Parkinsonian signs in patients with cervical dystonia treated with pallidal deep brain stimulation: a controlled and observer-blinded study

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Abbreviations: AMT = active motor threshold; DBS = Deep Brain Stimulation; EQ-5D-3L = European quality of life, 5 dimensions, 3 level version; FDI = first dorsal interosseous muscle; FOG = freezing of gait; GPI = globus pallidus internus; M-EDL = motor experiences of daily living; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; MEP = motor evoked potential; MNI = Montreal Neurological Institute; NIFTI = Neuroimaging Informatics Technology Initiative; OR = orbicularis oris muscle; PW = pulse width; RMT = resting motor threshold; TWSTRS-TSS = Toronto Western Spasmodic Torticollis Rating Scale—Torticollis Severity Scale; VTA = volume of neural tissue activated.
Abstract

Pallidal deep brain stimulation is an established treatment in patients with cervical and segmental dystonia. Anecdotal evidence suggests that it may lead in some patients to specific parkinsonian symptoms such as freezing of gait, micrographia, and bradykinesia. However, so far no study has examined parkinsonian signs in these patients in a controlled and systematic manner. Therefore, we investigated parkinsonian signs using the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (observer-blinded) in a group of 29 patients treated with pallidal stimulation for cervical dystonia and a non-surgical control group of 22 patients with predominant cervical dystonia. Additional assessments included MRI-based models of volume of neural tissue activated to investigate areas of stimulation responsible for symptom control and those likely to induce parkinsonian signs as well as an EMG analysis to investigate functional vicinity of stimulation fields to the pyramidal tract.

Compared with controls, stimulated patients had significantly higher MDS UPDRS motor scores (median, 25th-75th percentile: 14.0, 8.0–19.5 versus 3.0, 2.0–8.0; p<0.0001) as well as bradykinesia (8.0, 6.0–14.0 versus 2.0, 0.0–3.0; p<0.0001) and axial motor subscores (2.0, 1.0–4.0 versus 0.0, 0.0–1.0; p=0.0002), while rigidity and tremor subscores were not different between groups. When switching stimulation off in a subset of 19 patients tolerating this condition, the same parkinsonian signs were partially alleviated (all p<0.012).

Furthermore, the stimulation group reported more features of freezing of gait (p=0.0420) and trended towards reporting more parkinsonism related disability (p=0.0518) on a questionnaire basis. Quality of life was better in stimulated patients compared with control patients, but linear regression analysis revealed that parkinsonian signs had a significant negative impact on quality of life. In The imaging analysis showed that maximum efficacy for dystonia improvement was achieved by stimulating projected to the posteroventrolateral internal pallidum with overlapping clusters driving severity of bradykinesia and axial motor symptoms. The severities of parkinsonian signs were not correlated with functional vicinity to the pyramidal tract as assessed by EMG. In conclusion, parkinsonian signs, particularly bradykinesia and axial motor signs, due to pallidal stimulation in dystonic patients are frequent and negatively impact on motor functioning and quality of life. Therefore, patients with palilidal stimulation should be monitored closely for such signs both in clinical routine and future clinical trials. Spread of current outside the GPi internal pallidum is an unlikely explanation for this phenomenon, which seems to be caused by stimulation of neural elements within the stimulation target volume.
Introduction

Pallidal DBS has been established for over 10 years as an effective and safe treatment for patients with severe generalised or segmental dystonia (Kupsch et al., 2006; Vidailhet et al., 2005). Following case series and smaller non-randomized studies (Hung et al., 2007; Kiss et al., 2007; Walsh et al., 2013) the efficacy of GPi-DBS has also been demonstrated in cervical dystonia in a more recent large randomized and blinded multicentre trial (Volkmann et al., 2014). Most randomized controlled trials of DBS in dystonia have reported a low frequency of adverse events with no serious side effects on cognitive and neuropsychiatric functions. Negative consequences of current spread to surrounding areas such as the pyramidal tract (including severe dysarthria) are also infrequent (Vidailhet et al., 2013). However, anecdotal reports have suggested that dystonia patients with pallidal DBS can develop troublesome specific parkinsonian symptoms such as freezing of gait or micrographia (Berman et al., 2009; Blahak et al., 2011; Schrader et al., 2011; Tisch et al., 2007; Zauber et al., 2009). Also, one systematic study in 10 patients with cervical dystonia observed mild hypokinesia of gait and a relevant decrease in gait variability upon GPi-DBS as compared to with no stimulation (Wolf et al., 2016). However, the pathophysiology of these phenomena and their relevance to the overall outcome of pallidal stimulation for dystonia remain poorly understood. None of the studies mentioned above has used a universal instrument for assessment of parkinsonism nor has any study conducted a direct comparison of dystonia patients on pallidal DBS with patients on non-surgical treatment regimens, since the latter patient group can also exhibit mild parkinsonian features (Haggstrom et al., 2016). Moreover, it remains unknown whether the appearance of parkinsonian features has an impact on quality of life.

Therefore, we sought to assess parkinsonism and its impact on daily motor functioning and quality of life in patients with predominant cervical dystonia with validated universal tools, comparing patients treated with chronic pallidal DBS with matched patients under conservative treatment regimes. Moreover, we performed a probabilistic imaging analysis on VTAs in and around the GPi related to 1) reduction of dystonia and 2) induction of parkinsonian signs, in order to elucidate potential mechanisms by which pallidal DBS produces these effects. Lastly, we assessed whether current spread to the pyramidal tract due to pallidal stimulation as assessed by EMG is related to the advent of parkinsonism in a subgroup of DBS treated patients.
Methods

Participants and DBS implantation
Patients with bilateral GPi-DBS for cervical dystonia or segmental dystonia with predominant involvement of the neck were consecutively recruited from our movement disorders outpatient clinic. All patients had been carefully selected to undergo DBS lead implantation between 2004 and 2014. Clinically relevant parkinsonian signs had been excluded before surgery as part of our routine clinical preoperative assessment performed by movement disorder experts (TF and PL). Patients had undergone DBS lead implantation between 2004 and 2014. Operations were performed using an MRI-guided and MRI-verified approach under general anaesthesia as previously published (Tisch et al., 2007). In brief, implantation of bilateral quadripolar DBS electrodes (MDT-3389 Medtronic, Minneapolis, USA or STJ-6164-6149 St Jude, St. Paul, Minnesota, USA) was performed with direct targeting of the posteroventral GPi, as visualised on proton density sequence stereotactic MRI at 1.5 Tesla without microelectrode recording (Hirabayashi et al., 2002; Holl et al., 2010; Nakajima et al., 2011). Intraoperative dynamic impedance recording was used to delineate grey and white matter boundaries (Zrinzo and Hariz, 2009). Confirmation of electrode placement in the posteroventral GPi was obtained in all patients with immediate post-implantation stereotactic MRI. Stimulation parameters were postoperatively individualized in each patient for the best clinical effect and the least side effects. At the time of the present evaluation, all patients received monopolar stimulation on one or two adjacent active contacts, except for 3 patients who had been switched to an interleaved stimulation mode on two adjacent contacts and 2 patients who had been switched to a bipolar stimulation mode on two adjacent contacts. Stimulation was set at a frequency of 130 Hz in all patients (except 125 Hz for the 3 on interleaved stimulation mode) and on pulse widths ranging from 60 to 120 μs. Stimulation parameters had been kept constant at least 6 months prior to the present assessment. A group of patients with predominant cervical dystonia on conservative treatment regimens (without DBS) were also consecutively recruited from our movement disorders outpatient clinic and included as controls. Patients were not systematically screened for inherited dystonia, but two patients included in our study (both in the GPi-DBS group) had a known gene mutation – one a TOR1A mutation (DYT 1) and one a THAP1 (DYT 6) mutation. All patients provided written informed consent for the study according to the Declaration of Helsinki, which was approved by the local ethics committee.

Experimental design
In this case-control and multimodal study clinical and neurophysiological—Patient assessments of patients were performed within one day (DG and FB). Three different investigators independently performed clinical, imaging, and neurophysiological assessments: each blinded to the other two assessments. Clinical assessments were videotaped and videos were rated by a clinician blinded to treatment group and stimulation condition (PM). Imaging data was retrieved from intraoperative MRI scans and analysed as detailed below (HA).

Clinical assessments
For this study, DBS treated patients and control patients underwent clinical assessment in 2015 consisting of standardized neurological examination with validated rating scales complemented by validated questionnaires. The motor section of the MDS-UPDRS (Goetz et al., 2008) as well as the TWSTRS-TSS torticollis severity scale (Comella et al., 1997) were employed. Furthermore, the TWSTRS disability scale, TWSTRS pain scale, MDS-UPDRS motor experiences of daily living questionnaire, FOG questionnaire (Giladi et al., 2000), and the descriptive system of the EQ-5D-3L were applied to assess disability and quality of life. After initial assessment, GPi-DBS was switched off and, in the 19 patients who tolerated this condition without excessive recurrence of dystonia, stimulation was kept off for a median of 90 (25th–75th percentile: 60–100) minutes before reassessing TWSTRS-TSS torticollis severity and MDS-UPDRS-III motor sores.

All clinical assessments were videotaped and later assessed by a movement disorder neurologist (PM) experienced in the rating of the two scales and blinded to unaware of group assignment and stimulation condition. In the GPi-DBS group TWSTRS torticollis severity scores were compared with TWSTRS scores that had been recorded preoperatively in order to determine the benefit of chronic pallidal stimulation in reducing severity of cervical dystonia. MDS-UPDRS motor ratings did not include the item for neck rigidity in any of the patients, nor any other items in dystonic body parts with significant dystonia in individual patients. Rigidity ratings for non-dystonic body parts were taken from the actual clinical assessments. MDS-UPDRS motor scores were subgrouped into a rigidity subscore (item 3), a bradykinesia subscore (items 4 to 8), an axial motor subscore (items 9 to 14), and a tremor subscore (items 15 to 18).

MRI acquisition and procession
DBS contacts’ VTAs modelling was performed on MRI scans obtained intraoperatively on a 1.5 Tesla Siemens Avanto interventional MRI scanner. SureTune® (Medtronic Inc.
Minnesota), a DBS therapy planning platform, was used to model VTAs around individual contacts. The platform applies neuron models coupled to finite element simulations in order to generate DBS therapy VTAs. Homogeneous finite element simulations of the distribution of the electric potential together with coupled axon cable models (Aström et al., 2009), where the latter were composed of 21 nodes, with a diameter of 2.5 µm. Intraoperative MRI scans were uploaded and post-implantation MPRAGE (magnetization-prepared rapid gradient-echo) used to fit the DBS lead model within the MRI artefact produced by the leads. Individual VTAs were then generated according to that the respective patient’s chronic stimulation DBS settings in terms of stimulation amplitude and pulse width as previously described (Aström et al., 2009). Binary image files of VTAs along with corresponding transformation matrices were exported and processed in Matlab (Mathworks Inc.) using in-house software to generate NIfTI (Neuroimaging Informatics Technology Initiative) files. MPRAGE MRI scans were then registered to the MNI (Montreal Neurological Institute) ICBM (International Consortium of Brain Mapping) 152 non-linear 6th Generation Symmetric Average Brain Stereotaxic Registration Model (Grabner et al., 2006) using non-linear registration. The resulting transformation warps were in turn used to transform all VTAs to MNI space. Transformed VTAs were thresholded at 95% using Fslmaths (FSL 5.0) to remove the interpolation effect.

**EMG Recordings**

In order to estimate the functional proximity to the pyramidal (corticobulbar and corticospinal) tract, EMG activity of the orbicularis oris muscle and the EDL-first dorsal introsseous muscle upon contralateral pallidal stimulation was recorded in 14 patients, who tolerated being off high frequency stimulation for the necessary time period. Recordings were performed using 9mm Ag-AgCl surface cup electrodes with the same equipment in a standardized fashion as recently reported in a cohort of patients with Parkinson’s disease with subthalamic stimulation (Mahlknecht et al., 2017). In brief, signal amplification gain was set at 2000, recording frequencies at 10kHz, and a band pass frequency filter at 20–1000Hz. The signal was digitized and saved for offline analysis blinded to the conditions tested patients’ clinical examination using Signal V4.08 (CED, Cambridge, UK). For the orbicularis oris muscle, the active electrode was placed 1cm lateral to the mouth corner, and the reference 2cm lateral, for the first dorsal introsseous the muscle belly and the tendon of the same muscle were used, respectively. First, MEPs were assessed while patients were sitting in a comfortable armchair and instructed to relax but not speak or sleep. Monopolar stimuli were elicited by the impulse
generator at contacts used for chronic stimulation on each electrode. In patients with interleaved stimulation the contact with the higher stimulation amplitude and in patients with bipolar stimulation the contact representing the cathode were used. Stimulation at a low frequency of 3 Hz (allowing enough time for MEP recordings before subsequent stimuli) and at pulse width used for chronic stimulation was increased in 0.5 mA steps up to 8.0 mA or until bothersome side effects appeared. Thirty sweeps of EMG triggered by the stimulation artefact were averaged per condition to detect the RMT of pyramidal tract activation. RMTs were determined as the lowest stimulus intensity inducing MEPs clearly recognizable above background activity upon visual inspection (in most instances this was the case when MEPs reached >10 µV in amplitude).

Furthermore, AMT were assessed during sustained muscle contraction of approximately 25% of maximum voluntary force production (provided to the participants as visual feedback with a line on the EMG screen, which they were asked to match), first of the FDI first dorsal interosseous muscle by squeezing a roll of tape and second of the OO orbicularis oris muscle by forming a smiling mouth. Stimuli were elicited via the clinically used contacts on each side as for the RMT. AMT was determined as the lowest stimulus intensity inducing MEPs clearly recognizable above background activity upon visual inspection.

**Statistical analysis**

As data were largely non-normally distributed, as shown by the Shapiro-Wilk test, we used non-parametric tests for comparative statistics. Continuous variables are uniformly given by medians and 25th–75th percentiles. For the descriptive analysis we used two-sided Mann-Whitney U tests to compare age, disease duration, and scale scores between GPi-DBS versus control patients and paired two-sided Wilcoxon tests to compare scale scores under off versus on stimulation condition. Binary variables were compared using the chi-squared test. Spearman rank test was used for all correlation analyses. The impact of parkinsonian signs on quality of life was assessed using the spearman rank test adjusted for age, sex, disease duration, cervical dystonia severity, and treatment group. Additionally, an ordinal regression analysis adjusted for the same confounders was performed. For the latter analysis continuous variables were log-transformed to normal distribution. As dystonia is known to potentially cause (postural and/or action) tremor, the same analyses were done leaving tremor out from the MDS-UPDRS motor score. Linear regression analyses were additionally performed to assess the influence of various factors on the occurrence of parkinsonism. SPSS 22.0 (IBM Corp., Armonk, NY) was used for all statistical analyses. The significance level was set at two-sided p-value of <0.05. A statistical trend was defined as a two-sided p-value of <0.1.
Efficacy and side-effect cluster analysis of imaging data
A group average VTA was generated from the MNI (Montreal Neurological Institute) warped individual VTAs by using the (FMRIB) fslmaths function with -Tmean flag, which is equivalent to a sum of all voxels in all VTAs. To generate efficacy and side-effect average clusters, patients were independently ranked according to dystonia reduction as measured by the TWSRTS torticollis severity scale, as well as appearance of axial motor symptoms and bradykinesia (hemi-body) as measured by the respective MDS-UPDRS derived scores, and on a composite hemi-body score of tremor, bradykinesia and rigidity. Individual VTAs were weighted by multiplying each VTA by the rank for each of these three effect categories separately. Group averages were then generated from the resulting, weighted VTAs.

Results

Patient characteristics
Twenty-nine CD patients with GPi-DBS and 22 CD patients without DBS were recruited and included in the present study. At the time of the present evaluation, all patients received monopolar stimulation on one or two adjacent active contacts, except for 3 patients who had been switched to an interleaved stimulation mode on two adjacent contacts and 2 patients who had been switched to a bipolar stimulation mode on two adjacent contacts. Stimulation was set at a frequency of 130 Hz in all patients (except 125 Hz for the 3 on interleaved stimulation mode). Median pulse widths were 60 (60–90) μs on both sides and median stimulation amplitudes 3.7 (3.5–4.6) V on the left side and 3.7 (3.3–4.6) V on the right side. At the time of assessment at a median of 5.0 (2.0–7.0) years after DBS implantation, patients with GPi-DBS had significantly better TWSTRS torticollis severity scores compared with their preoperative scores (11.0, 5.5–14.5 versus 18.0, 11.3–20.0; Z = -3.4, p=0.0008). In a linear regression analysis, percent improvement was predicted by younger age (Beta-coefficient = -2.5, 95% confidence interval -3.6 to -1.3; p=0.0003), shorter disease duration before surgery (-1.3, -2.7 to -0.1; p=0.0693), and higher preoperative TWSTRS-TSS scores (2.5, -0.1 to 5.1; p=0.0551).
Patient controls did not significantly differ from GPi-DBS patients in terms of age, sex, disease duration, or dystonia severity (GPi-DBS patients on stimulation). Characteristics of the two patient groups are presented in Table 1.
Comparison between groups in terms of parkinsonian signs, disability, pain and quality of life

GPI-DBS patients had significantly higher MDS-UPDRS III\textsubscript{motor} scores as well as bradykinesia and axial motor subscores compared with controls (Fig. 1, see supplementary Table 1 for numerical data). Tremor subscores were higher in the control group, but his difference was not statistically significant. Tremor was mainly a postural and/or action tremor. Only two patients had a rest tremor component (one in the GPI-DBS group and one in the control group). Rigidity was not different. Furthermore, on a questionnaire basis, GPI-DBS patients had a statistical trend towards less torticollis related disability but more parkinsonism related disability (Table 1), although this was not statistically significant. FOG scores were significantly higher in the stimulation group. EQ-5D-3L scores were lower in DBS patients compared with control patients indicating better quality of life.

A correlation analysis and an ordinal linear regression analysis adjusted for potential confounders age, sex, disease duration, and treatment group showed that higher MDS-UPDRS motor scores were significantly associated with decreased quality of life (Table 2). Out of the individual parkinsonian sub-domains bradykinesia, axial motor symptoms, and tremor all significantly impacted on quality of life.

Off stimulation condition

As a sensitivity analysis, clinical assessments were repeated in an off stimulation condition in the GPI-DBS group to examine parkinsonism domain severity changes upon switching off stimulation. In the 19 participants tolerating this condition there was a trend towards lower preoperative TWSTRS–TSS torticollis severity scores compared with those not tolerating being off stimulation were lower (14.0, 7.8–20.0 versus 18.5, 17.3–21.5; Z = -3.4, p=0.0879). All other baseline characteristics outlined in Table 1 were not different between these two groups (all p>0.3). Switching off stimulation led to a significant reoccurrence of dystonic symptoms (Fig. 2, see supplementary Table 2 for numerical data). The percentage TWSTRS–TSS torticollis severity increase when stimulation was switched off significantly correlated with the percentage TWSTRS–TSS torticollis severity reduction on stimulation versus the preoperative status (Spearman’s r=0.599, p=0.0099). Switching stimulation off significantly lowered MDS-UPDRS scores as well as bradykinesia and axial motor subscores (Fig. 2 and supplementary Table 2).

Potential factors driving the occurrence of parkinsonian features
Neither TWSTRS TSS torticollis severity on stimulation nor the percentage reduction of torticollis severity upon stimulation (pre- versus postoperative status) correlated with the MDS-UPDRS motor scores or any of its subscales (all Spearman rank correlations $p>0.4$). Similarly, upon switching stimulation off, the percentage increase in torticollis severity did not correlate with the decrease in MDS-UPDRS motor scores or any of the subscales (all Spearman rank correlations $p>0.5$). The stimulation amplitude did not correlate with the MDS-UPDRS motor or any of the subscales (all Spearman rank correlations $p>0.2$). A linear regression analysis (see Table 3) showed that having DBS was the factor most significantly associated with higher total MDS-UPDRS scores as well as bradykinesia and axial motor subscores.

**Imaging analysis**

The descriptive imaging analysis showed that averaged volumes of tissue activated projected to the area of the posterolateral GPi (Fig. 3). The “sweet spot” for dystonia reduction upon stimulation was localized in the posteroventrolateral GPi. On visual inspection the clusters associated with bradykinesia, axial motor symptoms, and hemiparkinsonism according to a composite score out of tremor, bradykinesia, and rigidity largely overlapped with the “sweet spot”, but tended to be located more inferiorly, medially and anteriorly.

**Motor evoked potentials**

A total of 28 DBS electrode contacts in 14 patients were assessed while at rest and upon activation using stimulation at a low frequency (3 Hz) at the clinically used contacts. RMT and AMT in the contralateral OOr orbicularis oris muscle were elicited in 21 contacts and 27 contacts and in the contralateral FDI first dorsalis interosseus muscle in 15 contacts and 26 contacts, respectively, using stimulation strengths up to 8 mA. In those contacts where RMT or AMT could not be elicited, putative thresholds of 9 mA were assumed for correlation analysis in order to eliminate avoiding missing values. Median thresholds are presented in supplementary table 3 and were lower in the OOr orbicularis oris muscle compared with the FDI first dorsalis interosseus and upon activation compared with the resting condition. None of the thresholds were correlated with the MDS-UPDRS motor scores or with single parkinsonian sings (all $p>0.15$, n data points $= 14$). Also, lateralized scores for parkinsonian features were not correlated with any of the thresholds (all $p>0.3$, n data points $= 28$).

**Discussion**
This controlled and observer-blinded study evaluated parkinsonian symptoms in patients with predominant cervical dystonia treated with bilateral pallidal DBS and compared findings with those of a group treated with conservative treatment regimens. This is one of the largest long-term follow-up cohorts of dystonia patients demonstrating sustained benefit of Gpi-DBS; after a mean of 5 years of stimulation. Torticollis severity was still improved by 32% as compared with the preoperative status, in line with improvements seen after 6 months of open-label stimulation in recent randomized controlled trials (Volkmann et al., 2014). These findings underline the representativeness of this cohort of patients with cervical dystonia treated with long-term pallidal DBS. Degree of improvement on stimulation was significantly predicted by younger age at surgery and a trend was seen with shorter disease duration before surgery and higher preoperative TWSTRS-TSS scores.

To the best of our knowledge, this study is the first to compare parkinsonian symptoms in dystonia patients with and without pallidal DBS. Patients with GPi DBS, while significantly improved compared to their pre-operative status, had similar dystonia severity to the control group of patients on non-surgical treatments. However, Gpi-DBS treated patients had median MDS-UPDRS scores of 14 points overall parkinsonian symptoms were significantly higher as measured by the MDS-UPDRS (difference in median scores of 11 points), which exceeds the “minimally clinically important difference” of approximately 4 points in most patients (Horváth et al., 2015). Parkinsonian features that drove this difference were bradykinesia and axial motor symptoms, similar to descriptions in earlier case series and uncontrolled studies in selected patients (Berman et al., 2009; Blahak et al., 2011; Schrader et al., 2011; Tisch et al., 2007; Zauber et al., 2009). These findings therefore confirms the anecdotal notions of parkinsonian signs emerging due to Gpi-DBS in dystonia patients that by far exceed the amount of mild parkinsonian features known to accompany idiopathic and inherited isolated dystonias (Haggstrom et al., 2016). Various forms of tremor occur more commonly in dystonia patients, potentially resembling Parkinson's disease tremor and being a frequent cause of ‘subjects without evidence of dopaminergic deficit’ (Erro et al., 2016; Gigante et al., 2016). In line with these observation, in this cohort there was a trend towards less tremor in DBS patients compared with control patients (not statistically different), which may be due to the therapeutic effect of pallidal DBS on dystonic tremor (Fasano et al., 2014; Volkmann et al., 2014). Rigidity was not different between groups.

After switching stimulation off for a median of 90 minutes, a significant reoccurrence of dystonic symptoms (worsening of 29%) and significant reduction of overall parkinsonian
symptoms (improvement of 18%) was observed. Reduction in parkinsonism was seen in the same subdomains bradykinesia (improvement of 19%) and axial motor symptoms (improvement of 39%), whereas changes were not seen for rigidity nor for tremor. Interestingly, in two of our DBS treated patients, dopamine transporter scans had been performed as part of their clinical workup because parkinsonian symptoms were severe enough to warrant exclusion of nigrostriatal dopaminergic deficit. Although both patients were markedly bradykinetic, one with a severe hypokinetic gait disorder (MDS-UPDRS of 42 points) and the other a rest tremor (MDS-UPDRS of 23 points), imaging results in both patients were normal. This further argues against a nigrostriatal deficit accounting for parkinsonian signs seen in GPi-DBS treated patients with dystonia. Also the observed median of 14 points on the MDS-UPDRS scale is much lower compared with MDS-UPDRS scores in patients with Parkinson’s disease even in early disease stages where mean scores range around 20–30 points (Holden et al., 2018).

Patients with DBS tended to experience less torticollis related disability compared with patients on non-surgical treatments, but experienced significantly more parkinsonism related disability, which also exceeded the minimally clinically important difference (Horváth et al., 2017). Although we have not applied objective measures of gait such as kinematic assessment, questionnaire-assessed features of freezing of gait were significantly greater in the stimulation group compared with the control group and indicated decreased mobility. Quality of life was significantly better in patients with DBS, as expected from results from large randomized controlled trials (Kupsch et al., 2006; Mueller et al., 2008; Volkmann et al., 2014). However, there was a variability of quality of life across patients in the two groups and some of this variability can be accounted for by parkinsonian symptoms that have a significant negative impact on quality of life as shown in a logistic correlation and regression analysis adjusted for age, sex, disease duration, cervical dystonia severity and treatment group. All factors together explained 41% in variance of quality of life, of which 27% was explained by overall parkinsonian symptoms. Out of the single parkinsonian subdomains, bradykinesia, axial motor symptoms and tremor were negatively associated with quality of life highlighting the importance of a thorough screening of dystonia patients treated with pallidal DBS for features of parkinsonism.

The mechanism by which pallidal DBS induces parkinsonism is largely unknown. It could be speculated that parkinsonism occurring upon pallidal stimulation is a result of current spread outside the GPi and subsequent activation of adjacent fibre tracts such as the pyramidal tract. However, our EMG assessment of resting and activation motor thresholds of
the corticospinal and corticobulbar tract in association with pallidal DBS did not correlate with the severity of overall parkinsonism or any parkinsonian features. This underlines the observation of an earlier case study that did not find any correlation between bradykinesia and the structural proximity of GPi DBS electrodes to the internal capsule as assessed on neuroimaging (Berman et al., 2009).

Another speculation concerns the stimulation of different functional zones within the GPi as observed in GPi-stimulated patients with Parkinson’s disease, where activation of lower contacts may lead to pronounced improvement in levodopa-induced dyskinesias but development of akinesia (Krack et al., 1998). In contrast, stimulation of more dorsal contacts may lead to moderate improvements of akinesia and may even induce dyskinesias in some patients.

In our descriptive imaging analysis, the “sweet spot” for dystonia reduction with chronic stimulation was located only few millimetres above the ventral border of posteroventrolateral GPi, and in proximity of the medial medullary lamina. This ideal target for stimulation coincides with previously published coordinates from two imaging studies (Cheung et al., 2014; Schönecker et al., 2015) and one neurophysiological study using local field potential recordings (Neumann et al., 2017). In addition to confirming this sweet spot, the “hot spot” of stimulation potentially responsible for the advent of parkinsonian bradykinesia and axial motor symptoms, was assessed. Clusters for bradykinesia, axial motor symptoms, and hemiparkinsonism, according to a composite score out of tremor, bradykinesia, and rigidity, largely overlapped with the sweet spot but tended to be located more inferiorly, medially and anteriorly. This finding allows for two possible interpretations: 1. Stimulation of the neural elements within the GPi that are responsible for alleviation of dystonia are also responsible for the induction of parkinsonian symptoms, both most likely attributable to altered outflow activity of pallido-thalamo-cortical pathways. 2. Different functional neural elements within the GPi are responsible for the two potential effects. The observation that not all GPi DBS dystonia patients had high MDS-UPDRS motor scores would speak to this second hypothesis. Moreover, decreasing amplitude of stimulation, moving the stimulation field towards higher contacts, or lower frequency of stimulation, have been showed to potentially help decrease parkinsonian symptoms (Ba et al., 2016; Berman et al., 2009; Schrader et al., 2011; Tisch et al., 2007). This may, however, come at the cost of partially losing dystonic symptom control. Another recent study found that high-frequency stimulation led to a deterioration in a finger tapping task as compared with no and low frequency stimulation, thus suggesting a frequency-specific modulation of hand motor function in pallidal DBS (Huebl et al., 2015). In our sample the advent of parkinsonian features was independent from
clinical variables such as dystonia severity and amplitude of stimulation. Future interventional studies should systematically assess the potential of changing stimulation parameters such as employing low frequency stimulation of 60–100Hz, manipulating pulse width, directional stimulation with novel, commercially available DBS leads in preventing or alleviating parkinsonism. Interestingly, subthalamic DBS has also been successfully employed in dystonia patients (Cao et al., 2013; Ostrem et al., 2011, 2016). These studies, however, were rather small and did not include an assessment of parkinsonism. Whether STN-DBS in dystonia patients can provoke dyskinesia also requires careful study.

There are some limitations that should be taken into account when interpreting the findings of our study. There was no preoperative assessment of parkinsonism in our dystonia patients, and the temporal course of the advent of parkinsonian signs due to GPi-DBS in dystonic patients remains unknown. Nevertheless, the use of a comparable control group with blinded assessment confirms that troublesome parkinsonian signs occur frequently in many dystonia patients under pallidal stimulation after some years of stimulation. Also, most but not all dystonia patients tolerated switching stimulation off in order to examine whether parkinsonian signs were alleviated. However, those evaluated for this sub-analysis were not different in any of the characteristics compared with those not being switched off. Lastly, we did not adjust analysis for multiple comparisons as this was a hypothesis-driven study in a small (but considering the disease and the treatment still considerable) sample of patients. Strengths of our study include the standardized and multimodal approach of our study in a large group of dystonia patients. Of note, torticollis severity was still improved by 32% as compared with the preoperative status, in line with improvements seen after 6 months of open label stimulation in recent randomized controlled trials (Volkmann et al., 2014). These findings underline the representativeness of our cohort of patients with cervical dystonia treated with long-term pallidal DBS.

In summary, parkinsonian signs, particularly bradykinesia and axial motor signs due to pallidal stimulation in dystonic patients are frequent and negatively impact on motor functioning and quality of life. Therefore, patients under pallidal stimulation should be monitored closely for such signs both in clinical routine and future clinical trials. Spread of current outside the GPi is an unlikely explanation for this phenomenon, which seems to be caused by stimulation of neural elements within the stimulation target volume. Future
Interventional studies should systematically look into the effect of switching active contacts, manipulating frequency and/or pulse width of stimulation, or using directional stimulation strategies with regard to the prevention or alleviation of parkinsonian signs in dystonia patients under pallidal DBS.

**Funding**

This study was funded by a grant from the Brain Research Trust (BRT). The Unit of Functional Neurosurgery, UCL Institute of Neurology, Queen Square, London is also supported by the Parkinson's Appeal and the Sainsbury Monument Trust. This work was done both at UCL and UCL Hospitals NHS Trust and was funded in part by the Department of Health National Institute for Health Research Biomedical Research Centres funding scheme. PM was supported by a research grant from the Austrian Society of Neurology.
**Table 1: Baseline characteristics including questionnaire-based assessments**

<table>
<thead>
<tr>
<th></th>
<th>CD controls</th>
<th>GPI-DBS CD (On stimulation)</th>
<th>Z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at assessment (y)</td>
<td>60.0 (52.0–68.3)</td>
<td>63.0 (56.0–68.0)</td>
<td>-0.7</td>
<td>0.487</td>
</tr>
<tr>
<td>Sex (n female/male)</td>
<td>17/5</td>
<td>19/10</td>
<td></td>
<td>0.536</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>16.0 (9.0–30.0)</td>
<td>18.0 (11.5–27.5)</td>
<td>-0.2</td>
<td>0.827</td>
</tr>
<tr>
<td>Stimulation duration (y)</td>
<td>NA</td>
<td>5.0 (2.0–7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinumtoxin treatment (n)</td>
<td>22</td>
<td>6</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Antidystonic oral medications (n)</td>
<td>5</td>
<td>13</td>
<td></td>
<td>0.180</td>
</tr>
<tr>
<td>TWSTRS-TSS</td>
<td>12.0 (8.8–15.5)</td>
<td>11.0 (5.5–14.5)</td>
<td>-1.2</td>
<td>0.229</td>
</tr>
<tr>
<td>TWSTRS Disability</td>
<td>7.0 (5.0–10.3)</td>
<td>4.5 (1.0–10.3)</td>
<td>-1.9</td>
<td>0.0620</td>
</tr>
<tr>
<td>TWSTRS Pain</td>
<td>5.4 (3.7–9.6)</td>
<td>3.5 (0.0–11.5)</td>
<td>-1.3</td>
<td>0.211</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>6.0 (6.0–7.0)</td>
<td>5.0 (5.0–6.0)</td>
<td>-2.9</td>
<td>0.0032</td>
</tr>
<tr>
<td>FOG Quest</td>
<td>1.0 (0.0–3.5)</td>
<td>4.0 (1.0–8.8)</td>
<td>-2.3</td>
<td>0.0240</td>
</tr>
<tr>
<td>MDS-UPDRS M-EDL</td>
<td>5.0 (2.5–7.0)</td>
<td>8.5 (2.8–13.5)</td>
<td>-1.9</td>
<td>0.0518</td>
</tr>
</tbody>
</table>

Results are reported in medians (25th–75th percentile). Higher scoring on all scales given indicate worse outcome. Two-sided Mann-Whitney U test was used to calculate significance levels of comparisons between the GPI-DBS and the control group for continuous variables and the chi-square test for categorical variables.

Abbreviations: CD = Cervical Dystonia; EQ-5D-3L = European Quality of Life, 5 dimensions, 3 level version; GPI-DBS = Deep Brain Stimulation of the Globus Pallidus internus; M-EDL = motor experiences of daily living; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; TWSTRS-TSS = Toronto Western Spasmodic Torticollis Rating Scale – Torticollis Severity Scale.
### Table 2: Impact of parkinsonian symptoms on quality of life

<table>
<thead>
<tr>
<th></th>
<th>Spearman correlation coefficient</th>
<th>p-Value</th>
<th>OR (95%CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-UPDRS motor score</td>
<td>0.383</td>
<td>0.0085</td>
<td>4.4 (1.9–10.0)</td>
<td>0.0005</td>
</tr>
<tr>
<td>MDS-UPDRS motor score without tremor</td>
<td>0.353</td>
<td>0.0160</td>
<td>3.1 (1.5–6.5)</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

Both spearman rank correlation and ordinal regression analysis and were adjusted for age, sex, disease duration, cervical dystonia severity, and treatment group. OR are given for 1 level higher Quality of Life (EQ5D-3L) score per doubling MDS-UDPRS motor score and MDS-UPDRS derived scores. Abbreviations: 95%CI = 95% confidence interval; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; OR = Odds Ratios

### Table 2: Impact of parkinsonian symptoms on quality of life

<table>
<thead>
<tr>
<th></th>
<th>Beta-coefficient (95%CI)</th>
<th>Significance</th>
<th>Overall r²</th>
<th>r² for single factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-UPDRS motor score</td>
<td>0.052 (0.011–0.093)</td>
<td>p=0.0146</td>
<td>0.410</td>
<td>0.109</td>
</tr>
<tr>
<td>MDS-UPDRS rigidity</td>
<td>-0.091 (-0.524–0.341)</td>
<td>p=0.671</td>
<td>0.305</td>
<td>0.004</td>
</tr>
<tr>
<td>MDS-UPDRS bradykinesia</td>
<td>0.081 (0.016–0.145)</td>
<td>p=0.0154</td>
<td>0.408</td>
<td>0.107</td>
</tr>
<tr>
<td>MDS-UPDRS axial</td>
<td>-0.107 (-0.007–0.211)</td>
<td>p=0.0647</td>
<td>0.365</td>
<td>0.064</td>
</tr>
<tr>
<td>MDS-UPDRS tremor</td>
<td>0.414 (0.034–0.794)</td>
<td>p=0.0337</td>
<td>0.385</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Linear regression analysis adjusted for age, sex, disease duration, cervical dystonia severity, and treatment group was carried out to calculate B-coefficients, significances and r². B-coefficients are reported per 1 Unit change in respective MDS-UPDRS and MDS-UPDRS-derived scores. Abbreviations: MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale.
Table 3: Linear regression analysis on potential factors driving the occurrence of parkinsonian symptoms

<table>
<thead>
<tr>
<th></th>
<th>MDS-UPDRS motor scores</th>
<th>MDS-UPDRS Rigidity</th>
<th>MDS-UPDRS Bradykinesia</th>
<th>MDS-UPDRS Axial</th>
<th>MDS-UPDRS Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>0.08</td>
<td>0.01</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>(-0.12 – 0.29)</td>
<td>(-0.02 – 0.02)</td>
<td>(-0.10 – 0.16)</td>
<td>(-0.01 – 0.14)</td>
<td>(-0.07 – 0.02)</td>
</tr>
<tr>
<td></td>
<td>p=0.412</td>
<td>p=0.916</td>
<td>p=0.672</td>
<td>p=0.0937</td>
<td>p=0.198</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>0.11</td>
<td>0.04</td>
<td>0.03</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>(-0.06 – 0.28)</td>
<td>(-0.02 – 0.01)</td>
<td>(-0.09 – 0.14)</td>
<td>(-0.02 – 0.10)</td>
<td>(0.02 – 0.09)</td>
</tr>
<tr>
<td></td>
<td>p=0.182</td>
<td>p=0.644</td>
<td>p=0.637</td>
<td>p=0.190</td>
<td>p=0.0013</td>
</tr>
<tr>
<td><strong>Pallidal DBS vs. no DBS</strong></td>
<td>9.44</td>
<td>0.32</td>
<td>7.54</td>
<td>2.19</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>(5.45 – 14.42)</td>
<td>(-0.10 – 0.74)</td>
<td>(4.91 – 10.12)</td>
<td>(0.74 – 3.64)</td>
<td>(-1.76 – 0.02)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p=0.128</td>
<td>p&lt;0.0001</td>
<td>p=0.0038</td>
<td>p=0.0222</td>
</tr>
</tbody>
</table>

Abbreviations: DBS = Deep Brain Stimulation; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale

Linear regression analysis including age, disease duration, and group assignment was carried out to calculate B-coefficients (95% confidence intervals) and significances. B-coefficients were given for a 1-point/unit change in respective measures.
Figure 1. Differences in clinical assessments in the GPi-DBS treated patients versus control patients. Comparisons are made with a two-sided Mann-Whitney U test. Abbreviations: DBS = Deep Brain Stimulation; GPi = globus pallidus internus; MDS-UPDRS-III = Movement Disorder Society Unified Parkinson’s Disease Rating Scale motor section; TWSTRS-TSS = Toronto Western Spasmodic Torticollis Rating Scale – Torticollis Severity Scale. For numerical data please see supplementary table 1.
Figure 2. Differences in clinical assessments in the GPi-DBS treated cases on versus off stimulation (n=19). Comparisons are made with the two-sided, paired Wilcoxon signed rank test. The median change was calculated within each individual as measurements were paired.

Abbreviations: DBS = Deep Brain Stimulation; MDS-UPDRS-III = Movement Disorder Society Unified Parkinson’s Disease Rating Scale motor section; TWSTRS-TSS = Toronto Western Spasmodic Torticollis Rating Scale - Torticollis Severity Scale. For numerical data please see supplementary table 2.
Figure 3. Mapping of dystonia improvement and parkinsonian symptoms apparent upon chronic GPi stimulation are illustrated superimposed on sagittal (1st column), coronal (2nd column), and axial (3rd column) sections of the standard atlas of the Montreal Neurological Institute (MNI). The green area represents the mean volume of tissue activated across the entire group. The sweet spot for dystonia improvement (red, 1st and 5th row) is located in the posterolateral ventral GPi. The cluster for bradykinesia (cyan, 2nd row) and axial motor symptoms (black, 3rd row)
to a composite scores out of tremor, bradykinesia, and rigidity (blue 4th row) overlap with the sweet spot but tend to be located more inferiorly, medially, and anteriorly.
### Supplementary table 1: Clinical assessments in the GPi-DBS treated versus control patients.

<table>
<thead>
<tr>
<th></th>
<th>CD controls</th>
<th>GPi-DBS CD (On stimulation)</th>
<th>Z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWSTRS-TSS</td>
<td>12.0 (8.8–15.5)</td>
<td>11.0 (5.5–14.5)</td>
<td>-1.2</td>
<td>0.229</td>
</tr>
<tr>
<td>MDS-UPDRS Total</td>
<td>3.0 (2.0–8.0)</td>
<td>14.0 (8.0–19.5)</td>
<td>-4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDS-UPDRS Rigidity</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–1.0)</td>
<td>-1.6</td>
<td>0.117</td>
</tr>
<tr>
<td>MDS-UPDRS Bradykinesia</td>
<td>2.0 (0.0–3.0)</td>
<td>8.0 (6.0–14.0)</td>
<td>-4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDS-UPDRS Axial</td>
<td>0.0 (0.0–1.0)</td>
<td>2.0 (1.0–4.0)</td>
<td>-3.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>MDS-UPDRS Tremor</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–0.5)</td>
<td>1.7</td>
<td>0.0973</td>
</tr>
</tbody>
</table>

Results are reported in medians (25th–75th percentile). Two-sided Mann-Whitney U test was used to calculate significance levels of comparisons between the GPi-DBS and the control group. **P-Values in bold are below the Bonferroni-adjusted level of significance of <0.0084.**

Abbreviations: CD = Cervical Dystonia; EQ-5 = European Quality of Life

GPi-DBS = Deep Brain Stimulation of the Globus Pallidus internus; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale – Torticollis Severity Scale.
Supplementary table 2: Differences in clinical assessments in the Gpi-DBS treated cases On versus Off stimulation (n=19)

<table>
<thead>
<tr>
<th></th>
<th>Gpi-DBS CD</th>
<th>Gpi-DBS CD</th>
<th>Median Change</th>
<th>Z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On stimulation</td>
<td>Off stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n assessed</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWSTRS-TSS</td>
<td>9.0 (5.0–15.0)</td>
<td>15.0 (7.0–19.0)</td>
<td>2.0 (-7.0–0.0)</td>
<td>-2.6</td>
<td>0.0092</td>
</tr>
<tr>
<td>MDS-UPDRS Total</td>
<td>14.0 (8.0–19.5)</td>
<td>10.0 (6.0–14.0)</td>
<td>-2.0 (0.0–5.0)</td>
<td>2.7</td>
<td>0.0073</td>
</tr>
<tr>
<td>MDS-UPDRS Rigidity</td>
<td>0.0 (0.0–1.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>-0.1</td>
<td>0.915</td>
</tr>
<tr>
<td>MDS-UPDRS Bradykinesia</td>
<td>8.0 (6.0–14.0)</td>
<td>8.0 (4.0–10.0)</td>
<td>-1.0 (0.0–4.0)</td>
<td>-2.5</td>
<td>0.0117</td>
</tr>
<tr>
<td>MDS-UPDRS Axial</td>
<td>2.0 (1.0–4.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>-1.0 (0.0–2.0)</td>
<td>-2.8</td>
<td>0.0045</td>
</tr>
<tr>
<td>MDS-UPDRS Tremor</td>
<td>0.0 (0.0–1.0)</td>
<td>0.0 (0.0–1.0)</td>
<td>0.0 (-1.0–0.0)</td>
<td>-0.2</td>
<td>0.829</td>
</tr>
</tbody>
</table>

Results are reported in medians (25th–75th percentile). Two-sided, paired Wilcoxon signed rank test was used to calculate significance levels of comparisons between on versus off stimulation. **P-values in bold** are below the Bonferroni-adjusted level of significance of <0.0084.

Abbreviations: CD = Cervical Dystonia; Gpi-DBS = Deep Brain Stimulation of the Globus Pallidus internus; MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale - Torticollis Severity Scale.
Supplementary table 3: Thresholds for motor evoked potentials

<table>
<thead>
<tr>
<th></th>
<th>Resting motor thresholds</th>
<th>Active motor thresholds</th>
<th>Significance (Z-score, P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contralateral OOr</strong></td>
<td>6.0 (4.5–8.0)</td>
<td>4.0 (3.5–6.0)</td>
<td>-4.4 &lt;0.0001</td>
</tr>
<tr>
<td><strong>Contralateral FDI</strong></td>
<td>8.5 (6.5–9.0)</td>
<td>4.5 (4.0–8.0)</td>
<td>-4.2 &lt;0.0001</td>
</tr>
<tr>
<td><strong>Z-value</strong></td>
<td>-3.4</td>
<td>-2.2</td>
<td></td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0006</td>
<td>0.0295</td>
<td></td>
</tr>
</tbody>
</table>

Two-sided, paired Wilcoxon signed rank test was used to calculate significances.

Abbreviations: FDI = first dorsal interosseous muscle; OOr = orbicularis-oris muscle.

Results are reported in medians (25\textsuperscript{th} - 75\textsuperscript{th} percentile)
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Zauber SE, Watson N, Comella CL, Bakay R a E, Metman LV. Stimulation-induced parkinsonism after posteroven