Brain Stimulation 15 (2022) 582–585

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Efficacy of superolateral medial forebrain bundle deep brain stimulation in obsessive-compulsive disorder

Keywords:
Obsessive-compulsive disorder
OCD
Deep brain stimulation
DBS
Superolateral medial forebrain bundle

Letter to the editor

The superolateral medial forebrain bundle (slMFB) is a white-matter structure connecting established targets for deep brain stimulation (DBS) in obsessive-compulsive disorder (OCD) [1]. Recently, it has been proposed as a stimulation target itself [2] (see supplement S1 for presumed mode of action). The authors now present clinical outcome data of this treatment approach in form of an open label case series.

Nine consecutive patients (4 female) suffering from severe treatment-resistant OCD (mean duration of disease = 23.4 years, range 11–39 years) with a mean age of 39.2 years (range 25–52 years) have been treated with DBS of the slMFB by our research group (see supplement S2 for sample selection). All patients received various disease-specific prior treatments, reported substantial impairment in their daily life due to OCD symptoms and were classified as treatment-resistant by our multi-professional and specialized team (psychiatrists and psychologists) based on comprehensive visits and provided medical documents. They underwent DBS surgery between December 2017 and January 2020 and were followed up. The neurosurgical procedure including imaging, fiber tracking, surgery and postoperative care has been described in detail in patients with treatment-resistant depression [3]. The target region is located in the corridor between red nucleus, substantia nigra/subthalamic nucleus and the mammillothalamic tract [2–4]. In contrast to Ref. [3] all patients received segmented DBS electrodes (Vercise Cartesia, Boston Scientific, Valencia, USA). Eight patients received a rechargeable pulse generator (Vercise Gevia, Boston Scientific); one patient received a non-rechargeable pulse generator (Vercise PC, Boston Scientific). Pulse generators were placed subclavicularly.

Comprehensive symptom development (clinical outcome) was assessed regularly up to 36 months following stimulation onset, using clinician-based psychometric measurements (see supplement S3 and S4). We here focus on the Yale-Brown obsessive compulsive scale (Y-BOCS) [5] as measurement of symptom severity.

At baseline, mean Y-BOCS sum score of the sample was 31.0 ($SD = 5.7$). After three months of active stimulation three patients reached response criterion (>35% reduction of Y-BOCS sum score [6]) and three other patients reached >20% reduction of Y-BOCS sum score at this time point.

Mean duration until response criterion was reached for the first time was three months (ranging from stimulation onset to eight months). After one year of stimulation (range 10–13 months) seven patients were classified as responders and sustained response until last follow-up (FU, ranging from 11 to 36 months of stimulation, depending on date of surgery). Two patients responded occasionally only (Fig. 1F). As three-month data is available for six out of nine patients, this time point has been selected for short-term evaluation: By this time, mean Y-BOCS sum score had decreased by 43.1% ($SD = 23.6$, $n = 6$) compared to baseline. This score had decreased by 55.9% ($SD = 20.0$) after one year of stimulation and by 53.5% ($SD = 23.7$) at last FU. In absolute numbers this refers to a mean reduction of 12.2 points ($SD = 6.7$, $n = 6$) at three months, 16.9 ($SD = 5.4$) after one year and 16.2 ($SD = 6.7$) at last FU. For absolute scores see supplement Table S1, where improvement of depressive symptoms and global functioning is depicted, as well.

Current applied therapeutically ranged between 1.4 and 5.5mA. For detailed information on stimulation settings see supplement S7. Stimulation related side effects resembled the ones described in previous publications on slMFB DBS in depression [4] and could be resolved immediately by adjustments of the stimulation parameters. All further adverse events are listed in the supplement material (S8).

Comparing our data to existing literature, after three months of stimulation our results resemble the Y-BOCS reduction rates 45.1% (*95% CI* = [29.4%; 60.8%]) reported in a meta-analysis on DBS in OCD [8] but exceed this rate notably in the long run. Regarding size equivalent studies, some agreement with the clinical effects we report here, was achieved by DBS of the anteromedial subthalamic nucleus (amSTN) in a comparably affected sample with OCD ($n = 8$) [7]. Three months of amSTN stimulation resulted in 13 points reduction of Y-BOCS score whereas we achieved 12.2 points reduction ($n = 6$) in the same time frame. The long-term outcome with 51.2% ($SD = 21.2$) reduction rate after 46 months ($n = 12$) and 9/11 responders [9] is similar to our last follow-up results, as well. The amSTN is an anatomically distinct target from ours. However, especially with respect to other publications [1], principal overlap of the stimulated area is conceivable. Surprisingly, diplopia is not reported as side effect in Ref. [7], although we consider it a characteristic side effect in slMFB stimulation [4]. The comparison with existing literature demonstrates that DBS of the slMFB might

https://doi.org/10.1016/j.brs.2022.03.004

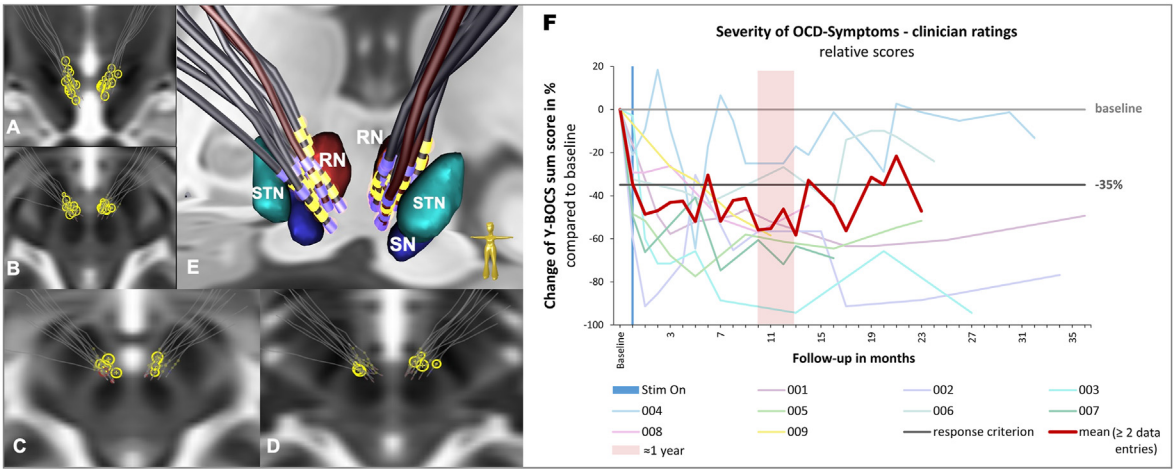

Fig. 1. Electrode positions of all patients in MNI normative space and clinical outcome.
Legend: RN red nucleus; SN, substantia nigra; STN, subthalamic nucleus. For information on methods see supplement S6.
All electrodes are located in the ventral tegmentum anterior to the red nucleus (red) and medial of the subthalamic nucleus indicating involvement of a separate system (hence slMFB) as opposed to Ref. [7]. **A**, coronal template with contacts (yellow spheres); **B-D**, axial templates. **E**, 3D reconstruction with effectively stimulated contacts three months after stimulation onset in yellow. Non-responder electrodes are displayed in brown/red. Electrodes are curled due to individual registration to normative space. **F,** Relative change regarding the Y-BOCS sum scores compared to baseline as indicator of severity regarding OCD over time for each patient. Mean has been calculated only if at least two data entries were available for the time of measurement. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reduce OCD symptoms just as much or even more than DBS of other targets and supports further research on efficacy and safety of this target.

Beyond OCD symptoms, eventually depressive symptoms decreased quickly after stimulation onset in seven patients (supplement Table S1). This antidepressant effect is not surprising but expectable as previous studies on DBS of the slMFB in treatment-resistant depression have demonstrated rapid response onsets [4]. This result supports the idea of a shared disease-network and is in line with the underlying hypothesis of a normalization of the reward network induced by the modulation of the slMFB-activity [1,2,10]. Further imaging studies proving this hypothesis on a functional level are pending.

Generally, results of this report have to be interpreted cautiously as this is an open-label case series. Although visits at our unit are standardized, we did not follow a formalized research protocol. This results in continuous open stimulation without controlled sham-phases and might result in an overestimation of improvement as well as the unstable concomitant medication and psychotherapy. Therefore, future studies should be designed as RCTs to generate deeper insight into the efficacy and safety-profile of the treatment. Nevertheless, considering the enormous burden of illness of OCD in its severest form as reported here, the large effect, the long-term efficacy data and the safety-profile reported, we believe that this report clearly makes the point of adding the slMFB to brain stimulation target studies for this disease.

Previous presentation

This manuscript has not been previously published other than in form of abstracts and is not currently under consideration by any other journal. Part of the data have been presented in abstracts/poster sessions at the ACNP annual meetings 2018 (Hollywood, FL) and 2019 (Orlando, FL) and at the DGPPN Congress 2018 (Berlin, Germany). We have since then acquired additional data that make our results more reliable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of competing interest

The authors disclose the following:

Dora M Meyer's and Susanne Spanier's positions are funded by a research grant provided to Thomas E Schlaepfer by Boston Scientific (USA).

Hannah M Kilian reports no financial relationships with commercial interests.

Marco Reisert reports no financial relationships with commercial interests.

Horst Urbach

received honoraria from Biogen, Eisai, mbits.
serves as an advisory member for Biogen.

Bastian E A Sajonz receives a research grant from CereGate unrelated to this project.

Peter C Reinacher

receives research support from Else Kröner-Fresenius Foundation (Germany) and Fraunhofer Foundation (Germany).
Received personal honoraria for lectures or advice from Boston Scientific (USA) and Brainlab (Germany).
Is consultant for Boston Scientific (USA), Inomed (Germany) and Brainlab (Germany).

Claus Normann

received speakers honoraria and advisory panel payments from Janssen; and DMC panel payments from Novartis.
is an investigator in clinical trials for Janssen, Intracellular Therapeutics and Ketabon.

Katharina Domschke is a member of the Janssen Pharmaceuticals, Inc. Steering Committee Neurosciences.

Volker A Coenen

serves on the scientific advisory boards of CereGate (Munich, Germany),CorTec (Freiburg, Germany) and InBrain (Barcelona, Spain).
has received honoraria and travel support for talks from Boston Scientific.
has received grants for IITs from Medtronic and Boston Scientific.
receives an ongoing collaborative grant from BrainLab (Munich, Germany).

Thomas E Schlaepfer.
Received honoraria for an expert opinion from LivaNova Inc.

was reimbursed for attendance fees for congresses or training sessions with a topic related to this article and travel expenses by Medtronic Inc.
received honoraria for the preparation of lectures or scientific conferences or training events related to this article's topic from Medtronic Inc., LivaNova Inc., Medforum Sp. zo.o., Neuro-Consil GmbH, Sage Therapeutics Inc.
received honoraria for a clinical contract study related to the topic of this article by LivaNova Inc.
received honoraria for an investigator initiated trial (IIT) related to the topic of this article from Boston Scientific.

Acknowledgements

We thank our patients for their trust and their consent to this publication. We thank Lars Greβ for data preparation and Pauline Turk for literature search.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.03.004.

References

[1] Coenen VA, Schlaepfer TE, Sajonz B, Döbrössy M, Kaller CP, Urbach H, et al. Tractographic description of major subcortical projection pathways passing the anterior limb of the internal capsule. Corticopetal organization of networks relevant for psychiatric disorders. NeuroImage Clin 2020:102165. https://doi.org/10.1016/j.nicl.2020.102165.
[2] Coenen VA, Schlaepfer TE, Goll P, Reinacher PC, Voderholzer U, Tebartz van Elst L, et al. The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder. CNS Spectr 2017;22(3):8. https://doi.org/10.1017/S1092852916000286.
[3] Coenen VA, Sajonz B, Reisert M, Bostroem J, Bewernick B, Urbach H, et al. Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression. NeuroImage Clin 2018;20:580–93. https://doi.org/10.1016/j.nicl.2018.08.020.
[4] Coenen VA, Bewernick BH, Kayser S, Kilian H, Boström J, Greschus S, et al. Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. Neuropsychopharmacology 2019;44:1224–32. https://doi.org/10.1038/s41386-019-0369-9.
[5] Goodman W, Price L, Rasmussen S, Mazure C, Fleischmann R, Hill C, et al. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch Gen Psychiatr 1989;46(11):1006–11. https://doi.org/10.1001/archpsyc.1989.01810110048007.
[6] Farris SG, McLean CP, Van Meter PE, Simpson HB, Foa EB. Treatment response, symptom remission, and wellness in obsessive-compulsive disorder. J Clin Psychiatr 2013;74(7):21639.
[7] Mallet L, Polosan M, Jaafari N, Baup N, Welter M-L, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive–compulsive disorder. N Engl J Med 2008;359(20):2121–34.
[8] Alonso P, Cuadras D, Gabriels L, Denys D, Goodman W, Greenberg BD, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. PLoS One 2015;10(7). https://doi.org/10.1371/journal.pone.0133591.
[9] Mallet L, Du Montcel ST, Clair A-H, Arbus C, Bardinet E, Baup N, et al. Long-Term effects of subthalamic stimulation in obsessive-compulsive disorder: follow-up of a randomized controlled trial. Brain Stimulation. Basic, Translational, and Clinical Research in Neuromodulation 2019;12(4):1080–2.
[10] Schlaepfer TE, Bewernick BH, Kayser S, Hurlemann R, Coenen VA. Deep brain stimulation of the human reward system for major depression—rationale, outcomes and outlook. Neuropsychopharmacology 2014;39(6):1303–14. https://doi.org/10.1038/npp.2014.28.

Dora M. Meyer, Susanne Spanier, Hannah M. Kilian
Department of Psychiatry and Psychotherapy/Division for Interventional Biological Psychiatry, Medical Center - University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Marco Reisert
Department of Stereotactic and Functional Neurosurgery, Medical Center – University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Horst Urbach
Department of Neuroradiology, Medical Center – University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Center for Deep Brain Stimulation (scientific), Faculty of Medicine, Freiburg University, Germany

Bastian EA. Sajonz
Department of Stereotactic and Functional Neurosurgery, Medical Center – University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Peter C. Reinacher
Department of Stereotactic and Functional Neurosurgery, Medical Center – University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Fraunhofer Institute for Laser Technology, Aachen, Germany

Claus Normann
Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Center for Deep Brain Stimulation (scientific), Faculty of Medicine, Freiburg University, Germany

Center for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Germany

Katharina Domschke
Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Center for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Germany

Volker A. Coenen
Department of Stereotactic and Functional Neurosurgery, Medical Center – University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Center for Deep Brain Stimulation (scientific), Faculty of Medicine, Freiburg University, Germany

Center for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Germany

Thomas E. Schlaepfer*
Department of Psychiatry and Psychotherapy/Division for Interventional Biological Psychiatry, Medical Center - University of Freiburg, Faculty of Medicine University of Freiburg, Germany

Center for Deep Brain Stimulation (scientific), Faculty of Medicine, Freiburg University, Germany

* Corresponding author. Division for Interventional Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Hauptstr. 5 79104 Freiburg, Germany.
E-mail address: thomas.schlaepfer@uniklinik-freiburg.de (T.E. Schlaepfer).

15 March 2022
Available online 26 March 2022