

Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting

INTRODUCTION

Deep brain stimulation (DBS) for Parkinson's disease (PD) is currently limited by costs, partial efficacy and surgical and stimulation-related side effects. This has motivated the development of adaptive DBS (aDBS) whereby stimulation is automatically adjusted according to a neurophysiological biomarker of clinical state, such as β oscillatory activity (12–30 Hz). aDBS has been studied in parkinsonian primates and patients and has been reported to be more energy efficient and effective in alleviating motor symptoms than conventional DBS (cDBS) at matched amplitudes.^{1 2}

However, these studies have not considered whether side effects can also be avoided with clinically effective stimulation. In PD, it is well recognised that a significant proportion of patients develop speech deterioration following DBS of the subthalamic nucleus (STN), which may be reversible.³

Here we test bilateral stimulation, optimising parameters for aDBS, and evaluate speech intelligibility. We hypothesised that acute aDBS would be more effective and more efficient than cDBS at matched stimulation parameters while causing less speech impairment.

METHODS

We recruited 10 patients with advanced idiopathic PD following implantation of DBS electrodes into the STN.² Recordings took place 3–6 days following electrode placement during a temporary period of externalisation. All participants gave informed written consent, and were tested following overnight withdrawal of dopaminergic medication (see online supplementary material). Two patients were excluded due to external stimulator failure leading to no voltage delivery under aDBS and cDBS conditions.

aDBS stimulation was delivered bilaterally, only when β amplitude exceeded a threshold as previously described.² aDBS contacts, voltages and trigger thresholds were independently set for the two sides according to motor benefit versus induced paraesthesiae, with the same contacts/voltages used for cDBS.

Stimulation in each block continued for 15 min prior to evaluation. Participants

were assessed during blinded and randomised aDBS, cDBS and OFF conditions using the standardised and validated speech intelligibility test (SIT) in which participants read sentences totalling 110 words.^{4 5} Speech was recorded, and % intelligibility was assessed by a speech and language therapist (blinded to condition). Six of the eight participants completed an MDS-UPDRS-III assessment, which was videoed and rated off-line (rigidity excluded, vUPDRS total=112) by two blinded movement disorder specialists. Two participants did not perform the MDS-UPDRS-III assessment due to fatigue/discomfort related to prolonged off states. Our primary outcome measures were a comparison of aDBS with cDBS for speech (SIT), and for motor impairment (vUPDRS). Statistical testing was performed by repeated measures ANOVA (rmANOVA) and the Student's t-test.

RESULTS

The mean voltage (fixed across cDBS and aDBS) was 2.7 ± 0.2 V, with stimulation in the aDBS condition delivered $42.6 \pm 3.7\%$ of the time.

Speech scores

Baseline SIT scores OFF medication were $67.9 \pm 9.2\%$. rmANOVA (Off DBS, aDBS and cDBS) demonstrated a significant main effect of stimulation type ($F_2=4.153$, $p=0.038$). Our planned contrast demonstrated better speech intelligibility with

aDBS ($70.4 \pm 6.4\%$) than with cDBS ($60.5 \pm 8.2\%$; $t_7=2.8$, $p_{\text{two tailed}}=0.02$; **figure 1**). In secondary exploratory comparisons, aDBS was no different to off DBS, but cDBS was worse than off DBS ($t_7=2.55$, $p_{\text{two tailed}}=0.038$).

Motor scores

Baseline vUPDRS-III scores, OFF medication, were 28.8 ± 4.5 (6 participants). This was compared to a mean preoperative score of 36.4, suggestive of a microlesional effect of surgery. The vUPDRS-III score across the three conditions (Off DBS, aDBS and cDBS) was compared by rmANOVA (6 participants) and demonstrated a significant main effect of stimulation ($F_{df=2}=5.4$, $p=0.025$). Our planned contrast revealed a significant improvement of aDBS compared to cDBS (vUPDRS-III means: 19.7 ± 1.0 vs 31.6 ± 4.3 ; $t_5=2.71$, $p_{\text{two tailed}}=0.042$).

DISCUSSION

Recent work has demonstrated that aDBS may be more effective at improving motor symptoms than conventional stimulation in PD with stimulation amplitudes optimised for cDBS.^{1 2} Here, we investigate acute stimulation-induced speech deterioration with parameters optimised for aDBS contrasted with cDBS using these same parameters. We found that in this acute setting, the stimulation parameters optimal for aDBS significantly reduced reversible speech side effects and

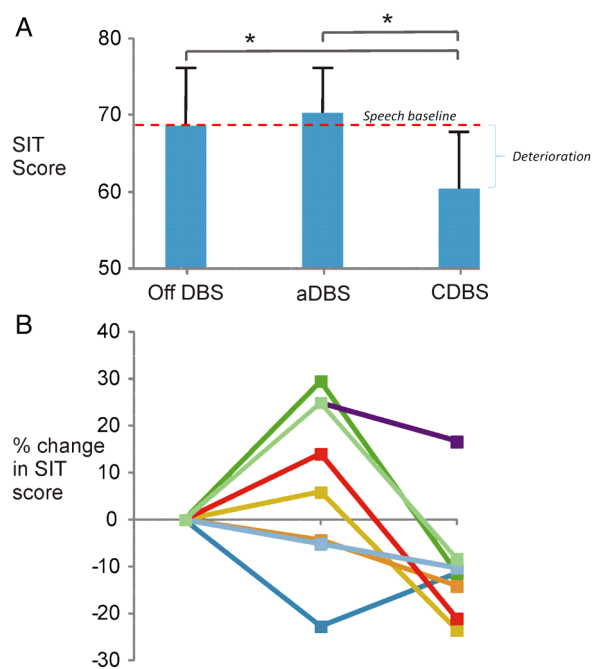


Figure 1 (A) Bar chart showing the mean \pm SEM speech intelligibility across the three stimulation conditions for all eight patients. (B) Data show individual percentage change for all participants across stimulation conditions, normalised to the Off DBS state. aDBS, adaptive DBS; cDBS, conventional DBS; DBS, deep brain stimulation; SIT, speech intelligibility test.

improved motor function, whereas these same stimulation parameters failed to produce a beneficial effect with cDBS and led to impairment in speech intelligibility. Together these findings suggest that stimulation parameters adapted to aDBS may potentially have a wider therapeutic window than cDBS with the same parameters. This dual effect whereby aDBS appears to have a lower efficacy threshold but spares speech may be related to the temporal targeting of β bursts by stimulation.

The average deterioration in the SIT score when stimulated by cDBS as opposed to aDBS was clinically relevant (9.9%). For quantitative comparison, the average deterioration when the STN is stimulated at 4 V compared to 2 V is reported as 16.5%,⁴ and the average improvement with Lee Silverman Voice Treatment was most recently reported as 4.7%.⁵

The present study has some acknowledged limitations mostly stemming from its acute nature in the postoperative period resulting in a temporary microlesional effect. Consequently, the responses to stimulation may not necessarily be representative of the chronic state. Furthermore, the postoperative period also introduced time constraints and patients were significantly fatigued by testing, and only short stimulation blocks were performed that may have lessened the mean effect of stimulation and increased the variability. In addition, our sample size was limited, and the use of blinded video-based assessments, which necessitates excluding rigidity scores and provides smaller effect sizes than non-blinded observations, may have obscured beneficial effects of cDBS. In sum, the current study cannot confirm whether aDBS will prove more effective or tolerable than independently optimised cDBS in the chronic setting but does provide proof of concept data that aDBS may, at least acutely, have less propensity for causing unwanted side effects than cDBS.

In conclusion, our study provides the first blinded group data demonstrating that aDBS has the potential to be more efficacious, with lower stimulation efficacy thresholds and less speech side effects than cDBS, although this will need confirmation in trials in chronically implanted patients.

Simon Little,¹ Elina Tripoliti,¹ Martijn Beudel,² Alek Pogosyan,³ Hayriye Cagnan,³ Damian Herz,³ Sven Bestmann,¹ Tipu Aziz,⁴ Binith Cheeran,⁴ Ludvic Zrinzo,¹ Marwan Hariz,¹ Jonathan Hyam,¹ Patricia Limousin,¹ Tom Foltynie,¹ Peter Brown³

¹Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, London, UK

²Department of Neurology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

³MRC Brain Network Dynamics Unit (BNDU), Department of Pharmacology and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

⁴Nuffield Department of Surgical Sciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

Correspondence to Professor Peter Brown, Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6, West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK; peter.brown@ndcn.ox.ac.uk

Twitter Follow Martijn Beudel at @mbeudel

Contributors SL designed the study, collected and analysed the data and wrote the manuscript. ET helped with the design of the study, speech ratings and writing of the manuscript. MB, HC, DH and SB helped with data collection, analysis and review and improvement of the manuscript. AP helped with design of the study and technical aspects of aDBS that facilitated its implementation, guidance and discussion of results, as well as review and improvement of the manuscript. TA provided help with trial facilitation and review and improvement of the manuscript. BC helped with UPDRS-III ratings, analysis and review and improvement of the manuscript. LZ, MH, JH and PL helped with design and ongoing trial facilitation, review and improvement of the manuscript. TF helped with design and ongoing trial facilitation, MDS-UPDRS-III blinded ratings, review and improvement of the manuscript. PB designed the study, collected and analysed the data and wrote the manuscript.

Funding This study was funded by clinical research training grants (SL—093929/Z/10/Z and 105804/Z/14/Z) from the Wellcome Trust and supported by the Medical Research Council (MC_UU_12024/1), National Institute for Health Research Oxford Biomedical Research Centre and Rosetrees Trust. The Unit of Functional Neurosurgery is supported by the Parkinson Appeal UK and Monument trust.

Competing interests SL has been a participant in a DBS teaching course funded by Medtronic, the manufacturer of the electrodes used in this study. TA has performed consultancy for and received speaking fees from Medtronic. BC has received travel support and unrestricted educational grants for organising CPD events from Medtronic, St Judes and Boston scientific (manufacturers of DBS electrodes), and some of which were used in this study. LZ, MH, TF and PL have received speaking fees and travel support from Medtronic and St Judes, and some of which were used in this study. PB has received fees and non-financial support from Medtronic and personal fees from Boston Scientific, and some of which were used in this study.

Ethics approval NRES Committee South Central—Oxford A.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This study resulted in a small volume of clinical scoring data which we would be happy to share on request by email to the corresponding author.

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2016-313518>).

Open Access This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>



CrossMark

To cite Little S, Tripoliti E, Beudel M, *et al.* *J Neurol Neurosurg Psychiatry* 2016;**87**:1388–1389.

Received 10 March 2016

Revised 26 July 2016

Accepted 27 July 2016

Published Online First 16 August 2016

J Neurol Neurosurg Psychiatry 2016;**87**:1388–1389.

doi:10.1136/jnnp-2016-313518

REFERENCES

- Rosin B, Slovik M, Mitelman R, *et al.* Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 2011;**72**:370–84.
- Little S, Pogosyan A, Neal S, *et al.* Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;**74**:449–57.
- Skodda S, Grönheit W, Schlegel U, *et al.* Effect of subthalamic stimulation on voice and speech in Parkinson's disease: for the better or worse? *Front Neurol* 2014;**4**:218.
- Tripoliti E, Zrinzo L, Martinez-Torres I, *et al.* Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. *Mov Disord* 2008;**23**:2377–83.
- Cannito MP, Suiter DM, Beverly D, *et al.* Sentence intelligibility before and after voice treatment in speakers with idiopathic Parkinson's disease. *J Voice* 2012;**26**:214–19.



OPEN ACCESS



Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting

Simon Little, Elina Tripoliti, Martijn Beudel, Alek Pogosyan, Hayriye Cagnan, Damian Herz, Sven Bestmann, Tipu Aziz, Binith Cheeran, Ludvic Zrinzo, Marwan Hariz, Jonathan Hyam, Patricia Limousin, Tom Foltynie and Peter Brown

J Neurol Neurosurg Psychiatry 2016 87: 1388-1389 originally published online August 16, 2016
doi: 10.1136/jnp-2016-313518

Updated information and services can be found at:
<http://jnp.bmj.com/content/87/12/1388>

These include:

References

This article cites 5 articles, 0 of which you can access for free at:
<http://jnp.bmj.com/content/87/12/1388#BIBL>

Open Access

This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See:
<http://creativecommons.org/licenses/by/4.0/>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections
[Open access](#) (219)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>