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Clinical short communication

Exploring the clinical outcomes after deep brain stimulation in Tourette syndrome

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ABSTRACT

Introduction: Deep brain stimulation (DBS) of the thalamic centromedian-parafascicular (CM-Pf) region is the most common target to treat refractory Tourette syndrome (TS), but the improvement among the patients is quite variable. This study describes the outcomes of stimulation in TS patients and attempts to determine whether the volume of tissue activated (VTA) inside the thalamus or the structural connectivity between the area stimulated and different regions of the brain is associated with tic improvement.
Methods: The DBS patient response was measured as the percentage change in the Yale Global Tic Severity Scale (YGTSS) before and 12 months after surgery. The sum of the two overlapping VTA/CM-Pf volumes from both hemispheres was correlated with the percent change in YGTSS scores to assess whether the area stimulated inside the CM-Pf affects the clinical outcome. Structural connectivity estimates between the VTA (of each patient) and different regions of the brain were computed using a normative connectome that was taken from healthy subjects.
Results: Five male patients aged 26.8 ± 9.3 years were included. No relationships were found between the areas stimulated and the changes in patient tics (p = .374). However, the right frontal middle gyrus (R = 0.564, p = .03), the left frontal superior sulci region (R = 0.900, p = .030) and the left cingulate sulci region (R = 0.821, p = .045) structurally correlated with tic improvement.
Conclusion: These data suggests that the volume of thalamic area that is stimulated does not explain the variance in outcomes in TS, however, the pattern of connectivity between the region stimulated and specific brain cortical areas is linked to patient outcome.

1. Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric disease characterized by motor and phonic tics that begins during childhood [1]. TS is frequently associated with other neuropsychiatric comorbidities such as obsessive-compulsive disorder. Overall, treatment of TS with behavioral interventions and/or a variety of medications is effective. Nevertheless, in a subset of patients these approaches are ineffective. Deep brain stimulation (DBS) may be an alternative treatment for these refractory cases [2].

To date, DBS has been used on several TS patients and is typically targeted to the globus pallidus internus or the centromedian nucleus-parafascicular region (CM-Pf) in the thalamus. Although most studies have shown a beneficial effect of DBS on tics, the results also reveal wide variations in treatment outcome [1–3], which highlights the need to determine why some patients improve after surgery and others do not, i.e., which factors predict individual patient responsiveness. These heterogeneous outcomes of DBS in TS treatment reflect (in part) a multi-faceted disorder with motor and behavioral aspects that may not respond equally to a single intervention [4].

Recent studies have demonstrated that the benefit of DBS may rely on the modulation of distant brain areas that are connected to the stimulation spot [5,6]. This remote influence of DBS can be measured by studying the fiber tracts that structurally connect both the volume of the stimulated tissue and the corresponding distant area. In this way, hypothetically, the connectivity of the stimulation site to a specific brain network may be responsible for some of the DBS response. Here, we describe clinical outcomes of DBS that was applied to a few patients

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with TS in an attempt to determine whether the electrode location and the connectivity profile between each patient correlates with tic improvement.

2. Methods

Five patients with TS underwent CM-Pf DBS between 2011 and 2018 at the University of São Paulo, Brazil due to medically refractory TS and according to the Movement Disorders Society recommendation [2]. We retrospectively analyzed data from this cohort who underwent bilateral DBS (Medtronic, Minneapolis, MN, USA) after an informed consent was signed. Clinical variables including medications, age, sex and disease duration were recorded before surgery. The DBS response was measured as a percentage change in the Yale Global Tic Severity Scale (YGTSS) before and 12 months after surgery. Neuropsychological assessment was made before the surgery in all patients, which included the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). This study was approved by a local ethics committee.

2.1. Lead location and volume of tissue activated

Postoperative tomography was linearly coregistered to preoperative MRI using SPM12 and subsequently normalized into ICBM 2009b NLIN asymmetric space using the SyN method (http://stnava.github.io/ANTs/) using the baseline MRI. The DBS electrode contacts were located within MNI space using Lead-DBS software (www.lead-dbs.org) [7].

Once localized the electrode, the volume of tissue activated (VTA) of the active contact was estimated using a heuristic stimulation algorithm previously described by Dembek et al. [8]. The overlap between the VTA and the CM-Pf was calculated in mm^3. The sum of the two overlapping VTA/CM-Pf volumes from both hemispheres was correlated with the percent change in YGTSS scores to analyze whether the area stimulated inside the CM-Pf may have influenced the clinical outcome.

2.2. Connectivity analysis

Using VTAs as seed regions, structural connectivity estimates were analyzed using a normative structural connectome, which consists of high density normative fibertracts that are based on 20 subjects. Global fiber-tracking was performed using Gibb's tracking method [9]. Structural connectivity was calculated by extracting tracts passing through the VTA and calculating the fiber counts in a voxel-wise manner through the entire brain [10]. Brain parcellations were defined according to the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA), which includes pairs of homotopic regions of interest. One hundred and twenty-two regions of interest, anatomically belonging to 37 gyri, and 50 regions of interest overlapped with 14 sulci [11].

2.3. Statistical analysis

Clinical pre-operative factors (age at surgery, age at tic onset, disease duration, YGTSS at baseline) that could predict YGTSS changes after surgery were analyzed using a logistic regression. The connectivity from VTAs was calculated for each patient. Structural connectivity strength was defined as the number of fiber tracts between the VTA and the corresponding cortical area. The connectivity map of each VTA was designed to determine whether changes in tics (the independent variable was defined as the YGTSS change 12 months after surgery, expressed as %) were associated with different brain connectivity patterns. The correlation between the independent (YGTSS) and dependent variable (fiber tracts) was expressed as an R-value.

3. Results

All five patients were male (age at tic onset = 8 ± 2 years; age at surgery = 26.8 ± 9.3 years). The mean disease duration at the time of surgery was 18.4 ± 7.7 years. Medications were kept constant after surgery, except for the patient 3, who suspended all medications due to side-effects (Supplementary File 1). No comorbidities were related, except for patients 2 and 5, who presented mild obsessive-compulsive disorder (YBOCS = 13 and 11, respectively). Table 1 summarizes the clinical outcomes 12 months after surgery. Patients 1, 2 and 3 responded positively after surgery; the symptoms of patient 4 and 5 did not improve (poor responders). The changes in YGTSS after surgery could not be explained by patient age at the time of surgery, age at the time of tic onset, baseline YGTSS or disease duration ($p > .05$).

Table 1
Thalamic-DBS effect on tics before and 12 months after surgery.

	YGTSS total		
	Preoperative	Postoperative	Improvement (%)
Patient 1	79	43	45
Patient 2	96	45	53
Patient 3	72	36	50
Patient 4	78	81	−4
Patient 5	85	82	3

YGTSS = Yale Global Tic Severity Scale.

3.1. Imaging analysis

The active contacts and the VTAs of all patients reached the CM-Pf. Visually, there were no major differences between the active contacts and the clinical outcomes (Fig. 1).

There was no significant relationship between the VTA intersection of the CM-Pf and the YGTSS changes after surgery ($p = .374$, Fig. 2).

Using the connectivity between the VTAs and the cortical areas (described above), we determined that the frontal and limbic regions structurally correlated with YGTSS improvement. Unlike patient 4 and 5 (poor responders), the VTA of the three good responders correlated positively with the right frontal middle gyrus ($R = 0.564$, $p = .03$), the left frontal superior sulci region ($R = 0.900$, $p = .030$) and the left cingulate sulci region ($R = 0.821$, $p = .045$) (Fig. 3).

4. Discussion

Our primary conclusions are: i) the motor outcome after CM-Pf DBS in TS may differ between patients and the VTA inside the target (CM-Pf) does not explain this variability in clinical outcomes; ii) the pattern of the connectivity between the region stimulated and specific brain cortical area may be responsible for the variance in outcome. These two points reinforce recent evidence that, although the targets for DBS in neurological disorders are normally determined by specific anatomical regions (nucleus or tracts), the ideal target may not necessarily be an anatomical structure in itself, but rather, a structurally connected region.

We found a strong correlation between the connectivity of the VTA from the three good responders with the frontal and limbic areas. This is expected because TS presents with motor (probably more related to frontal areas) and behavioral symptoms (limbic areas). The poor responders (patients 4 and 5), despite having his VTAs inside the CM-Pf nucleus, had no activated fibers connected with these regions. Additionally, there were no notable differences between the active contacts inside the CM-Pf among the patients. This is crucial because a misplacement lead could account for the poor outcomes.

Functional imaging proposes that tic improvement is related to the activation of the prefrontal cortex. A PET study revealed an association between tics and brain activity in the dorsolateral-rostral prefrontal cortex and cingulate cortex. In addition, transcranial magnetic stimulation studies indicate that tics originate from compromised inhibition

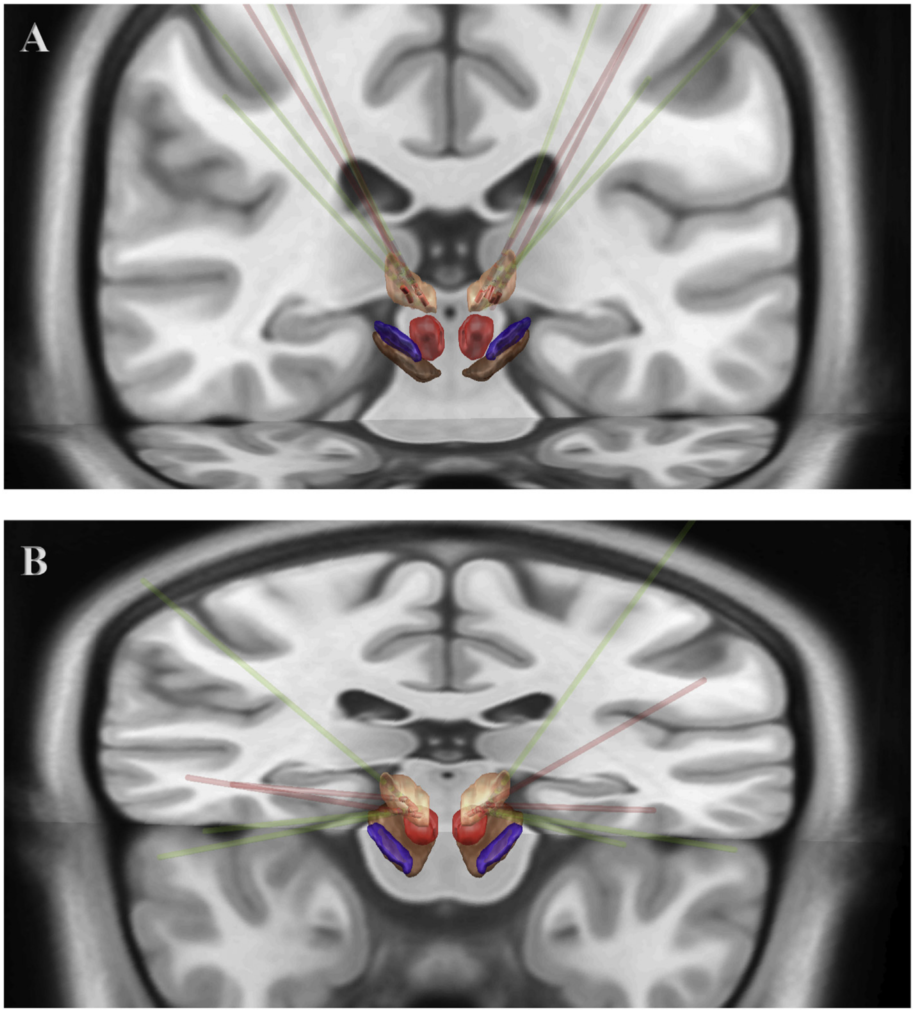

Fig. 1. The figure shows the lead placement and the active contact (red highlighted) between the good responders (green leads) and the poor responders (red leads). All the active contacts reached the centromedian nucleus-parafascicular region. A = Frontal view; B = Upper view. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in the motor cortex [12]. Taken together, we can hypothesize that the effectiveness of CM-Pf/dB is related to the effects of high-frequency stimulation of frontal and limbic cortical regions [13].

Recent data published by the International Deep Brain Stimulation Database and Registry revealed a mean improvement in the YGTSS of 45.1% in 157 patients with TS, 12 months after surgery [14]. Although individual data or interquartile ranges were not available, the large SD implies that the level of improvement among the TS patients was quite variable. A complex interplay between the severity and the chronicity of tics, baseline characteristics, psychiatry comorbidities, electrode placement and VTA connectivity may together account for this variability. Studies focusing on the most important predictive factors are

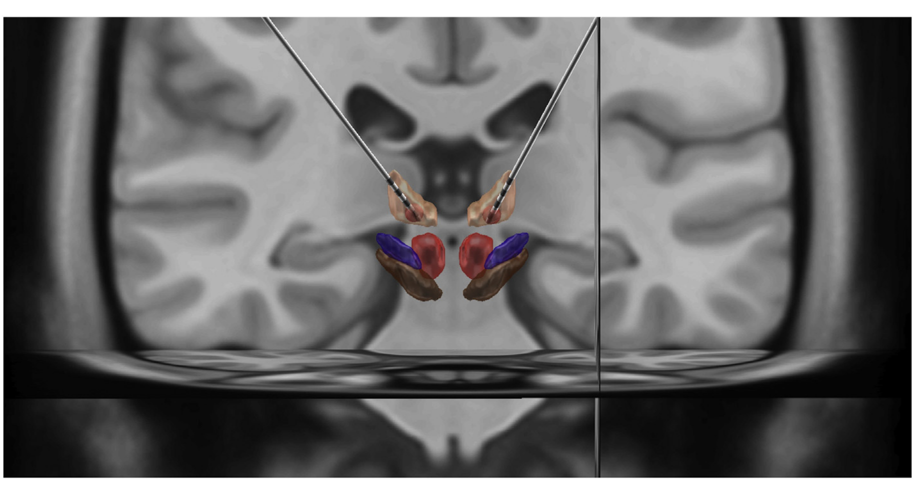

Fig. 2. Representation of the volume of tissue activated inside the centromedian nucleus-parafascicular region from Patient 2. The figure illustrates the VTA (red sphere) that reaches the centromedian nucleus-parafascicular region of patient 2. The volume of each VTA did not differ between patients. Pink nucleus = centromedian nucleus-parafascicular region; red nucleus = red nucleus; purple nucleus = subthalamic nucleus; brown nucleus = substantia nigra. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

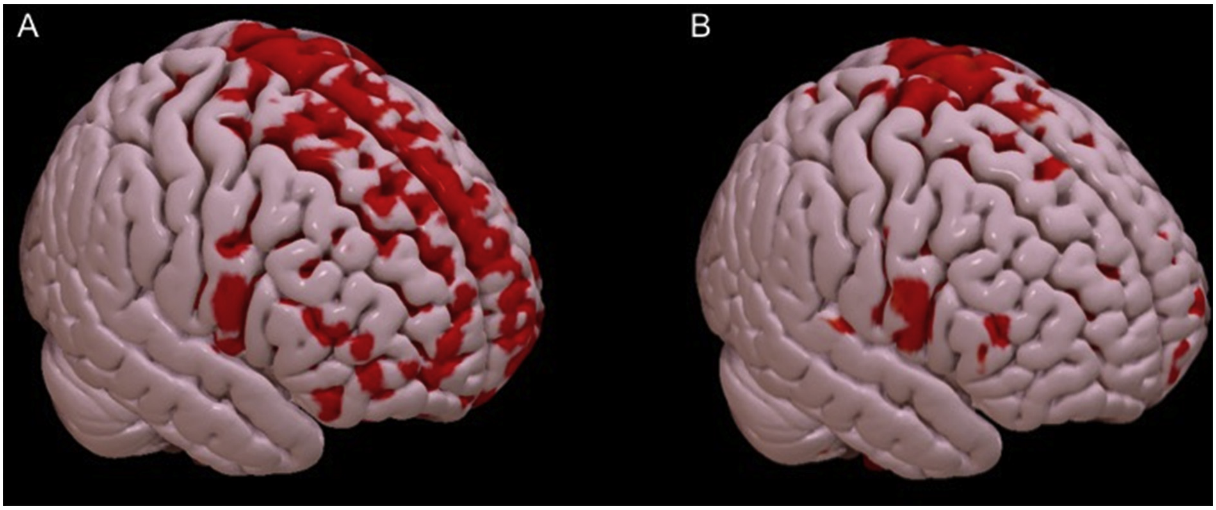

Fig. 3. Structural connectivity between the volume of tissue activated and the cortical areas.
The brain map represents the cortical areas that were structurally connected with the VTA in a good responder (patient 2, A) and a poor responder (patient 4, B). There is a stronger connectivity with the frontal areas in the good (compared to the poor) responder.

warranted.

This study has several clear limitations. Our goal was to present work conducted to test the hypothesis that the influence of thalamic-DBS on specific cortical regions may be, in part, responsible for motor outcomes in TS. This investigation is a proof-of-concept study with investigations of only five patients that attempted to determine why two patients did not improve after surgery, despite having their active contacts inside the CM-Pf.

5. Conclusion

Results in this study suggest that the thalamic volume stimulated does not explain the variance in outcome in TS, but rather, the pattern of connectivity between the region stimulated and specific brain cortical area does affect treatment outcome. Studies with larger patient cohorts will be necessary to confirm our initial findings.

Conflict of interests

The authors report no conflict of interest involved in this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.05.011.

References

[1] R.J. Bajwa, A.J. de Lotbinière, R.A. King, B. Jabbari, S. Quatrano, K. Kunze, L. Scahill, J.F. Leckman, Deep brain stimulation in Tourette's syndrome, Mov. Disord. 22 (2007) 1346–1350, https://doi.org/10.1002/mds.21398.

[2] L.E. Schrock, J.W. Mink, D.W. Woods, M. Porta, D. Servello, V. Visser-Vandewalle, P.A. Silburn, T. Foltynie, H.C. Walker, J. Shahed-Jimenez, R. Savica, B.T. Klassen, A.G. Machado, K.D. Foote, J.-G. Zhang, W. Hu, L. Ackermans, Y. Temel, Z. Mari, B.K. Changizi, A. Lozano, M. Auyeung, T. Kaido, Y. Agid, M.L. Welter, S.M. Khandhar, A.Y. Mogilner, M.H. Pourfar, B.L. Walter, J.L. Juncos, R.E. Gross, J. Kuhn, J.F. Leckman, J.A. Neimat, M.S. Okun, Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group, Tourette syndrome deep brain stimulation: a review and updated recommendations, Mov. Disord. 30 (2015) 448–471, https://doi.org/10.1002/mds.26094.

[3] E. Cannon, P. Silburn, T. Coyne, K. O'Maley, J.D. Crawford, P.S. Sachdev, Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome, Am. J. Psychiatry 169 (2012) 860–866, https://doi.org/10.1176/appi.ajp.2012.11101583.

[4] S.C.B. Casagrande, R.G. Cury, E. Alho, E.T. Fonoff, Deep Brain Stimulation in Tourette's Syndrome: Evidence to Date, (2019), pp. 1016–1075, https://doi.org/10.2147/NDT.S139368.

[5] A. Horn, M. Reich, J. Vorwerk, N. Li, G. Wenzel, Q. Fang, T. Schmitz-Hübsch, R. Nickl, A. Kupsch, J. Volkmann, A.A. Kühn, M.D. Fox, Connectivity predicts deep brain stimulation outcome in Parkinson disease, Ann. Neurol. 82 (2017) 67–78, https://doi.org/10.1002/ana.24974.

[6] J.M. Henderson, "Connectomic surgery": diffusion tensor imaging (DTI) tractography as a targeting modality for surgical modulation of neural networks, Front. Integr. Neurosci. 6 (2012) 15, https://doi.org/10.3389/fnint.2012.00015.

[7] A. Horn, A.A. Kühn, Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations, NeuroImage 107 (2015) 127–135, https://doi.org/10.1016/j.neuroimage.2014.12.002.

[8] T.A. Dembek, M.T. Barbe, M. Åström, M. Hoevels, V. Visser-Vandewalle, G.R. Fink, L. Timmermann, Probabilistic mapping of deep brain stimulation effects in essential tremor, NeuroImage Clin. 13 (2017) 164–173, https://doi.org/10.1016/j.nicl.2016.11.019.

[9] M. Reisert, I. Mader, C. Anastasopoulos, M. Weigel, S. Schnell, V. Kiselev, Global fiber reconstruction becomes practical, NeuroImage 54 (2011) 955–962, https://doi.org/10.1016/j.neuroimage.2010.09.016.

[10] A. Horn, D. Ostwald, M. Reisert, F. Blankenburg, The structural-functional connectome and the default mode network of the human brain, NeuroImage 102 (Pt 1) (2014) 142–151, https://doi.org/10.1016/j.neuroimage.2013.09.069.

[11] M. Joliot, G. Jobard, M. Naveau, N. Delcroix, L. Petit, L. Zago, F. Crivello, E. Mellet, B. Mazoyer, N. Tzourio-Mazoyer, AICHA: an atlas of intrinsic connectivity of homotopic areas, J. Neurosci. Methods 254 (2015) 46–59, https://doi.org/10.1016/j.jneumeth.2015.07.013.

[12] G.H. Moll, S. Wischer, H. Heinrich, F. Tergau, W. Paulus, A. Rothenberger, Deficient motor control in children with tic disorder: evidence from transcranial magnetic stimulation, Neurosci. Lett. 272 (1999) 37–40.

[13] H.S. Singer, Tourette's syndrome: from behaviour to biology, Lancet Neurol. 4 (2005) 149–159, https://doi.org/10.1016/S1474-4422(05)01012-4.

[14] D. Martinez-Ramirez, J. Jimenez-Shahed, J.F. Leckman, M. Porta, D. Servello, F.-G. Meng, J. Kuhn, D. Huys, J.C. Baldermann, T. Foltynie, M.I. Hariz, E.M. Joyce, L. Zrinzo, Z. Kefalopoulou, P. Silburn, T. Coyne, A.Y. Mogilner, M.H. Pourfar, S.M. Khandhar, M. Auyeung, J.L. Ostrem, V. Visser-Vandewalle, M.-L. Welter, L. Mallet, C. Karachi, J.L. Houeto, B.T. Klassen, L. Ackermans, T. Kaido, Y. Temel, R.E. Gross, H.C. Walker, A.M. Lozano, B.L. Walter, Z. Mari, W.S. Anderson, B.K. Changizi, E. Moro, S.E. Zauber, L.E. Schrock, J.-G. Zhang, W. Hu, K. Rizer, E.H. Monari, K.D. Foote, I.A. Malaty, W. Deeb, A. Gunduz, M.S. Okun, Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep brain stimulation public database and registry, JAMA Neurol. 75 (2018) 353–359, https://doi.org/10.1001/jamaneurol.2017.4317.