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White matter structural alterations in pediatric obsessive–compulsive disorder: Relation to symptom dimensions

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ABSTRACT

The aims of this study were to identify gray matter (GM) and white matter (WM) volume abnormalities in pediatric obsessive–compulsive patients, to examine their relationship between these abnormalities and the severity of disorder, and to explore whether they could be explained by the different symptom dimensions. Methods: 62 child and adolescent OCD patients (11–18 years old) and 46 healthy subjects of the same gender and similar age and estimated intellectual quotient were assessed by means of psychopathological scales and magnetic resonance imaging (MRI). Axial three-dimensional T1-weighted images were obtained in a 3T scanner and analyzed using optimized voxel-based morphometry (VBM). Results: Compared with healthy controls, OCD patients showed lower white matter (WM) volume in the left dorsolateral and cingulate regions involving the superior and middle frontal gyri and anterior cingulate gyrus ($t = 4.35$, $p = 0.049$ FWE (family wise error)-corrected). There was no significant correlation between WM and the severity of obsessive–compulsive symptomatology. There were no regions with lower gray matter (GM) volume in OCD patients than in controls. Compared with healthy controls, only the "harm/checking" OCD dimension showed a cluster with a near significant decrease in WM volume in the right superior temporal gyrus extending into the insula ($t = 5.61$, $p = .056$ FWE-corrected). Conclusion: The evidence suggests that abnormalities in the dorsolateral prefrontal cortex, anterior cingulate cortex, temporal and limbic regions play a central role in the pathophysiology of OCD. Moreover, regional brain volumes in OCD may vary depending on specific OCD symptom dimensions, indicating the clinical heterogeneity of the condition.

1. Introduction

Obsessive–compulsive disorder (OCD) is a clinically heterogeneous condition characterized by recurrent intrusive and distressing thoughts (obsessions) and repetitive ritualistic behaviors (compulsions), which cause severe distress. It has a lifetime prevalence of up to 4% (Fontenelle et al., 2006; Valleni-Basile et al., 1994; Yoldascan et al., 2009), and as many as 80% of all OCD cases emerge during childhood and adolescence (Pauls et al., 1995; Rasmussen and Eisen, 1990; Stein et al., 1997). In recent years, considerable attention has been paid to the symptomatic heterogeneity of OCD in an attempt to find biological markers, genetic transmission mechanisms, or ways of predicting treatment response (Mataix-Cols et al., 2005). Brain-imaging and genetic studies (Alsobrook et al., 1999; Mataix-Cols et al., 2004) have provided evidence for the biological validity of the dimensions (aggressive, sexual, and religious obsessions and checking compulsions; symmetry obsessions and repeating, counting, and ordering compulsions; contamination obsessions and washing compulsions; and hoarding obsessions and compulsions). In addition, another promising approach in relation

Abbreviations: AAL, Anatomical Automatic Labeling; ACC, anterior cingulate cortex; CSF, cerebrospinal fluid; CSTC, cortico-striato-thalamo-cortical; CY-BOCS, Children's Yale–Brown Obsessive–Compulsive; DARTEL, The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra; DLPFC, dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, 4th; DTI, diffusion tensor imaging; GM, gray matter; FWE, family wise error; ICV, intracranial cerebral volume; IQ, intelligence quotient; K-SADS-PL, Kiddy-schedule for affective disorders and schizophrenia for school-age children—present and lifetime version; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; OFC, orbitofrontal cortex; OCI-CV, Obsessive–Compulsory Inventory—Child Version; CDI, Children's Depression Inventory; SCARED, Screen for Childhood Anxiety Related Emotional Disorders; SD, standard deviation; SPSS, statistical package for the social sciences; SSRI, selective serotonin reuptake inhibitors; TPM, tissue probability maps; VBM, voxel based morphometry; WAIS, Wechsler Adult Intelligence Scale; WFU, Wake Forest University; WISC, Wechsler Intelligence Scale; WM, white matter.

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to reducing phenotypic heterogeneity involves the identification of homogeneous subtypes of OCD based on clinical characteristics such as age at onset. Notably, pediatric OCD differs from adulthood OCD in that it is more common in boys than girls, and it also shows greater heritability and a pattern of comorbidity that involves more comorbid tic disorders and attention-deficit/hyperactivity disorder.

Although the pathophysiology of OCD is not yet understood, the last 20 years have seen accumulating evidence for abnormalities of fronto-striatal–thalamic circuitry, and neuroanatomical models of obsessive–compulsive symptoms have been proposed (Evans et al., 2004; Jenike et al., 1996; Menzies et al., 2008; Saxena et al., 1998; Stein, 2000). Meta-analysis of whole-brain structural MRI studies using VBM techniques has revealed that in comparison with control subjects, OCD patients present: decreased bilateral regional gray matter (GM) volume in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC); increased bilateral regional GM volumes in the lenticular nucleus (mainly the ventral anterior putamen) extending to the caudate nucleus, as well as in the anterior prefrontal cortex (Radua and Mataix-Cols, 2009; Rotge et al., 2010); and increased volume of the internal capsule and reduced frontal and parietal WM (Piras et al., 2013). More specifically, structural MRI studies comparing pediatric OCD patients with healthy controls have sometimes shown inconsistent abnormalities. Regarding GM, increased volume was found in the OFC, ACC, putamen (Szeszko et al., 2008), and thalamus (Gilbert et al., 2000), while decreased volume was observed in the superior and medial frontal gyrus (Gilbert et al., 2008a), globus pallidum (Szeszko et al., 2004a), and parietal cortex (Carmona et al., 2007; Lazaro et al., 2009). As for WM, an increased volume in orbitofrontal areas (MacMaster et al., 2010) and a decreased volume in the frontal (Carmona et al., 2007) and parietal lobes (Lazaro et al., 2009) have been described. One longitudinal study reported that the lower GM and WM volumes observed in the parietal regions of OCD subjects compared with controls were normalized after six months of pharmacological treatment and clinical improvement, and they became similar to the volumes in the brains of controls (Lazaro et al., 2009). A recent study of 29 medication-free pediatric OCD patients and 29 controls found that orbitofrontal GM and external capsule WM increased after 16 weeks of cognitive behavioral therapy (CBT) (Huyser et al., 2012). Interestingly, the authors showed that the observed changes persisted at two-year follow-up (Huyser et al., 2013).

Several meta-analyses of functional neuroimaging studies have reported findings that are largely consistent with structural MRI results, namely altered regional activation in the aforementioned brain structures during performance of cognitive tasks and after symptom provocation (Brem et al., 2012; Del Casale et al., 2011; Rotge et al., 2008). All these findings have contributed to the widely accepted neuroanatomical model of OCD involving the cortico-striato-thalamo-cortical (CSTC) loops, as well as the involvement of other brain regions such as the ACC and parietal, temporal, and occipital areas (Kim et al., 2001; Koprivová et al., 2009; Valente et al., 2005; Yoo et al., 2008) that are functionally connected to the CSTC loops.

In recent years VBM neuroimaging studies have investigated the association between symptom dimension and brain matter volume in OCD. However, the findings have been inconsistent. Pujol et al. (2004) reported a relative decrease in GM volume in the right amygdala region in adult OCD patients with prominent "aggressive" obsessions and "checking" compulsions as compared with controls, while Gilbert et al. (2008b) described a significant association between the "washing" symptom dimension and reduced volume in the right prefrontal gyrus in adult OCD patients. Other authors have reported a negative correlation between 1) the "contamination/washing" dimension and GM volume in bilateral caudate nucleus and WM volume in right parietal region, 2) between the "harm/checking" dimension and GM and WM in bilateral temporal lobes, and 3) between the "symmetry/ordering" dimension and GM volume in the right motor cortex, left insula, and left parietal cortex (Van den Heuvel et al., 2009). Conversely, a positive correlation has been documented between the "aggression" dimension and GM volume in lateral parietal cortex, and between the "sexual/religious" dimension and GM volumes in the right middle lateral OCF and DLPFC (Alvarenga et al., 2012). These inconsistent findings can be partially attributed to methodological limitations such as prior medication intake and lack of an adequate instrument to assess severity of the obsessive–compulsive symptom dimensions (Alvarenga et al., 2012).

Neuroanatomical models of OCD have focused on the cortico-striato-thalamic circuits. However, other structures such as the anterior cingulate and parietal areas have recently been included in these circuits. Due to the heterogeneity of results published to date the aim of the present study was to compare a large sample of children and adolescents with OCD with a healthy control group (matched for age, gender, and estimated intelligence quotient) so that the brain abnormalities involved could be determined. We hypothesized that, above and beyond alterations in the orbitofrontal cortex, pediatric OCD patients would show structural GM and WM abnormalities in the DLPFC cortex extending into the cingulate area and the parietal cortex. We expected that GM and WM volumes in these structures would correlate with symptom severity. In addition, we aimed to investigate whether these abnormalities differ between patients according to symptom dimensions (contamination/washing, harm/checking, and symmetry/ordering) and whether they are consistent with previous results derived from adult OCD patients.

2. Methods

2.1. Participants

The sample comprised 62 children and adolescents and 46 healthy controls of both genders and ranging in age from 11 to 18 years. All patients had a current diagnosis of OCD according to DSM-IV criteria (American Psychiatric Association, 1994). The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL: Kaufman et al., 1996), validated in Spanish (Ulloa et al., 2006) and adapted for use in Spain by Cesar Soutullo (University of Navarra), was administered with both parents and the child as informants. Exclusion criteria were psychiatric comorbidity with psychotic disorder, autism spectrum disorder, somatic or neurological illness, and intelligence quotient (IQ) <70. The standard score on the Vocabulary subtest of the corresponding Wechsler scale was used to estimate IQ. The Wechsler Intelligence Scale for Children—Revised (WISC-IV) (Wechsler, 2003) was used for subjects under 16.11 years, while the WAIS-III was administered to those over 17 (Wechsler, 2001). All patients received naturalistic pharmacological treatment and/or CBT. This consisted of two or three sessions covering psycho-educational aspects of OCD (nature of OCD, etiology, clinical characteristics, psychopharmacological treatment and principles of behavior therapy) and twelve weekly cognitive–behavioral sessions based on exposure and response prevention. Nevertheless, the intensity and frequency of sessions depend on the severity of the disorder. None of the patients had participated in any of the previous VBM studies conducted by our research group.

The healthy control group was recruited from several schools in the same geographical region. Age, gender, and estimated IQ were matched between OCD cases and healthy controls. Subjects with a personal history of neurological and psychiatric disorders were excluded. The neuroimaging protocol was the same as in OCD patients.

Patients with contraindications for magnetic resonance imaging (e.g., those with orthodontic braces) were also excluded (N = 3). In three cases, the examination was terminated due to claustrophobia before the neuroimaging exam was completed, and two patients refused to scan. A neuroradiologist checked that all MRI scans were free of gross structural abnormalities. One OCD patient was excluded due to a parietal cystic gliotic lesion, while two healthy controls were excluded due, respectively, to a low-grade glioma and an arachnoid cyst. One patient (but no control subject) was omitted because of low-quality imaging data.