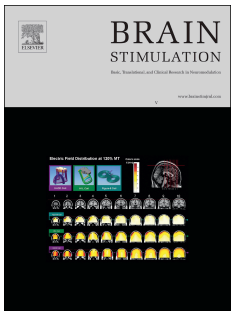


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PII: S1935-861X(23)01977-0

DOI: https://doi.org/10.1016/j.brs.2023.12.012

Reference: BRS 2527

To appear in: *Brain Stimulation*

Received Date: 24 October 2023

Accepted Date: 22 December 2023

Please cite this article as: Cuartero M-C, Grabli D, Flamand-Roze E, Karachi C, Rouaud T, Derkinderen P, Damier P, Raoul S, Krack P, Moro E, Fraix Valé, Chabardès Sté, Burbaud P, Guehl D, Cuny E, Pinto S, Vidailhet M, for the SPIDY3 study group, Lessons from multitarget neurostimulation in isolated dystonia: Less is more?, *Brain Stimulation* (2024), doi: https://doi.org/10.1016/j.brs.2023.12.012.

**Letter to the Editor**

# Lessons from multitarget neurostimulation in isolated dystonia: less is more?

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Word count: 992 words; 1 Table; 13 References; 5 Supplementary materials

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Dear Editor,

Deep brain stimulation (DBS) is an established therapeutic for disabling dystonia.[1,2] The internal globus pallidus (GPi-DBS) and subthalamic nucleus (STN-DBS) are the most frequently used targets to improve dystonia.[3] In selected patients with dystonia, thalamic stimulation targeted the ventral intermediate nucleus (dystonia plus tremor[4] and myoclonus-dystonia[5]), the ventralis oralis anterior and the posterior nuclei (post-traumatic dystonia with damaged GPi).[6] The centromedian-parafascicular complex (Cm-Pf) has attracted less attention. The Cm-Pf has connections with the striatum and the GPi and is involved in movement performance,[7] sensorimotor coordination (Cm), arousal and attention (Pf).[8] Our aim was to modulate dystonia networks by targeting key structures (Cm-Pf, STN), to evaluate the clinical effects from simple or combined (with GPi-DBS) stimulation, and to explore the potential therapeutic gain of dual stimulation to improve sub-optimal benefit of GPi stimulation alone.

We designed a prospective, randomized, multicenter study in patients with medically refractory dystonia, to assess the efficacy and safety of several DBS conditions: i) GPi-DBS alone, ii) alternative target alone (STN-DBS or Cm-Pf-DBS), and iii) combined GPi+alternative target DBS. We assessed motor (dystonia severity and disability) and non-motor (anxiety, depression) symptoms, with a double-blind evaluation. Our multicenter (Paris, Nantes, Bordeaux, Grenoble) clinical trial (AP-HP protocol number: P060235; Ethics Committee: CPP3207, IDRCB2006-A00477-44) had a parallel-group design and followed the CONSORT statements (Supplementary material 1), and was performed in accordance with the Declaration of Helsinki. Inclusion criteria were: clinically-diagnosed isolated dystonia refractory to medical treatments, age between 18 and 70 years, at least one year of disease duration, normal neurologic examination, normal cognitive functions, normal brain MRI. Exclusion criteria were psychiatric disorders, or other medical condition that could increase surgical risk or interfere with trial completion.

Twelve patients (Supplementary material 2) were included and underwent simultaneous bilateral electrode implantation in two targets: the sensorimotor part of the GPi, and an *alternative* target – STN or Cm-Pf – randomized according to 1:1 design prior to surgery. The two leads for each target were connected to an implantable pulse generator. DBS was switched-on 3 months after surgery. Acute testing was performed to allow for contact mapping of the DBS targets (pre-defined standardized procedure), optimal DBS parameter setting (based on the location of contacts on post-operative scan), and threshold identification for side effects. The order of the tested DBS conditions was determined by a random assigned sequence prior to surgery for each patient, blind to the target/stimulation conditions (Supplementary material 3). Particular attention was paid to optimization of stimulation settings (Supplementary material 4). Monopolar cathodal stimulation was used for all patients. All electrodes were set and maintained at 130 Hz (except for STN-DBS set at 20 Hz for patient 10). Pulse width (60 to 90 μs) and amplitude (1.5 to 4 V) were in the usual range. At the end of the study, all patients were set at their optimal condition: either GPi-DBS (n=10) or GPi+STN-DBS (n=2). Clinical assessments and patient self-evaluation were carried out pre- and post-surgery at the optimal setting of the DBS conditions, and for each DBS condition. The primary outcome measures, dystonia severity and disability, were evaluated with the Burke-Fahn-Marsden Dystonia Rating Scale movement (BFMDRS-M) and disability (BFMDRS-D) scores. Two neurologists (M.V. and D.Gr.), blinded to the DBS conditions, conjointly rated all patients based on video recordings obtained at each follow-up visit. Quality of life (36-Item Short Form Health Survey–SF-36, cranio-cervical dystonia questionnaire–CDQ-24), depression and anxiety (Hospital anxiety and depression scale–HAD) were also assessed (secondary outcome measures). We initially planned to include 20 patients (10 for each alternative target), but the recruitment was stopped prematurely as bilateral GPi-DBS became available as standard of care for dystonia in France during the study period. This explains the main limitation of the study, which is the small patient sample.

As in earlier studies[1,2,9], and despite variability of outcome among patients,[10] our results confirmed the efficacy and safety of bilateral GPi-DBS in dystonia (**Table 1**): patients experienced 44% improvement in dystonia severity (BFMDRS-M scores; p<0.001), quality of life (CDQ24; p<0.01) and anxiety (HAD-A; p=0.03) at 3 months with DBS. Our results were globally negative as a group, both for STN and Cm-Pf stimulation alone. Again, as a group, we did not observe any additional benefit of dual targets stimulation (GPi+STN or GPi+ Cm-Pf), with some exceptions at the individual level (Supplementary material 5). Such contrast between our results and the literature on STN-DBS[3, 10, 11, 12] has several explanations: i) most likely, the optimal settings and effects were not reached within the relatively short time-frame of the stimulation protocol and ii) time to optimal improvement may be quite variable.[10,11]

We explored, for the very first time in dystonia, the effect of Cm-Pf stimulation, alone or in combination with GPi-DBS. The choice of this particular target may have been relevant as movement-related neuronal activity in the Cm-Pf was identified per-operatively in cervical dystonia, suggesting its participation in movement performance.[7] The Cm-Pf connectivity reflects its modulatory influence on the sensorimotor[13] (Cm-related), and the limbic and associative (Pf-related) networks, potential therapeutic targets to control abnormal movements. However, no motor effect was observed in our study with Cm-Pf-DBS or GPi+Cm-Pf-DBS. Yet, considering the complex properties of Cm-Pf related motor and non-motor networks, the BFMDRS-M scale may not have been appropriate to detect subtle motor effects.

In conclusion, this study on multitarget stimulation is overall negative: we failed to demonstrate the efficacy of STN-DBS and Cm-Pf-DBS, or the added value of combined targets (GPi+Cm-Pf-DBS and GPi+STN DBS), We confirmed the global effect of bilateral GPi stimulation, albeit with inter-individual disparities in therapeutic effects targets. This heterogeneity of response, known with GPi-DBS, was also observed with STN-DBS in our study. Deciphering inter-individual disparities of therapeutic responses may be the "Rosetta stone": heterogeneous responses may shed new

light on disease heterogeneity and networks dysfunctions. This may pave the way toward a more personalized medicine (and research) based on individual results (by analogy to "N-of-one" type of research), and contribute to decipher brain networks functions and dysfunctions in dystonia.

**Credit author statement**

*Conceptualization:* D.Gr., M.V.; *Methodology:* D.Gr., M.V.; *Formal analysis:* D.Gr., M-C.C., M.V., S.P.; *Investigation:* C.K., D.Gr., D.Gu., E.C., E.F-R, E.M., M.V., T.R., P.B., P.Da., P.De., P.K., S.C., S.R., V.F.; *Resources:* C.K., D.Gr., D.Gu., E.C., E.F-R, E.M., M.V., T.R., P.B., P.Da., P.De., P.K., S.C., S.R., V.F.; *Data Curation:* D.Gr., M-C.C., M.V., S.P.; *Writing - Original Draft:* D.Gr., M-C.C., M.V., S.P.; *Writing - Review & Editing:* C.K., D.Gu., E.C., E.F-R, E.M., T.R., P.B., P.Da., P.De., P.K., S.C., S.R., V.F.;*Visualization:* M-C.C., S.P.; *Supervision:* D.Gr., M.V.; *Project administration:* D.Gr., M.V.; *Funding acquisition:* D.Gr., M.V.

**Funding**

The SPIDY3 clinical trial was funded by a French Programme Hospitalier de Recherche Clinique (PHRC), project number AOM06096, for which the sponsor was the *Département de la Recherche Clinique et du Développement (DRCD)* of the *Assistance Publique des Hôpitaux de Paris (AP-HP)*.

**Declaration of competing interest**

None.

**Acknowledgements**

The authors wish to thank all of the collaborators of the French SPIDY3 study group: in Paris, Welter M-L., Czernecki V., Cornu P., Navarro M-S., Dormont D., Lehéricy S., Pidoux B. and Yelnik J; in Nantes, Auffray-Calvier E. and Péréon Y.; in Grenoble, Ardouin C., Seigneuret E., Lebas J-F., Grand S. and Pollak P.; in Bordeaux, Benazzouz A., Machado S., and Rougier A.; in Lille, Defebvre L., Kreisler A., Simonin C., Destee A., Dujardin K., Blond S., Touzé G., Delmaire C. and Cassim F.; in

Lyon, Broussolle E., Thobois S., Bouvard M., Mertens P., Guenot M. and Hermier M. They also wish to thank the Département de la Recherche Clinique et du Développement (DRCD) of the Assistance Publique Hôpitaux de Paris (AP-HP), Cécile Jourdain and the Clinical Investigation Centre (CIC) of Paris, France, for helpful support.

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**Table 1. Dystonia severity and disability scores, and self-assessment of quality of life, anxiety and depression.**

| Conditions | **BFMDRS-M** (0-120) | **BFMDRS-D** (0-30) | **SF-36** (0-100) | **CDQ-24** (0-100) | **HAD-A** (0-21) | **HAD-D** (0-21) |
|---|---|---|---|---|---|---|
| **Pre-surgery** | **38.27±24.61** | **11.10±5.36** | **57.56±19.33** | **44.97±16.03** | **9.50±4.06** | **4.90±4.63** |
| **GPi** (mean ± SD) | **21.13±18.16** | **8.08±6.08** | **62.60±19.26** | **29.77±23.09** | **5.55±3.14** | **3.27±3.04** |
| *p-value, size effect* | *p=0.001, d=-1.01* | *p=0.13, d=-0.49* | *p=0.46, d=0.26* | *p=0.01, d=-0.82* | *p=0.03,d= -1.31* | *p=0.50, d=-0.58* |
| **STN** (mean ± SD) | **31.05±26.62** | **9.00±7.59** | **54.25±23.88** | **26.44±13.58** | **6.17±3.54** | **4.00±3.16** |
| *p-value, size effect* | *p=0.18, d=-0.30* | *p=0.18, d=-0.30* | *p=0.43, d=-0.35* | *p=0.06, d=-0.91* | *p=0.17, d=-1.00* | *p=0.58, d=-0.28* |
| **Cm-Pf** (mean ± SD) | **37±17.76** | **9.25±8.18** | **60.56±25.87** | **39.79±23.33** | **5.75±5.56** | **3.25±5.19** |
| *p-value, size effect* | *p=0.71, d=-0.06* | *p=0.86, d=-0.30* | *p=0.31, d=0.39* | *p=0.31, d=-0.54* | *p=0.33, d=-0.66* | *p=0.90, d=-0.23* |
| **GPi+STN** (mean ± SD) | **33.50±18.54** | **10.17±4.96** | **57.09±23.69** | **29.62±20.79** | **5.83±4.36** | **3.16±1.29** |
| *p-value, size effect* | *p=0.44, d=-0.21* | *p=0.75, d=-0.10* | *p=0.31, d=-0.50* | *p=0.06, d=-0.63* | *p=0.10, d=-0.88* | *p=0.65, d=-0.54* |
| **GPi+Cm-Pf** (mean±SD) | **18±11.47** | **9.20±4.55** | **71.39±18.09** | **28.91±13.90** | **5.20±4.71** | **2.60±2.61** |
| *p-value, size effect* | *p=0.06, d=-1.06* | *p=0.76, d=-0.42* | *p=0.19, d=0.10* | *p=0.06, d=-1.51* | *p=0.06, d=-0.84* | *p=0.28, d=-0.46* |

DBS effects were analyzed with R (Rstudio, version 1.4.1106; https://www.r-project.org/), using non-parametric Wilcoxon's tests (significant threshold set at $p<0.05$) and Cohen's *d* size effect since data were not distributed normally (Shapiro-Wilk test < 0.05). SD: standard deviation; BFMDRS: Burke Fahn Mardsen Rating Scale; M: motor; D: Disability; SF-36: Short Form (36) Health Survey; CDQ-24: Cranio-cervical dystonia questionnaire; HAD-A & HAD-D: Hospital Anxiety and Depression scale. The range of size effects being: very small ($0.01 < d < 0.2$), small ($0.2 < d < 0.5$), medium ($0.5< d < 0.8$), large ($0.8 < d < 1.20$), very large ($1.20 < d < 2$) and huge ($> 2$).

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: