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Neuronal activity correlated with checking behaviour in the subthalamic nucleus of patients with obsessive–compulsive disorder

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Doubt, and its behavioural correlate, checking, is a normal phenomenon of human cognition that is dramatically exacerbated in obsessive–compulsive disorder. We recently showed that deep brain stimulation in the associative-limbic area of the subthalamic nucleus, a central core of the basal ganglia, improved obsessive–compulsive disorder. To understand the physiological bases of symptoms in such patients, we recorded the activity of individual neurons in the therapeutic target during surgery while subjects performed a cognitive task that gave them the possibility of unrestricted repetitive checking after they had made a choice. We postulated that the activity of neurons in this region could be influenced by doubt and checking behaviour. Among the 63/87 task-related neurons recorded in 10 patients, 60% responded to various combinations of instructions, delay, movement or feedback, thus highlighting their role in the integration of different types of information. In addition, task-related activity directed towards decision-making increased during trials with checking in comparison with those without checking. These results suggest that the associative-limbic subthalamic nucleus plays a role in doubt-related repetitive thoughts. Overall, our results not only provide new insight into the role of the subthalamic nucleus in human cognition but also support the fact that subthalamic nucleus modulation by deep brain stimulation reduced compulsive behaviour in patients with obsessive–compulsive disorder.

Keywords: OCD pathophysiology; checking task; subthalamic nucleus; doubt-related neuronal activity; deep brain stimulation in OCD

Abbreviations: ROC = receiver operating characteristic; STN = subthalamic nucleus

Introduction

The subthalamic nucleus (STN) is known to play a critical role in the regulation of motor behaviour and represents the most frequently used therapeutic target for deep brain stimulation in Parkinson's disease (Bergman *et al*., 1990; Bar-Gad *et al*., 2003; Benabid *et al*., 2009). However, evidence from experimental studies in rodents (Baunez and Robbins, 1997; Baunez *et al*., 2002, 2007) and monkeys (Baup *et al*., 2008; Karachi *et al*., 2009), as well as from clinical observations in humans (Berney *et al*., 2002; Mallet *et al*., 2002; Kuhn *et al*., 2005; Houeto *et al*., 2006; Brucke *et al*., 2007; Frank *et al*., 2007; Kempf *et al*., 2007; Mallet *et al*., 2007, 2008), suggests that the STN is also involved in the processing of cognitive and emotional information. This point of view is supported by the anatomical description of both associative and limbic domains within the STN (Parent and Hazrati, 1995; Berney *et al*., 2002; Mallet *et al*., 2002; Hamani *et al*., 2004; Karachi *et al*., 2005; Kuhn *et al*., 2005; Houeto *et al*., 2006; Brucke *et al*., 2007; Frank *et al*., 2007; Kempf *et al*., 2007; Mallet *et al*., 2007, 2008). The role of the STN in the underlying pathological processes, and more generally in the processing of non-motor information, remains largely unknown. So far, few recordings of individual neuron activity have been made in the STN during behavioural tasks either in non-human primates (Georgopoulos *et al*., 1983; Matsumura *et al*., 1992; Wichmann *et al*., 1994; Isoda and Hikosaka, 2008) or in human patients (Fawcett *et al*., 2005; Williams *et al*., 2005; Gale *et al*., 2009; Zaghloul *et al*., 2012).

We previously noted that obsessive–compulsive disorder symptoms were improved in patients with Parkinson's disease operated for their motor fluctuations when the electrodes were positioned in the associative limbic part of the STN (Mallet *et al*., 2002). These observations were confirmed by the fact that stimulation of the same area in the monkey suppressed motor stereotypes (Baup *et al*., 2008) induced by pharmacological manipulations of the external pallidum (Grabli *et al*., 2004). On this basis, a double-blind multicentre study targeting the associative-limbic part of the STN was proposed to patients with medically resistant obsessive–compulsive disorder. These data confirmed that deep brain stimulation applied to this target reduced obsessive–compulsive disorder symptoms (Mallet *et al*., 2008). Although the reason for this improvement remained unclear, recent electrophysiological data suggest a dysfunctioning of the STN in obsessive–compulsive disorder (Piallat *et al*., 2011; Welter *et al*., 2011). Because surgery in these patients makes it possible to record neuronal activity perioperatively in the therapeutic target, we took advantage of this opportunity to test two hypotheses: (i) individual neurons located in the associative-limbic region of the STN might be influenced by cognitive and emotional information; and (ii) doubt revealed by checking behaviour might modify their activity.

We used a cognitive task based on a delayed matching-to-sample visuospatial paradigm that allowed unrestricted repetitive checking after the subjects had made a choice. The cognitive

task was previously found to discriminate checking and choice behavioural patterns in patients with obsessive–compulsive disorder and normal healthy volunteers, providing an objective quantification of doubt and checking (Rotge *et al*., 2008*a*). Indeed, pathological doubt, the core of the obsessional process, is related to a permanent error perception in the representation of one's actions and compulsive checking, a behavioural strategy used to cope with obsession-related anxiety (Aouizerate *et al*., 2004). This phenomenological view suggests that cognitive processes such as error detection and doubt monitoring may be altered in obsessive–compulsive disorder (Schwartz, 1998) owing to the disruption of the cortico–subcortical networks passing through the orbitofrontal, anterior cingulate cortices and STN (Rauch *et al*., 1994; Rotge *et al*., 2008*b*).

Materials and methods

Patients

All the patients included in the clinical study exhibited severe and refractory obsessive–compulsive disorder with checking behaviour in their everyday life as attested by the Yale–Brown Obsessive–Compulsive Scale checklist (Mallet *et al*., 2008). They gave informed consent and were enrolled for surgery according to strict inclusion criteria. The study had ethics approval from the institution (Programme Hospitalier de la Recherche Clinique Assistance Publique–Hôpitaux de Paris—AOM 03141). The initial clinical study included 17 patients operated with bilateral implantation of electrodes for chronic stimulation in the associative-limbic part of the STN [mean Yale–Brown Obsessive–Compulsive Scale score 32.3, standard deviation (SD) = 3.0 before surgery and 19.4 (SD = 8.5) after 3 months of STN chronic stimulation] (Mallet *et al*., 2008). In the present article, we analysed the electrophysiological data obtained in a sample of 10 patients in whom the recordings were performed in good conditions (no artefact, successful completion of the task with optimal awareness during surgery, stable electrophysiological recordings). The clinical features of these 10 patients are given in Table 1. Only one patient (Patient 16) did not exhibit checking symptoms but experienced verbal repetitions and magic thoughts. Among the nine remaining patients, checking was the first complaint for four, the second complaint for two and the third complaint for two, the final patient experiencing checking symptoms but not in the main complaints. Their mean Yale–Brown Obsessive–Compulsive Scale score was 32.0 (SD = 2.7) before surgery and 21.1 (SD = 7.1) after 3 months of STN chronic stimulation.

Task design

The behavioural task is based on a delayed matching-to-sample paradigm with a verification option, as shown in Fig. 1A. Patients had to match two images presented sequentially (presentation of the first image = study phase; presentation of the second image = matching phase). The patient's right hand was positioned on a panel comprising three buttons (Fig. 1B). This panel could not be seen, and thus movements were performed without visual control. The central button corresponded to the resting position. Two other buttons (green on the left and red on the right) were used to select one of the two possible responses during the matching and the decision phases. Then, the patients had to return to the resting position (central button, i.e. return movement) to reach the next phase. After the matching phase, during the decision phase, the opportunity was given to: (i) go back to the study phase by pressing the left button, which corresponds to checking behaviour or (ii) confirm their answer by pressing

Table 1 Clinical features of the 10 patients with obsessive–compulsive disorder enrolled in the present study

Patient number	Sex	Age (years)	Age of onset (years)	YBOCS	YBOCS obsession	YBOCS compulsion	Major depressive disorder	GAF	CGI	MADRS	BAS	Current medication	% YBOCS decrease at 3 months of stimulation
2	F	37	8	34	18	16	Past	35	7	14	12	CMI Li T3	21
3	M	56	10	31	16	15	Past	35	6	25	16	SNRI TC ANL NL Li	68
6	M	50	27	27	13	14		30	5	12	9	CMI ß- V NL BZ	7
7	M	34	8	35	18	17	Past, current	25	7	8	18		14
10	M	53	11	35	18	17		21	6	6	12	SRI ANL BZ	20
11	F	45	6	30	12	18		30	6	4	12	SRI Bs ANL BZ	40
12	M	50	14	35	20	15		35	7	7	2	SRI Bs ANL BZ	43
13	F	47	17	31	13	18		30	6	5	6	SRI CMI Bs BZ	29
16	F	43	11	32	14	18		32	6	18	21	SRI ANL BZ	72
17	F	42	17	30	15	15	Past	36	5	15	26	SRI SNRI V NL BZ	27

The Yale–Brown Obsessive–Compulsive Scale (YBOCS) (Goodman *et al*., 1989) score ranges from 0 to 40 with higher scores indicating worse function. The two YBOCS subscores range from 0 to 20. The presence of major depressive disorder was assessed by the Mini-International Neuropsychiatric Inventory (MINI 5.0.0.) (Sheehan *et al*., 1998). 'Past' = one or more episodes during lifetime, 'current' = an episode present at inclusion.
The Global Assessment of Functioning (GAF) score ranges from 1 to 90 with higher scores indicating more normal global functional status (APA, 2000).
The Clinical Global Impression (CGI) score ranges from 1 to 7 with higher scores indicating the severity of the disease (Guy, 1976).
The Montgomery and Asberg Depression Scale (MADRS) (Montgomery and Asberg, 1979) scores range from 0 to 60 with higher scores indicating the severity of depressive symptoms.
The Brief Anxiety Scale (BAS) (Tyrer *et al*., 1984) scores range from 0 to 60 with higher scores indicating more severe anxiety symptoms.
The percentage of decrease in Yale–Brown Obsessive–Compulsive Scale scores for each patient of the study is calculated at the end of a 3-month stimulation period during the crossover of the seminal study (Mallet *et al*., 2008).
ANL = atypical neuroleptic; ß- = ß-blocker; Bs = buspirone; BZ = benzodiazepine; CL = clonazepam; CMI = clomipramine; Li = lithium; NL = neuroleptic; SNRI = serotonin and norepinephrine reuptake inhibitor; SRI = serotonin reuptake inhibitor; T3 = thyroid hormone; TC = tetracyclic; V = valproate.

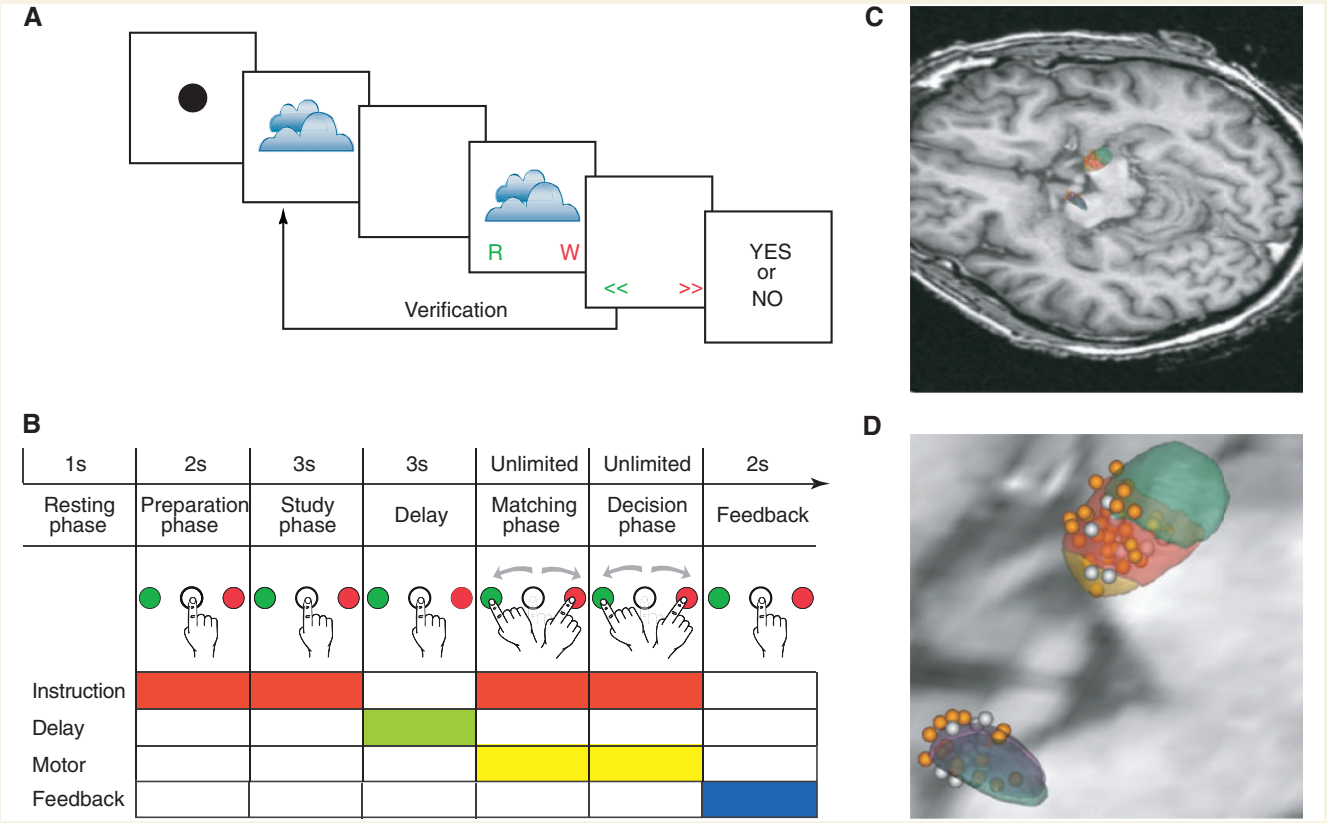

Figure 1 Experimental task and neuronal localization methods. (**A**) Sequence of the different displays presented during the task. (**B**) Different phases of the task; duration of each phase at the *top*; hand position and movement in the *middle*, colour code for event-related changes (instruction, delay, movement, feedback) at the *bottom*. (**C**) Location of the STN determined from the 3D deformable histological atlas. (**D**) Enlarged view of the STN showing the location of the task-related (orange) and unrelated (grey) recording sites within the functional subdivisions of the STN: motor (green), associative (red) and limbic (yellow).

the right button. After confirmation, feedback was provided ('Yes' for success and 'No' for error). Participants were instructed to respond 'as efficiently and correctly as possible'. Response accuracy, number of checkings and choice reaction time were monitored throughout the 20 test trials. To ensure that patients were familiar with the procedure, the task was explained in detail, and they completed 10 successive training trials before the beginning of neuronal recording, being secondarily completed with the 20 test trials. The image sets were selected from the open clipart library of Microsoft® PowerPoint® 2001 for Macintosh (examples of images are given in Supplementary Fig. 1).

Electrophysiological recordings

The obsessive–compulsive disorder target in the STN was preoperatively targeted 2 mm anterior and 1 mm medial to the Parkinson's disease target as identified in stereotactic MRI (Bejjani *et al*., 2000). In this frontal section, the dorsoventral position was adjusted so as to be at the boundary of STN associative and limbic territories (Supplementary Fig. 2). This targeting relies on clinical observations in human (Mallet *et al*., 2002) and experimental data in monkeys (Grabli *et al*., 2004; Baup *et al*., 2008; Karachi *et al*., 2009). Intraoperative microrecordings were performed under local anaesthesia in patients fully awake without medication. This procedure was maintained in parallel to atlas-based target localization because it both increases the accuracy of electrode placement to the patient's benefit (i.e. verification that the more anterior and medial trajectory was definitely within the STN) and provides irreplaceable data about neuronal activities in the human STN. Extracellular neuronal activity was recorded with three to five parallel tungsten microelectrodes (including a central tungsten recording microelectrode: diameter, 25 µm; impedance, 1 MΩ; and an external tube for macrostimulation; FHC Instruments). Electrodes were lowered stereotactically to 5 mm above the predetermined target, along five parallel trajectories using a microdrive (Natus). Four of the leads were arranged, at a distance of 2 mm, around a central lead positioned according to the stereotactic coordinates, permitting stimulation and recording from the central, anterior, posterior, medial and lateral parts of the STN. Signals were amplified ($\times 10$), filtered (300 Hz–3 kHz), monitored acoustically and recorded digitally using a Leadpoint (Natus) or an Alpha-Omega system (Alpha-Omega). Neuronal activity was stored when stable single unit activity was encountered in the STN (Welter *et al*., 2011). Great care was taken during recording to ensure that a superimposable spike was obtained throughout the whole recording session (Supplementary Fig. 3). To avoid any approach that would have biased the sample tested towards a particular type of cell, no attempt was made on-line to study the correlation between neuronal activity and task events. Spikes were recorded during task completion, event markers being digitized on-line (2 kHz), in parallel with the storage of neuronal activity.

Spike train analysis

Spikes were exported off-line as compatible files (.txt) to a PowerLab system (AD Instruments). Sorting was performed *post hoc* using a Chart 5.0 soft (AD instruments) and single unit activity analysed using Neuroexplorer software (Plexon Inc) and the Matlab 7.1 package (The MathWorks). To identify task-related changes, spike trains were analysed during epochs centred on task events (±500 ms). Nine different events were considered (Fig. 1B): (i) appearance of the black target spot corresponding to the onset of the preparation phase; (ii) first image presentation (study phase); (iii) onset of the delay (beginning with the disappearance of the first picture); (iv) second image presentation (beginning of the matching phase); (v) onset of the choice movement during the matching phase; (vi) end of the first movement (followed by the return movement to the resting position); (vii) appearance of the arrows; (viii) onset of the movement to confirm or verify the previous choice during the decision phase; and (ix) onset of feedback. Neuronal firing rate during these time-windows was compared with that measured during the 1500 ms preceding appearance of the target spot (reference period; Fig. 1A). If activity during a given epoch differed significantly from that recorded during the resting phase (Wilcoxon paired-ranks test, $P < 0.05$) for $\geqslant$100 ms, it was defined as task-related, and the corresponding neuron was identified as a task-related neuron (Fujii and Graybiel, 2003). Neurons were categorized as unimodal when changes occurred in relation with only one type of event (e.g. visual information, but not other events). They were categorized as multimodal when neurons responded to at least two types of events (e.g. both visual information and movement execution). A spike density function was generated by convolving spike trains with a combination of growth and decay exponential functions (Kernel function) that resembles a postsynaptic potential (Hanes *et al*., 1995; Ito *et al*., 2003).

$$r_{est.}(t) = \int_{-\infty}^{+\infty} A(\tau)\rho(t-\tau)d\tau$$

with $A(\tau) = \left(1 - \exp(-t/\tau_d)\right).\left(\exp(-t/\tau_d)\right)$; $(\tau_g = 1, \tau_d = 20)$

τ_g = time constant for the growth phase;

τ_d = time constant for the decay phase.

To estimate the point at which a significant change in discharge frequency occurred with respect to different types of events on a large sample of trials, we considered three situations: (i) response to visual instructions, i.e. first, second image; (ii) movement onset (in the matching and in the decision phases; and (iii) feedback appearance. In this situation, the reference period was calculated just before task event (Supplementary Fig. 5). The change point in neuronal activity corresponded to the point where the signal curve cuts the ±2 SD line for at least 50 ms.

A population analysis was performed to compare firing rate between different situations: (i) on-going trials with or without checking, depending on checking or not during the previous trial and (ii) on-going trials after a success or an error, depending on verification or not during the previous trial, depending on success or error during the previous trial. All trials for all task-related neurons were pooled to form a single ensemble. The firing rates were normalized, as the firing rate divided by the firing rate during the reference period. The mean discharge frequency for the population was then calculated. Curves were smoothed with a moving average window of 10 ms. For each time bin, a Wilcoxon rank sum ($P < 0.05$) was performed to compare the different conditions.

To study the predictability of neuronal activity changes for checking behaviour, we performed a receiver operating characteristic (ROC) curves analysis using the mean normalized discharge frequency of discharge based on population analysis data (Lasko *et al*., 2005). A ROC curve was built for each event of interest using PASW Statistics software (Version 18.0.3, September 2010). To construct the ROC curve, we separated the average firing rate according to the 'checking' or 'no checking' status of the trial. For each ROC curve, we determined a cut-off frequency discrimination value of 1.0, corresponding to baseline frequency. Based on this threshold, we calculated the predictivity for a checking trial. The latter was defined as the ratio of the true positive (checking trials detected as superior to the threshold) on the true and false positive (non-checking trials detected as superior to the threshold). The predictability for a non-checking trial for a given firing frequency was calculated in the same way but using negative values (true negative on true and false negative).

Location of recorded neurons

The location of each recorded neuron (x = lateral, y = anterior, z = depth) was carefully noted during surgery and then plotted on anterior commissure–posterior commissure (AC–PC) stereotactic coordinates of each patient. During surgery, the depth of the microrecording electrodes was systematically noted for each single unit recorded. The trajectory of each recording electrode was precisely localized with reference to the AC–PC reference system by identifying both the stereotactic frame and the AC–PC landmarks in the preoperative MRI. The x, y, z coordinates of each single unit recording were localized precisely within the AC–PC system (Supplementary Fig. 4). Then, its localization within the functional subdivisions of the STN was determined by using a 3D deformable histological atlas (Yelnik *et al*., 2007), which includes basal ganglia regions and their motor, associative and limbic functional subdivisions, and which was adjusted to the individual brain geometry of each patient (Bardinet *et al*., 2009). As atlas/patient registration was made on the preoperative MRI, the absence of a preoperative brain shift that would displace significantly the region of the STN was verified on postoperative MRI. Atlas-based localization of single unit neuronal recordings was performed independently and blindly from the electrophysiological analysis.

Results

Checking behaviour improves performance

Behavioural data were analysed on a series of 31 sessions including 578 trials during which we presented 282 similar and 296 different images between the study and the choice phases. During these sessions, 207 checkings (160 trials with verification) were performed. The mean number of correct responses was 11.9 [Standard error of the mean (SEM) = 0.693, 64.1%] for the 20 successive samples presented in each session (Supplementary Fig. 4A). The mean number of checkings over all the patients was 6.7 (SEM = 1.7); there was no difference in the number of checkings ($P = 0.153$, paired t-test) when similar images (mean 3.0; SEM = 0.51) and different images (mean 3.7; SEM = 0.693) were presented. The type of image did not influence the rate of checking (one-way ANOVA, $F = 2.02$, $P = 0.118$), and no difference was found between the four series of images. All subjects, except one, performed the 20 trials of each session. We analysed

subjects' performances taking into account whether they checked during the session. In trials without checking, the percentage of success was 64.2% (268/418). The virtual performance of subjects during the first trial in trials with checking was statistically different (45% 72/160; *t*-test, $P < 0.001$), suggesting that checking improved performance. Further, we first analysed the impact of checking on each subject's performance (Supplementary Fig. 4B). When the subject checked, there was a performance improvement (in term of number of correct responses) between the first (72/160) and the last (103/160) choice ($\chi^2 = 11.8$, $P < 0.001$, chi-square). Second, we compared the impact of changing the initial choice on the subjects' performance (Supplementary Fig. 4C). This occurred in 103/160 trials (64.3%), the number of changes leading to correct responses (67/103) was higher ($\chi^2 = 33.5$, $P < 0.001$, chi-square) than the number of changes leading to incorrect responses (36/103). Thus, checking and changes in strategy improved performance.

Behavioural response time (i.e. time between visual information and motor response during the matching and decision phases) was shorter when the patient decided not to check (versus deciding to check) ($P < 0.001$) (Supplementary Fig. 4D), whereas movement times (i.e. time to complete movement) was similar during the different phases (Supplementary Fig. 4D).

Individual neurons in the associative-limbic subthalamic nucleus process context-dependent multimodal information

The recording of single unit activity during task completion was performed in 87 individual STN neurons isolated and recorded continuously over the duration of the task. Sixty-three (72%) were task-related, i.e. they showed a significant change in firing rate for $\geqslant 1$ task events. The mean number of task-related neurons recorded by patients was 6.3 ± 2.9 (range 3–12). Task-related neurons were located mainly in the associative (72%) and more rarely in the limbic (16%) and motor (12%) domains of the STN (Fig. 1D).

In the associative-limbic part of the STN, activity changes of individual neurons occurred in relation to all classes of events (Fig. 2A). They could be related to movement execution (73%), visual instruction (60%), delay (24%) and feedback (37%) (Fig. 2B). They were observed both in the left and right STN, and movement was performed with the right hand (Supplementary Fig. 5). Study of the timing of neuronal changes revealed that instruction-related changes occurred 200–300 ms after visual signals (Supplementary Fig. 6A), whereas movement-related changes preceded movement onset by ~500 ms (Supplementary Fig. 6B). Feedback-related changes frequently took the form of an inhibition with a mean duration of 430 ms with a decrease in firing rate much below that observed during the reference period (Supplementary Fig. 6C). However, an increased firing rate could also be observed, and for some cells, inhibition during feedback could be the only neuronal change occurring during the task. The location of recorded neurons revealed that neurons responding to visual information, movement or feedback

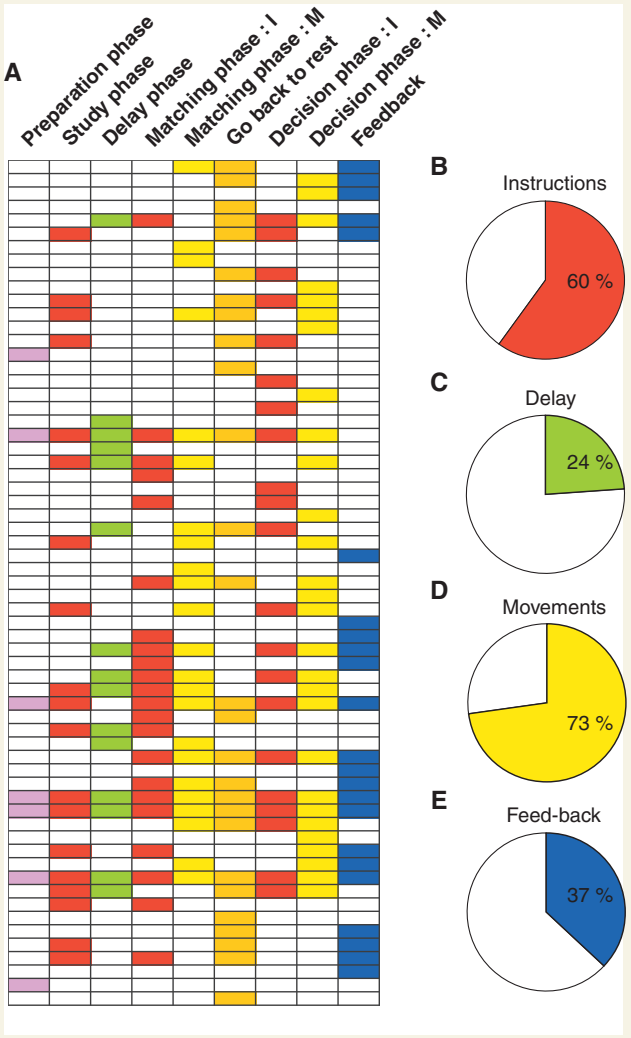

Figure 2 Task-event related changes in the associative STN. (**A**) Event-related changes in the 63 task-related neurons. Each line corresponds to one neuron. Significant neuronal changes with respect to the reference period are illustrated for the nine task events: (i) preparation phase: black target spot during the reference period (purple area); (ii) study phase: instructions during the study phase (red area); (iii) delay (green area); (iv) matching phase I: instructions during the choice period (red area); (v) matching phase M: movement during the matching phase (yellow area); (vi) return to rest: return movement to the resting position (orange area); (vii) decision phase I: instruction during the decision phase (red area); (viii) decision phase M: movement during the decision phase (yellow area); and (ix) feedback (blue area). Responses can be multimodal (in relation to several events, e.g. line 5) or unimodal (in relation to only one event, e.g. line 7). (**B–E**) Percentage of instruction-related changes (**B**), delay-related changes (**C**) movement-related changes (**D**) and feedback-related changes (**E**).

were grouped in the anteromedial part of the STN corresponding to the associative-limbic region (Supplementary Fig. 6G–I).

Although unimodal neuronal changes were observed (25/63, i.e. 39.7% of task-related neurons), neuronal changes were frequently multimodal (38/63, i.e. 60.3% of task-related neurons) occurring for different types of events (visual instruction, delay, movement execution, feedback) (Fig. 2A). This multimodal processing is illustrated in Fig. 3A for a representative neuron that exhibited a significant firing rate increase in relation to instructions at the study phase (Fig. 3A), movement execution during the matching phase (Fig. 3C), return movement (Fig. 3D), checking phase (Fig. 3E) and inhibition during the feedback (Fig. 3E). This neuron had a directional specificity, as changes in discharge frequency occurred before movement directed to the right button only (Fig. 3C2 versus C1). No verification was performed during this session (Fig. 3E).

Another critical point was that event-related changes were frequently context dependent. For instance, instruction-related changes could occur only for the first or the second image (Fig. 2A and 3), mediating a response to specific visual information. Indeed, response to the first image might be related to visual exploration and memory encoding, whereas response to the second image also presumes a comparison of both images within working memory. Likewise, movement-related changes of the same neuron could be different for movement in the matching phase and movement in the decision phase (Fig. 2A). For instance, the neuron shown in Fig. 4 had a similar discharge frequency for the two movement directions during the matching phase, i.e. green to the left and red to the right (Fig. 4C1 and C2), but its firing rate increased more strongly during the decision phase when the patient confirmed his response (Fig. 4E2) than when he checked (Fig. 4E1). Overall, the activity of this neuron was modulated by goal-directed movements with cognitive demand.

Subthalamic nucleus neuronal activity is influenced by checking behaviour

As stated above, checking behaviour frequently occurred during task completion. We investigated whether this behaviour was associated with specific neuronal changes and observed that individual neurons had different discharge frequencies depending on whether the subject went on to check during a given trial. The population analysis performed on all task-related neurons showed that the discharge frequency after visual instructions was higher if the subject went on to check (Fig. 5A and B, green line) than when he did not (Fig. 5A and B, red line). A similar result was found before movement execution (Fig. 5C and D). However, the difference between the two types of trials disappeared when the subject was engaged in motor aspects of behaviour (200 ms before movement onset, the red and the green lines tended to join, Fig. 5C and D). No difference was observed during the reference period, the preparation phase and after feedback. Thus, checking behaviour, which improved performance for a given trial, was associated with a higher STN firing rate.

Furthermore, we investigated the impact of checking behaviour during one trial on the discharge frequency of STN neurons during the next trial. When the subject checked in a given trial ('high doubt' condition, Fig. 6A and C), STN activity during the study phase (Fig. 6A) and decision phase (Fig. 6C) was not different between the two situations (solid line for a previous trial with checking, dotted line for a previous trial without checking). On the other hand, when the subject did not check during the current trial ('low doubt condition', Fig. 6B and D), checking during the previous trial increased STN discharge frequency between the matching and decision phases (Fig. 6D).

To test whether a given neuronal discharge frequency was predictive of subsequent behaviour, we performed a ROC analysis (Supplementary material). This type of analysis makes it possible to predict whether a quantitative parameter (mean neuronal discharge frequency) is predictive of a given factor (here, the checking or non-checking behaviour). The ROC curves are illustrated in Supplementary Fig. 7 for three different events: the first, second picture and movement onset during the choice situation. We found that below a normalized frequency of 1.0 (equal to baseline), the predictability for the current trial to be a non-checking trial was 80.4%, 72.5% and 82.3% for the three events, respectively. On the other hand, above the same frequency, the predictability for the current trial to be a checking trial was 34.8%, 41.6% and 37.5% for the three events, respectively. In other words, it seems that a low discharge frequency is predictable for a non-checking behaviour, whereas a high frequency is only weakly predictable for a checking behaviour.

Despite frequent feedback-related changes (37%, Fig. 2A), only four neurons (17%) modified their activity differently according to success ('yes') or failure ('no') in the preceding trial. The population analysis revealed no influence of performance during the previous trial on STN neuronal activity (Supplementary Fig. 8).

Discussion

Scientific investigation of cognitive functions in human subjects in the operating theatre is an extremely difficult challenge that has only rarely been undertaken. During surgery, the considerable stress and unusual position the patient must undergo is particularly distressing for severely ill patients with obsessive–compulsive disorder exhibiting a high level of anxiety. Despite these difficulties, we managed to achieve the task. The results revealed two previously unknown critical points: (i) individual neurons in the associative limbic region of the human STN display complex event-related changes in relation to diverse information and (ii) neuronal activity is influenced by the state of the subject's doubt during task completion. These results may explain why chronic STN stimulation improved obsessive–compulsive disorder symptoms in such patients.

In a previous study based on the same task, we found that patients with obsessive–compulsive disorder demonstrated a greater number of verifications and a longer response time for choice before checking than normal control subjects, especially those exhibiting checking behaviour in ecological conditions (Rotge *et al*., 2008*b*). This does not mean that the nature of doubt *per se* was different between patients with obsessive–compulsive disorder and normal subjects, but that doubt occurs more

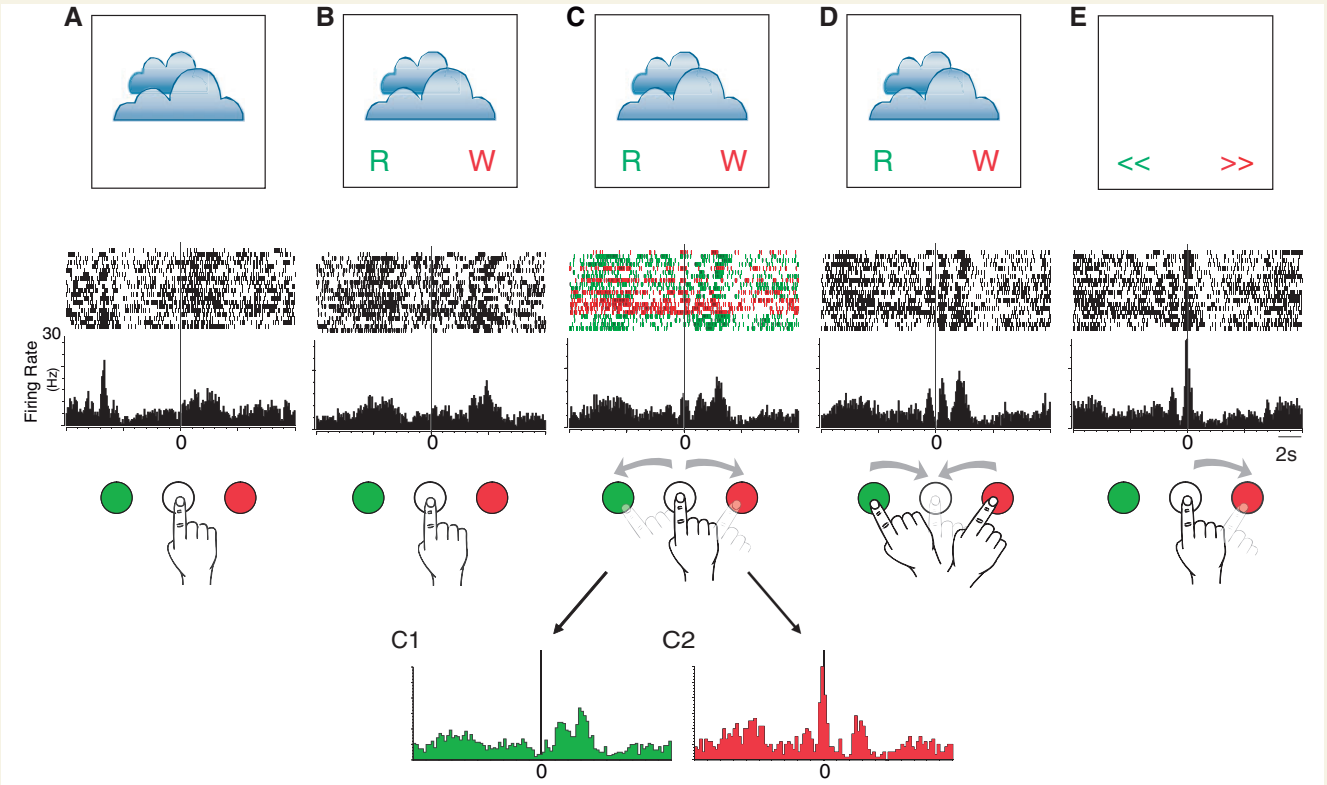

Figure 3 Multimodal neuronal activity changes in the associative STN. Neuronal activity (raster display, *top*) and corresponding peri-event histogram (*bottom*) are aligned (vertical line i.e. 0) with different events: study phase onset (**A**), instruction onset during matching phase (**B**), movement onset during the matching phase (**C**), movement end (**D**) and movement onset during the decision phase (**E**). During the matching phase, trials were shared between the two directions (to the left in **C1** and to the right in **C2**); changes were observed during movement directed to the right only (**C2**). In **D**, the peak after movement onset corresponds to the return movement; in **E**, movements were always performed to the right, as there was no checking behaviour during this session. Significant neuronal changes occurred in relation to the presentation of the first image (**A**, $z = -3.86$, $P < 10^{-4}$), before execution of the first movement (**C**, $z = -4.05$, $P < 10^{-4}$), during the return to the resting position (**D**, $z = -3.93$, $P < 10^{-4}$), before the second movement (**E**, $z = -4.05$, $P < 10^{-4}$). An inhibition of activity was observed after feedback (400 ms after movement onset in **E**, $z = -2.23$, $P = 0.026$).

frequently in obsessive–compulsive disorder sufferers and tends to increase over time. Here, we found that checking improved performance in line with data showing that performance accuracy was higher in obsessive–compulsive disorder that in control subjects on a delayed matching-to-sample task (Ciesielski *et al.*, 2005). This suggests that when subjects with obsessive–compulsive disorder are engaged in a task with a strong cognitive issue, checking may be an adaptive behavioural strategy intending to optimize performances, as in normal subjects, but also to refrain the possible increase in doubt throughout the task.

So far, few studies have investigated the properties of STN neurons during the performance of behavioural tasks in humans. Those studies conducted in the sensorimotor region of the STN in parkinsonian patients during surgery for deep brain stimulation revealed neuronal activity changes related to visually guided saccades in oculomotor tasks (Fawcett *et al.*, 2005; Williams *et al.*, 2005), arm movements (Gale *et al.*, 2009) but also cognitive-related changes (Zaghloul *et al.*, 2012). In our study, neuronal recordings were performed in the associative territory of the STN located anterior and medial to the motor territory. We found that movement-related changes in this region occurred ~500 ms before movement onset, an earlier change to that reported in the motor territory (Williams *et al.*, 2005; Kempf *et al.*, 2007). Such an involvement of the STN at the early stages of motor planning is in line with previous local field potential studies showing STN activation during the preparation of self-initiated automated motor sequences (Purzner *et al.*, 2007; Boecker *et al.*, 2008), motor response inhibition (Li *et al.*, 2008) and orientation of attention (Sauleau *et al.*, 2009). The neuronal activity changes we observed in the associative STN were complex with a context-dependent pattern linked to specific types of movements. Contrary to the lateralized activation reported in the motor STN (Devos *et al.*, 2006), we found that movement-related changes in this region occurred bilaterally during unilateral hand movements. Taken together, these data suggest a complex role of the associative part of the STN in motor control. However, we cannot assert that polymodal changes are a characteristic trait of neuronal activity in the STN associative/limbic territory. Indeed, a recent

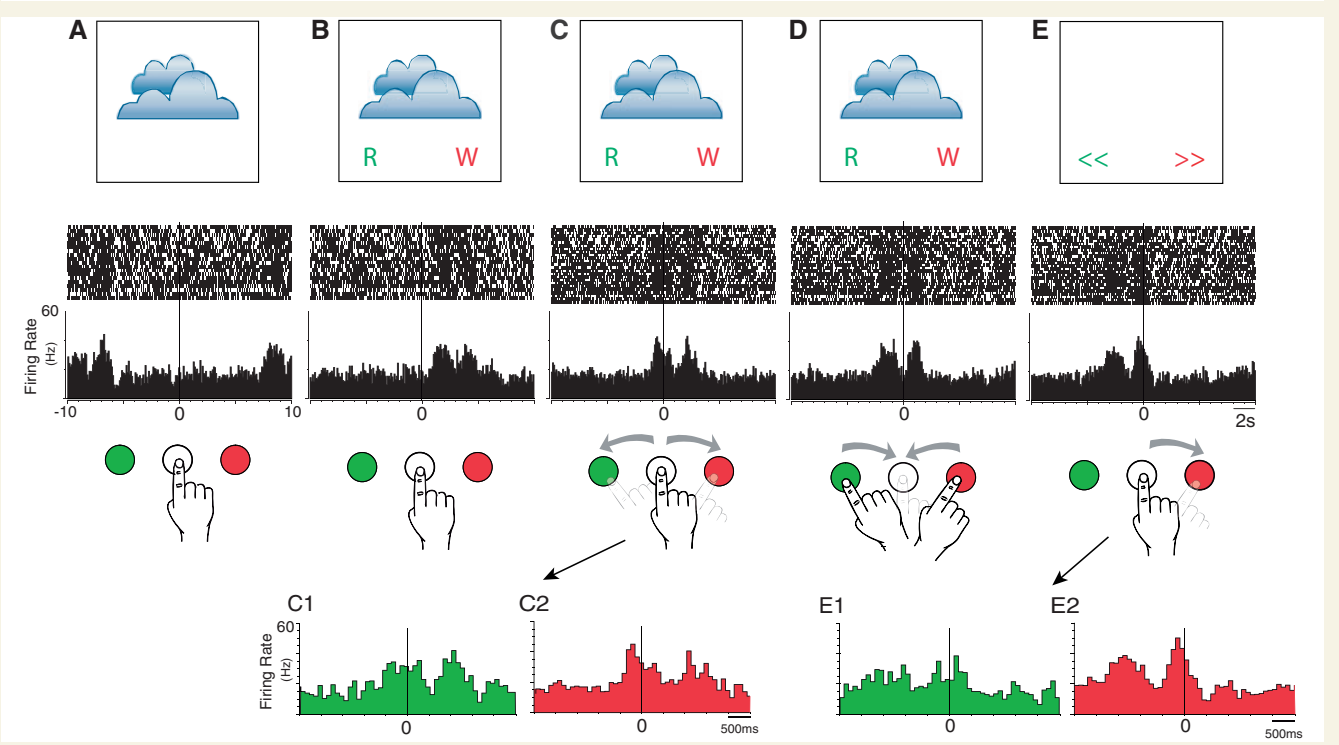

Figure 4 Context-dependent movement-related activity. Same legend as in Fig. 3. This neuron did not respond to cue presentation (**A** and **B**) but was activated before movement execution (**C–E**). Changes depended on the context in which the movement was performed. During the matching phase (**C**), movement-related changes occurred with respect to the reference period (U-test, $z = -3.42$, $P = 0.01$), but there was no significant difference in discharge frequency when movement was performed to the left (**C1**) or to the right (**C2**) (*U*-test, $z = -0.158$, $P = 0.88$). Return to the resting position (**D**) did not activate the neuron (*U*-test, NS). During the matching phase (**E**), movement-related changes were observed (*U*-test, $z = -2.83$, $P = 0.005$), but discharge frequency was significantly higher during the 500 ms preceding movement onset (U-test, $z = -3.11$, $P = 0.001$) when the patient confirmed (**E2**) versus when he checked his previous choice (**E1**).

article reported neuronal changes linked to both cognitive and motor processing during decision-making in the STN motor territory of patients with Parkinson's disease (Zaghloul *et al.*, 2012).

Moreover, neurons modified their activity in relation to non-motor information processing: visual instruction analysis, working memory during the delay and performance feedback at the end of each trial. As the STN is involved in action planning, integration of various types of cognitive information by STN neurons could play a role in decision-making processes (Mink, 1996; Frank *et al.*, 2007; Zaghloul *et al.*, 2012), as suggested by behavioural studies in rodents (Baunez *et al.*, 1995; Baunez and Robbins, 1997), local field potential recordings in humans (Brucke *et al.*, 2007; Balaz *et al.*, 2008) and the effects of neuromodulation (Mallet *et al.*, 2002; Baunez *et al.*, 2007; Mallet *et al.*, 2007, 2008; Baup *et al.*, 2008; Winter *et al.*, 2008). This involvement of the STN in the processing of cognitive information has been recently reported even in the motor territory of the STN (Zaghloul *et al.*, 2012). The fact that the activity of 60% of STN neurons was influenced by multimodal information in our study is a supplementary argument for the model of convergent information processing in the basal ganglia (Gdowski *et al.*, 2001; Bar-Gad *et al.*, 2003; Arkadir *et al.*, 2004; Turner and Anderson, 2005; Mallet *et al.*, 2007; Pasquereau *et al.*, 2007). Because multimodal activity has also been frequently encountered in various prefrontal cortical areas (Fujii and Graybiel, 2003; Michelet *et al.*, 2007; Watanabe and Sakagami, 2007), the complex pattern of neuronal changes in the associative STN could reflect the integration of different types of information in the prefrontal lobe, possibly through direct cortico-subthalamic projections (Kolomiets *et al.*, 2001).

The response of STN neurons during feedback could have several explanations. First, it is unlikely that it corresponds to a simple return to baseline firing rate or to a short period of inhibition after movement execution, as the decrease in firing rate was frequently prolonged, and excitation was occasionally observed. Second, a metacognitive (i.e. 'I am aware of how I performed') or a reinforcement dimension [i.e. 'I have (not) been rewarded because my choice was right (wrong)'] of neuronal changes could be evoked. However, the fact that only four neurons responded differently according to success or failure is not in favour of a role of the STN in the evaluation of behaviour. These data, in apparent contradiction with previous studies (Uslaner and Robinson, 2006; Bezzina *et al.*, 2008; Uslaner *et al.*, 2008; Lardeux *et al.*, 2009), must be interpreted with caution because of the limited sample of neurons in our study. Recently, an error detection signal was recorded in the ventral striatum of patients with

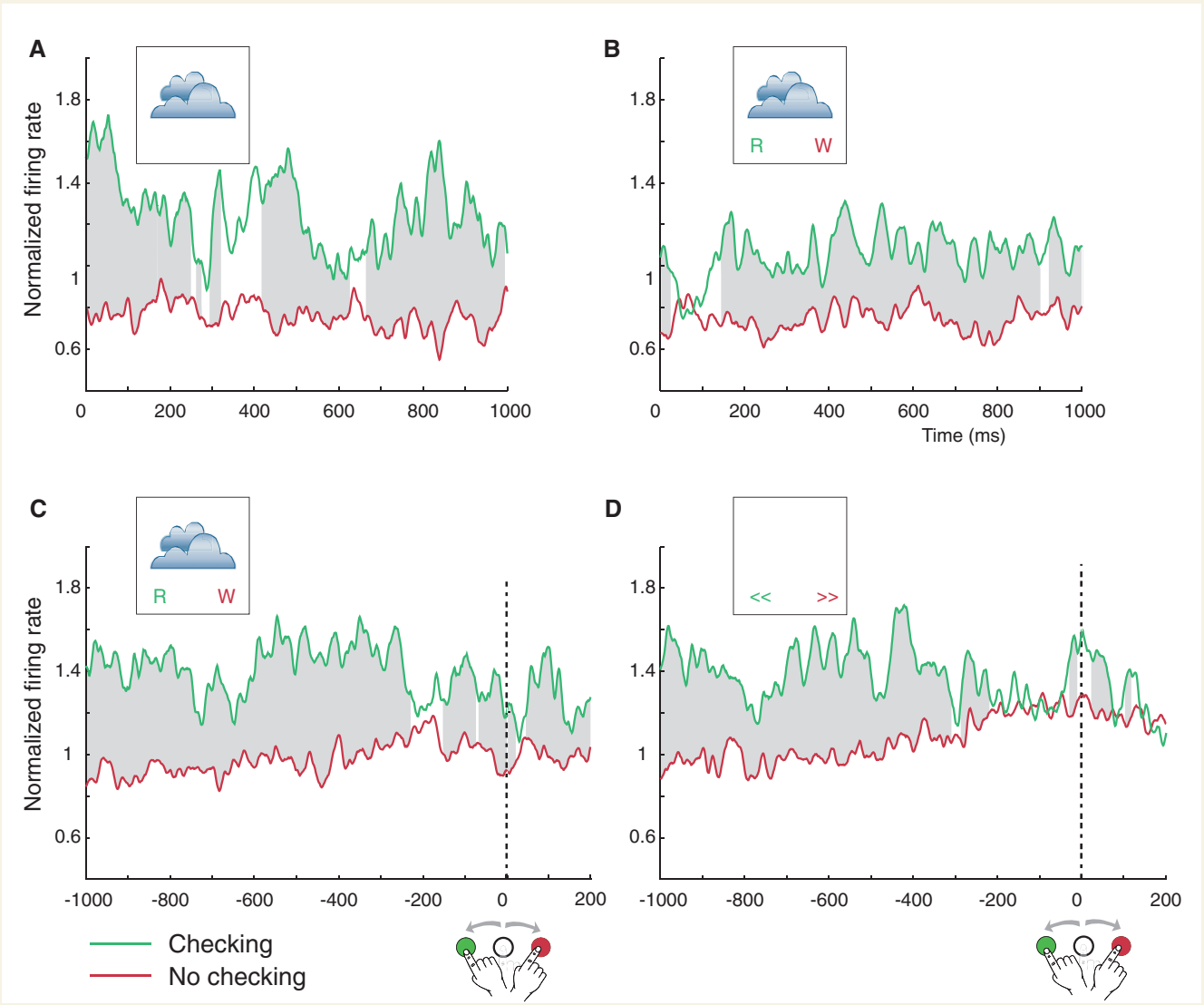

Figure 5 Influence of checking behaviour during the on-going trial on STN neuronal activity. (**A–D**) Population analysis for neuronal changes occurring for trials with and without checking ($n = 63$ neurons). Ordinate: normalized firing frequency aligned on specific task events during trials with checking (green line) and those without (red line). (**A**) Activity aligned with the presentation of the first image during the study phase. (**B**) Activity aligned with the presentation of the second image during the matching phase. (**C**) Activity aligned with the onset of the first movement (dashed line) during the matching phase. (**D**) Activity aligned with the onset of the second movement (dashed line) during the decision phase. In **A–B**, abscissa corresponds to the 1000 ms following image presentation. In **C–D**, abscissa corresponds to the 1000 ms preceding movement onset. The grey area between the green and red lines corresponds to significant differences (Wilcoxon rand sum test, $P < 0.05$).

obsessive–compulsive disorder in situations where the outcome did not match expectations (Patel *et al*., 2012). However, the design of the current study did not allow us to investigate this point. Third, the STN could be involved in the sequencing of actions requiring a signal for the end of each action in a sequence (Frank *et al*., 2007). The fact that inhibition was the most frequent type of neuronal change occurring during feedback is not in contradiction with this view. Although we cannot exclude the possibility that the 'end of the trial' signal is perceived as particularly salient by STN neurons, the nature of inhibition during feedback requires further investigation.

There are several limitations to the present study. First, we focused on a specific cognitive aspect of obsessive–compulsive disorder, i.e. checking behaviour, and a specific target, i.e. the associative-limbic region of the STN. As we could not cover all aspects of obsessive–compulsive disorder pathophysiology, our data provide only a partial view of the mechanisms subserving this complex disease. Indeed, the STN is only one of the relays of information processing in the complex cortico-subcortical networks involved in obsessive–compulsive disorder. It would have been interesting to compare our results with those collected in a different pathology e.g. Parkinson's disease. However, recordings

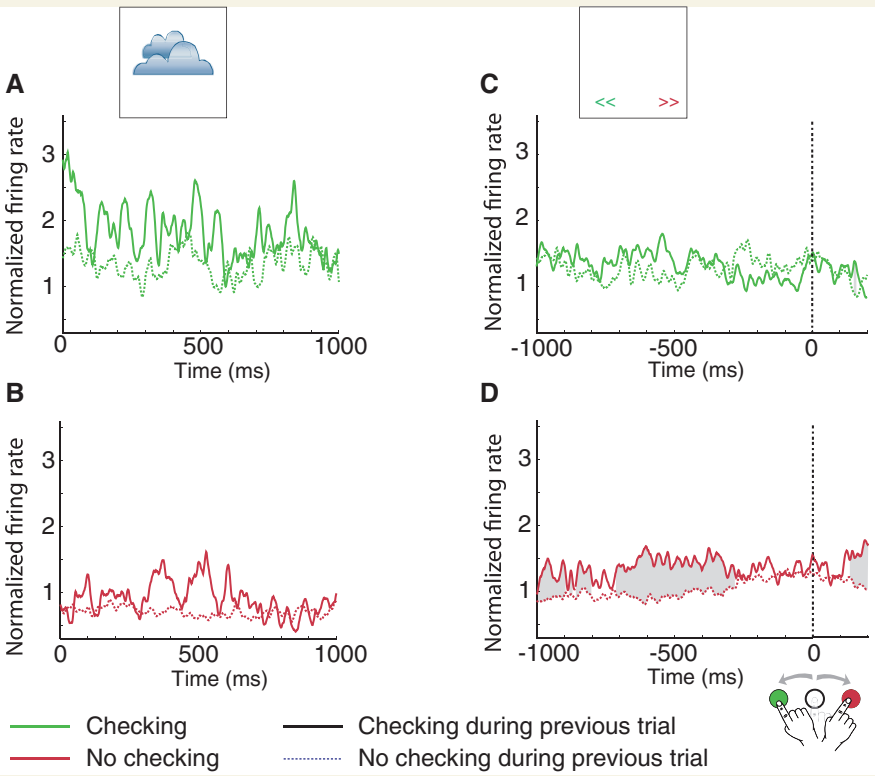

Figure 6 Influence of checking behaviour during the previous trial on STN neuronal activity. These graphs are derived from those in Fig. 5 and correspond to discharge frequency at the level of the neuronal population, in response to visual instructions in the study phase (**A–B**) and movement execution in the decision phase (**C–D**) when the subject is going to verify (green line) or not (red line) during the on-line trial. Normalized discharge frequency in represented in function of the occurrence of checking (continuous line) or not (dashed line) during the previous trial. The grey areas represent significant differences between the two curves. (**A**) Responses to visual instructions in the instruction phase when the subject checked during the on-line trial; (**B**) responses to visual instructions in the instruction phase when the subject did not check during the on-line trial; (**C**) responses during the decision phase when the subject checked during the on-line trial; (**D**) responses during the decision phase when the subject did not check during the on-line trial. Note that significant differences (grey area) were found when the subject had not verified during the previous trial (**B** and **D**).

in patients with Parkinson's disease are performed in a more lateral and dorsal part of the STN corresponding to the motor territory, and stable recordings during task completion are difficult to obtain in these patients. Moreover, further studies will be needed to explore the neural substrate of doubt in different anatomical structures (e.g. caudate nucleus in patients with obsessive–compulsive disorder) or to compare single unit recordings with those obtained with local field potentials. Second, the time dedicated to electrophysiology during the surgical procedure limits the possibility of performing control tasks because of the risk of infection correlated with the length of surgery. For instance, we did not control eye movements, although it is unlikely that they could have biased the results. Indeed, during the study and matching phases, they were multi-directional to explore and then compare the features of the two images. Furthermore, the patients were unable to see the response panel during motor responses, a fact that precludes any visual control of movement execution. In addition, we did not record EMG activity. It could be argued that increased EMG activity during checking trials might in part explain the difference in firing rate between checking and non-checking trials. This is unlikely because movements during the choice and decision phases were similar in the two situations (except for movement direction). In addition, the button that the patients had to press during rest before each motor response was very sensitive. This precludes the possibility of spontaneous movements, as when it occurred, the trial was aborted and consequently not considered for further analysis. To shorten the electrophysiological procedure, we also chose not to search for somatosensory receptive fields excluding an electrophysiological mapping of the STN motor territory. However, behavioural responses obtained with stimulation at the target location clearly induced emotional manifestations (feeling of anxiety or fear, on the other hand, decrease in anxiety, laughing), suggesting that we were indeed located in the associative/limbic territory. Finally, we postulated that most recordings were performed in the associative-limbic territory of the STN on the basis of previously published anatomical methods providing millimetric precision (Yelnik *et al*., 2007). However, histological data have shown that the boundaries between the STN's functional divisions are not clear-cut but correspond rather to a functional gradient (Karachi *et al*., 2002). Despite these restrictions, it is likely that a minority of neurons recorded in the present study were located outside the associative-limbic territory of the STN.

Pathological checking is thought to result from the intense feeling of doubt in patients with obsessive–compulsive disorder. The most salient finding of the present study is that checking behaviour favoured by doubt in a choice situation was associated with an increased STN neuronal activity, a modification that occurred several seconds before the patient had to check. These data support the idea that neuronal activity in the human STN is influenced by doubt. The fact that a low frequency of individual STN neurons was predictive of a non-checking behaviour is in line with the lowest discharge frequency during non-checking versus checking trials. Hence, when a subject had no doubt, STN discharge frequency was low. The low predictability of high STN discharge frequency for checking behaviour could be owing to the fact that several brain regions are involved in such a cognitive process, the STN being only one of the links among a complex network. A recent article showed that STN neuronal activity was high when participants were engaged in a decision, and that the level of spiking activity increased with the degree of decision conflict (Zaghloul *et al*., 2012). Taken as a whole, these results suggest that neuronal activity in the STN increases when the subject reaches a decision in a difficult context. On the other hand, when the subject was extremely uncertain, maintaining him in a checking state, the STN firing rate was already high, thus limiting any further increase in neuronal activity and consequently the influence of previous trials when they had to take the decision to check or not. The difference in activities between checking and non-checking trials disappeared 200 ms before response movement, and no further difference in neuronal activity was observed, whatever the decision (checking or otherwise). This suggests that all STN neurons were engaged at this time in motor aspects of behaviour and were no longer influenced by the cognitive context.

The abnormal recurrence of checking has been regarded as automated thought and behaviour strongly suggestive of basal ganglia involvement (Graybiel and Rauch, 2000; Graybiel, 2005). Several basal ganglia models identify the STN as having a role in the inhibition of unwanted programmes through the hyper-direct and indirect pathways (Nambu *et al*., 2002; Frank, 2006; Mink, 2006), as well as in time allocation and the withholding of responses in conflict situations (Frank *et al*., 2007). Thus, disruption of neuronal activity within the STN of patients with obsessive–compulsive disorder could play a role in the perpetuation of pathological repetitive behaviours such as checking. Because our data suggest that STN neurons are involved in the checking behaviour of obsessive–compulsive disorder, they support the fact that STN modulation by deep brain stimulation reduced compulsive behaviour in these patients (Mallet *et al*., 2008).

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Supplementary material

Supplementary material is available at *Brain* online.

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