Parkinsonism and Related Disorders 21 (2015) 597–602

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

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

A. Angeli, H. Akram, A. Zacharia, P. Limousin, M. Hariz, L. Zrinzo, T. Foltynie*

Unit of Functional Neurosurgery, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

ARTICLE INFO

Article history:
Received 11 December 2014
Received in revised form
9 March 2015
Accepted 16 March 2015

Keywords:
Parkinson's disease
Deep brain stimulation
Globus pallidus
GPi
GPe

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.

1. Introduction

Deep brain stimulation (DBS) of the Globus Pallidus pars interna (GPi) is a recognized 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 anti-dyskinetic 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 [5–7].

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 randomized controlled trials. In comparisons over 12–24 month periods, patients randomized 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 randomized study using UPDRS part 3 as the primary outcome

* Corresponding author. Box 146, National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG, UK. Tel.: +44 203 448 8726.
E-mail address: T.Foltynie@ucl.ac.uk (T. Foltynie).

http://dx.doi.org/10.1016/j.parkreldis.2015.03.019
1353-8020/

measure [12], is lower than that reported with STN DBS in several other studies [13–16].

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 fibers 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.

2. Methods

2.1. 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 optimized settings. As such, and after informal discussions, research ethics approval was not considered necessary.

2.2. 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 minimize the number of brain penetrations while ensuring targeting accuracy [21–25]. 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.

2.3. 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.

2.3.1. 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 60 us and a frequency of 130 Hz. 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.

2.3.2. 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.

2.4. 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.

3. Results

3.1. 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.

3.2. 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).