Brain Stimulation 12 (2019) 770–771

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Delusions following deep brain stimulation of the nucleus accumbens

To the editor:

Deep brain stimulation (DBS) is generally regarded as a safe and effective treatment for some psychiatric disorders, including major depressive disorder [1]. However, the novelty of the treatment requires a precise observation of possible side effects. Here, we present a case of voltage-related delusions following DBS of the nucleus accumbens (NAcc).

Case report

Mr. A, a 31-year old man who had been suffering from a chronic depressive disorder for ten years, was referred to our department. There were no signs or history of mania or psychosis. His Hamilton Depression Rating Scale (HDRS) score was 23 out of 52, corresponding with moderate-severe depression. Despite nine years of treatment involving antidepressants, psychotherapy and electroconvulsive therapy, Mr. A's symptoms never improved and he remained socially isolated and unable to work despite having a university degree.

Mr. A was included for experimental treatment with DBS and underwent implantation of an infraclavicular neurostimulator and two four-contact electrodes targeted at the NAcc and ventral limb of the anterior internal capsule (vALIC) [1]. DBS settings were adjusted according to titration protocol [1]. Therapeutic settings were only achieved after two years, with an unusual high current of 7.5V, monopolar stimulation, 90μs, 130Hz, at the two lowest contacts (0&1, corresponding to the gray matter of the NAcc). Depression scores dropped from 23 to 15 on the HDRS. Mr. A felt less depressed, became more talkative and regained interest in life.

In the following months, Mr. A was seen several times at our outpatient clinic. During that period, his depressive symptoms remained stable, no specific psychosocial events occurred and no medication changes were made. However, two weeks after his last visit, Mr. A was brought to our psychiatric emergency service following complaints from his neighbors about his behavior. He displayed paranoid delusions, being convinced that the brown spots on the wall of his living room were caused by asbestos and that his neighbors, the police and his medical practitioners were conspiring against him to expel him from his house. Mr. A's mood was anxious and agitated. He was admitted to our acute ward, where the current was lowered from 7.5V to 3.5V. Subsequently, delusions about asbestos disappeared completely within hours. Because depressive symptoms returned (HDRS 23), the current was increased again in small steps until 4.5V. However, every attempt to increase the current above 4.5V resulted in reappearance of delusional thinking within days, despite lower pulse widths, addition of quetiapine 800 mg/day or olanzapine 10 mg/day.

Eventually, clozapine 300 mg/day allowed for increasing the current to 7V, without recurrence of delusional thinking but also without a stable improvement of depressive symptoms. Over time, poor abstraction abilities and disorganized thinking became more apparent. More than one year after first occurrence of delusions, these thought disorders did not disappear during 2 weeks of DBS-discontinuation. Thought disorders further deteriorated after tapering off clozapine (due to side effects), together with recurrence of agitated mood and paranoid delusions, i.e. the conviction that he had been falsely treated with experimental DBS-settings. Considering the lack of anti-depressant effect of high-voltage DBS, the current was decreased to 3.5V and clozapine was continued at 250mg/day. DBS was continued at 3.5V because the patient reported that discontinuation of DBS caused worsening of depressive symptoms.

This case-report demonstrates that DBS of the NAcc may induce delusions in vulnerable patients. The delusions developed within hours and initially reversed rapidly after discontinuing stimulation or lowering the current. However, over time psychotic symptoms remained even after DBS discontinuation, and clozapine was required to manage psychosis. Reversible hypomanic symptoms as a side-effect during the first days of vALIC-DBS has been well documented, as well as reversible voltage-dependent manic symptoms following subthalamic DBS [2]. However, the current case is the first describing NAcc-DBS related voltage-dependent delusions that were reversible at first, but eventually triggered chronic psychosis.

Contemporary models of psychosis propose that increased striatal dopamine synthesis and release drives the attribution of motivational salience to irrelevant stimuli, underlying delusions [3]. We have previously demonstrated that vALIC/NAcc DBS induces striatal dopamine release within the time-frame of an hour after its activation [4]. Comparable increases in striatal dopamine are observed following Δ9-tetrahydrocannabinol infusion, which can similarly cause reversible psychotic symptoms, but may also trigger lasting psychosis in vulnerable individuals [5]. Individuals at-risk for psychosis have elevated baseline dopamine levels [6]. Dopamine levels might have not returned to baseline after initial onset of delusions in our patient. This may explain why high voltage DBS initially induced reversible delusions, while later delusions recurred already with much lower currents and eventually remained even without stimulation.

In addition, recent evidence suggests that hypo-function of the glutamate system may play a key role in the development of delusions [7]. DBS modulates glutamatergic pathways, as was demonstrated by glutamate-dependent decreases in orbitofrontal cortex

https://doi.org/10.1016/j.brs.2018.12.973

activity following NAcc DBS in an animal model [8]. Thus, increased striatal dopamine release and frontal glutamate antagonism are two possible mechanisms by which high voltage DBS of the NAcc may have triggered delusions and later psychosis.

Though animal models suggest NAcc DBS may be effective for schizophrenia by stabilizing striatal dopaminergic and prefrontal glutamatergic dysfunction [9], our case suggests that high voltage NAcc DBS may induce psychotic symptoms in vulnerable individuals. We would propose that experimentally applied DBS for schizophrenia should be restricted to low voltages. This warning is particularly relevant in the context of NAcc DBS as a currently proposed treatment for schizophrenia (https://www.clinicaltrials.gov/ct2/show/NCT02377505, NCT02377505).

At last, this case advocates for a careful selection of DBS patients. Our patient did not report any history of psychotic or manic symptoms at admission, but developed psychotic symptoms only during the course of DBS. Individuals that are prone for the development of psychotic symptoms have elevated striatal dopamine activity. DBS-induced striatal dopamine release might therefore only induce psychotic symptoms in patients that are vulnerable for psychosis [6]. We propose a careful screening of each DBS candidate for signs of psychosis, for example by conducting the Comprehensive Assessment of At Risk Mental State (CAARMS) [10].

Disclosure statement

P.R. Schuurman acts as independent advisor for Medtronic and Boston. The other authors have no disclosures to report.

References

[1] Bergfeld IO, Mantione M, Hoogendoorn MLC, Ruhé HG, Notten P, van Laarhoven J, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatr 2016:1–9. https://doi.org/10.1001/jamapsychiatry.2016.0152.

[2] Chopra A, Tye SJ, Lee KH, Matsumoto J, Klassen B, Adams AC, et al. Voltage-dependent mania after subthalamic nucleus deep brain stimulation in Parkinson's disease: a case report. Biol Psychiatry 2011;70:e5–7. https://doi.org/10.1016/j.biopsych.2010.12.035.

[3] Roiser JP, Howes OD, Chaddock CA, Joyce EM, McGuire P. Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. Schizophr Bull 2013;39:1328–36. https://doi.org/10.1093/schbul/sbs147.

[4] Figee M, de Koning P, Klaassen S, Vulink N, Mantione M, van den Munckhof P, et al. Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder. Biol Psychiatry 2014;75:647–52. https://doi.org/10.1016/j.biopsych.2013.06.021.

[5] Bossong MG, Mehta MA, Van Berckel BNM, Howes OD, Kahn RS, Stokes PRA. Further human evidence for striatal dopamine release induced by administration of δ9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology (Berl) 2015;232:2723–9. https://doi.org/10.1007/s00213-015-3915-0.

[6] Howes OD, Montgomery AJ, Asselin M-C, Murray RM, Valli I, Tabraham P, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatr 2009;66:13–20. https://doi.org/10.1001/archgenpsychiatry.2008.514.

[7] Marek GJ, Behl B, Bespalov AY, Gross G, Lee Y, Schoemaker H. Glutamatergic (N-methyl-D-aspartate receptor) hypofrontality in schizophrenia: too little juice or a miswired brain? Mol Pharmacol 2010;77:317–26. https://doi.org/10.1124/mol.109.059865.

[8] McCracken CB, Grace A a. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. J Neurosci 2007;27:12601–10. https://doi.org/10.1523/JNEUROSCI.3750-07.2007.

[9] Ma J, Leung LS. Deep brain stimulation of the medial septum or nucleus accumbens alleviates psychosis-relevant behavior in ketamine-treated rats. Behav Brain Res 2014;266:174–82. https://doi.org/10.1016/j.bbr.2014.03.010.

[10] Yung AR, Yuen HP, Mcgorry PD, Phillips LJ, Kelly D, Dell'olio M, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatr 2009;39(11-12):964–71.

Ilse Graat*
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Isidoor O. Bergfeld
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Amsterdam Neuroscience, Amsterdam, the Netherlands

Pelle de Koning, Nienke Vulink
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

P. Richard Schuurman
Amsterdam Neuroscience, Amsterdam, the Netherlands

Department of Neurosurgery, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Damiaan Denys
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Amsterdam Neuroscience, Amsterdam, the Netherlands

Netherlands Institute for Neurosciences, an Institute of the Royal Dutch Academy of Science, Amsterdam, the Netherlands

Martijn Figee
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Amsterdam Neuroscience, Amsterdam, the Netherlands

* Corresponding author. Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.
E-mail address: i.graat@amc.uva.nl (I. Graat).

21 December 2018
Available online 26 December 2018