Deep brain stimulation of the subthalamic, accumbens or caudate nuclei for patients with severe obsessive compulsive disorder: a randomized cross-over controlled study

Marie-Laure Welter, Joao Flores Alves Dos Santos, Anne-Helene Clair, Brian Lau, Hassimiou Mamadou Diallo, Sara Fernandez-Vidal, Hayat Belaid, Antoine Pelissolo, Philippe Domenech, Carine Karachi, Luc Mallet

From Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, Paris, France (MLW, AHC, BL, SFV, PD, CK, LM); Neurophysiology Department, CIC-CRB 1404, Rouen University Hospital, CHU Rouen, University of Rouen, France (MLW); Department of Mental Health and Psychiatry, Global Health Institute, University of Geneva, Geneva, Switzerland (JFADS, LM) ; INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, Paris, France (HMD) ; Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, Neurosurgery Department, Paris, France (HB, CK) ; INSERM U955, IMRB, Créteil, France (AP) ; Assistance Publique-Hôpitaux de Paris, DMU IMPACT, Département Médical-Universitaire de Psychiatrie et d'Addictologie, Neurosurgery Department, Hôpitaux Universitaires Henri Mondor - Albert Chenevier, Université Paris-Est Créteil, Créteil, France (AP, PD,LM)

Correspondance : Luc Mallet M.D., Ph.D., Univ Paris Est Creteil, Créteil, France; E-mail: luc.mallet@inserm.fr .

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For over ten years, electrical stimulation within the limbic cortico-subcortical network has been evaluated for treating patients with severe obsessive compulsive disorder (OCD) (1). High frequency deep brain stimulation (DBS) of various targets has been tested, including the anteromedial part of the subthalamic nucleus (amSTN), nucleus accumbens (NAc), ventral capsule/ventral striatum (VC/VS), anterior limb of the internal capsule (ALIC), bed nucleus of the stria terminalis, and inferior thalamic peduncle (1). So far, published data do not support superiority of any particular target, with a mean decrease of 45% in OCD severity whichever target is stimulated and about 25% of non-responders (2, 3). A recent randomized double-blind cross-over trial comparing the effects of amSTN or VC/VS DBS in 6 patients with severe OCD showed that both targets significantly reduced OCD symptoms one year after surgery, by 45% and 52.5% respectively (4). Here, we tested the effects of amSTN, NAc or caudate nucleus (CN) DBS in a randomized double-blind cross-over trial (NCT01807403) in 8 patients (7F/1M; mean±SD age = 42.5±8.4 yrs) with severe and refractory OCD (mean±SD Yale-Brown-Obsessive-Compulsive-Scale-Y-BOCS at inclusion= 33.5±4.31) (Figure 1A). The primary outcome was OCD severity measured using Y-BOCS during 3 months of active DBS compared to OCD severity at inclusion (Figure 1A,B). We also assessed anxiety, depression and quality of life (not shown). One patient (P06) prematurely ended the study at month 9 after attempting suicide; their OCD symptoms were unimproved during NAc or CN stimulation periods. The mean Y-BOCS score at the end of each double-blind active stimulation period was 24.1 (SD=6.99) for amSTN DBS, 24.3 (SD=6.21) for NAc DBS and 28.4 (SD=7.65) for CN DBS. During the randomized cross-over periods, we found that Y-BOCS was significantly decreased after active DBS of the amSTN (estimated marginal mean compared to baseline [SE]: 8.959 [1.955], $p<.001$), NAc (estimate [SE]: 8.561 [1.945], $p<.001$) and CN (estimate [SE]: 6.555 [1.855], $p=.003$). This corresponds to an average decrease of 25%, 22% and 19%, with amSTN, NAc and CN DBS, respectively. We found no significant differences in OCD severity between active DBS conditions during the randomized cross-over period, nor when considering only the last visit of each double-blind phase ($p>.10$ for all comparisons, Figure 1B). We did observe a significant decrease Off DBS (Sham) relative to inclusion (estimate [SE]: 7.158 [2.006], $p=.003$). We detected an order effect whereby the stimulation benefit was larger after the first double-blind phase (estimate [SE]: 3.70 [1.55], $p=.017$). For 3 patients, the largest improvements were obtained with amSTN DBS, while this was observed with NAc DBS for 2 patients and with CN DBS for one patient. For one patient amSTN DBS and

NAC DBS were equivalent, and better than CN DBS. Anxiety, depression (Figure 1C) and quality of life were not significantly modified during the randomized cross-over period. We tested for a lesioning effect, but found no significant change in the Y-BOCS (Figure 1B), anxiety, depression and quality of life scores (not shown) after surgery (M3) relative to inclusion ($p > .05$ for all comparisons). At the end of the randomized period, patients were asked about which stimulation period they preferred. Six of 7 patients chose the amSTN, which we used for the following open phase. One patient chose the NAc, but we switched to amSTN DBS after 4 months due to an absence of clear clinical benefit. At the end of the long-term follow-up period, all patients had amSTN DBS with a significant decrease in the Y-BOCS relative to inclusion (estimated marginal mean [SE]: 10.921 [2.004], $p < .001$). Three out of 7 patients had >35% improvement, and one had a 27% improvement. We found a significant correlation between the open phase stimulation of the amSTN and double-blind stimulation of the amSTN (Spearman $r = .794$, $p = .0328$). We also a significant correlation between the open phase stimulation of the amSTN and double-blind stimulation of the CN (Spearman $r = .833$, $p = .02$). Overall, we observed eight serious adverse events: three related to surgery (one misplaced electrode-P01, and two infections P02 and P05), three related to amSTN DBS with postural instability and falls in one patient (P02) and one transient hypomanic status (P03), and two related to the disease with increased anxiety in one patient (P08). Our study is the first to compare three distinct DBS targets in the same patients to treat severe and refractory OCD. Our Y-BOCS data suggest that amSTN DBS and NAc DBS are similarly effective for reducing OCD symptoms over a 3-month period of stimulation, with probably a weaker improvement with CN DBS. Despite this seemingly equivalent efficacy, almost all the patients blindly selected amSTN DBS when asked to identify the study period during which they felt the best in the double blind phase, a complex subjective judgment that goes beyond standard psychopathological assessment of OCD symptomatology (5). Consistent with our previous results (6,7), we observed a continuous and progressive improvement (66%) in OCD severity in 3 patients responsive to amSTN DBS in the long-term follow-up period, suggesting that time may be necessary for stimulation effects to manifest. However, amSTN DBS reduced OCD severity by less than 35% in 4 patients. Two of these patients had dysfunctional amSTN DBS electrodes thus preventing accurate evaluation of the efficacy, although they also did not respond to NAc/CN DBS despite in-depth testing during long-term follow-up (not shown). Interestingly, one of these two patients was the only hoarder of our sample, a condition identified as a

resistance factor to neurosurgical approaches (8, 9). Our results also suggest the possibility to determine quite early after stimulation initiation responders from non-responders. Overall, our results confirm the significant improvement of OCD symptoms using DBS of different limbic deep brain structures for patients with severe and highly resistant OCD (1). Our limited sample size limits our ability to fully rule out order, sequence and carryover effects. Further studies are needed to confirm our results, and identify the clinical features that predict DBS response in OCD patients, taking into account the relationship with the targeted structure (2–4) and the effects of DBS on cortico-subcortical network connectivity and activity (1).

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139 **Figure 1. Effects of DBS of the antero-medial Subthalamic, Accumbens and Caudate nuclei on OCD**
140 **severity in 8 patients with refractory and severe OCD. Upper panel. (A)** Study Flow Chart. The study
141 included a randomized double-blind crossover design period (months 3 to 14, with three 3-month
142 phases separated by a 1-month washout period), followed by an open-label period of 22 months.
143 Patients were evaluated before inclusion and at inclusion (baseline), less than 2 months before surgery;
144 once a month between month 3 and month 14, and 22 months after surgery (m+14). Double-blinding
145 was ensured by the fact that every month, a visit was made during which the stimulator was
146 manipulated, and that all periods, limits and durations were unknown to both patients and blind
147 evaluators. **(B)** Y-BOCS scores and **(C)** Depression (Montgomery and Asberg Depression Rating Scale
148 [MADRS]) scores in OCD patients before surgery (baseline), without active DBS 3 months after surgery
149 (M3), or following wash-out between targets (sham); caudate nucleus (CN), accumbens nucleus (NAc)
150 and anteromedial subthalamic nucleus (amSTN) DBS; and at the last follow-up assessment (Open). Each
151 color represents an individual patient, with each point corresponding to Y-BOCS assessments during
152 the different trial phases (points during the double-blind phases represent averages of 3 assessments).
153 Horizontal black lines represent the estimated marginal mean for each condition obtained from a linear
154 mixed model with patients as a random effect, and the upper and lower bounds of the grey rectangles
155 represent the corresponding 95% confidence intervals. **Lower panel.** The localization of the electrodes
156 and stimulating contacts (colored cylinders) within the basal ganglia structures (yellow in the CN, blue
157 in the NAc, red in the amSTN), are depicted on 3D reconstructions obtained with the computerized YeB
158 atlas (10). The sensori-motor (green), associative (purple) and limbic (yellow) territories are shown as
159 in Mallet et al (6) on posterior **(D)** and lateral views for the left **(E)** and right **(F)** hemispheres in the 7
160 OCD patients who completed the study.

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