Brain structural correlates of obsessive–compulsive disorder with and without preceding stressful life events

E. Real\textsuperscript{a,b,*}, M. Subira\textsuperscript{a,b,c}, P. Alonso\textsuperscript{a,b,c}, C. Segalas\textsuperscript{a,b}, J. Labad\textsuperscript{d,e}, C. Orfils\textsuperscript{a}, C. López-Sola\textsuperscript{a,b,c}, I. Martinez-Zalacain\textsuperscript{a}, E. Via\textsuperscript{a,c}, N. Cardoner\textsuperscript{a,d,e}, S. Jiménez-Murcia\textsuperscript{a,f}, C. Soriano-Mas\textsuperscript{a,b,g} and J.M. Menchón\textsuperscript{a,b,c}

\textsuperscript{a}Psychiatry Department, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain; \textsuperscript{b}Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Carlos III Health Institute, Spain; \textsuperscript{c}Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelona, Spain; \textsuperscript{d}Mental Health Department, Corporació Sanitària Parc Taulí, Sabadell, Spain; \textsuperscript{e}Department of Psychiatry and Forensic Medicine, Universitat Autònoma De Barcelona, Barcelona, Spain; \textsuperscript{f}Centro de Investigación Biomédica en Red-Fisiopatología de la Obesidad y Nutrición (CIBERobn), Carlos III Health Institute, Madrid, Spain; \textsuperscript{g}Department of Psychobiology and Methodology in Health Sciences, Universitat Autònoma de Barcelona, Barcelona, Spain

ABSTRACT

Objectives There is growing evidence supporting a role for stressful life events (SLEs) at obsessive–compulsive disorder (OCD) onset, but neurobiological correlates of such effect are not known. We evaluated regional grey matter (GM) changes associated with the presence/absence of SLEs at OCD onset. Methods One hundred and twenty-four OCD patients and 112 healthy controls were recruited. Patients were split into two groups according to the presence (n = 56) or absence (n = 68) of SLEs at disorder's onset. A structural magnetic resonance image was acquired for each participant and pre-processed with Statistical Parametric Mapping software (SPM8) to obtain a volume-modulated GM map. Between-group differences in socio-demographic, clinical and whole-brain regional GM volumes were assessed. Results SLEs were associated with female sex, later age at disorder's onset, more contamination/cleaning and less hoarding symptoms. In comparison with controls, patients without SLEs showed GM volume increases in bilateral dorsal putamen and the central tegmental tract of the brainstem. By contrast, patients with SLEs showed specific GM volume increases in the right anterior cerebellum. Conclusions Our findings support the idea that neuroanatomical alterations of OCD patients partially depend on the presence of SLEs at disorder's onset.

Introduction

There is growing evidence supporting a role for stressful life events (SLEs) at the onset and course of different mental conditions (Kendler et al. 1999; Morgan and Fisher 2007; Kessler et al. 2010; Horesh et al. 2011; Stegenga et al. 2012). Environmental factors interact with genetic predisposition to develop mental disorders (Moffitt et al. 2005) and recent studies also suggest a gene-by-environment interaction effect on treatment outcome (Keers et al. 2011; Real et al. 2012). In this context, some studies have focussed on the role of stress in obsessive–compulsive disorder (OCD) onset, specially, on the role of childhood traumatic experiences as potential triggers of symptom onset (Gershuny et al. 2002; Lochner et al. 2002). Non-traumatic but nonetheless SLEs have also been linked to a triggering effect of obsessive–compulsive symptoms in both children and adults (Lochner et al. 2002; Gothelf et al. 2004; Cath et al. 2008), but these have received less attention from researchers. These events are much more prevalent in the general population and are considered dateable occurrences involving changes in external social environment or the onset of a physical condition, being perceived by the patient as stressful. Some authors have suggested that stress plays a highly relevant role in clinical heterogeneity of OCD, given that specific clinical and familial patterns have been observed when a SLE precedes OCD onset. Thus, the presence of SLEs at disorder onset has been associated with variables such as female gender (Bogetto et al. 1999), older...
age at onset (Real et al. 2011), less family history of OCD (Albert et al. 2002; Labad et al. 2010; Real et al. 2011), contamination/cleaning symptoms (Labad et al. 2010; Real et al. 2011), the presence of obstetric complications (Real et al. 2011) and greater symptom severity (Cromer et al. 2007). Non-SLE-preceded OCD, by contrast, has been linked to factors considered to be more “genetically-influenced”, such as early onset, family history of OCD and gene-by-environment interaction effects on treatment resistance (Real et al. 2012). Overall, this is in line with previous work supporting that OCD is heterogeneous and a “stress-sensitive condition” (Miguel et al. 2005; Real et al. 2012), but specific studies assessing this issue are scarce.

Neuroimaging tools have been used to assess the neural correlates underlying clinical heterogeneity in OCD. In this line, structural magnetic resonance imaging studies have been particularly successful in detecting regional grey matter (GM) volume alterations associated with specific clinical features. For instance, from the clinical multidimensional model approach (Mataix-Cols et al. 2005; Rosario-Campos et al. 2006), aggressive/checking symptoms have been associated with volume alterations in temporolimbic regions including the amygdala as well as in the insula and putamen (Pujol et al. 2004; van den Heuvel et al. 2009; Alvarenga et al. 2012), contamination/cleaning symptoms have been associated with volume reductions in the dorsal caudate and insula, while the symmetry/ordering symptoms have been associated with volume reductions in sensorimotor cortex (van den Heuvel et al. 2009; Okada et al. 2014). Other clinical features have also been associated with regional volume alterations; for example, the presence of sensory phenomena preceding or accompanying obsessions-compulsive symptoms (Ferrao et al. 2012) has been associated with GM volume increases in the sensorimotor cortex (Subirà et al. 2015a), and the autogenous/reactive obsession classification scheme proposed by Lee (Lee et al. 2005) has been related with specific patterns of GM volume alteration in comparison with control subjects (Subirà et al. 2013).

The aim of the present study was to assess the pattern of regional GM change associated with the presence of SLEs at OCD onset. Patients with and without SLEs at disease onset were compared to a group of healthy controls (HC). In addition, we also assessed the correlations between such putative anatomical changes and clinical features known to differ between patients with and without SLEs, such as age at onset, disease duration or the presence of a family history of OCD, as well as with global disorder severity and the presence of specific clinical symptoms.

Material and methods

Participants

One hundred and twenty-four adult outpatients meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for OCD were consecutively recruited from the OCD Unit of Bellvitge University Hospital, Barcelona, Spain. They all had experienced OCD symptoms for at least 1 year before assessment, and two trained psychiatrists (P.A., C.S.) with extensive clinical experience in OCD confirmed the diagnosis through separate interviews using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Clinician Version (SCID-CV; First N et al. 1997). All the patients had been taking stable doses of medication during at least a 3-month period coinciding with scanning. Exclusion criteria were a lifetime history of psychotic disorders, mental retardation, a neurological disease other than tic disorder, lifetime history of substance abuse/dependence, presence of any contraindication to magnetic resonance imaging (MRI), or the presence of any abnormality in the MRI scan. Comorbidity with other DSM-IV-TR Axis I disorders was not considered an exclusion criterion if OCD was believed to be the primary diagnosis. This sample was partially overlapping with the group of patients (n = 412) reported in Real et al. (2011). Specifically, 82 patients of the current sample (66.1%) were also included in that previous study, which, however, did not include a neuroimaging assessment. Nonetheless, some of the brain scans included in this study were also used in other imaging studies of our group (de Wit et al. 2014; Subírà et al. 2015a, 2015b).

A sample of 112 HC was also recruited. The HC group was matched with the OCD group in age (OCD: 34.90 ± 9.53 years vs. HC: 33.76 ± 10.01 years; t = 0.989; P = 0.37) and gender (OCD, female percentage: 50% vs. HC, female percentage: 44.6%; χ² = 0.677; P = 0.437). Controls were assessed through the Structured Clinical Interview for DSM-IV-TR non-patient version (First MB et al. 2007) to exclude any Axis I psychiatric condition. Written informed consent was obtained from all subjects after being provided with a full description of the study, which was approved by the ethics committee of Bellvitge University Hospital (CEIC Ciutat Sanitària i Universitària de Bellvitge) and performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1964.
Clinical assessment

All subjects completed a semi-structured direct interview that included clinical and socio-demographic data assessing obstetric history and substance abuse, family history of OCD in first and second degree relatives (established by the Family History Research Diagnostic Criteria; Andreasen et al. 1977), as well as clinical OCD characteristics such as age at onset and comorbidity with another mental pathology or tic disorder (see Real et al. 2011). The severity of the obsessive-compulsive, depressive and anxiety symptoms was assessed through the clinician-administered version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al. 1989), Hamilton Depression Rating Scale (HDRS; Hamilton 1960) and the Hamilton Anxiety Rating Scale (HARS; Hamilton 1959), respectively. Lifetime presence of obsessive-compulsive symptoms was assessed with the clinician-administered version of the Y-BOCS Symptom Checklist (Goodman et al. 1989), as described elsewhere (Real et al. 2011).

Life events assessment

Patients were asked an open-ended question regarding their experiences of life events during the year before the onset of OCD symptoms. If they mentioned any event occurring 1 year prior to onset (either negative, positive or neutral), we carefully investigated the time of the occurrence of the life event and if the patient perceived it as stressful and related to the onset of OCD. The Paykel Scale of Stressful Life Events (Paykel et al. 1971) was then used to check whether the event identified fitted in any of the 61 events on the list, as in previous studies (Bogetto et al. 1999; Maina et al. 1999; Real et al. 2011; Rosso et al. 2012; Goldberg et al. 2015).

According to the above criteria, the OCD sample was split into two groups according to the presence (SLE-preceded OCD group) or absence (non-SLE-preceded OCD group) of an SLE at disorder’s onset (see Table 1).

Image acquisition and pre-processing

Images were acquired with a 1.5-T scanner (Signa Excite system, General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil. A high-resolution, T1-weighted, anatomical image was obtained for each subject and pre-processed according to a voxel-based morphometry (VBM) protocol. Further details regarding imaging acquisition and pre-processing are provided in Supplementary Material.

Statistical analyses

Sociodemographic and clinical variables were compared between SLE-preceded and non-SLE-preceded OCD groups, as well as with HC, by means of \( \chi^2 \) and independent sample \( t \)-tests using SPSS v.21. Significance threshold was set at \( P < 0.05 \).

We performed a VBM analysis to compare voxel-wise regional volumes across the three study groups by means of a one-way analysis of variance (ANOVA) model in SPM8 within the framework of the general linear model (omnibus \( F \)-test), with age, gender and total GM volume as covariates. As this was a whole-brain exploratory analysis, to protect findings against false positives, a stringent significance threshold of \( P < 0.05 \) family-wise error (FWE) corrected for multiple comparisons was used. In addition, pair-wise \( t \)-contrasts were also performed at the whole-brain level (\( P < 0.05 \) FWE corrected) to characterise the results of the omnibus \( F \)-test and identify putative between-group differences that might have gone undetected by this general comparison. Such pair-wise findings were further characterised in SPSS. Specifically, for each subject we extracted the voxel values from the significant peak coordinates and performed one-way ANOVAs with Tukey-B comparisons to illustrate, for each location, the progression of GM change across the three study groups. Finally, we performed a \( t \)-test comparison to compare the whole group of OCD subjects vs. HC.

Finally, to evaluate the putative effects of specific clinical features, the association between voxel values from the above analyses and variables such as disorder’s severity, age at onset, disease duration, presence of family history of OCD or symptom subtypes were assessed by means of Pearson’s correlations and Student’s \( t \)-tests. These analyses were controlled for the same confounders included in the SPM models, and threshold was set at \( P < 0.05 \).

Results

Sample characteristics

Fifty-six patients (45.16%) referred the presence of a life event associated with disorder’s onset (SLE-preceded OCD group). As reported in Table 1, a significantly higher number of females were observed in this subgroup of patients. Likewise, in comparison to the non-SLE subgroup, patients with SLEs reported a higher age at disorder onset, a higher percentage of contamination/cleaning symptoms, and a lower percentage of hoarding symptoms. No other significant
Sociodemographic or clinical differences were observed between both patient groups (Table 1 summarises sociodemographical and clinical characteristics of HC and OCD subgroups).

### Neuroimaging analysis

The omnibus F-test showed three GM clusters of significant across-group differences, located in the region of the central tegmental tract of the midbrain (x,y,z = 3,–31,–12; F = 18.02; P\text{FWE} = 0.001) and in bilateral dorsal-caudal putamen (right: x,y,z = 33,–13,0; F = 14.41; P\text{FWE} = 0.023; left: x,y,z = −32,−16,−2; F = 14.06; P\text{FWE} = 0.030). Planned pair-wise comparisons are summarised in Table 2. Specifically, in comparison with HC, patients in the non-SLE subgroup showed a GM volume increase in bilateral dorsal-caudal putamen (Figure 1A), as well as in the region of the central tegmental tract (Figure 2A). However, a GM volume increase in the right anterior cerebellum (hemispheric lobe VI) was observed in the SLE-preceded group (Figure 3A). This last finding, however, was not

### Table 1. Sample characteristics of non-SLE-preceded OCD, SLE-preceded OCD patients and healthy controls.

| Sample characteristics of non-SLE-preceded OCD, SLE-preceded OCD patients and healthy controls. | OCD (n = 124) |
|---|---|
| | Non-SLE-preceded OCD (n = 68) | SLE-preceded OCD (n = 56) |
| Gender, female (n, %) | 26 (38.2) | 36 (43.3) |
| Age (mean, SD) | 34.81 (9.65) | 35.02 (9.49) |
| Years of education\(c\) (mean, SD) | 25.96 (5.81) | 26.39 (5.65) |
| Age at onset of OCD\(d\) (mean, SD) | 19.79 (8.46) | 22.84 (7.94) |
| Y-BOCS (mean, SD) | 12.93 (3.04) | 12.98 (3.03) |
| Obsessions subscale | 30 (44.1) | 30 (53.6) |
| Compulsions subscale | 31 (45.6) | 38 (67.9) |
| Total score | 5.35 (118) | 6.17 (40) |
| Family history of OCD\(e\) (n, %) | 35 (53.6) | 50 (44.6) |
| HARS score (mean, SD) | 17 (25.0) | 14 (25.0) |
| Hoarding | 30 (44.1) | 31 (45.6) |
| Y-BOCS | 30 (44.1) | 30 (53.6) |
| Anxiet disorders | 14 (20.6) | 16 (28.6) |
| Mood disorders | 6 (8.8) | 5 (8.9) |
| Tic disorders | 1 (1.5) | 0 (0) |
| Eating disorders | 7.1 | 4.71 |
| Pharmacological treatment (n, %) | 4.71 | 4.71 |
| No treatment | 2 (2.9) | 2 (2.9) |
| SSRI | 23 (33.8) | 18 (22.1) |
| Clomipramine | 25 (36.8) | 19 (23.9) |
| SSRI/clomipramine + antipsychotic | 18 (26.5) | 15 (26.8) |

Data are N (%) for categorical variables or mean (SD) for continuous variables. HC, healthy controls; OCD, obsessive–compulsive disorder; SLE, stressful life event; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; SSRI, selective serotonin reuptake inhibitor; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale.

\(a\)Statistic value for the comparison between OCD groups, corresponding to Student’s t-test for continuous variables and chi-square test for categorical variables.

\(b\)Sociodemographic variables of HC are provided for reference. No significant differences were observed with the group of OCD patients in age and gender, although groups were slightly different in terms of years of education (t = −3.018, P = 0.003).

\(c\)There is one missing value for this variable (corresponding to a subject from the non-SLE-preceded OCD group).

\(d\)Age at onset was considered when symptoms became a significant source of distress and interfered with the patient’s social functioning.

\(e\)There are five missing values for this variable (three of them in the SLE-preceded OCD group and two in the non-SLE-preceded OCD group).

### Table 2. Regions with significant GM volume alterations characterising OCD subgroups.

| Peak coordinate | T value | KE (voxels) | Effect size (Cohen’s \(d\)) | Anatomical localization |
|---|---|---|---|---|
| Non-SLE-preceded OCD > Controls | (3,–31,–12) | 6.00 | 104 | 0.920 | Central tegmental tract |
| SLE-preceded OCD > Controls | (35,–40,–29) | 4.97 | 217 | 0.958 | Right anterior cerebellum (hemispheric lobe VI) |

\(x,y,z\) coordinates are reported in standard Montreal Neurological Institute space. KE, cluster extent; SLE, stressful life event.
observed in the omnibus $F$-test, where across-group differences for the cluster of the right anterior cerebellum were only marginally significant ($x,y,z = 35,-40,-29; F = 12.47; P_{FWE} = 0.101$). No significant GM volume decreases were observed in any of the OCD subgroups in comparison to HC. Likewise, at the whole-brain level, no significant differences were observed between OCD subgroups.

The above findings were further characterised in SPSS to illustrate, for each location, the progression of GM change across the three study groups. Thus, voxel-values from the peak coordinates of above analyses were analysed with Tukey-B comparisons. As expected, regarding GM volumes of the right putamen and the central tegmental tract, non-SLE patients and HC showed the highest and lowest values, respectively. Moreover, we observed that SLE patients showed intermediate values, equidistant from the other two groups (right putamen, $F_{(2,233)} = 14.99; p < 0.001$; central tegmental tract, $F_{(2,233)} = 18.98, P < 0.001$) (see Figures 1B and 2B, respectively). Conversely, regarding regional GM volume of the left putamen, despite being higher in non-SLE-preceded and SLE-preceded OCD and healthy control groups. Significance levels are reported for between-group comparisons (***$P < 0.0005$; n.s., non-significant).

Figure 1. Bilateral grey matter volume differences between non-SLE-preceded OCD patients and control group in putamen. (A) Increased GM volume in non-SLE-preceded OCD patients compared with the control group in the right and left putamen extended to the insula. Colour bar represents $t$ value. L indicates left hemisphere. Image presented at $P < 0.001$ for illustrative purposes. (B) Box-plot depicting adjusted GM volume corresponding to peak coordinate of the right putamen in both non-SLE-preceded and SLE-preceded OCD and healthy control groups. Significance levels are reported for between-group comparisons (***$P < 0.005$, **$P < 0.005$, ***$P < 0.0005$). (C) Box-plot depicting adjusted GM volume corresponding to peak coordinate of the left putamen in both non-SLE-preceded and SLE-preceded OCD and healthy control groups. Significance levels are reported for between-group comparisons (***$P < 0.0005$; n.s., non-significant).
SLE subgroup in comparison with HC, was also significantly larger in SLE patients in comparison with non-SLE-preceded patients ($F_{(2,233)} = 15.81; P < 0.001$), but this last group did not differ from HC (see Figure 3B). Similar results were observed when these analyses were repeated using the first eigenvariate instead of the peak voxel value as the summary measure of SPM clusters.

Voxel values from the peak coordinates of the neuroimaging analyses did not show significant correlations with age at disorder onset, disease duration, or symptom severity. Likewise, no associations were observed between the volumes from the above coordinates and family history of OCD or the presence of contamination/cleaning symptoms. Conversely, the presence of hoarding symptoms, which were more
frequent in patients without SLEs, was associated with larger volumes in the right dorsal putamen of this group of patients \( (r = 2.23; \text{df} = 122; P = 0.028) \). Nevertheless, hoarding symptoms did only partially account for the difference in right dorsal putamen volume between OCD groups, since the presence of SLEs continued to have a significant effect on right dorsal putamen volume after excluding from the analyses patients with hoarding symptoms \( (F_{(2,199)} = 7.93; P < 0.001) \). Further, although gender was included as a confounding covariate in all analyses, since our subgroups of patients differed in gender distribution we also compared voxel volumes from the above analyses between males and females, and no significant associations were found. Finally, we also explored whether main comorbidities (i.e., affective, other anxiety or tic disorders) had a significant effect on our imaging results by repeating the main analyses after excluding subjects with such disorders. Overall, comparisons were not significantly affected by the exclusion of subjects from any of the comorbidity groups.

A whole-brain voxel-wise comparison between the whole OCD group and HC is presented in supplementary material.

Discussion

To our knowledge, this is the first attempt to explore the neuroanatomical basis of OCD according to the presence/absence of SLEs at disorder onset. Specifically, we explored the role of non-traumatic SLEs on regional GM volumes at a whole brain level across patients with and without SLEs at disorder onset and HC. In comparison with HC, patients without SLEs showed GM volume increases in bilateral dorsal putamen and in the central tegmental tract of the brainstem, while patients with SLEs showed a GM volume increase in the right anterior cerebellar hemisphere. Importantly, according to our post-hoc analyses, GM volume increases in right dorsal putamen and central tegmental tract also discriminated between patient groups (patients without SLEs > patients with SLEs), although the volumes of these regions were also increased in patients with SLEs in comparison to control subjects. By contrast, OCD patients with and without SLEs did not differ in left putamen volume. Finally, GM volume increases in the right anterior cerebellum were specific to OCD patients with SLEs.

In our sample the frequency of patients reporting an SLE preceding OCD onset was higher than that found in a previous report from our group (45.16 vs. 37.4%) \( (\text{Real et al. 2011}) \). Although samples of these studies were partially overlapping (see Methods section), the present study assessed a smaller sample of subjects \( (n = 124 \text{ vs. } n = 412) \), which may account for the variations in the estimation of the prevalence of SLEs at OCD onset. Nevertheless, in another assessment of a large series of patients \( (n = 329) \) \( (\text{Rosso et al. 2012}) \), the frequency of OCD patients with SLEs at disorder’s onset (60.8%) was even higher than in our two studies. Despite the same scale being used for the assessment of SLEs in both research groups \( (\text{Paykel et al. 1971}) \), it is likely that methodological differences in the evaluation of patients may partially account for such discrepant findings. Thus, for instance, since the Paykel scale is not a screening scale, interview-based methods are considered the gold standard for evaluating the presence of life stress \( (\text{Monroe 2008}) \). Therefore, it is the interviewer, not the patient, who ultimately determines whether an event was of enough importance to lead to functional interference. In this sense, it is important to note that the assessment of SLEs preceding OCD onset is certainly a deficiently studied research topic, and further research efforts should be directed at developing unambiguous evaluation protocols to be shared by different research groups in order to obtain proper estimates of the prevalence of this clinical feature.

Our current results are nevertheless in agreement with these other two studies \( (\text{Real et al. 2011}; \text{Rosso et al. 2012}) \), and with earlier reports \( (\text{Bogetto et al. 1999}) \), in that SLE-preceded OCD is associated with female preponderance. Previous research has shown that women cope with SLEs in a way that exacerbates stress \( (\text{Bolger 1990}) \), as they are more vulnerable to develop anxiety and affective disorders after stress exposure \( (\text{Piccinelli and Wilkinson 2000}) \). This heightened female stress responsiveness seems to be mediated by biological factors (like reproductive steroid hormone-dependent modulation) \( (\text{Goel and Bale 2010}; \text{Donner and Lowry 2013}) \) and particular personality traits \( (\text{Mandelli et al. 2015}) \). We have also confirmed our previous findings relating SLEs with a later age at disorder onset \( (\text{Real et al. 2011}) \). In this sense, it is important to note that, contrary to other studies assessing traumatic life-events occurring at childhood \( (\text{Lochner et al. 2002}; \text{Brooks et al. 2015}) \), we assessed non-traumatic SLEs occurring during the year before the onset of OCD symptoms. This result may also indicate that non-SLE OCD is under stronger genetic control, and, indeed, the associations between SLEs and lower familial history of the disorder reported in previous studies \( (\text{Albert et al. 2002}; \text{Real et al. 2011}) \) are in agreement with this notion, although this association has not been confirmed here, plausibly because of the smaller sample size assessed. Likewise, the association between SLEs and contamination/cleaning symptoms has been
confirmed (Labad et al. 2008; Real et al. 2011). Since these symptoms are more prevalent in female OCD patients (Labad et al. 2008; Torresan et al. 2013), such a relationship may stem from the higher prevalence of SLEs within female populations. By contrast, we have not confirmed findings from other groups relating SLEs with aggressive/checking (Maina et al. 1999; Uguz et al. 2007) and somatic symptoms (Rosso et al. 2012), although, we reported a novel negative association with hoarding symptoms. As far as we know, this association has not been reported in the literature, although this lack of previous findings must be interpreted cautiously, since early studies may have mixed OCD patients with hoarding symptoms with patients with a hoarding disorder without OCD. In any case, in our sample, the presence of hoarding symptoms was associated with larger volumes in right dorsal putamen, an unexpected finding that, however, did not affect the interpretation of our main results, since the effect of SLEs on right dorsal putamen volumes remained significant after excluding patients with hoarding symptoms. Moreover, this correlation should also be interpreted with caution since it was observed at a lenient significance threshold.

Regarding our imaging findings, our results support the idea that, in addition to a different clinical profile, patients with and without SLEs at disorder onset have distinct neural correlates. Specifically, we observed that increased putamen volumes, a finding typically reported in general OCD samples (Pujol et al. 2004; Radua and Mataix-Cols 2009), were more manifest in OCD patients without SLEs, especially in the right hemisphere. This partial selectivity of putamen alterations for a particular subgroup of patients has been also observed in relation to other classification schemes, such as the division between patients with reactive vs. autogenous obsessions (Subirà et al. 2013). In that case, OCD patients with reactive obsessions displayed larger putamen volumes, a finding that was interpreted in association with the presence of overt compulsive behaviour as a distinguishing feature of this group of patients (Subirà et al. 2013). Indeed, large putamen volumes are not specific to OCD, these being also observed in other disorders involving a compulsivity component (Hollander et al. 2005; Chamberlain et al. 2008), and, in general, the dorsal putamen has been associated with habit formation and the development of stereotyped motor sequences and compulsive behaviours (Hollander et al. 2005; Balleine and O’Doherty 2010; Ruge and Wolfensteller 2013).

Interestingly, chronic stress exposure has been shown to cause neuronal hypertrophy in the sensorimotor striatum (Dias-Ferreira et al. 2009), and volume increases in the caudate-putamen have been described in stress susceptible animals (Delgado y Palacios et al. 2011). Therefore, the possibility exists that stress may lead to OCD by acting on the same neuronal substrates found to be altered in non-stress exposed patients. Speculatively, while the large putamen volumes observed in OCD patients without SLEs would not need to interact with environmental factors to lead to obsessive–compulsive symptoms, the intermediate putamen volumes observed in the SLE group might interact with the triggering effect of environmental stress, resulting in the development of obsessive–compulsive symptoms. Although further research is warranted to elucidate this issue, especially in samples of recently diagnosed subjects, our findings suggest that the extent to which putamen volume is increased in comparison to HC may be associated with a differential susceptibility to develop OCD.

The above notions imply that increased putamen volumes should be present from disorder onset. Nevertheless, contrary to these ideas, it might be argued that increased putamen volumes develop over the course of the disorder, as has been suggested in previous studies, where putamen volumes increased with patients’ age or disorder duration (Pujol et al. 2004; de Wit et al. 2014). Such findings have been interpreted in terms of structural neuroplasticity stemming from a protracted period of compulsive behaviour and putamen hyperfunctioning (de Wit et al. 2014). However, it is noteworthy that, despite the significant differences between our subgroups of patients in terms of age at onset, according to our post-hoc analyses, putamen volumes did not depend on the age at disorder onset or disease duration. Indeed, studies reporting an association between age and putamen volumes typically localise such findings in motivational-affective ventral-rostral regions of the nucleus (Pujol et al. 2004; de Wit et al. 2014), whereas our finding and others linking putamen volumes with specific OCD subtypes (Subirà et al. 2013) were located in the sensorimotor dorsal-caudal region of the nucleus. In this context, it should be noted that structural plasticity is more easily induced in limbic than in sensorimotor regions (Kolb 2003; Butz et al. 2009; Neufeld et al. 2009), which may partially account for the differential effects of age on specific putamen regions.

The GM area surrounding the central tegmental tract also discriminated between both patient subgroups, with greater differences, in comparison to HC, in non-stress exposed patients than in patients with SLE-preceded onsets. The same rationale described above may apply here; that is, the extent to which GM surrounding the central tegmental tract is increased in comparison to HC may be associated with a differential
susceptibility to develop OCD. Nevertheless, this region has not been typically reported in association with OCD or obsessive-compulsive symptoms. The central tegmental tract interconnects diencephalic and brainstem regions, such as the ventral posteromedial nucleus of the thalamus and the nucleus tractus solitaries (NTS), related to viscerosensory processing and interoceptive regulation (Kamali et al. 2009). In spite of interoception having been scarcely explored in OCD, previous data suggest that OCD patients may show structural alterations in the posterior insular cortex (Pujol et al. 2004; Nakamae et al. 2012), which has been considered as the primary interoceptive cortex (Craig 2003). Moreover, it has been recently shown that the brain regions interconnected through the central tegmental tract (i.e., ventral posteromedial thalamus and NTS) are involved in fear response (Fullana et al. 2015). Therefore, increased GM content within this area may be related with the heightened expression of fear responses observed in OCD (Simon et al. 2014). Regardless, it is also important to note that this is mainly a white matter region. Although we have carefully confirmed the location of this finding, this result should be interpreted with caution since with the current approach it is not possible to ascertain whether it implies a genuine volumetric change affecting a white matter tract, which may appear in GM segments due to the multi-class classification of voxels by the SPM tissue segmentation algorithm, or an alteration of the midbrain GM nuclei located in the vicinity of the tract.

In contrast to the above findings, a cluster of greater GM volume located in the right anterior cerebellum (hemispheric lobe VI) was specifically observed in OCD patients with SLEs at disorder onset. GM volume increases in the cerebellum have been previously reported in general OCD samples (Pujol et al. 2004; de Wit et al. 2014). Present volume increases were located in the right hemispheric lobe VI, which is related to sensorimotor functioning (Stoodley and Schmahmann 2010). Interestingly, some researchers have proposed that OCD may be considered as a sensorimotor disorder (Russo et al. 2014), and it is therefore tempting to speculate that patients with SLEs at disorder onset may show more sensorimotor disturbances. Unfortunately we did not assess this clinical feature in the present sample, although other groups have previously reported an association between the presence of SLEs and somatic (i.e., akin to sensorimotor) obsessions and compulsions (Rosso et al. 2012). Nevertheless, vermian and hemispheric components of lobule VI have also been found active during cognitive and affective processing (Stoodley and Schmahmann 2009), and previous studies have associated cognitive disturbances in OCD with alterations in cerebellar activity (Nakao et al. 2005; Nabeyama et al. 2008; Eng et al. 2015). However, no studies have assessed the association of these neurocognitive alterations and the presence of SLEs.

According to our estimates, general OCD populations should normally include a larger proportion of patients without SLEs at disorder onset. Hence, it is not surprising that putamen alterations have been previously reported in general OCD samples (Pujol et al. 2004; Radua and Mataix-Cols 2009), although, as discussed above, these have been typically reported in more ventral-rostral regions of the nucleus. At the same time, however, it seems surprising that volume increases in the central tegmental tract have not been reported before. Nevertheless, some studies have reported volume increases in the medial anterior cerebellum (vermis) extending to adjacent brainstem structures (Pujol et al. 2004; Soriano-Mas et al. 2007). A detailed evaluation of such findings is warranted to ascertain whether GM volume increases surrounding brainstem white matter tracts are a distinctive feature of OCD. Volume increases in cerebellar hemispheres reported here in association with SLEs, by contrast, might be more difficult to characterise in general OCD populations as these normally include a smaller proportion of patients with SLEs. Likewise, it should be mentioned that we have not described alterations involving other brain regions, such as the dorsal-medial prefrontal and the medial and lateral orbitofrontal cortices, typically reported in studies assessing general OCD populations (Pujol et al. 2004; Soriano-Mas et al. 2007; de Wit et al. 2014). Volumes of these regions may not, therefore, depend on the presence of SLEs, being most probably related to other clinical features. For instance, the presence of comorbid depression has been described to be particularly important in relation to orbitofrontal alterations (Cardoner et al. 2007) and this condition is not significantly different between our subgroups of patients.

Some limitations need to be considered in the interpretation of our results: (1) patients were recruited from an OCD referral unit and may not be representative of community samples; (2) almost all our patients were under pharmacological treatment. However, the dose of the medication had been stable during at least 3 months prior to the study and our subgroups of patients did not differ in treatment duration or type. Moreover, no significant effects of antidepressant treatment on brain morphology were detected in a meta-analysis of voxel-wise structural studies in OCD (Radua and Mataix-Cols 2009); (3) the potential influence of comorbidity on our findings cannot be totally ruled out, although our analyses showed that main comorbidities were not associated with the presence of SLEs and did
not affect imaging results; (4) we used a 1.5-T scanner, which probably limited the spatial resolution of our findings; (5) intellectual capacity was estimated by years of education, but premorbid IQ would have been preferable; (6) the cross-sectional design of the study limits making causal inferences between SLEs and volumetric changes; and (7) recall bias may affect reliability of retrospective measurements. However, to minimise this potential risk, all patients were assessed through a direct face-to-face interview, which allow the interviewer to evaluate the significance of SLEs for OCD onset and reduce possible recall distortions (Miller et al. 1986).

In summary, our findings add evidence to the notion that the causes of OCD may differ across patients, with genetic and other biological determinants, as well as contextual factors (e.g., stress), playing a variable role. Some structural alterations (i.e., putamen and brainstem volume increases) may be less evident and might act as a vulnerability factor in patients developing OCD subsequent to an SLE. Tentatively, we propose that, in these patients, the presence of an environmental factor could be needed for putative subclinical symptoms to become a full clinical expression of OCD. Moreover, such patients may exhibit specific morphological alterations (i.e., GM volume increases in cerebellar hemispheres) which may be related to specific symptoms, although further research both in the clinical characterisation of these patients and their biological correlates is needed to properly describe the causes and consequences of such putative stress-induced structural alterations. Our results may also provide new ideas to be considered regarding treatment approaches for OCD. Since SLE-preceded patients may be considered an “environmental-at-risk” OCD subgroup, more vulnerable to stress, perhaps these patients could benefit from specific training on stress coping strategies. Likewise, the increased GM volumes in critical neuroanatomical loci observed in non-SLE-preceded OCD patients suggest that this could be a relevant factor for treatment resistance to appear.

Acknowledgements

This work was supported by Instituto de Salud Carlos III (ISCIII) [CP10/00604, P111/210, P113/00918, P113/01958, P11/00413], FEDER funds (European Regional Development Fund (ERDF) – a way to build Europe –, AGAUR [2014 SGR 1672], Ministerio de Economía y Competitividad [PSI2011-28349] and PROMOSAM [PSI2014-56303-REDT]. CIBERSAM and CIBERonb are both initiatives of ISCIII. ER was supported by a Juan Rodés contract [JR14/00038] and CS-M was supported by a Miguel Servet grant [CP10/00604] from the ISCIII. MS was supported by a predoctoral grant from IDIBELL [Bellvitge Biomedical Research Institute, ID 06/IDB001]. CL-S was supported by the Ministerio de Educación, Cultura y Deporte de España [FPU12/01636]. The authors thank all of the study subjects as well as the staff from the Department of Psychiatry of Bellvitge University Hospital.

Disclosure statement
None to declare.

References

Albert U, Maina G, Ravizza L, Bogetto F. 2002. An exploratory study on obsessive-compulsive disorder with and without a familial component: are there any phenomenological differences? Psychopathology. 35:8–16.

Alvarenga PG, do Rosario MC, Batistuzzo MC, Diniz JB, Shavitt RG, Duran FL, Dougherty DD, Bressan RA, Miguel EC, Hoexter MQ, 2012. Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naïve patients. J Psychiatr Res. 46:1635–1642.

Andreasen NC, Endicott J, Spitzer RL, Winokur G. 1977. The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry. 34:1229–1235.

Balleine BW, O'Doherty JP. 2010. Human and rodent homologies in action control: corticostral determinants of goal-directed and habitual action. Neuropsychopharmacology. 35:48–69.

Bogetto F, Venturello S, Albert U, Maina G, Ravizza L. 1999. Gender-related clinical differences in obsessive-compulsive disorder. Eur Psychiatry. 14:434–441.

Bolger N. 1990. Coping as a personality process: a prospective study. J Pers Soc Psychol. 59:525–537.

Brooks SJ, Naadoo V, Roos A, Fouche JP, Lochner C, Stein DJ. 2015. Early-life adversity and orbitofrontal and cerebellar volumes in adults with obsessive-compulsive disorder: voxel-based morphometry study. Br J Psychiatry. 208:34–41.

Butz M, Worgotter F, van Ooyen A. 2009. Activity-dependent structural plasticity. Brain Res Rev. 60:287–305.

Cardoner N, Soriano-Mas C, Pujol J, Alonso P, Harrison BJ, Deus J, Hernandez-Ribas R, Menchon JM, Valdejo J. 2007. Brain structural correlates of depressive comorbidity in obsessive-compulsive disorder. Neuroimage. 38:413–421.

Cath DC, van Grootheest DS, Willemsen G, van Oppen P, Boomsma DI. 2008. Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins. Behav Genet. 38:108–120.

Craig AD. 2003. Interception: the sense of the physiological condition of the body. Curr Opin Neurobiol. 13:500–505.

Cromer KR, Schmidt NB, Murphy DL. 2007. Do traumatic events influence the clinical expression of compulsive hoarding? Behav Res Ther. 45:2581–2592.

Chamberlain SR, Menzies LA, Fineberg NA, Del Campo N, Suckling J, Craig K, Muller U, Robbins TW, Bullmore ET, Sahakian BJ. 2008. Grey matter abnormalities in trichotillomania: morphometric magnetic resonance imaging study. Br J Psychiatry. 193:216–221.

Delgado y Palacios R, Campo A, Henningsen K, Verhoye M, Poot D, Dijkstra J, Van Audekerke J, Benveniste H, Sijbers J, Wilborg O, et al. 2011. Magnetic resonance imaging and spectroscopy reveal differential hippocampal changes in...
anhedonic and resilient subtypes of the chronic mild stress rat model. Biol Psychiatry. 70:449–457.

de Wit SJ, Alonso P, Schwenk L, Mataix-Cols D, Lochner C, Menchon JM, Stein DJ, Fouche JP, Soriano-Mas C, Sato JR, et al. 2014. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. Am J Psychiatry. 171:340–349.

Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, Costa RM, Sousa N. 2009. Chronic stress causes frontostriatal reorganization and affects decision-making. Science. 325:621–625.

Donner NC, Lowry CA. 2013. Sex differences in anxiety and emotional behavior. Pflugers Arch. 465:601–626.

Eng GK, Sim K, Chen SH. 2015. Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. Neurosci Biobehav Rev. 52:233–257.

Ferrao YA, Shavitt RG, Prado H, Fontenelle LF, Malavazzi DM, de Mathis MA, Hounie AG, Miguel EC, do Rosario MC. 2012. Sensory phenomena associated with repetitive behaviors in obsessive-compulsive disorder: an exploratory study of 1001 patients. Psychiatry Res. 197:253–258.

First MB, Spitzer RL, Gibbon M, Williams JB. (2007). Structured Clinical Interview for DSM-IV-DSM-IV Axis I Disorders: Nonpatient Edition (SCID-I/NP). Biometrics Research, New York State Psychiatric Institute: New York, NY.

First N, Spitzer R, Gibbon M, Williams J. (1997). Structured Clinical Interview for DSM-IV Axis I disorders-Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press, Inc.

Fullana MA, Harrison BJ, Soriano-Mas C, Vervliet B, Cardoner N, Avila-Parcet A, Radua J. 2015. Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. Mol Psychiatry. doi:10.1038/mp.2015.88.

Gershuny BS, Baer L, Jenike MA, Minichillo WE, Wilhelm S. 2002. Comorbid posttraumatic stress disorder: impact on treatment outcome for obsessive-compulsive disorder. Am J Psychiatry. 159:852–854.

Goel N, Bale TL. 2010. Sex differences in the serotoninergic influence on the hypothalamic-pituitary-adrenal stress axis. Endocrinology. 151:1784–1794.

Goldberg X, Soriano-Mas C, Alonso P, Segalas C, Real E, Lópe-Solá C, Subira M, Via E, Jiménez-Murcia S, Menchon JM, et al. 2015. Predictive value of familiarity, stressful life events and gender on the course of obsessive-compulsive disorder. J Affect Disord. 185:129–134.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. 1989. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 46:1006–1011.

Gothelf D, Aharonovskiy O, Horesh N, Carty T, Aptar A. 2004. Life events and personality factors in children and adolescents with obsessive-compulsive disorder and other anxiety disorders. Compr Psychiatry. 45:192–198.

Hamilton M. 1959. The assessment of anxiety states by rating. Br J Med Psychol 32:50–55.

Hamilton M. 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry. 23:56–62.
and long-term difficulties, with some reflections on the concept of independence. Br J Psychiatry. 148:686–696.

Moffitt TE, Caspi A, Rutter M. 2005. Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry. 62:473–481.

Monroe SM. 2008. Modern approaches to conceptualizing and measuring human life stress. Annu Rev Clin Psychol. 4:33–52.

Morgan C, Fisher H. 2007. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. Schizophr Bull. 33:3–10.

Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, Yoshizato C, Yoshioka K, Tomita M, Kanba S. 2008. Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. Psychiatry Res. 163:236–247.

Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Kubota M, Miyata J, Fukui K. 2012. Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 37:90–95.

Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, Kudoh A, Tada K, Yoshioka K, Kawamoto M, et al. 2005. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol Psychiatry. 57:901–910.

Neufeld J, Teuchert-Noodt G, Grafen K, Winter Y, Witte AV. 2009. Synaplastic plasticity in motor, sensory, and limbic-prefrontal cortex areas as measured by degrading axon terminals in an environment model of gerbils (Meriones unguiculatus). Neural Plast. 2009:281561

Okada K, Nakao T, Sanematsu H, Murayama K, Honda S, Tomita M, Togao O, Yoshiura T, Kanba S. 2014. Biological heterogeneity of obsessive-compulsive disorder: A voxel-based morphometric study based on dimensional assessment. Psychiatry Clin Neurosci. 69:411–21.

Paykel ES, Prusoff BA, Uhlenhuth EH. 1971. Scaling of life events. Arch Gen Psychiatry. 25:340–347.

Piccinelli M, Wilkinson G. 2000. Gender differences in depression. Critical review. Br J Psychiatry. 177:486–492.

Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, Vallejo J. 2004. Mapping structural brain alterations in obsessive-compulsive disorder. Arch Gen Psychiatry. 61:720–730.

Radua J, Mataix-Cols D. 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry. 195:393–402.

Real E, Gratacos M, Labad J, Alonso P, Escaramis G, Segalas C, Subirà M, Lopez-Sola C, Estivill X, Menchon JM. 2012. Interaction of SLC1A1 gene variants and life stress on pharmacological resistance in obsessive-compulsive disorder. Pharmacogenomics J. 13:470–475.

Real E, Labad J, Alonso P, Segalas C, Jimenez-Murcia S, Bueno B, Subirà M, Vallejo J, Menchon JM. 2011. Stressful life events at onset of obsessive-compulsive disorder are associated with a distinct clinical pattern. Depress Anxiety. 28:367–376.

Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, Katovich S, Scahill L, King RA, Woody SR, et al. 2006. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol Psychiatry. 11:495–504.

Rosso G, Albert U, Asinari GF, Boggetto F, Maina G. 2012. Stressful life events and obsessive-compulsive disorder: clinical features and symptom dimensions. Psychiatry Res. 197:259–264.

Ruge H, Wolfenstein U. 2013. Functional integration processes underlying the instruction-based learning of novel goal-directed behaviors. Neuroimage. 68:162–172.

Russo M, Naro A, Mastroeni C, Morgante F, Terranova C, Muscatello MR, Zoccali R, Calabro RS, Quarantone A. 2014. Obsessive-compulsive disorder: a “sensory-motor” problem? Int J Psychophysiol. 92:74–78.

Simon D, Adler N, Kaufmann C, Kathmann N. 2014. Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction. Neuroimage Clin. 4:549–557.

Soriano-Mas C, Pujol J, Alonso P, Cardoner N, Menchon JM, Harrison BJ, Deus J, Vallejo J, Gaser C. 2007. Identifying patients with obsessive-compulsive disorder using whole-brain anatomy. Neuroimage. 35:1028–37.

Steegenga BT, Nazareth I, Grobbee DE, Torres-Gonzalez F, Svab I, Maaros Ho, Xavier M, Saldivia S, Bottomley C, King M, et al. 2012. Recent life events pose greatest risk for onset of major depressive disorder during mid-life. J Affect Disord. 136:505–13.

Stoodley CJ, Schmahmann JD. 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage. 44:489–501.

Stoodley CJ, Schmahmann JD. 2010. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex. 46:831–844.

Subirà M, Alonso P, Segalas C, Real E, Lopez-Sola C, Pujol J, Martinez-Zalacain I, Harrison BJ, Menchon JM, Cardoner N, et al. 2013. Brain structural alterations in obsessive-compulsive disorder patients with autogenous and reactive obsessions. PLoS One. 8:e75273.

Subirà M, Sato JR, Alonso P, do Rosario MC, Segalas C, Batistuzzo MC, Real E, Lopes AC, Cerrillo E, Diniz JB, et al. 2015a. Brain structural correlates of sensory phenomena in patients with obsessive-compulsive disorder. J Psychiatry Neurosci. 40:232–240:140118.

Subirà M, Cano M, de Wit SJ, Alonso P, Cardoner N, Hoexteter MQ, Kwon JS, Nakamae T, Lochner C, Sato JR, et al. 2015b. Structural Covariance of neostriatal and limbic regions in Obsessive-Compulsive Disorder. J Psychiatry Neurosci. 41:150012. doi:10.1503/jpn.150012.

Torresan RC, Ramos-Cerqueira AT, Shavitt RG, do Rosario MC, de Mathis MA, Miguel EC, Torres AR. 2013. Symptom dimensions, clinical course and comorbidity in men and women with obsessive-compulsive disorder. Psychiatry Res. 209:186–195.

Uguz F, Akman C, Kaya N, Cilli AS. 2007. Postpartum-onset obsessive-compulsive disorder: incidence, clinical features, and related factors. J Clin Psychiatry. 68:132–138.

van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, van Balkom AJ, Veltman DJ. 2009. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain. 132:853–868.