OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Case Reports

Rescue GPi-DBS for a Stroke-associated Hemiballism in a Patient with STN-DBS

Genko Oyama[1], Nicholas Maling[1], Amanda Avila-Thompson[1], Pam R. Zeilman[1], Kelly D. Foote[1], Irene A. Malaty[1], Ramon L. Rodriguez[1] & Michael S. Okun[1]*

[1] Departments of Neurology and Neurosurgery, Center for Movement Disorders & Neurorestoration, University of Florida, Gainesville, Florida, United States of America

Abstract

Background: Hemiballism/hemichorea commonly occurs as a result of a lesion in the subthalamic region.

Case Report: A 38-year-old male with Parkinson's disease developed intractable hemiballism in his left extremities due to a small lesion that was located adjacent to the right deep brain stimulation (DBS) lead, 10 months after bilateral subthalamic nucleus (STN)-DBS placement. He underwent a right globus pallidus internus (GPi)-DBS lead implantation. GPi-DBS satisfactorily addressed his hemiballism.

Discussion: This case offered a unique look at basal ganglia physiology in human hemiballism. GPi-DBS is a reasonable therapeutic option for the treatment of medication refractory hemiballism in the setting of Parkinson's disease.

Keywords: Globus pallidus internus, subthalamic nucleus, deep brain stimulation, hemiballism, stroke

Citation: Oyama G, Maling N, Avila-Thompson A, et al. Rescue GPi-DBS for a stroke-associated hemiballism in a patient with STN-DBS. Tremor Other Hyperkinet Mov 2014; 4. doi: 10.7916/D8XP72WF

*To whom correspondence should be addressed. E-mail: okun@neurology.ufl.edu

Editor: Elan D. Louis, Columbia University, United States of America

Received: November 22, 2013 **Accepted:** December 23, 2013 **Published:** February 4, 2014

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Introduction

Hemiballism is an involuntary hyperkinetic movement disorder characterized by unilateral, violent, and flinging movements of the limbs[1] and can result from a lesion in the contralateral or ipsilateral subthalamic nucleus (STN), the subthalamic region, the thalamus, and also several other brain regions.[2–4] Hemiballism is more severe when resulting from an STN lesion than when caused by involvement of other brain regions. In medically refractory cases, surgical interventions such as thalamotomy[5,6] and pallidotomy[7,8] have been applied sparingly, since it is generally believed that the hyperkinetic movements will lessen over time even without intervention.[4,9] We report a unique case where deep brain stimulation (DBS) of the globus pallidus internus (GPi-DBS) was utilized to suppress hemiballism resulting from a subthalamic stroke. This patient had bilateral STN-DBS performed in the remote past for Parkinson's disease (PD), and a new stroke was discovered to be adjacent to one of the previously implanted stimulators. We present the details of the case and also the physiological recordings from the DBS surgery.

Case report

A 38-year-old male with young-onset PD was initially referred to the University of Florida Center for Movement Disorders and Neurorestoration for evaluation. He had initially developed left-sided bradykinesia, rigidity, and tremor, and was treated with carbidopa/levodopa 25/100, one tablet, five times daily, which resulted in excellent benefit to his PD symptoms. Over the years he developed intolerable wearing off, and severe peak-dose dyskinesia that could not be improved by altering the dose (carbidopa/levodopa 25/100, two tablets, five times daily) and combinations of medications, including rasagiline 1 mg and entacapone 200 mg five times daily. His Unified Parkinson's Disease Rating Scale (UPDRS) motor score was 11 (on medication) and 25 (off medication).

He underwent a simultaneous, bilateral, STN-DBS implantation at the age of 44 years. Microelectrode recording (three passes on each hemisphere) was performed without anesthesia and was followed by macro-test stimulation. He reported excellent immediate implantation effects, with complete tremor suppression in both hands. One month

following his lead implantation, subclavicular generators (Soletra, Medtronic, Minneapolis, MN) were implanted and connected to the DBS leads under general anesthesia. The placement of the leads was confirmed postoperatively by a computed tomography (CT) scan fused to preoperative magnetic resonance imaging (MRI) (ventral lead tips: right 6.1 mm posterior, 10.6 mm lateral, 7 mm inferior; left 8.6 mm posterior, 10.1 mm lateral, 8 mm inferior). The lead locations were calculated as relative to the midpoint of the anterior posterior commissure (AC–PC) line. His chronic stimulation parameters were left STN, 2(−)C(+), 2.4 V, 90 μs, 135 Hz; right STN, 1(−)3(+), 2.0 V, 90 μs, 130 Hz. The postoperative UPDRS motor score was 33 (off medication/off stimulation), 27 (on medication/off stimulation), 24 (off medication/on stimulation), and 6 (on medication/on stimulation). At that time he reduced the dose of entacapone to 200 mg, taking only one tablet at night. He reported no "off" medication time, and he had minimal dyskinesia for the subsequent 9 months.

Approximately 10 months after DBS placement, while on vacation with family, he developed sudden-onset, severe left arm and leg dyskinesia. He turned off his DBS devices, and weaned off of all his PD medications, but the movements persisted. Four weeks later, he was admitted to the hospital for inpatient management of the ballistic movements. To suppress this hyperkinetic movement, lorazepam, 10 mg daily in three divided doses and olanzapine 5 mg three times daily were continued for 1 month, but these were only moderately helpful. The addition of clozapine, also in an attempt to control the hyperkinesia, only improved the hemiballism minimally.

After discussing the risks and benefits of potential surgery, a decision was made to place a right GPi-DBS device. As part of the preoperative protocol, high-resolution MRI was done and revealed a new T2 high- and T1 low-intensity lesion within the right STN that was directly adjacent to the right STN-DBS lead (Figure 1).

Microelectrode recording was performed without anesthesia, and single unit and local field potential (LFP) recordings were collected during the procedure. The recordings were split into two digitally filtered channels. Single units were sampled at 12.2 kHz and filtered from 500 Hz to 6 kHz. LFPs were sampled at 400.2 Hz and filtered from 0.5 to 200 Hz. During two passes, 14 single units were recorded from the target area, beginning at 8.3 and 9.7 mm from final depth (final depth was defined on the computer as the ventral/bottom of the optic track). The mean firing rate of the isolated neurons was 46.1 ± 29.2 Hz (n=14). The mean coefficient of variance for the inter-spike interval was 1.19 ± 0.28 ms. The mean burst index was 0.30 ± 0.3. Figure 2 illustrates a representative microrecording (Figure 2A) and histogram of inter-spike interval (Figure 2B).

Throughout both microelectrode passes, a high-pass hardware filter (125 Hz, 20 db/decade) was disabled to allow LFP recordings. Signal analysis was performed using MATLAB 7.7 software (Mathworks, Natick, MA). Total power spectrum analysis for each LFP was accomplished utilizing short time Fourier transform with a length of 4,096, and spectrograms were computed using a 256-point Hanning window with 50% overlap. The power spectra analysis revealed that strong beta activity was present at the baseline. During one recording,

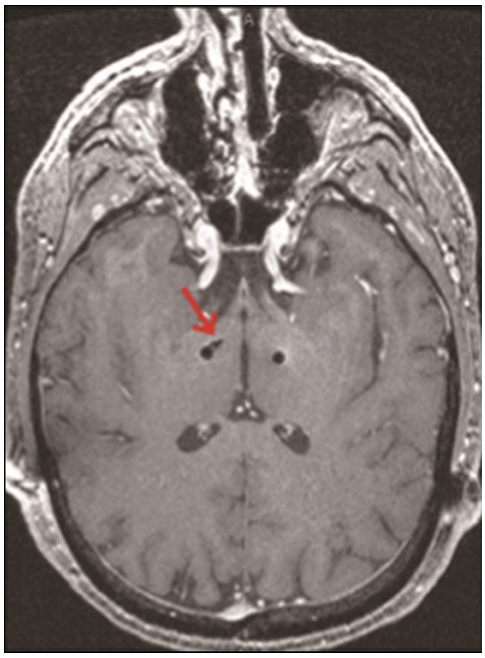

Figure 1. **STN infarction adsacent to the DBS lead.** Subthalamic nucleus infarction (red arrow) is seen adjacent to the previously placed deep brain stimulator.

stimulation from the previous implant in the left STN was enabled for 30 s. This stimulation had no effect on the beta band; on the other hand, theta band activity was increased (Figure 2C). Linear regression analysis suggested that theta would return to baseline levels 54.5 s after cessation of stimulation, though this was not recorded.

After microelectrode recording, macrostimulation was performed to confirm thresholds for side effects and benefits, and a 3387 DBS lead (Medtronic) was implanted and connected to the existing right-sided Soletra implantable pulse generators (IPGs) (Medtronic). A left-sided Soletra IPG was changed to a Kinetra IPG (Medtronic, Minnesota), which was then connected to the existing bilateral STN-DBS leads. The GPi lead was immediately activated and the stimulation settings were adjusted at 1 month to 1(−)C(+), 3.3 V, 90 μs, 135 Hz on right GPi, 2(−)C(+) 2.2 V, 60 μs, 135 Hz for the left STN-DBS, and 5(−)7(−) 1.5 V, 90 μs, 135 Hz for the right STN-DBS. The lead location was confirmed by postoperative CT–MRI fusion (ventral tip: 0.4 mm posterior, 21.5 mm lateral, 7.2 mm inferior relative to the midpoint of the AC–PC line). The hemiballistic movements abated in the operating theater during testing and the patient noticed improvement immediately on activation. By the end of the first postoperative week, the hemiballistic movements had completely resolved. He reported no dyskinesia or wearing off and was taking carbidopa/levodopa 25/100, one tablet, three times daily.

Discussion

There were several important observations in this case. First, the STN stroke with resulting hemiballism was located adjacent to the previously placed DBS lead. This finding was unique, and it is

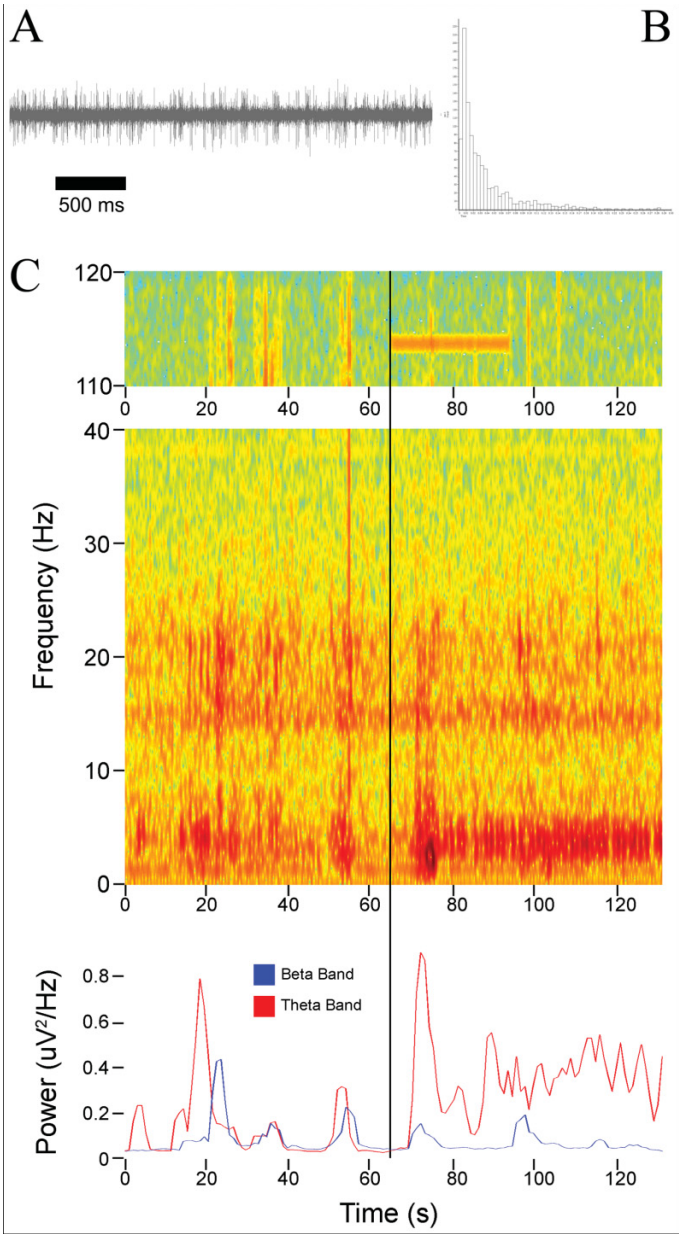

Figure 2. **Intraoperative physiological recordings.** The representative microrecording in globus pallidus internus (A) and histogram of inter-spike interval (B). (C) Spectral analysis of local field potential during stimulation. Spectrogram showing the occurrence of the stimulation artifact (107 Hz) from the previous ipsilateral deep brain stimulation implant in the subthalamic nucleus and oscillatory activity in the time vicinity of the stimulation. Quantification of theta (4–8 Hz) and beta (12–25 Hz) band oscillatory power revealed an increase in theta band activity.

unknown whether the DBS implantation itself influenced the occurrence of the stroke and when the stroke occurred. Second, we were able to treat the disabling movement disorder by adding a GPi-DBS system to the existing bilateral STN-DBS. To our knowledge, there is no existing report of GPi-DBS as applied for hemiballism, although thalamotomy[5,6] and pallidotomy[7,8] have been performed by other groups. Recently, Allert et al.[10] reported additional GPi-DBS rescue leads successfully applied for severe choreaform dyskinesias after a few years of STN-DBS implantation. The immediate cessation of this patient's movement matched the observations detailed in the previously published case reports that have utilized other surgical approaches. This current case offered us an opportunity to examine the human physiology, and to compare the physiology with the existing model of hemiballism.

The classical basal ganglia-thalamocortical motor circuit model has been previously proposed and can be applied to ballism.[11] Using the model, in hyperkinetic movements such as ballism, lesions within the circuitry have been postulated to reduce excitatory output from the STN that is directed to the GPi. Overall the model predicts a repeated word diminished basal ganglia output and enhanced thalamocortical activation.[2,12,13] The lesion in this area of basal ganglia has been postulated to produce ballistic movements. Our current DBS case offered us a unique opportunity to record from the pallidum, and to stimulate the STN in a patient with ballism.

In previous studies, Suarez et al.[7] reported that the firing rate of GPi in patients with hemiballism (30 ± 5 Hz) was lower than the observed rate in PD (on state $= 52 \pm 6$, off state $= 96 \pm 8$). Similarly, Vitek et al.[8] also reported the mean firing rate of GPi was lower in patients with hemiballism (33.7 ± 21.2 Hz) especially when compared with dystonia (50 ± 20.5 Hz). In Huntington's disease, which is known to be associated with chorea and in rare cases ballism, there has been a widely reported distribution of firing rates, but without correlation to chorea or hemiballism (29–81 Hz).[14–16]

In our case, it is possible that the patient initially had a typical firing rate and pattern in his basal ganglia indicative of PD, and then later developed a different firing pattern post stroke. Our intraoperative microrecording revealed a slightly lower activity from GPi than is typically observed in PD (46.1 ± 29.2 compared with 70–95 Hz).[14,17–19] The GPi firing rate in our case was higher than in the previously reported hemiballism cases.[7,8] On the other hand, the burst index in our case (0.30 ± 0.3) was lower than previously reported (1.5–2.5).[20,21] The markedly reduced burst index in our case may have been a result of pathological disruption of inputs from the STN. It is also possible that we observed heterogeneity from neurons recorded in the GPi, especially given the low sample number.

Abnormal synchronization of basal ganglia activity has been suggested to be associated with hyperkinetic movements.[7] Recently it has been shown that exaggerated beta oscillations in the 14–30 Hz bands are prominent and have been reported in STN PD cases[22–27] and also in GPi PD cases.[22,24,28–30] Beta synchronization in the basal ganglia circuitry has been shown to be suppressed by dopaminergic medication[22,24,25,29,30] and by high-frequency STN stimulation.[23,31–33] The suppression of oscillatory synchronization in the pallidum has also been correlated with levodopa-induced dyskinesia.[34] Our analysis of the LFP revealed the presence of a strong beta band that was similar to a previous report.[35] However, the beta band in our case was not suppressed by STN stimulation, which would not be the typical finding in PD, and we suspect the stroke altered the physiology. Additionally,

theta band activity in GPi was induced by stimulation. In dystonia patients, the low-frequency theta band is reported to be predominant in GPi and STN.[30,36,37] Similar to dystonia, low-frequency oscillations in basal ganglia may play a role in hemiballism or dyskinesia, but this hypothesis will need to be tested by a future study.

In conclusion, although only a single case, GPi-DBS was a reasonable therapeutic option for the treatment of medication refractory hemiballism in the setting of PD. More detailed human physiological studies of ballism in patients with and without PD are necessary, and may help us to better understand this entity.

References

1. Postuma RB, Lang AE. Hemiballism: revisiting a classic disorder. *Lancet Neurol* 2003;2:661–668.

2. Alarcon F, Zijlmans JC, Duenas G, Cevallos N. Post-stroke movement disorders: report of 56 patients. *J Neurology Neurosurg Psychiatry* 2004;75:1568–1574.

3. Chung SJ, Im JH, Lee MC, Kim JS. Hemichorea after stroke: clinical-radiological correlation. *J Neurol* 2004;251:725–729.

4. Lee MS, Marsden CD. Movement disorders following lesions of the thalamus or subthalamic region. *Mov Disord* 1994;9:493–507.

5. Bullard DE, Nashold BS, Jr. Stereotaxic thalamotomy for treatment of posttraumatic movement disorders. *J Neurosurg* 1984;61:316–321.

6. Levesque MF, Markham CH. Ventral intermediate thalamotomy for posttraumatic hemiballismus. *Stereotact Funct Neurosurg* 1992;58:26–29.

7. Suarez JI, Metman LV, Reich SG, Dougherty PM, Hallett M, Lenz FA. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. *Ann Neurol* 1997;42:807–811.

8. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999;46:22–35.

9. Dewey RB, Jr, Jankovic J. Hemiballism-hemichorea. Clinical and pharmacologic findings in 21 patients. *Arch Neurol* 1989;46:862–867.

10. Allert N, Schnitzler A, Sturm V, Maarouf M. Failure of long-term subthalamic nucleus stimulation corrected by additional pallidal stimulation in a patient with Parkinson's disease. *J Neurol* 2012;259:1244–1246.

11. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990;13:281–285.

12. Krauss JK, Pohle T, Borremans JJ. Hemichorea and hemiballism associated with contralateral hemiparesis and ipsilateral basal ganglia lesions. *Mov Disord* 1999;14:497–501.

13. Albin RL. The pathophysiology of chorea/ballism and Parkinsonism. *Parkinsonism Relat Disord* 1995;1:3–11.

14. Tang JK, Moro E, Lozano AM, et al. Firing rates of pallidal neurons are similar in Huntington's and Parkinson's disease patients. *Exp Brain Res* 2005;166:230–236.

15. Starr PA, Kang GA, Heath S, Shimamoto S, Turner RS. Pallidal neuronal discharge in Huntington's disease: support for selective loss of striatal cells originating the indirect pathway. *Exp Neurol* 2008;211:227–233.

16. Cubo E, Shannon KM, Penn RD, Kroin JS. Internal globus pallidotomy in dystonia secondary to Huntington's disease. *Mov Disord* 2000;15:1248–1251.

17. Lozano AM, Lang AE, Levy R, Hutchison W, Dostrovsky J. Neuronal recordings in Parkinson's disease patients with dyskinesias induced by apomorphine. *Ann Neurol* 2000;47:S141–146.

18. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: implications for models of dystonia. *Ann Neurol* 2003;53:480–488.

19. Starr PA, Rau GM, Davis V, et al. Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson's disease and normal macaque. *J Neurophysiol* 2005;93:3165–3176.

20. Zhao YQ, Zhou JA, Wang Y, Yu JC, Zhang H. Off-line analysis of single-unit neuronal discharge in the globus pallidus region in Parkinson's disease. *Chin Med J* 2010;123:1884–1887.

21. Favre J, Taha JM, Baumann T, Burchiel KJ. Computer analysis of the tonic, phasic, and kinesthetic activity of pallidal discharges in Parkinson patients. *Surg Neurol* 1999;51:665–672; discussion 72–73.

22. Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci* 2001;21:1033–1038.

23. Kuhn AA, Kempf F, Brucke C, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J Neurosci* 2008;28:6165–6173.

24. Priori A, Foffani G, Pesenti A, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;189:369–379.

25. Williams D, Tijssen M, Van Bruggen G, et al. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain* 2002;125:1558–1569.

26. Williams D, Kuhn A, Kupsch A, et al. Behavioural cues are associated with modulations of synchronous oscillations in the human subthalamic nucleus. *Brain* 2003;126:1975–1985.

27. Williams D, Kuhn A, Kupsch A, et al. The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *Eur J Neurosci* 2005;21:249–258.

28. Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J Neurosci* 2000;20:7766–7775.

29. Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain* 2002;125:1196–1209.

30. Silberstein P, Kuhn AA, Kupsch A, et al. Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. *Brain* 2003;126:2597–2608.

31. Brown P, Mazzone P, Oliviero A, et al. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp Neurol* 2004;188:480–490.

32. Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM. Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. *Exp Neurol* 2006;197:244–251.

33. Ray NJ, Jenkinson N, Wang S, et al. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp Neurol* 2008;213:108–113.

34. Silberstein P, Oliviero A, Di Lazzaro V, Insola A, Mazzone P, Brown P. Oscillatory pallidal local field potential activity inversely correlates with limb dyskinesias in Parkinson's disease. *Exp Neurol* 2005;194:523–529.

35. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci* 2007;30: 357–364.

36. Liu X, Wang S, Yianni J, et al. The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. *Brain* 2008;131:1562–1573.

37. Neumann WJ, Huebl J, Brucke C, et al. Enhanced low-frequency oscillatory activity of the subthalamic nucleus in a patient with dystonia. *Mov Disord* 2012;27:1063–1066.