

Effect of electrode contact location on clinical efficacy of pallidal deep brain stimulation in primary generalised dystonia

S Tisch, L Zrinzo, P Limousin, K P Bhatia, N Quinn, K Ashkan, M Hariz

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See end of article for authors' affiliations

Correspondence to:
Dr S Tisch, Unit of Functional Neurosurgery, Sobell Department, Institute of Neurology, University College London, Box 146, 8–11 Queen Square, London WC1N 3BG, UK; s.tisch@ion.ucl.ac.uk

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Primary generalised dystonia (PGD) is a movement disorder characterised by involuntary muscle contractions causing abnormal postures and spasms.¹ The failure of medical treatment has led to renewed interest in functional neurosurgical approaches to its treatment. Earlier positive reports of ablative pallidal surgery in dystonia² and the subsequent observations of improvement of dystonia in Parkinson's disease (PD) with posteroventral pallidotomy and DBS led to the first attempts to treat dystonia using globus pallidus internus (GPI) deep brain stimulation (DBS) by Coubes *et al* in 1996.³ Since then, GPI DBS has emerged as an effective treatment for PGD.^{4–5} Despite this progress and the more widespread acceptance of the technique, there is still debate about the optimal target within the GPI to achieve the best effect in dystonia. Most surgeons target the posteroventral portion of the GPI, the classical target for pallidotomy developed by Leksell and Laitinen.⁶ However, to date there have been few data to support the superiority of this target in dystonia, or whether within this region there may be an optimal zone to achieve the best effect.

We sought to explore the relationship between the precise location of the therapeutically stimulated electrode contact and the magnitude of clinical benefit in a consecutive series of patients with PGD who all underwent bilateral GPI DBS. We were interested to determine if within the GPI there is any regional stratification of the efficacy of stimulation for dystonia.

METHODS

Subjects

We studied a consecutive series of 15 patients with PGD. The clinical characteristics of the patients are summarised in table 1. Patient No 5 had a previous thalamotomy 23 years previously. The study was approved by the Joint Research Committee of

Objectives: To determine the effect of electrode contact location on efficacy of bilateral globus pallidus internus (GPI) deep brain stimulation (DBS) for primary generalised dystonia (PGD).

Subjects and methods: A consecutive series of 15 patients with PGD (10 females, mean age 42 years, seven DYT1) who underwent bilateral GPI DBS, were assessed using the Burke–Fahn–Marsden (BFM) dystonia scale before and 6 months after surgery. The position of the stimulated electrode contact(s) was determined from the postoperative stereotactic MRI. Contralateral limb and total axial BFM subscores were compared with the location of the stimulated contact(s) within the GPI.

Results: The mean total BFM score decreased from 38.9 preoperatively to 11.9 at 6 months, an improvement of 69.5% ($p < 0.00001$). Cluster analysis of the stimulated contact coordinates identified two groups, distributed along an anterodorsal to posteroventral axis. Clinical improvement was greater for posteroventral than anterodorsal stimulation for the arm (86% vs 52%; $p < 0.05$) and trunk (96% vs 65%; $p < 0.05$) and inversely correlated with the y coordinate. For the leg, posteroventral and anterodorsal stimulation were of equivalent efficacy. Overall clinical improvement was maximal with posteroventral stimulation (89% vs 67%; $p < 0.05$) and inversely correlated with the y (A–P) coordinate ($r = -0.62$, $p < 0.05$).

Conclusion: GPI DBS is effective for PGD but outcome is dependent on contact location. Posteroventral GPI stimulation provides the best overall effect and is superior for the arm and trunk. These results may be explained by the functional anatomy of GPI and its outflow tracts.

the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London, UK.

Surgical procedures and stimulation parameters

All patients underwent bilateral implantation of electrodes into the GPI and chronic stimulation. The quadripolar DBS electrode model 3389, with four platinum–iridium cylindrical surfaces (1.27 mm diameter, 1.5 mm in length and 2 mm centre-to-centre separation) and Kinetra model 7428 implanted pulse generator (Medtronic Neurological Division, Minneapolis, Minnesota, USA) were used in all except four patients where model 3387 (3 mm centre-to-centre separation) electrodes were used. Surgery was performed under general anaesthesia using the Leksell G frame (Elekta Instruments, Sweden) with direct targeting of the posteroventral GPI, as visualised on proton density sequence⁷ stereotactic MRI, 1.5 T, 2 mm contiguous slices. The entrance point into the skull was made 2–2.5 cm lateral to the midline at the level of the coronal suture, which provides an orthogonal approach. The ring angle (anteroposterior angle) was between 70 and 80°, and the arc angle 85–95°. Intraoperative impedance recording was used to delineate grey and white matter boundaries; microelectrode recording was not used. Confirmation of electrode placement in the GPI was obtained in all patients with immediate post-implantation stereotactic MRI. All patients received monopolar stimulation with one or two adjacent active contacts. Stimulation parameters were individualised in each patient and chosen for the best clinical effect and the least side effects. Eight patients were stimulated at ventral contacts; in seven patients (12 sides) the

Abbreviations: BFM, Burke–Fahn–Marsden; DBS, deep brain stimulation; Gpe, globus pallidus externus; Gpi, globus pallidus internus; PD, Parkinson's disease; PGD, primary generalised dystonia

Table 1 Patient characteristics

Patient No	Sex	Age (y)	Disease duration (y)	DYT1 gene status	Site of onset	Worst affected areas	BFM score pre-op/6 mo (0–120)	Medications	DBS parameters
1	F	18	9	+	R hand	Trunk, R limbs	48/1	Trihexyphenidyl	R: 4.5-, 3.9 v, 60 µs, 130 Hz L: 0.1-, 3.9 v, 60 µs, 130 Hz
2	M	24	16	–	R hand	Neck, trunk, R limbs	73/15	Clonazepam	R: 4.5-, 3.9 v, 90 µs, 130 Hz L: 0.1-, 3.8 v, 90 µs, 130 Hz
3	M	47	37	+	L leg	Neck, trunk, L side	52/22	Diazepam, Tetrabenazine	R: 4-, 3.5 v, 90 µs, 130 Hz L: 0.1-, 3.3 v, 60 µs, 130 Hz
4	F	23	12	–	R leg	Trunk, R leg	53/32	None	R: 5-, 4.0 v, 60 µs, 130 Hz L: 1-, 4.2 v, 60 µs, 130 Hz
5	F	52	36	+	L arm	L limbs	29/7	None	R: 4-, 3.0 v, 60 µs, 130 Hz L: 0-, 3.0 v, 60 µs, 130 Hz
6	F	16	7	+	R leg	R limbs, trunk	20/1	L-dopa, Trihexyphenidyl	R: 4-, 2.9 v, 60 µs, 130 Hz L: 0-, 2.9 v, 60 µs, 130 Hz
7	F	63	4	–	Trunk	Trunk, both legs	23/3	L-dopa, Trihexyphenidyl	R: 6-, 4.6 v, 90 µs, 130 Hz L: 2-, 4.6 v, 90 µs, 130 Hz
8	F	54	43	–	R hand	L limbs	24/9	None	R: 4-, 3.7 v, 60 µs, 130 Hz L: 1-, 3.7 v, 60 µs, 130 Hz
9	F	36	25	+	L foot	Trunk, L limbs	21/1	Trihexyphenidyl	R: 4-, 4.6 v, 90 µs, 130 Hz L: 0-, 4.2 v, 90 µs, 130 Hz
10	M	62	43	–	Neck	Neck, trunk, L arm	28/15	Trihexyphenidyl, Baclofen, Clonazepam	R: 6-, 3.7 v, 90 µs, 130 Hz L: 1-, 3.7 v, 90 µs, 130 Hz
11	F	22	15	+	L foot	Trunk, both legs	51/11	Trihexyphenidyl, Baclofen	R: 4-, 3.6v, 60 µs, 130 Hz L: 0-, 3.6 v, 60 µs, 130 Hz
12	F	64	50	–	R hand	Trunk, R limbs	46/13	None	R: 5.6-, 3.5 v, 60 µs, 130 Hz L: 1.2-, 3.5 v, 60 µs, 130 Hz
13	M	62	7	–	L leg	Neck, L leg, R arm	64/30	None	R: 4.5-, 3.5 v, 60 µs, 130 Hz L: 1.2-, 3.5 v, 60 µs, 130 Hz
14	M	47	26	–	Neck	Neck, R arm	25/12	None	R: 4.5-, 3.5 v, 90 µs, 130 Hz L: 0.1-, 3.5 v, 90 µs, 130 Hz
15	F	42	30	+	R foot	R arm, leg	27/6	None	R: 5-, 3.5 v, 60 µs, 130 Hz L: 1-, 3.5 v, 60 µs, 130 Hz

BFM, Burke–Fahn–Marsden; DBS, deep brain stimulation.

most ventral contacts (0 and 4) were not used for chronic stimulation. The reasons for not using the most ventral contacts were capsular (corticospinal) response with tension in the contralateral face or arm, or dysarthria (patient Nos 8, 10, 15), dizziness (patient No 4), better clinical effect of more dorsal contacts (patient No 7) and not tried for chronic stimulation from the outset (patient Nos 12 and 13). The stimulation parameters in each patient at 6 months are shown in table 1.

Clinical assessment

Clinical assessment was performed using the Burke–Fahn–Marsden scale (BFM), which is a validated clinical measure in generalised dystonia.⁸ Patients were assessed preoperatively and 6 months after surgery. Right and left hemibody scores were derived from the BFM movement scores for the arm and leg. The BFM movement scores for axial items (eyes, mouth, speech, neck, trunk), which are unpaired data, were analysed separately on a whole patient basis rather than by sides.

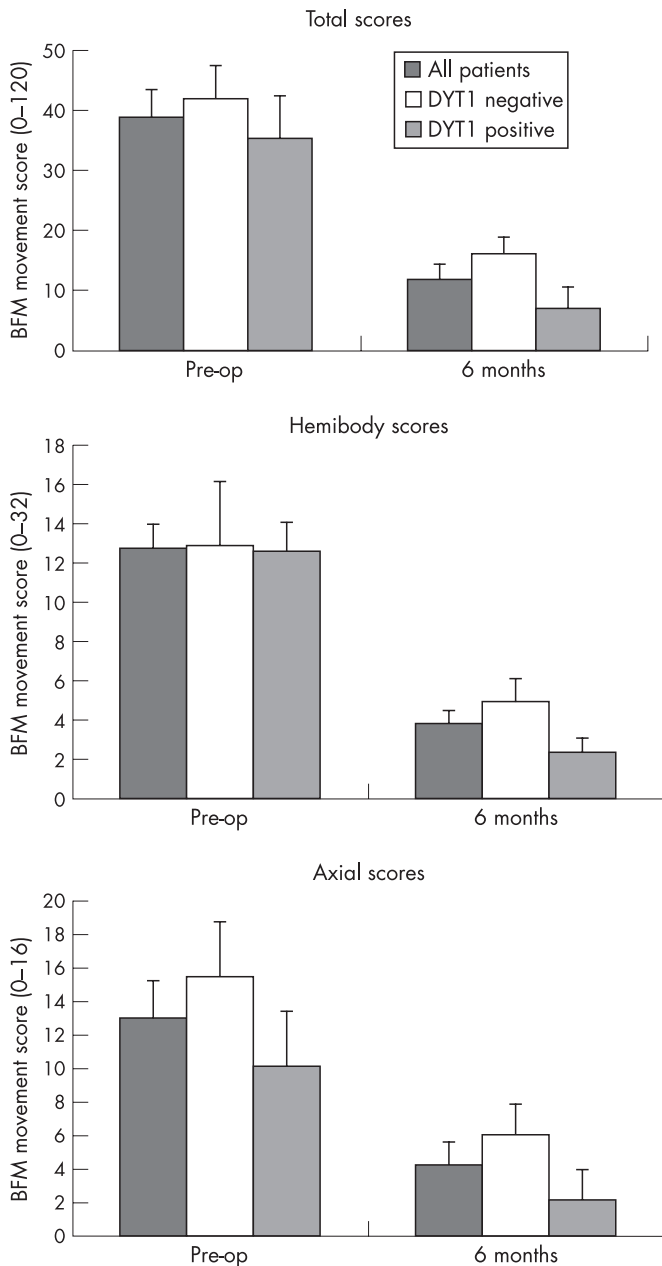


Figure 1 Mean Burke-Fahn-Marsden (BFM) movement scores for the whole body, hemibody (arm, leg) and axial (eyes, mouth, speech/swallow, neck and trunk), before and 6 months after bilateral globus pallidus internus deep brain stimulation. Values are mean (SEM). All decreases in BFM were significant at the $p < 0.05$ level.

MRI analysis and determination of electrode contact position

MRI images were analysed using the Stealth workstation (Framelink TM; Medtronic). The investigator determining contact location (LZ) was blinded to the clinical scores of the patients. Electrode contacts were identified on the postoperative stereotactic MRI. The centre of the electrode contact was determined as the centre of its artefact visible on the MRI image. Electrode contact position with respect to mid-commissural point, atlas defined target and the visible anatomical target was determined. The visible target was spatially normalised to atlas target of $x = 21$ mm, $y = 2$ mm, $z = -5$ mm in relation to the mid-commissural point. The Cartesian coordinates of the active contact after this transposition were then derived. This transposition normalised for anatomical variation

between and within patients. Where two adjacent contacts were stimulated (11 sides), the geometric mean of the two stimulated contacts was used. In addition to quantitative localisation of the stimulated electrode contacts, we also determined their position in relation to anatomical boundaries of the GPi visible on MRI images. Using the same MRI analysis methods, we also determined the targeting error for each electrode as the distance between the intended target and the electrode position.

Statistical analysis

Clinical and contact location data were cross tabulated so that total hemibody, arm and leg scores were paired with the coordinates of the contralateral active electrode contact (30 sides). Total scores and axial subscores were paired with the mean x , y and z coordinates of the active contacts of both electrodes (15 patients), to enable the data to be treated on a whole patient basis rather than by sides. Cluster analysis (K means cluster) was used to identify subgroups of electrode contacts within geographically distinct domains. Differences between groups were determined using χ^2 and two tailed unpaired t tests. Repeated measures ANOVA was used to explore the effects of coordinate and DYT1 status on clinical outcome. Correlations were performed using the Pearson correlation coefficient. A p value < 0.05 was considered significant. All statistics were performed using SPSS for Windows v 11.5.

RESULTS

Clinical outcome

Dystonia improved in all patients after surgery. The mean BFM movement score decreased from 38.9 preoperatively to 11.9 at 6 months, an improvement of 69.5% ($p < 0.00001$). The BFM disability score improved from 9.0 to 4.1, a 58% improvement ($p < 0.00001$). The mean percentage improvement in hemibody scores was 67.8% ($p < 0.0001$). There was no significant difference in outcome between arm and leg (63.8% vs 72.9%; NS) or right and left body sides (67.5% vs 68.0%; NS). Patients with DYT1 showed significantly greater improvement in total movement score (82.5% vs 61.5%; $p < 0.05$), hemibody score (81.8% vs 55.4%; $p < 0.01$) but not axial (89.4% vs 63.9%; NS) or disability score (69.5% vs 50.9%; NS). Improvement in hemibody score was non-significantly greater for 3387 than 3389 electrodes (79.0% vs 63.6%; NS). The clinical outcome results are summarised in fig 1. We observed in two patients (patient Nos 5 and 8) the development of delayed onset akinesia with gait slowing, and difficulty arising from sitting and turning in bed. In both patients these akinetic features occurred with stimulation of ventral contacts and improved by changing to more dorsal contacts.

Electrode contact location

Table 2 shows the electrode contact position in relation to pallidal anatomy, for each patient side.

The MRI of patient No 1 is shown in fig 2. For the entire cohort, the mean coordinates of the stimulated contact were $x = 20.8$ mm (18.3–22.4), $y = 3.2$ mm (1.2–5.1) and $z = -0.76$ mm (–5.3–2.2). Electrode contacts on the left brain side were more medial than on the right (20.2 mm vs 21.4 mm; $p < 0.001$), but for y and z coordinates there was no significant difference between right and left sides. The mean Euclidean targeting error for all of the electrodes was 0.9 (SD 0.5) mm and was not significantly different between right and left sides. As the targeting error was acceptably small and equal on both sides, the likely explanation of the left electrode being more medial is that the GPi is anatomically more medial on the left than on the right, as has been shown in a previous study.⁷

Table 2 Electrode contact position in relation to pallidal anatomy, for each patient side

Patient No	Left side				Right side			
	Contact 0	Contact 1	Contact 2	Contact 3	Contact 4	Contact 5	Contact 6	Contact 7
1	GPi*	GPi/MML*	GPe	GPe/LML	GPi*	GPi/MML*	GPe	GPe/LML
2	GPi*	GPi*	GPe	GPe/LML	GPi*	GPi/MML*	GPe	LML/PT
3	GPi*	GPi*	GPi/MML	GPe	GPi*	GPi/MML	GPe	GPe
4	GPi	GPi/MML*	MML/GPe	GPe/LML	GPi	GPi/MML*	GPe	GPe
5	GPi*	GPi/MML	GPe	GPe	GPi*	GPi/MML	GPe	GPe/LML
6	GPi*	GPi	GPi	GPi	GPi*	GPi/MML	MML/GPi	GPe
7	GPi	GPi	GPi*	GPi/MML	GPi	GPi	GPi*	GPi/MML
8	GPi	GPi*	GPi/MML	GPe	GPi*	GPi/MML	GPe	LML/PT
9	GPi*	GPi	GPi	GPi/MML	GPi*	MML/GPe	GPe	GPe/LML
10	GPi	GPi/MML*	MML/GPe	GPe	IC/GPi	GPi	GPi/MML*	MML
11	GPi*	GPi/MML	MML	GPe	GPi*	GPi/MML	MML	MML/GPe
12	GPi	GPi/MML*	GPe*	GPe	GPi	GPi*	GPi/MML*	GPe
13	GPi	GPi*	GPi/MML*	LML/PT	GPi*	GPi/MML*	MML/GPe	GPe
14	GPi*	GPi/MML*	MML	MML/GPe	GPi*	GPe*	GPe/LML	LML/PT
15	GPi	GPi*	GPi/MML	GPe	GPi	GPi/MML*	GPe/LML	GPe

GPe, globus pallidus externus; GPi, globus pallidus internus; IC, internal capsule; LML, lateral medullary lamina (separates GPe and putamen); MML, medial medullary lamina (separates GPi and GPe); PT, putamen.
*Stimulated contact(s).

Cluster analysis of the stimulated contact coordinates identified two spatially distinct groups with the following geometric centres: cluster 1 (10 sides) $x = 20.8$ mm, $y = 2.2$ mm, $z = -3.1$ mm and cluster 2 (20 sides) $x = 20.8$ mm, $y = 3.6$ mm, $z = 0.4$ mm. Clustering was influ-

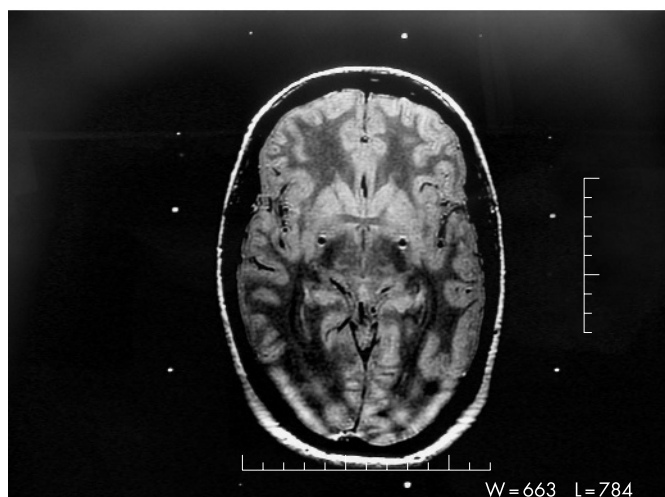
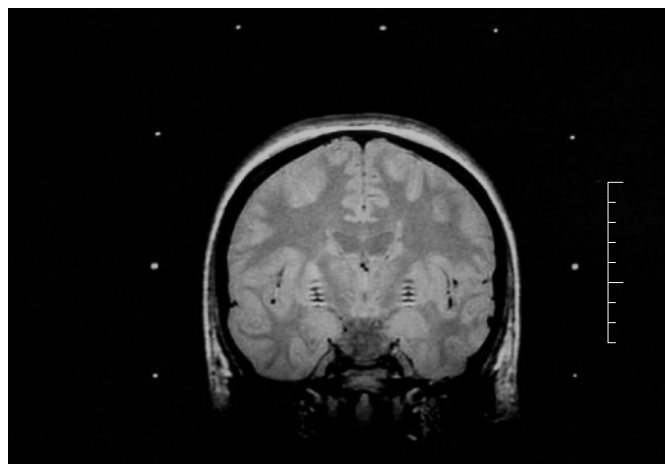


Figure 2 Immediate post-implantation coronal and axial MRI images of patient No 1 showing quadripolar 3387 electrodes located bilaterally in the globus pallidus internus.

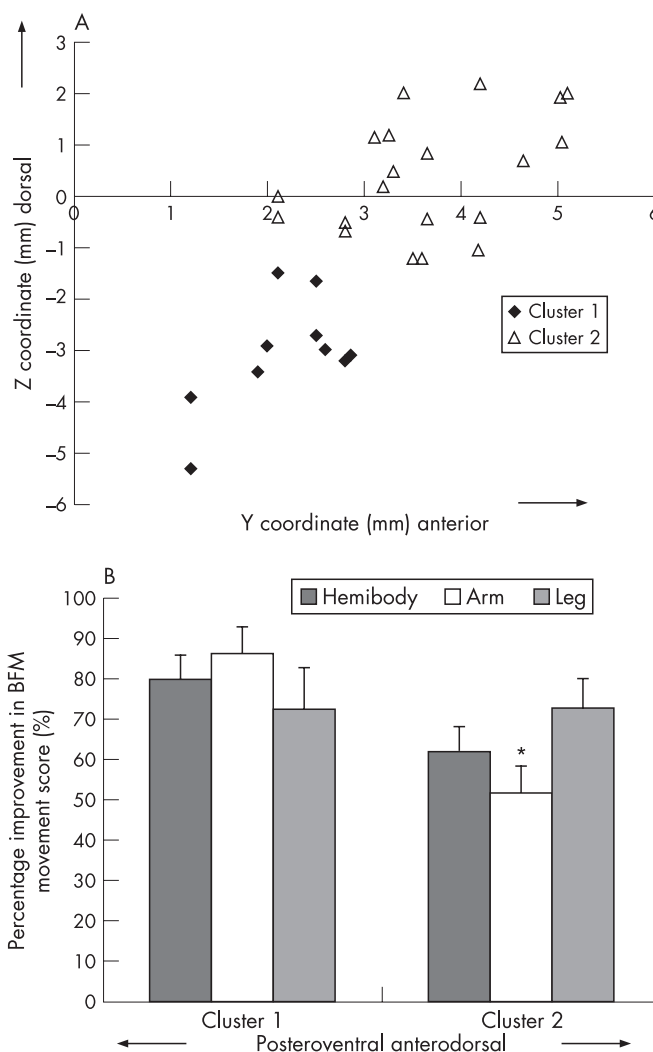


Figure 3 (A) Plot of y and z coordinate of the stimulated contact for 30 sides showing a linear distribution and the membership of spatial clusters. The origin of the plot is the mid point of the AC-PC line. Note cluster 1 is posteroventral and cluster 2 anterodorsal. (B) Mean percentage improvement in Burke-Fahn-Marsden (BFM) movement score for hemibody, arm and leg in clusters 1 and 2. For arm scores, improvement was significantly greater in cluster 1 than in 2 (* $p = 0.008$). Values are mean (SEM).

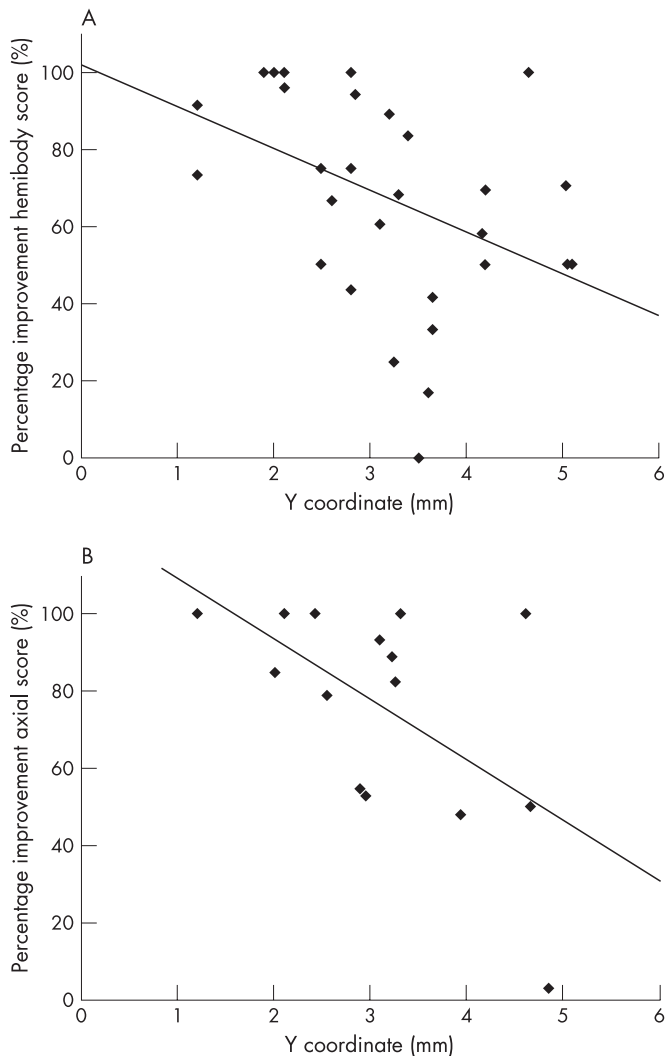


Figure 4 (A) Correlation between percentage change in hemibody Burke–Fahn–Marsden (BFM) score and the y coordinate of the stimulated contact in 30 sides ($r = -0.42$, $p = 0.022$). (B) Correlation between percentage change in axial BFM score and the average y coordinate right and left sides in 15 patients ($r = -0.57$, $p = 0.025$).

enced by the y ($F = 22.4$, $p < 0.0001$) and z ($F = 64.8$, $p < 0.0001$) coordinates but not by x ($F = 0.02$, $p = 0.89$), reflecting less variation in x. Cluster 1 is the most posteroventral, cluster 2 is more anterodorsal. When plotted in the y–z plane, the electrode contacts lie along a line reflecting the electrode trajectory and are significantly correlated ($r = 0.748$, $p < 0.001$) (fig 3A).

Effect of contact location on clinical outcome

The mean percentage improvement in BFM movement scores for the contralateral hemibody, arm and leg for clusters 1 and 2 are shown in fig 3B. The improvement in hemibody score was greater in cluster 1 than in cluster 2 (79.5% vs 61.9%) but this did not reach significance ($p = 0.071$). Analysis of arm and leg subscores revealed significantly greater improvement in cluster 1 than in cluster 2 for the arm (86.3% vs 51.9%; $p = 0.008$) but not the leg (72.6% vs 73%; NS) (fig 3B). We were also interested in the number of sides with superior outcome defined as $>80\%$ improvement in hemibody BFM score, a level of improvement used in a previous study of GPi DBS for dystonia using the BFM scale.⁹ Overall, there were 16 (of 30) sides with superior outcome, which occurred more frequently in cluster 1 (8/10) than in cluster 2 (8/20) ($\chi^2 = 4.29$, $p < 0.05$). The number of

DYT1 sides did not differ significantly between clusters 1 (6/10) and 2 (8/20) ($\chi^2 = 1.07$, NS). To further investigate if DYT1 status could account for the observed superior outcome for the arm in cluster 1, we performed repeated measures ANOVA on the arm subscores with the main factor of time (before and after surgery), between subjects factor of DYT1 and covariates of y and z coordinates. The x coordinate was omitted from the ANOVA because x did not contribute to electrode contact clustering. There was a significant main effect of time ($F(1,26) = 11.3$; $p < 0.005$), time \times y interaction ($F(1,26) = 4.6$; $p < 0.05$) but no time \times DYT1 interaction ($F(1,26) = 0.29$; $p = 0.596$). There was a significant inverse correlation between y coordinate and percentage improvement in hemibody BFM score ($r = -0.42$, $p = 0.022$), arm ($r = -0.43$, $p = 0.019$) but not leg ($r = -0.14$; NS). The same inverse correlation with y coordinate was observed for total axial scores ($r = -0.57$, $p = 0.025$) (fig 4).

We applied cluster analysis to the averaged x, y and z coordinates in each patient which again identified two spatially distinct groups: a posteroventral cluster (four patients; centre $x = 20.7$ mm, $y = 2.05$ mm, $z = -3.23$ mm) and more anterodorsal cluster (11 patients; centre $x = 20.86$ mm, $y = 3.55$ mm, $z = 0.14$ mm). The percentage improvement in axial BFM movement score was greater in the posteroventral than in the anterodorsal cluster (91% vs 70.3%), and for the trunk subscore this difference was significant (96% vs 65%; $p < 0.05$). Similarly, for the whole body BFM movement score, the percentage improvement was greater in the posteroventral than in the anterodorsal cluster (88.7% vs 67.2%; $p = 0.02$) and correlated with the y coordinate ($r = -0.62$, $p = 0.013$).

DISCUSSION

In the present study, our main finding is that superior improvement of dystonia is associated with chronic high frequency stimulation in the most posteroventral part of the GPi. The y (A–P) axis position of the electrode contact significantly influenced the efficacy of GPi DBS; the more posterior electrode contacts were therapeutically more effective.

The degree of improvement in patients with primary generalised dystonia following bilateral GPi DBS was similar to that previously reported.^{4,5} In contrast with these studies, we did observe a significantly better outcome in patients with DYT1. The superior outcome in DYT1 could act as a confounding factor, but we consider this unlikely for the following reasons. Firstly, DYT1 sides were not overrepresented in the posteroventral electrode contact cluster, and secondly, ANOVA showed no effect of DYT1 status and a clear effect of y coordinate on outcome. Our initial cluster analysis identified an anterodorsal–posteroventral gradient of electrode contact effectiveness, with better outcomes occurring more frequently in the posteroventral location. The subsequent finding of an exclusive correlation between the y coordinate and contralateral clinical outcome suggests y to be the more important predictor than z of electrode contact effectiveness.

The explanation for our findings may relate to pallidal anatomy. Anatomical and physiological studies in primates have shown that the sensorimotor territory of the GPi is ventral and posterior,^{10,11} the somatotopic arrangement such that the face and arm are posterior and ventral, and the leg central and more dorsal.¹² The pallidal anatomy supports our findings of superior efficacy of posteroventral stimulation as this is the sensorimotor area and modification of these circuits might be expected to alter the expression of dystonia. Pallidal somatotopy helps explain another aspect of our results; we found that posteroventral stimulation was best for the arm and overall, while for the leg, anterodorsal stimulation was of equivalent efficacy. These findings agree with GPi somatotopy, in that the

leg area extends more dorsally and centrally. Furthermore, our results agree with another study of GPi DBS contact location in PGD in which superior improvement for the leg was associated with electrode contact placement more centrally within the GPi, whereas posterior contact location was more efficient for the arm.⁹

Another relevant anatomical consideration is that the major routes of pallidal outflow, the ansa lenticularis and lenticular fasciculus, overlap in the posteroventral GPi,¹³ making both routes of pallidal outflow accessible to intervention in this region. It should be mentioned that although our findings have concentrated on GPi which was the targeted and stimulated structure, a contributory role of the globus pallidus externus (GPe), which lies in intimate relation to GPi, cannot be excluded. Congruent with our targeting results, groups using microelectrode recording during pallidal DBS for dystonia identify an optimal target area in the posteroventrolateral GPi close to the border with GPe.¹⁴ At the very least, our data confirm the superiority of the posteroventral pallidal target, which includes GPi but may also additionally include a contributing effect from the adjacent GPe.

Clinical observations also provide support for the importance of the posteroventral pallidum as an area for modification of motor symptoms. Leksell observed that the beneficial effects of pallidotomy improved as the lesions were made in a more posterior location,¹⁵ which led to the successful reintroduction of posteroventral pallidotomy for PD.⁶ In patients with PD, stimulation in the posteroventral GPi alleviates rigidity and abolishes dyskinesia but may worsen akinesia, while stimulation of dorsal contacts improves akinesia,^{16,17} suggesting functional segregation of effects. The volume of lesions in the posteroventral but not the anterodorsal part of the GPi correlates with the relief of dyskinesia in patients with PD.¹⁸ In addition, two of our patients developed akinesia with posteroventral stimulation, which resolved when more dorsal contacts were used. Taken together, these observations suggest that intervention in the posteroventral GPi is more “anti-kinetic” than in anterodorsal areas, and is consistent with our finding of optimal suppression of involuntary dystonic movements with stimulation in this region.

Our results raise an obvious and important question. Why did we not use the most ventral contacts in all patients? In most patients we did use the most ventral contacts; in some patients side effects limited their use and in one patient (patient No 7) more dorsal contacts were clinically superior to initial trials of more ventral contacts. However, in patient No 7, the stimulated contacts were 0.7 mm and 0.45 mm below AC-PC, therefore the good outcome in her case was still associated with more posteroventral rather than anterodorsal stimulation.

A limitation of our study is that it was not randomised or fully blinded, which may have introduced biases. Future studies randomising patients to either posteroventral or anterodorsal GPi stimulation with clinical assessment blinded to group would be an important next step to confirm our findings.

Our results confirm the superiority of the posteroventral GPi target for effective relief of dystonia with DBS. The accepted atlas target coordinates correspond well with the most effective contact location in our series. Our data would suggest that particular attention should be paid to targeting in the antero-posterior axis

to ensure sufficiently posterior placement of the electrode. Based on our findings, we would advocate that in patients with GPi DBS for dystonia, the lowermost contacts of the quadripolar electrode, without side effects, be tried for chronic stimulation first, since these, with conventional orientation of electrode trajectory, will be the most posteroventral. The identification of an anterodorsal to posteroventral gradient of contact efficacy may be explained by the functional organisation and anatomy of GPi and its outflow tracts.

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Authors' affiliations

S Tisch, L Zrinzo, P Limousin, K Ashkan, M Hariz, Unit of Functional Neurosurgery, Sobell Department of Motor Neuroscience, Institute of Neurology, London, UK

K P Bhatia, N Quinn, Sobell Department of Motor Neuroscience, Institute of Neurology, London, UK

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