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Deep Brain Stimulation of the Rat Subthalamic Nucleus Induced Inhibition of Median Raphe Serotonergic and Dopaminergic Neurotransmission

Subtalamik Nükleus Derin Beyin Stimülasyonu Sonrası Sıçan Median Raphe Nükleusunda Serotonerjik ve Dopaminerjik İletimin İnhibisyonu

Ersoy KOCABICAK[1,2*], Ali JAHANSHAHI[2*], Lisa SCHONFELD[2,3], Sarah-Anna HESCHAM[2], Yasin TEMEL[2], Sonny TAN[4]

[1]Ondokuz Mayıs University, School of Medicine, Department of Neurosurgery, Samsun, Turkey
[2]Maastricht University Medical Center, Departments of Neuroscience and Neurosurgery, Maastricht, Netherlands
[3]Hasselt University, Department of Morphology, Diepenbeek, Belgium
[4]University Hospital RWTH Aachen, Department of Neurosurgery, Aachen, Germany

**Authors contributed equally.*

Corresponding Author: Ersoy KOCABICAK / E-mail: ersoykocabicak@gmail.com

ABSTRACT

AIM: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) relieves motor dysfunction in advanced Parkinson's disease (PD). However, STN DBS treated patients can experience unpleasant and debilitating psychiatric side effects such as depression and impulsivity. The neural basis of these psychiatric effects has been linked to a dysfunction of 5-hydroxytryptamine (5-HT, serotonin) neurotransmission. STN DBS inhibited activity of 5-HT cell bodies in the dorsal raphe nucleus (DRN). Another important 5-HT source is located in the median raphe nucleus (MRN), which also contains a population of dopamine neurons. The effects of STN DBS on the MRN are unknown. Here, we test the hypothesis that STN DBS reduces 5-HT and dopaminergic function in the MRN, which may contribute to the psychiatric side effects of STN stimulation.

MATERIAL and METHODS: Bilateral STN DBS was applied in a freely moving rat model. Following STN DBS, rats were sacrificed and the brains were processed for c-Fos, 5-HT and tyrosine hydroxylase (TH) immunohistochemistry.

RESULTS: We found that STN DBS significantly lowered c-Fos expression compared to non-stimulated controls indicating reduced neuronal activity. Moreover, the mean optical density values of 5-HT and TH cells in the MRN was significantly lower compared to controls.

CONCLUSION: These results show that STN DBS inhibits 5-HT and dopamine neurotransmission in the MRN.

KEYWORDS: Subthalamic nucleus, Median raphe nucleus, Serotonin, Dopamine, Deep brain stimulation, Parkinson's disease, Psychiatric disorders

ÖZ

AMAÇ: İleri evre Parkinson hastalığında uygulanan subtalamik nükleus (STN) derin beyin stimülasyonu (DBS) tremor, bradikinezi ve rijidite gibi motor semptomların gerilemesini sağlar. Bununla beraber, STN DBS ile tedavi edilmiş hastalarda depresyon, duygu durum bozukluğu gibi istenmeyen bazı psikiyatrik yan etkiler oluşabilir. Bu psikiyatrik yan etkilerin nöral temelinde 5-hydroxytryptamine (5-HT, serotonin) iletimindeki değişikliklerin rol oynadığı düşünülmektedir. Dopaminerjik nöron kaynağı olarak da görev yapan median raphe nükleusu (MRN) , tıpkı dorsal raphe nükleusu gibi ratlarda bir diğer serotonerjik nöron kaynağıdır. STN DBS'in rat dorsal raphe nükleusunda serotonerjik aktivite gösteren hücreleri inhibe ettiği daha önce gösterilmiştir. Fakat STN DBS'in MRN üzerinde ne gibi etki gösterdiği bilinmemektedir. Çalışmamızda STN DBS'in sıçan median raphe nükleusunda serotonin ve dopaminerjik fonksiyonları azalttığına dair hipotezimizi araştırdık.

YÖNTEM ve GEREÇLER: Bilateral STN DBS serbest hareket eden sıçan modeline uygulandı. STN DBS sonrası sıçanlar sakrifiye edildi ve beyinleri c-Fos, 5-HT ve tirozin hidroksilaz (TH) ile immünohistokimyasal olarak işlendi.

BULGULAR: STN DBS'in, stimüle edilmemiş kontrol grubuyla karşılaştırıldığında c-Fos ekspresyonunu önemli oranda azalttığını tespit ettik. Ayrıca MRN içindeki 5-HT ve TH hücrelerinin ortalama optik dansite değerleri, kontrol grubuyla karşılaştırıldığında oldukça düşüktü.

SONUÇ: Bu sonuçlar, STN DBS'in median raphe nükleusunda 5-HT ve dopamin salınımını inhibe ettiğini göstermektedir.

ANAHTAR SÖZCÜKLER: Subtalamik nükleus, Median raphe nükleusu, Serotonin, Dopamin, Derin beyin stimülasyonu, Parkinson hastalığı, Psikiyatrik bozukluklar

INTRODUCTION

Patients with advanced Parkinson's disease (PD) suffering from severe motor fluctuations and medication side effects are potential candidates for deep brain stimulation (DBS) of the subthalamic nucleus (STN). Randomized controlled trials have demonstrated sustained improvement in PD motor disability after STN DBS (12, 51). Despite significant motor benefits, a number of patients develop post-operative behavioral problems, including increased impulsivity, suicide and depressive symptoms (7, 17, 19, 24, 35, 45, 50). In general psychiatry, these symptoms are associated with a dysfunctional serotonin (5-hydroxytryptamine, 5-HT) system (10, 28, 37). Recent animal studies showed STN DBS to inhibit 5-HT release in forebrain regions, including the striatum and hippocampus (11, 32, 41). Moreover, STN DBS induced 5-HT-dependent depressive-like behavior in the forced swim test (42, 44). This has been linked to STN DBS inhibited 5-HT neuronal activity in the midbrain dorsal raphe nucleus (DRN) (15, 44). However, another important population of 5-HT cell bodies is located in the median raphe nucleus (MRN) (38). The MRN also shows extensive innervation of the forebrain and has been implicated in psychiatric disorders (49). It should be noted that the MRN is a heterogenic structure not only containing 5-HT, but also dopamine cell bodies and fibers (21, 23). A dysfunction in both 5-HT and dopamine neurotransmission has been implicated in the development of psychiatric symptoms. Although research on STN DBS induced changes in 5-HT neurotransmission and psychiatric behavior has mainly focused on the DRN, it is unknown whether the MRN plays a role in these effects. The effects of STN DBS on MRN function have not been investigated before and it is unknown whether STN DBS alters MRN activity. Here we test the hypothesis that STN DBS reduces 5-HT and dopaminergic function in the MRN, which may contribute to the psychiatric effects of STN stimulation.

MATERIAL and METHODS

Twenty male albino Sprague Dawley rats (n = 10 per group; Charles River, the Netherlands) weighing 350-400g were used in this study. They were housed individually in standard transparent polypropylene cages with sawdust bedding in an air-ventilated room under a 12/12 h reversed light/dark cycle (lights on 19:00h – 07:00h) with the room temperature at 20-22°C and a humidity of 60-70%. Standard laboratory chow (Hopefarms, Woerden, the Netherlands) and water were available *ad libitum*. The experimental protocol was approved by the Animal Experiments and Ethics Committee of Maastricht University.

Rats underwent electrode implantation using a stereotactic frame (Stoelting, Wood Dale, USA) under general anesthesia with vaporized isoflurane. During surgery, body temperature was maintained at 37°C with a thermo-regulated heating blanket. Stimulation electrodes (bipolar coaxial gold-coated stimulation electrodes with platinum-iridium inner wire, shaft diameter 250µm, tip diameter 50µm; Technomed, Netherlands) were implanted bilaterally into the STN (coordinates from bregma: AP -3.8 mm, ML +/-2.5 mm, DV -8.0 mm (34)) and fixed to the skull using miniature screws and dental cement (Paladur, Heraeus Kulzer, Germany) (43).

For stimulations, each electrode was connected to a constant-current isolator (DLS100, World Precision Instruments, Germany) driven by a stimulus generator (DS8000, World Precision Instruments, Germany) and the following stimulation parameters were applied for one hour: 100 mA, 130 Hz and 60 µs pulse width, which previously inhibited 5-HT neurotransmission and induced non-motor behavioral changes in this rat model (15, 41, 43, 44, 46). Sham-stimulated rats also received bilateral STN electrode implantation. These rats were connected to the stimulator but were not stimulated. After a course of daily stimulations for 1 hour, the animals were sacrificed 2 hours after the last stimulation session. Animals were deeply anesthetized with pentobarbital (75 mg/kg) and perfused transcardially with Tyrode (0.02% KCl, 0.005% $MgCl_2$, 0.8% NaCl, 0.004% NaH_2Po_4, 0.1% $NaHco_3$ and 0.1% glucose; 0.1M) and fixative containing 4% paraformaldehyde, 15% picric acid and 0.05% glutaraldehyde in 0.1M phosphate buffer (pH 7.6). Brains were removed, post-fixed and cryoprotected with a sucrose solution before being frozen with carbon dioxide and stored at – 80°C. Subsequently, the brains were cut serially on a cryostat into 30 µm thick coronal sections.

Brain sections containing the electrode trajectories were mounted on gelatine-coated slides and processed for a standard hematoxylin-eosin staining to evaluate the location of the electrode tips. On sections containing the MRN, immunohistochemistry was carried out for c-Fos, a marker of neuronal activation, 5-HT and tyrosine hydroxylase (TH), the enzyme responsible for production of the dopamine precursor l-dopa. The sections were incubated with the following primary antibodies: rabbit anti-c-Fos (1:1000, Santa Cruz Biotechnology, Inc., USA), rabbit anti-5-HT (1:40,000 (38)) and mouse anti-TH (1:100, kindly supplied by Dr. C. Cuello, Canada). Antibodies were diluted in a 0.1% Bovine Serum Albumin (BSA) and Tris Buffered Solution (TBS)-Triton (TBS-T) solution. After three-night incubation for 5-HT and overnight incubation for TH and c-Fos, sections were incubated with the secondary antibody (donkey anti-rabbit and donkey anti-mouse biotine, Jackson Immunoresearch Laboratories Inc., Westgrove, USA) for 60 min. Subsequently, all sections were incubated with an avidin-biotin-peroxidase complex (Elite ABC-kit, Vectastatin; Burlingame, USA) for 2 hours. To visualize the immune complex of horseradish peroxide reaction product, sections were exposed to a nickel chloride enhanced 3,3'-diaminobenzidine tetrahydrochloride solution. Finally, the sections were mounted, dehydrated, and coverslipped with Pertex (Histolab Products ab, Goteborg, Sweden).

To avoid variability, all sections were stained in the same session and all conditions were kept equal. After the stainings, photographs were taken with an Olympus AX70 bright field microscope connected to a digital camera (F-view; Olympus, Tokyo, Japan) with analysis software (Imaging System, Münster, Germany). Images were taken from three

rostro-caudal anatomical levels from each rat: AP -7.30 mm, -7.64 mm and -8.0 mm from the bregma (34)). Light intensity and threshold conditions were kept identical for all sections. The investigators doing the measurements were blinded for different groups.

The number of c-Fos positive cells in the MRN was quantified in photographs taken with 10x magnification using Image J software (NIH, http://rsbweb.nih.gov/ij/) at three different anatomical levels of the MRN. A cell was regarded as being positive when its intensity was significantly higher than the background as described previously (42). The expression of c-Fos positive cells was corrected for the analyzed area surface (cells/mm2).

The amount of 5-HT and TH present in the MRN was assessed by measurement of cytoplasmatic optical densities in photographs taken at 40x magnification. The mean grey value of fifty 5-HT-immunoreactive neurons was measured. Since the MRN contains a small population of TH cells, all observed TH containing cells were subjected to optical density analysis. Each cell was analyzed using Image J software and the light intensity and threshold conditions were similar for all sections. The density of pixels ranged from 0 (black) to 255 (white). For the purpose of clarity, the grey values were converted, resulting in higher values for the dark cells and lower values for the less intensely stained cells. The optical density difference of the cytoplasm compared with the mean background was taken as the outcome parameter, representing cytoplasmic 5-HT and TH content (15, 20, 52).

All data are presented in mean ± standard error of the mean (S.E.M.). Statistical analysis was performed with the Independent sample's t-test using SPSS 16.0 version for Windows. P-values lower than 0.05 were considered significant.

RESULTS

Bilateral STN DBS caused a significant reduction in MRN c-Fos expression compared to non-stimulated controls (STN DBS 46 ± 4 vs controls 60 ± 3; $p<0.05$; Figures 1A-C). STN DBS caused a significant decrease in optical density measurements of MRN 5-HT and TH neurons compared to non-stimulated controls (5-HT for STN DBS 177 ± 3 vs controls 204 ± 10, $p<0.05$, Figures 2A-C; TH for STN DBS 206 ± 4 vs controls 226 ± 6, $p<0.05$, Figures 2D-F). This is indicative for lowered 5-HT and TH concentrations within the MRN.

The electrode tips of 4 rats from the STN DBS group were located outside the anatomical boundaries of the STN. Data from those rats were excluded from analysis. Overall there were no signs of excessive tissue damage due to surgery or stimulation, including intracranial hemorrhage or ischemia (Figure 3).

DISCUSSION

STN DBS has become a popular neurosurgical therapy in advanced PD. However, suicides are more frequent post-operatively and depressive symptoms negatively influence the quality of life (47, 50). Therefore, psychiatric side effects are an important issue and require understanding of their underlying mechanisms. Psychiatric symptoms are generally linked to a dysfunctional 5-HT system (10, 28, 37). Recent rat studies have shown STN DBS to induce 5-HT-dependent depressive-like behavior in the forced swim test (42, 44). Moreover, STN DBS decreased 5-HT release measured by *in vivo* microdialysis in forebrain regions, including the prefrontal cortex, striatum und hippocampus (11, 32, 41). Extracellular single cell recordings demonstrated STN DBS to inhibit 5-HT neuronal firing in the DRN, the largest source of 5-HT cell bodies in the central nervous system (15, 44). Another important 5-HT population is located in the MRN. Both DRN and MRN are implicated in psychiatric disorders but have distinct forebrain innervation patterns (16). However, the effect of STN DBS on MRN neurotransmission is unknown.

In the present study, we found a significant decrease in MRN c-Fos expression after STN DBS compared to non-stimulated controls. This indicates a decrease in local neuronal activity.

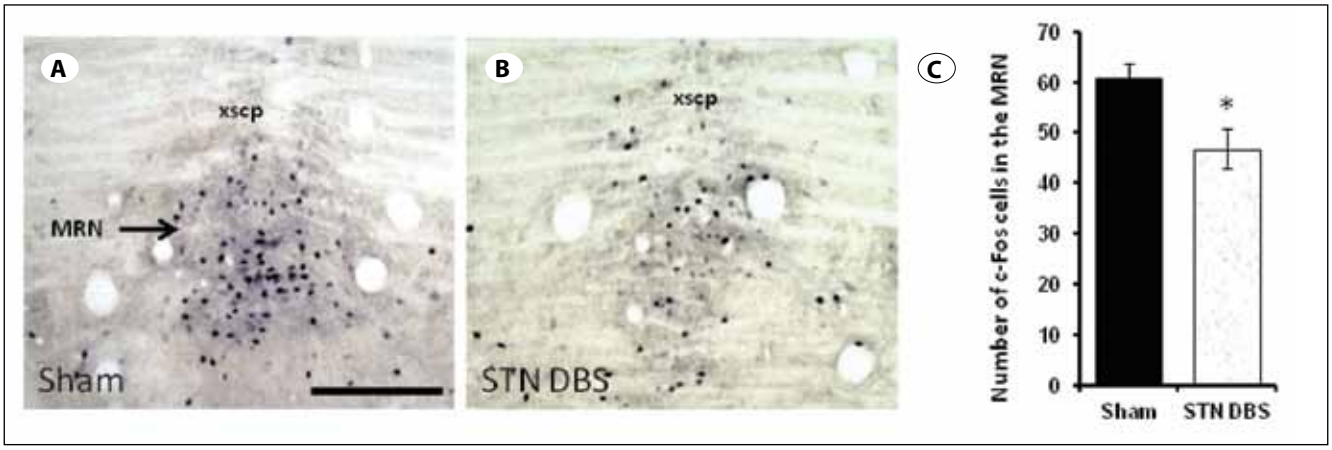

Figure 1: Representative low-power photomicrographs of c-Fos expression in the median raphe nucleus (MRN) of a sham **(A)** and STN DBS rat **(B).** Cumulative data of c-Fos expression in the MRN, expressed as the number of c-Fos positive cells per mm^2 (mean ± s.e.m.; STN DBS vs sham, * $p<0.05$) **(C)**. xscp, decussation of the superior cerebellar peduncle; Scale bar: 200 µm.

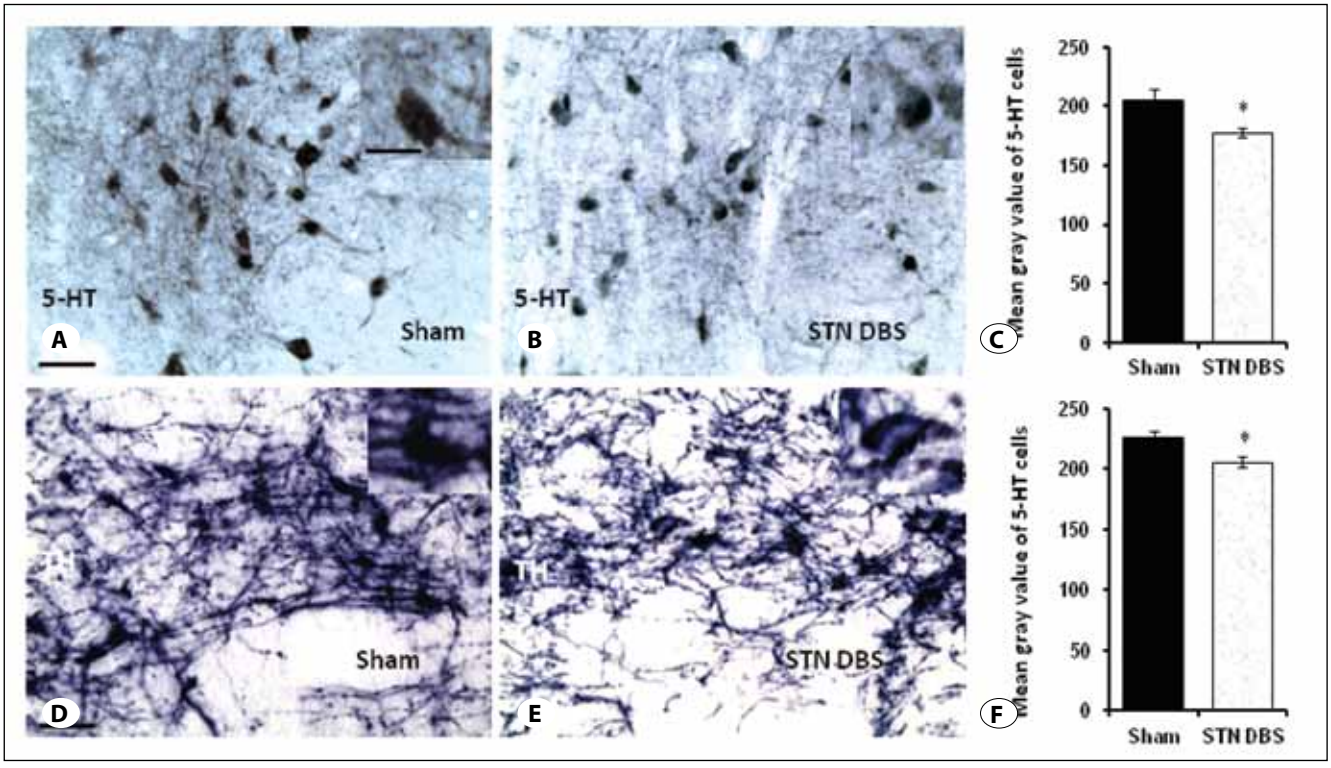

Figure 2: The figures represent high-power photomicrographs (40 x) of a 30µm-think section from the MRN of animals treated with DBS in the STN. **A, B)** 5-HT containing cells in the MRN of a sham, and STN DBS rat. **D, E)** TH containing cells in the MRN of a sham, and STN DBS rat. The graphs **(C and F)** represent the means ± S.E.M. of mean grey value of 5-HT and TH positive cells. Note that DBS induced a remarkable reduction of optical density of 5-HT and TH containing cells. * indicates significant difference as compared with sham animals (P<0.05). Scale bar: 50 µm.

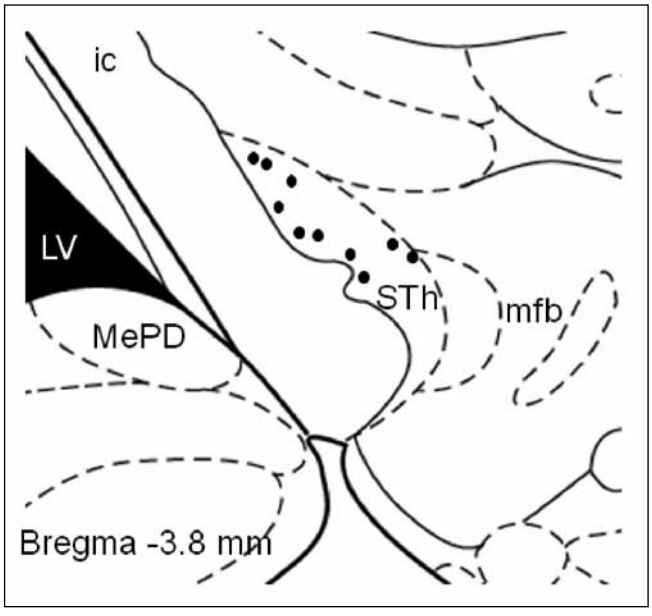

Figure 3: Schematic representation of the midbrain in rat (23), showing the localization of the electrode tips in the subthalamic nucleus **(STh)**. Medial forebrain bundle **(mfb)**, internal capsule **(ic)**, medial amygdaloid nucleus **(MePD)** and lateral ventricle **(LV)**.

In line with other STN DBS experiments a baseline c-Fos expression was expected in non-stimulated controls and was demonstrated earlier in regions including the DRN, lateral habenula and cerebellar nuclei (30, 42). The decreased MRN activity after STN DBS was anticipated based on 5-HT microdialysis experiments in rats showing decreased 5-HT release in the ventral hippocampus after STN DBS (32). The ventral hippocampus receives 5-HT innervation from both the DRN and MRN (29).

Recently, we also found a change in c-Fos expression in the DRN after STN DBS. Interestingly, stimulation caused a significant increase in DRN c-Fos expression in particular in the lateral DRN (42). The lateral DRN contains GABA interneurons important in inhibitory control of DRN 5-HT neurons (2, 48). These may be important in STN DBS induced decrease in neuronal activity of DRN 5-HT neurons (15, 44). Moreover, the MRN and DRN are interconnected with many bidirectional projections. Inhibition of DRN activity by STN DBS is likely to result in altered MRN activity as well.

We also found 5-HT density of MRN neurons to decrease significantly after STN DBS compared to non-stimulated controls, which reflects a decrease in MRN 5-HT concentration. Altered MRN 5-HT neurotransmission has been associated with mood disorders (3, 25). It is estimated that only circa 35%

of the MRN are 5-HT-containing neurons (27). The remaining include dopamine producing cell bodies among others (21). In our rat model STN DBS caused a decrease in MRN TH neuronal density. This suggests a STN DBS induced decrease in MRN dopamine concentration. We have also observed the presence of many TH-positive fibers in the MRN. This is in line with a previous study demonstrating the MRN to contain abundant dopamine-immunoreactive fibers (23). However, these fibers may originate outside the MRN in the ventral tegmental area or substantia nigra, which are important MRN afferents (4). STN DBS has demonstrated to increase neuronal activity of dopamine neurons in the substantia nigra pars compacta (5, 26). Some studies found increased striatal dopamine release in animal models, whereas clinical imaging studies did not support this observation (1, 8, 18). The effect of STN DBS on ventral tegmental dopamine neurons is unknown.

However, it should be kept in mind that the TH positive neurons and fibers may also represent other catecholamines. For example, noradrenaline terminals have been demonstrated in the MRN (33, 36). A staining for aromatic L-amino acid decarboxylase (AADC) would provide additional information for neuronal elements converting L-3,4-dihydroxyphenylalanine (L-dopa) into dopamine.

Anatomical tracing studies have not shown projections from the STN to the MRN or vice versa (4, 9, 49). Most likely it involves a multisynaptic pathway. Major STN projection targets, such as the ventral pallidum and substantia nigra, are important MRN afferents (4, 13, 22). The substantia nigra receives major STN input (14). Electrophysiological studies have demonstrated a decreased activity of substantia nigra pars reticulata neurons by STN DBS (6, 40).The ventral pallidum is connected to the medial STN, which is considered limbic subregion of the STN. However, the effects of STN DBS on the ventral pallidum are unknown. Moreover, another major MRN afferent originates in the lateral habenula (4). Although the STN does not directly project to the lateral habenula, we recently demonstrated STN stimulation induced activation of this region (42). The lateral habenula has been implicated in the regulation of both 5-HT and dopamine neurotransmission. In addition, hyperactivity of this structure has been associated with depression (31, 39). Therefore, one or more of these structures may mediate the inhibitory effect of STN DBS on MRN neurotransmission.

CONCLUSION

In this study, we have demonstrated that STN DBS decreased MRN neuronal activity. In addition, STN DBS reduced neuronal levels of 5-HT and TH in the MRN, suggesting a potential contribution of this region to the development of STN DBS-related behavioral side effects.

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