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Review article

Non-motor effects of deep brain stimulation in dystonia: A systematic review

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ABSTRACT

Introduction: Deep brain stimulation (DBS) has emerged as an effective treatment in medically intractable dystonia, with the globus pallidus internus (GPi) being most frequently targeted. Non-motor symptoms, including pain and psychiatric, cognitive and sleep disturbances, are increasingly recognized as important determinants of disease burden in dystonia patients. We reviewed non-motor outcomes of DBS in dystonia, focusing on GPi-DBS.

Methods: A systematic literature search of Pubmed and Embase was performed according to the PRISMA guidelines.

Results: Fifty-two studies were included. GPi-DBS reduced pain related to dystonia. No major effects on anxiety, mood, and cognition were found. In contrast to motor outcome, non-motor outcome seems more independent of the etiology of dystonia. However, the impact of potential confounders (e.g. patient factors, changes in pharmacological treatment) is unclear.

Conclusion: Despite the growing interest in non-motor symptoms in dystonia, DBS studies still focus primarily on motor outcome. We recommend systematic evaluation of both non-motor and motor features before and after DBS interventions to improve quality of life and management of patients with dystonia.

1. Introduction

Over the past decades, deep brain stimulation of the globus pallidus internus (GPi-DBS) has emerged as an important treatment strategy in the management of medically intractable dystonias [1]. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often patterned movements and/or postures and can be caused by a broad range of etiologies [2]. Motor outcome has been studied extensively, mainly in inherited and idiopathic isolated dystonia [3]. In addition to motor symptoms, patients with dystonia frequently experience mood, behavioral, cognitive, sleep, and pain issues [4,5]. These non-motor symptoms (NMS) are most likely to be part of the dystonia phenotype as they can only partially be explained as secondary to motor impairment, or as medication side-effect. Irrespective of the precise pathogenesis, NMS might be at least as important as motor symptoms when it comes to the perceived disease burden [6,7].

GPi-DBS is targeted at the sensorimotor area, located in the posteroventrolateral part of the GPi [3]. The possible (in)direct effects of GPi-DBS on the more antero-medial associative and limbic regions are of interest, especially because of their integration in subcortical-cortical circuits presumed to be important for executive functioning and behavior [8,9]. Reports on the influence of GPi-DBS on NMS in dystonia are contradictory, reporting improvements as well as deteriorations [10–13]. This review aims to systematically describe the impact of GPi-DBS on NMS in dystonia. A brief review on the NMS effect of other DBS targets is also provided.

2. Methods

A systematic literature search was independently performed by two authors (HE and SS) according to the PRISMA guidelines [14]. First all published articles regarding the effects of GPi-DBS in dystonia patients were searched, and later the articles reporting on the effects of DBS on NMS as primary or secondary outcomes were identified. Articles were extracted from Pubmed and Embase, covering a period from September 1999 until December 2017, using the following combination of MeSH terms and free text words: ‘deep brain stimulation’, ‘pallidal stimulation’, globus pallidus internus stimulation’ AND ‘dystonia’ (for full

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search strategy see supplement 1). Only English articles describing non-motor outcomes in quantitative outcome measures (including pre- and postoperative values and/or a percentage of change) were included in the review. Articles concerning DBS of the thalamus or the subthalamic nucleus (STN) were set aside for a separate evaluation. Due to the small numbers direct comparison of outcomes of thalamic and STN DBS with studies on GPi-DBS were not possible.

The most relevant non-motor outcomes were identified based on two previously published reviews concerning the NMS of dystonia, and subdivided into four categories: pain, psychiatry, cognition, and others [4,15]. The level of evidence was reported in the conclusions according to the levels evidence for therapeutic studies from the centre for Evidence-based medicine [16] (see supplement 1).

To deal with the heterogeneity of dystonia patients, results are presented for the different types of dystonia according to the etiology classification axis for dystonia [2]. Based on the available literature on DBS in dystonia, results from inherited and idiopathic dystonia (e.g. DYT1, DYT11, inborn errors of metabolism), and acquired dystonia (CP, tardive dystonia) are discussed separately.

3. Results

The systematic literature search revealed a total of 107 articles addressing the effectiveness of DBS upon one or more NMS (flowchart in supplement 1). Of these 107, 55 were excluded because of only qualitative data or overlap in patient population with other articles, leaving 52 eligible articles. RCTs and case series including more than five patients are discussed.

3.1. Pain

The effect of GPi-DBS upon pain in dystonia has been reported in 23 articles, using the Toronto Western Spasmodic Torticollis Rating Scale Pain Subscale (TWSTRS-P), the visual analogue scale (VAS), the Pediatric Pain Profile (PPP) and the Faces Pain Scale (Table 1).

3.1.1. Inherited and idiopathic dystonia

Most studies report on cervical dystonia, where the effects of GPi-DBS on pain were evaluated in a total of 154 patients. A RCT (n = 62) reported no significantly higher reduction in pain in the neuro- compared to the sham-stimulation group at 3-month follow-up [17]. After 6 months of non-blinded stimulation the mean pain reduction was 52% ($p < 0.001$), which was higher than the reduction in dystonia symptom severity (28%). In addition, nine case series (n = 6–14) showed a mean pain improvement from 48% to 73% which remained stable at follow-up ranging between 12 and 64 months [12,18–22]. No correlations between motor and pain outcome were reported, but six case series highlighted a dissociation between motor and pain response in timing and/or the extent [11,12,19,21,23,24].

In a RCT (n = 40) involving inherited or idiopathic generalized segmental dystonia, pain scores showed a larger reduction for neurostimulation patients in comparison to sham-stimulation patients (63% vs 0%, $p < 0.001$) at 3 months, which was maintained at 6-month and 5-year follow-up [25,26]. A case series (n = 24) found a mean pain improvement of 53%, comparable to relief in motor symptoms [27]. Six cranio-cervical dystonia patients had a mean improvement of 39%, a bit lower than motor improvement (45–90%) [28].

3.1.2. Acquired dystonia

Eleven patients (six children) with various forms of acquired dystonia reported a pain reduction varying from 48% to 100%, which was in contrast to a limited motor response (6–21%) [29–31].

3.1.3. Discussion

Pain is one of the most disabling and frequently present complaints in dystonia. Remarkably, the extent of pain is often not explained by the dystonia severity [32]. Current evidence suggests that pain may be due to changes in the thalamo-cortico-basal ganglia loops, integrating the multiple aspects of pain (e.g. motor, emotional and cognitive responses to pain) [33].

To this day, no studies have systematically looked into the correlation between motor and pain outcome of GPi-DBS for dystonia patients. Yet, there is a repeatedly reported difference in pain and motor response, supporting a possible role of pallidal stimulation in central pain processing [11,12,19,23,29,30,33,34]. Irrespective of the underlying pathophysiological mechanisms, this dissociation between pain and dystonia relief is intriguing, especially when it comes to the discussion regarding the effectiveness in acquired forms of dystonia, such as CP, where the motor outcome is less robust [35,36]. With pain being one of the most frequent complaints, this underscores the importance of a systematic evaluation of the effect of GPi-DBS on pain.

Although all studies used a medically refractory form of dystonia as inclusion criteria, the majority did not report, or only vaguely, on the continuation of botulinum toxin injections or oral medication after DBS. Therefore, it is impossible to conclude whether the pain response is influenced by changes in pharmacological treatment.

3.1.4. Conclusions

GPi-DBS in dystonia is likely to reduce pain both on the short- (6 months) and long-term follow-up (up to 6 year). The effect seems independent of dystonia etiology, with a higher level of evidence in isolated generalized and cervical dystonia (class II) compared to cranio-cervical and acquired dystonia (class IV). Pain response is repeatedly reported to be dissociated from motor response. However, blinded or correlational studies of pain and motor outcome are lacking as well the potential effect of confounding factors (e.g. change in pharmacological treatment or patient related factors).

3.2. Psychiatric issues

Twenty articles have quantitatively reported on the effects of GPi-DBS on mood and behavior (Table 2). The most used depression scales were the Beck Depression Inventory (BDI), Hamilton Depression Scale (HDS), and the Montgomery-Asberg Depression Rating Scale (MADRS). Anxiety was measured by the Beck Anxiety Inventory (BAI).

3.2.1. Inherited and idiopathic dystonia

A postoperative depression rating score (n = 85) or DSM axis diagnosis (n = 20) was available in 105 cervical dystonia patients. One RCT (n = 62) found a significant higher BDI reduction in the neuro- versus sham-stimulation group at 3-month follow-up (31% vs 4%, $p < 0.05$) [17]. Three case series (n ranged from 5 to 10) that excluded moderately and severe depressed patients reported a trend to, or a significant decrease between 28 and 59% in depression scores [18,37,38]. One prospective study (n = 20) that did not exclude depression found overall stable depressive and anxiety disorders up to 5 years of follow-up [39].

Depression rating scales were assessed in 130 generalized and segmental dystonia patients. A RCT (n = 40) found no significant difference in the BDI score changes after 3 months of neuro-versus sham-stimulation (39% vs 9%). Six months of GPi stimulation led to a mean reduction of 30% in the BDI scores that remained stable at 5-year follow-up [25,38]. Other case series (n ranged from 14 to 26) reported stable scores to mild improvements (−3%–27%), irrespective from whether depression was excluded [27,39–41] Anxiety was assessed in 81 patients, with overall stable outcomes up to 5 years postoperatively [25,38,39,41,42]. Since the last review on neuropsychiatric outcome of GPi-DBS highlighting the occurrence of suicide post-DBS [13], another suicide has been reported in a DYT1 generalized dystonia patient with a bipolar affective disorder and a good motor outcome (68%) after more than 2 years after DBS [39].

Table 1
Quantitative studies reporting on the impact of GPi-DBS on pain in dystonia.

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Inclusion criteria	Pain measure	FU in mth	% of improvement; pain score ± SD (range) per measurement point		Motor severity measure	% of improvement; motor score ± SD (range) per measurement point		Remarks
Inherited and idiopathic focal cervical dystonia											
Kulisevsky 2000 [23]	Case series (2)	Idiopathic cervical; Age 35–60; DD 7-20	Benzodiazepines, trihexyphenidyl, BTX and analgesics unsuccessful	VAS	0 17	75%	81 21	Tsui score	11%	19 17	- BTX was continued in one patient - Dissociation between pain and motor response possibly due to not always parallel motor and somatosensory circuit
Wöhlre 2003 [81]	Case report (1)	Idiopathic cervical; Age 60; DD 7	Minimal effect BTX and trihexyphenidyl	VAS	0 9	100%	4 0	BFMDRS-M	83%	49 8.5	- Risperidone was lowered (8 vs 2 mg)
Bittar 2005 [11]	Case series (6)	Idiopathic cervical; Age 38.5 (23–68); DD 8 (3–18)	Medically refractory	TWSTRS-P	24	59%		TWSTRS-S	58%		- Pain improved first symptom in the majority (95% of improvement in 4.4mnths versus 7.3mnths for severity)
Kiss 2007 [18]	Case series (10)	Idiopathic cervical; Age 58 (47–64); DD 17 (5–28)	Initial response and subsequent failure to BTX	TWSTRS-P	0 12	66%**	26.6 ± 3.6 9.1 ± 13.1	TWSTRS-S	44%**	14.7 ± 4.2 8.4 ± 4.4	- No BTX after DBS - 2/8 patients stopped their medication postoperatively
Loher 2008 [82]	Case series (4)	Idiopathic cervical; Age 28–52; DD 4-6	Anticholinergics insufficient or not tolerated	TWSTRS-P	0 12 36	45% 37%	6 (3–8) 3.3 (0–6) 3.8 (0–8)	TWSTRS-S	55% 28%	20.5 (19–22) 9.3 (6–14) 14.8 (10–20)	- 1/4 improvement in severity, not pain. - 2/4 improvement on severity and pain - 1/4 loss of effect at three year follow-up
Sakas 2009 [83]	Case report (1)	Idiopathic cervical, Age 49; DD 7	Pharmacological and BTX insufficient	TWSTRS-P	0 3 6 9	70% 70% 70%	10 3 3 3	TWSTRS-S	69% 81% 88%	16 5 3 2	- No specific data on medication use and continuation
Jeong 2009 [84]	Case series (6)	Idiopathic cervical; Age 54 ± 10; DD 6 ± 3	Insufficient benefit of BTX and other medical treatments	TWSTRS-P	0 3 6 12	65%** 61% 73%	6.0 ± 7.1 5.8 ± 2.1 6.2 ± 1.3 4.4 ± 0.7	TWSTRS-S	65%* 69% 77%	23.8 ± 6.4 8.6 ± 6.4 7.4 ± 4.2 5.6 ± 3.0	- No specific data on medication use and continuation - Severity scores diminished as fast as pain scores
Torres 2010 [85]	Case report (1)	Idiopathic cervical; Age 7; DD 9	Resistant to medical and BTX treatment	TWSTRS-P	0 3	79%	14 3	TWSTRS-S	41%	22 13	- No BTX postoperatively
Cacciola 2010 [19]	Case series (10)	Idiopathic cervical; Age 37–63; DD 2-26	Failure or exhaustion of medical treatment including BTX	TWSTRS-P	0 37	58%**	13.4 (6–18) 5.4 (0–14)	TWSTRS-S	67%**	23.8 (16–28) 8.4 (0–19)	- Correlation between pain and severity response revealed a dissociation in 4/10 (3; > 25% severity than pain response, 1; > 25% pain than severity improvement)

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Table 1 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Inclusion criteria	Pain measure	FU in mth	% of improvement; pain score ± SD (range) per measurement point		Motor severity measure	% of improvement; motor score ± SD (range) per measurement point		Remarks
Skogseid 2012 [38]	Case series (8)	Idiopathic cervical; Age 55 (47–72); DD 8 (5–20)	Non responders to BTX, clonazepam (7/8), paracetamol and opioids (5/8)	TWSTRS-P	0 3 6 12	73% 60% 73%	15 (11–19) 4 (0–14) 6 (0–14) 4 (0–7)	TWSTRS-S	46% 50% 64%	28 (23–31) 15 (6–19) 14 (5–24) 10 (2–19)	- Two patients used analgesics post-DBS and 50% clonazepam dose reduction in 5/7 patients - No BTX after DBS surgery
Kim 2012 [20]	Case series (14)	Idiopathic cervical; Age 48 (21–69); DD 5 (1–13)	Despite BTX and pharmacological treatment	TWSTRS-P	0 1 6 12 24	49%** 60%** 60%** 67%**	9.3 ± 2.8 5.1 4.1 4.1 3.5	TWSTRS-S	59%*** 66%*** 78%*** 78%***	15.6 ± 4.4 6.8 6.1 3.9 3.7	- Not certain if BTX and pharmacological treatment was continued after DBS
Yamada 2013 [24]	Case series (8)	Idiopathic cervical; Age 44 (27–74); DD 10 (1–14)	7/8 received BTX preoperatively	TWSTRS-P	64	87%*		TWSTRS-S	70%*		- Oral medication changed in 3/8 - Pain relief was striking and distinct from improvement in severity - Not certain if BTX was continued after DBS
Sadnicka 2013 [21]	Case series (11)	Idiopathic cervical; Age 56 ± 11; DD 16 ± 7	All BTX with various effect	TWSTRS-P	0 26	56%^{ns}	7.4 ± 4.5 2.9 ± 3.0	TWSTRS-S	61%**	23.0 ± 4.9 9.1 ± 4.4	- Not certain if BTX was continued after DBS - Reduction in pain (> 33%, n = 7) with reduction in severity (> 33%). - Stable or worsened pain score (n = 4) with reduction (> 33%, n = 3) or stable severity score (n = 1)
Walsh 2013 [12]	Case series (10)	Idiopathic cervical; Age 56 ± 13; DD 10 ± 12	Insufficient effect of medical treatment and BTX	TWSTRS-P	0 12 24 26 60	52%^{ns} 54%* 60%** 48% ^{ns}	12.6 ± 6.5 6.9 ± 6.4 6.7 ± 6.4 5.4 ± 6.4 8.5 ± 4.6	TWSTRS-S	41%* 50%** 49%** 53%**	21.5 ± 4.6 12.5 ± 3.6 11.0 ± 5.6 10.9 ± 4.8 9.9 ± 4.8	- Loss of pain improvement at 60 months was regained at 84 months (n = 7) - Pain differed from severity response, in some patients disappointing. - Late deterioration in pain may be due to progressive spinal disease or GPi functional anatomy

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Table 1 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Inclusion criteria	Pain measure	FU in mth	% of improvement; pain score ± SD (range) per measurement point		Motor severity measure	% of improvement; motor score ± SD (range) per measurement point		Remarks
Volkmann 2014 [17]	RCT (62)	Idiopathic or inherited cervical; Neuro-stimulation (n = 32) Age 57 ± 10 DD 15 ± 8; Sham-stimulation (n = 30) Age 57 ± 11; DD 15 ± 6	> 6 months after BTX treatment	TWSTRS-P (RCT) TWSTRS-P (open)	0 3 0 3 0 6	49% 27%^{ns} 52%***	Neuro-stim 10.8 ± 5.3 6.5 ± 5.6 Sham-stim 13.6 ± 4.6 9.9 ± 5.6 12.2 ± 4.7 6.1 ± 5.8	TWSTRS-S TWSTRS-S	26% 6%** 28%***	Neuro-stim 19.9 ± 3.7 14.7 ± 5.0 Sham-stim 20.9 ± 3.3 19.6 ± 3.9 20.4 ± 3.5 14.6 ± 5.2	- Pain improved in both neuro- and sham-stimulation, but not to a significantly extent in the two treatment groups. - No BTX after surgery. - Oral medication from 36 reduced to 11 different drugs after 6 months, no details on how many patients
Inherited and idiopathic segmental and generalized dystonia											
Krauss 2003 [29]	Case series (2)	Idiopathic generalized, Age 51–58; DD 12-39	Trihexyphenidyl insufficient or not tolerated	VAS	0 3 12 24	35% 65% 65%	14 9 5 5	BFMDRS-M	74% 74% 73%	81 21 21 22	- Both patients were on oral medication prior to surgery, one on morphine - No medication 3 months after DBS - Pain reduction in both > 33%
Kupsch 2006 [25]	RCT (40)	Idiopathic or inherited generalized and segmental cervical; Neuro-stimulation (n = 20) Age 41 ± 14; DD 22 ± 8; Sham-stimulation (n = 20) Age 38 ± 14; DD 17 ± 8	Despite optimal pharmacological treatment 5 year disease duration	VAS (RCT) VAS (open)	0 3 0 3 0 6	63% vs 0%*** 60%***	Neuro-stim 4.6 ± 2.9 1.7 ± 1.7 Sham-stim 4.8 ± 2.4 4. 8 ± 2.5; 4.7 ± 2.6 1.7 ± 1.8	BFMDRS-M	44% 5%*** 45%***	Neuro-stim 40.2 ± 24.9 24.5 ± 22.8 Sham- stim 32.6 ± 24.3 31.1 ± 24.0 36.4 ± 24.6 20.2 ± 18.0	- 20 patients received medical treatment at enrollment, average dosage reduction was 32.1% at 6 months with cessation in 5 patients (25%) - BTX in 13 at baseline, no details about continuation
Valldeoriola 2010 [27]	Case series (24)	Idiopathic or inherited generalized and segmental cervical; Age 30 ± 14; DD 10 ± 7	Functional limitation despite best medical treatment	Faces Pain Scale	0 6 12	54% 53%*	3.95 ± 2.9 1.83 ± 2 1.87 ± 1.1	BFMDRS-M	58%*** 59%***	42.2 ± 22 17.6 ± 12 17.5 ± 12	- Medication for dystonia were globally reduced after surgery
Idiopathic craniocervical dystonia											

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Table 1 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Inclusion criteria	Pain measure	FU in mth	% of improvement; pain score ± SD (range) per measurement point		Motor severity measure	% of improvement; motor score ± SD (range) per measurement point		Remarks
Capelle 2003 [86]	Case report (1)	Idiopathic cranial-cervical; Age 60; DD 5	Loss of efficacy of BTX, medical treatment limited by side effect	VAS	0 3 12 24	38% 38% 38%	8 5 5 5	BFMDRS-M	58% 58% 67%	18 7.5 7.5 6	- Preoperative medication was slowly tapered off (trihexyphenidyl, tiapride, tetrazepam, zopiclon). - At 24-month only zolpidem for sleeping disturbance
Ostrem 2007 [28]	Case series (6)	Idiopathic cranial-cervical; Age 66 (52–70); DD 8 (2–20)	Severe functional impairment despite optimal medical management	TWSTRS-P	0 6	39%^{ns}	8.1 ± 3.9 5.0 ± 4.6	TWSTRS-S BFMDRS-M	56%* 72%*	19 ± 4 8.4 ± 5.5 22 ± 8.3 6.1 ± 4.2	- Most patients continued to take the same medication, but BTX was stopped in 3/4 patients that received BTX pre-operatively
Acquired dystonia											
Krauss 2003 [29]	Case series (4)	Generalized due to cerebral palsy; Age 41 (36–46); DD 39 (24–44)	Trihexyphenidyl was tried but insufficient or not tolerated	VAS	0 3 12 24	52% 66% 66%	5.8 (4–9) 2.8 (0–6) 2 (0–5) 2 (0–5)	BFMDRS-M	11% 27% 21%^{ns}	70.5 (39–82) 62.5 (37–80) 50.8 (35–72) 55.8 (37–74)	- Drug dosage reduction in 2/4 post-DBS - All pain improvement > 33%, motor improvement < 33%
Gimeno 2012 [30]	Case series (6)	Generalized due to cerebral palsy (5) and glutaric aciduria type 1 (1); Age 10 (5–14); DD 10 (5–14)		PPP VAS	6 12 6 12	48% 55% 69% 80%		BFMDRS-M	6.3% 5.9%		- No information on pharmacological treatment or BTX - Clinically significant pain improvement (> 30%) in 3/3 measured at 6 months and 4/4 at 12 month follow-up
Kwon 2016 [34]	Case report (1)	Post-traumatic hemi; Age 47, DD 44	Medical treatment failed to alleviate symptoms	VAS	0 6 60	100% 100%	5 0 0	BFMDRS-M	20% 20%	26 21 21	- No information on pharmacological treatment or BTX

TWSTRS-P, Toronto Western Spasmodic Torticollis Rating Scale pain subscale (range 0–20); VAS, visual analogue scale (range 0–10); PPP, pediatric pain profile (range 0–60); TWSTRS-S, Toronto Western Spasmodic Torticollis Rating Scale severity subscale (0–35); BFMDRS-M, Burke-Fahn-Marsden dystonia rating scale motor subscale (0–120); BTX, botulinum toxin injections; ^{ns} non-significant; *p = 0.05; **p = 0.01; ***p = 0.001.

Table 2
Quantitative studies reporting on the impact of GPi-DBS on psychiatric symptoms in dystonia.

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Exclusion criteria	Symptom (outcome measure)	Follow up in months	% of improvement; score ± SD (range) per measurement		Motor severity measure	% of improvement; score ± SD (range) per measurement		Remarks
Inherited and idiopathic focal cervical dystonia											
Krauss 2002 [37]	Case series (5)	Idiopathic cervical; Age 46 (36–58); DD 12-44		Depression (HDS)	0 3 6 12 20	50% 37% 37% 67%	9 4.5^{ns} 5.7 ^{ns} 5.7 ^{ns} 3 ^{ns}	TWSTRS-S	38% 53% 55% 63%	20.5 12.7** 9.7** 9.2** 7.5**	- HDS improved with motor score improvement - No antidepressants
Kiss 2007 [18]	Prospective case series (10)	Idiopathic cervical; Age 58 (47–64); DD 17 (5–28)	Presence of psychiatric disturbances	Depression (BDI)	0 12	59%***	14.2 ± 7.2 6.0 ± 3.5	TWSTRS-S	44%**	14.7 ± 4.2 8.4 ± 4.4	- No antidepressants - One depression that was treated before stimulation was started but dystonia worsened on stimulation (−33%)
Skogseid 2012 [38]	Case series (8)	Idiopathic cervical; Age 55 (47–72); DD 8 (5–20)	Unstable depression	Depression (BDI)	0 18	28%^{ns}	9 (0–17) 6.5 (0–24)	TWSTRS-S	73%*	28 (23–31) 7 (3–19)	- At baseline 3/8 mild depressive, at follow up, 6/8 normal and 2/8 moderate depressive - 2/2 moderate depressions were treated pre-operatively - No report on antidepressants
Volkmann 2014 [17]	RCT (62)	Idiopathic or inherited cervical; Neuro-stimulation (n = 32) Age 57 ± 10 DD 15 ± 8; Sham-stimulation (n = 30) Age 57 ± 11; DD 15 ± 6	Moderate to severe depression (BDI > 25)	Depression (BDI - RCT) Psychiatric symptoms (BPRS-RCT) Depression (BDI - open) Psychiatric symptoms (BPRS-open)	0 3 0 3 0 3 0 3 0 6 0 6	31% 4%* 7% 8%^{ns} 21%** 9%**	Neuro-stim 10.8 ± 6.2 7.4 ± 6.1 Sham-stim 9.8 ± 5.8 9.4 ± 6.4 Neuro-stim 26.5 ± 9.4 24.7 ± 5.8 Sham-stim 25.6 ± 5.8 23.5 ± 5.9 10.3 ± 6.0 8.1 ± 6.8 26.0 ± 7.8 23.6 ± 5.1	TWSTRS-S TWSTRS-S	26% 6%** 28%***	Neuro-stim 19.9 ± 3.7 14.7 ± 5.0 Sham-stim 20.9 ± 3.3 19.6 ± 3.9 20.4 ± 3.5 14.6 ± 5.2	- Three possible stimulation related depressions of which two resolved and one needed patient counselling
Meoni 2015 [39]	Case series (20)	Idiopathic cervical; Age 54 ± 10; DD 15 ± 14	Psychosis or suicidal ideation	DSM IV – axis I diagnosis	0 28		14 diagnoses 13 diagnoses	TWSTRS-S	51%***	23.1 ± 3.2 11.6 ± 4.9	- 11 unchanged, 3 remission, 2 new-onset - Mood and anxiety disorders stable, one anxiety episode might be related to withdrawal of benzodiazepines.
Inherited and idiopathic segmental and generalized dystonia											
Capelle 2003 [86]	Case report (1)	Idiopathic cranial-cervical; Age 60; DD 5		Depression (HDS)	0 3 12 24	−29% 18% 24%	17 22 14 13	BFMDRS-M	58% 58% 67%	18 7.5 7.5 6	

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Table 2 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Exclusion criteria	Symptom (outcome measure)	Follow up in months	% of improvement; score ± SD (range) per measurement		Motor severity measure	% of improvement; score ± SD (range) per measurement		Remarks
Krauss 2003 [29]	Case series (2)	Idiopathic generalized, Age 51–58; DD 12-39	Major psychiatric disorders	Depression (HDS)	0 3 12 24	57% 64% 79%	14 6 5 3	BFMDRS-M	74% 74% 73%	81 21 21 22	- Preoperatively one moderate and one mild depressive score to normal scores at 2-year follow-up parallel to good motor response
Vidailhet 2005 [40]	Case series (22)	Idiopathic and inherited generalized dystonia; Age 30 (14–54); DD 18 (4–37)	Psychiatric disturbances	Depression (BDI)	0 12	27%^{ns}	11 ± 7 8 ± 8	BFMDRS-M	55%***	46.3 ± 21.3 21.0 ± 14.1	- 3/5 patients topped antidepressants, no details on correlation with motor response - Scores stable at 3-year FU [87]
Kupsch 2006 [25]	RCT (40) Neuro-stimulation (n = 20) Age 41 ± 14; DD 22 ± 8; Sham-stimulation (n = 20) Age 38 ± 14; DD 17 ± 8	Idiopathic or inherited generalized and segmental cervical;	Moderate to severe depression (BDI > 25) and no psychiatric co-existent disorders	Depression (BDI-RCT) Anxiety (BAI-RCT) Psychiatric symptoms (BPRS-RCT) Depression (BDI-open) Anxiety (BAI-open) Psychiatric symptoms (BPRS-open)	0 3 0 3 0 3 0 3 0 3 0 3 0 6 0 6 0 6	39 −9%^{ns} 42% 13%^{ns} 21% 11% 30%** 27%^{ns} 8%^{ns}	Neuro-stim 10.5 ± 7.3 6.4 ± 8.9 Sham-stim 9.7 ± 5.8 10.6 ± 10.1 Neuro-stim 13.7 ± 11.0 8.0 ± 6.5 Sham-stim 12.1 ± 10.5 10.5 ± 7.4 Neuro-stim 27.0 ± 7.3 21.4 ± 4.6 Sham-stim 27.8 ± 8.0 24.8 ± 5.5 10.1 ± 6.5 7.1 ± 6.7 12.9 ± 10.7 9.4 ± 7.6 27.4 ± 7.6 25.3 ± 7.1	BFMDRS-M	44% 5%*** 45%***	Neuro-stim 40.2 ± 24.9 24.5 ± 22.8 Sham- stim 32.6 ± 24.3 31.1 ± 24.0 36.4 ± 24.6 20.2 ± 18.0	- Improvements in mood remained stable at 5-year FU [26]
Valldeoriola 2010 [27]	Case series (24)	Idiopathic or inherited generalized and segmental; Age 30 ± 14; DD 10 ± 7	Active psychiatric symptoms	Depression (BDI)	0 6 12	18% 22%*	34.9 ± 12.3 28.7 ± 9.6 27.1 ± 11.0	BFMDRS-M	58%*** 59%***	42.2 ± 22 17.6 ± 12 17.5 ± 12	- Mood mildly improved, possibly secondary to motor response, but no report on associations motor and mood response
Jahanshahi 2014 [41]	(14)	Idiopathic or inherited generalized; Age 42 ± 19; DD 24 ± 17		Depression (BDI) Anxiety (BAI)	0 14 0 14	−3%^{ns} −4%^{ns}	7.2 ± 4.3 7.4 ± 6.4 11.9 ± 5.9 12.4 ± 10.3	BFMDRS-M	69%***	39.9 ± 17.4 13.3 ± 11.6	- Normal BDI and only mild anxiety on BAI at baseline
Meoni 2015 [39]	Case series (26)		Psychosis or suicidal ideation	DSM IV – axis I diagnosis	0 22		13 diagnoses 9 diagnoses	BFMDRS-M	67%***	31.9 ± 17.4 20.4 ± 22.4	

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Table 2 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Exclusion criteria	Symptom (outcome measure)	Follow up in months	% of improvement; score ± SD (range) per measurement		Motor severity measure	% of improvement; score ± SD (range) per measurement		Remarks
		Idiopathic or inherited generalized and segmental cervical; Age 54 ± 19; DD 24 ± 15									- 8 unchanged, 5 in remission 1 new-onset - Mood trend to improvement, possibly secondary to motor benefit, pain reduction and/or medication discontinuation - Stable anxiety disorders. One suicide
Acquired dystonia (Various)											
Meoni 2015 [39]	Case series (11)	Various acquired disorders; Age 37 ± 4; DD 19 ± 5	Psychosis or suicidal ideation	DSM IV – axis I diagnosis	0 10		10 diagnoses 9 diagnoses	BFMDRS-M	32%**	34.9 ± 22.1 23.8 ± 20.7	- 8 unchanged, 2 remission, 1 new-onset - Mood and anxiety disorders stable, one anxiety episode possibly due to benzodiazepines cessation. - 1 suicide
Acquired dystonia (Cerebral palsy)											
Vidailhet 2009 [45]	Case series (13)	Generalized; Age 33 (20–44)	Psychiatric disorders	Psychiatric symptoms (Hopkins checklist)	12	28%^{ns}	34.0 ± 9.3 24.6 ± 15.5	BFMDRS-M	21%**	44.2 ± 21.1 34.7 ± 21.9	- Trend to improvement OCD, depressive, paranoid, psychotic symptoms and stable anxiety, anger, sleep. - 5/13 anti-depressants for anxiety
Krauss 2003 [29]	Case series (4)	Generalized; Age 41 (36–46); DD 39 (24–44)		Depression (HDS)	0 3 12 24	25% 89% 100%	7.5 (0–12) 5.6 (1–15) 0.8 (0–2) 0	BFMDRS-M	11% 27% 21%^{ns}	71 (39–82) 63 (37–80) 51 (35–72) 56 (37–74)	- One mild depressive score preoperatively to normal with small motor benefit.
Acquired dystonia (Tardive dystonia)											
Pouclet-Coutremanche 2016 [44]	Case series (19)	Tardive dystonia; Age 52 (25–69); DD 6 (1–38)	PANNS < 50	Depression (MADRS) Schizophrenia (PANSS)	12	48%^{ns} 10%^{ns}	14.5 ± 10.9 7.6 ± 4.8 50.1 ± 15.5 45.4 ± 16.9	ESRS	58%		- Eight possible DBS-related psychiatric side effects: depression (4), anxiety (1), mania (1), delirium (1) and agitation (1) for which four needed hospitalization
Gruber 2009 [43]	Case series (9)	Tardive dystonia; Age 63 ± 13; DD 5 ± 3	Acute psychiatry, MADRS > 29	Depression (MADRS)	0 18	59%**	14.2 ± 7.0 6.5 ± 5.3	BFMDRS-M	82%***	30.9 ± 12.1 5.5 ± 4.8	
Kosel 2006 [88]	(1)	Tardive dystonia; Age 62; DD 10		Depression (BDI) Depression (MADRS)	0 18 0 18		22 17 26 13	BFMDRS-M	35%	27 17.5	- Depressive symptoms significantly improved in severely depressed patient
Various etiologies											
	Case series (15)		Lack of cooperation					BFMDRS-M	71%***		

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Table 2 (*continued*)

Author	Design (*n*)	Diagnosis; age and; disease duration (DD) in years	Exclusion criteria	Symptom (outcome measure)	Follow up in months	% of improvement; score ± SD (range) per measurement		Motor severity measure	% of improvement; score ± SD (range) per measurement		Remarks
Halbig 2005 [42]		Idiopathic, inherited and tardive dystonia; Age 46 (13–38); DD 13 (6–62)		Depression (BDI)	0	24%^{ns}	13.6 ± 9.5			33.8 ± 13.7	- SHPS and BPRS normal preoperatively - All improved depression scores (3/15 on BDI and 2/15 on MADRS) also showed a significant motor response - One deterioration on BDI with good motor response, but no exact scores were given.
					7	48%**	9.4 ± 11.3			13.7 ± 10.7	
				Depression (MADRS)	0	27%^{ns}	13.3 ± 7.7				
					7	69%*	7.7 ± 7.7				
				Anxiety (BAI)	0	67%*	15.0 ± 12.8				
					7	30%^{ns}	10.9 ± 12.3				
				Anhedonia (SHPS)	0		1.6 ± 1.1				
					7		0.5 ± 0.7				
				Mania (BRMRS)	0		1.2 ± 1.6				
					7		0.4 ± 1.3				
				Psychiatric symptoms (BPRS)	0		27.7 ± 11.4				
					7		19.4 ± 8.5				
De Gusmao 2017 [89]	Case series (12)	Focal, segmental and generalized dystonia of inherited, idiopathic and tardive; Age 42.3; DD 10.1	Not an intact cognition	Depression (BDI)	0	−36%*	10.5 ± 8.3	BFMDRS-M	61%	21.6 ± 11.5	- Total medication increase (1), stable (3), reduction (6) or stopped (2) - No information on the correlation between motor/non-motor outcome and influence of medication
					13	6%*	6.6 ± 5.7			8.4 ± 4.6	
				Anxiety (BAI)	0	5%^{ns}	10.2 ± 13.6				
					13		9.6 ± 13.6				
				Hopelessness (BHS)	0		2.8 ± 2.1				
					13		2.6 ± 3.3				

AES: Apathy Evaluation Scale (0–54); BAI, Beck Anxiety Inventory (range 0–63; 0–7 minimal, 8–15 mild, 16–25 moderate, 26–63 severe anxiety); BDI, Beck Depression Inventory (range 0–63; 0–9 mild, 10–18 minimal, 19–29 moderate, 30–63 severe depression); BRMRS, Bech–Rafaelsen Mania Rating Scale (range 0–44); BPRS, Brief psychiatric rating scale (range 18–126); HDS: Hamilton Depression Scale (range 0–56, 0–7 normal, 8–13 mild, 14–18 moderate, 19–22 severe, > 23 very severe); MADRS, Montgomery–Åsberg Depression Rating Scale (range 0–60, 0–6 normal, 7–19 mild, 20–34 moderate, 35–60 severe); PANNS: Positive and negative Syndrome Scale for Schizophrenia (range 30–210); SHPS: Snaith–Hamilton Pleasure Scale; SRPSS: Self-rated psychiatric symptom scale; BFMDRS-M, Burke-Fahn-Marsden dystonia rating scale motor subscale (0–120); ESRS, Extrapyramidal Symptom Rating Scale; TWSTRS-S, Toronto Western Spasmodic Torticollis Rating Scale severity subscale (0–35); ^{ns} non-significant; *p = 0.05; **p = 0.01; ***p = 0.001.

3.2.2. Acquired dystonia

Medication-induced dystonia or tardive dystonia (TD) is the largest acquired dystonia group. Since the majority of these patients develops dystonia after using neuroleptic medication, most of them had a positive psychiatric history. Two case series (n = 9 and n = 19) reported a trend or significant improvement of 48% and 59% respectively on the MADRS scores after 12–18 months, but four patients needed hospitalization for a possible DBS-related period of depression, agitation, anxiety or mania [43,44].

For dystonic CP, two case series (n = 13 and n = 4) found a 100% decrease in the HDS and stable psychiatric symptoms, although after DBS implantation anti-depressants were started for anxiety in 5/13 patients [29,45]. One suicide was reported in a depressed patient with a good motor response more than two years after combined Vim-GPi stimulation [39].

3.2.3. Discussion

Over the past decades, the psychiatric aspects of dystonia have gained more attention due to the relatively high prevalence of depression, anxiety and OCD in dystonia patients [4]. These symptoms are only partially explained by motor symptoms, and therefore likely to be part of the dystonia phenotype [4,5]. Also, they show to be important influencing factors of the quality of life [46]. Interestingly, from a psychiatric perspective there is also increasing evidence for the role of dysfunction of the cortical-limbic-striatal circuit in psychiatric disorders such as depression [5,47].

In dystonia patients with preoperative stable psychiatric symptoms, GPi-DBS seems to be safe. Most data is gathered in non-blinded studies comprising isolated, idiopathic or inherited dystonia, where the vast majority of patients did not experience onset or worsening of depressive symptoms. Although most studies excluded from surgery patients with moderate to severe depression, stable to improved mood and stable anxiety status were found in the two studies including patients with moderate to severe depression [27,39]. Mood improvement has been attributed to symptom relief, medication discontinuation or social impact [39]. However, as correlation studies between motor and psychiatric outcome are lacking, an intrinsic action of stimulation on subcortical limbic loops implicated in depression cannot be excluded.

Interestingly, although the presence of psychiatric symptoms is frequently highlighted in DYT11 myoclonus dystonia, there is no controlled study in these patient groups. Moreover, except from a report on worsening of psychiatric issues as well as one alleviation of panic attacks, no quantitative data is available for myoclonus dystonia [48–50]. Another distinct group is formed by Lesch-Nyhan patients, in which GPi-stimulation was repeatedly associated with decrease or disappearance of self-mutilating behavior, suggesting a central role for the GPi in behavioral networks [51–54].

In acquired dystonias, case series report overall stable to mildly improved mood scores in patients with TD or dystonic CP [44,45,55]. Although based on case series, psychiatric disturbances or exacerbations were reported in 5/17 CP patients and 8/29 TD patients during pallidal stimulation. However, patient samples were small and the associations between psychiatric disturbances and motor outcome are unclear. Nevertheless, these reports underscore the importance of careful psychiatric evaluation before and during DBS-treatment in this group of patients, and more thorough research on the possible pallidal stimulation effects on psychiatric symptoms.

Two suicides were reported in the past five years (one DYT1 and one CP patients), with no data to support a possible association between surgery and the suicide [39]. However, with an increasing number of DBS surgeries being performed in dystonia patients, the only small number of suicides might suggest that more attention has been paid to possibly vulnerable patients and consequently the prevention of suicide.

3.2.4. Conclusions

GPi-DBS appears a safe treatment option with regard to psychiatric outcomes in isolated, idiopathic or inherited dystonia patients with stable psychiatric symptoms (class II) as well as moderately to severe depressed patients (class IV). Despite only small reports (class IV), worsening of depression and anxiety during DBS treatment might occur more frequently in TD, DYT11 myoclonus dystonia and CP, highlighting the need for careful evaluation and follow-up of these patients.

3.3. Cognitive issues

Twenty-two studies reported on examination of cognition before and after GPI-DBS in dystonia, using a large variety of cognitive tests including the Mini Mental State Examination (MMSE) and the Mattis Dementia Rating Scale (MDRS). Studies of five or more patients are showed in Table 3.

3.3.1. Inherited or idiopathic isolated dystonia

In a total of 93 patients with cervical dystonia, no difference in global cognition scores were found between baseline and post-operative condition, and more extensive test batteries only reported a small decline in verbal memory and fluency of uncertain clinical relevance [17,18,22,37].

Global cognition screening in 88 generalized and segmental dystonia patient remained stable during DBS treatment [25,27,29,40]. Three case studies (n = 14, 22 and 24), including one pediatric cohort, in which cognition was extensively tested, reported improvement in attention, memory, and executive functioning [56,57], as well as slight worsening of verbal reasoning and memory [41,57]. Improvements were partially related to the decrease in anticholinergic medication and improved motor function.

Nine children with dystonia due to pantothenate-kinase-associated neurodegeneration (PKAN) were assessed at baseline and post-operatively at 24–36 months follow-up, showing overall stable to improved cognitive scores, presumably due to better concentration and the ability to finish more tests [58,59]. One patient deteriorated on almost all cognitive tests, which was attributed to disease progression.

3.3.2. Acquired dystonia

Global cognition, including MMSE and MDRS, was reported to remain stable during DBS treatment at 6–12 months follow-up in 19 TD patients [44,60]. One more extensive report in 9 TD patients found stable scores with a trend to improvement in verbal fluency [43]. For CP patients, one report in 40 pediatric DBS patients found no significant decline in scores postoperatively [61].

3.3.3. Discussion

The antero-medial GPi is integrated in the dorsolateral prefrontal and lateral orbitofrontal circuit, connecting the basal ganglia with the prefrontal cortex [8,9]. The dorsolateral prefrontal circuit is important for executive functioning and motor planning, whereas disruptions of the lateral orbitofrontal circuit can cause loss of interest and initiative. This probably explains why impairments in executive function, attention, verbal memory, and sequence learning have been frequently reported in dystonia patients, especially in DYT1, idiopathic cervical dystonia and DYT11 patients [62–65]. However, these findings have not always been consistent, and might be partially attributed to medication, discomfort, and depressive symptoms.

Based on the existing studies, GPi-DBS appears to have no major impact on the cognition of dystonia patients. These conclusions should be taken with caution in absence of blinded case-controlled studies and the heterogeneity of the neuropsychological assessments across studies. Although more thoroughly investigated in isolated generalized dystonia compared to acquired dystonia, the reported stability of cognitive functioning seems to be irrespective of the underlying dystonia etiology. Slight improvement in executive functioning and memory was

Table 3
Studies reporting on the impact of GPi-DBS on cognition in dystonia.

Author	Design (n)	Diagnosis; age and; disease duration (DD) in years	Follow-up in month	Exclusion criteria	Cognitive function (measure)	Cognitive outcome	Mean % of motor improvement	Change in medication	Remarks
Inherited and idiopathic focal cervical dystonia									
Krauss 2002 [37]	Case series (8)	Idiopathic cervical; Age 46 (36–58); DD 12-44	20		Global cognition (MMSE)	Nonsignificant increase of MMSE from 27 to 30	63% (BFMDRS)	No details on continuation of oral medication	- Lower MMSE pre-operatively partly due to interfering motor symptoms
Kiss 2007 [18]	Case series (10)	Idiopathic cervical; Age 58 (47–64); DD 17 (5–28)	12	Abnormal cognition	Test battery	Overall no significant changes except from small decline in verbal memory and learning (n = 3)	44%** (TWSTRS-S)	No BTX and 2/8 stopped their medication	- Uncertain clinical relevance of changes - One patient with decreased scores had worsening of dystonia and depression
Volkmann 2014 [17]	RCT, open label (62)	Idiopathic or inherited cervical; Age 57 ± 10; DD 15 ± 7	6	MDRS < 120	Global cognition (MDRS)	Stable scores	28%*** (TWSTRS-S)	Oral medication reduced from 36 to 11	- Observed no changes in cognitive status, no de-novo behavioral abnormalities
Dinkelbach 2015 [22]	Case series (13)	Idiopathic cervical, Age 54 ± 12; DD 15 ± 9	12	MDRS < 120	Memory, executive function, attention, visual perception, mental arithmetic, verbal intelligence (test battery)	No changes, except from a deterioration of verbal fluency task (cognitive flexibility)		Oral medication stable (2), reduced (1) or stopped (6)	- Deterioration not correlated with change in dystonia severity of quality of life
Inherited and idiopathic segmental and generalized dystonia									
Morrison 2000 [90]	Case series (2)	Unknown, Age 31–32; DD 5-21	1	Abnormal IQ	Attention, Language, visuo-spatial, executive, verbal learning, recall, memory	One patient showed improvement on attention and verbal recall.	Unknown (BFMDRS)	Unknown	
Capelle 2003 [86]	Case report (1)	Idiopathic cranial-cervical; Age 60; DD 5	24		Global cognition (MMSE)	MMSE improved from 24 to 28	67% (BFMDRS)	Medication was tapered of slowly	
Krauss 2003 [29]	Case series (2)	Idiopathic generalized, Age 51–58; DD 12-39	24		Global cognition (MMSE)	Stable scores	79% (BFMDRS)	2/2 able to stop antidystonic drugs	
Vidailhet 2005 [40]	Case series (22)	Idiopathic and inherited generalized; Age 30 (14–54); DD 18 (4–37)	12	MMSE < 24	Global cognition (MMSE)	Stable scores	55%*** (BFMDRS)	Oral medication increased (3), stable (4), reduced (11) or stopped (2)	- No details on association between cessation or reduction in medication and cognitive outcome
Kupsch 2006 [25]	RCT, open label (40)	Idiopathic or inherited generalized and segmental cervical; Age 39 ± 14; DD 20 ± 8	6	MDRS < 120	Global cognition (MDRS)	Stable scores	45%*** (BFMDRS)	Dosage reduction 32%	
Pillon 2006 [56]	Case series (22)	Idiopathic or inherited generalized; Age 30 (14–54); DD 18 (4–37)	12	MMSE < 24	Global cognition, abstract reasoning, verbal learning, fluency, executive functioning (test battery)	Mild but significant improvement on reasoning, executive functioning and memory.	55%***	Significant reduction in medical treatment	

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Table 3 (*continued*)

Author	Design (n)	Diagnosis; age and; disease duration (DD) in years	Follow-up in month	Exclusion criteria	Cognitive function (measure)	Cognitive outcome	Mean % of motor improvement	Change in medication	Remarks
									- Possibly partly due to better motor function and decrease in anticholinergic drugs and learning effect, no details. - Stable or more improved results at 3-year follow up (Vidailhet, 2007)
Valldeoriola 2010 [27]	Case series (24)	Idiopathic or inherited generalized and segmental; Age 30 ± 14; DD 10 ± 7	12	MMSE < 24	Global cognition (MMSE)	Stable scores	59%*** (BFMDRS)	Medication was globally reduced after surgery	
Jahanshahi 2014 [41]	Case series (14)	Idiopathic or inherited generalized; Age 42 ± 19; DD 24 ± 17	14		Global cognition, IQ, memory, language, executive function, task switching and attention (test battery)	No changes in IQ, memory, language and executive function. Only significant worsening of sustained attention.	69%*** (BFMDRS)	No changes in medication at baseline and follow-up	- No effect of DYT1 upon cognitive outcome.
Owen 2015 [57]	Case series (13)	Idiopathic or inherited generalized, 12 ± 4	12		Non-verbal and verbal intellectual abilities, memory and processing speed (test battery)	Overall stable and improved scores, except from deterioration in verbal comprehension (1), reasoning (1) and verbal or visual memory (2)		Oral medication reduced (5) or stopped (2)	- 4/5 patients with reduced anticholinergics improved on certain domains - Improved motor function likely to have contributed to improvements
Pantothenate-kinase-associated neurodegeneration									
Mahoney 2007 [58]	Case series (7)	Generalized, PANK2; Age 12 (8–17); DD 7 ± 3	24		Non-verbal and intellectual abilities, memory (test battery)	Stable scores and improvement in all but one		No details about oral medication	- Better scores due to better concentration and access to test materials. Worse scores (1) due to deterioration in dystonia
Adamovicová 2011 [59]	Case series (2)	Generalized, PANK2; Age 17–18; DD 9	36		IQ, verbal learning, executive function, verbal fluency (test battery)	IQ stable, verbal learning, executive functioning and verbal fluency better (1) or worsened (1)	40% (BFMDRS)	Medication was reduced in both	
Acquired dystonias (Cerebral palsy)									
Krauss 2003 [29]	Case series (4)	Generalized due to cerebral palsy; Age 41 (36–46); DD 39 (24–44)	24		Cognition (MMSE)	Stable MMSE scores		Benzodiazepine reduction in 2/4 post-DBS	
Owen 2017 [61]	Case series (40)	Dyskinetic CP, dystonia caused by IEM; Age 12.5 ± 3.5	12		Non-verbal and verbal intellectual abilities, memory (test battery)	No significant decline, improved scores on perceptual reasoning	Unknown	Overall oral medication reduced	

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Table 3 (*continued*)

Author	Design (n)	Diagnosis; age and; disease duration (DD) in years	Follow-up in month	Exclusion criteria	Cognitive function (measure)	Cognitive outcome	Mean % of motor improvement	Change in medication	Remarks
									- Improvement partly due to reduction in dystonia, reduction in medication
Acquire dystonia (Tardive dyskinesia)									
Damier 2007 [60]	Case series (10)	Severe tardive dyskinesia; Age 45 ± 5; DD 5 ± 1	6	MMSE < 24	Global cognition and frontal functioning (MMSE, MDRS, FAB and FBS)	Stable scores on all four scores.	62%** (ESRS)	No marked change in antipsychotics and antidepressants	
Gruber 2009 [43]	Case series (9)	Tardive dystonia; Age 63 ± 13; DD 5 ± 3	18	MDRS < 123	Global cognition, alertness, executive function, learning and memory, digit span	No changes with only a trend for improvement in verbal fluency			
Pouclet-Coutremanche 2016 [44]	Case series (19)	Age 52 (25–69); DD 6 (1–38)	12	MMSE < 24	Global cognition and frontal functioning (MMSE, MDRS, FAB)	Stable MMSE and FAB, improvement on MDRS	82%*** (BFMDRS)		Improvement on MDRS on subscores attention and conceptualization
Various etiologies									
Halbig 2005 [42]	Case series (15)	Idiopathic, inherited and tardive dystonia; Age 46 (13–38); DD 13 (6–62)	7	Not cooperative	Global cognition, alertness, attention and executive functions, learning and memory (test battery)	Improvement on trail-making test, likely due to improvement in motor function. Other cognitive measures stable or non-significantly improved.	71%*** (BFMDRS)	Reduction or cessation of antidystonic medication in 10/15 patients	- Postsurgical medication changes could mask neuropsychological deterioration induced by DBS - Reaction times increased in stable medication patients, but not significantly
De Gusmao 2017 [89]	Case series (12)	Focal, segmental and generalized dystonia of inherited, idiopathic and tardive; Age 42.3; DD 10.1	13	Not an intact cognition	Cognition; attention, WM and processing speed; language; visuo-spatial function and memory	Overall stable, improved working memory (letter-number sequencing (17.1 ± 4.4 vs 18.8 ± 4.1*) and cognitive set shifting (trails B 80.6 ± 34.7 vs 70.4 ± 33.3*)	61%[1]	Oral medication increased (1), stable (3), reduced (6) or stopped (2)	- No correlation between motor and cognitive outcome - No details regarding possible effect of change in medication and cognitive outcome

Test battery was used if there were more than five measures used in one study. FAB, frontal assessment battery; FBS frontotemporal behavioral scale; IQ, Intelligence quotient; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; BPVS, British Picture Vocabulary Scale; WISC, Wechsler Intelligence Scale for Children; BFMDRS-M, Burke-Fahn-Marsden dystonia rating scale motor subscale (0–120); ESRS, Extrapyramidal Symptom Rating Scale; TWSTRS-S, Toronto Western Spasmodic Torticollis Rating Scale severity subscale (0–35); PKAN, Pantothenate kinase-associated neurodegeneration; [ns] non-significant; *p = 0.05; **p = 0.01; ***p = 0.001.

reported in various dystonias [42,56–58,66]. However, the (additional) influence of learning effects on the tasks, decrease in medication (anticholinergics) and/or improved motor status upon reported improvements cannot be distinguished from the effects of GPi-DBS. Only one case series controlled for the use of medication by unchanged drug intake between baseline and follow-up [41]. These authors found no changes across multiple domains of cognitive function, except for worsening in sustained attention. This might be explained by a disturbance in the dorsolateral prefrontal circuit, but more studies are required to study this aspect and the consequences for daily functioning [67].

3.3.4. Conclusions

Based on current evidence, the influence of changes in medication and the heterogeneity in cognitive assessments across the studies, GPi-DBS does not have major impact on the cognition of dystonia patients (class IV). This stability seems to be irrespective of the underlying dystonia etiology.

3.4. Other non-motor symptoms

Sleep disturbances have been reported in patients with isolated, mainly focal dystonia. In one study, sleep disturbances were present in more than half of the focal cranial dystonia patients [68]. These disturbances were more closely related to depression than to dystonia severity. The absence of systematic analyses makes it impossible to differentiate between sleep disturbances being a primary or secondary feature in dystonia. Nevertheless, disturbances in sleep and fatigue seem to be associated with a lower quality of life in dystonia [69]. However, to our knowledge, the effect of GPi-DBS upon sleep with separate sleep measures has not been evaluated yet.

Two studies reported on *weight changes* following GPi-DBS. In one study there was no significant weight gain in 27 adult dystonia patients (median −0.045 kg, 95%-CI -1.17-0.78) [70]. In the other study, weight change was evaluated in 14 patients with segmental or generalized dystonia before and at 6, 17, and 72 months after GPi-DBS [71]. Although detailed results were only reported for the total group of GPi-DBS (n = 14) and thalamicVim-DBS (n = 3), there was a significant weight gain over the first 6 months postoperatively. This was desirable in two underweighted patients preoperatively, but led to overweight (BMI > 25) in five patients. The different outcomes in these two case series could be explained by the lower BMI at baseline in the latter. The weight gain was mainly attributed to decrease in dystonic movements, and recovery of dysphagia, rather than a direct effect of GPi stimulation.

One case series involving generalized (n = 2) and cervical (n = 9) dystonia patients investigated *bladder function* before and at least 3 months after the surgery [72]. Four out of the eleven patients showed a detrusor over-activity pre-DBS, which was not found in any patients after surgery.

3.5. Other DBS targets

Other DBS targets (STN and thalamus) have been investigated in a limited number of studies, mostly involving patients with isolated cervical dystonia (Table 4). No direct quantitative comparisons have been conducted.

Various NMS after *STN*-DBS have been evaluated in 34 dystonia patients in a total of 6 studies. With regard to the effect of STN-DBS on pain, an improvement has been reported in six out of seven dystonia patients with idiopathic dystonia and Fahr disease (n = 1) [73–75]. Psychiatric outcomes in STN-DBS showed overall stable BDI scores in 13 cervical dystonia patients and improvement on anxiety and depression scales in 10 tardive dystonia patients [73,76,77]. In 9 cervical dystonia patients a > 10% gain in body weight was observed in four patients [76]. In two studies reporting on cognitive outcome after STN-DBS no clinically significant changes were seen [73,76].

Non-motor outcome of *thalamic*-DBS has been mainly described in patients with tremulous or myoclonus dystonia. Seven cervical dystonia patients with head tremor, stimulated in the thalamus/subthalamic area reported a pain improvement of 90% [78]. For myoclonus dystonia, combined GPi-Vim stimulation showed no differences in affective status and cognition when either the GPi, Vim or both targets were stimulated (n = 7) [79]. One patient with postanoxic dystonia committed suicide during DBS treatment of the ventralis oralis anterior nucleus of the thalamus [80].

4. Conclusion

Despite growing experience with DBS as effective treatment for dystonic movements, systematic studies regarding the effect upon NMS such as pain, psychiatric issues and cognition in patients with dystonia are still lacking. With the existing knowledge, the impact of GPi-DBS on NMS seems to be more consistent across the whole dystonia population than motor outcome. GPi-DBS is likely to be beneficial for pain, whereas it does not have major impact on mood, anxiety, and cognition. In patients with DYT 11, CD and CP we detected new onset or worsening of mood disorders after GPi-DBS. Definite conclusions cannot be drawn as this was found only in case series and reports (level IV). These preliminary results underpin the importance of performing systematic evaluation on depression and anxiety in future studies. Overall, these conclusions should be interpreted with caution as the majority of the studies comprise small samples, are non-blinded, and the direct influence of GPi stimulation and the impact of potential confounders (e.g. patient factors, changes in pharmacological treatment) remains unclear.

Various reviewed studies described a potential dissociation or association between motor and non-motor response after GPi-DBS. Despite the possible interaction between motor and non-motor response, correlational studies are lacking underscoring the need for a more thorough evaluation of a possible confounding effect.

The use of impairment-based motor scales (such as the BFMDRS) as gold standard has led to a clear distinction in DBS efficacy between the favorable motor outcome in isolated, hereditary, and idiopathic dystonias, and the less robust outcome in lesional dystonias (CP, metabolic disorders, neurodegenerative) [3]. Therefore, the application of DBS in lesional dystonias often gives rise to discussion. However, the sole use of a motor score may not capture the true efficacy of DBS as other aspects might be at least as important for disability and quality of life in dystonia patients. Clinical practice and future studies should include systematic screening of both motor and non-motor features in dystonia DBS candidates [13]. With regards to non-motor symptoms, pain, anxiety and depression, and cognitive functioning (executive functioning, memory and attention) should be included in the pre- and post-operative evaluation. Future studies should also focus on the effect of DBS on sleep disturbances and fatigue to determine if systematic evaluation is required. In this context, it might be more suitable to use individualized, predefined goals on both motor as well as non-motor domains as primary outcome instead of dystonia severity measures.

Table 4
Quantitative studies reporting on the impact of STN-DBS and Th-DBS on non-motor symptoms in dystonia.

Target	Author	Design (n)	Diagnosis; Mean age; and disease durations DD ± SD in years (range)	Follow up in month	Exclusion criteria	Symptom (measure)	Conclusions
STN	Kleiner-Fisman 2007 [73]	Case series (4)	Idiopathic cervical and generalized; Age 50 (41–56); DD 25 (10–39)	12	Psychiatric illness, MMSE ≤24	Pain (TWSTRS-P) Depression and anxiety (BDI-II, S-TAI) Processing speed, verbal and visual memory, language, visual-spatial, attention and working memory, executive function (test battery)	Mean changes 2.9 ± 2,4, p = 0.38; improved in 3 and worsened in 1 Improvement in 3/4 (16–70%); non-relevant worsening in 1 (39%) 4/4 showed non-clinically significant decline in executive function. Baseline deficits in verbal and visual memory declined in 2/4. 2/4 in impaired range for language skills post-DBS
STN	Pahahill 2009 [74]	Case series (2)	Idiopathic, isolated cervical; Age 70 (68–71); DD 18 (15–21)	36		Pain (TWSTRS-P)	15 vs 3 and 11 vs 2; 80–83% improvement
STN	Ostrem 2011 [76]	Case series (9)	Idiopathic cervical dystonia; Age (24–71); DD 11 (2–34)	12		Depression (BDI-II) Processing speed, verbal memory and fluency, language, visual-spatial, attention and working memory, (test battery) Weight	18.0 ± 14.5 vs 14.8 ± 2^{ns}. 5/9 reported transient worsening of depression. 2/9 worsened anxiety Stable scores 4/9 wt gain, of which 3 > 10% increase
STN	Ma 2013 [75]	Case report (1)	Fahr disease; Age 26; DD 6	12		Pain (TWSTRS-P)	100% improvement; 7 vs 0
STN	Mills 2014 [91]	Case series (8)	Idiopathic cervical dystonia; Age 57 (45–68); DD 11 (3–27)	NA	MCAB < 22	Working memory (n-back test)	Stable scores
STN	Deng 2017 [77]	Case series (10)	Tardive dystonia; Age 29.8 ± 15.4	66		Axiety (HAMA) Depression (HDS)	19.3 ± 5.6 vs 3.7 ± 7.7 (p < 0.01) 22.9 ± 8.6 vs 3.8 ± 7.8 (p < 0.01) Growing hypothesis that the STN might participate in processing limbic system information
Thalamic/ subthalamic area	Pauls 2014 [78]	Case series (7)	Idiopathic, cervical dystonia with head tremor; Age 55 (23–76); DD 16 (2–32)	3	Psychiatric disease or cognitive deficits	Pain (VAS)	4.5 OFF vs 0.5 ON (90% better, p < 0.05)
GPi and nucleus VoA	Burkhard 2004 [80]	Case report (1)	Acquired, postanoxic generalized; Age 26; DD 6	4		Suicide	One completed suicide, had a pre-DBS history of depression, aggressive behavior and drug dependency
GPi versus VIM	Gruber 2010 [79]	Case series (10)	Myoclonus dystonia; Age 44 ± 16; DD 37 ± 4		MDRS < 123, MMSE < 24, hallucinations, severe depression MADRS > 29	Affective status (MDMQ) Alertness, executive functioning, learning, memory (test battery)	No significant effect of VIM, GPi or VIM + GPi-DBS upon affective status. No significant effect of VIM, GPi or VIM + GPi-DBS. Only impaired reaction time Gpi versus VIM (p = 0.04)
Gpi and VIM	Oropilla 2010 [92]	Case report (1)	Myoclonus dystonia; Age 23; DD 10	24		Pain (TWSTRS-P)	100% improvement; 11 vs 0

STN, subthalamic nucleus; GPI, globus pallidus internus; VIM, ventral intermediate nucleus; VoA, ventralis oralis anterior; BDI, Becks depression inventory; MADRS, Montgomery–Åsberg Depression Rating Scale; MCAB, Montreal Cognitive Assessment Battery; MDRS, Mattis Dementia Rating Scale; MDMQ, Multidimensional Mood State Questionnaire; Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; S-TAI, State-Trait Anxiety Inventory; TWSTRS-P, Toronto Western Spasmodic Torticollis Rating Scale pain subscale; VAS, visual analogue scale.

Contributors

HE and SS were involved in the design and conceptualizations of the study, analysis and interpretation of the data, drafting and revision of the manuscript. MAC, MEvE and EM critically revised the article. MAJT was involved in the design and conceptualization of the study, analysis and interpretation of the data and revision of the manuscript. All authors gave final approval of the version that was submitted.

Conflicts of interest

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Appendix A. Supplementary data

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