Differential frontal–striatal and paralimbic activity during reversal learning in major depressive disorder and obsessive–compulsive disorder

P. L. Remijnse[1,2]*, M. M. A. Nielen[1], A. J. L. M. van Balkom[1,3], G.-J. Hendriks[4,5], W. J. Hoogendijk[1,3], H. B. M. Uylings[2,6,7] and D. J. Veltman[1,2,3]

[1] *Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands*
[2] *Graduate School Neurosciences, Amsterdam, The Netherlands*
[3] *Out-patient Academic Clinic for Anxiety and Mood Disorders, GGZ Buitenamstel, Amsterdam, The Netherlands*
[4] *Out-patient Clinic for Anxiety Disorders, GGZ Nijmegen, The Netherlands*
[5] *Department of Psychiatry, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*
[6] *Department of Anatomy and Neuroscience, VU University Medical Center, Amsterdam, The Netherlands*
[7] *School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, University of Maastricht, The Netherlands*

Background. Several lines of research suggest a disturbance of reversal learning (reward and punishment processing, and affective switching) in patients with major depressive disorder (MDD). Obsessive–compulsive disorder (OCD) is also characterized by abnormal reversal learning, and is often co-morbid with MDD. However, neurobiological distinctions between the disorders are unclear. Functional neuroimaging (activation) studies comparing MDD and OCD directly are lacking.

Method. Twenty non-medicated OCD-free patients with MDD, 20 non-medicated MDD-free patients with OCD, and 27 healthy controls performed a self-paced reversal learning task in an event-related design during functional magnetic resonance imaging (fMRI).

Results. Compared with healthy controls, both MDD and OCD patients displayed prolonged mean reaction times (RTs) but normal accuracy. In MDD subjects, mean RTs were correlated with disease severity. Imaging results showed MDD-specific hyperactivity in the anterior insula during punishment processing and in the putamen during reward processing. Moreover, blood oxygen level-dependent (BOLD) responses in the dorsolateral prefrontal cortex (DLPFC) and the anterior PFC during affective switching showed a linear decrease across controls, MDD and OCD. Finally, the OCD group showed blunted responsiveness of the orbitofrontal (OFC)–striatal loop during reward, and in the OFC and anterior insula during affective switching.

Conclusions. This study shows frontal–striatal and (para)limbic functional abnormalities during reversal learning in MDD, in the context of generic psychomotor slowing. These data converge with currently influential models on the neuropathophysiology of MDD. Moreover, this study reports differential neural patterns in frontal–striatal and paralimbic structures on this task between MDD and OCD, confirming previous findings regarding the neural correlates of deficient reversal learning in OCD.

Introduction

Reversal learning is a neuropsychological function crucial for socio-emotional learning and behavior in primates (Rolls, 1999). It is defined as the ability to associate neutral stimuli with their rewarding or punishing values, and to alter these associations upon

* Address for correspondence : P. L. Remijnse, M.D., VU University Medical Center, Department of Anatomy and Neurosciences, room G102B, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.

(Email : PL.Remijnse@vumc.nl)

reversing reinforcement contingencies (Dias *et al.* 1996 ; Rolls, 1999). Several lines of evidence indicate that reversal learning (also termed affective switching) is disturbed in major depressive disorder (MDD), at a clinical, behavioral and neural level.

Clinically, MDD is by definition characterized by 'anhedonia' (APA, 1994) and patients with MDD experience a negative thought bias (Beck, 1963). Neurocognitive studies have reported aberrant responding to reward and punishment feedback in depressed patients (Henriques *et al.* 1994 ; Elliott *et al.* 1996 ; Must *et al.* 2006), and also a reduced ability to

exert inhibitory control during an affective switching (go/no-go) task (Murphy *et al.* 1999). At a neuro-chemical level, there is abundant evidence that the pathophysiology of MDD is characterized by under-lying dysfunctional serotonin [5-hydroxytryptamine (5-HT)] transmission (Mann *et al.* 1996), and various manipulations of 5-HT neurotransmission in human volunteers (Rogers *et al.* 1999; Chamberlain *et al.* 2006) have induced impaired performance on two-choice discrimination reversal tasks. For instance, acute tryptophan depletion (ATD) has been shown to affect reversal learning in healthy subjects (Murphy *et al.* 2002; Evers *et al.* 2005), and to induce a temporary re-lapse of depressive symptoms in recovered patients with MDD (Smith *et al.* 1997).

Finally, lesion and neuroimaging studies in non-human and human primates have implicated the or-bitofrontal (OFC)–striatal circuit in reversal learning (Dias *et al.* 1996; Fellows & Farah, 2003; Clark *et al.* 2004), which is one of the brain's parallel frontal–striatal circuits supposedly involved in the pathophy-siology of MDD (Alexander *et al.* 1990; Rogers *et al.* 2004). However, recent neuroimaging work has shown the engagement of additional frontal cortical brain areas in reversal learning, in particular the dorso-lateral prefrontal cortex (DLPFC), anterior PFC, an-terior insula, and anterior cingulate cortex (ACC) (Remijnse *et al.* 2005*a*; Budhani *et al.* 2006); that is, re-gions also implicated in MDD (Drevets, 2000; Phillips *et al.* 2003; Mitterschiffthaler *et al.* 2006).

Taken together, these findings suggest that per-formance of reversal learning may be impaired in MDD, associated with functional abnormalities in frontal–striatal and (para)limbic brain regions. To date, one neuropsychological study has reported a preserved ability to acquire and reverse a probabilistic discrimination, but an incapacity for depressed pa-tients to maintain response set in the face of mislead-ing negative feedback after having attained criterion for successful discrimination (Murphy *et al.* 2003).

Obsessive–compulsive disorder (OCD) is fre-quently a co-morbid disorder with MDD (Overbeek *et al.* 2002) and shares several features with MDD, including symptomatic overlap (Ninan & Berger, 2001) and clinical improvement following sero-tonergic antidepressants (Levine *et al.* 2001). However, MDD and OCD differ with respect to core clinical symptoms and neuropsychological profiles (Purcell *et al.* 1998; Joel *et al.* 2005). Ideally, identification of shared and distinct neural substrates for MDD and OCD may lead to a biologically grounded distinction between these disorders (Chamberlain *et al.* 2005; Chamberlain & Sahakian, 2006). We know of only two neuroimaging studies comparing these two disorders directly (Edmonstone *et al.* 1994; Saxena *et al.* 2001),

demonstrating increased activity in the bilateral putamen but diminished activity in the left hippo-campus (for MDD *versus* OCD) during the resting state. To date, neuroimaging activation studies using cognitive or mixed cognitive/emotional paradigms in MDD and OCD have not yielded consistent findings regarding differential involvement of brain areas in these disorders (Drevets, 2000; Phillips *et al.* 2003; Remijnse *et al.* 2005*b*), and comparative studies in this field are lacking.

We have recently published studies on the neural correlates of reversal learning in a group of healthy volunteers (Remijnse *et al.* 2005*a*) and also in com-parison with a sample of OCD patients (Remijnse *et al.* 2006). The aim of the present study was twofold: first, we sought to explore the neural correlates of reversal learning using functional magnetic resonance imaging (fMRI) in a sample of unmedicated patients with MDD, compared with our healthy control group that has been described before (Remijnse *et al.* 2005*a*). Based on existing neuropsychological and neuroima-ging data, we hypothesized impaired performance in the patient group, associated with abnormal OFC–striatal (Fellows & Farah, 2003; Clark *et al.* 2004), DLPFC and anterior PFC, ACC and insular activations (Remijnse *et al.* 2005*a*; Budhani *et al.* 2006). Second, we aimed to compare MDD and OCD directly in a single activation design. We recently demonstrated impaired reversal learning in OCD, associated with abnormal OFC–striatal, DLPFC, anterior PFC and anterior insular activity compared with healthy con-trols (Remijnse *et al.* 2006). However, as this previous OCD sample included patients with co-morbid de-pression, we assembled a new group of MDD-free, unmedicated OCD patients for the current study. Based on the sparse direct-comparison neuroimaging literature (Edmonstone *et al.* 1994), we hypothesized that patients with MDD may show increased putamen activity, compared with OCD patients.

Method

Subjects

Twenty patients with OCD-free MDD, 20 patients with OCD and currently (but not lifetime) free of MDD, and 27 healthy controls participated in this study (Table 1). The current OCD group consisted of 13 MDD-free OCD patients that also participated in our previous study (Remijnse *et al.* 2006), and seven newly recruited patients. Diagnoses and co-morbidity were established by experienced clinicians with the Structured Clinical Interview for DSM-IV Axis-I dis-orders (SCID; First *et al.* 1996). Exclusion criteria were the presence of alcohol or substance abuse at the time

Table 1. *Demographic and clinical data for patients with major depressive disorder* (MDD), *patients with obsessive–compulsive disorder* (OCD), *and for the healthy control group*

	MDD ($n=20$)	OCD ($n=20$)	Controls ($n=27$)	Between-groups comparison p value
Sex (female/male)	8/12	15/5	19/8	0.04*
Age in years (range)	35 (21–54)	34 (19–54)	32 (22–53)	0.64†
Handedness (R/L)	16/4	17/3	23/4	0.87*
Education (range 1–10)[a], mean (S.D.)	8.0 (2.1)	8.5 (1.1)	8.6 (1.4)	0.41†
Total YBOCS severity score, mean (S.D.), range		22.2 (5.1), 11–31		
Number of OCD patients with prior MDD/mean length in months since remission of MDD		8/36		
Padua-IR, mean (S.D.)	42.4 (32.5)[b]	59.7 (27.8)[b]	11.5 (10.4)	<0.001† MDD=OCD>CO‡
BDI, mean (S.D.)	25.6 (7.6)[b]	12.2 (7.7)[c]	1.7 (2.6)	<0.001† MDD>OCD>CO‡
HAMD-17, mean (S.D.)	19.1 (4.1)	6.9 (4.0)[d]	0.4 (0.9)	<0.001† MDD>OCD>CO‡
MADRS, mean (S.D.)	29.7 (4.7)	9.1 (6.5)[b]	0.6 (0.9)	<0.001† MDD>OCD>CO‡
HAMA, mean (S.D.)	19.9 (5.0)[b]			

Y-BOCS, Yale–Brown Obsessive–Compulsive Scale; Padua-IR, Padua Inventory Revised; BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CO, controls; S.D., standard deviation.

[a] 1 denotes primary school unfinished, 10 denotes university graduated. [b] Assessed in 18 patients. [c] Assessed in 17 patients. [d] Assessed in 15 patients.

* χ^2 test. † Analysis of variance (ANOVA). ‡ *Post-hoc* Tukey and Scheffe tests: $p<0.05$.

of study, and major internal or neurological disorders. In the MDD group, co-morbidity was as follows: social anxiety disorder ($n=3$), generalized anxiety disorder ($n=1$), panic disorder without agoraphobia ($n=1$), pain disorder ($n=1$), and cannabis abuse in early ($n=1$) and sustained ($n=1$) full remission. Twelve patients were free from co-morbidity, and six patients had their first lifetime depressive episode.

In the OCD group, nine patients were diagnosed with 'pure' OCD and the following disorders were co-morbid: post-traumatic stress disorder ($n=1$), panic disorder ($n=2$), generalized anxiety disorder ($n=4$), dysthymic disorder ($n=4$), social anxiety disorder ($n=4$), and opioid abuse in sustained full remission ($n=1$). Co-morbid Tourette disorder was clinically diagnosed in one patient. The mean duration of illness was 19.9 years in this group. At the time of the study, all patients and control subjects were free from psychotropic medication for at least 2 weeks, and in case of fluoxetine or antipsychotic medication for at least 1 month. Eight patients in the MDD group and seven patients in the OCD group were medication naïve, and the mean length of drug-free interval was 16 months

in the MDD sample and 30 months in the OCD group. All participants gave written informed consent and the study was approved by the ethical review board of the VU University Medical Center.

To assess symptom characteristics and severity scores, the Yale–Brown Obsessive–Compulsive Scale (YBOCS; Goodman *et al.* 1989) was administered in OCD patients only, and the Padua Inventory Revised (Padua-IR; Sanavio, 1988) was used to measure all participants' obsessive–compulsive (OC) characteristics. To rate the presence and severity of depressive symptoms in all three groups, the Beck Depression Inventory (BDI; Beck *et al.* 1961), the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1967) and the 10-item Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) were used. The Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) was administered in MDD patients only. Because of logistic problems in the patient groups, five patients with OCD failed to be interviewed with the HAMD-17 or with the MADRS ($n=2$), and two MDD patients failed to be interviewed with the HAMA.
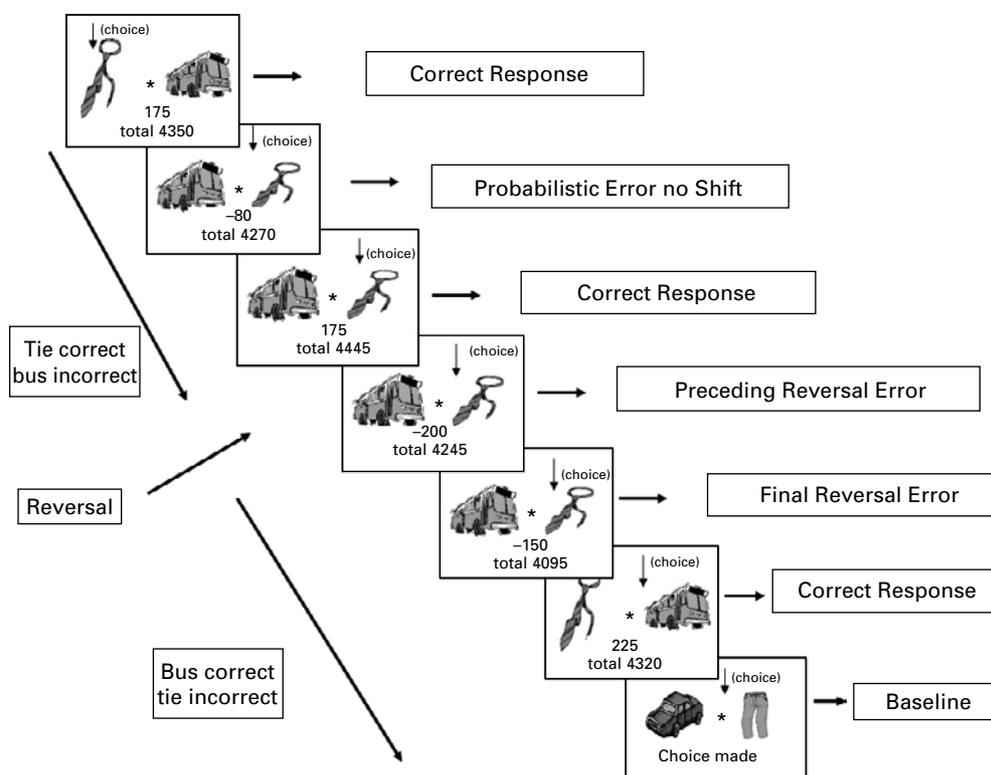
Fig. 1. The reversal learning task. In this example (consecutive trials are running from top-left to bottom-right) all events of interest are displayed. See Method section for details.

Two OCD patients and two MDD patients did not return the Padua-IR questionnaire. Three OCD patients and two MDD patients did not return the self-report BDI.

Reversal learning task and experimental procedure

We used a self-paced, probabilistic reversal learning task with an affectively neutral baseline (Fig. 1) that has been described previously (Remijnse *et al.* 2005*a*). Each trial in the experimental task consisted of two stimuli (a cartoon of a bus and a tie) presented at either side of a screen with randomized locations, for 3000 ms maximally. Subjects selected either stimulus by pressing the left or right button on a button box. Each trial ended with the presentation of positive or negative feedback in the form of a 2000 ms display of the number of points won or lost in that trial and the amount of accumulated points in the task up to that trial. This was followed by a fixation cross for 1000 ms.

Upon a correct response, either positive or negative feedback was given based on an 80:20 ratio, consisting of gaining or losing a random amount of 80–250 points. A correct response with a reward outcome was defined as a 'Correct Response'. A correct response that was probabilistically given negative feedback ('Probabilistic Error') could either lead to a shift in stimulus selection ('Probabilistic Error with Shift')

or not lead to such a shift ('Probabilistic Error no Shift'). The chance of a second, consecutive Probabilistic Error was 1:10 after a first Probabilistic Error. False responses ('Spontaneous Errors') were always given negative feedback. The criterion for reversal was reached after 6–10 correct responses (randomized). Immediately after reversal (unknown to the subject), a false response (according to the new criterion) not leading to a shift to the new correct stimulus was designated a Preceding Reversal Error, and the last false response prior to a shift a Final Reversal Error.

Affectively neutral baseline trials consisting of two different, equivalent stimuli (the cartoon of a car and a pair of trousers) were randomly presented interspersed with every seventh experimental trial on average. Baseline trials were never presented more than once consecutively, and put a minimal load on working memory (subjects were instructed in advance which of the two baseline stimuli to select), thus minimizing possible interference effects. Responses in this baseline task were given neutral feedback ('choice made') for 2000 ms, followed by a fixation cross for 1000 ms. The scanning session ended after 400 trials (including baseline trials) and lasted about 25 min. After the scanning session, participants received the total amount of accumulated points during the task divided by 1000 in euros.

Imaging procedure

Imaging data were collected using a 1.5-T Sonata MR system (Siemens, Erlangen, Germany) with a standard receiver head coil. Task stimuli were projected onto a screen at the end of the scanner table, visible through a mirror mounted above the subject's head. Two magnet-compatible response boxes were used to record the subject's responses.

T2*-weighted echo-planar images (EPIs) with blood oxygen level-dependent (BOLD) contrast were acquired. A customized EPI sequence sensitive to the OFC signal was used (Deichmann *et al.* 2003; Remijnse *et al.* 2006). The acquisition plane was tilted parallel to the air–tissue interface of the OFC for each subject ($0–15°$ from the anterior–posterior commissure line). Using this sequence with a repetition time of 2.18 s and an echo time of 45 ms, 35 slices (3×3 mm in-plane resolution; 2.5 mm slice thickness; matrix size 64×64) were obtained.

Data analysis

Demographic and behavioral data were analyzed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). For behavioral analysis, we assessed the mean number of baseline trials, Correct Responses, Probabilistic Errors no Shift, Final Reversal Errors, Preceding Reversal Errors, Probabilistic Errors with Shift, and Spontaneous Errors, the mean reaction times (RTs) for these events and the number of points accumulated by the end of the task. Performance differences between groups were assessed by one-way analyses of variance (ANOVAs) with Group (MDD *versus* OCD *versus* controls) as the between-subject factor and Event Type as the within-subject factor. In addition, correlations were calculated between performance measures and depression or OC severity measures for the MDD and the OCD group respectively.

Imaging analysis was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Images were reoriented, slice-timed and realigned to the first volume. The resulting mean image was then co-registered with the whole-brain EPI volume, and images were normalized to MNI space as defined by an SPM T2* template and spatially smoothed using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. Statistical analysis was carried out in the context of the general linear model, in which each event was modeled using a delta function convolved with the canonical hemodynamic response function (HRF). The following events were modeled to the onset of the feedback presentation, as defined previously: (1) baseline events, (2) Correct Responses, (3) Probabilistic Errors no Shift, (4) Preceding Reversal Errors, and (5) Final Reversal Errors. Two events were modelled as events of no interest: (6) Spontaneous Errors and (7) Probabilistic Errors with Shift. We excluded the latter from analysis because these were regarded as part of a subject's trial-and-error strategy instead of capturing a genuine set shift in stimulus–reinforcement associations. Movement parameters were included in the model as regressors of no interest.

The following contrasts were computed: (1) Correct Responses minus baseline trials to assess the main effect of reward, (2) Probabilistic Errors no Shift + Preceding Reversal Errors + Final Reversal Errors minus baseline trials to assess the main effect of all punishment events, and (3) Final Reversal Errors minus (Probabilistic Errors no Shift + Preceding Reversal Errors) to subtract punishment events not leading to a shift from punishment events prior to a shift, to isolate affective switching (Remijnse *et al.* 2005*a*). Contrasts (1) and (2) involved the affectively neutral baseline to assess the neural substrate of the main effect of reward and punishment respectively. This ensured that general aspects of motivational processing were not left undetected.

Contrasts were first performed at single-subject level. These were then entered into a second-level (random effects) analysis by calculating one-sample *t* tests on each individual's contrast images for contrasts 1–3. Group main effects for each contrast (Appendix A) were analyzed with one-way ANOVA. Next, we performed Group × Task interaction analyses for our contrasts of interest. Group main effects were adjusted for the whole-brain search volume using the false discovery rate (FDR) method implemented in SPM2 (Genovese *et al.* 2002), and reported at a significance level of $p < 0.05$. Interaction effects, masked with the relevant main effect, were reported at $p < 0.001$ uncorrected for multiple comparisons, or at a slightly lower threshold for regions of *a priori* interest as mentioned in the introduction ($p < 0.005$ uncorrected).

Results

Demographic and clinical data

The three groups were adequately matched for age, handedness and education level, but not gender (Table 1). A one-way between-groups ANOVA showed main effects for all depression symptom severity measures (BDI, HAMD-17 and MADRS), which was due to MDD patients scoring significantly higher than OCD patients, and OCD patients significantly higher than controls. On the Padua-IR, a one-way between-groups ANOVA revealed a main effect due to both patient groups scoring higher than controls.

A subsequent analysis of Padua-IR scores in the MDD group demonstrated that these were related to the rumination ($n=14$), precision ($n=1$), checking ($n=2$) and impulses ($n=1$) subdimensions (van Oppen *et al.* 1995).

Behavioral data

A one-way ANOVA showed performance differences across groups for mean RTs on baseline trials [$F(2, 64) = 4.6$, $p < 0.05$], Correct Responses [$F(2, 64) = 4.8$, $p < 0.02$], Probabilistic Errors no Shift [$F(2, 64) = 3.4$, $p < 0.04$], Preceding Reversal Errors [$F(2, 64) = 4.0$, $p < 0.03$] and Probabilistic Errors with Shift [$F(2, 64) = 6.2$, $p < 0.004$] (Table 2). Paired comparisons showed significant RT differences between patients with MDD and healthy controls on baseline trials (independent samples t test: $t = -2.9$, $p < 0.005$) and Preceding Reversal Errors ($t = -2.2$, $p < 0.04$); and between patients with OCD and controls on baseline trials ($t = -2.2$, $p < 0.05$), Correct Responses ($t = -3.1$, $p < 0.003$), Probabilistic Errors no Shift ($t = -2.6$, $p < 0.02$), Preceding Reversal Errors ($t = -2.9$, $p < 0.005$) and Probabilistic Errors with Shift ($t = -3.5$, $p < 0.001$); but not between MDD and OCD patients. Furthermore, in the MDD group, we found significant positive correlations between mean RTs and depression severity measures (MADRS, HAMD-17 and BDI) for Correct Responses, Probabilistic Errors no Shift, Final Reversal Errors, Preceding Reversal Errors, Spontaneous Errors and Probabilistic Errors with Shift (correlations ranging between $r = 0.44$ and $r = 0.62$; all $p < 0.05$). No significant correlations were detected between mean RTs and OC severity scores in the OCD sample.

One-way ANOVA did not reveal significant performance differences across groups for mean numbers of events or points accumulated by the end of the task.

There were no significant correlations between mean numbers of events and depression severity measures in the MDD group, or OC severity measures in the OCD group, except for a negative correlation between mean number of Spontaneous Errors and YBOCS scores ($r = -0.46$, $p < 0.04$).

Imaging data

Reward

Between-group interaction analyses (Table 3) demonstrated increased activity in MDD patients compared with healthy controls in the left gyrus precentralis, right superior temporal and occipital cortex, and the left putamen. Comparing MDD patients with OCD patients, MDD patients showed increased activity in the right medial OFC, right superior temporal cortex, left occipital cortex and right putamen.

Punishment

Interaction analyses (Table 3) demonstrated increased activity in the left insular cortex and right precuneus in MDD patients *versus* healthy controls. Between-patient group comparisons showed left insular cortex hyperactivity for MDD *versus* OCD patients, but no activations for OCD *versus* MDD patients.

Affective switching

Interaction analyses (Table 3) showed greater activation in the left anterior PFC, right DLPFC, left ACC, right insula, left inferior parietal cortex and right thalamus in healthy controls *versus* patients with MDD (Fig. 2). The reverse contrast (MDD > controls) showed an increased BOLD signal in the right inferior parietal and the left superior parietal cortex. When comparing MDD and OCD patients directly, we found activation in the left anterior PFC, right DLPFC, left insula, bilateral superior temporal and left superior parietal cortex for MDD > OCD (Fig. 2), but no activity for OCD > MDD.

Discussion

The present study on reversal learning revealed mean RT differences across two groups of unmedicated patients with either MDD or OCD, and a sample of healthy controls. Patients with MDD were significantly slower to respond on baseline trials and Preceding Reversal Errors compared with normal controls, and there were significant positive correlations between mean RTs and depression severity measures for most event categories in the MDD group. These observations are in line with findings that MDD affects psychomotor reaction speed (Kalb *et al.* 2006). We found no differences in mean numbers of experimental events or accumulated points between MDD patients and controls. This finding seems to be in accordance with Murphy *et al.* (2003), who reported preserved ability to learn stimulus–reinforcement associations and to perform affective switching in medicated MDD patients. However, these authors also reported an increased tendency for depressed patients to switch response following misleading negative feedback, a cognitive measure roughly equivalent to the number of Probabilistic Errors with Shift in our task. We failed to replicate this finding, possibly because of major differences in task implementation between studies; for example, our experimental design, compared with Murphy *et al.* (2003), comprised a fivefold larger total number of trials (400 *v.* 80), implemented many *versus* only two reversal stages, and included no probabilistic positive reinforcement to incorrect stimuli.

Table 2. *Behavioral data on the reversal learning task for the group of patients with major depressive disorder (MDD), with obsessive–compulsive disorder (OCD), and for the healthy control group*

Event type	MDD ($n=20$) Mean number (S.D.)	Mean RT (S.D.)	OCD ($n=20$) Mean number (S.D.)	Mean RT (S.D.)	Controls ($n=27$) Mean number (S.D.)	Mean RT (S.D.)	Group × Event Type for mean numbers (ANOVA) F value df $=2, 64$	Group × Event Type for mean RTs (ANOVA) F value df $=2, 64$
Baseline trials	47 (2.4)	0.86 (0.18)	46 (3.1)	0.82 (0.16)	47 (3.5)	0.73 (0.13)	0.9 N.S.	4.6* OCD>CO† MDD>CO†
Correct Responses	224 (24.8)	0.66 (0.15)	224 (23.2)	0.73 (0.18)	224 (17.1)	0.59 (0.12)	0.01 N.S.	4.8* OCD>CO†
Probabilistic Errors no Shift	18 (4.6)	0.64 (0.16)	19 (7.6)	0.69 (0.18)	19 (7.7)	0.57 (0.13)	0.24 N.S.	3.4* OCD>CO†
Final Reversal Errors	17 (5.3)	0.67 (0.18)	16 (5.2)	0.72 (0.23)	17 (5.8)	0.60 (0.14)	0.17 N.S.	2.5 N.S.
Preceding Reversal Errors	17 (11.0)	0.65 (0.19)	15 (10.5)	0.68 (0.19)	16 (9.4)	0.56 (0.89)	0.22 N.S.	4.0* OCD>CO† MDD>CO†
Spontaneous Errors	54 (29.2)	0.77 (0.16)	59 (25.3)	0.82 (0.20)	55 (23.1)	0.71 (0.19)	0.19 N.S.	2.1 N.S.
Probabilistic Errors with Shift	22 (7.0)	0.66 (0.16)	21 (8.0)	0.76 (0.18)	21 (8.2)	0.60 (0.13)	0.07 N.S.	6.2** OCD>CO†
Number of accumulated points by end of task	15659 (8195)		15228 (7561)		15524 (5998)		0.02 N.S.	

ANOVA, analysis of variance; df, degrees of freedom; N.S., not significant; RTs, reaction times; CO, controls; S.D., standard deviation.
* $p<0.05$, ** $p<0.005$. † Paired-comparison t tests: $p<0.05$; see text for further between-group details.

Table 3. *Brain regions showing group interaction effects for reward (Correct Responses minus baseline trials), punishment [(Probabilistic Errors no Shift + Final Reversal Errors + Preceding Reversal Errors) minus baseline trials] and affective switching [Final Reversal Errors minus (Preceding Reversal Errors + Probabilistic Errors no Shift)]*

| Region	L/R	MNI coordinates x	y	z	z value	Cluster size[a]	MNI coordinates x	y	z	z value	Cluster size[a]
Reward											
		MDD>Controls					MDD>OCD				
Medial OFC	R						12	33	−12	3.35	1
Gyrus temporalis superior	R	39	15	−30	3.14	1	39	15	−30	3.40	1
Gyrus precentralis	L	−36	−15	48	3.89	8					
Occipital cortex	R	30	−90	15	3.67	6					
	L						−27	−87	0	3.90	1
Putamen	L	−27	15	0	3.63	5					
	R						24	0	12	3.11	2
		Controls>MDD					OCD>MDD				
		No significant activations					No significant activations				
Punishment											
		MDD>Controls					MDD>OCD				
Insular cortex	L	−39	21	3	3.37	15	−33	18	3	3.00*	6
Precuneus	R	18	−69	51	3.18	5					
		Controls>MDD					OCD>MDD				
Occipital cortex	R	36	−93	3	3.10	5	No significant activations				
Affective switching											
		MDD>Controls					MDD>OCD				
Temporalis superior	R						39	15	−24	3.65	1
	L						−48	15	−18	3.28	7
Parietal inferior	R	39	−72	39	3.25	13					
Parietal superior	L	−21	−42	54	3.34	3	−21	−45	54	3.81	7
		Controls>MDD									
Insular cortex	L						−33	24	9	3.68	7
	R	33	21	6	3.13	11					
Anterior PFC	L	−33	48	−6	3.30	23	−18	51	0	3.61	3
		−24	57	9	3.01*	6					
Dorsolateral PFC	R	48	3	18	3.64	5	45	42	6	2.91*	3
Anterior cingulate	L	−3	36	18	3.65	10	OCD>MDD				
Parietal inferior	L	−48	−33	36	3.10	14	No significant activations				
Thalamus	R	6	−15	6	3.12	2					

L, Left; R, right; MNI, Montreal Neurological Institute; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; OFC, orbitofrontal cortex; PFC, prefrontal cortex.

All activations at $p<0.001$ uncorrected, except for z values* ($p<0.005$).

[a] Number of voxels.

In addition to these findings in the MDD group, patients with OCD performed slower during baseline trials, Correct Responses, Probabilistic Errors no Shift, Preceding Reversal Errors, and Probabilistic Errors with Shift, compared with healthy controls. This observation corroborates an earlier statement that slowness in OCD may be most apparent on executive tests requiring self-initiated organizational strategies, consistent with frontal–striatal abnormality (Roth *et al.* 2004). However, there were no significant differences in mean numbers of events or accumulated points for OCD subjects compared with the control group. This latter observation is at odds with an earlier study from our group using the same paradigm in a partially different sample of patients with OCD (Remijnse *et al.* 2006). This discrepancy may be due to differences in OCD patient characteristics: first, the current sample was free of co-morbid MDD and contained more patients having 'pure' OCD compared with our prior sample (45% *v.* 25%). Second, the groups differed with
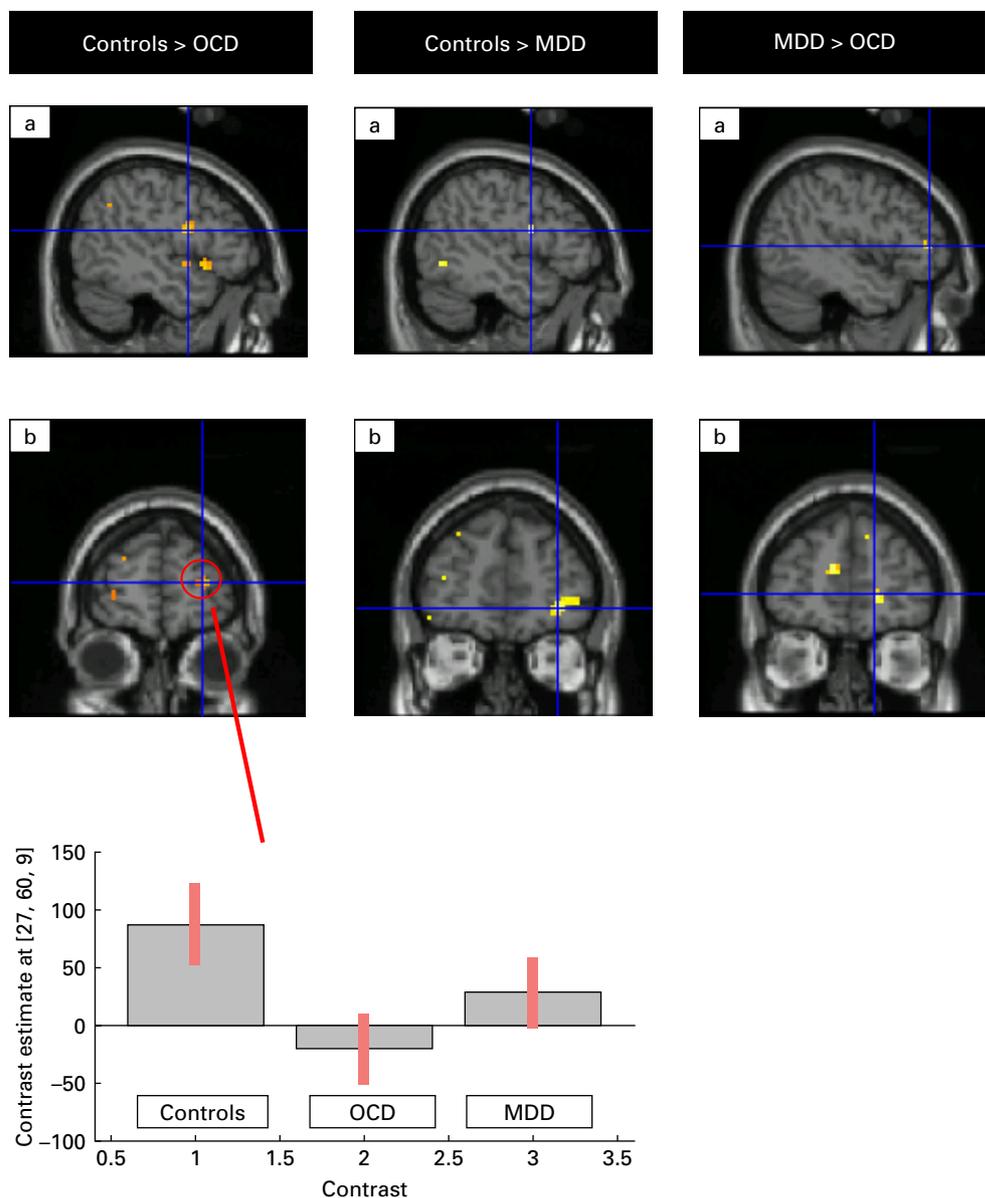
Fig. 2. Across-group interaction effects for affective switching, superimposed on sagittal and transaxial slices from a canonical [Montreal Neurological Institute (MNI) compatible] T1 image as supplied by SPM2. Increasing blood oxygen level-dependent (BOLD) responses for patients with obsessive–compulsive disorder (OCD), major depressive disorder (MDD) and healthy controls respectively are shown in (*a*) the right dorsolateral prefrontal cortex (DLPFC) (upper left: x = 48, y = 3, z = 18; upper middle: x = 48, y = 3, z = 18; upper right: x = 45, y = 42, z = 6) and (*b*) the left anterior PFC (lower left: x = −27, y = 60, z = 9; lower middle: x = −33, y = 48, z = −6; lower right: x = −18, y = 51, z = 0). A plot of effect size in the left anterior PFC is displayed for all three groups (x = −27, y = 60, z = 9).

regard to symptom subdimensions (the ratio checkers/non-checkers was smaller in the present sample compared with the former; data not shown).

With regard to the imaging results, we found that patients with MDD exhibited increased activity in the left insula on punishment, compared to both healthy control subjects and patients with OCD (the latter at a slightly lower statistical threshold; Table 3). In MDD, neuroimaging activation studies using affective

paradigms have reported increased insular responsiveness during presentation of negative stimuli in MDD (Fu *et al.* 2004; Anand *et al.* 2005; Keedwell *et al.* 2005). A recent model on the neuropathophysiology of depressive disorder postulates that the insula, together with the amygdala, may be the neurobiological substrate of an increased tendency to identify stimuli as emotional, and to experience predominantly negative affective states (Phillips *et al.* 2003). The current

finding of punishment-related anterior insular hyper-activity in patients with MDD, in corroboration with prior imaging studies, lends support to this model. In addition, it extends previous findings by showing that this assumed role of the anterior insula is specific to depression (at least with respect to OCD).

In addition to the MDD-specific insular hyper-activity on punishment, during reward events depressed patients recruited the putamen to a greater extent than healthy controls and patients with OCD. This latter finding is in line with our between-patient group hypothesis as outlined in the introduction section. The putamen has recently been demonstrated to be involved in stimulus–action–reward associations (Haruno & Kawato, 2006). Our finding of putamen hyperactivity upon reward is consistent with two previous imaging activation paradigms using positive valence stimuli in MDD (Kumari *et al.* 2003; Mitterschiffthaler *et al.* 2003), but it is in contrast with two other studies (Surguladze *et al.* 2005; Epstein *et al.* 2006). Differences in the nature of hedonic stimuli presented (i.e. positive words, happy faces, positive valence picture–caption pairs, or monetary reward) may account for these inconsistent results across studies. Further research is therefore warranted to clarify the role of the putamen in processing positive affect in MDD, and the significance of its apparent disorder-specific dysfunctional activity.

It is of note that the current study extends our earlier finding of reduced right orbitofrontal activity upon reward outcome for OCD patients compared with controls (Remijnse *et al.* 2006), by showing that reward-associated blunted right medial OFC responsiveness uniquely dissociated OCD from both depressed (see Table 3) and healthy individuals (Appendix B).

The neural correlates of affective switching have previously been localized both in (para)limbic brain regions (Cools *et al.* 2002; Remijnse *et al.* 2005*a*) and in areas involved in cognitive demands, that is the DLPFC and the anterior PFC (Remijnse *et al.* 2005*a*; Budhani *et al.* 2006; see also Appendix C). Of interest, the present experiment demonstrates a pattern of gradual decrease in DLPFC and anterior PFC activity during affective switching for healthy controls, MDD and OCD (Fig. 2). In addition, we found a diminished BOLD signal in the right insula and dorsal ACC in MDD patients relative to healthy controls. Our findings in the MDD group corroborate a recent fMRI study that reported in unmedicated depressed patients a failure to recruit the right ventrolateral PFC (using a region-of-interest analysis with a sphere that encompasses the area we designate as 'right insula') and the DLPFC (using a *post-hoc* whole-brain analysis), during affective switching (Taylor Tavares *et al.* 2008).

In MDD, decreased DLPFC and dorsal ACC metabolism and/or perfusion have frequently been observed in resting-state neuroimaging paradigms (Mayberg *et al.* 1994; Kennedy *et al.* 2001), and also in emotional (Bremner *et al.* 2007) and cognitive imaging activation designs (Okada *et al.* 2003; Siegle *et al.* 2007). Blunted activity in the DLPFC and dorsal ACC in MDD is generally considered the neural correlate of symptoms and psychological deficits in MDD, such as psychomotor retardation and executive impairments (Dolan *et al.* 1993; Rogers *et al.* 2004). In line with this interpretation, the diminished responsiveness of the DLPFC, anterior PFC and dorsal ACC during affective switching in MDD may reflect a reduced capacity for shifting a cognitive set and inhibiting the selection of a previously rewarded stimulus (Garavan *et al.* 2002; Smith *et al.* 2004). However, the present study did not show impaired *behavioral* performance during affective switching in depressed subjects. Therefore, the observed hyperactivity for MDD patients during affective switching in posterior (i.e. parietal) brain regions may be considered as compensatory recruitment for the relative failure to activate frontal areas. This converges with previous imaging activation studies that also reported increased parietal brain activity in MDD patients *versus* healthy subjects, in the presence of reduced ACC activation and equal task performance (Bremner *et al.* 2004, 2007).

The above-mentioned neuropathophysiological model of MDD (Phillips *et al.* 2003) posits that functional impairments in the DLPFC and dorsal ACC represent reduced effortful regulation of (negative) emotional states in this disorder. Again, our study is in agreement with this model by showing hypoactivity in these 'executive' brain regions upon a regulatory neuropsychological measure, that is affective switching.

Taken together, we suggest that the differential involvement of frontal–striatal and (para)limbic brain regions during reversal learning in MDD and OCD, as observed in the present study, may represent the neural correlates of biased emotional processing and reduced cognitive-behavioral flexibility in MDD and OCD. In addition, our findings in present and past papers (Remijnse *et al.* 2006) of distinct abnormalities in MDD and OCD seem to be in line with currently influential neurobiological models of these disorders. For OCD, the attenuated responsiveness in OFC–striatal and ACC structures during reward and affective switching events converge with the hypothesis of a dysfunctional (lateral) orbitofrontal loop as a key neurobiological underpinning of clinical and cognitive-behavioral manifestations of OCD (Chamberlain *et al.* 2005). Similarly, for MDD, the current results of increased insular but decreased dorsal ACC, DLPFC

and anterior prefrontal cortical activity lend support to the proposed limbic-cortical ('ventral–dorsal') dysbalance as a core feature of this disorder (Mayberg, 1997, 2003).

The present study is not without limitations. First, the MDD group differed significantly from the other two groups with regard to the male/female ratio. We know of no previously described direct relationship between gender and the neural substrate of reversal learning, but sex differences may exist with regard to the human 5-HT system (Jans *et al.* 2007). As outlined in the introduction, reversal learning is dependent on normal 5-HT neurotransmission, and both MDD and OCD have been associated with a dysfunctional serotonergic system. Therefore, we cannot rule out that group interaction neural effects on reversal learning may have been mediated by differential betweengroup 5-HT system functioning due to an inverse gender ratio. Second, although the OCD group was free of currently co-morbid MDD, these patients scored significantly higher on depression severity measures than the healthy controls. However, the ratings in our OCD sample were well below consensus- and computation-based cutoff scores for clinical remission in MDD, that is <7 for the HAMD-17 (Frank *et al.* 1991) and <10 for the MADRS (Zimmerman *et al.* 2004). In addition, a large and significant gap remained between OCD and MDD patients on all depression severity scores in this study.

In conclusion, our study shows differential frontal–striatal and paralimbic activity during reward, punishment and affective switching in unmedicated patients with either MDD or OCD compared with healthy controls. It would be of interest if future studies in MDD and OCD could further differentiate between cognitive and emotional aspects of these aberrant brain activations during reversal learning, for example by directly comparing BOLD responses during affective as opposed to cognitive switching behavior.

Acknowledgments

Declaration of Interest

None.

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Appendix A

'Glass brain' renderings showing task main effects and also group main effects for reward, punishment and affective switching. Overall, healthy control subjects showed more activations on reward and affective switching than patient group subjects, whereas activations on punishment were roughly equal across groups. Importantly, not all apparent between-group differences reached statistical significance. See text and tables for details.
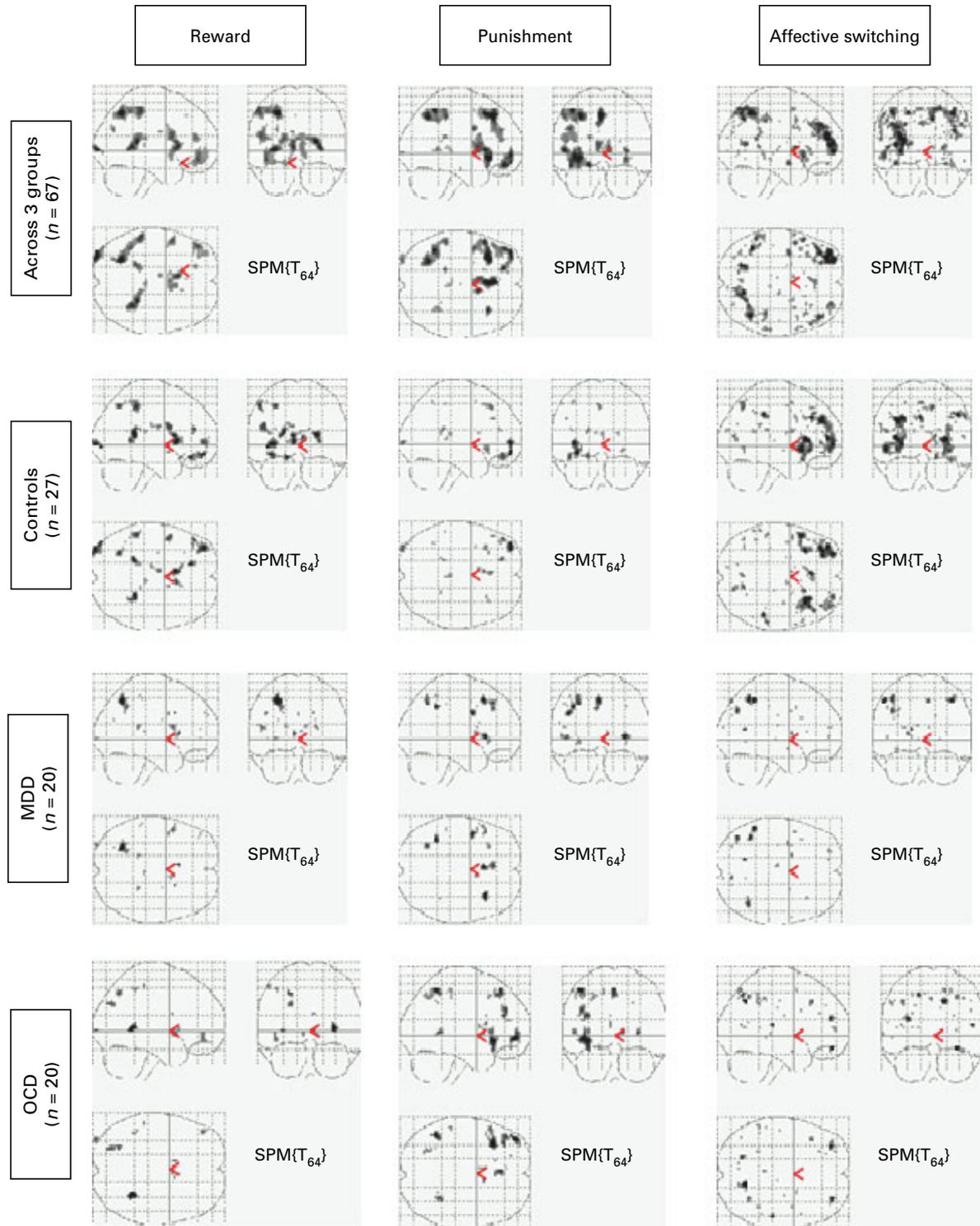
Appendix B. *Brain regions showing interaction effects for the obsessive–compulsive disorder* (OCD) versus *healthy control group on reward, punishment and affective switching*

OCD *versus* controls …	L/R	Reward MNI coordinates				Punishment MNI coordinates				Affective switching MNI coordinates			
Region	L/R	x	y	z	z value	x	y	z	z value	x	y	z	z value
		Controls > OCD				Controls > OCD				Controls > OCD			
Lateral OFC	R	36	54	−12	2.98*	No significant activations							
Medial OFC	R	15	36	−15	3.70								
Posterior OFC	L									−18	15	−15	3.28
Gyrus temporalis superior	R									54	−51	21	3.58
Parietal inferior	R									54	−36	30	3.57
Insular cortex	L									−30	21	9	5.08
	L									−36	15	9	4.24
	L									−36	27	−6	3.78
	R									33	18	12	3.35
Anterior PFC	L									−27	60	9	3.34
Dorsolateral PFC	R									48	3	18	3.47
Anterior Cingulate	L									−6	36	18	3.84
										OCD > Controls			
Cuneus	L	−30	−87	0	3.53	OCD > Controls							
Temporal medius cortex	R					No significant activations				60	−60	15	3.11
Caudate	R	6	18	6	2.43*								
		OCD > Controls											
		No significant activations											

L, Left; R, right; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PFC, prefrontal cortex.
All activations at $p < 0.001$ uncorrected, except for z values* ($p < 0.005$).

Appendix C. *Task main effects collapsed across the three groups for reward, punishment and affective switching*

Region	L/R	Reward MNI coordinates				Punishment MNI coordinates				Affective switching MNI coordinates			
		x	y	z	z value	x	y	z	z value	x	y	z	z value
Lateral OFC	R	42	45	−12	4.68	39	54	−3	5.25				
		33	51	−15	3.01	33	57	−9	5.04				
Medial OFC	R	18	42	−12	4.03	21	45	−15	5.15				
Posterior OFC	R	12	21	−15	3.41	33	21	−15	4.35				
Anterior PFC	R									36	54	9	4.92
										30	57	0	4.00
										27	51	18	4.74
	L									−27	57	3	3.61
Dorsolateral PFC	R	45	42	18	4.50	42	42	30	4.01	48	6	39	3.64
						48	33	30	4.03				
	L									−42	39	27	4.20
										−42	45	33	4.10
Gyrus frontalis inferior	R	51	9	21	4.70	45	3	30	4.56				
Dorsomedial PFC	R					3	27	48	5.69	3	27	36	3.69
						6	33	39	4.68				
Insular cortex	R					36	21	−6	5.96	48	6	6	4.15
						51	18	3	5.13	33	27	3	3.64
	L					−33	21	3	4.86				
						−33	24	6	4.40				
Temporal superior cortex	R									57	−48	18	3.68
Parietal cortex superior	R	57	−33	51	5.03					42	−54	51	4.56
		42	−48	51	4.52								
	L									−42	−57	48	4.75
Parietal cortex inferior	R					30	−60	45	5.40				
						54	−36	48	4.49				
Occipital cortex	R	33	96	0	6.33	30	−96	0	4.32				
		39	−87	−3	4.30								
Caudate nucleus	R	6	18	6	5.96	6	12	12	4.51				
	L	−6	9	0	4.39	−9	9	6	5.09				

L, Left; R, right; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PFC, prefrontal cortex.
All activations at $p < 0.05$ false discovery rate (FDR)-corrected for multiple comparisons.