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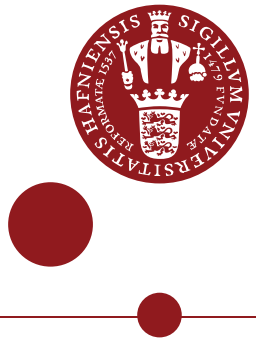

PhD Thesis

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Psychological and Neurobiological Perspectives on Pediatric Obsessive-Compulsive Disorder

Supervisor: Anne Katrine Pagsberg

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on April 9, 2022

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List of papers

This thesis includes the following four papers:

* = co-first authors

Paper I

Uhre, C. F.*, Uhre, V. F.*, Lønfeldt, N. N., Pretzmann, L., Vangkilde, S., Plessen, K. J., Gluud, C., Jakobsen, J. C., Pagsberg, A. K. (2020). Systematic review and meta-analysis: cognitive-behavioral therapy for obsessive-compulsive disorder in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 59(1), 64-77.

Paper II

Uhre, V. F., Uhre, C. F., Lønfeldt, N. N., Pretzmann, L., Vangkilde, S., Plessen, K. J., Gluud, C., Jakobsen, J. C., Pagsberg, A. K. (2020). Dr. Uhre et al. Reply. *Journal of the American Academy of Child and Adolescent Psychiatry*, 59(7), 787-791.

Paper III

Uhre, V. F., Larsen, K. M., Herz, D. M., Baaré, W., Pagsberg, A. K., Siebner, H. R. Inhibitory control in obsessive compulsive disorder: a systematic review and activation likelihood estimation meta-analysis of fMRI studies. *Manuscript*

Paper IV

Uhre, V. F., Larsen, K. M., Fuglsang, S. A., Madsen, K. H., Nejad, A. B., Baaré, W., Plessen, K. J., Siebner, H. R., Pagsberg, A. K. Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study. *Manuscript*

List of abbreviations

ABCD	Adolescent Brain Cognitive Development
ADHD	Attention deficit hyperactivity disorder
ALE	Activation likelihood estimation
BF	Bayes Factor
BOLD	Blood-oxygen-level dependent
CBT	Cognitive-behavioral therapy
C-GAS	Children's Global Assessment Scale
CGI-S	Clinical Global Impression Severity
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CSTC	Cortico-striato-thalamo-cortical
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
dACC	Dorsal anterior cingulate cortex
DALYs	Disability adjusted life years
DSM	American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders
EHI	Edinburgh Handedness Inventory
EPI	Echo planar images
ERP	Exposure and response prevention
FCBT	Family-based cognitive-behavioral therapy
FD	Framewise displacement
fMRI	Functional magnetic resonance imaging
FPRT	Family-based psychoeducation and relaxation therapy
FWE	Familywise error-corrected
GLM	General linear model
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HC	Healthy control
ICD	World Health Organization International Classification of Diseases
ICD-10	World Health Organization International Classification of Diseases – Tenth revision
IFG	Inferior frontal gyrus
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime
MD	Mean difference
MIREDIF	Minimum relevant difference
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PICO	Patients, Interventions, Comparisons and Outcomes
Pre-SMA	Pre-supplementary motor cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRT	Psychoeducation and relaxation therapy
RCT	Randomized controlled trial
RoB-2	Cochrane risk-of-bias tool, version 2019
ROI	Region-of-interest
RR	Risk ratio
RT	Reaction time
SD	Standard deviation
SMD	Standardized mean difference
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSD	Stop signal delay
SSRI	selective serotonin reuptake inhibitor
SSRT	Stop signal reaction time
SST	Stop signal task
TECTO	Treatment Effects of Cognitive-behavioral Therapy for Obsessive-Compulsive Disorder
TOCS	Toronto Obsessive-Compulsive Scale
TSA	Trial Sequential Analysis
VR	Virtual-reality
WAIS-IV	Wechsler Adult Intelligence Scale – Fourth edition
WISC-V	Wechsler Intelligence Scale for Children – Fifth edition
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

English summary

Background: Obsessive-compulsive disorder (OCD) is a serious psychiatric disorder that in some patients can be successfully treated using cognitive-behavioral therapy (CBT) with exposure and response prevention (ERP). However, other patients experience only few or no beneficial effects of CBT-ERP. In the ongoing randomized controlled trial (RCT) "Treatment Effects of Cognitive-behavioral Therapy for Obsessive-Compulsive Disorder" (TECTO), we compare the effects of CBT-ERP to psychoeducation and relaxation therapy in children and adolescents with OCD (8-17 years of age) on multiple outcomes. The TECTO RCT is coupled with multiple longitudinal case-control sub-studies that aim to identify features of pediatric OCD and factors that predict or moderate the treatment outcome. This thesis presents preliminary findings from the TECTO neuroimaging sub-study.

Objectives: To evaluate the existing evidence for beneficial and harmful effects of CBT for pediatric OCD, and to investigate the brain activation during inhibitory control in OCD compared with healthy controls, as it may be linked to symptomatology and treatment response.

Methods: To assess the evidence for beneficial and harmful effects of CBT for pediatric OCD, we used Cochrane review methods to conduct a systematic review and meta-analyses of trials that compared CBT to an alternative intervention or no intervention. The outcomes assessed were OCD symptom severity, psychosocial functioning, quality of life, adverse events, and remission from OCD. To evaluate the evidence for abnormal brain activation during inhibitory control in OCD, we performed a systematic review and coordinate-based activation likelihood meta-analyses of functional magnetic resonance imaging (fMRI) studies reporting coordinates of significant brain activation differences between OCD and healthy controls during inhibitory control. Finally, we used fMRI and a stop signal task to investigate neural and behavioral correlates of inhibitory control in a sample of unmedicated children and adolescents with OCD compared with age- and sex-matched healthy controls.

Results: Our systematic review of CBT trials suggested that CBT may be an effective treatment for pediatric OCD, but the certainty of the evidence was low for all assessed outcomes, and most trials only evaluated the effect of CBT on OCD symptom severity. Our systematic review of fMRI studies revealed statistically significant convergence of reported case-control differences during inhibitory control in the bilateral dorsal anterior cingulate cortex (dACC), but not enough data was

available to perform a meta-analysis restricted to pediatric samples. Preliminary findings from the TECTO neuroimaging sub-study showed moderate evidence against a group difference between children and adolescents with OCD and healthy controls in brain activation during inhibitory control and behavioral outcomes, but also a positive correlation in the OCD group between symptom severity and the activation of the right inferior frontal gyrus (IFG) during successful inhibition.

Conclusion: Additional RCTs that minimize risks of bias and evaluate the effect of CBT on other outcomes than OCD symptom severity are currently needed. The bilateral dACC may be a key functional locus of abnormal inhibitory control in adult OCD, but the evidence for abnormal brain activation during inhibitory control in pediatric OCD is less certain. The right IFG could play a central role in the development or maintenance of OCD symptoms, and future investigations in the TECTO study might relate the function of this region to treatment outcomes after CBT-ERP.

Dansk resumé

Baggrund: Obsessiv-kompulsiv tilstand (OCD) er en alvorlig psykiatrisk lidelse, som hos nogle patienter kan behandles med kognitiv adfærdsterapi (CBT) med eksponering og responsprævention (ERP). Andre patienter oplever dog kun få eller ingen gavnlige effekter af CBT-ERP. I det igangværende randomiserede kliniske forsøg (RCT) "Treatment Effects of Cognitive-behaioral therapy for Obsessive-Compulsive Disorder" (TECTO) sammenligner vi virkningen af CBT-ERP med psykoedukation og afspændingsterapi til børn og unge med OCD (8-17 år) på en række effektmål. TECTO RCT er koblet med flere longitudinelle case-kontrol sub-studier, der har til formål at identificere kendetegn for pædiatrisk OCD og faktorer, der forudsiger eller påvirker udbyttet af behandlingen. Denne afhandling præsenterer præliminære resultater fra TECTO billeddannelse sub-studiet.

Formål: At vurdere evidensen for gavnlige og skadelige virkninger af CBT til behandling af pædiatrisk OCD, og at undersøge hjerneaktiveringen ved inhibitorisk kontrol hos patienter med OCD sammenlignet med raske kontrolpersoner, idet den kan være relateret til symptomatologien og behandlingsrespons.

Metoder: For at vurdere evidensen for gavnlige og skadelige virkninger af CBT til behandling af pædiatrisk OCD, brugte vi Cochrane review-metoder til at udføre et systematisk review med metaanalyser af kliniske forsøg der har sammenlignet CBT med en alternativ intervention eller ingen intervention. Vi vurderede følgende effektmål: sværhedsgrad af OCD-symptomer, psykosocial funktion, livskvalitet, uønskede hændelser og remission. For at evaluere evidensen for abnormal hjerneaktivering ved inhibitorisk kontrol hos personer med OCD udførte vi et systematisk review og koordinatbaserede meta-analyser af studier med funktionel magnetisk resonans-billeddannelse (fMRI), som har rapporteret koordinater for signifikante hjerneaktiveringsforskelle for personer med OCD sammenlignet med raske kontrolpersoner ved inhibitorisk kontrol. Endelig brugte vi fMRI og en stopsignalopgave til at undersøge neurale og adfærdsmæssige korrelater ved inhibitorisk kontrol i en gruppe af ikkemedicinerede børn og unge med OCD sammenlignet med alders- og kønsmatchede raske kontrolpersoner.

Resultater: Vores systematiske review af CBT-forsøg viste, at CBT muligvis udgør en effektiv behandling for pædiatrisk OCD, men alle effektmål var forbundet med stor usikkerhed, og de fleste eksisterende forsøg har kun vurderet virkningen af CBT på sværhedsgraden af OCD-symptomer.

Vores systematiske review af fMRI-studier viste at koordinaterne for rapporterede gruppeforskelle i hjerneaktivering ved inhibitorisk kontrol konvergerede statistisk signifikant bilateralt i den dorsale del af gyrus cingularis anterior (dACC), men data var ikke tilstrækkelige til at udføre en meta-analyse begrænset til pædiatriske grupper. Foreløbige resultater fra TECTO-neuroimaging sub-studiet viste moderat evidens imod en gruppeforskel mellem børn og unge med OCD og raske kontrolpersoner i hjerneaktivering ved inhibitorisk kontrol og adfærdsmæssige præstationsmål, men samtidig også en positiv sammenhæng i OCD-gruppen mellem symptomsværhedsgrad og aktiveringen af højre inferior frontal gyrus (IFG) ved succesfuld inhibitorisk kontrol.

Konklusion: Der er behov for flere RCT'er, der minimerer risikoen for bias og inkluderer andre effektmål end OCD-symptomernes sværhedsgrad. Bilaterale dACC kan udgøre et centralt område for forandringer i hjerneaktivitet ved inhibitorisk kontrol hos voksne med OCD, men evidensen for forandringer i hjerneaktivitet ved inhibitorisk kontrol hos børn og unge med OCD er mindre sikker. Højre IFG kan spille en afgørende rolle for udviklingen eller vedligeholdelsen af OCD-symptomer, og fremtidige undersøgelser i TECTO-studiet kan muligvis relatere dette områdes funktion til virkninger af CBT-ERP.

Introduction

Clinical presentation and prevalence of OCD

Although aspects of what we now denote obsessive-compulsive disorder (OCD) can be traced back to the 14th century, the first description of OCD as it is defined in current classification manuals came much later, in 1877, by the German psychiatrist Karl Friedrich Otto Westphal [2]. Westphal recognized that obsessive-compulsive behaviors can occur despite intact intellectual and cognitive abilities, in the absence of any apparent affective causal pathology, and with the patient's awareness of the absurdity of the behaviors but inability to inhibit them. Westphal used the term "Zwangsvorstellung", which was translated to "obsessions" in England, but "compulsions" in the United States, and the term "obsessive-compulsive" emerged later when an agreement between health professionals on the definitions was made [2].

The cardinal symptoms of OCD are obsessions and compulsions [3]. Obsessions refer to persistent and intrusive thoughts, urges, or images that cause distress or anxiety, whereas compulsions are repetitive overt or mental acts that may be performed to reduce anxiety provoked by the obsessions [4], or due to an impaired ability to exert the necessary control over actions [5].

Almost everyone have experienced an irrational obsession with something or a compulsive urge to do an activity a certain way, as is reflected in the frequency with which the words "obsession" and "compulsion" are used to describe common occurrences (e.g., "I am obsessed with this band"). About 30% of the population have experienced distressing obsessions and compulsions at some point in their lives, and the conditional probability of a lifetime OCD diagnosis increases with the number of obsessions and compulsions [6]. For 2-3% of adults [6, 7], the distress or impairment is sufficient to merit a diagnosis of OCD according to the diagnostic criteria of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM; for a comparison of the criteria used in DSM and the WHO International Classification of Diseases [ICD], see [8]). The prevalence of OCD is similar in the pediatric population [9] and appear consistent across different countries [10].

The burden of OCD

The World Health Organization (WHO) ranks OCD among the 10 most debilitating psychiatric disorders measured in disability adjusted life years (DALYs) and estimates that over 6.1 million

DALYs will be lost by 2030 [11]. In addition, OCD imposes a substantial economic burden on society due to hospitalization, treatment services, and incapacitation [12, 13].

At the individual level, patients with OCD have markedly reduced quality of life and level of psychosocial functioning on a broad range of domains when compared to their healthy peers [14, 15]. One third of patients with OCD have had suicidal ideations, and about 10% have suicidal thoughts at the time of assessment [16, 17]. About one in ten patients with OCD have attempted suicide [16-18] and patients with OCD are estimated to be at a ten-fold risk of dying by suicide compared with matched controls from the general population [19]. Moreover, caregivers and families to patients with OCD are often profoundly affected and their level of burden is associated with the overall severity of the disorder [20-23].

Correct diagnosis of OCD is often delayed [24] and about 60% of individuals with OCD are not receiving any treatment for their illness [25]. Additionally, many individuals that do receive treatments experience limited beneficial effects [26]. In sum, the health-economic incentive to improve treatment for OCD is substantial.

The etiology of OCD

The precise etiology of OCD is unclear, but both polygenic and environmental factors are likely involved [4]. Studies of monozygotic and dizygotic twins indicate that about half of the phenotypic variation in OCD symptoms can be ascribed to non-shared environmental factors and about 40% to genetic variance [27], with slightly greater heritability for pediatric OCD than adult OCD [28]. Both somatic and psychosocial environmental risk factors or “stressors” have been suggested. For example, it has been proposed that a subgroup of patients with OCD clinically characterized by having a sudden onset of symptoms which fluctuate in severity and is accompanied by motor tics develop their symptoms in relation to streptococcal infections [29]. However, this hypothesis, known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), remains heavily debated [30, 31]. Stressful life events is a type of a psychosocial environmental factor that also may lead to phenotypic expression of pediatric OCD though environment-gene interactions [32, 33]. However, stressful life events and other types of psychosocial risk factors are not uniquely linked to OCD but constitute risk factors for a wide range of psychiatric conditions [34].

Common comorbid disorders

The reported lifetime rates of psychiatric comorbidity in OCD are similar across the lifespan and vary between 60% and 90% [6, 35-38], depending on the methodological approach. The most frequent comorbidities are anxiety and mood disorders [6, 18, 39], but also other disorders characterized by impulsivity or compulsivity (e.g., body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation, tic disorders, attention deficit hyperactivity disorder (ADHD), alcohol and substance use disorders and self-injurious behaviors) commonly co-occur in OCD [6, 40-44].

A cognitive-behavioral model for OCD

A cognitive-behavioral model can parsimoniously describe the functional link between obsessions and compulsions in OCD [45, 46] (Figure 1). In a nutshell, context-specific events, such as specific thoughts or bodily sensations, trigger obsessions. Obsessions are generally intrusive and persistent, and they are to varied degrees associated with doubt, guilt, negative thoughts, and unrealistic or superstitious beliefs. Obsessions cause a build-up of worry or anguish that is linked to an instinctual and compelling urge to engage in compulsive behaviors that provide a transient relief from anxiety and distress. However, in the long term, compulsions reinforce actions that are unrelated to the person's goals and often have negative consequences in the person's life. Over time, this cycle of obsessions and compulsions frequently result in avoidance behaviors and social isolation.

The heuristic cognitive-behavioral model is compelling in many ways, but for some cases the description offered is inadequate. For example, when the remaining diagnostic criteria are met, the presence of either obsessions or compulsions alone suffice for a diagnosis of OCD according to both ICD and DSM criteria (such cases are referred to as predominantly obsessive or predominantly compulsive). In these cases, the cognitive-behavioral model does not satisfactorily explain the etiology and maintenance of symptoms. There is also evidence to suggest that compulsive behaviors in OCD may arise from an imbalance between competing systems for automatic habitual behaviors and goal-directed behaviors, where the former dominates the latter [47]. This view is known as the "habit hypothesis" of OCD and proposes that compulsions are simple and goal-insensitive behaviors elicited by stimuli, rather than being oriented at reducing anxiety or neutralizing a perceived threat. The habit hypothesis is supported by the fact that many patients seem to develop compulsions before they develop obsessions [48]; in these cases, obsessions may be explained as the result of erroneous reverse inference, in which patients

mistakenly reason that ego-dystonic and goal-irrelevant compulsions must have been performed for a cause. Furthermore, normative ritualistic or compulsive-like behaviors, such as children requesting to hear the same story over and over, are common in childhood [49, 50], which supports the notion that compulsions may be a consequence of excessive habit formation. The cognitive-behavioral model of OCD appears to conflict with this perspective.

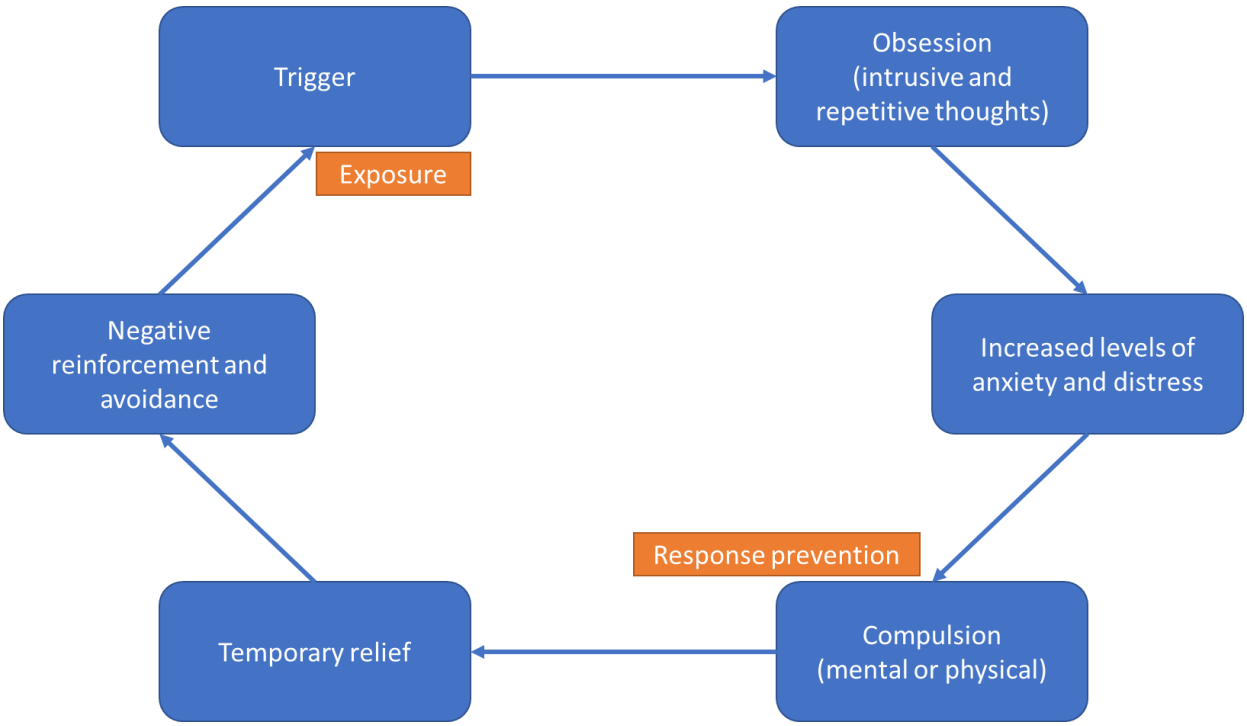

Figure 1. A cognitive-behavioral model for obsessive-compulsive disorder. The blue boxes illustrate the putative functional link between obsessions and compulsions and the orange boxes depict the treatment targets for cognitive-behavioral therapy with exposure and response prevention. According to the model, obsessions that are triggered by context-specific stimuli (e.g., touching an object that is perceived to be insanity) lead to a build-up of anxiety and distress, and a temporary relief is attained once a subsequent compulsion is performed (e.g., excessive hand washing). This compulsion is strengthened via negative reinforcement. Over time, this obsessive-compulsive cycle often leads to avoidance behaviors and social isolation. Exposure and response prevention involve progressive, prolonged, and repeated exposure to the stimuli triggering obsessions with subsequent prevention of the compulsive rituals (e.g., touching a doorknob and abstaining from washing hands afterwards), thereby over time facilitation the extinction of obsessional anxiety and distress. Original figure made with PowerPoint.

A cortico-striato-thalamo-cortical model for OCD

Several different lines of evidence have implicated parallel and partially segregated cortico-striato-thalamo-cortical (CSTC) circuits [51] in the pathophysiology of OCD [4, 52-54]. Earlier models have focused mostly on fronto-striatal circuits [55] (see Figure 2), but more recent evidence suggest that fronto-parietal [56] and fronto-limbic [57-59] networks are also involved. The CSTC loops are also known for their role in both hyperkinetic disorders (e.g., Huntington's disease) and hypokinetic disorders (e.g., Parkinson's disease), but contrary to movement disorders, there is no known locus of neurodegeneration in OCD [52]. Alterations to the functioning of CSTC circuits involved in the regulation of cognitions, emotions and behaviors have been probed in OCD using a variety of different research paradigms [60], and the precise locus for abnormal functioning appear to depend heavily on both the experimental context and the degree to which the brain is engaged in a task [61]. For example, when symptom provocation paradigms are used to induce OCD symptoms in patients, there seems to be increased activation of especially ventral fronto-striatal circuits, including the anterior cingulate and orbitofrontal cortices [62] and the bilateral amygdala [63]. Findings from symptom provocation experiments indicate that affective dysregulation is a central component in OCD and is consistent with the suggestion that OCD and the frequently co-occurring anxiety disorders and affective disorders to some extend have overlapping pathophysiology [58, 59, 64]. When patients with OCD are engaged in a cognitive task relying on executive functions, including goal-directed actions and inhibitory control, the locus of abnormality seem to be more lateral and dorsal fronto-striatal and fronto-parietal circuits [65-67].

As previously mentioned, persisting and ego-dystonic compulsions in OCD have been ascribed to maladaptive habit formation, and the inability of individuals with OCD to disengage from ritualistic behavior may reflect an imbalance between the largely dissociable neurocircuits underlying habits and goal-directed behaviors [5, 68, 69]. Habits are remarkably fixed repetitive behaviors or sequences of actions that are performed automatically and without conscious awareness [70]. Functionally, habits are in opposition to the more flexible goal-directed behaviors that are performed consciously and with a specific goal in mind [71]. Habits are acquired through repetition of an action in a stable context, leading to the subsequent automatic activation of that action when exposed to the contextual stimulus [72, 73]. Since the initiation of the habitual action is triggered by external cues (as opposed to internal goals), dependence on motivational processes or attentional resources is reduced. Consequently, habits may occur in the absence of conscious motivation, and can persist despite negative outcomes, and insensitivity to reward devaluation is

potentially pronounced in patients with OCD [74]. A large body of literature suggest both excess activation of regions critical to habit formation (including the basal ganglia) and decreased activation of circuits underlying goal-directed control over actions in OCD as well as other disorders characterized by compulsivity [68, 74-79].

Compulsive behaviors in OCD have also been linked to deficient inhibitory control over actions [80-83]. Inhibitory control has been assessed with a range of different tasks which have in common that participants occasionally must deviate from a pre-potent response tendency [84]. In cognitive

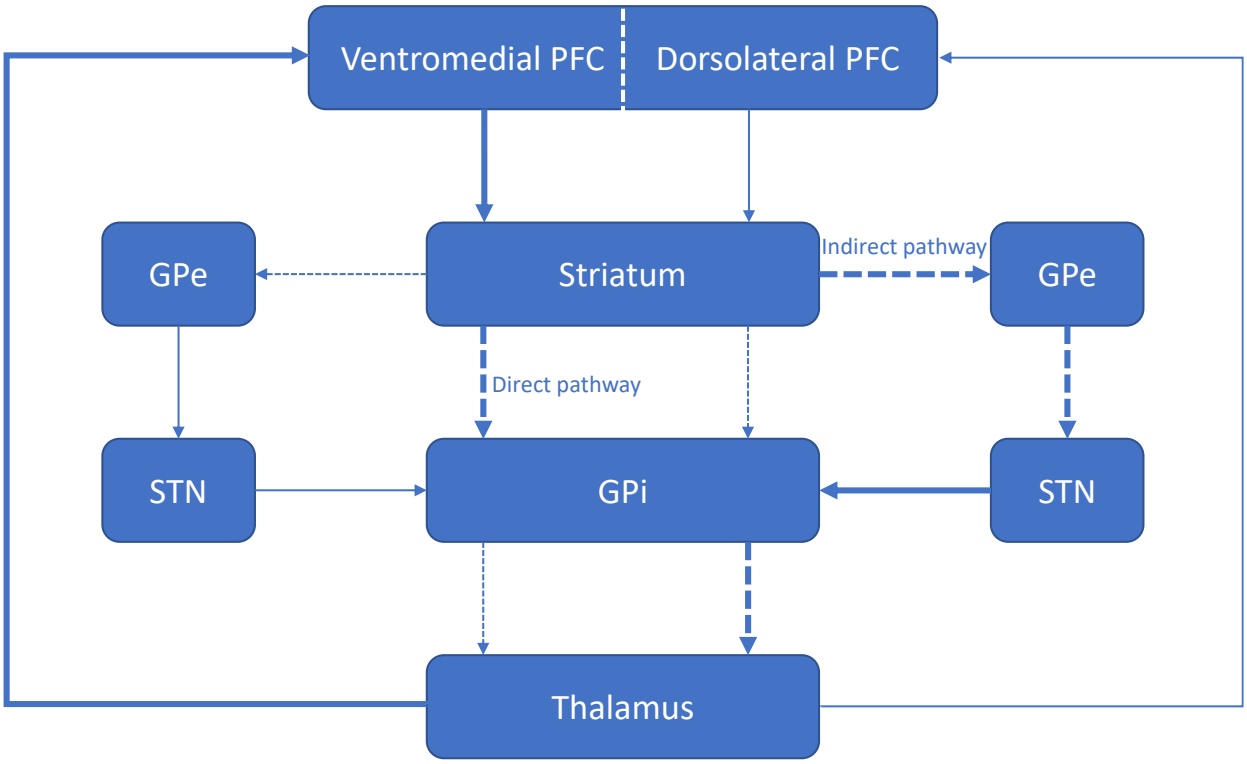

Figure 2. A simplified cortico-striato-thalamo-cortical (CSTC) model for obsessive-compulsive disorder. Solid arrows depict excitatory pathways and dashed arrows depict inhibitory pathways. The width of arrows indicates the strength of the projection. Fronto-striatal projections lead to excitation of the striatum (comprising the caudate and putamen) and the release of dopamine. This dopamine influences the activity of neurons in a direct pathway and an indirect pathway. In the indirect pathway, inhibitory projections from striatum to GPe and STN lead to excitation of GPi, thereby increasing the inhibitory influence of GPi on thalamus and thus decreasing the excitation of the PFC. Note that the direct pathway form a net excitatory (pro-kinetic) feedback loop which is central to the initiation and continuation of behaviors, whereas the indirect pathway form a net inhibitory (anti-kinetic) feedback loop that facilitates the inhibition of behaviors and the switching between behaviors. In OCD, the balance between the direct pathway and the indirect pathway is putatively disrupted, such that the ventromedial "affective" CSTC circuit is more activated, and the dorsolateral "cognitive" CSTC circuit being less activated. Abbreviations: GPe = external globus pallidus, GPi = internal globus pallidus, PFC = prefrontal cortex, STN = subthalamic nucleus. Original figure made with PowerPoint.

inhibition tasks, participants must control interference from distracting stimuli that are presented alongside a target stimulus (e.g., Flanker, Stroop, Simon, and Multisource interference) or from previously valid target-response associations (Switching and Shifting). In response inhibition tasks, participants must overcome a pre-potent tendency to respond induced by a high frequency of "go" trials by withholding their response on occasional "no-go" trials (go/no-go) or cancelling their response on "stop" trials (stop signal). Interference control, action restraint and action cancellation tasks probe different stages and aspects of inhibitory control [81], and action cancellation is potentially associated with the greatest load on inhibitory control processes [85] (for a review, see [86]). Interference control, action withholding and action cancellation engages only partially overlapping networks [87]. Interference control predominantly engages dorsal fronto-striatal brain networks, whereas response inhibition, and especially action cancellation, appear to consistently engage right-lateralized frontal brain regions, including the right inferior frontal gyrus (IFG) and pre-supplementary motor area (pre-SMA) [87], in addition to the bilateral insula [88]. Inhibition tasks using emotional stimuli appear to engage more left-lateralized and ventral frontal brain regions [89], and affective versus motor-cognitive inhibition likely lies on a neuroanatomical ventral-to-dorsal gradient within the prefrontal cortex [90]. Meta-analyses of fMRI data on patients with OCD indicate aberrant activation of multiple regions within CSTC circuits during inhibitory control [91-93] as well as other executive functions [65-67, 94]. Importantly, impairments of inhibitory control have also been detected in unaffected relatives of patients with OCD, indicating that it could be a candidate endophenotype of OCD [95]. However, precisely how impairments in inhibitory control are related to the symptomatology of OCD remains elusive.

Cognitive-behavioral therapy with exposure and response prevention for OCD

Cognitive-behavioral therapy (CBT) was pioneered by Aaron Beck and Albert Ellis in the 1960s [96, 97]. Today, CBT represents a family of practices that focus on changing maladaptive cognitions and behaviors in the treatment of psychopathology. CBT exists in many forms, but most CBT interventions share the core assumption that maladaptive cognitions are central to the development and maintenance of psychiatric disorders and distress [98, 99].

According to cognitive theory, intrusive thoughts are not themselves problematic. In fact, the vast majority of the general population have experienced obsessive intrusive thoughts [100]. Rather, it is the appraisal of thoughts that can lead to problematic obsessive-compulsive behaviors. When a person interprets a thought to be highly meaningful or exaggerates its significance, then what

would otherwise have been a small nuisance may start to cause distress. In turn, the person may use avoidance or engage in compulsive behaviors to alleviate this distress. This implied relationship between obsessions and compulsions is the primary target of CBT with exposure and response prevention (ERP; see Figure 1) [101-104]. During CBT with ERP, the patient with OCD learn to identify dysfunctional appraisals of thoughts and challenge them [105]. In brief, the patient with OCD is guided to intentionally expose themself to "trigger" stimuli and subsequently abstaining from performing compulsions. For example, an individual with contamination obsessions might expose themself to a public bathroom and subsequently refrain from compulsive handwashing. The aim for the patient with OCD is to remain in the exposure situation until distress subsides and is perceived as tolerable. This experience contradicts the patient's expectation that the trigger stimulus would be dangerous or intolerable, which allow new non-threatening associations to be formed and breaks the reinforcement cycle of the compulsive behavior. Other key components of CBT with ERP include psychoeducation, various homework assignments, and family involvement [106, 107].

CBT with ERP is the current recommended first-line treatment for children and adolescents with OCD [108, 109], which is supported empirically by results from systematic reviews and meta-analyses [110-120]. However, many of the existing reviews have not included an assessment of the risks of bias in included trials [113-115, 117, 118]. Moreover, results from randomized controlled trials (RCTs) and uncontrolled trials have sometimes been pooled [115, 117, 119], which may inflate the estimated treatment effect [121]. Finally, several existing reviews included only OCD symptom severity as an outcome measure [111, 112, 120] and did not assess additional patient-reported (or patient-centered) outcomes from trials, such as level of functioning, quality of life or adverse events. Patient-reported outcomes are crucial because they reflect the patient's experienced benefit of the treatment [122].

Differences between childhood-onset and adult-onset OCD

The age at onset in OCD is bimodal, with an early peak in incidence in late childhood that only vary moderately, and a later peak in late adolescence and early adulthood with greater variation [123-125]. Although many OCD symptoms present similarly in children, adolescents and adults, several important differences exist between childhood-onset OCD and adult-onset OCD, which makes it difficult to extrapolate findings from adult OCD to pediatric OCD [126]. For example, although comorbid anxiety disorders and affective disorders are common in both pediatric OCD and adult OCD, other comorbid disorders are more prevalent in pediatric OCD, including ADHD,

autism spectrum disorders, and tic disorders [124, 127, 128]. The heritability appears to be greater in childhood-onset OCD compared with adult-onset OCD [129]. There may be a slight male predominance in childhood-onset OCD, whereas the gender distribution is more equal in adult-onset OCD [128] (although data from the Danish population-based registers suggest that girls have a higher risk of OCD than boys [130]). Patients with OCD are sometimes unable to identify any obsessions as causing compulsive behaviors, but nevertheless report being at unease and having an urge to perform ritualistic compulsions until achieving a "just right" feeling. These "just right" compulsions preferentially present in pediatric OCD and may be linked to the higher frequency of co-occurring tic disorders [131]. Neurocognitive deficits appear to be fewer and more subtle in pediatric OCD than in adult OCD [132-134], and some neurocognitive dysfunctions may only

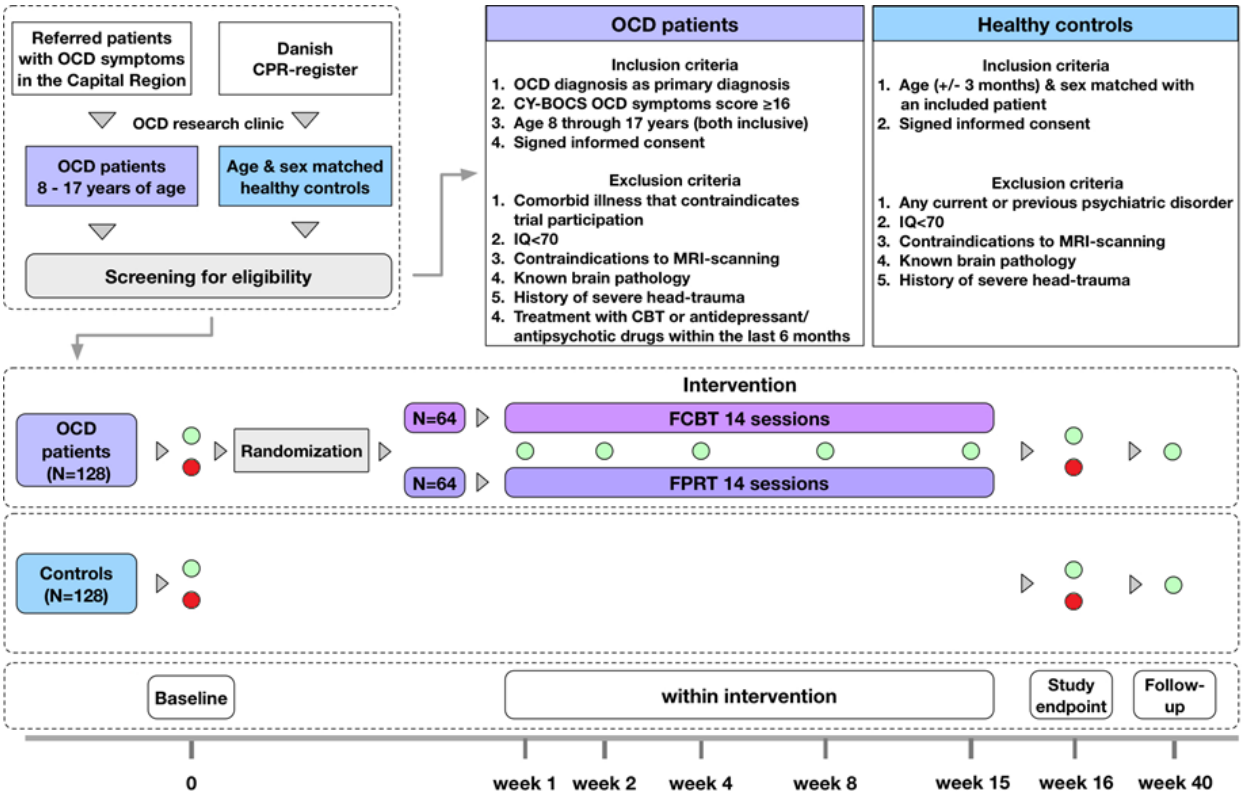

Figure 3. The TECTO trial study design. Individuals aged 8 through 17 years with a suspected diagnosis of OCD are referred by the Central Visitation Unit to our OCD team situated in the Child and Adolescent Psychiatric Center, Mental Health Services, Capital Region. Healthy controls are recruited from the same municipality via age- and sex-matched (within 3 months) random samples from the Danish Central Person Registry. Both groups are screened for eligibility (top right) by staff in the TECTO team using best-practice assessment procedures. Eligible participants that provide informed consent are enrolled in the trial (bottom) and (optionally) in TECTO sub-studies. Green dots indicate the time of assessment of clinical outcomes and red dots indicate the time of MRI assessment in the neuroimaging sub-study. Abbreviations: FCBT = family-based cognitive-behavioral therapy, FPRT = family-based psychoeducation and relaxation therapy, OCD = obsessive-compulsive disorder, IQ = intelligence quotient, MRI = magnetic resonance imaging. Figure courtesy of William Baaré (DRCMR).

emerge with the progression of the disorder [135]. The substantial differences between childhood-onset and adult-onset OCD have led to the suggestion that pediatric OCD may be a neurodevelopmental subtype of OCD [124, 136].

The neuroimaging sub-study of the TECTO trial

The TECTO trial is an ongoing RCT in which we compare the effects of 16 weeks of family-based CBT (FCBT) to 16 weeks of family-based psychoeducation and relaxation therapy (FPRT) in unmedicated and predominantly treatment-naïve children and adolescents with OCD (8 through 17 years of age; see the study design in Figure 3). FCBT is based on the manual by March and Mulle [106] and FPRT is based on the manual by Cautela and Groden [137]. FCBT and FPRT have carefully been tailored to be comparable regarding many key components of psychotherapy, including the number and duration of treatment sessions, the amount of homework assignments

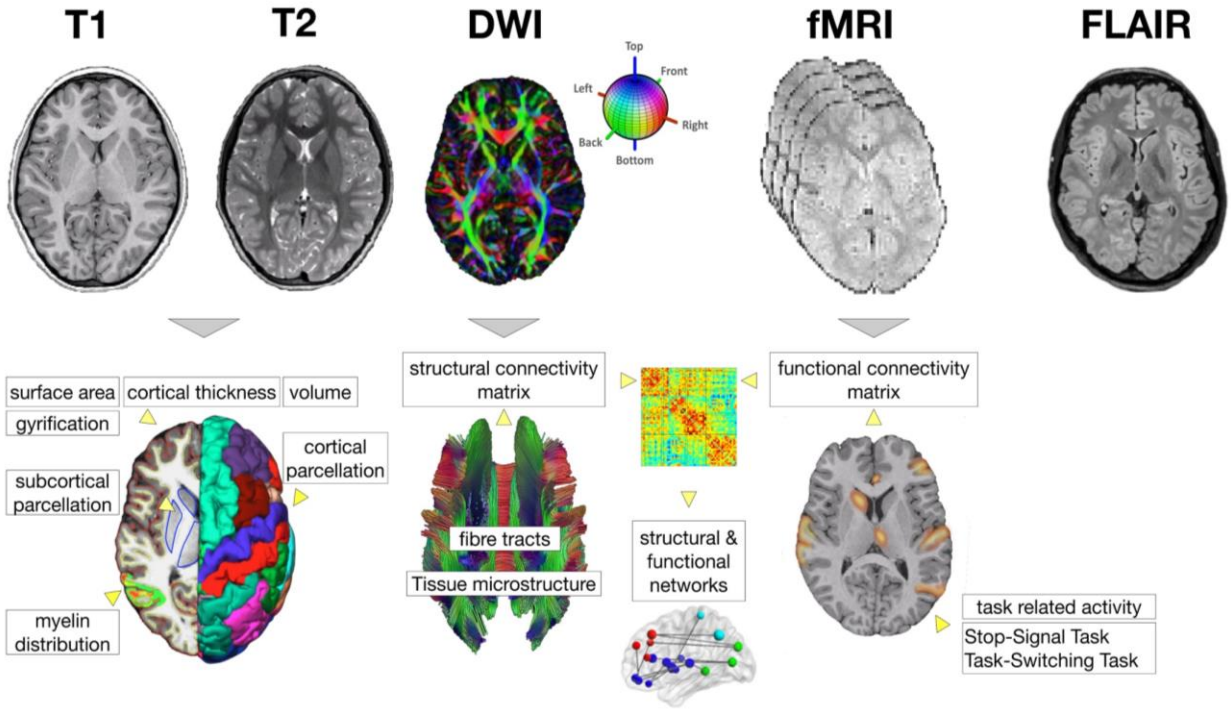

Figure 4. Brain imaging in the TECTO neuroimaging sub-study. T1-weighted images have good contrast between grey and white matter. T1 and T2 data is used to estimate regional cortical thickness, surface area, gyrification, myelin distribution in brain tissue, and cortical and subcortical brain structure volumes. Diffusion weighted imaging (DWI) provides insight into the microstructure of grey and white matter. Tractography is used to extract white matter fibres from DWI data and to investigate the structural connectivity in brain networks. The primary diffusion direction of water molecules is colour coded: green = front/back, blue = bottom/top, red = left/right. fMRI is used to measure brain activation during inhibitory control and investigate functional connectivity in brain networks. FLAIR is used to screen for signs of brain pathology. Figure courtesy of William Baaré (DRCMR).

and psychoeducation, and the involvement of the family in the treatment. In addition, all therapists deliver both treatments and receive supervision in both treatments. However, a crucial difference between the two treatments is that FCBT includes ERP whereas FPRT instead includes relaxation training. We purposefully isolated the ERP component to elucidate potential ERP-specific effects on treatment outcomes.

The neuroimaging sub-study of TECTO is one of multiple ongoing longitudinal case-control sub-studies that together aim to investigate the treatment effects on clinical, neural, cognitive, emotional and neuroendocrine outcomes and identify markers of pediatric OCD and factors that may predict or moderate the treatment response. Emerging evidence suggests that structural and functional changes may occur in many of the same regions of the CSTC circuits for different types of interventions [138]. The neuroimaging sub-study of TECTO takes a multimodal approach to brain imaging (Figure 4) to get a comprehensive picture of the neural correlates of the ERP component in FCBT and of the neural signatures of pediatric OCD.

From fMRI BOLD response to coordinate-based activation likelihood estimation meta-analysis

This thesis uses task-based fMRI and coordinate-based activation likelihood estimation (ALE) meta-analysis to investigate the neural correlates of inhibitory control in OCD. Specific neurocognitive functions are subserved by specific brain regions – a phenomenon known as functional specialization. In brief, fMRI is used to detect the blood-oxygen-level-dependent (BOLD) signal, which reflects changes in deoxyhemoglobin caused by local changes in blood flow and blood oxygenation that are coupled with changes in the underlying neuronal activity by a process called neurovascular coupling [139]. In principle, a particular neurocognitive function, such as inhibitory control, can therefore be localized by recording the BOLD response in a person performing an inhibitory control task during fMRI. Different complex methods are used to improve the spatiotemporal properties of fMRI and record the BOLD signal, but precisely how neuronal activity, hemodynamics and the fMRI BOLD signal are related is still not fully understood (see e.g., [140-142]).

The advent of fMRI has led to major advances in neuroscience, but task-based fMRI is also associated with several limitations. Most studies include small samples (as compared to clinical research or the social sciences). Reliability of the results is limited by both the biological confounds of the method and the flexibility in processing steps and statistical procedures [143-

145]. Furthermore, due to logistic expenses, the effects of variations in the precise experimental setup (e.g., variations in the types and timings of stimuli) are seldomly tested. Thus, it is often unknown whether a finding is robust or if it largely reflects the specific approach for analysis or experimental setup, which in turn discourage replication studies and lead to what has been dubbed the "publication of isolated findings" [146] (see also [147]). The fact that findings are at risk of being biased and context-specific [148] means that individual fMRI studies sometimes are not very informative.

A major advantage of published task-based fMRI studies, however, is the consistency with which the coordinates of activation foci are reported in a standardized stereotaxic space (i.e., the locations of significant findings are almost unanimously described in x, y, and z coordinates). This makes the fMRI literature well suited for meta-analysis. Coordinate-based ALE meta-analysis takes advantage of this by considering only the coordinates for the peak-level (maxima) activation differences between two groups of subjects or two experimental conditions while ignoring information pertaining to the magnitude of the effect (e.g., T-values and z-values) [149]. The strength of this extremely sparse representation of data is that almost the entire body of extant neuroimaging literature can be integrated without having to obtain additional data from the original authors. Unlike conventional meta-analyses, which tests the significance of a pooled effect size, coordinate-based ALE meta-analysis instead tests whether the *spatial convergence* of activation foci is greater than what would be expected by chance. This is essentially done in three steps (see e.g., [146]). First, each activation focus is modelled as the center of a 3D Gaussian probability distribution to represent the uncertainty arising from between-subject variances attributable to, for example, differences in normalization procedures across laboratories or neuroanatomical variability [150]. The width of this distribution is furthermore determined by the sample size of the study: a larger sample means greater likelihood of "true" activation near the location reported in the study. Second, all the probability distributions of activation foci from one experiment are combined into a single activation map. A final ALE map is determined by taking the union of activation maps across experiments. In effect, the ALE map is a 3D representation of the convergence across different experiments. Third, the computed ALE map is compared to a null distribution that reflects random spatial association between individual activation maps. More precisely, the null distribution represents the expected voxel-wise ALE values if the experiments considered converged at random. The null-distribution can be obtained using permutation-based procedures [151] or analytically [152].

Objectives

The overarching aim of this thesis

The purpose of this thesis is twofold. The first aim is to evaluate the efficacy of CBT for children and adolescents with OCD. The second aim is to uncover the neural underpinnings of inhibitory control in OCD, which is putatively linked to the symptomatology of the disorder and may be a mediator of treatment response. Individual aims of the papers included in this thesis are outlined here.

Paper I: Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents

The aim of Paper I was to assess beneficial and harmful effects of CBT for pediatric OCD in a systematic review and meta-analysis. To do this, we assessed the effect of CBT on a range of clinical outcomes and evaluated the risks of systematic errors (bias) and random errors (play-of-chance) of trials included in the review.

Paper II: Uhre et al. Reply to Storch et al.

The aim of Paper II was to address concerns raised over the methodology used in Paper I. We did this in a rebuttal letter-to-the-editor that also contained a revised risk-of-bias assessment.

Paper III: Inhibitory control in obsessive compulsive disorder: a systematic review and activation likelihood estimation meta-analysis of fMRI studies

The aim of Paper III was to evaluate the evidence from fMRI experiments for abnormal brain activation during inhibitory control in pediatric and adult OCD using coordinate-based ALE meta-analyses.

Paper IV: Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study

The aim of Paper IV was to investigate behavioral and neural correlates of response inhibition during performance of a stop signal task in a sample of unmedicated children and adolescents with OCD compared to healthy controls without past or current psychiatric disorders. Paper IV presents preliminary findings from data on participants enrolled in the TECTO trial prior to September 2021.

Methods

Ethical and legal permits and approvals

Paper IV was conducted in compliance with the Helsinki Declaration. The study was approved by the National Research Ethics Committee (H-18010607) and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark (VD-2018-263, l-suite 6502). Data was collected and stored in accordance with the Danish personal and health data regulations (the Danish Act on Processing of Personal Data, and the Danish Health Act, Section 43, Subsection 1). The TECTO trial is furthermore registered on ClinicalTrials.gov: NCT03595098 (July 23, 2018). No permits and approvals were required or obtained for Paper I, Paper II and Paper III.

Paper I: Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents

Pre-registration

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [153] and was conducted in accordance with the comprehensive guidelines specified in the Cochrane Handbook for Systematic Reviews of Interventions [version 5.1.0, available at https://handbook-5-1.cochrane.org/] [154]. We registered the protocol for our systematic review of CBT for pediatric OCD on PROSPERO on November 28, 2017 (registration ID: crd42017079118, link: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79118). The protocol contains additional information about many aspects of the review, and all deviations from the protocol were described in the review. The primary purpose of registering a protocol and making it publicly available is to minimize the risk of bias in the review process. Methodological choices should not depend on the data assessed in the review. In principle, any prior knowledge about potentially eligible studies could be problematic, as it may affect the definition of the research question, criteria for study eligibility or the choice of comparison groups and outcomes (see e.g., [122], section 2.1). We took a pragmatic approach of ensuring that our search strategy identified three trials that we a priori knew ought to be eligible, but otherwise tried to refrain from looking at potentially eligible trials prior to registering our protocol.

Search strategy

We searched for eligible trials on Cochrane's CENTRAL, MEDLINE, PsycINFO, EMBASE, LILACS, Science Citation Index Expanded on Web of Science, SSCI, and BIOSIS. This was complemented by a search for registered trials on ClinicalTrials.gov (www.ClinicalTrials.gov), Google Scholar (https://scholar.google.dk/), The Turning Research into Practice Database (https://www.tripdatabase.com/), European Medicines Agency (http://www.ema.europa.eu/ema/), United States Food and Drug Administration (www.fda.gov), China Food and Drug Administration (http://eng.sfda.gov.cn/WS03/CL0755/), Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatoryagency) and The WHO International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/). Finally, we manually checked reference lists of eligible trials and previous systematic reviews for unidentified potentially eligible trials. The search strategy for each database with the corresponding number of hits is provided in Appendix 1.

Criteria for inclusion

We used Cochrane's recommended PICO acronym (Patients, Interventions, Comparisons and Outcomes) to define our criteria for inclusion. Participants must have a primary ICD [155] or DSM [3] diagnosis of OCD. We accepted any intervention with CBT (as defined by trialists) irrespective of format (e.g., individual, group, or internet-based). Comparison groups were any intervention that was not CBT: 1) no intervention (e.g., wait-list or placebo), 2) treatment as usual (or similar terms), 3) pharmacological intervention (e.g., selective serotonin reuptake inhibitors [SSRI]), and 4) any other comparison intervention (e.g., relaxation therapy). We allowed co-interventions only if delivered similarly in both groups (e.g., CBT+SSRI versus SSRI).

Outcomes

We wanted our choice of outcomes to reflect the fact that pediatric OCD is associated with reduced quality of life and impairments of psychosocial functioning across a range of different dimensions (see e.g., [156, 157]). Additionally, because dropouts are common during CBT across a range of psychiatric disorders [158], we wanted to assess potential adverse effects associated with CBT. We therefore chose the following as primary outcomes: 1) OCD symptom severity (as assessed with Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS] [159]), 2) proportion of participants with serious adverse events (e.g., death, attempted suicide or life-threatening self-harm, hospitalization, persistent or significant loss of function, disability or incapacity), and 3) level of functioning measured on any validated scale (including both self-reported and parent-reported level of functioning). Secondary outcomes were: 1) quality of life measured on any

validated scale and 2) proportion of participants with non-serious adverse events (e.g., school drop-out, falling out with friends or family, or being thrown out of home). In addition, we included remission from OCD as an exploratory outcome. We defined remission as no longer meeting the DSM or ICD criteria for a diagnosis, or having a CY-BOCS score of below 12 in combination with a Clinical Global Impression – Severity (CGI-S) [160] score of below 3 [161].

Following the recommendations of Jakobsen, Wetterslev [162], we set the thresholds for significance of primary outcomes at $p \leq .025$. This corresponds to halfway between no adjustment and Bonferroni adjustment of the conventional threshold of $p \leq .05$. This pragmatic approach recognizes that the Bonferroni procedure would be too conservative because different health-related outcomes are interdependent, but still tries to account for problems with multiplicity due to multiple outcomes.

Risk of bias

We evaluated the risk of bias in included trials using Cochranes 2011 version of the risk-of-bias tool [154]. According to the guidelines, a trial is at an overall high risk of bias if it is rated at high risk of bias on one of seven bias risk domains: 1) allocation sequence generation, 2) allocation concealment, 3) blinding of participants and treatment providers, 4) blinding of outcome assessors, 5) incomplete outcome data, 6) selective outcome reporting, or 7) other bias (e.g., vested interest). The specific criteria we used to judge for each domain if a trial was at unclear risk of bias, low risk of bias, or high risk of bias are specified in the protocol. This is justified by evidence from meta-epidemiological studies of exaggerated effect estimates when one of these domains is at high risk of bias [163-171].

Data synthesis and meta-analyses

We followed state-of-the-art Cochrane methodology [154] and an eight-step procedure for synthesizing and meta-analyzing data [162]. We used Cochrane's review manager [172] to conduct the analyses. We contacted authors of included trials to obtain any information that we needed but which was not provided or sufficiently described in their publication (e.g., mean and standard deviation [SD] of outcomes or information related to bias risk domains).

Trial Sequential Analysis

Positive results from meta-analyses sometimes occur due to either systematic errors (bias) or random errors (play-of-chance), rather than because of a true effect of the intervention: these findings are therefore false positives (or type I errors). Similarly, negative (non-positive) results

may be caused by a lack of statistical power, rather than an absence of a true effect: such findings are therefore false negatives (or type II errors) [173]. On the other hand, if a meta-analysis is sufficiently powered, then a negative finding is more likely to reflect a true absence of an effect, in which case additional trials may not be needed. We performed Trial Sequential Analysis (TSA) [174] on all outcomes to control the risk of false-positive (type I error) and false negative (type II error) findings and estimate the information size (i.e., the cumulated sample size) required to detect or reject an anticipated minimum relevant difference (MIREDIF) between comparison groups [175]. Note, although the TSA takes into consideration the observed diversity across trials (i.e., between-trial variance due to heterogeneity in patient groups, interventions, or methods) in the calculation of the required information size for a pre-specified MIREDIF, it does not control for systematic errors (i.e., bias-related type I errors). In other words, results from the TSA are reliable only if bias in the included trials is negligible.

Sources of heterogeneity

In addition to TSA, we carried out several procedures to test the robustness of the findings in our meta-analyses. We investigated potential sources of heterogeneity present in the meta-analyses by visual inspection of the forest plots (i.e., by looking for any outlier results). For the primary outcomes (i.e., CY-BOCS, serious adverse events, and quality of life), we also investigated sources of heterogeneity by conducting planned and post-hoc subgroup analyses (see the protocol for additional information) when at least two trials or comparisons provided data. To do so, we used the formal test for subgroup interactions in Review Manager [172].

Sensitivity analyses

We performed sensitivity analyses to assess the potential impact of missing outcome data using the "best/worst" and "worst/best" data imputation procedure [162]. We also performed both fixed-effect meta-analyses and random-effects meta-analyses. Fixed-effect and random-effects meta-analyses makes different assumption about how weights are assigned to individual trials in the calculation of the combined effect [176]. In brief, the fixed-effect model assumes that all trials in the meta-analysis are measuring the same true effect, whereas the random-effects model allow that the true effect can vary between trials (e.g., the effect size may be greater in one trial than in another due to sample differences in the severity of the disorder, age, duration of intervention, etc.). In the fixed-effect model, the only source of error in the effect estimate is random error within trials. In the random-effects model, each trial is assumed to be a random sample from a distribution of effects, which introduces an additional source of error related to random error between trials. Consequently, with a sufficiently large sample size in the fixed-effect model, the error tends

toward zero regardless of whether this sample is confined to only a single trial or distributed across many. In contrast, even if every trial has an infinitely large sample in the random-effects model, uncertainty in the estimated effect size would remain present because these trials were assumed to be randomly drawn from a larger distribution of trials. Note, it is not always trivial to determine which model provides the best estimate of the combined effect. For instance, the random-effects model may provide inaccurate estimates of the between-trial variance when only few trials are included in the meta-analysis. On the other hand, the fixed-effect model may give inappropriately much weight to a single large-sample trial and effectively ignore smaller-sample trials in the meta-analysis. Because of this, we compared the results obtained with each model.

Certainty of the evidence

We evaluated the certainty of the evidence for each outcome with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) procedure [177]. This procedure starts by assuming the highest level of confidence in the estimate of an effect and then addresses each of five reasons to downgrade the confidence: 1) limitations in study design or execution (i.e., risk of bias), 2) inconsistency of results, 3) indirectness of evidence, 4) imprecision, 5) publication bias. Subsequently, three factors are considered which can provide reason to upgrade the confidence: 1) large magnitude of effect, 2) all plausible confounding variables would reduce the effect, or increase the effect if no effect was observed, 3) the presence of a dose-response gradient. We provided reasons for downgrading and upgrading the certainty of the evidence for each outcome in summary of findings tables. Because the reasons influencing each decision are additive, an outcome may be rated at the highest level of certainty even when some limitations are present.

Paper II: Uhre et al. Reply to Storch et al.

Risk of bias

In Paper I, we assessed the risk of bias in included trials using the 2011 version of Cochrane's risk of bias tool [154]. The tool is widely used, has transparent procedures, and has a firm basis in both empirical and theoretical evidence [178]. Nevertheless, it has several limitations. One drawback that is especially pertinent to Paper I is the fact that psychotherapeutic trials, which by necessity are unblinded, are judged to be at high risk of bias on the "blinding of participants and treatment providers" domain, and, in effect, are always assessed at an overall high risk of bias. A second limitation is that the tool only evaluates risks of bias at the trial level and thereby ignores the fact that different outcomes from the same trial can have different risks of bias (e.g., the amount of

missing data may differ across outcomes, or an outcome assessor may be blinded only for some outcomes). A revised Cochrane risk-of-bias tool (RoB-2) was released in 2019 to address previous limitations [179, 180]. We therefore used RoB-2 to reassess risks of bias for CY-BOCS end-ot-treatment scores of trials included in Study 1 on five domains: 1) randomization process, 2) deviations from intended intervention, 3) missing outcome data, 4) measurement of outcome, and 5) selection of reported result.

Paper III: Inhibitory control in obsessive compulsive disorder: a systematic review and activation likelihood estimation meta-analysis of fMRI studies

Search strategy

Following PRISMA guidelines [181] and best-practice recommendations for conducting coordinate-based meta-analysis [182], we searched for eligible articles on Web of Knowledge, ScienceDirect, Scopus and PubMed on March 19, 2021 (Table 1 presents the combination of search terms used). We conducted an additional search on the BrainMap database (Fox & Lancaster, 2002) for publications within the imaging modality of "fMRI", the diagnosis of "Obsessive Compulsive Disorder" and the behavioral domain of "action inhibition". Finally, we looked for additional articles in reference lists of included articles and relevant reviews. The search strategy for each database with the corresponding number of hits is provided in Appendix 2.

Articles included

By convention, "experiment" is used in coordinate-based ALE meta-analyses to denote the set of coordinates relating to a single contrast of interest. Because the terms study and experiment are

Table 1. An overview of the search terms used to search for eligible articles on Web of Knowledge, ScienceDirect, Scopus and PubMed.

		AND	
	OCD "obsessive compulsive disorder"	fMRI "functional magnetic resonance imaging"	Inhibition "Go/no-go" Stroop Flanker Interference Switching Stop Simon
OR			

sometimes used interchangeably, we instead used the term article to refer to a single published manuscript, which may contain one or multiple experiments. We only included articles that:

- Were peer-reviewed
- Were published in English
- Reported fMRI group coordinates of case-control (i.e., OCD versus healthy controls) differences in brain activation related to inhibitory control

The articles identified measures inhibitory control by comparing one of the contrasts stop, no-go, switch, mixed or incongruent with one of the contrasts failed-stop, go, odd-ball, repeat or congruent.

We excluded articles that:

- Did not report coordinates in either Montreal Neurological Institute (MNI) space or Talairach space
- Only presented region of interest results, if these regions were pre-defined (as opposed to functionally-defined based on a task main effect)
- Did not find any significant case-control differences for an eligible inhibitory control contrast.

Activation likelihood estimation

We performed coordinate-based ALE meta-analyses on the coordinates of case-control activation differences using the revised procedure [152, 183] in MATLAB (MathWorks). Coordinates that were reported in Talairach space were converted to MNI coordinates using the tal2icbm method [184]. Following best-practice guidelines, we only performed meta-analyses on contrasts based on activation foci from at least 17 experiments [183] and used a cluster-level familywise error-corrected threshold of $P<.05$ to assess the significance of convergence of activation foci [150, 152, 183, 185].

Contrasts of interest

Our contrasts of interest were: 1) OCD ≠ HC (convergence of activation foci for case-control differences irrespective of the direction of the difference), 2) OCD > HC (convergence of activation foci from experiments reporting hyperactivation in OCD), and 3) OCD < HC (convergence of activation foci from experiments reporting hypoactivation in OCD).

Because different subprocesses of inhibitory control have only partially overlapping neural underpinnings (see e.g., [81, 87, 89]), we repeated our analyses restricted to 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) to isolate these two aspects of inhibitory control. We furthermore performed sub-group analyses restricted to adult samples (defined as a sample mean age of >18 years).

Paper IV: Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study

Participants

Participants were recruited from the ongoing TECTO trial (Figure 5). Data from a total of 65 patients with OCD and 26 age- and sex-matched HCs, 8 through 17 years of age, was analyzed in the study. The included patients had a primary ICD-10 [155] diagnosis of OCD, did not have a comorbid diagnosis of schizophrenia, psychosis, mania, bipolar disorder, substance dependence syndrome, or pervasive developmental disorder (not including Asperger's syndrome), and had not received treatment with CBT, psychoeducation and relaxation therapy (PRT), antidepressants, or antipsychotics within the past six months. HCs were recruited from the same municipality through a random sample from the Danish Central Person Registry stratified to match patients with OCD on sex and age (within 3 months). The included HCs did not meet the ICD-10 criteria for any past or current psychiatric disorder. The evaluation of the presence (or absence) of psychiatric diagnoses in OCD and HC was based on combined data from the Danish patient journal system, school statements, questionnaires, and clinical interviews. All included participants had an estimated intelligence quotient of at least 70, were without any known neurological illness, and confirmed they had a history free of any severe head trauma. Additional details on the recruitment and assessment of participants are available in the TECTO trial protocol [186].

Clinical and demographic measures

Kiddie schedule for affective disorders and Schizophrenia – present and lifetime

We used the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL) [187] to assess OCD and comorbidities in patients and to ascertain absence of current and lifetime psychiatric disorders in HCs. K-SADS-PL is a semi-structured diagnostic interview that screens for the most prevalent DSM psychiatric disorders. We therefore made small adaptations to the interview to ensure that it completely covered the diagnostic criteria of corresponding ICD-10 diagnoses.

Children's Yale-Brown Obsessive Compulsive Scale

We assessed the severity of OCD symptoms in patients with CY-BOCS [159]. CY-BOCS is a semi-structured interview on which five items about obsessions and five items about compulsions are scored on a 0-4 Likert scale, giving a total score of 0-40, and two sub-scores of 0-20 representing the severity of obsessions and compulsions, respectively.

Clinical Global Impression – Severity

CGI-S [160] is a clinician-reported measure that asks the following question about the patient: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?". Seven options to choose among are provided on a Likert scale ranging from 1 (Not at all ill, no symptoms of the disorder present during the past seven days) to 7 (Among the most extremely ill patients – pathology drastically interferes in many life functions; patient may

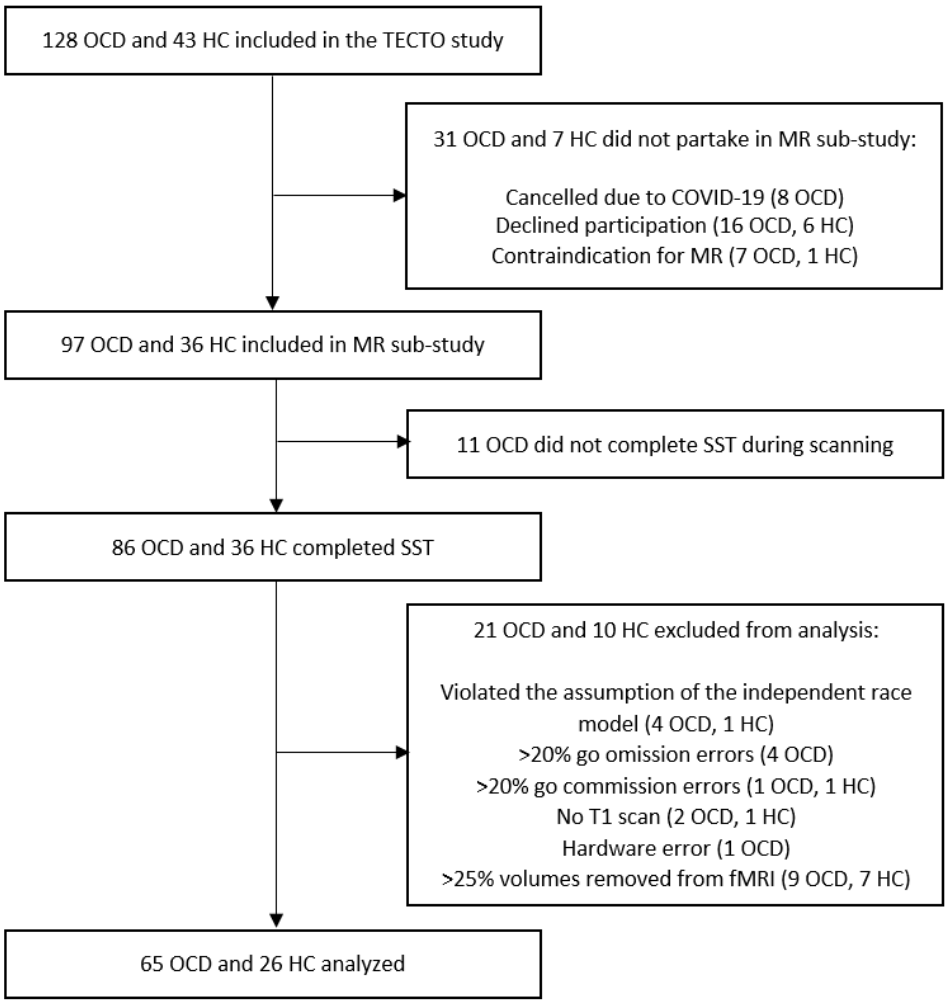

Figure 5. Participant flow diagram. Abbreviations: HC = healthy control, OCD = obsessive-compulsive disorder, SST = stop signal task.

be hospitalized). We rated CGI-S with respect to OCD symptoms (e.g., comorbid ADHD symptoms were not considered in the rating).

Children's Global Assessment Scale

We assessed global level of functioning in both patients with OCD and HCs with the Children's Global Assessment Scale (C-GAS) [188]. The scale is used to estimate global functioning during the past 2 weeks on a scale from 0 (needs constant supervision) to 100 (superior functioning in all areas).

Toronto Obsessive-Compulsive Scale

We used the Toronto Obsessive-Compulsive Scale (TOCS) [189] to measure self-reported and parent-reported clinical and sub-clinical obsessive-compulsive traits in both patients with OCD and HCs. The questionnaire consists of 21 items (e.g., "Needs to wash his/her hands") that are scored on a 7-point Likert scale ranging from -3 (far less often than average) to 3 (far more often than average), resulting in a total score between -63 and 63.

Edinburgh Handedness Inventory

We obtained a single continuous measure of hand preference with the Edinburgh Handedness Inventory (EHI) laterality quotient [190]. The laterality quotient has a value between -100 (left hand preference) and 100 (right hand preference) that is calculated based on self-reported hand preferences for 10 common activities (e.g., writing).

Purdue Pegboard Test

We used the Purdue Pegboard Test [191] to measure motor dexterity and speed. The Purdue Pegboard Test is a rectangular board with two rows of each 25 equidistant holes running parallel to the long sides of the board. Metal pegs are placed in concave cups and the participant is asked to place the pegs vertically in each hole on the side being tested as quickly as possible using only the corresponding hand(s). In a subsequent assembly task, the participant is asked to as quickly as possible assemble pins with washers and collars using both hands simultaneously. We recorded the time spent on left hand pin placement, right hand pin placement, both hand pin placement, and assembly.

Tanner Scale

We estimated the stage of puberty of each participant with the Tanner scale [192]. The scale consists of pictures showing five different stages of the physical development of the breasts (females), the testicular volume (males), the genitals and pubic hair (both sexes) and the participant identifies the picture best corresponding to their current stage of puberty.

Wechsler Intelligence Scales

We estimated the full-scale intelligence quotient with the age-appropriate version of Wechsler Intelligence Scales (either Wechsler Intelligence Scale for Children – Fifth edition [WISC-V] [193] or Wechsler Adult Intelligence Scale – Fourth edition [WAIS-IV] [194]).

The stop signal task

We used PsychoPy [version 1.84.2] [195] to code a modified version of the canonical stop signal task (SST) by Logan [196] optimized for fMRI. The task is comprised of three types of trials: go-trials, stop-trials, and null-trials (Figure 6). The major proportion of trials were go-trials, during which the participant was instructed to respond as quickly and accurately as possible to the direction of a vertical arrow. However, on infrequent stop-trials, a stop signal (red circle) was presented alongside the go-arrow with a variable stop signal delay (SSD), in which case the participant was instructed to attempt to refrain from responding. A linear staircase algorithm adjusted the SSD after each stop-trial (decreasing the SSD after failed stop-trials and increasing the SSD after successful stop-trials) to maintain a rate of successful response inhibition of approximately 50% for each participant. Our implementation of the SST followed recently published recommendations [197]. We included six commonly used behavioral outcomes:

- mean go-trial reaction time (RT)
- coefficient of variation in go-trial RT (i.e., the ratio of the SD to the mean, also known as the relative SD)
- mean correct go-trial RT
- stop signal reaction time (SSRT), estimated using the integration method with replacement of go-trial omission errors [197]
- go-trial omission error rate (i.e., proportion of go-trials with no response)
- go-trial commission error rate (i.e., proportion of go-trials with incorrect response)

Image acquisition

We used BOLD fMRI to map task-related regional brain changes during SST performance in a 3T Philips Achieva scanner with a 32-channel head coil at the Danish Research Centre for Magnetic Resonance. We acquired a total of 530 single-shot spin-echo echo planar images (EPI; FOV 120

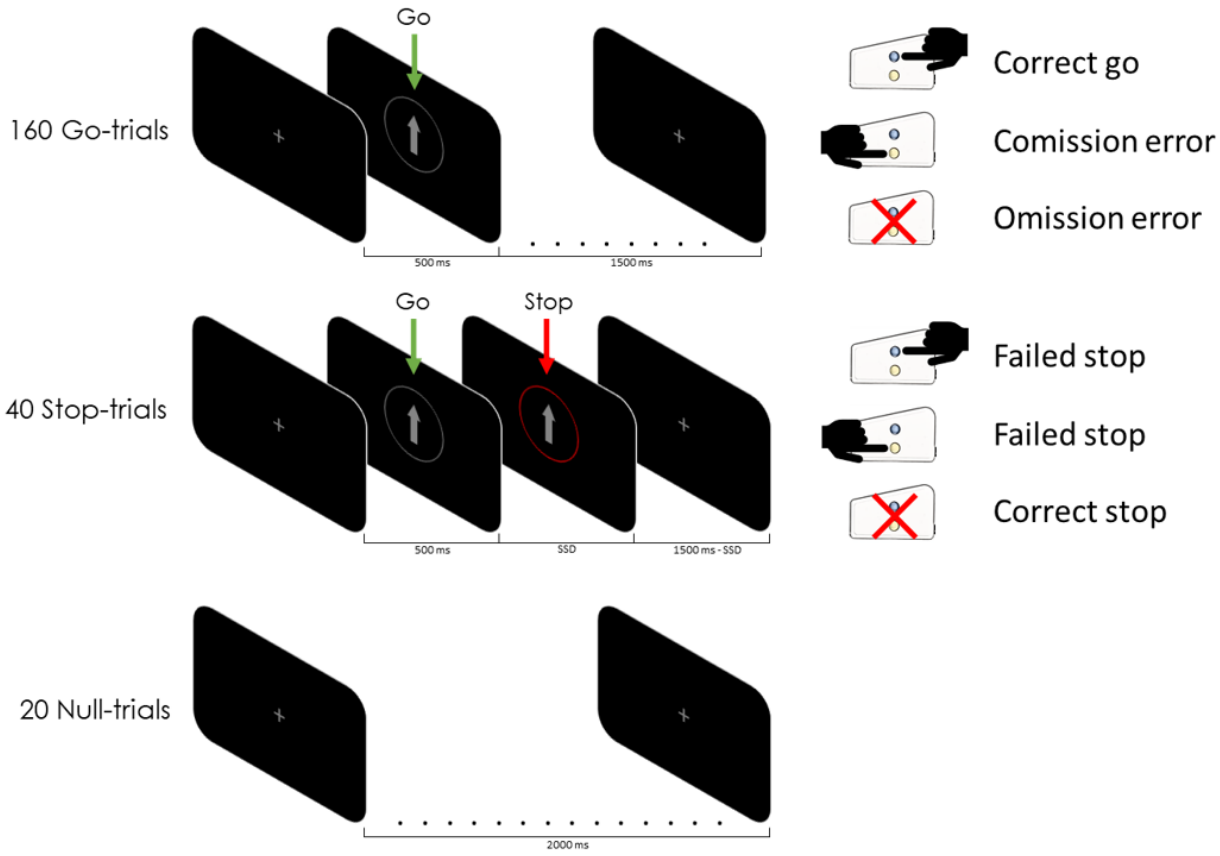

Figure 6. Trial outline for the stop signal task. The task consisted of go-trials (top) stop-trials (middle) and null-trials (bottom) presented in pseudo-random order with a jittered inter-trial interval. The behavioral outcomes for go-trials were correct go (correct button press), commission error (incorrect button press) and omission error (no button press). The behavioral outcomes for stop-trials were failed stop (any button press) and correct stop (no button press). On stop-trials, a circle surrounding the arrow changed color to red (the stop signal) after a variable SSD, in which case the task was to refrain from responding. Abbreviations: SSD = stop-signal delay.

mm, slice thickness 3.4 mm, slice gap 0.6 mm, TR 1700 ms, TE 30 ms, FA 71 degrees, 32 slices in the axial orientation, interleaved slice excitation in ascending order) and an additional five EPIs with opposing direction of phase encoding. Slices were angled along the anterior commissure-posterior commissure line and covered the entire cerebrum, partially cutting off the cerebellum when required. We also acquired a high-resolution T1-weighted image for each participant (voxel size approximately 1 mm isotropic, 245 sagittal slices, TR 6000 ms, TE 30 ms, FA 8 degrees). We used navigator-based prospective motion correction to improve image quality [198].

Pre-processing

We converted from PAR-REC file format to NifTi with the dcm2niix conversion tool [199] and pre-processed images using SPM12 software [version 7219] [200] implemented in MATLAB R2020a. We used the DARTEL toolbox [201] to create a study-specific template from segmented

T1-weighted images [202] and used the batch image calculator tool (https://robjellis.net/tools.html) to create a mask consisting of voxels that with at least 50% probability belong to tissue class 1 through 3. We slice-time corrected [203] EPI scans and realigned them to the mean EPI image of the time series to correct for head movements. We also performed a second realignment step to align images acquired with opposing direction of phase encoding (AP-direction/PA-direction), used these pairs to estimate the susceptibility-induced off-resonance field [204], and used the FSL TOPUP tool [205] to combine them into single images that were corrected for distortions. We did a final realignment to create mean replaced images of the unwarped images, which were co-registered to the masked anatomical T1-weighted image, spatially normalized to MNI-space using the subject-specific flow-fields, resampled to 2 mm isotropic voxels, and smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel.

First level modelling

We used a first-level general linear model (GLM) [206] to analyze BOLD fMRI data from each subject. We modelled correct go-trials, failed go-trials, correct stop-trials, and failed stop-trials separately for left-hand and right-hand responses at the arrow onset time as events convolved with the hemodynamic response function. We did not explicitly model null-trials (i.e., they constituted an implicit baseline). The analysis furthermore incorporated a high-pass filter with a 128 Hz cut-off frequency and included 24 regressors of no interest resulting from the Volterra expansion of motion parameters estimated from the rigid body realignment procedure [207]. We estimated the framewise displacement (FD) of each volume using the procedure described in [208] and flagged volumes whose FD exceeded 1 mm and the immediately following volume as outliers in the GLM analysis [209].

Whole-brain analyses

We entered the contrasts correct stop>correct go (successful inhibition) and failed stop>correct go (failed inhibition) into separate second-level models and compared the two groups in two-sample t-tests that included age and sex as covariates. We set the threshold for significance at a cluster-level familywise error-corrected (FWE) threshold of $p<.05$ using a cluster-forming threshold of $p<.001$ (uncorrected).

Region-of-interest analyses

We performed post-hoc functionally-defined region-of-interest (ROI) analyses. We first contrasted stop-trials with correct go-trials in the whole sample to determine the peak activation

coordinates of inhibition-related effects. We then used MarsBar [210] to extract the mean parameter estimates of activation within 10 mm spheres that were centered at each coordinate. We evaluated activation separately for successful inhibition (correct stop>correct go) and failed inhibition (failed stop>correct go).

Classical inference and Bayesian inference

We used both frequentist statistics with *p*-values and Bayesian hypothesis testing using Bayes factor (BF). Both the *p*-value and the BF are probabilities, but they signify different things [211] and the *p*-value is frequently misinterpreted [212]. The *p*-value denotes the conditional probability of observing an effect at least as extreme as the effect observed, on the condition that the null-hypothesis is true. Bayesian hypothesis testing uses Bayes' Theorem (Equation 1) and the Bayes Factor (BF) to compare competing hypothesis.

$$\underbrace{\frac{\mathrm{p}(\mathcal{H}_1|data)}{\mathrm{p}(\mathcal{H}_0|data)}}_{Posterior\ odds} = \underbrace{\frac{\mathrm{p}(\mathcal{H}_1)}{\mathrm{p}(\mathcal{H}_0)}}_{Prior\ odds} \times \underbrace{\frac{\mathrm{p}(data|\mathcal{H}_1)}{\mathrm{p}(data|\mathcal{H}_0)}}_{Bayes\ factor\ BF_{10}} \quad (1)$$

The general principle in Bayesian analysis is surprisingly straightforward (see e.g., [213-215]). Our goal is to evaluate whether OCD and HCs perform differently on a measure. We can formulate this as two rival hypotheses: the null-hypothesis ($\mathcal{H}_0$), which is the hypothesis that the performance of the groups is equal, and the alternative hypothesis ($\mathcal{H}_1$), which is the hypothesis that the performance of the groups is different. Before analysing any data, we specify our prior beliefs about how plausible we think these hypotheses are. This is done with probabilities, such that p($\mathcal{H}_1$) denotes the prior probability that $\mathcal{H}_1$ is true, and p($\mathcal{H}_0$) denotes the prior probability that $\mathcal{H}_0$ is true. Their ratio, or the *prior odds*, reflects the relative plausibility of the two hypotheses before making any observations; if we assign them equal probabilities of 0.5, then the relative plausibility is 1, reflecting our prior belief that $\mathcal{H}_0$ and $\mathcal{H}_1$ are equally likely. After observing data, we update our beliefs. Our new beliefs about the likelihood of $\mathcal{H}_1$ and $\mathcal{H}_0$ are reflected in the *posterior odds*, which denotes the relative plausibility of the hypotheses conditioned on the data observed. Since the posterior odds is a combination of our prior knowledge about the hypotheses (the prior odds) and what we learned from observing the data, the degree to which our beliefs are changed by observing the data is quantified by the BF. By convention, BF_{10} is used to denote the ratio of p(data|$\mathcal{H}_1$) relative to p(data|$\mathcal{H}_0$), whereas BF_{01} indicate the reverse, such that $BF_{10}=1/BF_{01}$. In

effect, a BF_{10} of 5 means that the data are five times more likely under $\mathcal{H}_1$ than $\mathcal{H}_0$, or, equivalently, that $\mathcal{H}_1$ predicts data five times better than $\mathcal{H}_0$ does.

We used Jeffreys' Amazing Statistical Program (JASP) [216] see also [1, 217] to quantify the relative predictive performance of $\mathcal{H}_0$ and $\mathcal{H}_1$ and the classification scheme provided by Lee and Wagenmakers [213] to describe the strength of the evidence (See Figure 7). Our use of Bayesian inference allowed us to quantify the evidence in favor of the null-hypothesis. This allowed us to differentiate between "absence of evidence of an effect" and "evidence of absence of an effect", which would not have been possible using frequentist statistics.

We evaluated the effects of group on demographic, clinical and SST performance variables using two-sided Bayesian independent-samples *t*-tests for normally distributed continuous data, Bayesian Mann-Whitney *U*-test for non-normally distributed continuous data (the Bayesian Mann-Whitney *U*-test is non-parametric and is robust to non-normality), and Bayesian contingency tables for dichotomous data. Normality was assessed with the Shapiro-Wilk test. For the Bayesian Mann-Whitney *U*-test, we increased the number of samples from 1.000 to 10.000, which in all cases achieved a potential scale reduction factor ($\hat{R}$) of <.1.05 [218]. We used Bayesian repeated-measures ANCOVAs with age and sex as covariates to compare the activation of ROIs in the OCD group and HC group during successful inhibition and failed inhibition. Here, we assessed for violation of the assumption of normality by visual inspection of the Q-Q plots. Finally, we used Bayesian Pearson Correlations to evaluate the evidence for correlations of SSRT with successful-inhibition-related activity within ROIs in both groups, and for correlations of OCD symptom severity with inhibition-related activity within ROIs in the OCD group.

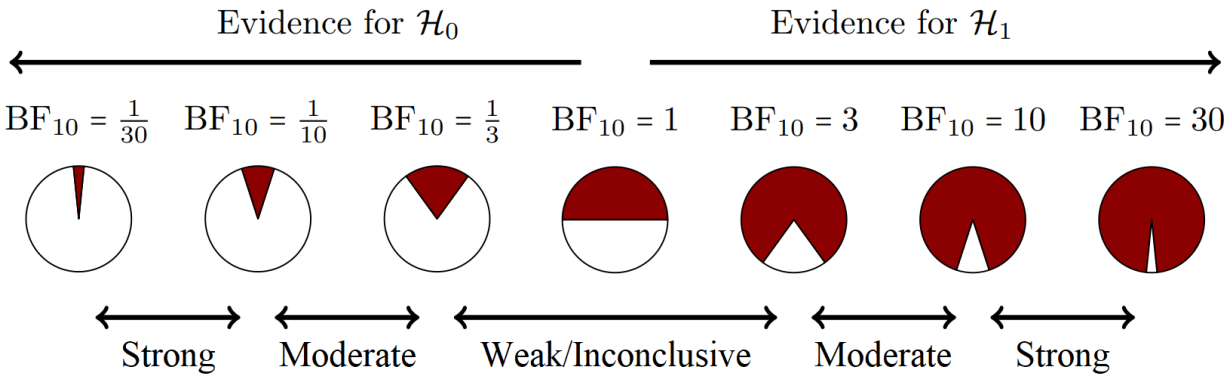

Figure 7. Graphical representation of the Bayes Factor classification table. The proportion of the circle colored red represent the support for $\mathcal{H}_1$ relative to $\mathcal{H}_0$. Figure adapted from van Doorn, van den Bergh [1], with permission under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Summary of results

Paper I: Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents

Trials included

The search is presented in the populated PRISMA flow diagram (Figure 8) and characteristics for the included trials found in the Supplementary Table S1 of the published paper [219]. We included

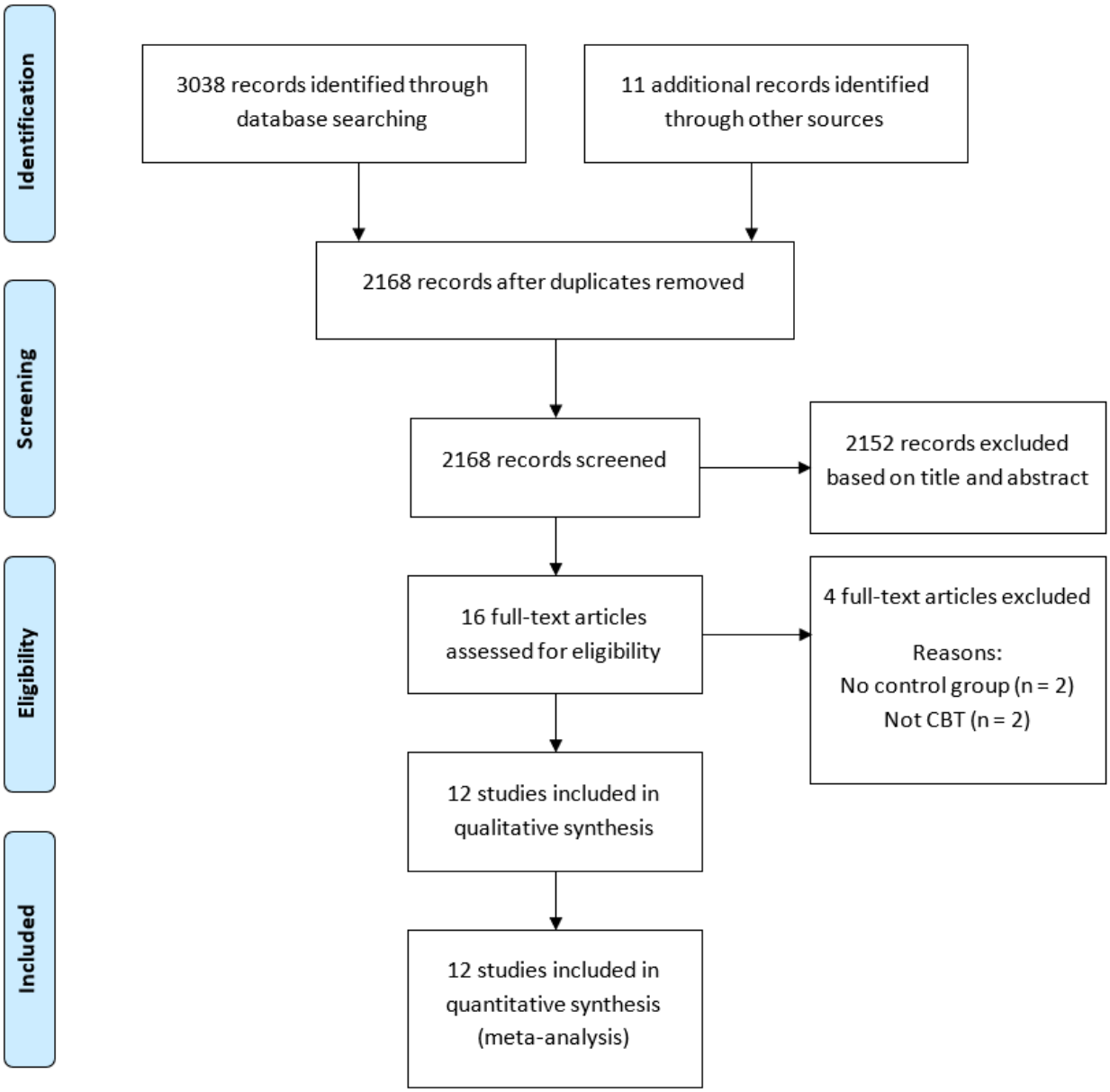

Figure 8. PRISMA flow diagram for the search and inclusion of trials in the meta-analysis. Abbreviations: CBT = cognitive-behavioral therapy. Figure from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

a total of twelve RCTs that investigated effects of CBT in 819 children and adolescents with OCD (age range of 4 to 18 years). Approximately 52% of the patients were females, and 65% had at least one comorbid disorder (most commonly an anxiety disorder). These proportions are comparable to estimated population rates [6]. In the trials, between 5 and 14 CBT sessions were delivered over 12 to 14 weeks. The identified trials allowed us to assess the effects of CBT in two comparisons:

1) CBT versus "no intervention" (waitlist, placebo psychotherapy, or no intervention with a co-intervention)

2) CBT versus SSRIs.

Note, only the forest plots for CY-BOCS are shown in the sections below. Forest plots for the remaining meta-analyses are available in the published paper and its supplementary materials.

Risk of bias

The assessment of risks of bias in included trials is presented in Figure 9. Unsurprisingly, considering the nature of psychotherapy, all trials were at high risk of bias on the "blinding of participants and treatment providers" domain. Consequently, all trials were evaluated to be at an overall high risk of bias. Only a single trial had low risk of bias on all other domains and might therefore be less affected by bias.

Sensitivity analyses

Detailed information pertaining to the results of TSA and results of subgroup analyses is available in the supplementary materials of the published paper. Table 2 and Table 3 shows the results from both random-effects and fixed-effects meta-analyses, which were similar for all outcomes. Results from missing outcome data imputations are shown for CBT versus "no intervention" in Table 4 and for CBT versus SSRIs in Table 5. These results are referenced in the following sections and demonstrate that some findings from the meta-analyses are sensitive to bias in missing outcome data.

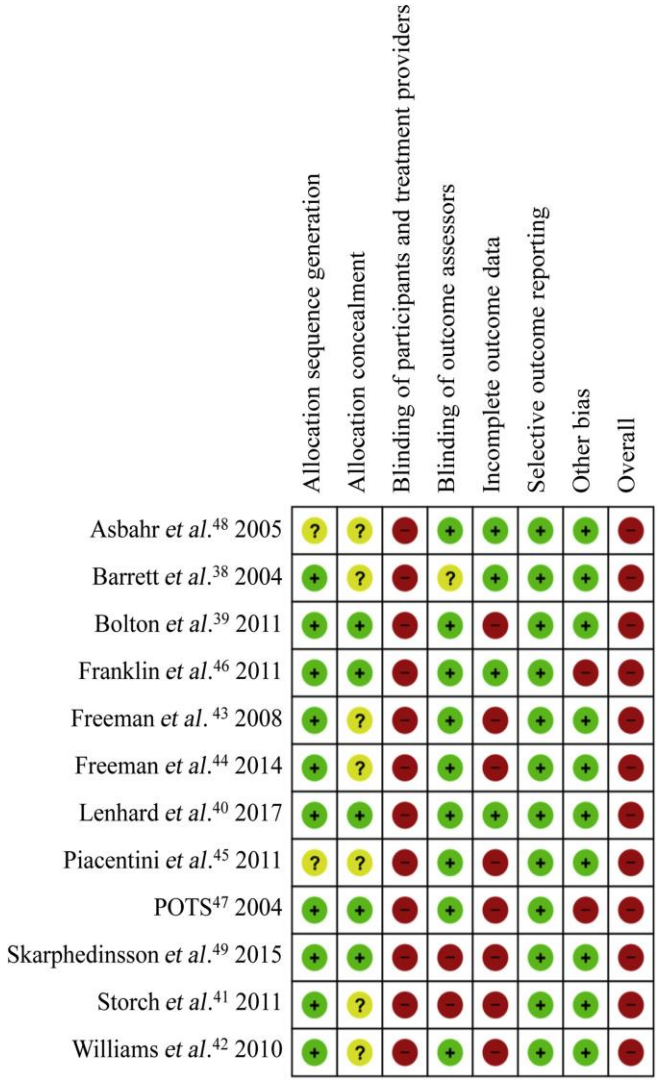

Figure 9. Risks of bias in trials included in the meta-analyses. Red (-) = high risk of bias, yellow (?) = unclear risk of bias, green (+) = low risk of bias. Note: the numbers next to authors corresponds to references in the published paper. Figure from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 2. Results from random-effects and fixed-effect meta-analysis for CBT versus 'no intervention'.

Outcome	N CBT	N control	Random-effects meta-analysis result	Fixed-effect meta-analysis result
OCD symptom severity (CY-BOCS)	400	301	MD=-8.51 (95% CI -10.84 to -6.18, p<.00001)	MD=-8.03 (95% CI -9.02 to -7.04, p<.00001)
Serious adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, patient-rated	160	90	SMD=-1.08 (95% CI -1.80 to -0.37, p =.003)	SMD=-0.90 (95% CI -1.19 to -0.62, p<.00001)
Level of functioning, parent-rated	223	154	SMD=-0.68 (95% CI -1.12 to -0.23, p =.003)	SMD=-0.56 (95% CI -0.78 to -0.34, p <.00001)
Quality of life	135	88	SMD=-0.39 (95% CI -0.77 to -0.02, p =.04)	SMD=-0.36 (95% CI -0.64 to -0.08, p=.01)
Adverse events	137	138	RR=1.06 (95% CI 0.93 to 1.22, p =.39)	RR=1.11 (95% CI 0.92 to 1.35, p =.28)
Lack of remission	295	185	RR=0.50 (95% CI 0.37 to 0.67, p<.00001)	RR=0.54 (95% CI 0.48 to 0.62, p<.00001)

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, MD = mean difference, RR = risk ratio, SMD = standardized mean difference. Table from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 3. Results from random-effects and fixed-effect meta-analysis for CBT versus SSRI.

Outcome	N CBT	N control	Random-effects meta-analysis result	Fixed-effect meta-analysis result
OCD symptom severity (CY-BOCS)	76	70	MD=-0.75 (95% CI -3.79 to 2.29, p =.63)	MD=-0.70 (95% CI -3.46 to 2.07, p =.62)
Serious adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, patient-rated	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, parent-rated	-	-	Meta-analysis not possible	Meta-analysis not possible
Quality of life	-	-	Meta-analysis not possible	Meta-analysis not possible
Adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Lack of remission	56	50	RR=0.85 (95% CI 0.66 to 1.09, p =.20)	RR=0.84 (95% CI 0.66 to 1.09, p =.19)

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, MD = mean difference, RR = risk ratio, SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitors. Table from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 4. Results from the missing outcome data imputation for CBT versus 'No Intervention'.

Outcome	Result from meta-analysis	Worst/best (2SD)	Worst/best (1SD)	Best/worst (2SD)	Best/worst (1SD)
OCD symptom severity (CY-BOCS)	MD=-8.51, 95% CI -10.84 to -6.18, p<.00001	MD=-6.11, 95% CI -8.91 to -3.30, p<.00001	MD=-7.28, 95% CI -9.81 to -4.74, p<.00001	MD=-10.59, 95% CI -13.00 to -8.18, p<.00001	MD=-9.70, 95% CI -11.96 to -7.43, p<.00001
Level of functioning (patient-rated)	SMD=-0.90, 95% CI -1.19 to -0.62, p<.00001	SMD=-0.52, 95% CI -0.79 to -0.25, p=.0001	SMD=-0.70, 95% CI -0.97 to -0.43, p<.00001	SMD=-1.14, 95% CI -1.42 to -0.86, p<.00001	SMD=-1.11, 95% CI -1.39 to -0.83, p<.00001
Level of functioning (parent-rated)	SMD=-0.68, 95% CI -1.12 to -0.23, p=.003	SMD=-0.35, 95% CI -0.81 to 0.12, p=.14	SMD=-0.50, 95% CI -0.98 to -0.02, p=.04	SMD=-0.89, 95% CI -1.32 to -0.47, p<.00001	SMD=-0.84, 95% CI -1.28 to -0.41, p=.0002
Quality of life	SMD=-0.39, 95% CI -0.77 to -0.02, p=.04	SMD=-0.11, 95% CI -0.47 to 0.26, p=.57	SMD=-0.26, 95% CI -0.65 to 0.13, p=.19	SMD=-0.60, 95% CI -0.92 to -0.27, p=.0003	SMD=-0.53, 95% CI -0.90 to -0.16, p=.005
Adverse events	RR=1.06, 95% CI 0.93 to 1.22, p=0.39	RR=1.14, 95% CI 1.01 to 1.28, p=.03		RR=0.92, 95% CI 0.47 to 1.79, p=.80	
Lack of remission	RR=0.50, 95% CI 0.37 to 0.67, p<.00001	RR=0.58, 95% CI 0.45 to 0.74, p<.00001		RR=0.41, 95% CI 0.30 to 0.55, p<.00001	

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, MD = mean difference, RR = risk ratio, SD = standard deviation, SMD = standardized mean difference. Table from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 5. Results from the missing outcome data imputation for CBT versus SSRI.

Outcome	Result from meta-analysis	Worst/best (2SD)	Worst/best (1SD)	Best/worst (2SD)	Best/worst (1SD)
OCD severity	MD=-0.75, 95% CI -3.79 to 2.29, p=.63	MD=1.94, 95% CI -5.32 to 9.21, p=.60	MD=0.91, 95% CI -4.96 to 6.79, p=.76	MD=-4.32, 95% CI -7.36 to -1.28, p=.005	MD=-2.70, 95% CI -5.41 to 0.01, p=.05
Lack of remission	RR=0.85, 95% CI 0.66 to 1.09, p=.20	RR=1.03, 95% CI 0.66 to 1.61, p=.89		RR=0.77, 95% CI 0.54 to 1.10, p=.15	

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, MD = mean difference, RR = risk ratio, SD = standard deviation, SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitors. Table from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Cognitive behavioral therapy versus "no intervention"

Primary outcomes

Ten trials assessed the effect of CBT on OCD symptom severity measured with CY-BOCS versus a control condition considered to be ineffective for OCD (waitlist, co-interventions or placebo). The meta-analysis showed a large effect of CBT over control conditions in reducing OCD symptom severity (mean difference [MD] = -8.51, 95% confidence interval [CI] = -10.84 to -6.18, $p < .00001$; See Figure 10). TSA indicated that this finding was unlikely to result from lack of statistical power or multiple testing, and missing outcome analyses indicated that the finding was unlikely to be explained by bias in missing outcome data. Subgroup analyses showed no evidence to suggest a difference in the effect of individual control conditions. However, conventional CBT was associated with a significantly larger reduction in OCD symptom severity than internet-delivered CBT.

Three trials monitored serious adverse events, and one serious adverse event was reported (attempted suicide by a patient with comorbid major depressive disorder).

Five trials evaluated the effect of CBT on a validated measure of level of functioning. The meta-analyses indicated that CBT compared with "no intervention" improved both patient-rated level of functioning (standardized MD [SMD] = -0.90, 95% CI = -1.19 to -0.62, $p < .00001$) and parent-rated level of functioning (SMD = -0.68, 95% CI = -1.12 to -0.23, $p < .003$). Subgroup analyses did not reveal any evidence of differences between control conditions for either patient-rated or parent-rated level of functioning but did indicate a larger effect of conventional CBT than internet-delivered CBT on patient-rated level of functioning. TSA and missing outcome analysis indicated that the effect on patient-reported level of functioning was unlikely to reflect problems with lack

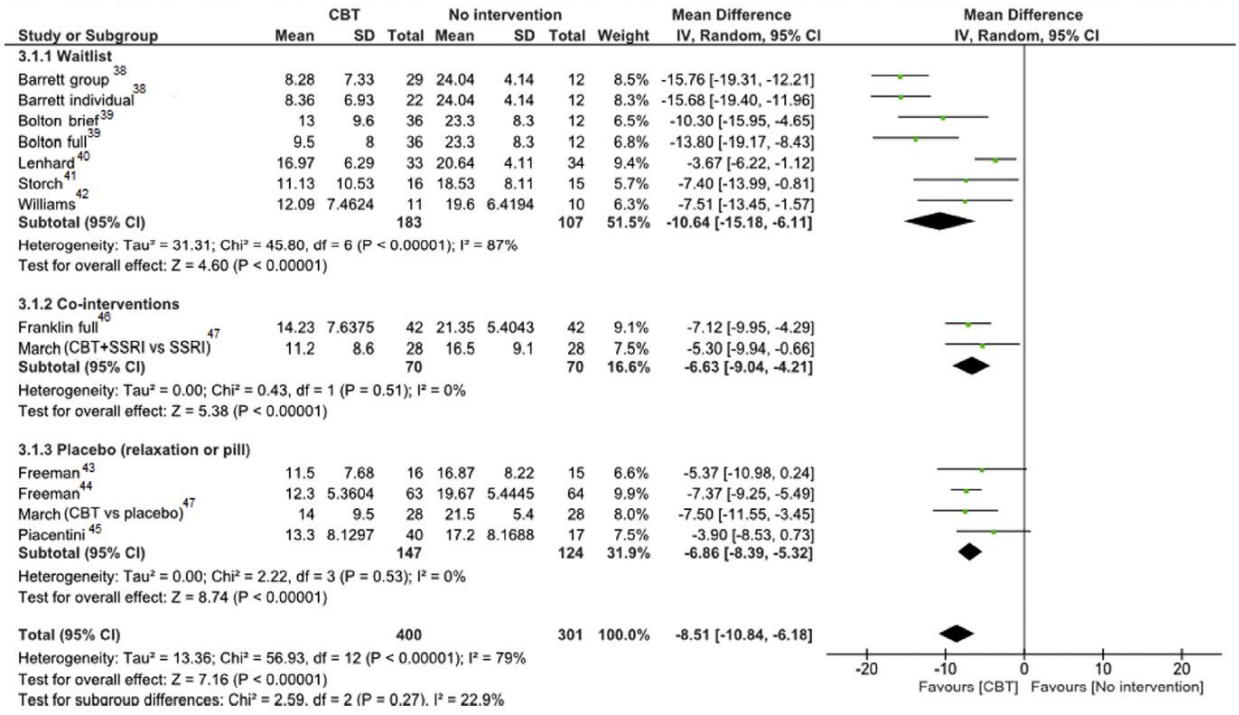

Figure 10. The effect of cognitive-behavioral therapy versus 'no intervention' on OCD symptom severity measured with the Children's Yale-Brown Obsessive-Compulsive Scale. Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitors. Note: the numbers next to authors corresponds to references in the published paper. Figure from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

of power, multiple testing, or missing outcome data. In contrast, TSA and missing outcome analysis showed that the finding of a beneficial effect of CBT over "no intervention" on parent-rated level of functioning is sensitive to bias in missing outcome data and may have been a spurious finding caused by lack of power or repeated testing.

Secondary outcomes

Two trials assessed the effect of CBT versus "no intervention" on measures of quality of life. The meta-analysis suggested a potential small beneficial effect of CBT over "no intervention" (SMD = -0.39, 95% CI = -0.88 to -0.02, p = .04), but this effect did not exceed our predefined threshold for significance.

Three trials monitored adverse events. 49 of 137 patients (35.8%) in CBT compared with 44 of 138 patients (31.9%) in "no intervention" experienced an adverse event during treatment. The meta-analysis did not suggest a difference in the risk of experiencing an adverse event for CBT versus "no intervention" (Risk ratio [RR] = 1.06, 95% CI = 0.93 to 1.22, p = 0.39). However, adverse events may have been related to high rates of concomitant pharmacotherapy using SSRIs

in the CBT and "no intervention" group (36.2% and 34.3%, respectively) and should therefore be interpreted with caution.

Exploratory outcome

Seven trials evaluated the risk of still having OCD after CBT versus "no intervention" using six different definitions of remission. The meta-analysis suggested that patients receiving CBT compared with patients receiving "no intervention" were less likely to still have OCD after treatment (RR = 0.50, 95% CI = 0.37 to 0.67, p < .00001). TSA and missing outcome analysis indicated that this result is not likely to be a random finding owing to insufficient statistical power, multiple testing, or bias in missing outcomes. Still, since no trial used a diagnostic interview to assess remission, and because remission was arbitrarily defined in a variety of ways, this finding may have questionable validity.

Cognitive behavioral therapy versus SSRIs

Three trials investigated the effect of CBT versus SSRIs on OCD symptom severity. The meta-analysis suggested similar efficacy of CBT and SSRIs in reducing OCD symptom severity (MD = -0.75, 95% CI = -3.79 to 2.29, p = .63) (See Figure 11). Importantly, TSA indicated that this finding is not likely to reflect random errors (i.e., it is unlikely that a clinically meaningful difference exists between the effect of CBT and SSRIs on OCD symptom severity). Analysis of missing outcome data furthermore indicated that the result is not likely to have been caused by bias in missing outcome data.

Data on other outcomes than OCD symptom severity were sparse. Two trials reported data on rates of remission, and the meta-analysis did not indicate any evidence of a difference between CBT and SSRIs in the risk of still having OCD after treatment (RR = 0.85, 95% CI = 0.66 to 1.09, p =

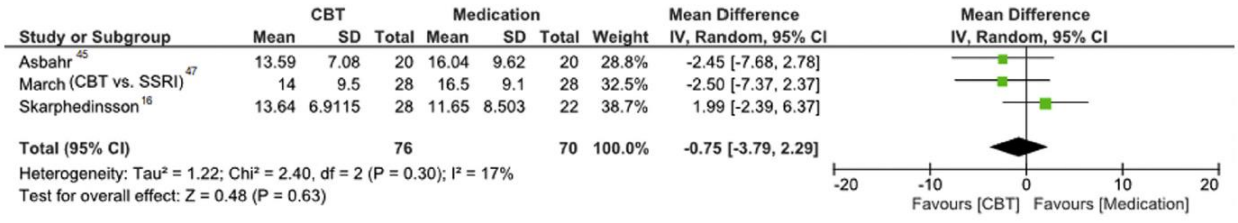

Figure 11. The effect of cognitive-behavioral therapy versus selective serotonin reuptake inhibitors on OCD symptom severity measured with the Children's Yale-Brown Obsessive-Compulsive Scale. Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitors. Note: the numbers next to authors corresponds to references in the published paper. Figure from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

0.20). However, TSA indicated that this finding may have been a spurious finding owing to lack of data.

Certainty of the evidence

The certainty of the evidence was evaluated to be low or very low for all outcomes (all reasons for downgrading are provided in the published paper in summary of findings tables). The certainty of all outcomes was downgraded due to high risk of bias in included trials. Importantly, even if the "blinding of participants and treatment providers" domain was removed from the evaluation, all but a single trial would remain at overall high risk of bias. The certainty of all outcomes, except CY-BOCS and remission for the CBT versus "no intervention" comparison, were furthermore downgraded due to the sample size being insufficient to calculate a precise effect estimate (as evident from the results of TSA).

Paper II: Uhre et al. Reply to Storch et al.

Risk of bias in CY-BOCS evaluated with RoB-2

Concerns have been raised over the methodology we used in Paper I, including our method for evaluating risk of bias in included trials [220]. Results from a new risk of bias assessment using the RoB-2 tool for the CY-BOCS outcome of the CBT versus 'no intervention' comparison in Paper I are presented in Figure 12 (additional information on the new evaluation are available

Study	Randomization process	Deviations from intended intervention	Missing outcome Data	Measurement of outcome	Selection of reported result	overall
Asbahr *et al.*, 2005[6]	?	?	+	+	?	?
Barrett *et al.*, 2004[7]	?	?	+	−	?	−
Bolton *et al.*, 2011[8]	+	−	?	+	+	−
Franklin *et al.*, 2011[9]	?	−	?	+	+	−
Freeman *et al.*, 2008[10]	?	+	+	+	+	?
Freeman *et al.*, 2014[11]	?	−	−	+	+	−
Lenhard *et al.*, 2017[12]	+	+	+	+	+	+
Piacentini *et al.*, 2011[13]	?	+	−	+	+	−
March, 2004[14]	+	+	+	+	+	+
Skarphedinsson *et al.*, 2015[15]	+	−	−	?	+	−
Storch *et al.*, 2011[16]	−	+	−	−	?	−
Williams *et al.*, 2010[17]	?	+	−	+	?	−

Figure 12. Risks of bias for the CY-BOCS outcome of the CBT versus 'no intervention' comparison in Paper I. (-) = high risk of bias, (?) = unclear risk of bias, (+) = low risk of bias. Note: the numbers next to authors corresponds to references in the published paper. Figure from Uhre et al. 2020, with permission under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

online at https://ctu.dk/media/13946/ITT-CYBOCS-EOT.xlsx). The results showed that CY-BOCS end-of-treatment results were at an overall low risk of bias in only 2 of the 12 trials included in Paper I. Notably, a cursory meta-analysis restricted to CY-BOCS scores from these two trials reduced the difference in favor of CBT versus "no intervention" from a mean difference for all trials of -8.51 (95% CI = -10.84 to -6.18, p<.00001) to a mean difference of -5.01(95% CI = -7.31 to -2.74, p<.00001).

Paper III: Inhibitory control in obsessive compulsive disorder: a systematic review and activation likelihood estimation meta-analysis of fMRI studies

Articles and samples included

The selection of articles included in the review is presented in the populated PRISMA flow diagram (Figure 13). A total of 21 articles reported significant differences in inhibition-related activity for OCD versus HC in a total of 35 experiments. Tables in the manuscript contain

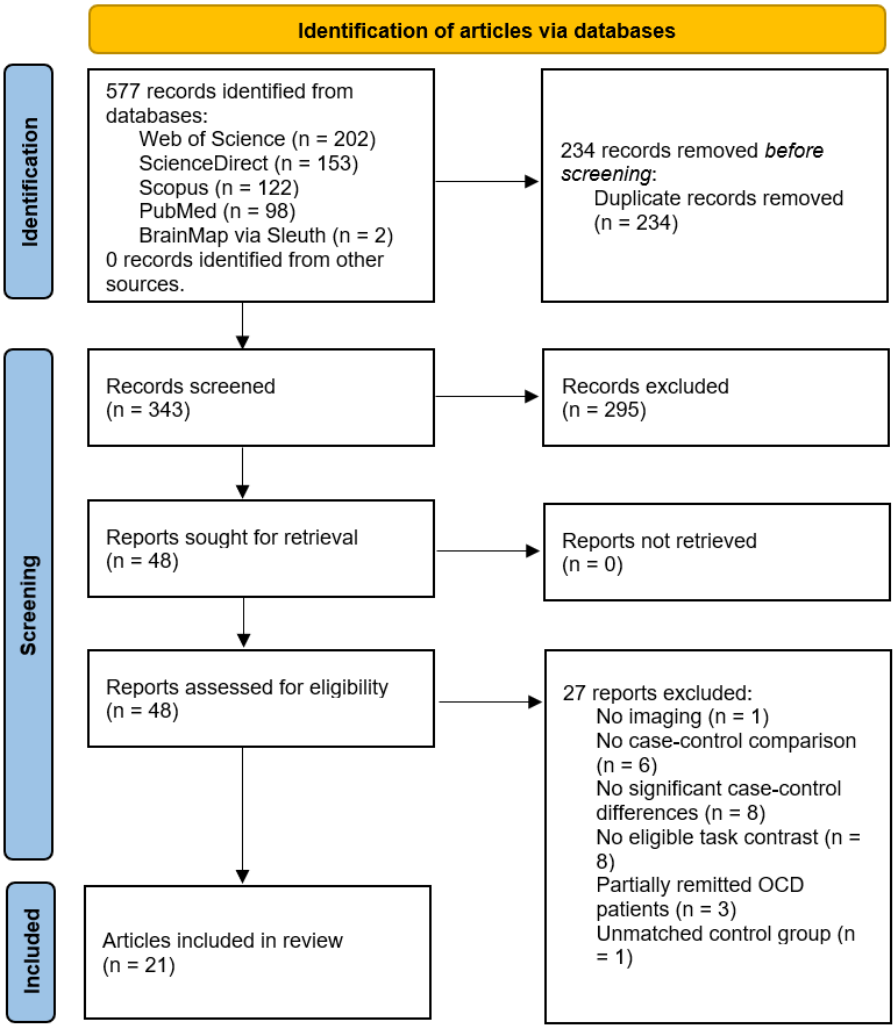

Figure 13. PRISMA flow diagram for the search and inclusion of articles in the review.

extensive details on the experiments and samples included. All articles determined the presence of OCD according to DSM criteria using a semi-structured clinical interview combined with the age-appropriate Yale-Brown Obsessive Compulsive Scale (Y-BOCS) or CY-BOCS. On average, the patients were moderately-to-severely ill (Figure 14, top panel). Only 22.8% were reported to be on medication at the time of scanning. The samples were mostly adolescents or young adults (mean age range of 13.5 to 39.1 years), and the OCD and HC groups were well-matched on both age (Figure 14, middle panel) and sex (Figure 14, bottom panel).

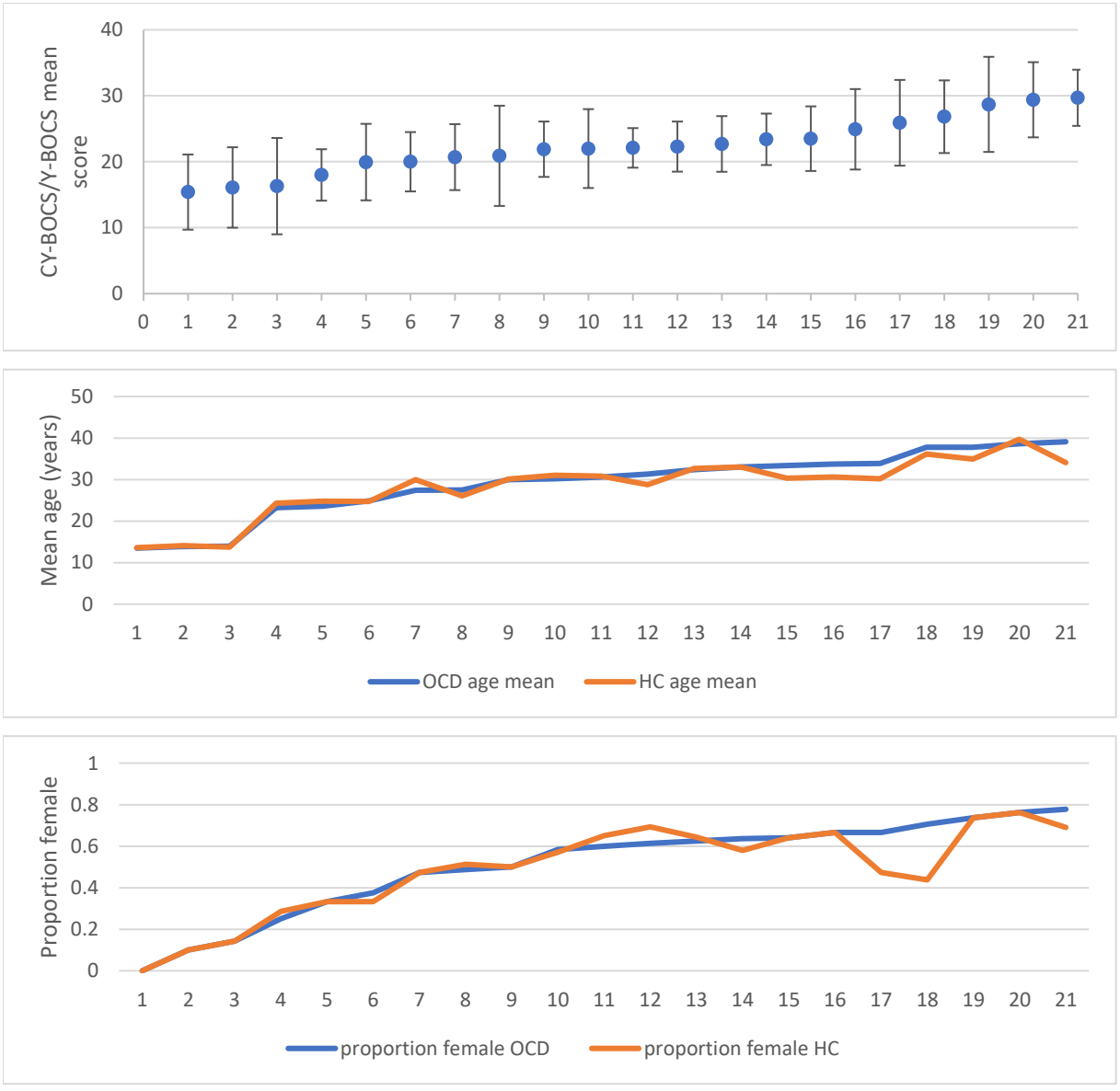

Figure 14. Information on the 21 included samples (x-axes). Patients with OCD had moderate-to-severe symptoms (top panel; range of mean score=15.4-29.7, weighted mean score=22.7 [SD=5.4], error bars indicate the SD). All 21 included samples were adequately matched on age (middle panel; OCD weighted mean age = 29.3 years [SD=7.8 years], HC weighted mean age = 28.5 years [SD=7.1 years]) and sex (bottom panel; OCD = 53.6% females, HC = 51.2% females. Abbreviations: CY-BOCS/Y-BOCS = (Children's) Yale-Brown Obsessive Compulsive Scale. Note, the numbers on the x-axes do not correspond to the same sample for different graphs.

Activation likelihood estimation

Primary analyses

We first assessed the spatial convergence of brain activation foci across all types of experiments. Thirty-five experiments reported foci of significant activation differences during inhibitory control. However, the spatial convergence of activation foci for the undirected (OCD ≠ HC) contrast was not significant ($P_{cFWE} = .116$). We did not assess the convergence of activation foci for hyperactivation in OCD (OCD > HC) because less than the required 17 experiments reported results for this contrast. Twenty experiments reported activation foci for hypoactivation in OCD (OCD < HC), but the convergence of these foci was not significant after family-wise error-correction ($P_{cFWE} = .073$).

Subgroup 1 - Cognitive inhibition experiments

We then assessed the spatial convergence of activation foci restricted to cognitive inhibition experiments. Twenty-five experiments reported foci of significant activation differences during cognitive inhibition. The ALE meta-analysis revealed significant convergence of activation foci for the undirected (OCD ≠ HC) contrast bilaterally in the dorsal anterior cingulate cortex (dACC, BA32) in a cluster that extended into the medial frontal gyrus (including BA6 and BA9; $P_{cFWE} = .04$; Figure 15). The size of this cluster was approximately 824 mm^3. We did not assess the convergence of activation foci for either hyperactivation (OCD > HC) or hypoactivation (OCD < HC), as both contrasts were based on data from less than the pre-specified minimum of 17 experiments.

Subgroup 2 – Response inhibition experiments

There were not sufficient data available to assess convergence of activation foci for any of the contrasts when restricting the analyses to response inhibition experiments.

Subgroup 3 – Experiments on adults

All the performed meta-analyses were repeated when excluding experiments from the three articles on pediatric samples. Excluding these experiments did not substantially alter the results.

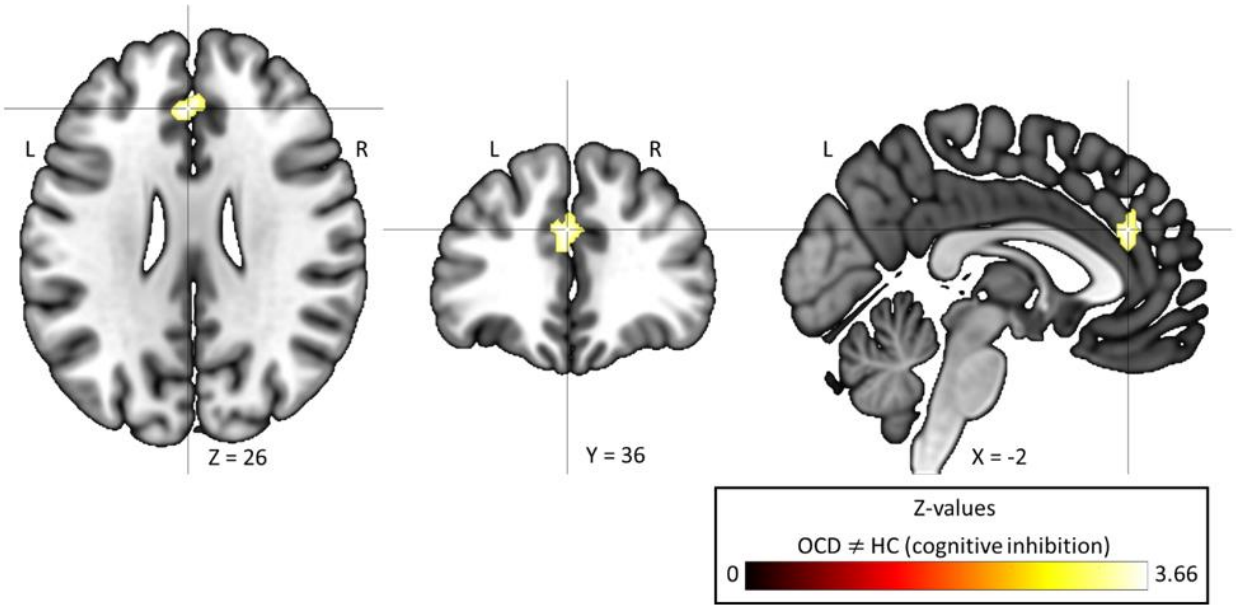

Figure 15. Results from the ALE meta-analysis of cognitive inhibition experiments shown in MNI space at a cluster-level familywise error-corrected threshold of p<.05. Abnormal activation during cognitive inhibition was observed in a cluster of voxels in the dorsal anterior cingulate cortex (BA32) extending into the medial frontal gyrus (BA6 and BA9).

Paper IV: Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study

Sample characteristics

Clinical and demographic characteristics of the sample are presented in Table 6. The OCD and HC group were adequately matched on potentially confounding demographic variables. The level of functioning in the OCD group was decisively worse than in the HC group (C-GAS BF_{10}=1.512e+18) and had more self-reported and parent-reported obsessive-compulsive traits (TOCS [child] BF_{10}=4.658e+6; TOCS [parent] BF_{10}=3.286e+11). The proportion of patients with OCD with at least one comorbid disorder was 53.8%.

Task performance

Measures of SST performance are presented in Figure 16. We found moderate evidence to suggest that the group performed comparably on all outcomes (Table 7). These results did not change when age and sex were included as covariates in the analyses, or when patients with a comorbid disorder were excluded from the analyses.

Whole-brain analyses of task-related brain activation

Our planned whole-brain analyses comparing successful inhibition (successful stop>correct go) and failed inhibition (failed stop>correct go) did not reveal any significant group differences in either direction (OCD>HC or OCD<HC). We also did not find any group differences when excluding patients with a comorbid disorder, or when comparing patients without a comorbid disorder to patients with at least one comorbid disorder. For these reasons, we proceeded with post-hoc ROI analyses.

Table 6. Demographic and clinical variables for the OCD group and HC group.

Variable	OCD group (n=65) Mean (SD) or n (%)	HC group (n=26) Mean (SD) or n (%)	BF_{10}
Demographic measures			
Female	33 (50.8%)	14 (53.8%)	0.291
Age in years	14.01 (2.66)	13.04 (2.25)	0.762
Tanner	3.06 (1.39)	2.88 (1.27)	0.281
EHI laterality quotient	61.29 (74.93)	80.62 (56.05)	0.432
Purdue Pegboard			
Right hand	14.44 (2.05)	14.68 (2.39)	0.268
Left hand	13.71 (1.59)	14.00 (2.25)	0.297
Both hands	11.77 (1.45)	11.52 (2.06)	0.293
Assembly	35.34 (7.56)	39.00 (10.17)	1.010
Full-scale IQ (WISC-V/WAIS-IV)	101.28 (12.79)	106.08 (14.48)	0.652
Parental education level in years	15.53 (2.12)	16.65 (2.12)	1.478
Clinical measures			
CY-BOCS total score	24.80 (4.96)		
Obsessions	12.43 (2.57)		
Compulsions	12.37 (2.79)		
CGI-S	4.51 (0.89)		
C-GAS	56.29 (9.29)	88.10 (9.29)	1.512e+18
TOCS (child)	7.54 (25.11)	-39.00 (22.25)	4.658e+6
TOCS (parent)	11.10 (19.87)	-39.75 (21.66)	3.286e+11
Total with at least one co-occuring disorder	35 (53.8%)		
Phobic anxiety disorders (F40)	1 (1.5%)		
Other anxiety disorders (F41)	2 (3.1%)		
Stress-related disorders (F43)	7 (10.8%)		
Eating disorders (F50)	3 (4.6%)		
Personality disorders (F61)	1 (1.5%)		
*Pervasive developmental disorders (F84)**	9 (13.8%)		
Other developmental disorders (F88)	3 (4.6%)		
Attention-deficit hyperactivity disorders (F90)	7 (10.8%)		
Conduct disorders (F91)	1 (1.5%)		
Emotional disorders with childhood onset (F93)	4 (6.2%)		
Tic disorders (F95)	7 (10.8%)		
Other behavioral and emotional disorders with childhood onset (F98)	1 (1.5%)		

Abbreviations: BF_{10} = Bayes Factor in favor of the alternative hypothesis (OCD different from HC) relative to the null hypothesis (OCD equal to HC), C-GAS = Children's Global Assessment Scale, CGI-S = Clinical Global Impression – Severity, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, EHI = Edinburgh Handedness Inventory, HC = healthy control, IQ = Intelligence Quotient, OCD = Obsessive-compulsive disorder, SD = standard deviation, TOCS = Toronto Obsessive-Compulsive Scale, WAIS-IV = Wechsler Adult Intelligence Scale version IV, WISC-V = Wechsler Intelligence Scale for Children version V. * = All cases were Asperger's syndrome (F84.5).

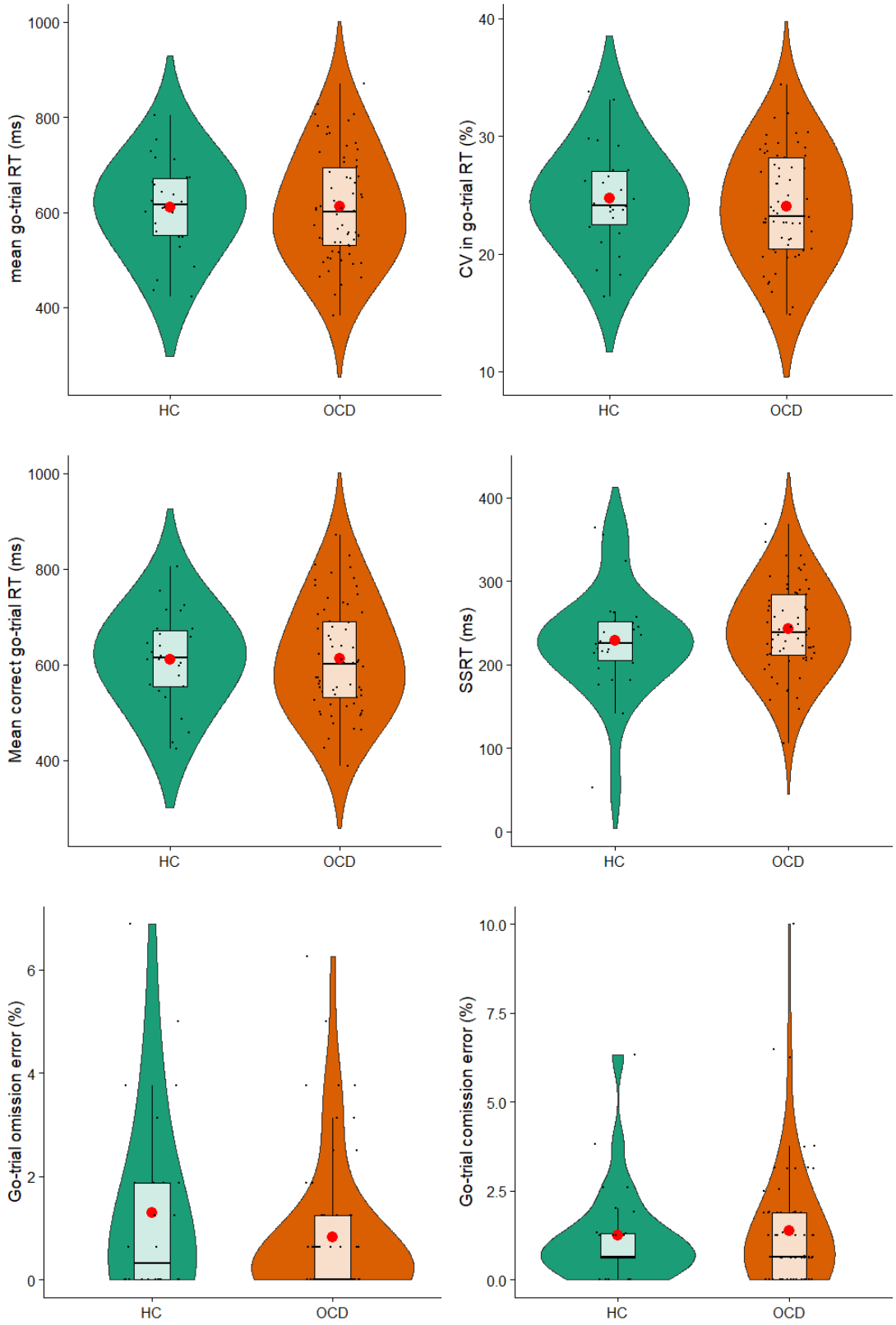

Figure 16. Mean estimates of stop signal task performance (red dots) for the OCD and HC group (the length of whiskers indicates 1.5 times the interquartile range and the black dots are the subject estimates). Abbreviations: CV = coefficient of variation (SD/mean), HC = healthy control, OCD = obsessive-compulsive disorder, RT = reaction time, SST = stop signal task.

Table 7. Stop signal task performance

	OCD Mean (SD) or %	HC Mean (SD) or %	BF_{10}
Mean go-trial RT (ms)	612 (111)	611 (96)	0.242
CV in go-trial RT	24.1%	24.7%	0.265
Mean correct go-trial RT (ms)	612 (111)	612 (96)	0.241
SSRT (ms)	243 (52)	229 (62)	0.323
Go-trial omission error	0.8%	1.3%	0.318
Go-trial commission error	1.4%	1.3%	0.242
SSD (ms)	338	349	0.259

Abbreviations: BF_{10} = Bayes Factor in favor of the alternative hypothesis (OCD different from HC) relative to the null hypothesis (OCD equal to HC), CV = coefficient of variation (SD/mean), HC = healthy control, OCD = obsessive-compulsive disorder, RT = reaction time, SD = standard deviation, SSD = stop-signal delay, SSRT = stop-signal reaction time.

Post-hoc region-of-interest analyses of task-related brain activation

Go-related and stop-related activation

We conducted a three-way ANOVA with condition (stop or correct go) and response side (left or right) as within-subject factors and group (OCD or HC) as a between-subject factor. The main (positive) effects of the correct go condition and stop condition are presented in Figure 17. We found go-related activation bilaterally in cerebellum, the occipital lobe, the anterior insula, the pre-SMA and the motor cortices and right-lateralized activation of thalamus, putamen, and pallidum. We found stop-related activation in what appeared to be the brain stem, bilaterally in the occipital lobe, the anterior insula, and the pre-SMA, and right-lateralized activation of the supramarginal gyrus, putamen, pallidum, and the IFG. These patterns of activation are consistent with findings from neuroimaging meta-analyses [88, 221] and other studies [84, 222].

Inhibition-related activation

The stop-related activation reflects not only processes initiated in relation to the stop-signal, but also processes initiated in related to the go-signal on the same trial (See Figure 6). To isolate the processes specifically related to inhibition, we therefore contrasted stop-related activity with go-related activity. This contrast revealed inhibition-related activation of the bilateral insula, the right IFG (pars opercularis) and the right pre-SMA (Figure 18, top). A Bayesian repeated-measures ANOVA of the ROI mean parameter estimates showed moderate evidence to suggest that the OCD and HC groups were similar in their activation of these regions during both failed inhibition (BF_{10}=0.331) and successful inhibition (BF_{10}=0.370; Figure 18, bottom).

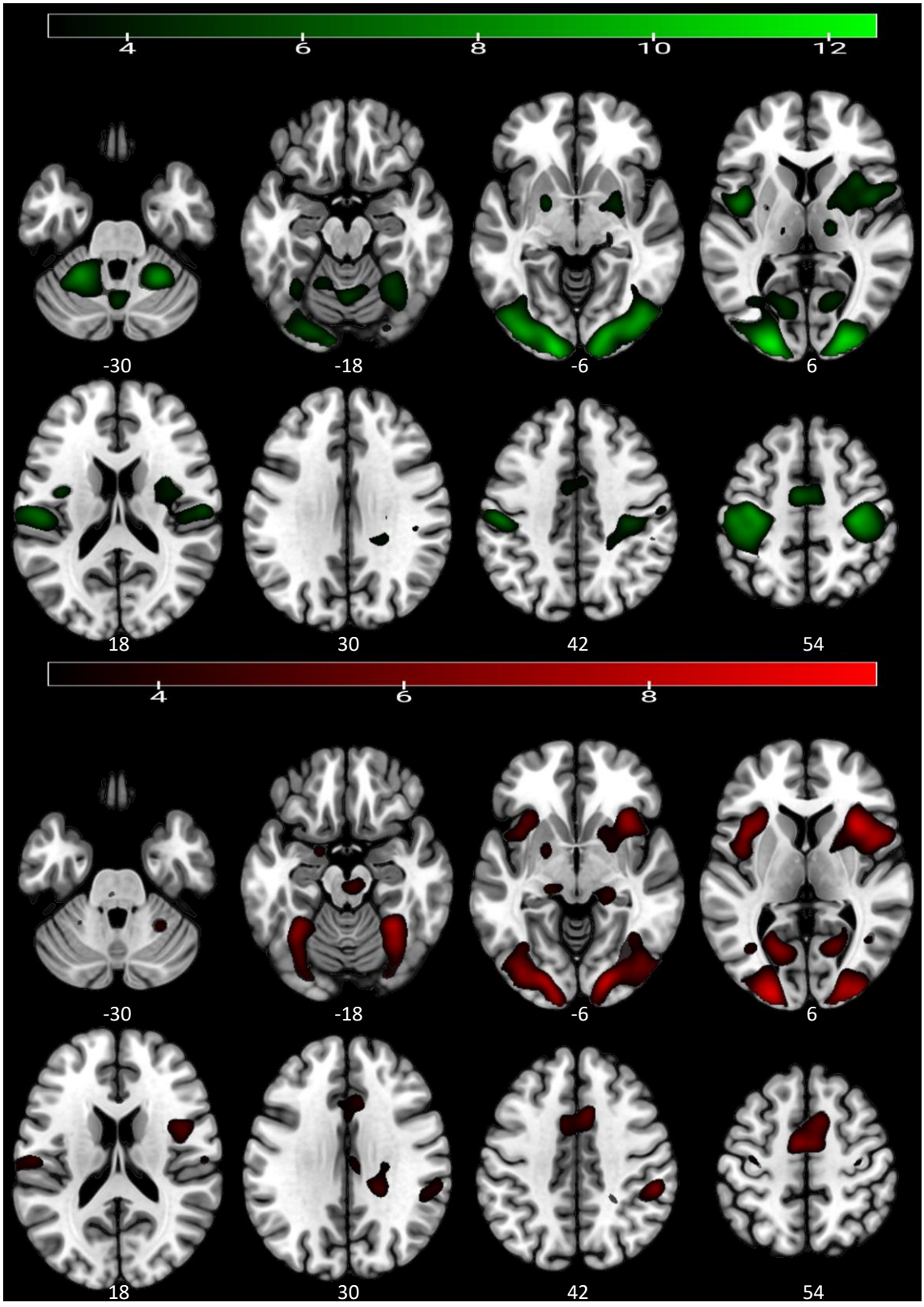

Figure 17. Task-related brain activation for go-trials (green; top) and stop-trials (red; bottom) shown in MNI space at p<.001 (uncorrected). The numbers below each horizontal slice indicate the z-coordinate and the images are in neurological format (right = right). The numbers on the color bars are T-values.

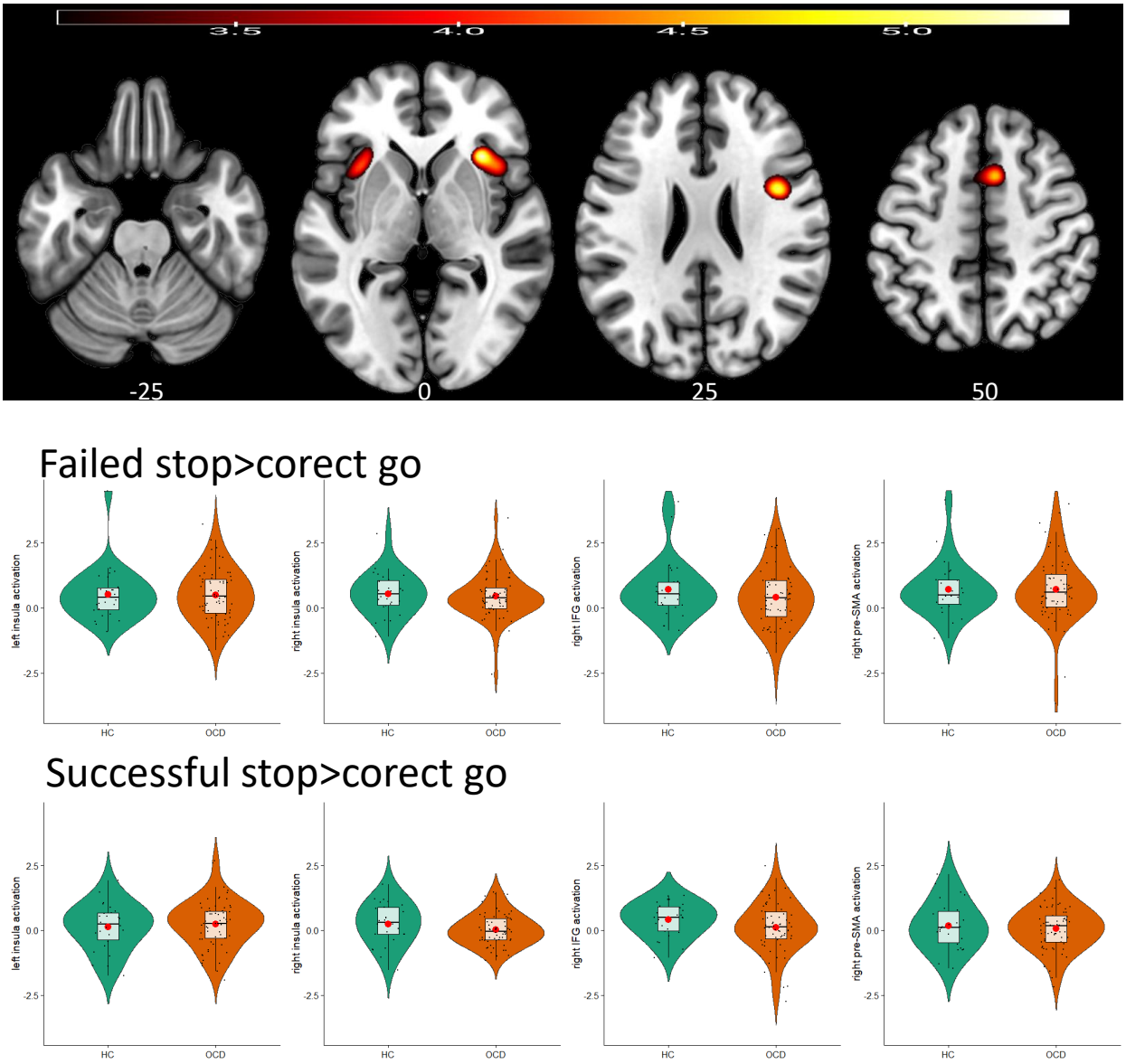

Figure 18. *Top*: task-related brain activation for stop-trials minus correct go-trials shown in MNI space at p<.001 (uncorrected). This contrast revealed inhibition-related activation of four ROIs: the bilateral insula, the right IFG and the right pre-SMA. The numbers below each horizontal slice indicate the z-coordinate and the images are in neurological format (right = right). The numbers on the color bar are T-values. *Bottom*: mean parameter estimates (red dots) of each ROI for the OCD group and HC group during failed inhibition (failed stop > correct go) and successful inhibition (successful stop > correct go). The length of whiskers indicates 1.5 times the interquartile range and the black dots are the subject estimates. Abbreviations: HC = healthy control, IFG = inferior frontal gyrus, OCD = obsessive-compulsive disorder, ROI = region-of-interest, pre-SMA = pre-supplementary motor area.

Brain-behavior correlations

The opercular part of the right IFG together with the right pre-SMA likely play a crucial role in the initial generation of the stop-command during inhibition (see e.g., [86]). We therefore performed Bayesian correlation analyses aimed at exploring whether activation of these regions was predictive of the SSRT in both groups and symptom severity in the OCD group. During successful inhibition, we found moderate evidence against a correlation between both ROIs and SSRT when considering the OCD and HC groups together (right IFG r=-.026, BF_{10}=0.135; right pre-SMA r=.036, BF_{10}=0.139). Restricting the analysis to either group did not alter the result. Interestingly, we found moderate evidence to suggest that the activation of the right IFG was predictive of OCD symptom severity during successful inhibition (r=.329, BF_{10}=5.166), but not during failed inhibition (r=.158, BF_{10}=0.335). Moderate evidence suggested that activation of the right pre-SMA was not predictive of OCD symptom severity during successful inhibition (r=.075, BF_{10}=0.184), whereas the data was inconclusive during failed inhibition (r=.186, BF_{10}=0.454).

Discussion

Contributions to our understanding of the treatment of pediatric OCD with CBT

Paper I assessed beneficial and harmful effects of CBT for pediatric OCD in a systematic review and meta-analysis. Overall, our findings indicated that CBT may be an effective treatment for pediatric OCD and have comparable effects to treatment with SSRIs. However, the certainty of the evidence was low for all evaluated outcomes, and many of the included trials were assessed at high risk of bias on multiple domains. Moreover, the review highlighted an overall lack of data on clinical outcomes of CBT beyond OCD symptom severity.

Our review updated and extended previous findings from systematic reviews of CBT for pediatric OCD. To our knowledge, the effects of CBT on adverse events, level of functioning, and quality of life had not previously been evaluated. Furthermore, our use of TSA and rigorous sensitivity analyses allowed us to assess for each outcome whether clinically meaningful and statistically significant differences between comparison groups, or absence thereof, were likely to be a random finding due to lack of statistical power, repeated testing of accumulating data, or missing outcome data bias.

The overall lack of data on beneficial and harmful effects of CBT for pediatric OCD beyond effects on OCD symptom severity is surprising when considering the substantial impairments of social, familial and occupational functioning and reduced quality of life associated with OCD [156, 157] (see section “The burden of OCD” in the introduction). Stated bluntly, significant reductions in OCD symptom severity may be important to a patient only insofar they lead to improved function or quality of life, and that may not always be the case. For example, a review of patients with depressive and anxiety disorders that enter clinical trials showed that, for patients with OCD, only 14% of the variation in quality of life was explained by symptom severity [14]. In a similar vein, the lack of data on potential differences between CBT and SSRIs in harmful effects (i.e., adverse events) is valuable information that is missing for clinicians and patients choosing between CBT and SSRIs, especially considering their comparable beneficial effects.

Based on the data review in Paper I, we make four tangible recommendations for future trials of CBT for pediatric OCD. We believe that adherence to these recommendations will significantly improve the state of the evidence. First, we suggest trialists use the Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) guidelines [223, 224] when planning their trial and report their findings in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [225]. The SPIRIT and CONSORT guidelines are checklists aimed at ensuring transparency and completeness in the development of trial protocols and reporting of trial outcomes. Second, we suggest that future trials define remission from OCD as no longer meeting the DSM or ICD criteria for a diagnosis and assess remission with a standardized and blinded diagnostic interview (as opposed to defining remission as having an end-of-treatment CY-BOCS score below an arbitrary cut-off, although see [226]). Third, in accordance with Cochrane's recommendations for systematic reviews [122], we encourage trialists to also measure the effect of treatment on patient-reported outcomes, such as level of functioning or quality of life. Fourth, we recommend that future trialists systematically assess and report adverse events for all compared groups (see e.g., [227]).

Contributions to our understanding of inhibitory control in OCD

Paper III assessed the evidence for abnormal inhibition-related brain activation in 394 patients with OCD compared with 410 HCs using coordinate-based ALE meta-analyses. Contrary to previous meta-analytic findings of widespread functional abnormalities [91-93], we found minimal evidence of convergence of activation foci for differences between the OCD and HC groups. Only the ALE meta-analysis for the undirected (OCD ≠ HC) contrast restricted to cognitive inhibition experiments revealed convergence of activation foci; this convergence occurred in the bilateral dACC. The dACC have strong connections with both the dorsal PFC and the striatum and therefore may play a key role in modulating activity of the CSTC circuits affected in OCD [228]. Moreover, the finding of abnormal activation substantiates similar previous findings [91-93] and suggest that the role of dACC may be especially prominent during cognitive inhibition.

Still, it seems implausible that dACC should be the only region abnormally activated in OCD during inhibitory control. Our ALE meta-analyses adhered to recent recommendations of not assessing convergence of activation foci based on less than 17 experiments and using a cluster-level familywise error-corrected threshold of $p<.05$ [183]. This stringent approach minimizes the risk that findings are largely driven by one dominant experiment and the risk of spurious findings. In effect, positive findings are very likely to reflect true abnormalities in activation during inhibitory control. However, the cost of this is that true and potentially important case-control activation differences are also more likely to be missed.

In sum, our review emphasizes the dACC as a potential key locus of abnormal activation during cognitive inhibition in OCD and highlight a need for experiments that are tailored to assess how different facets of inhibitory control are affected in OCD (see e.g., [87, 89, 229-231]).

In Paper IV, we assessed the neural and behavioral correlates of response inhibition in a large sample of unmedicated children and adolescents with OCD and age- and sex-matched HCs. Whole-brain analyses did not reveal any group differences during inhibition in the SST. Post-hoc analyses demonstrated that participants activated distinct go-related and stop-related networks during task performance in line with results from existing data on brain activation during SST performance [84, 88, 221, 222]. Contrasting stop-related activity with go-related activity revealed inhibition-related activation of the bilateral insula, the right IFG and the right pre-SMA. ROI analyses that putatively had increased sensitivity to potential group differences in these inhibition-relevant regions showed moderate evidence against an effect of group during both successful inhibition and failed inhibition, thereby corroborating our findings from the whole-brain analyses. These findings were further substantiated by moderate evidence to suggest that the groups performed comparably on all behavioral outcomes.

Several previous small-sample studies on pediatric OCD have found aberrant activation during inhibitory control [232-237]. In contrast, other studies, including two recent large-sample studies, have not found any significant group difference in inhibition-related brain activation [238-240]. However, these studies included both unmedicated patients and patients receiving pharmacological treatment for OCD, most often with SSRIs. Beneficial effects of SSRIs on motor functions [241], SSRT [242] or the activation of networks involved in inhibitory control [243-245] might have attenuated any existing group differences in these studies. Our findings of intact inhibitory control in unmedicated children and adolescents with OCD therefore extend previous null-findings by excluding medication use as an explanation for the absence of significant group differences in brain activation in our study.

The notable differences between pediatric-onset OCD and adult-onset OCD and the fact that pediatric OCD is associated with more subtle neurocognitive deficits suggest that pediatric OCD may represent a neurodevelopmental subtype of the disorder (see section “Differences between childhood-onset and adult-onset OCD” in the introduction). During late childhood and adolescence, there is increased plasticity in multiple regions that are critical to inhibitory control and other executive functions, including medial frontal, frontoparietal and motor regions, and

abnormal maturation of these regions may occur during this time [246, 247]. Our findings of comparable brain activation during inhibitory control in pediatric OCD and HCs are consistent with this perspective. At the same time, our exploratory correlational analyses indicated that activation of the right IFG during successful inhibition scales positively with OCD symptom severity, suggesting a functional role of this region in OCD symptomatology despite normal activation at the group level. Right IFG activation during successful inhibition may be associated with treatment response in pediatric OCD [236], and this is something that the TECTO neuroimaging sub-study can explore in the future.

Methodological considerations

Controlling the type I and type II error rates with TSA

Traditional meta-analysis using unadjusted confidence intervals and thresholds for significance do not account for the fact that updating a meta-analysis with results from newly conducted trials result in repeated testing on the same set of data. With a threshold for significance of $p<.05$ for the meta-analytic result, the actual risk of type I errors resulting from repeated testing is between 10% and 30% [175, 248]. Also, traditional meta-analyses do not differentiate between null-findings that most likely reflect an absence of a clinically meaningful difference between the compared interventions and null-findings that are spurious and may change as more data accumulates [249]. In Paper I, we used TSA to calculate the required information size and controlled the type I and type II error rates for the meta-analytic results. However, TSA is not a fool-proof procedure and has its own set of assumptions that may not always be met [250, 251]. In particular, results from TSA may sometimes be too conservative [174]. Still, in Paper I, TSA strengthened our meta-analytic findings in several cases by demonstrating that they were unlikely to have been caused by multiple testing.

Assessing risk of bias

In Paper II [252] we addressed concerns that have been raised over some aspects of the methodology employed in Paper I [220], including our use of the 2011 version of Cochrane's risk of bias tool [154]. Paper II therefore included a re-evaluation of the risk of bias for the OCD symptom severity outcome of the CBT versus 'no intervention' comparison using RoB-2 [180]. This re-assessment corroborated our initial evaluation of risk of bias in showing low risk of bias for the outcome in only 2 of 12 trials (16.7%). Moreover, our concerns regarding the risk of bias in CBT trials mirror those from a recent review of CBT with ERP for OCD in which only 8 of 36 trials (22.2%) were evaluated to be at an overall low risk of bias [253]. This review additionally

demonstrated suspected researcher allegiance (i.e., indications that trialists expected or considered one treatment to be superior to the other) in 28 of 36 trials (77.8%), and restricting the meta-analysis to trials without suspected researcher allegiance almost completely abolished the estimated effect of CBT with ERP versus control conditions [253]. Similarly, restricting the meta-analysis to low risk of bias trials in Paper II reduced the estimated effect of CBT on OCD symptom severity. This suggests that, although a high risk of bias may not always result in reflated effect estimates, the effect estimates obtained in Paper I may be exaggerated.

Assessing the evidence for convergence of activation foci for case-control differences using an undirected contrast

In Paper III, we used an undirected contrast (OCD ≠ HC) to assess the evidence for convergence of activation foci during inhibitory control irrespective of the direction of difference. To our knowledge, no prior meta-analyses of inhibitory control in OCD have done this. It has previously been suggested that an inverted U-shaped relationship between inhibition-related activity and task load is shifted in OCD relative to HCs, such that patients with OCD may show hyperactivation of inhibition-related brain areas when task demands are low, but hyperactivation in the same areas when task demands are high [81, 254]. Indeed, one study that used a combined stopping and shifting task have found hypoactivation during stopping, but hyperactivation during shifting, of the thalamus, the bilateral caudate, and the right precuneus, in patients with OCD relative to carefully matched HCs [231]. This implies that deficits in inhibitory control may not be attributable to global under- or over-activation of specific CSTC circuits (including the patterns of activation alluded to in Figure 2). From this perspective, opposing activations of the same region during different inhibitory control tasks should not be viewed as inconsistent findings, but rather a key characteristic of CSTC dysfunction. The undirected contrast is suitable for identifying such regions.

The stop-signal task

The SST has been widely used across a multitude of disciplines and is a valuable tool for studying response inhibition in clinical populations [197, 255]. However, a potential limitation in some previous versions of the SST, such as the version used in the landmark Adolescent Brain Cognitive Development (ABCD) study, is the simultaneous offset of the go-stimulus with the presentation of the stop-signal on stop-trials, resulting in shorter go-stimulus durations on stop-trials than on go-trials [256] (see also [257, 258]). This violates the assumed context independence of the go process and stop process in the estimation of the SSRT [196]. In Paper IV, we attempted to alleviate this problem by allowing the go-stimulus to remain onscreen during the presentation of

the stop-signal on stop-trials. Nevertheless, full context independence is likely difficult to attain, and new computational models that accommodate context dependence in the estimation of SSRT are currently being developed [259]. We tried to conduct Paper IV in accordance with consensus guidelines for the SST [197] and hope that this have led to reasonably precise estimates of SSRT.

MRI of children and adolescents

Major efforts were made in Paper IV to reduce discomfort and improve the quality of imaging data. Prior to the day of scan, participants engaged in a narrated virtual-reality (VR) environment designed specifically for this study to closely mimic the actual experience of being MR-scanned. On the day of scanning, participants furthermore underwent a practice session in a full-scale mock replica of the MR scanner. VR and mock MRI may reduce discomfort and head movement during MR-scanning [260, 261]. The acquisition of T1-weighed images utilized a navigator-based prospective motion correction to improve image quality [198]. The processing of imaging data included a study-specific template to improve the fMRI sensitivity [262] and several motion-scrubbing procedures to lessen the effect of head motion during image acquisition on image quality. Despite these efforts, some participants were unable to complete the full scanning protocol due to discomfort, and some of the acquired imaging data were discarded due to poor quality.

Conclusions and future perspectives

The overarching goals of this thesis were to evaluate the efficacy of CBT for pediatric OCD and to investigate the neural underpinnings of inhibitory control in OCD. Results from Paper I and Paper II indicated that CBT may be an effective treatment for pediatric OCD, but they also showed high risks of bias in many existing trials. Results from Paper III highlighted the bilateral dACC as a key functional locus of abnormal inhibitory control, and Paper IV suggested a role of the right IFG in pediatric OCD symptomatology. However, significant contributions of the studies are also reflected in what we did not find. Paper I showed a paucity of data on the effects of CBT on patient-reported outcomes, such as functioning, quality of life, or adverse events, and highlighted marked inconsistencies in how remission have been defined in the included RCTs. This information is useful in the planning of future trials. In Paper III, the lack of spatial convergence of activation foci of reported hypo- or hyperactivation in OCD during inhibitory control may suggest that different experimental setups have diverse and non-trivial effects on the activation of CSTC circuits that previous studies have found to be affected. Paper IV showed an absence of hypo- and hyperactivation of task-relevant ROIs in pediatric OCD during inhibitory control, which could suggest that any neural abnormalities present in pediatric OCD are likely not confined to abnormal activation of individual regions.

Clearly, the preliminary findings of the TECTO neuroimaging sub-study presented in this thesis leaves much to be desired. In the future, neuroimaging data collected at follow-up (after FCBT or FPRT, or after 16 weeks in the HC group) will be analyzed. This data may elucidate the neural underpinnings of successful treatment with ERP. We should also investigate abnormalities in pediatric OCD at the brain network level [138]. In this regard, we may use tractography to analyze the collected diffusion-weighted imaging data and delineate any abnormalities in structural connectivity and relate them to measures of functional connectivity from task-based fMRI. Additionally, the approach employed in Paper IV of regressing out the effect of age in the analyses does not take advantage of the wide age range included in the study. For example, it is possible that developmental variability in the different age groups outweigh the between-group variability in the neural and behavioral correlates of inhibitory control [254]. Although our follow-up period is short (16 weeks), our longitudinal design does provide some opportunities to investigate developmental and age-related effects.

Factor analyses indicate that the heterogeneous symptom profile in OCD can be adequately summarized in four to five symptom dimensions [263, 264]. These symptom dimensions have been differentially linked to different clusters of comorbidities [265-267], and may even have distinct neural correlates [268, 269]. This suggests that specific OCD subtypes may share etiological factors with different comorbidities and potentially have overlapping pathophysiology. A promising approach to gain a better understanding of obsessive-compulsive behaviors may therefore be to identify transdiagnostic dimensions, such as compulsivity [57, 270], and link them to well-defined psychological and neurobiological mechanisms [61, 64]. This may turn the lack of diagnostic specificity in OCD into an advantage, since this approach can reveal treatment targets that are present not only in subgroups of patients with OCD, but also in other psychiatric populations. In this regard, integration of data from the different sub-studies in TECTO may help to get a more differentiated understanding of the protean and heterogeneous disorder that OCD is, and perhaps eventually even push the treatment of pediatric OCD toward one that is more personalized.

Appendices

Appendix 1 – database search terms employed in Paper I

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2018, Issue 11) (463 hits)

#1 MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees

#2 OCD or obsess* or compuls*

#3 #1 or #2

#4 MeSH descriptor: [Behavior Therapy] explode all trees

#5 ((cognitive or behaviour*) and therap*) or CBT or BT or CT

#6 #4 or #5

#7 MeSH descriptor: [Child] explode all trees

#8 MeSH descriptor: [Infant] explode all trees

#9 Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*

#10 #7 or #8 or #9

#11 #3 and #6 and #10

MEDLINE Ovid (1946 to November 2018) (361 hits)

1. exp Obsessive-Compulsive Disorder/

2. (OCD or obsess* or compuls*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. exp Behavior Therapy/

5. (((cognitive or behaviour*) and therap*) or CBT or BT or CT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. 4 or 5

7. exp Child/

8. exp Infant/

9. (Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 7 or 8 or 9
11. 3 and 6 and 10
12. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. 11 and 12

Embase Ovid (1974 to November 2018) (922 hits)

1. exp obsessive compulsive disorder/
2. (OCD or obsess* or compuls*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. 1 or 2
4. exp behavior therapy/
5. (((cognitive or behaviour*) and therap*) or CBT or BT or CT).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. 4 or 5
7. child/
8. infant/
9. (Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
10. 7 or 8 or 9
11. 3 and 6 and 10
12. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
13. 11 and 12

Science Citation Index Expanded (1900 to November 2018), Conference Proceedings Citation Index – Science (1990 to November 2018), Social Sciences Citation Index (1956 to November 2018) and Conference Proceedings Citation Index- Social Science & Humanities (1990 to November 2018) (Web of Science) (543 hits)

#6 #5 AND #4

#5 TS=(random* or blind* or placebo* or meta-analys*)

#4 #3 AND #2 AND #1

#3 TS=(Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*)

#2 TS=(((cognitive or behaviour*) and therap*) or CBT or BT or CT)

#1 TS=(OCD or obsess* or compuls*)

BIOSIS (1969 to November 2018; Web of Science) (130 hits)

#6 #5 AND #4

#5 TS=(random* or blind* or placebo* or meta-analys*)

#4 #3 AND #2 AND #1

#3 TS=(Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*)

#2 TS=(((cognitive or behaviour*) and therap*) or CBT or BT or CT)

#1 TS=(OCD or obsess* or compuls*)

LILACS (Bireme; 1982 to November 2018) (58 hits)

(OCD or obsess$ or compuls$) [Words] and (((cognitive or behaviour$) and therap$) or CBT or BT or CT) [Words] and (Child$ or Paediatric$ or Pediatric$ or Juvenile$ or Youth$ or Young$ or Adolesc$ or Teenage$ or kid$ or infant$ or toddler$ or boy$ or girl$) [Words]

PsycINFO (EBSCOhost; 1806 to July 2017) (542 hits)

S13 S11 AND S12

S12 TX (random* or blind* or placebo* or meta-analys*)

S11 S3 AND S6 AND S10

S10 S7 OR S8 OR S9

S9 TX (Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*)

S8 MA infant

S7 MA child

S6 S4 OR S5

S5 TX (((cognitive or behaviour*) and therap*) or CBT or BT or CT)

S4 MA Behavior Therapy

S3 S1 OR S2

S2 TX (OCD or obsess* or compuls*)

S1 MA Obsessive-Compulsive Disorder

Appendix 2 – database search terms employed in Paper III

Web of Science (195 hits, 09-07-2020) (202 hits, 19-03-2021)
4 #3 AND #2 AND #1
3 TS=(inhibition OR "go/no-go" OR stroop OR flanker OR interference OR switching OR stop OR simon)
2 TS=(fmri OR "functional magnetic resonance imaging")
1 TS=(ocd OR "obsessive compulsive disorder")

ScienceDirect (140 hits, 09-07-2020) (153 hits, 19-03-2021)
("ocd" OR "obsessive compulsive disorder") AND ("fmri" OR "functional magnetic resonance imaging") AND ("inhibition" OR "go/no-go" OR "flanker" OR "stroop OR "interference" OR "switch" OR "stop" OR "switching" OR "simon")

Scopus (116 hits, 09-07-2020) (122 hits, 19-03-2021)
(TITLE-ABS-KEY (ocd OR "obsessive compulsive disorder") AND TITLE-ABS-KEY (fmri OR "functional magnetic resonance imaging") AND TITLE-ABS-KEY (inhibition OR "go/no-go" OR stroop OR flanker OR interference OR switching OR stop OR simon))

PubMed (92 hits, 09-07-2020) (98 hits, 19-03-2021)
(ocd AND fmri AND inhibition [Title/Abstract]) OR
(ocd AND fmri AND “go/no-go” [Title/Abstract]) OR
(ocd AND fmri AND stroop [Title/Abstract]) OR
(ocd AND fmri AND flanker [Title/Abstract]) OR
(ocd AND fmri AND interference [Title/Abstract]) OR
(ocd AND fmri AND switch* [Title/Abstract]) OR
(ocd AND fmri AND stop [Title/Abstract]) OR
(ocd AND fmri AND simon [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND inhibition [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND “go/no-go” [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND stroop [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND flanker [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND interference [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND switch* [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND stop [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND simon [Title/Abstract]) OR

(”obsessive compulsive disorder” AND fmri AND inhibition [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND “go/no-go” [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND stroop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND flanker [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND interference [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND switch* [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND stop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND simon [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND inhibition [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND “go/no-go” [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND stroop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND flanker [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND interference [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND switch* [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND stop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND simon [Title/Abstract])

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Paper I

Systematic review and meta-analysis: cognitive-behavioral therapy for obsessive-compulsive disorder in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 2020; 59(1), 64-77.

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REVIEW

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Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents

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Ms. C.F. Uhre and Mr. V.F. Uhre are co-first authors of this article.

Objective: To assess benefits and harms of cognitive-behavioral therapy (CBT) versus no intervention or versus other interventions for pediatric obsessive-compulsive disorder (OCD).

Method: We searched for randomized clinical trials of CBT for pediatric OCD. Primary outcomes were OCD severity, serious adverse events, and level of functioning. Secondary outcomes were quality of life and adverse events. Remission from OCD was included as an exploratory outcome. We assessed risk of bias and evaluated the certainty of the evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: Nine trials (N = 645) were included comparing CBT with no intervention and 3 trials (N = 146) comparing CBT with selective serotonin reuptake inhibitors (SSRIs). Compared with no intervention, CBT decreased OCD severity (mean difference [MD] = −8.51, 95% CI = −10.84 to −6.18, $p < .00001$, low certainty), improved level of functioning (patient-rated: standardized MD [SMD] = −0.90, 95% CI = −1.19 to −0.62, $p < .00001$, very low certainty; parent-rated: SMD = −0.68, 95% CI = −1.12 to −0.23, $p = .003$, very low certainty), had similar proportions of participants with adverse events (risk ratio = 1.06, 95% CI = 0.93−1.22, $p = .39$, GRADE: low certainty), and was associated with reduced risk of still having OCD (risk ratio = 0.50, 95% CI = 0.37−0.67, $p < .00001$, very low certainty). We had insufficient data to assess the effect of CBT versus no intervention on serious adverse events and quality of life. Compared with SSRIs, CBT led to similar decreases in OCD severity (MD = −0.75, 95% CI = −3.79 to 2.29, $p = .63$, GRADE: very low certainty), and was associated with similar risk of still having OCD (risk ratio = 0.85, 95% CI = 0.66−1.09, $p = .20$, very low certainty). We had insufficient data to assess the effect of CBT versus SSRIs on serious adverse events, level of functioning, quality of life, and adverse events.

Conclusion: CBT may be more effective than no intervention and comparable to SSRIs for pediatric OCD, but we are very uncertain about the effect estimates.

Key words: cognitive-behavioral therapy, obsessive-compulsive disorder, systematic review

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Obsessive-compulsive disorder (OCD) is among the most common psychiatric disorders, with an estimated prevalence of 1% to 3% in children and adolescents.[1,2] Pediatric OCD is associated with reduced quality of life, as well as familial, social, and occupational impairment.[3-7]

The recommended first-line treatment for pediatric OCD is cognitive-behavioral therapy (CBT) including exposure and response prevention.[5,8] Previous reviews support the recommendation of CBT for pediatric OCD,[9-18] but limitations such as not assessing risk of bias in included trials,[9-13] pooling results from randomized trials and noncontrolled studies,[9,13,14] or including only symptom severity as an outcome measure[15-17] may have led to inaccurate conclusions regarding the efficacy of CBT.

In this systematic review, we assessed beneficial and harmful effects of CBT versus no intervention and versus other interventions, in terms of symptom severity, level of functioning, quality of life, lack of remission, and adverse events, for OCD in children and adolescents. We assessed risk of bias in included trials, controlled for random errors due to sparse data or multiple testing using trial sequential

analysis (TSA),[19] and evaluated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[20]

METHOD

Protocol and Registration

The protocol for this systematic review was registered with PROSPERO on November 28, 2017 (CRD42017079118).

Search Strategy

We systematically searched for eligible trials in Cochrane's CENTRAL, MEDLINE, PsycINFO, EMBASE, LILACS, Science Citation Index Expanded on Web of Science, SSCI, and BIOSIS. The search strategy for MEDLINE is provided in Supplement 1, available online. Details on the search are provided in the protocol.

Trial Selection

Three authors (CU, VU, and LP) independently screened titles and abstracts and retrieved and screened all relevant full-text articles for eligibility. A fourth author (NL) was consulted to solve any discrepancies. We included all randomized clinical trials of CBT for children and adolescents (as defined by trialists) with a primary diagnosis of OCD, according to a standard diagnostic system (ie, the *International Classification of Diseases* [*ICD*][21] or the *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*][22]). We included trials irrespective of language, setting, publication status, and publication year. We accepted any type of CBT defined as CBT by trialists. We accepted any non-CBT control intervention. Trials comparing CBT plus a co-intervention with the co-intervention alone (eg, CBT + selective serotonin reuptake inhibitors [SSRIs] versus SSRI) were included if the co-intervention was delivered similarly in the experimental and control groups.

Data Extraction and Outcomes

Three reviewers (CU, VU, and LP) independently extracted the following information from full-text articles of each included trial: author names; publication year; trial location; participant characteristics; sample size; interventions (number of sessions/dosage, duration, and format); mean scores and SDs for each specified outcome at baseline, end of treatment, and maximum follow-up; and information for risk of bias assessment. Our primary outcomes were: (1) symptom severity assessed with the Children's Yale−Brown Obsessive-Compulsive Scale (CY-BOCS)[23]; (2) serious adverse events, defined as death, any life-threatening event, hospitalization, persistent or significant loss of function, or disability[24]; and (3) level of functioning measured on any validated scale. Our secondary outcomes were: (1) quality of life measured on any validated scale; and (2) adverse events, defined as any adverse event not classified as a serious adverse event. Our exploratory outcome was lack of remission from OCD diagnosis.

Risk of Bias Evaluation

We used the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* to evaluate risk of bias in the included trials.[25] Three authors (CU, VU, and LP) independently classified the trials according to specific criteria (detailed in the protocol). Disagreements were resolved with a third author (JJ). We assessed selection bias (allocation sequence generation and allocation concealment), performance bias (blinding of trial participants and treatment providers), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias (eg, vested interest bias). Only trials assessed at low risk of bias within all assessed domains were classified as trials at overall low risk of bias.

Data Synthesis and Meta-analyses

We followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions,*[25] Keus *et al.*,[26] and the eight-step assessment for meta-analyses described by Jakobsen *et al.*[27] We used Cochrane's Review Manager 5[28] to analyze data.

For continuous outcomes, we calculated mean differences (MDs) with 95% CIs. When different scales were used to measure the same outcome type, we calculated standardized mean differences (SMDs) by dividing the MD between a CBT and control group by the pooled SD at end of treatment. To aid interpretation of the intervention effect, we re-expressed SMDs in the unit of the scale most commonly used in the included trials by multiplying the SMD with the pooled SD at end of treatment of the CBT and control groups that had scores on this scale.[29] We multiplied scores by −1 for scales on which increases represent beneficial outcomes, to ensure consistent directionality across scales. For dichotomous outcomes, we calculated risk ratios with 95% CIs. For all outcomes, the intervention effects were assessed with both random-effects[30] and fixed-effect[31] meta-analyses, and the most conservative estimate was reported as the main result.[27] If the two estimates were similar, we used the estimate with the widest CI. We planned to assess three primary and two secondary outcomes. Following the recommendations of Jakobsen *et al.*, we therefore considered a p value of $\leq .025$ for primary outcomes and of $\leq .033$ for secondary outcomes as thresholds for statistical significance.[27] We used the

conventional p value of .05 for the exploratory outcome. We inspected forest plots and trial characteristics to identify potential sources of heterogeneity. We assessed the presence and quantities of statistical heterogeneity by the I^2 statistic, with significance set at $p < .10$.[32,33] When multiple intervention groups were reported in a single trial, we included only the relevant groups. If two comparisons from the same trial were combined in the same meta-analysis, we halved the control group to avoid double counting.[25]

We contacted trial authors to obtain missing data for quantitative analyses and risk of bias assessment. For continuous outcomes, we calculated SDs using other reported data when necessary (eg, calculating SDs from reported CIs or standard errors).

Trial Sequential Analysis

Meta-analyses run the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews.[19,34] We controlled for risks of false-positive results (type I errors) and false-negative results (type II errors), and estimated the information size required to detect or reject an anticipated minimal clinically relevant difference between comparison groups by performing TSA[19] on each outcome (details are provided in the protocol and the TSA manual[35]).

Planned Subgroup Analyses

We performed the following planned subgroup analyses for the primary outcomes (CY-BOCS score, serious adverse events, and level of functioning) when at least two trials or comparisons provided data for the analysis: type of control intervention, type of CBT assessed (ie, individual, group format, or Internet-based), and trials with blinded outcome assessors compared to trials without blinded outcome assessors. We had insufficient data for the following planned subgroup analyses for all primary outcomes: trials at low risk of bias versus trials at high risk of bias, children (<13 years of age) versus adolescents (≥13 years of age), severe OCD versus mild to moderate OCD, and OCD with one or more comorbid psychiatric disorders versus OCD without comorbidity. We used the test for subgroup differences in Review Manager.[28]

Sensitivity Analyses

We performed sensitivity analyses to assess the potential impact of missing data. A "best/worst" scenario was assessed for continuous outcomes by assuming that all patients lost to follow-up in CBT had a beneficial outcome (the group mean plus 2 SD) and that all patients lost to follow-up in the control group had a harmful outcome (the group mean minus 2 SD). A "best/worst" scenario was assessed for dichotomous outcomes by assuming that no patients lost to follow-up in CBT had an event and that patients lost to follow-up in the control group had an event. In addition, we assessed the reverse "worst/best" scenarios for all outcomes. As supplementary analyses, we repeated all analyses for continuous outcomes with 1 SD instead of 2 SD.[27]

Protocol Deviations

In our protocol, we defined remission as not meeting the criteria for OCD as assessed with a diagnostic interview or having a CY-BOCS score ≤12 in combination with a Clinical Global Impression–Severity (CGI-S) score of 1 (not at all ill) or 2 (borderline mentally ill).[36] However, as only three trials assessed remission in either of these ways, we accepted any reported measure of remission.

RESULTS

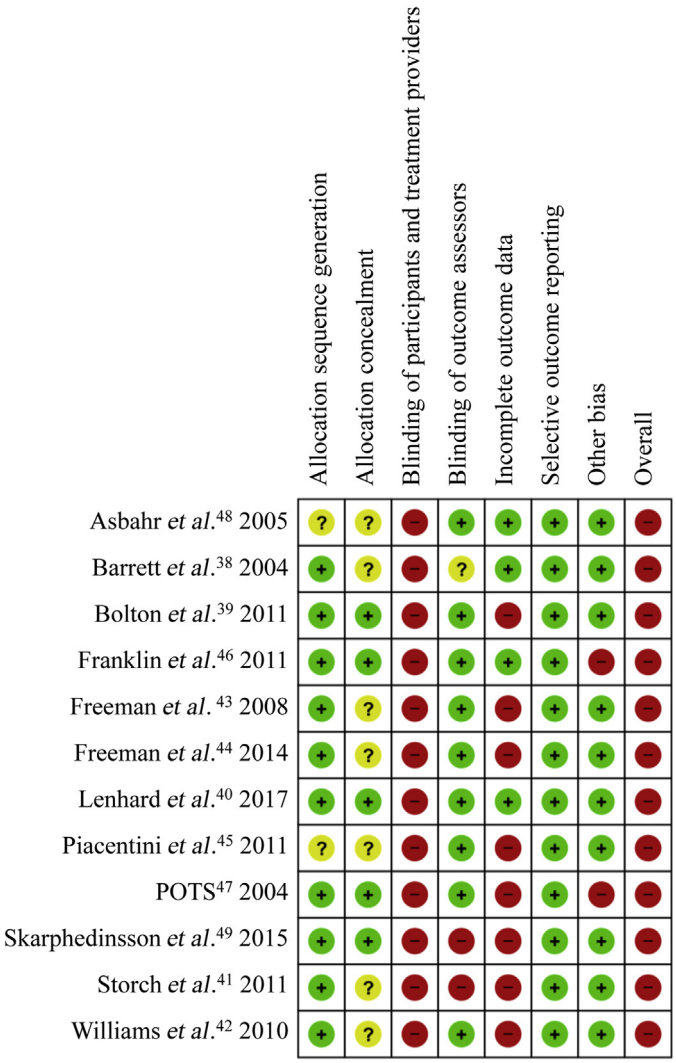
Study Selection and Characteristics

We completed the primary search on July 27, 2017, and the latest search on November 21, 2018 (see the PRISMA flow diagram[37] in Figure S1, available online). Study characteristics are presented in Table S1, available online. Twelve randomized clinical trials were eligible for inclusion in the review ($n_{analyzed} = 819$; age range 4−18 years; 52% female patients; 65% patients with ≥1 comorbid disorder; baseline mean CY-BOCS score = 23.9; 5−14 planned CBT sessions delivered over 12−14 weeks). Five trials[38-42] compared CBT with waitlist. Three trials[43-45] compared CBT with a control intervention including psychoeducation and relaxation training, defined as placebo psychotherapy in all three trials. Two trials[46,47] compared CBT with "no intervention" with SSRI co-intervention delivered similarly in both groups (ie, CBT+SSRI versus SSRI); one of these trials[47] also included an active control comparison of CBT versus pill-placebo. In total, three eligible trials[47-49] compared CBT with SSRI. Based on the trials identified, we did two comparisons: (1) CBT versus "no intervention" (including waitlist, placebo, and no intervention, with a co-intervention delivered similarly in the experimental and control groups); and (2) CBT versus SSRIs. We calculated effects of interventions only at end of treatment, as we had insufficient data to evaluate long-term effects. We found no substantial discrepancies between effect estimates from random-effects and fixed-effect meta-analyses (see Table S2, available online).

Risk of Bias Assessment

Details on the assessment of risk of bias are presented in Figure 1. All trials and all meta-analysis results were rated at overall high risk of bias. Given the nature of psychotherapeutic interventions, no trial had adequate blinding of

FIGURE 1 Risk of Bias in the Included Randomized Clinical Trials



Note: Random allocation sequence generation was adequate in 10 of 12 trials (83%); allocation concealment was adequate in 5 of 12 trials (42%); blinding of trial participants and treatment providers was adequate in 0 of 12 trials (0%); blinding of outcome assessors was adequate in 9 of 12 trials (75%); there was low risk of bias for "incomplete outcome data" in 4 of 12 trials (33%); there was low risk of bias for "selective outcome reporting" in 12 of 12 trials (100%); and the "other bias" domain (eg, vested interest) was adequate in 10 of 12 trials (83%). Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (–) = high risk of bias. Please note color figures are available online.

participants and treatment providers. Only one trial[40] had low risk of bias in the remaining bias domains and was therefore potentially less affected by bias.

Comparison 1: CBT Versus "No Intervention"

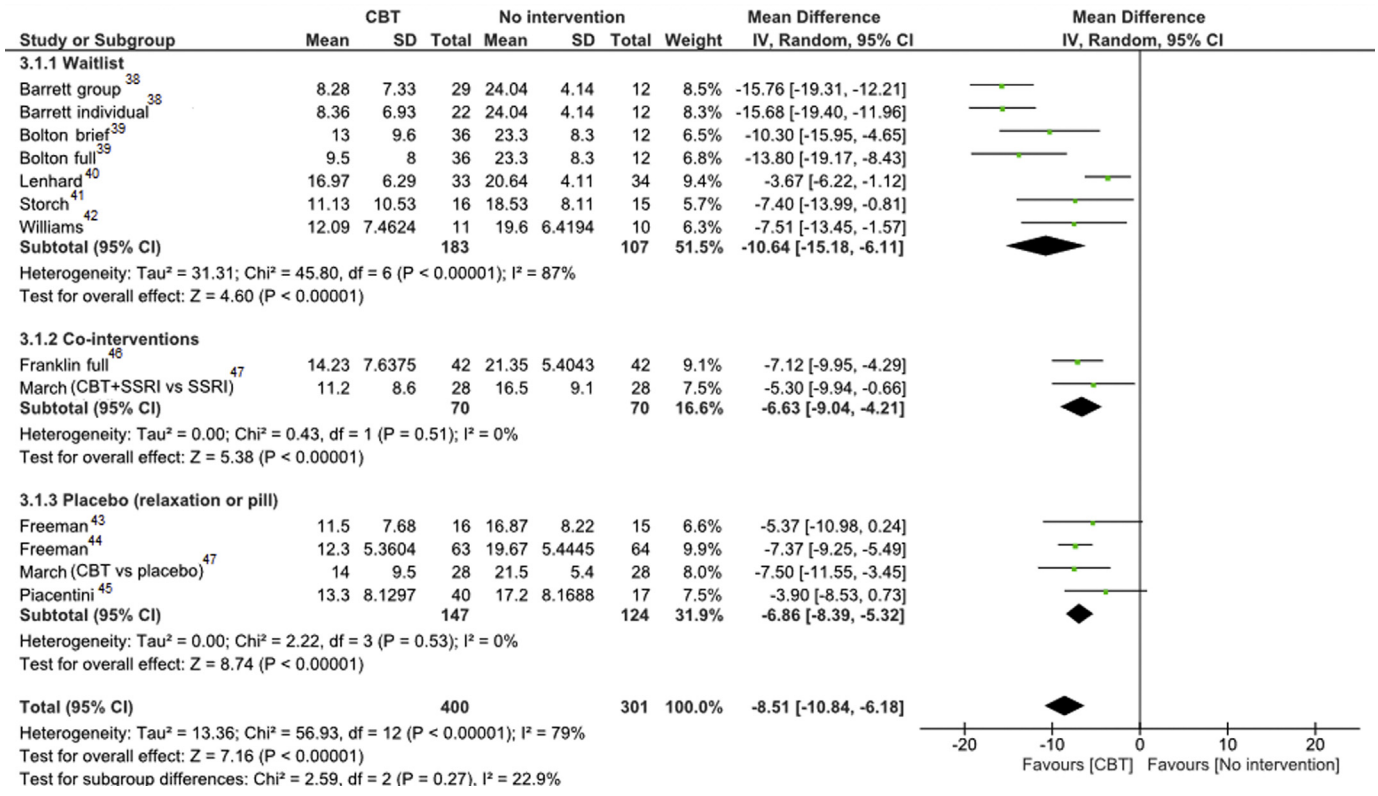
Primary Outcome: Children's Yale–Brown Obsessive-Compulsive Scale. Ten trials[38-47] ($n_{analyzed}$ = 701; 13 comparisons) tested the efficacy of CBT in reducing OCD symptom severity on the CY-BOCS scale versus a control condition considered ineffective for OCD. Five trials[38-42] used waitlist control; two trials[46,47] used "no intervention" with an SSRI co-intervention applied equally in both comparison groups (one of these trials[47] also included a control condition with pill-placebo); and three trials[43-45] used placebo psychotherapy. Random-effects meta-analysis showed evidence of a difference in favor of CBT versus "no intervention" (MD = −8.51, 95% CI = −10.84 to −6.18, $p < .00001$) (Figure 2). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S2, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online).

The I^2 was 79% ($\chi^2 = 56.93$, $p < .00001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated heterogeneity primarily in the CBT versus waitlist comparison. In 2[38,41] of the 5 trials comparing CBT with waitlist, the waitlist duration was considerably shorter than the CBT duration (eg, 12 weeks of CBT versus 4 weeks of waitlist). Excluding these trials from the analysis reduced I^2 to 45% but did not substantially alter the meta-analysis result (MD = −6.81, 95% CI = −8.45 to −5.18, $p < .00001$). Subgroup analyses showed no evidence of differences between the types of control conditions, but did show evidence of a difference in favor of conventional CBT versus Internet-delivered CBT (see Supplement 2, available online).

Primary Outcome: Serious Adverse Events. Three trials[40,44,46] assessed serious adverse events for CBT versus a control considered ineffective for OCD. One trial[40] used waitlist control, one trial[46] used "no intervention" with an SSRI co-intervention, and one trial[44] used placebo psychotherapy. None of the 137 patients in CBT experienced a serious adverse event compared with one of 138 patients (0.7%) in the "no intervention" group. The reported event was a suicide attempt by a participant with comorbid depression in a "no intervention" with SSRI in the co-intervention group. We did not perform meta-analysis, missing outcome analysis, or TSA for serious adverse events, because no events were observed for CBT and only one event was observed for "no intervention."

Primary Outcome: Level of Functioning. Five trials[39-41,44,45] ($n_{analyzed}$ = 377, 6 comparisons) assessed the effect of CBT on level of functioning versus a control considered ineffective for OCD. Three trials[39-41] used a waitlist control, and two trials[44,45] used placebo psychotherapy. Three trials[39,41,45] used the Child Obsessive-Compulsive Impact Scale–child rated (COIS-C) and –parent rated (COIS-P); one trial[40] used the Education, Work and

FIGURE 2 Effect of Cognitive-Behavioral Therapy Versus "No Intervention" on Severity of Obsessive-Compulsive Disorder Measured on the Children's Yale–Brown Obsessive-Compulsive Scale



Note: *CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors. Please note color figures are available online.*

Social Adjustment Scale–child rated (EWSAS-C) and –parent rated (EWSAS-P); and one trial[44] used only COIS-P.

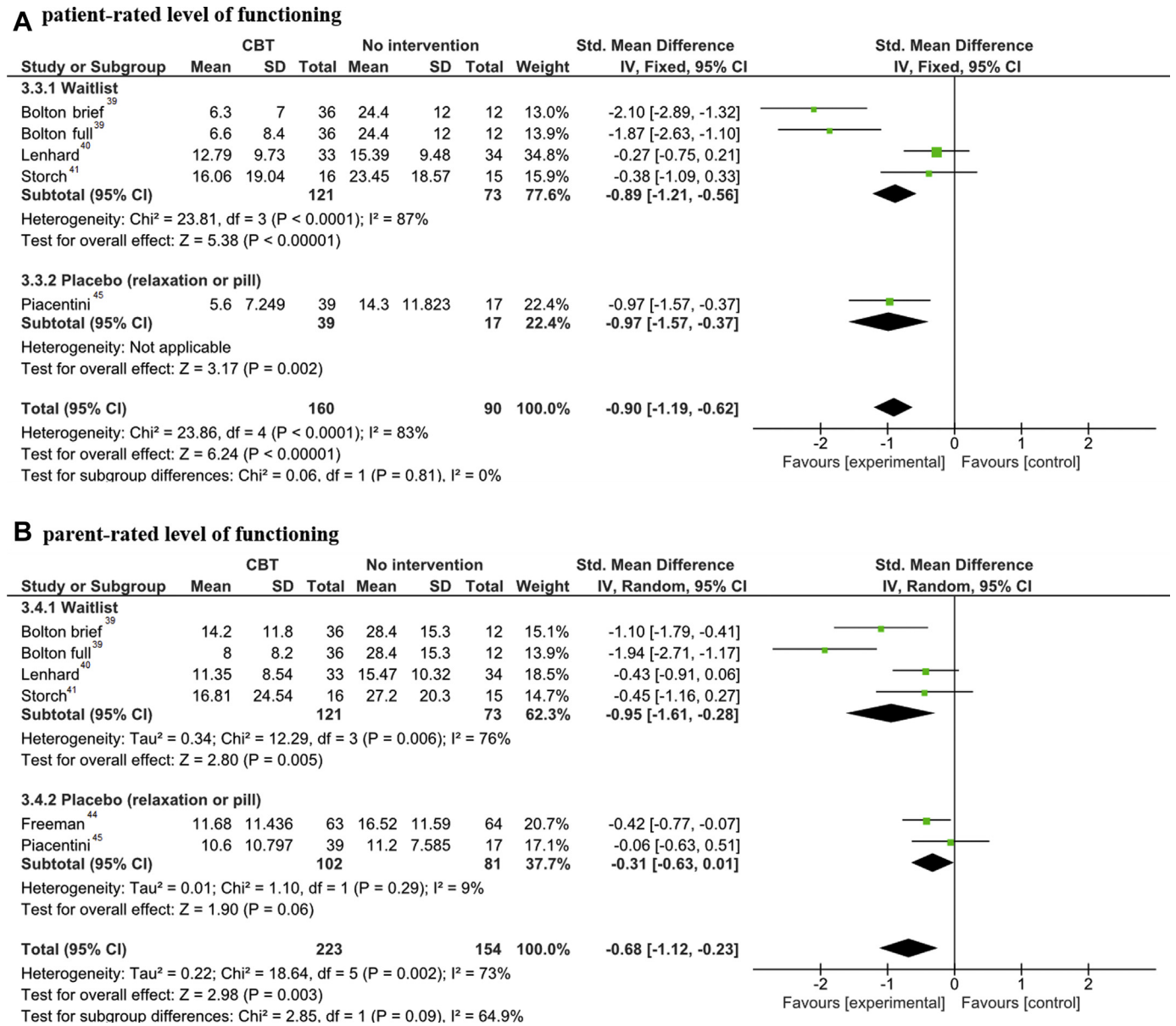
Patient-Rated Level of Functioning. Fixed-effect meta-analysis on patient-rated level of functioning showed evidence of a difference in favor of CBT versus "no intervention" (SMD = –0.90, 95% CI = –1.19 to –0.62, $p <$ .00001) (Figure 3a). Missing outcome analysis showed that this finding is unlikely to have been caused by missing outcome data bias (Table S3, available online). Restricting the analysis to the three trials reporting results from COIS-C did not substantially alter the meta-analysis result. TSA restricted to the trials reporting results from COIS-C showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S3, available online).

The I^2 was 83% ($\chi^2 = 23.86$, $p < .0001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[39] had a markedly larger intervention effect estimate. Excluding this trial from the analysis reduced I^2 to 40% but did not substantially alter the meta-analysis result. Subgroup analyses showed no evidence of differences between the types of control conditions, but did show evidence of a difference in favor of conventional CBT versus Internet-delivered CBT (Supplement 2, available online).

Parent-Rated Level of Functioning. Random-effects meta-analysis on parent-rated level of functioning showed evidence of a difference in favor of CBT versus "no intervention" (SMD = –0.68, 95% CI = –1.12 to –0.23, $p = .003$) (Figure 3b). Missing outcome analysis showed that this finding is sensitive to missing outcome data bias (Table S3, available online). TSA restricted to the trials reporting results from COIS-P showed that this finding may be a random finding due to lack of power or multiple testing (Figure S4, available online).

The I^2 was 73% ($\chi^2 = 18.64$, $p = .002$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[39] had a markedly larger intervention effect estimate. Excluding this trial from the analysis reduced I^2 to 0% but did not substantially alter the meta-analysis result. Subgroup analyses showed no evidence

FIGURE 3 Effect of Cognitive-Behavioral Therapy Versus "No Intervention" on Patient-Rated Level of Functioning (a) and Parent-Rated Level of Functioning (b)



Note: *CBT = cognitive-behavioral therapy. Please note color figures are available online.*

of differences between the types of control conditions (Supplement 2, available online).

Secondary Outcome: Quality of Life. Two trials[39,44] ($n_{analyzed}$ = 223, 3 comparisons) assessed the effect of CBT on quality of life versus a control considered ineffective for OCD. One trial[39] used waitlist control and assessed quality of life with the Manchester Short Assessment of Quality of Life (MANSA). One trial[44] used placebo psychotherapy and assessed quality of life with the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Random-effects meta-analysis suggested a difference in favor of CBT versus "no intervention" (SMD = –0.39, 95% CI = –0.77 to –0.02, p = .04) (Figure S5, available online), although this effect did not meet our predefined significance threshold of $p \leq 0.025$. Missing outcome analysis showed that this finding is sensitive to missing outcome data bias (Table S3, available online). The I^2 was 33% (χ^2 = 2.98, p = .23), suggesting negligible heterogeneity. We had insufficient data for TSA.

Secondary Outcome: Adverse Events. Three trials[40,44,46] ($n_{analyzed}$ = 275, 3 comparisons) assessed adverse events for CBT versus a control considered ineffective for OCD. One trial[40] used waitlist control, one trial[46] used "no intervention" with an SSRI co-intervention, and one trial[44] used placebo psychotherapy. A total of 49 of 137 patients (35.8%) in CBT experienced an adverse event compared with 44 of 138 patients (31.9%) in the "no intervention." Two of the trials[40,44] reported the types of adverse events. In one trial,[40] the events recorded were mood problems (9%), OCD-related symptoms (6%), anxiety (4%), and sleep problems (1%). The overall occurrence was similar between the groups, and no type of event was more common in either group. The other trial[44] recorded a single event of aggressive impulsive behavior in the CBT group. Random-effects meta-analysis showed no evidence of a difference between CBT and "no intervention" in the risk of experiencing an adverse event (RR = 1.06, 95% CI 0.93–1.22, $p = 0.39$) (Figure S6, available online). TSA showed that this finding may be a random finding due to lack of power or multiple testing (Figure S7, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online). The I^2 was 0% ($\chi^2 = 1.08$, $p = .58$), suggesting negligible heterogeneity.

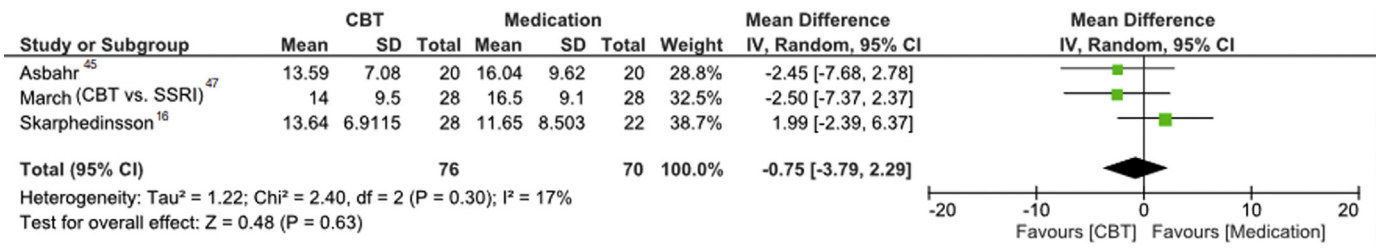
Exploratory Outcome: Lack of Remission. Seven trials[38-41,43,45,47] ($n_{analyzed}$ = 480, 10 comparisons) assessed the risk of still having OCD at end of CBT compared with a control considered ineffective for OCD. Four trials[38-41] used waitlist control; one trial[47] used "no intervention" with an SSRI co-intervention and included an additional control condition with pill-placebo; and two trials[43,45] used placebo psychotherapy. Two trials[38,39] used the Anxiety Disorders Interview Schedule–parent version (ADIS-P) clinical interview to assess remission; one trial[40] used a combination of CY-BOCS score ≤12 and CGI-S score ≤2; one trial[41] used a combination of ADIS-P severity rating ≤3 and CY-BOCS score ≤10; one trial[47] used CY-BOCS score ≤10, one trial[45] used CY-BOCS score ≤11; and one trial[43] used CY-BOCS score ≤12. A total of 141 of 295 patients (47.8%) in CBT compared with 171 of 185 patients (92.4%) in the "no intervention" group still had OCD at the end of treatment. Random-effects meta-analysis showed that patients were less likely to still have OCD at the end of treatment in the CBT versus "no intervention" group (RR = 0.50, 95% CI = 0.37–0.67, $p < .00001$) (Figure S8, available online). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S9, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online).

The I^2 was 82% ($\chi^2 = 50.34$, $p < .00001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[40] had a smaller intervention effect estimate and markedly smaller CI. Excluding this trial from the analysis reduced I^2 to 58% but did not substantially alter the meta-analysis result.

Comparison 2: CBT Versus Pharmacological Intervention

Primary Outcome: Children's Yale–Brown Obsessive-Compulsive Scale. Three trials[47-49] ($n_{analyzed}$ = 146, 3 comparisons) tested the efficacy of CBT in reducing OCD symptom severity assessed with CY-BOCS versus an SSRI intervention. One trial[48] did not report end-of-treatment CY-BOCS scores and SDs. As we were unable to obtain these data from the trial authors, we used values retrieved by authors of a previous review.[50] Random-effects meta-analysis showed no evidence of a difference between CBT and SSRI (MD = –0.75, 95% CI = –3.79 to 2.29, $p = .63$) (Figure 4). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S10, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S4, available online). The

FIGURE 4 Effect of Cognitive-Behavioral Therapy Versus Selective Serotonin Reuptake Inhibitors on Severity of Obsessive-Compulsive Disorder Measured on the Children's Yale–Brown Obsessive-Compulsive Scale



Note: *CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors. Please note color figures are available online.*

I^2 was 17% ($\chi^2 = 2.40$, $p = .30$), suggesting negligible heterogeneity.

Primary Outcome: Serious Adverse Events. Three trials[47-49] assessed serious adverse events for CBT versus an SSRI intervention. However, two of these trials[47,49] assessed only SSRI-related serious adverse events. The remaining trial[48] reported having assessed serious adverse events in both comparison groups but did not report numbers of events or participants affected.

Primary Outcome: Level of Functioning. One trial[49] ($n_{analyzed} = 50$, one comparison) assessed the effect of CBT on level of functioning versus an SSRI intervention. This trial assessed patient-rated level of functioning with COIS-C and parent-rated level of functioning with COIS-P. There was no evidence of a difference between CBT and SSRI on parent-rated level of functioning (MD = 1.70, 95% CI = –6.45 to 9.85, $p = .68$) or patient-rated level of functioning (MD = 6.95, 95% CI = 0.15–13.75, $p = .05$).

Secondary Outcome: Quality of Life. No trials assessed the effect of CBT on quality of life versus an SSRI intervention.

Secondary Outcome: Adverse Events. Three trials[47-49] assessed adverse events for CBT versus an SSRI intervention. However, two of these trials[47,49] assessed only SSRI-related adverse events. The remaining trial[48] assessed adverse events in both comparison groups. This trial reported more weight loss in the SSRI group and more nausea and abdominal discomfort in the CBT group, but did not report numbers of events or participants affected.

Exploratory Outcome: Lack of Remission. Two trials[47,49] ($n_{analyzed} = 106$, 2 comparisons) assessed the risk of still having OCD at end of CBT compared with an SSRI intervention. Both trials defined remission as CY-BOCS score ≤ 10. A total of 36 of 56 patients (64.3%) in CBT compared with 38 of 50 patients (76.0%) in the SSRI intervention still had OCD at the end of treatment. Random-effects meta-analysis showed no evidence of a difference between CBT and SSRI intervention in the likelihood of still having OCD (RR = 0.85, 95% CI = 0.66–1.09, $p = .20$) (Figure S11, available online). TSA showed that this finding may be a random finding due to lack of power or multiple testing (Figure S12, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S4, available online). The I^2 was 0% ($\chi^2 = 0.53$, $p = .47$), suggesting negligible heterogeneity.

Publication Bias

We did not have enough trials, and the clinical heterogeneity was too substantial, to perform any of the assessments of publication bias specified in our protocol.

GRADE Assessment

The GRADE assessments are presented in Table 1. The certainty of evidence was low or very low for all outcomes.

DISCUSSION

We included 12 randomized clinical trials in the present systematic review of CBT for pediatric OCD. First, we compared CBT with "no intervention." Our primary analyses showed that CBT may substantially reduce OCD symptom severity and may moderately improve level of functioning when compared with "no intervention", whereas we were unable to assess the effect on serious adverse events due to sparse data. Our secondary analyses showed that CBT and "no intervention" may have similar effects on quality of life, and may lead to similar proportions of participants experiencing adverse events, although TSA analysis suggested that the latter may be a random finding due to lack of power or multiple testing. Our exploratory analysis showed that CBT may have a substantial beneficial effect on remission when compared with "no intervention", although approximately one-half of patients in CBT were classified as nonremitters at the end of treatment.

It is possible that the relatively high proportion of participants affected by adverse events in the CBT and "no intervention" groups (35.8% and 31.9%, respectively) is partly related to high rates of concomitant use of SSRI in the 2 groups (36.2% and 34.3%, respectively). Indeed, some overlap exists between the adverse events reported here and known SSRI side effects in children and adolescents,[51] and the trial[44] reporting the lowest proportions of participants experiencing adverse events (1 of 63 participants in CBT and 0 of 64 participants in the "no intervention" group) also had the lowest rate of concomitant use of SSRI (2%). Nevertheless, as we do not have data to disentangle CBT-related adverse events and adverse events related to concomitant use of SSRI, the main finding is that knowledge about harmful effects of CBT is lacking.

Next, we compared CBT with SSRI interventions. Our primary analyses showed that CBT and SSRIs may have comparable effects on OCD symptom severity, whereas we were unable to assess the effect on serious adverse events and level of functioning due to sparse data. Secondary analyses on quality of life and adverse events were not possible. Our exploratory analysis showed that CBT and SSRI may have comparable beneficial effects on remission, although TSA

TABLE 1 Summary of Findings Tables for Cognitive-Behavioral Therapy Versus "No Intervention" and Versus Selective Serotonin Reuptake Inhibitors

CBT vs. "No Intervention" for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With "No intervention"	Risk With CBT				
Severity of OCD		Mean severity of OCD was 8.51 lower in CBT (10.84 lower to 6.18 lower)	—	701 (10)	⊕⊕◯◯ LOW [a,b]	CBT may result in a large reduction in severity of OCD.
Serious adverse events	7 per 1,000	2 per 1,000 (0—58)	RR 0.33 (0.01— 7.96)	275 (3)	⊕◯◯◯ Very low [a,c,d]	We are very uncertain about the effect of CBT on serious adverse events.
Level of functioning (patient-rated)	—	SMD 0.90 lower (1.19 lower to 0.62 lower)	—	250 (4)	⊕◯◯◯ Very low [a,b,c,e]	CBT may improve level of functioning (patient-rated) but we are very uncertain. Note: lower scores represent higher level of functioning.
Level of functioning (parent-rated)	—	SMD 0.68 lower (1.12 lower to 0.23 lower)	—	377 (5)	⊕◯◯◯ Very low [a,b,c,e,f]	CBT may improve level of functioning (parent-rated) but we are very uncertain. Note: lower scores represent higher level of functioning.
Quality of life	—	SMD 0.39 higher (0.02 higher to 0.77 higher)	—	223 (2)	⊕◯◯◯ Very low [a,c,f]	We are very uncertain about the effect of CBT on quality of life.
Adverse events	319 per 1,000	338 per 1,000 (297—389)	RR 1.06 (0.93— 1.22)	275 (3)	⊕⊕◯◯ LOW [a,c]	CBT appears to result in little to no difference in adverse events.
Lack of remission	924 per 1,000	462 per 1,000 (342—619)	RR 0.50 (0.37— 0.67)	480 (7)	⊕◯◯◯ Very low [a,b,e,g]	CBT may reduce lack of remission, but we are very uncertain.

(continued)

TABLE 1 Continued

CBT vs. SSRI for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With SSRI	Risk With CBT				
Severity of OCD		The mean severity of OCD was 0.75 lower in CBT (3.79 lower to 2.29 higher)	—	146 (3)	⊕◯◯◯ Very low [a,c]	CBT appears comparable to SSRI in reducing severity of obsessive-compulsive disorder, but we are very uncertain.
Serious adverse events	0 per 1,000	0 per 1,000 (0—0)	Not estimable	40 (1)	-	There was insufficient data to evaluate the effect on serious adverse events.
Level of functioning (patient-rated)	-	MD 6.95 lower (0.15 lower to 13.75 lower)	—	50 (1)	⊕◯◯◯ Very low [a,c,f]	We are uncertain about the effect of CBT compared to SSRI on level of functioning (patient-rated). Note: lower scores represent higher level of functioning.
Level of functioning (parent-rated)	-	MD 1.70 lower (9.85 lower to 6.45 higher)	—	50 (1)	⊕◯◯◯ Very low [a,c,d]	We are uncertain about the effect of CBT compared to SSRI on level of functioning (parent-rated). Note: lower scores represent higher level of functioning.
Quality of life	Not estimable	Not estimable	Not estimable	0	-	There were no available data to evaluate the effect on quality of life.
Adverse events	Not estimable	Not estimable	Not estimable	0	-	There were no available data to evaluate the effect on adverse events.

(continued)

TABLE 1 Continued

CBT vs. SSRI for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With SSRI	Risk With CBT				
Lack of remission	760 per 1,000	646 per 1,000 (502−828)	RR 0.85 (0.66− 1.09)	106 (2)	⊕◯◯◯ Very low[a,c,d,g]	We are uncertain about the effect of CBT compared to SSRI on remission.

Note: The risk with CBT (and the 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence are as follows: High certainty = We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. CBT = cognitive-behavioral therapy; MD = mean difference; OCD = obsessive-compulsive disorder; RR = risk ratio; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

[a]*All trials were at an overall high risk of bias.*

[b]*Substantial statistical heterogeneity was present and was not explained by planned or post hoc subgroup analyses.*

[c]*The sample size was insufficient to calculate a precise effect estimate.*

[d]*The CI around the effect estimate included both meaningful benefit and harm.*

[e]*There was wide variation in effect estimates across trials.*

[f]*The CI around the effect estimate included both meaningful benefit and no effect.*

[g]*Remission was assessed in nonstandardized and potentially invalid manners.*

analysis suggested that this may be a random finding due to lack of power or multiple testing.

All included trials were assessed at high risk of bias, and the certainty of the evidence was rated as low or very low for all outcomes for both comparisons. Trials evaluating effects of psychotherapy are inherently more prone to performance bias compared to trials evaluating effects of medication,[52-54] as it is not feasible to blind psychotherapists to the treatment they are providing. However, issues remained that could have been avoided. Several trials used unblinded outcome assessors or had unclear allocation concealment. Intervention effects on subjectively assessed outcomes (eg, CY-BOCS score) have been shown to be exaggerated by 25% in trials with inadequate or unclear blinding compared to trials with adequate blinding, and by 31% in trials with inadequate or unclear allocation concealment compared to trials with adequate allocation concealment.[52] Allocation concealment is always feasible, and the use of credible control interventions (eg, placebo psychotherapy) can limit performance bias.[18] Only one of the included trials[40] was assessed at low risk of bias on all other domains than the performance bias domain, highlighting a need for additional rigorous trials.

This review updates and extends findings from previous reviews. To our knowledge, this is the first review to assess the effects of CBT on adverse events, level of functioning, and quality of life in children and adolescents with OCD. In addition, we performed sensitivity analyses to assess the potential impact of missing data, and used TSA to control for risks of false-positive and false-negative results. This allowed us to determine whether a clinically meaningful and statistically significant difference, or lack of a difference, between CBT and a control intervention was likely to be a random finding due to missing outcome data bias, lack of power, or multiple testing.

Our review revealed an overall lack of data on beneficial and harmful effects of CBT beyond OCD symptom severity. All included trials assessed symptom severity measured on the CY-BOCS as a primary outcome. Most trials also included a measure of remission, but methodological limitations, such as dichotomizing a continuous outcome (CY-BOCS) and using varying arbitrary definitions of remission instead of assessing remission with a standardized diagnostic interview, raises serious concerns about both the reliability and validity of this outcome.[55] Few trials

assessed adverse events, level of functioning, and quality of life. Although symptom reduction is arguably an important outcome, a comprehensive and more complete evaluation of CBT efficacy should also include assessment of potential harmful effects (ie, adverse events), quality of life, and level of functioning.[56] Psychotherapy is often assumed to be associated with minimal harm, but adverse events are rarely systematically monitored in psychotherapy trials.[57] Differences in the frequency or severity of harmful effects could be decisive factors for clinicians and patients when choosing between CBT and SSRIs, especially considering our finding of comparable beneficial effects. Moreover, symptom reduction may have little relevance to patients if not accompanied by noticeable improvements in daily life well-being and functioning.

A potential methodological issue with the assessment of OCD symptom severity in all included trials is that 4 of the 10 items that comprise the CY-BOCS total score specifically address the patient's ability to resist and control obsessions and compulsions, which is a major focus of exposure and response prevention in CBT. Although inability to resist and control obsessions and compulsions are core features of OCD symptomatology, the heavy emphasis on items addressing these features might inflate estimates of the effect of CBT when CBT is compared with interventions that do not include exposure and response prevention (eg, psychoeducation and relaxation training or SSRI interventions). This potential issue may be circumvented by testing whether group differences persist when scores on these items are excluded from the total CY-BOCS score, or by including additional measures of benefits in future trials and reviews.

In conclusion, CBT may be more effective than no intervention and comparable to SSRI for pediatric OCD, but high risk of bias in included trials and low certainty of the evidence prevent firm conclusions regarding the efficacy of CBT. In addition, we had insufficient data to adequately explore potential reasons behind statistical heterogeneity in the meta-analyses. For all outcomes, we were unable to perform planned subgroup analyses based on overall risk of bias, participant age, OCD severity, and comorbidity status.

Based on the data reviewed, we have four recommendations for future trials in this field. First, future trials should be designed in accordance with the standard protocol items: recommendations for interventional trials (SPIRIT) guidelines[58] and reported according to the consolidated standards for reporting of trials (CONSORT) guidelines.[59] Second, we recommend that future trials define remission from OCD as not fulfilling the diagnostic criteria according to *ICD* or *DSM* and determine remission with a blinded standardized diagnostic interview. Third, we encourage trialists to include additional outcomes pertaining to treatment effects beyond symptom reduction, such as measures of quality of life and level of functioning. Fourth, we urge authors of future trials to systematically monitor and report adverse events for all comparison groups.

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Supplement 1 - Search Strategy for MEDLINE (OvidSP; 1946 to November 2018)

1. exp Obsessive-Compulsive Disorder/

2. (OCD or obsess* or compuls*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. exp Behavior Therapy/

5. (((cognitive or behaviour*) and therap*) or CBT or BT or CT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. 4 or 5

7. exp Child/

8. exp Infant/

9. (Child* or Paediatric* or Pediatric* or Juvenile* or Youth* or Young* or Adolesc* or Teenage* or kid* or infant* or toddler* or boy* or girl*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. 7 or 8 or 9

11. 3 and 6 and 10

12. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 11 and 12

Supplement 2 - Comparison 1: CBT versus 'No intervention' – Subgroup Analyses

Subgroup analyses for the primary outcome: Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)

The test for subgroup differences between the types of control conditions was not significant (χ^2=2.59, p=.27). The MD in favor of CBT versus waitlist was -10.64 (95% CI -15.18 to -6.11, p<.00001); versus 'no intervention' with SSRI co-intervention it was -6.63 (95% CI -9.04 to -4.21, p<.00001); and versus placebo it was -6.86 (95% CI -8.39 to -5.32, p<.00001). Substantial heterogeneity was present in the CBT versus waitlist subgroup (I^2=87%, p<.00001), but not in the CBT versus 'no intervention' with co-interventions subgroup (I^2=0%, p=.51) or the CBT versus placebo subgroup (I^2=0%, p=.53).

The test for subgroup differences between conventional CBT and internet-delivered CBT was significant (χ^2=6.98, p=.008). The MD in favor of conventional CBT versus 'no intervention' was -9.12 (95% CI -11.59 to -6.65, p<.00001) and in favor of internet-delivered CBT versus 'no intervention' was -4.25 (95% CI -6.89 to -1.60, p=.002).

Subgroup analyses for the primary outcome: level of functioning

Patient-rated level of functioning

The test for subgroup differences between waitlist control and placebo psychotherapy was not significant (χ^2=0.81, p=.81). The SMD in favor of CBT versus waitlist was -0.89 (95% CI -1.21 to -0.56, p<.00001), corresponding to -9.29 points on the COIS-C. The SMD in favor of CBT versus placebo was -0.97 (95% CI -1.57 to -0.37, p=.002), corresponding to -10.12 points on the COIS-C.

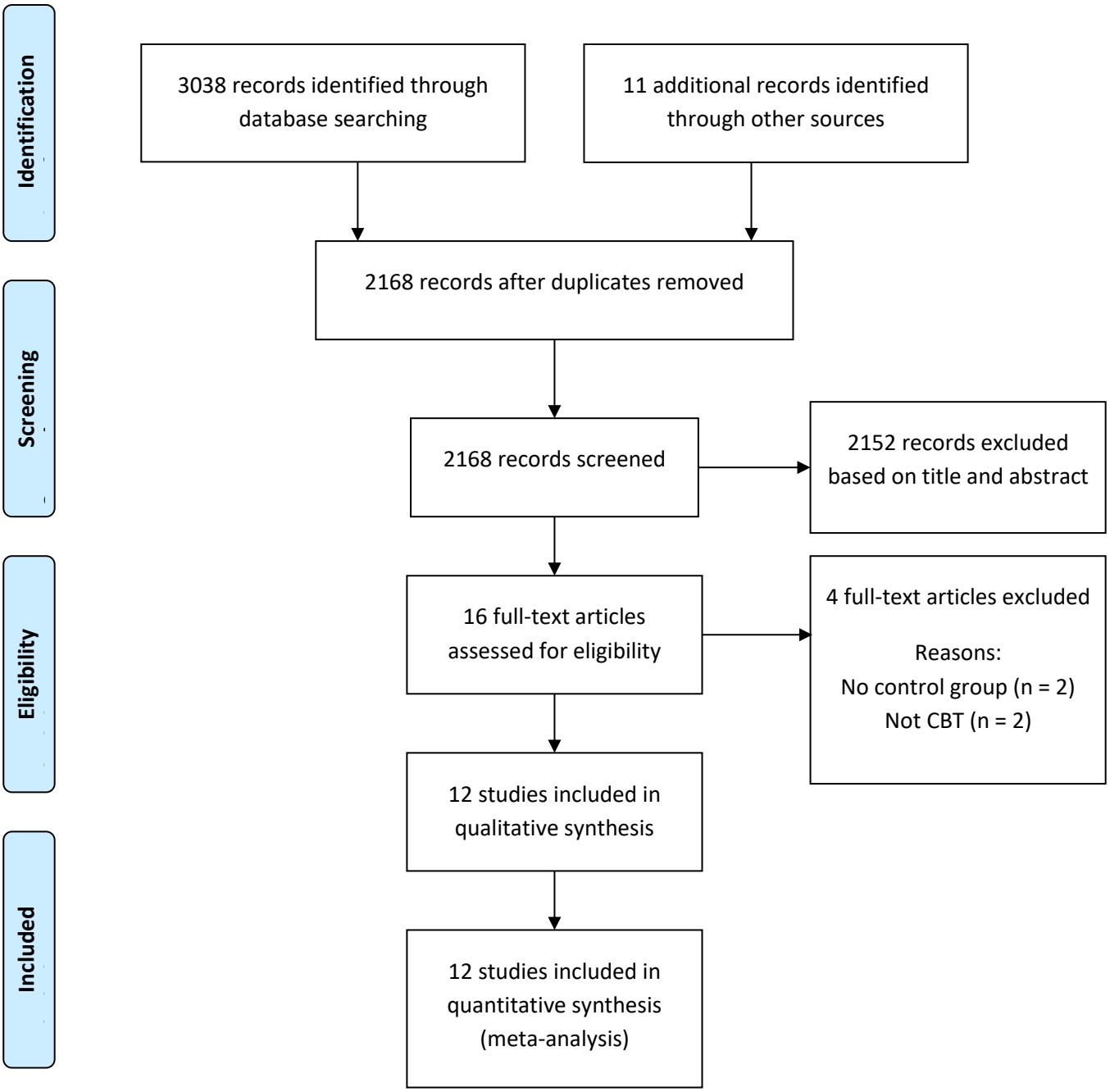
The test for subgroup differences between conventional CBT and internet-delivered CBT was significant (χ^2=17.65, p<.0001). The SMD in favor of conventional CBT versus 'no intervention' was -1.52 (95% CI -1.92 to -1.12, p<.00001), corresponding to -15,86 points on the COIS-C. We found

no evidence of a difference between internet-delivered CBT and ‘no intervention’ on patient-rated level of functioning (SMD=-0.30, 95% CI -0.07 to 0.10, p=.14).

Patient-rated level of functioning

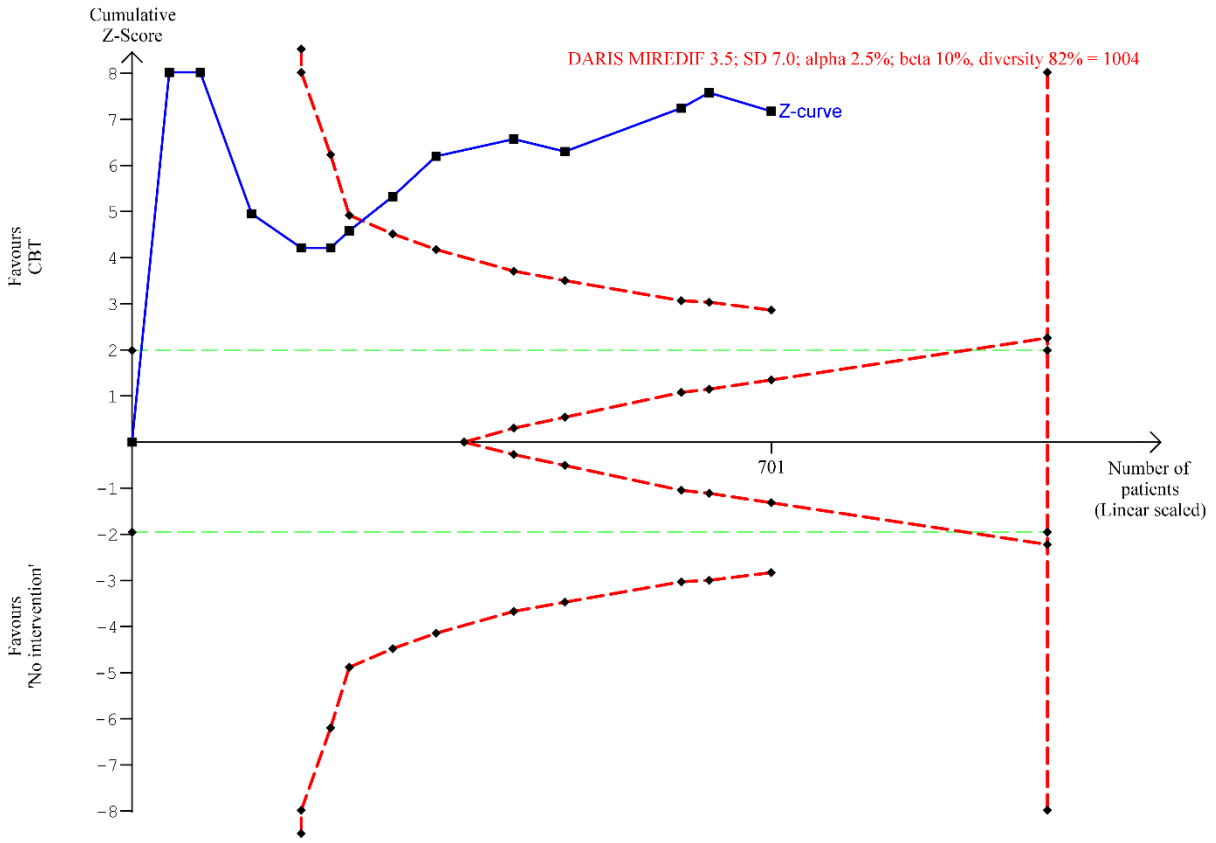
The test for subgroup differences between waitlist control and placebo psychotherapy was not significant (χ^2=2.85, p=.09). The SMD in favor of CBT versus waitlist was -0.83 (95% CI -1.14 to -0.51, p=.006), corresponding to -10.17 points on the COIS-P. There was no evidence of a difference between CBT and placebo psychotherapy (SMD=-0.31, 95% CI -0.63 to 0.01, p=.06).

Figure S1 PRISMA Flow Diagram



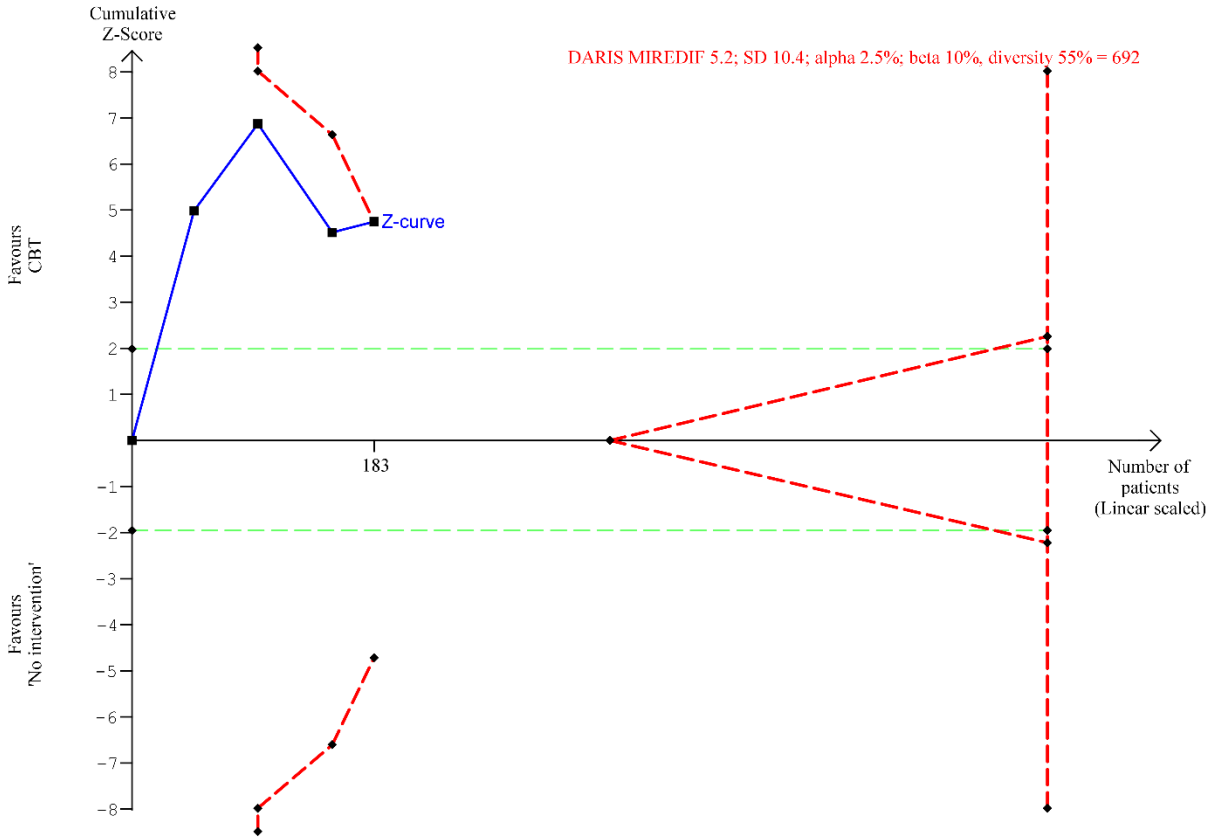
Note: CBT = cognitive behavioral therapy.

Figure S2 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus 'No Intervention' on Obsessive-Compulsive Disorder Symptom Severity



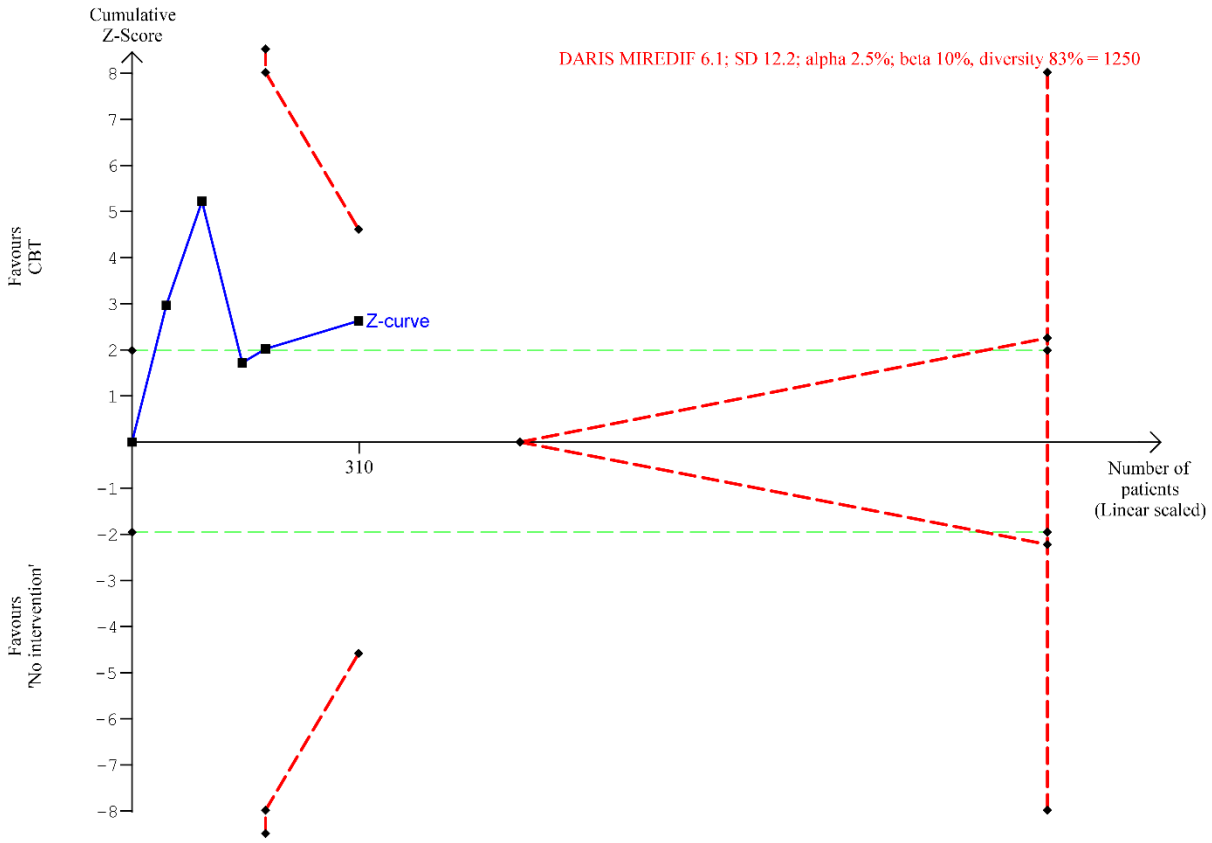
Note: The diversity-adjusted required information size for Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) was calculated to 1004 patients based on a minimal relevant difference of 3.5 CY-BOCS points, a standard deviation of 7.0, an alpha of 2.5%, a beta of 10%, and the observed diversity of 82%. Ten trials with an accrued 701 patients reported results from CY-BOCS. However, the cumulative Z-curve crossed the trial sequential monitoring boundary for benefit (outer wedge). The finding in the conventional meta-analysis of a statistically significant and substantial superiority of cognitive behavioral therapy compared with 'no intervention' in reducing symptom severity is therefore unlikely to be a random finding due to lack of power or multiple testing if bias could be ignored. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S3 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus 'No Intervention' On Patient-Rated Level of Functioning



Note: The diversity-adjusted required information size for Child Obsessive-Compulsive Impact Scale – child rated (COIS-C) was calculated to 692 patients based on a minimal relevant difference of 5.2 COIS-C points, an SD of 10.4, an alpha of 2.5%, a beta of 10%, and the observed diversity of 55%. Three trials with an accrued 183 patients reported results from COIS-C. However, the cumulative Z-curve crossed the trial sequential monitoring boundary for benefit (outer wedge). The finding in the conventional meta-analysis of a statistically significant and substantial superiority of cognitive behavioral therapy compared with 'no intervention' in improving patient-rated level of functioning is therefore unlikely to be a random finding due to lack of power or multiple testing if bias could be ignored. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S4 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus 'No Intervention' On Parent-Rated Level of Functioning



Note: The diversity-adjusted required information size for Child Obsessive-Compulsive Impact Scale – parent rated (COIS-P) was calculated to 1250 patients based on a minimal relevant difference of 6.1 COIS-P points, an SD of 12.2, an alpha of 2.5%, a beta of 10%, and the observed diversity of 83%. Four trials with an accrued 310 patients reported results from COIS-P. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (outer wedge) or the futility boundary (inner wedge), indicating that the finding in the conventional meta-analysis of a statistically significant superiority of cognitive behavioral therapy compared with 'no intervention' in improving parent-rated level of functioning may be a random finding due to lack of power or multiple testing. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S5 Effect of Cognitive Behavioral Therapy versus 'No Intervention' on Quality of Life

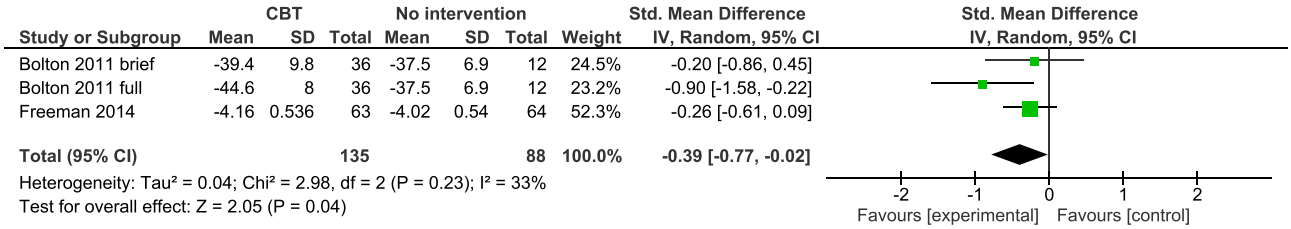


Figure S6 Effect of Cognitive Behavioral Therapy versus 'No Intervention' on Adverse Events

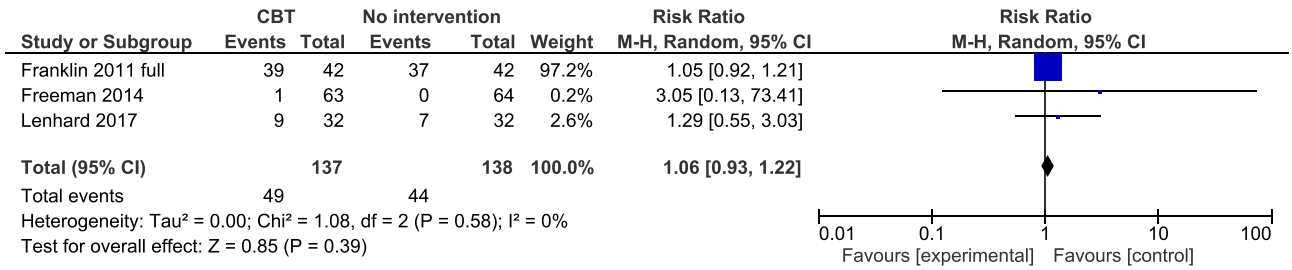
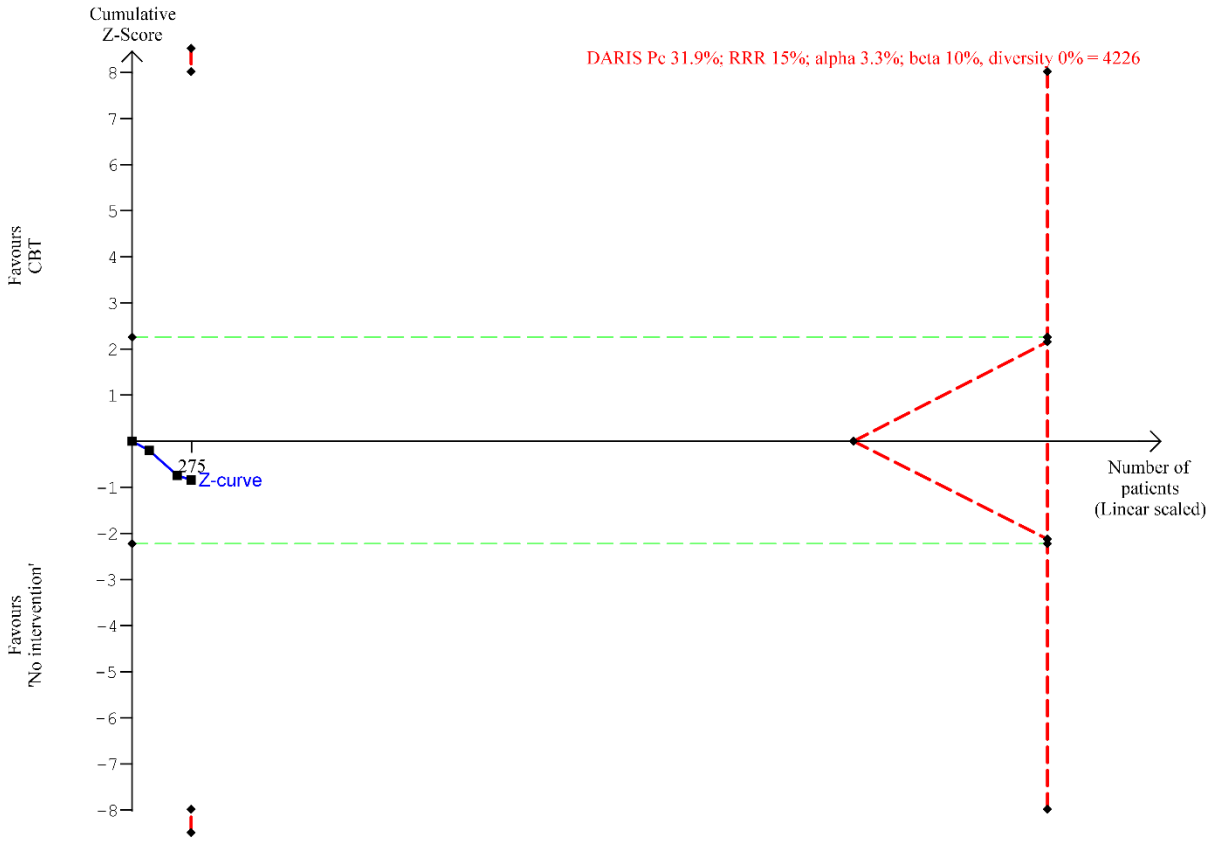


Figure S7 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus 'No Intervention' on Adverse Events



Note: The diversity-adjusted required information size for adverse events was calculated to 4226 patients based on a minimal relevant relative risk reduction of 15%, an alpha of 3.3%, a beta of 10%, and the observed diversity of 0%. Three trials with an accrued 275 patients reported proportions of patients with adverse events. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (outer wedge) or the futility boundary (inner wedge), indicating that the finding of no difference in risk reduction between cognitive behavioral therapy and 'no intervention' in the conventional meta-analysis may be a random finding due to lack of power or multiple testing. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S8 Effect of Cognitive Behavioral Therapy Versus 'No Intervention' on Lack of Remission

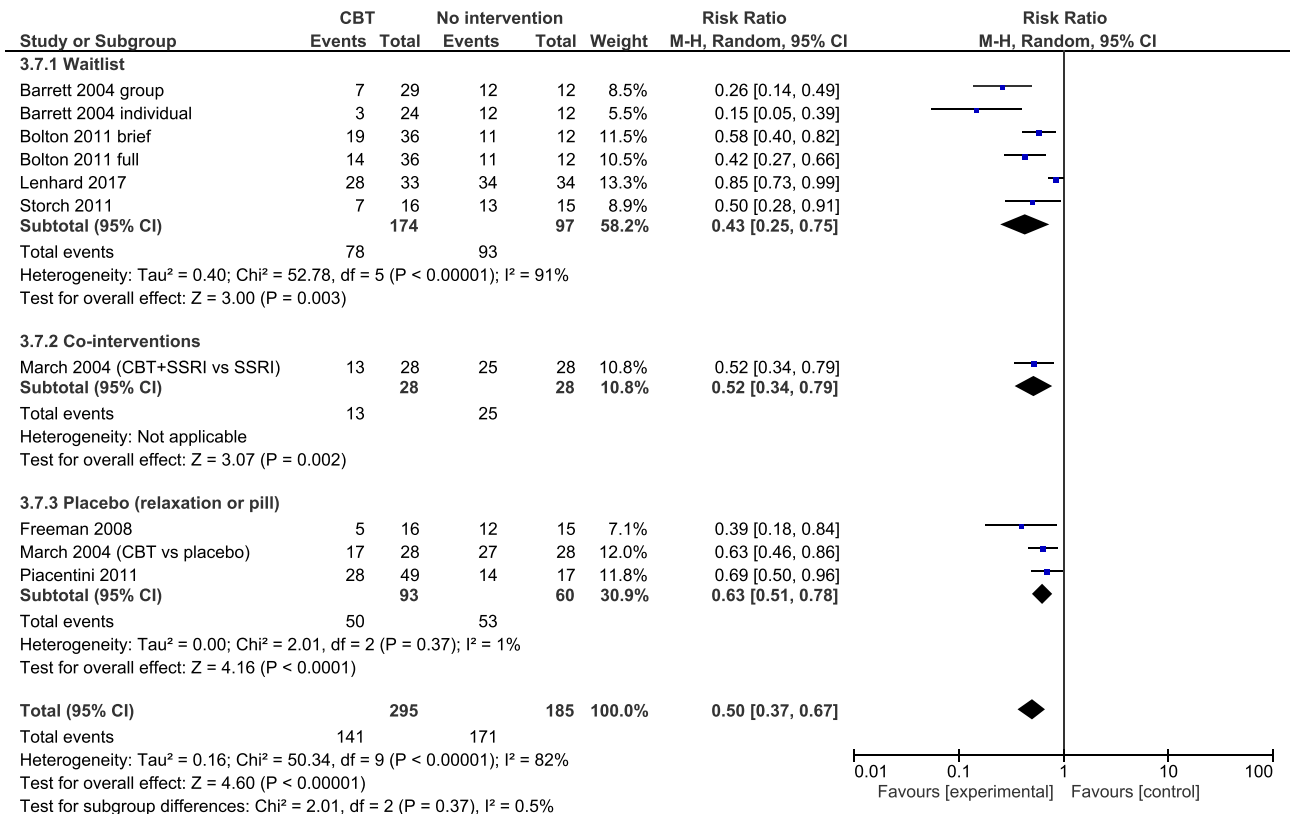
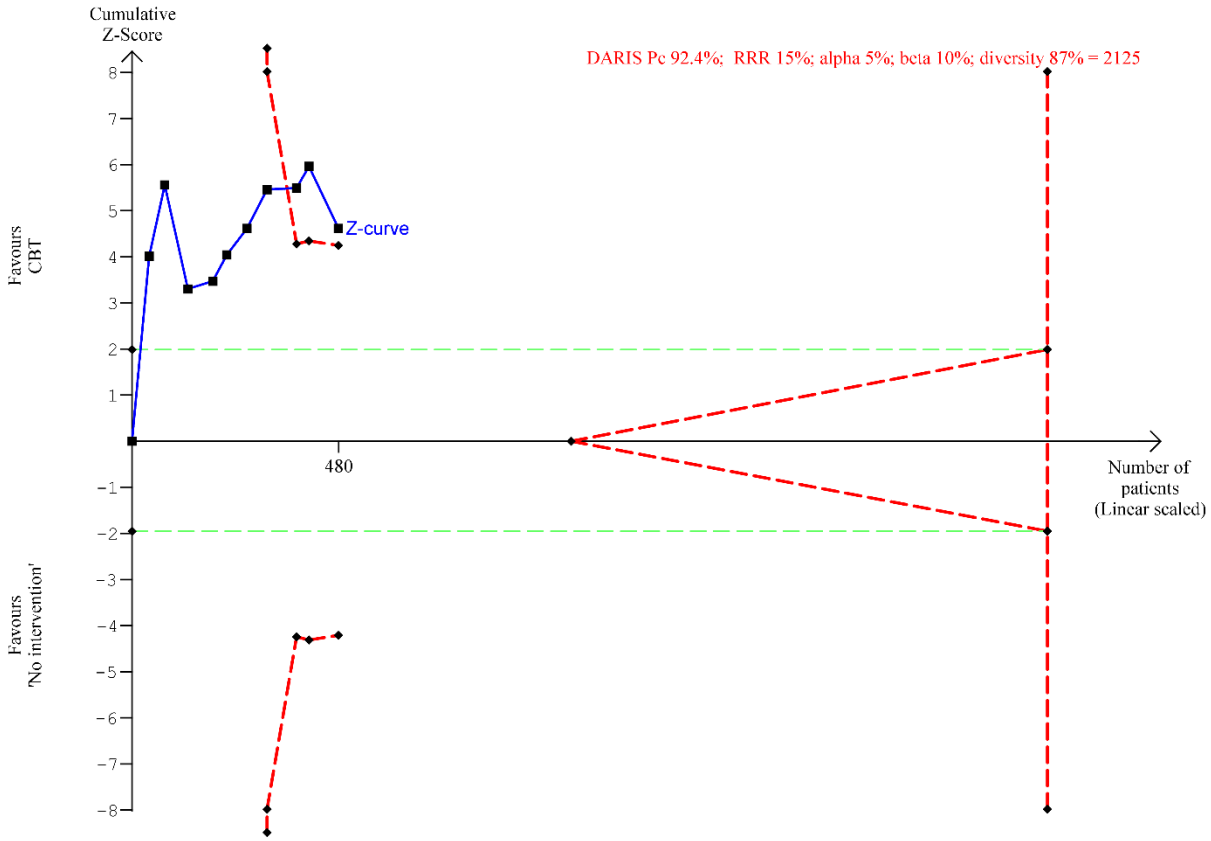
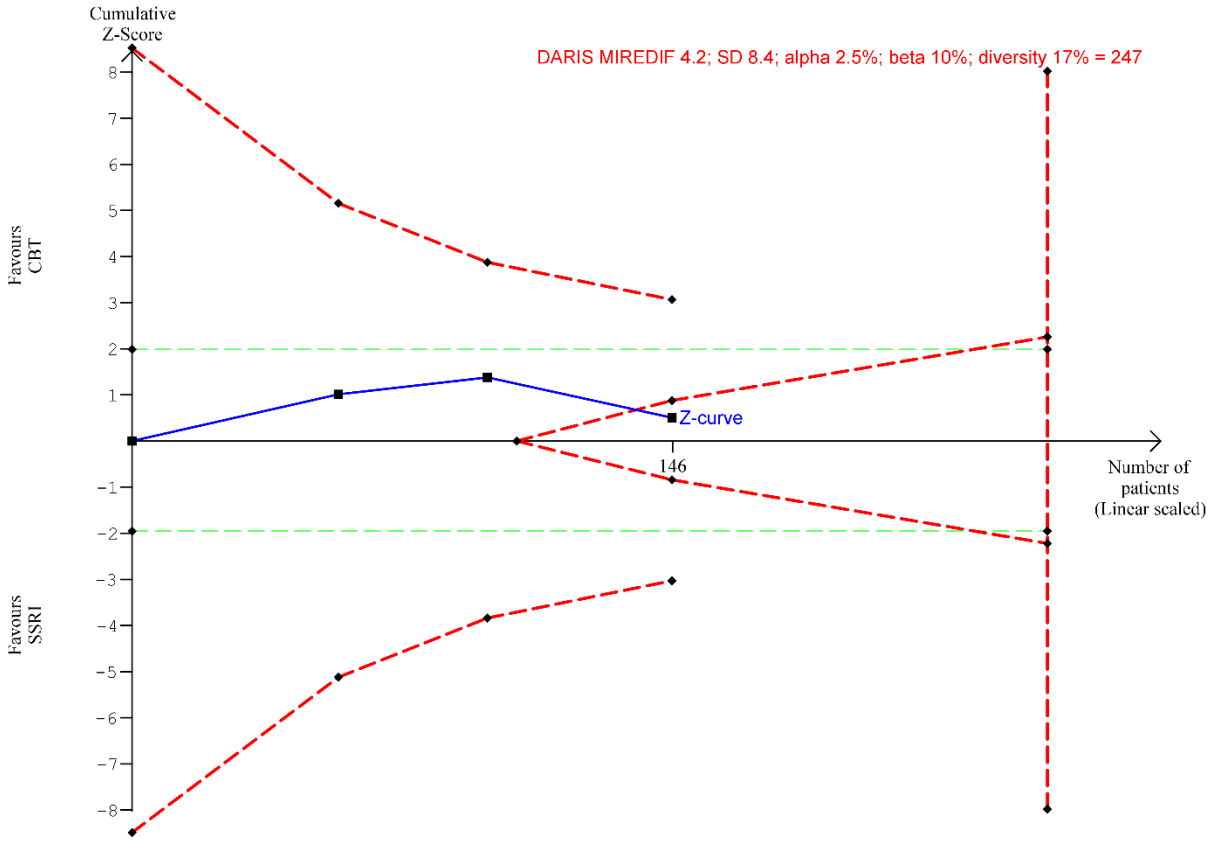


Figure S9 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus 'No Intervention' on Lack of Remission



Note: The diversity-adjusted required information size for lack of remission was calculated to 2125 patients based on a minimal relevant relative risk reduction of 15%, an alpha of 2.5%, a beta of 10%, and the observed diversity of 87%. Seven trials with an accrued 316 patients reported proportions of patients still having obsessive-compulsive disorder. The cumulative Z-curve crossed the trial sequential monitoring boundary for benefit (outer wedge). The finding in the conventional meta-analysis of a statistically significant and substantial superiority of cognitive behavioral therapy compared with 'no intervention' in reducing the proportion of participants still having obsessive-compulsive disorder is therefore unlikely to be a random finding due to lack of power or multiple testing if bias could be ignored. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S10 Trial Sequential Analysis and Diversity-Adjusted Required Information Size for The Effect of Cognitive Behavioral Therapy versus Selective Serotonin Reuptake Inhibitors on Obsessive-Compulsive Disorder Symptom Severity



Note: The diversity-adjusted required information size for Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) was calculated to 247 patients based on a minimal relevant difference of 4.2 CY-BOCS points, a SD of 8.4, an alpha of 2.5%, a beta of 10%, and the observed diversity of 17%. Three trials with an accrued 146 patients reported results from CY-BOCS. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (outer wedge). However, the cumulative Z-curve crossed the futility boundary (inner wedge), indicating that the finding in the conventional meta-analysis of no difference in reduction of symptom severity between cognitive behavioral therapy and selective serotonin reuptake inhibitors is unlikely to be a random finding due to lack of power or multiple testing if bias could be ignored. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Figure S11 Effect of Cognitive Behavioral Therapy versus Selective Serotonin Reuptake Inhibitors on Lack of Remission

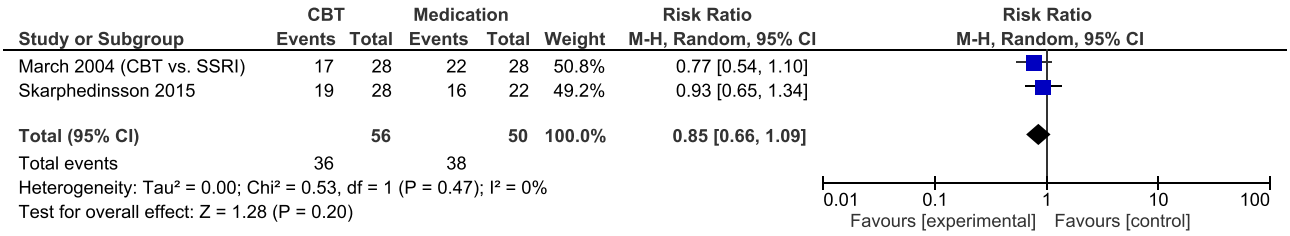
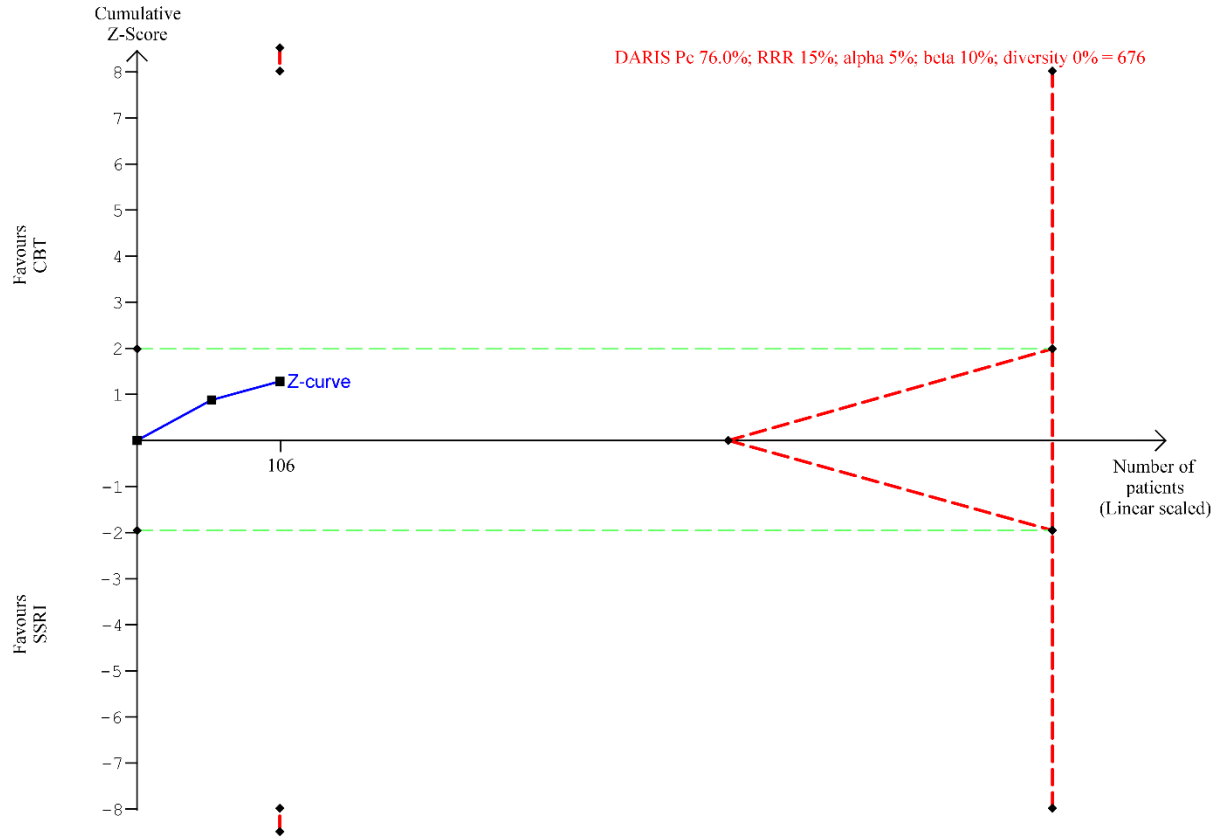


Figure S12 Trial Sequential Analysis and Diversity-Adjusted Required Information Size For The Effect of Cognitive Behavioral Therapy versus Selective Serotonin Reuptake Inhibitors on Lack Of Remission



Note: The diversity-adjusted required information size for lack of remission was calculated to 676 patients based on a minimal relevant relative risk reduction of 15%, an alpha of 2.5%, a beta of 10%, and the observed diversity of 0%. Two trials with an accrued 106 patients reported proportions of patients still having obsessive-compulsive disorder. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (outer wedge) or the futility boundary (inner wedge), indicating that the finding of no difference in risk reduction between cognitive behavioral therapy and selective serotonin reuptake inhibitors in the conventional meta-analysis may be a random finding due to lack of power or multiple testing. CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors.

Table S1

Table S1 Study Characteristics for Trials Included in The Systematic Review and Meta-Analysis

Author	Trial location	Participants	Comparisons included in meta-analyses	Baseline CY-BOCS mean (SD)	Duration of intervention
Asbahr et al. 2005	Brazil	DSM-IV OCD Comorbidity: 70% No previous or concurrent treatment for OCD (either pharmacotherapy or CBT) Age: 9-17 yr (mean=13.05, SD=2.54) 35% females	Group CBT (n=20) vs. SSRI (n=20)	Group CBT: 26.3 (4.9) SSRI: 27.0 (6.65)	12 weeks
Barrett et al. 2004	Australia	DSM-IV OCD Comorbidity: 79% (60% generalized anxiety disorder, 35% specific phobia, 19% social phobia, 17% separation anxiety disorder, 5% dysthymic disorder, 3% major depressive disorder) 22% concurrent pharmacotherapy for OCD Age: 7-17 yr (mean=11.87, SD=2.61) 51% females	Individual CBT (n=24) vs. Group CBT (n=29) vs. waitlist (n=24)	Individual CBT: 23.64 (4.3) Group CBT: 21.38 (5.62) Waitlist: 22.95 (5.49)	CBT: 14 weeks Waitlist: 4-6 weeks
Bolton et al. 2011	UK	DSM-IV OCD Comorbidity: 70% any anxiety disorder, 14% oppositional defiant disorder, 9% major depressive disorder, 8% attention deficit hyperactivity disorder, 2% tic disorder 40% concurrent pharmacotherapy for OCD Age: 10-18 yr (mean=14.50, SD=2.35) 59% females	Full individual CBT (n=36) vs. brief individual CBT (n=36) vs. waitlist (n=24)	Full CBT: 22.3 (5.0) Brief CBT: 22.0 (6.9) Waitlist: 24.2 (5.0)	12 weeks
Franklin et al. 2011	USA	DSM-IV OCD Comorbidity: 60% (44% any anxiety or mood disorder, 22% attention deficit hyperactivity disorder, 15% tic disorder) No concurrent pharmacotherapy for OCD (other than trial intervention) Partial response to SSRI in previous trial (POTS) Age: 7-17 yr (mean=13.53, SD=2.70) 54% females	Individual CBT+SSRI (n=42) vs. SSRI (n=42)	CBT+SSRI: 25.45 (5.18) SSRI: 26.08 (5.12)	12 weeks
Freeman et al. 2008	USA	DSM-IV OCD Comorbidity: 55% internalizing disorders, 36% externalizing disorders, 19% attention deficit hyperactivity disorder, 10% tic disorder 14% concurrent pharmacotherapy for OCD Age: 4-8 yr (mean=7.11, SD=1.26) 57% females	Individual CBT (n=22) vs. relaxation training (n=22)	CBT: 22.95 (3.84) Relaxation: 21.7 (4.52)	14 weeks
Freeman et al. 2014	USA	DSM-IV-TR OCD Comorbidity: 59% (23% tic disorder, 21% specific phobia, 20% generalized anxiety disorder, 13% separation anxiety disorder, 11% social phobia, 14% attention deficit hyperactivity disorder, 14% oppositional defiant disorder, 6% elimination disorder, 2% any mood disorder) 2% concurrent pharmacotherapy for OCD Age: 5-8 yr (mean=7.2, SD=1.2) 53% females	Individual CBT (n=63) vs. relaxation training (n=64)	CBT: 25.13 (4.46) Relaxation: 25.97 (3.98)	14 weeks

Lenhard et al. 2017	Sweden	DSM-5 OCD Comorbidity: 43% (13% specific phobia, 13% generalized anxiety disorder, 9% social anxiety disorder, 9% attention deficit hyperactivity disorder, 7% panic anxiety disorder, 7% major depressive disorder, 6% tic disorder, 3% dysthymia, 1% post-traumatic stress disorder) 18% concurrent pharmacotherapy for OCD Age: 12-17 yr (mean=14.60, SD=1.71) 46% females	Internet-based CBT (n=33) vs. waitlist (n=34)	CBT: 23.0 (4.31) Waitlist: 22.12 (3.91)	12 weeks
POTS 2004	USA	DSM-IV OCD Comorbidity: 80% (63% any anxiety/mood disorder, 27% any externalizing disorder, 16% tic disorder) No concurrent pharmacotherapy for OCD (other than trial intervention) Age: 7-17 yr (mean=11.78, SD=2.75) 50% females	Individual CBT (n=28) vs. individual CBT+SSRI (n=28) vs. SSRI (n=28), vs. pill-placebo (n=28)	CBT: 26.0 (4.7) CBT+SSRI: 23.8 (3.0) SSRI: 22.5 (4.7) Placebo: 25.2 (3.3)	12 weeks
Piacentini et al. 2011	USA	DSM-IV OCD Comorbidity: 66% (34% generalized anxiety disorder, 14% social anxiety disorder, 10% separation anxiety disorder, 7% specific phobia, 1% panic disorder, 14% attention deficit hyperactivity disorder, 4% oppositional defiant disorder, 4% mood disorder) No concurrent pharmacotherapy for OCD Age: 8-17 yr (mean=12.2, SD=2.5) 63% females	Individual CBT (n=49) vs. relaxation training (n=22)	CBT: 24.7 (N/A) Relaxation 25.3 (N/A)	14 weeks
Skarphedinsson et al. 2015	Denmark, Sweden, Norway	DSM-IV OCD Nonresponders from previous open trial randomized to continued treatment with either CBT or SSRI. Comorbidity: 46% (24% any anxiety disorder, 24% tic disorder, 14% attention deficit hyperactivity disorder, 6% any depressive disorder) No concurrent pharmacotherapy for OCD in the CBT group. Age: 7-17 yr (mean=14.0, SD=2.7) 52% females	Individual CBT (n=28) vs. SSRI (n=22)	CBT: 21.3 (4.0) SSRI 21.1 (3.7)	16 weeks
Storch et al. 2011	USA	DSM-IV-TR OCD Comorbidity: 97% 48% concurrent pharmacotherapy for OCD Age: 7-16 yr (mean=11.10, SD=2.65) 39% females	Internet-based CBT (n=16) vs. waitlist (n=15)	CBT: 25.38 (3.61) Waitlist: 21.27 (2.74)	CBT: 12 weeks Waitlist: 4 weeks
Williams et al. 2010	UK	ADIS-C OCD Comorbidity: 48% (13% generalized anxiety disorder, 13% specific phobia, 13% separation anxiety disorder, 6% attention deficit hyperactivity disorder, 6% social phobia, 3% dysthymia) 19% concurrent pharmacotherapy for OCD Age: 9-18 yr (mean=13.58, SD=N/A) 38% females	Individual CBT (n=11) vs. waitlist (n=10)	CBT: 23.09 (N/A) Waitlist: 21.05 (N/A)	12 weeks

Note: ADIS-C = Anxiety Disorders Interview Schedule – child version; CBT = cognitive behavioral therapy; DSM = the Diagnostic and Statistical Manual of Mental Disorders; N/A = not available; OCD = obsessive-compulsive disorder; SSRI = selective serotonin reuptake inhibitors.

Table S2

Table S2 Results of Random-Effects and Fixed-Effect Meta-Analyses on Each Assessed Outcome for Comparison 1: CBT versus No Intervention and Comparison 2: CBT versus SSRI

Comparison 1: CBT versus 'no intervention'

Outcome	N CBT	N control	Random-effects meta-analysis result	Fixed-effect meta-analysis result
OCD symptom severity (CY-BOCS)	400	301	MD=-8.51 (95% CI -10.84 to -6.18, p<.00001)	MD=-8.03 (95% CI -9.02 to -7.04, p<.00001)
Serious adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, patient-rated	160	90	SMD=-1.08 (95% CI -1.80 to -0.37, p =.003)	SMD=-0.90 (95% CI -1.19 to -0.62, p<.00001)
Level of functioning, parent-rated	223	154	SMD=-0.68 (95% CI -1.12 to -0.23, p =.003)	SMD=-0.56 (95% CI -0.78 to -0.34, p <.00001)
Quality of life	135	88	SMD=-0.39 (95% CI -0.77 to -0.02, p =.04)	SMD=-0.36 (95% CI -0.64 to -0.08, p=.01)
Adverse events	137	138	RR=1.06 (95% CI 0.93 to 1.22, p =.39)	RR=1.11 (95% CI 0.92 to 1.35, p =.28)
Lack of remission	295	185	RR=0.50 (95% CI 0.37 to 0.67, p<.00001)	RR=0.54 (95% CI 0.48 to 0.62, p<.00001)

Comparison 2: CBT versus SSRI

Outcome	N CBT	N control	Random-effects meta-analysis result	Fixed-effect meta-analysis result
OCD symptom severity (CY-BOCS)	76	70	MD=-0.75 (95% CI -3.79 to 2.29, p =.63)	MD=-0.70 (95% CI -3.46 to 2.07, p =.62)
Serious adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, patient-rated	-	-	Meta-analysis not possible	Meta-analysis not possible
Level of functioning, parent-rated	-	-	Meta-analysis not possible	Meta-analysis not possible
Quality of life	-	-	Meta-analysis not possible	Meta-analysis not possible
Adverse events	-	-	Meta-analysis not possible	Meta-analysis not possible
Lack of remission	56	50	RR=0.85 (95% CI 0.66 to 1.09, p =.20)	RR=0.84 (95% CI 0.66 to 1.09, p =.19)

Note: We found no substantial discrepancies between results from the random-effects and fixed-effect models. CBT = cognitive behavioral therapy; CI = confidence interval; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; MD = mean difference; RR = risk ratio; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

Table S3

Table S3 Imputation of Missing Outcome Data for Trials Assessing Cognitive Behavioral Therapy versus 'No Intervention' for Pediatric Obsessive-Compulsive Disorder

Outcome	Result from meta-analysis	Worst/best (2SD)	Worst/best (1SD)	Best/worst (2SD)	Best/worst (1SD)
OCD severity	MD=-8.51, 95% CI -10.84 to -6.18, p<.00001	MD=-6.11, 95% CI -8.91 to -3.30, p<.00001	MD=-7.28, 95% CI -9.81 to -4.74, p<.00001	MD=-10.59, 95% CI -13.00 to -8.18, p<.00001	MD=-9.70, 95% CI -11.96 to -7.43, p<.00001
Level of functioning (patient-rated)	SMD=-0.90, 95% CI -1.19 to -0.62, p<.00001	SMD=-0.52, 95% CI -0.79 to -0.25, p=.0001	SMD=-0.70, 95% CI -0.97 to -0.43, p<.00001	SMD=-1.14, 95% CI -1.42 to -0.86, p<.00001	SMD=-1.11, 95% CI -1.39 to -0.83, p<.00001
Level of functioning (parent-rated)	SMD=-0.68, 95% CI -1.12 to -0.23, p=.003	SMD=-0.35, 95% CI -0.81 to 0.12, p=.14	SMD=-0.50, 95% CI -0.98 to -0.02, p=.04	SMD=-0.89, 95% CI -1.32 to -0.47, p<.00001	SMD=-0.84, 95% CI -1.28 to -0.41, p=.0002
Quality of life	SMD=-0.39, 95% CI -0.77 to -0.02, p=.04	SMD=-0.11, 95% CI -0.47 to 0.26, p=.57	SMD=-0.26, 95% CI -0.65 to 0.13, p=.19	SMD=-0.60, 95% CI -0.92 to -0.27, p=.0003	SMD=-0.53, 95% CI -0.90 to -0.16, p=.005
Adverse events	RR=1.06, 95% CI 0.93 to 1.22, p=0.39	RR=1.14, 95% CI 1.01 to 1.28, p=.03		RR=0.92, 95% CI 0.47 to 1.79, p=.80	
Lack of remission	RR=0.50, 95% CI 0.37 to 0.67, p<.00001	RR=0.58, 95% CI 0.45 to 0.74, p<.00001		RR=0.41, 95% CI 0.30 to 0.55, p<.00001	

Note: CI = confidence interval; MD = mean difference; RR = risk ratio; SMD = standardized mean difference.

Table S4

Table S4 Imputation of Missing Outcome Data for Trials Assessing Cognitive Behavioral Therapy versus Selective Serotonin Reuptake Inhibitors for Pediatric Obsessive-Compulsive Disorder

Outcome	Result from meta-analysis	Worst/best (2SD)	Worst/best (1SD)	Best/worst (2SD)	Best/worst (1SD)
OCD severity	MD=-0.75, 95% CI -3.79 to 2.29, p=.63	MD=1.94, 95% CI -5.32 to 9.21, p=.60	MD=0.91, 95% CI -4.96 to 6.79, p=.76	MD=-4.32, 95% CI -7.36 to -1.28, p=.005	MD=-2.70, 95% CI -5.41 to 0.01, p=.05
Lack of remission	RR=0.85, 95% CI 0.66 to 1.09, p=.20	RR=1.03, 95% CI 0.66 to 1.61, p=.89		RR=0.77, 95% CI 0.54 to 1.10, p=.15	

Note: CI = confidence interval; MD = mean difference; RR = risk ratio; SMD = standardized mean difference.

Paper II

Uhre et al. Reply to Storch et al.. *Journal of the American Academy of Child & Adolescent Psychiatry*, 2020; 59(7), 787-791.

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Published manuscript.

(PUTS) assessment tools, all of which are in the public domain and therefore no royalties are received. He has received honoraria and travel support for lectures at academic institutions and from TLC Foundation for BFRBs, Tourette Association of America, and International OCD Foundation for behavior therapy trainings. He has received publication royalties from Guilford Press and Oxford University Press. Dr. Bloch has received grant or research support from Therapix Biosciences, Neurocrine Biosciences, Janssen Pharmaceuticals, Biohaven Pharmaceuticals, NIH, National Alliance for Research on Schizophrenia and Depression (NARSAD), Lesbian Health Fund, Yale Foundation for Lesbian and Gay Studies (FLAGS), and Patterson Foundation. He has served on the advisory board/data monitoring and safety board of Therapix Biosciences. He has served as associate editor of *Journal of Child Psychology and Psychiatry* and on the editorial boards of *Journal of Child and Adolescent Psychopharmacology* and *Depression and Anxiety*. He has received royalties from Wolters Kluwer for *Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, Fifth Edition*. He has received moonlighting pay from the Veteran's Administration. Dr. Cervin has received current funding from Bror Gadelius Foundation, Lions Research Foundation Skåne, Lindhaga Foundation, Sven Jerring Foundation, and Region Skåne. Dr. McGuire has received support from Tourette Association of America, American Academy of Neurology, Brain Research Foundation, American Psychological Foundation, and Hilda and Preston Davis Family Foundation. He has received royalties from Elsevier and has served as a consultant for Signant Health, Syneos Health, and Luminopia. Dr. McCracken has received consultant income from Roche, Octapharma, GW Biosciences, and Tris Pharmaceuticals, and he has received clinical trial research contracts from Roche. Dr. McKay has received royalties from Springer Publishing, Wiley, Elsevier, and Guilford Press. Dr. Franklin has received book royalties from Guildford Press. Dr. Walkup has received funding from Hartwell Foundation and Tourette Syndrome Association. He has served on the speakers' bureau for Tourette Syndrome Association. He has received book royalties from Guilford Press and Oxford University Press. Dr. Stewart has received grant or research support from American Academy of Child and Adolescent Psychiatry, Anxiety and Depression Association of America, International OCD Foundation, Canadian Institutes of Health Research, Michael Smith Foundation for Health Research, BC Children's Hospital Foundation, and Provincial Health Services Authority. She has served on the Scientific Clinical Advisory Board of International OCD Foundation and on the Scientific Advisory Board of Anxiety Canada. She is an author of the OCD Family Functioning (OFF) Scale. She has served on the editorial board of *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. She has received honoraria from National Institute of Mental Health and Neuroscience, Yale Child Study Center, Aarhus University Hospital, International Anxiety Disorder Symposium, SickKids Hospital, Toronto, and Canadian Academy of Child and Adolescent Psychiatry. Dr. Goodman has received research funding from NIH, Biohaven Pharmaceuticals, and Mater Foundation. He has received honoraria from Biohaven Pharmaceuticals and Neurocrine. Drs. De Nadai, Farrell, Riemann, Wagner, Schneider, Williams, Abramowitz, and Fitzgerald have reported no biomedical financial interests or potential conflicts of interest.

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Dr. Uhre *et al.* Reply:

In a recent letter to the editor, a group of clinician-researchers posit that the conclusions in our published systematic review[1] on cognitive-behavioral therapy (CBT) for pediatric obsessive-compulsive disorder (OCD) are based on inappropriate methodology. In this reply, we address the concerns expressed by Storch *et al.*[2]

Storch *et al.* specify our use of the 2011 version of the Cochrane risk-of-bias tool[3] to assess risk of bias in included trials as their main concern. The 2011 version of the Cochrane risk-of-bias tool is the most commonly used tool to assess risk of bias and has been widely used in both Cochrane and non-Cochrane reviews.[4] However, as mentioned by Storch *et al.*,[2] a revised Cochrane risk-of-bias tool for randomized trials (RoB-2)[5] was released in 2019 to address limitations of the previous version. In the 2011 version, lack of blinding of participants and treatment providers domain in unblinded trials is always rated at high risk of bias. Because a judgment of high risk within any domain results in the trial being considered at an overall high risk of bias, psychotherapeutic trials, which typically are unblinded by design, would de facto be assessed at an overall high risk of bias. We discuss this potential limitation in the discussion section of our review. Only one of the included trials had low risk of bias in the remaining bias domains and was therefore potentially less affected by bias. RoB-2 was not released in time for us to have used it in our review, and we acknowledge that our risk of bias assessment may have benefited from the updates in RoB-2. Therefore, two authors (V.F.U. and N.N.L.) independently reassessed risk of bias for Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) end-of-treatment scores using RoB-2. A final consensus assessment was reached through

TABLE 1 Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) End-of-Treatment Results

Study	Randomization process	Deviations from intended intervention	Missing outcome Data	Measurement of outcome	Selection of reported result	overall
Asbahr *et al.*, 2005[6]	?	?	+	+	?	?
Barrett *et al.*, 2004[7]	?	?	+	−	?	−
Bolton *et al.*, 2011[8]	+	−	?	+	+	−
Franklin *et al.*, 2011[9]	?	−	?	+	+	−
Freeman *et al.*, 2008[10]	?	+	+	+	+	?
Freeman *et al.*, 2014[11]	?	−	−	+	+	−
Lenhard *et al.*, 2017[12]	+	+	+	+	+	+
Piacentini *et al.*, 2011[13]	?	+	−	+	+	−
March, 2004[14]	+	+	+	+	+	+
Skarphedinsson *et al.*, 2015[15]	+	−	−	?	+	−
Storch *et al.*, 2011[16]	−	+	−	−	?	−
Williams *et al.*, 2010[17]	?	+	−	+	?	−

***Note**: Risk of bias for CY-BOCS end-of-treatment scores of included trials as assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB-2). + = low risk; ? = some concerns; − = high risk.*

discussion of any discrepancies in the independent assessments. Our new assessment showed that the CY-BOCS end-of-treatment result has an overall low risk of bias in only 2 of 12 included trials (Table 1). Restricting the random-effects meta-analysis to the two trials with overall low risk of bias reduced the difference in favor of CBT versus no intervention (trials with overall low risk of bias: mean deviation = −5.01, 95% CI = −7.31 to −2.74, $p <$ .00001; all trials: mean deviation = −8.51, 95% CI = −10.84 to −6.18, $p <$ .00001). Additional information on the risk of bias judgments is available online at http://www.ctu.dk/media/13946/ITT-CYBOCS-EOT.xlsx.

Storch *et al.*[2] also assert that our use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in our evaluation of the certainty of the evidence is inappropriate. According to Storch *et al.*,[2] the certainty of the evidence should not be rated as low because our sensitivity analyses did not alter the results of the original analyses and because "CBT efficacy is supported by both definitive meta-analyses and large trials that are rated at low risk of bias by authoritative sources," but the authors do not cite these supposed "authoritative sources." As stated in our review, "previous reviews support the recommendation of CBT for pediatric OCD, but limitations such as not assessing risk of bias in included trials, pooling results from randomized and noncontrolled trials, or including only symptom severity as an outcome measure may have led to inaccurate conclusions regarding the efficacy of CBT."[1] To our knowledge, ours is the first review of CBT for pediatric OCD to assess both systematic errors (risk of bias) and random errors (play of chance). We followed the guidelines described in the GRADE handbook.[18] Briefly, GRADE includes a separate assessment of the certainty of the evidence for each outcome based on five factors: study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. In our review, we provide the reasons for downgrading the certainty of the evidence for each outcome of each meta-analysis. For example, the certainty of the evidence for CBT versus no intervention on severity of OCD was downgraded twice: once owing to study limitations (all trials were at an overall high risk of bias) and once owing to inconsistency of results (substantial statistical heterogeneity was present and was not explained by planned or post hoc subgroup analyses). The certainty of the evidence after having downgraded twice is, by GRADE definition, low. Moreover, our sensitivity analyses assessed only the potential impact of missing data and therefore did not account for all factors that may result in downgrading of the certainty of the evidence. Thus, the certainty of the evidence can be low or very low even for outcomes for which the conclusions of

the original analyses are unchanged by subsequent sensitivity analyses.

Storch *et al.*[2] incorrectly state that we included only 9 of 29 existing randomized controlled trials (we included 12 trials) and claim that we "exclude relevant CBT studies as well as pharmacotherapy only trials." The alleged narrow focus stems from our decision to focus exclusively, but extensively, on the evidence base of (any type of) CBT for pediatric OCD. While we acknowledge that other randomized controlled trials, such as pharmacotherapy only trials or CBT versus CBT trials (eg, brief versus full CBT), are also useful and important, they do not evaluate CBT versus a non-CBT comparison group and are therefore not within the scope of our review (see our predefined inclusion and exclusion criteria in our protocol[19]).

Storch *et al.*[2] further claim that "some of the included CBT studies were inappropriately grouped despite dramatically different protocols (eg, Internet CBT grouped with minimal in-person contact) and treatment doses." Many study characteristics that differ between included CBT trials could potentially result in substantial heterogeneity in a meta-analysis. For this reason, our review included the following planned subgroup analyses for all primary outcomes (CY-BOCS score, serious adverse events, and level of functioning) when at least two trials or comparisons provided data for the analysis: type of control intervention, type of CBT assessed (ie, individual, group format, or Internet-based), and trials with blinded outcome assessors compared with trials without blinded outcome assessors. We had insufficient data for the following planned subgroup analyses for all primary outcomes: trials at low risk of bias versus trials at high risk of bias, children ($<$13 years of age) versus adolescents ($\geq$13 years of age), severe OCD versus mild to moderate OCD, and OCD with one or more comorbid psychiatric disorders versus OCD without comorbidity. In our CBT versus no intervention meta-analyses, subgroup analyses showed evidence of a difference in favor of conventional CBT versus Internet-delivered CBT on CY-BOCS score and on patient-rated level of functioning (see Supplement 2 of our review).

Storch *et al.*[2] also note that we "seem to suggest that CBT may have significant side effects or risk of harm." In our Trial Sequential Analysis, the diversity-adjusted required information size for adverse events was calculated to be 4,226 patients based on a minimal relevant relative risk reduction of 15%, an α of 3.3%, a β of 10%, and the observed diversity of 0%. Only three trials with an accrued 275 patients reported proportions of patients with adverse events. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit or the futility boundary, indicating that the finding of no difference in risk reduction between CBT and no intervention in the conventional meta-analysis may be a random finding owing to lack of power or multiple testing (see Supplement 7 of our review). We state in our review: "as we do not have data to disentangle CBT-related adverse events and adverse events related to concomitant use of SSRI [selective serotonin reuptake inhibitor], the main finding is that knowledge about harmful effects of CBT is lacking."[1] We are pleasantly surprised to learn that Storch *et al.*[2] found evidence to suggest that adverse events happen in less than 0.01% of treated patients and will be eagerly awaiting the public availability of these data. We note, however, that even rare serious adverse events are important to identify.

Storch *et al.*[2] further state that our approach effectively prevents clinicians from recommending evidence-based therapies; that our review dismisses 15 years of cumulative evidence from randomized controlled trials; that our review misrepresents the state of the evidence to the detriment of children and families; and that our flawed findings have the potential to deter clinicians from using treatments that work, reduce third-party support for covering necessary care, and create ongoing and unnecessary access barriers for children and families, preventing patients from accessing a treatment likely to provide substantial and durable relief. These claims appear to rest on the misconception that we advise against the use of CBT for pediatric OCD, when, in fact, we only make recommendations concerning future trials in this field. Moreover, our recommendations as well as our conclusion that "CBT may be an effective treatment for pediatric OCD" are comparable to those of previous canonical reviews. For example, the most recent Cochrane review concluded that "behavioral or cognitive-behavioral therapy alone appears to be an effective treatment for OCD in children and adolescents" and "additional higher quality trials are needed to confirm these findings."[20]

In our view, it is important to be cognizant of how and to what extent limitations in trials potentially influence the intervention effect estimates and what can be done in future trials to alleviate these limitations. Evidence from meta-epidemiological studies show that effect estimates are exaggerated when the domains assessed in our review are at high risk of bias.[21–29] This is particularly important when reviewing the effects of a psychotherapy, where lack of blinding of participants and the use of subjectively rated outcomes (eg, CY-BOCS) are common practice, but it also pertains to medication trials, in which common adverse effects may lead to unblinding, which in RoB-2 is addressed with the signaling question: "did participants experience side effects or toxicities that they know to be specific to one of the interventions?" Storch *et al.*[2] believe that concerns about overall risk of bias should be mitigated for multiple

reasons that are misunderstandings on their part. They incorrectly state that "all participants in the OCD studies received an active intervention (ie, CBT versus RT)" (in fact, 5 of the 12 trials used waitlist control) and that "all outcome raters were blinded" (in fact, outcome assessors were not blinded in 3 of 12 trials). Storch *et al.*[2] further reference what they believe to be a disparate bias risk assessment in a previous review of CBT for pediatric OCD, but which, similar to our review, highlighted potential problems with random allocation sequence generation, allocation concealment, blinding of outcome assessors, and incomplete outcome data in included trials.[30]

Even if the claims made by Storch *et al.*[2] that "the quality of research in CBT rivals or exceeds that in many areas of biomedicine" and that "virtually all OCD stakeholders have achieved consensus regarding the efficacy of CBT for pediatric OCD and its place as a frontline intervention" are true, the need for additional rigorously designed trials to ascertain the estimated effects of the intervention stands—especially considering the prominent role of CBT as an evidence-based treatment for pediatric OCD.

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Paper III

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

Authors: Valdemar Funch Uhre, Kit Melissa Larsen, Damian Marc Herz, William Baaré, Anne Katrine Pagsberg, Hartwig Roman Siebner.

Unpublished manuscript.

Working title: 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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Conflicts of Interest:
Hartwig Roman Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark, and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora, Denmark, and Lundbeck AS, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers,

Amsterdam, The Netherlands. Hartwig Roman Siebner has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark. Valdemar Funch Uhre, Kit Melissa Larsen, Damian Marc Herz, William Baaré and Anne Katrine Pagsberg have no conflicts of interest to declare.

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Keywords:
response inhibition, cognitive inhibition, interference, functional magnetic resonance imaging, fMRI, anterior cingulate, ocd

Color:
Color should be used for Figure 1 and Figure 2.

Abstract

Background:

Patients with obsessive compulsive disorder (OCD) often show deficits in inhibitory control, which may underlie poor control over obsessions and compulsions. Inhibitory control in OCD has been examined in a series of functional magnetic resonance imaging (fMRI) articles using a variety of tasks. Evidence from previous coordinate-based activation likelihood estimation (ALE) meta-analyses suggests abnormal task-related activation in fronto-striatal circuits. However, new recommendations for conducting more rigorous ALE meta-analyses have since emerged.

Objectives:

First, to reevaluate the evidence for abnormal brain activation during performance of inhibitory control tasks in OCD adhering to the updated ALE guidelines, 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. We first performed ALE meta-analyses to elucidate brain areas in which case-control activation differences converged across articles. To extend previous work, we then separately evaluated response inhibition experiments (i.e., experiments requiring inhibition of a prepotent response without execution of an alternative response) and cognitive inhibition experiments (i.e., experiments requiring inhibition of a prepotent response and execution of an alternative response).

Results:

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:

Our findings partially corroborate a growing body of literature that implicates the dACC in impaired inhibitory control in OCD. Our findings also 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.

1. Introduction

Obsessive compulsive disorder (OCD) is a severe and disabling psychiatric disorder with a lifetime prevalence of 2% to 3% (Ruscio, Stein, Chiu, & Kessler, 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 ego-dystonic, excessive and repetitive overt or mental acts (e.g., extreme hand-washing or checking rituals) (American Psychiatric Association, 2013; Robbins, Vaghi, & Banca, 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 & Schachar, 2010; van Velzen, Vriend, de Wit, & van den Heuvel, 2014). Historically, the concept of inhibition has been used to describe several different phenomena (Bari & 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 withholding 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 (hereafter referred to as 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 (hereafter referred to as 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; L. A. Page et al., 2009; Roth et al., 2007). Also, small sample sizes and methodological flexibility in processing pipelines (Carp, 2012) and statistical procedures (Eklund, Nichols, & Knutsson, 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, Sim, & Chen, 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 and more stringent recommendations for conducting and reporting ALE meta-analysis have since been published (Eickhoff et al., 2016; Müller et al., 2018). 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, only partially overlapping, networks (Hung, Gaillard, Yarmak, & Arsalidou, 2018; Swick, Ashley, & Turken, 2011; Zhang, Geng, & Lee, 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 the new 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 (M. J. Page et al., 2021) and follows the best-practice recommendations for conducting coordinate-based meta-analyses (Müller et al., 2018). We systematically searched for eligible articles on Web of Knowledge, ScienceDirect, Scopus and PubMed (final search on March 19, 2021), using the search terms "ocd" OR "obsessive compulsive disorder" AND "fmri" OR "functional magnetic resonance imaging" AND "inhibition" 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 & 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, Milic, & Mast, 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 any inhibitory control task which compared one of the contrasts stop, no-go, switch, 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 region of interest analysis based on a priori assumptions about brain areas of interest or did not find significant case-control differences for an inhibitory control contrast. We did, however, include articles that presented results from region of interest analysis based on a task main effect or previous meta-analysis data, since these results are likely less affected by bias.

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, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2016), 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 best-practice standards, we assessed the significance of convergence of activation foci using a cluster-level familywise error-corrected threshold of $P < 0.05$ (Eickhoff et al., 2012; Eickhoff et al., 2009; Eickhoff et al., 2016; Turkeltaub et al., 2012). We restricted our ALE analyses to contrasts based on at least 17 experiments, as empirical simulations suggest that this minimum prevents excessive contribution of individual experiments (Eickhoff et al., 2016). Additional details on the ALE procedure is found elsewhere (Eickhoff et al., 2012; Eickhoff et al., 2009).

Our contrasts of interest were OCD ≠ HC, OCD > HC, and OCD < HC. In the interest of isolating different processes involved in inhibitory control, we repeated 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 48 full-text articles amongst 343 non-duplicate records retrieved from database search were selected for eligibility assessment (Figure 1). We did not identify any additional records from other sources. We included 21 articles that compared activation related to inhibitory control in 394 OCD patients and 410 healthy controls in 35 experiments in the review (Table 1). Twenty-six articles were excluded based on our pre-defined criteria, of which eight 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; Viard et al., 2005). Furthermore, one article (Tolin, Witt, & Stevens, 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 score=22.7 [SD=5.4]). 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

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 OCD relative to HC (i.e., OCD > HC) as only 15 experiments (233 unique subjects; average of 16.7 subjects per experiment) reported results for this contrast. Twenty experiments (314 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 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) ($P_{cFWE} = .04$, cluster volume of 824 mm^3; see Figure 2). This location was reported in four 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 the OCD > HC main effect and the OCD < HC main effect 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; average of 15.4 subjects per experiment) or hypoactivation in OCD relative to HC (15 experiments and 221 unique subjects; average of 15.4 subjects per experiment).

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 updated guidelines 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 ALE based on 35 experiments, comprising observations from 394 OCD patients and 410 HC subjects, identified no brain region that showed a consistent change in task-related activation between patients with OCD and HC subjects. We were 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 tasks, as all previous meta-analyses of inhibitory control or broader executive functions in OCD have reported abnormal activation. Carlisi et al. (2017), Norman et al. (2016) and Norman et al. (2019) used the anisotropic effect size version of seed-based *d* mapping (AES-SDM) to combine peak coordinates and t-maps, thereby increasing the statistical power of the meta-analysis (https://www.sdmproject.com/) (Radua et al., 2014). All three reviews used a voxel *p* value threshold of $p < .005$ (uncorrected) in combination with either or both of a cluster extend threshold and a peak SMD z value threshold of at least 1, which attempts to balance sensitivity and specificity (Radua et al., 2012). While AES-SDM tests for spatial convergence with spatial assumptions that are likely not met (Albajes-Eizagirre & Radua, 2018), a newer iteration of SDM instead relies on permutation of subject images (SDM-PSI) (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). However, although SDM-PSI is more sensitive than AES-SDM when multiple effects are present, both versions adequately control the family-wise error rate (Albajes-Eizagirre et al., 2019). Carlisi et al. (2017), Norman et al. (2016) and Norman et al. (2019) most consistently found abnormal activation related to inhibitory control in a cluster comprising the rostral and dorsal anterior cingulate cortex and the medial prefrontal cortex and subcortically in the caudate, putamen and insula. Brem et al. (2012), Del Casale et al. (2016), Eng, Sim & Chen (2015) and Menzies et al. (2008) used ALE in their reviews. However, Brem et al. (2012), Eng, Sim & Chen (2015) and Menzies et al. (2008) performed meta-analyses on activation differences obtained from less than the currently recommended minimum of 17 fMRI experiments (Eickhoff et al., 2016). Consequently, results from their meta-analyses were underpowered to detect even moderate sized effects and were furthermore

at high 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 neuroimaging data (Chumbley & Friston, 2009) and to entail both low sensitivity and high susceptibility to spurious, false positive findings (Eickhoff et al., 2016). However, 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.

Thirty-five experiments reported results for the OCD ≠ HC contrast. Using cluster-level FWE thresholding, this sample size 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). If abnormal activity related to inhibitory control in a brain area exists, why might most experiments not find activation differences within that area? One reason could be that the precise neural correlates of abnormal inhibitory control in OCD depend on the extent to which different subprocesses of inhibitory control are engaged by different task demands (Criaud & Boulinguez, 2013; Hung et al., 2018; Sebastian et al., 2013; Zhang et al., 2017). Most obviously, a distinction can be made at the behavioral level between inhibitory control tasks where the participant occasionally must inhibit a pre-potent response without initiating a different 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). Indeed, our meta-analyses restricted to cognitive inhibition experiments revealed abnormal activation in dACC for OCD relative to HC subjects, which was driven predominantly by hypoactivation in OCD patients. More precisely, this cluster was observed at the border between the rostral dACC and the pregenual region of the ventral ACC in an area of the ACC with strong connections to the dorsal PFC and striatum (Stevens, Hurley, & Taber,

2011). The dACC and PFC, together with striatum, are involved in functionally segregated parallel fronto-striatal circuits (Alexander, DeLong, & Strick, 1986), which converging lines of evidence have implicated in the pathophysiology of OCD (Burguière, Monteiro, Mallet, Feng, & Graybiel, 2015; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Pauls, Abramovitch, Rauch, & Geller, 2014).

Our finding of abnormal activation of the dACC was reported in only 4 of the 25 experiments included in the analysis (corresponding to 16%), suggesting that substantial heterogeneity was still present in this sub-group consisting of only cognitive inhibition experiments. Another potential major source of heterogeneity is the OCD samples included in the review. The incidence of OCD is bimodal, with an early peak at approximately 9 to 10 years of age and a later peak in the early 20's (Geller, Homayoun, & Johnson, 2021). Among other things, early-onset OCD is associated with different symptom types, poorer insight, higher rates of comorbidity, better treatment response and higher rates of remissions than is late-onset OCD (Geller et al., 2021). Moreover, the risk of OCD is twice as high for first-degree relatives to early-onset OCD patients than it is for first-degree relatives to late-onset OCD patients (do Rosario-Campos et al., 2005; Nestadt et al., 2000). Some even argue that early-onset OCD and late-onset OCD ought to be classified as distinct psychiatric disorders (Geller et al., 2001). While we were not able to assess potential effects of age of OCD onset on the neural underpinnings of inhibitory control, such effects would be worthwhile to explore in future neuroimaging studies.

Most recently, it has been suggested that impaired inhibitory control in OCD manifests only later in the trajectory of the disorder (Marzuki, Sahakian, & Robbins, 2020), although abnormal brain activation during the early phase of OCD has also been reported (Nakao et al., 2009). This raises an important question: is impaired inhibitory control a primary dysfunction that contributes to OCD symptomatology or something secondary that dynamically changes during the progression of the disorder? The structure and function of the brain may be altered not only by disease duration, but also by confounding factors such as previous or current treatments and compensatory behavioral strategies that emerge to cope with distressing symptoms.

These confounders are likely less pronounced in pediatric OCD where the rate of remission is greater and the duration of the disorder shorter. Thus, research on pediatric OCD may be better suited to reveal primary brain alterations in networks underlying inhibitory control. On the other hand, inhibitory control in pediatric OCD samples is potentially affected by age-specific abnormalities in the maturation of the underlying brain networks during childhood and adolescence (Huyser, Veltman, de Haan, & Boer, 2009). One study of age effects on striatal and thalamic connectivity to medial frontal cortex found reduced connectivity of the dorsal striatum to ACC only in the youngest OCD patients compared to HC subjects, whereas increased connectivity of the dorsal striatum to the ventral medial frontal cortex was observed at all developmental stages (Fitzgerald et al., 2011). Another study found an age-dependent abnormal error-related activation of ACC in pediatric OCD patients. Age-specific dysfunction of the ACC appears to be paralleled by altered volumetric maturation of ACC in pediatric OCD, which possibly reflects abnormal neuronal pruning during development (Rosenberg & Keshavan, 1998). However, our 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 pediatric samples. Although cross-sectional studies offer some insight into maturational effects on the underpinnings of inhibitory control in OCD, longitudinal studies which track and characterize the development of fronto-striatal networks over a longer period of time are needed to better elucidate the role of inhibitory control as the disorder progresses.

Several limitations of our review need mentioning. Our ALE approach relied on reported coordinates for peak activation differences rather than non-thresholded statistical maps for group differences. As such, information about the size of the effect was not modelled and true group differences may consequently have been lost. 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 cooccur with affective disorders (Gillan, Fineberg, & Robbins, 2017) and share features of affective dysregulation linked to abnormal dACC activity (Milad & Rauch, 2012; Wood & Ahmari, 2015). Comorbid affective disorders were

common in the OCD samples included in this review and may therefore also have contributed to the effects observed.

To conclude, using a stringent meta-analytic approach, our finding of abnormal dACC activation in OCD during inhibitory control substantiates similar findings in previous meta-analyses (Carlisi et al., 2017; Norman et al., 2016; Norman et al., 2019) and suggests that different inhibitory control subprocesses contribute to abnormal activation in OCD. Therefore, more detailed examination of these subprocesses represents an important avenue for further investigation.

5. Acknowledgements:

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Figure 1. PRISMA flow chart for the selection of articles included in the review.

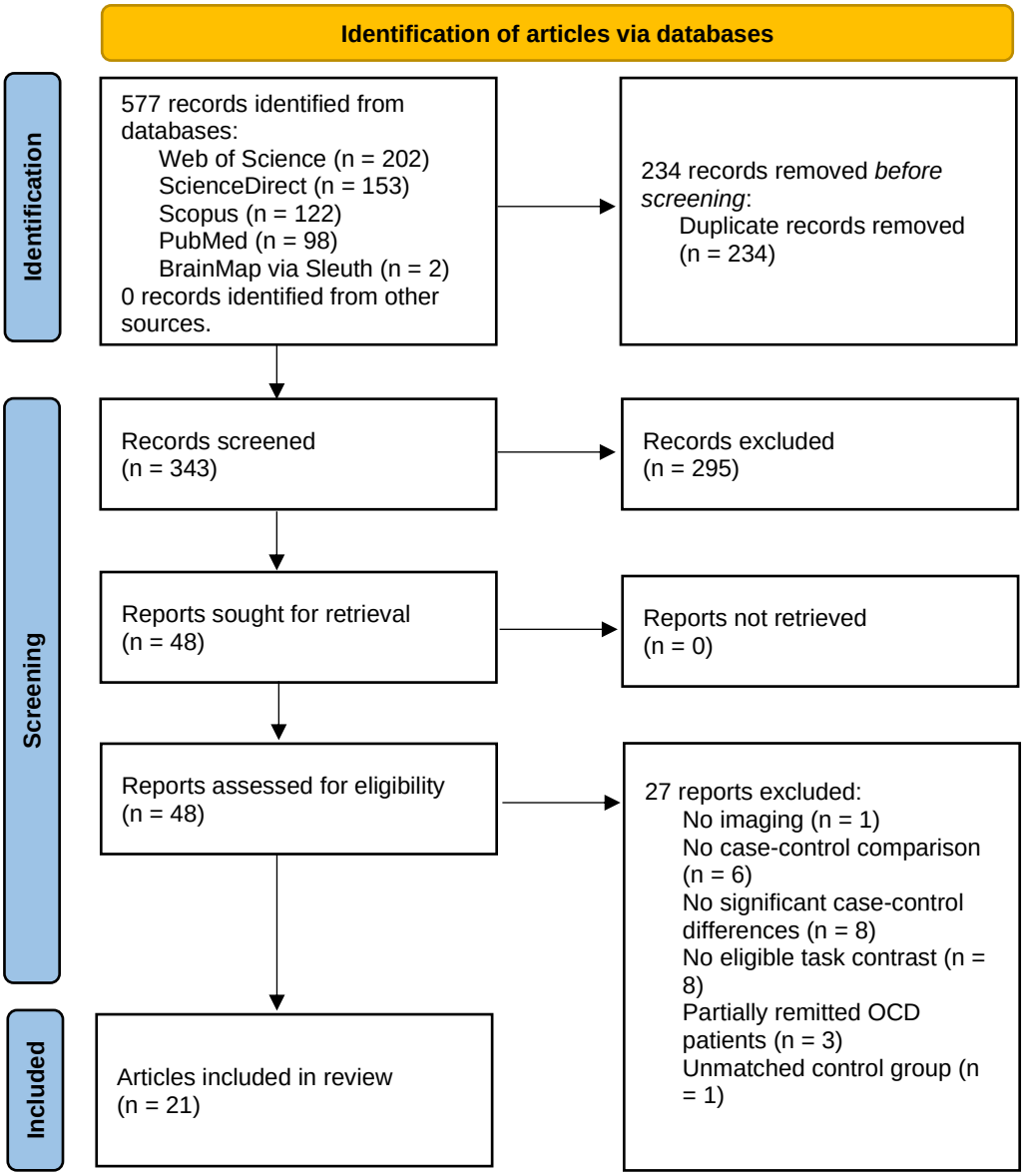

Figure 2. Meta-analysis results for cognitive inhibition experiments overlaid on the MNI-152 template brain. Abnormal activation during cognitive inhibition was observed for OCD patients when compared to HC subjects in a cluster in the dorsal anterior cingulate (dACC/BA32) extending into the medial frontal gyrus (BA6 and BA9). Note: HC = healthy control; OCD = obsessive compulsive disorder; L = left; R = right.

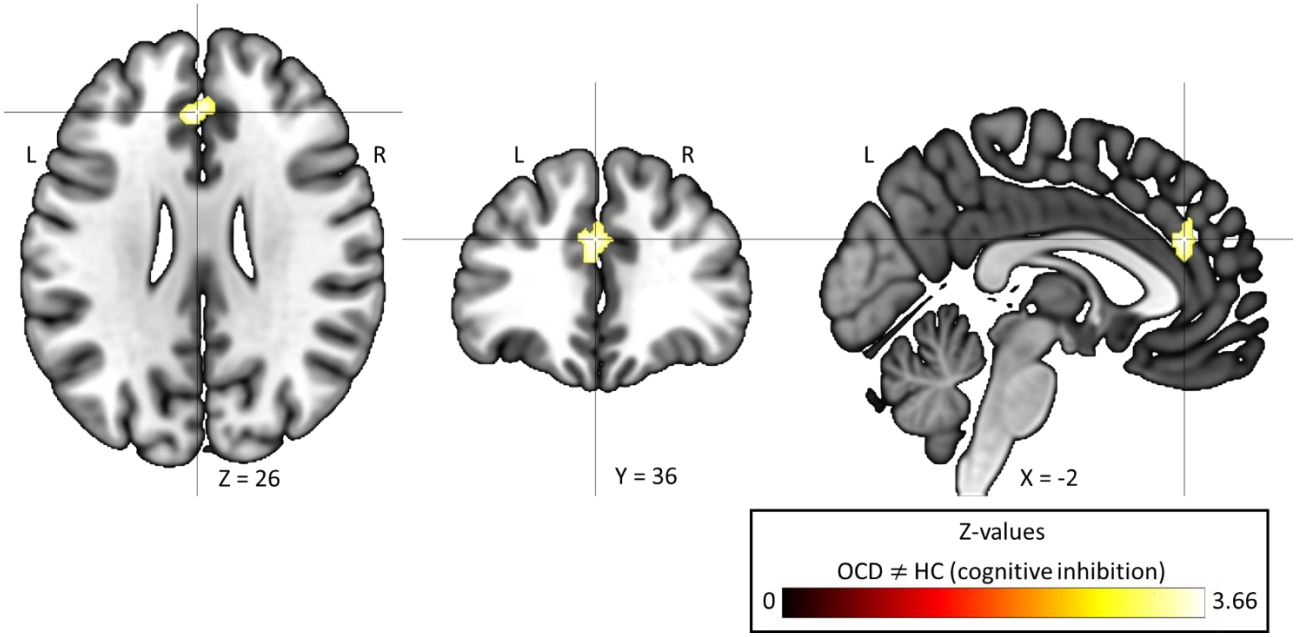

Table 1 Articles included in the meta-analysis

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	
Schlosser 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 task	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
Yucel et al., 2007	19	19	Multisource interference task	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.

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=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%).	20.0 (NA, 5.8)
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. Overall comorbidity: 10.5% (GAD=10.5%). Overall medication: 73.7% (SSRI=68.4%, tricyclic antidepressant=5.3%).	19.95 (NA, 5.98)
Nabeyama et al., 2008	OCD: 11 (63.6) HC: 19 (57.9)	OCD: 32.4 (NA, 10.6) HC: 32.7 (NA, 7.1)	DSM-III-R OCD assessed with SCI and Y-BOCS. Disease duration: mean=10.73 years, SD=6.95 years. Overall comorbidity: 0.0%. Overall medication: 0.0% (medication free for => 2 weeks).	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)	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)
Schlosser 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%. Overall medication: 9.5% (SSRI=9.5%).	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)	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)
Yucel 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.

Supplement 1. Search strategy for each database.

Web of Science (195 hits, 09-07-2020) (202 hits, 19-03-2021)
4 #3 AND #2 AND #1
3 TS=(inhibition OR "go/no-go" OR stroop OR flanker OR interference OR switching OR stop OR simon)
2 TS=(fmri OR "functional magnetic resonance imaging")
1 TS=(ocd OR "obsessive compulsive disorder")

ScienceDirect (140 hits, 09-07-2020) (153 hits, 19-03-2021)
("ocd" OR "obsessive compulsive disorder") AND ("fmri" OR "functional magnetic resonance imaging") AND ("inhibition" OR "go/no-go" OR "flanker" OR "stroop OR "interference" OR "switch" OR "stop" OR "switching" OR "simon")

Scopus (116 hits, 09-07-2020) (122 hits, 19-03-2021)
(TITLE-ABS-KEY (ocd OR "obsessive compulsive disorder") AND TITLE-ABS-KEY (fmri OR "functional magnetic resonance imaging") AND TITLE-ABS-KEY (inhibition OR "go/no-go" OR stroop OR flanker OR interference OR switching OR stop OR simon))

PubMed (92 hits, 09-07-2020) (98 hits, 19-03-2021)
(ocd AND fmri AND inhibition [Title/Abstract]) OR
(ocd AND fmri AND “go/no-go” [Title/Abstract]) OR
(ocd AND fmri AND stroop [Title/Abstract]) OR
(ocd AND fmri AND flanker [Title/Abstract]) OR
(ocd AND fmri AND interference [Title/Abstract]) OR
(ocd AND fmri AND switch* [Title/Abstract]) OR
(ocd AND fmri AND stop [Title/Abstract]) OR
(ocd AND fmri AND simon [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND inhibition [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND “go/no-go” [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND stroop [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND flanker [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND interference [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND switch* [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND stop [Title/Abstract]) OR
(ocd AND ”functional magnetic resonance imaging” AND simon [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND inhibition [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND “go/no-go” [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND stroop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND flanker [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND interference [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND switch* [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND stop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND fmri AND simon [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND inhibition [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND “go/no-go” [Title/Abstract]) OR

(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND stroop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND flanker [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND interference [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND switch* [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND stop [Title/Abstract]) OR
(”obsessive compulsive disorder” AND ”functional magnetic resonance imaging” AND simon [Title/Abstract])

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Paper IV

Working title: Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study

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Keywords: stop-signal task; obsessive-compulsive disorder; cognitive control; action cancellation; response inhibition; fMRI

Abstract

Obsessions and compulsions, the cardinal symptoms of obsessive-compulsive disorder (OCD), have been linked to impairments in inhibitory control in adult OCD and altered task-related activation of associated cortico-striato-thalamo-cortical networks. Although similar perturbations have been described in pediatric OCD, findings from the few existing neuroimaging studies are inconsistent. Here, we analyzed data from a total of 65 unmedicated patients with a primary diagnosis of OCD and 26 age- and sex-matched healthy controls, 8 through 17 years of age, that engaged in a modified stop signal task during functional magnetic resonance imaging. The effects of group on brain activation during successful inhibition and failed inhibition were first tested in whole-brain analyses using frequentist statistics. However, because these analyses did not reveal any significant group differences, additional analyses were performed using Bayesian inference instead, which allowed us to quantify the evidence against an effect of group. Bayesian repeated-measures ANOVAs revealed moderate evidence against an effect of group during both successful inhibition and failed inhibition in four functionally-defined regions-of-interest: left insula, right insula, right inferior frontal gyrus (IFG) and right pre-supplementary motor area (pre-SMA). Similarly, Bayesian t-tests revealed moderate evidence against an effect of group on all measures of task performance. Secondary Bayesian correlation analyses were used to explore associations of the stop-signal reaction time (SSRT) and OCD symptom severity with inhibition-related activation of the right IFG and right pre-SMA. Interestingly, activation of the right IFG scaled positively with OCD symptom severity during successful inhibition, indicating a potential compensatory function of this region in suppressing compulsive behaviors. In conclusion, while inhibitory control may not be affected in pediatric OCD at the group level, our results suggest that activation of the right IFG during inhibition may be tied to OCD symptomatology.

1. Introduction

Obsessive-compulsive disorder (OCD) is a debilitating disorder characterized by persistent and intrusive obsessions and repetitive compulsions (American Psychiatric Association, 2013) that affects 2-3% of the population (Ruscio, Stein, Chiu, & Kessler, 2010).

Obsessions and compulsions in OCD may be linked to impaired inhibitory control, that is, an impaired ability to stop ongoing actions and thoughts when circumstances demand it (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005). Different subprocesses of inhibitory control are assessed in experiments where responses are sometimes made in the presence of interfering stimuli (e.g. Flanker task), or where a pre-potent response occasionally must be either altered (e.g. Switching task), withheld (e.g. Go/No-go task) or cancelled (e.g. Stop signal task, SST) (Aron, 2011; van Velzen, Vriend, de Wit, & van den Heuvel, 2014).

Recent meta-analytic evidence from functional neuroimaging studies of OCD indicate aberrant activation of cortico-striato-thalamo-cortical (CSTC) networks during performance of inhibitory control tasks (Carlisi et al., 2017; Norman et al., 2016; Norman et al., 2019). However, this evidence is based mainly on findings from studies of adults with OCD and may not be extrapolated to pediatric OCD cases for several reasons. First, based on numerous findings of marked differences between pediatric-onset and adult-onset OCD in their clinical presentation, gender distribution, genetics, neurocognitive profile, and treatment response, some argue that pediatric-onset OCD constitute a developmental subtype of OCD, or even a distinct psychiatric disorder (Geller et al., 2001; Geller, Homayoun, & Johnson, 2021). Second, a recent review of candidate neurocognitive endophenotypes in OCD suggest that impairment of inhibitory control may manifest only at later stages of the disorder (Marzuki, Sahakian, & Robbins, 2020). Third, the distribution for the incidence of OCD as a function of age is bimodal with the first peak at about 9-10 years of age (Geller et al., 2021), at a time during which the neural mechanisms supporting inhibitory control are still not fully matured (Constantinidis & Luna, 2019). Consequently, potential age-specific abnormalities in the maturation of

inhibitory control networks may not yet have occurred in many pediatric OCD patients (Huyser, Veltman, de Haan, & Boer, 2009).

The few existing neuroimaging studies of inhibitory control in pediatric OCD are inconclusive. Studies with smaller samples have found both reduced interference-related activation in the multisource interference task (Fitzgerald et al., 2010) as well as increased interference-related (Huyser, Veltman, Wolters, de Haan, & Boer, 2011) and set-shifting-related (Britton et al., 2010) activation in the Flanker task and a set-shifting task, respectively, in multiple regions within CSTC networks. Additionally, several studies have found reduced interference-related, switching-related and successful-inhibition-related activation of CSTC networks in a small group of boys with remitted OCD when compared to healthy controls (HCs) during performance of multiple different inhibitory control tasks (Rubia et al., 2010; Rubia, Cubillo, Woolley, Brammer, & Smith, 2011; Woolley et al., 2008). Moreover, a recent large study included 69 pediatric patients with OCD (8 through 19 years of age) and 72 HCs and found no group effects on interference-related activation in the multisource interference task (Fitzgerald et al., 2018). This finding corroborates similar findings of no group differences in task-related activation during interference control in the multisource interference task (Fitzgerald et al., 2013) and during successful inhibition in the stop signal task (Gooskens et al., 2019). Most existing studies furthermore rely on data from pediatric OCD patients on medication, which may affect observed group differences (Boedhoe et al., 2018; Boedhoe et al., 2016). In sum, it remains unclear whether and to what extend different aspects of inhibitory control are associated with abnormal brain activation in pediatric OCD.

In the current study, we aimed to identify changes in brain activation during inhibitory control and relate them to behavioral performance and OCD symptom severity in a large sample of unmedicated pediatric OCD patients when compared with age- and sex-matched HCs without any current or past psychiatric disorders. We operationalized inhibitory control as the ability to withhold a prepotent motor response on infrequent stop-trials in a modified version of the SST (Logan, 1994) and estimated the stop-signal reaction time (SSRT).

The SST has proven effective in probing CSTC networks that underlies the cancellation of initiated actions (Hannah & Aron, 2021), which may be particularly relevant for OCD as many patients have difficulties in stopping compulsive behaviors that have been initiated (van Velzen et al., 2014).

2. Methods

2.1. Participants

A total of 128 children and adolescents with OCD and 43 HCs were enrolled between September 2018 and 2021 in the TECTO trial, which is an ongoing randomized clinical trial with a parallel case-control design (ClinicalTrials.gov Identifier NCT03595098). Of these participants, a subset of 97 OCD patients and 36 HCs were included in the present MR sub-study (Figure 1). Patients were recruited from psychiatric outpatient units in the Capital Region of Denmark. Inclusion criteria were 8 through 17 years of age, a primary diagnosis of OCD (F42, according to the criteria of the International Classification of Diseases, 10th revision, ICD-10) (WHO, 1992), and a Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997) score of at least 16 (corresponding to moderate-to-severe OCD). Patients were excluded if they met the ICD-10 criteria for a diagnosis of schizophrenia, psychosis, mania, bipolar disorder, substance dependence syndrome, or pervasive developmental disorder (not including Asperger's syndrome). Additionally, patients were excluded if they had received treatment within the past six months using cognitive behavioral therapy, relaxation therapy, antidepressant medication, or antipsychotic medication. HCs were from the same municipality and were recruited from a random sample drawn from the Danish Central Person Registry that was matched on sex and age (within 3 months). HCs were excluded if they met the ICD-10 criteria for any current or previous psychiatric disorder. Both HCs and OCD patients were excluded if they had a full-scale IQ below 70, had any neurological illness, or had previously sustained a severe head trauma. Additional details on the TECTO trial are available in the trial protocol (Pagsberg et al., 2022). The study was approved by the National Research Ethics Committee (H-18010607) and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark (VD-2018-263, l-suite 6502). All participants provided informed

consent prior to enrollment (participants below the age of 15 years gave their assent and consent was provided by their guardian). Consent to partake in the MR sub-study was not a prerequisite for participation in the TECTO trial.

2.2. Measures

OCD diagnosis in patients and absence of any current or lifetime psychiatric disorders in HCs was ascertained with the Kiddie Schedule for affective disorders and Schizophrenia – present and lifetime (K-SADS-PL)(Kaufman et al., 1997). OCD symptom severity was assessed with the CY-BOCS and the Clinical Global Impression – Severity (CGI-S)(Busner & Targum, 2007). In both OCD patients and HCs, level of functioning was assessed with the Children's Global Assessment Scale (C-GAS)(Shaffer et al., 1983) and obsessive-compulsive traits were assessed with the Toronto Obsessive-Compulsive Scale (TOCS)(Park et al., 2016). Handedness was assessed with the 10-item 5-alternative forced-choice version of the Edinburgh Handedness Inventory (EHI)(Oldfield, 1971) and summarized in a single laterality quotient. Additionally, motor coordination and speed were assessed with the Purdue Pegboard Test (PPBT)(Tiffin & Asher, 1948). Stage of puberty was assessed by self-report on the Tanner scale (Taylor et al., 2001). Finally, general cognitive ability (full-scale IQ) was assessed using age-appropriate versions of the Wechsler Intelligence Scales (WISC-V or WAIS-IV)(Wechsler, 2014; Wechsler, Coalson, & Raiford, 2008).

2.3. Virtual-reality and Mock MRI

Although the MRI procedure poses minimal risk of harm, it sometimes causes discomfort. The amount of discomfort may be notably higher in children and adolescents compared to adults, and in clinical groups with high anxiety levels (Everts et al., 2021). In addition, head motion during MRI is a major challenge in pediatric (Afacan et al., 2016) and psychiatric (Makowski, Lepage, & Evans, 2019) populations. Preparations using virtual-reality (VR) and mock MRI can reduce discomfort and the amount of head movement, thereby improving image quality. We administered a narrated VR experience of the MRI procedure prior to the day

of scan. The simulation was developed specifically for this study to closely mimic the actual procedures used and allow the subject to try them in a virtual environment. Additionally, subjects underwent a mock scan procedure immediately preceding the actual scan. The mock scanner (Model PST-100355, Psychology Software Tools, Inc.) was a full-scale MRI machine replica without internal magnets, but otherwise fully equipped with motorized MRI bed, head band with motion tracker, head coil with stabilizer system, systems for presentation of visual and auditory stimuli, and a response pad. The Mock scanner was used to practice the fMRI task, practice lying still while receiving visual live feedback on head movements and familiarize the subject with the scan environment and gradient sounds.

2.4. Stop signal task

The stop signal task was coded in PsychoPy [version 1.84.2] (Peirce, 2009) and comprised a total of 220 trials, of which 160 were go-trials, 40 were stop-trials, and 20 were null-trials (Figure 2). Go-trials and stop-trials were presented in different pseudo-randomized orders, with the constraints that the first 12 trials were go-trials, and a stop-trial could not be followed by another stop-trial. We used a linear staircase algorithm to adaptively increase the stop-signal delay (SSD) after successful stop-trials (thereby increasing task difficulty) and decrease the SSD after failed stop-trials (thereby decreasing task difficulty) in increments of 50 ms. The initial SSD was subject-specific and was determined by averaging the SSDs of the last half of the mock session stop-trails and rounding to nearest 50. The initial SSD in the mock session was 250 ms. The use of an initial subject-specific SSD ensures that the SSD distribution is adequately sampled around a subject's mean SSD during task performance. Subjects were excluded from further analysis if more than 20% of go-trials were omission errors, if more than 20% of go-trials were commission errors, or if the assumption of independence of go and stop processes was violated (i.e., if the mean RT on failed stop-trials was greater than the mean RT on go-trials). For the remaining subjects, we then calculated the stop-signal reaction time (SSRT) using the integration method with replacement of go omission errors (Verbruggen et al., 2019).

2.5. Image acquisition

MRI data were acquired from a 3T Philips Achieva scanner with a 32-channel head coil at the Danish Research Centre for Magnetic Resonance. For each subject, a total of 530 single-shot spin-echo echo-planar images (EPI; TR=1700 ms, TE=30ms, FA=71°, matrix size=68x70 mm, 32 slices in the axial orientation, interleaved slice excitation in ascending order, slice thickness=3.4 mm, slice gap=0.6 mm, FOV=120mm) were acquired in addition to another five EPIs with opposing phase encoding direction. Slices were angled parallel to the anterior commissure - posterior commissure line and covered the whole cerebrum, partially cutting off the cerebellum when necessary. In addition, a T1-weighted image was acquired for each subject (matrix size= 288x288 mm, voxel size=approximately 1 mm isotropic, TR=6000 ms, TE=30 ms, FA=8°, 245 slices in the sagittal orientation) with navigator-based prospective motion correction to improve image quality (Andersen, Björkman-Burtscher, Marsman, Petersen, & Boer, 2019). Foam pads were used to reduce head motion during scan. Subjects were shown a calming movie of fish and turtles during the structural scan to reduce head motion (Greene et al., 2018). Weighted blankets were available to help reduce movement and increase comfort.

2.6. Pre-processing

MRI data were preprocessed using SPM12 [version 7219] (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011) in MATLAB R2020a. T1w images were segmented into tissue classes (Ashburner & Friston, 2005) that were used to generate brain masks for each subject. Tissue probability images of grey and white matter for each subject were used to create a study-specific average template with DARTEL (Ashburner, 2007). Functional EPI scans were slice-time corrected and realigned to correct for head movements. EPI with opposite phase encoding direction were used to estimate the susceptibility-distortions using FSL TOPUP (Andersson, Skare, & Ashburner, 2003). Distortion-corrected images were co-registered to the masked anatomical T1w image,

spatially normalized to MNI space using the subject-specific flow fields and smoothed with an isotropic 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.7. Statistical analyses

2.7.1. Bayesian inference

All Bayesian analyses were performed in JASP version 0.15 (JASP Team, 2021) using default settings unless otherwise noted. We tested for group differences in demographics, clinical measures and SST performance using the appropriate Bayesian Student's t-tests, Bayesian Mann-Whitney *U*-test and Bayesian Contingency Tables. Results from Bayesian Mann-Whitney *U*-tests were based on a data augmentation algorithm with 5 chains and 10.000 iterations that in all cases achieved a potential scale reduction factor ($\hat{R}$) of <1.05 (Brooks & Gelman, 1998). We classified the strength of the evidence in favor of the alternative hypothesis relative to the null-hypothesis according to the guidelines provided by Wagenmakers and colleagues (2018), with the modification that anecdotal evidence for either hypothesis (i.e., a Bayes Factor [BF] between 1/3 and 3) was classified as insufficient data. As such, a BF_{10} above 3 means that the observed data favors the alternative hypothesis (a group difference or a correlation), whereas a BF_{10} below 1/3 means that the observed data favors the null-hypothesis (no group difference or no correlation).

2.7.2. Subject-level GLM

A first-level GLM was used to analyze BOLD fMRI data from each subject (Friston, Frith, Frackowiak, & Turner, 1995). Correct go-trials, failed go-trials (omission errors and commission errors), correct stop-trials and failed stop-trials were modeled separately for left-hand and right-hand responses at the onset time of the arrow as events convolved with the canonical hemodynamic response function. Null-trials were not explicitly modelled and constituted an implicit baseline. The analysis incorporated a high pass filter with a 128 Hz cut-off frequency. Volterra expanded motion parameters estimated from rigid-body motion correction were included as regressors of no interest, resulting in 24 parameters (Friston, Williams, Howard, Frackowiak, & Turner, 1996). Framewise displacement (FD) of each volume were estimated according to the procedure

described in Power, Barnes, Snyder, Schlaggar, and Petersen (2012), and volumes whose FD exceeded 1 mm, as well as the immediately following volumes, were flagged as outliers in the GLM analysis (Siegel et al., 2014). Subjects having more than 25% of volumes censored were excluded from all further analyses (Supplemental Figure S1). The proportion of outlier volumes for the remaining subjects were similar in the OCD and HC group (BF_{10}=0.323; Supplemental Figure S2).

2.7.3. Group-level whole-brain analyses

Contrasts images constructed for correct stop-trials versus correct go-trials (successful inhibition) and failed stop-trials versus correct go-trials (failed inhibition) were entered into separate second-level models that included age and sex as covariates. Clusters were displayed at an uncorrected peak threshold of p<.001 and group differences were considered significant at a cluster-level familywise error-corrected (FWE) threshold of p<.05 across the whole brain.

2.7.4. Region-of-interest analyses

We also performed post-hoc region-of-interest (ROI) analyses with a full-factorial 2x2x2 design, where condition (stop or correct go) and response side (left or right) were the within-subject factors and group (OCD or HC) was the between-group factor. We first determined the peak activation coordinates of inhibition-related effects in the whole sample by contrasting stop-trials with correct go-trials at an uncorrected p-value of <.001. We then placed 10 mm spheres centered at each coordinate and used MarsBar (Brett, Anton, Valabregue, & Poline, 2002) to extract the mean contrast estimates of activation within each ROI separately for successful inhibition and failed inhibition (the placement of each ROI is depicted in Figure 4B). Mean contrast estimates of OCD and HC were compared across ROIs in Bayesian repeated-measures ANCOVAs with group as a between-subject factor and age and sex as covariates (i.e., age and sex were included in all models).

Finally, we used Bayesian Pearson Correlations to explore correlations of inhibition-related activity within ROIs with SSRT in both groups, and with OCD symptom severity in the OCD group. For the latter, the ROIs were centered at the peak activation coordinates for inhibition-related effects in the OCD group only.

3. Results

3.1. Sample characteristics

The sample characteristics are presented in Table 1. We found moderate evidence that the groups were comparable in proportion of females (BF_{10}=0.291), stage of puberty (Tanner BF_{10}=0.281) and motor coordination and speed as assessed with the PPBT left hand, right hand, and both hands (BF_{10} between 0.268 and 2.93). We did not have sufficient data to determine whether the groups were equal or different in age (BF_{10}=0.762), handedness (EHI laterality quotient BF_{10}=0.432), PPBT assembly (BF_{10}=1.010), general cognitive ability (full-scale IQ BF_{10}=0.652) or parental education level (BF_{10}=1.478). Importantly, we did not find evidence to suggest a difference between the groups on any of the demographic measures.

We found decisive evidence of worse global level of functioning in the OCD compared to HC group (C-GAS BF_{10}=1.512e+18). Additionally, we found decisive evidence that the OCD group had more self-reported and parent-reported obsessive-compulsive traits than did the HC group (TOCS [child] BF_{10}=4.658e+6; TOCS [parent] BF_{10}=3.286e+11).

In the OCD group, 30 of 65 (46.2%) had only received a diagnosis of OCD, 25 of 65 (38.5%) had one comorbid disorder, and 10 of 65 (15.4%) had two comorbid disorders. The most common comorbid disorders were Asperger's syndrome (13.8%), stress-related disorders (10.8%), attention-deficit hyperactivity disorders (ADHD; 10.8%) and tic disorders (10.8%). On average, OCD patients had moderate to severe OCD symptoms (mean CYBOCS score of 24.80) that was associated with moderate to severe illness (mean CGI-S score of 4.51).

3.2. Task performance

Behavioral outcomes for SST performance are presented in Figure 3. We found moderate evidence against an effect of group on all behavioral measures (Table 2). We got similar results from auxiliary Bayesian

ANOCVAs that included age and sex as covariates and when excluding patients with at least one comorbid disorder from the analyses.

3.3. Task-related brain activation

Our planned comparison of successful inhibition and failed inhibition in the two groups did not reveal any suprathreshold clusters in either direction (OCD>HC and OCD<HC). We also did not find evidence of any group differences when excluding patients with comorbidities from the analysis, or when comparing patients with at least one comorbid disorder to patients without comorbidities.

To substantiate these null-findings, we conducted post-hoc ROI analyses. A three-way ANOVA with condition (stop or correct go), response side (left or right) and group (OCD or HC) showed go-related bilateral activation of the cerebellum, occipital lobe, anterior insula/central operculum, pre-supplementary motor area (pre-SMA) and motor cortical regions and unilateral activation of the right thalamus, right putamen and right pallidum (Figure 4A, Table S1-S2). We found stop-related activation of the brain stem, bilaterally in the occipital lobe, anterior insula and pre-SMA and unilateral activation of the right supramarginal gyrus (SMG), right putamen, right pallidum and right pars opercularis of the inferior frontal gyrus (IFG) (Figure 4A, Table S3-S4). This right-dominant network is consistent with existing evidence from neuroimaging meta-analyses (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015; Swick, Ashley, & Turken, 2011) and reflects both the stop process related to the stop signal and a concurrent go process which was initiated with the go signal about 340-350 ms earlier (Table 2). We therefore contrasted the stop-related activity with go-related activity to isolate the neural correlates specific to inhibition. This revealed inhibition-related activation of bilateral insula, right IFG (pars opercularis) and right pre-SMA (Figure 4B). Our ROI analysis showed anecdotal to moderate evidence against an effect of group on the activation of these four regions during failed inhibition (BF_{10}=0.331, Figure 4C top panel, Table S5) and successful inhibition (BF_{10}=0.370, Figure 4C bottom panel, Table S6).

In the canonical visual stop signal task, participants respond to leftward- or rightward pointing horizontal arrows using their corresponding hand. Because the mapping between target arrow and response hand is not counter-balanced in this design, the effects of arrow direction and response hand on task-related activation are conflated and difficult to estimate. Note, even if responses are made using fingers from the same hand, attentional biases related to arrow direction may remain present. We tried to mitigate this problem with our use of vertical arrows as go-stimuli, which permitted counter-balancing of the mapping between go-stimulus and response-hand across participants. We found a main effect of response side confined to the motor cortices, even when using a liberal threshold of $p<.001$ (uncorrected) (see Figure S3 and Table S7). Response hand did not interact with condition or group either alone or in combination. This is a strong indication that the observed task-related patterns of activation, including the predominantly right-lateralized inhibition-related activation, were not artifacts of mixing right-hand and left-hand responses.

3.4. Correlations between task performance and behavioral and clinical measures

The ventral pars opercularis of the right IFG and the right pre-SMA together play a critical role in generating the stop-command (Hannah & Aron, 2021). We therefore explored whether activity within these two regions related to SSRT during successful inhibition, and whether the activation of these regions was predictive of OCD symptom severity during either successful inhibition or failed inhibition (see Figure S4). We found moderate evidence that the activation of both ROIs during successful inhibition was uncorrelated with SSRT when considering both groups together (right IFG r=-.026, BF_{10}=0.135; right pre-SMA r=.036, BF_{10}=0.139), and when restricting the analyses to the OCD group (right IFG r=-.038, BF_{10}=0.162; right pre-SMA r=.047, BF_{10}=0.165) or the HC group (right IFG r=.085, BF_{10}=0.264; right pre-SMA r=.038, BF_{10}=0.247).

During successful inhibition, we found moderate evidence that OCD symptom severity was positively correlated with right IFG activation (r=.329, BF_{10}=5.166) and not correlated with right pre-SMA activation (r=.075, BF_{10}=0.184). During failed inhibition, the data was not sufficient to determine whether an association was present for either ROI (right IFG r=.158, BF_{10}=0.335; right pre-SMA r=.186, BF_{10}=0.454).

4. Discussion

The major aim of the present study was to assess neural and behavioral correlates of inhibitory control in a large sample of unmedicated pediatric OCD patients and HC. Our planned whole-brain analyses did not identify any significant group differences during either successful inhibition or failed inhibition in the SST. We replicated this null-finding in post-hoc functionally defined ROI analyses that had increased sensitivity to group differences within task-relevant regions. Similarly, we found moderate evidence to suggest that the groups were comparable on all our measures of task performance.

Our findings of no group differences in brain activation during inhibitory control mirror null-findings from two recent large studies (Grooskens et al., 2019; Fitzgerald et al., 2018), whereas several previous studies with small samples have found aberrant inhibition-related activation in in children and adolescents with OCD (Huyser et al., 2011; Fitzgerald et al., 2010; Britton et al., 2010; Woolley et al., 2010; Rubia et al., 2011; Rubia et al., 2010). However, in contrast to our study, the two recent studies included patients in pharmacological treatment for OCD, predominantly with selective serotonin reuptake inhibitors (SSRIs). Given the putative beneficial effect of SSRIs on the integrity of CSTC networks involved in inhibitory control (Kim, Jung, Shim, & Kwon, 2020; Saxena et al., 2002; Shin et al., 2014) our results are important replications of previous null-findings in an unmedicated sample.

Our functionally defined ROI analyses showed that four regions were reliably activated in the whole sample during response inhibition: the left and right insula, pars opercularis of the right IFG, and the right pre-SMA. These regions are all part of the CSTC networks that form the neural basis for response inhibition (Cieslik et al., 2015; Hannah & Aron, 2021; Swick et al., 2011). Aberrant activation of CSTC networks have been implicated in adult OCD during inhibitory control (Carlisi et al., 2017; Norman et al., 2016; Norman et al., 2019). In contrast, our analyses yielded moderate evidence against an effect of group on the activation of ROIs during both successful inhibition and failed inhibition. Late childhood and adolescence is a critical period of brain development that is characterized by a pronounced potential for plasticity across multiple brain regions, including frontoparietal, medial frontal and motor regions, but also increased susceptibility to

dysfunctional brain maturation (Kaufmann et al., 2017; Paus, Keshavan, & Giedd, 2008). Increasingly, pediatric OCD is being recognized as a disorder with a neurodevelopmental origin (Geller et al., 2021; Huyser et al., 2009), and problems with inhibitory control may emerge only later during disease progression (Marzuki et al., 2020). Our results are consistent with this view.

Our finding of comparable SSRT in the OCD and HC group (mean of 243 ms compared with 229 ms) converge with similar findings in previous fMRI studies using the SST (Gooskens et al., 2019; Rubia et al., 2010; Woolley et al., 2008), but these cohorts again included patients in treatment with SSRIs. SSRIs may modulate excitatory interneurons in the motor cortex (Gerdelat-Mas et al., 2005) and reduce SSRT (Skandali et al., 2018). While the inclusion of patients in pharmacotherapy for OCD may have affected the SSRT in prior studies, our inclusion of only unmedicated patients rules out that explanation for our finding of intact SSRT in pediatric OCD. In addition, our finding is consistent with results from a recent review and meta-analysis indicating only a minuscule deficit in SSRT in OCD across all ages, and a particularly small deficit in younger subjects (Mar, Townes, Pechlivanoglou, Arnold, & Schachar, 2021). Future longitudinal case-control studies using the SST are needed to determine whether impairments of SSRT manifest with the progression of the disorder, or if they represent a feature of adult-onset OCD.

Correlational analyses showed moderate evidence against an association between the activation of right IFG and right pre-SMA during successful inhibition and SSRT. Notably, we found moderate evidence that right IFG activation during successful inhibition correlates positively with OCD symptom severity, indicating a potential compensatory function in suppressing compulsive behaviors by a pronounced recruitment of the right IFG in patients with more severe symptoms. We found moderate evidence to suggest that activation of the right pre-SMA during successful inhibition does not correlate with OCD symptom severity.

Right IFG activation during successful inhibition have been found to correlate positively with response to treatment in partially remitted pediatric OCD patients (Rubia et al., 2010). In contrast, a recent study suggests that right IFG hypoactivation in adult OCD does not change after concentrated exposure and response

prevention treatment (Thorsen et al., 2020). Our cross-sectional design does not permit inferences about causality, but our finding may suggest a “training” effect related to frequently suppressing or compensating for compulsive urges in everyday life in patients with more severe symptoms, and those that do so may have better neural predispositions for successful treatment.

Our study has several important strengths. Our large sample size gave us increased statistical power to detect true effects and reduced the likelihood that any observed effects were spurious findings (Button et al., 2013). This is particularly important considering the inconsistent positive findings from previous studies of inhibitory control that had small sample sizes. We replicated null-findings from whole-brain analyses with functionally defined ROI analyses that had increased sensitivity to group differences. Because we compared moderately to severely ill OCD patients with significant functional impairments to healthy controls carefully screened for any prior and current psychiatric disorders, the absence of group effects cannot be explained by a mildness of symptoms in the OCD group or existing psychopathologies in the control group. The samples analyzed were furthermore well-matched on potentially confounding demographic variables, and the patients included were all unmedicated, which allowed us to preclude any effects that the use of medication may have had. Nevertheless, some limitations should also be considered. Despite our efforts to mitigate scan-related discomfort and head movements by using VR and a Mock scan session, we had significant data loss due to participant movement during fMRI. Also, the presence of comorbid disorders, such as ADHD, may have affected task performance in the OCD group (Arnold, Ickowicz, Chen, & Schachar, 2005). Finally, we used an adaptive algorithm for the SSD to individually control the task difficulty for each participant. This introduces systematic performance-related differences in task difficulty that may have affected our estimation of individual differences in inhibition-related activity (D'Alberto et al., 2018). However, since the average SSD was similar in the OCD and HC group (338 ms and 349 ms, respectively), it seems unlikely that our finding of evidence against an effect of group on inhibition-related activity was significantly influenced by group differences in objective task difficulty.

The present study presented preliminary baseline findings from an ongoing longitudinal trial, the TECTO trial (Pagsberg et al., 2022). The next step is to investigate the effects of intervention with cognitive-behavioral therapy or psychoeducation and relaxation therapy on neural and behavioral correlates of inhibitory control once the trial is complete. To conclude, our findings suggest that neural and behavioural correlates of inhibitory control in pediatric OCD are unaffected at the group level but highlight a putative role of the right IFG in pediatric OCD symptomatology.

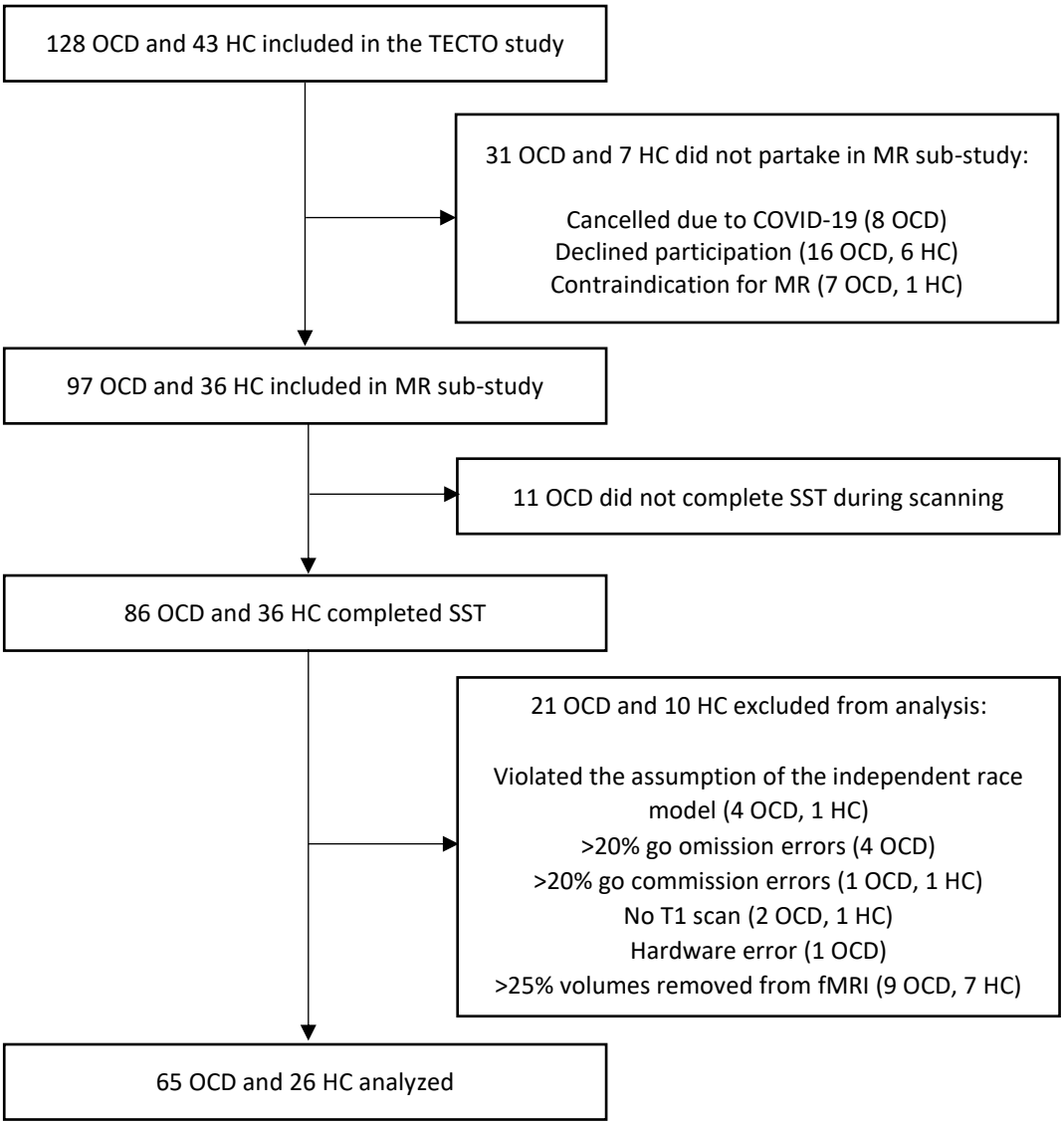


Figure 1. Participant flow diagram. Abbreviations: HC, healthy control; OCD, obsessive-compulsive disorder; SST, stop signal task.

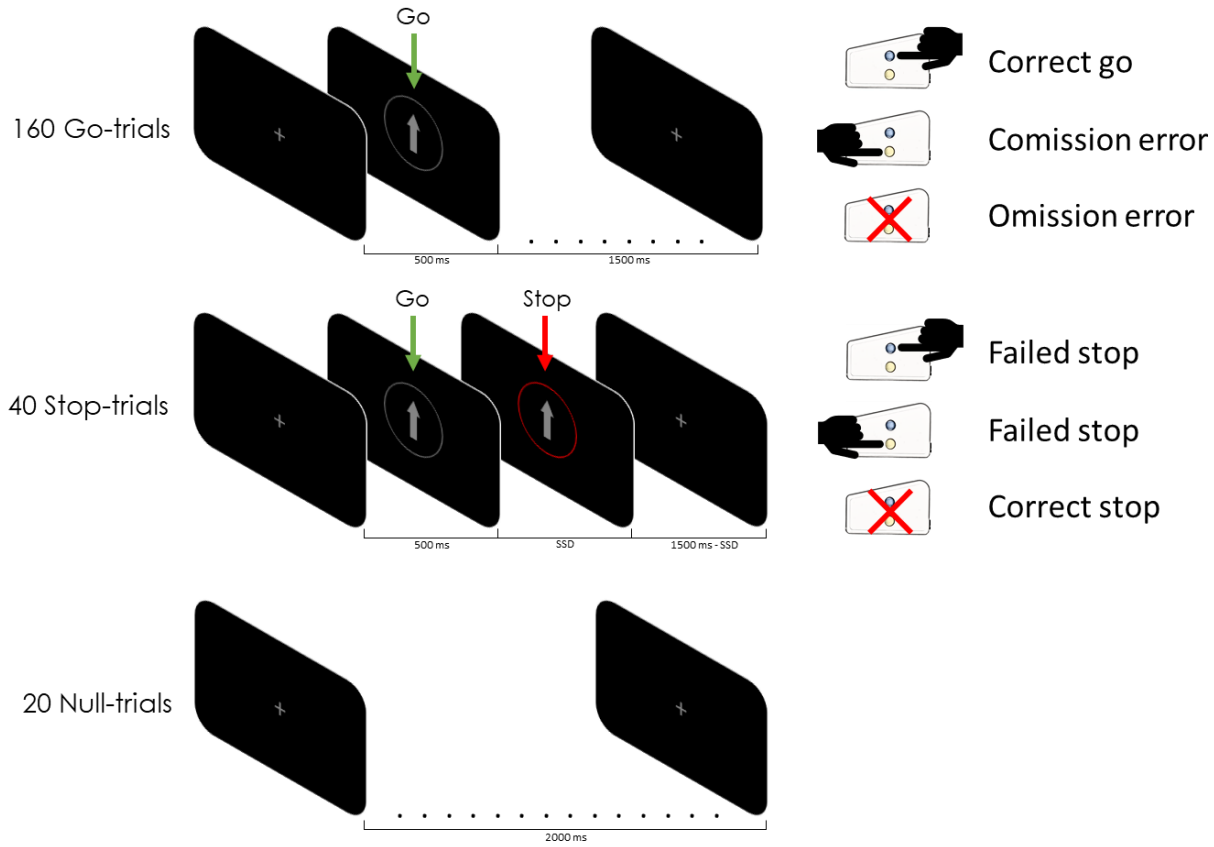


Figure 2. Trial outline for the stop signal task. Each trial started with a fixation cross presented for 500 ms. In go-trials, participants were instructed to respond as quickly and accurately as possible to the direction of a centrally presented arrow pointing upward or downward using a response pad. Go-trials were classified as correct go (correct button press), commission error (incorrect button press) or omission error (no button press). In stop-trials, a circle presented simultaneously with the arrow changed color to red (the stop-signal) after a variable SSD, and participants had to refrain from responding. Stop-trials were classified as failed stop (any button press) or correct stop (no button press). Null-trials occurred on every 11th trial and consisted of a prolonged presentation of the fixation cross matching the duration of go- and stop-trials. The mapping between arrow direction (up or down) and response hand (left or right) was counterbalanced. All trials terminated with a fixation cross presented for 1000-2000 ms (jittered). Abbreviations: SSD, stop-signal delay.

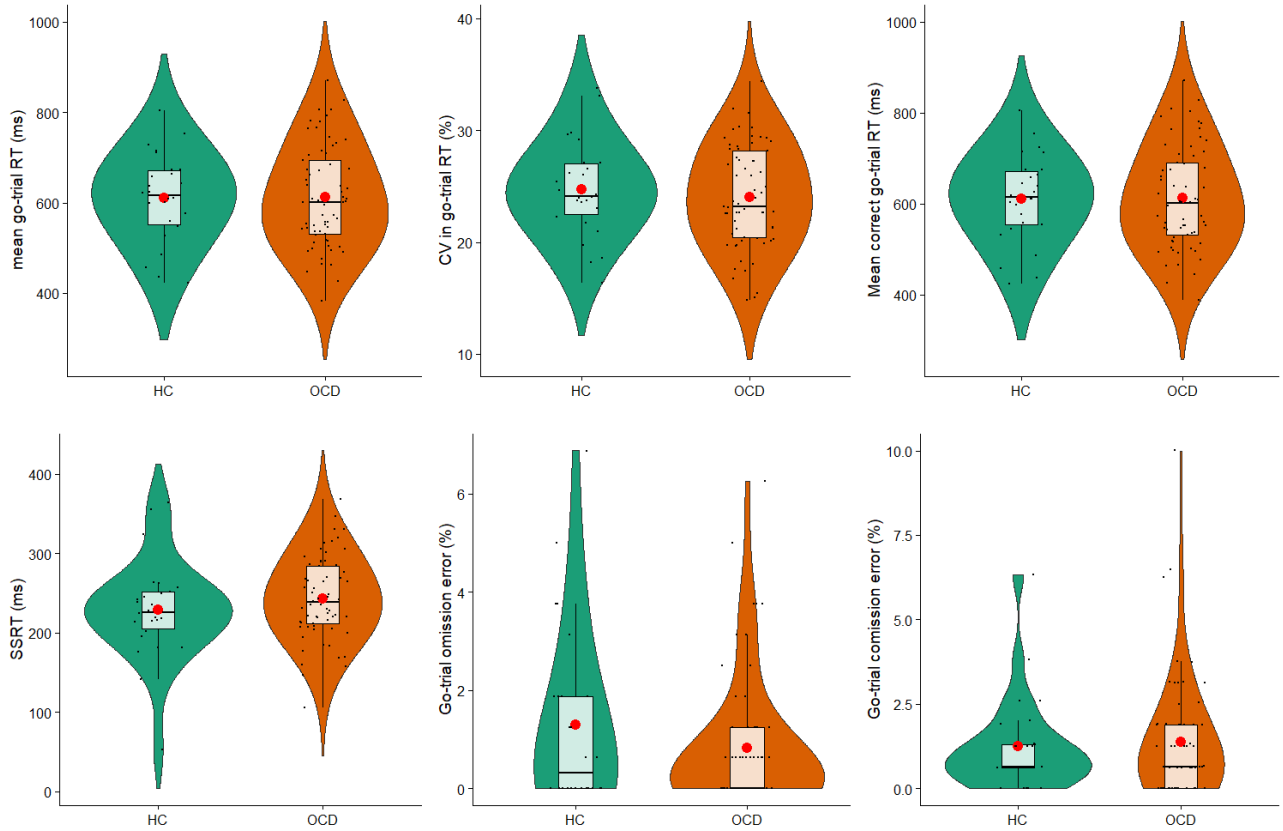
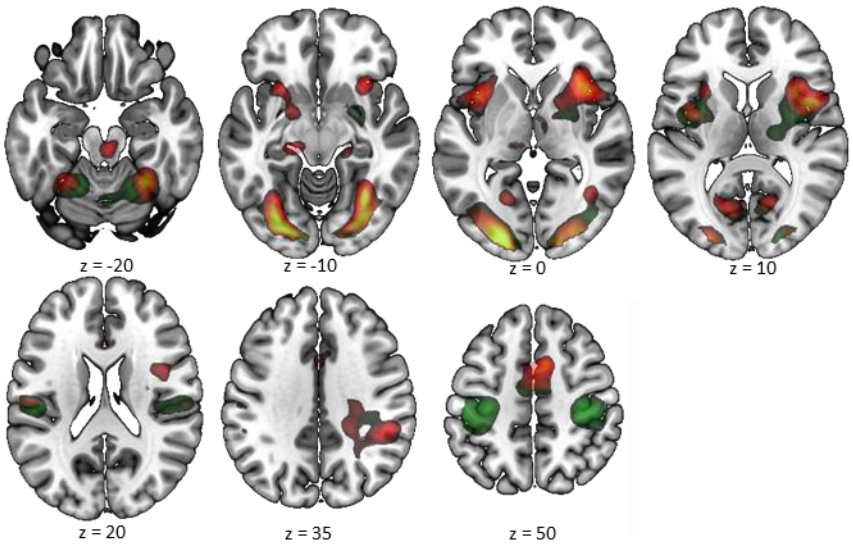
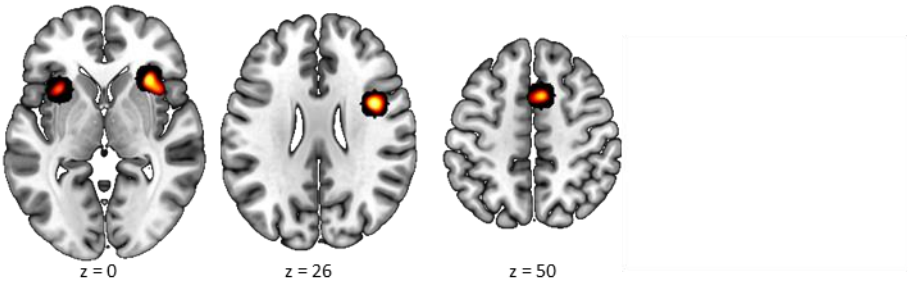


Figure 3. fMRI SST performance (red dots) for the OCD and HC groups (the boxplot shows the median and quartiles, the length of the whiskers represent 1.5 times the interquartile range, and the black dots show the subject estimates). We found moderate evidence that OCD and HC were equal on mean go-trial RT(top left), CV in mean go-trial RT (top middle), mean correct go-trial RT (top right), SSRT (bottom left), percent go-trial omission error (bottom middle) or percent go-trial omission error (bottom right). Abbreviations: CV, coefficient of variation (sd/mean); HC, healthy control; OCD, obsessive-compulsive disorder; RT, reaction time; SST, stop signal task.

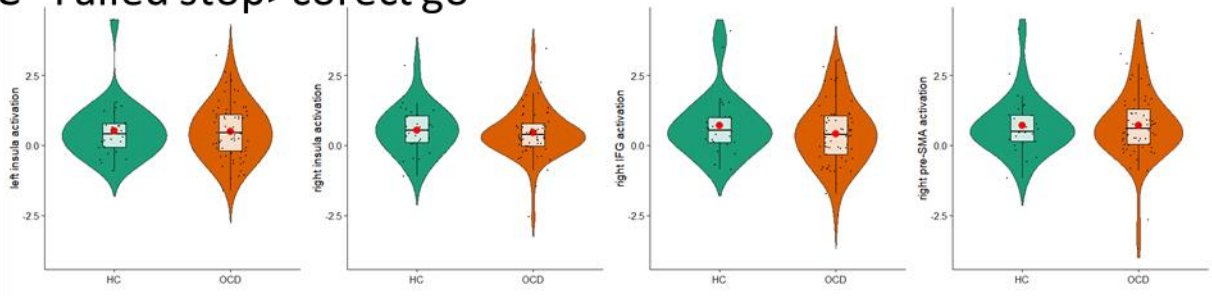
A Stop and correct go



B Stop>correct go



C Failed stop>corect go



Successful stop>corect go

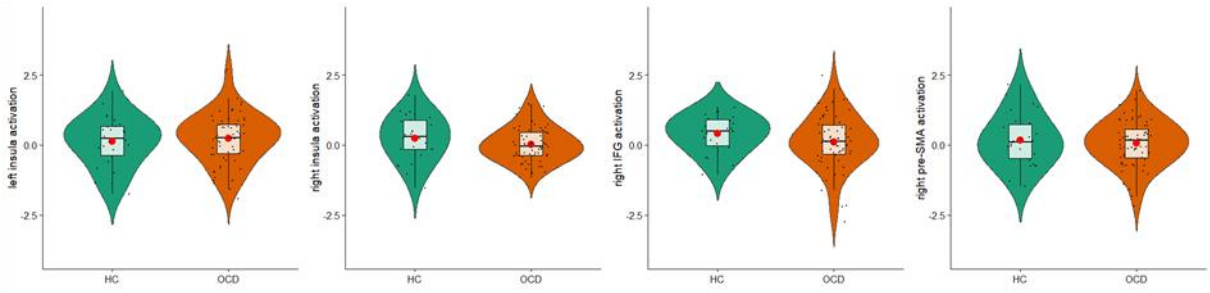


Figure 4. Brain activation during task performance. (A) Task-related activation for stop-trials (red) superimposed on task-related activation for correct go-trials (green) shown at p<.001 (uncorrected). (B) Task-related activation for stop-trials minus correct go-trials shown at p<.001 (uncorrected) superimposed on four ROIs (black disks); 1. left anterior insula, 2. right anterior insula, 3. right IFG (pars opercularis), 4. right pre-SMA. (C) Mean parameter estimates (red dot) of each group for failed stop-trials minus correct go-trials (top; failed inhibition) and correct stop-trials minus correct go-trials (bottom; successful inhibition) within each ROI (the boxplot shows the median and quartiles, the length of the whiskers represent 1.5 times the interquartile range, and the black dots show the subject estimates). Images are in neurological format (right = right). The numbers next to the color bars in A and B reflect T-values. Abbreviations: HC, healthy control; IFG, inferior frontal gyrus; OCD, obsessive-compulsive disorder; ROI, region-of-interest; pre-SMA, pre-supplementary motor area; SSRT, stop signal reaction time.

Table 1. Demographic and Clinical Characteristics of participants included in fMRI analyses

Variable	OCD group (n=65) Mean (SD) or n (%)	HC group (n=26) Mean (SD) or n (%)	BF_{10}
Demographic measures			
Female	33 (50.8%)	14 (53.8%)	0.291
Age in years	14.01 (2.66)	13.04 (2.25)	0.762
Tanner	3.06 (1.39)	2.88 (1.27)	0.281
EHI laterality quotient	61.29 (74.93)	80.62 (56.05)	0.432
Purdue Pegboard			
Right hand	14.44 (2.05)	14.68 (2.39)	0.268
Left hand	13.71 (1.59)	14.00 (2.25)	0.297
Both hands	11.77 (1.45)	11.52 (2.06)	0.293
Assembly	35.34 (7.56)	39.00 (10.17)	1.010
Full-scale IQ (WISC-V/WAIS-IV)	101.28 (12.79)	106.08 (14.48)	0.652
Parental education level in years	15.53 (2.12)	16.65 (2.12)	1.478
Clinical measures			
CY-BOCS total score	24.80 (4.96)		
Obsessions	12.43 (2.57)		
Compulsions	12.37 (2.79)		
CGI-S	4.51 (0.89)		
C-GAS	56.29 (9.29)	88.10 (9.29)	1.512e+18
TOCS (child)	7.54 (25.11)	-39.00 (22.25)	4.658e+6
TOCS (parent)	11.10 (19.87)	-39.75 (21.66)	3.286e+11
Total with at least one co-occuring disorder	35 (53.8%)		
Phobic anxiety disorders (F40)	1 (1.5%)		
Other anxiety disorders (F41)	2 (3.1%)		
Stress-related disorders (F43)	7 (10.8%)		
Eating disorders (F50)	3 (4.6%)		
Personality disorders (F61)	1 (1.5%)		
*Pervasive developmental disorders (F84)**	9 (13.8%)		
Other developmental disorders (F88)	3 (4.6%)		
Attention-deficit hyperactivity disorders (F90)	7 (10.8%)		
Conduct disorders (F91)	1 (1.5%)		
Emotional disorders with childhood onset (F93)	4 (6.2%)		
Tic disorders (F95)	7 (10.8%)		
Other behavioral and emotional disorders with childhood onset (F98)	1 (1.5%)		

Note: OCD and HC were compared pairwise using Bayesian Mann-Whitney *U*-test and Bayesian contingency tables. Data on the EHI is missing for four patients and two healthy controls. Abbreviations: BF_{10}, Bayes Factor in favor of the alternative hypothesis (OCD different from HC) over the null hypothesis (OCD equal to HC); C-GAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression - Severity; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; EHI, Edinburgh Handedness Inventory; HC, healthy control; IQ, Intelligence Quotient; OCD, Obsessive-compulsive disorder; SD, standard deviation; TOCS, Toronto Obsessive-Compulsive Scale; WAIS-IV, Wechsler Adult Intelligence Scale version IV; WISC-V, Wechsler Intelligence Scale for Children version V. * All cases were Asperger's syndrome (F84.5).

Table 2. Stop signal task performance

	OCD Mean (SD)	HC Mean (SD)	BF_{10}
Mean go-trial RT (ms)	612 (111)	611 (96)	0.242
CV in go-trial RT	24.1%	24.7%	0.265
Mean correct go-trial RT (ms)	612 (111)	612 (96)	0.241
SSRT (ms)	243 (52)	229 (62)	0.323
Go-trial omission error	0.8%	1.3%	0.318
Go-trial commission error	1.4%	1.3%	0.242
SSD (ms)	338	349	0.259

Abbreviations: BF_{10}, Bayes Factor in favor of the alternative hypothesis (OCD different from HC) versus the null hypothesis (OCD equal to HC); CV, coefficient of variation (sd/mean); HC, healthy control; OCD, Obsessive-compulsive disorder; RT, reaction time; SD, standard deviation; SSD, stop-signal delay; SSRT, stop-signal reaction time.

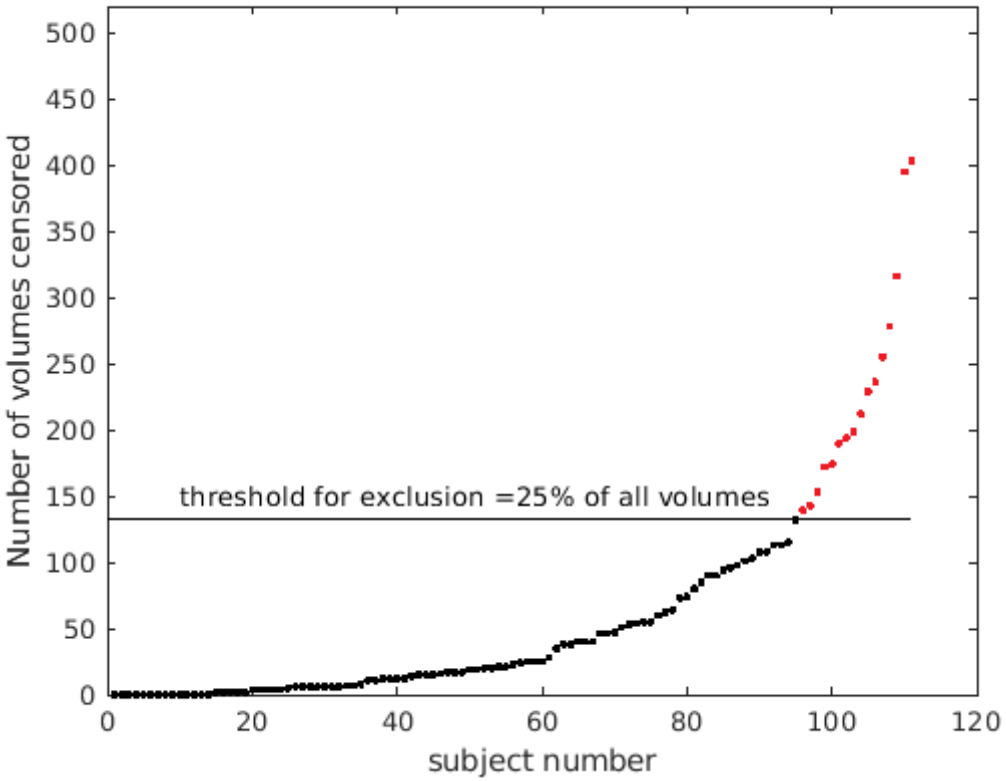


Figure S1. Number of volumes censored for each subject (sorted in ascending order). A total of 16 subjects (red dots) exceeded the predefined threshold for exclusion of 25% volumes censored (black line) and were therefore excluded from the fMRI analysis.

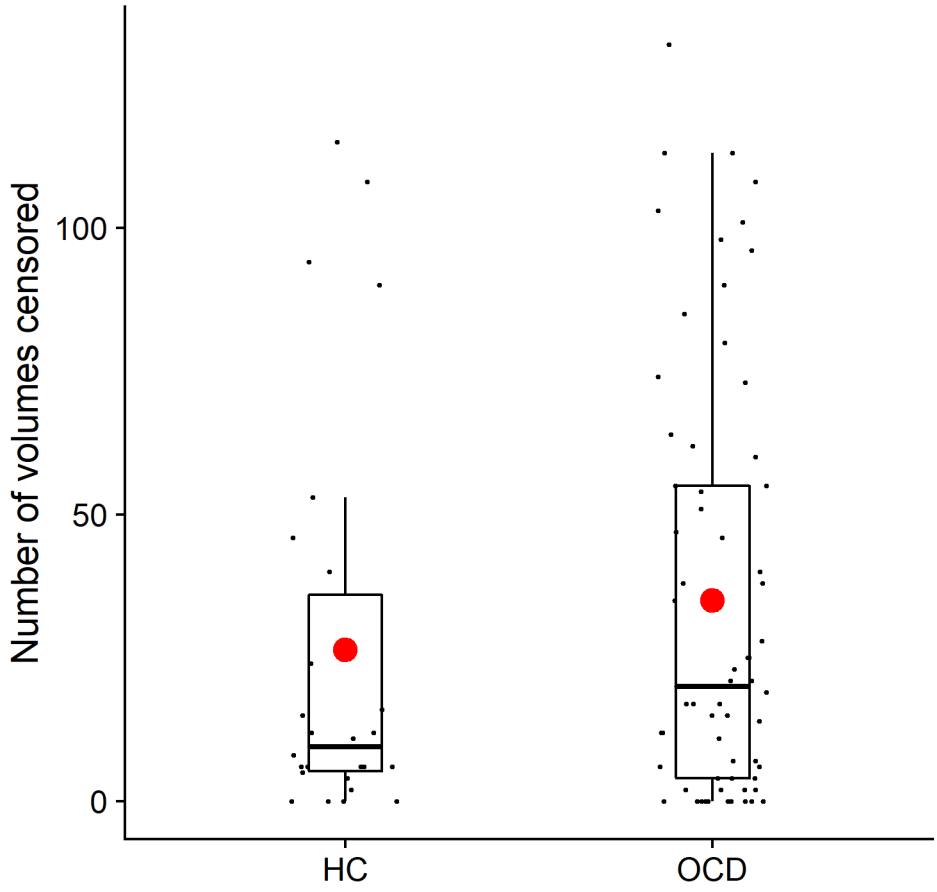


Figure S2. Mean number of volumes excluded from fMRI analysis (red dots) in the OCD and HC groups (the boxplot shows the median and quartiles, the length of the whiskers represent 1.5 times the interquartile range, and the black dots show the number for each subject. We found moderate evidence that OCD and HC were equal in the number of volumes that were censored for subjects that were included in the fMRI analysis (BF_{10}=0.323). Abbreviations: HC, healthy control; OCD, obsessive-compulsive disorder.

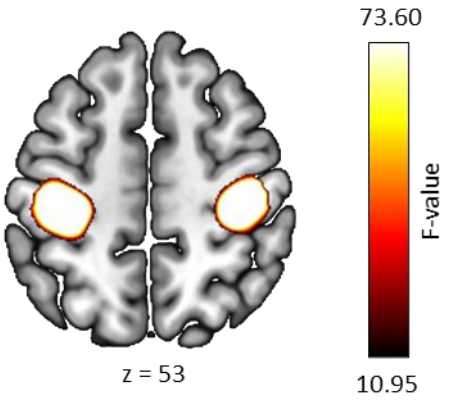


Figure S3. Task main effect of response finger. In a three-way ANOVA (hand x condition x group), a significant main effect of response hand (left vs. right) was present only in the primary motor cortices even at a liberal threshold of p<.001 (uncorrected), indicating that other task-related effects were not artifacts of mixing left hand and right hand responses in the analyses. The Image is in neurological format (right = right).

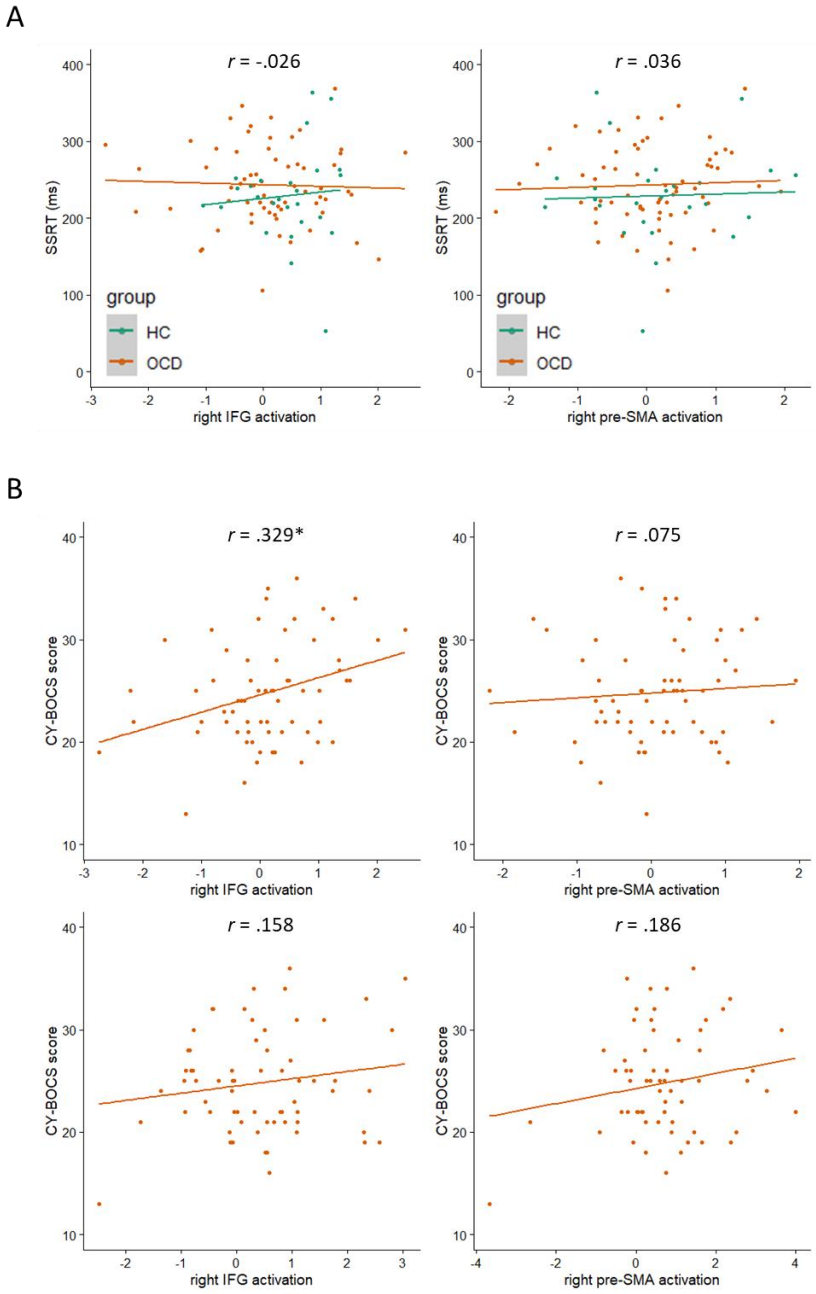


Figure S4. Brain-behavior correlations. (A) Correlations between mean parameter estimates for regions-of-interest and SSRT in each group during successful inhibition. We found moderate evidence against a correlation between SSRT and activation of both the right IFG (r=-.026, BF_{10}=0.135) and the right pre-SMA (r=.036, BF_{10}=0.139) when considering both groups together. Restricting the analysis to either group did not significantly alter the results. (B) Correlations between mean parameter estimates of regions-of-interest and OCD symptom severity (CY-BOCS score) in the OCD group during successful inhibition (top row) and failed inhibition (bottom row). During successful inhibition, there was moderate evidence to suggest that OCD symptom severity was positively correlated with the activation of right IFG (r=.329, BF_{10}=5.166), but not correlated with right pre-SMA activation (r=.075, BF_{10}=0.184). The data was insufficient to evaluate whether or not OCD symptom severity correlated with either region-of-interest during failed inhibition (right IFG r=.158, BF_{10}=0.335; right pre-SMA r=.186, BF_{10}=0.454). *=BF_{10}>3.

Table S1. Task-related activation for go-trials in the OCD group (wholebrain analysis).

	Cluster-level statistics*			
Region name	**$p_{FWE\text{-}corrected}$**	**Number of voxels**	**MNI x, y, z coordinates**	**T**
R occipital lobe	<.001	796	20, -94, 2	9.18
			28, -86, 2	8.78
			20, -86, -8	7.37
L occipital lobe	<.001	881	-14, -98, -4	8.41
			-20, -96, 4	7.96
			-34, -84, -4	7.72
L precentral gyrus/postcentral gyrus	<.001	647	-34, -22, 54	7.55
			-48, -26, 50	6.99
L anterior insula	<.001	162	-38, -2, 12	7.31
R cerebellum	<.001	222	20, -52, -22	6.39
L parietal operculum	<.001	162	-48, -22, 20	6.15
			-58, -18, 20	5.99
R precentral gyrus/postcentral gyrus/SMG	<.001	382	38, -30, 56	6.13
			34, -22, 56	6.12
			54, -22, 46	4.59
L pre-SMA	.005	43	-4, -8, 50	5.34
R putamen	.005	43	28, -4, 12	5.02
	.038	2	28, 4, 6	4.47
R central operculum	.032	4	56, -18, 20	4.69

Note: *significant at $p<.05$ with correction for the family-wise error rate across the whole brain. HC, healthy control; pre-SMA, pre-supplementary motor cortex; SMG, supramarginal gyrus.

Table S2. Task-related activation for go-trials in the HC group (wholebrain analysis).

	Cluster-level statistics*			
Region name	**$p_{FWE\text{-}corrected}$**	**Number of voxels**	**MNI x, y, z coordinates**	**T**
L occipital lobe	<.001	725	-20, -94, -2	8.18
			-30, -84, -12	6.86
			-40, -82, -2	6.09
	.021	11	-8, -76, 14	4.79
L cerebellum	<.001	252	-20, -54, -24	6.93
R occipital lobe	<.001	260	16, -96, -2	6.29
			24, -92, 6	6.29
			36, -86, -4	5.75
	.021	11	42, -72, -6	4.97
R postcentral gyrus	<.001	183	34, -28, 50	6.07
R cerebellum	.001	108	24, -52, -26	6.00
	.024	8	2, -64, -26	4.61
R anterior insula	<.001	129	42, 4, 10	5.87
			32, 16, 10	4.96
L anterior insula	.007	37	-36, -2, 12	5.20
L precentral gyrus	.005	43	-30, -26, 56	5.14
R pallidum	.032	4	16, -4, -4	4.69
L postcentral gyrus	.042	1	-42, -20, 54	4.49
	.042	1	-46, -30, 50	4.45

Note: *significant at p<.05 with correction for the family-wise error rate across the whole brain. HC, healthy control.

Table S3. Task-related activation for stop-trials in the OCD group (wholebrain analysis).

	Cluster-level statistics*			
Region name	**$p_{FWE\text{-}corrected}$**	**Number of voxels**	**MNI x, y, z coordinates**	**T**
R occipital lobe	<.001	503	20, -94, 2	7.48
			26, -80, -10	6.75
			28, -86, 2	6.59
	.007	36	30, -52, -18	5.10
L occipital lobe	<.001	487	-14, -98, -4	6.86
			-26, -94, 6	6.56
			-32, -82, -6	6.02
L anterior insula	.006	39	-38, -4, 14	5.29
L pre-SMA	.011	25	-2, -6, 54	4.84
L postcentral gyrus	.034	3	-58, -20, 22	4.55
R pre-SMA	.034	3	6, 4, 52	4.49

Note: *significant at p<.05 with correction for the family-wise error rate across the whole brain. OCD, obsessive-compulsive disorder; pre-SMA, pre-supplementary motor cortex.

Table S4. Task-related activation for stop-trials in the HC group (wholebrain analysis).

	Cluster-level statistics*			
Region name	**$p_{FWE\text{-}corrected}$**	**Number of voxels**	**MNI x, y, z coordinates**	**T**
R occipital lobe	<.001	445	32, -62, -8	7.10
			40, -60, 2	6.14
			30, -50, -18	5.78
	.007	35	20, -62, 6	4.91
R anterior insula/IFG (pars opercularis)	<.001	822	44, 6, 8	6.91
			34, 16, 6	6.69
			34, 18, -6	5.39
L occipital lobe	<.001	626	-24, -92, 4	6.83
			-22, -86, -8	6.43
			-28, -82, -12	6.42
	<.001	196	-18, -66, 6	6.63
R pre-SMA	.003	57	8, 8, 46	5.73
L anterior insula	.001	94	-40, 8, 4	5.38
	.026	7	-28, 14, -12	4.77
L hippocampus	.009	29	-16, -26, -10	5.26
L cerebellum	.010	27	-24, -52, -22	5.06
L putamen	.011	25	-20, 0, -12	5.05
R hippocampus	.019	12	32, -8, -14	5.01
			12, -70, 12	4.78
R SMG	.024	8	52, -36, 42	4.66

Note: *significant at $p<.05$ with correction for the family-wise error rate across the whole brain. HC, healthy control; IFG, inferior frontal gyrus; pre-SMA, pre-supplementary motor cortex; SMG, supramarginal gyrus.

Table S5. Bayesian repeated-measures ANCOVA with region-of-interest parameter estimates for failed inhibition (failed stop>correct go) as a within-group factor, group as a between-group factor and age and gender as covariates.

Models	P(M)	P(M|data)	BF_M	BF_{10}	error %
Null model (incl. sex, age, subject)	0.200	0.507	4.107	1.000	
ROI	0.200	0.234	1.222	0.462	6.850
group	0.200	0.168	0.805	0.331	5.344
ROI + group	0.200	0.085	0.370	0.167	7.310
ROI + group + ROI ✻ group	0.200	0.007	0.029	0.014	11.514

Note: All models include sex, age, and subject.

Table S6. Bayesian repeated-measures ANCOVA with region-of-interest parameter estimates for successful inhibition (correct stop>correct go) as a within-group factor, group as a between-group factor and age and gender as covariates.

Models	P(M)	P(M|data)	BF_M	BF_{10}	error %
Null model (incl. sex, age, subject)	0.200	0.693	9.025	1.000	
group	0.200	0.257	1.381	0.370	4.609
ROI	0.200	0.032	0.133	0.046	6.318
ROI + group	0.200	0.014	0.057	0.020	8.659
ROI + group + ROI ✻ group	0.200	0.004	0.017	0.006	10.658

Note: All models include sex, age, and subject.

Table S7. Task main effect of response finger (left or right) across conditions (go and stop) and groups (HC and OCD).

	Cluster-level statistics*			
Region name	**$p_{FWE\text{-}corrected}$**	**Number of voxels**	**MNI x, y, z coordinates**	**F**
L precentral gyrus (primary motor cortex)	<.001	552	-32, -24, 54	73.60
R precentral gyrus (primary motor cortex)	<.001	474	36, -24, 52	54.86

Note: *significant at p<.05 with correction for the family-wise error rate across the whole brain. HC, healthy control; OCD, obsessive-compulsive disorder.

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Declarations of co-authorship

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Valdemar Funch Uhre
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Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Psychological and neurobiological perspectives on pediatric OCD

2. The declaration applies to the following article	
Title of article	Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents
Article status	
Published ☒ Date: January 2020	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP), 2020; 59(1): 64-77. DOI: https://doi.org/10.1016/j.jaac.2019.08.480

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C
3. Planning of the experiments and methodology design and development	C

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	C
5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	C
8. Finalisation of the manuscript and submission	C

Provide a short description of the PhD student´s specific contribution to the article.[i]

VFU and CFU are co-first authors and worked together on most aspects of the study. These aspects include the formulation of the research question (with help from supervisors), the development of methods, the screening of records, obtaining access to and retrieving data (with help from SV), assessments concerning the trials included (together with LP and NNL) the analysis of data (with advice from CG and JCJ), interpretation of the results and making the figures and tables included in the article, writing the initial draft of the manuscript and finalizing and submitting the manuscript.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☒ No: ☐
If yes, please state name of the author and title of thesis / dissertation.	Camilla Funch Uhre; Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	VFU and CFU contributed equally to most aspects of the work, with a few exceptions: CFU contributed more to the formulation and preparation of the work (including drafting the protocol for the review) and to the collection of data from trial authors. VFU contributed more to the development of key methods and to the analysis of data and interpretation of the results.

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**

5. Signatures of the co-authors[iii]				
1.	020422	Camilla Funch Uhre	MSc	
2.	17/03/2022	Nicole Nadine Lønfeldt	MSc, PhD	
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9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 170322

Principal supervisor: anne katrine pagsberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 17-03-2022

PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Valdemar Funch Uhre
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Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Psychological and neurobiological perspectives on pediatric OCD

2. The declaration applies to the following article	
Title of article	Dr. Uhre *et al*. Reply:
Article status	
Published ☒ Date: July, 2020	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP), 2020; 59(7), 787-791. DOI: 10.1016/j.jaac.2020.04.013

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	F
3. Planning of the experiments and methodology design and development	A

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	F
5. Conducting the analysis of data	C
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]

For this work, no new methods were developed, and no new data were accessed or collected.

VFU identified the questions to address in the letter and planned the new RoB-2 assessment.

VFU and NNL conducted the risk of bias assessment independently.

VFU interpreted the results, wrote the manuscript, and finalised and submitted the manuscript, which was revised by all co-authors.

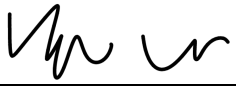
4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	02-04-2022	Camilla Funch Uhre	MSc	

5. Signatures of the co-authors[iii]				
2.	17/03/2022	Nicole Nadine Lønfeldt	MSc, PhD	
3.	17/03/2022	Linea Pretzmann	MSc	
4.	17/3 2022	Signe Vangkilde	MSc, PhD	
5.	17/03/2022	Kerstin Jessica Plessen	MD, PhD	
6.	17/3/22	Christian Gluud	MD, DrMedSci	
7.	01-04-2022	Janus Christian Jakobsen	MD, PhD	
8.	170322	Anne Katrine Pagsberg	MD, PhD	anne katrine pagsberg
9.				
10.				

6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 170322 Principal supervisor: anne katrine pagsberg

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 17-03-2022 PhD student: 

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[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Valdemar Funch Uhre
E-mail	Valdemar.uhre@regionh.dk
Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Psychological and neurobiological perspectives on pediatric OCD

2. The declaration applies to the following article	
Title of article	Inhibitory control in obsessive compulsive disorder: a systematic review and activation likelihood estimation meta-analysis of functional magnetic resonance imaging studies
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: Sep 13, 2021 (rejected with the possibility of resubmission on Nov 26, 2021)	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	A

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	B
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]

VFU, AKP and HRS identified the scientific problem and formulated key research questions.

VFU planned and developed the search strategy for the database search.

VFU conducted the initial and final database search and retrieved records.

VFU and WB independently screened retrieved records for eligibility.

VFU obtained data from eligible studies.

VFU and KML curated the data.

VFU and DM conducted the meta-analyses.

VFU interpreted the results and made the figures and tables.

VFU wrote the initial draft of the manuscript.

All authors revised the manuscript.

VFU finalized and submitted the manuscript.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	

If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]				
	Date	Name	Title	Signature
1.	16-03-2022	Valdemar Funch Uhre	MSc	
2.	23/3 22	Kit Melissa Larsen	Msc, Phd	
3.	23.03.22	Damian Marc Herz	MD, PhD	
4.	25.03.22	William Baaré	PhD	
5.	160322	Anne Katrine Pagsberg	MD, PhD	anne katrine pagsberg
6.	23/03/22	Hartwig Roman Siebner	MD, DMSci	
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 02-04-22 Principal supervisor: anne katrine pagsberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 16-03-2022

PhD student:

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DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Valdemar Funch Uhre
E-mail	Valdemar.uhre@regionh.dk
Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Psychological and neurobiological perspectives on pediatric OCD

2. The declaration applies to the following article	
Title of article	Moderate evidence of intact inhibitory control in pediatric obsessive-compulsive disorder: An fMRI study
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☒
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	A, B, C, D, E, F
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	B

3. **The PhD student's contribution to the article** *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	A, B, C, D, E, F
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	C
5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student's specific contribution to the article.[i]

VFU, KJP, HRS and AKP identified the scientific problem and formulated key research questions.

VFU coded and piloted the task.

VFU and ABN planned the experiments and piloted the experimental setup.

VFU, ABN, KWA and WB developed and tested key methods on pilot data.

VFU collected clinical, demographic, and scanning data on approximately 50 participants in the early stages of the data collection phase and supervised subsequent data collection of scanning data.

VFU cleaned and curated the data.

VFU, KML, SAF and KHM conducted the analysis of data.

VFU produced the tables and figures included in the manuscript.

VFU, KML, SAF, HRS and AKP interpreted the results.

VFU wrote the initial draft of the manuscript.

All authors revised the manuscript.

VFU finalized the manuscript.

4. **Material from another thesis / dissertation**[ii]	
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	Date	Name	Title	Signature
1.	23/03/22	Valdemar Funch Uhre	MSc	
2.	23/3 22	Kit Melissa Larsen	MSc, PhD	
3.	23/03 22	Søren Asp Fuglsang	MSc, PhD	
4.	30/03 22	Kristoffer Hougaard Madsen	MSc, PhD	
[redacted]				
6.	25/03/2022	Ayna Baladi Nejad		
7.	24/03/22	William Baaré	PhD	
8.	24/03/22	Kerstin Jessica Plessen		
9.	23/03/2022	Hartwig Roman Siebner		
10.	02-04-22	Anne Katrine Pagsberg	MD, PhD	anne katrine pagsberg

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

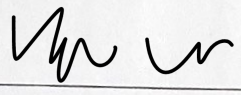
Date: 02-04-22

Principal supervisor: anne katrine pagsberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 01-04-2022

PhD student: 

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