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Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder

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Intrusive thoughts and compulsive urges to perform stereotyped behaviours are typical symptoms of obsessive-compulsive disorder. Emerging evidence suggests a cognitive bias towards habit formation at the expense of goal-directed performance in obsessive-compulsive disorder. In this study, we test this hypothesis using a novel individualized ecologically valid symptom provocation design: a live provocation functional magnetic resonance imaging paradigm with synchronous video-recording of behavioural avoidance responses. By pairing symptom provocation with online avoidance responses on a trial-by-trial basis, we sought to investigate the neural mechanisms leading to the compulsive avoidance response. In keeping with the model of habit formation in obsessive-compulsive disorder, we hypothesized that this disorder would be associated with lower activity in regions implicated in goal-directed behaviours and higher activity in regions implicated in habitual behaviours. Fifteen patients with obsessive-compulsive disorder and 15 healthy control volunteers participated in this functional magnetic resonance imaging study. Online stimuli were individually tailored to achieve effective symptom provocation at neutral, intermediate and strong intensity levels. During the symptom provocation block, the participant could choose to reject or terminate the provoking stimuli resulting in cessation of the symptom provocation. We thus separately analysed the neural correlates of symptom provocation, the urge to avoid, rejection and relief. Strongly symptom-provoking conditions evoked a dichotomous pattern of deactivation/activation in patients, which was not observed either in control conditions or in healthy subjects: a deactivation of caudate-prefrontal circuits accompanied by hyperactivation of subthalamic nucleus/putaminal regions. This finding suggests a dissociation between regions engaged in goal-directed and habitual behaviours. The putaminal hyperactivity during patients' symptom provocation preceded subsequent deactivation during avoidance and relief events, indicating a pivotal role of putamen in regulation of behaviour and habit formation in obsessive-compulsive disorder. Effective connectivity analysis identified the ventromedial prefrontal cortex/orbitofrontal cortex as the main structure in this circuitry involved in the modulation of compulsivity in obsessive-compulsive disorder. These findings suggest an imbalance in circuitry underlying habitual and goal-directed action control, which may represent a fundamental mechanism underlying compulsivity in obsessive-compulsive disorder. Our results complement current models of symptom generation in obsessive-compulsive disorder and may enable the development of future therapeutic approaches that aim to alleviate this imbalance.

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Abbreviations: ACC = anterior cingulate cortex; OCD = obsessive-compulsive disorder; PFC = prefrontal cortex

Introduction

A prominent feature of obsessive-compulsive disorder (OCD) is the propensity to perform compulsive behaviours despite negative consequences. OCD has been conceptualized as a disorder of self-control and behavioural inhibition (Milad and Rauch, 2012; Robbins *et al.*, 2012). Data from symptom evocation and provocation studies in OCD suggest hyperactivity of the orbitofrontal, dorsolateral prefrontal (PFC) and anterior cingulate cortices (ACC), caudate, insula and amygdala (McGuire *et al.*, 1994; Rauch *et al.*, 1994; Breiter *et al.*, 1996; Adler *et al.*, 2000; Hendler *et al.*, 2003; Mataix-Cols *et al.*, 2004; Nakao *et al.*, 2005; Schienle *et al.*, 2005; Simon *et al.*, 2010, 2013; Baioui *et al.*, 2013). These studies support a neurobiological model of OCD suggesting an important role for dysfunctional loops in cortico-striato-thalamo-cortical (CSTC) circuits (Graybiel, 2008; Milad and Rauch, 2012) as well as the involvement of limbic structures to the aetiology of this disease (Simon *et al.*, 2010, 2013; Admon *et al.*, 2012; Stern *et al.*, 2012). Symptom provocation studies commonly use exposure to words or images related to the symptoms and ask patients to recognize or recall contexts related to past symptoms (Mataix-Cols *et al.*, 2004; Nakao *et al.*, 2005; Schienle *et al.*, 2005; Gilbert *et al.*, 2009; Simon *et al.*, 2010; Baioui *et al.*, 2013). Some studies used mental imagery and others exposed patients to direct provocation, using real sensory stimulation (e.g. tactile exposure to triggers such as contaminated objects). However, these evocation and provocation studies have been studied separately from the compulsive avoidance behaviour. In this study we used a real-time tailored provocation task paired with online behavioural avoidance responses. Using a clearly defined chain of symptomatic events on a trial-by-trial basis we aimed to investigate the common neural correlates of symptom generation and mechanisms leading to the compulsive avoidance behaviour.

Studies of OCD point towards hyperactive regions implicated in action monitoring and response conflict such as the ACC (Menzies *et al.*, 2008; Milad and Rauch, 2012) and a shift from goal-directed to habitual behaviours implicating cortico-striatal circuitry (Gillan *et al.*, 2011). Deficits in error monitoring (Melcher *et al.*, 2008; Page *et al.*, 2009; Rao *et al.*, 2010; Schlosser *et al.*, 2010), response inhibition (Bannon *et al.*, 2002; Page *et al.*, 2009; Morein-Zamir *et al.*, 2013), task switching (Chamberlain *et al.*, 2007) and reversal learning (Chamberlain *et al.*, 2008) indexed by cognitive tasks such as Stroop, Go/No Go, Stop-Signal, Reversal Learning Intra/Extradimensional Shift tasks, have been consistently shown in OCD. This behavioural inflexibility, which has been associated with abnormal activity of a subregion likely within the rostral part of the dorsal ACC and orbitofrontal cortex (Fitzgerald *et al.*, 2005, 2010; Maltby *et al.*, 2005), may be closely related with difficulties to quickly shift between goal-directed and habitual behaviour strategies (Shenhav *et al.*, 2013). An incongruent or conflicting stimulus context requires inevitably more cognitive monitoring than a congruent one, which can easily be processed automatically, because no conflict is involved (Shenhav *et al.*, 2013). The studies by Gillan and colleagues (2011, 2014) suggesting a bias towards habit formation at the expense of goal-directed performance in patients with OCD seem to provide good evidence for this duality between controlled and automatic processes.

The dichotomy between goal-directed and habitual behaviours has been extensively studied in rodents (Dickinson, 1985; Dickinson and Balleine, 1993; Yin *et al.*, 2006; Balleine *et al.*, 2007; Dias-Ferreira *et al.*, 2009). According to this dual-system model, different behavioural strategies are used to respond to environmental demands and it is the ability to shift between them that enables successful decisions (Balleine, 2007). The goal-directed system encodes actions that are performed to achieve specific outcomes, whereas the habitual-system drives action selection based on stimulus-response associations (Dickinson and Balleine, 1993). The goal-directed system is vital for responding to permanent changes in the environment, but it is effortful to sustain its activity because it demands continuous monitoring of the environment. The habitual system is more efficient but can lead to behavioural inflexibility in case of over-learned stimulus associations (Adams, 1982). It has been suggested that rodent cortico-striatal circuits involving prelimbic cortex (Balleine and Dickinson, 1998) and dorsomedial (Balleine *et al.*, 2007) striatum are implicated in goal-directed actions whereas the dorsolateral striatum (Yin *et al.*, 2006) is involved in habit formation. Recent studies have highlighted the homologies between animal and human physiology of action control (de Wit and Dickinson, 2009; Tricomi *et al.*, 2009; Balleine and O'Doherty, 2010).

Here we used a novel symptom provocation design focusing on individualized real-time multisensory exposure with greater ecological validity to provoke compulsive behaviours. We measured, on a trial-by-trial basis, patient's avoidance responses thus linking the provocation to the compulsive avoidance behaviour. We compared within (across neutral and strong conditions) and between subject (healthy controls versus patients with OCD) provocation at

variable levels of intensity, and used baseline control blocks with silent counting. We then carried out functional connectivity analyses to identify direction of interactions in the network implicated in impaired response control and habit formation.

In line with the goal-directed/habitual behaviour dichotomy account and with the recent suggestion that compulsivity in OCD might arise from excessive avoidance habit formation that is related to a subjective urge to respond (Gillan *et al.*, 2014), we hypothesize that OCD would be associated with a decrease in caudate activity implicated in goal-directed behaviours and an increase in putaminal activity implicated in habitual behaviours. This simple dichotomy is well known in the motor and action control domains in neurological conditions such as Parkinson's disease. Hadj-Bouziane *et al.* (2012) addressed the idea that goal-directed behaviours are predominantly caudate-dependent whereas habitual responses are primarily putamen-dependent, at advanced Parkinson's disease stages, where dopamine depletion is greater in the putamen than in the caudate nucleus. The emergence of habitual responses was more vulnerable to the disease than the early phase of learning dominated by goal-directed actions, in line with the hypothesis. Our symptom provocation paradigm was designed to capture such imbalances using direct measures of avoidance responses modelled as compulsive actions.

Materials and methods

Participants

Fifteen patients with OCD and 15 healthy control subjects matched for gender, age and years of education [OCD: eight males/seven females; mean age = 32.3 years, standard deviation (SD) ± 9.02; mean years of education = 13.7, SD ± 3.7; healthy controls: eight males/seven females; mean age = 31.0 years, SD ± 8.9; mean years of education = 15.0, SD ± 3.4] participated in this study. Control subjects were recruited from the community, were unmedicated and had never suffered from a psychiatric illness. Patients with OCD were recruited from the Hospital of University of Coimbra. OCD diagnoses were established by a psychiatrist and clinical psychologists using the Structured Clinical Interview for the Diagnosis of DSM IV psychiatric disorders and the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) (DiNardo *et al.*, 1994). To assess the severity and characteristics of OCD symptoms, each patient completed the Yale-Brown Obsessive-Compulsive Scale and the symptom checklist (Goodman *et al.*, 1989). All patients scored >18 indicating at least moderate severity (mean score = 26, SD ± 6.20). Depression scores were obtained with the Beck Depression Inventory (Beck *et al.*, 1961) (mean score = 13.8, SD ± 8.7). Anxiety was measured using the Hamilton Anxiety Rating Scale (Hamilton, 1959) (mean score = 7.2, SD ± 3.51). Exclusion criteria included the presence of comorbidity with other Axis I diagnoses, neurological disorders, history of drug, alcohol addiction and any serious medical condition. Although five of our patients scored >16 on the Beck Depression Inventory scale, this was not sufficient, based on the clinical interview, to establish a diagnosis. Nevertheless, we used this measure as a covariate in the analysis. All patients had recently initiated cognitive behavioural therapy, and 14 patients were on antidepressant and/or anxiolytic medication. A handedness inventory (Oldfield, 1971) was administered and average laterality quotient was 95. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Commissions of the Faculty of Medicine of the University of Coimbra. Written informed consent was obtained after a detailed explanation of the study and after a pre-experimental interview to tailor the experimental conditions to each participant.

Symptom provocation task

We used ANOVA between-group and within-group (provocation condition) analyses including interaction effects. The within-group repeated-measures crossover design is considered an optimal approach to assess the effects of an intervention within the same population (Hedayat and Yang, 2005) (e.g. symptom provocation versus neutral provocation). We used individually tailored stimulation, which has been shown to be effective for symptom provocation (Baioui *et al.*, 2013). For patients, the choice of stimuli resulted from a pre-experimental interview between the patient, two members of the experimental team (P.B. and M.C.B.), a clinician (J.R.) and a psychotherapist (F.P.), to identify the maximum degree of natural symptom provocation acceptable to each patient. Thus, the online stimulation was individually tailored both in the type of stimuli and the degree of stimulation. For healthy controls, the stimuli included the most salient set of stimuli of the patients' database (also likely to perturb healthy subjects due to their generic intrusive nature), and new ones designed to cause similar intrusive thoughts (such as contamination fears). This mixed strategy was preferred because some stimuli identified to trigger symptoms in patients would not have any impact in healthy controls.

The experiment consisted of 30-s blocks of provocation of variable intensity, then 30 s of a silent counting baseline followed by a 6-s intertrial interval for the control motor response (Fig. 1C). This sequence was repeated 12 times per session, for a total of four sessions in each participant. The provocation stimuli were delivered at three intensity levels (neutral, intermediate or strong) in pseudo-randomized order. The pseudo-randomization was based on predefined session lists prescribing an arbitrary order of stimulation by balanced perturbation of the three intensity levels (four neutral, four intermediate and four strong provocation blocks) with the restriction that no two adjacent stimulation blocks offered the same intensity level. Thus, a total of 48 blocks of provocation were delivered to each participant, 16 at each intensity level. Within a session, the stimuli at each intensity level were held constant, but between the four sessions, four different stimuli per intensity level were used to avoid habituation over sessions.

The silent counting task baseline between the provocation blocks was intended to allow the patients to shift their focus of attention away from the previous provocation stimuli. By engaging in a neutral task, patients were distracted from any ruminative or obsessive thoughts triggered by previous stimuli.

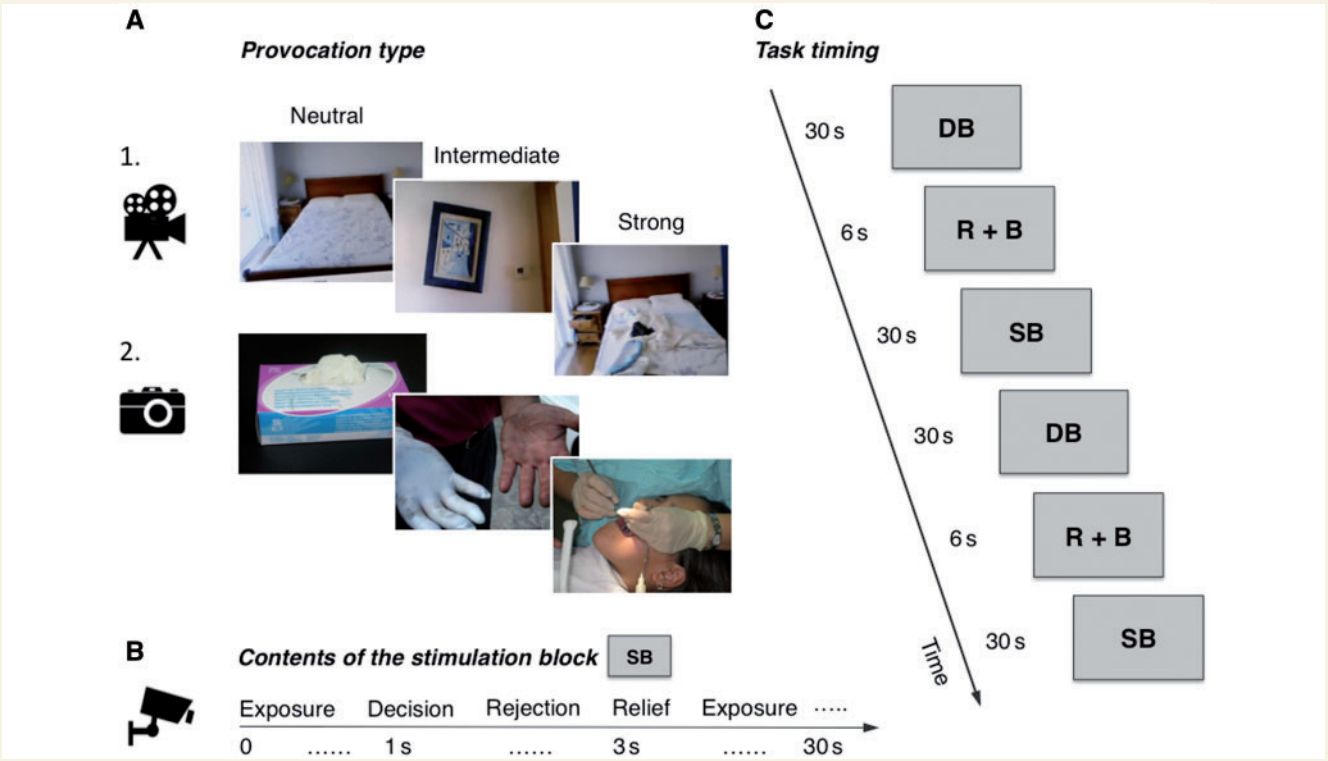

Figure 1 Experimental paradigm. (**A**) Examples of the two different modalities used for the symptom provocation task. (1) Online video-streaming of scenarios from the patients' homes (remote provocation). Strong blocks were live videos capturing the experimenter disorganizing the patients' homes while neutral videos showed the rooms as the patients had left them; (2) The tactile modality in which the experimenter directly delivered the provoking stimuli to the patient's hand. In this case, the patient would see an image of a glove that she would touch. The visual presentation was intended to inform the patient about the type of stimuli delivered to the hand. (**B**) Contents of the stimulation block. Both modalities used a video-recording system to record and timestamp the exposure, decision to reject, rejection and relief events within the stimulation blocks. (**C**) Task timing. The experiment consisted of 30 s of provocation blocks of variable intensity (SB = stimulation blocks), 30 s of a baseline-counting task (DB = distractive baseline) and 6 s of response plus baseline block (R + B = response plus baseline). This sequence was repeated 12 times per run, for a total of four runs in each participant.

In the counting task, participants observed a random sequence of two numbers (1 and 2) over a 30-s period and were instructed to count the number of times the number 1 appeared. Subjects then reported the answer from one of two options presented on the screen during the 6-s intertrial interval.

During the provocation blocks, participants were instructed to spontaneously signal if they were no longer able to tolerate the provocation stimulus. Using a single hand gesture, participants would signal to the experimenter to cease the exposure. The provocation would then cease for a 3-s period of relief, as described below, after which exposure would return. When the exposure continued, participants were allowed to reject it again. Thus, depending on the number and duration of rejections, the number of provocation events presented within the 30-s provocation blocks would vary between sessions and subjects (for details, see the 'Results' section). The timing of these rejection events was synchronously acquired using a MRI compatible video recording system. We explicitly discussed with the participant before the study to use this hand gesture only when they were no longer able to tolerate the provocation. As expected, rejection events did not occur in healthy controls and in patients during neutral blocks. They occurred mainly in patients during the strong provocation blocks. In patients, some of the provocation events in the intermediate condition had to be relabelled after the exposure. This happened occasionally when a stimulus was rejected during a planned intermediate provocation block. In the subsequent analyses, the stimulation in that block was labelled as strong to reflect the real experience of the patient during the provocation. No strong or neutral blocks were relabelled. Rejection events therefore indicated that symptom provocation was effective, and the number of rejections inside a provocation block indexed how effective the provocation was perceived by the patient. Given that the number of events and their impact on the neural response is taken into account in the statistical model of the event-related analysis, this added additional information to the block design analysis.

In healthy controls, the three intensity levels were defined based on the scores collected from a stimulus rating scale.

There were two types of tailored provocation stimuli: tactile provocation near bore and visual provocation online (Fig. 1A). In the near-bore provocation, for example, a patient with biological contamination obsession and washing compulsions would touch with their left hand three different provocation stimuli of varying provocation intensity. During these provocations, the patient experienced live provocation with their left hand while visual stimuli were presented to indicate the level of provocation while in the scanner. The live provocation for

this patient was as follows: neutral: the patient touched clean and untouched gloves; intermediate: the patient touched gloves, which had been previously categorized by him/her as potentially contaminated because they had been used by known individuals (e.g. the experimenter or the psychotherapist); strong: the patient touched gloves that they believed to be biologically contaminated because they had been used by individuals who were ill or by unknown individuals in high risk jobs (e.g. dentists, nurses). The stimuli were placed in the participant's hand by the experimenter (P.B.) during the scanning session. A rejection hand gesture was accommodated by removal of the glove from the participant's hand followed by the 3-s relief period and concomitant disinfecting of the hand with an antibacterial wipe.

In other participants, to achieve a realistic and efficient provocation, we streamed online videos in real-time from the patients' homes. For example, for a patient with obsessions for symmetry, organization and cleanliness, they watched real-time videos from within their homes in which the experimenter (P.B.) would disorganize and litter the home. For this procedure, custom Matlab software was used to capture online footage using Internet and synchronous Skype connection. Such real-time video exposure also allowed online rejection requests. Rejection hand gestures followed the same design as near bore provocation. For details about the type of provocation used for each patient, see Supplementary Table 1. Healthy subjects underwent the tactile provocation near bore type, because it was found to be most effective in this group.

The visual stimulation consisted of natural scenes of similar complexity for all subjects. Visual provocation stimuli always contained a scene with at most one provoking agent. All visual stimuli were presented at high contrast levels and had identical durations.

In summary, participants were exposed to individualized provocation stimuli of differing intensity (neutral, intermediate and strong) in a mixed block-event related design in which individual rejection events were video-recorded and time-stamped. Rejection events occurred when participants could no longer tolerate the provocation and modelled the compulsive or avoidance behavioural response. This allowed the analysis of the provocation stimuli, the decision to reject, the rejection event and the relief period. This design involved intensive patient interviewing and preparation, and it required strict control for recording artefacts caused by movement inside the scanner.

Data acquisition

Visual stimuli were presented using Presentation software (Neurobehavioural Systems) and natural tactile stimuli were used with simultaneous video recording. Custom Matlab software was used for synchronization with remote and local video recording.

Participants were scanned in a 3 T Siemens Magnetom TimTrio scanner, at the Portuguese Brain Imaging Network, using a 12-channel head coil. For each participant, and before functional runs, 160 anatomical slices were acquired with the following parameters: one T_1-weighted MPRAGE sequence, repetition time = 2.3 s, echo time = 2.98 ms, voxel size = $1 \times 1 \times 1\,mm^3$, flip angle = 9°, field of view = 256 × 256. To minimize the motion of the subject's head during the study, foam padding was used. Functional MRI data were acquired using blood oxygen level-dependent contrast whole brain echo planar imaging (EPI). We used two slightly different protocols: (i) $n = 5$, repetition time = 3 s, echo time = 39 ms, voxel size = $2 \times 2 \times 3\,mm^3$, 3-mm thick slices with no interslice gap, with an in-plane matrix of 128 × 128 voxels, flip angle = 90°, field of view = 256 × 256, 39 interleaved axial slices, 295/run; (ii) $n = 10$, repetition time = 2 s, echo time = 39 ms, voxel size = $3 \times 3 \times 4\,mm^3$, 4-mm thick slices with no interslice gap, with an in-plane matrix of 84 × 84 voxels, flip angle = 90°, field of view = 256 × 256, 29 interleaved axial slices per volume, in a total of 420 volumes per run. The acquisition protocol was changed to improve connectivity analyses, for which a lower repetition time is advantageous.

Image processing and data analysis

Analyses were carried out using BrainVoyager QX 2.6 (Brain Innovation). Preprocessing included intensity inhomogeneity correction, slice-scan-time correction, temporal high-pass filtering to remove low frequency drifts, realignment, and rigid-body transformation of data to the first image to correct for motion. Functional data were coregistered to anatomical data and subsequently transformed into Talairach space. A spatial smoothing using a Gaussian filter (full-width at half-maximum 4 mm) was performed. Four sessions were excluded from further analysis because of motion artefacts.

Statistical analyses were performed on individual and group data using a random effects general linear model to implement a repeated-measures ANOVA. The design matrix was based on regressors separately created for each type of blocked conditions (baseline and neutral, intermediate and strong provocation) and event onset times derived from video recordings from each scan session. The time-stamped video-recorded events were rejection onset time, rejection duration and relief periods. Additionally, decision to reject was defined as an event 1 s before initiation of the hand gesture signalling rejection. In this way, block onset times were predetermined by the experimental design (Fig. 1C), whereas event onset times were based on the behavioural response of the participants during the stimulation (Fig. 1B). To account for haemodynamic delay and dispersion, each of the predictors was convolved with a double-gamma haemodynamic response function as implemented in BrainVoyager. Statistical maps were corrected for multiple comparisons using false discovery rate correction and the cluster threshold estimator plugin for BrainVoyager QX (Forman *et al.*, 1995). Each map was first thresholded at $P < 0.05$ and then submitted to cluster threshold estimation based on a Monte Carlo simulation with 1000 iterations, which yields a value of $P < 0.05$ corrected for multiple comparisons.

Time course analysis was performed with a focus on the putamen because of its surprising results at the event level, in patients. We first extracted the time varying blood oxygen level-dependent response for left and right putamen based on the clusters found on the statistical general linear model maps (Contrast: decision to reject > rejection events). To estimate the underlying neuronal signal, we deconvolved the haemodynamic response from the blood oxygen level-dependent signal using the PPI module in SPM8. This procedure also removes confounds such as the DC component. We then characterized the individual event-related response as the average

of sequences of estimated neuronal signal time-locked to the rejection event. The plots show the average neuronal signal relative to rejection normalized across patients ± SEM (Fig. 4B).

Finally, after localizing the brain regions directly involved in OCD symptomatology, we ran an effective connectivity analysis by applying the Granger Causality Mapping method (Roebroeck *et al.*, 2005). The purpose was to get information about the functional interactions between those brain areas, as well as information about the direction of these interactions to infer their causal relationship. As Granger Causality Mapping requires the specification of seed regions, after which measures of effective connectivity for all voxels in the brain are calculated in reference to the time course in the seeded clusters, several seed regions were individually created. These seeds were spheres of 3 mm centred at the peaks of activation clusters obtained from the general linear model analysis. The seed regions were selected based on their direct involvement in OCD symptomatology observed consistently in our block and event-related analyses, and consistent with previous studies in OCD reporting abnormal activation in these regions (Del Casale *et al.*, 2011; Milad and Rauch, 2012). The resulting seed regions were: dorsal ACC [Brodmann area (BA) 24], ventromedial PFC/orbitofrontal cortex, amygdala, caudate head, and putamen. Random effect Granger Causality Maps were first calculated for each individual patient. Statistical thresholds for these maps were computed using a bootstrap method (Roebroeck *et al.*, 2005) with corrections for multiple comparisons based on false discovery rate ($q < 0.05$) (Genovese *et al.*, 2002). A mean group Granger Causality Mapping was then created, using *t*-tests, yielding effective connectivity information to the seed regions throughout the entire brain. The obtained granger causality maps pointed up which areas in the brain are influenced by activity in each seed and which areas whose activity influences the activation in the specified seed region.

Results

Patients with OCD performed rejection events during the strong provocation blocks. As expected, the neutral blocks did not evoke any rejection response confirming their role as control conditions, for the within-subject design. Furthermore, healthy control subjects did not yield rejection events.

The presence of rejection events in patients allowed us to divide the 30 s strong rejection blocks into exposure, rejection events and relief periods. The exposure event was further subdivided by separately assessing the 1-s duration before the rejection event, modelling the decision to reject. The mean (SD) number of rejection events (submitted to random effects analysis) was 25.33 (6.20) and their mean (SD) duration was 2.14 s (1.64). Their coefficient of variation of 0.24 implies low variability in symptom provocation across subjects. It was expected that some subjects would exhibit a higher number of rejection episodes than others, but our patients showed a sufficient number of rejections for statistical analysis, and across-subject variability was useful for random-effects analysis. The mean (SD) duration of the strong exposure conditions (submitted to the event-related analysis) was 9.56 s (5.83).

Brain activity was modelled both as a function of strong 'blocks' containing symptomatic provocation as well as a function of the real-time presence of effective symptom evoking stimuli ('event'-related analysis) (see 'Materials and methods' section). Both approaches yielded converging results.

We first conducted a random effects block analysis comparing patients with OCD and healthy controls. In the main group effect (irrespective of condition), patients with OCD showed greater activity in bilateral caudate, right putamen, right thalamus and right sensory-motor areas (S1/M1) and lower activity in left parahippocampal gyrus and hippocampus, cerebellum and parietal areas including precuneus as compared to healthy controls. In the main provocation effect, strong provocation as compared to neutral provocation was associated with greater activation in bilateral anterior insula, presupplementary motor area, ACC, putamen, thalamus, substantia nigra and left subthalamic nucleus. It was also associated with lower activation in the bilateral ventromedial PFC, including orbitofrontal cortex, pregenual cingulate cortex, dorsolateral PFC, posterior cingulate cortex, left parahippocampal gyrus and hippocampus. A significant Group × Provocation interaction was observed: patients with OCD had enhanced bilateral putamen, globus pallidus, thalamus, caudal subregion of dorsal cingulate cortex (dorsal cingulate cortex in BA 24), insula, subthalamic nucleus, substantia nigra and presupplementary motor area and lower activity in bilateral ventromedial PFC, posterior cingulate and left dorsal caudate for the strong versus neutral contrast relative to healthy controls (Fig. 2 and Supplementary Table 2).

We then performed an event-related general linear model analysis in the OCD group focusing on the strong blocks separately modelling the following: (i) exposure events (excluding decision, rejection and relief events); (ii) the decision to reject (modelled as 1 s before the rejection event); (iii) rejection events modelling the avoidance behavioural response; and (iv) the relief periods. These separate events are represented graphically in Fig. 1B. Strong exposure > neutral condition showed a pattern similar to the one observed with the interaction block analysis: deactivation of the ventromedial PFC, pregenual ACC, dorsolateral PFC and the dorsal caudate, and hyperactivation of the caudal subregion of dorsal cingulate cortex (in BA 24), thalamus, substantia nigra and presupplementary motor area. In other words this event-related analysis replicated into a large extent the OCD-specific pattern found in the general linear model block analysis. In contrast, the bilateral putamen, subthalamic nucleus, amygdala and insula activity seen in the general linear model analysis above appeared to be involved only in the decision to rejection, rejection and relief phases. During both the decision to reject and rejection events, patients showed hyperactivation of the caudal (near to presupplementary motor area) part of dorsal cingulate cortex, amygdala, subthalamic nucleus,

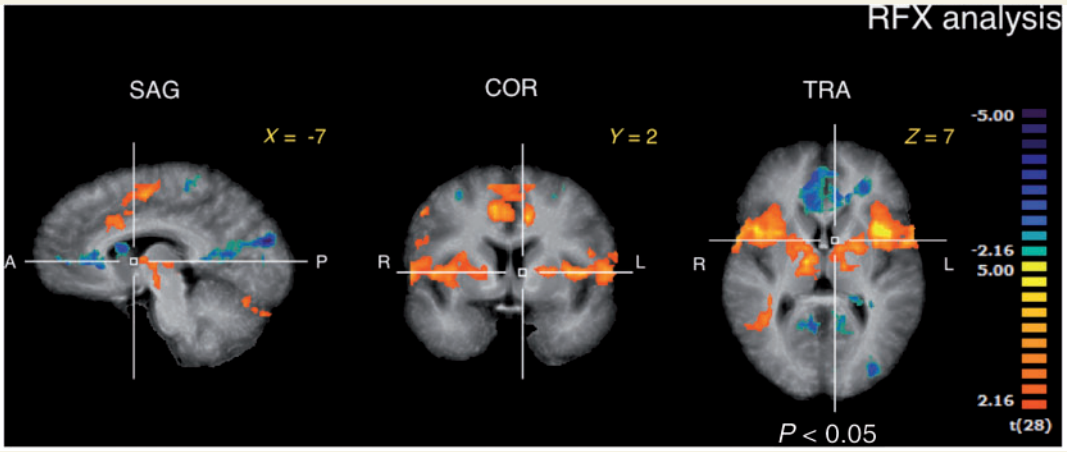

Figure 2 Between-group **random effects general linear model analysis.** Group × Provocation interaction for the strong > neutral provocation contrast. OCD patients showed greater bilateral putamen, globus pallidus, subthalamic nucleus, thalamus, dorsal ACC, insula, pre-supplementary motor area and substantia nigra relative to healthy controls and lower activity in ventromedial PFC, posterior cingulate and left dorsal caudate ($P < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 35 voxels). See Supplementary Table 2 for details regarding peak voxel coordinates, cluster size, *t* and *P*-values for random-effects analysis. COR = coronal; SAG = sagittal; RFX = random effects; TRA = transverse.

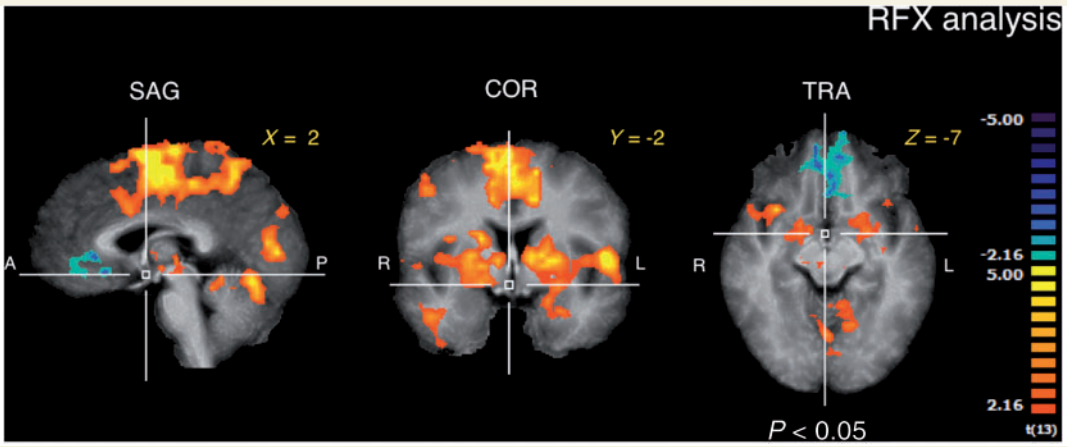

Figure 3 **Random effects analysis at the event level in the OCD patient group.** Hyperactivation of caudal dorsal cingulate cortex, amygdala, insula, putamen, globus pallidus and right caudate and deactivation of ventromedial prefrontal cortex. Peak deactivation coordinates (*x*,*y*,*z*): (SAG) left caudal dorsal cingulate cortex, BA 24, (−10,19,30), right caudal dorsal cingulate cortex, BA 24, (2,7,30); (TRA) right amygdala (23,−8,−9), left amygdala (−22,−3,−10), right ventromedial PFC/orbitofrontal cortex (8,52,−6), left ventromedial PFC/orbitofrontal cortex (−7,46,−6): (COR) left putamen (−19,−2,6), right putamen (23,1,2), right caudate (17,1,18), right palidum (12,1,6), left palidum (−16,−2,9), left insula (−34,19,9) right insula (31,13,18). Contrast: decision to reject + reject events > neutral condition, $P < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 104 voxels. COR = coronal; SAG = sagittal; RFX = random effects; TRA = transverse; A = anterior; P = posterior; L = left; R = right.

thalamus, insula, putamen, globus pallidus and right caudate whereas the ventromedial PFC remained deactivated (decision to reject + reject events > neutral condition) (all $P < 0.05$ corrected) (Fig. 3). When these phases were considered separately, bilateral putaminal hyperactivation was only found in the decision to reject phase (Fig. 4, left panel A), deactivating immediately after the stimulus withdrawal (contrast: decision to reject > reject event) ($P < 0.05$ corrected) (Fig. 4A). During relief periods (relief > neutral), patients showed activation in bilateral amygdala and deactivation in bilateral caudate and putamen (all $P < 0.05$ corrected) (Fig. 4C).

There were no correlations between the imaging results and the Beck Depression Inventory and anxiety scores, suggesting that these covariates were not explaining our results.

Considering that OCD is a clinically heterogeneous disorder, characterized by different symptom dimensions that

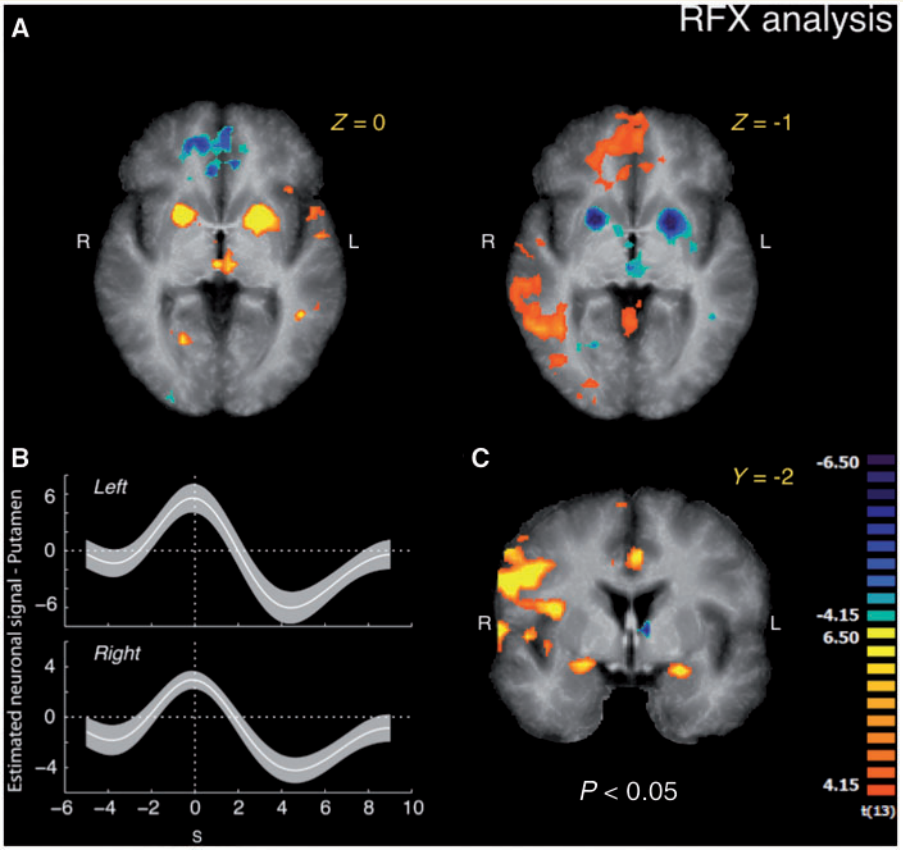

Figure 4 Analyses at the event level in the OCD patient group. (**A**) *Left*: Hyperactivation of bilateral putamen just before rejection events in the OCD patient group. Contrast: decision to reject > reject events, $P < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 17 voxels. Peak activation coordinates (*x*,*y*,*z*): left putamen (−19,4,0), right putamen (20,4,3). *Right*: Hypoactivation of bilateral putamen during stimulus withdrawal, $P < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 8 voxels. Peak activation coordinates: left putamen (−19,4,0), right putamen (20,4,3). (**B**) Estimated neuronal signal from the putamen (left and right) obtained by haemodynamic deconvolution of the blood oxygen level-dependent response. Zero represents the timing in which the rejection event started. (**C**) Activation of amygdala during relief periods. Peak activation coordinates: left amygdala (−25,1,−12) and right amygdala (17,−5,−9). Deactivation in bilateral caudate and putamen is not shown in this slice. Contrast: relief events > baseline, FFX general linear model, $P < 0.05$ FDR corrected, minimum cluster size = 103 voxels.

may have partially distinct neural correlates (Mataix-Cols *et al.*, 2007) we followed the factor analytic approach and methodology based on the Yale-Brown Obsessive-Compulsive Scale checklist scores used by Katerberg *et al.* (2010) to perform a multiple regression analysis to predict blood oxygen level-dependent responses in the regions of interest observed in patients. We found that putaminal hyperactivation was predicted by the contamination/cleaning factor (left putamen: $P = 0.010$; right putamen: $P = 0.023$), with a positive correlation (Pearson r = 0.68, $P = 0.008$ and Pearson r = 0.54, $P = 0.036$, respectively); right caudate head deactivation was predicted by symmetry/hoarding factor ($P = 0.03$), with a trend for negative correlation (Pearson r = −0.45, $P = 0.06$); and left insula hyperactivation was predicted by almost all factors (contamination/cleaning, $P = 0.011$; doubts, $P = 0.012$; superstitions/rituals, $P = 0.008$; and symmetry/hoarding $P = 0.005$).

Our random effects analysis highlighted hyperactivity and deactivations of specific networks in response to strong exposure in the OCD group: (i) deactivation of ventromedial/orbitofrontal, pregenual frontal cortex and caudate structures; and (ii) hyperactivation of putamen, amygdala, insula, subthalamic nucleus and dorsal caudal cingulate (BA 24) and their neighbouring presupplementary motor area structures. Given the identification of this dichotomous circuitry, we ran a Granger causality analysis (Roebroeck *et al.*, 2005). We selected seed regions based on the regions identified in the random-effects analysis to analyse a data-driven search for causal network activation: caudate head, ventromedial PFC/orbitofrontal cortex (deactivated areas) putamen, amygdala and the posterior subregion of dorsal ACC (BA 24) (hyperactivated areas). The effective connectivity analysis identified two main structures causally influencing the circuitry shown in our provocation paradigm: the ventromedial PFC causally influenced caudate head, amygdala and putamen and the putamen causally influenced the caudal part of the ACC, that is near the presupplementary motor area (Fig. 5A).

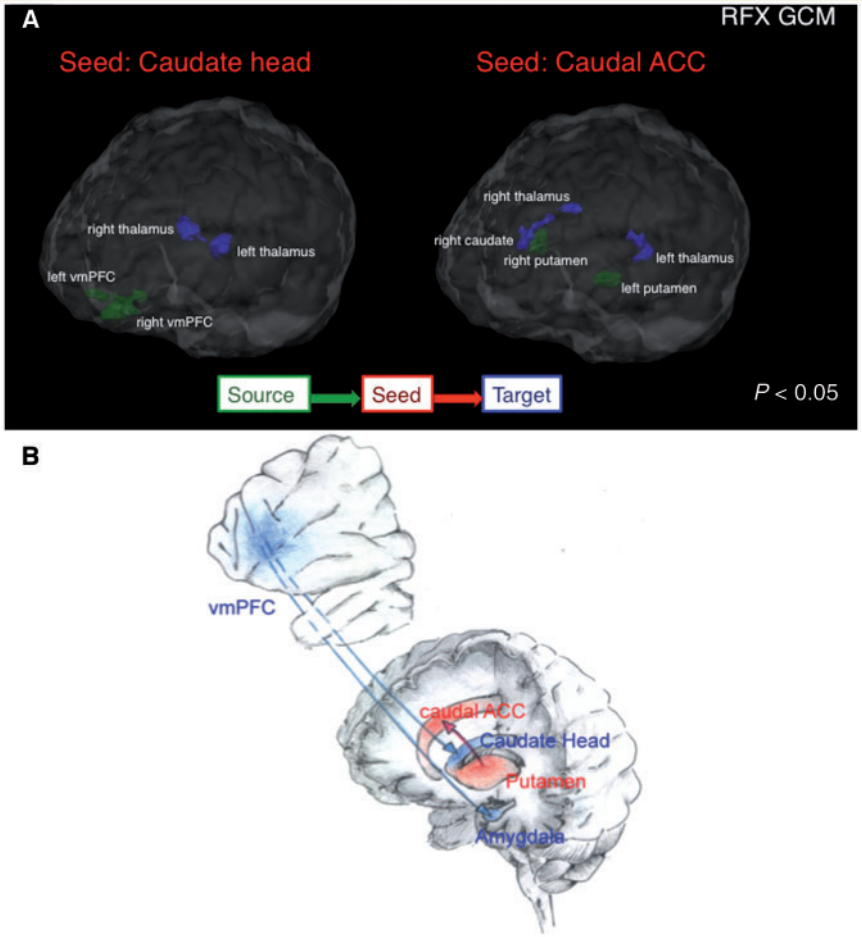

Figure 5 Connectivity analysis and causal model. (**A**) Connectivity analysis. Granger causality analysis shows that the head of the caudate (seed region from random effects general linear model analysis) is causally influenced by ventromedial prefrontal cortex (vmPFC) and that the caudal dorsal cingulate cortex (seed region for analysis) is influenced by the putamen. Putamen and amygdala seed region analyses are not shown in this figure but are referred to in the Results section. (**B**) Causal model inspired by integrating functional MRI and causality results: prefrontal structures (ventromedial prefrontal cortex) gate the modulation of basal ganglia (caudate and putamen) and limbic areas (amygdala). Putamen, by turn, a structure involved in repetitive and habitual behaviour, gates the activation of structures mediating action monitoring and repeated action patterns such as the caudal dorsal cingulate cortex and the presupplementary motor area (not shown). GCM = Granger Causality Modelling; RFX = random effects.

Discussion

In this study we focused on the neural correlates of symptom generation in OCD, by using a novel symptom provocation stimulation task in which subjects were exposed to individually tailored stimuli in real-time and further paired with a measure of the avoidance response. We presumed this avoidance or rejection responses modelled the compulsive behaviour and that our task design would allow us to examine their neural correlates as well as their preceding and subsequent phases. Our study design thus allowed the dissociation of neural correlates underlying phases of exposure, the decision to perform the compulsive action, rejection and relief.

We identified a dichotomous pattern of activation/deactivation during exposure to symptom provocation specifically in patients with OCD, which was not observed in healthy controls: (i) decreased activity in ventromedial and dorsolateral PFC and dorsal caudate; and (ii) hyperactivity of bilateral putamen, caudal cingulate cortex (BA24), presupplementary motor area and supplementary motor area, subthalamic nucleus and limbic regions such as amygdala and insular cortex. Hyperactivity of bilateral putamen in particular was localized to the decision phase before a rejection event. Effective connectivity analysis using Granger Causality Modelling identified two main structures causally influencing this circuitry shown in OCD symptom provocation: the ventromedial PFC and the putamen. The former may underlie the integration of affective meaning

and behaviour regulation, whereas the latter may be critically involved in habit formation and repetitive response selection.

This dichotomous circuitry contrasts with patterns of fronto-striato-limbic hyperactivation shown in previous OCD studies, which is likely related to differences in task nature and design, leading to distinct functional interpretation. For instance, several studies in OCD show increased activity in frontal areas using different behavioural tasks; however, these studies focus on testing different cognitive processes and tasks rather that symptom generation (Fitzgerald *et al.*, 2005; Maltby *et al.*, 2005; Chamberlain *et al.*, 2008). Moreover, some symptom evocation and provocation studies asked patients to imagine, recognize or recall contexts related to past symptoms using exposure to images or words (Mataix-Cols *et al.*, 2004; Nakao *et al.*, 2005; Schienle *et al.*, 2005; Gilbert *et al.*, 2009; Simon *et al.*, 2010; Baioui *et al.*, 2013) or using real sensory stimulation (physical objects) (McGuire *et al.*, 1994; Rauch *et al.*, 1994; Breiter *et al.*, 1996; Adler *et al.*, 2000; Hendler *et al.*, 2003). However, these previous studies did not include subject-driven feedback, and were not designed to address the link between symptom provocation and compulsive behaviour. This novel feature used in our task may be one of the main reasons for the identification of differential involvement of frontal areas known to be related to executive control and behaviour regulation (Hare *et al.*, 2009; Roy *et al.*, 2012). Another possible reason may be related to differences in the efficacy of the symptom provocation across the studies. A study in children (Gilbert *et al.*, 2009) showed a deactivation pattern similar to that observed in our study although this study did not assess efficacy of symptom provocation or specifically test avoidance events at the event level.

Our results are consistent with the account that ventromedial PFC gates activity of regions involved in goal-oriented behaviour such as the caudate nucleus and interconnected regions such as the dorsolateral PFC. Additionally, activation of the putamen, a critical structure in repetitive, habitual behaviour, leads in turn to overactivation of other structures such as the caudal part of dorsal ACC known to be involved in conflict monitoring and response selection (BA 24) and presupplementary motor area (Graybiel, 2008; Robbins *et al.*, 2012) (Fig. 5B). These latter regions may mediate repeated-action patterns and action control under conflict. Our findings thus dovetail with animal models of compulsivity (Dias-Ferreira *et al.*, 2009; Gremel and Costa, 2013) and are corroborated by human structural connectivity data, suggesting a duality that predicts differences in the balance between habitual and goal-directed action control (de Wit *et al.*, 2012; Meunier *et al.*, 2012). This duality is also present in diseases with impaired action control such as Parkinson's disease, with differential effects on goal-directed and habitual processes (Hadj-Bouziane *et al.*, 2012).

The ventromedial PFC is suggested to be a key structure in the integration of value-guided stimulation and in mediating affective behavioural and physiological responses (Roy *et al.*, 2012). Alternatively, the ventromedial PFC may also be related to impairments in conditioned fear extinction. Milad *et al.* (2013) have recently shown that patients with OCD show deficits in conditioned fear extinction, particularly in recalling extinction memory, an effect associated with reduced activation in ventromedial PFC (Milad *et al.*, 2013). Lesions in the ventromedial PFC in rodents are also associated with increased recovery of fear a day after extinction training, demonstrating the role of the ventromedial PFC in consolidation of extinction learning and consequent inhibition of inappropriate behaviours (Quirk *et al.*, 2000). Recall of a fearful memory and consequent ventromedial PFC deactivation triggered by the provocation stimuli may also play a role in the provocation aspect of our study. Thus, deficits in affective integration of stimuli that trigger OCD-related fears, which in turn result in failure to activate the ventromedial PFC/orbitofrontal cortex and consequent impairment of activity in the network involved in goal-directed behaviours shifting instead to salient stimuli, might induce pathological habitual behaviours.

We showed an important functional role for the putamen in OCD with greater bilateral putaminal hyperactivation during the decision phase, in the course of stimulus exposure, before the rejection event (Fig. 3). Our findings are consistent with a model in which the provocation stimulus is encoded as a potential threat or activation of a fearful memory via a ventromedial PFC-putamen-caudal ACC and presupplementary motor area network involved in repetitive behaviours. With sufficient exposure, the urge for the compulsive avoidance behaviour is then mediated via putaminal activation, which biases the OCD cognitive system towards the potential threat stimuli, activating the habitual-system and producing automatic responses. Previous studies demonstrated dorsal ACC involvement in conflict monitoring (Shackman *et al.*, 2011). The dorsal ACC is a wide structure containing several areas and the subdivisions that seem to be hyperactive in our paradigm are related to response selection and conflict monitoring. Accordingly, a notable meta-analysis that performed a connectivity-based parcellation of the human cingulate cortex, focusing on its relations to functional specialization, suggested that a more anterior part of the dorsal ACC (anterior cingulate sulcus and paracingulate cortex) monitors action errors and conflict whereas a more posterior zone underlies response selection (Beckmann *et al.*, 2009). We found hyperactivity in mid-cingulate and caudal dorsal cingulate regions that mediate both cognitive components in conflict monitoring and response selection components. Two theories predominate about the overall function of this region of cortex: 'conflict monitoring' and 'attention/selection for action' (Botvinick *et al.*, 1999). A role for cognitive evaluation seems to be relevant. This is also consistent with the activation of the presupplementary motor area, which has a more cognitive function than the supplementary motor area proper and is involved in monitoring of action switching (Picard and

Strick, 2001). This view is supported by the results of Pardo *et al.* (1990), who found activation in the presupplementary motor area during the Stroop conflict task (Pardo *et al.*, 1990). Overall presupplementary motor area function is more closely related to maintenance of relevant sensory information than response selection or production.

As expected, we observed increased activity in paralimbic regions such as the amygdala (in particular during post-rejection appraisal) and insular cortex, similar to other studies on symptom provocation and fear (Shapira *et al.*, 2003; Schienle *et al.*, 2005; Simon *et al.*, 2010, 2013; Admon *et al.*, 2012; Stern *et al.*, 2012). These structures have consistently been associated with emotional processing, especially in detecting and appraising potential threats (amygdala) (Fiddick, 2011) and pain perception (insula) (Apkarian *et al.*, 2005; Mutschler *et al.*, 2012). Interestingly, we found hyperactivity in subthalamic nucleus and substantia nigra during exposure to strong provocation in patients as compared to healthy controls. Importantly, the subthalamic nucleus has been successfully targeted for neurosurgical treatment with deep brain stimulation both in Parkinson's disease (Limousin *et al.*, 1995) and OCD (Mallet *et al.*, 2008).

There were some limitations to this study. First, the majority of our patients with OCD were taking selective serotonin reuptake inhibitors and/or anxiolytic medication, which might potentially influence the neuronal and behavioural responses. However, as we used a within-patient repeated-measures design with each subject acting as their own control, in addition to the between-group analyses, we could control for confounding variables and within-subject variability (Hedayat and Yang, 2005). Second, our study sample size did not allow for splitting into subgroups to investigate a neuronal differentiation of OCD subtypes. However, we performed a multiple regression analysis with the five mean dimensional scores resulting from the Yale-Brown Obsessive-Compulsive Scale checklist to predict patients' blood oxygen level-dependent responses in regions of interest. This analysis provided additional evidence for corticostriatal dissociation, with putaminal hyperactivation being better predicted by the contamination/cleaning factor. Follow-up investigations further aiming to differentiate neuronal indices symptomatically may therefore be interesting to pursue in the future and should also address the direct influence of comorbidities in different OCD subtypes.

The existence of a dichotomous pattern of deactivation/hyperactivation may provide evidence for a novel functional parcellation of the neural circuitry involved in OCD at the event level and possibly other neuropsychiatric disorders of impulse control and/or compulsive behaviour. This is consistent with behavioural and anatomical data from an animal model (Dias-Ferreira *et al.*, 2009; Gremel and Costa, 2013) and human connectivity findings (de Wit *et al.*, 2012; Meunier *et al.*, 2012). Our results also put in a new context previous studies that failed to show activation of ventromedial PFC/medial orbitofrontal cortex in OCD, albeit in tasks where nature is not directly related to symptom generation (Rauch *et al.*, 2007). Our results favour the perspective that this dichotomy may represent a generic phenomenon, supporting the existence of a circuit underlying habitual behaviour that is overactivated in impulse control disorders. Dias-Ferreira *et al.* (2009) have proposed that stress can cause compulsive behaviours in the rat due to abnormal cortico-striatal activation, and Gremel and Costa (2013) have shown that inhibition of orbitofrontal cortex disrupts goal-directed actions, whereas activation of this structure specifically increases goal-directed performance. These results are compatible with our findings.

Our results also support the recent suggestion that dysfunction in the goal-directed response system and increased reliance on the habitual-response system are fundamental mechanisms that may underlie the urge to perform compulsive acts (Gillan *et al.*, 2011). The ventromedial PFC-putaminal-dorsal cingulate cortex (BA 24) pathway points towards abnormal affective integration of stimuli, conflict monitoring and decision-making, favouring repetitive actions based on increased error signalling (Botvinick *et al.*, 2004; Robinson *et al.*, 2013). Cingulotomy has been shown to significantly reduce OCD (Dougherty *et al.*, 2002; Richter *et al.*, 2008) in line with this model. Finally, our findings corroborate results using transcranial magnetic stimulation on frontal regions and supplementary motor area and deep brain stimulation focusing on the caudate nucleus (Bourne *et al.*, 2012; Jaafari *et al.*, 2012). They are also in agreement with the view that exogenous stimulation may restore behavioural control from the striatum back to PFC regions, thereby reversing the state of pathological imbalance (Mian *et al.*, 2010).

Taken together, our findings may inform the development of therapeutic interventions, for instance using transcranial magnetic stimulation, aiming to target regions specifically involved in action control or repetitive behaviour in order to enhance or downregulate the brain activity that specifically underlies the experienced symptoms.

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Supplementary material

Supplementary material is available at *Brain* online.

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