ARTICLE

Bilateral globus pallidus stimulation for severe Tourette syndrome – a double-blind, randomized crossover trial

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Summary

Background

Deep brain stimulation (DBS) has been proposed as a treatment option for severe Tourette syndrome (TS), based on open-label series and blinded data from a small number of individuals. This study aimed to further evaluate the safety and efficacy of bilateral globus pallidus internus (GPi) DBS in this patient group.

Methods

In this randomized, double-blind, crossover trial, eligible patients (severe medically refractory TS, aged ≥20 years old) were recruited from 2 tertiary movement disorders clinics in the UK, received GPi DBS surgery, then were randomly assigned (1:1) to either "stimulation-ON first" or "stimulation-OFF first" for a three-month period followed by a switch to the opposite condition for a further three-month period. Neither patients nor rating clinicians were aware of their computer-generated treatment allocation. An unmasked clinician was responsible for programing the stimulation. The primary endpoint was the difference in Yale Global Tic Severity Scale (YGTSS) total score between the two blinded conditions using repeated measures ANOVA. After completing the double-blind crossover period, patients continued to have open-label stimulation adjustments and objective assessments of tic severity until database lock one month after the final patient's final trial related visit. The trial was registered with ClinicalTrials.gov, number NCT01647269.

Findings

Data were collected between August 2011 and December 2014. Of the 15 patients enrolled, 13 patients completed the double-blinded period. The mean YGTSS total score was 87·9 (SD 9·2) at baseline, 80·7 (SD 12·0) with DBS OFF and 68·3 (SD 18·6) with DBS ON. Repeated measures ANOVA revealed a significant interaction between timepoint and YGTSS total scores (Wilks Lamba =0·45, F(2,11)= 6·6, p=0·013). Pairwise comparisons in YGTSS total scores after Bonferroni correction were significantly lower at the end of the ON

compared to the OFF blinded stimulation condition with a mean improvement of 12·4 points (95% CI 0·10- 24·7, p=0·048) equivalent to 15·3%. Between trial commencement and database lock, 3 serious adverse events were observed; 2 DBS hardware infections, (2 & 7 weeks post-operatively) & 1 episode of DBS induced hypomania, during the blinded ON stimulation phase, all of which resolved with treatment.

Interpretation
Globus pallidus stimulation led to a significant improvement in tics during the ON compared to the OFF blinded condition, with an overall acceptable safety profile. Future research should concentrate on identifying the most effective deep brain stimulation target to control both tics and associated comorbidities, and further clarify those factors predicting individual patient responses to this treatment option.

Funding
This was an investigator-initiated study with funding provided through UK National Health Service (NHS) Individual Funding Requests.

Keywords: Tourette's syndrome, deep brain stimulation, randomized controlled trial, globus pallidus internus.

Introduction

The clinical hallmark of Tourette syndrome (TS) is the presence of multiple motor and vocal tics, often preceded by premonitory sensations or urges and frequently complicated by neurobehavioral comorbidities, including attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), impulse control disorder, self-injurious behaviour (SIB), as well as personality and mood disorders.[1–3]

The majority of TS patients experience a pre-pubertal increase in tic severity, followed by a remission towards late adolescence or early adulthood. Nevertheless, a significant number of patients may continue to experience disabling symptoms in adulthood and require lifelong treatment.[4] Behavioural therapies, alpha-2 adrenergic agonists, antipsychotic agents, anticonvulsant drugs, benzodiazepines, and botulinum toxin injections may all offer some symptomatic relief.[2,3] Nevertheless in a proportion of patients, these approaches are insufficiently effective or accompanied by intolerable side effects and among this group there remain a number of *severely* affected patients for whom surgical approaches such as deep brain stimulation (DBS), may present an alternative treatment option.[5]

The first report of DBS for the treatment of refractory TS was published in 1999 by Vandewalle et al, targeting the same thalamic nuclei, (i.e. centromedian /parafascicular complex -CM/Pf, and ventral oral internus nuclei) which were subject to stereotactic ablation by Hassler & Dieckmann in the 1970s.[6,7] Since then, various areas of the brain have been targeted by DBS including the centromedian–parafascicular complex of the thalamus, the subthalamic nucleus, nucleus accumbens and anterior limb of the internal capsule, and the globus pallidus internus and externus, providing variable but generally positive results.[5]

Supportive evidence is however mostly based on case reports or in small case series typically in non-blinded studies involving limited number of patients. Open-label beneficial effects of DBS targeting the CM/Pf thalamic nuclei have been partially supported by two small randomized trials including 5 and 6 patients respectively, but have raised significant issues about the safety and tolerability of this target.[8–10]

There is extensive evidence for the efficacy of GPi DBS in other hyperkinetic movement disorders, L-dopa induced dyskinesia, or various forms of dystonia that support the use of GPi as an attractive alternative target for DBS in TS.[11,12] In a series of 3 patients comparing bilateral thalamic and bilateral anteromedial GPi stimulation, combined and sham

stimulation, Welter and co-workers demonstrated an advantage of anteromedial GPi DBS that was sustained for 20–60 months of follow-up.[13] Further open-label studies have also suggested that GPi DBS might be a promising therapeutic alternative for severe medically refractory TS with an acceptable safety profile.[14–16]

However, there remain a number of unanswered questions regarding DBS for TS including; the objective demonstration of its efficacy on different aspects of TS, the factors that predict individual patient responsiveness, as well as the methods for deriving optimal stimulation parameters, and the precise optimal choice of brain target. Thus, DBS for TS is still considered as an experimental approach. Well-designed randomized double-blind trials, involving a multi-disciplinary team approach are needed to help address these questions. In the current trial, we assessed the clinical efficacy and safety of bilateral GPi DBS in a cohort of 15 patients with treatment refractory, severe TS, using a randomized, double-blind, crossover design followed by ongoing open-label evaluation.

Methods

Patients

Patients were eligible for inclusion if they were adults with stable Tourette's syndrome; had chronic and severe tic disorder with severe functional impairment in Yale Global Tic Severity Scale (YGTSS) of at least 35/55 for at least 12 months prior to surgery; had failed conventional medical treatment at therapeutic doses of three classes of medication; behavioural intervention had been considered inappropriate or had been unsuccessful; had optimised treatment of co-morbid conditions for at least 6 months; and were compliant with any psychosocial interventions/ with surgical treatment plans. The exclusion criteria were: tic disorder attributable to another condition; presence of other medical or psychiatric disorders that might increase the risk of the procedure; psychosocial factors which might impede operative/post-operative care and research participation; coagulation problems; other disease compromising life expectancy; still likely to benefit from psychological intervention; pregnancy; age < 20 years.

Study design

The study was sponsored by University College London, and was conducted in two academic centres in the UK (UCL Institute of Neurology, London and Salford Royal NHS Foundation Trust, Manchester). The study was designed to compare tic severity during 3 months "ON-stimulation" with 3 months "OFF-stimulation" in a randomized double-blind, sham stimulation controlled, crossover manner. The trial conformed to the Declaration of Helsinki, Good Clinical Practice guidelines, and was approved by the ethics committees at participating centres. All patients provided written informed consent before enrolment. The trial was registered with ClinicalTrials.gov, number NCT01647269.

Procedures

Each patient was screened for eligibility at a multidisciplinary evaluation, including assessment by at least one neurologist, functional neurosurgeon, neuropsychiatrist and neuropsychologist (figure 1). All patients underwent a baseline assessment, followed four weeks later by stereotactic implantation of bilateral DBS electrodes (model 3387 or 3389, Medtronic, Minneapolis, MN, USA) into the GPi. In London, implantation of bilateral DBS electrodes was guided by individual targeting on stereotactic proton density MRI, visualizing the individual pallidal target. A Leksell stereotactic frame was used, without microelectrode recording and with immediate postoperative stereotactic MRI to document electrode location in relation to the patient's individual anatomy. All patients were operated under general anaesthesia. Full details of this neurosurgical procedure have been published previously.[17,18] In Salford, target verification was confirmed using MR imaging of bilateral plastic stylettes prior to the insertion of the final DBS electrodes that followed the same trajectory.[19] All patients received Activa® PC, (Medtronic, Minneapolis, MN, USA) implantable pulse generators (IPGs).

All participants were scheduled for a first post-operative assessment six weeks following DBS implantation. Following this assessment, patients were screened for the effects of stimulation. Stimulation parameters were adjusted during a one-week un-blinded period. The optimal settings were determined by using the most effective parameters on tics with the lowest energy, without causing side effects. Patients were then randomly assigned in pairs to “stimulation-ON first” or “stimulation-OFF first”, for the subsequent three months, following which they would switch to the opposite condition. The patients were routinely contacted at least once monthly and intermediate blinded adjustments/ pseudo-adjustments were performed by a non-blinded member of the trial team, as instructed by the blinded clinician according to tic control/reported side effects. Detailed assessments were scheduled at the end of each of the three-month blinded periods (figure 1).

At the end of the blinded trial period patients were given the option of having their stimulators permanently switched ON. Patients were invited to routine follow-up and assessed in an open-label fashion at least every 6 months until database lock, with further adjustments to their stimulation parameters made as necessary.

Formal assessments were performed at each visit as per trial protocol by a clinician blinded to stimulation status, and included the completion of the following scales: Yale Global Tic Severity Scale (YGTSS), Yale-Brown Obsessive Compulsive scale (Y-BOCS), Modified Rush Video Rating Scale (MRVRS), Diagnostic Confidence Index (DCI), MOVES scale, and Tourette Quality of Life Scale (GTS-QOL). They also completed the Beck Depression inventory (BDI), the State-Trait Anxiety Index (STAI), the Neuropsychiatric Inventory (NPI) as well as a battery of neuropsychological tests; the California Verbal Learning test (CVLT), Recognition memory for faces (RMF), Verbal fluency, Trail Making test B (TMT-B), Stroop interference test, Letter Cancellation test, Paced Auditory Serial Addition test (PASAT), Corsi blocks. Adverse events were systematically recorded throughout the trial.

Randomization and masking

Participants were randomly assigned to either “stimulation-OFF first” during which they received no stimulation, or “stimulation-ON first”. Computer-generated pairwise randomization was performed according to order of enrolment so that comparable numbers of patients were recruited to receive each condition first. The randomization sequence was generated by the chief investigator and only revealed to the unblinded clinician responsible for the programming of the stimulation. The patients and the clinicians directly involved in the scoring were not aware of the condition of stimulation. The unblinded clinician responsible for the DBS programming spent the same time adjusting the stimulator of the patients at the start of the ON or OFF-stimulation periods. Adjustment/ pseudo-adjustments were performed in an identical manner during both blinded phases based on instruction from the blinded clinician that response to treatment was sub-optimal and using increments of 0·1-0·2V. The electrical parameters were selected to avoid side effects and amplitudes gradually increased at the start of the ON period to avoid any sensation of stimulation being perceived by the patients.

Outcome measures

The pre-specified primary end point was the difference in tics between the two blinded stimulation conditions including all individuals that completed both blinded phases, as assessed using the YGTSS total score. Pre-specified secondary outcomes were change in the following validated scales: Y-BOCS, GTS-QOL, BDI, NPI, STAI and the battery of neuropsychological tests in OFF- versus ON-stimulation conditions. Additional post-hoc analyses were performed to evaluate the impact of surgery on tic severity prior to stimulation; to compare changes in MRVRS, MOVES scale, motor and vocal tic and impairment subscores of the YGTSS and to assess the change between baseline and open-label assessments among all patients utilising the latest available open-label follow-up.

Statistical Analysis
The sample size of this study was based on practical considerations, given that available data with regards to efficacy/variance of pallidal DBS for Tourette's syndrome were insufficient to enable a formal power calculation. Raw scores for the primary endpoint for each recruited patient are presented to maximise transparency of the range of outcomes. The primary and secondary endpoints were compared at baseline, OFF– and ON-stimulation using repeated measures ANOVA. Pairwise comparisons (with Bonferroni correction) were performed for those endpoints with significant main effects of timepoint. The effect of randomisation sequence on the difference between blinded ON and OFF YGTSS scores was compared using an unpaired t test. Post hoc comparisons of baseline against open label scores were performed using paired t tests. All data were analysed using Statistical Package for the Social Sciences version 21·0 software (SPSS, Chicago, IL, USA).

Funding
This was an investigator-initiated study with no commercial sponsorship or funding. Funding for DBS procedures was sought from each individual's National Health Service (NHS) primary care trust using individual funding requests in advance of the surgery. The NHS had no role in the design, data collection, analysis or interpretation of the trial or the writing of the report. All authors had full access to all of the data. Dr Foltynie had responsibility for the final decision to submit the report for publication.

Results
Study population
Of 18 patients assessed for eligibility, 15 patients (11 male, mean age 34·7) were enrolled (figure 2). Table 1 summarizes their clinical characteristics.

DBS Surgery
All DBS procedures were performed between August 2011 and April 2014. Thirteen patients had bilateral electrodes in the anteromedial GPi. Two patients with concurrent dystonia/dystonic tics had bilateral electrodes placed slightly more posteriorly towards the posteroventral GPi aiming to maximise improvement in their dystonia while still adhering to the trial protocol, and given the absence of evidence regarding which subregion of the GPi may be most effective for tic suppression (figure 3).

Protocol withdrawals/deviations
Two patients withdrew from the ON/OFF blinded crossover phase of the trial, one before and one soon after randomization, because of their concerns of the additional delay in potential therapeutic effects associated with the crossover period. In accordance with their ethics committee approved trial consent, both immediately received open-label continuous stimulation. Thirteen patients completed the randomization period; 6 randomly assigned to "stimulation-ON first" and 7 to "stimulation-OFF first" (figure 2). Three of these had protocol deviations, including 1 patient withdrawing from the blinded phase of the trial 1 month early due to increased anxiety associated with the blinding, and 2 patients having incomplete assessments at trial visits due to patient fatigue. Two patients had medication changes during the 6 months of the blinded protocol (1 patient had initiation of diazepam 5mg and fluoxetine 20mg halfway during stimulation-ON period and continued during stimulation-OFF period due to exacerbation of anxiety, and a second patient discontinued haloperidol during stimulation-OFF period due to intolerance of pre-existing sedative side effects).

Efficacy of stimulation – Primary outcome YGTSS
Table 2 presents the individual and mean YGTSS total scores for all 15 patients. Repeated measures ANOVA revealed a significant interaction between timepoint and YGTSS total scores (Wilks Lamba =0·45, $F(2,11)= 6·6$, $p=0·013$). Pairwise comparisons of YGTSS total scores after Bonferroni correction confirmed significantly lower scores at the end of stimulation-ON blinded period in comparison to the end of the stimulation-OFF blinded

period (n=13) with a mean improvement of 12·4 points (95% CI 0·1-24·7, p=0·048), equivalent to 15·3%.

Additional pair-wise comparisons between baseline and OFF stimulation showed an improvement of 7·2 points (95% CI -0·2 – 14·7) of marginal significance (p=0·059 after Bonferroni correction), while between baseline and ON stimulation confirmed an improvement of 19·6 points (95% CI 5·0-34·3, p=0·009 after Bonferroni correction). There was no between group difference in the primary outcome according to the sequence of the randomization (t= 0.023, p=0.98).

Efficacy of stimulation- Pre-specified Secondary Outcomes

There was a significant effect of timepoint on GTS-QOL and CVLT immediate recall scores (Table 3) but no significant differences comparing blinded ON vs OFF stimulation scores after Bonferroni correction (GTS-QOL (p=1.0), CVLT immediate recall (p=0.07)). There were no other significant changes in other secondary outcomes comparing baseline, blinded ON and OFF stimulation timepoints.

Post hoc analyses

Seven patients had an improvement in tic severity based on the 6 week post-operative, pre-stimulation assessment possibly indicating a residual microlesion effect of the surgery (Table 2.) In the blinded period comparison of the sub-items of the YGTSS, there was a significant effect of timepoint for the mean motor tic, vocal tic and impairment sub-scores, but only the motor subscore remained significant in the ON compared to the OFF condition after Bonferroni correction (p=0.039). There was also a significant effect of timepoint in the mean MRVRS observed and unobserved scores, together with a significant improvement in the ON compared to OFF condition in the mean observed MRVRS score (p=0.031)(table 3).

Beyond the blinded crossover trial period, all 13 patients opted to have their stimulators permanently switched-ON and (alongside the 2 patients who withdrew from the blinded phase of the trial) were followed on an open-label basis for a mean of 16·7 months (range 8-36) post-operatively. Open-label YGTSS total scores (n=15) at latest follow up were reduced by 40·1% compared with baseline (mean score 51·5 *vs* 87·9, p<0·0001) (table 2). At this timepoint, all secondary outcome measures were also significantly improved except Y-BOCS and STAI (table 3).

Optimising stimulation parameters

During the blinded period, electrical stimulation was delivered as single monopolar stimulation in 9 patients and as double monopolar stimulation in the remaining 4. The stimulation amplitudes were deliberately constrained to avoid unblinding ON/ OFF status during this period. During the subsequent open-label period, stimulation was further adjusted to achieve maximal symptom control, including further titrations of voltage, pulse-width and frequency, the addition of contacts in 3 patients, and complete change of active contacts in 4 patients. For DBS parameters- See Supplementary material.

Adverse events

Surgery was well tolerated and all patients were ambulatory within 24h. Adverse events were recorded until database lock (mean period of 16·7 months (range 8-36). Three serious adverse events (20%) were reported of which 2 were surgery related and 1 was stimulation related. Patients 3 and 7 developed infection of the DBS hardware which necessitated the removal of leads, extension cables and IPG and administration of antibiotics. Both patients opted to re-enter the trial and were re-implanted 22 months and 6 months post initial operation and completed the trial protocol as above. One patient experienced deterioration of tics and hypomanic behaviour during the ON-stimulation condition. Hospital admission was necessary, following re-screening and alteration of stimulation settings accompanied by addition of medications. Over the whole study period, including the open-label extension of

the study, an additional 23 adverse events occurred in 10 patients, 15 of which resolved (table 4).

Discussion

In this double-blind, crossover trial of 15 patients with severe medically refractory TS, globus pallidus stimulation led to a significant improvement in tics during the ON compared to the OFF blinded condition, with an overall acceptable safety profile. There was a wide range of improvements observed during the rigorous double-blind evaluation with greater consistency following the initiation of open-label stimulation adjustment. To our knowledge, this is the largest double-blind trial of DBS in TS patients published to date, although we are aware that other teams are also evaluating this potential target in this population.

The modest improvement we observed in the mean YGTSS and video-based tic counts during the blinded phase of the trial, was not reflected in a significant improvement in mean quality of life (GTS-QOL) scores or any of the co-morbid psychiatric conditions assessed. However, long-term open-label assessment of the patients revealed further mean improvement in tics (40·1%) compared with pre-operative baseline, and at latest follow-up, continuous GPi stimulation led to a significant mean improvement (38·9%) in quality of life. Mood, assessed by BDI also significantly improved, whereas only modest, non-significant effects were seen in obsessive compulsive behaviours (Y-BOCS), and anxiety (STAI). Greater improvements were seen in motor compared with vocal tics in blinded evaluations, although efficacy was similar for tic subtypes in the open-label analysis.

The individual patient responses were presented to maximise transparency; in 6 patients there was no clear benefit from stimulation during the blinded phase of the trial (< 10% improvement in YGTSS). In the majority of these individuals, a clear improvement was obvious in open-label assessment following further changes of the stimulation parameters which was consistently contact-specific and reproducible. This is an issue for DBS related trials, where adjusting the stimulation while maintaining treatment blinding can compromise the identification/use of optimal settings therefore suboptimal stimulation parameters may be used out of necessity. In addition, anxiety associated with uncertainty whether stimulation was switched ON or OFF, was a particular issue in some patients, which could also at least partly explain the more limited effect in patients' quality life during the blinded period. The additional contribution of a transient/persisting post-operative microlesion effect impacting on subsequent ON verses OFF stimulation YGTSS assessments in certain patients, cannot be excluded.

During open-label optimisation of the stimulation, there were clear improvements in quality of life considering the group as a whole. Nevertheless, four patients had less than 20% improvement in YGTSS scores compared with baseline without obvious explanation. A complex interplay between severity and chronicity of tics on an individual's learned behaviour, comorbid psychiatric symptoms, stimulation related side effects, and also patients' expectations may explain the variability of response to stimulation in these patients.

Most patients responded to average stimulation parameters comparable to those used in Parkinson's disease, with higher levels of stimulation sometimes having a negative impact. However, in several patients, and in those showing good response patterns in particular, progressive increases in amplitude of stimulation and number of active contacts was necessary over time. This raises a concern that tolerance to stimulation may occur and also of accelerated battery depletion, both important issues for the long-term care of this relatively young population of patients. Of note is that the most dorsal contacts on the electrodes were frequently associated with optimal tic responses possibly indicating that stimulation of the globus pallidus externus (GPe) might be involved in the mechanism of tic relief.[20]

To date, the thalamic DBS target probably remains the best explored in TS.[8–10,21–24] However, despite impressive benefits seen in open-label studies, results have also been more modest in small double-blind trials of thalamic DBS for TS. The potential role of thalamic DBS for TS with respect to both efficacy and side effects remains a source of debate with some centres continuing to report positive open label results[24].

In our trial, GPi stimulation was generally well tolerated and stimulation related side effects were amenable to stimulation adjustment. Of concern is the infection rate (13%) which is higher than expected, and may reflect that higher infection rates are indeed associated with DBS in this population, previously estimated to be as high as 18%.[25,26] Whether this is due to patients' behaviour or distinct immunological profiles in this population remains unclear.

A limitation of our study remains the relatively small sample size and that in 2 individuals electrodes were placed more posteriorly in the GPi as directed by their concurrent dystonic features. We cannot conclude whether anteromedial GPi DBS is superior to posteroventral GPi DBS for tic suppression based on our results. Moreover, in 2 patients medication changes occurred during the blinded period (1 increased, 1 decreased) and thus any influence of these changes aside from DBS cannot be excluded. Due to the immediate and often obvious effects of DBS adjustment, both blinding and subsequent adherence to trial protocol can be easily compromised unless adjustments are limited to minor potentially sub-therapeutic changes. Even so, delivery of effective stimulation in severely affected patients can make maintenance of double-blinding difficult. These challenges may be overcome in future trials by randomising patients to different targets, or comparing different targets within patients. However, the common coexistence of significant psychiatric comorbidity, the subjective nature of TS related outcome measures and their potential ceiling effects in the most severely affected patients, add to the difficulties of trial conduct in TS patients and interpreting the results based on individual scales.

In conclusion, our data support the GPi as an attractive alternative for DBS in TS. The mean effect size observed in the blinded period is greater than that seen in double-blind trials of medications for TS, and with further follow-up, GPi DBS appears to have major effects on tic severity and quality of life of this extremely disabled patient group. The anteromedial GPi is considered as part of the same limbic pathways that are thought to be involved in tic generation,[27–30] and while it is likely that tics emerge from network based neuronal dysfunction, bilateral DBS surgery appears to be well tolerated when targeting the pallidum. Additionally the pallidal target can be easily visualized on pre-operative stereotactic MRI allowing uniformity of targeting across patients. Future trials comparing the optimal target for DBS for TS should include a comparator arm with electrodes in bilateral anteromedial GPi/ GPe, and continue to try and identify those factors, which predict individual patient responsiveness.

Panel: Research in context

Evidence before this study

We searched PubMed up to December 2014 with the terms Tourette's syndrome, Gilles de la Tourette, or Tourette and deep brain stimulation, or DBS for double-blind randomized trials. We identified 4 small trials incorporating double-blind randomized methodology. In two trials including 5 and 6 patients respectively, the efficacy of thalamic DBS (centromedian–parafascicular (CM–Pfc) and ventralis oralis complex of the thalamus) was evaluated.[9,10] In another two trials, the effect of thalamic and anteromedial GPi stimulation was compared in 1 and 3 patients respectively.[13,31] These studies, including very small numbers of patients each report a benefit from stimulation, and thus partially support the overall positive outcomes presented in open-label studies. However, the literature of DBS for the treatment of Tourette syndrome consistently highlights the paucity of the highest level of evidence for its use. There remains a need for double-blind, randomized, controlled trials, with a sufficient number of patients to address a number of unresolved issues including; the magnitude and

consistency of the efficacy of this treatment, its clinical relevance, its effect on comorbid conditions, and the overall safety of this approach. The brain target as well as stimulation settings that can optimally address the abovementioned issues also remain to be determined.

Added value of this study
Our prospective, randomized trial is the largest double-blind trial of DBS in TS patients to date, assessing the safety and efficacy of pallidal DBS. Our results provide high-quality evidence that GPi DBS can significantly improve tics and can have major effects in quality of life in the long-term, while having an acceptable safety profile.

Implications of all the available evidence
The outcomes of this study provide further justification for the use of GPi DBS as a treatment for patients with severe medically refractory TS, which to date was supported by limited evidence. Future trials will likely require cross-centre collaboration to recruit larger numbers and evaluate the relative merits of different DBS targets, and identify factors predictive of useful response to surgery.

Authors contributions:
Chief Investigator- Thomas Foltynie supervised all aspects of the trial conduct, was responsible for randomisation and masking and provided statistical and methodological advice but had no direct role in data collection or data analysis.
Study design: Ludvic Zrinzo, Eileen Joyce, Marjan Jahanshahi, Thomas Foltynie;
Data collection: All authors except Thomas Foltynie.
Analysis of data: Zinovia Kefalopoulou, Ludvic Zrinzo,;
Statistical analysis: Zinovia Kefalopoulou;
Interpretation of data- All authors.
Drafting of the manuscript: Zinovia Kefalopoulou;
Critical revision of the manuscript: All authors.

Conflict of Interest
Dr Kefalopoulou is supported by a European Union FP-7 grant (TRANSEURO); Dr Zrinzo, Mr Candelario and Mrs Milabo report personal fees from Medtronic Inc; Mr Hyam and Prof Hariz report personal fees from Medtronic Inc and St Jude Medical; Prof Limousin reports personal fees from Medtronic Inc, St Jude Medical, and Boston Scientific; Dr. Foltynie reports personal fees from Medtronic Inc, personal fees from St Jude Medical, grants from Michael J Fox Foundation, grants from Cure Parkinson's Trust, grants from Parkinson's UK, grants from Brain Research Trust, personal fees from Abbvie Pharmaceuticals. There is no actual or potential conflict of interest in relation to this article.

Acknowledgements
We are grateful to all the patients who participated in this trial, as well as their referring clinicians. This work was undertaken partly at UCL/UCLH and was funded in part by the Department of Health NIHR Biomedical Research Centres funding scheme. The Unit of Functional Neurosurgery, UCL Institute of Neurology, Queen Square, London, is supported by the Parkinson’s Appeal and the Monument Trust. Dr Kefalopoulou is supported by a European Union FP-7 grant (TRANSEURO).

We gratefully acknowledge the contribution of the Birmingham, UK Tourette syndrome/team in particular Dr Andrea Cavanna, who contributed to the initial trial protocol design, but was unable to participate in the trial itself.

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Figure legends

Figure 1. Randomized double-blind crossover design of the study.

Figure 2. Trial profile.

Figure 3. Axial view from Schaltenbrand atlas to indicate location of active DBS contacts during blinded phase (patients a,b,d,e,f,g,h,j,k,l,m,n,o) and open label phase (patients c, i) within Left and Right Globus Pallidus. Depth in relation to the midcommissural plane is shown on the left. Selected abbreviations: GPi: globus pallidus pars interna; Pl: pars lateralis (pars externa) of pallidum; P.m.e: pars medialis externa and P.m.i: pars medialis interna of GPi; Ru: red nucleus; Sth: subthalamic nucleus; (Adapted from Schaltenbrand G, Wahren W. Atlas for Stereotaxy of the Human Brain, 2nd ed. New York: Thieme; 1977. Plates 53-55. Reprinted by permission.)

Table legends

Table 1. Baseline clinical characteristics of the study population. M: Male; F: Female. All patients had tried at least 3 classes of medication including dopamine blocking agents.

Table 2. Individual results on YGTSS total score in all 15 patients, at baseline, ON/OFF blinded, and open-label assessments.
Yale Global Tic Severity Scale (YGTSS) total score, 0-100. This scale comprises of a total tics severity score (-this score provides an evaluation of the number, frequency, intensity, complexity and interference of motor and vocal tics and ranges from 0-50) and an impairment score (-this score takes into account difficulties in self-esteem, family life, social acceptance, or school or job functioning due to tics and ranges from 0-50), with higher scores indicating greater severity. During trial recruitment, for the purposes of inclusion the impairment sub-score was transformed to a 0-5 analogue and added to the total tics severity score (range 0-55). Positive difference means improvement. *For purposes of maintaining confidentiality the patient sequence presented in tables 2 (and supplementary table 5) do not correspond to the sequence presented in table 1. # Primary endpoint analysis. § Post hoc analysis.

Table 3. Pre-specified secondary outcomes & post hoc analyses
Yale–Brown Obsessive Compulsive Scale (Y-BOCS) is a clinician-administered scale for the evaluation of obsessive compulsive symptoms and consists of 10 sub-items, items 1-5 are about obsessive thoughts and 6-10 about compulsions, total scores range from 0-40. The Modified Rush Video Rating Scale (MRVRS) scores are based on 5minute tic counts considering motor and vocal tic frequency and severity during two 5-minute periods, one observed and one unobserved, scores ranging from 0-20 each. The Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QoL) is a disease-specific patient-reported scale for the measurement quality of life in Tourette's patients: it consists of 27 items covering psychological, physical, obsessional, and cognitive aspects of the disorder, score range 0-108. MOVES is a clinician administered scale, consisting of 20 items evaluating motor and vocal tics, obsession and compulsions and associate features with scores ranging from 0-60. Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory measuring the severity of depression and scores range from 0-63. The State-Trait Anxiety Inventory (STAI) consists of 20 questions on a self-report basis measuring the severity of anxiety with scores ranging from 20-80. The Neuropsychiatric inventory (NPI) is a comprehensive assessment of 12 behavioural disturbances capturing frequency, severity of each behaviour and distress caused. The Trail Making test is a neuropsychological test of visual attention and task switching, measuring time (s) taken to complete the task. In the Paced Auditory Serial Addition test (PASAT), subjects are given a number every 4 seconds

and asked to add it to the number before (scores 0-30). For these scales higher scores indicate more severe condition. The California Verbal learning test (CVLT) was used to measure immediate recall of a list of 16 words over 5 trials. The Recognition memory for faces (RMF) measures accuracy of recall of 25 faces. The Verbal Fluency test measures how many words can be produced for each of 3 letters for 1 minute per letter. The Letter cancellation test (NAB Numbers and letters test) is used to evaluate deficits in attention and calculates an efficiency score based on errors and speed (maximum score 200). The Corsi block test is a neuropsychological test that assesses visuospatial short term working memory (maximum score 16). For these tests, lower scores indicate a more severe condition.
* The comparison between baseline and open label follow up is a post hoc analysis.

Table 4. Adverse events in all 15 patients during the whole study period.
* refers to percentage of patients; ¥ refers to percentage of events

Table 5. Stimulation parameters (supplementary data). *For purposes of maintaining confidentiality the patient sequence presented in tables 2 (and supplementary table 5) do not correspond to the sequence presented in table 1.

Tables

Table 1.

Patient	Sex	Age at onset (years)	Age at surgery (years)	Co-morbidities	Medication at inclusion
1	M	11	33	Obsessive compulsive disorder, Generalised anxiety disorder	NIL
2	F	7	55	Tardive dystonia History of depression	Diazepam 10mg
3	M	8	26	Depression, Generalised anxiety disorder, History of alcohol/substance misuse	Fluoxetine 10mg
4	M	7	24	Generalised anxiety disorder, Panic disorder, Depression	NIL
5	M	5	26	Obsessive compulsive behaviour, history of depression	Fluoxetine 20mg
6	M	6	38	Obsessive compulsive disorder, Depression, Generalised anxiety disorder, self-injurious behaviour	Venlafaxine 225mg Promethazine 100mg Diazepam 15mg Zolpidem 10mg
7	M	7	25	Obsessive compulsive behaviour	NIL
8	F	12	49	Depression	Amitriptyline10mg Citalopram 20mg Clonidine 500mg Zopiclone 11.25mg
9	M	7	49	Obsessive compulsive disorder, Depression	Fluoxetine 20mg
10	F	23	34	Obsessive compulsive disorder	Clonazepam 1mg
11	M	2	29	NIL	NIL
12	M	6	39	Obsessive compulsive disorder, Depression, self-injurious behaviour	Fluoxetine 40mg Haloperidol 2mg
13	M	6	43	History of obsessive compulsive disorder	Fluoxetine 40mg Risperidone 3mg
14	F	3	25	History of obsessive compulsive disorder, borderline personality disorder, eating disorder, self-injurious behaviour, psychotic episode	Clozapine 150mg Gabapentin 3600mg Sertraline 200mg Clonidine 250mg Zopiclone 15mg Topiramate 200mg
15	M	7	25	Obsessive compulsive disorder, Generalised anxiety disorder, Depression	Baclofen 80mg Diazepam 10-30mg

Table 2.

Patients 1-15*	**Baseline**	**6 weeks post-op**	**RANDOM-ISATION SEQUENCE**	**Blinded OFF-STIM**	**Blinded ON-STIM**	**Open-label ON-STIM**	**Change Blinded OFF-STIM vs Blinded ON-STIM (%)**	**Change Baseline vs open-label ON-STIM (%)**
a.	80	48	OFF, ON	68	39	33	29 (42·6%)	47 (58·6%)
b.	99	98	OFF, ON	99	78	42	21 (21·2%)	47 (57·6%)
c.	93	92		*n/a*	*n/a*	4	*n/a*	89 (95·7%)
d.	87	74	OFF, ON	85	66	63	19 (22·4%)	24 (27·6%)
e.	81	81	OFF, ON	81	81	66	0 (0%)	15 (18·5%)
f.	93	70	ON, OFF	67	59	48	8 (11·9%)	45 (48·4%)
g.	74	75	ON, OFF	75	77	74	-2 (-2·7%)	0 (0%)
h.	93	79	OFF, ON	82	63	49	19 (23·2%)	44 (47·3%)
i.	82	83	ON, OFF	*n/a*	*n/a*	47	*n/a*	35 (42·7%)
j.	80	55	ON, OFF	67	62	62	5 (7·5%)	18 (22·5%)
k.	96	96	ON, OFF	70	55	46	15 (21·4%)	50 (52·1%)
l.	71	59	OFF, ON	71	71	59	0 (0%)	12 (16·9%)
m.	98	97	ON, OFF	94	97	83	-3 (-3·1%)	15 (15·3%)
n.	99	100	OFF, ON	98	100	51	-2 (-2·0%)	48 (48·5%)
o.	92	40	ON, OFF	92	40	46	52 (56·5%)	46 (50%)
Mean (SD)	***87·9 (9·2)***	***76·5 (19·1)***		***80·7 (12·0)***	***68·3 (18·6)***	***51·5 (18·5)***	***12·4 (15·9) 95%CI (0·1-24·7) p=0.048*** #	***36.3 (22.6) 95%CI (23·8-48·9) p<0.0001*** §
Mean % difference (SD)							***15·3% (18·6)***	***40·1% (23·7)***

Outcome measure (range)	**Baseline**	**6 weeks post-op**	**Blinded OFF-STIM**	**Blinded ON-STIM**	**Open-label ON-STIM**	***Repeated measures ANOVA (F statistic) P value***	***Baseline vs open-label Paired T test* (T statistic) p value***

Table 3.

Pre-specified Secondary outcome measures	Mean (SD)						
GTS-QoL (0-108)	71·5 (21·8)	55·5 (23·6)	62·0 (24·7)	54·3 (28·4)	43·7 (29·6)	(3·3) 0·038	*(4.1) 0·001*
Y-BOCS (0-40)	13·8 (10·1)	12·7 (9·6)	14·6 (10·3)	12·8 (10·0)	10·7 (9·3)	(0·02) 0·979	*(1.8) 0·090*
BDI (0-63)	25·7 (12·5)	19·3 (12·4)	20·5 (14·3)	21·0 (13·8)	14·6 (12·4)	(2·6) 0·127	*(2.6) 0·025*
STAI (20-80)	56·9 (14·1)	52·3 (13·6)	55·1 (15·8)	56·3 (15·9)	47·6 (16·1)	(1·2) 0·352	*(2.1) 0·057*
NPI total (0-144)	19·7 (15·8)	13·2 (11·1)	15·4 (14·8)	16·8 (11·9)	-	(3·7) 0·071	
NPI distress (0-60)	9·5 (7·5)	7·1 (7·1)	7·7 (6·5)	7·9 (6·1)	-	(2·6) 0·137	
CVLT Trial 1 (0-16)	6·6 (1·1)	6·5 (1·4)	8·6 (1·9)	6·9 (1·6)	-	(10·4) 0·005	
CVLT Trial 5 (0-16)	12·9 (1·7)	12·8 (2·2)	13·5 (1·8)	13·5 (3·1)	-	(0·7) 0·522	
RMF (0-25)	23·8 (1·3)	24·1 (1·4)	24·1 (1·9)	24·3 (0·9)	-	(0·9) 0·446	
Verbal Fluency	41·5 (12·1)	39·9 (9·3)	44·7 (10·7)	45·6 (12·7)	-	(0·2) 0·828	
Trail Making Test –B (seconds)	84·7 (27·8)	71·3 (12·3)	70·6 (23·8)	71·7 (16·5)	-	(3·2) 0·095	
Stroop Interference (seconds)	57·3 (16)	58·5 (13·8)	53·6 (15·1)	56·3 (15·3)	-	(1·9) 0·213	
PASAT Errors (0-30)	9·3 (5·8)	10·3 (6·8)	6·5 (4·0)	7·6 (2·3)	-	(0·8) 0·477	
Letter Cancellation test (0-200)	90·5 (16·2)	94·5 (13·9)	98·1 (13·7)	95·4 (19·0)	-	(3·3) 0·092	
Corsi Blocks (0-16)	7·3 (1·4)	7·8 (1·5)	7·5 (2·2)	7·5 (1·1)	-	(0·1) 0·949	
Post-hoc Analyses	Mean (SD)						
YGTSS Motor (0-25)	22·3 (2·0)	20·5 (4·3)	20·9 (2·0)	17·9 (4·1)	13·7 (4·3)	(9·2) 0·005	(6.7) <0·0001
YGTSS Vocal (0-25)	19·5 (3·6)	17·9 (4·4)	19·1 (3·7)	16·5 (4·4)	12·5 (5·4)	(5·2) 0·026	(5.2) <0·0001
YGTSS Impairment (0-50)	46·0 (5·1)	38·0 (11·5)	40·8 (8·6)	33·9 (11·9)	25·3 (11·9)	(6·0) 0·018	(5.8) <0·0001
MDRVS observed (0-20)	15·5 (3·2)	14·7 (3·6)	14·9 (3·1)	12·8 (3·3)	10·6 (3·6)	(7·7) 0·010	(5.4) <0·0001

MDRVS unobserved (0-20)	16·9 (2·3)	15·4 (3·4)	15·4 (3·1)	14·0 (2·8)	11·6 (3·7)	(12·2) 0·002	(5.6) <0·0001
MOVES (0-60)	35·0 (10·1)	30·2 (10·1)	34·9 (11·4)	30·8 (12·3)	25·9 (14·9)	(0·9) 0·425	(2.9) 0·013

Table 4.

Adverse Event		
Serious	Events	Resolved
Related to surgery or device		
Battery infection necessitated removal of system and re-implantation	2	2
Related to stimulation		
Deterioration of condition, hypomanic behaviour, admission to psychiatric ward	1	1
Total	3 (20%*)	3 (100%¥)
Non-serious		
Related to surgery or device		
Prolonged pain around IPG	1	1
Keloid scar formation	1	0
Burr hole cap discomfort	1	0
Connection cable discomfort	1	0
Upper respiratory tract infection	1	1
Related to stimulation		
Increased anxiety	2	1
Insomnia	2	2
Irritability	3	3
Tiredness/ lack of energy	2	1
Headaches	2	1
Mood deterioration	1	0
Emotional lability	1	1
Upper respiratory tract infection	1	1
Abdominal rush	1	1
Panic attacks	1	1
Mild dysarthria	1	0
Lower limb dyskinesia	1	1
Total	23 (66·7%*)	15 (60%¥)