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The ansa subthalamica as a substrate for DBS-induced manic symptoms

Over the years, important insight on the neurocircuitry of psychiatric symptoms have emerged from side effects recorded during deep brain stimulation (DBS). We have recently treated obesity in Prader Willi syndrome (PWS) using lateral hypothalamic region (LH) DBS [1,2] and noticed that two out of four patients developed stimulation-induced hypomania/mania.

Patient 1 was a 28y-old male who presented his first psychotic episode by the age of 12. At 14y, he developed hypomania and started treatment with lithium. Prior to DBS, he had mild obsessive-compulsive symptoms (Yale Brown Obsessive-Compulsive Scale, YBOCS, score of 12). Hypomanic or psychotic episodes were well-controlled with topiramate (300 mg/daily) and clozapine (150 mg/daily).

DBS electrodes (model 6149; St Jude Medical) were implanted in the LH under local anesthesia and sedation [1]. Targeting was based on the direct visualization of adjacent structures. Electrodes were implanted posterolateral to the fornix, anterolateral to the mammillary bodies, and posterior to the optic tract [1]. In a second procedure, electrodes were connected to a pulse generator (Libra XP6644; St Jude Medical) under general anesthesia. Contacts closer to the target were initially selected as cathodes (case anode).

Ten days after surgery, DBS was activated at 1.5 mA, 91 μsec, and 40 Hz. No hypomania was observed at this stage (Young Mania Rating Scale of 2; YMRS). The patient was reassessed every few days and stimulation increased by 0.5 mA until 3.5 mA. Over hours/days, he became more talkative, developed psychomotor agitation, irritability, impulsivity, had a reduced need for sleep and misidentification illusions. He was brought to our clinic, scoring 11 in the YMRS. DBS discontinuation led to prompt symptomatic amelioration. During the study, a lower current amplitude was administered with no recurrence of hypomania.

Patient 2 was an 18y-old female. By the age of 8, she had a brief psychotic episode. Since early adolescence the patient developed compulsive feeding, impulsivity, disinhibition, aggressive behaviour and hypersexuality. Also present were moderate OCD symptoms (YBOCS score of 24), skin picking and nail biting. Over the years she has taken topiramate, fluoxetine, sertraline, quetiapine, and methylphenidate. Prior to DBS she was receiving topiramate (25 mg/daily) and alprazolam (sporadically at night).

Surgery and the initial stimulation protocol were similar to those reported above. Prior to DBS activation, the patient's YMRS score was 7. Ventral contacts were the ones found to be closer to LH. During the titration phase, she progressively developed increased agitation, hypersexuality, aggressive and defying behaviours when receiving 3.5 mA (YMRS of 22). Discontinuing stimulation partially ameliorated her symptoms and topiramate 50 mg/day was given. Three weeks later, after the patient was relatively stable, the DBS system was reactivated with a relapse of impulsivity, emotional lability, aggressive behaviour and skin picking. DBS was discontinued and topiramate progressively increased to 150 mg/day and 200 mg/day. The administration of lower current amplitudes during the study was not associated with symptomatic recurrence.

Postoperative computed tomography (CT) and preoperative T1 images were co-registered and normalized to MNI, along with the USP-Würzburg atlas, as previously described [3,4]. The volume of tissue activated (VTA) was calculated using the finite element method-based model within Lead DBS [3,4]. VTA fields were exported as nifti files and imported into Amira. Scaled electrode models were built in 3Dsmax 7 (Autodesk Inc., USA) and imported to Amira (v 5.4.1, Visage Imaging GmbH, Germany) to fit the electrode trajectory reconstructed from post-op CTs. Using this method, 3D histological structures were merged to postoperative electrodes. VTAs were calculated in MNI space and displayed in Amira.

Fig. 1 reveals that structures potentially modulated by DBS at settings that induced hypomanic symptoms were the LH and the ansa subthalamica (AS), a fiber bundle that connects limbic portions of the subthalamic nucleus (STN) with anteroventral aspects of the globus pallidus internus (GPi) and ventral pallidum [5]. In patient 2, the right medial forebrain bundle (MFB) was within the VTA, while the left MFB was adjacent to it. In patient 1, only the right MFB was adjacent to the VTA. The medial aspect of the subthalamic nucleus was within the VTA in patient 2 but only next to it in patient 1.

By conveying information between limbic regions of basal ganglia structures [5], the ansa subthalamica may represent a potential substrate for the psychiatric side effects of DBS. According to our calculated VTA, DBS at settings that induced mania may have potentially activated the AS bilaterally.

In recent studies, DBS delivered to the superolateral division of the MFB induced significant clinical improvements in patients with depression [6]. In our study, the right MFB was within the VTA in patient 2 but adjacent to this tract in patient 1. This suggests that the MFB was unlikely involved in the development of manic symptoms in our patients. Additional structures potentially recruited but probably not associated with psychiatric side effects were the lateral hypothalamus and the anteromedial STN. In our previous study, the administration of lower currents was shown to affect the lateral hypothalamus in the absence of hypomania [1]. As for the STN, while medial aspects of the nucleus were within the VTA in patient 2, this was not the case for patient 1. As patients who did not developed hypomania in our previous trial did not

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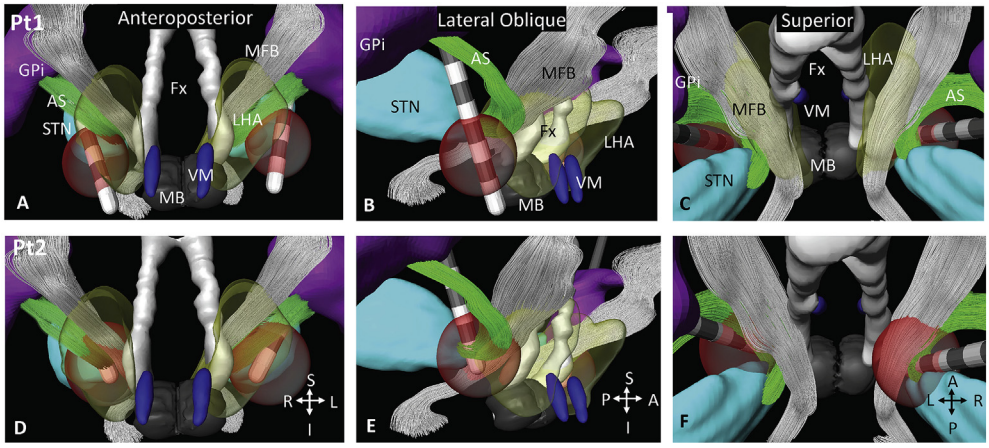

Fig. 1. Schematic representation of the electrode location in two patients with Prader Willi Syndrome treated with deep brain stimulation. Anteroposterior (A, D), lateral oblique (B, E) and superior (C, F) views in patients 1 (A, B, C) and 2 (D, E, F) are represented. At stimulation settings that induced hypomania/mania, structures within the volume of tissue activated by DBS (VTA; red spheres) were the ansa subthalamica and the lateral hypothalamus, bilaterally. In patient 2, the right medial forebrain bundle (MFB) was within the VTA while the left bundle was adjacent to it. In patient 1, the MFB was adjacent to the right but not the left VTA. The medial aspect of the subthalamic nucleus was near the VTA in patient 2 but not in patient 1. The lateral hypothalamic area [1] is represented in yellow (LHA), columns of the fornix in light grey (Fx), mammillary bodies in dark grey (MB), ventromedial nuclei (VM) in blue, the subthalamic nucleus in light blue (STN), the ansa subthalamica (AS), and the globus pallidus internus in purple (GPi). The medial forebrain bundle is represented in grey. pt-patient. A-anterior; P- posterior; R-right; L-left; S-superior; I- inferior.

receive stimulation at high currents [1], it is unlikely that neither the STN or AS were recruited.

The effects of DBS are comprised by a complex interplay of cellular, dendritic and axonal mechanisms [7]. If we consider that high frequency stimulation would drive the AS, potential consequences would be an excitation of the ventral pallidum and anteromedial GPi, the inhibition of associated thalamic regions and a reduced activation of prefrontal and orbitofrontal regions. Though we acknowledge this is a simplistic view, it may help to explain the reduced prefrontal metabolic activity observed in patients with OCD treated with anteromedial STN DBS [8], which would supposedly modulate the AS as well. This would also be in line with work suggesting that patients with mania have an attenuated metabolic activation of prefrontal and orbitofrontal cortical regions during multiple tasks [9,10].

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Declaration of competing interest

The authors declare no conflict of interest related to this work. CH was part of an unrelated advisory board for Medtronic.

References

[1] Franco RR, Fonoff ET, Alvarenga PG, Alho EJL, Lopes AC, Hoexter MQ, et al. Assessment of safety and outcome of lateral hypothalamic deep brain stimulation for obesity in a small series of patients with prader-willi syndrome. JAMA Netw Open 2018;1(7):e185275.
[2] Talakoub O, Paiva RR, Milosevic M, Hoexter MQ, Franco R, Alho E, et al. Lateral hypothalamic activity indicates hunger and satiety states in humans. Ann Clin Transl Neurol 2017;4(12):897–901.
[3] Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity Predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol 2017;82(1):67–78.
[4] Horn A, Kuhn AA. Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. Neuroimage 2015;107:127–35.
[5] Alho EJL, Alho A, Horn A, Martin M, Edlow BL, Fischl B, et al. The ansa subthalamica: a neglected fiber tract. Mov Disord 2020;35(1):75–80.
[6] Coenen VA, Bewernick BH, Kayser S, Kilian H, Bostrom J, Greschus S, et al. Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. Neuropsychopharmacology 2019;44(7):1224–32.
[7] Hamani C, Florence G, Heinsen H, Plantinga BR, Temel Y, Uludag K, et al. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. eNeuro 2017;4(5).
[8] Le Jeune F, Verin M, N'Diaye K, Drapier D, Leray E, Du Montcel ST, et al. Decrease of prefrontal metabolism after subthalamic stimulation in obsessive-compulsive disorder: a positron emission tomography study. Biol Psychiatr 2010;68(11):1016–22.
[9] Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. Biol Psychiatr 2005;58(10):763–9.
[10] Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biol Psychiatr 2004;55(12):1163–70.

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