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Increased dopamine transporter levels following nucleus accumbens deep brain stimulation in methamphetamine use disorder: A case report

Methamphetamine (MA) and related stimulants are the world's second most commonly abused drug class with an estimated 24 million users worldwide [1]. MA use is associated with marked medical and psychiatric morbidity, increased mortality, and functional impairments, with estimated costs of $85 million per year globally. Current treatments consist primarily of behavioral interventions which have limited efficacy. To date, no medications or other biological treatments have been approved for the treatment of methamphetamine use disorder (MUD).

Deep brain stimulation (DBS) utilizes electrodes to deliver high frequency stimulation in an effort to resolve pathological network activity in the brain. DBS is a safe, reversible, effective, and US Food and Drug Administration approved treatment for movement disorders and obsessive compulsive disorder [2]. More recently, a number of case series have explored the utility of DBS in treating alcohol and heroin use disorder [3,4]. Here we describe a patient with a methamphetamine use disorder (MUD) who was successfully treated using DBS of the nucleus accumbens and ventral capsule.

Methamphetamine (MA) is a potent psychoactive drug that increases synaptic dopamine levels by blocking the reuptake of dopamine and increasing reverse transport via the dopamine transporter (DAT). Relative to other psychostimulants, MA has a more prolonged action on dopamine function. MA acutely increases dopaminergic neurotransmission in the basal ganglia implicated in motor function, motivation, learning, and reward. The chronic use of MA is associated with cognitive impairments, mood and sleep disturbances, and brain structural and functional changes. A meta-analysis of human imaging studies shows that chronic psychostimulants are linked to long-term downregulation of dopaminergic neurotransmission (4). While lower dopamine release and D2/D3 receptor levels can be found across all psychostimulants, MUD seems to be associated specifically with lower DAT levels. Brain functional changes can persist in some cases even after prolonged drug abstinence, although partial or full recovery can also be observed.

Both preclinical and clinical studies have highlighted the brain's dopaminergic system in the pathophysiology of drug addiction. The dopaminergic system has also been considered a potential target in the treatment of MUD [5]. The decrease in DAT levels seen with chronic MA use has been attributed to: functional adaptations to decreased synaptic dopamine; a direct effect of internalization of transporters; and a neurotoxic effect on dopaminergic nerve terminals, which is consistent with reports of enhanced risk of Parkinson's disease with chronic MA use. In this case report, we describe the extinction of drug-taking behavior along with a marked increase in striatal DAT levels in a MUD patient following one year of DBS targeting the nucleus accumbens and ventral capsule.

A 33-year-old male with a 5-year history of treatment refractory MUD underwent DBS targeting the nucleus accumbens and ventral capsule. The patient started using MA in 2012, typically using every other day. Prior to surgery his average use was 0.5 g per day. The patient underwent multiple attempts at detoxification characterized by short abstinent periods and relapses. The present case fulfilled the diagnostic criteria for MUD with no other comorbid psychiatric or personality disorders (Structured Clinical Interview for DSM-IV Axis I/II Disorders). The patient volunteered to participate in a DBS clinical trial for MUD (ClinicalTrials.gov: NCT03347474). Informed consent was obtained; the ethics was approved through the Ruijin Hospital, Shanghai Jiao-Tong University ethics board. In September 2017, DBS leads (1242, Scenery, Suzhou, China) [4,6] were implanted into the bilateral nucleus accumbens and ventral capsule. Following lead location verification with post-operative computerized tomography, stimulation of the two middle contacts was initiated (3.0 V 210μs 130Hz). The patient underwent 11C-CFT PET imaging of DAT levels prior to DBS treatment and one year after continuous DBS. At one-year follow-up, PET scanning occurred while DBS was 'on'.

Following DBS treatment, the patient remained abstinent for a full year as assessed by self-report and urine and hair drug testing. The DBS parameters were adjusted in the first post-surgical month (2.5 V, 90μs, 130Hz) to avoid agitation and hypomania, which can be a side effect of the DBS treatment. One year after surgery, the patient's self-reported craving on a Visual Analogue Scale score decreased from 8 pre-surgery to 0. Similarly, on the Obsessive-Compulsive Drug Use Scale, the patient had become less focused on drugs and experienced less functional interference from his urge to seek and take drugs (items score changed from 29 before surgery to 11 after one year of treatment). He also experienced a diminished desire to use drugs and an increased control over his drug-taking behavior (items score changed from 17 to 5). Additionally, he felt better able to resist drug thoughts and intentions to use (items score changed from 8 to 3). Comparing pre-versus post-surgery he showed improved scores on questionnaires of mood, anxiety, quality of life and functional impairment. Cognitive testing showed either

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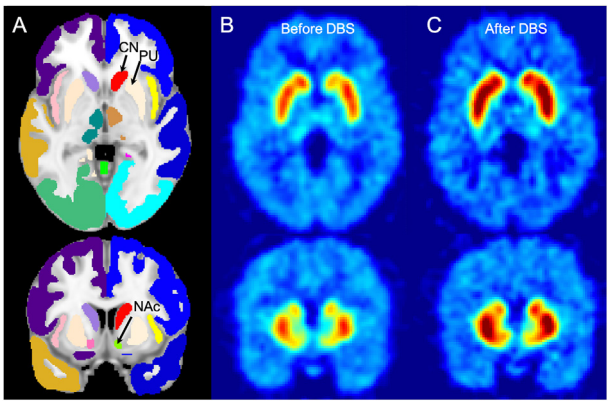

Fig. 1. Comparison of 11C-CFT positron emission tomography (PET) imaging in a patient with a methamphetamine use disorder before and one year after chronic deep brain stimulation of the nucleus accumbens (NAc) and ventral capsule. (A) Region of interest definitions shown in the MNI152 space. The ROIs were defined using the AAL2 atlas combined with NAc definition (https://neurovault.org/images/56777/). (B) Striatal PET images before and (C) 1-year post-DBS (right; PET image acquired 'on' DBS). After DBS, 11C-CFT PET shows enhanced dopamine transporter binding in the caudate nucleus (CN), putamen (PU) and nucleus accumbens (NAc). Average binding potential (pre, post): caudate, 1.92, 2.31; putamen, 2.35, 2.96; nucleus accumbens, 2.04, 2.46; frontal, 1.10, 1.06. We performed 11C-CFT PET dopamine transporter neuroimaging using a Siemens Biograph 64 HD PET/CT (Siemens, Erlangen, Germany) in 3-dimensional mode. Anatomically-based volume of interests (VOIs) for the CN, anterior and posterior PU, and occipital cortex were placed manually on the mean image summed over central slices encompassing the striatal structures. For the 11C-CFT PET images, we calculated the ratio of specific to nonspecific activity in the CN and anterior and posterior PU VOIs by subtracting occipital from striatal activity and dividing by occipital activity [7].

no change or improvements in psychomotor function, speed of visual processing, attention, visual learning, working memory and planning. There were no significant side effects or complications. Paralleling the clinical benefits, the patient displayed a marked increase in striatal DAT density at one-year follow-up (20.5% increase in the caudate, 25.6% increase in the putamen; in contrast to −3.2% change in frontal cortex) (Fig. 1).

Our case report highlights the safety, feasibility and potential efficacy of DBS of the nucleus accumbens and ventral internal capsule for treatment refractory MUD. One plausible DBS mechanism may be related to the effects of DBS on normalizing brain dopaminergic dysfunction following chronic MA use. Indeed, DBS targeting the nucleus accumbens in obsessive-compulsive disorder has been shown to enhance striatal dopamine release (7). Whether our findings are related to DBS-related enhancement of dopamine function hence increasing DAT levels, or are secondary to prolonged abstinence rather than DBS-related remains to be addressed. We emphasize that this is an open label case report and placebo effects may play a role on the clinical improvement but notably this is a patient with chronic severe MUD with a history of multiple treatment failures. Our observations highlight the need for randomized clinical trials to assess efficacy of DBS for MUD.

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References

[1] Ballester J, Valentine G, Sofuoglu M. Pharmacological treatments for methamphetamine addiction: current status and future directions. Expert Rev Clin Pharmacol 2017;10:305–14. https://doi.org/10.1080/17512433.2017.1268916.
[2] Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;33:474–84. https://doi.org/10.1016/j.tins.2010.07.002.
[3] Spagnolo PA, Goldman D. Neuromodulation interventions for addictive disorders: challenges, promise, and roadmap for future research. Brain 2017;140:1183–203. https://doi.org/10.1093/brain/aww284.
[4] Chen L, Li N, Ge S, Lozano AM, Lee DJ, Yang C, et al. Long-term results after deep brain stimulation of nucleus accumbens and the anterior limb of the internal capsule for preventing heroin relapse: an open-label pilot study. Brain Stimul 2018. https://doi.org/10.1016/j.brs.2018.09.006.
[5] Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine a systematic review and meta-analysis. JAMA Psychiatry 2017;74:511–9. https://doi.org/10.1001/jamapsychiatry.2017.0135.
[6] Zhang C, Li D, Jin H, Zeljic K, Sun B. Target-specific deep brain stimulation of the ventral capsule/ventral striatum for the treatment of neuropsychiatric disease. Ann Transl Med 2017;1:1–6. https://doi.org/10.21037/atm.2017.07.13.
[7] Liu FT, Ge JJ, Wu JJ, Wu P, Ma Y, Zuo CT, et al. Clinical, dopaminergic, and metabolic correlations in Parkinson disease: a dual-tracer PET study. Clin Nucl Med 2018;43:562–71. https://doi.org/10.1097/RLU.0000000000002148.

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