

Anatomical Alterations and Symptom-Related Functional Activity in Obsessive-Compulsive Disorder Are Correlated in the Lateral Orbitofrontal Cortex

To the Editor:

Several neuroimaging studies have reported the presence of anatomical and functional brain alterations in obsessive-compulsive disorder (OCD). The identification of brain alterations is critical to the understanding of the pathophysiology and, thus, the cause of this disease. Developments in neuroimaging techniques over the last few years have greatly improved our capacity to identify anatomical and functional brain alterations in OCD (1,2). However, it remains unknown whether anatomical alterations directly support functional changes, specifically those changes involved in symptom mediation. This issue is critical for identifying the brain regions that are closely related to OCD etiopathogenesis, in contrast to those regions whose abnormal activity may represent a secondary phenomenon that adapts to some primary network abnormalities.

In the present report, we tested the hypothesis that anatomical alterations and symptom-related functional activity are related in OCD. For this, we used data from two voxel-based meta-analyses of neuroimaging studies in OCD. The first study is a meta-analysis of voxel-based morphometry (VBM) studies that assessed changes in gray matter density (GMD) between OCD patients and control subjects (1), and the second study is an analysis of paradigm-driven functional neuroimaging studies that explored brain correlates of induced OCD symptoms (2). For our research, we compiled data from both meta-analyses to identify brain regions that were anatomically altered and also functionally involved in the mediation of OCD symptoms.

The literature search included articles were fully described in the original publications for both meta-analyses (1,2). We repeated the database search to ensure that no original article fulfilling the selection criteria had been published since the publication of both meta-analyses. The meta-analysis of functional studies included 8 articles with 77 OCD patients (102 foci), and the meta-analysis of VBM studies included 10 articles with 343 OCD patients (66 foci). Because the meta-analyses were performed using different statistical thresholds, we performed new activation likelihood estimation (ALE) analyses with the data using exactly the same thresholds. Activation likelihood estimation analyses were completed using Scribe, Sleuth, and Ginger ALE software (BrainMap, University of Texas, San Antonio) (3–5). A full-width half-maximum of 12 mm was used. A permutation test of randomly distributed foci allowed us to determine the statistical significance of the resulting ALE values, corrected for multiple comparisons. Five thousand permutations were performed using the same full-width half-maximum value and the same number of foci that had been used to compute the ALE values. A conservative threshold for statistical significance was set at $p < .05$ (false discovery rate corrected), with a minimum cluster size of 400 mm³. Finally, to test our main hypothesis,

we created an overlap ALE map with both functional and anatomical maps. We used MRICron software (<http://www.sph.sc.edu/comd/rorden/mricron/>) to visualize ALE maps overlaid onto a high-resolution brain template generated by the International Consortium for Brain Mapping (6).

We thus obtained two maps—an anatomical map reporting changes in GMD between OCD patients and control subjects and a functional map reporting activity during symptom provocation in OCD patients (1,2). Finally, an overlap map was created to test the main hypothesis (Figure 1). The only brain region that had anatomical alterations and was involved in the mediation of OCD symptoms was the lateral part of the left orbitofrontal cortex (OFC) (left inferior frontal gyrus; Brodmann area 47; Montreal Neurological Institute atlas: $x = -22$; $y = 22$; $z = -17$).

This is the first demonstration of a close relationship between structural and functional brain alterations in OCD. The left lateral OFC is greater in OCD patients relative to healthy subjects, and it mediates OCD symptoms. This finding suggests that this brain region is closely related to OCD etiopathogenesis. Accordingly, Chamberlain *et al.* (7) have recently shown that, in comparison with healthy control subjects, lateral OFC activation is reduced during a task that assesses behavioral flexibility in OCD patients and in unaffected relatives. These findings suggest that the lateral OFC could play a central role in cognitive flexibility deficits and, thus, in the genesis of pathological habits. The present findings, representing data from 420 OCD patients, together with those of Chamberlain *et al.* (7) strongly suggest that the lateral OFC has a primary role in OCD genesis. Future studies should replicate our findings in a same sample of patients and further investigate the molecular and cellular mechanisms responsible for the alterations of the lateral OFC in OCD.

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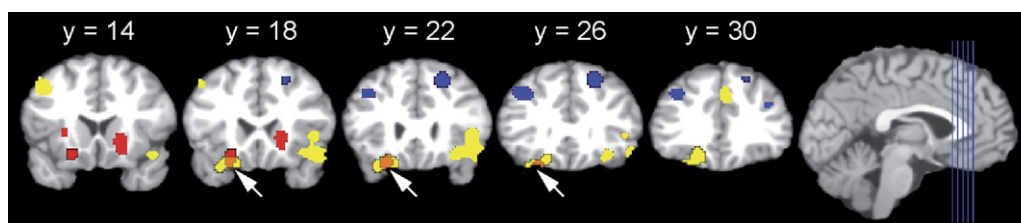


Figure 1. Overlap of the anatomical and functional maps. Coronal views are centered in the brain region where anatomical alterations and symptom-related functional activity overlap (left inferior frontal gyrus; Brodmann area 47; MNI atlas: $x = -22$; $y = 22$; $z = -17$). Red indicates brain regions with greater GMD in OCD than control subjects. Blue indicates brain regions with smaller GMD in OCD than control subjects. Yellow indicates brain regions with functional activity during symptom provocation in OCD. Orange indicates overlap between the red and yellow regions. GMD, gray matter density; MNI, Montreal Neurological Institute; OCD, obsessive-compulsive disorder.

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