Orbitofrontal Dysfunction in Patients with Obsessive-Compulsive Disorder and Their Unaffected Relatives

Samuel R. Chamberlain, *et al.*

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Supporting Online Material

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Orbitofrontal Dysfunction in Patients with Obsessive-Compulsive Disorder and Their Unaffected Relatives

Samuel R. Chamberlain,[1,2,3]* Lara Menzies,[1,2,3] Adam Hampshire,[4] John Suckling,[1,2] Naomi A. Fineberg,[1,3] Natalia del Campo,[1,2] Mike Aitken,[2,5] Kevin Craig,[1,2,3] Adrian M. Owen,[4] Edward T. Bullmore,[1,2,6] Trevor W. Robbins,[2,5] Barbara J. Sahakian[1,2]

Obsessive-compulsive disorder (OCD) is characterized by repetitive thoughts and behaviors associated with underlying dysregulation of frontostriatal circuitry. Central to neurobiological models of OCD is the orbitofrontal cortex, a neural region that facilitates behavioral flexibility after negative feedback (reversal learning). We identified abnormally reduced activation of several cortical regions, including the lateral orbitofrontal cortex, during reversal learning in OCD patients and their clinically unaffected close relatives, supporting the existence of an underlying previously undiscovered endophenotype for this disorder.

Obsessive-compulsive disorder (OCD) is a debilitating neuropsychiatric condition characterized by recurrent intrusive thoughts (obsessions) and/or repetitive rituals (compulsions), often performed according to rigid rules (*1*, *2*).

OCD is frequently familial, and first-degree relatives of patients exhibit up to an eightfold increased risk of also developing clinically meaningful OC symptoms (*3*). Nonetheless, attempts to delineate contributory genes have met with limited success. It is probable that top-level symptoms are too distal from the underlying pathogenesis of the disorder to provide sufficient power to detect underlying genetic diatheses. Consequently, there is an ongoing search for objective brain-based measurable traits, or endophenotypes, that decompose top-level phenotypes into meaningful markers more proximally related to the etiology (*4*, *5*). Such markers should be present in unaffected first-degree relatives of patients, even in the absence of clinically meaningful symptoms (*4*).

OCD is associated with abnormal function in corticostriatal circuitry mediating inhibitory control and flexible responding (*6*, *7*). The orbitofrontal cortex (OFC) is central to our understanding of OCD (*8*) because structural and functional alterations of this region are the most frequently reported neuroimaging findings in patient studies (*6*, *7*, *9*). The OFC subserves reversal learning, a cognitive function important in day-to-day life whereby behavior is flexibly altered after negative feedback (*10*). Reversal learning is dependent on the serotoninergic system (*11*, *12*) and is impaired by lesions to the OFC (but not the dorsolateral prefrontal cortex) across species (*13*, *14*). Reduced activation of the OFC has previously been reported in patients with OCD during reversal learning (*15*), but many patients in that study were also depressed. This was a potential confounder because depression itself is associated with OFC dysfunction and increased feedback sensitivity (*16*). In addition, relatives were not assessed, and thus the state-versus-trait nature of the OFC dysfunction could not be discerned.

In the search for neurocognitive endophenotypes in OCD, we measured brain activation in comorbidity-free patients and their unaffected first-degree relatives. We used a functional magnetic resonance imaging task capable of fractionating different components of behavioral flexibility, including reversal of responses, a plausible psychological deficit in OCD (*17*). The sample comprised 14 patients, 12 unaffected never-treated first-degree relatives of these patients, and 15 matched controls without a family history of the disorder. The three groups were matched in terms of age, handedness, and intelligence quotient (table S1).

On each trial, volunteers observed two pictures presented on screen, each of which comprised a face and house superimposed. The aim of the task was for volunteers to work out through trial and error which object (which face or house) was correct (fig. S1). If volunteers believed that the left-hand stimulus contained the correct object, they pressed a left button, and vice versa. After every second response, feedback was given on screen ("CORRECT" or "INCORRECT") to indicate whether the chosen object was indeed correct. Once a criterion of six consecutive correct responses was reached, either the correct object was changed or a new stimulus set was presented; the volunteer was then required to learn the new correct object (*17*, *18*).

We first examined the volunteers' brain activation when they were working out solutions, minus their brain activation when the solutions were known. This provided an overview of the neural circuitry generally involved in undertaking the task. We then examined their brain activations corresponding to reversal learning and set-shifting, cognitive functions dependent on the OFC and ventrolateral prefrontal cortices, respectively (*10*, *17*). We hypothesized that patients with OCD and their unaffected relatives would show reduced activation of the OFC in the reversal contrast (*6*) as compared with controls. The groups did not differ significantly in number of errors on the task, because all participants were pretrained to minimize the likelihood of behavioral confounders. However, relatives exhibited slower response times when working out solutions than the patients and controls (fig. S2).

Regions activated when working out solutions and during reversal learning, across all subjects, are indicated in fig. S4, A and B. When working out solutions, OCD patients and their unaffected relatives showed under-activation in regions including, bilaterally, the lateral OFC [Brodmann areas (BA) 10, 11, and 47], lateral prefrontal cortex (PFC) (BA 45 and 46), and left

[1]Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Box 189, Cambridge CB2 0QQ, UK. [2]Behavioral and Clinical Neuroscience Institute (BCNI), University of Cambridge, Cambridge CB2 3EB, UK. [3]National OCD Treatment Service, Queen Elizabeth II Hospital, Welwyn Garden City AL7 4HQ, UK. [4]Medical Research Council (MRC) Cognition and Brain Sciences Unit, Cambridge CB2 7EF, UK. [5]Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, UK. [6]Clinical Unit Cambridge, GlaxoSmithKline, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.

*To whom correspondence should be addressed. E-mail: srchamb@gmail.com

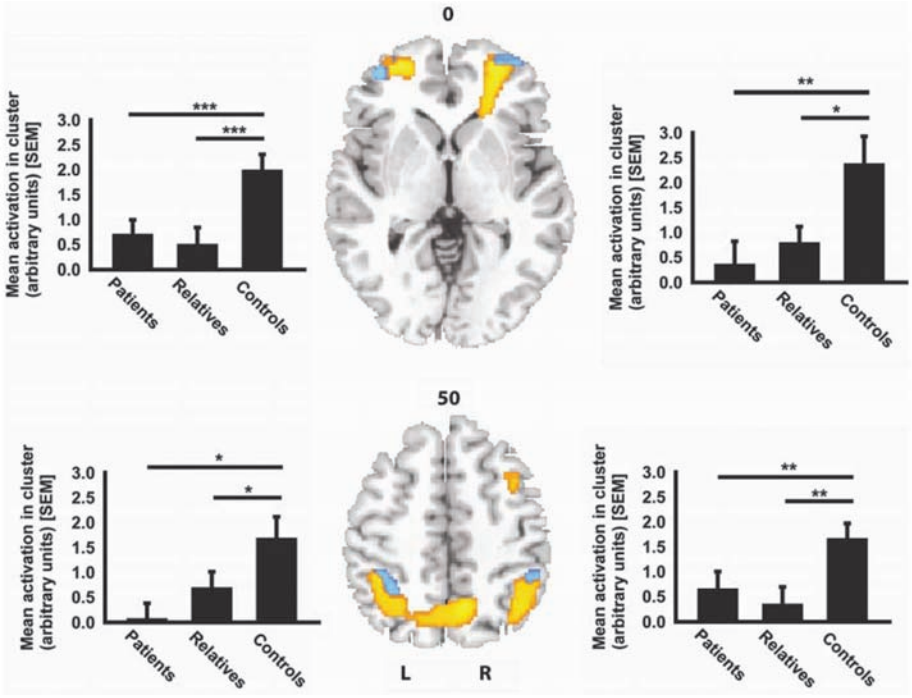

Fig. 1. Patients with OCD and their unaffected relatives showed underactivation during reversal learning bilaterally in the lateral OFC, lateral PFC, and parietal cortices. The images are of representative brain slices showing regions activated during reversal learning across all subjects (yellow areas; false discovery rate–corrected, $P < 0.05$) and regions in which there was a significant effect of group (blue areas; corrected to less than one false-positive cluster across the whole map) (*19*). Peripheral graphs indicate mean group activations for each of the four identified clusters where there was a significant effect of group. (**Top left**) Cluster 1, left lateral OFC (BA 10, 11, and 47) and left lateral PFC (BA 46). (**Top right**) Cluster 2, right lateral OFC (BA 10, 11, and 47) and right lateral PFC (BA 46). (**Bottom left**) Cluster 3, left parietal lobe (BA 40). (**Bottom right**) Cluster 4, right parietal lobe (BA 40). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ are the significant differences in brain activation between groups, using non-parametric permutation.

parietal cortex (BA 40) as compared with controls (*18*). During reversal learning, OCD patients and relatives showed significant underactivation bilaterally in the lateral OFC (BA 10, 11, and 47), lateral PFC (BA 46), and parietal cortex (BA 40) as compared with controls (Fig. 1). Brain activation during extradimensional shifting was not significant at the whole-study level and thus was not entered into between-group analysis (*18*).

This study found reduced lateral OFC, lateral PFC, and parietal responsiveness during reversal learning not only in patients with OCD but also in their unaffected never-treated relatives. These findings emphasize the centrality of these regions not only in day-to-day flexibility but also in the genesis of pathologic habits. Reversal-learning–related hypofunction appears to be a vulnerability marker (or candidate endophenotype) for OCD that exists in people at increased genetic risk, even in the absence of chronic treatment or symptom confounders. Such brain-based markers may thus be of considerable utility in the search for underlying genetic diatheses.

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