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Review article

Meta-analytic investigations of common and distinct grey matter alterations in youths and adults with obsessive-compulsive disorder

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a disabling illness with onset generally in childhood. OCD-youths differ from OCD-adults with regard to gender distribution, comorbidity patterns and treatment options. However, little is known about the neural correlate differences underpin those two populations. The current meta-analysis summarizes voxel based morphometry findings to elucidate whether differences of neural correlates exist between these two populations. Both OCD-youths and OCD-adults demonstrated greater striatal volume and smaller prefrontal grey matter volume (GMV). However, smaller GMV in left visual cortex was observed in OCD-youths only, while smaller GMV in anterior cingulate gyrus and greater GMV in cerebellum were demonstrated only in OCD-adults. Meta-regression showed greater GMV in left putamen was most prominent in samples with higher percentages of medicated OCD-adults. Our findings confirmed the most consistent GMV alterations in OCD were in prefrontal-striatal circuitry. Besides, other regions may involve at different developmental stages including deficits of visual cortex in OCD-youths and abnormalities of limbic-cerebellar circuit in OCD-adults. Medication effect may be more pronounced in the striatum, especially the putamen.

1. Introduction

Obsessive-compulsive disorder (OCD) is one of the most common chronically debilitating psychiatric disorders; it has a lifetime prevalence rate of approximately 2.3% in the general population (Ruscio et al., 2010). It is characterized by the presence of obsessions in the form of intrusive and distressing thoughts, ideas or images and by the urge to perform repetitive or ritualistic behaviours, known as compulsions (Abramowitz et al., 2009).

During the past few years, OCD in children and adolescents (hereafter referred to as OCD-youths) has received increasing attention as 30%-50% of adults with OCD (hereafter referred to as OCD-adults) have an onset in childhood (often before 10 years of age) rather than in adulthood (Pauls et al., 2014). Nevertheless, OCD-youths differ from OCD-adults with regard to gender distribution (more common in boys), patterns of comorbidity (OCD-youths are more likely to present with comorbid tic disorders and attention-deficit/hyperactivity disorder) (Zarei et al., 2011) and treatment options (OCD-youths are less likely to respond to selective serotonin reuptake inhibitors (SSRI) than to cognitive behavioural therapy) (Huyser et al., 2009). However, little is known about the differences between these groups in terms of the neural mechanism based on cerebral cortex changes. The discovery of brain alterations that might distinguish OCD-youths from OCD-adults might provide new options for better preventive strategies and treatment targets.

In recent decades, neuroimaging techniques have played an important role in exploring brain structures and functions in normal and diseased states. High-resolution structural MRI is thought to provide evidence about the neural bases of cerebral abnormalities in mental disorders and offers the advantage of relative stability and easy operability in clinical settings. Voxel-based morphometry (VBM), a fully automated computational-based technique for measuring morphological changes throughout the brain without confinement to specific regions, has enhanced the practical application of structural images by introducing an era of quick evaluation for group comparisons (Ashburner and Friston, 2001; Davies et al., 2009). It has been widely

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used in psychiatric disorders, including OCD. Grey matter volume (GMV) changes have been detected in various brain regions in OCD-adults. These changes include smaller GMV in the prefrontal cortex and the anterior cingulate cortex (ACC) and greater striatal and cerebellar GMV (Kim et al., 2001; Pujol et al., 2004; Valente et al., 2005; van den Heuvel et al., 2009). VBM studies of OCD-youths have also revealed GMV abnormalities in the prefronto-striatal circuit (Gilbert et al., 2008a; Zarei et al., 2011), but GMV alterations outside this prevailing circuit in OCD-youths are reported in the parietal and occipital cortex (Lazaro et al., 2009; Szeszko et al., 2008). Given these differences in clinical profiles and structural neuroanatomy between OCD-youths and OCD-adults, we raised an important question: are there different patterns of neural alterations in OCD-youths and OCD-adults?

To our knowledge, no original VBM study has been published to directly compare the structural abnormalities of OCD-youths and OCD-adults. A prior multicentre VBM mega-analysis supported the prevailing prefronto-striatal models of OCD and revealed a clear group x age effect in the striatum (de Wit et al., 2014). Another recent worldwide multicentre FreeSurfer study combining both meta-analysis and mega-analysis demonstrated different patterns of subcortical abnormalities in paediatric and adult OCD patients and highlighted the potential importance of neurodevelopmental alterations in OCD (Boedhoe et al., 2016). One meta-analysis integrating the region of interest (ROI) literature identified structural alterations in the thalamocortical pathways in OCD using RevMan software (Rotge et al., 2009). Previous VBM meta-analyses (Peng et al., 2012; Radua and Mataix-Cols, 2009; Radua et al., 2010; Rotge et al., 2010) that included 10–15 partially overlapping paediatric and adult studies consistently showed that a specific network of cortico-striato-thalamic regions was associated with OCD. Only Rotge et al. performed a subgroup meta-analysis comparing grey matter density differences between OCD-youths and OCD-adults using activation likelihood estimation (ALE) method (Rotge et al., 2010). However, Rotge et al. failed to find any significant differences between OCD-youths and OCD-adults, possibly because of the small number of published primary studies at that time. They identified ten VBM studies, only four of which were based on OCD-youths. Furthermore, other confounding factors, such as drug treatments and clinical profiles, were not considered in their meta-analysis. Because additional primary OCD VBM studies have been published in recent years, it is worthwhile to conduct an updated meta-analysis to help explore the neural differences between OCD-youths and OCD-adults. For example, one recent meta-analysis of fMRI studies described the functional neural correlates of bipolar disorders (BD) from a developmental aspect by comparing the voxel-wise convergence of fMRI findings in BD-youths vs. BD-adults (Wegbreit et al., 2014). Neuroimaging meta-analysis not only can pool statistically significant results to further improve predictive power but can also detect the emergent properties of neural systems through large-scale data mining and computational modelling, which is not feasible in a single study (Fox et al., 2014). In addition, recent advancements in meta-analysis methodology have also made it possible to quantitatively correlate imaging results with clinical profiles (Radua and Mataix-Cols, 2009; Radua et al., 2012).

Thus, the aims of this study were threefold: first, we conducted separate VBM meta-analyses for OCD-youths and OCD-adults using Anisotropic Effect Size Signed Differential Mapping (AES-SDM) software (Radua et al., 2014). Second, we conducted subgroup meta-analyses to assess the robustness and heterogeneity of the main findings. Specifically, we performed subgroup meta-analyses regarding medication status (drug-free OCD and medicated OCD). Stratified meta-analyses of pure OCD and the subgroup meta-analyses regarding age of onset in OCD-adults were subsequently conducted. We also performed subgroup meta-analyses regarding magnetic field strength (1.5 T and 3.0 T). Finally, we used meta-regression methods to examine the potential moderating effects of medication and other relevant clinical variables, such as onset age, illness duration, symptom severity and comorbidity on the reported GMV abnormalities. We hypothesized that both OCD-youths and OCD-adults would show common structural alterations in prefronto-striatal circuit and relevant structures. Additionally, we hypothesized that OCD-adults and OCD-youths would show distinct GMV abnormalities outside the prefronto-striatal network.

2. Materials and methods

2.1. Study selection

Systematic and comprehensive searches of the PubMed, ISI Web of Science, PsycINFO, Medline, Cochrane Library, and EMBASE databases were performed to identify studies published between January 1994 and October 2014 and “in press” articles. The keywords for the search were “obsessive-compulsive disorder” plus any of the following terms: “voxel*” or ‘voxel based morphometry’ or “VBM” or “whole-brain” or “grey matter”. The reference lists of identified articles and review articles were manually scrutinized to obtain additional papers.

A study was considered for inclusion if it (i) was published as a peer-reviewed original paper; (ii) included patients with a primary diagnosis of OCD based on DSM criteria; (iii) reported a VBM comparison between OCD patients and healthy control subjects (HCS); (iv) reported the whole-brain results of GMV alterations in a stereotactic space in three-dimensional standard coordinates; (v) used significance thresholds for data that were either corrected for multiple comparisons or uncorrected with spatial extent thresholds. The corresponding authors were contacted by e-mail to provide additional details not included in the original manuscripts.

Studies were excluded if (i) it was impossible to obtain the three-dimensional coordinates in stereotactic space; (ii) the data overlapped with those of another publication (in cases of overlap, the study with larger sample size was selected for meta-analysis); (iii) there was no HCS group; (iv) only region of interest (ROI) findings were reported instead of whole-brain results; (iv) the reporting findings were based on small volume correction. In our analyses, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009).

Three authors (X.Y.H., M.Y.D. and L.Z.C.) independently searched the literatures, examined the retrieved articles, extracted and cross-checked data. The results were compared, and any inconsistent results were discussed and resolved by consensus. The coordinates in each study were extracted for meta-analysis according to the AES-SDM method (Radua et al., 2014).

2.2. Voxel-wise meta-analysis

Regional differences in GMV between patients and HCS were analysed using AES-SDM for the OCD-youths and OCD-adults separately. The SDM approach incorporates useful features from previous methods, such as ALE (Turkeltaub et al., 2002) and multilevel kernel density analysis (Wager et al., 2007). The approach also embodies some improvements and new features. For example, in the SDM approach, unlike other coordinate-based meta-analytic methods (Turkeltaub et al., 2002), both positive and negative coordinates are reconstructed on the same map to prevent a particular voxel from erroneously appearing to be positive and negative at the same time (Radua and Mataix-Cols, 2009). Second, rather than assigning voxels a conventional value (e.g., “0” or “1”), the SDM approach assigns each voxel a measure of the effect size, namely, the standardized mean (for one-sample designs) and the standardized mean difference (for two-sample designs), referred to as Hedges d at the sample level. The use of effect sizes allows reported peak coordinates to be combined with statistical parametric maps, thereby allowing more exhaustive and accurate meta-analyses. Third, complementary analyses, such as jack-knife, subgroup and meta-regression analyses, were used to assess the robustness and heterogeneity of the results (Radua et al., 2012). Finally, the SDM approach considered null findings, which would cause a number of voxels to