

Prefrontal Cortical Stimulation in Tourette Disorder: Proof-of-concept Clinical and Neuroimaging Study

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ABSTRACT: Background: The benefits of neurosurgery in Tourette Syndrome (TS) are still incompletely understood. Prefrontal cortical electrical stimulation offers a less invasive alternative to deep brain stimulation. Objective: To perform a pilot assessment on safety and efficacy of prefrontal cortical bilateral electrical stimulation in TS using clinical and brain metabolic assessments. Methods: Four adult TS patients underwent tic assessment using the Yale Global Tic Severity Scale and the Rush Video Rating Scale at baseline and 1, 3, 6, and 12-months after implant; whereas FDG-PET scans were acquired at baseline and after 6 and 12 months. Results: Tic clinical scores were improved at 6 months after implant, meanwhile they showed a tendency to re-emerge at the 12-month follow-up. There was a correlation between FDG-PET and tics, mainly consisting in a reduction of baseline brain hypermetabolism, which paralleled tic score reduction. Conclusion: Epidural stimulation in TS is safe and yields a modulation of tics, paralleled by FDG-PET metabolic modulation.

Introduction

Tourette disorder (TS) is an early-onset neurological disorder characterized by motor and vocal tics that have persisted for more than one year since first tic onset.¹ First-line treatment is based on behavioral and medical therapy; deep brain stimulation (DBS) has been used for severe cases refractory to medical treatment² as it can provide symptomatic improvement, but is not devoid of important adverse events.³ Moreover, there is uncertainty concerning the most appropriate DBS target, suggesting further treatment options are worth being explored. Among these, epidural cortical brain stimulation emerges as a possible alternative to DBS in hyperkinetic movement disorders.^{4,5} Tics are the hallmark movement disorder observed in TS.⁶ Various clinical, neuroimaging, and neurophysiological observations indicate that abnormal functioning of the basal ganglia and related

thalamocortical circuits constitutes the major pathophysiological basis of tics in TS.⁷ It is assumed that the basal ganglia play a major role in the “timing and sequencing” of motor and behavioral programs by selecting desired and by suppressing unwanted programs to be executed. In this way, the basal ganglia “assist” the prefrontal cortex by facilitating or suppressing behavioral or motor responses. Evidence that the motor cortex is hyperexcitable in TS patients comes from neurophysiological studies. Transcranial magnetic stimulation (TMS) studies demonstrated several changes of motor cortex excitability in TS, including reduced short-interval intracortical inhibition, reduced short latency sensory afferent inhibition, and shortened cortical silent periods.⁸

Imaging studies in TS have revealed that, during tic execution, glucose metabolism is increased in premotor, prefrontal, and motor cortex, indicating neural hyperactivity in these brain areas.^{9,10} A recent fMRI study in TS has shown that premotor

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and prefrontal areas have increased activation for hand motor tasks and that activation during motor imagery (a mental rehearsal of a motor task) also involved rostral prefrontal and temporoparietal regions in the right hemisphere.¹¹ Positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG-PET) played an important role in revealing the involvement of brain circuits outside the basal ganglia.¹² The main consistent finding in TS is a concurrent increase of glucose metabolism in the lateral and medial premotor cortices and cerebellum combined with a decrease in the basal ganglia and thalamus.^{13,14}

Building on these premises, we performed a proof-of-concept clinical trial on the safety and efficacy of bilateral epidural prefrontal cortex stimulation in TS patients.

Materials and Methods

We selected patients with a diagnosis of TS based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) criteria:¹⁵ the patient was over the age of 18; the chronic tic disorder was adversely affecting quality of life; failure to reduce the severity of tics or intolerable side effects using adequate doses of oral medications administered for at least 3 months; and the absence of cognitive deficits or psychiatric disorders of Axis I. Patients with comorbid attention deficit hyperactivity disorder were excluded. Additional exclusion criteria were: significant structural brain lesions on imaging studies, history of severe head trauma preceding the onset of tics, use of dopamine receptor blockers before the recognition of tics, previously implanted electrical devices, electroconvulsion therapy in the past 24 months, suicide attempts in the past 12 months, significant sociopathic personality, and current or planned pregnancy. The study protocol was approved by the institutional review board and the patients signed an informed consent.

A multidisciplinary team, composed of a neurologist, a neurosurgeon, a neuropsychologist, and a psychiatrist examined all the patients. An independent neurologist and a psychiatrist reviewed screening data for each patient and certified their suitability for participation in the trial. The following scales were used: Yale Global Tic Severity Scale (YGTSS, which includes subscales for motor and phonic tics),¹⁶ Rush Video Rating Scale (RVRS),¹⁷ and the Hamilton Rating Scales for Depression and Anxiety (HAM-D; HAM-A).^{18,19}

An assessment of the acute effects stimulation with a frequency of 60 Hz and a pulse width of 60 μ sec was initially performed in all patients one day after surgery. Based on previous reports,^{4,20} stimulation settings were kept within the following ranges: amplitude 2.5 to 3.0 V; pulse width 60 to 90 μ s; frequency 50 to 120 Hz. The internal pulse generators were set at constant voltage. At each visit, stimulation settings were reviewed and optimized to minimize side effects and maximize potential motor improvement (Supporting Table 1). The same stimulation settings were applied on both sides.

The epidural placement of the electrodes was performed under general anesthesia, as previously described.⁵ The cortical

target was the prefrontal area, set between Brodmann areas 9 and 46. Cortical stimulation was delivered continuously for 24 hours, using individualized stimulation settings (Supporting Table 1).

FDG-PET Study

FDG-PET acquisitions were performed at baseline, 6-months and 12-months after implant, as previously described.²¹

Voxel-based Single Subject Analysis

Single patient FDG-PET scans were spatially normalized to a specific FDG-PET template²² to allow voxel-based comparisons based on a validated optimized statistical parametric mapping (SPM) procedure.²¹ This procedure statistically compares single-subject FDG-PET scans with a large database ($N = 112$) of healthy controls scans, delivering SPM-t maps showing patterns of regional metabolic increases and decreases at the single-subject level, which are thresholded at $p < 0.05$, corrected for multiple comparisons with Family-Wise Error (FWE) correction.

Voxel Level Analysis

We adopted a second level flexible factorial design (repeated measures ANOVA) in SPM5, setting standardized clinical scales^{17,23} as variables of interest. In the present design, three time levels (T0, T1, T2) were entered as factors, adding a covariate of interest-containing clinical scores on the chosen scale and testing for positive and negative correlations. As for the within-subject factor, given the dependency between the measurements over time, variance was coded as dependent and equal, thus accounting for non-sphericity violations.²⁴

The single-subject SPM contrast images of hypermetabolism resulting from the first level analyses were used for the correlation analysis. In the present design, a positive correlation indicates that decreases in glucose metabolism are associated with decreases in tic severities, and vice versa. On the other hand, a negative correlation indicates that increases in glucose metabolism are associated with decreases in tic severities (e.g., interpreted as compensatory effect), and vice versa. A statistical threshold of $p < 0.001$ (uncorrected for multiple comparisons) was adopted, with a minimum cluster extent set at $k:100$ voxels. Additionally, the results were deemed significant only if surviving cluster-level FWE-corrected $p < 0.05$ threshold.

Region of Interest Analysis

Regions of Interest (ROIs) were obtained with the Wake Forest University PickAtlas (WFUPickAtlas) toolbox,²⁵ adopting the Automated Anatomical Labeling atlas²⁶ for SPM, while the ROI analysis was run with MarsBar Toolbox for SPM. Due to the limited number of patients, we decided for a confirmatory ROIs approach based on a priori hypothesis on the basis of the results in previous literature on TS, reporting alterations in specific neural networks.^{7,13,14,27,28} We focused on the following regions: (1) the sensorimotor network, including primary sensorimotor

and the premotor cortex; (2) the associative cortices, namely the dorsolateral frontal cortex (inferior, middle, superior frontal gyri, and frontal operculum), the lateral temporal cortex (inferior, middle, and superior temporal gyri), the inferior and superior parietal cortex, and the rolandic operculum; (3) the limbic network, including insula, hippocampal structures, anterior cingulate cortex, and orbitofrontal cortex (inferior, middle, and superior frontal orbital definitions of the AAL atlas); and (4) the caudate nucleus, putamen, and the thalamus. At consistence with voxel-based analysis, the same statistical threshold of $p < 0.001$ was adopted. Additionally, at the ROI-level, a Bonferroni multiple comparisons correction was performed considering the total number of included ROIs.

Results

The population recruited consisted of four men aged 36.3 years (± 8.6 SD) at implant. Their demographic and clinical characteristics are summarized in Table 1. All had a severe tic disorder leading to functional impairment; in all, tics were considered the main source of disability and a main limitation to social integration and quality of life. Behavioral abnormalities were instead minor and not significantly disabling. Although none of them fulfilled DSM criteria for anxiety or depression, patients three and four scored positive at HAM-A and patient four also at HAM-D. Continuous epidural stimulation was well tolerated with no reported side effects. There were no surgical complications, device failures, or malfunctions.

The individual RVRS scores are shown in Supporting Table 2. In summary, at month 6 RVRS improved in patient 1 (P1) by 33% compared to baseline; in patient 2 (P2) by 26%; in patient (P3) by 40%; and patient 4 (P4) by 7%. At 12 months, P1 and P4 stayed stable, while P2 and P3 relapsed compared to month 6. At 1 year, P1 was still 13% better than baseline, while P3 was 10% worse than baseline.

The YGTSS scores are shown in Supporting Table 2 with all components and totals. At month 6, the YGTSS total motor and total phonic tic score was reduced in P1 by 52% compared to baseline, in P2 by 20%, in P3 by 62% and in P4 by 2.7%. At month 12, this score was still improved in P1 by 60% compared to baseline, it had deterioration in P2 by 7%, again improved by 24% in P3 and by 3% in P4. At month 6, the YGTSS Global score improved in P1 by 28% compared to baseline, in P2 by 44%, in P3 by 81% and in P4 by 12%; at month 12, there was a 77% improvement of P1 compared to baseline, a 3% deterioration of P2, a 28 % improvement and of P3, and a 13 % improvement of P4.

HAM-A and HAM-D values at baseline and at follow-up visits are reported in Supporting Fig. 1.

At baseline, the FDG-PET SPM analysis at single-subject level did not reveal a significant reduction in regional brain glucose hypometabolism compared to healthy controls ($p_{FWE} < 0.05$, Family-Wise Error corrected for multiple comparisons). A significant ($p_{FWE} < 0.05$) increase of brain metabolism was otherwise

TABLE 1 Demographic and clinical features of the patients

Patient number	Age at onset	Age at implant	Symptoms at onset	OCD	HAM-A baseline	HAM-D baseline	RVRS baseline	YGTSS Motor baseline	YGTSS Vocal baseline	Baseline medication	Medication after Cortical Stimulation
P1	14	43	Motor tics: head, shoulder and arms Phonic Tic: Developed Later	None	15	3	12	16	9	Pimozide, tetrabenazine, sulpiride, aripiprazole	None
P2	7	35	Motor tics: limbs Phonic Tic: none	None	16	7	15	16	13	Clonidine, olanzapine, quetiapine, risperidone	Quetiapine, fluvoxamina
P3	8	23	Motor tics: head, shoulders, right limbs Phonic Tic: none	None	21	10	10	18	11	Prazepam, pimozide, trihexyphenidyl, sulpiride, aripiprazole, haloperidol	Haloperidol
P4	8	37	Motor tics: limbs Phonic Tic: none	None	22	15	14	25	12	Haloperidol, pimozide, clonidine, paroxetine, sertraline, tetrabenazine	Quetiapine, Valproic acid

Abbreviations: OCD (obsessive compulsive disorder according to DSMIV-TR); HAM-A, Hamilton scale for anxiety; HAM-D, Hamilton scale for depression.

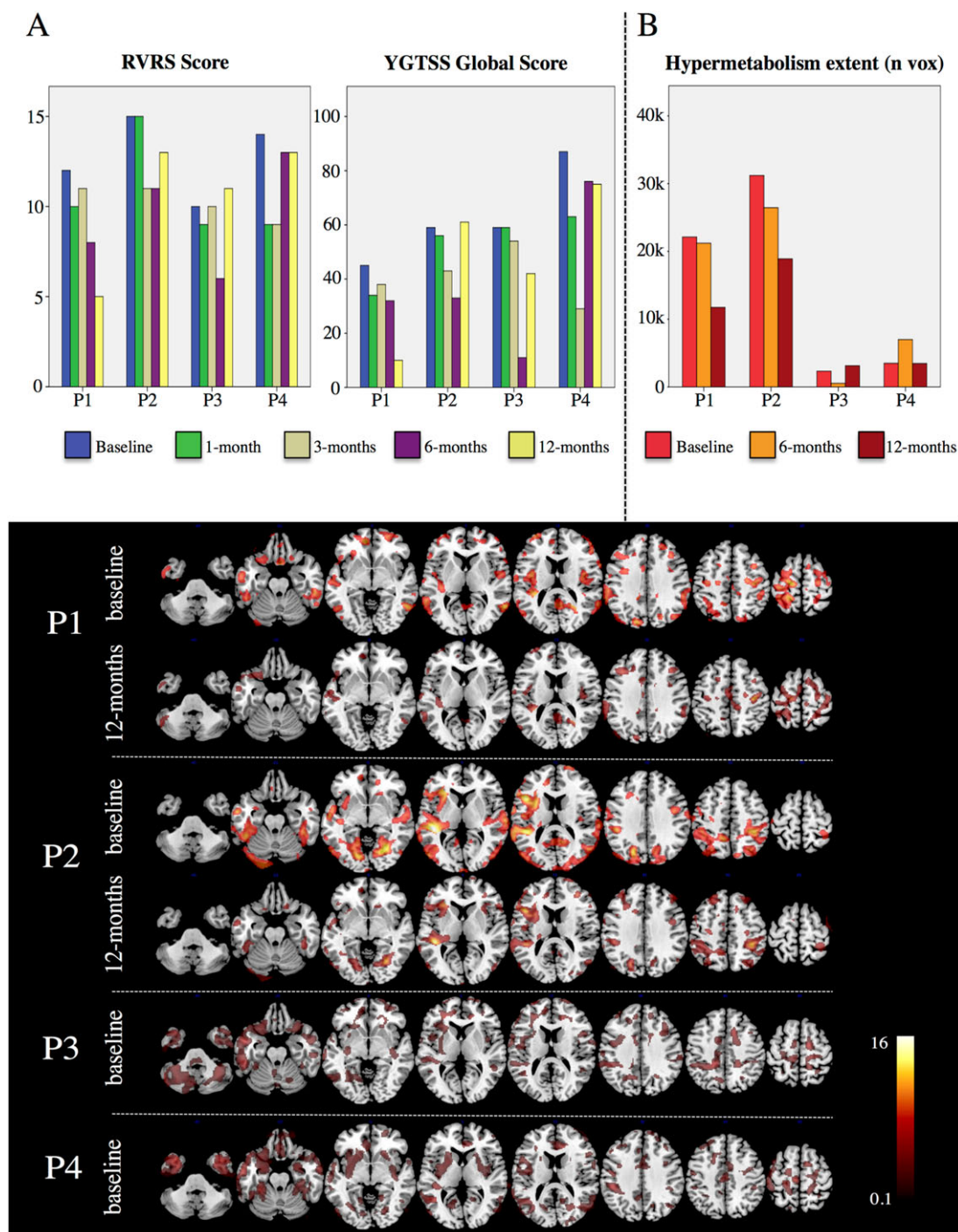
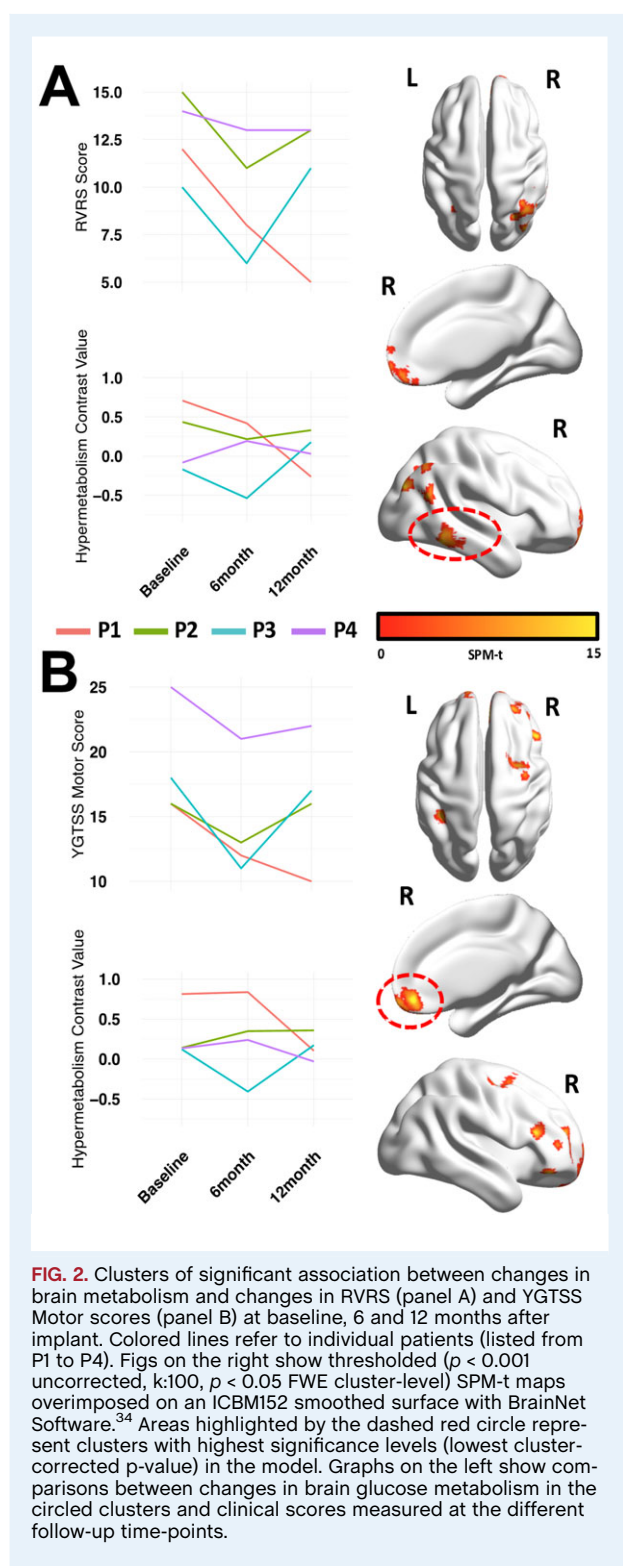


FIG. 1. Longitudinal assessment of clinical and FDG-PET brain metabolism in individual patients (listed from P1 to P4). (A) Barplots show longitudinal variations of RVRs scores and YGTSS global scores at preset follow-up times; (B) Barplot showing the longitudinal variations of hypermetabolic cluster extent (0-40K number of voxels) at preset follow-times, as measured at $p_{FWE} < 0.05$ (minimum cluster extent 100 voxels); (C) Hypermetabolic patterns observed in patients at baseline and 12 months (only for patients 1 and 2, who showed the most significant changes at follow-up. Patients 3-4 showed limited regional metabolic increases and negligible FDG-PET metabolism fluctuations at follow up (see Fig. 1B). SPM-t maps ($p_{FWE} < 0.05$) are overlaid on a standard anatomical T1 template with a multislice transaxial view.



found in the primary sensorimotor cortex, premotor cortex, frontal and rolandic operculum, orbitofrontal cortex, lateral temporal cortex and parahippocampal structures, inferior parietal cortex, left primary auditory cortex, insula and posterior cingulate cortex, with some cerebellar involvement. These metabolic

increases were more evident in P1 and P2 compared to P3 and P4, although anatomically co-localized (Fig. 1B–C).

The extent of the significant regional hypermetabolism was reduced 12 months after implant by 47% and 40%, respectively, in patients one and two. Instead, P3 and P4, who presented less severe hypermetabolism at baseline, had inconsistent changes after 12 months of cortical stimulation.

ROI-based and voxel-level correlation analyses showed consistent results. At the voxel-level, significant association ($p < 0.001$ uncorrected, $p < 0.05$ FWE-corrected at the cluster-level) was found between clinical improvement and regional brain metabolism reduction, for both the RVRS and YGTSS scores (Fig. 2). Although these associations did not survive primary FWE-correction for multiple comparisons, $p < 0.001$ was considered as a reasonably stringent threshold to balance Type I and Type II errors.

ROI-based analyses provided consistent results at the same statistical threshold, additionally surviving Bonferroni multiple comparisons correction. Table 2 and Supporting Table 3 provide further anatomical and statistical details.

A variability of tic scores was observed between patients after implant, consisting in improvements or relapses of symptomatology that were paralleled by decreases or increases of cortical metabolism in specific brain regions (Fig. 2). Such metabolic changes were significant in the following cortical regions with a marked prevalence in the right hemisphere: orbitofrontal, dorsolateral frontal, inferior/middle temporal and inferior parietal cortex.

Discussion

This study explored the safety and efficacy of bilateral epidural prefrontal cortex stimulation administered for one year to TS patients without psychiatric features. We aimed at influencing the generation of tics by stimulating frontal Brodmann areas 9 and 46. This minimally invasive treatment was well tolerated. P1 showed an overall reduction of tics, with an almost complete cessation of moderate to severe tics (Fig. 1A). However, in the remaining patients, an early beneficial response was followed by a progressive partial relapse after the first month. These results disappointed the hypothesis underlying the study design.

Considering that a YGTSS total tic severity score reduction of 35% is considered a reliable measure for determining treatment response,²⁹ only P1 achieved a consistent tic reduction above such threshold. P3 had an improvement above 35% at month 6, which was not confirmed at month 12. The other patients were below such threshold.

Motor and phonic tics improved during the first 6 months of treatment and relapsed afterward in all but P1. By contrast, the main effect on FDG PET metabolism was at 12 months rather than at the time of maximum clinical effect. One year after implant, neuroimaging changes were still appreciable. FDG-PET data at baseline showed metabolic increases in sensorimotor, premotor, and primary auditory cortex, with some cerebellar involvement, as expected.^{7,14,28}

TABLE 2 Confirmatory ROI analysis. Significant correlations between decreases in regional HYPERmetabolism and clinical improvements are shown with respective *p*-values and ROI xyz MNI stereotaxic coordinates. Significance for all the regions survived Bonferroni correction for multiple comparisons

Correlations	Anatomical area	<i>p</i> -value	x	Y	z
RVRS total score - Positive correlation	Temporal_Inf_R	0.000547	53	-32	-24
YGTSS Motor - Positive correlation	Frontal_Mid_R	0.000659	37	32	33
	Frontal_Sup_R	0.000517	22	30	42
	Frontal_Orb_R	0.000479	33	41	-14

All the stimulation settings tested were safe. No immediate changes of tic severity were observed when stimulation settings were changed. Of note, comparable changes in stimulation settings were adopted for all the patients, in particular for the first three patients (Supporting Table 1), in terms of gradual increases of both frequency and amplitude of the stimulation along the follow-up. Despite this, the patients presented individual variable trajectories in terms of modulation of metabolism, thus making it unlikely that stimulation changes could have played a primary role in the PET results.

We found a correlation between changes in FDG-PET brain metabolism and variations in RVRS and YGTSS motor scores, mainly consisting in a reduction of baseline regional brain hypermetabolism that paralleled tic score reduction. This suggests that prefrontal cortical stimulation modulated brain metabolism in correlation with clinical improvement, an action likely exerted by influence on the cortico-striato-pallido-thalamic network that is abnormal in TS.³⁰ Changes in motor scores were directly associated with metabolic changes in premotor regions, which are known to be crucial for motor imagery³¹ and are hyperactive during tics.¹⁰ To sum up, when clinical amelioration was observed, it was associated with a modulation of brain glucose metabolism. This finding also supports a pathogenic role of abnormal premotor and motor cortex activations in the pathophysiology of tics, possibly dysregulating prefrontal suppression of involuntary movements.³²

In our study, we selected patients who had no significant psychiatric comorbidity such as OCD and depression which indeed seem to benefit significantly from DBS. Given to the wide-ranging of the clinical course of TS, the lower percentage of clinical improvement might be due to the restriction on the type of patients enrolled in this study. At baseline, two patients had a HAM-A total score of 21 and 22, respectively and one had a HAM-D total score of 15. These patients did not fulfil DSM-IV-TR criteria for Depressive Disorder or Anxiety Disorder. In all, however, anxiety and depressive scores improved after surgery (Supporting Fig. 1).

Prefrontal cortical stimulation may possibly be useful in a subset of TS patients with a predominantly motor phenotype. This proof-of-concept study in a highly selected TS population provides heterogeneous outcomes. Two main issues need to be addressed before planning further controlled trials based on cortical stimulation. First, long-term efficacy is still untested: this one-year observation showed a partial relapse that warrants longer follow-up observations. Second, heterogeneity of tic improvement following prefrontal cortical stimulation suggests

that different brain network abnormalities may produce overlapping phenotypes. This may indicate that better-refined selection of patients, based on some yet undiscovered endophenotype, may be needed. A similar explanation may also apply to inconsistent outcomes observed after DBS implants in TS.³³

Whether prefrontal cortical stimulation is specifically indicated in tics or applies instead to the broader category of hyperkinetic disorders is a matter for investigation. In patients with “mobile” cervical dystonia motor and FDG-PET improvement were observed over one year after implant.⁵ In patients with fixed cervical dystonia, including a previously published patient who had transient benefit after cortical stimulation,²⁰ no appreciable improvement occurs. Tics have different pathophysiology from dystonia, although they may have similarities in the common final pathway to the motor cortex.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

D.P.: 3A, 3B

S.L.: 1B, 1C, 3A, 3B

L.I.: 2B

P.A.: 2B

O.G.: 3B

A.F.: 1C, 3B

A.A.: 1A, 1B, 2C, 3B

Disclosures

Ethical Compliance Statement: The ethics committee of the Istituto Neurologico Carlo Besta approved the study. Patient consent was obtained in written form and documented in the hospital record. The authors confirm that have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Supporting File 1. This file contains Supporting Tables 1–3 and Supporting Fig. 1.

Prefrontal cortical stimulation in Tourette disorder: proof-of-concept clinical and neuroimaging study

Supplementary tables and figures

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Supplementary Tables

Supplementary Table 1. Stimulation settings in individual patients at different follow-up times.

Pts	Month 0	Month 1	Month 3	Month 6	Month 12
1	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 80 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V
2	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 80 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V
3	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 80 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V
4	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 60 Hz Duration: 60 µs, Amplitude: 2.5 V	Cathode: Case+ Anode: 0-1-2-3- Frequency: 90 Hz Duration: 60 µs, Amplitude: 3.0 V

Supplementary Table 2. Individual data for items of the Rush Video Rating scale (RVRS) and the Yale Global Tic Severity Scale (YGTSS) at follow-up times.

Patients	Month 0	Month 1	Month 3	Month 6	Month 12
Rush Video Rating Scale (RVRS)					
P1	12	10	11	8	8
P2	15	15	11	11	13
P3	10	9	10	6	11
P4	14	9	9	13	13
YGTSS Total Motor Tic score					
P1	16	14	18	12	10
P2	16	14	14	13	16
P3	18	18	17	11	17
P4	25	20	15	21	22
YGTSS Total Phonic Tic score					
P1	9	10	0	0	0
P2	13	12	9	10	15
P3	11	11	7	0	5
P4	12	13	4	15	13
YGTSS Total Tic Score (a summation of the Total Motor Tic and Total Phonic Tic Scores)					
P1	25	24	18	12	10
P2	29	26	23	23	31
P3	29	29	24	11	22
P4	37	33	19	36	36
YGTSS overall TS impairment					
P1	20	10	20	20	0
P2	30	30	20	10	30
P3	30	30	30	0	20
P4	50	30	10	40	40
YGTSS global severity					
P1	45	34	38	32	10
P2	59	56	43	33	61
P3	59	59	54	11	42
P4	87	63	29	76	75

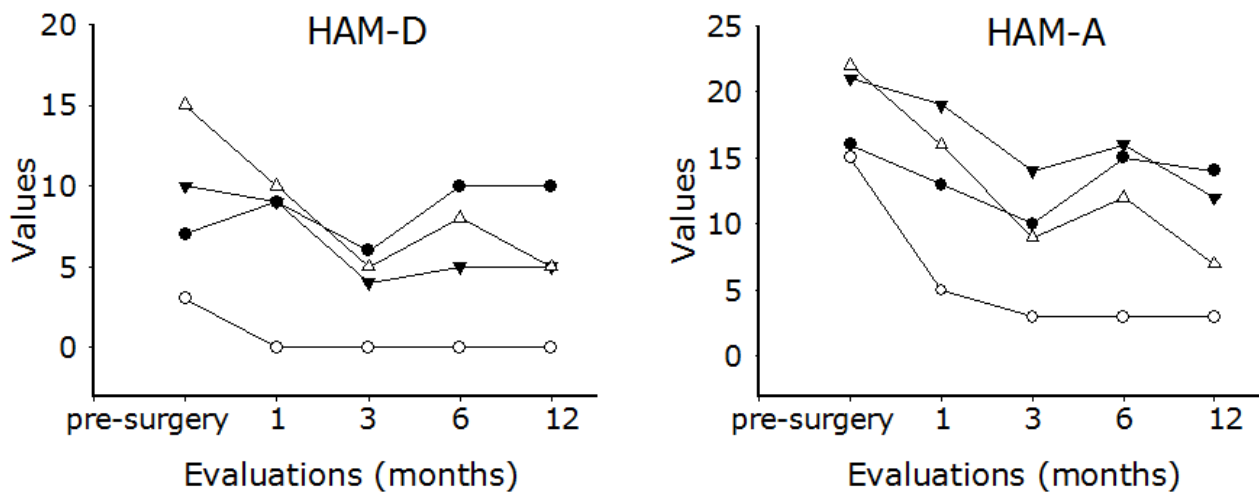
Supplementary Table 3. Voxel-based correlation analyses. All results shown survived $p < 0.001$ (uncorrected) and $p < 0.05$ FWE cluster-level statistical thresholds. P-values (cluster-level corrected), cluster sizes (k), MNI stereotaxic coordinates of the peaks and relative anatomical labeling (AAL atlas ¹) are provided.

RVRS	p-value	K	Anatomical Label	SPM-z	x	y	z
	<0.000	117	Angular_L	4.90	-34	-60	34
	<0.000	476	Temporal_Inf_R	4.78	58	-48	-20
	<0.000	531	Temporal_Mid_R	4.64	56	-68	12
	<0.000	406	Frontal_Mid_Orb_R	4.59	12	48	-10
	<0.000	120	Parietal_Inf_R	4.29	50	-46	52
YGTSS	p-value	K	Anatomical Label	SPM-z	x	y	z
Motor	<0.000	873	Frontal_Mid_Orb_R	5.13	4	46	-14
Subscore	<0.000	240	Precentral_R	4.44	64	8	20
	<0.000	182	Frontal_Inf_Orb_R	4.39	46	36	-14
	<0.000	158	Parietal_Inf_L	4.39	-38	-46	50
	<0.000	340	Frontal_Sup_R	4.35	28	-2	72
	<0.000	122	Frontal_Sup_L	4.08	-16	64	6

Abbreviations: RVRS, Rush Video Rating Scale; YGTSS, Yale Global Tic Severity Scale.

Supplementary Figures

Supplementary Figure 1. Individual data of the Hamilton Rating Scales for Depression and Anxiety (HAM-D; HAM-A) at different follow-up times. HAM-A scores >17-24 is taken to indicate mild anxiety; whereas HAM-D total scores between 8 and 17 is taken to indicate a mild depressive symptoms. Both HAM-A and HAM-D include a variety of somatic symptoms, which can correlate with the occurrence of tics.



Legend: P1: hollow circles; P2: full circles; P3: full triangles; P4: hollow triangles

References

1. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273-289.