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

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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

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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

motor component, the control epochs were selected when patients had to passively fixate a cross at the centre of a screen. Spectral power was computed from every epoch on each contact-pair and a logarithmic transformation was applied to the power distribution (Kiebel, Tallon-Baudry, & Friston, 2005). Unpaired *t*-test was performed to measure the effect of OCD on STN oscillatory power averaged within different frequency bands (delta: 1–4 Hz; alpha: 8–12 Hz; low beta: 13–24 Hz; high beta: 25–35 Hz, gamma: 60–80 Hz) (df = 634 and 954 respectively for P1 and P2). Permutation tests were then used to assess the significance of the measured *t*-values. OCD and CON conditions were shifted 10 000 times, to estimate random unpaired student *t*-test distributions from the 10 000 surrogate *t*-values. Those distributions were used to define the statistical threshold on measured *t*-values, corresponding to the upper and lower bound of the distribution (two-tailed test with a statistical risk alpha set to .05). To take into account the multiple tests performed (6 contact-pairs × 5 frequency bands), the alpha level was adjusted using a Bonferroni correction.

Fig. 1 shows the STN power spectrum (normalized by power between 1 and 80 Hz as a global scaling factor) at rest, of the two patients under study here (P1 and P2) and of 5 other ones (P3 to P7) implanted and recorded in the exact same conditions but who did not have any acute OCD symptoms during LFP recordings (clinical information in Table 2). Interestingly, one can note that the difference in the shape of STN spectrum between P1–P2 and the other patients (P3–P7) was the clearest in ventral contacts, particularly on the right side.

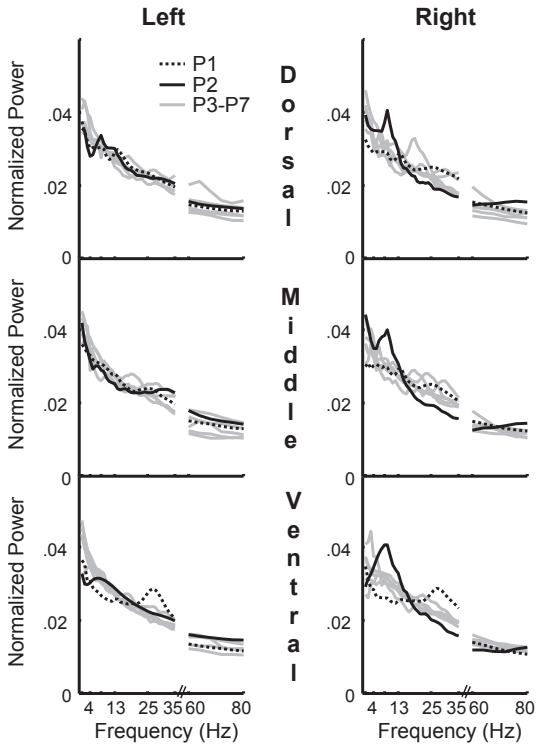

Fig. 1 – Normalized power spectra in the dorsal, middle and ventral STN estimated from recordings selected during visual fixation in the seven OCD patients.

However, the main frequency of STN activity differed between P1 (26 Hz, beta band) and P2 (9 Hz, alpha band).

Considering P1 and P2 separately, statistical analyses of the spectral differences between OCD and CON conditions revealed that in the more dorsal STN contacts, oscillatory power was higher during acute OCD symptoms in low and high frequencies for P1 and only in low frequencies for P2 (Fig. 2). For P1, this effect was also observed in middle and ventral contacts, but was inverted in the beta band of the right STN. For P2, reduced beta and gamma activity during OCD symptoms was also observed in the right ventral STN. However, it remained higher in low frequencies (delta band) for all contacts and in all frequencies for the middle STN contacts.

This short study of two rare cases indicates that significant increase of STN oscillations can be found during OCD symptoms, on the majority of STN contacts in distinct frequency bands. We also observed in the right ventral STN a decrease of oscillatory activity in the beta and gamma frequency bands. These results thus suggest that the STN is involved during OCD symptoms, but the specificity of STN LFP changes remains clearly to be addressed. This was not possible here because of the heterogeneity in reported findings that is inherent to case studies. Although some findings were shared by P1/P2, we indeed found non reproducible results between the two patients, such as the main frequency of STN spectrum.

There are also some limitations to this study. First, we could not perform an event-related analysis of OCD rituals because it was difficult to determine the exact onset and duration of OCD symptoms. Second, we could record the STN of only 2 patients during acute OCD symptoms (in a recent series of 7 very rare patients). Moreover, the duration of OCD symptoms was different between patients, leading to different sensitivity of statistical analyses. In particular the number of OCD epochs, which was larger for P2 (455) than for P1 (179), may partly explain the observed differences between P1 and P2. Third, differences of motor activity during the stop signal task and during rituals might have biased STN oscillatory activity. This possibility is somewhat limited because patients' behaviour during OCD symptoms largely differed: P1 had some motor rituals whereas P2 suffered from a sort of "cognitive freezing", which was not accompanied by motor activity. Therefore, the motor hypothesis, which predicts a decrease of beta activity for P1 and an increase for P2, is invalidated by the fact that we observed an increase of beta activity in both P1 and P2, and even stronger in P1.

Despite these limitations, we propose below to interpret some of our main observations, which are the first pieces of evidence on the potential role of STN in OCD. First, our results provide preliminary electrophysiological evidence that obsessions or "cognitive freezing" might not be strictly related to enhanced beta oscillations, which were proposed to "reflect the maintenance of a cognitive set and a relative dominance of endogenous signals that override the effect of unexpected external events" (Engel & Fries, 2010). According to this hypothesis, but extended to all frequency bands, one could interpret that endogenous obsession signals reflected by enhanced STN activity were too strong for the patients to be able to perform a simple motor inhibition task during OCD symptoms. Second, it should be noted the presence of decreased STN activity in the right hemisphere, as well as an

Table 2 – Clinical characteristics of OCD patients at time of recordings. OCD type (1; 2; 3) corresponded to the main type of symptom observed: contamination/cleaner (1), doubt/checker (2) and miscellaneous OCD + repeating (3); Y-BOCS = Yale-Brown Obsessive Compulsive Scale (with Obsessions + Compulsions subscores); GAF = Global Assessment of Functioning; CGI = Clinical Global Impression; SNRI = serotonin and norepinephrine reuptake inhibitors; SRI = serotonin reuptake inhibitors; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics.

	Sex	Age, years	Duration of symptoms, years	OCD type	Clinical scales			Medication, total daily dose (mg)		
					Y-BOCS	CGI	GAF	SNRI and SRI	FGA and SGA	Other medications
P1	M	34	13	2	16 + 16	6	35	Clomipramine 187.5 mg	Cyamemazine 150 mg	Oxazepam 150 mg
P2	M	27	10	3	17 + 17	6	30	Sertraline 150 mg	Amisulpride 300 mg	
P3	M	36	17	1	17 + 15	5	40	Paroxetine 40 mg		
P4	F	38	11	1	18 + 18	6	32	Sertraline 100 mg		Clonazepam 4 mg
P5	F	40	15	1	19 + 17	6	34	Fluvoxamine 200 mg Clomipramine 75 mg		Gabapentin 600 mg Clonazepam 3 mg
P6	F	54	22	2	17 + 16	5	30	Paroxetine 50 mg		Lorazepam 3 mg Zopiclone 7.5 mg
P7	F	30	23	2	16 + 18	6	35	Venlafaxine 75 mg		Levothyrox 125 µg

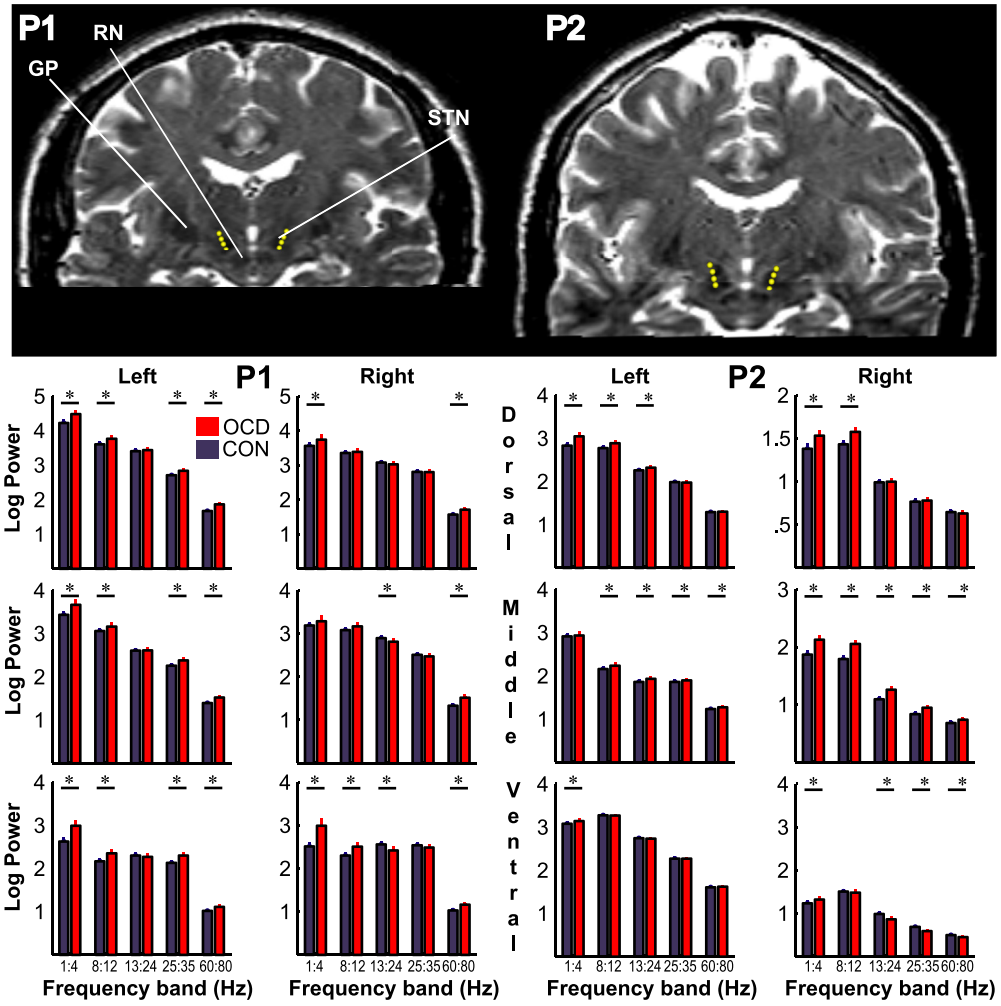

Fig. 2 – Top: DBS electrode locations superimposed on the preoperative MRI of each patient (Left: P1; Right P2). Yellow spheres show individual DBS contacts. Bottom: LFP log power of dorsal, middle and ventral STN contacts in delta, alpha, low beta, high beta and gamma bands. Stars indicate frequency bands showing a significant difference between OCD symptoms and control (CON) condition ($p < .05$, bootstrapping tests). RN: red nucleus; GP: globus pallidus; STN: subthalamic nucleus.

asymmetry of the shape of STN spectrum between left and right hemisphere. This may support an asymmetry of the STN pathophysiology in OCD as already reported from spontaneous per-operatory single-unit recordings where more burst neurons (suspected to be a marker of neuronal network dysfunction) were reported on the left side (Piallat et al., 2011; Welter et al., 2011).

Put together, these two cases suggest that acute OCD symptoms may be related to abnormally high oscillatory activity in the STN, particularly in the left hemisphere and in the delta-alpha (1–12 Hz) frequency range. In PD, increased cortico-subthalamic oscillatory activity in the alpha-beta bands (8–30 Hz) correlates with akinesia (Hirschmann et al., 2013). In OCD, increased oscillatory activity has also been observed in the STN and was found to correlate with the severity of OCD (Welter et al., 2011). Furthermore, some subthalamic neurons specifically increased their firing rate when doubt occurred during a verification task (Burbaud et al., 2013). Thus, we speculate that the increase in STN oscillations during acute OCD symptoms might correspond to a compensatory mechanism that aims at overcoming obsessions. Furthermore, these results suggest first an extension of the role of alpha-beta (8–30 Hz) oscillations to its already "antikinetic" role hypothesized in previous studies performed in movement disorder patients (Jenkinson & Brown, 2011): abnormally alpha–beta oscillations may not only over-stabilize the motor system, but they would also prevent cognitive flexibility (Engel & Fries, 2010). Another theoretical interpretation of the increased level of STN oscillations is that it could correspond to modulation of the bursting activity of STN neurons (Welter et al., 2011) and might reflect an abnormal excitation of the STN during OCD. In EEG research, slow rhythms have been proposed to reflect inhibition of thalamo-cortical loops for action selection (Jensen & Mazaheri, 2010; Schroeder & Lakatos, 2009). Thus, abnormal low frequency activity in the STN during acute OCD might reflect pathological (repetitive) action selection that is the hallmark of OCD. However, the involvement of both low and high LFP frequencies may highlight a more general dysfunction of the associative-limbic circuitry (Graybiel & Rauch, 2000; Krack, Hariz, Baunez, Guridi, & Obeso, 2010), which translates into an over-stabilization of the stream of behaviour, thoughts and motivations that characterize OCD patients.

We thus propose that during OCD symptoms, the modified level of LFP activity in the STN would reflect a mixture of both pathological activity corresponding to repetitive unsuccessful action selection in OCD 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 known to dysfunction in OCD is an interesting question for future research in larger series of patients.

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