Augmentation Effect of Repetitive Transcranial Magnetic Stimulation Over the Orbitofrontal Cortex in Drug-Resistant Obsessive-Compulsive Disorder Patients: A Controlled Investigation

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Background: The orbitofrontal cortex (OFC) plays a major role in the pathophysiology of obsessive-compulsive disorder (OCD); functional neuroimaging studies indicate that OCD symptoms are associated with increased activity in the OFC, caudate nucleus, thalamus, and anterior cingulate gyrus. The goal of our single-blind study was to assess whether repetitive transcranial magnetic stimulation (rTMS) over the left OFC would influence OCD symptoms in drug-resistant patients.

Method: Twenty-three consecutively admitted right-handed inpatients with *DSM-IV-TR*–diagnosed drug-resistant OCD were given rTMS (80% motor threshold, 1 Hz seconds per minute for 10 minutes every day for 15 days) to the left OFC parallel (active: n = 16) or perpendicular (sham: n = 7) to the scalp. The patients' OCD symptoms, mood, and anxiety were rated at baseline, at the end of treatment, and once every 2 weeks for 3 months after treatment. Data were gathered from June 2006 to November 2007.

Results: Considering changes in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores with 2-way analysis of variance for repeated measures for a total of 8 observations (before rTMS, after treatment, and every 2 weeks for 12 weeks' follow-up), we found significant reduction of YBOCS scores comparing active versus sham treatment for 10 weeks after the end of rTMS ($P < .02$), with loss of significance after 12 weeks ($P < .06$). We also found a reduction of anxiety and depression symptoms but not a significant difference in the 2 groups.

Conclusions: Low-frequency rTMS of the left OFC produced significant but time-limited improvement in OCD patients compared to sham treatment.

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Obsessive-compulsive disorder (OCD) is a highly debilitating condition with a lifetime prevalence of 2%–3%.[1,2] Although the introduction of selective serotonin reuptake inhibitors (SSRIs) has improved the treatment and prognosis of OCD, a notable percentage of patients (from 40% to 60%) do not respond to treatment, and the response has a latency of 4–8 weeks.[3] This low rate of overall response to first-line strategies has led to the development of several augmenting pharmacologic and nonpharmacologic strategies, including cognitive-behavioral therapy, clomipramine, low doses of atypical antipsychotics,[4,5] deep brain stimulation (DBS), functional neurosurgery, and transcranial magnetic stimulation (TMS).

Transcranial magnetic stimulation is a noninvasive technique that delivers magnetic pulses to the cortex by means of a hand-held stimulating coil applied directly to the head. One single pulse produces an intense magnetic field that causes depolarization of lower neurons. The limit is 2.5–3 cm under the scalp, but TMS can influence subcortical neurons with a transsynaptic mechanism, as seen in positron emission tomographic studies.[6]

Six trials of TMS on OCD patients have been published to date, and their findings are promising[7–12]; however, the small sample size, a considerable variability in the stimulation site, and parameters used have prevented the drawing of definitive conclusions about its clinical efficacy. Available data show positive effects after stimulation of the right and left prefrontal cortex[11] and of the supplementary motor area,[7] with response rates in drug-resistant OCD ranging from 25% to 60% with a Yale-Brown Obsessive Compulsive Scale (YBOCS) score reduction > 40%. The results over the prefrontal cortex were not confirmed after controlled studies (sham condition).[10,12,13]

The orbitofrontal cortex (OFC) plays a major role in the pathophysiology of OCD. Functional neuroimaging studies indicate that OCD symptoms are associated with increased activity in the OFC, caudate nucleus, thalamus, and anterior cingulate gyrus. Baxter et al[14] proposed that OCD symptoms are mediated by hyperactivity in orbitofrontal-subcortical circuits due to an imbalance of

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- A large percentage of patients with obsessive-compulsive disorder are drug resistant.
- Additional nonpharmacologic approaches are needed.
- Repetitive transcranial magnetic stimulation was found to be effective in reducing obsessive-compulsive symptoms in drug-resistant patients.

tone between direct and indirect striatopallidal pathways. Increased functional activity in the OFC was found bilaterally[14–18] or restricted to the left side.[19,20] Functional magnetic resonance imaging studies evidenced dysfunctions in the same orbitofrontal-subcortical circuits[21,22]; thus, a stimulation over the OFC could be OCD specific.

No study has attempted to improve response to drug treatment by combining repetitive TMS (rTMS) in the OFC. In the present exploratory study, we evaluated the effect of combined rTMS over the left OFC and drug treatment in drug-resistant OCD patients.

METHOD

Subjects

Twenty-three consecutively admitted right-handed inpatients with *DSM-IV-TR*–diagnosed OCD were studied. Exclusion criteria included other Axis I diagnoses, major medical or neurologic conditions, age younger than 18 years or older than 75 years, and a YBOCS score < 16. In accordance with the safety criteria for rTMS,[23] patients with a history of seizure or bearing pacemakers, mobile metal implants, implanted medical pumps, or metal clips placed inside the skull were also excluded.

All patients gave written informed consent after complete description of the study. The study was approved by the Ethical Committee of San Raffaele Hospital, Milan, Italy, and was conducted in accordance with the declaration of Helsinki and the Good Clinical Practice Guidelines. The study was registered by the Ethical Committee of the Azienda Sanitaria Locale, Milan, Italy (study code: 708S0). Data were gathered from June 2006 to November 2007.

Treatment

Patients were randomly administered real (n = 16) or sham (n = 7) rTMS, given every day for 5 days a week for 3 weeks. Randomization was performed by a computer-generated schedule with a 2:1 ratio (active:sham).[24] We chose this large proportion because of the ethical problem of administering drug-resistant patients the same unsuccessful therapy for an additional 3 months.

The patients included in the study had failed adequate trials for at least 2 antiobsessional drugs and cognitive-behavioral therapy; an adequate trial of pharmacotherapy was at least 12 weeks of treatment with the maximum dosage of drug. Drug-resistant OCD literature indicates an absence of a significant reduction in YBOCS scores (> 35%) after at least 2 trials with SSRIs and 1 trial with clomipramine. At the beginning of the study, pharmacologic treatments included serotonin reuptake inhibitors (23/23), atypical neuroleptics (2/23), antiepileptics (6/23), and benzodiazepines (18/23); these drugs were continued without modifications throughout the study.

Stimulation Procedure

The rTMS was performed with a Magstim Rapid Stimulator for biphasic pulses (Magstim Company Ltd, Whiteland, London) with a focal 70-mm 8-shaped coil. To determine the resting motor threshold, we used the thumb movement visualization method, stimulating the left primary motor cortex.[25]

The brain target was the left OFC, which corresponds to Fp1 (International 10–20 EEG System).[26] For sham treatment, the coil was placed over the same area but perpendicular to the scalp. The patients received 10 minutes of 1 Hz left-sided subthreshold rTMS (intensity 80% of the resting motor threshold) over the left frontopolar cortex targeting the OFC for 15 sessions (1 session per day, 5 sessions per week for 3 weeks).

Data Collection and Statistical Analysis

The YBOCS,[27,28] Hamilton Depression Rating Scale (HDRS),[29] and Hamilton Anxiety Rating Scale (HARS)[30] were administered at baseline, after 15 rTMS sessions, and every 2 weeks for 3 months after the end of rTMS. Effects of treatment over time were assessed with 2-way analysis of variance (ANOVA) repeated measures, with time and treatment (active vs sham) as independent factors and rating scale scores as dependent variables. Post hoc analysis was performed with the Scheffé test.

RESULTS

All patients completed the study and the procedure was well tolerated. Patients belonging to distinct treatment options (sham vs active rTMS) did not differ in terms of clinical and demographic characteristics (age, age at onset of OCD, insight into disease, and baseline YBOCS, HDRS, and HARS scores).

We considered first the effect of the treatment in terms of reduction of total YBOCS scores after 3 weeks of ac-

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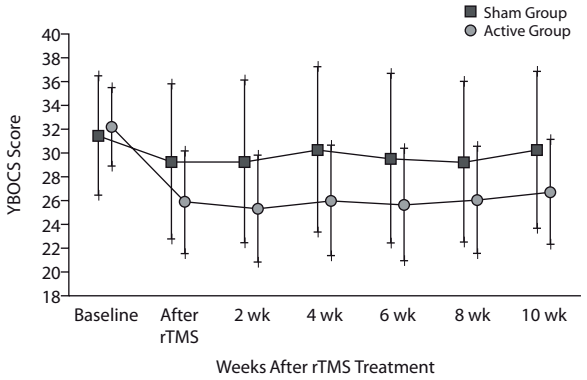
Figure 1. Comparison of YBOCS Scores for Active vs Sham rTMS Groups[a,b]



[a]Significant difference between baseline, poststimulation, and follow-up ratings according to repeated-measures analysis of variance ($P < .02$).
[b]$F_{6,126} = 2.4839$; $P = .02640$.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

tive rTMS treatment versus sham: ANOVA of YBOCS total score showed a nonsignificant effect of group ($F_{1,21} = 0.17$; $P < .68$), a highly significant effect of time ($F_{1,21} = 18.73$; $P < .00$), and a significant time × group interaction ($F_{1,21} = 4.55$; $P < .04$), meaning that the pattern of changes of obsessive-compulsive symptoms did not follow parallel slopes of time course.

We then performed an ANOVA analysis with the YBOCS total scores over time (8 observations: baseline, after rTMS treatment, and every 2 weeks for 3 months after the end of rTMS treatment), finding a significant difference between active and sham stimulation until week 10 after the end of rTMS ($F_{6,126} = 2.48$; $P < .02$; Figure 1). After this time, significance was lost ($F_{7,147} = 1.93$; $P < .06$).

Post hoc analysis with the Scheffé test revealed no significant difference among sham group YBOCS scores. In post hoc analysis, sham versus active group single observations were not significantly different, while in the active group, the comparison between the after-treatment observations and the basal YBOCS scores were significant. The absence of significance was probably due to the small number of patients (it was an exploratory study) and the large number of observations (8 in total).

Using 2-way ANOVA analysis for repeated measures, we observed that depression symptoms measured by the HDRS did not significantly decrease after active treatment (after rTMS: $F_{1,21} = 2.33$; $P < .14$; after 12 weeks' follow-up: $F_{7,147} = 0.64$; $P < .71$). The same analysis was performed for anxiety scores (HARS); we found no significant decrease comparing active and sham stimulation (after rTMS: $F_{1,21} = 0.07$; $P < .79$; after 12 weeks' follow-up: $F_{7,147} = 0.50$; $P < .82$). We could conclude that the rTMS effect in OCD drug-resistant patients is specific for obsessive-compulsive symptoms. We decided not to covariate YBOCS decreasing scores for depression or anxiety because depressive and anxiety symptoms are part of the OCD clinical presentation.

An analysis of the percentage of reduction in YBOCS scores after rTMS treatment found that 15 of 16 patients who received active rTMS had a reduction; 8 of 16 patients had a reduction ≥ 25%; and 4 of 16 patients had a reduction ≥ 35%. One of 7 patients who received sham stimulation had a YBOCS score reduction of 26% (Table 1).

DISCUSSION

To our knowledge, this is the first study of OFC stimulation in the treatment of OCD. Ours is an exploratory study: the number of patients is small, especially considering that it is divided into 2 groups; the sample is well characterized and selected (OCD patients with no Axis I codiagnosis, especially for depression, drug resistant with stable therapy, and no drug changing for 3 months); and the site and the paradigm of stimulation is innovative.

We report a clinically significant improvement in OCD symptoms in a sample of drug-resistant OCD patients with benefits lasting up to 10 weeks after the end of rTMS treatment. This time-limited efficacy of rTMS could indicate the necessity of administering a second session of rTMS after 2 months in those patients who received benefit from a first session of rTMS; this could be the subject of future studies.

Placebo effect was found only in 1 patient of 7 who received sham stimulation. There was also a benefit in terms of depressive and anxiety symptoms, but it did not reach significance. We can conclude that the effect of rTMS over the left OFC is specific for OCD symptoms and only secondary in influencing depression and anxiety symptoms in OCD patients.

The results we found are similar to those reported in DBS studies.[31] Deep brain stimulation of the anterior limb of the internal capsule has been shown to be beneficial in the short term for OCD patients who exhaust conventional therapies. Nuttin et al,[32] who published the first DBS for OCD series, found promising results using a capsule target immediately rostral to the anterior commissure. In a collaborative study,[33] 10 adult OCD patients meeting stringent criteria for severity and treatment resistance received DBS. Four of 8 patients had a ≥ 35% decrease in YBOCS score severity at 36 months; in 2 patients, scores declined between 25% and 35%. This open study found promising long-term effects of DBS in highly treatment-resistant OCD.

A report[34] using DBS for refractory OCD showed a benefit in 2 patients. Follow-up positron emission tomographic studies revealed decreased OFC activation in these 2 responding patients, which suggested to the

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Table 1. Clinical Characteristics and Drug Treatment of Patients With Obsessive-Compulsive Disorder Who Received Active or Sham Repetitive Transcranial Magnetic Stimulation (rTMS)

Group and Patients	Pharmacologic Treatment	Baseline YBOCS Score	YBOCS Score After rTMS	YBOCS Score After rTMS (12-wk follow-up)					
				2 wk	4 wk	6 wk	8 wk	10 wk	12 wk
Active rTMS									
1	Fluvoxamine	36	34	34	34	33	33	33	33
2	Venlafaxine, risperidone	26	18	19	22	19	19	19	19
3	Fluvoxamine	25	15	15	15	15	15	15	15
4	Fluvoxamine	32	30	30	30	30	30	30	30
5	Fluoxetine	37	24	27	29	27	25	25	25
6	Fluvoxamine, paroxetine	28	17	17	17	17	17	16	16
7	Fluvoxamine, clomipramine, risperidone	31	21	21	21	21	21	21	21
8	Clomipramine	34	34	34	34	34	34	34	34
9	Fluvoxamine	31	28	28	28	28	28	28	28
10	Clomipramine	39	36	35	40	40	40	39	39
11	Sertraline	16	10	6	6	6	6	6	6
12	Clomipramine, risperidone	34	25	25	25	25	25	30	30
13	Fluvoxamine	38	33	33	33	34	34	34	34
14	Clomipramine	36	24	12	12	12	20	28	36
15	Fluvoxamine	38	36	36	36	36	36	36	36
16	Fluvoxamine	34	33	33	34	34	34	34	34
Sham rTMS									
17	Venlafaxine	26	26	26	26	26	26	26	26
18	Fluvoxamine, clomipramine	22	22	22	22	22	22	22	22
19	Clomipramine	28	28	28	28	28	28	28	28
20	Clomipramine, risperidone	37	37	37	37	37	37	37	37
21	Clomipramine	29	24	24	29	24	24	29	24
22	Fluvoxamine	40	40	40	40	40	40	40	40
23	Fluoxetine	38	28	28	30	30	28	30	30

Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

authors that a successfully disrupted cortical-subcortical circuit mediated the clinical effect.[34] These results are comparable to those achieved with ablative, anterior capsulotomy,[35] which has not been amenable to study in blinded protocols.

To date, there have been only 6 studies of TMS in OCD.[7,9–13] These trials were promising but inconclusive for several reasons. The studies differed in design in important ways: site stimulation, parameters, and treatment duration. In addition, the samples were small, few of them[9,10,12,13] were double-blind, and they included patients with comorbidity for major depression[7,9,11] and patients who were drug resistant and drug naive.[9,10] A uniform target area for stimulation, such as the left prefrontal cortex for major depression, has not been established; there are reports of symptom reduction following stimulation in both the right[9] and left prefrontal cortex[11] and the supplementary motor area.[7] For all of these reasons, it is difficult to compare our results to the previous studies using rTMS to treat OCD patients.

We decided to stimulate with a proven paradigm over the left OFC in consideration of OCD pathophysiology. Functional neuroimaging studies indicate that OCD symptoms are associated with increased activity in the OFC, caudate nucleus, thalamus, and anterior cingulate gyrus. Increased functional activity in the OFC was found bilaterally[14–18] or restricted to the left side.[19,20] This is the reason why a stimulation over the OFC is OCD specific. Schutter and colleagues[36] obtained an improvement in memory for happy faces after 3 daily sessions of 1 Hz rTMS over the left OFC in comparison with sham condition in a sample of 12 healthy volunteers. The authors proved the tolerability of this technique and its efficacy.

Limitations of this study are the small sample size and the absence of a neuroimaging or neuorophysiologic technique supporting clinical assessments in order to show neural patterns associated with clinical improvement and to better understand the specific neuronal action of rTMS over the OFC. Our clinical results together with those of Schutter et al[36] seem to prove the efficacy of this technique, but it is necessary to give a direct demonstration of the interaction between rTMS and the OFC. Another limitation is the imprecision of the stimulation that can be avoided using neuronavigators.

Further investigation involving larger groups of patients should be performed to clarify whether rTMS could be a useful therapy in OCD patients and to determine the optimal stimulation characteristics for its delivery.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, risperidone and venlafaxine are not approved by

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the US Food and Drug Administration for the treatment of obsessive-compulsive disorder.

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REFERENCES

1. Karno M, Golding JM, Sorenson SB, et al. The epidemiology of obsessive compulsive disorder in five US communities. *Arch Gen Psychiatry.* 1988;45(12):1094–1099.
2. Weissman MM, Bland RC, Canino GJ, et al. The cross national epidemiology of obsessive compulsive disorder. *J Clin Psychiatry.* 1994;55(suppl):5–10.
3. Pallanti S, Hollander E, Bienstock C, et al. Treatment non-response in OCD: methodological issues and operational definitions. *Int J Neuropsychopharmacol.* 2002;5(2):181–191.
4. Albert U, Bergesio C, Pessina E, et al. Management of treatment resistant obsessive-compulsive disorder: algorithms for pharmacotherapy. *Panminerva Med.* 2002;44(2):83–91.
5. Ipser JC, Carey P, Dhansay Y, et al. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. *Cochrane Database Syst Rev*. 2006;(4):CD005473.
6. Husain FT, Nandipati G, Braun AR. Stimulating transcranial magnetic stimulation during PET with a large-scale neural network model of the prefrontal cortex and the visual system. *Neuroimage.* 2002;15(1):58–73.
7. Mantovani A, Lisanby SH, Pieraccini F, et al. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). *Int J Neuropsychopharmacol.* 2006;9(1):95–100.
8. Martin JL, Barbanoj MJ, Pérez V, et al. Transcranial magnetic stimulation for treatment of obsessive-compulsive disorder. *Cochrane Database Syst Rev*. 2003;(3):CD003387.
9. Greenberg BD, George MS, Artin JD, et al. Effect of prefrontal transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry.* 1997;154(6):867–869.
10. Alonso P, Pujol J, Cardoner N, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double blind, placebo-controlled study. *Am J Psychiatry.* 2001; 158(7):1143–1145.
11. Sachdev PS, Mc Bride R, Loo CK, et al. Right versus left prefrontal transcranial stimulation for obsessive-compulsive disorder: a preliminary investigation. *J Clin Psychiatry.* 2001;62(12):981–984.
12. Prasko J, Pasková B, Záleský R, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive-compulsive disorder: a randomized, double-lind, sham-controlled study. *Neuroendocrinol Lett.* 2006;27(3):327–332.
13. Sachdev PS, Loo CK, Mitchell PB, et al. Repetitive transcranial magnetic stimulation for the treatment of obsessive-ompulsive disorder: a double-blind controlled investigation. *Psychol Med.* 2007;37(11):1645–1649.
14. Baxter LR, Schwartz JM, Mazziotta JC, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry.* 1988;145(12):1560–1563.
15. Rubin RT, Villanueva-Meyer J, Ananth J, et al. Regional xenon 133 cerebral blood flow and cerebral technetium 99m HMPAO uptake in unmedicated patients with obsessive-compulsive disorder and matched normal control subjects: determination by high-resolution single-photon emission computed tomography. *Arch Gen Psychiatry.* 1992;49(9):695–702.
16. Rubin RT, Ananth J, Villanueva-Meyer J, et al. Regional 133xenon cerebral blood flow and cerebral ^{99m}Tc-HMPAO uptake in patients with obsessive-compulsive disorder before and during treatment. *Biol Psychiatry.* 1995;38(7):429–437.
17. Alptekin K, Degermenci B, Kivircik B, et al. Tc-99m HMPAO brain perfusion SPECT in drug-free obsessive-compulsive patients without depression. *Psychiatry Res.* 2001;107(1):51–56.
18. Molina V, Montz R, Martin-Loeches M, et al. Drug therapy and cerebral perfusion in obsessive-compulsive disorder. *J Nucl Med.* 1995;36(12):2234–2238.
19. Baxter LR, Phelos ME, Mazziotta JC, et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder: a comparison with rates in unipolar depression and in normal controls. *Arch Gen Psychiatry.* 1987;44(3):211–218.
20. Swedo SE, Schapiro MB, Grady CL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1989;46(6):518–523.
21. van den Heuvel OA, Veltman DJ, Groenewegen HJ, et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 2005;62(3):301–309.
22. Remijnse PL, Nielen MM, van Balkom AJ, et al. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 2006;63(11): 1225–1236.
23. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108(1):1–16.
24. Saghaei M. Random allocation software for parallel group randomized trials. *BMC Med Res Methodol.* 2004;4:26.
25. Pridmore S, Fernandes Filho JA, Nahas Z, et al. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J ECT.* 1998;14(1):25–27.
26. Okamoto M, Dan H, Sokamto K, et al. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. *Neuroimage.* 2004;21(1):99–111.
27. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. *Arch Gen Psychiatry.* 1989;46(11):1006–1011.
28. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, II: validity. *Arch Gen Psychiatry.* 1989;46(11):1012–1016.
29. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56–62.
30. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959;32(1):50–55.
31. Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery.* 2007;61(1):1–11.
32. 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(9189):1526.

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