



AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Stimulation of the subthalamic area modulating movement and behavior

This is the author's manuscript	
Original Citation:	
Availability:	
This version is available http://hdl.handle.net/2318/149489	since 2015-07-03T13:51:21Z
Published version:	
DOI:10.1016/j.parkreldis.2014.07.013	
Terms of use:	
Open Access	
Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from convright	

(Article begins on next page)

protection by the applicable law.



UNIVERSITÀ DEGLI STUDI DI TORINO

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in PARKINSONISM & RELATED DISORDERS, 20, 2014, 10.1016/j.parkreldis.2014.07.013.

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

(1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.

(2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.

(3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en), 10.1016/j.parkreldis.2014.07.013

The definitive version is available at: http://linkinghub.elsevier.com/retrieve/pii/S1353802014002946

Stimulation of the subthalamic area modulating movement and behavior

L. Ricciardi¹, L. Morgante², A. Epifanio², M. Zibetti³, M. Lanotte³, L. Lopiano³, F. Morgante⁴.

¹ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

⁴ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

Keywords

Apathy; Parkinson's disease; Subthalamic nucleus; Zona incerta; Hemiballism; Deep brain stimulation.

Abbreviations

AES: apathy evaluation scale; BDI: Beck Depression Inventory; DBS: deep brain stimulation; FF: Forel Field; ICD: impulse control disorders; LEDD: levodopa equivalent daily dose; PD: Parkinson's disease; STN: subthalamic nucleus; ZI: zona incerta.

Apathy has been reported as a frequent symptom following deep brain stimulation (DBS) of the sub thalamic nucleus (STN) in patients with Parkinson's disease (PD) but the mechanism is still matter of debate^[1]. Here we report a PD patient in whom apathy was acutely induced by stimulation of the fibers surrounding the STN.

A 55-year-old man, with a 15-year history of PD complicated by impulse control disorders (ICD) (compulsive shopping and hypersexuality) and severe motor fluctuations underwent bilateral STN–DBS. At that time, he did not show any sign of depression or apathy and did not take any anti-depressant. Before surgery, he was treated with levodopa/carbidopa (1125 mg/day) and pramipexole (0.75 mg/day) and his levodopa equivalent daily dose (LEDD) was 1200 mg. Post-surgery thin slice MRI scan merged with pre-Op MRI showed correct anatomical placement of the electrodes within the STN region, with the most dorsal contact lying bilaterally in the zona incerta (ZI)/Forel Field (FF) area (Fig. 1).



Fig. 1: Postoperative sagittal T1-weighted MRI with Schaltenbrand and Wahren atlas superimposed showing the most dorsal contact of electrode lying into the ZI/FF area. ZI: zona incerta; FF: Forel's Field; STN: subthalamic nucleus; SN: substantia nigra.

² Department of Neuroscience, University of Messina, Messina, Italy.

³ Department of Neurosciences, University of Torino, Italy.

One month after surgery, he had improvement of motor fluctuations and increase in daily ON time with monopolar stimulation at 130 Hz and 60 mcs stimulus duration (contacts: 5-, 2.9 V; 1-, 2.7 V). However, gait was severely impaired because of ballism in the left lower limb, which had started immediately after surgery and worsened progressively. Ballism was not modified by turning OFF the stimulator or by levodopa administration (LEDD = 750 mg; pramipexole had been withdrawn) but significantly decreased with gait improvement, when switching the stimulation to the dorsal contacts. However, with this stimulating setting the patient developed apathy. He explained that he felt no emotional involvement neither for positive nor for negative stimuli, he did not have pleasure in going out, meeting people, doing his favorite activities, such as swimming, eating or having sex. He did not feel depressed, he just did not feel any drive in doing anything. He did not show any ICD. Apathy persisted despite increasing the LEDD up to 950 mg and reintroducing 0.75 mg/day of pramipexole.

Six months after DBS, we performed an acute stimulation challenge in the ON medication condition with different DBS settings and we probed motor, affective and behavioral outcomes. A signed written consent for using the video for publication was obtained by the patient, who was blinded to DBS conditions. Due to the lack of a validated scale able to detect acute changes in mood and motivation, we used the Apathy evaluation scale (AES) and Beck's Depression Inventory (BDI) instructing the patient to refer the questions to that particular moment. The following conditions were applied: A) bilateral monopolar stimulation of contacts 1- and 5- (previously found be the best contacts for parkinsonian signs); B) bilateral monopolar stimulation of the two most dorsal contacts (3-, 7-); C) bilateral monopolar stimulation of contacts 1- and 5-; D) unilateral monopolar stimulation of left STN at contact 3-; E) bilateral turning OFF of STN-DBS for 5 days; F) unilateral monopolar stimulation of right STN at contact 7-. For each stimulation condition, frequency and stimulus duration were kept constant at 130 Hz and 60 mcs, respectively. Conditions A to D were applied on the same day for 2 h each; condition F was applied for 2 h on the sixth day after bilateral turning OFF of STN-DBS. Voltage was gradually increased in each contact and chosen according to the best medical benefit obtained on motor symptoms and/or ballism. Bilateral stimulation of contacts 1- and 5- improved parkinsonism, did not produce apathy, but was associated to severe ballism of the left lower limb. Ballism was present in all stimulation conditions, including stimulation of the dorsal contact on left STN and when turning off STN-DBS, but there was no evidence of apathy. Only bilateral activation of the most dorsal contacts or stimulation of the dorsal contact on right STN determined resolution of ballism, improvement of gait disturbance and occurrence of severe apathy within 5 min (Fig. 2 and Video). The results of the acute stimulation challenge allowed us to conclude that stimulation of the most dorsal contact on right STN was capable to treat ballism, at expense of determining significant apathy. At latest follow-up (4 years after surgery), stimulating parameters were contact 1- (3.1 V) on left STN and contact 7-/5-(interleaving stimulation, 3.2/2.9 V) on right STN (both 60 mcs, 125 Hz). This setting allowed to control left lower limb ballism with mild apathy (AES = 10).



Fig. 2: Pre- and post-operative motor, affective and behavioral data in the ON medication state. After surgery, involuntary movements were present in all stimulation condition (A, C, E) and when turning off STN-DBS (D), but there was no evidence of apathy. Only bilateral activation of the most dorsal contacts (B) or stimulation of the dorsal contact of right STN (F) determined resolution of involuntary movements, improvement of gait disturbance and occurrence of severe apathy by AES increase. UPDRS-III = Unified Parkinson's disease rating scale, motor section; BDI = Beck Depression Inventory; LEDD = levodopa equivalent daily dose; AIMS = abnormal involuntary movement scale; AES = apathy evaluation scale; GF-Q = gait and falls questionnaire.

This PD patient with post-surgical ballism showed stimulation-locked apathy occurring when switching on the most dorsal contact on the right STN, which was also the one capable to reduce left lower limb ballism. Post-surgical hemiballism is a rare adverse effect of stereotactic surgery and has been also described after lesions involving the ZI and partially the STN^[2]. Stimulation of the most dorsal contact located within the ZI/FF lead to a significant reduction of post-surgical hemiballism, likely by stimulating the pallidofugal fiber tracts. Interestingly, activation of the same contact was also associated to quick occurrence of severe apathy. Apathy has been defined as a lack of feeling, emotion or interest leading to reduction of goal-directed behaviors and has been described as a feature of PD, independent from depression. Neuroimaging studies suggested that it might be produced by a dysfunction in the mesial frontal/anterior cingulate cortex-ventral tegmental connections. Apathy has been reported to occur in PD after STN-DBS and it has been considered as complication due to dopamine-agonists withdrawal. However, longitudinal studies showed no correlation between post-DBS apathy and decrease of dopaminergic drugs^[1], suggesting that dopaminergic denervation in the mesolimbic pathways or modulation of limbic networks by STN stimulation^[3] might be causative. Our case supports the hypothesis that apathy might partially depend on stimulation of fibers adjacent to STN and functionally involved in the mesocorticolimbic pathways. Two other cases with post-DBS apathy were described where the stimulating contact was lying in the ZI/FF^{[4], [5]}. Functional MRI during stimulation of right electrode on the ZI/FF producing apathy was performed in one of these cases^[5] and showed increased activity in many cortical and sub-cortical areas, including the superior prefrontal cortex and anterior cingulate area^[5].

We acknowledge among the limitations of our study, the use of assessment scales such as AES and BDI to evaluate acute changes in mood and motivation. However, due to the lack of a validated scale able to detect acute changes in these domains, we used AES and BDI instructing the patient to refer the questions to that particular moment. Moreover, to achieve resolution of left side ballism and optimal control parkinsonian signs, stimulation with the most dorsal contacts was delivered using a slight higher voltage; however, it is unlikely that a 0.1 V difference would account for the behavioral changes we described.

In conclusion, we suggest that apathy associated to STN-DBS is a multi-factorial phenomenon, not simply due to dopamine-agonist withdrawal syndrome but partly linked to the spreading of stimulation to the white matter tracts adjacent to the STN, a crucial crossway integrating motor and non-motor pathways.

Competing interests

This study did not receive any industry, government, institutional sponsorship or funding. Lucia Ricciardi received honoraria for lectures and educational activities from Chiesi Farmaceutici. Antonio Epifanio and Letterio Morgante received honoraria for lectures and educational activities from GlaxoSmithkline, Lundbeck, UCB pharma, and Novartis. Francesca Morgante received honoraria for speaking engagements from Allergan, Lundbeck, Novartis, Chiesi Farmaceutici, UCB pharma. Maurizio Zibetti, Leonardo Lopiano and Michele Lanotte did not report any disclosures.

References

^[1] S. Thobois, C. Ardouin, E. Lhommee, H. Klinger, C. Lagrange, J. Xie, *et al.* Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation.« Brain», 2010, 133, pp. 1111-1127.

^[2] J. Guridi, J.A. Obeso. The subthalamic nucleus, hemiballismus and Parkinson's disease: reappraisal of a neurosurgical dogma. «Brain», 2001, 124, pp. 5-19.

^[3] D. Drapier, S. Drapier, P. Sauleau, C. Haegelen, S. Raoul, I. Biseul, *et al.* Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? « J Neurol», 2006, 253 (8), pp. 1083-1091.

^[4] V. Czernecki, M. Schupbach, S. Yaici, R. Levy, E. Bardinet, J. Yelnik, *et al.* Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. « Mov Disord», 2008, 23, pp. 964-969.

^[5] T. Stefurak, D. Mikulis, H. Mayberg, A.E. Lang, S. Hevenor, P. Pahapill, *et al.* Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. «Mov Disord», 2003, 18, pp. 1508-1516.