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Letter to the Editor

Variable frequency stimulation of subthalamic nucleus for freezing of gait in Parkinson's disease

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High frequency stimulation (HFS) of the subthalamic nucleus (STN) provides consistent, long-term improvement of the cardinal signs of Parkinson's disease (PD), such as bradykinesia, tremor and rigidity. Freezing of gait (FOG) responds poorly to HFS and deteriorates over time, but this can be alleviated by using relatively low frequency stimulation (LFS) [1]. There are two major concerns when applying LFS in clinical practice, the first being the duration of clinical benefit. Evidence indicates that LFS-STN can improve axial signs in some but not all PD patients, but most of them experienced loss of efficacy in the short term. Then patients are left with little improvement or increasing tremor, rigidity and bradykinesia, which consists of the three main signs of PD. Thus even if axial problems can be ameliorated by LFS in the long term, patients might find deterioration of motor symptoms difficult to tolerate. Strategies to bypass this tolerance phenomenon to LFS are needed. Here, we describe a patient with FOG who received variable frequency stimulation (VFS) where the stimulation frequency was set to alternate between high and low frequencies.

In August 2012 after signing informed consent, a 66-year-old man was implanted with Deep Brain Stimulation systems [2] (PINS Medical). STN was chosen for the target. He developed rigidity in his limbs in the middle of 2007 and was diagnosed with PD in September of that year. Over time, his levodopa dose was increased from 250 mg to 1000 mg per day and 0.375 mg pramipexole was added. The levodopa equivalent dosage was decreased to 750 mg/day one month after implantation and UPDRS score decreased from 57 to 21. Six months later he developed FOG. The parameters of active contacts, amplitude and frequency were changed, but had no effect on the gait. Variable frequency stimulation was then applied with a remarkable improvement in the FOG observed with little deterioration of the limb rigidity. Parameters were 2.7 V, 60 us, 60 Hz & 130 Hz (60 Hz for 20 s and 130 Hz for 30 s per cycle) to the right side and 1.7 V, 60 us, 60 Hz & 130 Hz (60 Hz for 20 s and 130 Hz for 30 s per cycle) to the left side. A Timed up and go (TUG) test was conducted and videoed to show the improvement in the FOG (Table 1). The patient was followed-up by telephone after 4 months of VFS, and the benefit was still remarkable compared with traditional HFS, in spite of some deterioration.

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.parkreldis.2015.10.002.

Studies have shown that frequency stimulation significantly influences the effect of deep brain stimulation. Bradykinesia and hypokinetic FOG have been reported as adverse effects of HFS. Khoo et al. [1] found in randomized, double blind, prospective comparisons that alternating the frequency between 60 Hz and 130 Hz yielded a better response of the axial symptoms than just using the 60 Hz frequency. Moro et al. [3] showed that stimulating the pedunculopontine nucleus (PPN), which lies caudal to the STN, at 25 Hz in advanced PD patients resulted in significant improvement in FOG. Steffani and colleagues [4] demonstrated further synergism between STN (HFS) and PPN (LFS) with improved axial symptoms beyond that of stimulating either target individually. Based on these findings, we hypothesize that PD patients with FOG might benefit from STN-VFS. In order to prevent the STN from adapting to either frequency, we set the time duration of one cycle to be as short as possible. In addition, based on the beneficial results of HFS to appendicular symptoms and LFS to axial ones, we hypothesize that the time ratio used for each frequency should be programmed according to relevant PD symptoms. Thus, adding two additional parameters, such as time period for each cycle and ratio for each frequency, to the VFS programming will require additional time.

As Alfonso Fasano et al. [5] has indicated that frequency modulation is the encoding of information in a carrier wave by varying the instantaneous frequency of the wave. Although the beneficial results for FOG in our patient has lasted for four months in this study, we recognize that further studies are necessary to evaluate the effect of VFS in a larger sample size and longer study duration.

Author roles

Fumin Jia-conception, organization, and execution of research project; writing of the first draft; Yi Guo-implantation of DBS systems; Sen Wan-execution of research project; writing a part of first draft; Hao Chen-execution of research project; Hongwei Hao-organization of research project; Jianguo Zhang-medical assessment; Luming Li-conception and organization of research project; design; review and critique of manuscript, the corresponding author of this article.

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Table 1
Evaluation of FOG with constant frequency and variable frequency stimulation.

	Constant frequency	Variable frequency
	130 Hz	60 Hz & 130 Hz
Typical start hesitation episode (s)	20	3
Typical turning hesitation time (s)	14	3
Velocity (m/s)	0.75	0.83
Stride length (m)	0.40	0.42
FOG-Q Score	20	8
UPDRS III gait subscore (item 30)	2	0

The constant frequency stimulation applied 130 Hz to both the right and left sides.
The variable frequency stimulation applied 60 Hz & 130 Hz (60 Hz for 20 s and 130 Hz for 30 s per cycle) to both the right and left sides.
The gait evaluation used the FOG-Q (freezing of gait questionnaire) and UPDRS, the patient was off medication during the whole study.

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References

[1] H.M. Khoo, H. Kishima, K. Hosomi, T. Maruo, N. Tani, S. Oshino, T. Shimokawa, M. Yokoe, H. Mochizuki, Y. Saitoh, T. Yoshimine, Low-frequency subthalamic nucleus stimulation in Parkinson's disease: a randomized clinical trial, Mov. Disord. 29 (2014) 270–274, http://dx.doi.org/10.1002/mds.25810.

[2] H.G. Liu, Y. Ma, K. Zhang, M. Ge, F.G. Meng, T. Feng, X.H. Wan, Y. Guo, R.Z. Wang, A.C. Yang, W.H. Hu, J.Z. Guo, J.G. Zhang, Subthalamic deep brain stimulation with a new device in Parkinson's disease: an open-label trial, Neuromodulation 16 (2013) 212–218, http://dx.doi.org/10.1111/ner.12050.

[3] E. Moro, C. Hamani, Y.Y. Poon, T. Al-Khairallah, J.O. Dostrovsky, W.D. Hutchison, A.M. Lozano, Unilateral pedunculopontine stimulation improves falls in Parkinson's disease, Brain 133 (2010) 215–224, http://dx.doi.org/10.1093/brain/awp261.

[4] A. Stefani, A.M. Lozano, A. Peppe, P. Stanzione, S. Galati, D. Tropepi, M. Pierantozzi, L. Brusa, E. Scarnati, P. Mazzone, Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease, Brain 130 (2007) 1596–1607. http://dx.doi.org/10.1093/brain/awl346.

[5] A. Fasano, A.M. Lozano, The FM/AM world is shaping the future of deep brain stimulation, Mov. Disord. 29 (2014) 161–163, http://dx.doi.org/10.1002/mds.25834.

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