Inhibitory control in obsessive compulsive disorder: A systematic review and activation likelihood estimation *meta*-analysis of functional magnetic resonance imaging studies

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ARTICLE INFO

ABSTRACT

Background: Patients with obsessive compulsive disorder (OCD) often show deficits in inhibitory control, which may underlie poor control over obsessions and compulsions. Several functional magnetic resonance imaging (fMRI) experiments utilizing a variety of tasks have investigated the neural correlates of inhibitory control in OCD. Evidence from existing *meta*-analyses suggests aberrant activation of regions in fronto-striatal circuits during inhibitory control. However, new fMRI articles have since been published, and a more rigorous methodology for neuroimaging *meta*-analyses is now available.
Objectives: First, to reevaluate the evidence for abnormal brain activation during performance of inhibitory control tasks in OCD while adhering to current best practices for *meta*-analyses, and second, to extend previous findings by separately assessing different subprocesses of inhibitory control.
Method: We systematically searched Web of Knowledge, ScienceDirect, Scopus, PubMed and the functional BrainMap database for fMRI articles that compared activation during performance of inhibitory control tasks in patients with OCD and healthy control (HC) subjects. Thirty-five experiments from 21 articles met our criteria for inclusion. We first performed activation-likelihood-estimation *meta*-analyses to elucidate brain areas in which case-control activation differences converged across articles and tasks. We then aimed to extend previous work by separately evaluating experiments requiring inhibition of a prepotent response without execution of an alternative response (i.e., response inhibition) and experiments requiring inhibition of a prepotent response and execution of an alternative response (i.e., cognitive inhibition).
Results: The 35 experiments included a total of 394 patients and 410 controls. We did not find evidence of abnormal brain activation in OCD during inhibitory control when pooling data from all experiments. Analysis restricted to cognitive inhibition experiments showed abnormal activation of the dorsal anterior cingulate cortex (dACC; $P = .04$, cluster-level familywise error-corrected, cluster volume of 824 mm^3). We did not have sufficient data to evaluate response inhibition experiments separately.
Conclusion: Findings of abnormal brain activation in OCD from different inhibitory control tasks do not appear to converge on the same brain regions, but the dACC may be implicated in abnormal cognitive inhibition. Our findings highlight a need for experiments that specifically target subprocesses of inhibitory control to achieve a more differentiated understanding of the neural correlates for impaired inhibitory control in OCD.

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1. Introduction

Obsessive compulsive disorder (OCD) is a severe and disabling psychiatric disorder with a lifetime prevalence of 2 % to 3 % (Ruscio et al., 2010). Clinically, OCD is characterized by two core symptoms: obsessions, which are recurrent, persistent and intrusive thoughts or urges (e. g., about contamination or harm), and compulsions, which are egodystonic, excessive and repetitive overt or mental acts (e.g., extreme hand-washing or checking rituals; American Psychiatric Association, 2013; Robbins et al., 2019) .

Poor control over obsessions and compulsions in patients with OCD has been attributed to impairments in inhibitory control (Fineberg et al., 2014; Fineberg et al., 2010; Lipszyc and Schachar, 2010; van Velzen et al., 2014). Historically, the concept of inhibition has been used to describe several different phenomena (Bari and Robbins, 2013). In cognitive neuroscience, inhibitory control is commonly assessed with tasks requiring control over a prepotent response tendency (Aron, 2011). These tasks include Stop signal, Go/no-go, Flanker, Simon, Stroop, Multisource interference, and Switching/Shifting. In Stop signal and Go/no-go, a prepotent response tendency is induced by a higher frequency of go trials than trials requiring inhibition (i.e., stop and no-go trials). Stop signal requires the cancellation of an already triggered motor response, whereas Go/no-go requires the witholding of a prepotent go response that has not yet been initiated. Flanker, Simon, Stroop and Multisource interference requires the response to a target in the presence of interfering distractors that are associated with an alternative response. Switching/Shifting requires the response to a target with interference from previous targets that were associated with a different response (i.e., the task to perform switches) or interference from a previously relevant feature dimension (i.e., the relevant feature to attend switches). We use the term inhibitory control to denote the neural processes underlying successful performance of these tasks. To investigate different subprocesses of inhibitory control, we also make a distinction between tasks where the participant occasionally must inhibit a pre-potent response without initiating an alternative motor response (i.e., response inhibition) and tasks where the participant, in addition to inhibiting their pre-potent motor response, must also plan and execute an alternative motor response (i.e., cognitive inhibition).

Previous task-related functional magnetic resonance imaging (fMRI) articles suggest that patients with OCD show abnormal brain activation during inhibitory control. However, findings from individual articles are sometimes inconsistent. For example, some articles report increased activation of the posterior medial prefrontal cortex (de Wit et al., 2012; Yücel et al., 2007), whereas other articles report decreased activation of the same area (Nabeyama et al., 2008; Nakao et al., 2005; Page et al., 2009; Roth et al., 2007). Also, small sample sizes and methodological flexibility in processing pipelines (Carp, 2012)and statistical procedures (Eklund et al., 2016; Yeung, 2018) increase the risk of biased and context specific findings that do not generalize (Botvinik-Nezer et al., 2020; David et al., 2013).

Meta-analyses are critical to show and quantify consistencies of results from different experiments, thereby allowing for generalization beyond the experimental setup of individual articles. Previous *meta*-analyses of OCD fMRI data sets indicate abnormal activation of the rostral and dorsal anterior cingulate cortex, the medial prefrontal cortex, and the striatum during inhibitory control (Carlisi et al., 2017; Norman et al., 2016; Norman et al., 2019) , and during broader executive functions (Brem et al., 2012; Del Casale et al., 2016; Eng et al., 2015; Menzies et al., 2008). Many previous *meta*-analyses tested for convergence of reported coordinates for abnormal task-related activity in OCD using activation likelihood estimation (ALE) (Brem et al., 2012; Del Casale et al., 2016; Eng et al., 2015; Menzies et al., 2008). However, new studies have since been published, and existing ALE *meta*-analyses do not meet the current standards for type I error control (Eklund et al., 2016). Moreover, several recent experiments have not found significant case-control differences during inhibitory control (Hollestein et al.,

2021; Hough et al., 2016; Pagliaccio et al., 2019; Suñol et al., 2020) , and recent prominent publications have sparked serious concerns over the reliability and reproducibility of neuroimaging research (Marek et al., 2022; Poldrack et al., 2017). This raises the question of whether previous *meta*-analytical findings are replicable when integrating data from new studies while adhering to contemporary recommendations for conducting *meta*-analyses. In addition, inhibitory control is not a unitary construct. Rather, inhibitory control is an umbrella term which includes dissociable subprocesses that are underpinned by distinct and only partially overlapping networks (Hung et al., 2018; Swick et al., 2011; Zhang et al., 2017). These networks are differentially engaged by different types of inhibitory control tasks (Hung et al., 2018; Zhang et al., 2017). With the present review and *meta*-analyses, we reassess the evidence for abnormal activation during inhibitory control in OCD following best-practice guidelines and extend previous findings by separately evaluating response inhibition and cognitive inhibition.

2. Methods

2.1. Search strategy

This review adheres to the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) guidelines (Page et al., 2021) and follows the best-practice recommendations for conducting coordinate-based *meta*-analyses (Müller et al., 2018; Tahmasian et al., 2019). We systematically searched for eligible articles on Web of Knowledge, ScienceDirect, Scopus and PubMed (final search on April 28, 2022), using the search terms ("ocd" OR "obsessive compulsive disorder") AND ("fmri" OR "functional magnetic resonance imaging") AND ("inhibitory" OR "inhibition" OR "multisource" OR "conflict" OR "cancel" OR "go/no-go" OR "flanker" OR "stroop" OR "interference" OR "switching" OR "stop" OR "simon"). The search strategy for each database is provided in Supplement 1. We also searched the functional BrainMap database (Fox and Lancaster, 2002) using Sleuth version 3.0.4 (http://brainmap.org) within the imaging modality of "fMRI", the diagnosis of "Obsessive Compulsive Disorder" and the behavioral domain of "action inhibition". We manually searched the reference lists of retrieved articles and relevant review papers for additional articles.

2.2. Article selection

We use the term "article" to refer to a published manuscript and the term "experiment" to denote the set of coordinates, or activation foci, relating to a single case-control contrast. Hence, one article may include more than one experiment. Two authors independently screened title/ abstract and full-texts in separate steps using a procedure optimized for the EndNote software (Bramer et al., 2017). We resolved any discrepancies through discussion. We included peer-reviewed articles published in English that reported group coordinates for case-control differences in activation related to inhibitory control. We only included fMRI articles to maximize data homogeneity (e.g., by avoiding heterogeneity associated with differences in spatial and temporal resolutions between different imaging techniques). We included all relevant contrasts from inhibitory control tasks irrespective of whether the task was defined in the search terms or referred to as an inhibitory control task by the authors. The included experiments compared one of the contrasts stop, no-go, switch, shift, mixed or incongruent to one of the contrasts failed-stop, go, odd-ball, repeat or congruent. We excluded articles that did not report coordinates in either Talairach or Montreal Neurological Institute (MNI) space, only presented results with interactions from non-fMRI methods (e.g. brain-behavior correlations), only presented results from a priori region of interest analysis, or did not find significant case-control differences for an inhibitory control contrast. We did not exclude articles that masked the case-control comparisons based on either task-related activity in the control group or the combined group (n = 3) or data from a *meta*-analysis of the task (n = 1) as these masks are not based

on a priori assumptions about brain regions of interest.

2.3. Data extraction and data synthesis

One author extracted information pertaining to sample characteristics and activation foci from full-text articles and supplementary materials. Another author independently validated all extracted data. Discrepancies were resolved through discussion. We converted all mean standard errors to standard deviations by multiplying with the square root of the sample size. We transformed coordinates that were reported in Talairach space to MNI space using the tal2icbm method (Lancaster et al., 2007). We contacted article authors to retrieve any missing data.

2.4. Activation likelihood estimation meta-analyses

We performed a *meta*-analysis on the extracted activation foci for case-control differences using the revised activation likelihood estimation (ALE) procedure (Eickhoff et al., 2012; Eickhoff et al., 2016; Turkeltaub et al., 2012) , implemented in MATLAB (MathWorks). In brief, ALE tests whether the convergence of reported activation foci across experiments is greater than what is expected by chance. This is done by modelling the location of each activation foci in an experiment by a 3-dimensional Gaussian probability distribution, where the reported coordinate is treated as the center of the distribution, and the size of the distribution depends on the number of participants in the experiment. The union of modeled activations across experiments provides a whole-brain voxel-wise distribution of ALE scores that is tested against a null distribution of spatially independent foci (the null hypothesis that activation foci are randomly distributed throughout the brain). Following current best-practice guidelines, we assessed the significance of convergence of activation foci using a voxel-level threshold of and a cluster-level familywise error-corrected threshold of , and performed ALE *meta*-analyses only when at least 17 experiments reported activation foci for a contrast (Eickhoff et al., 2016; Tahmasian et al., 2019). Additional details on the ALE procedure is found elsewhere (Eickhoff et al., 2012; Eickhoff et al., 2009).

Our primary analysis aimed to identify brain areas with aberrant activity during inhibitory control in patients with OCD by evaluating differences between patients and controls irrespective of the sign of the difference (i.e., OCD ≠ HC). Our use of an unsigned contrast was partly motivated by the fact that existing experiments have reported opposing activation differences between patients with OCD and HC subjects for many of the same regions, and sometimes even for different conditions within the same experiment (e.g., Morein-Zamir et al., 2016). Specifically, it is hypothesized that individual regions in patients with OCD may show hyperactivation for low task demands but hypoactivation for high task demands (van Velzen et al., 2014). This implies that opposing activations of the same region in inhibitory control tasks with varying cognitive load might not reflect irreconcilable findings, but instead a key characteristic of fronto-striatal dysfunction in OCD. Next, we sought to find areas with consistent hyperactivation or hypoactivation by separately *meta*-analyzing reported activation foci of greater brain activity in patients compared with controls (OCD > HC) and activation foci of less activity in patients than controls (OCD < HC). In the interest of isolating different processes involved in inhibitory control, we wanted to repeat our analyses restricted to two different classifications of inhibitory control: cognitive inhibition experiments (i.e., Flanker, Simon, Stroop, Multisource interference, and Switching/Shifting) and response inhibition experiments (i.e., Stop signal and Go/no-go). Finally, because only three articles included pediatric samples, we decided post-hoc to conduct the same *meta*-analyses restricted to experiments on adult samples (as defined by a cut-off of 18 years of age).

3. Results

3.1. Article selection and sample characteristics

A total of 56 full-text articles amongst 351 non-duplicate records retrieved from database search were selected for eligibility assessment (Fig. 1). We did not identify any additional records from other sources. We included 21 articles (Britton et al., 2010; de Wit et al., 2012; Fitzgerald et al., 2010; Fitzgerald et al., 2005; Gu et al., 2008; Han et al., 2011; Huyser et al., 2011; Kang et al., 2013; Marsh et al., 2014; Morein-Zamir et al., 2016; Nabeyama et al., 2008; Nakao et al., 2009; Nakao et al., 2005; Page et al., 2009; Remijnse et al., 2013; Roth et al., 2007; Schlösser et al., 2010; Theiss et al., 2019; Thorsen et al., 2020; van den Heuvel et al., 2005; Yücel et al., 2007) that compared activation related to inhibitory control in 394 OCD patients and 410 HC subjects in 35 experiments in the review (Table 1). Thirty-four articles were excluded based on our pre-defined criteria, of which 9 articles were excluded solely because they did not find significant case-control differences for the appropriate task contrast (Fitzgerald et al., 2018; Fitzgerald et al., 2013; Gooskens et al., 2019; Hollestein et al., 2021; Hough et al., 2016; Pagliaccio et al., 2019; Stern et al., 2011; Suñol et al., 2020; Viard et al., 2005). Furthermore, one article (Tolin et al., 2014) was excluded post-hoc because the OCD and HC groups differed substantially in their respective mean ages (33.5 years and 51.3 years) and gender distributions (25 % females and 83 % females). The included OCD samples comprised predominantly adolescents and young adults (range of mean ages = 13.5–39.1 years) with moderate to severe OCD symptoms assessed with the age-appropriate version of the (Child) Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989; Scahill et al., 1997) (CY-BOCS/Y-BOCS) (range of mean score = 15.4–29.7, weighted mean age = 22.7 years [SD = 5.4 years]). Among the OCD patients, 22.8 % were on medication at the time of scanning (most commonly with selective serotonin reuptake inhibitors [SSRIs]). The remaining were medication-free at the time of scanning and at least two weeks prior. All articles ascertained OCD according to Diagnostic and statistical manual of mental disorders (DSM; American Psychiatric Association, 2013) criteria using a semi-structured clinical interview in combination with either CY-BOCS or Y-BOCS. All articles adequately matched OCD patients and healthy controls on gender (53.6 % females compared with 51.2 % females across articles) and age (weighted mean age of 29.3 years [SD = 7.8 years] compared with 28.5 years [SD = 7.1 years]). Additional details on included samples are presented in Table 2.

3.2. Activation likelihood estimation

The locations of activation foci from experiments reporting case-control differences are shown in Fig. 2. We first assessed experiments that showed case-control differences irrespective of the direction of difference. Thirty-five experiments (372 unique subjects; average of 16.7 subjects per experiment) reported results for the OCD ≠ HC contrast. We did not find evidence to suggest convergence of reported case-control differences irrespective of the direction of difference (P_{cFWE} = .116). We did not have sufficient data to assess experiments that found hyperactivation in patients relative to controls (OCD > HC) as only 15 experiments (233 unique subjects) reported results for this contrast. Twenty experiments (314 unique subjects) reported results for the OCD < HC contrast. We did not find evidence to suggest convergence of reported case-control differences in experiments reporting hypoactivation in OCD relative to HC (P_{cFWE} = .073).

To evaluate different subprocesses of inhibitory control, we first restricted our analyses to cognitive inhibition experiments. Twenty-five experiments (279 unique subjects; average of 15.4 subjects per experiment) reported results for the OCD HC contrast in cognitive inhibition experiments. The *meta*-analysis revealed convergence of case-control activation differences bilaterally in the dorsal anterior cingulate (dACC; BA32) extending into the medial frontal gyrus (BA6 and BA9;
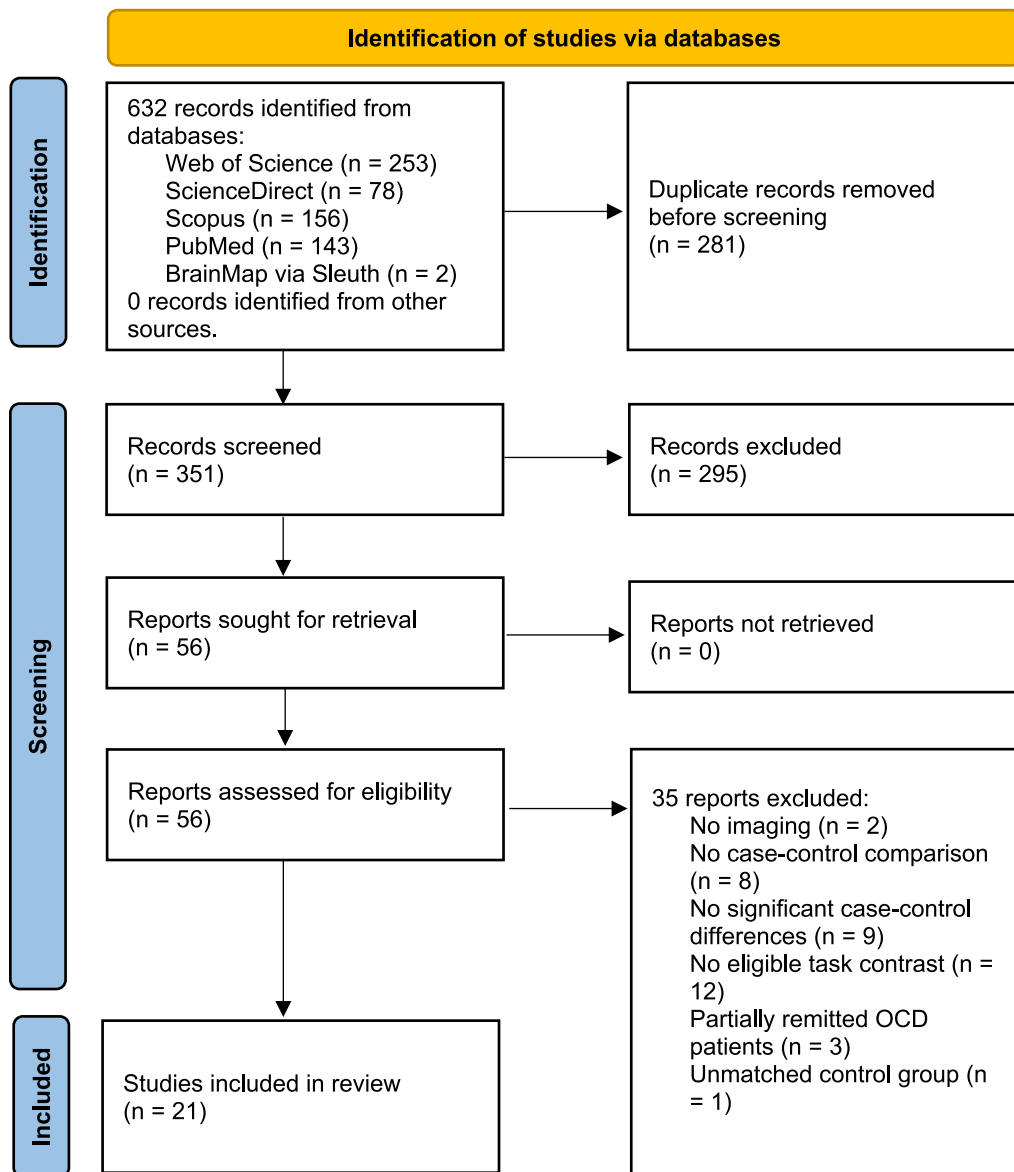
Fig. 1. PRISMA flow chart for the selection of articles included in the review.

cluster volume of 824 mm^3; see Fig. 3). This location was reported in 4 of the 25 experiments (corresponding to 16 % of the experiments) and came from four different articles (Gu et al., 2008; Han et al., 2011; Nakao et al., 2005; Yücel et al., 2007). The relative contribution of activation foci for hyperactivation and activation foci for hypoactivation to the OCD HC contrast were approximately 0.1 % and 99.9 %, respectively, indicating that the difference between OCD and HC was predominantly driven by hypoactivation in the OCD group. We did not have sufficient data to individually assess cognitive inhibition experiments that found hyperactivation in OCD relative to HC (10 experiments and 147 unique subjects) or hypoactivation in OCD relative to HC (15 experiments and 221 unique subjects).

We then wanted to restrict our analyses to response inhibition experiments. However, we did not have sufficient data to perform any *meta*-analysis restricted to response inhibition experiments, as only 10 response inhibition experiments reported case-control differences.

Finally, we repeated our analyses restricted to experiments on adult samples, because only 3 articles included pediatric samples. Excluding experiments on pediatric samples from the analyses did not alter the overall results.

4. Discussion

Applying best-practice methodology for conducting and reporting ALE, our *meta*-analyses assessed the evidence for abnormalities in activation related to inhibitory control in patients with OCD compared to HC subjects. Our primary *meta*-analysis did not reveal evidence to suggest consistent differences in inhibition-related brain activation between patients with OCD and HC subjects. Notably, this null-finding occurred in a well-powered *meta*-analysis: the sample of 35 experiments is considered adequate by present guidelines for neuroimaging *meta*-analyses (Müller et al., 2018; Tahmasian et al., 2019) and gave us more than 80 % power to detect a convergence of activation differences in areas that were identified in just 7 (20 %) of the experiments (Eickhoff et al., 2016) Existing fMRI *meta*-analyses of fewer experiments found aberrant activation of several brain regions, most consistently the prefrontal cortex, the anterior cingulate cortex, insula, and the dorsal striatum (Brem et al., 2012; Carlisi et al., 2017; Del Casale et al., 2016; Eng et al., 2015; Menzies et al., 2008; Norman et al., 2016; Norman et al., 2019). We were therefore surprised to not find evidence of convergence of activation differences between OCD patients and HC subjects when considering the entire body of available data from inhibitory control

Table 1
Articles included in the meta-analysis.

Author, year	OCD, n	HC, n	Task	Task contrasts	Case-control contrasts	Foci, n	Analysis
(Britton et al., 2010)	15	20	Shifting	Mixed > Repeat	HC > OCD	1	Whole brain
(de Wit et al., 2012)	41	37	Stop-signal	Successful stop > go	OCD > HC	1	ROI based on main task effect
					HC > OCD	2	
(Fitzgerald et al., 2010)	18	18	Multisource interference	Correct incongruent > correct congruent	OCD > HC	2	ROI based on main task effect
(Fitzgerald et al., 2005)	8	7	Flanker	High interference > low interference	HC > OCD	1	Whole brain
				High interference > no interference	OCD > HC	1	
					OCD > HC	3	
(Gu et al., 2008)	21	21	Switching	Switch > Repeat	HC > OCD	21	Whole brain
(Han et al., 2011)	10	20	Switching	Switch > Repeat	HC > OCD	22	Whole brain
(Huyser et al., 2011)	25	25	Flanker	Correct incongruent > correct congruent	HC > OCD	2	Whole brain
(Kang et al., 2013)	18	18	Stop-signal	Successful stop > successful go	HC > OCD	13	Whole brain
					OCD > HC	5	
(Marsh et al., 2014)	22	22	Simon spatial incompatibility	Post-congruent incongruent > post-congruent congruent	OCD > HC	1	Whole brain
				Correct incongruent > correct congruent	OCD > HC	1	
(Morein-Zamir et al., 2016)	19	19	Combined shifting and go/no-go	Complex stop > go	OCD > HC	3	Whole brain
				Shift > go	HC > OCD	13	
(Nabeyama et al., 2008)	11	19	Stroop	Color naming incongruent > Color naming congruent	HC > OCD	2	Whole brain
(Nakao et al., 2009)	17	16	Stroop	Color naming incongruent > Color naming congruent	HC > OCD	7	Whole brain
(Nakao et al., 2005)	24	14	Stroop	Color naming incongruent > Color naming congruent	OCD > HC	1	Whole brain
					HC > OCD	7	
(Page et al., 2009)	10	11	Go/no-go	Correct no-go > correct go	HC > OCD	3	Whole brain
					OCD > HC	6	
			Simon spatial incompatibility	Incongruent > congruent	HC > OCD	4	
					OCD > HC	1	
			Switching	Switch > repeat	HC > OCD	2	
(Remijnse et al., 2013)	18	29	Switching	Switch > repeat	HC > OCD	1	ROI based on main task effect
					OCD > HC	3	
(Roth et al., 2007)	12	14	Go/no-go	No-go > go	HC > OCD	7	Whole brain
					OCD > HC	4	
(Schlösser et al., 2010)	21	21	Stroop	Color naming incongruent > color naming congruent	OCD > HC	2	Whole brain
					HC > OCD	1	
(Theiss et al., 2019)	16	15	Conflict	Post-incongruent incongruent > post-congruent incongruent	HC > OCD	1	Whole brain
(van den Heuvel et al., 2005)	18	19	Stroop	Color naming incongruent > color naming congruent	OCD > HC	3	Whole brain
(Yücel et al., 2007)	19	19	Multisource interference	Incongruent > congruent	OCD > HC	1	Whole brain
					HC > OCD	1	
(Thorsen et al., 2020)	31	26	Stop-signal	Successful stop > successful go	HC > OCD	1	ROI based on meta-analysis data

Note: HC = healthy control; OCD = obsessive compulsive disorder; ROI = region-of-interest.

tasks. Differences in the scope, the *meta*-analytical approach and the experiments included in the *meta*-analyses may have contributed to this discrepancy. For example, Carlisi et al. (Carlisi et al., 2017); Norman et al. (Norman et al., 2016) and Norman et al. (Norman et al., 2019) used the anisotropic effect size version of seed-based *d* mapping (AES-SDM) to combine peak coordinates and non-thresholded *t*-maps (https://www.sdmproject.com/; Radua et al., 2014). In contrast to ALE, AES-SDM can include *t*-maps from experiments that did not find significant case-control differences in the *meta*-analysis and is therefore able to identify consistent differences in brain activation that do not reach whole-brain significance in individual experiments. On the other hand, AES-SDM must rely on assumptions to impute the effect size of a peak coordinate if it is not reported in the article and the *t*-map is not available. ALE ignores all the information about the size of the effect and is therefore potentially less prone to be biased by systematic differences in the availability of data. Brem et al. (2012); Del Casale et al. (2016); Eng et al. (2015) and Menzies et al. (2008) used ALE in their reviews. However, Brem et al. (2012); Eng et al. (2015) and Menzies et al. (2008) performed *meta*-analyses on activation differences obtained from less than the recommended minimum of 17 fMRI experiments (Eickhoff et al., 2016). Consequently, their *meta*-analyses were not adequately powered to detect even moderate sized effects and were furthermore at an increased risk of being driven largely by a single dominant

experiment. Additionally, Brem et al. (2012) and Menzies et al. (2008) used the false-discovery rate correction for multiple comparisons (Laird et al., 2005), which has been shown to be inappropriate for neuro-imaging data (Chumbley and Friston, 2009) and to entail both low sensitivity and high susceptibility to spurious, false positive findings (Eickhoff et al., 2016). Del Casale et al. (2016) performed adequately powered ALE *meta*-analyses on activation differences between OCD patients and HC subjects in executive function fMRI experiments and found that only hypoactivation of the right caudate body in OCD patients survived thresholding using the optimal cluster-level FWE correction at $P < .05$. Nevertheless, because this review assessed a broader range of cognitive functions, it is possible that the reported hypoactivation of the right caudate in OCD patients was related to cognitive processes other than inhibitory control.

Differences in the experimental design of included experiments may have contributed to our null finding. Prior work has shown that the precise neural correlates of inhibitory control depend on the extent to which different subprocesses of inhibitory control are engaged by different task demands (Criaud and Boulinguez, 2013; Hung et al., 2018; Sebastian et al., 2013; Zhang et al., 2017). Our *meta*-analyses restricted to cognitive inhibition experiments revealed abnormal activation of the dACC in a cluster at the border between the rostral dACC and the pre-genual region of the ventral ACC in an area of the ACC with strong

Table 2

Samples included in the *meta*-analysis.

Author, year	*n* (% females)	mean age in years (range, SD)	Clinical characteristics of OCD sample	Mean symptom severity (range, SD)
(Britton et al., 2010)	OCD: 15 (60.0) HC: 20 (65.0)	OCD: 13.5 (10–17, 2.4) HC: 13.6 (10–17, 2.4)	DSM-IV OCD assessed with K-SADS-PL and CY-BOCS. Disease duration: mean = 4.1 years, SD = 2.0 years. Overall comorbidity: NA (GAD = 13.3 %, specific phobia = 13.3 %, agoraphobia = 6.7 %, MDD = 13.3 %, depression-NOS = 6.7 %, TS = 6.7 %, ADHD = 13.3 %). Overall medication: 100 % (primary: SSRI = 80.0 %, tricyclic antidepressants = 20.0 %; secondary: mood stabilizers = 20.0 %, stimulants = 26.7 %, desyrel = 6.7 %, clonidine = 6.7 %, memantine = 6.7 %, atomoxetine = 6.7 %, lorazepam = 6.7 %).	15.4 (7–26, 5.7)
(de Wit et al., 2012)	OCD: 41 (48.8) HC: 37 (51.3)	OCD: 38.6 (18–65, 9.8) HC: 39.7 (18–65, 11.6)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 54 % (specific phobia = 24.4 %, mood disorder = 22.0 %, social phobia = 12.2 %, panic disorder = 7.3 %, eating disorder = 4.9 %, agoraphobia = 2.4 %, somatoform disorder = 2.4 %, TS = 2.4 %). Overall medication: 0.0 % on psychoactive medication (medication free for => 4 weeks).	21.9 (NA, 6.1)
(Fitzgerald et al., 2010)	OCD: 18 (66.7) HC: 18 (66.7)	OCD: 13.9 (8–18, 2.6) HC: 14.1 (8–18, 2.6)	DSM-IV OCD assessed with K-SADS-PL and CY-BOCS. Disease duration: mean = 3.0 years, SD = 1.5 years. Overall comorbidity: NA (separation anxiety disorder = 27.8 %, GAD = 5.6 %, anxiety-NOS = 16.7 %, depression-NOS = 11.1 %, tics = 11.1 %). Overall medication: 66.7 % (SSRI = 66.7 %).	16.1 (NA, 7.3)
(Fitzgerald et al., 2005)	OCD: 8 (25.0) HC: 7 (28.6)	OCD: 27.4 (NA, 8.5) HC: 30.0 (NA, 8.6)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 0.0 %. Overall medication: 62.5 % (fluoxetine = 25.0 %, fluoxetine + clonazepam = 12.5 %, fluoxetine + risperidone = 12.5 %, sertraline = 12.5 %)	18.0 (NA, 3.9)
(Gu et al., 2008)	OCD: 21 (14.3) HC: 21 (14.3)	OCD: 23.6 (NA, 4.5) HC: 24.8 (NA, 3.7)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 14.3 % (panic disorder =	20.0 (NA, 5.8)

Table 2 (*continued*)

Author, year	*n* (% females)	mean age in years (range, SD)	Clinical characteristics of OCD sample	Mean symptom severity (range, SD)
			4.8 %, obsessive–compulsive personality disorder = 4.8 %, schizotypical personality disorder = 9.5 %). Overall medication: 52.4 % (SSRI = 14.3 %, SSRI + anti-anxiety = 9.5 %, SSRI + atypical antipsychotics = 4.8 %, SSRI + anti-anxiety + atypical antipsychotics = 23.8 %).	
(Han et al., 2011)	OCD: 10 (10.0) HC: 20 (10.0)	OCD: 23.2 (NA, 4.5) HC: 24.3 (NA, 2.9)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: mean = 4.4 years, SD = 3.3 years. Overall comorbidity: 10.0 % (obsessive–compulsive personality disorder = 10.0 %). Overall medication: 0.0 % (medication free for => 4 weeks).	20.9 (NA, 4.5)
(Huyser et al., 2011)	OCD: 25 (64.0) HC: 25 (64.0)	OCD: 13.95 (9.0–19.0, 2.52) HC: 13.71 (8.7–18.8, 2.85)	DSM-IV OCD assessed with Anxiety and Depression Inventory Schedule, Child and Parents' version and CY-BOCS. Disease duration: NA. Overall comorbidity: NA (anxiety disorders = 48 %, affective disorders = 12 %, externalizing disorder (ADHD and ODD) = 12 %, tic disorder = 8 %). Overall medication: 0.0 % (fluoxetine 6 months prior = 4.0 %, risperidone 14 days prior = 4.0 %, methylphenidate + dexamphetamine + atomoxetine 1 year prior = 4.0 %).	24.92 (16–35, 5.0)
(Kang et al., 2013)	OCD: 18 (33.3) HC: 18 (33.3)	OCD: 24.9 (NA, 5.9) HC: 24.7 (NA, 2.7)	DSM-IV OCD assessed with SCI for Axis I disorders and Y-BOCS. Disease duration: mean = 6.5 years, SD = 5.5 years. Overall comorbidity: 0.0 %. Overall medication: 0.0 % (medication free for => 4 weeks).	22.1 (NA, 7.6)
(Marsh et al., 2014)	OCD: 22 (50.0) HC: 22 (50.0)	OCD: 30.0 (NA, 9.09) HC: 30.14 (NA, 9.35)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: mean = 13.95 years, SD = 9.28 years. Overall comorbidity: 0.0 %. Overall medication: 0.0 %.	25.91 (NA, 4.2)
(Morein-Zamir et al., 2016)	HC: 19 (73.7) OCD: 19 (73.7)	OCD: 37.79 (NA, 10.1) HC: 36.16 (NA, 11.27)	DSM-IV OCD assessed with unstructured interview, MINI and Y-BOCS. Disease duration: NA.	19.95 (NA, 5.98)

(*continued on next page*)

Table 2 (*continued*)

| Author, year	n (% females)	mean age in years (range, SD)	Clinical characteristics of OCD sample	Mean symptom severity (range, SD)
(Nabeyama et al., 2008)	OCD: 11 (63.6) HC: 19 (57.9)	OCD: 32.4 (NA, 10.6) HC: 32.7 (NA, 7.1)	Overall comorbidity: 10.5 % (GAD = 10.5 %). Overall medication: 73.7 % (SSRI = 68.4 %, tricyclic antidepressant = 5.3 %). DSM-III-R OCD assessed with SCI and Y-BOCS. Disease duration: mean = 10.73 years, SD = 6.95 years.	29.7 (25–33, 3.0)
(Nakao et al., 2009)	OCD: 17 (70.6) HC: 16 (43.8)	OCD: 30.6 (18–60, 9.7) HC: 30.8 (18–60, 7.9)	Overall comorbidity: 0.0 %. Overall medication: 0.0 % (medication free for => 2 weeks). DSM-III-R OCD assessed with SCI and Y-BOCS. Disease duration: mean = 5.5 years, SD = 3.1 years. Overall comorbidity: 0.0 %. Overall medication: 0.0 % (medication free for => 2 weeks).	28.7 (NA, 3.8)
(Nakao et al., 2005)	OCD: 24 (62.5) HC: 14 (64.3)	OCD: 33.9 (21–54, 8.08) HC: 30.2 (24–43, 5.13)	DSM-III-R OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 0.0 %. Overall medication: 0.0 % (medication free for => 2 weeks).	29.4 (18–37, 4.22)
(Page et al., 2009)	OCD: 10 (0.0) HC: 11 (0.0)	OCD: 39.1 (18–60, 10.2) HC: 34.1 (18–60, 10.1)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 20.0 % (dysthymic disorder = 20.0 %). Overall medication: 0.0 % (medication free for => 6 weeks).	23.5 (NA, 3.9)
(Remijnse et al., 2013)	OCD: 18 (77.8) HC: 29 (69.0)	OCD: 33.0 (19–54, NA) HC: 33.0 (22–53, NA)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 55.6 % (PTSD = 5.6 %, panic disorder = 11.1 %, GAD = 22.2 %, dysthymic disorder = 22.2 %, social phobia = 22.2 %, opioid abuse in sustained full remission = 5.6 %, TS = 5.6 %). Overall medication: 0.0 % (medication free for => 2 weeks).	22.7 (11–31, 4.9)
(Roth et al., 2007)	OCD: 12 (58.3) HC: 14 (57.1)	OCD: 37.8 (NA, 13.2) HC: 34.9 (NA, 13.2)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 16.7 % (MDD = 16.7 %, social phobia = 8.3 %). Overall medication: 50.0 % (SSRI = 50.0 %).	22.3 (NA, 6.1)
(Schlösser et al., 2010)	OCD: 21 (76.2) HC: 21 (76.2)	OCD: 31.3 (NA, 10.2) HC: 28.8 (NA, 8.3)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: mean = 8.6 years, SD = 7.8 years. Overall comorbidity: 0.0 %.	20.7 (NA, 6.5)
(Theiss et al., 2019)	OCD: 16 (37.5) HC: 15 (33.3)	OCD: 27.5 (NA, 5.33) HC: 26.06 (NA, 4.45)	Overall medication: 9.5 % (SSRI = 9.5 %). DSM-IV OCD assessed with MINI and Y-BOCS. Disease duration: NA. Overall comorbidity: 63 % (anxiety disorder = 37 %, MDD = 31 %). Overall medication: 43.8 % ("mostly" SSRI).	22.0 (NA, 5.51)
(van den Heuvel et al., 2005)	OCD: 18 (66.7) HC: 19 (47.4)	OCD: 33.4 (NA, 10.18) HC: 30.3 (NA, 8.28)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: 0.0 %. Overall medication: 0.0 % (medication free for => 4 weeks).	23.4 (NA, 7.21)
(Yücel et al., 2007)	OCD: 19 (47.4) HC: 19 (47.4)	OCD: 33.7 (NA, 10.7) HC: 30.6 (NA, 7.2)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: mean = 13.4 years, SD = 11.3 years. Overall comorbidity: 0.0 %. Overall medication: 57.9 % (fluoxetine hydrochloride = 21.1 %, fluvoxamine maleate = 5.3 %, citalopram hydrobromide = 10.5 %, venlafaxine hydrochloride = 5.3 %, clomipramine hydrochloride = 15.8 %)	16.3 (NA, 5.7)
(Thorsen et al., 2020)	OCD: 31 (61.3) HC: 26 (69.2)	OCD: 30.19 (NA, 9.21) HC: 31.0 (NA, 10.73)	DSM-IV OCD assessed with SCI and Y-BOCS. Disease duration: NA. Overall comorbidity: NA (MDD = 29.0 %, GAD = 29.0 %, social phobia = 22.6 %, specific phobia = 12.9 %, panic disorder = 9.7 %, hypochondriasis = 9.7 %, dysthymia = 6.5 %, PTSD = 3.2 %, ADHD = 3.2 %, somatization disorder = 3.2 %, panic disorder = 3.2 %). Overall medication: 22.6 % (SSRI = 19.4 %, methylphenidate = 3.2 %).	26.83 (NA, 4.26)

Note: ADHD = attention-deficit hyperactivity disorder; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; GAD = generalized anxiety disorder; HC = healthy control; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime; MDD = major depressive disorder; MINI = Mini-International Neuropsychiatric Interview; NA = not available; NOS = not otherwise specified; OCD = obsessive–compulsive disorder; ODD = oppositional defiant disorder; PTSD = post-traumatic stress disorder; SCI = Structured Clinical Interview; SD = standard deviation; SSRI = selective seretonin reuptake inhibitor; TS = Tourette's disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

connections to the dorsal PFC and striatum (Stevens et al., 2011). This finding was driven predominantly by hypoactivation in OCD patients relative to HC subjects and aligns with similar findings in previous *meta*-analyses. The dACC and PFC, together with striatum, represent key nodes of functionally segregated parallel fronto-striatal circuits
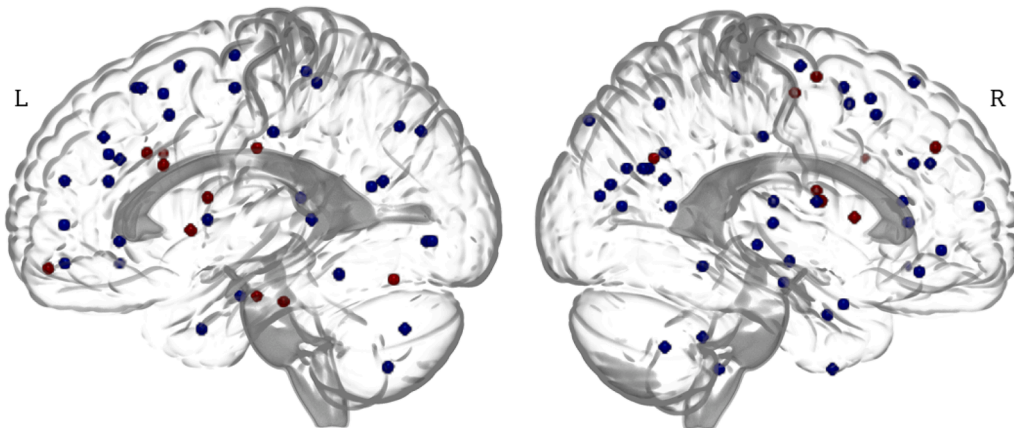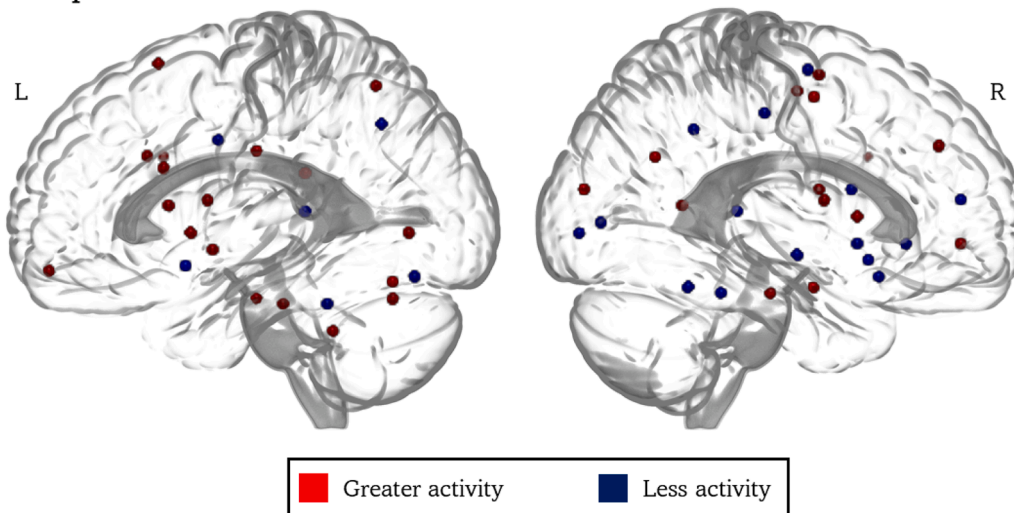
Cognitive inhibition

Fig. 2. Distribution of foci from cognitive inhibition experiments (top) and response inhibition experiments (bottom) reporting significant activation differences between patients with obsessive–compulsive disorder and healthy control subjects. Activation foci were widely distributed in both types of experiments. Red foci show the locations of activation differences in experiments reporting greater inhibition-related activation in patients, whereas blue foci denote the coordinates in experiments reporting reduced inhibition-related activation in patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Response inhibition

■ Greater activity   ■ Less activity

(Alexander et al., 1986), which converging lines of evidence have implicated in the pathophysiology of OCD (Burguière et al., 2015; Jahanshahi et al., 2015; Pauls et al., 2014). The functional role of the dACC during inhibitory control remains to be fully elucidated (Long et al., 2021), but it is likely involved in an error-processing circuit which monitors performance and signals frontal executive control regions to adjust the selection of actions upon detection of errors (Kerns, 2006). Interestingly, a recent *meta*-analysis of 10 inhibitory control tasks that concurrently included both an error and an inhibition contrast found error-related hyperactivation of the dACC, but inhibition-related hypo-activation of the same region (Norman et al., 2019). Moreover, decreased activation of the dACC has previously been associated with increases in task demands (Koch et al., 2012). Together with previous findings, our result support the notion that any existing perturbations of dACC activation during inhibitory control in OCD are likely dependent on the precise cognitive and contextual demands. Still, not a lot of confidence should be placed in this one positive finding: it was only marginally significant (P_{cFWE} = .04) and was derived from a subgroup *meta*-analysis, which was not corrected for multiple comparisons. Moreover, abnormal activation of the dACC was reported in only 4 of the 25 experiments included in the *meta*-analysis (corresponding to 16 %), and merely 4 of a total of 34 experiments (12 %) when also considering the nine experiments that were excluded solely because they had null results.

Heterogeneity driven by differences in sample characteristics may

also have contributed to inconsistencies across experiments. Marked differences exist between pediatric OCD and adult OCD (Geller et al., 2021), and impairments of inhibitory control may manifest only later in the trajectory of the disorder (Marzuki et al., 2020). Although we were not able to assess the effects of age or disease duration on our findings, a post-hoc sub-group analyses restricted to experiments on adults suggested that the results of our *meta*-analyses were not notably affected by data from the 3 pediatric samples. Additionally, the frequent use of medication (most commonly selective serotonin reuptake inhibitors) in many of the included samples may have altered brain function during inhibitory control (Kim et al., 2020; Shin et al., 2014), but the diversity in medication status across samples made it difficult to conduct appropriate sub-analyses to investigate this.

Several limitations of our review need mentioning. Our ALE approach relied on reported coordinates for significant activation differences rather than non-thresholded statistical maps for group differences. As such, our method may have missed patterns of brain activation abnormalities that do not reach whole-level significance in experiments, but which otherwise converge when non-thresholded maps are integrated. Additionally, we did not assess potential effects of medication status (Boedhoe et al., 2018) or duration of illness (Nakao et al., 2009) in the included OCD samples. Finally, OCD frequently co-occur with affective disorders (Gillan et al., 2017) and share features of affective dysregulation linked to abnormal dACC activity (Milad and Rauch, 2012; Wood and Ahmari, 2015). Comorbid affective disorders were
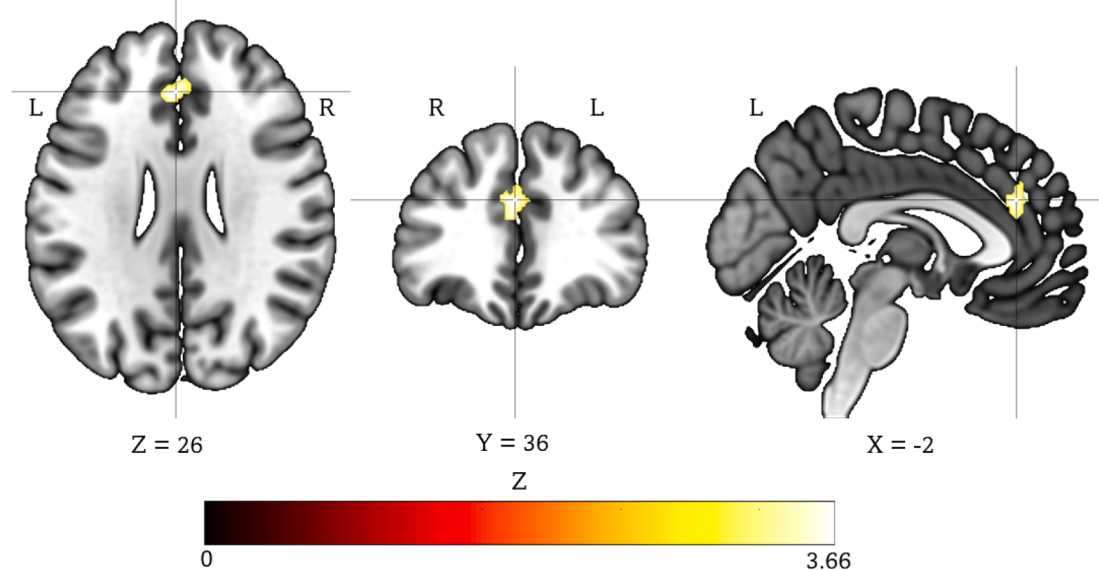
Fig. 3. Meta-analysis results for cognitive inhibition experiments overlaid on the MNI-152 template brain. Abnormal activation during cognitive inhibition was observed for OCD patients when compared to HC subjects in a cluster in the dorsal anterior cingulate (dACC/BA32) extending into the medial frontal gyrus (BA6 and BA9). Note: HC = healthy control; OCD = obsessive compulsive disorder; L = left; R = right.

common in the OCD samples included in this review and may therefore also have affected our findings.

To conclude, this systematic review used a stringent *meta*-analytic approach to quantitatively synthesize experiments reporting abnormal brain activation during inhibitory control in patients with OCD. We did not find evidence to suggest that observed activation differences across a variety of inhibitory control tasks converged onto the same brain regions. However, a subgroup analysis suggested limited convergence of activation differences during cognitive inhibition in the dACC. Overall, our findings suggest that if abnormalities in brain activation during inhibitory control are present in OCD, the activation pattern is likely not robust or consistent across tasks. As the field matures and additional data becomes available, future *meta*-analyses will be better equipped to provide more detailed examinations of different facets of inhibitory control and task-specific effects in OCD.

CRediT authorship contribution statement

Valdemar Funch Uhre: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Kit Melissa Larsen Data:** Validation, Writing – review & editing. **Damian Marc Herz:** Formal analysis, Writing – review & editing. **William Baaré Data collection:** Writing – review & editing. **Anne Katrine Pagsberg:** Conceptualization, Writing – review & editing, Supervision. **Hartwig Roman Siebner:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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