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Changes of oscillatory activity in the subthalamic nucleus during obsessive-compulsive disorder symptoms: Two case reports

Julien Bastin [a,b,*], Mircea Polosan [a,b,c], Brigitte Piallat [a,b], Paul Krack [a,b,d], Thierry Bougerol [c], Stéphan Chabardès [a,b,e] and Olivier David [a,b]

[a] Fonctions Cérébrales et Neuromodulation, Université Joseph Fourier, Grenoble, France
[b] Grenoble Institut des Neurosciences, INSERM, U836, Grenoble, France
[c] Clinique de Psychiatrie, Pôle Neurologie Psychiatrie, Centre Hospitalier Universitaire, Grenoble, France
[d] Clinique de Neurologie, Pôle Neurologie Psychiatrie, Centre Hospitalier Universitaire, Grenoble, France
[e] Clinique de Neurochirurgie, Pôle Tête et Cou, Centre Hospitalier Universitaire, Grenoble, France

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has positive and negative effects on mood and cognition, as shown in patients suffering from Parkinson's disease (PD) and severe obsessive-compulsive disorders (OCD). Such behavioural and clinical effects suggest that the STN has an important function in limbic circuitry, which still needs to be clarified from electrophysiological recordings. Here we report two exceptional cases of OCD patients in whom local field potentials (LFP) of the anterior STN were directly recorded during acute obsessive-compulsive symptoms. We found significant symptom-related changes in different frequency bands, with no clear preferential oscillatory pattern. The overall modified STN activity during OCD symptoms suggests a mixture of both pathological and compensatory mechanisms that would reflect the maintenance of an over stable motor/cognitive/emotional set. Whether this activity propagates throughout the entire cognitive-limbic loops that are impaired in OCD is an interesting question for future research in larger series of patients.

Research in how the brain processes information is important for understanding obsessive-compulsive disorder (OCD). Beyond factors such as attention, learning, memory that are known to be involved in OCD psychopathology, emotional processing, namely affective and reward processing, depends on the involvement of specific neural networks within and beyond the cortico-striato-thalamo-cortical circuits in the context of specific cognitive-affective paradigms (Becker et al., 2013; Cannistraro et al., 2004; Fitzgerald et al., 2005; van den Heuvel et al., 2005; Milad et al., 2013).

Recently it has been shown that severe refractory OCD symptoms can be improved by high frequency stimulation of the subthalamic nucleus (STN) (Chabardès et al., 2012; Fontaine et al., 2004; Mallet et al., 2008). The STN is a key

* *Corresponding author*. Grenoble Institut des Neurosciences, Chemin Fortuné Ferrini – Bât EJ Safra – CHU, 38700 La Tronche, France.
E-mail address: julien.bastin@ujf-grenoble.fr (J. Bastin).
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structure of basal ganglia connecting motor, limbic and associative systems, because it is known from Parkinson's disease (PD) patients that deep brain stimulation (DBS) of the STN can have significant effects on mood and cognition, including mirthful laughter (Krack et al., 2001), acute depression (Bejjani et al., 1999), aggressiveness (Bejjani et al., 2002), hypomania or full blown mania (Krack et al., 2001; Mallet et al., 2007; Ulla et al., 2011). Those transient effects are usually seen as "side effects" in PD, but are clues to the heretofore-underappreciated role that STN plays in limbic circuitry, whose precise functions are as yet unknown and under active investigation (Buot et al., 2012; Kühn et al., 2005; Péron, Frühholz, Vérin, & Grandjean, 2013). Studies on PD patients highlighted the relationship between STN alpha activity (oscillations) and valence-related emotional information processing, but there are still insufficient data elucidating the involvement of STN in OCD symptomatology. While the baseline firing pattern of STN neurons was shown to differ from that of PD patients (Piallat et al., 2011) and to correlate with the severity of OCD symptoms (Welter et al., 2011), the modulation of STN activity during OCD symptoms is unknown. Here, we report two exceptional cases of OCD patients implanted for DBS therapy, from whom STN local field potentials (LFP) were recorded during unexpected OCD symptoms that occurred during a cognitive task performed at the patient's bedside, within a few days between the implantation of the DBS leads and of the stimulator. In each patient separately, we describe below (1) whether baseline STN frequency spectrum was comparable to that of 5 other OCD patients we similarly recorded but who did not show any acute OCD symptoms; (2) how STN oscillatory activity changed during acute OCD symptoms using as a baseline the fixation periods, i.e., when they were able to perform the task.

Both patients (P1 and P2, two males, 34 and 27 years old) gave their informed consent to participate to the study, which was approved by the ethical committee in charge of Grenoble University Hospital. The main OCD symptoms for P1 were severe obsessions/doubts concerning his spatial position accompanied by checking and touching compulsions (P1 has suffered from OCD for 13 years; pre-surgical Yale-Brown Obsessive Compulsive Scale – Y-BOCS – score was 32 on a scale of 40). For P2, the main dimensions of OCD symptoms focused on contamination and washing, as well as "just right" obsessions (P2 has a 10-year history of OCD; pre-surgical Y-BOCS score: 34). The severe OCD state of both patients benefitted of STN DBS, with significant clinical improvement after one year DBS ON of 40% and 47% for P1 and P2 respectively. The percentage of clinical improvement was assessed after 1 year of DBS with the parameters obtained after an optimization period of DBS parameters during the first 3 months; it represents the percentage of improvement of the Y-BOCS score with the pre-operatory state. Parameters of stimulation were the following: monopolar bilateral stimulation at 1.8 V, frequency = 130 Hz, pulse width = 60 μsec: contacts 1–2 and 5–6 for P1 and contacts 2 and 6 for P2. Medication at the time of the surgery and of LFP recordings was: Clomipramine 2,5 × 75 mg/Oxazepam 50 mg/Cyamemazine 50 mg/day for P1; Sertraline 150 mg/Amisulpride 300 mg/day for P2.

Patients were bilaterally implanted for STN DBS therapy (Chabardès et al., 2012; Mallet et al., 2008) with 4 contacts DBS electrodes (3389 Medtronic, Minneapolis, USA), and from which LFP recordings were obtained with a portable EEG amplifier (Micromed SD32, Treviso, Italy). An anti-aliasing hardware low-pass filter at 270 Hz was used and the sampling rate was 2048 Hz. To stimulate preferentially the presumed non-motor STN, the DBS electrode was positioned on the track in which no side effects was obtained during per-operatory micro-stimulation, and in which no sensori-motor cells were recorded during micro-electrode recordings. Depth of the electrode was chosen according to per-operatory micro-recordings so that middle DBS contacts were positioned within the electrophysiological estimate of the non-motor STN. Table 1 indicates final positions of the DBS contacts. A longitudinal bipolar montage was used to improve the spatial specificity of STN recordings, and therefore three STN contact-pairs were analysed for each patient's hemisphere. We compared STN recordings during OCD symptoms (OCD condition) to recordings obtained when the patients were able to perform a stop signal task (control condition, CON). Behavioural and electrophysiological results concerning the stop signal task specifically are not relevant for the present study and are described in a companion paper (Bastin et al., in revision). During OCD condition, patients could not perform anything other than their rituals (P1) or felt "cognitively freezing" while having severe "just right" obsessions (P2).

We processed recordings during 3–5 min, a duration assumed to be longer than unspecific transient fluctuations within each condition. Continuous recordings were epoched into non-overlapping successive time windows of 1 sec (179 OCD epochs for P1, 457 OCD epochs for P2). The number of epochs of the control condition was 457 for P1 and 499 for P2, which was set for each patient according to the number of trials performed by each patient during the SST and to artefact free periods during visual fixation. In order to limit the contamination of the control recordings by any cognitive or

Table 1 – DBS electrode positions in the Talairach coordinate system with posterior commissure (PC) as origin. *X* coordinates: laterality relative to the midline. *Y* coordinates: anteriority relative to the anterior border of PC. *Z* coordinates: depth relative to the AC–PC line. By convention, DBS contacts are labelled contacts 0,1,2,3 on the right side and contacts 4, 5, 6, 7 on the left side.

Patient	Laterality	DBS contact	X (mm)	Y (mm)	Z (mm)
P1	Left	4	−8.77	12.99	−5.20
		5	−9.59	13.68	−3.55
		6	−10.41	14.37	−1.90
		7	−11.23	15.06	−.25
	Right	0	8.15	8.18	−4.71
		1	8.89	9.30	−3.22
		2	9.63	10.42	−1.73
		3	10.37	11.54	−.24
P2	Left	4	−7.10	10.34	−5.92
		5	−7.66	11.41	−4.21
		6	−8.22	12.48	−2.50
		7	−8.78	13.55	−.79
	Right	0	8.96	10.99	−6.10
		1	9.90	12.06	−4.40
		2	10.84	13.13	−2.70
		3	11.78	14.20	−1.00