



Original article

Neural correlates of affective and non-affective cognition in obsessive compulsive disorder: A meta-analysis of functional imaging studies



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ABSTRACT

Obsessive compulsive disorder (OCD) is characterized by intrusive thoughts and repetitive ritualistic behaviors and has been associated with diverse functional brain abnormalities. We sought to synthesize current evidence from functional magnetic resonance imaging (fMRI) studies and examine their alignment to pathogenetic models of OCD. Following systematic review, we identified 54 task-fMRI studies published in the last decade comparing adults with OCD ($n = 1186$) to healthy adults ($n = 1159$) using tasks of affective and non-affective cognition. We used voxel-based quantitative meta-analytic methods to combine primary data on anatomical coordinates of case-control differences, separately for affective and non-affective tasks. We found that functional abnormalities in OCD cluster within cortico-striatal thalamic circuits. Within these circuits, the abnormalities identified showed significant dependence on the affective or non-affective nature of the tasks employed as circuit probes. In studies using affective tasks, patients overactivated regions involved in salience, arousal and habitual responding (anterior cingulate cortex, insula, caudate head and putamen) and underactivated regions implicated in cognitive and behavioral control (medial prefrontal cortex, posterior caudate). In studies using non-affective cognitive tasks, patients overactivated regions involved in self-referential processing (precuneus, posterior cingulate cortex) and underactivated subcortical regions that support goal-directed cognition and motor control (pallidum, ventral anterior thalamus, posterior caudate). The overall pattern suggests that OCD-related brain dysfunction involves increased affective and self-referential processing, enhanced habitual responding and blunted cognitive control.

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1. Introduction

Obsessive-compulsive disorder (OCD) affects approximately 1–2% of the general population worldwide and is characterized by intrusive thoughts (obsessions) and ritualistic repetitive behaviors (compulsions) [1,2]. Patients also typically report affective symptoms relating to increased distress and physiological arousal and excessive fear of specific stimuli and situations [3].

Neuroimaging has significantly improved our understanding of the pathophysiology of OCD as structural and functional imaging studies have provided evidence of case-control differences in brain morphometry and task-related activation. The largest brain structural studies have been conducted by the OCD working group of the enhancing neuroimaging genetics through meta-analysis

(ENIGMA) consortium [4] and by the international OCD brain imaging consortium (OBIC) [5,6] using meta- and mega-analytic approaches. The ENIGMA-OCD consortium compared subcortical and ventricular volumes from 1830 patients and 1759 healthy participants and the OBIC consortium compared gray matter density and cortical thickness from 412 adult patients and 368 healthy participants. These studies found that OCD was associated with larger pallidal volumes [4] while the volumes of hippocampus [4,6], and the anterior, dorsomedial and ventrolateral prefrontal cortex (PFC) were decreased [5]. OCD was further associated with reduced cortical thickness of the dorsal and ventral PFC, the inferior parietal and posterior cingulate cortex (PCC) and the precuneus [6]. In parallel, meta-analyses of brain structural studies have also implicated the thalamus and the insula [7–11].

Early functional studies in OCD used positron emission tomography (PET) or single-photon emission computed tomography (SPECT) and reported overactivation in patients within the

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ventromedial PFC and the caudate [80]. Recent literature is dominated by functional magnetic resonance imaging (fMRI) studies that have been subject to meta-analyses; these commonly report OCD-related underactivation in the caudate, the medial PFC and the anterior cingulate cortex (ACC) coupled with overactivation in the insula and putamen [10,12–15].

Several pathogenetic mechanisms for OCD have been proposed on the basis of the imaging findings. The cortico-striatal-thalamic (CST) model postulates an overactive ventral/affective CST loop and a hyporesponsive dorsal/cognitive CST loop [16–18]. The ventral/affective loop encompasses the ventromedial PFC, the ACC, the ventral striatum and the mediodorsal thalamus and the dorsal/cognitive loop involves the dorsolateral PFC and the parietal cortices, the head of the caudate, the ventral anterior thalamus and the globus pallidus [19]. More recent models focus either on the compulsivity of OCD rituals and thoughts or the fear and anxiety related nature of obsessions. The former model considers OCD in terms of deficient cognitive control, indexed by hypofunction of dorso-parietal cortical regions, resulting in uninhibited automatic or habitual actions [20]. The latter model considers deficient fear extinction as the core pathogenic mechanism of OCD and emphasizes the involvement of the medial and ventromedial PFC, the ACC and the amygdala, which are part of the fear conditioning/extinction network [21].

The aim of the current study was to investigate the alignment between currently available fMRI evidence and the prevailing OCD models. We conducted a systematic review of the literature to identify relevant studies and we used Activation Likelihood Estimation (ALE), a quantitative co-ordinate based meta-analytic approach, to integrate the findings of the primary studies [22]. A variety of activation paradigms were used in the primary studies. Based on the key processes involved we classified each task as assessing either affective or non-affective cognition. We predicted that brain functional abnormalities in OCD will show task-dependence that may reconcile the different OCD models. Specifically, we hypothesized that affective processing tasks would primarily reveal abnormalities in affect-processing medial prefrontal and striatal regions while non-affective processing tasks would primarily uncover abnormalities in dorsal prefrontal and lenticular regions involved in cognitive control and habit formation.

2. Methods

2.1. Primary literature search and study selection

We conducted a systematic review of the major electronic databases (and reference lists of primary studies) in accordance with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria [23] to identify studies investigating patients with OCD using task-related fMRI published in peer-reviewed, English-language journals from January 1st 2005 – December 31st 2016. The search keywords were, “obsessive compulsive disorder”, “functional” and “neuroimaging”. Studies were subsequently selected for inclusion in the quantitative meta-analysis if they:

- reported comparisons between adult patients with OCD and healthy volunteers;
- employed functional magnetic resonance imaging (fMRI);
- assessed task-related brain function;
- used image subtraction methodology to identify foci of task-related neural changes contrasting an active to control condition;

- reported their results in standard stereotactic coordinates in either Talairach or Montreal Neurological Institute (MNI) space.

Studies were excluded if they:

- examined pediatric, elderly or special populations (e.g., patients with brain lesions);
- included patients with comorbid psychosis.

The level of significance employed across studies varied but we accepted the results reported as significant based on the criteria of the individual studies. Two of the authors checked independently checked all identified studies for eligibility.

2.2. Database construction

Data on sample size, age and sex were recorded separately for patients and healthy participants. For patients, we extracted medication status (%medicated), class of current medication (e.g. antidepressants, anxiolytics, antipsychotics or other), mean and standard deviation in symptoms severity assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS) [24] and the method used to ascertain diagnosis (i.e., structured interview, unstructured clinical assessment, health records). For each study, we recorded the field strength of the MRI scanner, type of task, peak coordinates of the case control-differences and the direction of signal change compared to healthy participants. When required, MNI coordinates were transformed into the Talairach standard space using *icbm2tal* [25]. Two of the authors checked and reconciled the data extracted.

2.3. Classification of fMRI paradigms

Paradigms were further subdivided as affective (i.e., involving affective or reward processing or symptom provocation) or non-affective (i.e., involving affectively neutral functions). This grouping reflects the most current formulations of the relationship between experimental tasks and corresponding brain networks. Specifically, as brain imaging evidence has accrued over the last two decades, it has become apparent that the human brain is organized into distributed and domain-general functional networks. Affective and social cognition and non-affective cognition are constructed from interactions within and between respective superordinate networks for affective/social and non-affective processing [26–28]. In addition to this broad classification, we also categorized tasks in domains and constructs as defined by the Research domain criteria (RDoC) initiative [29–31]. The RDoC initiative posits that psychiatric diagnoses result from disruption in brain circuits associated with the domains of reward (positive valence systems), threat sensitivity (negative valence systems), cognitive processes, interpersonal interactions (social processes) and biological activation (arousal and regulation) [30] that can be probed by behavioral tasks.

2.4. Quantitative meta-analysis method

Data from affective and non-affective tasks were analysed separately following the same procedure. We used the activation likelihood estimation (ALE) algorithm implemented in *GingerALE* version 2.3.6 (www.brainmap.org/ale) to identify consistent clusters of case-control differences across studies employing affective and non-affective tasks. The ALE algorithm tests whether peak coordinates from the primary studies converge in brain regions more than expected by chance. For each study, each coordinate was modelled as the centre of a 3D Gaussian distribution which full width at half maximum is determined by

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