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Editorial

After 19 years of deep brain stimulation in Tourette's syndrome: From multiple targets to one single target?

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The medical scientific community drives toward standardization of procedure. In deep brain stimulation (DBS) for motor diseases, there are two main targets; the subthalamic nucleus and the globus pallidus internus (GPi). In contrast, in DBS for Tourette's syndrome (TS), currently there is no consensus as to target choice. Multiple potential targets are proposed and are used, furthermore in single or combined fashion. Is a single target for DBS in TS ultimately possible? DBS for medication refractory TS was proposed in 1999 by the Dutch team led by Vandewalle[16] stimulating the thalamic centromedian-parafascicular nucleus (CM/Pf). The medial thalamus was lesioned already at the beginning of the 1970s by Hassler and Dieckmann for TS.[4] Target coordinates selected by the Dutch group were 5 mm lateral to the anterior commissure–posterior commissure line (AC–PC), 2 mm posterior to mid-commissural point, vertically at the AC–PC plane. Since then, several DBS targets have been proposed for TS, which is considered a disorder due to fronto-striatal dysfunction paired with a strong behavioral alteration.[18,19] In the whole TS spectrum, 90% of patients present with at least one comorbidity, such as obsessive-compulsive disorder (OCD), learning difficulty, poor impulse control, self-injury behavior, attention-deficit-hyperactivity disorder, nonobscene socially inappropriate behavior, and autistic spectrum disorder.[12] Coexisting symptoms are also depression and anxiety.[12] In clinical practice, obsessive-compulsive symptoms (OCS) and behaviors (OCB) are the most important comorbidities, as they are responsible for a substantial social impairment along with an economic burden for both patients and their families.[2] OCS and OCB are frequently observed in TS patients, where tics are the main component in childhood and OCD along with other psychopathological traits are encountered more frequently in adolescence and adulthood. However, it is well known that tics happen in OCD patients as well.[3]

To address such a variable range of symptoms and reduce social impairment, clinicians have progressively shifted their attention from a simple treatment of tics to a wider control of comorbidities. During the last two decades, beside the CM/Pf of the thalamus, new DBS targets have been investigated for a better control of comorbidities. Currently, there is the tendency to select targets based on the specific phenotypic presentation,[14] a patient-to-patient basis is adopted.[10] The CM/Pf is mostly taken into consideration in patients with a predominant tic phenomenology and a low comorbidity charge, whereas the nucleus accumbens (NAc), the ventral striatum, the anterior limb of the internal capsule, and the antero-medial limbic section of the globus pallidus internus (a-GPi) are preferred in patients with a predominant comorbidity burden.

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Currently, based on double-blind studies, the most robust data come from thalamic and pallidal stimulation [Figure 1].[1,6,14,15]

To the best of our knowledge, we have worldwide the largest data pool on DBS in TS. We performed 66 DBS procedures on 61 TS patients between 2004 and 2017. From 2004 to 2012, we treated 42 TS patients targeting the ventro-oralis-internus centromedian parafascicular thalamus (Voi-CM/Pf), which is located 2 mm anteriorly to the target described by Vandewalle. Since the beginning, we decided to locate the DBS-lead anteriorly for a better stimulation of the associative-limbic connections, in order to modulate both motors as behavioral features of TS.[11] In patients still suffering from debilitating OCS and OCB despite a previous thalamic DBS, the NAc has been used as an add-on rescue DBS target. In 2012, we performed the first GPi DBS targeting the a-GPi. Since then, we implanted eight TS patients at the antero-medial GPi, while for the same time lapse, we treated only one TS patient at the Voi-CM/Pf. Change of the chosen target came slowly, as we realized that the a-GPi DBS in TS is as good as the Voi-CM/Pf in reducing motor tics, but it is more effective in controlling comorbidities, especially the OCS and the OCB [Figures 2 and 3]. More importantly, our patients treated with the a-GPi DBS showed a stable response over an extended period of time and a lower risk of developing hardware-related adverse events compared to the Voi-CM/Pf (13 DBS system explantation procedures in a population of 43 patients implanted at the Voi-CM/Pf group vs. no DBS system explantation procedures in a population of 8 patients implanted at the a-GPi). Published data on the a-GPi for TS show equally encouraging long-term results compared to the CM-Pf and the Voi-CM/Pf. Regardless of the chosen target, the associated risks are the general risks of DBS intervention. In TS-DBS, the recent large trial by Martinez-Ramirez *et al.*[8] showed that the majority of adverse effects are stimulation related and transient. From a surgical point of view, the GPi is preferred to the thalamic target for its more defined boundaries, as it is a real nucleus and not a cluster of neurons. In the literature, there are several case reports and double blind studies on the feasibility of pallidal stimulation echoing our findings. In 2011, Martínez-Fernández *et al.* performed pallidal DBS in five patients, three patients were implanted in the limbic a-GPi, and the other two patients in the sensorimotor postero-ventral GPi. The mean Yale Global Tic Severity Scale (YGTSS) reduction following limbic stimulation was greater than following motor stimulation (74% vs. 42%). The authors concluded that despite the low number of treated patients' limbic, a-GPi DBS appears to be superior than motor GPi DBS in TS.[7] In 2013, Massano *et al.* reported a young TS patient treated with a-GPi DBS. At 1-year follow-up, they reported an YGTSS improvement of 37% and at 2-year follow-up an improvement rate of

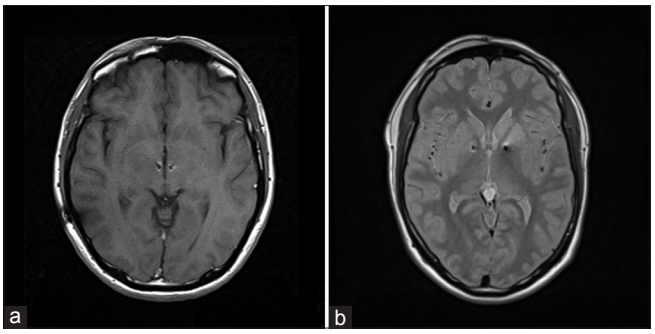

Figure 1: Postoperative brain MRI. (a) DBS leads at the ventro-oralis-internus centromedian parafascicular thalamus (Voi-CM/Pf). (b) DBS leads at the antero-medial globus pallidus internus (a-GPi)

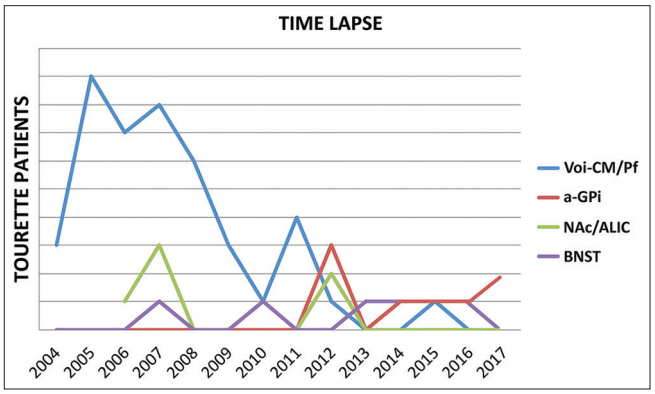

Figure 2: Procedure targeting evolution from 2004 to 2017. The ventro-oralis-internus centromedian parafascicular thalamus (Voi-CM/Pf) depicted in blue, the nucleus accumbens/anterior limb of the internal capsule (NAc/ALIC) depicted in green, the bed nucleus of stria terminalis (BNST) depicted in purple, and the antero-medial globus pallidus internus (a-GPi) depicted in red

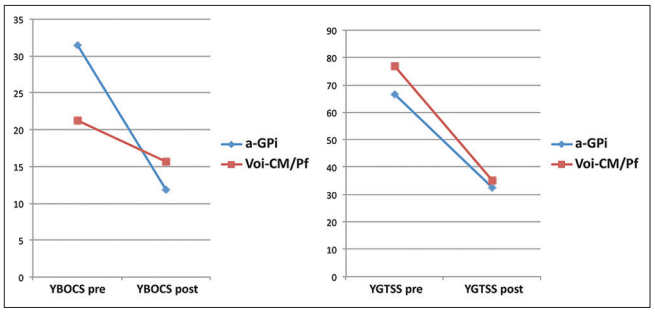

Figure 3: Comparison of the Yale-Brown Obsessive-Compulsive Scale (YBOCS) and the Yale Global Tic Severity Scale (YGTSS) score changes after DBS at the ventro-oralis-internus centromedian parafascicular thalamus (Voi-CM/Pf) and at the antero-medial globus pallidus internus (a-GPi)

60%. More importantly, patient comorbidities improved as well after DBS.[9] In 2014, Huasen *et al.* reported a case of a-GPi DBS in a patient with violent neck extension tics that had caused a myelopathy. YGTSS improvement was from 83 to 37 at 1-year follow-up.[5] In 2014, Sachdev *et al.* published a 4-year follow-up study on 17 patients suffering from TS implanted at the a-GPi. The authors reported a 48.3% reduction in motor tics and a 41.3% reduction in phonic tics at the 1-month follow-up. This improvement

remained unchanged at the 4-year follow-up.[13] Different results have been reported by Welter *et al.* in 2017 when the French group published data on a randomized, double-blind, controlled trial conducted on medically refractory TS patients from eight hospitals specialized in movement disorders. Enrolled patients were implanted with bilateral a-GPi DBS and 3 months later they received either active or sham stimulation; for the subsequent 3 months from the activation or non-activation, patients have been followed up in a double-blind fashion. Of a total of 25 patients who completed the study, 16 were stimulated whereas 9 received a sham stimulation. Between the beginning and the end of the 3-month double-blind period, two groups of clinicians noted no significant difference in YGTSS score change. They concluded that a 3-month period of a-GPi DBS is insufficient to decrease tic severity for patients with TS.[17] The recently published trial "The Prospective International Deep Brain Stimulation Database and Registry" (31 institutions in 10 countries worldwide) arrived to similar conclusions as our analysis regards target choice based on 185 TS patients treated with DBS (one-third of cases were from our institute). The anterior GPi showed the greatest improvement (YGTSS total score at 1-year follow-up 50.5% vs. centromedian thalamic region 46.3%).[8]

On a concluding note:

The current most critical aspect in DBS TS remains the standardization of target choice. Our center has to the best of our knowledge the worldwide largest data pool on DBS in TS. Based on our experience and from the published data, it appears that a single target in TS is possible. We think that the limbic a-GPi is a promising target in pharmacologic refractory TS for motor and for limbic symptoms. With our short communication, we hope to drive the DBS community to pay more attention to this target to achieve a consensus on target selection in TS. Consensus on target selection would aid significantly in standardizing further the procedures in DBS for TS, in order to improve patient care.

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