ARTICLE

Varying time-course of effects of high frequency stimulation of sub-regions of the Globus pallidus in patients with Parkinson's disease

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ABSTRACT

Introduction: Deep Brain stimulation of the globus pallidus can be a highly effective treatment for patients with Parkinson's disease (PD), experiencing Levodopa-induced-dyskinesia (LID). Stimulation programming can focus simply on eliminating dyskinesia, or can also attempt to relieve the rigidity, tremor or akinesia of PD itself.

Methods: In this study, we explored whether additional benefit on the "off" symptoms and signs of PD, could be achieved in post-operative PD patients with good LID control, by making further adjustment to existing stimulation parameters directed towards the more superior electrode contacts, located in the Globus Pallidus pars externa (GPe).

Results: Acutely, GPe-DBS led to clear improvement in the akinesia, rigidity and tremor of PD in the off-medication state compared with Globus Pallidus pars interna (GPi) DBS (p=0.003), however this was accompanied by the development of off-medication dyskinesia. Combined GPi-GPe DBS allowed maintained improvement but without dyskinesia. Follow up of patients over the subsequent 6-12 weeks showed gradual loss of this initial improvement. Switching back to GPi-DBS alone provided greater improvement in off medication symptoms than had been observed using the same GPi-DBS setting, 6-12 weeks previously.

Conclusions: Benefits on the off-medication symptoms of PD obtained acutely with GPe-DBS are in general not sustained. Similarly, the effects of GPi-DBS on the off medication symptoms of PD, can evolve over short periods of time presumably as a result of changes in network-wide neuronal plasticity. These clinical observations provide further insight into DBS mechanism of action, and can also help inform optimal methods of GPi-DBS programming.

Introduction

Deep brain stimulation (DBS) of the Globus Pallidus pars interna (GPi) is a recognised treatment for patients with Parkinson's disease (PD) [1]. The original pioneers of this surgery in Zurich, Switzerland [2] then in Grenoble, France [3], observed and reported the beneficial effects of chronic GPi DBS for the long-term amelioration of L-dopa induced dyskinesia (LID). These antidyskinetic effects of GPi DBS have been shown to persist for greater than 5 years [4]. In parallel, GPi DBS has been found to be helpful in a range of other hyperkinetic

movement disorders including Dystonia, Huntington's chorea and Tourette's syndrome [5,6,7].

The role of GPi DBS in the treatment of *hypokinetic* signs i.e. akinesia, rigidity and tremor has also been studied. Early series of patients undergoing GPi DBS reported conflicting results [2,8], and subsequent open label series have also shown markedly variable improvements in UPDRS 3 off-medication scores: 10% [9], 39% [10] and 54% [11], with the latter studies suggesting beneficial effects on rigidity, akinesia, tremor and axial signs persisting for at least 12 months. Nevertheless, patients tend to be able to make only small reductions in L-dopa equivalent dose as compared to patients undergoing subthalamic nucleus (STN) DBS. More recently, the efficacy of GPi DBS in relieving the motor symptoms of PD (as measured by the UPDRS part 3) has been the subject of several randomised controlled trials. In comparisons over 12-24 month periods, patients randomised to GPi DBS had improvements in UPDRS part 3 off medication scores of 26- 29% [12,13], which, although equivalent to the improvement seen with STN DBS in the only randomised study using UPDRS part 3 as the primary outcome measure [12], is lower than that reported with STN DBS in several other studies [13,14,15,16].

The globus pallidus is substantially larger than the STN, which perhaps explains some of the variable/contrasting effects seen. Following a series of acute experiments comparing the effects of stimulation through different contacts on a GP electrode, the Paris group [17], then the Grenoble group [3] reported that stimulation of the ventral pallidum (GPi) could alleviate rigidity but at the same time blocked the anti-akinetic effect of levodopa, while stimulation of the dorsal GPi or Globus Pallidus pars externa (GPe) alleviated akinesia, and induced dyskinesia but had little or no effect on rigidity. They concluded that these effects are mediated through stimulation of either pallidofugal fibres from cells in the lateral GPi forming the ansa lenticularis, in contrast to the effects of stimulation of cells in medial GPi which form the lenticular fasciculus, these pathways terminating in different thalamic subnuclei. They suggested activation of intermediate contacts on a GP electrode for a beneficial compromise between these effects [3].

Similarly, in other series of patients with GPi DBS studied in the acute setting, it appeared that ventral GPi stimulation improved dyskinesia but worsened akinesia, while GPe DBS relieved akinesia but provoked dyskinesia. Stimulation of either target improved rigidity [18,19].

It has also been observed that *chronic* ventral GPi DBS can provoke features of parkinsonism in patients with cervical dystonia [20]. Furthermore, the effects of GPi DBS in patients with dystonia are known to evolve over days, weeks or even months suggesting downstream effects on synaptic plasticity as one mechanism of action of this therapy. The beneficial effects of GPi DBS in PD are therefore somewhat nuanced and clearly depend on the exact anatomical position of the contact delivering the stimulation as well as the timepoint at which the effects are observed.

While the acute and chronic benefits of posteroventral GPi DBS for L-dopa induced dyskinesia are no longer a subject of debate, differences between *acute and longer lasting* effects of stimulating dorsal sub-regions of the globus pallidus (GP) have not been comprehensively studied. This issue has clinical relevance not only for surgical targeting but also to help advise clinicians responsible for DBS programming and deriving conclusions regarding optimal stimulation parameters. Acute effects may be profoundly different from effects of prolonged stimulation over subsequent weeks or months. In this study, the aim was to systematically explore the effects of stimulation delivery to different regions of the GP in patients with chronically implanted electrodes, both acutely and over a 6 and 12 week follow up period. These data were used to inform not only on the consistency and longevity of DBS related effects, but also to ensure that every patient was receiving the optimal

stimulation parameters taking into account both OFF motor symptoms and signs, as well as Levodopa induced dyskinesias.

Methods

Patients

All participants were patients with PD who had undergone bilateral GPi DBS and were under long term follow up at the National Hospital for Neurology & Neurosurgery, Queen Square, London. All patients had undergone GPi DBS surgery with the primary aim of ameliorating their disabling levodopa-induced dyskinesia (LID). For the purposes of this study, all adjustments to DBS parameters were performed to improve the clinical status of the patients. In the absence of clinical improvement, DBS parameters were reset to previously optimised settings. As such, and after informal discussions, research ethics approval was not considered necessary.

DBS Surgery

All DBS Surgeries were performed between 2003 and 2011 using a standard operative technique carried out by 1 or 2 functional neurosurgeons that has been described in detail previously, with emphasis on stereotactic MRI-guided and stereotactic MRI-verified electrode placement to minimise the number of brain penetrations while ensuring targeting accuracy [21,22,23,24,25]. All patients were implanted with bilateral 3389 DBS electrodes (Medtronic, Minneapolis) connected to either a Kinetra or Activa PC Implantable Pulse Generator (IPG). Using a surgical trajectory to avoid the lateral ventricle, all our electrodes targeted to GPi, pass through the GPe, resulting in the most inferior contacts of the electrodes lying in the ventral GPi, whereas the most superior contacts lie in the border of GPi- GPe (laminar zone) or in the superior and posterior part of GPe. (Supplementary Figure)

All patients underwent a stereotactic MRI scan immediately after lead implantation, for verification of precise anatomical lead positioning prior to connection to the IPG. Post-operative programming had been previously performed in the On medication state, and had satisfactorily ameliorated levodopa induced dyskinesia (LID) which had been the primary indication for surgery.

Patient assessments

The purpose of this study was to ensure that a cohort of patients already receiving chronic GPi DBS as a treatment for PD dyskinesia were receiving optimal stimulation parameters, as judged in both the OFF medication and ON medication condition, rather than solely focusing on severity of dyskinesia. Patient assessments were performed in 3 formal sessions of stimulation adjustment each separated by 6 weeks.

Baseline Assessment

All patients attended after an overnight cessation of medications. All patients underwent a systematic motor evaluation, in four states in a consistent sequence: 1) Off medication - ON ventral GPi i.e. DBS through inferior contacts previously used to control LID, 2) Off-medication - ON GPe DBS i.e. through superior contacts (verified on post operative imaging to lie in the GPe/ laminar region- for the purpose of this manuscript these will be referred to as GPe DBS) 3) Off-medication - ON combined GPi-GPe i.e. DBS through combined inferior and superior contacts, 4) On-medication - ON "optimal" DBS. All assessments throughout the study were performed using a fixed pulse width of 60us and a frequency of 130Hz. At each setting, changes to the stimulation amplitude were titrated against the degree of symptom control and development of side effects.

Motor evaluations were performed using Part 3 of the Unified Parkinson's disease rating scale (UPDRS). At least five to ten minutes was allowed to elapse following each change in DBS parameters before motor evaluations were performed. At the end of the assessment, the "optimal" stimulation parameters were selected for each patient taking into account the

objective motor evaluation in both the presence and absence of medication, the occurrence of side effects (in particular dyskinesia) and the patient's own "subjective" views. At the end of each session, patients returned home with their new "optimal" DBS setting.

Follow-up Assessments

Each patient that had an objective benefit from changing DBS parameters was invited to return for a repeat assessment at 6 weeks after an overnight period Off medication, and were evaluated 1) Off medication - ON newly derived "optimal" DBS parameters, followed by 2) Off medication - ON original GPi DBS setting and 3) On medication - ON "optimal" stimulation parameters. The same procedure was repeated at 12 weeks in those patients who had persisted with a new setting compared with their baseline DBS parameters.

Statistical Analysis

All statistical tests were performed using Stata version 8. Data were checked for normality using Shapiro-Wilk test. For normally distributed variables, paired t-tests were used to compare scores noted with different DBS parameters. For non-normally distributed variables, Wilcoxon signed rank tests were used.

Results

Patient Data

Thirteen PD patients (9 male) with chronically implanted GPi electrodes agreed to participate in this study. Their mean age at onset was 45.5 (range 24-58), mean disease duration of 18.9 years (range 9-39 years), and duration since GPi DBS surgery was 3.6 years (range 1-9 years). No patients received adjustment to their medication regime during this period of study.

Contact positions

Post-operative stereotactic MRI sequences confirmed that the inferior contacts on each electrode were anatomically situated in the GPi, while the superior contacts of each electrode were in the GPe and/or laminar zone between GPi and GPe (for example see Supplementary Figure).

Off medication baseline assessment:

Effects of GPi DBS and acute GPe DBS – OFF medication

The sequence of assessments throughout the study is presented in Figure 1. At baseline, the mean Off medication - ON GPi UPDRS part 3 score was 50.2 (SD 8.1). In the Off medication - ON GPe state, this score fell to 41.1 (SD 11.4) ($p = 0.003$) (Fig 2). The individual UPDRS scores and stimulation parameters are presented in Table 1. 11/13 patients had better part 3 scores ON GPe DBS than ON GPi DBS. Comparison of the UPDRS part 3 sub-scores of akinesia, rigidity, tremor and axial symptoms all favoured GPe stimulation ($p<0.05$).

In the Off medication - ON GPe DBS state, (hyperkinetic) dyskinesia or dystonia was observed in nine patients. This resembled L-dopa induced dyskinesia and was aggravated by increases in amplitude of GPe stimulation. Three patients described numbness contralateral to stimulation site, dizziness and an unpleasant feeling closely related to increasing stimulation amplitude. During these assessments eight out of the thirteen patients also reported a "subjective" improvement in their function in the Off medication - ON GPe DBS state in comparison to the Off medication - ON GPi DBS state, while five patients perceived no functional difference between these two states.

Combination of GPi & GPe DBS

In the Off medication - ON GPi-GPe DBS condition, mean UPDRS part 3 total score was 35.3 (SD 10.2), representing a further improvement compared with GPe HFS (Mean difference 5.1 points, $p = 0.01$). One patient did not undergo this evaluation because of

fatigue. Off medication dyskinesia/dystonia was completely eliminated by the acute combination of inferior (GPi DBS) and superior (GPe DBS) contacts with preservation of the benefits noticed in the ON GPe DBS state. The eight patients that experienced a beneficial response ON GPe DBS continued to report a subjective beneficial response on the ON GPi-GPe DBS state as well.

ON Medication ON GPi-GPe
Further small improvements in mean UPDRS part 3 score were seen with medication (mean 30.6 (SD 12.1). None of the patients had LIDs using the combined GPi-GPe DBS setting. The eight patients with both an objective and subjective sense of PD improvement chose to maintain their new DBS settings and agreed to attend a follow up visit at 6 weeks.

Follow up assessment at 6 weeks
One patient did not manage to attend the 6-week follow up assessment for personal reasons but attended the 12 weeks time point. In the other seven patients, in the off medication state, there was still a significant advantage of GPi-GPe DBS in comparison to GPi DBS ($p=0.02$); although this was less compared with the corresponding baseline GPi-GPe DBS assessment ($p=0.01$) (Table 3).

Four of these patients reported a subjective gradual loss of the initial benefit from the change to combined GPi-GPe DBS. These patients were switched back to their original GPi DBS setting, and an On-medication ON GPi DBS evaluation performed.

Follow up Assessment at 12 weeks
The four patients still persisting with the GPi-GPe DBS setting were evaluated having completed 12 weeks of combined GPi-GPe DBS. In all of these individuals there was now an advantage of using GPi DBS alone compared with the combined GPi-GPe DBS. All four patients were therefore switched back to their original GPi DBS settings and an On-medication - ON GPi assessment performed.

Comparing UPDRS part 3 scores in the Off-medication - ON GPi-GPe DBS state between baseline and the time point of exit from the study (4 patients at 6 weeks and 4 patients at 12 weeks) showed a significant decline of acute GPi-GPe DBS effectiveness. In contrast, there was significant improvement of UPDRS part 3 with GPi -DBS in comparison with the same setting at baseline ($p=0.006$).

Discussion
In this study, we have explored the acute and short-term effects of DBS through different parts of the GP in an attempt to improve the symptom control of patients already receiving chronic GPi DBS as a treatment for LID. Acute changes in stimulation through superior contacts lying within the GPe had consistent beneficial effects on akinesia and rigidity although at the expense of provoking off-medication dyskinesia. Combining stimulation through both GPi and GPe contacts resulted in the best control of akinesia and rigidity, without dyskinesia, in both Off and On-medication states in the acute setting, but with short term follow up, this did not lead to sustained advantages over GPi DBS alone. Of particular interest was the observation that reinstating GPi DBS alone after an interval of combined GPi-GPe DBS had greater impact on Off-medication signs than that seen with previous chronic GPi DBS at the same settings.

The change in therapeutic response to GPi DBS, suggests that the intervening period during which patients received combined GPi & GPe DBS might have had neuromodulatory effects on the basal ganglia motor network, perhaps mediated via changes in synaptic plasticity i.e. long term potentiation/depression. A previous non-human primate study has similarly suggested that therapeutic effects on parkinsonism may not be immediate following GPi DBS, and indeed may be preceded by a period of aggravated symptoms, although in this

study observations occurred over minutes rather than weeks [26]. Pallidotomy studies in the same primate models have shown that lesions in the GPe exacerbate parkinsonism [27], further distinguishing the mechanism of action of GPe DBS which appear to be mediated through neuronal activation rather than suppression [26, 28]. This is also supported by case reports where human patients with a pallidotomy in the GPe had either worsened or had no beneficial effect, requiring a re-operation with a new pallidotomy into the GPi [29,30]

Explanations of DBS mechanisms, based purely in terms of stimulating/inhibiting the rate or pattern of firing in 1) orthodromic GPi- thalamic pathway, 2) antidromic striatum- GPi "direct pathway" or 3) antidromic STN-GPi pathway are likely to be over-simplistic. Whole network based changes occur as a result of STN DBS as has been demonstrated using resting state fMRI and measuring effective connectivity using stochastic dynamic causal modelling [31]. It is thus tempting to speculate that similar network based changes occur over time with GPi DBS and thus explain the variable clinical responses seen over time.

The acute effects of GPe DBS were more reminiscent of those seen with acute STN DBS i.e. a major reduction of akinesia and rigidity, accompanied by an increase in dyskinesia. The GPe is highly connected to the STN, and acute effects of GPe stimulation may be mediated via a change in the synchronized oscillatory beta activity in the GPe-STN projection. However, given that the clear clinical effects of GPe DBS do not appear to be sustained, one possible explanation is that the orthodromic influence of GPe DBS on STN activity is unable to impact to the same extent on network-wide effective connectivity changes seen in the direct and hyperdirect pathways associated with STN stimulation [31].

The current study has several limitations. The number of patients included was inevitably limited by the small number of patients undergoing GPi DBS in our centre in comparison to STN DBS. In addition, the aim of the study was to ensure that all patients received optimal symptom control using combined GP DBS and medications throughout, therefore patients wishes were kept paramount and patients were not compelled to complete OFF stimulation assessments. Those experiencing negative effects or loss of efficacy, were able to switch back to former settings at either the 6 or 12 week stage introducing variability in the results. Furthermore, settings were chosen without the clinical assessor, nor the patient being blinded to stimulation parameters, which is a potential source of bias. A further limitation is that the patients' original "GPi" settings were not homogeneous and included any GPi contacts 0-, 1-, or 2- for either electrode although no patients were receiving stimulation through the most superior GPe contacts (3-) at baseline, while all were stimulated through the most superior contacts (3-) throughout the "GPe" study period. Given that we used a fixed pulse width and frequency throughout the study, we cannot extrapolate our results to patients receiving other stimulation parameters.

Despite the marked benefits seen with acute combined GPi-GPe DBS, all patients experienced a gradual loss of the initial beneficial effect, with the result that at the end of the study period, all patients preferred to pursue with GPi DBS alone. These observations are important not only in helping our understanding of the role of the GPi/ GPe in PD pathophysiology, and its manipulation by DBS, but also on a practical level, i.e. programming of individual patients. It is tempting to speculate that the beneficial effects of GPe DBS might be prolonged or even enhanced by an adaptive DBS type setting i.e. using a closed loop system to detect abnormal patterns of brain activity and delivering stimulation accordingly [32]. However the slower and varied clinical responses seen using GPi DBS, especially as a treatment for LID, may remain a challenge even for adaptive DBS systems.

Ultimately, we conclude that patients selected for GPi DBS in view of severe troublesome dyskinesia, considered unsuitable for STN DBS in view of borderline cognition or speech, receive substantial benefit for their LIDs from combined stimulation and medication. However, while attempting to make further improvements in "OFF" period fluctuations in this

group of patients through stimulation adjustment is tempting, especially in patients with limited alternative treatment options, this study suggests that acute beneficial effects associated with stimulation through the dorsal contacts may not be sustained.

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Legend to Figures:

Supplementary Figure.

a) Wire mesh 3D figure of 3389 DBS lead lying within the posterior GPi and GPe. Software used to create figure courtesy of Dr Mattias Astrom. b) Stereotactic proton density MRI: axial view of (i) inferior and (ii) superior active contacts within the ventral GPi and dorsal GPe respectively and (iii) coronal view.

FIG 1.

Flow chart of patient assessments throughout the study.

FIG 2.

Graphical comparison of UPDRS part 3 OFF medication scores on different DBS stimulation parameters at baseline and at study exit.