j.jns.2018.08.016, indexed in Pubmed: 30153572.
23. Weintraub D, Duda JE, Carlson K, et al. CSP 468 Study Group. Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease: results from a randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2013; 84(10): 1113–1118, doi: 10.1136/jnnp-2012-304396, indexed in Pubmed: 23667214.
24. Bernal-Pacheco O, Oyama G, Foote KD, et al. Taking a better history for behavioral issues pre- and post-deep brain stimulation: issues missed by standardized scales. Neuromodulation. 2013; 16(1): 35–9; discussion 39, doi: 10.1111/j.1525-1403.2012.00477.x, indexed in Pubmed: 22748071.
25. Pham U, Skogseid IM, Pripp AH, et al. Impulsivity in Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation-An exploratory study. PLoS One. 2021; 16(3): e0248568, doi: 10.1371/journal.pone.0248568, indexed in Pubmed: 33711081.
26. Voon V, Kubu C, Krack P, et al. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord. 2006; 21 Suppl 14: S305–S327, doi: 10.1002/mds.20963, indexed in Pubmed: 16810676.
27. Orth M, Handley OJ, Schwenke C, et al. European Huntington's Disease Network, Investigators of the European Huntington's Disease Network. Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. PLoS Curr. 2010; 2(12): RRN1184–1412, doi: 10.1371/currents.RRN1184, indexed in Pubmed: 20890398.
28. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci. 2012; 24(1): 53–60, doi: 10.1176/appi.neuropsych.11030057, indexed in Pubmed: 22450614.
29. van Duijn E, Craufurd D, Hubers AAM, et al. European Huntington's Disease Network Behavioural Phenotype Working Group. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry. 2014; 85(12): 1411–1418, doi: 10.1136/jnnp-2013-307343, indexed in Pubmed: 24828898.
30. Sellers J, Ridner SH, Claassen DO. A Systematic Review of Neuropsychiatric Symptoms and Functional Capacity in Huntington's Disease. J Neuropsychiatry Clin Neurosci. 2020; 32(2): 109–124, doi: 10.1176/appi.neuropsych.18120319, indexed in Pubmed: 31466515.
31. Xu S, Wang W, Chen Si, et al. Deep brain stimulation complications in patients with Parkinson's disease and surgical modifications: a single-center retrospective analysis. Front Hum Neurosci. 2021; 15: 684895, doi: 10.3389/fnhum.2021.684895, indexed in Pubmed: 34177503.
32. Radziunas A, Deltuva VP, Tamasauskas A, et al. Neuropsychiatric complications and neuroimaging characteristics after deep brain stimulation surgery for Parkinson's disease. Brain Imaging Behav. 2020; 14(1): 62–71, doi: 10.1007/s11682-018-9971-4, indexed in Pubmed: 30267364.
33. Sobstyl M, Stapińska-Syniec A, Kupryjaniuk A, et al. Deep brain stimulation procedure complicated by intracerebral infection of DBS lead due to outbreak of COVID-19 pandemic. Neurol Neurochir Pol. 2021; 55(6): 598–600, doi: 10.5603/PJNNS.a2021.0062, indexed in Pubmed: 34541636.
34. Przytuła F, Dulski J, Sobstyl M, et al. Battery for deep brain stimulation depletion in Parkinson's Disease and dystonia patients - a systematic review. Neurol Neurochir Pol. 2021; 55(4): 346–350, doi: 10.5603/PJNNS.a2021.0041, indexed in Pubmed: 34056704.