

## Discontinuation of Superolateral Medial Forebrain Bundle Deep Brain Stimulation for Treatment-Resistant Depression Leads to Critical Relapse

### To the Editor:

Deep brain stimulation (DBS) is investigated as a possible therapy for treatment-resistant depression (TRD) (1–7). DBS of the superolateral medial forebrain bundle (sIMFB) is associated with rapid and sustained antidepressant effects (8). Little is known about the effect of DBS cessation after long-term treatment in psychiatric disorders. Previous clinical studies showed aggravation of depression after DBS discontinuation in TRD. Prediscontinuation level could be recaptured following different timelines after reinitiation of stimulation (2,9,10).

These results hint that permanent stimulation is needed to maintain response. The acute effect of discontinuing sIMFB DBS is unknown and is regarded as an important safety aspect. Typical events such as sudden battery depletion, misuse of the recharging device, or device dysfunction could cause a relapse.

In this article, we report on 5 cases treated with sIMFB DBS (patients included in the study trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov): [NCT01778790](https://clinicaltrials.gov/ct2/show/study/NCT01778790) and [NCT01095263](https://clinicaltrials.gov/ct2/show/study/NCT01095263)) experiencing a discontinuation either unintentionally (cases 1–4) or planned (case 5).

Case 1 (male, 49 years of age, 31-year history of depression, sIMFB DBS since June 2014) responded immediately after DBS onset and response remained stable in the following 3 years. In October 2017, he started the pilgrimage on the Camino de Santiago (11). Two weeks before the end of his trip, the battery was depleted. He reported an increase of rumination and difficulties in decision making. Two days after reonset of stimulation, depressive symptoms disappeared.

Case 2 (male, 49 years of age, 27-year history of depression, sIMFB DBS since November 2014) showed an acute antidepressant effect, but response did not remain stable. In August 2017, stimulation was discontinued for 2 days (battery depletion), leading to an acute symptom aggravation and slow improvement after reonset. In October 2017, stimulation was discontinued in error and symptoms worsened immediately within 2 hours. Depressive symptoms disappeared 1 day after the restart of stimulation.

Case 3 (female, 38 years of age, 11-year history of depression, sIMFB DBS since May 2011) showed immediate and sustained antidepressant efficacy. In January 2017, depressive symptoms worsened. Using the patient programmer, she noticed that the battery was fully depleted. After recharging and parameter adaptation in our clinic, depressive symptoms remitted again fully.

Case 4 (male, 51 years of age, 17-year history of depression, sIMFB DBS since December 2013) showed a slow effect and a variable antidepressant response over the whole period. In April 2017, he switched the stimulation off in error with the patient programmer. Two weeks later, depressive symptoms worsened. He noticed the off-state stimulation, turned it on

again by himself, and reported an amelioration of symptoms 1 to 2 days later.

For Case 5 (male, 61 years of age, 21-year history of depression, sIMFB DBS since January 2015), before DBS onset, the depressive episode had been persisting for 2 years and the patient was classified as treatment resistant and not responding to psychotherapy, antidepressants, and electroconvulsive therapy. Five weeks after DBS onset, symptoms were remitted, and antidepressant efficacy remained stable over the last 2.5 years (Figure 1). After 2 years of successful stimulation, he was convinced that he had no need for DBS anymore. We reluctantly agreed to discontinue stimulation against medical advice in a controlled setting. During the time of discontinuation, the patient stayed at a friend's house and was in close contact with our research group via mobile phone. The next scheduled visit was planned after 4 days. Severity of depressive symptoms was assessed with Montgomery-Åsberg Depression Rating Scale (12), Hamilton Depression Rating Scale (13), Depression Acute Effects Scale (14), and Beck Depression Inventory (15). Additionally, Global Assessment of Functioning was assessed (16).

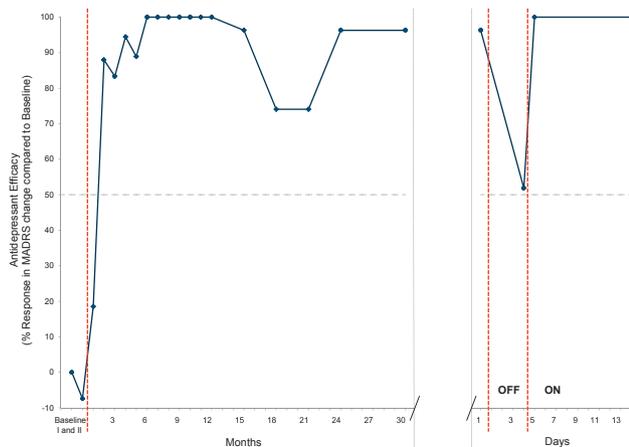
The day stimulation was discontinued, the patient was remitted from depression. Acute effects did not occur within the next few hours. Twenty-four hours later, he reported a relapse with strong loss of drive, ideas, and feelings. He felt like being restored to the time when he had severe depression. A change in the Depression Acute Effects Scale was rated from 0 to 66. During the next 3 days, symptoms were less severe compared with the morning of the second day, sleep and appetite remained well, and activities were possible. After 80 hours of discontinuation, the patient wished to turn stimulation on again. At this time point, depressive symptoms were classified as mild (worst outcome since February 2015) (Figure 1). The day after reonset, prediscontinuation level was recaptured and remission of symptoms remained stable until the next follow-up.

We have described experiences of 5 patients with discontinuation of sIMFB DBS either unintentionally or planned. The acute and sustained antidepressant effects of this target could be shown already (8,14). This is the first time data on the need for chronic stimulation and the timeline to relapse after sIMFB DBS discontinuation have been presented.

A significant reoccurrence of depression was observed in all 5 patients within days. This is in line with the findings of other clinical studies suggesting that permanent stimulation is needed in psychiatric disorders (2,9,10). Thus, unintended cessation of sIMFB DBS is an important safety risk in the treatment of TRD—especially regarding the different timelines (1 day to several weeks) to recapture the prediscontinuation level (9,10).

Changes in brain functioning after DBS seem to be transient, indicating a functional and temporal phenomenon (1–3,17). Cerebral metabolism decreases occurred 48 hours after DBS discontinuation in 7 TRD patients (18). Brain metabolism changes were not associated with an apparent aggravation of symptoms suggesting that they may proceed clinical changes.

DBS for psychiatric disorders is a new treatment method, and data on lasting antidepressant effects after long-term



**Figure 1.** Case 5. Time course before, during, and after discontinuation of stimulation. Antidepressant efficacy measured as Montgomery-Åsberg Depression Rating Scale (MADRS) percent response change compared with baseline.

stimulation are needed. Our observations make placebo effects as an explanation for the antidepressant effect of sIMFB DBS in TRD improbable.

We suggest that continuous sIMFB DBS in TRD is necessary. The discontinuation of sIMFB stimulation can result in rapid worsening of depression within days. Future sIMFB DBS studies should include a controlled blinded discontinuation in the trial design [see other DBS studies with a discontinuation (9,10,19)]. Close monitoring of patients during this study phase is necessary to prevent relapse into severe depression.

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### References

- Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH (2008): Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 64:461–467.
- Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. (2005): Deep brain stimulation for treatment-resistant depression. *Neuron* 45:651–660.
- Bewernick BH, Hurlmann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. (2010): Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry* 67:110–116.
- Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, et al. (2011): Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. *Am J Psychiatry* 168:502–510.
- Schlaepfer TE, Bewernick BH, Kayser S, Mädlar B, Coenen VA (2013): Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry* 73:1204–1212.
- Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, de Diego-Adeliño J, Gironell A, et al. (2012): Deep brain stimulation of the subcallosal cingulate gyrus: Further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol* 15:121–133.
- Bewernick BH, Kayser S, Sturm V, Schlaepfer TE (2012): Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: Evidence for sustained efficacy. *Neuropsychopharmacology* 37:1975–1985.
- Bewernick BH, Kayser S, Gippert SM, Switala C, Coenen VA, Schlaepfer TE (2017): Deep brain stimulation to the medial forebrain bundle for depression—long-term outcomes and a novel data analysis strategy. *Brain Stimul* 10:664–671.
- Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barocas A, et al. (2012): Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69:150–158.
- Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhé HG, Notten P, van Laarhoven J, et al. (2016): Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry* 73:456–464.
- Simon A (2018): Camino de Santiago. Available at: <http://santiago-compostela.net/>. Accessed September 3, 2018.
- Montgomery SA, Åsberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
- Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
- Bewernick BH, Kayser S, Gippert SM, Coenen VA, Schlaepfer TE (2017): Acute antidepressant effects of deep brain stimulation—Review and data from sIMFB-stimulation. *Pers Med Psychiatr* 3:1–7.
- Hautzinger M, Keller F, Kühner C (2006): Beck Depressions-Inventar (BDI-II). Frankfurt, Germany: Harcourt Test Services.
- Jones SH, Thornicroft G, Coffey M, Dunn G (1995): A brief mental health outcome scale—reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* 166:654–659.
- Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessaer D, Axmacher N, et al. (2008): Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33:368–377.
- Martin-Blanco A, Serra-Blasco M, Pérez-Egea R, de Diego-Adeliño J, Carceller-Sindreu M, Puigdemont D, et al. (2015): Immediate cerebral metabolic changes induced by discontinuation of deep brain stimulation of subcallosal cingulate gyrus in treatment-resistant depression. *J Affect Disord* 173:159–162.
- Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, et al. (2010): Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 67:1061–1068.