

# Basal ganglia dysfunction in OCD: subthalamic neuronal activity correlates with symptoms severity and predicts high-frequency stimulation efficacy

M-L Welter<sup>1,2,3,4,5</sup>, P Burbaud<sup>6,7</sup>, S Fernandez-Vidal<sup>1,8</sup>, E Bardinet<sup>1,8</sup>, J Coste<sup>9</sup>, B Piallat<sup>10</sup>, M Borg<sup>11</sup>, S Besnard<sup>12</sup>, P Sauleau<sup>13</sup>, B Devaux<sup>14</sup>, B Pidoux<sup>15</sup>, P Chaynes<sup>16</sup>, S Tézenas du Montcel<sup>17</sup>, A Bastian<sup>1,2,3,4</sup>, N Langbour<sup>6</sup>, A Teillant<sup>1,2,3,4</sup>, W Haynes<sup>1,2,3,4</sup>, J Yelnik<sup>1,2,3,4</sup>, C Karachi<sup>1,2,3,4,18</sup> and L Mallet<sup>1,2,3,4</sup>, for the French ‘Stimulation dans le Trouble Obsessionnel Compulsif (STOC)’ Study Group<sup>19</sup>

Functional and connectivity changes in corticostriatal systems have been reported in the brains of patients with obsessive-compulsive disorder (OCD); however, the relationship between basal ganglia activity and OCD severity has never been adequately established. We recently showed that deep brain stimulation of the subthalamic nucleus (STN), a central basal ganglia nucleus, improves OCD. Here, single-unit subthalamic neuronal activity was analysed in 12 OCD patients, in relation to the severity of obsessions and compulsions and response to STN stimulation, and compared with that obtained in 12 patients with Parkinson’s disease (PD). STN neurons in OCD patients had lower discharge frequency than those in PD patients, with a similar proportion of burst-type activity (69 vs 67%). Oscillatory activity was present in 46 and 68% of neurons in OCD and PD patients, respectively, predominantly in the low-frequency band (1–8 Hz). In OCD patients, the bursty and oscillatory subthalamic neuronal activity was mainly located in the associative–limbic part. Both OCD severity and clinical improvement following STN stimulation were related to the STN neuronal activity. In patients with the most severe OCD, STN neurons exhibited bursts with shorter duration and interburst interval, but higher intraburst frequency, and more oscillations in the low-frequency bands. In patients with best clinical outcome with STN stimulation, STN neurons displayed higher mean discharge, burst and intraburst frequencies, and lower interburst interval. These findings are consistent with the hypothesis of a dysfunction in the associative–limbic subdivision of the basal ganglia circuitry in OCD’s pathophysiology.

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## Introduction

Obsessive–compulsive disorder (OCD) is a common disabling disease, but its neural substrate remains poorly understood. A large set of imaging and neurophysiological data obtained in OCD patients have suggested, however, a dysfunction of the ventromedial corticosubcortical loop.<sup>1–9</sup> In the light of these results, deep brain stimulation (DBS) of the caudate nucleus and adjacent structures has been proposed for the treatment of severe and refractory OCD patients.<sup>10–15</sup> Recently, the subthalamic nucleus (STN) has appeared as another potential target for DBS following serendipitous results from Parkinson’s disease (PD) patients<sup>16–18</sup> and its

role in associative and limbic information processing in human and non-human primates.<sup>19–21</sup> Data obtained in rats and human also suggest that the STN is implicated in the ability to stop or inhibit an already initiated response, highlighting its potential role in impulse control disorders.<sup>22,23</sup> We have recently confirmed the efficacy of stimulation applied in the medial part of the STN in OCD patients with a multicentre clinical trial.<sup>24</sup> The usefulness of STN stimulation has also been investigated in rats and monkeys with induced compulsive-like behaviour.<sup>25–28</sup> The fact that modulation of the STN neuronal activity by DBS improves OCD symptoms suggests that this basal ganglia structure may be dysfunctional in human patients.

<sup>1</sup>Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière (CRICM), Université Pierre et Marie Curie-Paris 6, UMR-S975, Paris, France; <sup>2</sup>Inserm, U975, Paris, France; <sup>3</sup>CNRS, UMR 7225, Paris, France; <sup>4</sup>Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris Centre d’Investigation Clinique, Paris, France; <sup>5</sup>Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Département de Neurologie, Bâtiment Paul Castaigne, Paris, France; <sup>6</sup>Laboratoire Mouvement, Adaptation, Cognition, CNRS UMR 5227, Université Victor Segalen Bordeaux 2, Bordeaux, France; <sup>7</sup>Service de Neurophysiologie, Hôpital Universitaire Pellegrin, Bordeaux, France; <sup>8</sup>Groupe Hospitalier Pitié-Salpêtrière, Centre de Neuroimagerie de Recherche (CENIR), Paris, France; <sup>9</sup>Service de Neurochirurgie A, CHU Clermont-Ferrand, Clermont-Ferrand, France; <sup>10</sup>INSERM, U836, Grenoble Institute of Neuroscience, Grenoble, France; <sup>11</sup>Service de Neurologie, CHU Nice, Nice, France; <sup>12</sup>Service de Neurophysiologie Clinique, CHU Poitiers, Poitiers, France; <sup>13</sup>Service de Neurophysiologie, CHU Rennes, Rennes, France; <sup>14</sup>Service de Neurochirurgie, Hôpital Sainte-Anne, Paris, France; <sup>15</sup>Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Service de Neurophysiologie Clinique, Paris, France; <sup>16</sup>Service de Neurochirurgie, CHU Toulouse, Toulouse, France; <sup>17</sup>Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Département de Biostatistiques et Information Médicale, ER4 (ex EA3974) Modélisation en Recherche Clinique, Paris, France and <sup>18</sup>Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Service de Neurochirurgie, Paris, France

Correspondence: Dr ML Welter, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Département de Neurologie, Bâtiment Paul Castaigne, 47-83 bd de l’Hôpital, Paris 75013, France.

E-mail: marie-laure.welter@psl.aphp.fr

<sup>19</sup>Members of the French STOC Study Group are listed in the Appendix.

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One way to understand the potential role of the basal ganglia system and its dysfunction in OCD symptoms is to investigate subcortical structures electrophysiologically. Neuronal recordings of the striatum have already been reported in three OCD patients where an increased and more irregular pattern was found during obsessions.<sup>29</sup> As the STN is the main target for DBS in patients with Parkinson's disease (PD), a large set of electrophysiological data have been reported in patients and non-human primate models of PD, and consistently show increased neuronal activity, occurrence of bursts, synchrony and oscillations.<sup>30–34</sup> In such patients, an electrophysiological analysis has allowed, at least in part, to understand how STN dysfunction is linked to the motor symptoms<sup>33,35</sup> and how these electrophysiological characteristics are related to the clinical outcome of STN stimulation.<sup>36,37</sup> In OCD patients, compared with PD patients, the firing rate of subthalamic neurons has been shown to be lower with, however, the same proportion of bursting neurons.<sup>38</sup>

This study aimed to further explore the relationship between STN neuronal activity and OCD symptoms. Subthalamic electrophysiological recordings were obtained in OCD patients during surgery for DBS and analysed in relation to both OCD severity and STN stimulation outcome.<sup>24</sup> Subthalamic neuronal activity recorded in PD patients operated under the same conditions was used for comparison. Previous studies led us to hypothesise that (1) subthalamic neuronal activity would be differentially affected in OCD compared with PD patients, especially in the ventromedial (associative–limbic) subdivision; and (2) the neuronal activity characteristics would be linked to clinical severity or response to STN stimulation of OCD symptoms.

## Materials and methods

**Participants.** A total of 12 patients with severe and refractory OCD and 12 patients with severe form of PD were included in this study. Patients with OCD were operated for bilateral high-frequency STN stimulation in a therapeutic trial (ClinicalTrials.gov number, NCT00169377)<sup>24</sup> (see Supplementary Material and Table S1). All patients gave informed written consent and the protocol was approved by the local ethics committee. Patients with PD were operated for bilateral STN stimulation as routinely performed in our centre<sup>39</sup> (see Supplementary Material). None of the patients showed contraindication to surgical procedure, dementia or abnormal brain imaging.

**Neurosurgical procedure.** The surgery was performed as described previously.<sup>24,40</sup> Briefly, the implantation of bilateral stimulating electrodes (Medtronic, model 3389, Minneapolis, MN, USA) was performed the same day using both preoperative anatomical and perioperative electrophysiological targeting. Subthalamic nuclei were preoperatively targeted by means of stereotactic magnetic resonance imaging, with additional ventriculography in some OCD patients (depending on the local protocol).<sup>24</sup> In OCD patients, the target was defined 2 mm anterior and 1 mm medial to the PD target at the boundary of STN associative and limbic subdivisions.<sup>41,42</sup>

**Micro-electrode recordings.** Perioperative electrophysiological recordings were performed in awake patients, at rest (see Supplementary Material). Drug treatment was discontinued the evening before surgery in all patients. Extracellular single-unit neuronal activity was recorded simultaneously from 3 to 5 leads, used to identify and localise the STN for 2 min at rest, each 200–500  $\mu\text{m}$  within the STN.<sup>31,32</sup>

**Off-line analysis.** Neuronal recordings were exported off-line as text files to a PowerLab system (ADI instruments; Phymep, Paris, France) and analysed using the Spike 2 software suite (Version 5; Cambridge Electronic Device, Cambridge, UK). Spikes were discriminated from noise and the mean firing rate, mean interspike interval (ISI) and coefficient of variation were calculated for each neuron (see Supplementary Material, and Figure S1A, D and G). Discharge patterns were classified as regular, irregular or bursting and the spike trains with bursting activity were detected for each neuron<sup>43</sup> (see Supplementary Material). The mean bursting index ( $S$ ), burst frequency, duration, intraburst frequency and interval interburst were calculated for each neuron.<sup>34</sup> Analysis of oscillatory activity was performed by frequency band using a Matlab program<sup>44</sup> ( $\delta$ : 1–4 Hz;  $\theta$ : 4–8 Hz;  $\alpha$ : 8–12 Hz;  $\beta$  low: 12–20 Hz;  $\beta$  high: 20–35 Hz;  $\gamma$ : > 35 Hz) (see Supplementary Material).

**Imaging.** The location of each recorded neuron within the functional subdivisions, that is, motor, associative and limbic, of the STN was determined by using a three-dimensional deformable histological atlas adjusted to the individual brain geometry of each patient<sup>45,46</sup> (see Supplementary Material).

**STN stimulation in OCD patients.** A 3-month STN stimulation period was tested in the 12 OCD patients.<sup>24</sup> At the end of the on-stimulation period, the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) score was decreased by 22% (see Supplementary Material).

**Statistical analysis.** Results for continuous variables are reported as mean  $\pm$  s.d. To compare neuronal activity between OCD and PD cells, we used mixed models (analysis of variance with random effect) with a random effect for patients and two fixed effects for the group (OCD vs PD) as the between-subject factor and neuronal recording localisation (sensorimotor, associative, limbic) as the within-STN factor, and the interaction between these two fixed factors. When significant effects were found, pairs of means were compared using a Tukey–Kramer correction. For categorical data, generalised linear models with a logistic link function were used with similar effects as for the linear mixed model used for continuous data.

As changes in STN neuronal activity have been reported, we examined the differences in STN neuronal activity between OCD patients with ( $n=4$  subjects, 48 cells) and without ( $n=4$  subjects, 50 cells) neuroleptic treatment,<sup>47</sup> and between left and right sides,<sup>38</sup> using the Student'  $t$ -test for continuous variables and the Fisher's exact test for categorical variables. The relationship between the severity of

obsessions and compulsions (Y-BOCS global and obsession and compulsion subscores), the improvement in OCD symptoms induced by STN stimulation and the STN neuronal activity characteristics were also evaluated using the non-parametric Spearman's correlation test. For these purposes, the mean discharge frequency, ISI, coefficient of variation, S index, burst frequency and duration, intraburst frequency and interval interburst, the proportion of STN neurons displaying oscillatory activities, power and peak in each band frequency were calculated for each subject. The postoperative percentage improvement in OCD symptoms was calculated for each patient, as follows: (score before the on-stimulation period – score at the end of the 3-month STN stimulation period) × 100/score before the on-stimulation period (see Supplementary Material).

Statistical analyses were performed with the SAS 9.2 software (SAS Institute, Cary, NC, USA). The level of significance for all statistical tests was fixed at  $P < 0.05$ . No Bonferroni correction was applied.

## Results

In all, 138 cells were isolated and recorded from the STN of the 12 OCD patients and 173 cells from the STN of the 12 PD patients. The average recording duration was  $59.6 \pm 39.4$  s and the average number of spikes  $1417 \pm 1191$ .

**Discharge frequency and pattern.** The mean STN firing rate in OCD patients (STN-OCD) was significantly lower, with a higher mean ISI, compared with STN neurons of PD patients (STN-PD; Table 1). The distribution of the three types of discharge pattern in STN neurons did not differ between OCD and PD patients ( $P = 0.14$ ), with a predominant burst-like firing pattern (Table 1). The mean bursting index, burst duration and interval interburst were significantly higher and the mean burst frequency and intraburst frequency significantly lower in STN-OCD neurons compared with STN-PD neurons (Table 1).

**Oscillatory activity.** Over the entire bandwidth analysed, the proportion of neurons displaying oscillatory activity was lower in STN-OCD compared with STN-PD (46 vs 68%; Figure 1). In both groups, about half of the oscillatory neurons showed peaks in more than one frequency band (Figure 1). The distribution of oscillatory activity was similar in the two groups of patients, but for the presence of more  $\theta$  activity in STN-OCD neurons and in the  $\beta$ -low band in STN-PD neurons (Figure 1A;  $P < 0.02$ ). The mean frequency in the  $\beta$ -low band was significantly lower in STN-OCD compared with STN-PD neurons (Table 1).

**Influence of the neuroleptic treatment.** No significant difference in neuronal activity was found between STN neurons ( $n = 48$  cells) recorded in OCD patients undergoing neuroleptic treatment compared with those without ( $n = 50$  cells) (see Supplementary Material).

**Localisation of STN neuronal activity in OCD and PD patients.** A total of 81 right and 57 left STN neurons and 123

**Table 1** Discharge frequency, pattern and oscillatory activity of subthalamic neurons in 12 OCD and 12 PD patients

	OCD patients (n = 138 cells)	PD patients (n = 173 cells)
Discharge frequency (Hz)	22.4 ± 13.7*	31.6 ± 13.5
Mean ISI (ms)	71.8 ± 63.5*	40.1 ± 26.3
Coefficient of variation	1.3 ± 0.4	1.2 ± 0.3
<i>Pattern of discharge: proportion of (%)</i>		
Regular	13%	8%
Irregular	18%	24%
Burst-type	69%	67%
Burst (S) index	9.8 ± 4.0*	8.3 ± 3.1
<i>Burst frequency (Hz)</i>		
Burst duration (ms)	823.5 ± 665.0*	340.3 ± 246.1
Intraburst frequency (Hz)	53.7 ± 52.6*	74.4 ± 34.7
Interburst interval (s)	5.2 ± 7.0*	2.9 ± 2.6
<i>Oscillatory activity</i>		
$\delta$ band (1–4 Hz)		
Peak frequency (Hz)	3.3 ± 0.5	3.1 ± 0.6
Peak power	1.52 ± 1.44	1.10 ± 1.23
$\theta$ band (4–8 Hz)		
Peak frequency (Hz)	5.5 ± 1.5	5.7 ± 1.2
Peak power	1.16 ± 1.26	1.10 ± 1.24
$\alpha$ band (8–12 Hz)		
Peak frequency (Hz)	9.9 ± 1.5	10.2 ± 1.2
Peak power	1.66 ± 1.92	2.05 ± 3.49
$\beta$ low (12–20 Hz)		
Peak frequency (Hz)	14.4 ± 2.8*	15.8 ± 2.5
Peak power	1.41 ± 2.57	1.59 ± 3.04
$\beta$ high (20–35 Hz)		
Peak frequency (Hz)	24.5 ± 3.3	23.2 ± 2.32
Peak power	1.24 ± 1.62	1.72 ± 3.06
$\gamma$ band (> 35 Hz)		
Peak frequency (Hz)	52.3 ± 14.1	56.3 ± 16.7
Peak power	0.35 ± 0.27	0.48 ± 0.25

Abbreviations: ISI, interspike interval; OCD, obsessive-compulsive disorder; PD, Parkinson's disease.

Results are expressed as mean ± s.d.

\* $P < 0.05$  when compared with PD patients.

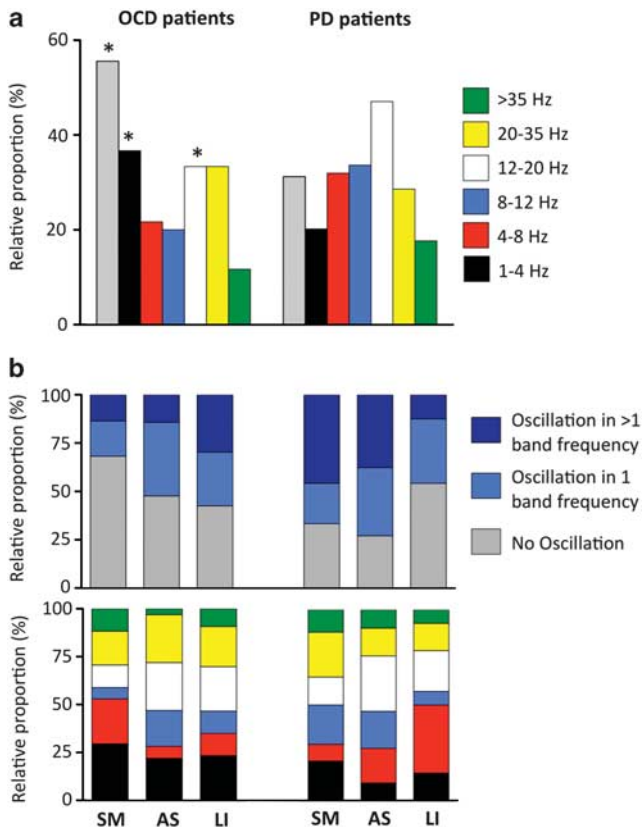
right and 50 left STN neurons were recorded in OCD and PD patients, respectively.

STN-OCD neurons were located more anteriorly than STN-PD neurons, with no difference in mean laterality or depth (Table S2 and Supplementary Material). The majority of recorded neurons were located in the associative STN in both groups (Figure 2a).

## Neuronal activity as a function of laterality and position within the STN.

No significant differences in neuronal activity were found between right and left STN neurons in OCD patients (not shown). However, the mean bursting index, number of spikes per burst and burst duration were significantly lower in the second ( $n = 36$  cells) vs the first ( $n = 102$  cells) STN operated ( $P < 0.04$ , not shown). In PD patients, compared with the first-side STN neurons (right STN,  $n = 123$  cells), second-side STN neurons (left STN,  $n = 50$  cells) exhibited less burst-type and more regular patterns (burst-type: 72 vs 54%; regular: 5 vs 14%,  $P < 0.04$ ) and lower mean power in  $\beta$  band oscillation ( $P < 0.02$ , not shown).

The mean discharge frequency of STN-OCD neurons was significantly lower compared with STN-PD neurons in all subdivisions of the STN (Figure 2b;  $P < 0.05$ ), with no



**Figure 1** Distribution of oscillatory activity of subthalamic neurons recorded in obsessive-compulsive disorder (OCD) and Parkinson's disease (PD) patients. (a) Relative proportion of the 138 and 173 subthalamic nucleus (STN) neurons showing oscillatory activity in OCD and PD patients. Asterisks indicate significant differences ( $P < 0.05$ ) between neurons of OCD and PD patients. (b) Subthalamic oscillatory activity as a function of subthalamic subdivisions in OCD and PD patients. Top histogram: relative proportion of neurons recorded in the sensorimotor (SM), associative (AS) and limbic (LI) subdivisions and showing none, one or more than one period of significant oscillatory activity. Bottom histogram: relative proportion of neurons recorded in the SM, AS and LI subdivisions and showing significant oscillatory activity in the  $\theta$ ,  $\alpha$ ,  $\beta$ -low,  $\beta$ -high and  $\gamma$  band frequencies.

interaction between the subjects (OCD vs PD) and the neuronal recording locations (motor vs associative vs limbic) (Figure 2b;  $P = 0.098$ ). A significant interaction between subjects and localisation was found for the mean ISI (interaction:  $P < 0.03$ ). The mean ISI of the STN-OCD neurons located in the motor part was significantly higher compared with the mean ISI of the STN-OCD neurons located in the associative and limbic parts in OCD patients and with all subdivisions for STN-PD neurons ( $P < 0.005$ , not shown).

No significant interaction between subjects and location was found either for the pattern of discharge or for the bursting index (not shown). However, the mean bursting index of STN-OCD neurons was significantly higher in the motor and associative parts compared with STN-PD neurons recorded in the same STN territories (Figure 2c;  $P < 0.008$  and  $P < 0.005$  for the motor and associative parts, respectively). No significant interaction between subjects and location was found for the burst characteristics (burst frequency, duration of burst, intraburst frequency—not shown). However, the

mean burst duration of STN-OCD neurons was significantly greater (not shown,  $P < 0.03$ ) and the mean intraburst frequency significantly lower in the motor part compared with STN-PD neurons recorded in the same STN territory (Figure 2d;  $P < 0.01$ ). A significant interaction between subjects and location was found for the interburst interval (interaction:  $P < 0.007$ ), which was higher in the motor part of the STN compared with the other subdivisions in OCD patients (not shown).

Over the whole frequency range, STN-OCD neurons showed more oscillation in the limbic part, whereas STN-PD neurons showed more oscillation in the motor part (Figure 1b;  $P < 0.04$ ). The frequency analysis showed more oscillation for STN-PN neurons in the  $\delta$  and  $\alpha$  bands in the motor compared with either the associative or limbic parts of the STN (interaction:  $P = 0.03$ ; Figure 1b). STN-OCD neurons showed more oscillation in the  $\alpha$  band in the limbic compared with other STN subdivisions (interaction:  $P < 0.001$ ; Figure 1b). No significant interaction between subjects and location was found for the presence of  $\beta$ -low,  $\beta$ -high or  $\gamma$  oscillatory activity (Figure 1b).

#### Subthalamic neuronal activity as a function of obsessions and compulsions.

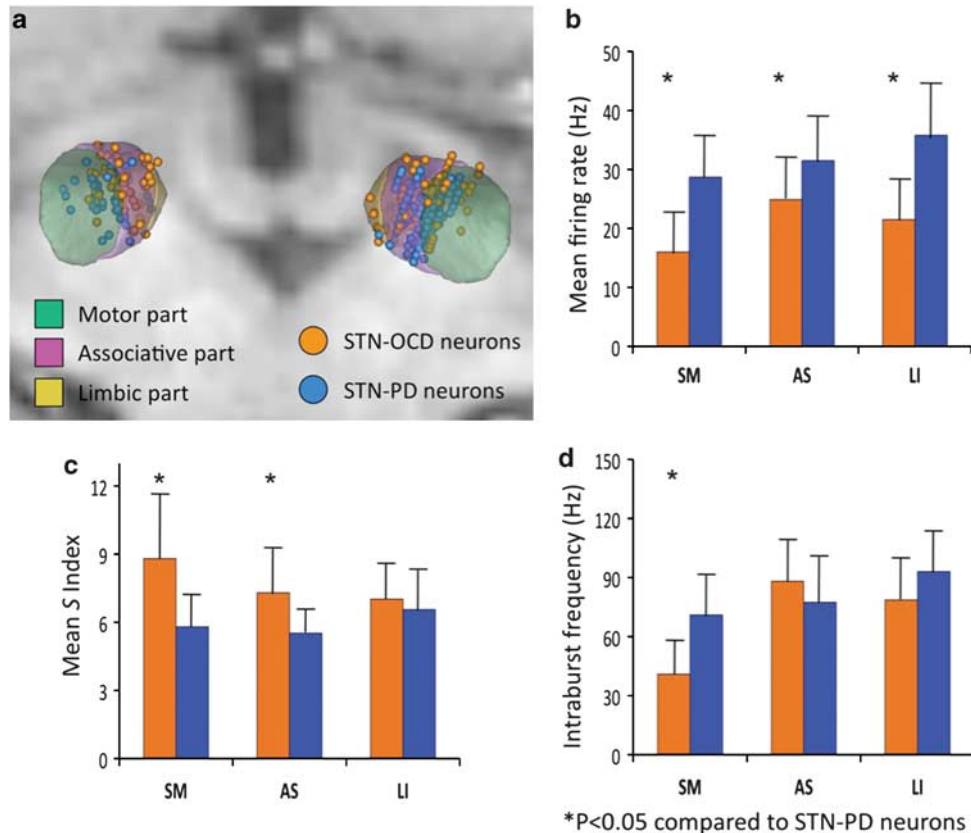
No significant relationship was found between the preoperative severity of OCD symptoms and mean discharge frequency, bursting index and burst frequency of STN-OCD neurons (Table 2). Obsessions and compulsions severity were significantly correlated with burst duration and mean intraburst frequency and interburst interval (Table 2).

No significant relationship was found between OCD severity (Y-BOCS, obsession and compulsion subscores) and the mean proportion, peak frequency and power in the  $\theta$ ,  $\beta$ -low,  $\beta$ -high and  $\gamma$  band frequencies. The Y-BOCS global and obsession subscores were correlated with the mean peak frequency in the  $\delta$  band. OCD severity was also significantly correlated with mean power in the  $\delta$  frequency band and with the mean proportion of STN neurons with  $\alpha$  oscillations and the mean  $\alpha$  band peak frequency.

In summary, the more severe the obsessions, the lower the burst duration and interburst interval, and the higher the mean discharge and intraburst frequencies, peak and power in the  $\delta$  band frequency. The more severe the compulsions, the higher the intraburst frequency and the proportion of STN neurons with  $\alpha$  oscillations with lower peak frequency.

#### STN neuronal activity as a function of the STN stimulation efficacy.

The improvement in Y-BOCS global and obsession subscores with STN stimulation was significantly correlated with the mean discharge frequency ( $r = 0.86$ ,  $P < 0.01$ ; Figure 3a), burst frequency ( $r = 0.69$ ,  $P < 0.04$ ; Figure 3b), intraburst frequency ( $r = 0.76$ ,  $P < 0.02$ ; Figure 3c) and the mean interburst interval ( $r = -0.96$ ,  $P < 0.004$ ; Figure 3d) of STN neurons. The improvement in compulsion subscores with STN stimulation was significantly correlated with the mean discharge frequency ( $r = 0.78$ ,  $P < 0.02$ ; Figure 3a) and the mean interburst interval ( $r = -0.81$ ,  $P < 0.02$ ). No significant correlation was found between the improvement in OCD symptoms (Y-BOCS global, obsession and compulsion subscores) and the



**Figure 2** Subthalamic neuronal activity as a function of subthalamic subdivisions in obsessive-compulsive disorder (OCD) and Parkinson's disease (PD) patients. (a) Localisation by means of the three-dimensional (3D) digitised distortable basal ganglia atlas of all the neurons recorded in OCD and PD patients. The motor part is represented in green, the associative part in pink and the limbic part in yellow in a 3D posterior view of both sides. Each sphere represents an individual neuron (orange for subthalamic nucleus (STN)-OCD neurons and blue for STN-PD neurons). (b–d) Mean firing rate, burst index and intraburst frequency plotted against the three subthalamic subdivisions (sensorimotor, SM; associative, AS; limbic, LI) for STN neurons recorded in OCD (orange bars) and PD (blue bars) patients. Asterisks indicate significant differences ( $P < 0.05$ ) between a given subdivision in OCD patients and the same subdivision in PD patients.

presence and characteristics (peak frequency and power) of STN oscillatory activities (not shown).

## Discussion

This study reports for the first time the relationship between spontaneous subthalamic neuronal activity and symptom severity in OCD patients and their response to STN stimulation. We found that the mean firing rate of subthalamic neurons was significantly lower in OCD patients than in PD patients, with a predominantly burst-type activity, less frequent but longer bursts, and a predominant oscillatory activity in the  $\delta$  band (Table 1 and Figures 1–3). In patients with the most severe OCD, STN neurons exhibited bursts with higher intraburst frequency and more oscillations in the low-frequency bands. In OCD patients with best postoperative clinical outcome with STN stimulation, STN neurons displayed higher mean discharge, burst and intraburst frequencies, but lower mean interburst interval. Neuronal activity differences observed between OCD and PD patients could result from the fact that neurons recorded in both groups were not similarly localised within the STN (Figure 2 and Supplementary Table S2). The fact that, to our knowledge, no data in the literature

have shown that STN neurons are morphologically and physiologically different in different subregions of the STN,<sup>48</sup> except for the presence of more passive movement-responsive neurons in the dorsolateral part of the STN (motor subregion),<sup>30,32</sup> does not favour this hypothesis, however.

The mean firing rate of STN-OCD neurons was close to that reported in normal monkeys,<sup>49</sup> essential tremor,<sup>34</sup> dystonic<sup>50</sup> and OCD patients.<sup>38</sup> No significant relationship was found between firing rate and OCD severity. In our PD patients, the higher mean firing rate of STN neurons was similar to that reported previously,<sup>31,32,34</sup> and thought to result from the disinhibition of the subthalamic activity secondary to the degeneration of nigral dopaminergic neurons.<sup>30,51</sup> These data suggest that in OCD patients symptoms are not related to an increase or decrease in the STN neuronal discharge.

Conversely, the firing patterns were similarly distributed between OCD and PD patients, with a predominant burst-type activity (Table 1). In PD patients, the increase in burst-type activity is thought to result from the degeneration of nigral dopaminergic neurons<sup>30,52,53</sup> and resolves with dopaminergic treatment.<sup>54</sup> In OCD patients, the increase in the burst-type activity, also reported previously,<sup>38</sup> could be related to the

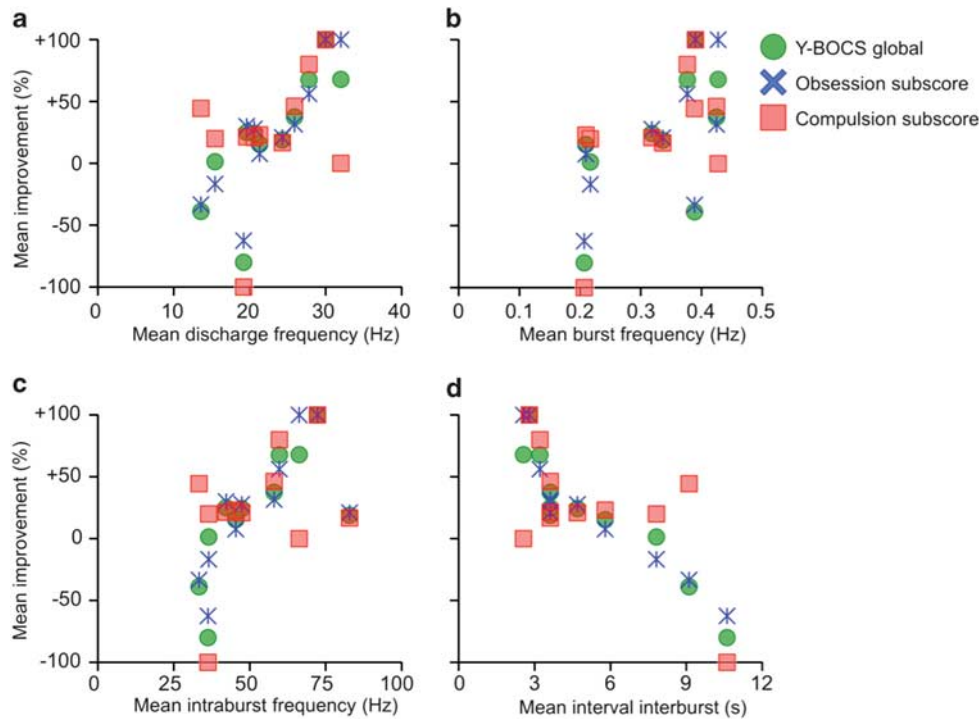
**Table 2** Relationship between severity of obsessions and compulsions and subthalamic neuronal activity in OCD patients

	<i>Y-BOCS</i>	<i>Obsessions</i>	<i>Compulsions</i>
Mean discharge frequency	0.46	0.54	0.31
<i>Burst discharges</i>			
Mean burst (S) index	-0.32	-0.40	-0.32
Mean burst frequency	0.02	0.14	-0.03
Mean burst duration	-0.46	<b>-0.60*</b>	-0.40
Mean intraburst frequency	<b>0.68*</b>	<b>0.78*</b>	<b>0.60*</b>
Mean interburst interval	-0.55	<b>-0.65*</b>	<b>-0.58*</b>
<i>δ band (1–4 Hz)</i>			
Mean proportion of neurons	0.11	-0.13	0.37
Mean peak frequency	<b>0.79*</b>	<b>0.81*</b>	-0.08
Mean power peak frequency	0.38	<b>0.61*</b>	-0.02
<i>θ band (4–8 Hz)</i>			
Mean proportion of neurons	-0.48	-0.50	-0.05
Mean peak frequency	-0.07	0.01	-0.11
Mean power peak frequency	0.17	0.10	0.38
<i>α band (8–12 Hz)</i>			
Mean proportion of neurons	-0.45	-0.45	<b>0.73*</b>
Mean peak frequency	-0.12	0.06	<b>-0.62*</b>
Mean power peak frequency	-0.26	0.02	<b>-0.85*</b>
<i>β-low band (12–20 Hz)</i>			
Mean proportion of neurons	-0.56	-0.04	-0.02
Mean peak frequency	0.02	-0.33	0.01
Mean power peak frequency	-0.26	0.34	-0.07
<i>β-high band (20–35 Hz)</i>			
Mean proportion of neurons	-0.50	-0.30	0.12
Mean peak frequency	-0.04	-0.10	-0.27
Mean power peak frequency	0.40	0.27	0.20
<i>γ band (&gt; 35 Hz)</i>			
Mean proportion of neurons	-0.22	0.03	-0.49
Mean peak frequency	-0.32	0.11	-0.01
Mean power peak frequency	-0.32	-0.34	-0.40

Abbreviations: OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale. Values are correlation coefficients (non-parametric Spearman's regression). Entries shown in bold \* $P < 0.05$  after univariate analysis.

intake of neuroleptic treatment resulting in a dopaminergic receptors blockage, as previously reported in animal studies.<sup>47</sup> However, the fact that the proportion of bursting STN neurons was similar in the four OCD patients who received neuroleptic treatment in the days before surgery compared with the four OCD patients without neuroleptic treatment (64 vs 74%) fails to support this hypothesis, as discussed previously.<sup>38</sup> Compared with STN-PD neurons, STN-OCD neurons have a higher bursting index with longer but less frequent bursts (Table 1), and OCD severity was significantly related to some burst characteristics (Table 2). Moreover, OCD improvements with STN stimulation were dependent on a number of burst characteristics, with a higher response for patients with lower interburst interval, but higher intraburst frequency (Figure 3). Some burst characteristics decreased in neurons recorded in the second STN side operated, whichever the side. This could reflect a lesioning effect provoked by the implantation of the first lead resulting in a microsubthalamotomy,<sup>55</sup> as previously reported with unilateral STN lesion<sup>56</sup> or stimulation,<sup>57</sup> and not a pathological marker *per se* as suggested previously.<sup>38</sup> With respect to the functional connectivity of the basal ganglia network, the increase in bursting activity in the STN observed in our OCD patients

could be related to a decrease in the inhibitory phasic input from the GPe, which has been proposed to scale its activity depending on the basal ganglia cortical input via the striatum.<sup>58</sup> It is known that the functional alterations in basal ganglia circuitry observed in OCD patients occur mainly along the ventral frontostriatal axis, with heightened activity in the orbitofrontal cortex and caudate nuclei.<sup>8,59</sup> Moreover, an increase in striatal neuronal activity with more irregular pattern has been observed in OCD patients experiencing obsessions.<sup>29</sup> Given the neuroanatomical connectivity of the basal ganglia, one might expect that an increase in striatal activity would result in an increase in inhibitory phasic input from the striatum to the GPe provoking a decrease of inhibitory GPe input to the STN, leading in turn to an increase in bursting activity.<sup>42,51,60</sup> Cortical activity may also influence STN neuronal activity through the so-called hyperdirect pathway.<sup>61</sup> Abnormal ventral STN and striatal neuronal activity could then result in a disruption of information processing at the level of basal ganglia output and the thalamocortical pathway in line with the abnormal activity observed at the cortical level in OCD patients, especially in the orbitofrontal and anterior cingulate cortices.<sup>62–65</sup> Finally, the improvement in OCD symptoms by modulation of the STN neuronal activity with high-frequency



**Figure 3** Improvement in obsessions and compulsions with subthalamic nucleus stimulation as a function of subthalamic neuronal activity in obsessive–compulsive disorder patients. The graphs represent the relationship between the improvement in the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) global (green circles), obsession (blue crosses) and compulsion (red squares) subscores and the mean (a) discharge frequency, (b) burst frequency, (c) intraburst frequency and (d) interburst interval.

stimulation may be related to changes in these cortical regions, as recently reported in the same group of patients.<sup>66</sup>

In our OCD patients, about half of the STN neurons displayed oscillatory activity (Figure 1). Conversely, in other non-parkinsonian patients, such as those suffering from essential tremor or dystonia, only 18 and 6.5% of STN neurons show oscillatory activity in the 3–30 Hz band frequency, respectively.<sup>34,50</sup> This observation suggests that oscillatory activity is augmented in the STN of OCD patients. A simple explanation could be that the high proportion of oscillations observed in STN-OCD neurons is related to neuroleptic treatment; however, the fact that oscillations tended to be less frequent in STN neurons of OCD patients undergoing neuroleptic treatment (42%) compared with STN neurons of OCD patients without (74%) fails to support this hypothesis. In PD patients, STN oscillation predominated in the STN motor part, as reported previously.<sup>34,67</sup> In the  $\delta$  and  $\alpha$  band frequencies, oscillations appear to be related to tremor,<sup>30,67</sup> and in the  $\beta$  band to movement inhibition and akinesia<sup>33,35,68,69</sup> and predictive of STN stimulation outcome.<sup>36,37</sup> In OCD patients,  $\delta$  and  $\alpha$  frequency band oscillation, which predominated in the STN associative and limbic parts, was significantly related to OCD symptom severity (Table 2). Our results are in line with reports obtained with EEG techniques in such patients who show an increase in low-frequency ( $\delta$ ,  $\theta$  and  $\alpha$ ) oscillation, in resting state activity, at both cortical (in frontal and frontotemporal regions)<sup>70–72</sup> and subcortical (in the thalamus and the striatum)<sup>2</sup> levels, and related to symptom severity.<sup>70,71,73</sup> Lastly, whereas  $\beta$  band

STN oscillatory activity has been identified as a marker of akinesia in PD patients,<sup>33,69</sup> about 35% of STN neurons exhibited  $\beta$  band oscillations in OCD patients (Figure 1). This result is in line with the report of a relationship between the severity of symptoms and  $\beta$  band power in frontal cortical regions in untreated OCD patients.<sup>71</sup> An increase in the  $\beta$  power frequency has also been identified as one of the bioelectrical markers in various anxious states,<sup>74,75</sup> and the question remains as to whether oscillations in the  $\beta$  band activity observed in the STN of OCD patients could be related to anxiety. Finally, the increase in low frequencies observed in the STN in our OCD patients, predominantly in the limbic portion, is consistent with changes reported at the limbic cortical level and support the hypothesis of an involvement of cortico-subcortical functional connections in this disorder.<sup>1</sup>

Significant relationships between STN neuronal activities, which resembled parkinsonian STN neuronal activity (higher firing rate, burst and intraburst frequencies, and lower interburst interval), and STN stimulation efficacy were found in our OCD patients. This could mean that the main dysfunction in OCD patients improved by STN stimulation is one of the nigrostriatal dopaminergic system. However, this hypothesis seems unlikely as these neuronal activities were not identified as being predictive of the STN stimulation efficacy in PD patients.<sup>36,37</sup> This result would rather suggest that OCD patients with a more disturbed STN neuronal activity are better candidates for this surgical treatment. The electrophysiological effects of high-frequency STN stimulation are not fully understood; however, a decrease in neuronal

activity in the STN with retrograde and anterograde activations of input (cortex and GPe) and output (GPI and SNr) structures has been reported in patients and animal models of PD.<sup>43,47,57,76–81</sup> Finally, the therapeutic effect of high-frequency stimulation of the STN is thought to result from complex changes in the neuronal activity of the entire cortico-basal ganglia circuitry, leading to a disruption of the pathological neuronal activity.

In conclusion, STN neurons in OCD patients display increased bursting activity with a high proportion of oscillatory activity, in relation to symptom severity and response to STN stimulation. In line with the accepted role of the STN in decision making and action sequencing,<sup>58,82</sup> one might expect that dysfunction of this subcortical region could result in the setting of an inappropriate (increase or decrease) decision threshold in the context of reinforcement and decision conflicts. Consequently, an increase in this threshold could result, at least in part, in an inability to make a decision or a difficulty in terminating an action sequence, thereby resulting in obsessions and compulsions. Lastly, the fact that some STN neuronal activity characteristics are predictive of the STN stimulation-induced improvement suggests that some patients may be considered as good candidates for this treatment regarding the predominant involvement of the STN in the occurrence of their symptoms. This hypothesis will be explored in future studies.

### Conflict of interest

The authors declare no conflict of interest.

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**Author contributions:** Dr Welter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (<http://www.nature.com/tp>)

## Appendix

Members of the French STOC Study Group were as follows: Trial Coordination: L. Mallet (Centre d'Investigation Clinique, CHU Pitié-Salpêtrière, Paris). Steering Committee: Y. Agid, B. Aouizerate, C. Arbus, T. Bougerol, P. Damier, D. Fontaine, J.L. Houeto, M.O. Krebs, J.J. Lemaire, L. Mallet, B. Millet, P. Pollak. Logistics and Monitoring: D. Hourton, S. Aprelon, C. Jourdain (Assistance Publique-Hôpitaux de Paris, Direction de la Recherche Clinique, Paris). Coordinating teams: Anatomy: E. Bardinnet, J. Yelnik; Electrophysiology: P. Burbaud, M.L. Welter, A.H. Clair; Neuropsychology: C. Czernecki, M. Vérin. Data Management and Statistical Analysis: S. Tézenas du Montcel, D. Madar (Unité de Recherche Clinique, CHU Pitié-Salpêtrière, Paris). Writing Committee: L. Mallet, A. Pelissolo, S. Tezenas du Montcel, M.L. Welter, J. Yelnik. Centers (Principal Investigator: PI, Co-investigators: psychiatrist (P), neurosurgeon (N), neurologist (NI), electrophysiologist (E), radiologist (R), neuropsychologist (Np)): Coordinating Center, Paris Pitié-Salpêtrière Hospital: L. Mallet (PI, P), A. Pelissolo (PI, P), Y. Agid (NI), P. Cornu (N), S. Navarro (N), M.L. Welter (E, NI), A. Hartmann (NI), B. Pidoux (E), D. Grabli (NI), V. Czernecki (Np), D. Dormont (R), D. Galanaud (R), J. Yelnik, E. Bardinnet,

C. Béhar (Np), Y. Worbe (NI), A.H. Clair (Np), B. Moutaud, CIC staff and nurses; Bordeaux: B. Aouizerate (PI, P), P. Burbaud (E), E. Cuny (N), D. Guehl (NI); Clermont-Ferrand: P.M. Llorca (PI, P), I Chéreau (P), J.J. Lemaire (N), F. Durif (NI), P. Derost (NI), J. Coste (E); J. Gabrillargues, M. Barget, I. de Chazeron; Grenoble: T. Bougerol (PI, P), M. Polosan (P), A.L. Benabid (N), S. Chabardès (N), E. Seigneuret (N), P. Krack (NI), P. Pollak (NI), C. Ardouin (Np), J.F. Le Bas (R); Nantes: P. Damier (PI, NI), Y. Lajat (N), S. Raoul (N); Nice: V. Mattei (PI, P), D. Fontaine (N), M. Borg (NI), P. Paquis (NI), E. Michel (Np), P. Robert (P); E. Michel, F. Papetti (P); Paris Sainte-Anne Hospital: N. Baup (PI, P), B. Devaux (N), M.O. Krebs (P), C. Oppenheimer (R); J.P. Olié (P), D. Ranoux (NI), M. Chayet (Np); Poitiers: J.L. Houeto (PI, NI), N. Jaafari (P), B. Bataille (N), V. Mesnage (NI); R. Gil (NI), V. Audouin (Np), J.L. Senon (P); Rennes: B. Millet (PI, P), M. Vérin (NI), D. Drapier (P), P. Sauleau (E); S. Drapier (NI); Toulouse: C. Arbus (PI, P), Y. Lazorthe (N), P. Chaynes (N), N. Fabre (NI), M. Simonetta (E), L. Schmitt (P), J.A. Lotterie (R), C. Camassel. Sponsor: N. Best (Assistance Publique-Hôpitaux de Paris, Direction de la Recherche Clinique, Paris). Independent Safety Committee: J.C. Aussilloux, S. Blond, J. Feingold, D. Sicard. Independent Selection Committee: J. Adès, J. Cottraux, M. Goudemand.