Long-term effects of subthalamic stimulation in Obsessive-Compulsive Disorder: Follow-up of a randomized controlled trial

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Obsessive-Compulsive Disorder (OCD) is characterized by intrusive, anxious thoughts with repetitive, ritualized behaviors, and has negative impacts on family relationships and social life. Its lifetime prevalence is estimated to be 2–3% [1]. Cognitive and behavioral therapy and selective serotonin reuptake inhibitors are the standard treatments for OCD; nevertheless, despite these treatments, between 25 and 40% of patients display persistent symptoms leading to severe functional disability [2]. Neurosurgical treatment targeting different parts of the orbito-fronto-striato-thalamo-cortical circuit has been proposed for the most severe and refractory forms, including both gamma knife non-invasive stereotactic lesions and invasive deep brain stimulation (DBS) [3] (Supplementary Information). However, the long-term efficacy (>3 years) and safety of DBS for OCD is not fully reported. We prospectively followed 14 OCD patients treated with subthalamic DBS (STN-DBS, STOC study) for 46 months [4] (ClinicalTrials.gov Number: NCT00169377) (Supplementary Information). The primary outcome was the change in the total Yale Brown Obsessive Compulsive Scale (Y-BOCS) score between inclusion (baseline) and month 46 with STN-DBS, or month 34 in the case of missing data at month 46 (Supplementary Fig. 1). We also assessed other psychiatric symptoms, global functioning and tolerance (Supplementary Information) [4]. Twelve patients completed the follow-up study (Supplementary Fig. 1). The Y-BOCS total score between inclusion (baseline) and the end of the follow-up period showed a median decrease of 15.5 points (IQR = −31 to −6), with a median change of 50% (IQR = −86.1 to −19.4%, Table 1). At the final follow-up, 11 patients (92%) were considered at least partial responders (>25% of Y-BOCS decrease) and 9 (75%) full responders (>35% of Y-BOCS decrease) (Table 1). The Y-BOCS score was also significantly improved at month 46 compared to month 16 (Table 1) and decreased by an average of 1 (SE = 0.04) point per year between month 16 and month 46 (Time effect p = 0.027, Supplementary Fig. 2). At the end of the follow-up period (month 46), the compulsion, obsession, anxiety and depression scores, but also global functioning and social and family life subscores were significantly improved (Supplementary Table 1). We found a significant positive relationship between the severity of OCD at month 46 and the age at onset (r = 0.61, p = 0.045, Supplementary Fig. 3) with early onset patients having fewer OCD symptoms with STN stimulation. During the follow-up, the medication had not changed significantly (not shown) but stimulation voltage was significantly increased (p = 0.042, Supplementary Table 2). Twenty-three serious adverse events occurred, 5 being transient and related to STN-DBS (hypomania, impulsivity, dysarthria or fall) and 18 related to the disease (increased anxiety and obsessive and compulsive symptoms, and major depressive episodes with suicide attempts, Supplementary Table 3). Our results show that STN-DBS can effectively treat OCD symptoms in severe and refractory patients over a period more than 3 years, with a 53% decrease in OCD severity and 11 out of 12 patients being considered responders at the final assessment with improvements in global functioning and social life. The fact that DBS of other limbic structures within the cortico-basal ganglia circuitry, such as the nucleus accumbens and the bed nucleus of the Stria terminalis, induce a median decrease in Y-BOCS scores of 45%, with two thirds of responders, favors the hypothesis that modulation of the neuronal activity within the limbic basal ganglia circuitry by DBS leads to OCD reduction [5]. In our patients, we observed a continuous and progressive significant improvement with time, concomitantly with increased DBS voltage. This suggests that a certain threshold of electric charge is needed to obtain an optimal outcome, but also that chronic and continuous STN-DBS might promote brain plasticity with additional improvement over time. Such plasticity phenomena have been suggested to explain the long-term results for GKC treatment [6]. Finally, even though ablative neurosurgery such as GKC may have some advantages over DBS and be seen as a “quick-fix”, “minimal-invasiveness” and “low-cost” paradigm [7] (Supplementary Information), it is, however, a “high-cost” procedure, with the need for prolonged hospitalization, regular outpatient visits and neurostimulator replacements. In our study, the fact that these beneficial effects were obtained with low voltage and that no stimulator replacement was needed during the follow-up period would suggest that STN-DBS is less expensive with high cost-effectiveness compared to other DBS procedures [8]. One patient (P12) showed no OCD reduction over the course of the study, and in the two patients who withdrew during the follow-up study (P05 and P14) there was no significant improvement. This is unlikely to have been related to the electrode placement, because the therapeutic contacts were correctly located within the associative-limbic part of the STN in all patients.
now needed to assess the health-economic benefits and minimize potential side-effects. Larger studies are required to confirm the long-term efficacy of STN-DBS in treating OCD patients [1]. In conclusion, the study suggests that STN-DBS can lead to a significant improvement in global functioning, social and familial disability, providing very high response rate, good long-term outcome and improving quality of life. A month follow-up study demonstrated that STN-DBS represents a feasible treatment option for OCD patients.

(Supplementary Fig. 4). This suggests that about 20% of our patients are unresponsive to STN-DBS, as also previously reported with other DBS targets [5]. Four of our 12 patients (33%) developed hypomania and impulsivity and 3 patients (23%) attempted suicide, with coexistent stimulation-induced impulsivity, acute alcoholism or increased anxiety, depressive signs and/or OCD. This rate of psychiatric signs is high in comparison to that previously reported for patients with DBS of the nucleus accumbens or Stria terminalis in OCD patients [5]. This suggests that the occurrence of these psychiatric signs could result from DBS of these limbic structures [10], but also from an aggravation of the disease in these severe and refractory OCD patients [1]. In conclusion, the findings from this 46-month follow-up study demonstrate that STN-DBS represents a new therapeutic option for severe and refractory OCD, with a very high response rate, good long-term outcome and improvement in global functioning, social and familial disability, providing a multidisciplinary approach to optimize stimulation parameter settings and minimize potential side-effects. Larger studies are now needed to assess the health-economic benefits of STN-DBS and to compare this treatment with other stimulation targets, with the use of study designs taking into account the advantages of DBS's adaptability.

Conflicts of interest

Dr. Mallet reports grants from Fondation pour la Recherche Médicale, grants from Agence Nationale de la Recherche, grants from Fondation Privée des HUG, grants from Fondation ICM, grants from Halphen Foundation, outside the submitted work; Dr. Bardinet reports grants from Medtronic, during the conduct of the study; Dr. Chabardes reports personal fees from Medtronic, personal fees from Boston Scientific, outside the submitted work; Dr. Fontaine reports grants and personal fees from Medtronic, outside the submitted work; Dr. Houeto reports personal fees from Medtronic, outside the submitted work; Dr. Krakoff reports grants and other from Medtronic during the conduct of the study; grants and personal fees from Medtronic, grants and personal fees from Boston Scientific, grants from St Jude Medical France, grants from Edmond J & Lily Safra Foundation, grants and personal fees from Movement Disorder Society, grants from French Ministry of Health (PHRC), grants from Inserm, grants from France Parkinson, grants from Swiss National Science Foundation, grants from Roger de Spoelberch Foundation, grants from Centre National de la Recherche Scientifique, personal fees from European Society Stereotactic Functional Neurosurgery, grants and personal fees from UCB, grants from Orkyn, grants from Homeper, outside the submitted work; Dr. Millet reports grants and personal fees from Medtronic, grants and personal fees from Syneika, personal fees from Lundbeck, personal fees from AstraZeneca, personal fees from Celgene, personal fees from Janssen, outside the submitted work; Dr. Polosan reports personal fees from Medtronic, grants from Boston Scientific, grants from Agence Nationale de la Recherche, outside the submitted work; Dr. Tezenas du Montcel reports personal fees from Boston Scientific, outside the submitted work; Dr. Welter reports personal fees from Medtronic, grants from Michael J Fox Foundation for Parkinson's Disease, grants from Agence Nationale de la Recherche, outside the submitted work. The other authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

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References


