Target-specific deep brain stimulation of the ventral capsule/ventral striatum for the treatment of neuropsychiatric disease

Chencheng Zhang[1], Dianyou Li[1], Haiyan Jin[2], Kristina Zeljic[3], Bomin Sun[1]

[1]Department of Functional Neurosurgery, [2]Department of Psychiatry, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; [3]Institute of Neuroscience, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

Correspondence to: Bomin Sun, MD, PhD. Department of Functional Neurosurgery, Ruijin Hospital of the Shanghai JiaoTong University School of Medicine, Shanghai 200025, China. Email: sbm11224@rjh.com.cn.

Abstract: Deep brain stimulation (DBS) is a well-established therapy for Parkinson's disease and other movement disorders. An accumulating body of evidence supports the extension of DBS application for the treatment of refractory psychiatric disorders. The ventral capsule/ventral striatum (VC/VS) is the most common anatomical target for obsessive-compulsive disorder (OCD), addiction, and depression. However, no specific electrode is available for the clinical targeting of these areas for DBS. According to the anatomical features of the VC/VS, a novel electrode was developed for simultaneous and independently programmed stimulation of the nucleus accumbens (NAc) and the anterior limb of the internal capsule (ALIC). This VC/VS-specific electrode has the potential to enhance stimulus intensity, provide independent and flexible target stimulation.

Keywords: Deep brain stimulation (DBS); nucleus accumbens (NAc); ventral striatum (VS); obsessive-compulsive disorder (OCD); addiction; anorexia nervosa

Submitted Apr 02, 2017. Accepted for publication Jul 04, 2017.
doi: 10.21037/atm.2017.07.13
View this article at: http://dx.doi.org/10.21037/atm.2017.07.13

Introduction

Deep brain stimulation (DBS) involves neurosurgical implantation of a nerve stimulator device that delivers electrical signals to a specific brain area. DBS is primarily used to address motor symptoms in the treatment of movement disorders or emotional and behavioral symptoms in the treatment of intractable mental disorders (1,2). The clinical efficacy of DBS in movement disorders disease is well established, whereas its implementation in mental disorders has produced mixed results (3,4). DBS is applied to different targets for various conditions using a straight quadripolar electrode with 1.5-mm contacts and an inter-space of 0.5 or 1.5 mm between contacts irrespective of the target; identical stimulation parameters must be applied at each contact of one electrode, with both electrodes using the same frequency. The ventral anterior limb/ventral striatum (VS) is the most common target of neurosurgery for DBS in the treatment of obsessive-compulsive disorder (OCD) and depression (5-9). For this target area, the more ventral portion of the anterior limb is associated with a greater therapeutic benefit (10-12). Thus, the electrode configuration for DBS should be specifically tailored to the geometry and properties of this target area (12,13). We therefore developed a configuration of the SceneRay 1242 according to the anatomy of the ventral capsule (VC)/VS to deliver stimulation at an increased intensity and density, allowing independent stimulation parameters while maintaining a consistent safety profile.

Materials

The SceneRay 1242 electrode

The SceneRay 1242 (*Figure 1*) electrode was designed to have a diameter of 1.27 mm and 4 contacts. The contact length is 3.0 mm and the spacing between the ventral and dorsal contacts is 2, 4, and 4 mm, with a total length of 22.5 mm (3+2+3+4+3+4+3 and 0.5 projecting from the electrode tip). The electrode material, that is, the stimulating contacts and the inner spring wire, is a platinum-iridium alloy; the insulating material is polyurethane. Regarding the

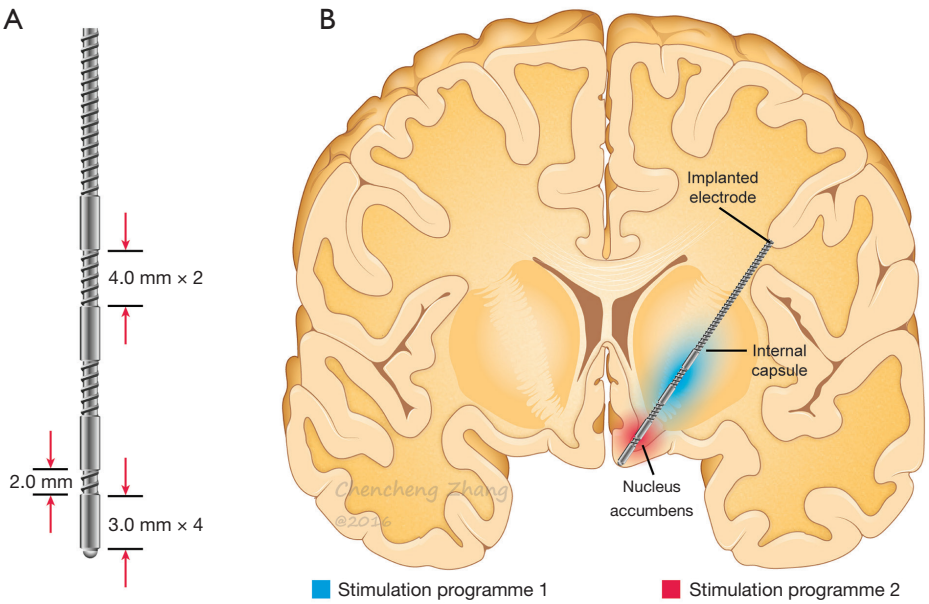

Figure 1 Electrode and stimulation program setting.

Table 1 Stimulating program of each contact

	Left brain	Right brain	Brain region	Programing group
Contacts	0	4	NAc	Stimulating program 2
	1	5		
	2	6	ALIC	Stimulating program 1
	3	7		

NAc, nucleus accumbens; ALIC, anterior limb of the internal capsule.

mechanical properties with chronic implantation, after implantation the electrode lead can withstand a variety of twisting forces that may occur in the human body, and the entire electrode is resistant to cracks. The electrode wire can withstand tension above 2 N such that it does not break and there is no damage to the connection, joints, or insulating layer. The electrodes were designed to enable independently programmed stimulation after implantation, spanning from the anterior limb of the internal capsule (ALIC) to the nucleus accumbens (NAc), with two ventral contacts located within the ventral NAc and two dorsal contacts located within the ALIC.

The electrode contact size was set to 3 mm for several reasons, and primarily based on anatomical studies suggesting that the human NAc is approximately 8 mm in length. Thus, a 3-mm contact length combined with a 2-mm contact interval should completely cover the NAc (14,15). Moreover, under the same stimulation parameters, the electric field distribution increases as the electrode contact length increases, such that a larger contact interval enables a greater electric field distribution. However, if the contact gap is too large, the surrounding scope of the electrode is effectively activated and can lead to off-target effects (16,17). Considering the size of the NAc, we hypothesized that an electrode contact length of 3 mm with a 2-mm contact interval would be optimal for NAc stimulation. Additionally, these parameters allow for two stimulating contacts within the NAc with independent stimulation parameters, and thus provide additional options for optimization (*Table 1*).

The total length of the electrode is 22 mm, based on the stereotactic coordinates of the NAc and ALIC. That is, the distance from the ventral edge of the ALIC to the NAc ventral margin is approximately 13 mm. For the ventral electrode, 4 mm was used for the second and third spacing (ventral to the lower edge of the third contact space, 12 mm) so that the third electrode contacts would be located in the fuselage of the ALIC. A total ventral-to-dorsal length of 22 mm positioned the fourth contacts in the medial and

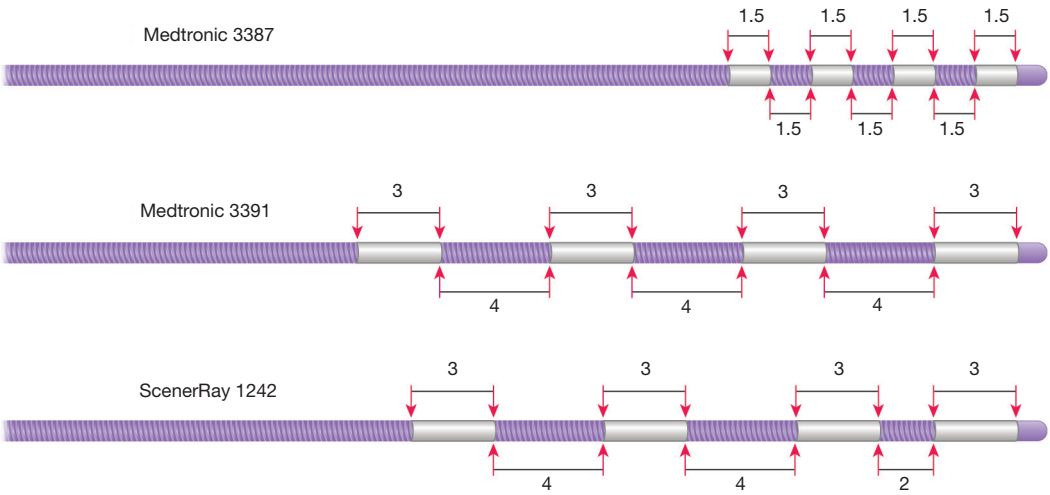

Figure 2 Medtronic 3387 and 3391 versus SceneRay 1242.

lateral third of the ALIC, which is a common target for capsulotomy. Therefore, the design of the electrode contact length was consistent with human anatomy and facilitated dual target stimulation of the NAc and ALIC.

The Medtronic electrodes

The Medtronic 3387 electrode is commonly used for ALIC stimulation in OCD, while the 3391 electrode was used in early studies as well as in studies conducted under humanitarian device exemption (18). The main differences between the SceneRay 1242 and the Medtronic 3391 electrodes are as follows: (I) the spacing of the two ventral contacts differs by 2 mm, which takes into account the anatomical size of the NAc; (II) the 3391 is used as a contact-type electrode positioned entirely within the NAc, whereas the SceneRay 1242 electrode in the present study positions two contacts within the NAc, and allows for a choice between the stimulation contacts; and (III) the SceneRay 1242 electrode in the present study was designed with consideration of the impulse generator (IPG) so that the two ventral and two dorsal contacts can be programmed with different stimulation parameters, i.e., voltage, pulse width, and frequency (*Figure 2*).

Discussion

The DBS method described here is widely used to treat Parkinson's disease, essential tremor, dystonia, and other movement disorders, as well as treatment-resistant depression (TRD), OCD, and drug addiction. DBS is a less invasive, reversible, safe, and effective option, but its exact mechanism of action has yet to be elucidated. Given the mixed results of DBS for the treatment of refractory mental illness, serious efforts should be made to fully explore its therapeutic utility and improve its effectiveness (19). Modern DBS for psychiatric indications was pioneered in 1999 for intractable OCD, when the initial target was the ALIC (20). Since then, DBS targets for OCD have evolved to include the VC/VS and specifically the NAc (21). From its inception for use in movement disorder surgery, the chief benefit of DBS over ablative neurosurgery has been the ability to perform bilateral procedures in motor areas of the basal ganglia and thalamus, with a reduced risk of affecting speech, swallowing, cognition, and balance as off-target effects. However, the rationale for DBS of non-motor subcortical areas in psychiatric disorders is less clear, except for its advantage as a non-ablative and therefore reversible therapy. Unlike the use of DBS versus ablative surgery for movement disorders, anterior capsulotomy has a better outcome than anterior capsule DBS, albeit with more side effects (20). Among potential target regions, the VC/VS is especially interesting because of its major involvement in the pathophysiology of numerous psychiatric indications, particularly OCD and TRD (22,23).

DBS targeting first emerged as a treatment for Parkinson's disease. Although conventional DBS stimulation systems can stimulate multiple contacts simultaneously, only one set of stimulation parameters (e.g., stimulation frequency, pulse width, and amplitude) can be implemented. Taking into account the neuronal composition of the NAc versus the white matter tract composition of the ALIC, different

stimulation parameters may be required to achieve efficacy. Thus, the ability to stimulate two brain areas according to two different sets of parameters is an important advantage, particularly to synchronize the effects within the ventral anterior limb/VS. Given the limitations of single electrode stimulation of an independent single functional area, and taking into account the contact hypothesis of neural networks in various diseases' loop structures, the ability to influence two or more brain regions with DBS may be beneficial in the regulation of psychiatric symptoms (19). An important measure of DBS optimization is the total electrical energy delivered (TEED) (24). TEED is determined by the programmed parameters of stimulation and the measured system impedance. In theory, optimized DBS settings will generate maximal clinical benefit at the lowest possible TEED, resulting in fewer stimulation-related complications and longer battery life. Voltage is the only factor that is exponentially related to TEED. The novel electrode described in this case report, which has bigger contacts compared to conventional contacts, has lower impedance and accordingly can provide a wide range of TEED. High voltages 3.5–5.5 V) are often reported in OCD DBS cases, which is beyond the voltage range used for movement disorder stimulation (2.0–3.5 V). Thus, use of a more target-appropriate electrode as in the present case study may be appropriate in future OCD DBS research.

The failure of the St. Jude trial (25) in which DBS of the subcallosal cingulate cortex (SCC) was applied in TRD may be explained, in some part, by over-reliance on structural images and a lack of fiber tract analysis during surgical planning. Fibers of passage rather than a gray matter target such as the subthalamic nucleus (STN) may mediate the therapeutic effects of DBS. Pre-operative diffusion tensor imaging data were acquired in a cohort with TRD to produce patient-specific white matter tractography maps (26). Post-operative field modeling analysis based on diffusion tensor imaging has shown that the DBS activation volumes of all responders to SCC DBS affect a particular combination of fiber bundles. Non-responders, in contrast, consistently share this association between activation volume and fiber connections. In addition, in OCD, structural connectome mapping in healthy subjects has been used to characterize high levels of variability in fiber tracts in the VC/VS, and combined with preoperative diffusion imaging to guide target selection in an OCD patient (27). Another group has investigated tractography activation patterns in a cohort of six patients with OCD who received VC/VS DBS. They created computational models to simulate the activation of fiber tracts and to identify their cortical connections. Modulation of the dorsolateral prefrontal cortex was associated with the best clinical response (28). The negative results of the VC/VS DBS trial for TRD by Dougherty and colleagues warrant the use of more stimulation parameter flexibility prior to a randomized off phase, and highlight the importance of stimulation of specific fiber pathways (22). A recent randomized double-blind placebo controlled trial demonstrated the efficacy of DBS of the ventral anterior limb of the internal capsule (vALIC) for TRD with a 52-week open-label titration (29). Together, these findings suggest that DBS surgical planning may benefit from the consideration of not only more refined anatomical coordinates but also fiber pathway activation data to help identify optimal lead placement and stimulation parameters.

The nerve fibers in the VC/VS form connections with the prefrontal cortex, dorsal anterior cingulate, orbital frontal cortex, ventral medial prefrontal cortex, and thalamus, as well as many other functional areas of the brain (27). Thus, implanted electrodes that stimulate the VC/VS region affect many different areas of the brain. Effects on the limbic system may also be considered in the context of depression, OCD, and other neuropsychiatric disorders; notably, through the cortico-striato-thalamo-cortical (CSTC) loop circuitry (30). Anatomical and functional abnormalities in CSTC loops are hypothesized to be the neurobiological basis of many neuropsychiatric diseases, and stimulation of this circuitry in the short-term produces emotional responses, anxiety, panic attacks, euphoria, and other relevant symptoms. Additionally, the NAc is the brain's reward center of the CSTC loop, and a hub for the regulation of emotion, motivation, and satisfaction. DBS stimulation of the NAc therefore has the potential to affect reward-seeking behavior, emotional behavior, and motivational behavior, which could have a major effect on disorders such as depression and drug addiction. Some research suggests that combining cingulotomy with accumbens stimulation does not yield better results than cingulotomy alone (31), as both targets ultimately influence the same common pathway where all four classical psychosurgical approaches (i.e., bilateral anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy) converge in their effects (32). However, this idea is based on observations in a small number of patients, and dismisses the possibility of a theoretically effective target that should be defined by its relative prominence, its functional, effective, and structural

connectivity, and its role within a circuit driving the target behavior or symptoms. Stimulating neuronal populations and elements to alter pathological baseline activity, and thereby influence local, regional, and up- and downstream projections, is the central unifying principle of DBS treatment, regardless of the clinical indication. Multiple targets with flexible stimulation parameters might be helpful for either driving activity in underperforming circuits or reducing activity in overactive or "error signal generating" regions, possibly leading to clinical improvements.

The effects of DBS on abnormal neural connectivity in the CSTC circuit of OCD patients could explain why stimulation in different brain regions can produce a similar improvement across patients. Stimulation of the STN has been reported to decrease activity in the orbital frontal cortex, medial prefrontal cortex, and anterior cingulate cortex, while stimulation of the ALIC has similarly been associated with decreased activity in the orbital frontal cortex, subgenual anterior cingulate cortex, and right dorsal lateral prefrontal cortex. Interestingly, although STN stimulation does not significantly alter comorbid depressive and anxiety symptoms, striatal stimulation produces a significant and quick improvement in mood and anxiety preceding changes in OCD severity. Future studies should address the local and distant effects of DBS of these areas, and the distinct mechanisms of action in order to optimize implantation and stimulation in patients based on illness presentation. Importantly, the electrode developed in the present study can be used in future work to more clearly distinguish the therapeutic effects of NAc versus ALIC stimulation.

We anticipate that the new stimulation method described here will improve the application of DBS for OCD, depression, drug addiction, anorexia, and other intractable mental illnesses, as well as improve the efficacy and safety of DBS treatment as a whole. We plan to use this electrode in China for a range of neuropsychiatric diseases within the next few years. Moreover, optimization of programming flexibility and electrophysiological recording with our new electrode design has the potential to increase our understanding of VS/VC DBS therapy.

Acknowledgements

We thank Judith Gault (PhD) for her valuable comments. The SHSMU-ION Research Center for Brain Disorders; and SceneRay Co. Ltd.
Funding: The National Natural Science Foundation of China (81471387 to B Sun).

Footnote

Conflicts of Interest: Dr. B Sun received research support from SceneRay (donated devices); Dr. D Li received travel sponsorship from Medtronic. Dr. C Zhang has received honoraria and travel expenses from the Deep Brain Stimulation industry (Medtronic, SceneRay, PINS). The other authors have no conflicts of interest to declare.

References

1. Okun MS. Deep-brain stimulation--entering the era of human neural-network modulation. N Engl J Med 2014;371:1369-73.
2. Miocinovic S, Somayajula S, Chitnis S, et al. History, applications, and mechanisms of deep brain stimulation. Jama Neurol 2013;70:163-71.
3. Nuttin B, Wu H, Mayberg H, et al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry 2014;85:1003-8.
4. Goodman WK, Alterman RL. Deep brain stimulation for intractable psychiatric disorders. Annu Rev Med 2012;63:511-24.
5. Pepper J, Hariz M, Zrinzo L. Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. J Neurosurg 2015;122:1028-37.
6. Alonso P, Cuadras D, Gabriëls L, et al. Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Predictors of Response. PLoS One 2015;10:e0133591.
7. Lopes AC, Greenberg BD, Canteras MM, et al. Gamma Ventral Capsulotomy for Obsessive-Compulsive Disorder: A Randomized Clinical Trial. JAMA Psychiatry 2014;71:1066-76.
8. Jung HH, Kim SJ, Roh D, et al. Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. Mol Psychiatry 2014;20:1205-11.
9. Zhan S, Liu W, Li D, et al. Long-term follow-up of bilateral anterior capsulotomy in patients with refractory obsessive-compulsive disorder. Clin Neurol Neurosurg 2014;119:91-5.
10. van den Munckhof P, Bosch DA, Mantione MH, et al. Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule. Acta Neurochir Suppl

2013;117:53-9.
11. Takashi M, Fayad SM, Goodman WK, et al. Surgical Neuroanatomy and Programming in Deep Brain Stimulation for Obsessive Compulsive Disorder. Neuromodulation 2014;17:312-9; discussion 319.
12. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol. Psychiatry. Mol Psychiatry 2010;15:64-79.
13. De Koning PP, Figee M, van Den Munckhof P, et al. Current status of deep brain stimulation for obsessive-compulsive disorder: A clinical review of different targets. Curr Psychiatry Rep 2011;13:274-82.
14. Lucas-Neto L, Neto D, Oliveira E, et al. Three dimensional anatomy of the human nucleus accumbens. Acta Neurochir 2013;155:2389-98.
15. Mavridis I, Boviatsis E, Anagnostopoulou S. Anatomy of the human nucleus accumbens: a combined morphometric study. Surg Radiol Anat 2011;33:405-14.
16. Mikos A, Bowers D, Noecker AM, et al. Patient-specific analysis of the relationship between the volume of tissue activated during DBS and verbal fluency. Neuroimage 2011;54 Suppl 1:S238-46.
17. Butson CR, Cooper SE, Henderson JM, et al. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34:661-70.
18. Vora AK, Ward H, Foote KD, et al. Rebound symptoms following battery depletion in the NIH OCD DBS cohort: clinical and reimbursement issues. Brain Stimul 2012;5:599-604.
19. Lozano AM, Lipsman N. Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation. Neuron 2013;77:406-24.
20. Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet. 1999;354:1526.
21. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology 2010;35:317-36.
22. Donald AM Jr, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry 2009;65:267-75.
23. Greenberg BD, Gabriels LA, Malone DA Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 2010;15:64-79.
24. Koss AM, Alterman RL, Tagliati M, et al. Calculating total electrical energy delivered by deep brain stimulation systems. Ann Neurol 2005;58:168-9.
25. Schlaepfer TE. Deep Brain Stimulation for Major Depression—Steps on a Long and Winding Road. Biol Psychiatry 2015;78:218-9.
26. Riva-Posse P, Choi KS, Holtzheimer PE, et al. Defining Critical White Matter Pathways Mediating Successful Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression. Biol Psychiatry 2014;76:963-9.
27. Makris N, Rathi Y, Mouradian P, et al. Variability and anatomical specificity of the orbitofrontothalamic fibers of passage in the ventral capsule/ventral striatum (VC/VS): precision care for patient-specific tractography-guided targeting of deep brain stimulation (DBS) in obsessive compulsive disorder (OCD). Brain Imaging Behav 2016;10:1054-67.
28. Hartmann CJ, Lujan JL, Chaturvedi A, et al. Tractography Activation Patterns in Dorsolateral Prefrontal Cortex Suggest Better Clinical Responses in OCD DBS. Front Neurosci 2016;9:519.
29. Bergfeld IO, Mantione M, Hoogendoorn M, et al. Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry 2016;73:456-64.
30. Gunaydin LA, Kreitzer AC. Cortico-Basal Ganglia Circuit Function in Psychiatric Disease. Annu Rev Physiol 2016;78:327-50.
31. Chang WS, Roh D, Kim CH, et al. Combined bilateral anterior cingulotomy and ventral capsule/ventral striatum deep brain stimulation for refractory obsessive-compulsive disorder with major depression: do combined procedures have a long-term benefit? Restor Neurol Neurosci 2013;31:723-32.
32. Schoene-Bake JC, Parpaley Y, Weber B, et al. Tractographic analysis of historical lesion surgery for depression. Neuropsychopharmacology 2010;35:2553-63.

Cite this article as: 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;5(20):402. doi: 10.21037/atm.2017.07.13

