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ORIGINAL ARTICLE

Abnormal processing of deontological guilt in obsessive–compulsive disorder

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Abstract Guilt plays a significant role in the occurrence and maintenance of obsessive–compulsive disorder (OCD). Two major types of guilt have been identified: one deriving from the transgression of a moral rule (deontological guilt DG), another (altruistic guilt AG), relying on the assumption of having compromised a personal altruistic goal. Clinical evidence suggests that OCD patients are particularly sensitive to DG, but not AG. In this functional magnetic resonance imaging (fMRI) study, we investigated brain response of OCD patients while processing DG and AG stimuli. A previously validated fMRI paradigm was used to selectively evoke DG and AG, and anger and sadness, as control emotions in 13 OCD patients and 19 healthy controls. Patients' behavioral results showed a prominent attitude to experience guilt, compared to controls, while accomplishing task. fMRI results revealed that patients have reduced activation in the anterior cingulate (ACC) and frontal gyrus when experiencing guilt, regardless of its specific type (DG or AG). When separately considering each type of guilt (against each of its control), patients showed decreased activation in the ACC, the insula and the precuneus, for DG. No significant differences were observed between groups when processing AG, anger or sad stimuli. This study provides evidence for an abnormal processing of guilt, and specifically DG, in OCD patients. We suggest that decreased activation may reflect patients' cerebral efficiency, which derives from their frequent exposure to guilty feelings ("neural efficiency hypothesis"). In conclusion, our study confirms a selective abnormal processing of guilt, and specifically DG, in OCD.

Keywords Obsessive–compulsive disorder · Neuroimaging · Guilt · Deontological guilt · Altruistic guilt · Emotional processing

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Introduction

In recent years, growing interest has been dedicated by affective neuroscientists to investigate the pathophysiology of aberrant emotional processing in psychiatric conditions (Edwards et al. 2002; Leppänen 2006). In obsessive compulsive disorder (OCD), which is the fourth-most-common mental disorder worldwide with a prevalence ranging from 1 to 4 % (Leonard et al. 2005; Fullana et al. 2009), guilt has been suggested to negatively impact patients' clinical severity and treatment outcome (Mancini and Gangemi 2004; Nissenson 2006). From an evolutionary perspective, guilt is considered as an adaptive complex social emotion that plays a role in protecting humans from one another (Trivers 1971). Abnormal guilty feelings have been frequently observed in psychiatric conditions, such as OCD

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(Shafran et al. 1996), depression (Gilbert 1992; O'Connor et al. 1999) and antisocial disorder (Pardini et al. 2003). The role of guilt in OCD has recently resurfaced (Mancini and Gangemi 2004; Nissenson 2006), as it appears to play a role in the occurrence and maintenance of obsessive–compulsive (OC) symptoms (Mancini and Gangemi 2004; Nissenson 2006). Harrison et al. (2012) has recently demonstrated using functional magnetic resonance imaging (fMRI), in OCD patients, that obsessive beliefs, such as inflated responsibility, modulate brain activation in response to a moral decision task. Guilt is regarded as the emotional response underpinning obsessive thinking, being further strengthened by feelings of regret, which might explain compulsive behaviors and decision-making dysfunctions in OCD.

Within literature, at least two distinct types of guilty feelings have been identified. One is related to the sense of guilt deriving from the transgression of an inner moral rule, with no concern for others to be damaged (deontological guilt DG). For instance, breaking a religious rule, as it may happen to a Roman Catholic who has sexual intercourse before marriage, might evoke a sense of deontological guilt (Haidt et al. 1993). The second type of guilt, defined as altruistic (AG), relies on the assumption of having compromised/disregarded a personal altruistic goal, even though no violation of an inner moral rule has occurred. For instance, an intense sense of guilt might arise for not having shared the destiny of a friend who has become a victim, for instance in an air crash, even though no moral rule has been disobeyed (Weiss et al. 1986; O'Connor et al. 2000). Evidence for the distinction between deontological and altruistic guilt derives from many behavioral studies (for a review, see Mancini and Gangemi 2011). Additional evidence comes from a recent fMRI investigation (Basile et al. 2011), demonstrating that, in healthy individuals, deontological guilt and altruistic guilt rely on the activation of distinct neuronal networks. Activation in the anterior cingulate cortex (ACC) and in the left insula is modulated by DG stimuli, while medial prefrontal areas (that are traditionally involved in the Theory of Mind, Shallice 2001) are more responsive to AG stimuli.

With respect to the distinction between DG and AG, it has been argued that OCD patients are particularly sensitive to the former type of feeling (Mancini et al. 2008). In fact, Lopatcka and Rachman (1995) and Shafran (1997) have demonstrated that the obsessive' concern over a harmful event (e.g., a gas explosion), is drastically reduced in OCD patients when they do not have a direct responsibility for the event. Patients' obsessive concern is indeed not for victims of the explosion, but for themselves, having violated a moral norm, in this case of prudence. It thus seems that both responsibility and guilt play a causal role to in the development and maintenance of this disorder.

According to the clinical relevance of abnormal guilty feelings in OCD, and to patients' specific sensitivity to DG (Mancini and Gangemi 2011), the current fMRI study aims at investigating the brain response of OCD patients when processing stimuli evoking DG and AG. For this purpose, we employed a previously validated fMRI paradigm (Basile et al. 2011) based on the presentation of emotional facial expressions (Ekman and Friesen 1976) followed by contextual sentences. As previously shown in healthy individuals, this paradigm is able to induce specific patterns of brain activation for DG and AG stimuli against their basic control emotions (i.e., anger and sadness). We hypothesize that patients with OCD will present an abnormal activation when exposed to guilty stimuli, and more specifically for those inducing DG.

Methods

fMRI paradigm

The event-related paradigm employed here was previously validated in healthy subjects (see supplementary material Figure 1). A detailed description of the task can be found in Basile et al. (2011). Briefly, each experiment consisted of 60 trials for each of four experimental conditions, namely DG and AG (target), and anger and sadness (control basic emotions), randomly intermixed (inter-trial-interval was jittered between 1,350 and 1,650 ms). Each trial consisted of an Ekman and Friesen (1976) face presentation followed by a short sentence. Typical target trials evoking DG were elicited by associating an angry face with sentences like: "How could I behave that immorally!". Conversely, AG was elicited by the association of a sad face and a sentence such as: "How unfair! I am doing so well, while she/he is so unlucky!". With respect to control conditions, anger statements, preceded by the same angry faces used in DG stimuli, included sentences like: "How dare she? Staring at me in such a way!". Sad sentences, associated with previously used sad facial expressions, included statements like: "He must be really sad! Crying in such a way!". As additional manipulation of the paradigm, for each condition, half of the trials were associated to neutral faces, in order to control for the effect of the face expression, as previously described (Basile et al. 2011). During fMRI, subjects were instructed to observe each face and to imagine that an external person was experiencing that specific emotion (or none, in the neutral condition) directed toward themselves. Then, they were instructed to interpret each statement (following each face presentation) as an inner dialogue in response to the facial expression shown previously. At the end of each trial, subjects were asked to answer the question: “Do you feel guilty?”, choosing for a YES/NO answer by button pressing.

In summary, the fMRI experiment resulted in eight equally balanced experimental conditions: (1) neutral face + DG sentence, (2) anger face + DG sentence, (3) neutral face + anger sentence, (4) anger face + angry sentence, (5) neutral face + AG sentence, (6) sad face + AG sentence, (7) neutral face + sad sentence, (8) sad face + sad sentence.

Subjects

Thirteen patients with OCD [F/M 3/10; mean (SD) age 37.0 (11.1) years; mean years of education (SD) 11.5 (2.6) and 19 healthy controls (HC) (F/M 8/11; mean (SD) age 26.2 (2.1); mean years of education (SD) 12.8 (2.3)] were enrolled in study. OCD patients were recruited from the association of cognitive psychotherapy centre of Rome and by internet announcements, through the Italian association web site for OCD (http://www.aidoc.it/). In each patient, the diagnosis of OCD was verified by an expert psychiatrist (F.M.) according to current DSM-IV-TR diagnostic criteria (APA 2000). Half of OCD patients ($N = 6$) were under medication with antidepressant drugs (selective serotonin reuptake inhibitor, SSRI, or tricycles), and nine patients had started a course of cognitive-behavioral therapy shortly before fMRI acquisition.

Psychological tools to assess/exclude the presence of OCD symptoms, and to quantify the attitude of experiencing guilty feeling were administered to all subjects (Table 1). Psychological measures assessing anxiety and depressive symptoms included: the State-Trait Anxiety Inventory (STAI, Spielberger et al. 1983), the Padua Inventory (PI, Sanavio 1988), and the Beck depression inventory-II (BDI-II, Ghisi et al. 2006). The Guilt Inventory (GI, Kulger and Jones 1992) was administered to assess the state-guilt, trait-guilt and moral standards in both groups of subjects. To assess symptoms severity and OCD typology the Yale-Brown obsessive–compulsive scale (Y-BOCS, Goodman et al. 1989) was administered only to patients. No patients met criteria for Tourette syndrome or psychotic disorders. Comorbid anxiety or depressive disorders were not considered as exclusion criteria in the patients' group as OCD was the primary diagnosis.

All tests were presented in their Italian validated version. *t* tests for independent samples were used to compare between-group scores. Healthy controls were screened for their OC symptoms through the Padua inventory, and volunteers scoring above 21 were excluded from study participation. All subjects had to be right handed and had normal or corrected-to-normal vision. Ethical approval from the ethics committee of Santa Lucia foundation and written informed consent from each participant were obtained before study initiation.

Image acquisition

MRI data were acquired from a 3 Tesla Allegra system (Siemens, Erlangen, Germany) equipped with a circularly polarized transmit-receive coil. The maximum gradient strength is 40 mT m^{-1}, with a maximum slew rate of 400 mT m^{-1} ms^{-1}.

Functional images were collected by echo-planar (EPI) T2* sequence using BOLD (blood oxygenation level dependent) contrast. Each acquired volume consisted of 32 axial slices with a 3 mm thickness and a 1.3 mm distance factor in order to cover the entire brain, with an effective repetition time of 2.08 s. The scanner was synchronized with the presentation of each session, and the ratio of inter-scan to inter-stimulus interval ensured that voxels were sampled at different phases relative to stimulus onset.

Data analysis

Each of the eight experimental conditions was presented in four fMRI sessions (duration 11 min and 26 s each). Two sessions included randomly occurring trials evoking DG and anger (conditions 1–4, see above in the “fMRI paradigm” section), while the other two included trials evoking AG and sadness (conditions 5–8 above). At the end of each trial, subjects were confronted with a forced-choice question, allowing us to assess whether guilt was elicited, or not, on a trial-by-trial basis. *t* tests for independent samples were used to compare fMRI behavioral responses and reaction times between HC and OC patients.

fMRI data were processed using MATLAB 7.0 (MathWork, Natick, MA) and SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), and analyzed with the general linear model (GLM) for event-related designs, using a random-effect analysis. For each fMRI session, the first four volumes were discarded to allow for T1 equilibration effects. All the acquired EPI images were then realigned to the first image of the first session using the ‘Realign’ routine in SPM5, normalized to a standard echo-planar image template, and smoothed with a Gaussian kernel of 8 mm full-width half maximum.

For each subject, the following conditions were modeled (independently of guilt-evoking ratings) using the time of sentence disappearance as onset: (1) neutral face + deontological guilt sentence, (2) anger face + deontological guilt sentence, (3) neutral face + anger sentence, (4) anger face + angry sentence, (5) neutral face + altruistic guilt sentence, (6) sad face + altruistic guilt sentence, (7) neutral face + sad sentence, (8) sad face + sad sentence.

The resulting contrast-images representing the amplitude of BOLD response for each subject and each condition were included in the random-effect level analysis, using a flexible-factorial design. Correction for non-sphericity was used to account for possible differences in error variance

Table 1 Psychometric results in studied subjects

Psychometric tool [mean (SD) scores]	HC ($N = 19$)	OCD patients ($N = 13$)	p value*
STAI state	36.0 (9.5)	39.4 (5.8)	NS
STAI trait	36.2 (9.3)	47.0 (4.9)	0.001
PI rumination	6.6 (5.7)	25.5 (11.9)	0.001
PI contamination	4.2 (3.0)	10.4 (11.7)	0.03
PI check	2.7 (3.4)	11.9 (7.6)	0.001
PI fear of losing control	0.2 (0.4)	4.0 (3.8)	0.001
PI total score	16.8 (11.4)	64.1 (33.3)	0.001
Guilt state	24.5 (5.0)	33.0 (7.6)	0.001
Guilt trait	48.5 (10.5)	62.7 (10.4)	0.001
Guilt morality	46.6 (5.4)	43.1 (13.4)	NS
BDI	5.0 (5.1)	17.4 (13.6)	0.001
Y-BOCS total score	–	19.3 (9.4)	–
Y-BOCS obsessions	–	12.5 (6.0)	–
Y-BOCS compulsions	–	8.8 (5.7)	–

BDI Beck depression inventory-II, *GI* guilt inventory, *HC* healthy controls, *NS* not significant, *OCD* obsessive compulsive disorder, *PI* Padua inventory, *SD* standard deviation, *STAI* state-trait anxiety inventory, *Y-BOCS* Yale-Brown obsessive compulsive scale

* Independent t tests: statistical threshold set at p values <0.05. See text for further details

across conditions and any non-independent error terms for the repeated measures analysis. Within the random-effect level analysis, we investigated the main effect of conditions and the critical between-group differences, using condition × group interactions. We assigned corrected p values at the cluster-level (p_{corr} <0.05; cluster size estimated at p uncorrected 0.005, voxel-level), considering the whole brain as the volume of interest.

Specifically, we first tested for the main effect of guilt (DG and AG) against basic emotions (anger and sadness), irrespective of group; and then compared this effect between groups, using a group × condition interaction. Next, we assessed the possible specificity for one or the other guilt-type (DG or AG) testing the condition × group interactions separately for the two types of guilt (e.g., "DG vs. anger", larger in HC than OCD). For completeness, we also compared the basic emotion conditions (anger and sadness) against the guilt conditions (DG and AG).

For those fMRI effects able to discriminate between patients and controls, additional multiple regression analyses were run to assess possible associations between regional brain activation and behavioral (performance during task) and psychometric measures (GI, PI, and Y-BOCS scores). Statistical significance was tested by Pearson correlation (p values <0.05).

Finally, to exclude that medications could interfere with changes in brain activation, we ran an additional analysis by contrasting the OCD patients as divided in those under treatment and in those drug free (p_{unc} <0.01).

Results

Psychometric data

Psychological tools confirmed the diagnosis of OCD in all patients, and excluded any abnormality in HC. Moreover, this assessment confirmed a higher attitude of OCD patients in experiencing guilt. Predominant symptom subtypes were checking (over or covert, $N = 12$) and comorbid washing (in $N = 5$ cases). Mean (SD) scores for psychological tools in HC and in patients are summarized in Table 1.

Behavioral performance during fMRI

Consistent with the psychometric evaluation, behavioral responses in fMRI experiments revealed that OCD patients felt significantly more guilty than HC in both conditions, DG and AG [$t\ (30) = -2.33$, $p < 0.02$, in DG; $t\ (32) = -2.78$, $p < 0.009$, in AG]. Patients also rated anger stimuli as more guilt-inducing than HC, although this result did not reach full statistical significance ($p < 0.06$). Conversely, no differences at all between HC and OCD patients were observed in guilt-judgments for the sadness condition (Fig. 1). Further, statistical analysis of patients' behavioral responses during fMRI task revealed significantly more frequent guilt responses during DG stimuli [Mdn = 41, mean (SD) = 38.2 (10.9)] processing, than AG ones [Mdn = 21, mean (SD) = 25.5 (19.2); Wilcoxon paired t test, $Z = -2.12$, $p = 0.03$). When considering subjects' reaction times (RTs), no significant difference was observed between HC and OCD patients.

Imaging findings

First we compared all guilt conditions versus basic emotion (DG and AG against anger and sadness) irrespective of group. This did not show any significant effect, as only HC showed a differential activation during the guilt conditions. Indeed the formal test (group × condition interaction) comparing the "guilt minus basic emotion" in HC vs. ODC

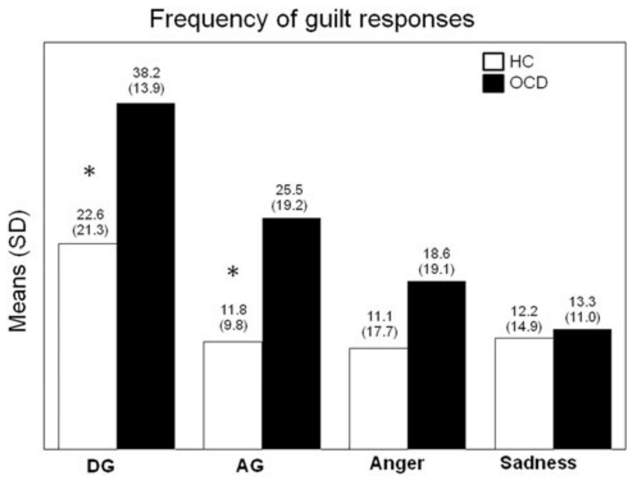

Fig. 1 Guilt responses. Mean frequencies of guilt responses in target-guilt and basic emotions answers across all conditions, in the two groups, are shown. Independent *t* tests were performed to check for between-group differences. A trend towards statistical significance was observed between groups within the anger condition. Significant for $*p < 0.005$

showed a significant effect in the anterior cingulate cortex (ACC), the superior and medial frontal gyri (sup/med FG, Fig. 2; Table 2). Figure 2 shows that HC, but not OCD patients, activated these areas (see signal plot in Fig. 2). The same comparison also revealed an analogous differential response to the guilt stimuli in the anterior insula bilaterally and in the left precuneus, albeit this did not survive whole-brain correction for multiple comparisons (p_{unc} <0.001). The insulae also showed a "facial emotion by group" interaction, with greater activity for emotional faces (anger and sadness) than neutral faces in HC, only (Table 2; signal in plot in Fig. 2).

The signal plot of the ACC indicated that the differential effect between OCD patients and HC during the processing of guilt stimuli was driven primarily by the DG stimuli. Indeed, comparing DG (minus anger) in HC versus OCD revealed a significant interaction in the ACC and sup/med FG (Table 2, and signal in plot in Fig. 2, yellow columns). By contrast, the comparison of AG (minus sadness) in HC versus OCD did not reveal any significant effect. The three-ways interaction ("DG: anger" versus "AG: sadness" in HC more than OCD) confirmed this specificity, but only at uncorrected level of significance (Table 3; Fig. 3).

For completeness we also tested for areas showing greater activation for basic emotions stimuli than guilt stimuli (i.e., "anger and sadness" minus "DG and AG"). This revealed a widespread pattern of activation including prefrontal, temporal and occipital areas. The pattern of activation in these areas was similar in both groups (see signal plots in Fig. 3). Indeed none of the interactions testing for differences between groups revealed significant effects.

When investigating the potential effect of medication in OCD patients, no significance between group difference (patients under treatment vs. drug free patients) was found in any contrast in either direction (statistical threshold set at $p_{unc} < 0.01$). To exclude the potential confound of age and levels of depression in accounting for the main results of the study, we added each of these variables, in isolation, as covariate of no interest. These additional analyses confirmed our results, despite the expected reduction in statistical power due to addition of covariates.

In summary, the fMRI analyses revealed that OCD patients activate the ACC (plus insulae and precuneus, at uncorrected level) less than HC when experiencing guilt, and that this effect is mainly driven by DG.

Brain–behavior associations

We found a significant negative association between patients' PI ratings of check subscale severity and activation in the right insula (Fig. 4a), and between Y-BOCS obsession severity scores and activation within the ACC (Fig. 4b). Conversely, a positive correlation was observed between neural activity in the ACC, the superior and medial frontal gyri and guilt-state (GI) scoring (Fig. 4c). When considering performance during task, we found that greater frequency of guilt responses was inversely associated with neural signal intensity in the medial FG and in the right insula, in the OCD, but not in the HC group (Fig. 4d).

Discussion

Guilt, and specifically the deontological type (associated with a sense of responsibility and regret), has been hypothesized to play a role in OCD's onset and maintenance (Shafran et al. 1996). So far, this hypothesis has been formulated on the basis of clinical and behavioral observations (Mancini and Gangemi 2004; Nissenson 2006). The current fMRI investigation, based on a previously validated fMRI paradigm (Basile et al. 2011), was designed to assess whether these clinical and behavioral observations in OCD patients might be explained in terms of an abnormal brain processing of guilt stimuli. To this purpose, we recruited a group of patients with OCD, and we compared them with a group of healthy individuals. Psychological assessment confirmed that OCD patients had higher levels of OC symptomatology and a higher attitude to guilty feeling than controls, thus confirming previous clinical and behavioral observations (Mancini and Gangemi 2004; Nissenson 2006). Further, OCD patients, compared to controls, showed significantly higher guilt rates also when performing the fMRI task. This indicates

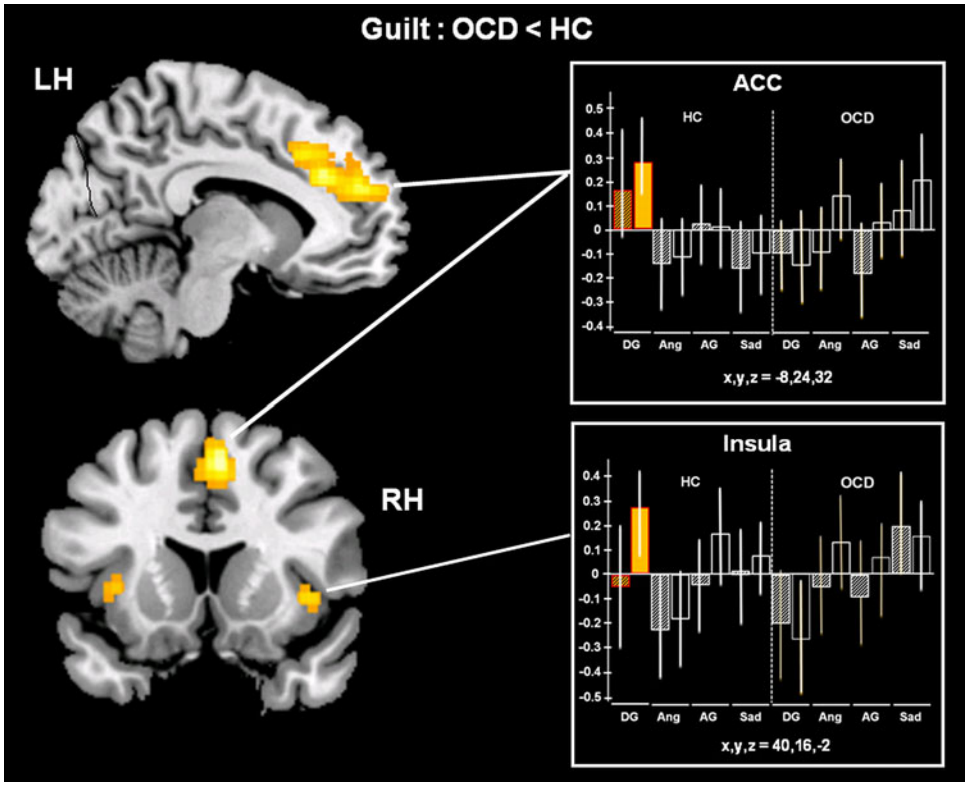

Fig. 2 Activation in guilt conditions. Maxima of regions showing significant BOLD signal differences between patients with obsessive–compulsive disorder (OCD) and healthy controls, when comparing both guilt conditions (deontological and altruistic) versus control basic emotions (i.e., anger and sadness). Between-group comparison revealed a pattern of decreased brain activation in OCD patients, including the anterior cingulate cortex (ACC, BA 32) and the medial and superior frontal gyrus (*top panel*), and both the insulae and the *left* precuneus (*bottom panel*). Plots showing BOLD signal changes across conditions indicate that this effect is mainly driven by DG. Dashed columns refer to trials containing neutral faces plus emotional sentence, while fully colored columns refer to trials containing emotional faces followed by emotional sentences. Statistical threshold is the same as in Table 2. *OCD* obsessive–compulsive disorder, *HC* healthy controls, *ACC* anterior cingulate cortex, *LH left* hemisphere, *RH right* hemisphere

Table 2 Between-group differences in brain activation for guilt

Brain area	HC > OCD patients: guilt (DG + AG)									HC > OCD patients: DG only						
	Cluster				Peak voxel					Cluster		Peak voxel				
	Size	Side	BA	p_{corr}	Coordinates			Z value	p_{unc}	Size	p_{corr}	Coordinates			Z value	p_{unc}
					x	*y*	*z*					*x*	*y*	*z*		
Ant cingulate	1,665	L/R	32/25	<0.001	8	24	32	3.79	<0.001	684	0.027	−2	18	46	3.59	<0.001
Sup frontal gyrus		L/R	9/10		4	14	52	3.59	<0.001							
Med frontal gyrus		L	9		−6	58	22	3.72	<0.001							
Insula	78	R	–	NS	40	12	−2	3.32	<0.001	188	NS	40	16	−2	3.27	<0.001
Insula	71	L	–	NS	−36	12	2	3.10	<0.001	228	NS	−38	12	2	3.60	<0.001
Precuneus	51	L	7	NS	−10	−64	50	3.30	<0.001	341	NS	−10	−66	50	3.95	<0.001

Stereotaxic coordinates are reported in Talairach space. See text for further details

Maxima of regions showing significant BOLD signal changes. In each statistical comparison, we assigned corrected *p* values at the cluster-level (p_{corr} <0.05; cluster size estimated at p_{unc} = 0.005, voxel-level), considering the whole brain as the volume of interest

corr corrected, *unc* uncorrected, *Ant* anterior, *Sup* superior, *Med* medial, *BA* Brodmann area, *OCD* obsessive compulsive disorder, *HC* healthy controls, *NS* not significant

Table 3 Main effect of basic emotions against both guilt emotions together

Brain area	Basic emotions > guilt, in HC and OCD								
	Cluster				Peak voxel				
	Size	Side	BA	p_{corr}	Coordinates			Z value	p_{unc}
					x	y	z		
Inf frontal gyrus	2,584	L/R	45	<0.000	−46	36	−2	5.91	<0.001
Lingual gyrus	1,686	R	18	<0.000	14	−82	−6	6.79	<0.001
Mid temporal gyrus	1,620	L/R	39	<0.000	−56	−8	−16	5.91	<0.001
Occipital pole	876	L	17	<0.000	−10	−98	2	4.38	<0.001

Stereotaxic coordinates are reported in Talairach space. See text for further details

Maxima of regions showing significant BOLD signal changes. Here the main effect of basic emotions in both, OCD patients and controls are reported. In each statistical comparison, we assigned corrected *p* values at the cluster-level (p_{corr} <0.05; cluster size estimated at p_{unc} = 0.005, voxel-level), considering the whole brain as the volume of interest

corr corrected, *unc* uncorrected, *Inf* inferior, *Mid* middle, *BA* Brodmann area, *OCD* obsessive compulsive disorder, *HC* healthy controls

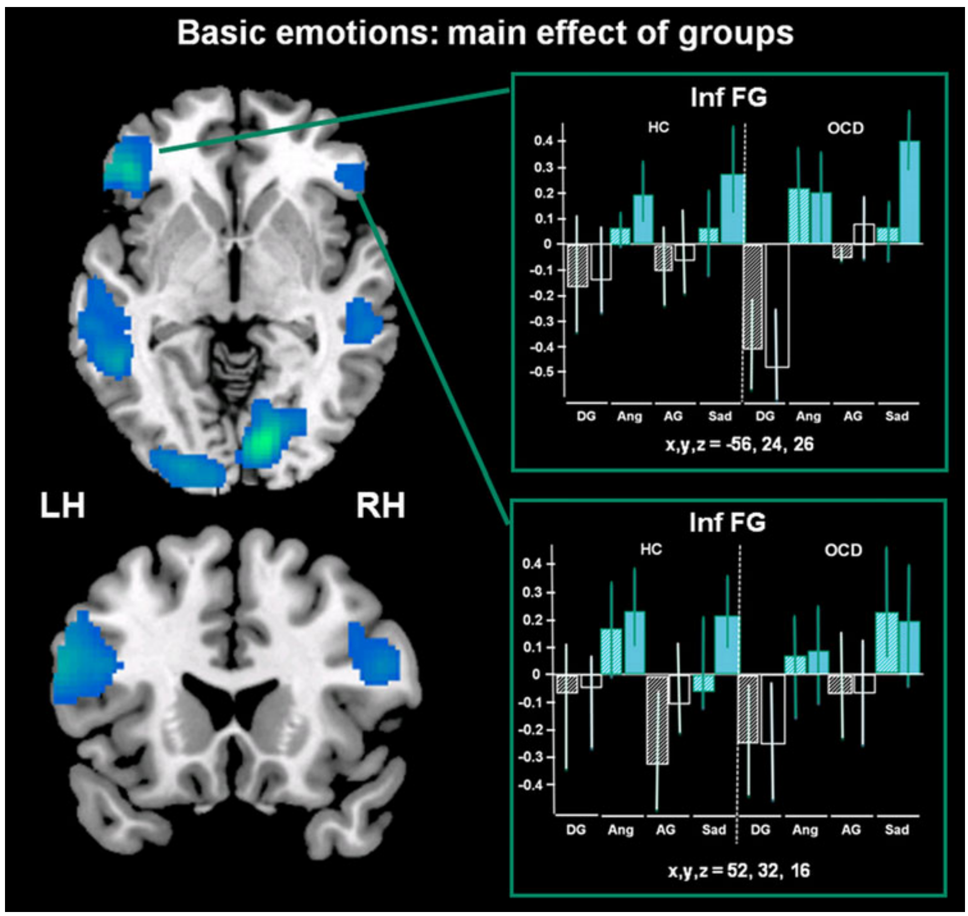

Fig. 3 Basic emotions main effect. Average activity for anger and sad conditions as compared with guilt conditions (DG and AG) across both groups is shown. Significant activation was observed in the inferior/middle frontal gyri, in the middle/superior temporal gyri, in the precuneus and in the occipital lobes. Almost all activations were bilateral, with a greater extent within the *left* hemisphere. *Dashed columns* refer to trials containing neutral faces plus emotional sentence, while *fully colored columns* refer to trials containing emotional faces followed by emotional sentences. The signal plots show that both groups activated similarly when exposed to basic emotions. *OCD* obsessive–compulsive disorder, *HC* healthy controls, *infFG* inferior frontal gyrus, *LH left* hemisphere, *RH right* hemisphere

that our paradigm was able to test our working hypothesis selectively, by manipulating the experimental variable thought to differentiate OCD patients from healthy individuals. Further, when considering OCD patients' performance during task in isolation, more frequent guilt feelings were reported when confronted with DG stimuli, as compared to AG ones. Again, this result confirms the specific sensitivity to a more deontological type of guilt in OCD patients.

fMRI results revealed that OCD patients have reduced activation in the ACC, extending to the superior/medial frontal gyrus, when experiencing guilt, regardless of its specific type (DG or AG). Previous functional neuroimaging studies in healthy subjects (Basile et al. 2011; Shin

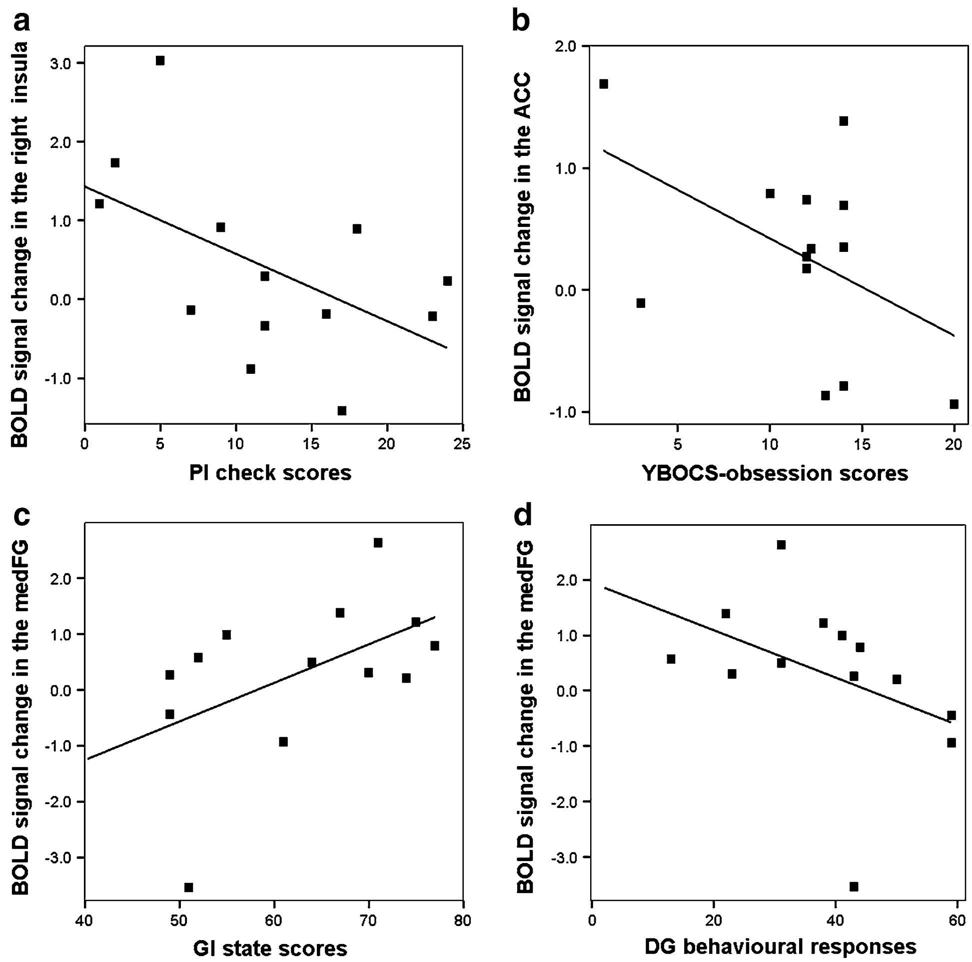

Fig. 4 Correlations between brain activation and psychometric and behavioral responses in patients' group. Unit change in BOLD signal per unit change in ratings. BOLD signal intensity and psychological or behavioral ratings are represented on the *vertical* and *horizontal axes*, respectively. **a** PI-check subscale ratings correlated inversely with activity in the right insula. **b** Y-BOCS obsessions scores correlated negatively with activity in the ACC. **c** Guilt-state correlated positively with activity in the medFG. **d** Frequency of DG responses during tasks correlated inversely with activity in medFG. *PI* Padua inventory, *Y-BOCS Yale-Brown* obsessive–compulsive scale, *GI* guilt inventory, *ACC* anterior cingulate cortex, *medFG* medial frontal gyrus, *DG* deontological guilt

et al. 2000; Takahashi et al. 2004; Moll et al. 2007; Kédia et al. 2008) reported a direct involvement of the ACC in the experience of guilt, considered as a single component emotion. As suggested by different authors (Moll et al. 2007; Kédia et al. 2008), the ACC might be directly implicated in empathic moral feelings, entailing both attachment towards another person (AG) and abstract moral rules (DG).

When considering the two types of guilt in isolation, OCD patients showed a more remarkable reduction of activation (than controls) in the ACC, in the anterior insulae bilaterally, and in the left precuneus, when experiencing DG. In contrast, no specific modulation of brain activity was found for AG stimuli. A selective implication of DG in the OCD is consistent with previous literature (Mancini and Gangemi 2011). The current study confirms that a selective dysfunctional processing of deontological (but not altruistic) guilt may occur in patients with OCD. Moreover, a selective involvement of DG is conceivable on the basis of our previous investigation (Basile et al. 2011), providing evidence for the existence, in healthy subjects, of distinct neuronal networks to subserve DG and AG processing. The network implicated in the experience of DG, which resulted to be selectively modulated in the presence of OCD, includes not only the ACC, but also the insula bilaterally. The anterior portion of the insula is traditionally implicated in the emotion processing of disgust (Lane et al. 1997; Phillips et al. 1997), to which OCD patients are generally hypersensitive too (for a review, see Berle and Phillips 2006). Further, disgust has also been defined as a moral emotion (Miller 1997), as it might arise from sensory experiences, but also from more abstract concerns, such as moral judgments. Our current findings confirm that DG is likely to be a complex emotion with more basic (disgust-related) and cognitive (moral judgment) aspects, and that specific brain structures (i.e., the insula and the ACC, respectively) might represent their corresponding neuronal substrate. Further, we argue that abnormal patterns of activation observed in the ACC and in the insula of OCD patients, might reflect their abnormal processing of DG stimuli. This interpretation is reinforced by the correlations found between patients' OCD symptom severity and frequency of DG behavioral responses during fMRI. Activation of the left precuneus was also modulated by DG in OCD patients. Although this region was not included in the network activated by healthy subjects when experiencing

DG (Basile et al. 2011), the precuneus is known to be implicated in higher-order cognitive functions (Cavanna and Trimble 2006), and might therefore contribute in accounting for the abnormal processing of DG stimuli in OCD patients. As mentioned above, DG can indeed be regarded as a complex emotion, with more basic components and more cognitive aspects.

When testing for differences in the processing of the two control basic emotions (i.e., anger and sadness), we did not find significant changes between OCD patients and controls. Both groups, while processing anger and sadness stimuli, activated similarly to each other a prefronto-temporo-occipital network. Again, this suggests that the clinical manifestations of OCD are not merely due to an abnormal processing of basic emotions, but they involve more cognitive aspects, such as those implicated in complex emotions.

Overall, patients' showed reduced brain activation than controls when processing guilt stimuli, especially those of deontological type. We can only speculate about the relationship between more intense guilty feelings and a negative neuronal modulation. One potential explanation might be found in the so called "neural efficiency hypothesis" (Neubauer and Fink 2009), which assumes that lower brain activation might reflect a more efficient (since less energy consuming) brain response during a specific task. Many studies showed that trained individuals, or experts, require fewer energy resources to cope with well-known task demands, this resulting in reduced patterns of brain activation (for a review see, Neubauer and Fink 2009). Similarly, we suggest here that there may be a relationship between OCD patients' frequent exposure to guilty feelings in the everyday life, and their pattern of reduced brain activation.

Previous neuroimaging studies (Mataix-Cols et al. 2004) based on symptom provocation in OCD have reported increases of brain activity in patients, compared to healthy controls. This apparent inconsistency with our findings is likely to be due to the substantial difference in the brain processing induced by the different fMRI paradigms. When investigating neural activity during a symptom provocation task, like showing disgusting/aversive pictures (Mataix-Cols et al. 2004), patients undergo an intense basic emotion perturbation that leads increased levels of anxiety and a higher general arousal. Both these aspects may be responsible for an increased brain activity. Conversely, guilt stimuli are likely to operate in a more ecological way, eliciting moral contents that regularly pervade the everyday experience of patients. In other words, guilt stimuli do not induce neural response such as those elicited by characteristic OC triggers, but in spite, we believe they interact with the cerebral activity underlying patients' "guilt-default" mental and emotional states. A recent fMRI study by Harrison et al. (2012) investigated moral decision-making (through moral dilemmas) in a large sample of OCD patients, showing increased neural activity in both frontal and middle temporal regions of patients, as compared against controls. Again, this hyperactivation might be explained by the more provocative features of this task, compared to the one we used in our study. In addition, the moral investigation by Harrison et al. (2012) was based on a cognitive task (decision-making) which, by definition, requires more effort to be accomplished, than our emotional paradigm. We suggest that a forced decision-making choice is likely to be more activating than a simple questioning about an inner emotional feeling. Consistent with this interpretation, the partial overlapping of anatomical areas implicated in the two studies, included structures such as the ACC and the prefrontal cortex, which are known to mainly subserve cognitive functions. On the other hand, the insula, which is traditionally involved in disgust and guilt processing, and in aversive emotions in general (Basile et al. 2011; Shin et al. 2000; Takahashi et al. 2004; Moll et al. 2007; Kédia et al. 2008), was found to be task modulated in our study, only.

One limitation of this study is the significantly older mean-age of patients, compared to HC. However, we do not think age affects emotional processing in young adults. A second limitation refers to the fact that almost half of OCD patients were receiving medication with antidepressant. However, the additional analysis we run by contrasting the two OCD patients' subgroups did not return any significant difference in brain activation, even when setting a permissive statistical threshold. This suggests that medications did not produce any effect on our experimental findings. On the other hand, even in previous literature, the effect of antidepressant drugs on functional brain activation remains a controversial issue. Some neuroimaging studies suggest an increase of specific regional metabolism, but with different effects depending on duration of administration (Page et al. 2009). One study in OCD patients treated with SSRI, revealed an increase of task-relevant brain activation during cognitive challenge, while another fMRI study (Fu et al. 2004) involving depressed patients treated with antidepressant, revealed decreases in neural response while processing emotional stimuli. These findings imply that medication might have a mitigating effect on brain dysfunction, which could have been more pronounced in patients under medication. On the other hand, another study (Page et al. 2009) involving OCD patients, found no difference in brain activation between treated and untreated patients.

In this fMRI study we observed an abnormal cerebral functioning during guilt, and more specifically DG, in the brain of patients with OCD. This alteration may underlie patients' increased sensibility to such emotional states, contributing to the disorder's onset and maintenance. Future follow-up studies comparing neural activity before and after efficacious treatment could help to explain eventual cerebral plasticity mechanisms, underlying patients' guilt proneness.

An abnormal processing of guilty feeling is likely to be present also in other psychiatric or neurological disorders. For instance, major depressive disorder (MDD) includes excessive or inappropriate guilt, along with feelings of worthlessness, as a diagnostic affective component. Specifically, depression might be associated with abnormal processing of altruistic (but not deontological) guilt, as suggested by previous clinical studies (Gilbert 1992; O'Connor et al. 1999). Future fMRI studies should address these aspects, by investigating the contribution of an abnormal guilt processing in patients with MDD. As recently shown by Green et al. (2012), patterns of reduced brain activity exist in the brain of remitted depressed patients. Finally, to further investigate the selective role of guilt in OCD psychopathology, it would also be interesting to use our fMRI paradigm in other disorders showing repetitive stereotyped or compulsive behaviors, such as Tourette syndrome or trichotillomania (Abramowitz et al. 2009; Rachman 2002).

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