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Robust clinical benefit of multi-target deep brain stimulation for treatment of Gilles de la Tourette syndrome and its comorbidities

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Dear Editor

Deep brain stimulation (DBS) has emerged as an efficacious modality for the treatment of medically refractory neuropsychiatric diseases. Traditional DBS approaches have used a single pair of bilateral leads to treat diseases with relatively well-defined disease networks and targets [1]. However, the optimal approach for Gilles de la Tourette syndrome (GTS) has yet to be determined. GTS is complicated by having more than 4 proposed DBS targets for the motor system and common comorbidities including major depressive depression (MDD) and obsessive-compulsive disorder (OCD) [2,3]. Networks implicated in these diseases involve targets including the centromedian-parafascicular complex (CM), the ventral capsule/ventral striatum (VC/VS), the anterior limb of the internal capsule (ALIC), and the nucleus accumbens (NAc) [4]. Clinical management is further complicated in patients with refractory pain secondary to motor tics who may be managed with opiates and develop dependence on these substances [5]. DBS of the NAc has been shown to ameliorate consumption of substances of abuse including alcohol, nicotine, and heroin, adding further support for multi-targeted DBS approaches [6].

A patient (right-handed, male) in his 20s presented to our institution with severe, medically refractory GTS, most significantly involving his head and neck, with comorbidities including OCD, MDD, and chronic pain. Clinical investigation was carried out in accordance with our institutional IRB-approved protocol (IRB-33146). Informed consent was obtained prior to initiation of this study. At the age of 11 years, the patient was diagnosed with GTS, OCD, and ADHD, that progressively worsened at the age of 20 (Fig. 1A). He developed chronic pain syndrome from chronic neck tics and subsequent opioid use disorder (OUD). Prior to DBS, the patient failed pharmacotherapy (haloperidol, risperidone, clonidine) as well as comprehensive behavioral intervention to control his tics. He failed 4 SSRIs (paroxetine, escitalopram, sertraline, fluoxetine), clomipramine, nortriptyline, and bupropion for his OCD and depression. Pain management included failed trials of tramadol, oxycodone, carisoprodol, gabapentin, topiramate, pregabalin, and methocarbamol.

The patient underwent bilateral DBS placement using a frameless approach (Medtronic, Inc, Minneapolis, MN, Model 3387) to the CM ($x = 5mm, y = -4mm, z = 0mm$ to the center of the AC-PC line) (Fig. 1) and VC/VS ($x = 5mm, y = 4mm, z = -6mm$ to the center of the AC-PC line) (Fig. 1B and C) [7]. Clinical outcomes of GTS severity were measured by tic frequency calculated during clinic visits and using the Yale Global Tic Severity Scale (YGTSS) that provides an evaluation of motor and phonic symptoms. The Yale-Brown Obsessive-Compulsive Scale (YBOCS) captured the severity of obsession and compulsions associated with OCD. For MDD measures, a 17-item version of the Hamilton Depression Scale (HDRS-17) gauged the patient's mood during clinic visits. DBS programming started two weeks after placement.

Prior to surgery, the patient had a YGTSS of 70 and over 200 tics/day. Initial monopolar threshold tolerance testing of CM lead contact 2, two weeks after surgery, resulted in adverse reactions of sensory disturbances and dizziness that have been previously reported [8]. At 4-months of programming, he had a prominent reduction in his tics (2–3 tics during 1-h exam) and a 60% reduction in YGTSS with absence of vocalizations. At 8 months post-operatively, CM lead contacts 1 and 3 remained activated with improvement in the patient's tics (no tics on exam), a YGTSS of 11, and resolution of visual disturbances.

Prior to surgery, the patient had a YBOCS score of 20 and a HDRS-17 score of 21. Initial activation of the VC/VS lead (c+, 2- at 2.5 V, 130 Hz, and 90 μs) contact 2, in the ALIC, resulted in marked improvement in his mood and affect on examination. Further, prominent MDD symptoms returned upon deactivation of this lead. There were no changes to his ongoing tics. He continued to have intermittent episodes of dysphoria due to inability to manage his pain and tic symptoms during this time. The voltage was steadily increased to 5 V and at 4 months post-surgery, the patient had a YBOCS score of 11 (45% decreased from 1-week pre-operative score). At 1-year post-operatively, the patient continued to improve with a YBOCS score of 6 and a HDRS-17 score of 1.

During the initial 3 months of programming, the patient's hydrocodone intake peaked at 12 times daily for post-operative pain control. Partway during management, we discovered that the patient self-administered increased opiate dosages and had concurrent kratom intake as well, demonstrative of an exacerbation of his baseline pain control. Following measures to manage the patient's opioid regimen, his VC/VS lead was activated at contact 0 in the ventral NAc to control his cravings. Notably, the patient was able to self-initiate a taper. Over the following several months, there was an overall reduction in self-reported opioid cravings

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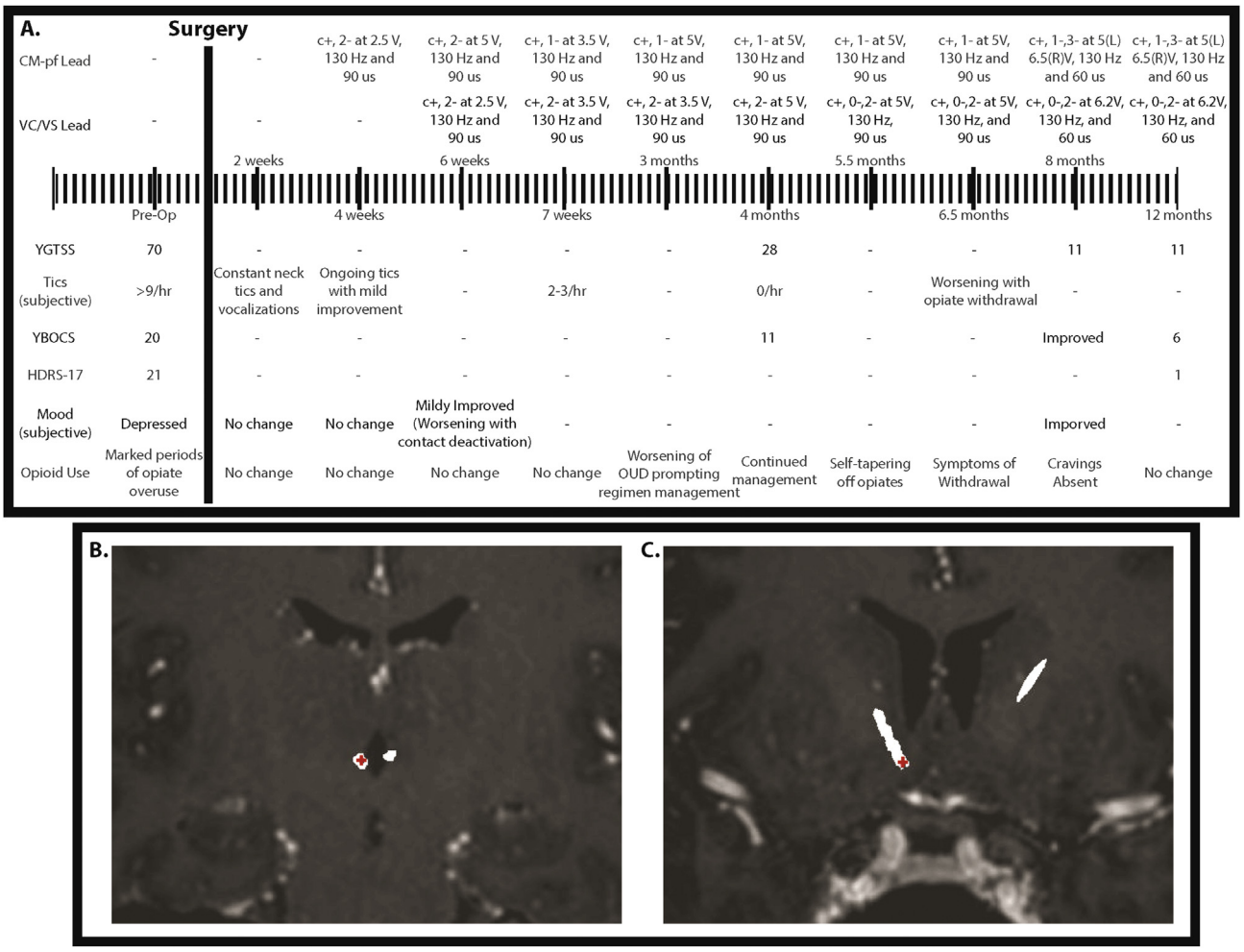

Fig. 1. Timeline infographic (A) displaying case history and clinical course outcomes. Merged pre-operative MRI and post-operative CT with anticipated targets in the left thalamus (B) and NAc (C) displayed. Coronal views of the base of the DBS lead (contact 0 or C0, red dot) in the (B) left CM thalamic nucleus and (C) left NAc. CM = centromedian nucleus of thalamus CT = computed tomography imaging, MRI = magnetic resonance imaging, NAc = nucleus accumbens. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and improved mood as well. The patient was able to be placed on a low dose of suboxone and held at this dose until the time of this publication.

The clinical course described highlights the complexities of managing GTS patients, 50–90% of whom may exhibit comorbid conditions including OCD, and MDD [3]. Failure to address these components may lead to ineffective control of GTS spectrum symptoms and may contribute to the broad range of DBS treatment outcomes seen in the literature [3,9]. Importantly, GTS can involve multiple, parallel networks. Effective treatment using DBS may require modulation of multiple brain networks [2]. Our case suggests that DBS approaches targeting multiple affected networks may provide control over the symptoms in a way that single DBS approaches simply cannot. Additionally, our results add to a growing body of the literature showing evidence of reduced rates of substance abuse following DBS [6]. Importantly, this case provides further evidence that DBS to the reward system holds promise for affecting addictive behaviors.

In conclusion, motor and non-motor complications of severe, medication-resistant GTS and its comorbidities can be effectively treated with bilateral, dual-target DBS to the CM and VC/VS. Relief of motor tics was specific to stimulation of thalamic nuclei. Unlike discernible borders of the ALIC and NAc targets, thalamic nuclei are difficult to visualize using standard MRI imaging due to their small size and poor inter-nuclei contrast. Target optimization in this region will require analysis of DBS lead localization to examine the pathologic underpinnings of the functional thalamic contacts.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Bina Kakusa, Sabir Saluja
Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, 94305, USA

William J. Tate, Flint M. Espil
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, 94305, USA

Casey H. Halpern*
Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, 94305, USA

Nolan R. Williams**
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, 94305, USA

* Corresponding author. Stanford University School of Medicine, 300 Pasteur Drive, Edwards Bldg./R 293, Stanford, CA, 94305, USA.

** Corresponding author. Stanford University School of Medicine, Psychiatry and Behavioral Sciences, 401 Quarry Rd, MC 5719, Stanford, CA, 94305, USA.
E-mail address: chalpern@stanford.edu (C.H. Halpern).
E-mail address: nolanw@stanford.edu (N.R. Williams).

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