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Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

PhD thesis

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Thesis title: Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

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List of papers

This thesis includes the following three papers:

Paper 1:

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.

Authors: Camilla Funch Uhre, Valdemar Funch Uhre, Nicole Nadine Lønfeldt, Linea Pretzmann, Signe Vangkilde, Kerstin Jessica Plessen, Christian Gluud, Janus Christian Jakobsen, Anne Katrine Pagsberg.

Paper 2:

Subtle and selective neurocognitive impairment in children and adolescents with obsessive-compulsive Disorder. *Submitted manuscript*.

Authors: Camilla Funch Uhre, Jens Richardt Møllegaard Jepsen, Valdemar Funch Uhre, Nicole Nadine Lønfeldt, Anne Dorothee Müller, Kerstin Jessica Plessen, Signe Vangkilde, and Anne Katrine Pagsberg.

Paper 3:

Probabilistic learning and decision-making appear intact in children and adolescents with obsessive-compulsive disorder. *Unsubmitted manuscript.*

Authors: Camilla Funch Uhre, Valdemar Funch Uhre, Jens Richardt Møllegaard Jepsen, Melanie Ritter, Linea Pretzmann, Nicoline Løcke Jepsen Korsbjerg, Christine Lykke Thoustrup, Julie Hagstrøm, Kerstin Jessica Plessen, Anne Katrine Pagsberg, Signe Vangkilde.

Abbreviations

ADHD = Attention-deficit/hyperactivity disorder

ANOVA = Analysis of variance

AST = Attention Switching Task

BF = Bayes' factor

BT = Behavioral Therapy

CANTAB = Cambridge Neuropsychological Test Automated Battery

CBT = Cognitive Behavioral Therapy

CGT = Cambridge Gambling Task

CI = Confidence interval

CSTC = Cortico-striato-thalamo-cortical

CY-BOCS = Children's Yale Brown Obsessive-Compulsive Scale

D-KEFS = Delis-Kaplan Executive Function System

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

FCBT = Family-based Cognitive Behavioral Therapy

fMRI = Functional magnetic resonance imaging

FPRT = Family-based Psychoeducation and Relaxation Therapy

GRADE = Grading of Recommendations Assessment, Development and Evaluation

ICD-10 = International Classification of Diseases – Tenth Revision

IQ = Intelligence quotient

IQR = Interquartile range

MANOVA = Multivariate analysis of variance

MANCOVA = Multivariate analysis of covariance

OCD = Obsessive-compulsive disorder

PRT = Psychoeducation and Relaxation Training

RoB = Risk of bias

SD = Standard deviation

SMD = Standardized mean difference

SOC = Stockings of Cambridge

SSRI = Selective serotonin reuptake inhibitor

SWM = Spatial Working Memory

TMT = Trail Making Task

TOF = Test Observation Form

TSA = Trial Sequential Analysis

WAIS-IV = Wechsler Adult Intelligence Scale – fourth edition

WHO = World Health Organization

WISC-V = Wechsler Intelligence Scale for Children – fifth edition

WPT = Weather Prediction Task

Thesis Summary

Neurocognitive dysfunction putatively underlies core symptoms of pediatric obsessive-compulsive disorder (OCD), but experimental findings are inconclusive. The only existing meta-analysis of neurocognitive studies with children and adolescents with OCD discovered a trend of underperformance compared to healthy controls, but no group differences were statistically significant. Moreover, the investigators concluded that the evidence was insufficient to determine a specific cognitive profile of pediatric OCD.

The main purpose of this thesis was to characterize neurocognitive functioning of children and adolescents with OCD. Two experimental studies and a systematic review of cognitive behavioral therapy (CBT) for pediatric OCD are included in this thesis. The experimental studies (Papers 2 and 3) reflect the neurocognitive focus of this thesis, whereas the systematic review (Paper 1) reflects the general preparation phase of the larger study which this work was a part of (The TECTO study).

In the systematic review, we assessed benefits and harms of CBT compared to no intervention, placebo, or other interventions. The main findings indicated that CBT is an effective treatment for pediatric OCD, superior to placebo, and similar to pharmacological treatment with selective-serotonin-reuptake-inhibitors (SSRIs). However, the twelve included trials were rated as having high overall risks of bias, and the certainty of the evidence was low for all evaluated outcomes (symptom severity, level of functioning, adverse events, quality of life, and remission). Additionally, the review revealed a lack of data on patient-reported outcomes.

In our experimental studies, children and adolescents with OCD performed moderately worse on an affective decision-making task and had slower processing speed compared to healthy controls. We found no evidence of impaired planning, working memory, verbal or nonverbal fluency (Paper 2), or probabilistic learning and decision-making in a neutral context (Paper 3). Our findings regarding cognitive flexibility were more ambiguous, with minor impairment on some outcomes (including accuracy and completion times on set-shifting tasks), but not on a more direct measure of cognitive flexibility (switch cost). Taken together, our findings suggest that children and adolescents with OCD may exhibit subtle and selective neurocognitive impairment, which future studies should investigate the potential real-life impact of.

Resumé (Danish Summary)

Obsessiv-kompulsiv tilstand (OCD) hos børn og unge formodes at være forbundet med neurokognitive forstyrrelser, men de eksperimentelle fund er inkonsistente. Den eneste metaanalyse af neurokognitive studier med børn og unge med OCD fandt en generel tendens til underpræstation i OCD-grupperne sammenlignet med kontrolgrupperne, men ingen statistisk signifikante forskelle. Forfatterne konkluderede desuden, at datagrundlaget var utilstrækkeligt til at kunne udlede en egentlig kognitiv profil for børn og unge med OCD.

Hovedformålet med denne ph.d.-afhandling var at karakterisere den neurokognitive funktion hos børn og unge med OCD. Afhandlingen inkluderer tre videnskabelige artikler: to eksperimentelle undersøgelser og et systematisk review med meta-analyse af kognitiv adfærdsterapi (KAT) til pædiatrisk OCD. De eksperimentelle undersøgelser (artikel 2 og 3) afspejler afhandlingens primære fokus på neurokognition, mens det systematiske review (artikel 1) afspejler forberedelsesfasen forud for påbegyndelsen af det større studie, som dette arbejde er en del af (TECTO-studiet).

I det systematiske review vurderede vi gavnlige og skadelige virkninger af KAT sammenlignet med ingen intervention, placebo eller anden intervention. Hovedresultaterne indikerede, at KAT er en effektiv behandling for børn og unge med OCD, mere effektiv end placebo og sammenlignelig med farmakologisk behandling med selektive serotoningenoptagshæmmere (SSRI). De tolv inkluderede kliniske forsøg var dog alle i høj risiko for bias, og der var stor usikkerhed forbundet med de absolutte effektestimater for samtlige mål (symptomsværhedsgrad, generelt funktionsniveau, uønskede hændelser/bivirkninger, livskvalitet og remission). Derudover afslørede gennemgangen af de kliniske forsøg en overordnet mangel på patient-rapporterede effektmål.

Vores eksperimentelle undersøgelser viste en moderat nedsat evne til beslutningstagen i en affektiv kontekst og let nedsat forarbejdningshastighed hos børn og unge med OCD sammenlignet med raske kontrolpersoner. Vi fandt ingen gruppeforskelle mellem OCD-gruppen og kontrolgruppen i forhold til planlægningsevne, arbejdshukommelse, verbal og nonverbal mobilisering (fluency, artikel 2), samt indlæring af sammenhænge mellem respons og udfald i en emotionelt neutral sammenhæng (artikel 3). Vores fund vedrørende kognitiv fleksibilitet var mere tvetydige, med let nedsat præstation i OCD-gruppen på visse mål (herunder let reduceret nøjagtighed og længere

gennemførelsestider på de relevante opgaver), men ikke på et mere direkte mål for kognitiv fleksibilitet (switch cost). Tilsammen peger vores resultater på, at børn og unge med OCD kan have subtile og selektive kognitive vanskeligheder, hvilket fremtidige undersøgelser bør undersøge den eventuelle betydning af i forhold til faktisk funktionsevne i dagligdagen.

Introduction

Obsessive-compulsive disorder in children and adolescents

Did you ever count the lampposts on your way to school, avoid stepping over cracks in the sidewalk, or mentally repeat certain phrases over and over?

Rituals often form integral parts of children's routines, e.g., at bedtime, dinner time, and getting to or from day care. The rituals seen in normal development are usually easy to maintain and provide comfort and structure for the child [1, 2]. Magical thinking (i.e. connecting unrelated actions and outcomes) is also common in childhood [1], and most people can recall rituals they performed to avoid a negative event, make something good happen, or simply feel satisfied. When rituals or magical thinking becomes disruptive to daily life or persists beyond early childhood, the behavior may reflect clinically relevant symptoms of obsessive-compulsive disorder [3].

OCD affects 0.63-3% of children and adolescents [4-6], causing impairment in school, at home, and with peers [7]. OCD is clinically defined by the presence of distressing and recurring thoughts, images or urges (obsessions) and/or repetitive mental or behavioral rituals (compulsions) that are frequently performed in response to obsessions [8, 9]. The specific content of obsessions and compulsions vary between individuals with OCD, but some symptoms are more common than others. The most common symptom group is contamination fear and excessive washing (often hand washing), seen in about 50% of pediatric OCD cases [10]. Other common symptoms include forbidden/taboo thoughts of a sexual or aggressive nature, fear of being harmed or causing harm to others, repeating specific action sequences (e.g., repeatedly opening and closing a door when leaving the house), and checking behavior (e.g., repeatedly checking if doors are locked and switches turned off) [11]. These symptom groups are found consistently across different cultures and age groups [11, 12]. OCD typically debuts early in life [11] and the average age of onset in children and adolescents is ten years [13]. Overall, two 'debut peaks' have been identified: one in childhood and one in early adulthood [14].

Most children and adolescents are aware that their obsessions and compulsions are excessive and will attempt to suppress or hide them, especially in public [1]. Since symptoms are often suppressed around others, childhood OCD can be overlooked. For example, in a large British mental health

survey, 25 children and adolescents met the criteria for OCD but all except three cases had been undetected [4]. Moreover, a review reported that the average age of assessment is 2.5 years after OCD onset in childhood [13]. Without treatment, OCD symptoms frequently persist in adulthood and assume a chronic course, fluctuating in severity throughout the lifespan [15].

Diagnostic criteria

Two diagnostic classification systems are used worldwide – the International Classification of Diseases (ICD), developed by the World Health Organization [9], and the Diagnostic and Statistical Manual of Mental Disorders (DSM), developed by the American Psychiatric Association [12]. The versions in use at the time of assessment of our study participants (ICD-10 and DSM-5) have very similar sections on OCD. According to the diagnostic criteria, obsessive and/or compulsive behavior must be time-consuming and present on most days, causing distress and disruption of daily life activities. Patients must recognize obsessions as their own thoughts or impulses and must be unable to resist at least one obsession or compulsion. The individual should also have insight into the senselessness of their obsessions and compulsions, although insight can vary greatly, especially in children and adolescents with OCD [16]. As a result, the level of insight has been added as a specifier in the DSM-5, allowing classification of OCD with poor or absent insight [12].

Co-occurring disorders

The course of OCD is often complicated by the co-occurrence of other psychiatric disorders [11, 17, 18] with comorbidity being associated with greater symptom severity and poorer response to treatment [19, 20]. Approximately 70% to 80% of children and adolescents with OCD have at least one co-occurring disorder [21-23]. Common co-occurring disorders include anxiety disorders, tic disorders (including Tourette's), attention-deficit hyperactivity disorder (ADHD), and mood disorders [24].

Differences between childhood-onset and adult-onset obsessive-compulsive disorder

While the diagnostic criteria and the common symptoms clusters are shared across age ranges, childhood-onset OCD and adult-onset OCD may differ in important ways, making it difficult to extend findings from one age group to the other [25]. Notably, the comorbidity pattern in children and adolescents with OCD differs from the pattern seen in adults [1]. Co-occurring mood and anxiety disorders are common in both pediatric and adult OCD, but other co-occurring disorders are predominantly seen in children and adolescents, including tic disorders [26], attention deficit-/hyperactivity disorder (ADHD), and autism spectrum disorders [1, 27]. The symptom presentation also appears to vary across age groups. Some children are unable to identify any obsessions that drive their rituals, but instead report feeling uneasy or uncomfortable, and a ritual is needed to feel "just right" again [1, 28]. The "just right" feeling is predominantly reported in children and adolescents with OCD and may be related to the high prevalence of co-occurrent tic disorder. Higher rates of ordering/symmetry compulsions and obsessions about harm to self or others have also been reported in children and adolescents with OCD, compared to adults [27]. Moreover, childhood-onset OCD is more often associated with a family history of OCD [1, 13], a predominance of males, and poor insight compared to adults [27]. In a study investigating insight in children and adolescents with OCD, 45% (n=35) displayed poor insight, as determined by clinician-ratings of the insight-item of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS [29]) [16]. Studies of insight in adults with OCD report poor insight in 13% to 30% of cases [30]. Children and adolescent also involve other people in their compulsions to a larger extent than adults with OCD [31, 32]. For example, parents may be asked to take part in a specific ritual or avoidance behavior. Parents commonly engage in such family accommodation which unintentionally reinforces symptoms [33], for example by agreeing to excessive washing of the child's items, arranging meals in particular ways, or repeating reassurances to alleviate distress [34]. Lastly, the only existing meta-analyses of neurocognitive functioning in children and adolescents with OCD [35] suggested that childhood-onset OCD is associated with fewer neurocognitive deficits than seen in adults [36, 37] (see details in later sections on the neurocognitive findings in children and adolescents with OCD and how they may differ from adults).

The apparent differences between children and adults with OCD have been interpreted in different ways. For instance, some researchers argue that childhood-onset OCD may be a distinct subtype of the disorder [1, 27]. On the other hand, at least some of the phenotypic variability seem to reflect different stages of normal development, with specific obsessive-compulsive "themes" occurring at expected ages – such as the higher rate of obsessions about harm to caregivers seen in children with OCD and sexual obsessions in adolescents with OCD.

Psychological models of obsessive-compulsive disorder

Psychological and cognitive theories link OCD to dysfunctional beliefs and exaggerated emotional processing of situations [38]. In cognitive-behavioral theory, which is the basis of standard therapeutic treatment of OCD, symptom development has traditionally been ascribed to classical conditioning processes: specific cues (external situations or mental events) come to trigger anxiety, which is then alleviated by compulsions, thereby maintaining obsessions and compulsions through negative reinforcement [39]. The conditioning model has greatly influenced the understanding of OCD symptom maintenance and effective treatment strategies, but is generally regarded inadequate as a theory of how OCD develops; the onset of OCD is often gradual rather than sudden, unlike a response to a specific traumatic event, and individuals with OCD often have multiple types of obsessions and compulsions without having multiple corresponding conditioning experiences [39]. According to modern cognitive behavioral theories, individuals with OCD attribute too much importance and moral value to their thoughts, a phenomenon termed "thought-action fusion" [40]. Thought-action fusion is assumed to manifest in two ways: 1) believing that thoughts and events are causally related (e.g., if I think of a disease, I am more likely to develop it), and 2) considering immoral thoughts to be equal to immoral actions (e.g., if I think about hurting my friends, it is as bad as actually hurting them). The theory is supported by some studies with children and adolescents [41, 42], but thought-action fusion does not seem to be specific to OCD [43, 44].

Treatment

Behavioral therapy (BT) and cognitive behavioral therapy (CBT) are first-line treatments for OCD in children and adolescents [45-47]. The main treatment component was developed in the 1960s to 1970s and is now known as "exposure and response prevention". During exposure and response prevention, the patient is exposed to a trigger situation (e.g., using a public restroom) and must

prevent the compulsive response (e.g., excessive or ritualistic handwashing) with therapist assistance [48, 49]. Other treatment components include psychoeducation, homework assignments (between-session exposures), and family involvement [50, 51]. Randomized clinical trials show medium to large effects of CBT for children and adolescents with OCD, although up to 40% of patients still have considerable symptoms after their first CBT/BT treatment [52, 53]. Importantly, a large Scandinavian cross-over study indicated that another dose of CBT may be as effective as switching to pharmacotherapy for initial non-responders [54]. In paper 1, we present a systematic review and meta-analysis of randomized controlled trials (RCTs) of CBT for OCD in children and adolescents, assessing treatment effects on a range of clinical outcomes. CBT was superior to no intervention, relaxation training (as a control intervention), and comparable to pharmacological treatment for OCD in children and adolescents. However, results of individual trials were inconsistent and the risk of bias was high, emphasizing the need for more rigorous trials with low risk of bias to evaluate the absolute treatment effect of CBT for children and adolescents with OCD [52].

Etiology

The etiology of OCD is unclear, but the symptom development is generally viewed within the framework of a 'vulnerability-stress model', suggesting that multiple genetic and environmental factors contribute to the disorder [8, 39]. According to a review of twin studies, the heritability of OCD symptoms are between 25% - 47% in adults with OCD, with higher estimates of 45% - 65% in children and adolescents with OCD [55].

Environmental risk factors may be both somatic and psychological stressors. Swedo and colleagues [56] proposed that OCD symptoms and tics could develop after an abnormal immune response to streptococcal infection, known as the PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) hypothesis. The PANDAS hypothesis is still debated, with recent studies finding no link between streptococcal infection and sudden onset or exacerbation of OCD symptoms or tics [57].

Psychological stress and trauma may also trigger OCD symptoms in children and adolescents who are genetically predisposed to the disorder. For example, in some studies, children and adolescents with OCD report having experienced significantly more stressful life events than healthy controls in

the year preceding symptom onset [58, 59]. In the largest study, including 263 pediatric OCD cases, children reported higher rates of traumatic life events, including domestic violence, sexual or physical assault, and forced home entry [59]. Studies with adult samples have also indicated an association between post-traumatic stress disorder and the development of OCD [60, 61]. However, stress and trauma are common risk factors across psychiatric disorders and not specific to OCD [39].

Neurobiological and cognitive models of obsessive-compulsive disorder

The neurobiological model of OCD highlights abnormal functioning in the cortico-striato-thalamo-cortical (CSTC) circuits of the brain, associated with the regulation of cognitions, emotions, and behavior [11, 62, 63].The CSTC circuits are parallel neural loops that link areas of the frontal cortex with deep brain structures including the thalamus and the basal ganglia (an overview of the circuitry is presented in Figure 1). In OCD, excessive activation of limbic and ventral CSTC circuity has been

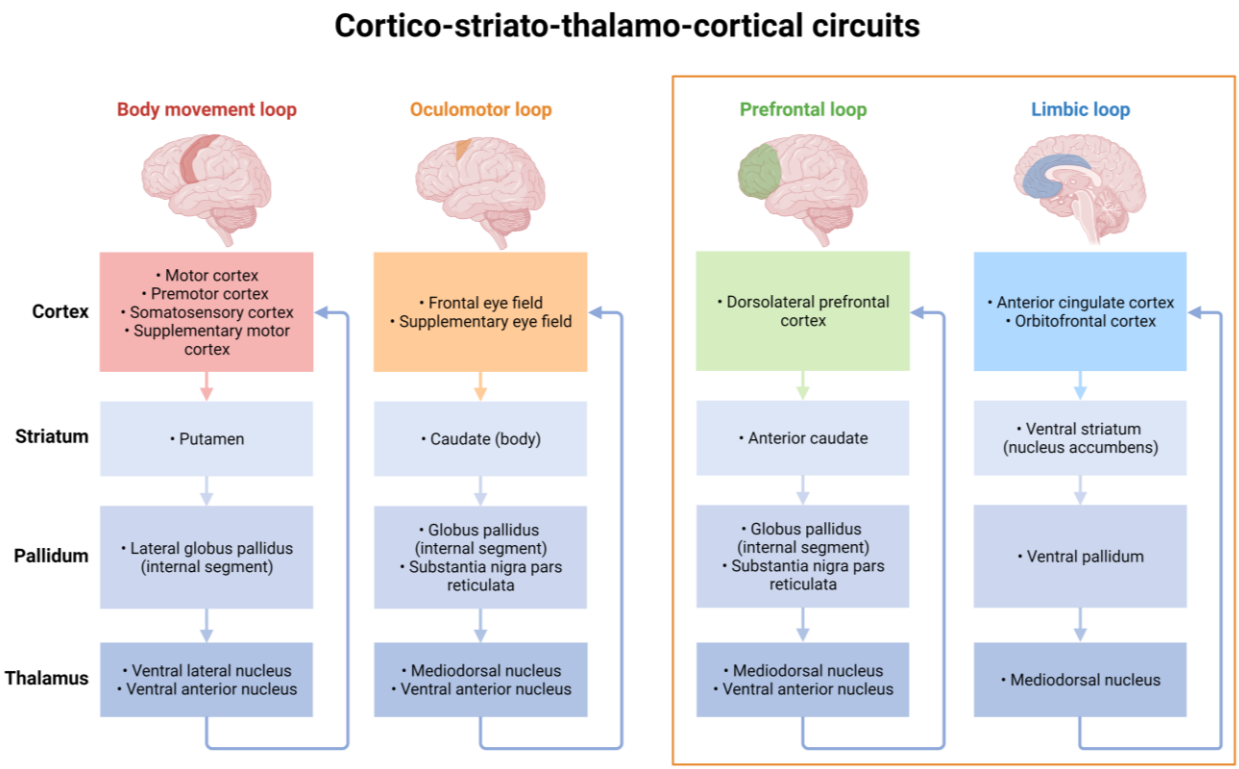

Figure 1. Overview of cortico-striato-thalamo-cortical (CSTC) circuits. The prefrontal and limbic loops (highlighted in orange) have been implicated in OCD, with excessive activation of limbic circuitry potentially underlying excessive emotional processing and decreased activation of dorsolateral circuitry underlying deficits in cognitive control. The CSTC circuits have also been implicated in other disorders, such as tic disorders that are associated with abnormal activity of the motor loops. The figure is adapted from the "Basal Ganglia Motor and Non-motor Loops" template from BioRender (BioRender.com).

proposed to underlie dysregulated emotions (e.g. distress and anxiety related to obsessions), while decreased activation of dorsal CSTC circuits may underlie deficits in cognitive control (e.g. the inability to inhibit unwanted behavior) [8, 64]. The CSTC model is generally supported by functional magnetic resonance imaging (fMRI) studies, showing aberrant activation of the orbitofrontal cortex, the anterior cingulate cortex, and the caudate nucleus in individuals with OCD compared to healthy control groups [65]. For example, adults with OCD show increased activation of limbic and ventral fronto-striatal regions compared to controls at rest and in response to symptom-provocation, as well as decreased activation of dorsal fronto-striatal regions during executive function tasks [66-69].

Building on the CSTC model, a recent neurocognitive model links obsessive-compulsive behavior to a disruption in the balance between a goal-directed system and a habit system for the control of actions, leading to excessive reliance on habits and thereby difficulties in updating and adapting behavior when required [70-72].

Whereas habits are fixed and automatic responses, goal-directed actions are flexible and intentional [73]. Habits often serve as cognitive 'short cuts' in situations that occur frequently and have a relatively defined set of appropriate responses, as is characteristic for many everyday situations [74, 75]. When you get ready for work in the morning, you breeze through your routines without much effort, almost as if your hands prepare your breakfast, and your feet transport you. In unfamiliar situations, actions need to be carefully selected and adapted to achieve a current goal. Ideally the goal-directed system and the habit system work in an efficient balance. In children and adolescents with OCD, the two systems appear out of balance, resulting in an overreliance on the habit system at the expense of flexibility [70, 76-78]. In this view, compulsions represent extreme and pathological habit responses.

The brain areas implicated in OCD overlap with areas involved in inhibition of unwanted actions (response inhibition) and selection of goal-directed actions - including the prefrontal cortex, the caudate nucleus, and the anterior cingulate cortex [63]. Additionally, the basal ganglia likely play a key role in the formation of habits [79]. In mice, the spiking activity of neurons in the striatum has been linked to start and end signals of automated actions [80, 81], while lesions in the basal ganglia induce compulsive-like behavior [82]. Recent studies with individuals with OCD show that both adolescents and adults with OCD default to learned responses that once yielded a desired outcome

instead of updating their response strategy along with changes in task demands and outcomes [65, 70, 76].

Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

Based on the CSTC model, individuals with OCD are expected to have difficulty exerting cognitive control, acting and thinking flexibly in a goal-directed manner [64]. Most neurocognitive OCD studies have therefore investigated potential deficits in executive functions [83].

Executive functions refer to the control processes that regulate thoughts, actions, and emotions, although the precise delimitation varies considerably in the psychological literature. Based on their extensive work on the subject, Miyake and Friedman proposed a widely acknowledged definition of executive functions, as *"(…) a set of general-purpose control mechanisms, often linked to the prefrontal cortex of the brain, that regulate the dynamics of human cognition and action. (…) a core component of self-control or self-regulation ability (or "willpower")"* (Miyake and Friedman, 2012, p. 8) [84]

Core executive functions include inhibitory control, working memory, and cognitive flexibility [85, 86]. Planning is also often referred to as an executive function, building on the core functions [83, 86] (see Figure 2).

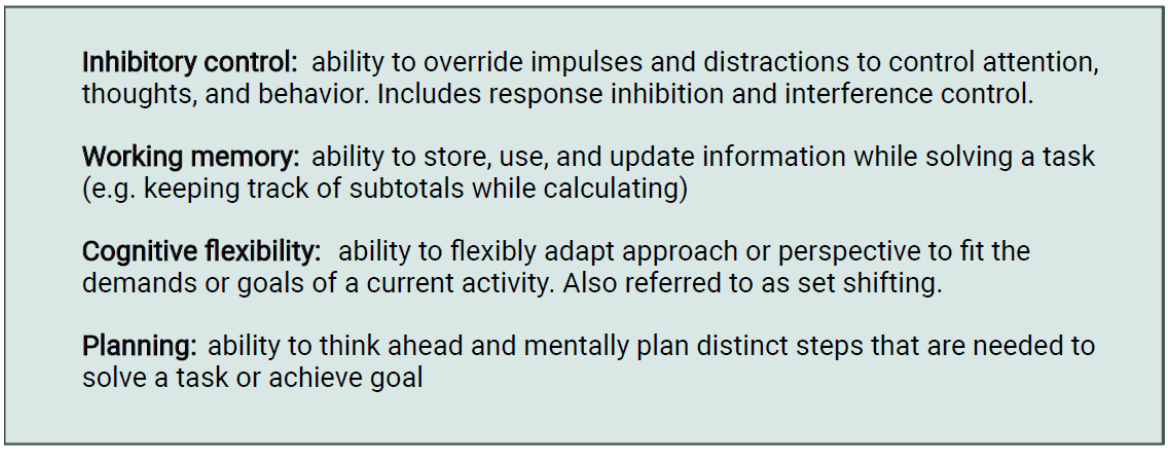

Figure 2. Executive functions and brief definitions.

In addition to executive functions, processing speed, visuo-spatial functions, attention, and decision-making has been investigated in children and adolescents with OCD [35, 87].

Experimental findings

The only existing meta-analysis of neurocognitive studies in children and adolescents with OCD (N studies = 11) reported a tendency of poorer performance relative to healthy controls, but no statistically significant differences were found between groups [35]. The authors concluded that *"Results indicate an overall small degree of underperformance on most subdomains, intact performance on response inhibition and interference control subdomains, and a small to moderate degree of underperformance in the subdomain of planning. It is important, however, to consider the small number of studies included, which highlights the urgent need for more research tapping neuropsychological functions in pediatric OCD."* (Abramovitch et al., 2015, p. 844) [35]. The review was restricted to case-control studies using validated tests of neurocognitive functions. A recent systematic review without meta-analysis evaluated findings on executive functions and memory from a broader range of neurocognitive studies (n = 43), including studies using novel tasks [87]. The authors concluded that children and adolescents with OCD may have impaired visual working memory, planning ability, decision-making under uncertainty (e.g. when response-outcome contingencies are ambiguous), as well as increased sensitivity to errors (increased error-related negativity in electroencephalography experiments) [87]. Additionally, slower processing speed has been reported in a large sample of children and adolescents with OCD (n=102) [88].

In contrast to the lack of significant findings in the meta-analysis of neurocognitive studies in children and adolescents with OCD [35], meta-analyses of neurocognitive findings in adults with OCD show mild to moderate impairment in executive and other functions, with the most consistent findings being impaired nonverbal memory, planning ability, and processing speed [36, 37, 89, 90]. This apparent disparity between pediatric and adult samples has sparked debate about whether neurocognitive functioning varies systematically across age groups, possibly reflecting different subtypes of OCD, or whether neurocognitive deficits become more pronounced with disorder progression or neurodevelopment [87]. For example, children and adolescents with OCD may perform comparably to healthy peers at earlier stages of development, but show more difficulties when the neural systems underlying executive functions mature through adolescence and adulthood [87]. Alternatively, neurocognitive functioning may be comparable in children and adults

with OCD, but pediatric studies are generally too small (typically including 14-35 patients) to detect the small to moderate impairments seen in adults [87]. Large neurocognitive studies with children and adolescents with OCD (including our own, presented in Paper 2), are needed to approach a conclusion, and determine the cognitive profile of childhood OCD.

The TECTO study

The work presented in this thesis is part of the TECTO study, which is an ongoing randomized controlled trial combined with a longitudinal case-control study [91]. The TECTO study compares the effects of family-based CBT (FCBT) with family-based psychoeducation and relaxation therapy (FPRT) in children and adolescents with OCD (Fig 3 outlines the TECTO study design). The two treatments are similar, but the supposed main treatment component – exposure and response prevention – is only delivered in the CBT arm (see Figure 4 for a brief overview of the treatment components). The attached case-control study is divided into a series of substudies exploring characteristics of children and adolescents with OCD at baseline as well as associations between treatment response at follow-up and a multitude of neurobiological, neurocognitive, emotional, neuroendocrine, and relational (parent-child and therapist-client dynamics) outcomes.

The experimental studies included in this thesis (Paper 2 and 3) presents data from the baseline neurocognitive assessments of children and adolescents with OCD and healthy controls. The specific aims of the neurocognitive sub-study are presented below.

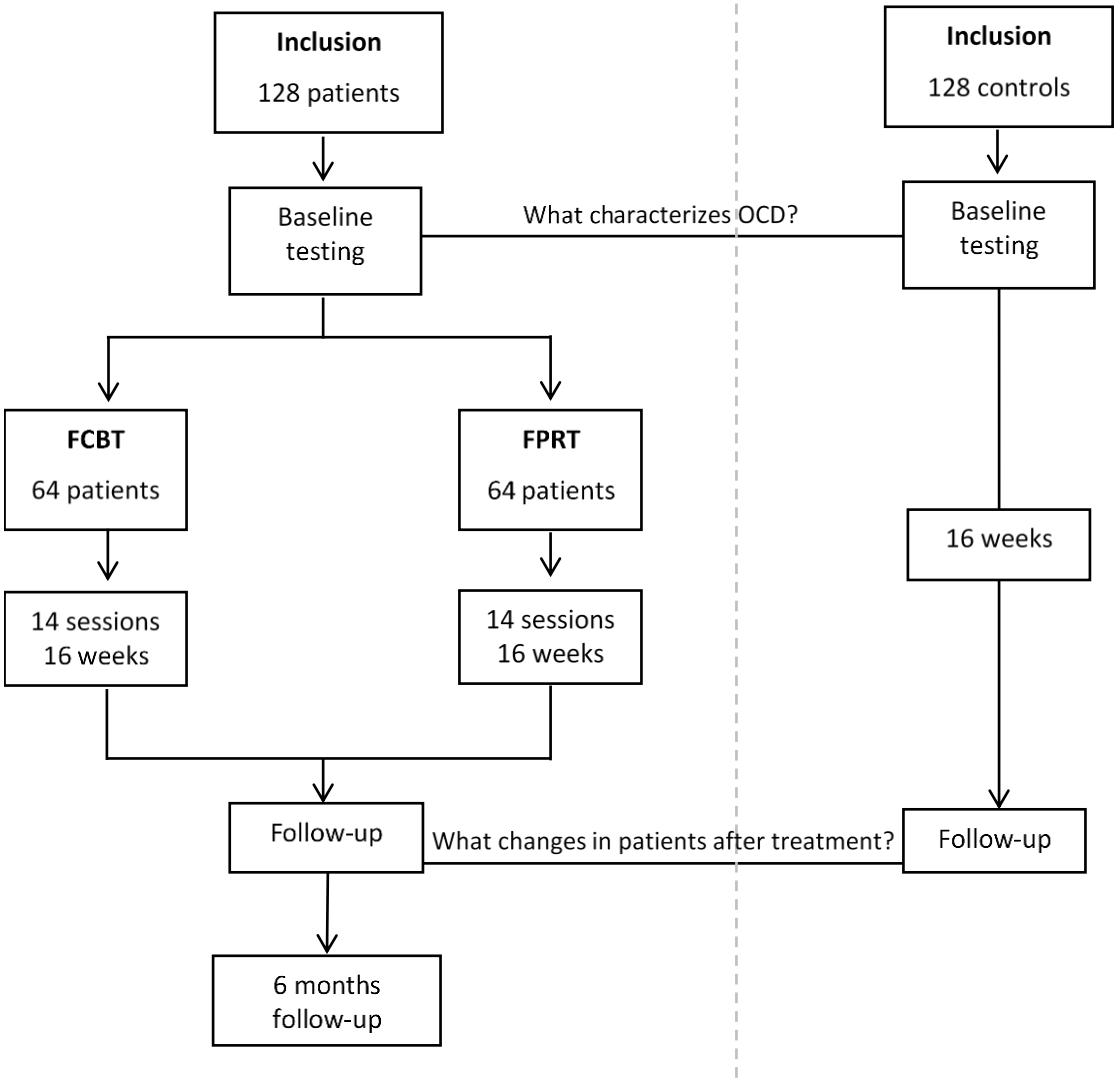

Figure 3. TECTO study design. The TECTO trial (left side of the figure) compares effects of family-based cognitive-behavioral therapy (FCBT) and family-based psychoeducation and relaxation training (FPRT). The case-control study compares children and adolescents with OCD to healthy controls across a range of outcomes (e.g., neuroimaging and neurocognitive tests) at baseline and follow-up.

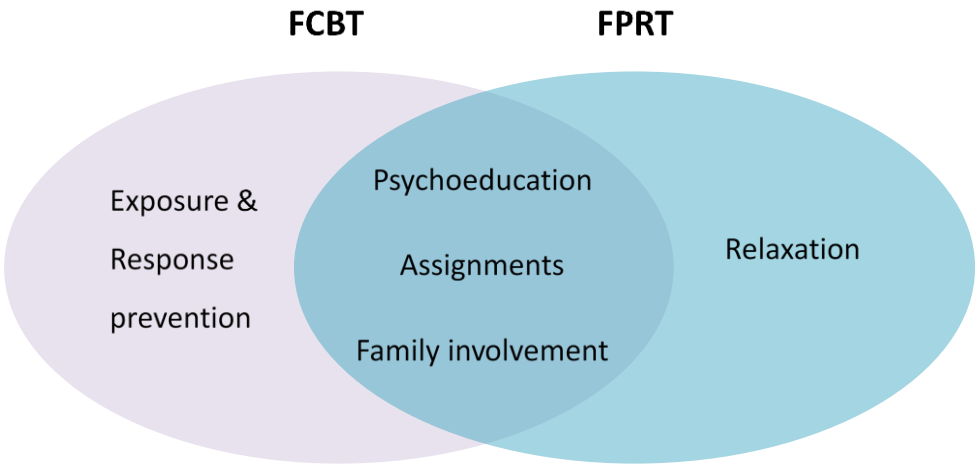

Figure 4. Brief overview of treatment components in family-based cognitive behavioral therapy (FCBT) and family-based psychoeducation and relaxation training (FPRT).

Thesis objectives

The overarching aim of this work was to characterize neurocognitive functioning of children and adolescents with obsessive-compulsive disorder. Neurocognitive dysfunction has long been assumed to play a central role in OCD, but findings from experimental studies are inconsistent, and the only meta-analysis of pediatric studies concluded that the current evidence does not allow for identification of a specific cognitive profile [35]. Moreover, childhood-onset OCD has been proposed to be a subtype of the disorder [27] with distinct neurocognitive presentation. Nevertheless, the potential neurocognitive differences across age groups are unclear [87], at least in part because pediatric studies are vastly underrepresented relative to adult studies (approximately 1:25 [92]). We therefore assessed a range of neurocognitive functions in a large sample of children and adolescents with OCD, compared to healthy controls. Based on the theoretical models of OCD, we hypothesized that children and adolescents would exhibit neurocognitive deficits, especially in cognitive flexibility.

The thesis includes three manuscripts. The experimental studies (Paper 2 and 3) reflect the neurocognitive focus of the thesis, while Paper 1 presents a systematic review of CBT for pediatric OCD, which was done in preparation for the TECTO trial. The individual aims of each paper are presented below.

Paper 1

The aim of the first study (Paper 1) was to obtain an overview of the findings from randomized controlled trials of CBT for children and adolescents with OCD, as part of the preparation for the TECTO trial. Several previous reviews and meta-analyses assessed the effect of CBT on alleviating symptom severity in pediatric OCD, without assessing effects on other important outcomes. In accordance with the broad scope of the TECTO trial, we wished to evaluate the state of the evidence of CBT for pediatric OCD on a broader range of outcomes. We systematically reviewed previous randomized CBT trials for children and adolescents with OCD regarding symptom severity, level of functioning, quality of life, adverse events, and remission.

Paper 2

The aim of the second study (Paper 2) was to determine whether neurocognitive functioning differs in children and adolescents with OCD compared to healthy controls. Individuals with OCD are expected to have executive function deficits (e.g., impaired cognitive control and flexibility) based on the CSTC model and the theory of impaired goal-directed control [64, 70]. Recent evidence supports the model, indicating that adolescents with OCD rely excessively on a habit system for the control of actions rather than a goal-directed system [76]. We therefore selected a test battery focused on executive functions and particularly on cognitive flexibility (i.e., set shifting tasks), hypothesizing that children and adolescents with OCD would perform worse than healthy controls.

Paper 3

The aim of the third study (Paper 3) was to investigate associations between pediatric OCD and deficits in probabilistic learning and decision-making. OCD is often associated with excessive doubt, overestimation of threat, and formation of irrational associations between actions and outcomes (e.g., thinking that maybe a feared negative event can be avoided by performing an arbitrary ritual). The clinical presentation of the disorder may reflect impaired learning of probabilistic contingencies, resulting in difficulties with monitoring and modifying thoughts and actions based on feedback from experiences. We assessed performance of children and adolescents with OCD and healthy controls on the Weather Prediction Task (WPT), which is a classic probabilistic learning and decision-making task (detailed in the Methods section). We added a questionnaire after task performance to assess

potential differences in explicit knowledge of the task contingencies between children and adolescents with OCD and healthy controls.

Methods

Systematic review of cognitive-behavioral therapy for obsessive-compulsive disorder in children and adolescents (paper 1)

Trial inclusion and data extraction

We systematically searched for trials comparing CBT to any control intervention for children and adolescent with OCD. We searched for relevant trials via the following databases/registers: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Psychological Information Database (PsycINFO), Excerpta Medica Database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), Web of Science, Social Science Citation Index (SSCI), and BIOSIS. We also searched through other sources, including e.g., ClinicalTrials.gov [93], Google Scholar [94], conference abstracts from major CBT conferences, and reference lists of eligible trial papers identified through database searches.

We included all trials that assessed the effects of CBT compared to any other control condition (including any other intervention, placebo, and wait-list control). Three authors independently screened all titles and abstracts from the initial searches, as well as full-text manuscripts of potentially eligible trials. The same authors independently extracted the following data from each eligible trial: author names, publication year, trial location, participant characteristics, sample size (total and for each intervention/control group), intervention characteristics (e.g., duration and number of treatment sessions), and mean scores and standard deviations for each outcome at baseline, end of intervention, and end of longest follow-up period. The primary outcomes were symptom severity (CY-BOCS total score), serious adverse events, and level of functioning (any validated scale). Secondary outcomes were adverse events and quality of life (any validated scale). Remission was included as an exploratory outcome. All methods were planned and detailed in a registered protocol ahead of conducting the review (PROSPERO registration ID: crd42017079118).

Assessment of risk of bias

We evaluated risk of bias in the included trials using Cochrane's risk of bias tool [95], covering the following domains:

- Selection bias (allocation method and concealment)
- Performance bias (blinding of trial participants and treatment providers)
- Detection bias (blinding of outcome assessors)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias (e.g., vested interests).

We contacted trial authors to obtain additional data or clarifications in case the information included in the trial manuscript was insufficient to evaluate a risk of bias domain (e.g., the manuscript included no or unclear description of the allocation process or blinding).

Data analyses

We followed the systematic review guidelines provided by Cochrane [95], and used Cochrane's Review Manager 5 [96] for data analyses. In case of missing data, we contacted trial authors to obtain the relevant values. We calculated mean differences (MDs) with 95% confidence intervals for continuous outcomes. In case different scales were used to measure the same outcome type, we calculated standardized mean differences (SMDs). For dichotomous outcomes, we calculated risk ratios with 95% confidence intervals. As we planned to assess three primary outcomes and two secondary outcomes, we adjusted the significance levels to $p \leq .025$ and $p \leq .033$, respectively [97]. The conventional threshold for significance (0.05) was used for exploratory outcomes. We used Trial Sequential Analysis (TSA) to assess risks of false-positive and false-negative findings, and estimate the total sample size needed to detect or reject a clinically relevant difference based on the observed data [98, 99]. We did subgroup analyses when at least two trials provided data for the comparison. Subgroup analyses addressed effects related to type of control intervention (e.g. active control or placebo), type of CBT intervention (e.g., individual CBT vs. group CBT), blinding of assessors (i.e., trials with blinded assessors versus trials without blinded assessors), risk of bias (i.e., low risk of bias trials vs. high risk of bias trials), age group (children vs. adults), symptom severity in the OCD group (e.g., mild versus severe OCD), and comorbidity status (i.e., OCD with comorbidity versus OCD only). We evaluated the strength of the evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines [100].

Experimental studies (Papers 2 and 3)

Participants

All participants in the neurocognitive studies (Papers 2 and 3) were part of a case-control study attached to a randomized clinical trial (The TECTO trial[91]). A total of 117 children and adolescents with OCD and 77 healthy controls were included in Paper 2, while a subgroup of 77 children and adolescents with OCD and 31 healthy controls were included in Paper 3.

Children and adolescents with OCD were recruited from the total pool of youths (8-17 years) referred with suspected OCD to the Child and Adolescent Mental Health Centre, Mental Health Services CPH, Copenhagen, Denmark. The eligibility criteria were:

- Age between 8 and 17 years (11 and 17 years in Paper 3)
- Full-scale IQ above 70
- OCD diagnosis according to ICD-10 (F42)
- Children's Yale-Brown Obsessive Compulsive Scale score $\geq$ 16 (CY-BOCS, range 0-40)[29]
- No CBT, PRT or pharmacological treatment with SSRIs, other antidepressants, or antipsychotic medication within the last six months prior to study entry
- No co-occurring bipolar disorder, mania, substance dependence disorder, schizophrenia, other psychotic disorder, or pervasive developmental disorder (except for Asperger's Syndrome).

Healthy controls were recruited via the Danish Central Person Registry [101] from a sample of children and adolescents in the same region and age range as participants with OCD. Healthy controls had to meet the same eligibility criteria as participants with OCD, with the exception that they did not previously or currently meet the diagnostic criteria for a psychiatric disorder, as assessed with a clinical interview (see details under "Procedures and approvals"). The demographic and clinical characteristics of the total sample are shown in Table 1 (adapted from Paper 2, Table 2).

Table 1. Demographic and clinical characteristics of the participants

Characteristic	OCD group Mean (SD) or n (%)	Healthy control group Mean (SD) or n (%)	*p* value
Number of participants	117	42	
Females/Males	58/59 (49.6/50.4)	18/24 (42.9/57.1)	.458
Age in years	13.31 (2.82)	12.36 (2.25)	.055
Parental education in years	15.55 (2.12)	16.73 (1.87)	.007
General Ability Index (WISC-V/WAIS-IV)	98.76 (13.54)	106.69 (13.17)	.001
TOF total score	17.38 (20.09)	6.14 (7.25)	<.001
OCD severity			
CY-BOCS total score	25.30 (4.98)		
CY-BOCS obsessions score	12.87 (2.99)		
CY-BOCS compulsions score	12.63 (2.82)		
Co-occurring disorders (ICD-10)			
Mood disorder (F30-F39)	1 (0.85)		
Phobic anxiety disorder (F40)	3 (2.56)		
Other anxiety disorder (F41)	8 (6.84)		
Stress-related disorder (F43)	15 (12.82)		
Eating disorder (F50)	4 (3.42)		
Personality disorder (F61)	2 (1.71)		
Asperger's syndrome (F84.5)	17 (14.53)		
Other developmental disorder (F88)	5 (4.27)		
ADHD (F90)	15 (12.82)		
Conduct disorder (F91)	1 (0.85)		
Emotional disorder with childhood onset (F93)	5 (4.27)		
Tic disorder (F95)	13 (11.11)		
Total with at least one co-occurring disorder	69 (58.97)		

Note: The data is from the full sample of participants included in the experimental studies of this thesis. The data provided in this table is identical to the data presented in Paper 2, Table 2. A subgroup of adolescents from the same sample were included in Paper 3. Abbreviations: ADHD, attention-deficit hyperactivity disorder; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; OCD, Obsessive-compulsive disorder; SD, standard deviation; TOF, Test Observation Form; WAIS-IV, Wechsler Adult Intelligence Scale Version IV; WISC-V, Wechsler Intelligence Scale for Children Version V.

Procedures and approvals

The study was conducted in compliance with the Helsinki Declaration [102] and was approved by the Danish authorities on research ethics and data protection (the Ethics Committee of The Capital Region of Denmark, and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark).

All participants were assessed for present and lifetime psychopathology with The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present & Lifetime version (K-

SADS-PL) [103]. Symptom severity in children and adolescents with OCD was assessed with the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [29]. Additionally, all children and adolescents were tested with a full Wechsler Intelligence Scale [104, 105]. The same assessor interviewed the child and parents with both the K-SADS-PL and the CY-BOCS. The K-SADS-PL was administered twice – once with the child/adolescent, and once with the parents. The CY-BOCS interview was done with the parents and the child/adolescent present, or with the child/adolescent alone, at the discretion of the assessor. Another assessor did intelligence testing. After the assessment, any detected diagnoses were conferred with a specialist in the outpatient clinic based on the criteria in the ICD-10 [9]. Neurocognitive testing was done on a separate day and included a comprehensive battery which took approximately 2.5 hours to complete. Each measure is detailed in the following.

Assessment of psychopathology

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present & Lifetime version (K-SADS-PL)

The K-SADS-PL is a semi-structured interview assessing symptoms of psychopathology according to DSM criteria [103]. The K-SADS-PL is the main diagnostic interview used in the Child and Adolescent Mental Health Centers of the Mental Health Services in Denmark, although final diagnoses are based on ICD-10 criteria. Accordingly, small adaptations to the interview are made in cases where the ICD criteria of a suspected disorder are not covered completely by the items in the K-SADS-PL. The K-SADS-PL starts with an introductory interview to gain rapport as well as insight into current problems at home, in school, and in social relationships. After the introductory interview, the assessor and respondent(s) go through a series of screening items that are scored on a scale going from zero (no relevant information was obtained) to three (clinically relevant symptom). The interview is conducted twice – once with the child/adolescent and once with parents/caregivers. Both interviews are scored separately, and the clinician makes a final evaluation of the scores.

Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)

The CY-BOCS is the gold standard semi-structured interview used to assess the presence and severity of obsessive-compulsive symptoms in children and adolescents [29]. The assessor and respondent go through checklists of common obsessions and compulsions, which the respondent

must answer if he/she experienced in the past week. After assessing symptom presentation, the symptoms are rated in terms of severity. The total score ranges from 0-40 with higher scores representing more severe OCD symptoms. In addition to the total score, the CY-BOCS includes a sub-score for the severity of obsessions and a sub-score for the severity of compulsions (both have score ranges of 0-20).

Neurocognitive assessment

The neurocognitive test battery included widely used and validated tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[106], the Delis-Kaplan Executive Function System (D-KEFS)[107], and the Wechsler scales [104, 105]. Intelligence was assessed with the age-appropriate Wechsler Scale for the individual participant – either The Wechsler Intelligence Scale for Children – Fifth edition (WISC-V)[104] or The Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV)[105]. The remaining neurocognitive battery assessed five neurocognitive functions: Cognitive flexibility, planning and decision-making, working memory, verbal and nonverbal fluency, and processing speed. All neurocognitive tests were administered and scored by trained psychologists and research assistants under the supervision of two senior neuropsychologists. The standard procedures for administration and scoring were followed. Table 2 provides an overview of the neurocognitive tests and outcomes. Each test is described in detail in the following.

Table 2. Neurocognitive test battery and outcomes

Neurocognitive function	Test	Outcomes
General cognitive ability	WISC-V / WAIS-IV	General Ability Index
Cognitive flexibility	CANTAB Attention Switching Task	Percent correct trials; Switch cost[a]
	D-KEFS Trail Making Test - Number-Letter Switching	Completion time in seconds
	D-KEFS Verbal Fluency – Switching	Number of correct switches
	D-KEFS Design Fluency - Switching	Number of correct figures
Planning and decision-making	CANTAB Stockings of Cambridge	Problems solved in minimum moves[b]
	CANTAB Spatial Working Memory	Spatial working memory strategy[c]
	Cambridge Gambling Task	Quality of decision making[d]; Risk adjustment[e]
Working memory	Wechsler Scales Working Memory Tests	Working memory index score
	CANTAB Spatial Working Memory	Total errors
Fluency	D-KEFS Verbal Fluency - Phonemic	Number of correct words
	D-KEFS Verbal Fluency - Semantic	Number of correct words
	D-KEFS Design Fluency – Empty Dots	Number of correct figures
Processing speed	D-KEFS Trail Making Test – Number Sequencing	Completion time in seconds
	D-KEFS Trail Making Test – Letter Sequencing	Completion time in seconds
Probabilistic learning	Weather Prediction Task	Proportion of optimal responses; Response time in seconds

Note: CANTAB = Cambridge Neuropsychological Test Automated Battery; D-KEFS = Delis-Kaplan Executive Function System; WAIS-IV = Wechsler Adult Intelligence Scale – fourth edition; WISC-V, Wechsler Intelligence Scale for Children – fifth edition. The Weather Prediction Task is reported on in Paper 3, while the remaining battery is reported on in Paper 2.

[a] Difference in mean reaction time in milliseconds between switch and repeat trials.

[b] Number of trials in which the participant used as few moves as possible to solve the task.

[c] Based on the number of times each search within a trial started in a new box rather than starting in the same box each time and following a systematic search pattern (lower scores represent more efficient strategy)

[d] The proportion of trials where the participant chose the most likely outcome – higher scores represent better decision making.

[e] The degree to which the participant adjusted the bet size according to the ratio of red:blue boxes – higher scores means higher degree of adjustment.

CANTAB Attention Switching Task

The Attention Swithcing Task (recently renamed "Multitasking Test") is a computerized test of cognitive flexibility, in which the participant is asked to make fast and accurate responses to an arrow shown on the screen. On each trial, the arrow appears on either the right or the left side of the screen, and points in either the right or left direction. The participant has to respond on a press pad with a right and left button, according to either the location of the arrow or the direction of the

arrow. The response rule (location or direction) is presented on the screen before each trial. The number of trials between each switch in response rule varies throughout the test, and some trials are congruent (e.g. arrow pointing right on the right side of the screen) while others are incongruent (e.g. arrow pointing left on the right side of the screen). We used two outcomes from the test to assess cognitive flexibility: Accuracy (correct trials in %) and switch cost (the difference in miliseconds between the average reaction time in switch versus repeat trials).

D-KEFS Trail Making Test

The Trail Making Test was used to assess processing speed as well as cognitive flexibility. We used three conditions from the test, including Number Sequencing, Letter Sequencing, and Number-Letter Switching. In the sequencing conditions, the participant connects target-items (either numbers or letters) in the correct order (ascending numerical order or alphabetical order) on a sheet of paper as quickly and accurately as possible. In the Number-Letter Switching condition, participants have to alternate between connecting letters and numbers in the correct order, continually switching between them (i.e. 1-A-2-B etc.). Any errors are corrected immediately by an experimenter, who then instructs the participant to continue from the last correct connection made. The main outcome of the Trail Making Test is completion time in seconds. We used completion time from the Number Sequencing and Letter Sequencing conditions to assess processing speed, while completion time in the Number-Letter Switcing condition was used to assess cognitive flexibility.

D-KEFS Verbal Fluency Test

The Verbal Fluency Test was used to assess verbal fluency and cognitive flexibility. We used three conditions from the task: Phonemic Fluency, Semantic Fluency, and Category Switching. In the Phonemic and Semantic conditions, the participant names as many words as possible in 60 seconds following a specific rule - words beginning with a specific letter (phonemic) or words from a specific semantic category (semantic). In Category Switching, the participant has to switch between naming words from two different semantic categories (fruit and furniture) for 60 seconds (e.g., apple-table-pear-sofa). We used the number of correct words from the Phonemic and Semantic conditions to assess fluency, while number of correct switches from the Category-Switching condition was used to assess cognitive flexibility.

D-KEFS Design Fluency Test

The Design Fluency test was used to assess non-verbal fluency and cognitive flexibility. We used two conditions of the task: Design Fluency (with empty dots), and Switching. The Fluency condition requires the participant to draw as many different figures as possible in a series of squares with filled and empty dots by connecting only empty dots, ignoring the filled ones. All figures need to be novel and made from only four straight lines. In the Switching condition, the participant needs to alternate between connecting filled and empty dots in addition to following the rules that also apply to the Fluency condition (i.e. create novel figures using four straight lines). We used the number of correct figures from the Fluency condition to assess non-verbal fluency, and the number of correct figures from the Switching condition to assess cognitive flexibility.

CANTAB Stockings of Cambridge

Stockings of Cambridge is a computerized planning test. On each trial, the participant needs to rearrange colored balls to match a model pattern, using as few moves as possible, planning the moves in advance. The test progresses in difficulty, starting with one move needed to copy the model and ending on five moves. We used the outcome “problems solved in minimum moves” to assess planning ability (i.e. the proportion of trials solved with the minimum moves needed).

CANTAB Spatial Working Memory

Spatial Working Memory (SWM) is a computerized working memory test in which several boxes are presented on the screen, and the participant is instructed to find a blue token behind each of them. When the participant finds the token, it is hidden behind a new box. On each trial, the participant needs to find the token behind each box, never returning to a box where a token has already been found. The number of boxes that needs to be searched increases gradually from three to eight boxes. Two types of errors are recorded: returning to an empty box within the same search trial, and returning to a box in which the token has already been found. We used two outcomes from the test: SWM total errors, as a measure of working memory function, and SWM strategy, as a measure of planning ability. The strategy outcome is based on the number of times the participant started each search within a trial with a new box instead of starting in the same box and following a systematic sequence – lower scores represent more efficient strategy use.

CANTAB Cambridge Gambling Task

The Cambridge Gambling Task is a computerized probabilistic decision-making test in which the participant has to guess if a token is hidden behind red boxes or blue boxes. On each trial, ten boxes are presented and the participant has to decide on either red or blue. The ratio between blue and red boxes varies, representing different probabilities of finding the token behind one or the other. The participant starts with 100 points and must select a proportion to bet on their decision. Points are added after succesful bets and subtracted after unsuccesful bets. We used two outcomes from the test to assess decision making: quality of decision making (i.e. the proportion of trials where the participant chose the most likely outcome) and risk adjustment (i.e. a measure of the degree to which the participant adjusted the bet size according to the proportion of red and blue boxes – higher scores means higher degree of adjustment).

Wechsler Scales Working Memory Index

The Working Memory Index from the Wechsler Scales of Intelligence (WISC-V for younger children and WAIS-IV for adolescents from age 16) was used as a measure of working memory capacity. The index is based on three digit span tests in which the test administrator reads a sequence of digits and asks the participant to relay them forwards in test one, backwards in test two, and in correct numerical order in test three.

Weather Prediction Task

The Weather Prediction Task (WPT) [108] is a probabilistic learning and decision-making test. In the WPT, participants predict weather outcome based on cue-cards displayed on a computer screen. The cue-cards are probabilistic predictors of two possible outcomes (rain or sun), and the participants must learn the cue-outcome contingencies through feedback. On each trial, either one, two, or three cue-cards are presented, and the participant responds either “rain” or “sun” by pressing corresponding keys on a keyboard. After each decision, the participant gets feedback on whether the predicted outcome occurred or not. We included a total of 350 trials in the task, divided into seven blocks. The outcomes were mean accuracy and mean response time (time in seconds from cue until response) for each block. Additionally, we assessed explicit knowledge of cue-outcome contingencies with a multiple-choice questionnaire, which participants answered immediately after completing the task.

Data analyses

Bayesian inference

We used classical inference (frequentist statistics) in Paper 2, and Bayesian inference in Paper 3. The key statistic in classical inference is the *p*-value, which denotes the probability of finding an observed effect, or a more extreme one, on the condition that the null-hypothesis is true. Bayesian inference instead uses the Bayes' equation (1) and the key statistic is the Bayes' factor (BF), which is the ratio of the probability of one hypothesis to the probability of an alternative hypothesis [109-111].

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

In the studies presented in this thesis, we were interested in evaluating whether children and adolescents with OCD differed from healthy controls on a range of neurocognitive and demographic outcomes. We therefore tested the probabilities of two main hypotheses: the null-hypothesis denoting that the effect was equal in the two groups ($\mathcal{H}_0$), and the alternative hypothesis ($\mathcal{H}_1$), denoting unequal effects in the groups (i.e. true differences between the OCD and healthy control groups). In Bayesian statistics, prior beliefs about the likelihood of the hypotheses are specified, such that p($\mathcal{H}_1$) denotes the assumed prior probability that $\mathcal{H}_1$ is true, and p($\mathcal{H}_0$) denotes the prior probability that $\mathcal{H}_0$ is true [109, 111]. Their ratio (the prior odds) reflects the relative plausibility of the two hypotheses before making any observations (i.e. before analyzing any data); if the two hypothesis are assumed to be equally likely, they are given equal prior probabilities of 0.5, resulting in prior odds of 1 [110, 111]. After observing data, the odds are updated accordingly, resulting in the *posterior odds* of $\mathcal{H}_1$ relative to $\mathcal{H}_0$. The degree to which the observed data changed the odds is represented by the BF. BF_{10} is the ratio of p(data|$\mathcal{H}_1$) relative to p(data|$\mathcal{H}_0$), whereas BF_{01} is the opposite, such that $BF_{10}=1/BF_{01}$. In effect, a BF_{10} of 4 means that the data are four times more likely under $\mathcal{H}_1$ than $\mathcal{H}_0$, or stated more plainly that $\mathcal{H}_1$ predicts the observed data four times better than $\mathcal{H}_0$ [110, 112]. The BF is a continuous measure, but some descriptive classifications have been proposed to ease interpretation [110, 112] (see Figure 5 as well as the visualization in Figure 6, both figures reproduced from Goss-Sampson 2020 [112] with permission under the Creative Commons license CC BY 4.0). These classifications were used to interpret findings in Paper 3.

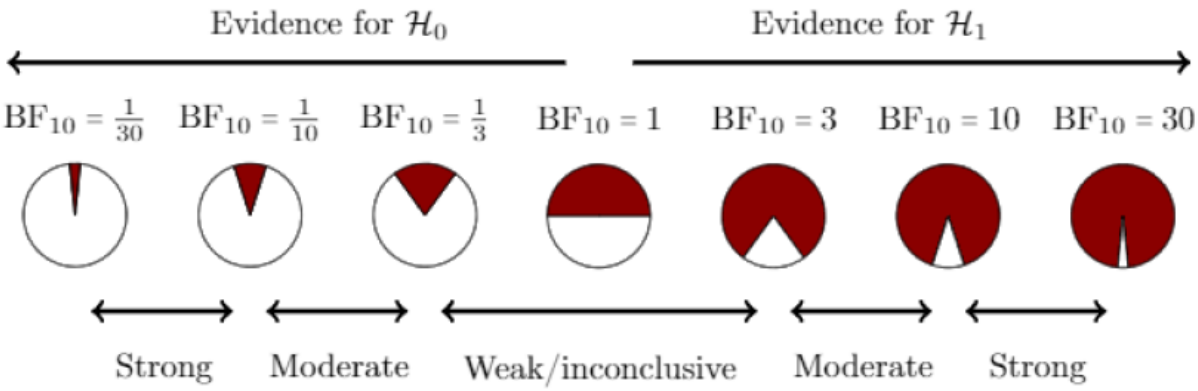

Figure 5. Visualization of the strength of the evidence based on the Bayes' factor (BF). The evidence for the alternative hypothesis ($\mathcal{H}_1$) relative to the null hypothesis ($\mathcal{H}_0$) is represented by the white relative to colored areas of each pie chart. Figure by Mark A. Goss-Sampson, copyright © May 2020, *Bayesian Inference in JASP. A Guide for Students*, reproduced with permission under the Creative Commons license CC BY 4.0.

BF_{10}	$Log_e BF_{10}$	Evidence	In favour of
>100	>4.6	Decisive	Alternative hypothesis
30 to 100	3.4 to 4.6	Very strong	Alternative hypothesis
10 to 30	2.3 to 3.4	Strong	Alternative hypothesis
3 to 10	1.1 to 2.3	Moderate	Alternative hypothesis
1 to 3	0 to 1.1	Anecdotal	Alternative hypothesis
1	0	No evidence	Neither
1 to 0.33	0 to -1.1	Anecdotal	Null Hypothesis
0.33 to 0.1	-1.1 to -2.3	Moderate	Null Hypothesis
0.1 to 0.033	-2.3 to -3.4	Strong	Null Hypothesis
0.033 to 0.01	-3.4 to -4.6	Very strong	Null Hypothesis
<0.01	< -4.6	Decisive	Null Hypothesis

Figure 6. Classification of the strength of the evidence based on the Bayes' factor (BF) value. The "anecdotal" classification is generally also referred to as "weak" or "inconclusive" (e.g. the evidence is insufficient to determine whether one hypothesis is more likely than the other). The "decisive" classification is also referred to as "extreme". Figure by Mark A. Goss-Sampson, copyright © May 2020, *Bayesian Inference in JASP. A Guide for Students*, reproduced with permission under the Creative Commons license CC BY 4.0.

Paper 2

Statistical analyses were done in IBM SPSS version 25 [113]. Missing values (1.3% of the neurocognitive data) were imputed using multiple imputation [114]. We defined outliers as data points more than 2.2 x IQR above the third quartile or below the first quartile [115]. Identified outliers (<1.5% of the neurocognitive data points) were modified to either the maximum or minimum value within the data distribution, depending on the direction of the outlier [115]. Data that violated the assumption of equal variances across groups (assessed with Levene's test)[32] was transformed prior to the analyses.

We compared participant characteristics in the OCD group and healthy control group using independent-samples t-tests for numerical data (e.g. age) and chi-square test for categorical data (sex). Neurocognitive test performance was compared using multivariate analysis of covariance (MANCOVA) with age and sex as covariates. The Holm-Bonferroni method [116] was used to adjust the significance levels due to the multiple significance tests included in the MANCOVA (comparing a total of 16 outcomes). We assessed potential associations between neurocognitive outcomes and symptom severity (CY-BOCS total score) using Pearson's correlation analyses. Potential associations between the neurocognitive outcomes and comorbidity (OCD only versus OCD + co-occurring disorder) was assessed with independent samples t-tests. All effect sizes were calculated as standardized mean differences (SMD), corresponding to Cohen's *d.* [117]

Paper 3

All analyses were done using Bayesian statistics in JASP [118]. Each analysis assessed the strength of the evidence of rival hypothesis: the null hypothesis, $\mathcal{H}_0$, indicating no group differences, and the alternative hypothesis, $\mathcal{H}_1$, indicating true differences between the groups. We reported the evidence in favor of $\mathcal{H}_1$ relative to $\mathcal{H}_0$ as the Bayes' factor, BF_{10} [119]. A BF_{10} of 1 favor none of the hypotheses, whereas values above 1 favor $\mathcal{H}_1$, and values below 1 favor $\mathcal{H}_0$. We used the guidelines provided by Wagenmakers and colleagues [110] to classify the strength of the evidence as either anecdotal/insufficient evidence, moderate, strong, very strong or decisive (Figures 5 and 6).

Participant characteristics in the OCD and healthy control group were compared using Bayesian independent-samples t-test for normally distributed data and Bayesian Mann-Whitney's *U*-test for non-normally distributed data. Categorical data (sex) was compared using a Bayesian contingency

table. We used Bayesian repeated-measures analyses to evaluate the effects of group on the average proportion of optimal responses and the average response time across WPT blocks. We used the default priors (assuming equal probability of $\mathcal{H}_1$ and $\mathcal{H}_0$). We assessed effects of group on cue-outcome awareness using Bayesian A/B test. Potential associations between WPT performance and either symptom severity (total CY-BOCS score) or comorbidity (OCD only versus OCD + co-occurring disorder) was assessed using Bayesian correlation analyses and Bayesian repeated measures analyses, respectively.

Results

Paper 1: Systematic review and meta-analysis: Cognitive-behavioral therapy for obsessive-compulsive disorder in children and adolescents.

Included trials

We included twelve randomized controlled trials of CBT versus any type of control intervention for pediatric OCD [54, 120-130] (see PRISMA flow diagram in Figure 7, adapted from Paper 1, Figure S1). The total sample size was 819 children and adolescents, aged 4-18 years. 52% of the sample were female and 65% had at least one co-occurring disorder.

Five trials compared CBT to a waitlist control [120-124]. Three trials compared CBT to a control condition defined by the authors as placebo psychotherapy (psychoeducation and relaxation training) [125-127]. Two trials compared CBT+SSRI to SSRI only [129, 131]. One of these trials also included a pill-placebo group, and a CBT only group, allowing for additional comparisons of CBT vs. placebo and CBT vs. SSRI [129]. In total, three trials included a comparison of CBT versus SSRI [54, 129, 130]. The included trials enabled us to do two main comparisons:

1) CBT versus “no intervention” (waitlist, placebo, co-intervention delivered similarly in both the intervention and control group)
2) CBT versus SSRI

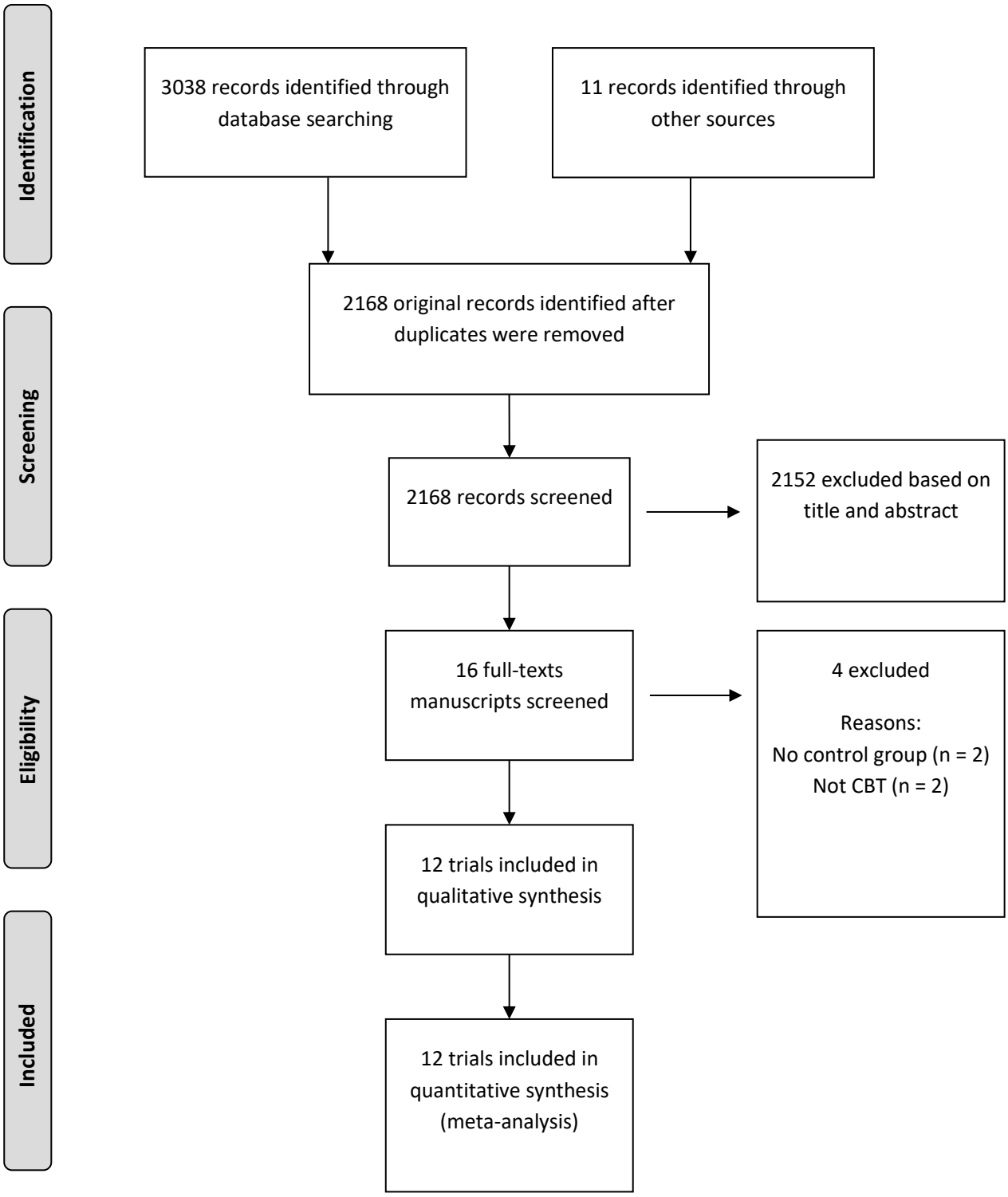

Figure 7. PRISMA Flow Diagram of the systematic search and inclusion of eligible trials. Figure from Uhre et al. 2020, Supplemental Figure S1 © 2019 The Authors, *American Academy of Child and Adolescent Psychiatry, Published by Elsevier Incorporated*.

Risk of bias

All trials were rated at an overall high risk of bias, due to having high or unclear risk of bias in at least one domain, frequently related to incomplete outcome data because of high drop-out rates, and lack of blinding of treatment providers/participants (see Figure 8). The latter is a general issue in psychotherapeutic trials, as treatment providers and participants cannot be blinded to the intervention type, resulting in high risk of "performance bias" for all trials. Only one trial had low risk of bias on all other domains [122].

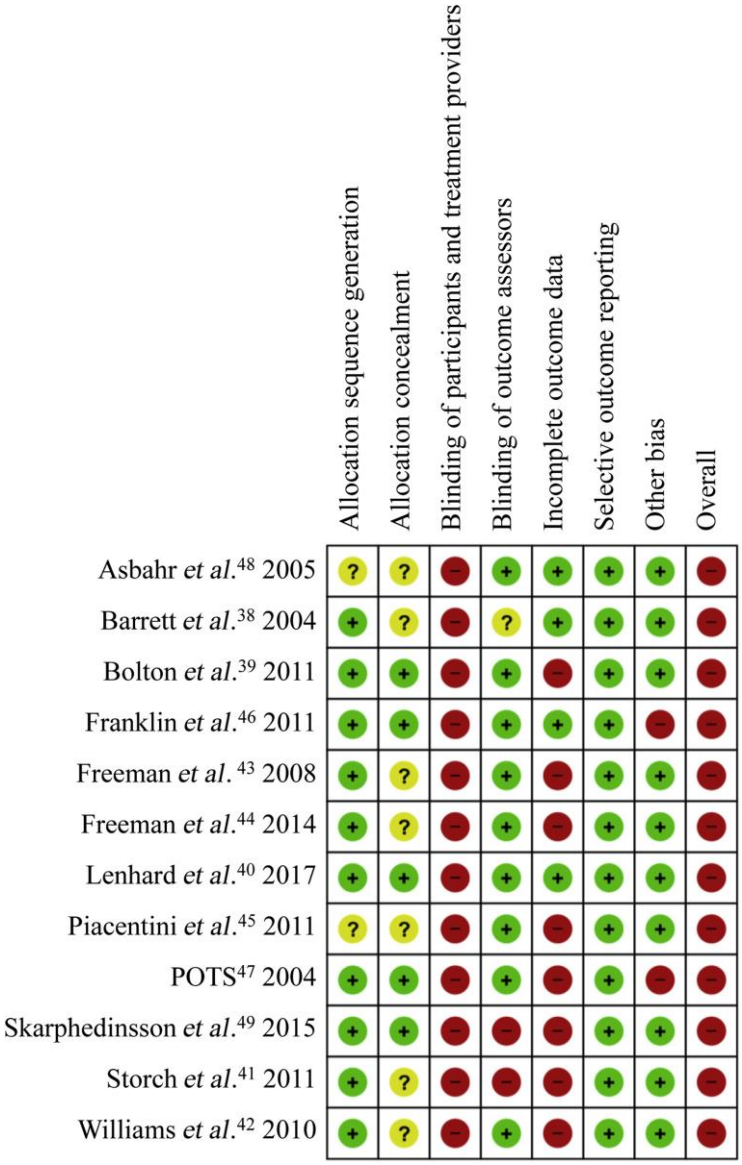

Figure 8. Risk of bias in the included trials. Red = high risk of bias, yellow = unclear risk of bias, green = low risk of bias. Note that the numbered references refer to the reference list in the published paper. Figure from Uhre et al. 2020, Figure 1 © 2019 The Authors, *American Academy of Child and Adolescent Psychiatry, Published by Elsevier Incorporated*.

CBT versus “no intervention”

Ten trials assessed effects on CY-BOCS total score of CBT versus a control condition considered ineffective for OCD [120-129]. The evidence favored CBT (MD = -8.51, 95% CI = -10.84 to -6.18, p < .001). Subgroup analyses showed no evidence of differences between the control conditions but indicated that conventional CBT may be superior to Internet-delivered CBT. Three of the trials assessed serious adverse events [122, 125, 128], but we did not perform any meta-analyses as only one event was reported (attempted suicide of a participant in a control group). Level of functioning was higher after CBT compared to “no intervention”, based on data from five trials [123, 126, 127, 132, 133] using different rating-scales (patient rated functioning: SMD = -0.90, 95% CI = -1.19 to -0.62, p < .001). Proportion of participants with adverse events were similar for CBT and “no intervention” groups (RR = 1.06, p = 0.39). OCD remission rates were higher after CBT compared to “no intervention” (based on seven trials, the risk ratio of non-remission after CBT was 0.50 relative to “no intervention”). We had insufficient data to evaluate intervention effects at long-term follow-up, as well as to evaluate effects on quality of life. The certainty of the evidence was low or very low for all outcomes as evaluated using GRADE guidelines.

CBT versus SSRI

Three trial compared effects on CY-BOCS total score of CBT versus pharmacological treatment with SSRIs s [54, 129, 130]. We found no evidence to suggest a difference between CBT and SSRIs (MD = -0.75, 95% CI = -3.79 to 2.29, p = .63). We were unable to evaluate potential differences in adverse events, as the two trials that systematically documented and reported adverse events did so only for the SSRI groups. We also had insufficient data to assess effects on level of functioning, and quality of life. OCD remission rates were reported in two of the trials [54, 129], showing no evidence of a difference in the risk of non-remission between CBT and SSRI (RR=0.85, p = .20). However, TSA indicated that this could be a random finding due to lack of power or multiple testing. The GRADE evaluation resulted in low or very low certainty of the evidence for the assessed outcomes.

Paper 2: Subtle and selective neurocognitive impairment in children and adolescents with obsessive-compulsive disorder

Participant characteristics

The sample comprised 117 children and adolescents with OCD and 42 healthy controls (see Table 1 under the section "Participants"). The OCD group and the healthy control group were matched in terms of age and sex, but intelligence and parental education level was higher (approximately 0.5 SD) in the control group. Children and adolescents with OCD had moderate to severe symptoms of OCD (mean CY-BOCS total score = 25.30, SD = 4.98), and approximately 59% had at least one co-occurring disorder. The most frequent co-occurring disorders were Asperger's Syndrome, stress-related disorders, ADHD, and tic disorder.

Neurocognitive functioning

Children and adolescents with OCD and healthy controls were compared on 16 neurocognitive outcomes (see Figure 9, identical to Figure 1 from Paper 2), assessing the following functions: cognitive flexibility, planning and decision-making, working memory, and processing speed. Children and adolescents with OCD performed significantly worse on five outcomes: accuracy in the CANTAB Attention Switching Task, quality of decision-making in the CANTAB Cambridge Gambling Task, and completion time in seconds in all three conditions of the D-KEFS Trail Making Task (Letter-Sequencing, Number-Sequencing, and Number-Letter Switching). The effect size was moderate (0.68) for quality of decision-making, and small for the remaining outcomes (0.30-0.35). We found no evidence of differences between children and adolescents with OCD and healthy controls in planning, working memory, fluency, or a more direct measure of cognitive flexibility than the accuracy measure from the Attention Switching Task (switch cost). We found no evidence of associations between performance on the neurocognitive tests and OCD symptom severity (total CY-BOCS score), or comorbidity status (having OCD only versus having OCD and at least one co-occurring disorder).

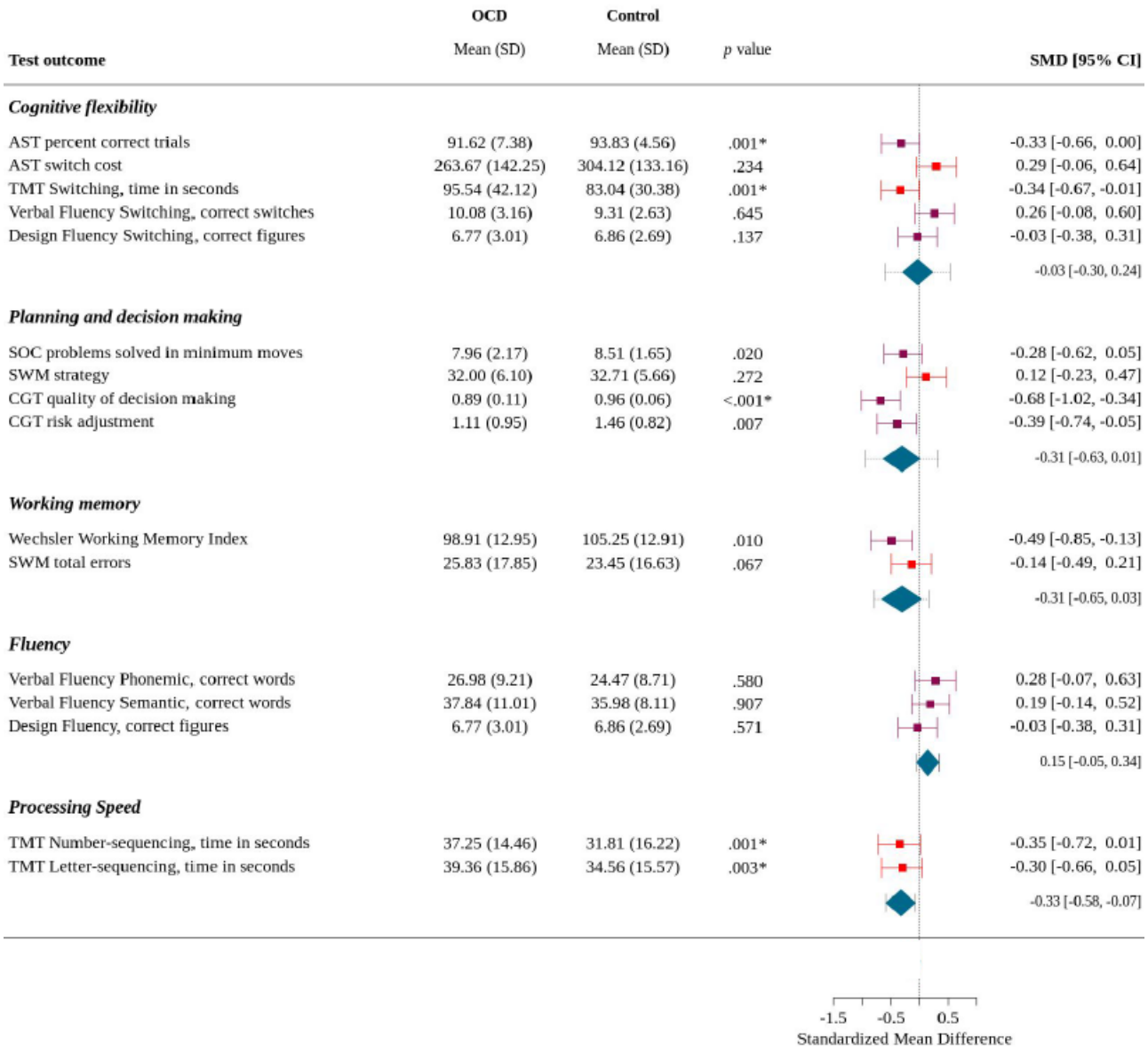

Figure 9. Performance on neurocognitive tests. Test performance was compared across groups with multivariate analysis of covariance (MANCOVA) with sex and age as covariates. The left side of the SMD plot represents poorer performance in the OCD group compared to the healthy control group. For most outcomes higher scores represent better performance, but for a few outcomes the opposite is true (e.g. completion time). We multiplied the SMD by -1 for outcomes on which lower scores are better to ensure consistent directionality on the plot – i.e. points on the left side of the plot represent worse performance in the OCD group, while points on the right side of the plot represent worse performance in the healthy control group. The SMDs that were corrected are highlighted in red. Abbreviations: AST, Attention Switching Task; CGT, Cambridge Gambling Task; SD, standard deviation; SMD, Standardized mean difference; SOC, Stockings of Cambridge; SWM, Spatial Working Memory; TMT, Trail Making Test. Figure and Figure text is reproduced from Paper 1, Figure 1 (unpublished paper). * = results that remained significant after Holm-Bonferroni correction.

Paper 3: Probabilistic learning and decision-making appear intact in children and adolescents with obsessive-compulsive disorder

Participant characteristics

A total of 77 children and adolescents with OCD and 31 healthy controls participated in the study. The OCD and healthy control group were similar in terms of sex, but we did not have sufficient evidence to determine if the age and intelligence distributions were equal in the two groups. Parental education was higher in the control group. Approximately 56% of the children and adolescents with OCD had at least one co-occurring disorder – most frequently Asperger's Syndrome, stress-related disorders, ADHD, and tic disorder.

WPT performance and cue-outcome awareness

We found moderate evidence against an effect of group on WPT performance (both regarding average proportion of optimal responses and response times). The data was inconclusive regarding whether cue-outcome awareness differed in children and adolescents with OCD compared to healthy controls. Nonetheless, both groups appeared to learn the cue-outcome contingencies explicitly, scoring above chance levels on the questionnaire. Moreover, we found moderate evidence against an effect of symptom severity on WPT performance in the OCD group, as well as moderate evidence against an effect of comorbidity on the average proportion of optimal responses. The data on whether comorbidity affected average response times in the OCD group were inconclusive.

Discussion

Treatment of children and adolescents with obsessive-compulsive disorder

In Paper 1, we evaluated benefits and harms of CBT compared to any other intervention for children and adolescents with OCD in a systematic review and meta-analysis. The main findings indicated that CBT is an effective treatment of pediatric OCD, superior to placebo, and comparable to SSRI treatment. However, the twelve included trials were rated at an overall high risk of bias, and the certainty of the evidence was low for all evaluated outcomes (symptom severity, level of functioning, adverse events, quality of life, and remission). Additionally, the review revealed a lack of data on treatment outcomes other than total symptom severity scores and remission rates.

Our review updated and extended previous findings from systematic reviews of CBT for children and adolescents with OCD. To our knowledge, our review is the first to evaluate the effects of CBT for OCD on level of functioning, adverse events, and quality of life. The fact that we found a general lack of data on such patient-reported outcomes was surprising, given the substantial negative impact of OCD on quality of life and functioning in school and social contexts [7]. The importance of evaluating treatment effects on patient-reported outcomes is also highlighted in the Cochrane Handbook for Systematic Reviews of Interventions, as they *"(…) provide crucial information for patients and clinicians facing choices in health care (…) and are often the outcomes of most importance to patients and families"* (Higgins and Thomas, Cochrane Handbook for Systematic Reviews of Interventions, version 6.3, 2022, part 3, available from: www.training.cochrane.org) [134]. Accordingly, the lack of data on adverse events during CBT hinders evaluation of potential differences in risk between CBT and SSRI treatment, which would be useful for clinicians and patients when deciding between the treatment types, especially given the comparable beneficial effects. Future trials should therefore make sure to include patient-reported outcomes.

A limitation of the current review is that we assessed the risk of bias in included trials using the 2011 version of Cochrane's risk of bias tool [95]. In this version of the tool, psychotherapeutic trials are judged at overall high risk of bias almost by default, due to participants and treatment providers being unblinded to the type of treatment delivered (e.g. CBT, SSRIs, or placebo). Another limitation of the tool is that risk of bias is assessed at the trial level, although the risk of bias could vary on the

outcome level (e.g. outcome assessors could be blinded for some outcomes but not others). A revised Cochrane risk of bias tool (RoB 2) was released in 2019 to address previous limitations [135]. In a letter-to-the-editor, a group of researchers and clinicians expressed concerns about our review methodology, highlighting the use of the original RoB tool as their main concern [136]. In our reply, we used RoB 2 to reassess the risks of bias for the symptom severity outcome (total CY-BOCS score) in the included trials [137]. The reassessment corroborated our initial finding of high risk of bias in most included trials, although two trials were assessed at low risk of bias[122, 129]. Restricting the meta-analyses to these low risk of bias trials reduced the estimated effect of CBT on alleviating symptom severity (mean difference in CY-BOCS total score based on low risk trials = -5.01, 95% CI= -7.31 to -2.74; mean difference based on all trials = -8.51, 95% CI = -10.84 to -6.18) [137]. Similarly, the most recent review and meta-analysis of CBT for OCD (all age groups, n trials = 36) found a large effect in favor of CBT compared with psychological placebo on alleviating symptoms, similar effects of CBT and other active treatments (including pharmacological treatment and other psychotherapy), while also finding high risk of bias in most studies which appeared to inflate the effect (i.e. the effect size was markedly lower in low risk of bias trials, compared to high risk of bias trials)[138].

Is neurocognitive functioning impaired in children and adolescents with obsessive-compulsive disorder?

In Paper 2, we investigated neurocognitive functioning in 117 children and adolescents with OCD and 42 healthy controls. The OCD group showed moderate impairment in probabilistic decision-making, and minor impairment in processing speed and some measures of cognitive flexibility (accuracy and completion times on set-shifting tasks). We found no group differences in planning, working memory, and fluency. We found no significant associations between any of the 16 neurocognitive outcomes and either OCD symptom severity (total CY-BOCS score) or comorbidity status (OCD only versus OCD + co-occurring disorder).

In Paper 3, we used the WPT to investigate probabilistic learning and decision-making in a subsample of 77 children and adolescents with OCD and 31 healthy controls. We found moderate evidence against effects of group on both response time and accuracy on the task, and no evidence of differences in explicit cue-outcome knowledge, suggesting that probabilistic learning and decision-making is intact in children and adolescents with OCD.

Taken together, our results indicate that children and adolescents with OCD show subtle and selective neurocognitive impairment, rather than widespread difficulties.

Our finding of slower processing speed in the OCD group relative to the healthy controls aligns with previous findings in both children and adolescents [88, 139, 140] and adults [36, 37, 89] with OCD. Slower processing speed may impact performance on other neurocognitive tests, intended to measure other functions [88]. For example, we included the Trail Making Number-Letter Switching Test as a measure of cognitive flexibility, but our finding of slower completion times on the test could also reflect the slower processing speed in our sample. Slower processing speed could also contribute to the lower accuracy score on the Attention Switching Task, as the inter-trial interval is short and demands rapid responding. Notably, we found no group differences in switch cost on the same task, suggesting that children and adolescents with OCD and healthy controls were equally capable of adjusting responses to changes in task demands, which is the hallmark of cognitive flexibility.

Our finding of moderately reduced quality of decision-making on the Cambridge Gambling Task suggests that children and adolescents with OCD are less able to use information about outcome probabilities to guide their choices, compared with healthy peers. Similarly, two recent studies found that children and adolescents with OCD were slower to learn response-outcome contingencies in an instrumental learning task, and slower to adopt new response strategies when previously rewarded actions were devalued, compared to healthy controls [76, 141]. Three previous studies investigated probabilistic learning and decision-making in pediatric OCD using gambling tasks [87]. Two of the studies demonstrated impaired decision-making on the Iowa Gambling Task [142, 143], while the last study found no significant differences on the Cambridge Gambling Task [144].

While our finding on the Cambridge Gambling Task appear to contradict our findings of intact probabilistic learning and decision-making on the WPT (Paper 3), the discrepancies may be explained by the notion that contingency-learning and decision-making in OCD is specifically impaired in emotional contexts [145, 146]. The Cambridge Gambling task contains no OCD-specific content, but is considered an affective task, as it involves risk (e.g. betting points and risking losses). In contrast, the WPT we employed was emotionally neutral. Two studies with adults with OCD found intact performance on the neutral WPT but impaired performance on an emotional version, with

the only differences in the tasks being what participants were told to predict – either weather outcome or epidemic outbreaks [145, 146]. Intolerance of uncertainty, over-evaluation of risk or threat, and risk aversion has also been associated with OCD [147, 148]. Perhaps executive function difficulties arise specifically in the context of negative emotion or high arousal, akin to how individuals with OCD experience a loss of control over actions and thoughts in the context of distressing obsessions.

Does neurocognitive functioning differ in children and adults with OCD?

Slower processing speed [36, 83], impaired decision-making, and increased sensitivity to errors, appear to be neurocognitive characteristics for both children and adults with OCD [87]. It is less clear if children and adolescents show other deficits in memory, cognitive flexibility, and inhibitory control, which have been reported in adult OCD [87, 149]. One possibility is that the few and subtle neurocognitive findings in pediatric OCD compared to adult OCD reflect neurodevelopmental processes with difficulties increasing with disorder progression [149]. Coherent with this view, several imaging studies found aberrant brain activity during executive function tests in pediatric samples, comparable to aberrations observed in adults with OCD [150], but no impairment on behavioral outcomes (e.g. group differences in test performance) [65, 87, 142, 151, 152]. Potential differences between children and adults with OCD could also be related to other factors such as illness duration or differential effects of pharmacological treatment on neurocognition at different stages during the lifespan [87]. However, as the effects reported in behavioural studies with adults with OCD are generally small to moderate [36], subtle neurocognitive impairment may be shared characteristics across age groups that have been found more consistently in adult samples due to the larger number of adequately powered studies [87]. For example, the small to moderate effects observed in our large sample (Paper 2) could have gone undetected in previous pediatric studies, which typically included small samples. If, on the other hand, neurocognitive deficits are in fact less pronounced in children and adolescents with OCD compared to adults, it speaks to the importance of early detection and treatment, as noted in a recent review: *"Functional brain abnormalities in the absence of cognitive deficit in child patients implies that early detection of the disorder is crucial, and that treatment needs to be delivered early on in the disorder trajectory to potentially impede cognitive decline"* (cited from Marzuki et al. 2020, p. 641) [87].

Strengths and limitations of the experimental studies

The experimental studies included in this thesis had several strengths. Mainly, our studies included large samples of children and adolescents with OCD compared to previous studies. To our knowledge, the study presented in Paper 2 is the largest study comparing neurocognitive functions in children and adolescents with OCD to healthy controls. Moreover, no participants received pharmacological treatment for OCD, which allowed us to investigate neurocognitive functions free from potential confounding effects of receiving SSRIs [153, 154].

Our studies also have important limitations. We aimed to include healthy controls that were representative of normally developing children and adolescents, but the demographic data suggested that the healthy controls were "super normal" in the sense that parental education in years was systematically higher in the control group, and intelligence was also significantly higher in the total sample of healthy controls included in Paper 2. In retrospect, the strict exclusion criteria – excluding any potential control participant who reported symptoms that met the diagnostic criteria for any disorder at any time – may have resulted in the recruitment of controls who did not represent the population of healthy peers. However, the differences in intelligence and parental education were relatively small (a difference of about 0.5 SD) and re-running the analyses with these factors as covariates did not notably change the results. A limitation specific to Paper 3 was that we only assessed probabilistic learning and decision-making in a neutral setting (predicting weather outcome), while studies published during our data collection phase indicated specific impairments in more emotional or high-arousal settings. Our study would have benefitted from the addition of an emotional version of the WPT to explore the proposed interaction of emotion and cognition in our large sample. Finally, our total sample spanned a large developmental range (8-17 years), which may have diluted effects and masked potential neurocognitive impairment in older participants [83, 149].

Conclusions and future perspectives

The overarching aim of this work was to investigate neurocognitive functioning of children and adolescents with moderate to severe OCD in a large, well-characterized clinical sample prior to initiation of psychological or pharmacological treatment. In our experimental studies, children and adolescents with OCD were moderately impaired on affective decision-making and showed slower processing speed compared to healthy controls. We found no evidence of impaired planning, working memory, fluency (Paper 2), or probabilistic learning and decision-making in a neutral context (the WPT, Paper 3). Our findings on cognitive flexibility were less clear, with minor impairment on some outcomes of set-shifting tasks (including accuracy and completion times), but not on more direct measures of cognitive flexibility (e.g., switch cost). Taken together, the results indicate that children and adolescents with OCD show subtle and selective neurocognitive impairment, in contrast to the more widespread difficulties reported in adults.

As the work presented in this thesis represents baseline results from a longitudinal case-control study, some future research steps are already planned. Longitudinal data will be used to evaluate associations between neurocognitive functioning and treatment effects. For example, treatment with exposure and response prevention might "normalize" executive functioning in the context of emotions, by promoting a more reality-based understanding of contingencies between actions and negative events, allowing feedback from experiences, rather than internal cues, to guide choices. If this is the case, probabilistic decision-making as measured by the Cambridge Gambling Task might improve in the OCD group at end of treatment. Moreover, neurocognitive findings will be related to the multitude of other outcomes assessed at baseline and follow-up in the TECTO study in both patients and healthy controls– including structural and functional brain imaging, salivary oxytocin levels, heart-rate variability during emotion regulation, family-dynamics, and a range of clinical outcomes such as symptom severity, level of functioning, and quality of life. Hopefully, the results will contribute with a clearer picture of neurocognition in pediatric OCD and how it may relate to other aspects of the disorder and treatment response.

Other future studies could explore the notion of specific deficits in executive functioning in the context of emotion/arousal, for example comparing contingency-learning and decision-making across neutral and emotional settings. In daily life, decisions must be made in all sorts of context,

and so excessive deliberation times and poorer decision-making – even if limited to emotionally charged situations - may well affect real-life functioning. Moreover, longitudinal studies are needed to evaluate the long-standing discussion of whether apparent differences between children and adults with OCD are spurious or true findings, perhaps reflecting neurodevelopmental processes that result in increasing neurocognitive difficulties with increasing age and illness duration.

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Paper 1

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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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

J Am Acad Child Adolesc Psychiatry 2020;59(1):64–77. CME

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

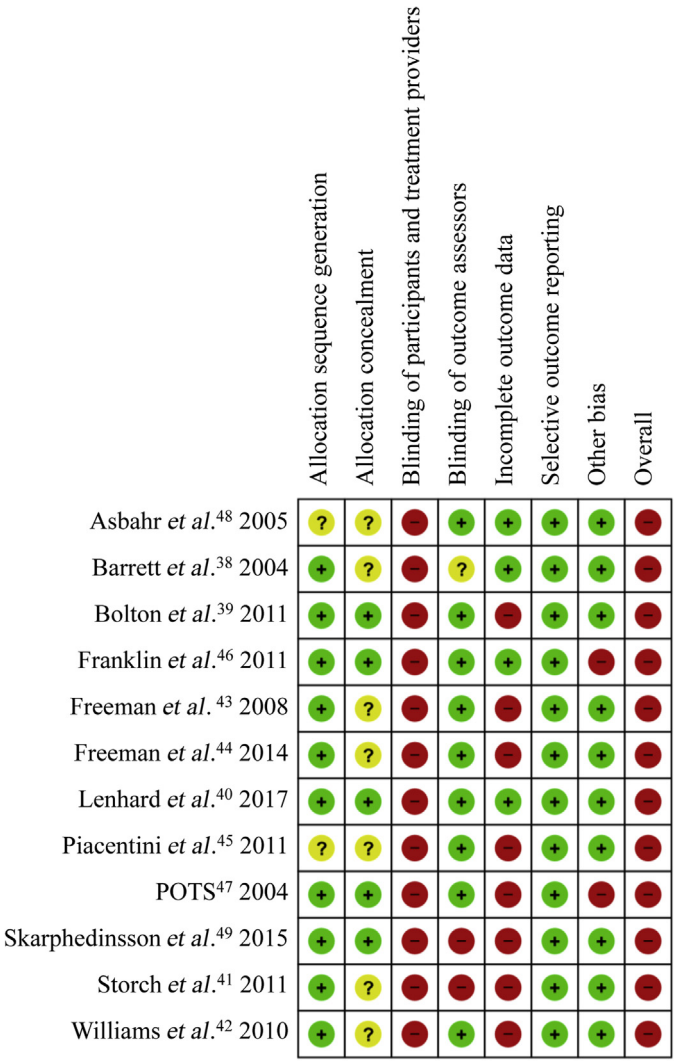
Study Selection and Characteristics

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"

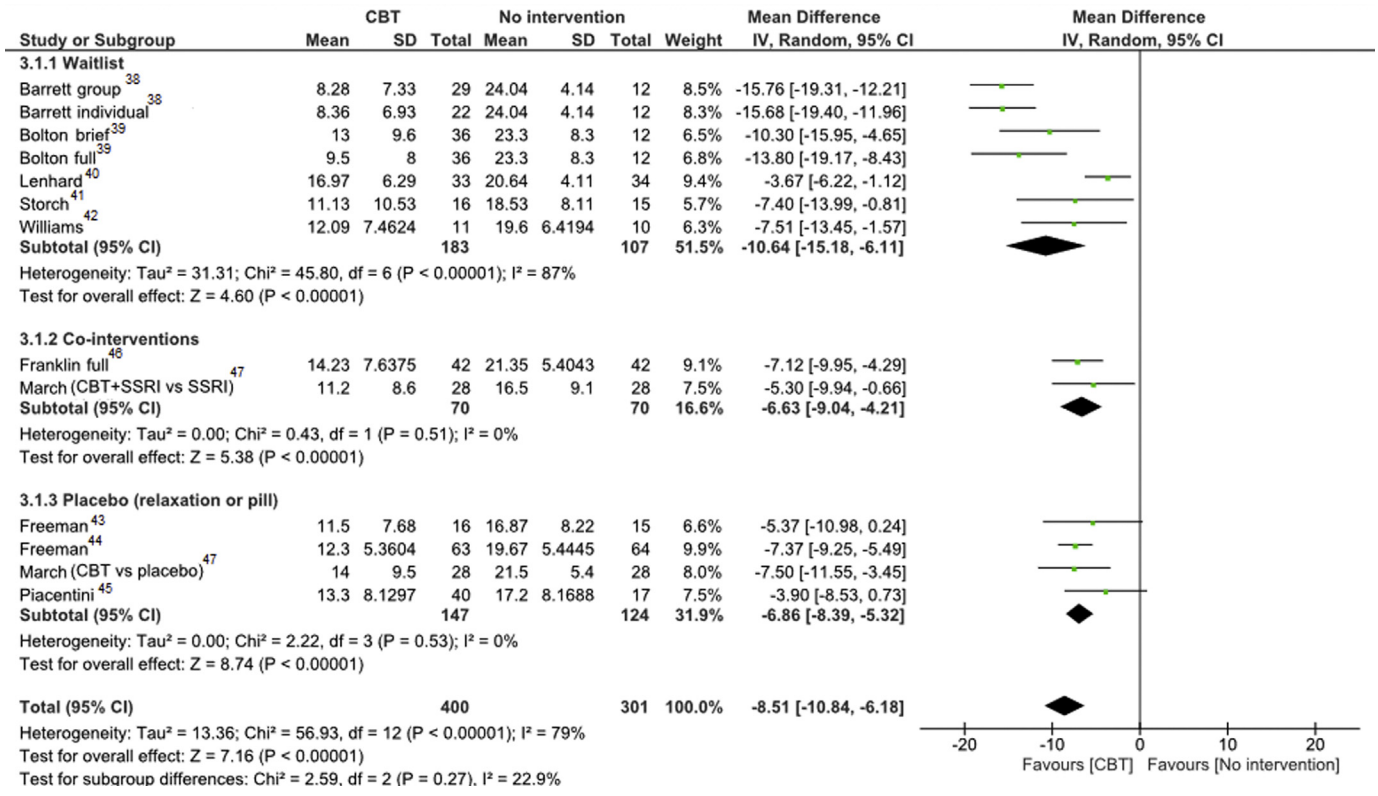
Primary Outcome: Children's Yale–Brown Obsessive-Compulsive Scale. Ten trials[38-47] ($n_{analyzed}$ = 701; 13 comparisons) tested the efficacy of CBT in reducing OCD symptom severity on the CY-BOCS scale versus a control condition considered ineffective for OCD. Five trials[38-42] used waitlist control; 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.

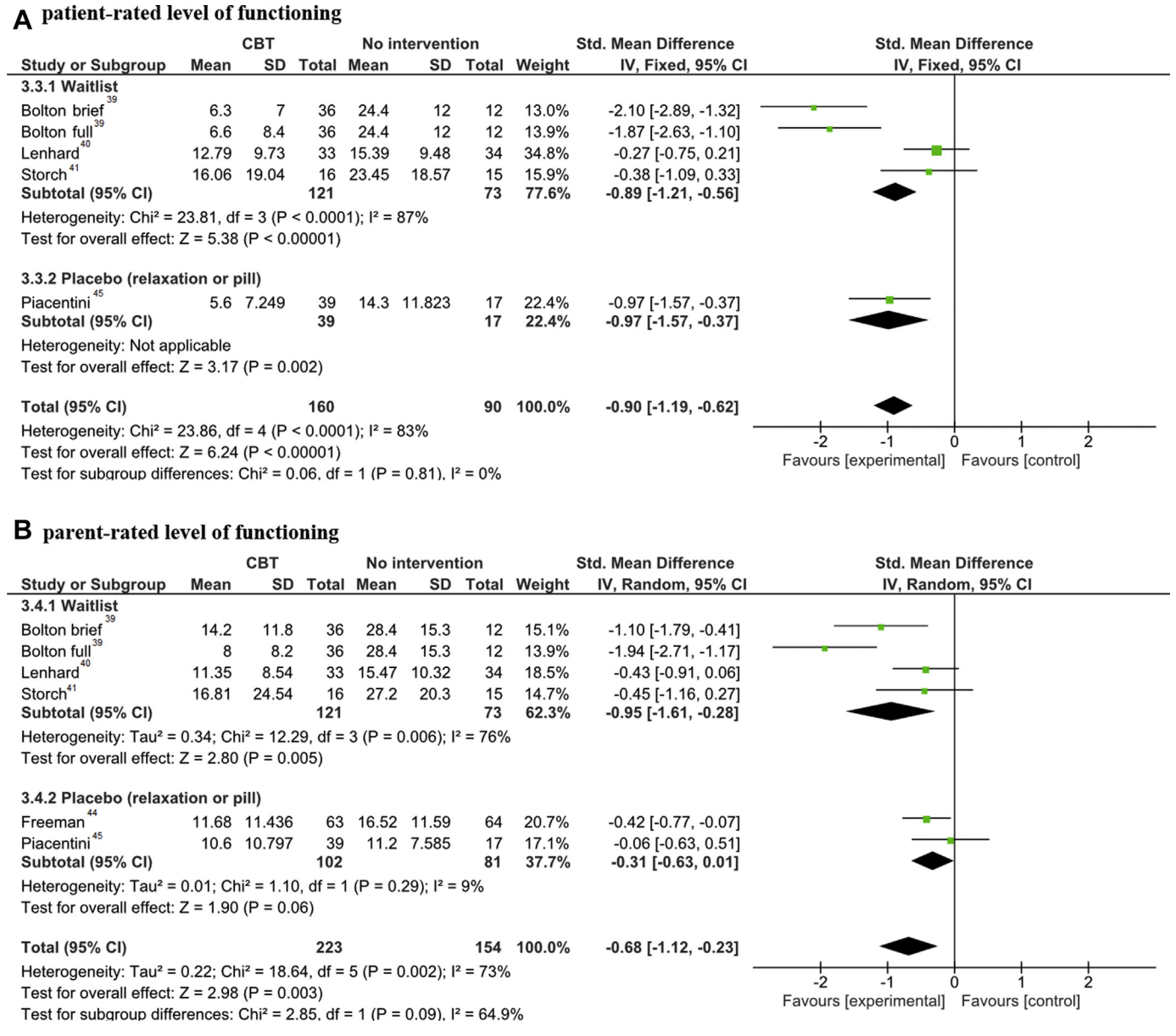
Patient-Rated Level of Functioning. Fixed-effect meta-analysis on patient-rated level of functioning showed evidence of a difference in favor of CBT versus "no intervention" (SMD = –0.90, 95% CI = –1.19 to –0.62, $p <$ .00001) (Figure 3a). Missing outcome analysis showed that this finding is unlikely 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.

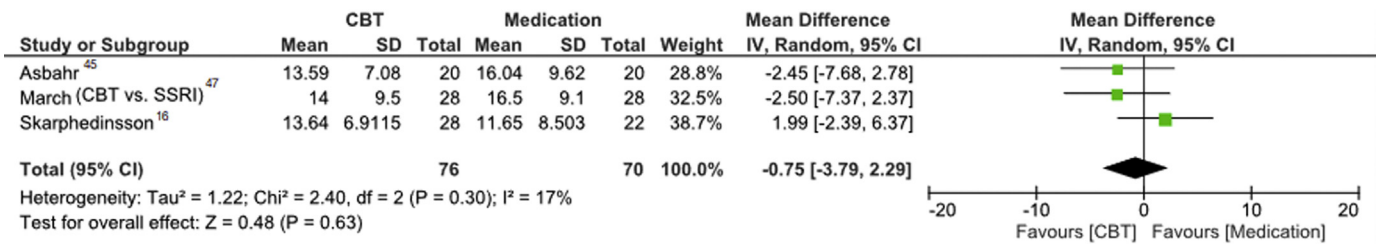
Exploratory Outcome: Lack of Remission. Seven trials[38-41,43,45,47] ($n_{analyzed}$ = 480, 10 comparisons) assessed the risk of still having OCD at end of CBT compared with a control considered ineffective for OCD. Four trials[38-41] used waitlist control; one trial[47] used "no intervention" with an 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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Paper 2

Subtle and selective neurocognitive impairment in children and adolescents with obsessive-compulsive Disorder.

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Title: Subtle and selective neurocognitive impairment in children and adolescents with obsessive-compulsive disorder

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Abstract

Objective: Neurocognitive impairment putatively underlies the core symptoms of pediatric OCD, but neurocognitive investigations within this population are few, underpowered, and show inconsistent results. In this study, we compare neurocognitive functioning in a large sample of untreated children and adolescents with OCD to healthy controls.

Methods: Children and adolescents with OCD (n=117) and healthy controls (n=42), age 8-17 years, completed psychopathological assessment, intelligence testing, and a neurocognitive test battery with 16 outcomes assessing cognitive flexibility, planning and decision-making, working memory, fluency, and processing speed. Participants with OCD were recruited from psychiatric outpatient units and healthy controls were recruited from the same catchment area via a Central Person Registry.

Results: Children and adolescents with OCD performed worse than healthy controls with small to moderate effects (Cohen's d = 0.30-0.68) on five outcomes assessing probabilistic decision-making, processing speed, and some aspects of cognitive flexibility (including slower completion times and lower accuracy on set-shifting tasks, but no significant group differences in switch cost). We found no evidence of differences in planning, working memory, verbal and nonverbal fluency. Moreover, we found no significant associations between OCD symptom severity or comorbidity status and any of the neurocognitive outcomes in children and adolescents with OCD.

Conclusion: Our results indicate that children and adolescents with OCD show selective and small to moderate impairment in neurocognitive functioning, which may have limited clinical relevance.

Key words: Cognition; Case-Control Studies; Child; Adolescent; Obsessive-compulsive Disorder

Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder, affecting 1-3% of children and adolescents worldwide[1,2]. Core symptoms include intrusive and distressing thoughts, urges, or mental images (i.e., obsessions) and repetitive behavioural or mental rituals (i.e., compulsions) [3].

The most widely accepted neurobiological model of OCD, the cortico-striato-thalamo-cortical (CSTC) model,[4] suggests that decreased activation of dorsal fronto-striatal circuitry underlies deficits in cognitive control (e.g., inability to inhibit unwanted thoughts and actions), whereas increased activation of limbic and ventral fronto-striatal circuitry underlies dysregulated emotions (e.g., anxiety and distress in relation to obsessions). This model is based on converging findings from imaging studies, primarily including adult samples.[4] However, neurocognitive OCD studies examining the functions associated with the CSTC network have yielded inconsistent results.

Meta-analyses of studies in adults show a tendency of mild to moderate impairment (effect size 0.3-0.6) across neurocognitive domains in individuals with OCD compared to healthy controls, with the most consistent findings being impaired nonverbal memory, planning ability, and processing speed[5-8]. The findings in adults with OCD may not apply to children and adolescents with OCD, given the differences in symptom presentation and pattern of comorbidity[9,10], as well as general neurocognitive differences between children and adults. Neurocognitive studies with children and adolescents with OCD are sparse and report fewer significant findings compared to studies with adults. To our knowledge, only one meta-analysis of neurocognitive outcomes in children and adolescents with OCD has been published[11]. The meta-analysis included eleven studies covering different neurocognitive domains and found no significant impairment in children and adolescents with OCD, as assessed with well-established tests[11]. The direction of effects was consistent with underperformance in the OCD groups relative to healthy controls, but no differences reached statistical significance and effect sizes were small, ranging from 0.04-0.4 across domains. A recent

systematic review (without meta-analysis) of 43 neurocognitive studies with paediatric OCD samples indicated that children and adolescents with OCD show impaired visual working memory, planning, decision-making under uncertainty (e.g., during implicit learning of rewards), and abnormal error sensitivity (defined as increased error-related negativity in electroencephalography experiments).[12]

The few significant neurocognitive findings in studies with children and adolescents with OCD seem to contrast with the numerous significant findings, albeit with small to moderate effect sizes, from adult studies. Methodological issues and study differences in the paediatric literature – including small samples, differences in sample comorbidity and medication status, as well as differences in the specific tests used – likely contribute to the inconsistent findings. For example, most paediatric studies included children and adolescents in pharmacological treatment for OCD without investigating potential effects of medication status on neurocognitive outcomes. Nevertheless, medication may affect neurocognitive performance in individuals with OCD[13] and has recently been linked with substantial and widespread changes in brain anatomy in large-scale analyses of structural neuroimaging data from the ENIGMA-OCD consortium[14].

To achieve a better understanding of neurocognitive functioning in children and adolescents with OCD, large controlled studies that assess neurocognitive functions using well-established tests are warranted.

In this study, we investigated neurocognitive functioning in a large clinical sample of children and adolescents (8-17 years) with moderate to severe OCD compared with healthy controls. Based on the theoretical and experimental literature, we hypothesized that participants with OCD would perform worse than healthy controls on the neurocognitive tests.

Methods

Participants

Children and adolescents with OCD and healthy controls were recruited between September 2018 and September 2021. All participants were part of a case-control study nested in a randomised clinical trial, which included neurocognitive assessment at baseline (pre-treatment) and follow-up (post-treatment) (The TECTO trial[15], ClinicalTrials.gov Identifier: NCT03595098). This paper presents results from the baseline assessment.

All participants with OCD were recruited from psychiatric outpatient units in the Capital Region of Denmark. Inclusion criteria were age 8-17 years, primary OCD diagnosis (International Classification of Diseases, 10th revision, ICD-10[16], and symptom severity score ≥16 on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [17]. We excluded children and adolescents with OCD if they had a full scale IQ <70 (as assessed with the age-appropriate Wechsler Intelligence Scale,[18,19] had received cognitive behavioural therapy (CBT), psychoeducation and relaxation therapy (PRT), antidepressant medication, or antipsychotic medication within the past six months; or had a diagnosis of schizophrenia, other psychotic disorder, mania, bipolar disorder, substance dependence disorder, or pervasive developmental disorder (except for Asperger's syndrome).[15]

Healthy controls were recruited from the regional population via a random sample of children and adolescents in the same age range and municipality as the participants with OCD, drawn from the Danish Central Person Registry.[20] Controls were excluded if they currently or previously met the diagnostic criteria for a psychiatric disorder (ICD-10) or fulfilled any of the exclusion criteria also used for participants with OCD (i.e., IQ < 70 or treatment within the past six months).

Procedures

All study procedures were approved by the Danish data protection and research ethics authorities (The Ethics Committee of Capital Region of Denmark, approval number: H-18010607, and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark: VD-2018-263, I-Suite no.: 6502). Participants and their families gave informed consent prior to participation, adhering to the Declaration of Helsinki[21]. Diagnostic assessments and neurocognitive tests were administered by trained clinicians and research staff and videotaped for supervision and scoring purposes. All participants received a gift card for their research activities (value 250 DKK / ~38 USD per visit).

Clinical assessment

Trained psychologists and physicians screened all participants for psychopathology using the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL).[22] Some of the healthy controls were screened by trained master-level psychology students, supervised by trained psychologists and physicians. The same assessor interviewed the children and their parents separately and assessed the OCD symptom severity in children and adolescents with OCD with the CY-BOCS.[17] To evaluate presence and severity of co-occurring disorders, children and adolescents with OCD were assessed with additional clinical tests when relevant (e.g., Autism Diagnostic Observation Schedule[23] for patients suspected to have an autism spectrum disorder). Diagnoses were conferred with a child and adolescent psychiatrist or a psychologist with specialisation in child and adolescent psychiatry in the outpatient clinic. Signs of behavioral or emotional problems during neurocognitive testing were assessed with the clinician-rated Test Observation Form (TOF).[24]

Neurocognitive tests

The test battery consisted of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[25] the Delis-Kaplan Executive Function System (D-KEFS),[26] and the Wechsler Intelligence Scales.[19,27] Intelligence was assessed with the General Ability Index from the Wechsler Intelligence Scales, using the age-appropriate version of the scale for the individual participant: The Wechsler Intelligence Scale for Children – Fifth edition (WISC-V)[27] or The Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV).[19] The remaining test battery assessed cognitive flexibility, planning and decision-making, working memory, verbal and nonverbal fluency, and processing speed (Table 1). Primary outcomes from each test were chosen prior to study initiation, based on comparability with previous studies and consensus in the author group on which outcomes best reflected each of the functions assessed. All neurocognitive tests were administered and scored by trained psychologists and research assistants under the supervision of two senior neuropsychologists. Standard administration and scoring procedures were followed.

< Table 1 should be inserted here >

Statistical Analysis

Analyses were done in SPSS version 25.[28] Missing values analyses were carried out for all neurocognitive outcomes. The total number of missing values was low (1.3%) and we did not detect any systematic patterns in missing values. Missing values were imputed using the SPSS fully conditional specification Markov Chain Monte Carlo (MCMC) procedure for multiple imputations,[29] using all neurocognitive outcomes, age, and sex as predictors. Convergence was assessed using the Gelman and Rubin approach and by visual inspection of the trace plots.[30,31] First, we ran an

exploratory analysis with two imputations and 1000 iterations to assess MCMC convergence. The exploratory analysis revealed convergence of parameters within the first 100 iterations of each run. We repeated the analysis with 20 imputations and 200 iterations for each run. Visual inspection of trace plots indicated convergence of individual chains within few iterations. The potential scale reduction factor (PSRF) was $\hat{R}$<1.01, suggesting that chains converged to the equilibrium distribution.

Outlier analyses were carried out for all neurocognitive outcomes, with outliers defined as data points more than 2.2 x IQR above the third quartile or below the first quartile.[32] A total of 36 outliers (<1.5% of the total values) were identified. The proportion of values identified as outliers was similar across groups – 28 outliers (1.4%) in the OCD group, and 8 outliers (1.2%) in the healthy control group. Outliers were winsorised by modifying their values to either the maximum or minimum value within the data distribution (i.e. 2.2 x IQR above the third quartile or 2.2 x IQR below the first quartile).[32]

Levene's test[33] was used to check if data was normally distributed. The AST accuracy score (percentage correct trials) and the CGT quality of decision-making score violated the assumption of equal variances across groups and were arcsine square root transformed.

Demographic and clinical characteristics of the groups were compared using independent-samples t-tests for numerical data (e.g. age) and chi-square test for categorical data (sex). Parental education in years was calculated as a mean for both parents, as done in a previous study.[34] If only one parent participated in the trial, then that parent's value was used. Neurocognitive test performance was compared across participants with OCD and healthy controls using multivariate analysis of covariance (MANCOVA) controlling for potential effects of age and sex. In secondary analyses, we used MANCOVAs to control for potential effects of differences in intelligence and parental education level. To minimize the risk of false discoveries due to multiple comparisons, we adjusted the significance levels using the Holms-Bonferroni method.[35]

Symptom severity (CY-BOCS total score) and comorbidity was assessed as potential moderators of neurocognitive outcomes using Pearson's correlation analyses and independent samples t-tests respectively. We analysed correlations between overall comorbidity status (comorbid disorder present vs. OCD only) and neurocognitive outcomes, and between neurocognitive outcomes and specific comorbid disorders, if they occurred in at least 15% of the children and adolescents with OCD.[36]

Effect sizes were calculated as standardized mean differences (SMD), also known as Cohen's *d*.[37]

Results

Demographic and clinical characteristics

A total of 117 children and adolescents with OCD and 42 healthy controls participated in the study. The OCD group and the healthy control group had similar ratios of female:male participants and similar mean age but differed significantly in general cognitive ability (intelligence) and parental education level (see Table 2).

The OCD group had relatively high symptom severity scores and rates of comorbidity (Table 2). More than half of the participants with OCD had at least one co-occurring disorder, most commonly attention-deficit/hyperactivity disorder (ADHD), stress-related disorder, Asperger's syndrome, and tic disorder (including Tourette's Syndrome). The OCD group was untreated for OCD (no psychotherapy or SSRI treatment). We did not systematically assess the use of medication other than antidepressants and antipsychotics at the time of inclusion, but a retrospective screening of the health records found that a small number of patients received medication for other reasons, primarily sleep aid (melatonin, n = 8, methylphenidate, n = 1, antihistamine, n = 1, valproate, n = 1, cannabidiol drops, n =1). Participants with OCD showed more symptoms of psychopathology during testing than healthy controls, as assessed with the TOF. Inspection of all TOF subscales revealed significantly

higher ratings of symptom-behaviour in the OCD group compared to the healthy control group within each of the five symptom scales: withdrawn/depressed, language/thought problems, anxious, oppositional, and attention problems (p <.05).

< *Table 2 should be inserted here* >

Neurocognitive functions

Children and adolescents with OCD and healthy controls were compared on 16 outcomes, assessing cognitive flexibility, planning and decision making, working memory, verbal and nonverbal fluency, and processing speed (for statistics, see Figure 1). After correction for multiple testing, group differences were significant on five of the 16 outcomes: accuracy in the Attention Switching Task, quality of decision-making in the Cambridge Gambling Task, and completion time in seconds on the Trail Making Test Number-sequencing Test, Letter-sequencing Test, and the Number-letter Switching Test. The effect size was moderate for the quality of decision-making outcome (0.68 *d*), with controls choosing the most likely outcome in 7% more trials. Effect sizes were small (0.30-0.35 *d*) for the four remaining outcomes. Compared to the healthy controls, the OCD group had a 2.2% percent lower accuracy score in the Attention Switching Task, and their mean completion times were between 4.8 and 12.5 seconds slower across the conditions of the Trail Making Test. A MANCOVA with parental education in years as covariate yielded comparable results, as did a MANCOVA controlling for potential effects of differences in the General Ability Index. The plot in Figure 1 displays the standardized mean differences (effect sizes) for the neurocognitive outcomes. Points on the left side of the plot represents poorer performance in the OCD group compared to the healthy control group.

< Figure 1 should be inserted here >

Exploratory analyses

We evaluated associations between neurocognitive outcomes and symptom severity and co-occurring disorders. For symptom severity, we found no significant correlations between CY-BOCS total score and the 16 neurocognitive outcomes (p-values ≥ 0.15). For the comorbidity analyses, we grouped OCD participants into two groups: 'OCD only' and 'OCD + co-occurring disorder'. We did not perform any specific analyses of the association between a single disorder and neurocognitive functioning, as no disorder was present in at least 15% of the children and adolescents with OCD. Independent samples t-tests showed no significant differences on any of the neurocognitive outcomes between participants with OCD and co-occurring disorders vs. OCD only (p-values ≥ 0.18).

Discussion

We compared neurocognitive functioning in 117 children and adolescents with OCD and 42 healthy controls aged 8-17 years on 16 outcomes, assessing cognitive flexibility, planning and decision making, working memory, fluency, and processing speed. All participants were thoroughly assessed with diagnostic interviews and intelligence testing. The OCD group was representative of clinical OCD populations in terms of intelligence and comorbidity rates and types,[10,38] and matched the healthy control group in terms of age and sex.

Our main findings revealed that participants with OCD performed significantly worse than healthy controls on five cognitive outcomes, spanning cognitive flexibility, decision-making, and processing speed. As expected, participants with OCD also had more observable symptoms of emotional and behavioural problems during neurocognitive testing than healthy controls, as assessed with the TOF.

However, we found no significant group differences on tests of planning, working memory, or fluency.

The quality of decision-making was moderately reduced in participants with OCD compared to healthy controls, assessed with the Cambridge Gambling Task, which requires participants to gamble a proportion of points based on the probability of reward. This finding implies that children and adolescents with OCD have a harder time learning and using probabilistic information or understanding response-outcome contingencies than their healthy peers. Accordingly, two recent studies found that adolescents with OCD were slower to learn response-outcome relationships and worse at adapting response strategy when previously rewarded actions were devaluated compared to healthy controls.[39,40] Additionally, Marzuki and colleagues[40] found normal performance in the OCD group on all outcomes of the Wisconsin Card Sorting Test, in which response-outcome relationships are deterministic rather than probabilistic. Selective difficulties with learning probabilistic response-outcome relationships may be related to the clinical manifestations of OCD with individuals having obsessional fears that highly unlikely events may occur and beliefs that compulsions influence the likelihood. Excessive doubt is a common clinical characteristic of OCD and may be triggered or enhanced when response-outcome relationships are uncertain.[40] While our exploratory analysis did not reveal a significant correlation between the excessive doubt outcome of the CY-BOCS and decision-making ability on the Cambridge Gambling Task, the potential link could be worth exploring in future studies, using comprehensive and reliable measures of contingency-learning. Two other studies evaluated probabilistic decision-making in childhood OCD using the Iowa Gambling Task[41] in which probabilities of rewards vs. losses must be learned over time.[42,43] Similar to our finding, children with OCD showed poorer decision-making ability than healthy controls in both studies and one of the studies found related fronto-striatal aberration using fMRI.[42] To our knowledge, only one other paediatric study used the Cambridge Gambling Task, and this study found no significant differences in the quality of decision-making between participants with OCD and healthy controls.[34]

Based on the findings from these prior studies, a review noted that children and adolescents with OCD may show impaired decision-making ability when the probability of reward is ambiguous (as in Iowa Gambling Task), but not when probabilities are more obvious (as in Cambridge Gambling Task)[12]. Our finding of moderately worse performance on the Cambridge Gambling Task suggests that children and adolescents with OCD may show more general difficulties with probabilistic decision-making.

Our finding of reduced processing speed in the OCD group compared to the healthy control group is consistent with previous studies with adults[5-7] as well as children and adolescents with OCD.[36,44,45] Moreover, reduced processing speed was the primary finding in a recent large paediatric case-control study.[36] The authors found worse performance in the OCD group compared to controls on timed tests only, arguing that slower processing speed could explain the apparent underperformance on other neurocognitive tests. Reduced processing speed has also been proposed as the main cause of neurocognitive underperformance in adults with OCD.[46,47]

In our assessment of cognitive flexibility, we found significant differences between the groups on two outcomes. Participants with OCD were slower to complete the Trail Making Number-Letter Switching Test and less accurate than controls in the Attention Switching Task (effect sizes of 0.3 *d*). Our finding of reduced cognitive flexibility contrasts previous findings with most studies showing comparable cognitive flexibility in children and adolescents with OCD and healthy controls.[12] Several studies specifically used the Trail Making Number-Letter Switching Test,[34,44,45,48-50] with just one study reporting significantly slower completion times in children and adolescents with OCD compared to healthy controls.[45] Although we included the Trail Making Number-Letter Switching Test to assess cognitive flexibility, our finding of slower completion time on this test could also be explained by the slower processing speed observed in the OCD group in our study (see e.g. Lamberty et al.).[51] The Attention Switching Task also involves time pressure, as participants are instructed to

respond rapidly and the response window between trials is short. Slower processing speed could contribute to the lower accuracy seen on this task in the OCD group compared to the control group, especially since we found no significant differences in switch cost assessed with the same task. That is, participants with OCD and healthy controls were equally capable of adjusting their reactions to changes in task demands, which is a more direct measure of cognitive flexibility.

Overall, we found that children and adolescents with OCD compared to healthy controls had slightly reduced processing speed, moderately reduced probabilistic decision-making ability, as well as slower completion time and lower accuracy on two outcomes intended to measure cognitive flexibility. Across all outcomes where participants with OCD performed significantly worse than healthy controls, the average scores in the OCD group were within the normal range for the tests and between 0.3-0.68 standard deviation from the mean of the healthy control group. While we found selective and subtle differences on the group level, individual children and adolescents with OCD may still experience clinically significant neurocognitive impairment. Our analyses of potential associations between symptom severity and comorbidity status on neurocognitive outcomes yielded no significant results, in line with previous work with both children and adolescents[36,44,48] and adults with OCD[5]. However, other factors, such as illness duration, could be associated with neurocognitive impairment in OCD.

The few and subtle neurocognitive findings in children and adolescents with OCD have been suggested to reflect successful neural compensation during cognitive performance, as several imaging studies have reported aberrant brain activity during task performance, while displaying no behavioural performance differences.[12,52] For example, aberrant brain activity in children and adolescents with OCD has been observed in paradigms assessing error-monitoring [53,54], cognitive flexibility [50,55,56], working memory [57], and decision-making [42] in the absence of significant differences in behavioural task performance compared to healthy controls. Such findings could indicate that

neurocognitive changes in children and adolescents with OCD are predominantly neural and possibly manifest behaviourally later in the course of the illness.[12] This could partially explain why more significant differences are seen across neurocognitive domains in adults. However, as the effects reported in behavioural studies with adults with OCD are generally small (effect sizes 0.3-0.6 *d*)[5], subtle neurocognitive impairment may be shared across age groups. Moreover, the fact that more significant findings are found in adult samples could be due to the larger number of adequately powered studies conducted with this age group. The emergence of large neurocognitive studies with children and adolescents with OCD is an important step towards resolving this debate.

Our study has several strengths. First, it is the largest neurocognitive study comparing children and adolescents with OCD to healthy controls. To our knowledge, only one other case-control study included more than 100 children and adolescents with OCD.[36] Additionally, our sample was unmedicated for OCD, thereby avoiding potential confounding effects of SSRI treatment.[13,14] Also, our healthy controls were thoroughly screened for psychopathology and recruited from the Danish Central Person Register to achieve the lowest possible risk of selection bias. Finally, we used a comprehensive battery of well-established tests, assessing functioning within several neurocognitive domains, whereas most prior studies focused on a single domain or included few different tests.

Our study also has several limitations. For example, since the data presented here are cross-sectional, we were unable to evaluate if the observed neurocognitive underperformance is moderated by e.g. illness duration, pharmacological or therapeutic intervention, or age of onset (i.e., onset in childhood vs. adulthood). Additionally, although we aimed to recruit healthy controls that were representative of the background population, their average intelligence score was 0.5 SD above the norm average, and parental education level was also higher in the control group than in the OCD group. However, controlling for intelligence and parental education level in secondary analyses had no discernible effect on our results.

Future studies should investigate neurocognitive functions in OCD using a longitudinal study design to evaluate if neurocognitive performance worsens with disorder progression or if neurocognitive performance is predicted or moderated by clinical or treatment-related factors. Future studies would also benefit from incorporating assessments of neurocognitive functioning in daily life to evaluate if the observed neurocognitive underperformance is associated with any real-life impairment or neurocognitive complaints. Also, an updated meta-analysis of neurocognitive findings in children and adolescents with OCD is due, given the emergence of large paediatric studies that will help overcome power limitations and bring the paediatric neurocognitive investigations on par with the investigations of neurocognition in adults with OCD.

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Table 1. Neurocognitive tests and outcomes

Functions and tests	Test description	Outcomes
Cognitive flexibility		
Attention Switching Task[24]	Computerized test in which the participant responds "right" or "left" quickly and accurately based on either the direction or location of an arrow. The response rule switces continually throughout the task.	Percent correct trials; Switch cost[a]
Trail Making Test Number-Letter Switching[25]	Paper-pencil test in which the participant draw a line as quickly and accurately as possible, connecting numbers and letters in ascending order while alternating between them (i.e. 1-A-2-B etc.).	Completion time in seconds
Verbal Fluency Switching[25]	Verbal test in which the participant names as many words as possible in 60 seconds, alternating between two categories (e.g. apple-table-pear-sofa).	Number of correct switches
Design Fluency Switching[25]	Paper-pencil test in which requires the participant draws as many different figures as possible in 60 seconds by connecting dots with straight lines, continually switching between filled and empty dots.	Number of correct figures
Planning and decision-making		
Stockings of Cambridge[24]	Computerized test in which the participant copies a model by rearranging items (balls) to match the model, trying to use the minimum moves required.	Problems solved in minimum moves[b]
Spatial Working Memory[24]	Computerized test in which an increasing number of boxes are presented on the screen, and the participant is instructed to find a blue token behind each of them. When the token is found, it is hidden behind a new box and the participant is asked to avoid returning to a box where a token has already been found.	Spatial working memory strategy[c]
Cambridge Gambling Task[24]	Computerized test in which the participant guesses whether a token is hidden behind red boxes or blue boxes. On each trial, ten boxes are presented and the ratio of blue:red boxes is varied. The participant bets points on their decision, and points are won or subtracted according to outcome and bet-size.	Quality of decision making[d]; Risk adjustment[e]
Working memory		
Wechsler Scales Working Memory Test[19,26]	Verbal digit span test in which the administrator reads a sequence of digits and asks the participant to relay them forwards in Condition 1, backwards in Condition 2, and in ascending numerical order in Condition 3.	Working memory index score
Spatial Working Memory[24]	*See previous description in this table*	Total errors
Fluency		
Verbal Fluency Phonemic[25]	Verbal test in which the participant has 60 seconds to name as many words as possible beginning with a specific letter. Three subtests are administrered.	Number of correct words
Verbal Fluency Semantic[25]	Verbal test in which the participant has 60 seconds to name as many words as possible from a specific semantic category. Two subtests are administrered.	Number of correct words
Design Fluency Empty dots[25]	Paper-pencil test in which the participant is draws as many different figures as possible for 60 seconds, connecting empty dots and ignoring filled dots.	Number of correct figures
Processing speed		
Trail Making Test Number sequencing[25]	Paper-pencil test in which the participant draws a line, connecting numbers in ascending order as quickly and accurately as possible	Completion time in seconds
Trail Making Test Letter sequencing[25]	Paper-pencil test in which the participant draws a line that connects letters in alphabetical order as quickly and accurately as possible.	Completion time in seconds

Note: The test battery spanned tests from the CANTAB battery [25], the D-KEFS battery (Delis et al. 2001), and the Wechsler Scales (Wechsler 2008; Wechsler 2014b). CANTAB tests include: Attention Switching Task, Stockings of Cambridge, Cambridge Gambling Task, and Spatial Working Memory. D-KEFS tests include: the Trail Making Test, Verbal Fluency, and Design Fluency. The Wechsler tests include: Working Memory subtests.

[a]The difference in the average reaction time in milliseconds between switch and repeat trials.

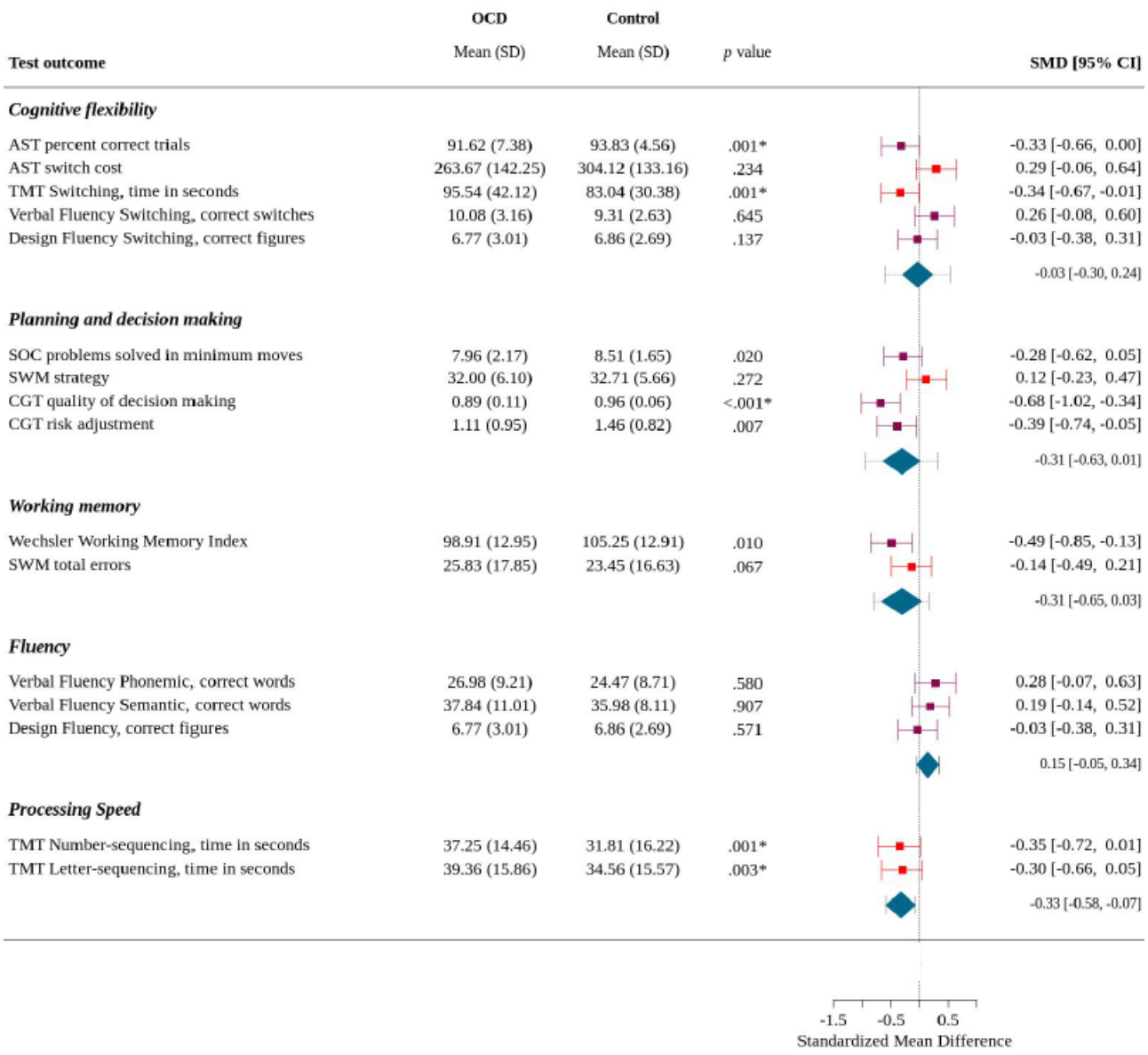
[b]The number of trials in which the participant matched the model by using as few moves as possible.
[c]Based on the number of times the participant started each search within a trial with a new box instead of starting with the same box and following a systematic sequence – lower scores represent more efficient strategy use.
[d]The proportion of trials where the participant chose the most likely outcome – higher scores represent better decision making.
[e]The degree to which the participant adjusted the bet size according to the ratio of red:blue boxes – higher scores means higher degree of adjustment.

Table 2. Demographic and Clinical Characteristics

Characteristic	OCD group Mean (SD) or n (%)	Healthy control group Mean (SD) or n (%)	*p* value
Number of participants	117	42	
Females/Males	58/59 (49.6/50.4)	18/24 (42.9/57.1)	.458
Age in years	13.31 (2.82)	12.36 (2.25)	.055
Parental education in years	15.55 (2.12)	16.73 (1.87)	.007
General Ability Index (WISC-V/WAIS-IV)	98.76 (13.54)	106.69 (13.17)	.001
TOF total score	17.38 (20.09)	6.14 (7.25)	<.001
OCD severity			
CY-BOCS total score	25.30 (4.98)		
CY-BOCS obsessions score	12.87 (2.99)		
CY-BOCS compulsions score	12.63 (2.82)		
Co-occurring disorders			
Mood disorder (F30-F39)	1 (0.85)		
Phobic anxiety disorder (F40)	3 (2.56)		
Other anxiety disorder (F41)	8 (6.84)		
Stress-related disorder (F43)	15 (12.82)		
Eating disorder (F50)	4 (3.42)		
Personality disorder (F61)	2 (1.71)		
Asperger's syndrome (F84.5)	17 (14.53)		
Other developmental disorder (F88)	5 (4.27)		
ADHD (F90)	15 (12.82)		
Conduct disorder (F91)	1 (0.85)		
Emotional disorder with childhood onset (F93)	5 (4.27)		
Tic disorder (F95)	13 (11.11)		
Total with at least one co-occurring disorder	69 (58.97)		

Note: ADHD, attention-deficit hyperactivity disorder; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; OCD, Obsessive-compulsive disorder; SD, standard deviation; TOF, Test Observation Form; WAIS-IV, Wechsler Adult Intelligence Scale Version IV; WISC-V, Wechsler Intelligence Scale for Children Version V.

Figure 1. Performance on neurocognitive tests



Note: Test performance was compared across groups with multivariate analysis of covariance (MANCOVA) with sex and age as covariates. The left side of the SMD plot represents poorer performance in the OCD group compared to the healthy control group. For most outcomes higher scores represent better performance, but for a few outcomes the opposite is true (e.g. completion time). We multiplied the SMD by -1 for outcomes on which lower scores are better to ensure consistent directionality on the plot – i.e. points on the left side of the plot represent worse performance in the OCD group, while points on the right side of the plot represent worse performance in the healthy control group. The SMDs that were corrected are highlighted in red. Abbreviations: AST, Attention Switching Task; CGT, Cambridge Gambling Task; SD, standard deviation; SMD, Standardized mean difference; SOC, Stockings of Cambridge; SWM, Spatial Working Memory; TMT, Trail Making Test.
* = results that remained significant after Holm-Bonferroni correction.

Key points

- Neurocognitive impairment has been proposed to underlie the core symptoms of pediatric OCD, but neurocognitive investigations of children and adolescents with OCD are few and characterized by small samples and inconsistent findings.
- We investigate neurocognitive functioning in a large and representative sample of children and adolescents with moderate to severe OCD compared with healthy controls, using well-established tests assessing cognitive flexibility, planning and decision-making, working memory, fluency, and processing speed.
- Children and adolescents with OCD showed moderate impairment in probabilistic decision-making, and subtle underperformance in processing speed and some aspects of cognitive flexibility (lower accuracy and slower completion times in set-shifting tasks).
- We found no evidence of differences between children and adolescents with OCD and their healthy peers in planning, working memory, fluency, or a more direct measure of cognitive flexibility (switch cost).
- Children and adolescents with OCD may show subtle and selective neurocognitive impairment which future studies should directly address to further explore the potential real-life impact of these deficits.

Paper 3

Probabilistic learning and decision-making appear intact in children and adolescents with obsessive-compulsive disorder.

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Unsubmitted manuscript.

Title: Probabilistic learning and decision-making appear intact in children and adolescents with obsessive-compulsive disorder

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Abstract

Background: Probabilistic learning and decision-making may be impaired in children and adolescents with obsessive-compulsive disorder (OCD), who often lack insight into the irrational nature of their symptoms and the contingencies between them. However, experimental studies of probabilistic learning and decision-making in OCD are few and inconclusive. In this study, we evaluate the strength of the evidence for or against impaired probabilistic learning and decision-making in a large sample of children and adolescents with OCD.

Methods: Seventy-seven children and adolescents with OCD and 31 healthy controls (11-17 years) completed the probabilistic Weather Prediction Task (WPT), in which cue-outcome contingencies must be learned through feedback. We assessed proportion of optimal responses (predicting the most likely outcome) and response time (time in seconds from cue until response) from the WPT. We tested explicit cue-outcome knowledge with a multiple-choice questionnaire. We used Bayesian statistics to evaluate the strength of the evidence for or against differences in WPT performance between the OCD group and the healthy control group.

Results: We found moderate evidence against an effect of group on proportion of optimal responses and response time in the WPT. Both children and adolescents with OCD and healthy controls gained explicit knowledge of the cue-outcome contingencies but we were unable to determine whether the groups differed in this awareness.

Conclusion: Our results suggest that probabilistic learning and decision-making is intact in children and adolescents with OCD.

Introduction

Obsessive-compulsive disorder (OCD) affects 1-3% of children and adolescents[1,2] and is characterised by recurring and distressing thoughts (obsessions) and mental or behavioural rituals (compulsions)[3,4]. OCD is associated with excessive doubt and indecisiveness, overestimation of threat, and irrational beliefs that highly unlikely events may occur[5,6]. The clinical manifestations of OCD may be underpinned by difficulties in learning and using probabilistic information[7,8], leading to difficulties updating thoughts and behaviour based on experiences and feedback. Such issues may be especially pronounced in children and adolescents compared to adults with OCD, as lack of insight into the irrational nature of obsessive-compulsive symptoms and their contingencies is common in childhood-onset OCD[9]. However, experimental studies of probabilistic learning in OCD show inconsistent results and have almost exclusively been conducted with adults. For example, adults with OCD have been shown to deliberate longer and feel more uncertain about probabilistic predictions[10], exhibit excessive loss aversion by rejecting relatively low-risk gambles at a higher rate[11], and learn response-outcome contingencies at a slower rate[12] compared to healthy controls. The latter finding has also been reported in adolescents[13]. Yet, other studies report no performance differences between adults with OCD and healthy controls on probabilistic learning tasks[14-16]. The inconsistent results may be partly explained by differences in participant characteristics and type of task used across studies. For example, most of the adult studies included both unmedicated and medicated participants (treated with selective serotonin reuptake inhibitors [SSRIs]). Nonetheless, a recent study suggested a moderating role of medication, reporting impaired probabilistic learning only in a subgroup of unmedicated adults with OCD[12]. Moreover, some studies indicate that probabilistic learning impairments in OCD may be context-specific, perhaps only captured by tasks that trigger obsessions.[17,18]

In this study, we investigated probabilistic learning and decision-making in a large sample of children and adolescents with OCD, using a classic probabilistic test - the Weather Prediction Task (WPT).[19] We evaluated the strength of the evidence for or against differences in probabilistic learning and decision-making in the OCD group versus the healthy control group using Bayesian hypothesis-testing.

Methods

Participants

Participants were recruited between September 2018 and December 2021. All participants were part of a case-control study nested in an ongoing randomised controlled trial, which will be reported on elsewhere (The TECTO trial[20], ClinicalTrials.gov Identifier: NCT03595098).

Children and adolescents with OCD were recruited from psychiatric outpatient units of the Mental Health Services in Copenhagen, Denmark, and had to meet the following criteria: age between 11 and 17 years old, full-scale IQ > 70, established OCD diagnosis, and symptom severity score ≥16 on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)[21] (corresponding to moderate to severe OCD symptoms). Participants with OCD were excluded if they had received treatment with cognitive-behavioural therapy (CBT), psychoeducation and relaxation therapy (PRT), antidepressant or antipsychotic medication within the last six months prior to study entry. We also excluded participants with OCD if they had co-occurring bipolar disorder, mania, substance dependence disorder, schizophrenia, other psychotic disorder, or pervasive developmental disorder (except for Asperger's syndrome).[20]

Healthy controls were recruited via the Danish Central Person Registry[22], and were from the same municipality as children and adolescents with OCD. Healthy controls were excluded if they currently

or previously met the diagnostic criteria for any psychiatric disorder and otherwise had to meet the same eligibility criteria as participants with OCD.

Procedures

The study procedures were approved by the Ethics Committee of The Capital Region of Denmark (approval no. H-18010607), and The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark (approval no. VD-2018-263). We obtained informed consent for all participants, following the Declaration of Helsinki[23]. Participants received a gift card of 250 DKK (~34 EUR) for their research activities.

Clinical assessment

Participants were assessed for psychopathology using the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL)[24]. OCD symptom severity was assessed with the CY-BOCS[21]. OCD diagnosis and any co-occurring diagnoses were based on the criteria of the International Classification of Diseases, 10th revision (ICD-10)[3], and established in consensus between the assessor and a specialist in the outpatient unit (either a psychiatrist or a psychologist with specialization in child and adolescent psychiatry). Intelligence was assessed with the age-appropriate version of the Wechsler Intelligence Scales - either the digital version of the Wechsler Intelligence Scale for Children - Fifth edition (WISC-V)[25] or The Wechsler Adult Intelligence Scale - Fourth edition (WAIS-IV).[26] As Pearson Assessment notified us of technical issues with two subtests from the digital WISC-V during the data collection period, potentially resulting in overestimated full IQ scores, we assessed intelligence with the unaffected General Ability Index.

Weather Prediction Task

The WPT is a computer test in which participants predict the weather (either rain or sun) based on cue-cards shown on the screen. Either one, two, or three cue-cards were shown on each trial. Each card had a fixed probability of predicting either rain or sun, but the cue-outcome contingencies were unknown to participants. Based on feedback on their predictions, participants should gradually learn the contingencies and therefore make more qualified predictions as the task progresses.

The WPT was coded in PsychoPy[27] version 1.83.04. The task mirrors the WPT available from the open source PEBL software[28], but with the addition of a multiple-choice questionnaire in the end to assess cue-outcome awareness in participants. The task consisted of 350 trials, divided into seven blocks of 50 trials. Each trial consisted of cue-card presentation (presentation of 1-3 cue-cards), decision, and feedback (see trial outline and cue-outcome contingencies in Figure 1). The decision phase was self-paced with the cue-cards remaining on screen until the participant responded either "rain" or "sun" by pressing corresponding keys on a keyboard. The feedback screen showed a smiling face for correct predictions, and a frowning face for incorrect predictions. Each cue-card predicted each outcome (rain/sun) with a fixed probability. On trials with two or three cue-cards, the outcome probability was calculated based on the probabilities of the individual cards in the set. As the relationships between cues and outcomes were probabilistic, the most likely outcome did not always occur. For the analyses, a correct response was therefore defined as predicting the most likely of the two outcomes, irrespective of the actual outcome. The main test outcomes of the WPT were the average proportion of optimal responses and the average response time (time in seconds from cue-card presentation until response) for each block.

< Figure 1 should be inserted here >

Assessment of cue-outcome awareness

After completing the WPT, participants answered a four-option multiple-choice questionnaire that assessed explicit knowledge of the cue-outcome contingencies. The questions were: 1) how many different cards were in the test? 2) which card was the best predictor of sun? 3) which card was the best predictor of rain? For the two questions about prediction, all four cue-cards were presented as possible answers.

Data analyses

All analyses were done using Bayesian statistics in the open source statistics program JASP[29]. In each analysis, we quantified the relative predictive performance of rival hypotheses: the null hypothesis, $\mathcal{H}_0$, predicting that the size of an effect was equal for the OCD and healthy control group, and the alternative hypothesis, $\mathcal{H}_1$, predicting that the size of an effect was unequal for the OCD and healthy control group. We report the evidence in favour of $\mathcal{H}_1$ relative to $\mathcal{H}_0$ as the Bayes' factor, BF_{10}[30]. We classified the strength of the evidence in accordance with the guidelines provided by Wagenmakers and colleagues[31], ranging from a classification of anecdotal/inconclusive to decisive evidence. For example, a BF_{10} of 1-3 corresponds to anecdotal/inconclusive evidence for $\mathcal{H}_1$, a BF_{10} of 3-10 corresponds to moderate evidence for $\mathcal{H}_1$, and a BF_{10} of 10-30 corresponds to strong evidence for $\mathcal{H}_1$[31]. Conversely, a BF_{10} of 0.3-1 corresponds to anecdotal/inconclusive evidence for $\mathcal{H}_0$, a BF_{10} of 0.1-0.3 corresponds to moderate evidence for $\mathcal{H}_0$, and a BF_{10} of 0.03 to 0.1 corresponds to strong evidence for $\mathcal{H}_0$ etc.[31]

We assessed group effects on demographic and clinical variables using Bayesian independent-samples *t*-test for normally distributed data and Bayesian Mann-Whitney's *U*-test for non-normally distributed data, as assessed with a Shapiro-Wilk test of Normality. A Bayesian contingency table was used to compare sex ratios in the two groups.

We used Bayesian repeated-measures analyses to assess the effect of group (OCD versus healthy control) on average proportion of optimal responses and response time in each block with age and sex as covariates. Normality was assessed by visual inspection of the Q-Q plots.

Effects of group (OCD versus healthy control) on the explicit knowledge of cue-outcome contingencies were analysed with a Bayesian A/B test.

Bayesian correlation analyses were used on data from the OCD group to assess potential associations between WPT performance and symptom severity (total CY-BOCS score). Moreover, we used Bayesian repeated-measures analyses to assess associations between WPT performance and comorbidity status in participants with OCD (having OCD only versus having OCD and at least one co-occurring disorder).

Results

Seventy-seven children and adolescents with OCD and 31 healthy controls completed the WPT (see group characteristics in Table 1). Participants with OCD and healthy controls were similar in terms of sex ratio. We did not have sufficient data to determine whether the groups differed in terms of age distribution ($BF_{10} = 0.55$) and intelligence ($BF_{10} = 1.87$). Length of parental education in years was longer in the control group ($BF_{10} = 26.54$). More than half of the participants with OCD had at least one co-occurring psychiatric disorder (primarily stress-related disorders, Asperger's syndrome, and attention-deficit hyperactivity disorder [ADHD]). The participants in the OCD group were untreated for OCD. We did not systematically assess the use of medication other than SSRIs, other antidepressants and antipsychotics at the time of inclusion, but retrospective screening of the health records found that a few patients received medication for other reasons, primarily sleep aid (melatonin, n = 8; antihistamine, n = 1; methylphenidate, n = 1; valproate, n = 1; cannabidiol drops, n =1).

< Table 1 should be inserted here >

WPT performance

WPT performance for the OCD group and healthy control group is presented in figure 2 (optimal responses) and figure 3 (response time).

We found moderate evidence against an effect of group on both optimal response rate (BF_{10} = 0.24) and response time (BF_{10} = 0.28), indicating that participants with OCD and healthy controls performed comparably across the WPT blocks (Tables 2 and 3). Block number was decisively the strongest predictor of WPT performance based on the data, being 2,500 times better at predicting the optimal response rate compared to the null hypothesis, and $1.96*10^{55}$ times better at predicting the response time. We did not run post hoc analyses, as the purpose of the study was to determine the effect of group, and no effect was observed.

< Table 2 should be inserted here >

< Table 3 should be inserted here >

< Figure 2 should be inserted here >

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Awareness of cue-outcome relationships

The proportion of correct responses on questions in the cue-outcome questionnaire are presented in Table 4, along with the predictive performances of the possible hypotheses. The average accuracy scores suggest that both children and adolescents with OCD and healthy controls learned the cue-outcome contingencies explicitly, scoring above chance on all questions. The observed data did not favour any of the alternative hypotheses, and the strength of the evidence was weak for all possible models of the data - including the null hypothesis - indicating that we had insufficient data to determine whether the groups were equally aware of the cue-outcome contingencies.

< *Table 4 should be inserted here* >

Effects of symptom severity and comorbidity

We found moderate evidence against a correlation of symptom severity with both optimal response rate and response time (BF_{10} range 0.14-0.28 across all blocks). Moreover, we found moderate evidence against an effect of comorbidity on proportion of optimal responses in the OCD group (BF_{10} = 0.23). We did not have sufficient data to determine whether comorbidity affected the response time (BF_{10} = 2.04).

Discussion

To our knowledge, our study is the first to assess probabilistic learning and decision-making in children and adolescents with OCD using the WPT. We assessed WPT performance in 77 children and adolescents with OCD and 31 healthy controls. Participants with OCD were unmedicated, had moderate to severe OCD symptoms, and approximately 55% had at least one co-occurring psychiatric

disorder. We found no evidence to suggest that the groups differed on any of the demographic variables apart from parental education in years, which was approximately one year longer in the healthy control group.

We found moderate evidence against an effect of group on WPT performance, both in terms of accuracy (proportion of optimal responses) and response time (time in seconds from cue-card presentation until response). Block number was the only strong predictor of performance, showing similar learning curves for the OCD group and the healthy control group, resulting in higher proportions of optimal responses and faster response times as the experiment progressed. We did not have sufficient data to determine whether participants with OCD and healthy controls differed in explicit awareness of cue-outcome relationships. Finally, we found moderate evidence against effects of symptom severity and comorbidity on WPT performance in the OCD group, in line with previous findings[32].

Our study supports previous findings of intact probabilistic learning in adults with OCD[14,15,17,18]. In contrast to our findings, one prior study found subtle impairments on the WPT in a group of unmedicated adults with OCD compared to an SSRI-medicated OCD group and a healthy control group, arguing that null findings in other studies may be confounded by pharmacological treatment[12]. However, all children and adolescents with OCD in our study were medication-free and still performed comparably to healthy controls, with moderate strength of the evidence. The previous finding could be a false-positive finding due to the relatively small samples tested[33] (26 unmedicated patients vs. 25 SSRI-medicated patients). Alternatively, the discrepancy could reflect true differences in neurocognitive functioning in children and adolescents with OCD compared to adults with OCD, which requires further investigation in future adequately powered studies.

Two previous studies compared probabilistic learning in adults with OCD and healthy controls, using the standard WPT and an emotional version of the task, in which participants predicted epidemic

outbreaks[17,18]. In both studies, individuals with OCD were impaired only on the emotional task, leading the authors to conclude that probabilistic learning is impaired specifically in an emotional or high-arousal context. Similarly, two studies found impaired decision-making in children and adolescents with OCD, assessed with the Iowa Gambling Task, in which probabilities of rewards and losses must be learned through feedback[34,35]. Impaired probabilistic learning and decision-making in OCD could therefore result from the interaction of cognition and emotion, consistent with the neurobiological model of OCD, which links obsessive-compulsive behavior to dysregulated emotions and impaired cognitive control[36]. Our finding of intact probabilistic learning in a non-emotional context is compatible with this model.

Our assessment of cue-outcome awareness did not yield firm evidence for or against a difference in explicit knowledge of the task contingencies between the OCD group and the healthy control group. Nonetheless, our findings suggest that both groups explicitly learned the cue-outcome associations. Two other studies have investigated cue-outcome awareness in OCD, albeit using a deterministic learning task [37,38]. In one study, adults with OCD were able to identify the correct responses to each cue but were less aware of the resulting outcomes compared to healthy controls.[37] The authors suggested that individuals with OCD may experience difficulties with learning specific contingencies between events, and therefore rely mostly on habits rather than more goal-directed behaviour. However, in another study using the same task, adolescents with OCD showed no impairment on explicit knowledge of cue-outcome contingencies[38]. More research is therefore needed to determine whether explicit knowledge of contingencies is impaired in OCD, and whether the current disparate findings are spurious or reflect differences between children and adults with OCD.

The main strength of our study is the inclusion of a large sample of children and adolescents with OCD, providing us with enough data to evaluate the strength of the evidence on the main WPT outcomes using Bayesian hypothesis testing. Also, because our OCD group was unmedicated, we

were able to investigate probabilistic learning and decision-making without the potential confounding effects of pharmacological treatment. The main limitation of our study is that we did not compare performance across different contexts. Future research should extend the current findings by assessing probabilistic learning and decision-making in children and adolescents with OCD using both neutral and emotional content to determine whether specific impairments emerge in the context of emotion.

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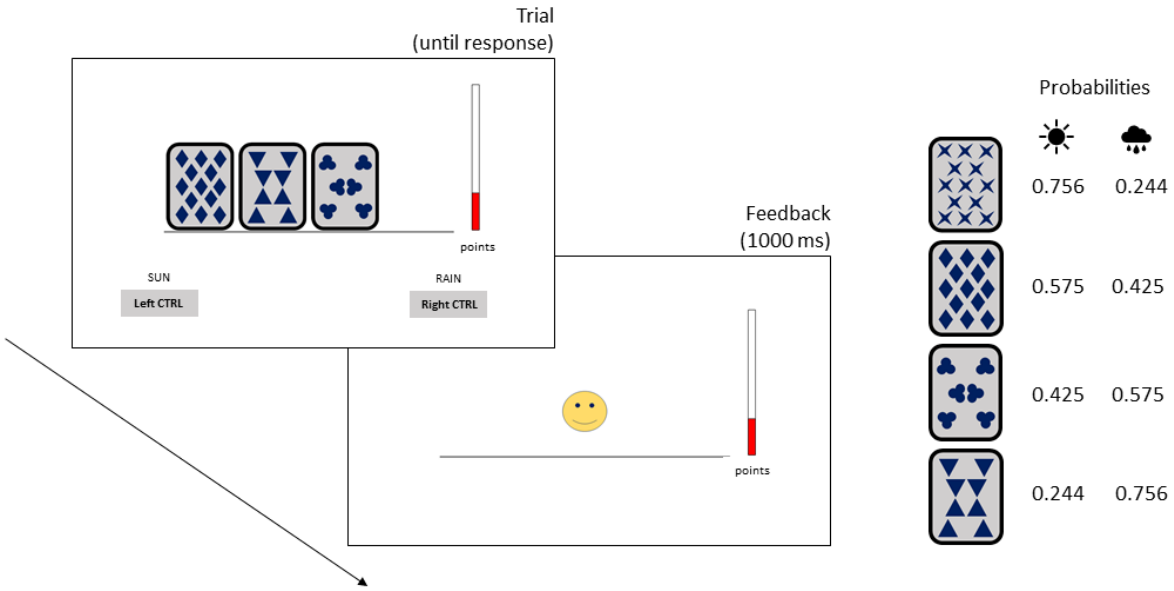

Figure 2. Trial outline and cue-outcome contingencies for the Weather Prediction Task (WPT). On each trial, participants were presented with either 1, 2 or 3 cue-cards and asked to predict the weather – either sun or rain – by pressing corresponding keys on a keyboard. Each cue-card had a fixed prediction ratio, as shown in the figure. The participants had no prior knowledge of the cue-outcome contingencies and had to learn from feedback (smiling face for correct predictions and frowning face for incorrect predictions). A point-bar was always visible, filling up for each correct prediction and draining for each incorrect prediction. The task consisted of 350 trials, divided into 7 blocks of 50 trials each.

Table 1. Participant characteristics

Characteristic	OCD group Mean (SD) or n (%)	Healthy control group Mean (SD) or n (%)	BF_{10}
Number of participants	77	31	
Females/males	45/32 (58.44/41.56)	17/14 (54.84/45.16)	0.25
Age in years	14.50 (2.13)	13.85 (2.12)	0.55
General Ability Index (WISC-V/WAIS-IV)	99.81 (12.86)	105.84 (12.70)	1.87
Parental education in years	15.60 (2.10)	17.18 (1.17)	26.54*
OCD severity			
CY-BOCS total score	25.32 (5.08)		
CY-BOCS obsessions score	12.70 (2.88)		
CY-BOCS compulsions score	12.62 (2.60)		
Co-occurring disorders			
Mood disorder (F30-F39)	1 (1.30%)		
Phobic anxiety disorders (F40)	2 (2.60%)		
Other anxiety disorders (F41)	8 (7.79%)		
Stress-related disorders (F43)	10 (12.99%)		
Eating disorders (F50)	4 (5.19%)		
Personality disorders (F61)	2 (2.6%)		
Asperger's syndrome (F84.5)	9 (11.69%)		
Other developmental disorders (F88)	2 (2.60%)		
ADHD (F90)	7 (9.09%)		
Conduct disorders (F91)	1 (1.30%)		
Emotional disorders with childhood onset (F93)	4 (5.19%)		
Tic disorders (F95)	7 (9.09%)		
Total with at least one co-occurring disorder	43 (55.84%)		

Note: For all tests, the alternative hypothesis ($\mathcal{H}_1$) specifies that the OCD group is unequal to the healthy control group. The Bayes' Factor (BF_{10}) reflects the evidence in favour of $\mathcal{H}_1$ relative to $\mathcal{H}_0$. Co-occurring diagnoses are listed with diagnosis title and ICD-10 F-code. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; OCD, obsessive-compulsive disorder; SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; *= strong evidence in favour of $\mathcal{H}_1$.

Table 2. Model comparisons of effects on proportion of optimal responses in the Weather Prediction Task.

Models	P(M)	P(M|data)	BF_M	BF_{10}	Error%
Null model (incl. age, sex, subject)	0.20	3.27e-4	1.31e-3	1.00	
Block	0.20	0.79	15.19	2423.18	7.82
Block + group	0.20	0.21	1.04	630.37	8.86
Block + group + Block * group	0.20	2.06e-3	8.26e-3	6.31	20.58
Group	0.20	7.89e-5	3.16e-4	0.24	5.55

Note. All models include age, sex, subject. The Bayes' factor (BF_{10}) determines how well the alternative models predict the observed data compared to the null model that the proportion of optimal responses across blocks is unaffected by block number and group (OCD vs. healthy controls). P(M) is the assumed probability of each model prior to the analyses (we assumed equal probabilities). P(M|data) is the updated probabilities given the experimental data from WPT. BF_M shows how much the data changed the prior probabilities. BF_{10} shows the Bayes' factor for each hypothesis relative to the null hypothesis.

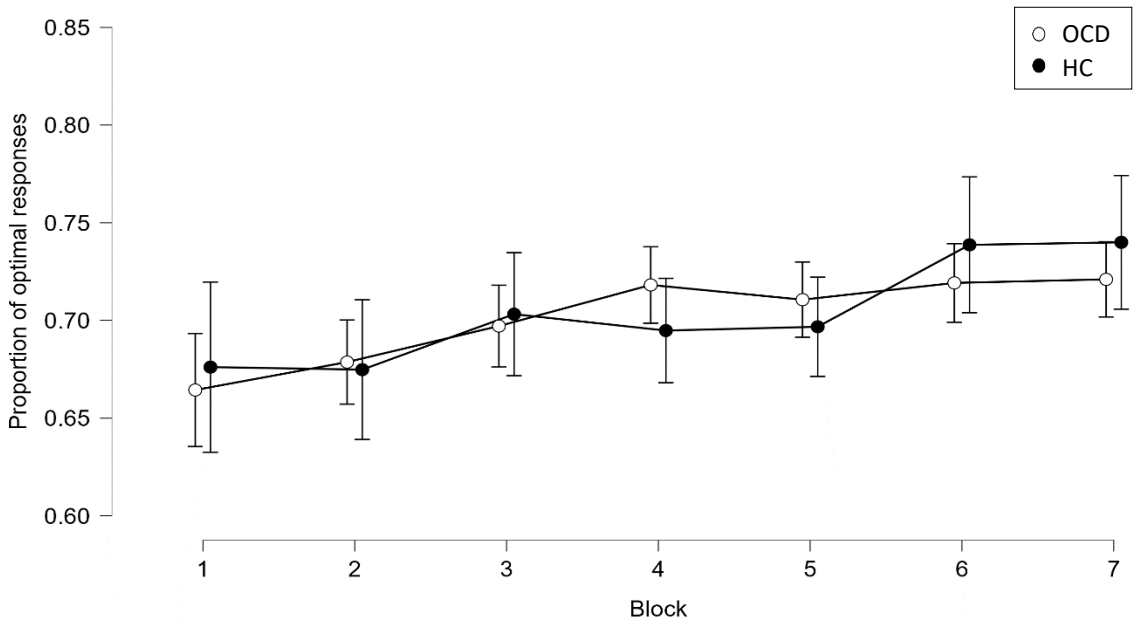

Figure 2. Proportion of optimal responses as a function of block number. The average proportion of optimal responses in each block of 50 trials is presented with 95% credible intervals (i.e., the range that contains the true value with a 95% probability, given the observed data). Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder.

Table 3. Model comparisons of effects on response time in the Weather Prediction Task.

Models	P(M)	P(M|data)	BF_M	BF_{10}	Error%
Null model (incl. age, sex, subject)	0.20	3.85e-56	1.54e-55	1.00	
Block	0.20	0.75	12.20	1.96e+55	6.50
Block + group	0.20	0.24	1.29	6.34e+54	7.67
Block + group + Block * group	0.20	3.00e-3	0.01	7.79e+52	11.62
Group	0.20	1.09e-56	4.37e-56	0.28	5.55

Note. All models include age, sex, subject. The Bayes' factor (BF_{10}) determines how well the alternative models predict the observed data compared to the null model that the response time across blocks is unaffected by block number and group (OCD vs. healthy controls). P(M) is the assumed probability of each model prior to the analyses (we assumed equal probabilities). P(M|data) is the updated probabilities given the experimental data from WPT. BF_M shows how much the data changed the prior probabilities. BF_{10} shows the Bayes' factor for each hypothesis relative to the null hypothesis.

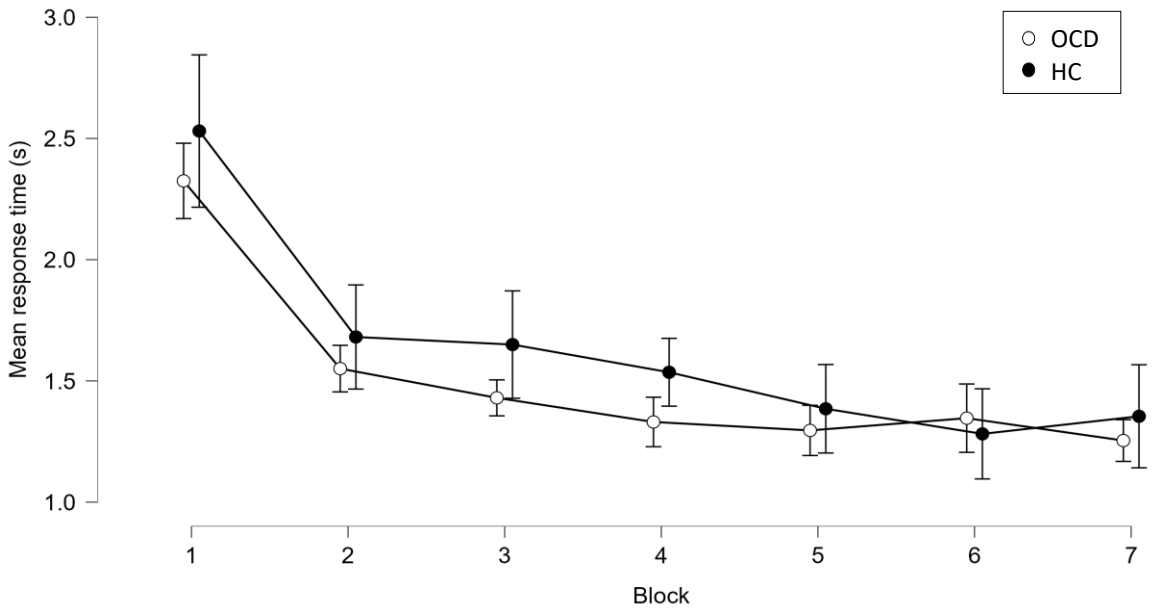

Figure 3. Response time as a function of block number. The plot shows the average response time in seconds from cue-card presentation until response in each block of 50 trials with 95% credible intervals (i.e., the range that contains the true value with a 95% probability, given the observed data). Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder.

Table 4. Evaluation of cue-outcome awareness.

Question	Proportion of correct responses		Predictive model	BF_{10}
	OCD group	Healthy controls		
Number of cards	0.79	0.90	OCD = HC	1.00
			OCD < HC	1.47
			OCD > HC	0.24
Best predictor of sun	0.64	0.71		
			OCD = HC	1.00
			OCD < HC	0.71
			OCD > HC	0.26
Best predictor of rain	0.79	0.84		
			OCD = HC	1.00
			OCD < HC	0.65
			OCD > HC	0.36

Note. The effect of group on the proportion of correct responses was assessed with a Bayesian A/B test, testing the predictive power of three competing models: the null-model (OCD = HC) and the two alternative models (the proportion of correct responses is lower in the OCD group, OCD < HC; the proportion of correct responses is higher in the OCD group, OCD > HC). The full questions in the cue-outcome questionnaire were: How many different cards were in the test? Which card was the best predictor of sun? Which card was the best predictor of rain? Four options were given for each question. Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder.

Co-authorship declarations

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	Camilla Funch Uhre
E-mail	Camilla.funch.uhre@regionh.dk
Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

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: 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. 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	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	C
6. Interpretation of the results	C
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] CFU and VFU are co-first authors of the manuscript and both were involved in all aspects of the study from the initial conceptualization to the data analyses, writing and finalisation of the manuscript. CFU drafted the protocol for the review, independently screened all records from the systematic search and extracted data from all eligible trial papers, and contacted trial authors to obtain additional data when relevant.	

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.	Valdemar Funch Uhre, tentative title: Psychological and Neurobiological Perspectives on Pediatric Obsessive-Compulsive Disorder (thesis in preparation, not yet submitted)
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.	CFU and VFU are co-first authors on the manuscript and contributed equally to the work, with few exceptions – CFU contributed more to the formulation/preparation of the work (e.g. drafted the protocol for the review) and data collection from trial authors, whereas VFU contributed more to development of methods and the data analyses.

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
1.	13.3.2022	Valdemar Funch Uhre	MSc	
2.	13.03.2022	Nicole Nadine Lønfeldt	MSc, PhD	
3.	11.3.2022	Linea Pretzmann	MSc	
4.	12/3 2022	Signe Vangkilde	MSc, PhD	
5.	11/3/2022	Kerstin Jessica Plessen	MD, PhD,	
6.	11/3 2022	Christian Gluud	MD, DrMedSci	
7.	11.3.2022	Janus Christian Jakobsen	MD, PhD	
8.	11.3.2022	Anne Katrine Pagsberg	MD, PhD	
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: 13.3.2022

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: 18.3.2022

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	Camilla Funch Uhre
E-mail	Camilla.funch.uhre@regionh.dk
Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

2. The declaration applies to the following article	
Title of article	Subtle and selective neurocognitive impairment in children and adolescents with obsessive-compulsive disorder
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 25.2.2022	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	C

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3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	C
5. Conducting the analysis of data	A
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] CFU contributed considerably to formulation of aims and methods (including selection of the test battery and outcomes) and to recruitment and data collection (clinical assessments and neurocognitive assessments). CFU cleaned and curated the data and conducted the analyses of clinical and neurocognitive data. CFU wrote the manuscript, revised it after feedback from supervisors and other co-authors, 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.	15.3.2022	Valdemar Funch Uhre	MSc	

5. Signatures of the co-authors[iii]				
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3.	13.03.2022	Nicole Nadine Lønfeldt	MSc, PhD	
4.	15.3.2022	Anne Dorothee Müller	MSc	
5.	15.3.2022	Kerstin Jessica Plessen	MD, PhD	
6.	12/3 2022	Signe Vangkilde	MSc, PhD	
7.	15.3.2022	Anne Katrine Pagsberg	MD, PhD	
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: 15.3.2022
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: 18.3.2022

PhD student:

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Name of PhD student	Camilla Funch Uhre
E-mail	Camilla.funch.uhre@regionh.dk
Name of principal supervisor	Anne Katrine Pagsberg
Title of the PhD thesis	Neurocognitive functioning in children and adolescents with obsessive-compulsive disorder

2. The declaration applies to the following article	
Title of article	Probabilistic learning and decision-making appear intact in children and adolescents with obsessive-compulsive disorder
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**
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2. Development of the key methods	B

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5. Conducting the analysis of data	A
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] CFU contributed considerably to formulation of aims/scientific problem. CFU designed parts of the experimental task which was coded by the second author (e.g., task stimuli and questionnaire), and contributed considerably to recruitment/data collection. CFU cleaned and curated the data and conducted the analyses of clinical and neurocognitive data. CFU wrote the manuscript and revised it after feedback from supervisors and other 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]				
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5. Signatures of the co-authors[iii]				
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3.	11.3.2022	Melanie Ritter	MSc	
4.	11.3.2022	Linea Pretzmann	MSc	
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8.	11.3.2022	Kerstin Jessica Plessen	MD, PhD	
9.	11.3.2022	Anne Katrine Pagsberg	MD, PhD	anne katrine pagsberg
10.	12/3 2022	Signe Vangkilde	MSc, PhD	

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: 13.3.2022

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: 18.3.2022

PhD student:

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