A STUDY OF NEUROCOGNITION IN OCD-AFFECTED YOUTH, AT-RISK SIBLINGS,

AND HEALTHY CONTROLS

by

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Abstract

OCD is a neuropsychiatric illness that often begins in childhood, has significant impact on family, academic, occupational, and social functioning. OCD has complex genetic underpinnings, with a 10-fold increased risk among siblings of OCD-affected youth. Attempts to identify OCD vulnerability contributory genes have had suboptimal results partially due to the heterogeneous nature of OCD that prevents the differentiation of external symptoms in genetically homogenous subgroups. Although genetic influences are greater in childhood-onset OCD, most studies have used adult samples. There is increasing interest in determining intermediate markers of brain dysfunction (endophenotypes) that are associated with vulnerability for OCD through neurocognitive assessment.

This study examined neurocognition in OCD-affected youth (N=29), in comparison to their siblings (N=18), and healthy controls (N=31), in the areas of executive function, attention, visual memory, intelligence, state anxiety, and OCD symptom severity. It was hypothesized that OCD-affected youth and their siblings would have lower performance on all neurocognitive tasks in comparison to healthy controls, with the exception of attention and visual memory. Only the OCD group would present with behaviour challenges associated with executive dysfunction. There would be no relationship between symptom severity and test performance and state anxiety and test performance in the sample. Analysis of covariance (ANCOVA) and mixed model ANCOVA with family membership as a random factor were used to assess group effects on the outcome variables.

OCD-identified youth presented with significant deficits in planning and daily behaviour associated with executive dysfunction in comparison to healthy controls. Siblings demonstrated poorer decision-making when compared to OCD and healthy control participants. No significant

group differences were found in other examined neurocognitive areas. Symptom severity was not associated with neurocognitive performance of OCD-affected youth, whereas high state anxiety was associated with poorer decision-making across all groups.

Impaired planning has been implicated as a potential endophenotype in OCD, similar to previous adult studies. This study contributes to the limited research on neurocognitive functioning of OCD-affected youth and their siblings, increases awareness about neurocognitive deficits in OCD, and provides information for the advancement in school and clinical interventions and early identification of those at risk for developing OCD.

Preface

This work was conducted through Dr. Evelyn Stewart's lab at the Child and Family Research Institute (CFRI) under the supervision of Dr. Lynn Miller and Dr. Evelyn Stewart. I was responsible for study design, data collection, data analysis, and manuscript writing. I also conducted the majority of the assessments, wrote all the assessment feedback reports, and met with the participants' parents to debrief the results of the assessment.

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List of Abbreviations

Abbreviation	Full Name
ADIS-P	*Anxiety Disorders Interview Schedule, Parent Form* (Silverman & Albano, 1996)
ADHD	Attention-Deficit/Hyperactivity Disorder
AICC	Akaike's Information Criteria (corrected)
BCCH	British Columbia Children's Hospital
BRIEF	*Behavior Rating Inventory of Executive Function* (Gioia et al., 2001)
CANTAB	*Cambridge Neuropsychological Test Automated Battery* (Cambridge Cognition, 2013a).
Subtests	
IED	Intra-Extra Dimensional Set Shift
IST	Information Sampling Task
SOC	Stockings of Cambridge
SST	Stop Signal Task
SWM	Spatial Working Memory
RVP	Rapid Visual Information Processing
SRM	Spatial Recognition Memory
CBT	Cognitive Behaviour Therapy
CFRI	Child and Family Research Institute
CY-BOCS/YBOCS	*Children's Yale-Brown Obsessive Compulsive Scale (*Scahill et al., 1997) / *Yale-Brown Obsessive Compulsive Scale* (Goodman, et al., 1989)
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (APA, 2000)
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (APA, 2013)
EF	Executive Function
GEC	*Global Executive Composite*
HC	Healthy Control
ICD-10	*International Statistical Classification of Diseases and Related Health Problems 10th Revision* (World Health Organization, 2010)
MANCOVA	Multivariate analysis of variance with covariates
MLE	Maximum Likelihood Estimation
OCD	Obsessive-Compulsive Disorder
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus infections
REML	Restricted Estimation of Maximum Likelihood
SIB	Genetically At-Risk Siblings
SSRI	Selective serotonin reuptake inhibitor
STAI/STAI-C	*State-Trait Anxiety Inventory, Form Y* (Spielberger, 1973)/ *State-Trait Anxiety Inventory for Children* (Spielberger, 1983)

Abbreviation	Full Name
State anxiety	Performance based on *STAI* or *STAI-C* scores
WASI-II	*Wechsler Abbreviated Scale of Intelligence – Second*
Index	*Edition* (Wechsler, 2011)
FSIQ	Full Scale Intelligence Quotient

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Dedication

I dedicate my dissertation study to my *amado* husband, Donat, who has supported every step of

my personal, academic, and professional development throughout graduate school, and to my

soon-to-be born daughter who had the closest experience one could have in the completion of

this research project.

Chapter 1: Introduction

Obsessive-Compulsive Disorder (OCD) is a prevalent and debilitating illness

characterized by obsessions and/or compulsions that are time-consuming and cause significant

distress or impairment in one's functioning (American Psychiatric Association [APA], 2013a).

OCD affects 1-3% of the general population (Weissman et al., 1994), and the World Health

Organization has identified OCD as one of the top 10 leading causes of global disability (Ayuso-

Mateos, 2006). OCD often begins in childhood, and genetic and family studies suggest that early

onset increases familial risk of developing the disorder, with a 10-fold increased risk among

siblings of OCD-affected youth (Hanna, Himle, Curtis, & Gillespie, 2005). Evidence from twin

studies suggests that genes play a major role in the onset of this disorder (van Grootheest, Cath,

Beekman, & Boomsma, 2005). Although no specific genes associated with OCD have been

consistently identified (Stewart et al., 2012), researchers agree that OCD is characterized by

phenotypic heterogeneity described via "dimensional phenotypes" (Geller, Faro, Brown, & Levy,

2012). At this point, there are no specific biological tests to determine genetic risk or to diagnose

OCD. There is a need to better understand the systems-level brain function and organization

among those affected by OCD to determine whether pathology is heritable at the systems-level

(Chamberlain & Menzies, 2009). In addition to neuroimaging measurement, neuropsychological

evaluation has been utilized in an attempt to elucidate pathology.

Preliminary evidence suggests that youth with OCD exhibit neurocognitive impairment

across different subdomains (Andres et al., 2007; Ornstein, Arnold, Manassis, Mendlowitz, &

Schachar, 2010; Shin et al., 2008). Differences in brain functioning in those with OCD may be a

direct contributor to the observed functional impairment across diverse settings, including home,

school, and community (Piacentini et al., 2003; Sukhodolsky et al., 2005). The primary purpose

of this study was to rigorously investigate neurocognitive functioning in youth with OCD, as a means to increase awareness about neurocognitive deficits in OCD and to gain a better understanding of potential heritability of neuropsychological traits in OCD. Neurocognitive functioning was assessed in OCD-affected youth, their unaffected siblings, and healthy controls, via standardized performance measures and rating scales. The following review highlights the characteristics and developmental course of OCD, summarizes the impact of OCD on an individual's functioning, discusses biological and cognitive-behavioural models used to explain this disorder, describes the neurocognitive characteristics of OCD, and provides a rationale for conducting the present study.

Characteristics of OCD

OCD is a neuropsychiatric condition characterized by the presence of obsessions and/or compulsions that cause significant distress or impairment in daily functioning, as affected individuals tend to spend significant amounts of time (greater than one hour per day) engaged in obsessive and/or compulsive behaviours (APA, 2013a). According to the American Psychiatric Association [APA] (2013a), most individuals with OCD have both obsessions and compulsions. Obsessions are defined as unwanted, intrusive, and repetitive thoughts, images, or urges related to themes such as contamination, symmetry, aggression, sex, religion or scrupulosity, harm, illness, perfectionism, and incompleteness (e.g., "just so"). Compulsions are repetitive behaviours or mental acts that are performed according to rigid rules and serve as coping mechanisms to temporarily neutralize and alleviate anxiety or distress. Typical compulsions include washing/cleaning, ordering or arranging, touching, checking, repeating as well as performing mental rituals such as counting, praying, or repeating words silently. While compulsions tend to be performed to reduce the distress caused by the obsessions or to prevent feared events, they are either unconnected to the feared events in a realistic way or they are

clearly excessive (APA, 2013a). Most individuals with OCD recognize at some point in their lives that their OCD-related beliefs and actions are unreasonable or not true. However, it has been reported that between 15 and 30% of OCD-affected individuals are unable to make this realization (Catapano et al., 2010). In the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] (APA, 2013a), one's level of insight is specified according to "good or fair insight," "poor insight", or "absent insight/delusional beliefs" (p. 237). It is important to note that the new DSM-5 has eliminated OCD from the Anxiety Disorder diagnostic category and included it in a new classification category, entitled 'Obsessive-Compulsive and Related Disorders'. This change is based on evidence that the following disorders are associated with one another in terms of diagnostic validator and treatment approaches: OCD, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder Due to Another Medical Condition, Other Specified Obsessive-Compulsive and Related Disorder, and Unspecified Obsessive-Compulsive and Related Disorder (APA, 2013a). Table 1 provides information about the DSM-5 diagnostic criteria for OCD. Controversy remains with respect to the validity of diagnostic categories that are based solely upon clinical observation (Insel, 2013). The importance of examining less subjective aspects of brain functioning, such as neurocognitive performance, within psychiatrically ill populations has been increasingly recognized (National Institute of Mental Health [NIMH], 2011).

Table 1. DSM-5 Diagnostic Criteria for OCD (APA, 2013a, p. 237)

OCD Diagnostic Criteria
Obsessions are defined by (1) and (2): 1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety and distress.

2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsion are defined by (1) and (2):

1. Repetitive behaviours (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels drive to perform in response to an obsession or according to rules that must be applied rigidly.

2. The behaviours or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

Note: Young children may not be able to articulate the aims of these behaviours or mental acts.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking disorder]; stereotypies, as in stereotypic movement disorder; ritualized eating behaviour, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having a illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulsive-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behaviour, as in autism spectrum disorder).

Specify if:

With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:

Tic-related: The individual has a current or past history of a tic disorder.

Developmental Course of OCD

OCD affects 1-3% of the general population and can onset throughout the lifespan, ranging between preschool age and adulthood (typically by age 40; Karno, Golding, Sorenson, & Burnam, 1988; Kessler et al., 2005; Merikangas, Nakamura, & Kessler, 2009). Before diagnosing OCD in young children, it is important to discriminate age-appropriate repetitive behaviours from pathological symptoms. The majority of children present with typical age-dependent repetitive and superstitious behaviours related to mastery and control of key developmental transitions during early childhood that disappear by adolescence (for review see Leonard, Goldberger, Rapoport, Cheslow, & Swedo, 1990; March & Mulle, 1998). For example, while young children typically display behaviours involving bedtime rituals and childhood games as a means to master separation anxiety, such behaviours are often replaced in middle childhood by focused interest, hobbies, or collecting (Adams & Burke 1999; Leonard et al., 1990; March & Mulle, 1998). In contrast, OCD-related behaviours are perceived as excessive or persisting beyond developmental appropriate periods (APA, 2013a), and result in dysfunction rather than mastery of important developmental transitions (March & Mulle, 1998). Typically, when such rituals are interrupted, children with OCD become significantly distressed causing impairment in family functioning (Stewart et al., 2011). According to Leonard et al. (1990), what differentiates obsessive-compulsive age-dependent behaviours from OCD is the time that these behaviours occur and the content and severity of the obsessions and compulsions. The exception to this rule occurs when OCD-like behaviours overlap with culturally dependent beliefs, such as religious responsibilities or appropriate cleanliness expectations (March & Mulle, 1998).

Although the onset of OCD is relatively common during childhood and adolescence, and a significant number of adult patients report that the onset of their OCD occurred at an early age (Presta et al., 2003). OCD tends to be clinically recognized in individuals several years after it

begins (Fireman, Koran, Leventhal, & Jacobsen, 2001). Geller and colleagues (1998) reviewed 11 studies on childhood-onset OCD and indicated that while the mean age of onset in children and youth was 10.3 years, the mean age of accurate diagnosis was 13.2 years, pointing to a nearly 3-year lag between onset and proper identification. Childhood-onset OCD is marked by male predominance, with a 3:2 male to female ratio before puberty, a ratio that evens out by middle childhood (Albano, Chorpita, & Barlow, 2003). Evidence also suggests that a significant proportion of childhood-onset symptoms remit over time (Stewart et al., 2004). In contrast, studies conducted with adults report a mean age at onset of 21 years (Karno et al., 1988), without gender differences in distribution. According to Pinto et al. (2006), there is a lag of approximately 17 years between the onset of obsessive and compulsive first symptoms and one's access to first treatment, and an 11-year gap between meeting diagnostic criteria for OCD and receiving treatment for the first time. Geller (2006) concludes that the distribution of incidence of OCD has two peaks: one in childhood and another in early adulthood. Despite the increasing awareness of its detrimental impact, OCD in children is often overlooked and, consequently, undiagnosed (Fireman et al., 2001). Some reasons contributing to the fact that OCD tends to be under-recognized, under-diagnosed, and under-treated in youth include poor insight or secretiveness about one's illness, evolution of symptoms combined with developmental challenges over time, lack of trained healthcare providers in OCD symptom identification and appropriate treatment, and limited access to treatment resources (Geller et al., 2012; March & Mulle, 1998).

OCD Impact on Functioning

Evidence suggests that OCD symptoms have significant impact not only on family relationships, but also on academic and occupational performance, and socialization (Hollander et al., 1998). Geller and colleagues (1998) reviewed 67 articles on childhood-onset OCD and

reported that many studies determined that children with OCD face significant challenges at school, including school avoidance, school refusal, and limited academic performance. It has been suggested that students with OCD tend to perform significantly below their academic potential (Parker & Stewart, 1994) partially due to the interference of OCD symptoms with concentration and productivity (APA, 2000). There is a lack of research on the effects of OCD symptomology on psychosocial functioning in children and youth (Piacentini Bergman, Keller, & McCracken, 2003; Valderhaug & Ivarsson, 2005). To address this issue, Piacentini and colleagues (2003) conducted a study with 151 children with OCD (mean age 11.8 years) and their primary caregivers. Subjects were asked to complete a questionnaire regarding the impact of OCD on three functional domains, including social, home/family, and academic/school functioning. Results suggested that approximately 90% of the children with OCD described at least one area that was significantly impacted by OCD symptoms, and nearly half of the sample reported substantial impairments in each of the three functional domains assessed. Overall, concentration while doing schoolwork and completion of homework were the two most commonly endorsed problematic areas by both groups. There was also a wide range of specific functional impairments reported by the subjects, which is consistent with the heterogeneity of OCD. It is possible that OCD-affected students may have difficulty with tasks that require attention (e.g., concentration and homework completion) due to their tendency to process task-irrelevant information related to threat (i.e., attention bias) rather than focus on the task at hand (Muller & Robert, 2004).

While school functioning challenges have been traditionally explained as a secondary effect of OCD symptoms and their associated distractions, it is quite possible that neurocognitive deficits may contribute to suboptimal performance. There is a need to better understand the

impact of OCD on school functioning through the exploration of academic and cognitive skills in youth with OCD. To begin to address this need, the hypothesis that OCD-affected youth have neuropsychological impairments that may underlie academic challenges (Andres et al., 2007) is further investigated in this dissertation study.

Students with OCD may also exhibit deficits in social functioning (Adam & Burke, 1999). Friendships and interpersonal skills are often negatively affected by difficulties with processing social-emotional information (Adams, 2004; Adams & Burke, 1999). Social information processing deficits have been associated with executive dysfunction and can be perceived as age-inappropriate emotional responses and behavioural actions (Anderson, 2002). Children with executive function difficulty may have challenges regulating their mood, affect, initiative, energy level, and moral and social behaviour. For example, they may ask embarrassing questions, make hurtful statements, and ignore social rules and conventions. As a result, their interpersonal skills and ability to maintain meaningful social relationships may be significantly impacted (Anderson, 2002).

Difficulty with peer relationships in OCD-affected youth may also be a consequence of bullying or peer victimization. Youth with OCD are frequently bullied or victimized at school due to their compulsive behaviours (Storch et al., 2006). Attempts to hide their compulsions from peers and to avoid triggers for their obsessions or escape bullies may contribute to their limited friendship networks, thereby increasing social isolation (Leininger, Dyches, Prater, Heath, & Bascom, 2007). Co-occurring diagnosis with ADHD or oppositional defiance disorder (ODD) may further complicate OCD-affected youth's behavioural and academic functioning (Adams, Smith, Bolt, & Nolten, 2007).

Given the significant challenges that youth with OCD experience at school, school-based accommodations and/or modifications and special education or related services may be necessary to promote youth's successful educational functioning (Adams et al., 2007). While there is a very limited number of professionals well trained in schools to support the needs of OCD-affected students (Sloman, Gallant, & Storch, 2007), "school psychologists are uniquely positioned to facilitate the identification of youth with OCD and provide appropriate services by facilitating early identification and formulating healthy consultative relationships with school staff in efforts to inform and train teachers, counselors, and parents about OCD symptoms" (p. 301). Evidence indicates that many school psychologists have limited knowledge about assessment and treatment of OCD-affected youth (Gallant et al., 2006, unpublished, cited in Sloman et al., 2007). The strong connection between students' mental health and optimal learning outcomes (Becker & Luthar, 2002) further emphasizes the need for school psychologists to implement interventions that promote mental health of OCD-affected youth (Adams et al., 2007).

Currently, there is no cure for OCD. While pharmacological and cognitive-behavioural treatments have shown to be effective to treat the disorder, OCD symptoms in childhood-onset may persist in 41% of the cases (Stewart et al., 2004). Rasmussen and Eisen's (2002) review of the course and clinical features of OCD indicates that 85% of patients have persistent symptoms that vary in content, intensity, and frequency overtime. Thus, there is a need to recognize and treat OCD early due to its persistent course, significant associated impairments in social, academic, and occupational functioning, and considerable social and economic burden (Chamberlain & Menzies, 2009; Stewart et al., 2004). Untreated OCD in adults has been associated with higher rates of unemployment, less work productivity, adverse effects upon

family members, and lower rates of marriage (for review see Fireman et al., 2001). Demonstrating this, the World Health Organization (WHO) Global Burden of Disease 2000 study identified OCD as a leading global cause of non-fatal illness burden in the world, accounting for 2.5% of total global Years Lived with Disability (YLD; Ayuso-Mateos, 2006). Thus, it is critical to identify OCD early and to introduce intervention during the school years to prevent further deleterious effects in adulthood.

Heterogeneity of OCD

Significant variability in OCD symptom presentation and an ongoing debate regarding its unitary versus multidimensional nature have been stressed in the literature. Its diagnostic criteria are defined by the *DSM-5* (APA, 2013a) and the *International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10]* (World Health Organization, 2010*)*. These guidelines are relatively arbitrary and subjective, suggesting that OCD is a unitary nosological entity (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008), and that OCD diagnosis is based on subjective interpretation of the criteria (Chamberlain & Menzies, 2012).

Empirical consensus indicates that OCD-affected individuals exhibit diverse symptoms, providing evidence that OCD is rather a clinically heterogeneous condition characterized by at least four factor dimensions (Mataix-Cols, Pertusa, & Leckman, 2007). To investigate the hypothesis of a multidimensional model of OCD, several studies have been conducted over the two past decades. Results from meta-analyses of the symptom structure of OCD in adult populations point to four main factors associated with the disorder, including (a) symmetry: symmetry obsessions and ordering, repeating, and counting compulsions; (b) forbidden thoughts: aggression, religious, sexual, and somatic obsessions and checking compulsions, (c) cleaning: contamination obsessions and cleaning compulsions, and (d) hoarding: hoarding obsessions and

compulsions (for review see Bloch et al., 2008; Mataix-Cols, Rosario-Campos, & Leckman, 2005). When determining the factor structure of OCD in pediatric populations, evidence suggests a similar four-factor structure to that involving adults only, with differences only related to checking compulsions (which loaded highest on the symmetry factor) and somatic obsessions (which loaded highest on the cleaning factor; Bloch et al., 2008). In general, a four-factor structure of OCD symptoms is expressed across lifespan age groups (i.e., children, adolescents, and adults; Stewart et al., 2008). In the DSM-5, the chapter on Obsessive-Compulsive and Related Disorders includes a description of a similar four-factor dimension (i.e., cleaning, symmetry, forbidden or taboo thoughts, and harm), and acknowledges that some individuals present with hoarding behaviours as a result of obsessions and compulsions associated with fears of hurting others (APA, 2013a).

OCD often co-occurs with other psychiatric disorders. Based on Stewart et al.'s (2004) review of the literature on the long-term outcome of childhood-onset OCD, comorbid disorders that most frequently accompany OCD in youth include mood disorders (9–66%), anxiety disorders (10–54%), tic disorders and Tourette syndrome (9–59%), disruptive behavior disorders (20–30%) and developmental/personality disorders (12–68%). The authors note, however, that not all studies reviewed reported the types and rates of comorbid diagnoses, which could have been a consequence of exclusion criteria in the reviewed studies. Findings from this review suggest that comorbid psychiatric conditions might predict the severity, persistence, treatment outcome, and global functioning in OCD-affected youth.

Evidence supports high rates of comorbidity between childhood-onset OCD and attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, and tic disorders (for review see Geller et al., 2012). Based on findings from twin studies, it is hypothesized that some

components of these three disorders may be genetically linked to childhood-onset OCD. Thus, a genetic susceptibility for these disorders would result in overlapping neurologically mediated behaviours. It has been suggested that the comorbidity between OCD and ADHD, Tourette syndrome, and tic disorders may represent a distinct familial subtype that can guide genetic studies as well as clinical studies aimed at improving treatment responses and outcomes. It is possible that neurocognitive deficits in these comorbidities may partially account for deficits observed in OCD-affected youth (Hanna et al., 2002). Thus, it may be difficult to determine whether neurocognitive impairments derive from one disorder or another in individuals with OCD-ADHD/Tourette syndrome/tic disorders comorbidity.

Models of OCD

To best understand OCD, combining components of several OCD models based on biology and cognitive-behavioural characteristics may provide evidence that cognition and behaviour play a role in biological systems, helping explain how biology affects learning. Based on family, genetic, neuroimaging, and efficacy of pharmacotherapy studies (Decloedt & Stein, 2012), a combination of complex neurobiological, neurochemical, and genetic factors contribute to the onset, development, and severity of the disorder, which have been associated with cognitive and behavioural responses (Murphy, Stewart, & Obregon, in press).

Neurobiological abnormalities in the cortical-striatal-thalamic circuit and disruption in neurotransmitters (i.e., glutamaergic, serotonergic, and dopaminergic systems) have shown to play a crucial role in the etiology and course of OCD (Rosenberg, MacMaster, Mirza, Easter, & Buhagiar, 2007; Wu et al., 2013), and to be associated with neurocognitive dysfunction (Andres et al., 2007; Ornstein et al., 2010; Shin et al., 2008). Review of the literature on neurobiological studies conducted with OCD-affected youth (MacMaster, O'Neill, & Rosenberg, 2008) indicates that when compared to healthy controls, youth with OCD present with significantly greater gray

matter density in the orbital frontal cortex (associated with emotion regulation and social behaviour) and in the anterior cingulate (associated with cognitive and affective/motivational processing; Zillmer et al., 2008). At the subcortical level, youth with OCD have been found to have significantly smaller striatal volumes than healthy controls (Rosenberg et al., 1997), which were inversely correlated with OCD symptom severity but not illness duration. The striatum is embedded in the basal ganglia and associated with control of movement and support of higher-order cognitive functions (Zillmer Spiers, & Culbertson, 2008). Some studies indicate that OCD symptoms may arise or be aggravated as a consequence of streptococcal infection, which is caused by inflammation to the basal ganglia thought to be triggered by antistreptococcal antibodies (i.e., Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus infections [PANDAS]; da Rocha et al., 2008; March & Mulle, 1998).

To specify the neural correlates of higher-order cognitive deficits in OCD, functional magnetic resonance imaging (fMRI) experiments have been conducted using a cognitive activation paradigm. Results of such studies indicate that both OCD-affected youth and adults exhibit decreased frontal-striatal activation, which has been associated with OCD participants' poorer performance on a set-shifting task in comparison to healthy controls (Britton et al., 2010; Gu et al., 2008). These findings point to the effect of an imbalance between the dorsal and ventral frontal-striatal circuits on OCD-affect individuals' cognitive flexibility. Abnormalities in the glutamate system have also been associated with OCD (Griest, Jefferson, Kobak, Katzelnick, & Serlin, 1995), as imaging studies suggest that cortical-striatal-thalamic-cortical (CSTC) abnormalities in OCD patients may be related to frontocortical hyperglutamatergic dysfunction (Alonso et al., 2012). Some preliminary data have also linked glutamate transporter genes to the disorder (Stewart et al., 2007). Finally, as selective serotonin reuptake inhibitors (SSRIs) are the

most commonly used medication-class to treat OCD, dysregulation in the brain's serotonin system has been related to OCD and associated with deficits in decision-making processes (Homberg, 2012).

In addition to the frontal-striatal-thalamic model of OCD, other brain regions, such as the corpus callosum, the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, and the pituitary gland have been implicated in childhood-onset OCD (for review see MacMaster et al., 2008). Findings from a meta-analysis on gray matter alterations in OCD indicated no significant differences between youth and adult subjects and pointed to significant differences in grey matter density in the parieto-frontal areas (i.e., significantly lower density) and the basal ganglia (i.e., significantly higher density) between OCD patients and healthy controls (Rotge et al., 2010).

Overall, review of neuroimaging studies in OCD indicates that while structural neuroimaging findings have been inconsistent, functional neuroimaging research provides strong support for developmental brain abnormality and the CSTC circuitry alteration that may affect emotion processing and cognitive functions in youth and adults with OCD (Murphy et al., in press). Based on evidence supporting a biological basis of OCD, brain imaging is considered a valuable tool to study OCD. A combination of neuroimaging and neurocognitive testing may provide a more comprehensive picture of how the structure and function of the brain of OCD-identified individuals affect behaviour (Chamberlain & Menzies, 2009).

Moreover, evidence supports a moderate to strong genetic influence in OCD depending on the age of onset. Estimates of heritability for OCD symptoms range between 27% and 47% in adult samples, and 45% and 65% in pediatric populations (Abramowitz, Taylor, & McKay, 2009; van Grootheest et al., 2005). Twin studies of adults with OCD suggest that environmental factors have a significant contribution to adulthood-onset, whereas genes appear to be the main

contributors to the disorder in pediatric populations (van Grootheest et al., 2005; 2007). Review of family studies conducted with children and adolescents with OCD support the argument that approximately 50% of OCD and subclinical OCD cases are familial (Pauls, 2012). The prevalence of OCD within families ascertained through childhood-onset (i.e., 10-fold higher than controls and/or the population prevalence) is also significantly higher than the adult-onset counterpart (i.e., 2-fold higher than controls and/or the population prevalence; Pauls, 2012). A recent article written by researchers at the International OCD Foundation Genetics Collaborative (IOCDF-GC; Stewart et al., 2012) indicated that solid evidence points to an estimate of four- to ten-fold increase in risk of developing OCD among first-degree relatives of adults and youth with OCD, respectively, in comparison to relatives of healthy controls, suggesting that potential gene variants may contribute to risk for OCD.

An increasing number of studies on endophenotypes have been conducted with psychiatric populations to help identify markers in genetics (Gottesman & Gould, 2003). According to Gottesman and Gould (2003), endophenotypes are markers of brain dysfunction that are (a) associated with illness in the population, (b) heritable, (c) state-independent, as they manifest in individuals whether or not the illness is active, (d) in families, co-segregate with the illness, and (e) found among unaffected family members at a higher rate than in the general population. While the presence of an endophenotype does not necessarily result in the expression of the disease itself, investigating endophenotypes has promising utility, especially in detecting those individuals at risk before the disorder develops. Understanding vulnerability and resiliency in OCD may be key to deconstructing the brain and its mechanisms into more manageable and understandable markers that can be associated with genes, and potentially helping differentiate diagnostic classification of disorders presented with similar behaviours (Chamberlain &

Menzies, 2009; 2012). A review of the literature on endophenotypes in OCD is provided later in this paper. To conclude, biological models support developmental brain dysfunction and abnormalities of specific neurotransmitter systems in the CSTC circuitry that are implicated in emotional processing (e.g., dorsal striatum/medial prefrontal cortex) and cognitive functions (dorsolateral prefrontal cortical-parietal network, orbitofrontal, anterior cingulate corticies). Genes also contribute to the disorder.

Different cognitive-behavioural models have been developed over the years in an effort to explain psychological processes in OCD that can also provide insight into the associations between obsessive and compulsive behaviour and neurocognitive dysfunction. In a review of these models, Shafran (2005) identified five major theories: (a) Salkovskis' cognitive-behavioural theory of OCD (Salkovskis, 1985), (b) Rachman's cognitive theory of obsessions (Rachman, 1997), (c) Purdon and Clark's cognitive theory emphasizing the importance of thought control (Purdon & Clark, 1999), (d) Jones and Menzies' cognitive-behavioural model emphasizing danger expectancies (Jones & Menzies, 1997), and (e) Rachman's cognitive theory of compulsive checking (Rachman, 2002). Shafran (2005) emphasized that such models presented with more similar than different characteristics, especially related to the idea that obsessions arise from evaluation of otherwise normal intrusive thoughts, images, and urges as highly meaningful or threatening. These appraisals are considered the main cognitive process that leads to an increase in the intensity and frequency of obsessive intrusive thoughts. While most people experiencing intrusive thoughts would perceive such thoughts as unpleasant but meaningless events without harm-related implications, in individuals with OCD, these thoughts may evoke distress, prompt attempts to suppress or remove the unwanted intrusion, and efforts to prevent harmful events associated with the intrusion through compulsive rituals (Abramowitz et

al., 2009). According to cognitive-behavioural models of OCD, intrusive thoughts evolve into obsessions when they are perceived as highly significant or threatening, whereas compulsions become excessive and persistent when they are strengthened by immediate decrease in distress or temporary elimination of the unwanted thoughts. In addition, the presence of compulsive behaviours prevents individuals from learning that their appraisals are unrealistic, thus reinforcing the misguided belief that they are responsible for the threat (Shafran, 2005).

Although these five cognitive-behavioural models of OCD are supported by some empirical data, limitations of methods used, both via self-report questionnaires and controlled laboratory experiments, have prevented conclusions. For example, data derived from self-report questionnaires are subject to recall bias and often are cross-sectional, preventing the determination of causality. Likewise, results from self-reports regarding dysfunctional beliefs and misappraisal of intrusive thoughts are not characteristic of all cases of OCD, reflecting the disorder's heterogeneity (Abramowitz et al., 2009). In terms of experimental laboratory research, results may be considered artificial and lacking ecological validity due to the artificially controlled conditions where the studies are conducted (Shafran, 2005). Despite critiques, most of the more recent psychological approaches to treat OCD are based on cognitive-behavioural models with a common goal of changing biased cognitive processes as a means to reduce OCD symptoms (Shafran, 2005).

The abovementioned models suggest specific therapeutic approaches for treating OCD based on cognitive and behavioural strategies (Franklin, Goss, & March, 2012), that target obsessive and compulsive behaviours hypothesized to be mediated by neurocognitive deficits (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Isik Taner, Bakar, & Oner, 2011). The aim of cognitive-behavioural treatment (CBT) interventions is to modify

psychological processes, such as erroneous assumptions and automatic thoughts, to provide corrective information about both the world and obsessive fears, and to use response prevention strategies to disrupt self-perpetuating mechanisms (Rachman, 2002). While biological and genetic models strive to explain OCD from a structural and/or functional perspective, cognitive-behavioural conceptual models attempt to explain the disorder based on learning principles and cognitive processes (Shafran, 2005), emphasizing that changing maladaptive beliefs or dysfunctional behaviours may reduce OCD symptomology (Franklin et al., 2012). In particular, prolonged exposure to obsessional triggers and refraining from performing rituals (i.e., exposure and response prevention [ERP]) are an empirically supported behavioural intervention to treat OCD (Barrett et al., 2004; Bolton et al., 2008; Freeman et al., 2008; 2013; Franklin et al., 2012). ERPs may address potential deficits associated with neurocognition, including (a) difficulty suppressing repetitive behaviour (i.e., response inhibition), (b) difficulty changing repetitive behaviour based on environmental feedback (i.e., cognitive flexibility), (c) need to gather more information before making a decision or tendency to experience excessive uncertainty and doubt (i.e., decision-making), (d) selective and biased attention towards feared stimuli (i.e., attention), and (e) limited confidence in memory for actions (i.e., memory; Chamberlain & Menzies, 2012).

Based on findings from large-scale Randomized Control Trial (RCT) CBT studies (Pediatric OCD Treatment Study [POTS] Team, 2004) and meta-analyses (Barrett et al., March, 2004; Freeman et al., 2013), CBT is the first-line treatment recommended before medication for mild to moderate cases of childhood-onset OCD. Supporting this clinical approach, CBT alone has shown significantly higher remission rates than medication alone (O'Kearney, 2007). For moderate to severe cases of OCD-affected youth, a combination of both medication and CBT has demonstrated best outcomes (American Academy of Child and Adolescent Psychiatry, 2012),

with 54% of participants reaching full remission (POTS, 2004). Nonetheless, meta-analysis of long-term outcome studies for childhood-onset OCD suggests that symptoms may persist in 41% of the cases (Stewart et al., 2004), indicating suboptimal improvement from standard treatment approaches.

To conclude, biological and cognitive-behavioural models have attempted to explain the causes of and to develop treatment for OCD using different methods (i.e., medication versus CBT). Although such models have received support in the literature, they also present with key limitations. While biological models do not address symptom heterogeneity, cognitive-behavioural models do not provide a full explanation for the disorder either, making it difficult to clearly determine a unitary cause for OCD (Abramowitz et al., 2009). It seems clear that both biological and behavioural-cognitive theories are necessary to develop a comprehensive explanation for the disorder and to plan treatment.

Neurocognitive Characteristics in OCD

To better understand the relationship between brain functioning, cognition, and behaviour, it is important to consider how specific structures or functions of the brain relate to cognitions and result in particular behaviours. A growing number of studies have investigated neurocognitive characteristics of individuals with OCD. Due to the potential involvement of frontal-striatal systems in OCD, neuropsychological assessment focusing on executive functions (EFs), attention, memory, and visuo-spatial integration (Geller et al., 2006), has been recognized as a valuable approach to understanding the underlying neuroanatomical structures of the brain of OCD-affected individuals (Kuelz, Hohagen, & Voderholzer, 2004). Increased awareness about neurocognitive deficits in OCD, especially associated with EF, may help enhance treatment and school interventions that would improve youth with OCD's functioning across environments (Freeman et al., 2013).

Executive function. EF has been broadly defined and is considered an "umbrella term" that describes a number of inter-related complex cognitive processes associated with purposeful, goal-directed behaviours (Anderson, 2002; Baron, 2004; Guy, Isquith, & Gioia, 2004). EF helps individuals to guide and manage their cognitive functioning, emotional control, and behaviour, particularly during problem-solving tasks or in adapting to novel situations (Anderson, 2002; Dawson & Guare, 2004). Given its broad definition, a number of processes or subdomains have been associated with EF, including but not limited to planning, organization, strategy formation, cognitive flexibility, inhibition, working memory, decision-making, self-monitoring, goal-directed persistence, initiative, attentional control, anticipation, and volition (Anderson, 2002; Baron, 2004; Dawson & Guare, 2004; Singer & Bashir, 1999). EF is activated by novel or complex situations that require one's strategic planning, attentional control, temporal organization of strategies and behaviour, flexibility of thought and action, and monitoring to achieve long-term goals (Baron, 2004; Dawson & Guare, 2004; Lehto et al., 2003; Lezak, Howieson, & Loring, 2004). As a result, EF processes and skills are necessary for engaging in behaviours that are independent, purposeful, and self-serving (Baron, 2004). This includes selecting and achieving goals, developing problem-solving solutions, displaying socially appropriate behaviours and interactions, controlling emotions, and having adequate cognitive and academic development (Anderson, 2002; Lezak et al., 2004). EF is of great importance to the human functioning and has shown strong correlation to and to be predictive of academic achievement (Best, Miller, & Naglieri, 2011).

Issues with EF definition. Historically, issues related to the conceptualization and assessment of EF have interfered with its specific definition, including the interchangeable use of cognitive and anatomical constructs and terminology (i.e., EF and frontal lobe; Stuss &

Alexander, 2000). While EF was initially a synonym of frontal lobe functions, the current neurological center of EF is considered to be in the frontal and especially dorsolateral prefrontal cortex in addition to adjacent areas (e.g., basal ganglia; Baron, 2004). Impairment at any level of this neural system may result in deficits in one or more EF processes, affecting cognitive and/or emotional functioning. Impaired cognitive responses due to executive dysfunction may be expressed via poor impulse control and reasoning ability, difficulties in monitoring or regulating performance, limited use of feedback, lack of inhibition, and planning problems. Deficits in emotional responses and behaviour caused by EF impairment may be explained via negative mood, flat affect, low energy level, limited use of social rules and conventions, lack of initiative or motivation, impulsivity, and disruptive moral and social behaviour (Anderson, 2002; Gioia et al., 2001). A number of psychiatric disorders, such as OCD (Ornstein et al., 2010; Shin et al., 2008), ADHD (Barkley, 2003; Brown, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and autism spectrum disorders (Bishop, 1993; Wong, 2004), have been partially characterized by deficits in EF. Youth with executive dysfunction may display inflexible and rigid behaviour and have difficulty in learning from mistakes, in modifying previously learned behaviours, and in seamlessly dealing with change and transitions (Anderson, 2002).

Overall, debate continues as to whether EF is a unitary concept similar to general level of intelligence versus a complex group of inter-related but distinct processes (Lehto et al., 2003). Most researchers agree, however, that EF is responsible for management of the brain's cognitive functions, which promote the mechanism for self-regulation needed for purposeful, goal-directed behaviour (Anderson, 2002; Brown, 2006). In this dissertation study, EF is considered as a higher order multi-component construct that involves different inter-related domains, including cognitive flexibility, decision-making, planning, response inhibition, and working memory.

Development of EF. EF emerges in basic forms in young children, gradually becoming more complex as the brain matures throughout childhood, adolescence, and early adulthood (Brown, 2006). EF processes may follow different developmental trajectories (Anderson, 2002) and evolve in interaction with other cognitive domains (Dawson & Guare, 2004; Hongwanishkul, Happaney, Lee & Zelazo, 2005). Early in life, young children present with concrete, impulsive, stimulus-bound behaviours. As EF develops, children's problem solving, planning, self-monitoring, and self-regulation skills develop. Overall, EF processes are thought to mature at a similar rate during childhood for boys and girls (Anderson, 2002). However, evidence points to significant gender differences in test performance with males performing better on spatial and motor tasks, and females performing better on verbal, memory, and social cognition tasks (for review see Gur et al., 2012).

Genetic makeup as well as biological and social environments are also thought to influence the development of EF (Dawson & Guare, 2004; Hongwanishku et al., 2005). Biologically, EF has been associated with the prefrontal brain systems and its connections with posterior and subcortical regions (Dawson & Guare, 2004; Miller, 2007; Zelazo Müller, Frye, & Marcovitch, 2003; Zelazo, Craik, & Booth, 2004). Throughout childhood and adolescence, increasing myelination of the prefrontal connections in the brain network results in more rapid transmission of nerve impulses and subsequent progressive integration of cognitive processes with gradual improvement of EF (Anderson, 2002). As the prefrontal cortex and its connections mature into late adolescence, some EF processes develop later than others. For example, verbal reasoning and complex problem solving tasks are among the final EF domains to evolve (Lehto et al., 2003). A number of studies and review papers on the developmental trajectory of EF have been published in recent years (e.g., Anderson, 2002; Best & Miller, 2011; Miyake et al., 2000b;

Romine & Reynolds, 2005). With some discrepancies, it is generally agreed that EF first emerges in infancy, around 12 months, and that the other executive domains follow distinctive trajectory rates throughout the lifespan. Anderson (2002) suggested that a rapid growth in attentional control (e.g., selective attention, inhibition) occurs between birth and age 5 years, simultaneously with frontal cortex development. Cognitive flexibility, information processing (i.e., efficiency, fluency, and speed of processing), and goal setting (i.e., initiative, conceptual reasoning, planning, strategic organization) domains significantly improve between ages 7 and 9 years, and typically reach maturity by age 12 years. However, other executive processes, such as self-regulation and decision-making, may regress between ages 11 and 13 year due to a transitional period between evolving cognitive processes (Anderson, 2002), and then continue to develop throughout adolescence. Romine and Reynold's meta-analysis (2005) on frontal lobe functioning development suggested that, inhibition and cognitive flexibility do not significantly change after age 14 years, whereas planning and verbal fluency skills continue to develop into early adulthood. The authors stressed that the development of frontal functioning is intertwined with development of other related processes, including language, attention, memory, and emotion.

EF development is also influenced by social and environmental contexts. Children develop EF not only by learning from their own experiences, but also from being taught norms and given expectations on how EF processes should be used in adult life. Adults often shape children's behaviour by setting limits, providing cues, prompts, structure, and scaffolding (Dawson & Guare, 2004; Holmes Beremstein & Waber, 2007). Academically, children become increasingly successful as they learn how to regulate their behaviour in order to learn and meet academic expectations. According to Zelazo et al. (2004), EF develops in an inverted U-shape curve, with

age-related deterioration of some skills (e.g., working memory) that typically starts in late adulthood. Although researchers have not consistently explained why specific EF processes deteriorate over time, it has been suggested that the decline in other cognitive functions may negatively impact EF processes. It has alternatively been hypothesized that a reduced need for social acceptance may contribute to the observed decline in late life (Zelazo et al., 2004).

Challenges in the assessment of EF. Operationalizing the term "executive function" has been an ongoing challenge, resulting in methodological limitations such as the development of assessment tools with appropriate psychometric characteristics (Chan, Shum, Touloupoulou, & Chen, 2008; Wong, 2004). First, EF research, theory, and assessment have been primarily conducted with adult populations and downscaled to children (Baron, 2004; Wong, 2004). Consequently, most assessment tools are neither developmentally appropriate nor properly standardized for use with children and adolescents (Anderson et al., 2001; Baron, 2004; Strauss, Sherman, & Spreen, 2006). The development of EF measures for children has also been delayed because of the traditional neuropsychological perspective that the frontal lobes primarily mature in adolescence or early adulthood (Culbertson & Zillmer, 1998). More recent understanding suggests that EF processes can be assessed when they are partially developed but not fully functional (Anderson, 2002). Currently, a few assessment instruments developed for younger populations exist. Nonetheless, creating tasks that are age-appropriate across the developmental trajectory continues to be a significant challenge (Anderson, 2002; Baron, 2004). In particular, EF task instructions are usually complex, and children must have sufficient language skills to perform specific activities. Consequently, apparent EF deficits from these tasks may actually reflect verbal comprehension limitations and language barriers (Wong, 2004).

Second, given its broad definition, there is no consensus on which EF processes should be assessed. Most researchers agree, however, that EF tasks must be novel or complex for individuals performing them, and that information should be integrated through formulation of plans and strategies and monitoring of performance (Strauss et al., 2006). Because individuals have different experiences, it is difficult to develop a task that is novel or complex for everyone, thus threating the validity of EF tools (Anderson, 2002). Likewise, test-retest reliability of EF tasks tends to be lower than the normally acceptable levels for clinical use due to practice effects (e.g., tests can only be novel once; Strauss et al., 2006). In children, however, EF tasks tend to remain novel for longer periods of time (Wong, 2004).

Concerns with task impurity of EF measures are also acknowledged in the literature (Miyake et al., 2000a; Strauss et al., 2006). As EF tasks measure both executive and non-executive processes (e.g., EF operates on other cognitive processes such as memory and attention), it may be difficult to determine whether the source of failure derives from executive or other functions (Strauss et al., 2006). Because EF tasks require a simultaneous coordination of different processes, it is challenging to control non-EF processes related to specific task contexts (Miyake & Friedman, 2012). Task impurity may be reduced with younger populations due to the need for task demands to be simpler (Wong, 2004). To address issues related to low reliability and task impurity, the use of multiple tasks for each executive process is suggested (Miyake et al., 2000b). In addition, new EF test batteries, such as the *Delis–Kaplan Executive Function System* (*D-KEFS;* Delis, Kaplan, & Kramer, 2001), have been developed in an attempt to isolate component skills underlying different processes and to overcome task impurity limitations (Strauss et al., 2006).Another issue related to assessing EF is the low process and behaviour correspondence; similar behaviours can have different causes (Jurado & Rosselli, 2007). In other

words, a specific EF deficit may result in a range of behaviours, whereas a particular behaviour may be caused by a variety of EF deficits.

Furthermore, ecological and predictive validity of EF tasks represent another limitation of assessing such a construct (Anderson, 2002; Baron, 2004). According to Baron (2004), the absence of EF deficits on neurocognitive testing does not provide enough evidence that EF processes are intact. Inconsistency between test performance and real life behaviours has been extensively documented in the literature (Strauss et al., 2006). In artificial assessment settings, activities are delivered in a one-on-one fashion and in a well-structured manner. The environment is usually quiet and has minimal distractions, not reflecting real-life situations in which individuals are required to use their EF (Dawson & Guare, 2004; Lezak et al., 2004). It is suggested that since assessment tests only modestly predict everyday behaviour, information derived from alternative sources, including questionnaires, interviews, and observation, should be incorporated in the assessment process (Sbordone & Guilmette, 1999). In a review of EF tools appropriate for use with children, Baron (2004) and Dawson and Guare (2004) suggested that combining qualitative measures, such as observations, work samples, behaviour checklists, or interviews, with quantitative measures would provide a comprehensive picture of one's EF processes. While behavioural rating scales may identify the individual's ability to function with or without distraction or support in their regular environment, direct testing provides information about one's executive functioning under ideal environmental conditions (e.g., quiet setting, free from distractions). Thus, using both direct and indirect measures in the assessment of EF is important, as these tools may identify somewhat different manifestations of impairment in EF (Isquith, Roth, & Gioia, 2013; Strauss et al., 2006). In the present study, EF will be assessed using direct and indirect tools.

EF in OCD. In an attempt to integrate biological and cognitive-behavioural models of OCD, it has been suggested that specific functional or structural impairments (i.e., frontal-striatal dysfunction) negatively affect higher-order cognitive functions (i.e., EF) and secondary processes (i.e., attention and memory) in OCD-affected individuals (Penades, Catalan, Andres, Salamero, & Gasto, 2005). It has been hypothesized that neurocognitive dysfunctions mediate obsessive and compulsive behaviours (e.g., repetitive mental acts or behaviour performance according to a rigid set of rules; Chamberlain et al., 2005; Isik et al., 2011). According to Isik Taner and colleagues (2011), obsessions and compulsions in OCD derive from impairments in inhibition of repetitive thoughts and behaviours, and selective and biased attention and memory processes directed towards stimuli considered threating. The authors emphasize "dysfunction in memory and visuospatial processes in patients with OCD are not a result of memory impairment *per se*, but rather arise from an impaired ability to apply efficiently elaborated strategies" (p. 273).

A growing number of neuropsychological studies conducted with OCD-affected individuals have investigated potential EF abnormalities and impairments in attention and/or memory processes. Most of these studies have been conducted with adult populations with results indicating that OCD-affected individuals have more difficulty with specific EF tasks, including executive planning, switching cognitive set, response inhibition, and visual-spatial working memory (for review see Purcell, Maruff, Kyrios, & Pantelis, 1998a; 1998b) as well as with memory and visual-constructional skills (for review see Olley, Malhi, & Sachdev, 2007). In contrast, no firm evidence of attention deficits in OCD has been found in the literature (for review see Kuelz et al., 2004), suggesting that the primary neuropsychological deficit in OCD is

executive dysfunction, and that memory impairments in OCD may be secondary to executive deficits (Olley et al., 2007).

Compelling empirical evidence indicates specific neuropsychological impairments in two main domains related to the clinical presentation of adult OCD: (a) inhibitory control associated with limited control over obsessions and lack of ability to supress compulsions, and (b) cognitive flexibility linked to compulsions that are performed according to rigid rules and a focus on irrelevant stimuli instead of larger whole (Freeman et al., 2013). Difficulties with decision-making have also been suggested, as OCD patients tend to request more information before making decisions, and to spend excessive time considering low-risk scenarios and decisions related to their OCD (Dittrich & Johansen, 2013; Foa et al., 2003).

However, far fewer studies have investigated such impairments in pediatric populations (Geller et al., 2006). Review of neurocognition in childhood-onset OCD suggests similar neuropsychological deficits to adults. Some evidence points to impairments in response suppression and motor inhibition, set shifting, conceptual thinking, spatial-perception, planning abilities, working memory, visual memory, and fluency (Andres et al., 2007; Ornstein et al., 2010; Shin et al., 2008). However, some studies have not identified any neurocognitive impairments in either youth (Beers et al., 1999) or adults (Simpson et al., 2006) with OCD. Furthermore, others have suggested that putative neuropsychological deficits in OCD-affected youth who receive treatment are not stable overtime (Andres et al., 2008).

Inconsistent findings of childhood-onset OCD studies may be explained by the limited systematic description of relevant sample characteristics (e.g., medication status, matching of control groups, comorbidity with other psychiatric disorders), small sample sizes, lack of sensitivity of neuropsychological tests as well as limited control for the effects of anxiety,

intelligence, or age on test performance (Kuelz et al., 2004; Jang et al., 2010). Despite some indication of executive dysfunctions in youth with OCD, overall results have been mixed or inconclusive (e.g., Beers et al., 1999; Rao, Reddy, Kumar, Kandavel, & Chandrashekar, 2008; Shin et al., 2008), making it difficult to determine whether or not OCD-affected youth have a unique neuropsychological profile. Documenting neurocognitive deficits in childhood-onset OCD may improve the understanding of the neurobiology of the disorder and enhance treatment efficacy by incorporating strategies that address executive dysfunction into existing CBT treatment packages and stand-alone interventions (Freeman et al., 2013).

EF impairments in unaffected relatives of individuals with OCD. As OCD is a heritable neuropsychiatric disorder, first-degree relatives are at a greater risk for developing the disorder than the general population (Chamberlain et al., 2005). Attempts to identify contributory genes in OCD over the years have had limited results. This is believed to be due to the heterogeneous nature of OCD, preventing the differentiation of external symptoms or signs (phenotypic markers) into genetically homogenous subgroups (Chamberlain et al., 2007b). Consequently, there is increasing interest in identifying endophenotypes (i.e., intermediate markers of brain dysfunction) that are associated with vulnerability markers for the development of OCD (Chamberlain et al., 2007b). Endophenotypes have a particular utility in helping deconstruct the brain and its mechanisms into more manageable and understandable markers that can be potentially associated with genes (Chamberlain & Menzies, 2009). According to Chan and Gottesman (2008), neurocognitive dysfunctions in individuals with psychiatric disorders are one of the most promising candidate endophenotypes.

In addition to neuroimaging measurement, neuropsychological assessment of specific domains associated with genetic risk has been considered an important supplemental form of

assessment that could lead to future gene discovery studies (Chan & Gottesman, 2008). As an example, neuropsychological testing has been widely used to investigate potential endophenotype markers in other complex genetic psychiatric disorders such as schizophrenia. In Gur et al.'s (2007) study, schizophrenia probands demonstrated greatest neurocognitive impairment (i.e., mental flexibility, attention, verbal, face, and spatial memory, spatial processing, sensorimotor processing, and emotion intensity discrimination) in comparison to healthy controls, followed by relatives. Overall findings derived from studies conducted with schizophrenia-affected individuals and their unaffected relatives support the hypothesis of heritability of neurocognitive traits, emphasizing the role that neurocognitive assessment may have in determining candidate endophenotypes in other psychiatric disorders such as OCD (Gur et al., 2007).

Very limited research on endophenotypes in OCD is currently available, limiting conclusions about potential neurocognitive markers in OCD (Chamberlain et al., 2007). To date, eight studies (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Chamberlain et al., 2007b; Delorme et al., 2007; Li, Su, Li, & Yang, 2012; Rajender et al., 2011; Segalas et a., 2010; Viswanath, Reddy, Kumar, Kandavel, & Chandrashekar, 2009; de Wit, et al., 2012) have assessed the neuropsychological performance of unaffected first-degree relatives of OCD-affected individuals. Although all studies pointed to potential endophenotype candidates in OCD, findings were inconsistent. None of these studies was conducted with young populations. This is a notable absence, given the dramatically higher heritability in early-onset OCD theoretically improving the chances of endophenotype identification. Results from eight OCD endophenotype studies to date are summarized in Table 2.

Chamberlain et al.'s findings (2007) indicated that unaffected first-degree relatives and OCD patients exhibited deficits in cognitive flexibility and motor inhibition, but intact decision-making skills. In Delorme et al.'s study (2007), both unaffected relatives of patients with autism and OCD presented with executive deficits in planning and spatial working memory, but contrasting from Chamberlain et al.'s work (2007), they also exhibited intact cognitive flexibility and mental set shifting. Viswanath et al. (2009) reported that unaffected siblings of OCD probands had significant deficits in decision-making and behavioural reversal, but average performance in the other EF domains and memory and attention. Cavedini et al. (2010) reported that OCD probands and their relatives demonstrated impairments in decision-making, planning, and mental flexibility in comparison to healthy controls, and suggested that decision-making and planning aggregate in OCD families and might be a heritable component in OCD (Cavedini et al., 2010). Segalas et al. (2010) found that both OCD probands and their unaffected first-degree relatives presented with deficits in visual memory. Consistent with Chamberlain et al.'s (2007) findings, Rajender and colleagues (2011) indicated that both OCD patients and their unaffected first-degree relatives had significant impairments in set-shifting and inhibitory control, and proposed that visuo-constructive abilities and delayed verbal recall were also potential trait markers in OCD. Li et al. (2012) suggested that delayed verbal and visual memory and problem solving (measured by a planning task) were potential endophenotypes in OCD. Finally, de Wit et al. (2012) used functional MRI (fMRI) to assess response inhibition in OCD probands and their siblings and reported impaired response inhibition among OCD and sibling groups, although for the latter this did not reach statistical significance. It was suggested that hyperactivity in the presupplementary motor area was a candidate neurocognitive endophenotype of OCD.

Table 2. Previous Research Findings on Endophenotypes in OCD

Study	Participants	Main Statistical Analysis	Measure with worse performance between OCD/Relatives [a] versus HC (Measure)	Measure with no different performance across groups
Chamberlain et al. (2007b)	20 OCD [a, b] 20 Relatives [c] 20 HC	ANOVA	Cognitive Flexibility (IED)*** Motor inhibition (SST)***	Decision-making (CGT)
Delorme et al. (2007)	58 Relatives of Autism [c] 64 Relatives of OCD [c] 47 HC	Kruskal-Wallis/ Pearson's Chi-Square	Planning (TOL)*	Flexibility/Mental Set Shifting (TMT) Visual Fluency (DF) Verbal Fluency (VF)
Viswanath et al. (2009)	25 SIB of OCD 25 HC	Wilcoxon Signed Rank/ Mc Nemar / Pearson's Chi-Square	Decision-making (IGT)* Behaviour Reversal (DAT)*	Set-Shifting (Stroop) Planning (TOL) Cognitive Flexibility (WCST) Verbal Fluency (COWA) Visual Memory (WMS; RCFT) Verbal Memory (WMS) Attention (CPT; TMT)
Cavedini et al. (2010)	35 OCD [a] -Relative [c] pairs 31 HC- Relative [c] pairs	Independent t-tests	Decision-making (IGT)*** Planning (ToH)***	Mental Flexibility (WCST)
Segalas et al. (2010)	25 OCD 25 SIB of OCD 25 HC	ANCOVA[e]	Visual Memory (RCFT)*** Verbal Memory (TAVEC)**	Attention (WAIS)
Rajender et al. (2011)	30 OCD [a,b, d]-Relative pairs [a,c] 30 HC	ANOVA	Delayed Verbal Memory (RAVT)*** Visual Memory (RCFT)** Set-Shifting (WCST)*** Response Inhibition (Stroop)***	Planning (TOL) Attention (CT; DVT; TT)
Li et al. (2012)	40 OCD [a, d] 48 parents of OCD 40 HC 47 parents of HC	ANOVA	Delayed Verbal Memory (WMS)*** Delayed Visual Memory (WMS)*** Planning (ToH)***	Cognitive Flexibility (Stroop) Mental Flexibility (TMT) Set-shifting (WCST) Verbal Fluency (VF)
de Wit et al. (2012)	41 OCD [d] 17 SIB of OCD 37 HC	ANOVA Two-sample t-test[f]	Response Inhibition (SST)**	

Discrepancy of results in OCD endophenotype studies. Despite somewhat contradictory results, it is important to note that all studies examining EF, attention, and/or memory impairments in OCD patients, unaffected relatives, and healthy controls have been conducted with adult samples. Adults with OCD have shown to be less susceptible to genetic influence than OCD-affected youth (van Grootheest et al., 2005). In Delorme et al. (2007), Chamberlain et al.'s (2007), Rajender et al. (2011), and Li et al. (2012) studies, multiple generation relatives were included in the sample, a factor that could bias the results because the subjects were at different neurodevelopmental stages (Viswanath et al., 2009). It is difficult to compare results across studies given the mismatch between tests used and the constructs they propose to measure. For example, while Li et al. (2012) used the Trail-Making test to assess mental flexibility, Cavedini et al. (2010) and Viswanath et al. (2009) used the WCST to assess this construct. In contrast, Delorme et al. (2010) indicated that the Trail-Making is a measure of set shifting, whereas Rajender et al. (2011) suggested that the WCST assesses set shifting. Thus, lack of consensus regarding the EF domains and their interpretation may contribute to inconsistent results in the literature. Moreover, most studies did not address issues related to ecological validity or potential confounding factors such as IQ and anxiety-related test performance. Given such limitations,

there is a need for more studies that investigate potential endophenotype markers of OCD, especially in pediatric populations.

Finally, previous OCD endophenotype studies have used different analytic methods. For example, in Chamberlain et al.'s (2007), Rajender et al.'s (2011), and de Wit et al.'s (2012) studies, one-way analysis of variance (ANOVA) was performed to investigate group differences (i.e., OCD, Relatives, HC). Similarly, Li et al. (2012) used ANOVA to compare effects between four groups (i.e., OCD and OCD parents, OCD and HC, OCD parents and HC parents, OCD and HC parents). Further, Segalas et al. (2010) analyzed group differences using analysis of covariance (ANCOVA), and adjusting for the covariates age, level of anxiety, and depression. As family members are not considered independent observations, the abovementioned studies violated the assumption of independency of groups (i.e., OCD and first-degree relative), which may have potentially impacted the results. In contrast, Cavedini et al. (2010) acknowledged that due to the lack of independence between probands and relatives in their sample, only diagnostic specificity pairwise comparison using independent t-tests was performed. While group effect comparisons were not analyzed, comparisons between OCD probands and HC probands, OCD relatives and HC probands, and OCD relatives and HC relatives were conducted. Lastly, Delorme et al.'s (2007) and Viswanath et al.'s (2009) samples did not include OCD probands. Inter-group comparisons were made using Kruskal-Wallis (continuous variables) or Pearson Chi Square test (categorical variables) and Wilcoxon Signed Rank (continuous variables) or Mc Nemar/Pearson's Chi Square test (categorical variables), respectively. Discrepant findings among previous OCD endophenotype studies could also be due to different analytic methods, violation of independence of groups in analysis of variance-based methods, and different sample composition.

Rationale for the Proposed Study

　　OCD is a neuropsychiatric illness that often begins in childhood and has significant impact on family, academic, occupational, and social functioning. Based on biological and cognitive-behavioural models of OCD, neurobiological abnormalities in cortical-striatal-thalamic circuits and neurocognitive deficits in EF have demonstrated a role in OCD symptomology, which could contribute to OCD-affected individuals' impaired functioning across diverse settings, including home, school, work, and community (Piacentini et al., 2003; Sukhodolsky et al., 2005). The majority of empirical studies have included OCD-affected adult subjects in their sample. Among the fewer studies conducted with children and adolescents, results regarding a specific neuropsychological profile in OCD have been mixed (Andres et al., 2007; 2008; Beers et al., 1999; Behar et al., 1984; Isik Taner et al., 2011; Ornstein et al., 2010; Rosenberg et al., 1997; Shin et al., 2008; Woolley et al., 2008). Neuropsychological studies that assess neurocognitive functioning in first-degree relatives of OCD-affected individuals have shown great promise in the identification of potential cognitive traits that could be linked to genes concerning vulnerability to the disorder. To date, only eight studies on neuropsychological intermediate markers of brain dysfunction in OCD have been published in the literature. One of the main drawbacks of these studies is that they only included adults in their samples, who have lower predisposition to genetic influence than childhood-onset OCD participants (van Grootheest et al., 2005). Other limitations are that most studies did not address the ecological validity of their results via indirect means, or control for anxiety test performance. There is a need to identify neurocognitive deficits and their functional impact in youth with OCD and their unaffected siblings, and to investigate whether such deficits are trait-like markers in OCD. Increased awareness of neurocognitive deficits in OCD may enhance the understanding of a potential neurocognitive profile and the heritability of cognitive traits in OCD, providing (a) further

support to the qualification of EF as an endophenotype candidate (Cavedini et al., 2010), (b) help

with early identification of those at risk for developing OCD (Chamberlain & Menzies, 2012),

and (c) information for the advancement of school and clinical interventions (Freeman et al.,

2013).

Purpose of Study

The primary purpose of this study was to investigate neurocognitive functioning in youth

with OCD compared to their unaffected siblings and healthy controls, as a means of increasing

knowledge of neurocognitive deficits in OCD and of better understanding the heritability of

neuropsychological traits in OCD. In the present study, neurocognitive functions that were

previously addressed in the adult OCD literature, including EF (i.e., cognitive flexibility,

decision-making, planning, response inhibition, and working memory), attention (i.e., sustained

attention), and memory (i.e., visual memory) were directly assessed in youth, as well as

intelligence (i.e., Full Scale IQ; FSIQ). Indirect assessment of EF (i.e., parent-rated *BRIEF*) was

conducted to address the ecological validity of the test results, and the participants' state anxiety

was measured before the assessment began to account for its potential influence on performance.

Finally, the severity of obsessive and compulsive symptoms was assessed to allow for

comparisons with the subjects' neurocognitive performance. The following research questions

guided the study:

Research question 1. Is there a significant difference in neurocognitive performance on

specific direct tests (i.e., EF, attention, and visual memory) between youth with OCD, at-risk

siblings, and healthy controls?

Specific hypothesis. Youth with OCD and their siblings will demonstrate significant

performance deficits on specific EF subdomains (i.e., cognitive flexibility, decision-making,

planning, response inhibition, and visual working memory), but not on visual memory and

sustained attention, in comparison to healthy control participants. Thus, both OCD-affected youth and their siblings will demonstrate lower performance on neurocognitive tasks, suggesting potential neurocognitive trait makers in OCD.

Research question 2. Is there a score difference from an indirect assessment of EF (*BRIEF* Global Executive Composite [gec]) between youth with OCD, at-risk siblings, and healthy controls?

Specific hypothesis. Only OCD-affected youth will demonstrate significantly different *BRIEF* gec scores, suggesting that despite similar neurocognitive profiles, deficits in EF impact daily functioning of youth with OCD, but not unaffected siblings.

Research question 3. Is there a relationship between OCD symptom severity and neurocognitive performance of youth with OCD?

Specific hypothesis. There will be no relationship between symptom severity and neurocognitive performance within the OCD group, suggesting that potential neurocognitive trait markers are independent of obsessive and compulsive symptom severity.

Research question 4. Is there a relationship between state anxiety and neurocognitive performance on tests in the sample?

Specific hypothesis. There will be no relationship between neurocognitive performance and state anxiety in the sample.

The next chapters describe the implementation, results, and discussion of the findings from this study. Chapter 2 provides a detailed description of the methods used to collect and analyze the data. Chapter 3 describes the analyses of the research questions. Chapter 4 provides an in-depth discussion of the results, emphasizing relevant elements of the literature review.

Strengths and limitations, implications of the findings, and directions for future studies are also described in this section.

Chapter 2: Method

Design Overview

  This section describes the selection criteria and recruitment procedure of participants, the setting where the study was conducted, and the procedure used to collect data, including a description of measures and the data analytic strategy. The present study was completed within a 17 month-period (October 2012 to February 2014), with data collection between months 4 and 13 and data analysis between months 11 and 16. The study was approved by the Behavioural Research Ethics Board (BREB) at the University of British Columbia (UBC) in compliance with Tri-council Policies for research at Canadian universities. In this quasi-experimental study, data were collected on subjects' executive functioning (direct and indirect assessment), attention, visual memory, intellectual ability, OCD symptom severity, and state of anxiety.

Participants

  There were a total of 78 participants in this study: 29 youth with a current diagnosis of OCD (Group 1), 18 unaffected siblings of OCD probands (Group 2), and 31 healthy controls (Group 3). Recruitment of siblings was challenged by a number of factors, including absence of siblings among OCD-affected subjects (N=7), siblings not falling within the 8-18 age range required for inclusion (N=5), siblings disinterested in participation (N=2), and sibling exclusion based on diagnosis identified by semi-structured interview (N=1).

  Eligibility criteria. The *Anxiety Disorder Interview Schedule for Parents (ADIS-P*; Silverman & Albano, 2004) served as one of the main tools to assess the participants' eligibility for study inclusion. Group 1 was comprised of youth who met *DSM-IV-TR* criteria for OCD, as determined via the *ADIS-P* and the *Children's Yale-Brown Obsessive Compulsive Scale* (*CY-BOCS*; Goodman, et al., 1989; Scahill et al., 1997). Assessments were administered by a British Columbia Children's Hospital (BCCH) team psychiatrist and/or psychologist during initial

assessment at the Pediatric OCD Program. To establish sibling (Group 2) and healthy control (Group 3) eligibility by assessing for lifetime psychiatric diagnoses, a parent of potential subjects was administered the *ADIS-P* and a screening questionnaire over the phone by trained graduate students (see Appendix A for telephone screening questionnaire). The telephone interview was typically approximately one hour in duration. For instances when potential participants were determined to have clinically relevant symptoms related to OCD and/or other psychiatric disorders, a list of community resources for assessment and treatment was provided.

The inclusion criteria to participate in the study were as follows: (a) age 8-18 years old, (b) ability of subjects and parents to provide informed assent/consent, and (c) ability of subjects and parents to communicate effectively in English. For Group 1, OCD-affected subjects had a current *DSM-IV-TR* Axis I diagnosis of childhood-onset OCD. The exclusion criteria for OCD-affected subjects (Group 1) were as follows: (a) current diagnosis of major depressive disorder, bipolar disorder, psychosis, mental retardation or pervasive developmental disorder (e.g., autism), and (b) lifetime substance dependence/abuse disorder. The exclusion criteria for at-risk siblings (Group 2) were as follows: (a) non-biological full sibling, (b) current diagnosis of major depressive disorder, bipolar disorder, psychosis, mental retardation or pervasive developmental disorder (e.g., autism), (c) lifetime diagnosis of OCD, and (d) lifetime substance dependence/abuse disorder. The exclusion criteria for healthy controls (Group 3) were as follows: (a) lifetime *DSM-IV-TR* Axis I psychiatric disorder, and (b) OCD or Tourette syndrome in a first-degree relative. Among the individuals consenting to participate, only one sibling and four healthy controls were excluded based on results of the *ADIS-P*.

Consent and assent. OCD-affected youth and their siblings were recruited from assenting/consenting patients referred to the BCCH OCD clinic, whereas healthy controls were

recruited through community poster advertisements and word of mouth (e.g., Craigslist postings and flyers). OCD-affected youth and their siblings initially received a description of the study and copies of consent/assent forms in the mail prior to their initial OCD clinic assessment, and were asked by their psychiatrist or psychologist if they were interested in participating. Families willing to participate were contacted by a member of the research team and briefly screened for eligibility via telephone questionnaire. Healthy controls contacting the research team also received information about the study and copies of consent/assent forms via email (see Appendix B for consent and assent forms). A member of the research team contacted the families at least 24 hours after they received consent/assent forms and briefly screened those expressing interest via phone call questionnaire. *ADIS-P* interviews were scheduled after the research team received signed consent/assent forms.

Participant reimbursement. All subjects received a $30 gift card for completing the neurocognitive assessment (approximately 2 hour-time commitment). At-risk siblings and healthy controls received an additional $30 gift card after a parent completed the *ADIS-P* (approximately 1-2 hour time commitment). Travel and parking expenses were not reimbursed.

Summary report of assessment results. Parents of all OCD-affected subjects and their at-risk siblings received a written report summarizing assessment results written by the author (see Appendix C for report template). The author also met with families as desired to discuss results. Upon request, parents of healthy controls received either verbal feedback or a written assessment report. A list of recommended readings to describe executive function was given to parents expressing interest. In total, 42 assessment reports were written and mailed to the families, 19 assessment reports were both written and directly reviewed with the families, seven

assessment reports were verbally debriefed with families, and 10 subjects did not receive feedback regarding assessment results.

Setting

Data were gathered between January and October 2013. The assessment sessions occurred either in a quiet room at an office located at the Child and Family Research Institute (CFRI) at BCCH or at the subject's house, depending on the family's preference. Most participants were assessed in a single session with duration of approximately two hours.

Data Collection

The author conducted the majority of study assessments (70%; N=55). Four School Psychology graduate students with experience in standardized testing were trained and supervised by the author to assist in administration of measures used in the study. All collected data were quality checked by the author and double-checked by a trained research assistant to ensure that scores were accurately recorded in the database. Seventy percent of the *ADIS-P* interviews were recorded for interrater reliability check, and of these, 25% were randomly checked by a blinded, trained reviewer for diagnostic accuracy and confirmation of study eligibility.

Privacy and data security. All collected data were recorded with unique study code numbers for each subject and was securely stored in Dr. Stewart's laboratory within the BC Mental Health & Addictions Research Institute (BCMHARI), located in the CFRI building. Study forms containing personally identifying information of subjects (e.g., signed consent/assent forms, screening interview forms) were stored separately in locked filing cabinets at BCMHARI. Only Dr. Stewart, her immediate team members, and selected lab/research colleagues had access to the data. Given the need for large sample sizes to study psychiatric illnesses, the participants' de-identified data may be sent to other research labs to study OCD and

psychiatric disorders, which will be at the discretion of the study Principal Investigator (i.e., Dr. Stewart). No personal identifying information will be forwarded with these samples.

Measurement

The main goal of this study was to investigate neurocognitive functioning (i.e., EF, attention, and visual memory) in youth with OCD compared to their unaffected siblings and healthy controls, as a means to increase awareness about neurocognitive deficits in childhood-onset OCD and better understand the potential heritability of neuropsychological traits. In addition to the *ADIS-P* diagnostic interview, participants were assessed across a number of domains, including neurocognitive functioning, intellectual ability, obsessive and compulsive symptom severity, and state anxiety. Parents completed two questionnaires, one of which inquired about their child's daily behaviour associated with eight EF domains (*BRIEF*), and another of which captured demographics and academic history. Standardized testing procedures were implemented to optimize performance, including sitting arrangement, minimal distraction, and use of standardized instructions. Test administration occurred in a fixed order that was selected to maintain subject engagement. Assessment breaks were provided according to the participants' needs. The measures used in this study are described below in the order that they were administered or according to the assessed neurocognitive domains (i.e., *ADIS-P, STAI/STAI-C, CY-BOCS/YBOCS, CANTAB, BRIEF*, and background and academic questionnaire).

Diagnostic interview. To determine eligibility for study participation, all participants were interviewed by qualified research team members using the *ADIS-P*.

Anxiety Interview Schedule for Parent IV (ADIS-P). The *ADIS-P* (Silverman & Albano, 1996) is a semi-structured interview widely used in clinical trials to assess anxiety disorders in youth. In particular, several studies conducted with youth have used this tool to diagnose OCD

(e.g., Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005). The reliability of the *ADIS-P* has been thoroughly tested and found to range from good to excellent (internal consistency of 0.73 to 0.92 for youth; Silverman, Saavedra, & Pina, 2001). One of the parents of all participants were administered the *ADIS-P* to confirm or disconfirm a diagnosis of OCD or other disorders and determine eligibility for participation.

State of anxiety. Given criticism in the neuropsychological literature regarding the lack of control for test anxiety in studies conducted with OCD-affected individuals (Rao et al., 2008), participants' current level of anxiety was evaluated immediately prior to the assessment using either the *State-Trait Anxiety Inventory for Children* or the *State-Trait Anxiety Inventory, Form Y (STAI-C;* Spielberger, 1983; *STAI;* Spielberger, 1973).

State-Trait Anxiety Inventory for Children (STAI-C) and State-Trait Anxiety Inventory, Form Y (STAI). The *STAI-C* (Spielberger, 1983) and *STAI* (Spielberger, 1973) are both self-report questionnaires designed to assess and differentiate between anxiety as a general trait (i.e., relatively stable personality trait) and a state (i.e., temporary condition of state anxiety). The age range for the *STAI-C* is 8 to 13 years and for the *STAI* is 14 years and older. These questionnaires are divided into two forms, each comprised of 20 items rated on a 3-point (*STAI-C*) and 4-point scale (*STAI*). The administration time is approximately five minutes. Normative data for the *STAI-C* derived from 1,554 subjects from grades 4 to 6 in the state of Florida. Reliability data for the *STAI-C* include internal consistency (0.80s range) and test-retest coefficients (state 0.31-0.41; trait 0.67-0.71). Validity data include convergent and divergent validity. Normative data for the *STAI* is provided for high school, college students, working adults, and clinical patients. In a reliability generalization study that reviewed 816 research articles utilizing the *STAI* between 1990 and 2000, average reliability coefficients were

acceptable for both internal consistency (state 0.91; trait 0.89) and test-retest (state 0.70; trait 0.88; Barnes, Harp, & Jung, 2002). In the present study, participants completed one of these forms depending on their age in an electronic format in order to assess their present level of anxiety before the assessment started.

Severity of obsessions and compulsions. To assess the presence and severity of participants' obsessive and compulsive symptoms, the *CY-BOCS* or *YBOCS* was administered to all participants.

***Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and Yale-Brown Obsessive Compulsive Scale (YBOCS)*.** The *CY-BOCS* (Scahill et al., 1997) and the *YBOCS* (Goodman, et al., 1989) are clinician-administered, semi-structured questionnaires of symptoms and severity of OCD in individuals over the previous week. The age range for the *CY-BOCS* is 6 to 14 years and for the *YBOCS* is 15 years and older. These 10-item questionnaires are rated on a 5-point Likert scale (total 0-40) and are considered a gold-standard tool in clinical and research settings (Lewin & Piacentini, 2010). The *CY-BOCS* and the *YBOCS* are divided into two sections: the first section is an obsessive-compulsive checklist, and examines current and life-long presence of OCD symptoms. The second section assesses obsessions and compulsions related to their frequency, distress, interference, one's ability resist the obsessions, and perceived control over symptoms resulting in subscores for both obsessions (0-20) and compulsions (0-20; Lewin & Piacentini, 2010). Only the second part of these forms was used in the present study, with an administration time of approximately 5 minutes, and scores ranging between subclinical (0-8) and extreme (32-40). The *CY-BOCS* and the *YBOCS* have strong psychometric properties, including reliability and validity. In this study, all subjects were administered the second part of

these questionnaires to permit analysis examining relationship between symptom severity and neurocognitive performance.

Intelligence. Although it has been recognized that successful intelligence test performance does not guarantee success in EF test performance (Baron, 2004), empirical evidence suggests a positive correlation between specific domains of intelligence (i.e., crystallized intelligence and fluid reasoning) and EF domains. These include working memory (Friedman et al., 2006), shifting, and inhibition (Lehto et al., 2003). To consider this in analyses, intellectual functioning was assessed using the *Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)*.

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II). The *WASI-II* (Wechsler, 2011) is a revised brief cognitive measure of intelligence for individuals between ages 6 and 90 years, 11 months. The *WASI-II* is comprised of four subtests, including Vocabulary, Similarities, Matrix Reasoning, and Block Design. The Verbal IQ (VIQ) includes the Vocabulary and Similarities subtests, whereas the Performance IQ (PIQ) includes the Matrix Reasoning and Block Design subtests. To estimate general cognitive ability (FSIQ), full-scale scores were derived either from all four subtests or from the Vocabulary and Matrix Reasoning subtests. The *WASI-II* has updated norms derived from representative sample of 2,300 individuals according to the 2008 United States (US) Bureau Census. At this time, limited data on its psychometric properties are available given its recent release in the fall of 2011. It is reported that *WASI-II* has high reliability coefficients for children and adults greater than 0.80 (Zhou & Raiford, 2011). As its previous version (i.e., *WASI*) had strong support regarding its validity, it is anticipated that the *WASI-II* will also demonstrate acceptable psychometric properties as a screening measure of intelligence (Pierson et al., 2012). Subtest results are

reported in t-scores and for indexes as standard scores. In the present study, all four subtests comprising the FSIQ were administered (administration time: 30 minutes).

Executive Function. Direct, objective (i.e., *CANTAB*) and indirect, subjective (i.e., *BRIEF*) measures of EF were used, in addition to separate assessment of attention and visual memory domains.

Cambridge Neuropsychological Test Automated Battery (CANTAB). The *CANTAB* (Cambridge Cognition, 2013a*)* is a set of computerized cognitive tests presented on a high-resolution color monitor with a touch-sensitive screen, developed to assess cognitive abilities associated with the frontal and medial temporal areas of the brain, such as working memory/planning, visual memory, and visual attention (Robbins et al., 1994; Strauss et al., 2006). The *CANTAB* was adapted for use in humans from research conducted on animals with brain damage, especially in frontal and temporal regions. The *CANTAB* comprises 25 tests that target the following domains and purposes: introduction and test orientation (two tests), visual memory (four tests), executive function (six tests), attention (five tests), semantic/verbal memory (two tests), decision making and response control (four tests), social cognition (one test), and other tests (one test). The *CANTAB* task stimuli are nonverbal, comprised of simple shapes or geometric designs. Minimal English language proficiency is required to understand instructions before each task begins (Luciana & Nelson, 2002), and most tests include examples or teaching items to ensure comprehension of the task demands. Floor and ceiling effects are minimized by having subtests graded in difficulty, allowing use with different age groups and diagnoses (Ozonoff et al., 2009). The age range for these tests is between 4 and 90 years. The *CANTAB* has been used by researchers in more than 50 countries and cited in more than 1,000 peer-reviewed

empirical studies (Cambridge Cognition, 2013b). Thirty-one of these studies included OCD subjects and more than 120 studies included children and adolescents.

The *CANTAB* has been standardized in over 2,000 typical English-speaking U.K. resident subjects (aged 4-90; Robbins et al., 1994; Strauss et al., 2006), mostly adults. The manual does not provide information on gender or average National Adult Reading Test (NART) estimate IQ data for the standardization sample. Normative data samples of children have been growing in recent years (de Luca et al., 2003; Luciana, 2003; Luciana & Nelson, 2002). Luciana and Nelson (1998; 2002) provided normative data on six *CANTAB* subtests for approximately 400 children aged 4-12 years old who resided in Minnesota, USA. Normative data included gender, ethnicity, English as a primary or secondary language, parents' level of education, and children's handedness. Participants' verbal and nonverbal IQ was also assessed and found to be positively correlated with the *CANTAB* performance. Children who had English as a second language performed at comparable levels on the *CANTAB* tests in relation to English native speakers. Internal consistency ranged between adequate and high (0.73 to 0.95) depending on the task (Luciana, 2003). No information on test-retest reliability is available for pediatric populations. Lowe and Rabbit (1998) collected test-retest reliability data on an elderly sample (N=162) and reported that coefficients ranged from low (<0.59) to high (0.80-0.89) with most tasks falling in the low range. Practice effects were modest. Such finding is relatively expected based on requirements for EF tasks to be sensitive to novelty (Strauss et al., 2006). No information on alternate forms of *CANTAB* tests is currently available.

Validity of the *CANTAB* has been widely documented with adult populations, supporting test sensitivity to the presence of brain dysfunction, and discrimination among brain disorder subtypes (e.g., frontal versus temporal lobe pathology; Luciana, 2003). In younger populations,

construct and discriminant validity was established by comparing *CANTAB* data between functional and neural development of the frontal cortex of children with and without clinical conditions.

Overall, review of clinical and research applications for the *CANTAB* with pediatric populations indicates that this computerized battery is more sensitive to developing neural networks than traditional tests as it is able to record aspects of performance that rarely captured by psychometrics. As a result, the *CANTAB* may have the potential to improve the assessment process for children, including both normative and clinical samples. However, prior to the incorporation of this test into routine pediatric neuropsychological assessments, some limitations have to be addressed. These include collection of more normative and reliability data for pediatric populations and adaptation of its format to adjust to social-interactional needs or limitations of specific young individuals (Luciana, 2003).

In the present study, nine tests from the *CANTAB* battery measuring EF, attention, and visual memory were administered to all subjects in a specific order. The administration time for individual tests ranged between 2 and 20 minutes. The total administration time of the *CANTAB* battery was approximately 60 minutes. Below are the *CANTAB* tests used in the current study to assess EF.

Motor Screening Task (MOT) was administered at the beginning of the battery as a simple introduction for the participant to the touch screen format of the assessment. On this test, crosses appear on the screen in turn and participants are asked to touch it using the forefinger of their dominant hand. The cross disappears when it is touched properly. The MOT is a screening test for visual, movement, and comprehension difficulties. MOT scores are not reported in this research (administration time: 2 minutes).

Big/Little Circle (BLC) test was used as a training test to prepare participants for the Intra/Extradimensional Shift (IED) test. The BCL assesses comprehension, learning, and reversal, giving participants experience in following and reversing a rule, before proceeding to the IED test. On the BLC test, participants are shown a series of circle pairs containing one large and one small, with the instruction to touch the small circle. After 20 trials, participants are instructed to touch the big circle for subsequent 20 trials. Similar to the MOT, no BCL score is reported in this study (administration time: 2 minutes).

Intra-Extra Dimensional Set Shift (IED) is a cognitive flexibility test analogue of the Wisconsin Card Sorting Test (WCST) that assesses rule acquisition and reversal, which is sensitive to brain changes in the fronto-striatal areas (Cambridge Cognition, 2013). On this task, participants are presented with two pictures and instructed to select the "correct" one. There is an underlying rule determining which picture is correct in every trial, and participants learn this rule through trial and error ("correct" or "incorrect" feedback). When the learning criterion is achieved (after six correct trials), the computer changes the rule. Thus, it requires that subjects "maintain attention to different examples within a reinforced stimulus dimension (ID shift), and then shift attention to the previously irrelevant stimulus dimension (ED shift)" (Nielen & Den Boer, 2003, p. 919). This test is comprised of nine stages, with scores based upon the total number of errors made, and adjusted scores to account for when all stages are not completed [IED (total error correct)] (administration time: 7 minutes).

Stockings of Cambridge (SOC) is derived from the Tower of London task and assesses spatial planning, spatial working memory, and motor control. This is considered to be a measure of frontal lobe function. On this task, the participant is shown two displays containing three coloured balls and instructed to use balls in the lower display to copy the pattern shown in the

upper display, with the minimum number of moves. Subjects are encouraged to plan their moves before moving the balls. The number of minimum moves required ranges between two and five moves across 12 *copying* trials. For each *copying* trial, a control condition (*following* trial) is presented in which subjects are required to follow as *quickly as possible* a sequence of moves shown at the top half of the screen by moving the corresponding balls in the bottom half of the screen. The *following* trials are exact replications of the participants' earlier planning moves during the *copying* trials (Purcell et al., 1998a). Scores are based on (a) the mean number of movements for five move solution problems [SOC (mean of move)], (b) the mean speed of movement after the initial move has been performed on 5 move solution problems, which is calculated by the difference between the first move and the completion of the problem [SOC (subsequent thinking)], and (c) the number of problems successfully solved using the minimum number of moves [SOC (perfect solutions)] (administration time: 10 minutes).

Information Sampling Task (IST) tests impulsivity and decision-making. This test assesses pre-decisional processing, as participants are required to gather and evaluate information before making a decision. It is reported to assess a similar underlying process, known as reflection impulsivity, to the Matching Familiar Figures Test (Chamberlain et al., 2007a). On this test, subjects are presented with a grid of 25 closed boxes located above two coloured panels. By touching the grey boxes one at a time, the boxes open up and remain open, showing one of the two colours displayed at the bottom of the screen. Participants are instructed to decide which of the two colours is in the majority of the 25 boxes. Immediate feedback indicating whether the response was correct or incorrect is provided once the choice has been made, and the colours change with boxes from trial to trial. There are two conditions, including the *fixed win condition* and the *decreasing win condition.* In the *fixed win condition,* participants

can open as many boxes as they wish, and they are awarded 100 points for making a correct decision, regardless of the number of boxes opened. In the *decreasing win condition*, the number of points awarded for a correct decision starts at 250 and decreases by 10 points for every box opened (Cambridge Cognition, 2013b). Incorrect decisions result in a loss of 100 points in either condition. The main scores for this test include (a) the number of trials in which the correct colour is chosen for each condition, [IST (total correct fixed] and [IST (total correct decreasing)], and (b) the mean number of boxes opened in each condition, [IST (mean box open fixed)] and [IST (mean box open decreasing)], which provides information about differences between responses in separate task structures (e.g., opening fewer boxes in the decreasing win condition than in the fixed win condition; Chamberlain et al., 2007a; administration time: 15 minutes).

Stop Signal Task (SST) is a stop signal response inhibition test requiring participants to make rapid responses to a series of directional arrows appearing consecutively in the center of the computer screen ("go trial") and to inhibit a prepotent response when hearing an auditory beep ("stop signal"). On this test, participants are introduced to a press pad and instructed to press the left hand button when they see a left-pointing arrow, and the right hand button when they see a right-pointing arrow. They are also instructed to refrain from pressing any button when they hear a beep. There are five blocks lasting approximately 2 minutes and 10 seconds each. After each block, subjects are presented with a bar graph displaying their response time, in addition to a written message that is previously verbally explained by the examiner. The SST is considered to be an inhibitory control test. It provides a stop-signal reaction time score [SST (ssrt)] reflecting the time relapse between presentation of the "go" cue and of the "stop signal" stimulus at which the individual is able to accurately withhold a button push response 50% of the

time. A longer SST (ssrt) reflects poorer motor inhibitory control (Chamberlain & Menzies, 2012; administration time: 20 minutes).

Spatial Working Memory (SWM) test assesses ability to retain and manipulate spatial information using working memory. It also measures the ability to reach a goal using heuristic strategy. On this task, participants are instructed to search for a token that is hidden in one of the several boxes. After a token is found, it will never appear in the same box again. As a result, subjects can gradually narrow down the search within boxes that have not previously contained hidden tokens. The number of potential tokens to be found corresponds to the number of boxes displayed on the screen, ranging between three and eight boxes. Each trial is completed when all tokens have been found. Scores are based on the total number of times that participants return to boxes where tokens were found during previous searching sequence [SWM (between error)] (Chamberlain et al., 2007a; Purcell et al., 1998a; administration time: 8 minutes).

Behavior Rating Inventory of Executive Function (BRIEF). The *BRIEF* (Gioia et al., 2001) defines EF as the ability for individuals to self-regulate cognitive and social problem solving. The main purpose of the *BRIEF* is to assess deficits in behaviours associated with EF at home and school settings (Maricle & Avirett, 2012). The *BRIEF* is an 86-item-questionnaire in which parents and teachers of youth ages 5 to 18 years are asked to report on a 3-point Likert scale how often the child exhibits specific problem behaviours. The *BRIEF* is designed to assess eight different aspects of EF, including inhibition, shifting, emotional control, initiation, working memory, planning/organization, organization of materials, and monitoring. An overall score [BRIEF (gec)] and two clinical scale scores (Behavioural Regulation and Metacognition) are determined from combinations of different scales. Each questionnaire form takes approximately 10 to 15 minutes to complete.

The *BRIEF* normative sample (N=1,419) was based on the 1999 US Census drawn from one US state (Maryland), thus limiting its representativeness. Additional data were also gathered to assess reliability and validity in clinical samples (Strauss et al., 2006). Reliability data demonstrate high internal consistency (range 0.80 - 0.98), test-retest reliability (range 0.76 - 0.85 after an average interval of two weeks), practice effects (i.e., magnitude of changes in t-scores over time for test-retest groups) and teacher-parent interrater reliability (average r =0.32; low coefficient is consistent with expectations for different environmental settings). Validity data include content, construct, convergent and predictive validity, which range from modest to strong. Scores for scales and composites are reported as t-scores. Clinically significant concerns are indicated when t-scores exceed 65. Using a multitrait-multi-method matrix, individual scales and summary indexes have been found to correlate with other partially or unrelated measures of attention and other behaviours. Review of studies conducted with clinical populations indicate that clinical conditions characterized by executive dysfunction, such as ADHD, Autism Spectrum Disorder (ASD), reading disorder, and traumatic brain injury (TBI), exhibit expected profiles on the *BRIEF,* may be distinguishable between diagnostic groups (Isquith, Roth, & Gioia, 2013). Some evidence suggests relationships between biological markers of EF (e.g., frontal-lobe volume, cortical thickness, white-matter integrity, corpus callosum length) and ratings of everyday EF on the *BRIEF* (for review see Isquith et al., 2013). Data are also available from preliminary studies of other clinical populations such as high functioning autism, Tourette syndrome, low birth weight, frontal lobe lesions, and mental retardation. Overall, results from the *BRIEF* can provide information about etiology and help delineate interventions for youth with a variety of diagnoses (Gioia et al., 2000).

Some critiques regarding use of the *BRIEF* as an indirect assessment of EF include the following: (a) EF is measured based on an adult's subjective perception of a child's EF rather than objectively measuring cognitive EF, (b) weak correlation between the *BRIEF* and direct measures of EF, and (c) the *BRIEF* may capture behaviour or attention more than EF (Maricle & Avirett, 2012). Such critiques may also reflect a lack of ecological validity for direct EF measures, supporting the notion that the *BRIEF* may be more sensitive to executive deficit impacts on daily functioning (Vriezen & Pigott, 2002). In the present study, the *BRIEF* (parent form) was completed by a parent of each subject to provide a more comprehensive assessment of EF weaknesses and strengths. The *BRIEF* (gec) score was used in this study to represent overall EF difficulty on daily functioning at home (administration time: 10-15 minutes).

Attention. Research has shown that although OCD-affected individuals do not exhibit deficits on attention tasks (Kuelz et al., 2004), they do present with selective and biased attention in real-life situations (e.g., towards threat-relevant stimuli; Isik Taner et al., 2011). However, attention is considered as a central component of neuropsychological assessment. Because attentional processes are intertwined with EF and memory, it is difficult to isolate and measure this construct separately from other processes (Miller & Maricle, 2012). Strauss et al. (2006) recommend the use of different measures to assess attention, including a test specifically designed for attention. The Rapid Visual Information Processing (RVP) test from the *CANTAB* was used to assess this construct.

Rapid Visual Information Processing (RVP) is a 4-minute modified version of the Continuous Performance Task (CPT) that assesses sustained attention and that sensitively measures parietal and frontal lobe functions. On this test, a box in the center of the computer screen displays sequential random numbers (ranging from 2 to 9), at a rate of 100 digits per

minute. Participants are requested to detect target sequences of three digits and to register responses using the press pad when the last digit of the sequence appears. The target sequence remains on the screen during the test. While subjects aged 8 to 14 years are presented with only one target sequence, participants aged 15 years and older are presented with three different target sequences. The main scores used for this test are: (a) [RVP (a)]: indicates how efficient the subject is at detecting target sequences incorporating correct responding (hit) and incorrect responding (false alarm); (b) [RVP (probability hit)]: provides the number of correct responses; (c) [RVP (probability false alarm)]: indicates the number of incorrect responses; and (d) [RVP (mean latency)]: indicates the mean of delay to response (Cambridge Cognition, 2013a; administration time: 7 minutes).

Memory. Evidence suggests that memory deficits in OCD may be secondary to an executive failure of organizational strategies during encoding, identifying executive dysfunction as the primary abnormality in OCD-affected individuals (Olley et al., 2007). Most studies have found deficits in spatial memory and working memory, rather than in verbal memory among individuals with OCD (for review see Olley et al., 2007; Purcell et al., 1998a, 1998b). In the present study, visual memory was assessed using the *CANTAB* Spatial Recognition Memory test.

Spatial Recognition Memory (SRM) test assesses spatial recognition memory in a 2-choice forced discrimination paradigm (Cambridge Cognition, 2013a). Subjects are presented with a sequence of five individual boxes located at different places on the screen and are instructed to remember the location of the boxes for future recall in a forced-choice paradigm. At the end of the sequence, two squares are displayed, one of which is in the correct location and the other of which is in a different position. Subjects are required to choose the box in the correct location. There are four trials, each of which uses a set of novel stimuli locations (Purcell et al.,

1998a). Scores are calculated based on the percentage of correctly recalled locations [SRM (percent correct)] (administration time: 5 minutes).

Subject background and academic functioning. To supplement analysis of the data, participants' parents were asked to complete a questionnaire to capture information regarding the child's demographics (e.g., parents' age, education, marital status, child's ethnicity, language spoken at home) and general academic functioning (e.g., area of academic difficulty, school personnel involved, tutoring; see Appendix D for Background and Academic Functioning Questionnaire).

Statistical Analysis Procedure

A series of analysis of variance with covariates (ANCOVAs) were performed using the SAS software (SAS, version 9.3, the Mixed procedure; SAS, 2013). Group (OCD, SIB, HC) was included as the explanatory variable, and age, gender, FSIQ, and state anxiety served as covariates. Due to violation of the assumption of independence for groups, family membership was considered as a possible random factor for inclusion in the model. The interactions between group and age (group*age) and between group and IQ (group*IQ) were also considered for inclusion in the model. In instances when the random effect for family was retained in the model, mixed models ANCOVA was used. F-tests were used to assess the association between the explanatory variables and the response variable. Skewness and kurtosis values were obtained for the residuals of the response variables of all models.

A significant result (α-level $= 0.05$) for group is considered evidence as of between-group differences for means of the response variable. In the presence of a significant group effect, pairwise comparisons between group means were performed using t-tests. Cohen's d values and 95% confidence limits for response variables were calculated based on least squares means and

standard deviations. The standard deviation was calculated using either the model residual or a combination of the model residual and covariance parameter for family, as appropriate.

A decision was made prior to data analyses that derived p-values would not be corrected for multiple testing, based upon the small number of subjects in the sample and the exploratory nature of this research. A number of researchers on OCD endophenotype and childhood-onset OCD have also not adjusted p-values for multiple comparisons (Beers et al., 1999; Chamberlain et al., 2007; Delorme et al., 2007; de Wit et al., 2013; Ornstein et al., 2010; Shin et al., 2008). Moreover, Bonferroni correction, which assumes independence between tests, is considered too conservative (Purcell, 1998a). In this study, unadjusted p-values indicate significance ($p<0.05$).

Akaike's Information Criteria (corrected) [AICC] was considered for each response variable to assess whether model fit was improved by inclusion of the group*age or the group*FSIQ interactions or by the random effect for family. The inclusion of the group*age and group*FSIQ interactions was an exploratory component of model building. Therefore, these terms were removed from the model if their presence did not improve model fit. As the majority of the families represented in the data had only one member, the benefit of including family effects in the model may not be sufficient to justify the loss of degrees of freedom available for performing the statistical tests. Therefore, family was only included in models when it improved fit.

The models were subsequently fitted using maximum likelihood estimation (MLE), which allows for comparison between models with different fixed effects (e.g., with and without interactions with group). The model with the smallest AICC was selected for each response variable. If the AICC was the same for two models, the simpler model (e.g., without family) was

selected; having the same AICC for two models suggests that the additional term (e.g., family) does not contribute to the model fit.

The following models were considered:

1) Fam_Both: This model includes a random effect for family and interaction effects for both group*age and group*FSIQ

2) Fam_Age: This model includes a random effect for family and an interaction effect only for group*age

3) Fam_FSIQ: This model includes a random effect for family and an interaction effect only for group*FSIQ

4) Fam_NoInt: This model includes random effect for family and omits both interaction effects

5) NoFam_Both: This model omits random effect for family and includes both interaction effects

6) NoFam_Age: This model omits random effect for family and includes an interaction effect only for group*age

7) NoFam_FSIQ: This model omits random effect for family and includes an interaction effect only for group*FSIQ

8) NoFam_NoInt: This model omits both the random effect for family and both of the interaction effects.

The selected models were then rerun using restricted maximum likelihood (REML) estimation in order to obtain less biased estimates of the variance parameters and thus less biased tests of the fixed effects. If an interaction was significant, estimated slopes for the relationship between covariate and response variable for each group were obtained by refitting the model

without the covariate while retaining the covariate by group interaction.

There were a total of 16 response variables for all eight measures, including IED (N=1), IST (N=4), SOC (N =3), SST (N =1), SWM (N=1), RVP (N =4), SRM (N =1), and *BRIEF* (N=1). The response variables were all counts, scores, or continuous data. Most of the counts and scores had enough distinct, ordinal values that they could be treated as continuous. Table 3 provides a brief description of the neurocognitive tests and scores used in this study.

Table 3. Description of Neurocognitive Tests and Score Interpretation

Construct [Measure]	Response Variable	Description	Meaning of Higher Score
Cognitive Flexibility [IED]	total error correct	Total errors in intra- and extra-dimensional conditions or adjusted scores with stage incompletion	Worse
Decision-Making [IST]	total correct fixed	Total trials with correct response in fixed condition	Better
	total correct decreasing	Total trials with correct response in decreasing condition	Better
	mean box open fixed	Mean boxes opened in fixed condition	Better
	mean box open decreasing	Mean boxes opened in decreasing condition	Worse
Planning [SOC]	mean move	Mean movement for five move problems	Better
	mean subsequent thinking	Mean speed after initial move in 5 move problems	Worse
	perfect solutions	Problems solved using minimum number of moves	Better
Response Inhibition [SST]	ssrt	Time between "go" and "stop" stimulus at which 50% of trails are successful	Worse
Working Memory [SWM]	between error	Times token-containing boxes are reopened	Worse
Attention [RVP]	a	Sensitivity to target	Better
	probability hit	Probability of correct response	Better
	probability false alarm	Probability of incorrect response	Worse
	mean latency	Mean time to response	Worse

Construct [Measure]	Response Variable	Description	Meaning of Higher Score
Visual Memory [SRM]	percent correct	Correct recall percentage	Better
Indirect EF [*BRIEF*]	gec	Overarching summary of daily behaviours associated with EF across eight domains	Worse

All potential explanatory variables in this study (i.e., age, gender, FSIQ, and state anxiety) were continuous, except for gender. Age was reported to the second decimal place in years, for example translating 12.75 to 12 years, 8 months. Gender, a categorical variable, was coded as 0=female and 1=male and then analyzed using mixed models logistic regression. FSIQ scores were reported as standard scores (mean=100; SD=15). Because the available normative sample of state anxiety measure is fairly limited (i.e., *STAI-C*: grades 4-6; *STAI*: high school), all study participants did not receive scaled scores. In addition, four subjects inadvertently completed the form that did not correspond to their correct age range. As a result, the state anxiety raw scores from both forms (i.e., *STAI-C* and *STAI*) were scaled in order to represent a single variable. Means, minimums, and ranges were computed for each age group (*STAI-C*: 8-13 years and *STAI*: 14+ years). The final state anxiety variable was calculated for group i as follows: $anxiety_i = (anxiety_i - minimum_i)/range$; where i =1 (*STAI-C*), 2 (*STAI*).

To investigate distribution differences for continuous explanatory variables, including age, FSIQ, state anxiety, and *CY-BOCS*, between-group comparisons were conducted using analysis of variance. Based on AICC, family as a random factor was included in analysis if the model fit was improved. For gender (categorical variable), logistic regression was employed. In the presence of a significant group effect, pairwise comparisons between group means were performed using t-tests.

To answer the third research question examining a potential relationship between symptom severity and neurocognitive performance, models were fitted including *CY-BOCS.* All but one of the OCD subjects presented with a nonzero *CY-BOCS* score, whereas all but one *CY-BOCS* value for the SIB and HC groups were equal to zero. Therefore, there was insufficient overlap in values of *CY-BOCS* between the OCD group and the SIB and HC groups to allow a comparison between groups at a value of *CY-BOCS* that occurred within the range of the data for all groups. Thus, only the OCD subjects were included in the data set for this analysis and group was omitted from the models. Multiple regression was performed and resulting F-tests using parameter estimates tested whether there was an association between *CY-BOCS* and response variables for OCD subjects. Finally, a post-hoc power analysis for a one-way between groups ANCOVA was conducted using the program G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2007), to determine the effect size for significant group differences based on the total sample size of the current study.

Chapter 3: Results

This section provides an overview of the results of this study. First, the research questions will be restated. Next, a description of the sample used in the study is provided. Subsequently, the statistical analyses and results for each of the four research questions are presented.

Research Questions

The main goal of the current study was to investigate neurocognitive functioning in youth with OCD (i.e., OCD) compared to unaffected, at-risk siblings (i.e., SIB) and healthy controls (i.e., HC) in efforts to increase awareness about neurocognitive deficits in OCD and better understand the potential heritability of neuropsychological traits as endophenotypes in OCD. Neurocognitive functioning was assessed using direct (objective, standardized testing) and indirect (subjective, parent report) tools, with the aim of answering the four main questions:

(1) Is there a significant difference in neurocognitive performance on specific direct tests (i.e., EF, attention, and visual memory) between youth with OCD, at-risk siblings, and healthy controls?

(2) Is there a significant score difference from an indirect assessment of EF, *BRIEF* (gec), between youth with OCD, at-risk siblings, and healthy controls?

(3) Is there a relationship between symptom severity and neurocognitive performance of youth with OCD?

(4) Is there a relationship between state anxiety and neurocognitive performance on tests in the sample?

Sample Description

The total number of participants in this study was 78, including 49 females and 29 males, ranging between 8 and 18 years of age. The average participants' age was 13 years, 1 month (SD = 2.8). The majority of the sample was female (N=49; 63%), Caucasian (N=52; 67%), and had

English as a primary language (N=56; 72%). Most of the participants' parents had completed at

least some post-secondary education (N=138; 89%). Table 4 presents the demographic

characteristics of the sample.

Table 4. Demographic Characteristics of OCD-Affected Youth, At-Risk Siblings, and Healthy
Controls

	OCD		SIB		HC		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	13.79	2.7	13.08	3.1	12.5	2.8	13.12	2.8
	N	%	N	%	N	%	N	%
Gender								
Male	10	34.5	9	50	10	32.3	29	37
Female	19	65.5	9	50	21	67.7	49	63
Ethnicity								
Caucasian	22	75.9	12	66.7	18	58.1	52	67
Other	3	10.2	2	11.1	5	16.1	10	20
Caucasian and other	4	13.8	4	22.2	8	25.8	16	13
Primary language								
English	22	75.9	16	77.8	18	58.1	56	72
Other	0	0	0	0	2	6.5	2	2
English and Other	7	24.1	2	11.1	11	35.5	20	26
Parental education level completed								
Less than high-school	0	0	0	0	1	0	1	0
High-school	9	15	5	14	3	7	17	11
College/ university	44	76	26	72	31	50	101	65
Graduate school	5	9	5	14	27	43	37	24
Parental marital status								
Married	26	89.7	16	88.9	28	90.3	70	90
Separated/divorced	3	10.3	2	11.1	3	9.7	8	10
Youth's school progress								
Typical	26	89.7	18	100	30	96.8	74	95
Skipped grade	0	0	0	0	1	3.2	1	1
Repeated grade	3	10.3	0	0	0	0	3	4
Special education program								
None	22	75.9	17	94.4	27	87.1	66	85
Gifted	2	6.9	1	5.6	4	12.9	7	9
Other	5	17.2	0	0	0	0	5	6
Area identified as a concern								
Reading	5	17.2	1	5.6	1	3.2	7	9
Math	8	27.6	2	11.1	1	3.2	11	14

	OCD		SIB		HC		Total	
	N	%	N	%	N	%	N	%
Spelling	4	13.8	0	0	0	0	4	5
Writing	8	27.6	3	16.7	0	0	11	14
Social Adjustment	4	13.8	3	16.7	0	0	7	9
Behaviour	6	20.7	1	5.6	0	0	7	9
Attention/Concentration	11	37.9	3	16.7	0	0	14	18
Organization	12	41.4	2	11.1	1	3.2	15	19
At least one area of concern	17	58.6	6	33.3	3	9.7	26	33.3

Information about comorbidity with other psychiatric disorders, medication intake, age of onset of OCD symptoms, and subtypes of obsessions and compulsions were collected for 27 OCD participants (93% of the OCD group). Results from the *ADIS-P* interview and diagnostic assessment indicated that in the OCD group, 17 subjects (59%) were identified as having one or more of the following comorbid diagnoses: ADHD (N=4), Generalized Anxiety Disorder (N=10), Social Phobia (N=1); Specific Phobia (N=1), Anxiety Disorder Not Otherwise Specified (N=3), Body Dysmorphic Disorder (N=1), Enuresis (N=1), Tourette syndrome (N=2), and tic disorder (N= 2). In terms of medication, nine (31%) of the 27 participants were taking psychotropic medication. The average age of onset of OCD was 10 years, 4 months. Table 5 summarizes the frequency of obsessions and compulsions based on *CY-BOCS* symptom checklist results for 27 OCD-affected participants.

Table 5. Frequency of Obsessions and Compulsions on the *CY-BOCS*

	Frequency [a]	Percent
Obsessions		
Aggression	17	59%
Contamination	18	62%
Hoarding	4	13%
Religious/Moral	10	35%
Symmetry/Exactness/Order	11	38%
Sexual	2	7%
Health Related	4	13%
Miscellaneous	16	55%
Compulsions		
Cleaning/Washing	23	79%
Checking	17	59%

	Frequency [a]	Percent
Hoarding/Collection	4	13%
Counting	5	17%
Repeating	14	48%
Ordering/Arranging	15	52%
Miscellaneous	26	90%

[a] Number of OCD-affected youth

In the siblings group, eight (44%) sibling subjects either met criteria for a *DSM-IV-TR* diagnosis or were identified as potentially having one of the following diagnosis: ADHD (N=2), Generalized Anxiety Disorder (N=1), Specific Phobia (N=1), Specific Learning Disability (Rule out; N=1), Specific Phobia (Rule out; N=1), and Social Phobia (Rule out; N= 2).

To investigate between-group differences in distributions regarding the continuous explanatory variables (i.e., FSIQ, state anxiety, and *CY-BOCS*), comparisons via ANOVA were employed, not including family as a random effect. For age, based on AICC, family membership improved the model slightly and, thus, the random effect for family was included in the analysis. For gender, logistic regression with no random factor for family was performed.

There were no significant group differences in age and gender (p>0.05). Significant differences between groups were identified for FSIQ (p=0.023), state anxiety (p=0.039), and the *CY-BOCS* (p<0.001). HC participants had significantly higher estimated mean FSIQ scores in comparison to OCD probands (p=0.009), but not SIB subjects (p=0.059). OCD and SIB groups did not significantly differ with respect to FSIQ (p=0.069). OCD participants had significantly higher estimated mean state anxiety scores in comparison to SIB (p=0.015), but not HC subjects (p=0.085). HC and SIB groups did not significantly differ with regard to state anxiety (p=0.315). Finally, OCD subjects had higher different estimated mean scores on the *CY-BOCS* compared to SIB and HC subjects (p<0.001). No significant group differences were identified between siblings and healthy controls (p=0.865). Table 6 presents the clinical characteristics of the groups in relation to each explanatory variable (i.e., age, gender, FSIQ, *CY-BOCS*, and state anxiety).

Table 7 shows pairwise comparisons for significant groups differences on the explanatory variables.

Table 6. Clinical Characteristics of OCD-Affected Youth, At-Risk Siblings, and Healthy Controls

Explanatory Variables	OCD	SIB	HC	P-Value
	Estimated Mean (Std Error)	Estimated Mean (Std Error)	Estimated Mean (Std Error)	
Age (years)	13.79 (0.53)	12.92 (0.66)	12.38 (0.54)	0.165
Gender [a]	0.34 (0.09)	0.50 (0.12)	0.32 (0.08)	0.439
FSIQ [b]	103.24 (2.29)	104.78 (2.90)	111.77 (2.21)	0.023*
CY-BOCS [c]	17.34 (0.81)	0.22 (1.03)	0 (0.00)	<0.001*
State Anxiety [d]	0.43 (0.04)	0.28 (0.05)	0.34 (0.04)	0.039*

[a] Estimated probabilities of gender (male=1)
[b] Average range: Between 90 and 109
[c] Clinical levels of OCD symptomology: Scores at or above 16
[d] Raw scores only were analyzed
*Significant group differences (p<0.05); Std Error: standard error; FSIQ: Full Scale Intelligence Quotient; *CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale*; State Anxiety*: State-Trait Anxiety Inventory-State* form

Table 7. Pairwise Comparisons for Significant Group Differences on Explanatory Variables

Explanatory Variable	OCD vs SIB (p-value)	OCD vs HC (p-value)	SIB vs HC (p-value)
FSIQ	0.069	0.009*	0.059
CY-BOCS	<0.001*	<0.001*	0.865
State Anxiety	0.015*	0.085	0.315

*Significant group differences (p<0.05)

Selection of Best Fitting Model

Maximum Likelihood Estimation (MLE) was used to select and determine the best model using AICC. For most response variables, the model omitting both random effect for family and interactions had the smallest AICC value and, therefore, the best fit. Only two models [SST (ssrt) and BRIEF (gec)] provided evidence that interaction (i.e., group*FSIQ) or that random effect for family contributed to the overall model fit. The best fitting model for the response variable BRIEF (gec) included the group*FSIQ interaction. This indicates that the relationship between

BRIEF (gec) and group may depend on the value of FSIQ. For the SST (ssrt), the random factor

family with no interactions represented the best fitting model. This indicates that random factor

family explains sufficient variability to justify retaining it in the model (see Appendix E for

intraclass correlation coefficients calculated using the model with only family and no fixed

effects). Table 8 displays the AICC values used in selecting the best-fitting model from the eight

possible models for each response variable.

Table 8. Akaike's Information Criteria (corrected) for Selecting Best Fitting Model

Domain	Variable	Fam_ Both	Fam_ Age	Fam_ FSIQ	Fam_ NoInt	NoFam _Both	NoFam _Age	NoFam _FSIQ	NoFam _NoInt	Selected Model
Cognitive Flexibility	IED (total error correct)	719.5	715.2	715.0	711.1	716.7	712.5	712.6	**708.7**	NoFam_ NoInt
Decision-making	IST (total correct fixed)	243.8	239.7	238.8	234.9	243.8	239.7	238.8	**234.9**	NoFam_ NoInt
	IST (total correct decreasing)	296.4	293.6	291.5	289.0	293.8	291.2	289.1	**286.8**	NoFam_ NoInt
	IST (mean box open fixed)	488.0	483.0	481.6	477.1	485.2	480.3	481.6	**477.1**	NoFam_ NoInt
	IST (mean box open decreasing)	445.4	442.9	441.4	439.2	445.4	442.9	441.4	**439.2**	NoFam_ NoInt
Planning	SOC (mean move)	300.9	295.7	296.0	291.0	300.9	295.7	296.0	**291.0**	NoFam_ NoInt
	SOC (mean subsequent thinking)	1293.8	1289.7	1293.3	1289.7	1293.8	1289.7	1293.3	**1289.7**	NoFam_ NoInt
	SOC (perfect solutions)	343.6	339.9	338.0	334.6	340.8	338.1	335.4	**333.1**	NoFam_ NoInt
Response Inhibition	SST (ssrt)	897.9	896.9	893.2	**891.6**	905.5	902.1	900.0	897.0	Fam_ NoInt

Domain	Variable	Fam_Both	Fam_Age	Fam_FSIQ	Fam_NoInt	NoFam_Both	NoFam_Age	NoFam_FSIQ	NoFam_NoInt	Selected Model
Working Memory	SWM (between error)	594.2	588.9	590.7	586.1	592.0	586.9	588.5	**584.0**	NoFam_NoInt
Attention	RVP (a)	-268.1	-272.2	-272.8	-276.6	-268.1	-272.2	-272.8	**-276.6**	NoFam_NoInt
	RVP (probability hit)	-60.2	-64.0	-65.3	-68.7	-60.2	-64.0	-65.3	**-68.7**	NoFam_NoInt
	RVP (probability false alarm)	-352.0	-357.1	-351.9	-357.0	-354.8	-359.7	-354.6	**-359.6**	NoFam_NoInt
	RVP (mean latency)	927.1	922.6	924.7	920.2	924.6	920.4	922.1	**917.8**	NoFam_NoInt
Visual Memory	SRM (percent correct)	601.7	596.2	600.3	595.0	601.7	596.2	597.7	**592.5**	NoFam_NoInt
Indirect EF	BRIEF (gec)	566.4	575.2	560.9	570.1	565.4	573.9	**560.0**	568.9	NoFam_FSIQ

The model includes: Fam_Both: a random effect for family and interaction effects for both group*age and group*FSIQ; Fam_Age: a random effect for family and an interaction effect only for group*age; Fam_FSIQ: a random effect for family and an interaction effect only for group*FSIQ; Fam_NoInt: a random effect for family and omits both interaction effects

The model omits: NoFam_Both: random effect for family and includes both interaction effects; NoFam_Age: random effect for family and includes an interaction effect only for group*age; NoFam_FSIQ: random effect for family and includes an interaction effect only for group*FSIQ; NoFam_NoInt: both the random effect for family and both of the interaction effects.

Analysis Results and Estimates

REML was used to obtain estimates of slopes for the relationships between covariates and the response variable for each group. For the *BRIEF* (gec), AICC results indicated that the group*FSIQ interaction was significant [F-test=7.29; p<0.001] and improved the model fit when using a significance criteria of p-value<0.05.

Statistical Analyses and Results for Research Questions

Based on AICC results, ANCOVA was the main type of analysis conducted to examine

group effects on response variables associated with the following domains: cognitive flexibility,

decision-making, planning, working memory, attention, visual memory, and indirect EF. Mixed

model ANCOVA employing family as a random factor was used to assess group differences on

the SST (ssrt), measure of response inhibition. Overall, distributions of the response variables

were considered sufficiently normal for the purposes of analysis of variance. Exceptions

included IST (total correct fixed) and IST (total correct decreasing), which were limited by

relatively few values. The distributions for these variables did not resemble any standard

distribution (e.g., normal, poisson, or binomial). Therefore, they were treated as being

approximately normally distributed. As analysis of covariance is considered to be robust to

deviations from normality, it is assumed that the study findings were not strongly impacted by

deviations from the normal distribution. Estimated means were computed as the mean values of

the covariates (see Appendix F for skewness and kurtosis values of the residuals from the

models).

To determine the effect size for significant group differences based on the total sample size

of the current study, a post-hoc power analysis for a one-way between groups ANCOVA was

conducted using the program G*Power 3.1 (Faul et al., 2007). The analysis indicated that the

current sample achieved power $(1 - \beta)$ of 0.47 when detecting medium effect size, $f = 0.25$, and

power, $(1 - \beta)$ of 0.88 when detecting large effect size, $f = 0.40$ (Cohen, 1977) while employing

the traditional 0.05 criterion of statistical significance.

Statistical analysis and results for research questions 1 and 2. The following

paragraphs summarize the results according to each domain, to address the first two research

questions regarding groups differences in neurocognitive performance based on direct and indirect measures.

Cognitive flexibility. For the IED, there is no statistical evidence for a difference between groups (p=0.938). There was a significant negative association, however, between IED (total error correct) and the covariate FSIQ [slope=-0.657; t(71)=-3.26; p=0.002]. This indicates that the higher the subjects' FSIQ, the less likely they were to make shifting errors in the intra- and extra-dimensional conditions.

Decision-making. Four IST scores were used to assess decision-making. A significant difference was found between groups regarding the IST (mean box open decreasing) [F (70,2)=5.35, p=0.007)]. Pairwise comparisons revealed that SIB subjects opened significantly more boxes in the decreasing condition (least square mean = 12.62; standard error = 0.94) compared to OCD probands (least square mean = 9.92; standard error = 0.81) [t(70)=-2.15; p=0.035)] and healthy controls (least square mean = 8.69; standard error = 0.75) [t(70)=3.26; p=0.002)]. This means that siblings tended to gather more information (i.e., open more boxes) before making a decision, despite being penalized for increased information sampling. OCD and HC groups did not have significantly different performance on this measure. No significant group differences were identified for the remaining scores [i.e., IST (total correct fixed), IST (total correct decreasing), and IST (mean box open fixed)].

There was a negative association between the IST (total correct decreasing) and the covariate state anxiety [slope=-1.701; t(70) =-2.04; p=0.045]. This indicates that more state anxiety of subjects before the session was associated with fewer correct trials in the fixed condition.

Planning. Three SOC scores were used to assess planning. A significant difference between groups was found for the SOC (perfect solutions) [F (71,2)=4.24, p=0.018]. Pairwise comparisons indicated that OCD probands had a significantly lower number of perfect solutions (least square mean = 7.00; standard error = 0.39) than that of HC subjects (least square mean = 8.59; standard error= 0.37) [t(71)=-2.91; p=0.005)]. OCD probands' performance did not significantly differ from that of SIB participants (least square mean = 7.82; standard error = 0.46) [t(71)=-1.35; p=0.18)]. No significant difference in performance between SIB and HC subjects were found [t (71)=-1.30; p=0.199)]. In terms of SOC (mean of move), measure of the number of moves in excess of the minimum pre-determined, there is no evidence of significant differences between groups (p=0.087). Similarly, for the SOC (mean subsequent thinking), measure of mean of the speed of movement after the initial move, no significant differences were identified between groups (p=0.409).

There was a positive association between SOC (perfect solutions) and age [slope=0.195; t (71)=2.46; p=0.016] and FSIQ [slope=0.056; t(71)=3.10; p=0.003]. This suggests that as age or FSIQ increased, subjects were more likely to solve problems using the pre-determined number of moves (i.e., making perfect solutions).

Response inhibition. No significant group difference was found for the SST (ssrt). This indicates that the groups did not differ in terms of their stop-signal reaction time [i.e., length of time spent between "go" and "stop" stimulus when subjects were able successfully inhibit a response on 50% of trials; SST (ssrt) p=0.273]. However, there was a negative association between SST (ssrt) and age [slope=-10.933; t(19)=-3.82; p=0.001]. This suggests that the younger the subjects, the lower their motor inhibitory control (i.e., longer ssrt scores).

Working memory. No significant group differences were found with regard to the number of times that token-containing boxes were reopened during a previous searching sequence [SWM (between error)] (p=0.417). There was a negative association between SWM (between error) and the covariate age [slope=-1.449; t(71)=-3.65; p<0.001]. This suggests that the younger the subjects, the more errors they made in their search for tokens.

Attention. Four scores were used to assess group differences in sustained attention. There were no significant differences between the groups for any RVP scores, including RVP (a), which refers to how efficient subjects were at detecting target sequences using correct and incorrect responding (p=0.159); RVP (probability hit) and RVP (probability false alarm), measures of the probability of individuals responding either correctly or incorrectly to a sequence of numbers (p=0.105; p=0.147, respectively), and RVP (latency), a measure of the mean of time taken to respond (p=0.286).

There was a negative association between RVP (probability hit) and RVP (probability false alarm) and age [slope=-0.014; t(71)=-2.39; p=0.019; slope=-0.003; t(71)=-3.45; p=0.001, respectively]. This suggests that the younger the subjects, the higher the probability of responding both correctly and incorrectly to a sequence of numbers. There was also a positive association between RVP (probability false alarm) and the covariate gender [t(71)=4.48; p=0.038]. Males' score on this measure (estimated mean = 0.023; standard error = 0.004) was higher than females' (estimated mean = 0.012; standard error = 0.003). This suggests that males were more likely to respond incorrectly to a sequence of numbers than females.

Visual memory. There was no significant difference between groups for visual memory [SRM (percent correct); p=0.178]. There was a positive association between SRM (percent

correct) and age [slope=1.283; t(71)=2.88; p=0.005]. This suggests that the older the subjects, the higher the percentage of correct recall of boxes locations in a forced-choice paradigm.

Indirect EF. The *BRIEF* (gec) score provided an overarching summary of daily behaviours associated with EF subdomains, including inhibition, shifting, emotional control, initiation, working memory, planning/organization, organization of materials, and monitoring (see Appendix G for subdomain estimated mean scores). According to parents' perspectives, there was a significant difference in performance on the *BRIEF* (gec) between the groups [F(69,2)=9.15; p<0.001]. Pairwise comparisons revealed that OCD probands (estimated mean = 55.89, standard error = 1.68) had significantly higher scores (i.e., more deficits) on ratings of daily behaviours associated with EF compared to SIB (estimated mean = 45.08, standard error = 1.97) [t(69)=4.07, p<0.001] and HC subjects (estimated mean = 44.74, standard error = 1.63; [t(69)=4.84, p<0.001]. SIB and HC participants did not have a significantly different performance on this indirect measure of EF (p=0.897).

Given the group*FSIQ interaction, results from parameter estimates (i.e., estimated slopes) regarding the association between FSIQ and *BRIEF* (gec) indicated that only the estimated slope for the OCD group was significantly different from zero (p<0.001). The negative estimated slope indicates that *BRIEF* (gec) decreases as FSIQ increases.

Table 9 reports on the estimated group means, standard errors, F-tests, degrees of freedom (DF), and p-values for all response variables. Table 10 indicates pairwise comparisons for the response variables where F-tests were significant, with Cohen's d values and 95% confidence limits for significant response variables (see Appendix I for Cohen's d values on all response variables). Figures 1 and 2 provide a visual representation of significant group differences on direct and indirect measures of EF based on adjusted mean square for each group.

Table 11 displays the parameter estimates for the response variables that had significant

association with the covariates. Table 12 reports on the parameter estimates for *BRIEF* (gec)

based on the group*FSIQ interaction.

Table 9. Neurocognitive Performance of OCD-Affected Youth, At-Risk Siblings, and Healthy Controls based on Adjusted Means (Standard Error)

Domain	Variable	OCD	SIB	HC	F-statistic	DF	P-value
Cognitive Flexibility [a]	IED (total error correct)	28.74 (4.30)	30.15 (5.11)	30.90 (4.08)	0.06	71	0.938
Decision-making [a]	IST (total correct fixed)	9.03 (0.21)	9.39 (0.25)	8.78 (0.20)	1.81	70	0.171
	IST (total correct decreasing)	7.69 (0.30)	7.80 (0.35)	7.17 (0.28)	1.28	70	0.285
	IST (mean box open fixed)	19.74 (1.03)	19.31 (1.20)	19.14 (0.96)	0.09	70	0.913
	IST (mean box open decreasing)	9.92 (0.81)	12.62 (0.94)	8.69 (0.75)	5.35	70	0.007*
Planning [a]	SOC (mean move)	7.40 (0.30)	7.65 (0.35)	6.71 (0.28)	2.52	71	0.087
	SOC (mean subsequent thinking)	595.02 (178.24)	776.84 (211.83)	933.38 (168.93)	0.91	71	0.409
	SOC (perfect solutions)	7.00 (0.39)	7.82 (0.46)	8.59 (0.37)	4.24	71	0.018*
Response Inhibition [a]	SST (ssrt)	222.08 (14.34)	194.85 (16.90)	198.76 (14.60)	1.39	19	0.273
Working Memory [a]	SWM (between error)	14.73 (1.93)	14.92 (2.29)	11.64 (1.83)	0.89	71	0.417
Attention [a]	RVP (a)	0.93 (0.01)	0.96 (0.01)	0.94 (0.01)	1.89	71	0.159
	RVP (probability hit)	0.76 (0.03)	0.86 (0.03)	0.80 (0.03)	2.33	71	0.105
	RVP (probability false alarm)	0.01 (0.00)	0.02 (0.00)	0.01 (0.00)	1.97	71	0.147
	RVP (mean latency)	365.20 (16.43)	383.60 (19.53)	344.27 (15.57)	1.27	71	0.286
Visual Memory [a]	SRM (percent correct)	73.72 (2.18)	76.96 (2.54)	79.43 (2.03)	1.77	70	0.178
Indirect EF [b]	*BRIEF* (gec)	55.89 (1.68)	45.08 (1.97)	44.74 (1.63)	9.15	69	<0.001*

[a] Raw scores only were analyzed
[b] Clinically significant concern: Scores at or above 65

Table 10. Pairwise Comparisons for Significant Response Variables

		OCD vs SIB			OCD vs HC			SIB vs HC		
Domain	Response Variable	T-value	P-value	Cohen's d	T-value	P-value	Cohen's d	T-value	P-value	Cohen's d
Decision-making	IST (mean box open decreasing)	-2.15	0.035*	-0.69	1.09	0.278	0.31	3.26	0.002*	0.31
Planning	SOC (perfect solutions)	-1.35	0.18	-0.43	-2.91	0.005*	-0.83	-1.30	0.199	1
Indirect EF	*BRIEF* (gec)	4.07	<0.001*	1.35	4.84	<0.001*	1.39	0.13	0.897	0.04

$*p < 0.05$

Figure 1. Significant Response Variables of Direct Measures of EF Based on Adjusted Mean Square for Each Group

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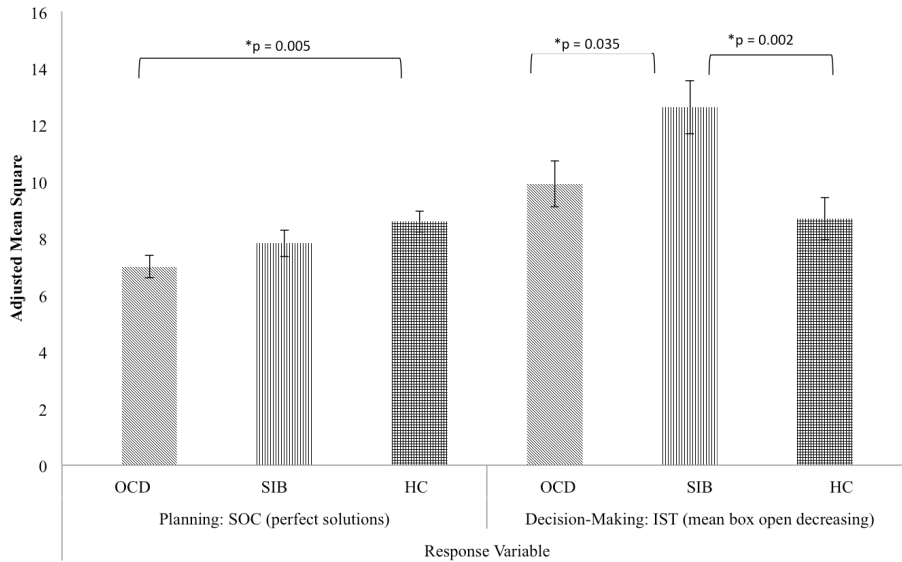
Figure 2. Significant Response Variables of Indirect Measure of EF Based on Adjusted Mean Square for Each Group
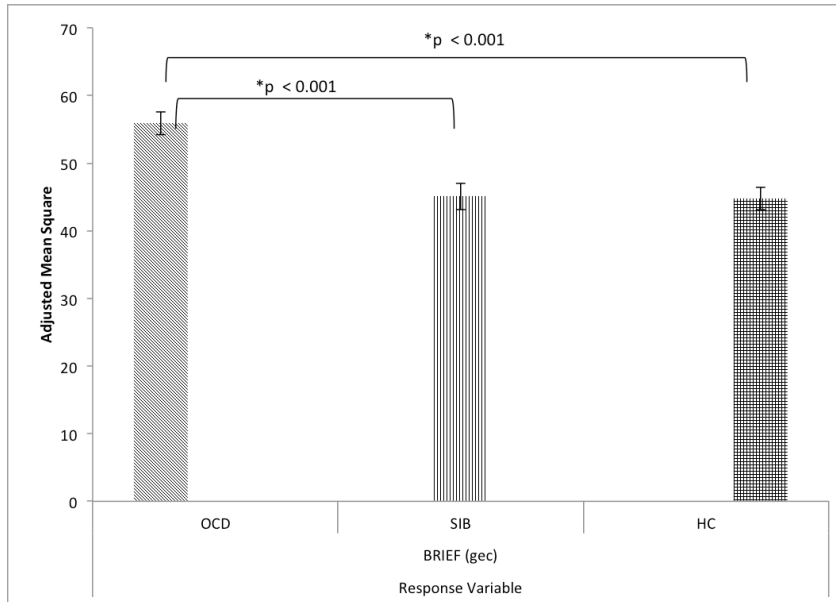
Table 11. Parameter Estimates for Response Variables with Significant Covariates

Covariate	Response Variable	Estimated Slope	Standard Error	DF	T-value	P-value
Age	SOC (perfect solutions)	0.195	0.080	71	2.46	0.016
	SST (ssrt)	-10.933	2.865	19	-3.82	0.001
	SWM (between error)	-1.449	0.400	71	-3.65	<0.001
	RVP (probability hit)	-0.014	0.006	71	-2.39	0.019
	RVP (probability false alarm)	-0.003	<0.001	71	-3.45	0.001
	SRM (percent correct)	1.283	0.445	70	2.88	0.005
Gender	RVP (probability false alarm)			71	4.48	0.038
	Females	0.012	0.003	71	3.52	0.001
	Males	0.023	0.004	71	5.52	<0.001
FSIQ	IED (total error correct)	-0.657	0.201	71	-3.26	0.002
	SOC (perfect solutions)	0.056	0.018	71	3.10	0.003
	BRIEF (gec)[a]	-0.515	0.113	69	-4.54	<0.001
State anxiety	IST (total correct decreasing)	-1.701	0.834	70	-2.04	0.045

[a] Significant association only for OCD group

Table 12. Parameter Estimates for *BRIEF* (gec) Based on Group*FSIQ Interaction

Variables	Parameter Estimate	Standard Error	T-Value	P-Value
OCD*FSIQ	-0.515	0.113	-4.54	<0.001*
SIB* FSIQ	-0.156	0.193	-0.81	0.422
HC* FSIQ	0.119	0.126	0.95	0.346

*p<0.05

Statistical analysis and results for research question 3. To address the third research question about the relationship between symptom severity and neurocognitive performance, multiple regression was performed on the OCD subjects group. Results from this analysis based on parameter estimates indicate that there is no evidence of a significant relationship between neurocognitive performance and severity of obsessive and compulsive symptoms between OCD probands. Table 13 displays F-test results and p-values for the association between *CY-BOCS* and response variables for OCD subjects.

Table 13. F-tests Results for Association Between Response Variables and *CY-BOCS* for OCD group

Variables	F-Statistics	P-value
IED (total error correct)	0.05	0.821
IST (total correct fixed)	0.01	0.905
IST (total correct decreasing)	3.18	0.088
IST (mean box open fixed)	0.24	0.627
IST (mean box open decreasing)	0.84	0.369
SOC (mean move)	0.55	0.466
SOC (mean subsequent thinking)	3.24	0.085
SOC (perfect solutions)	0.28	0.601
SST (ssrt)	0.91	0.349
SWM (between error)	0.87	0.362
RVP (a)	1.16	0.293
RVP (probability hit)	1.07	0.312
RVP (probability false alarm)	0.51	0.484
RVP (mean latency)	0.04	0.845
SRM (percent correct)	0.09	0.761
BRIEF (gec)	0.00	0.965

*p<0.05

Statistical analysis and results for research question 4. The fourth research question regarding a relationship between state anxiety and neurocognitive performance was addressed using state anxiety as a covariate. As previously reported, results of the F-tests indicate that there was no evidence of significant association between state anxiety and most response variables, with the exception of IST (total correct decreasing). There was a negative association between the IST (total correct decreasing) and the covariate state anxiety [slope=-1.701; t(70)=-2.04; p=0.045], suggesting that the more state anxiety subjects experienced before the session, the lower the number of correct trials in the fixed condition. Thus, state anxiety was associated with worse performance. Table 14 indicates F-test results and p-values for each response variable in relation to the state anxiety covariate.

Table 14. F-tests Results for Response Variables Based on Covariate State Anxiety

Variables	F- Statistics	P-value
IED (total error correct)	0.02	0.886
IST (total correct fixed)	3.19	0.079
IST (total correct decreasing)	4.16	0.045*
IST (mean box open fixed)	0.49	0.484
IST (mean box open decreasing)	2.05	0.156
SOC (mean move)	2.61	0.112
SOC (mean subsequent thinking)	1.78	0.186
SOC (perfect solutions)	0.92	0.340
SST (ssrt)	0.02	0.895
SWM (between error)	0.02	0.897
RVP (a)	0.00	0.997
RVP (probability hit)	0.02	0.878
RVP (probability false alarm)	0.05	0.831
RVP (mean latency)	1.93	0.170
SRM (percent correct)	0.00	0.981
BRIEF (gec)	2.02	0.160

*p<0.05

Summary of Results

Models were successfully developed for separate neurocognitive domains in the search for group differences between OCD-affected youth, at-risk siblings, and healthy controls. Based on AICC values, the best fitting model for most response variables omitted both random effect

for family and interaction effects. Only the SST (ssrt) model included a random effect for family, whereas the best fitting model for the *BRIEF* (gec) included the group*FSIQ interaction.

Overall results derived from a series of ANCOVAs and from mixed model ANCOVA [for SST (ssrt)] addressed the four research questions proposed in this study. Neurocognitive performance was determined to be significantly different between the groups during decision-making [IST (mean box open decreasing)] and planning [SOC (perfect solutions)] tasks, and with respect to EF impact on daily behaviour [*BRIEF* (gec)]. Post-hoc pairwise comparisons indicated that on the decision-making task, siblings opened significantly more boxes in the decreasing condition compared to OCD probands and healthy controls, suggesting that they tended to gather more information before making a decision, despite being penalized for increased information sampling. OCD and HC groups did not have significantly different performance in this domain. On the planning task, OCD probands had significantly less number of perfect solutions compared to HC subjects, but not SIB subjects, reflecting deficits in the planning domain. SIB and HC subjects did not present with significantly different performance in planning. Finally, only OCD probands had significantly worse scores on a measure of daily behaviour associated with EF [*BRIEF* (gec)] when compared to SIB and HC subjects. No significant difference in performance between SIB and HC subjects were found on this indirect assessment of EF. For the remaining neurocognitive measures (i.e., cognitive flexibility, response inhibition, working memory, sustained attention, and visual memory), there was no evidence to support group differences.

Significant associations between response variables and covariates were identified. Age was determined to be a significant covariate in all response variables, except for cognitive flexibility, decision-making, and indirect measure of EF. Age was negatively associated with

performance on tasks of response inhibition, working memory, and sustained attention. The younger the subjects, the lower their motor inhibitory control (i.e., longer response inhibition scores), the more errors they made in their search for tokens (i.e., working memory), and the higher the probability of responding both correctly and incorrectly to a sequence of numbers (i.e., sustained attention). Age was also positively associated with measures of planning and visual memory. The older the subjects, the more likely they were of solving problems using the pre-determined number of moves (i.e., planning) and the higher the percentage of correct recall of boxes locations in a forced-choice paradigm (i.e., visual memory). In addition, FSIQ was positively associated with planning. As FSIQ increased, the more likely subjects were of solving problems using the pre-determined number of moves (i.e., making perfect solutions). FSIQ was negatively associated with measures of cognitive flexibility and daily behaviours associated with EF. The higher the subjects' FSIQ, the less likely they were of making shifting errors in the intra- and extra-dimensional conditions (i.e., cognitive flexibility) and their parents of reporting EF deficits (lower *BRIEF* scores). Gender was associated with a measure of sustained attention, where males were more likely to respond incorrectly to a sequence of numbers than females. Symptom severity (*CY-BOCS*) was not associated with any response variables describing neurocognitive performance of OCD subjects. Finally, state anxiety was negatively associated with a measure of decision-making, suggesting that the more state anxiety subjects experienced before the session, the lower the number of correct trials in the fixed condition.

The hypothesis that OCD-affected youth and their siblings would present with executive dysfunction on all five domains and intact visual memory and sustained attention (research question #1) was partially confirmed. OCD-affected youth presented with deficits in planning, in comparison to both their siblings and healthy controls. Only siblings presented with impaired

decision-making in comparison to the OCD and healthy control groups. No other significant group differences across the other assessed neurocognitive areas were found. Consistent with the second and third hypotheses, only the OCD group exhibited behaviour challenges associated with executive function deficits; there was no relationship between symptom severity of OCD-affected youth and their test performance across any neurocognitive domains. The final hypothesis was partially confirmed, indicating that there was no significant association between state anxiety and test performance in the sample, with the exception of a negative association between state anxiety and decision-making.

Chapter 4: Discussion and Conclusions

This chapter is divided into five sections. First, a discussion of findings from direct and indirect neurocognitive assessments is offered, comparing results with previous studies and examining potentially responsible factors for similarities and differences across studies. Second, implications of the findings and contributions of this study to current understanding in the field will be discussed. Third, strengths and limitations of the study will be highlighted. Next, future directions for research focusing on neurocognitive traits in OCD will be addressed. This chapter will end with a summary and final conclusions.

Discussion of Research Findings

Direct assessment of neurocognitive functioning. Results regarding the first research question about group differences on direct measures of neurocognitive functioning indicate that youth with OCD demonstrated impairment in planning that was not observed in healthy control subjects. Only siblings of OCD probands exhibited deficits in decision-making. No significant performance differences were found for the remaining neurocognitive domains (i.e., cognitive flexibility, response inhibition, working memory, sustained attention, and visual memory). Results from this study are comparable to several previous studies conducted with unaffected relatives of OCD probands (e.g., Cavedini et al., 2010; Delorme et al., 2007; Viswanath et al., 2009). Table 13 provides a summary of the current study's findings in relation to the OCD endophenotype literature. An in-depth discussion of potential reasons for discrepant results across OCD endophenotype studies is highlighted at the end of this section.

Planning. Planning was assessed in this study using three scores derived from the SOC, a computerized version of the Tower of London task. When required to solve problems using a minimum number of moves [SOC (perfect solutions)], youth with OCD performed significantly worse than healthy controls, but not siblings. Although siblings had a lower number of perfect

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solutions on this task in comparison to healthy controls, this difference was not statistically significant. It is possible that the small number participants in the siblings group (N=18) compromised the result due to low power. Overall, dysfunction in planning, in terms of perfect solutions, was primarily observed in OCD participants followed by siblings. With regard to the remaining planning scores, OCD probands and siblings made more moves in excess for five-move problems [SOC (means of move)], but spent less time solving the planning problems [SOC (mean subsequent thinking)] in comparison to healthy controls. Such differences between groups did not reach statistical significance.

It is important to note that covariates of age and FSIQ were positively associated with the number of perfect solutions on the SOC. This means that as age and FSIQ increased, the more likely participants were to solve problems using the optimal number of moves (i.e., more developed planning ability). Such finding points to the important role of brain maturation and cognitive development in planning.

The current study also demonstrated that OCD probands' neurocognitive performance in planning was not associated with obsessive and compulsive symptom severity (*CY-BOCS* scores). This suggests that deficits in planning could be independent of OCD symptom severity, and thus may be manifested in individuals whether or not the illness is active. The lack of relationship between symptom severity and neurocognitive performance is one of the key features for considering an executive deficit (e.g., planning) as a potential trait marker candidate in OCD.

When comparing the current findings to that of other research in the field, three previous OCD endophenotype studies also indicated that planning deficits were present in OCD patients and/or first-degree relatives (Cavedini et al., 2010; Delorme et al., 2007; Li et al. 2012). Delorme

et al. (2007) reported that unaffected first-degree relatives of OCD probands demonstrated significantly fewer perfect solutions at five-move problems compared to healthy controls, but intact speed to solve these five-move problems. Li et al. (2012) reported that both OCD probands and their parents demonstrated worse performance time on the Tower of Hanoi (ToH) task. Cavedini et al. (2010) indicated that both OCD probands and their first-degree relatives made significantly more moves on the ToH compared to HC subjects and HC relatives.

In contrast to the findings described above, two studies did not report significant planning differences between OCD and/or first-degree relative groups and healthy controls (Rajender et al., 2011; Viswanath et al., 2009). Although Rajender et al. (2011) indicated that OCD probands spent significantly more time solving planning tasks (small effect size = 0.2) in comparison to first-degree relatives and healthy controls, no significant group differences were found for the number of excess moves. The authors concluded that OCD participants presented with poorer performance on planning due to psychomotor slowing rather than pure planning deficits. It is important to note that in Rajender et al.'s (2011) study, only nonmedicated adults without comorbidities and with checking/washing symptoms were included in the OCD sample. The participants in Rajender's study may present with distinct neurocognitive correlates in comparison to the current study's heterogeneous OCD-affected youth sample. Moreover, Viswanath et al. (2009) did not include OCD participants in their sample, and only reported absent significant differences between SIB (from families with more than two affected members) and HC groups, which are consistent with the current findings. Overall, findings from three of five previous OCD endophenotype studies agree with the current findings that planning deficits may be a potential trait marker in OCD.

Neurocognitive studies conducted only with OCD probands and healthy controls have documented planning difficulties on tasks similar to the Tower of London [TOL], although findings are mixed (Gousse et al., 2005; Purcell et al., 1998a; 1998b; van den Heuvel et al., 2005; Veale et al., 1996). In particular, Ornstein et al. (2010) reported that youth with OCD made more moves than necessary while the TOL task became more difficult. In contrast, Beers et al. (1999) did not find differences in performance on the Tower of Hanoi task between 21 non-depressed and nonmedicated youth with recently diagnosed OCD and healthy controls matched for age, IQ, gender, and socio-economic status. It is possible that intact performance in planning was due to differences in structural features and administration directions that resulted in the use of different strategies for solution between the Tower of Hanoi and the Tower of London tasks (Bull, Espy, & Senn, 2004).

Difficulties with planning tasks are consistent with the proposed neurobiological model of OCD involving frontal–striatal circuits. In an fMRI study, OCD adult probands had decreased frontal-striatal activation during planning tasks, mainly in the dorsolateral prefrontal cortex and caudate nucleus (van den Heuvel et al., 2005). The authors proposed that structural deficits in these areas are independent of OCD symptom severity, reinforcing the hypothesis that planning could be a potential endophenotype (Delorme et al., 2007). No study has yet examined whether similar dysfunction in the fronto-striatal circuits are present among unaffected relatives.

Based on the current study's findings and previous research, planning may be a potential trait marker in OCD, as both OCD and SIB groups had more difficulty executing the planning task than healthy controls, and OCD probands' planning performance was not associated with OCD symptom severity (*CY-BOCS*). More studies that investigate planning as a trait marker in childhood-onset OCD are still needed to support this hypothesis.

Decision-making. In the present study, decision-making was assessed using a measure of pre-decisional processing and reflection impulsivity, in which individuals were required to gather and evaluate information prior to making a decision and testing their hypothesis (Clark, Robbins, Ersche, & Sahakian, 2006). Among the four scores analyzed, siblings had a significantly different performance on the number of boxes opened in the decrementing reward condition [IST (mean box open decreasing)] in comparison to OCD probands and healthy control subjects. This suggests that when the conflict between reinforcement and certainty was introduced (i.e., decreasing condition), siblings minimized their reinforcement in favour of sampling more information until they were certain about their decision (e.g., lower tolerance for uncertainty). No other group differences were found for the remaining IST scores (i.e., number of trials in which subjects made the correct decision in both conditions, or the number of boxes opened in the fixed condition).

Symptom severity was not associated with OCD participants' performance in decision-making. However, there was a negative association between state anxiety and the total number of correct trials in the decreasing condition. This indicates that individuals who reported feeling more anxious before the session tended to choose the incorrect colour more often in the decreasing condition than those who had lower levels of state anxiety. Based on this finding, it appears that individuals with lower anxiety symptoms have increased tolerance for uncertainty.

Review of the literature in neurocognition in OCD indicates that Chamberlain et al. (2007a), Fadda et al. (2011), and Veale et al. (1996) have used the same task that was used in the present study (IST) to assess what they termed "reflection-impulsivity" and "set-shifting". None of the three studies identified significant group differences in the number of boxes opened across conditions. Chamberlain et al. (2007a) highlighted, however, that OCD patients exhibited limited

sensitivity to change in task structure (i.e., they opened a similar number of boxes in both conditions), pointing to higher levels of cognitive rigidity in relation to comparison groups.

Most of the studies on neurocognition in OCD (Lawrence et al., 2006; da Rocha et al., 2008; Tolin, Villavicencio, Umbach, & Kurtz, 2011), including the endophenotype research (Cavedini et al., 2010; Chamberlain et al., 2007b; Viswanath et al., 2009), have used the Iowa Gambling Task (IGT) or a similar measure to assess decision-making. Both Cavedini et al. (2010) and Viswanath et al. (2009) found that unaffected first-degree relatives of OCD probands demonstrated impairments in decision-making. In Cavedini et al.'s (2010) study, OCD probands and their unaffected relatives chose from the advantageous decks less frequently than HC probands and their relatives. Using the same task, Viswanath et al. (2009) reported that unaffected siblings of OCD probands tended to choose from the disadvantageous deck more frequently and from the advantageous deck less frequently. Disadvantageous decision-making on the IGT demonstrates a preference for immediate gains and limited thought about future consequences (Mata et al., 2011). Chamberlain et al. (2007b), however, did not report significant group differences on a comparable task to the IGT (i.e., Cambridge Gamble Task).

In contrast to Cavedini et al.'s (2010) heterogeneous OCD sample, Chamberlain et al. (2007b) recruited OCD adults with only washing/checking symptoms, who may have exhibited distinct neurocognitive traits. The only study that has investigated children's performance on the IGT (Kodaira et al., 2012) indicated impaired decision-making of the OCD group in comparison to matched healthy controls. None of the previous studies, however, controlled for state anxiety, a covariate that did show significant association with decision-making in the current study.

In terms of brain functioning, decision-making has been primarily associated with the medial part of the prefrontal cortex, which plays a significant role in goal-directed behaviour and

the updating of attentional biases or rules (Homberg, 2012). Review of the literature on neurobiological studies of decision-making processes in OCD (Sachdev & Malhi, 2005) indicates that OCD patients present with impairments in the dorsolateral, orbitofrontal, and anterior cingulate cortices, and its interaction with limbic regions, especially the amygdala and the basal ganglia. Furthermore, da Rocha et al. (2008) suggested that impairments in decision-making in OCD (measured by the IGT) are associated with serotonin transporter promoter polymorphism, which involves the orbitofrontal cortex and serotonergic system (Viswanath et al., 2009). Similarly, in children, Kodaira et al.'s findings (2012) suggested that OCD is associated with orbitofrontal-striatal-thalamic circuitry dysfunction.

Overall, it is challenging to compare this study's results with those of previous studies as decision-making has generally been measured using a different task (i.e., IGT). The few studies conducted with OCD participants using the IST did not identify deficits in decision-making in probands, consistent with this study's findings. However, to date, no first-degree relatives have been assessed using the IST, and no study has controlled for the effect of state anxiety on individual's test performance. It is possible that only siblings exhibited lower tolerance for uncertainty in the present study due to factors associated with family dynamics or family environment. For example, healthy siblings may experience a high degree of uncertainty in decision-making developed due to their OCD sibling's symptomology. As a result, siblings may prioritize being certain and making correct decisions (e.g., opening more boxes) over taking the chance to earn higher-valued rewards (e.g., receive more points in the decreasing condition).

When assessing decision-making using the IGT, two out of three OCD endophenotype studies have identified decision-making impairments in probands and first-degree relatives (Cavedini et al., 2010) or only in siblings of OCD subjects (Viswanath et al., 2009). Moreover,

the only study conducted with youth using the IGT also suggested deficits in decision-making. Based on neurobiological and OCD endophenotype findings as well as some evidence in the OCD neurocognition literature conducted with pediatric populations (using IGT), it is possible that decision-making deficits in OCD-affected youth may be present and better captured by the IGT test. Thus, future studies may administer an adapted version of the IGT to investigate decision-making deficits in childhood-onset OCD as well as include state anxiety as a covariate in their analyses.

  Cognitive flexibility. There was no evidence for differential performance between groups in cognitive flexibility using the IED. OCD participants' performance on this measure was not associated with symptom severity. However, cognitive inflexibility was negatively associated with FSIQ, suggesting that individuals with higher cognitive functioning tended to make fewer shifting errors than those with lower IQ. Consistent with this study's findings, three previous studies indicated that OCD probands and their first-degree relatives (Cavedini et al., 2010; Li et al. 2012) or unaffected siblings (Viswanath et al., 2009) did not demonstrate deficits in cognitive flexibility or set shifting on the WCST (a comparable measure to the IED). Using a different test (TMT), Delorme et al. (2007) and Li et al. (2012) reported that unaffected first-degree relatives of OCD probands also showed intact mental flexibility. In contrast, Chamberlain et al. (2007b) and Rajender et al. (2011) identified impaired cognitive flexibility in OCD probands and first-degree relatives using the IED and WCST, respectively. Although both studies matched the OCD with the HC group for age, sex, and IQ, their OCD samples were comprised of adult probands only with checking or washing symptoms, who could exhibit specific neural correlates.

  In the childhood-onset OCD literature, most studies pointed to intact cognitive flexibility on the WCST test (Beers et al., 1999; Kodaira et al., 2012; Ornstein et al., 2010), with the

exception of Shin et al. (2008). Although Shin et al. (2008) used age, IQ, and gender as covariates, it is possible that deficits in cognitive flexibility in their study may reflect type I error due to the small number of participants in each group (e.g., 17 OCD children, 23 healthy controls) combined with the large number of response variables (N=26) that were not corrected for multiple testing. In addition, no information regarding power and effect size was provided. Based on the current study's results, neither the OCD nor the SIB group presented with significantly different performance on the IED in comparison to healthy controls, which is generally consistent with the childhood-onset OCD and the OCD endophenotype literature. Discrepancy between the present study and Chamberlain et al.'s (2007b) and Rajender et al.'s (2011) findings could be due to the inclusion of specific OCD subtype participants in their samples.

Response inhibition. The current study did not find evidence for group differences in response inhibition, as measured by the SST, and symptom severity was not associated with OCD-affected youth's performance on this task. There was a negative association between SST scores and age, suggesting that younger subjects from all groups tended to display lower motor inhibitory control (larger SST scores). In contrast to this study's findings, Chamberlain et al. (2007b) identified impaired motor inhibition in OCD probands and first-degree relatives, and de Wit et al. (2012) reported that only OCD probands had impaired response inhibition (SST), compared to siblings and control subjects. While Chamberlain et al.'s (2007b) OCD sample exhibited specific washing/checking symptoms, in de Wit et al.'s study (2012), significant group differences between OCD and HC groups fell short of significance (p=0.04). Using a different task (i.e., Stroop), Rajender et al. (2011) also indicated deficits in inhibition in OCD probands

and their first-degree relatives. None of these researchers, however, used age as a covariate in the analyses, which was negatively associated with motor inhibitory control in the current study.

Review of the literature in childhood-onset OCD provides mixed support for deficits in response inhibition among OCD subjects. Ornstein et al. (2010) and Woolley et al. (2008) did not find significant differences between groups, and Beers et al. (1999) reported that, in fact, children with OCD performed better than healthy controls on a similar test to the SST. In contrast, Rosenberg et al. (1997) indicated that 18 medication free, nondepressed children with OCD showed impaired response suppression in comparison to their matched healthy controls on a oculomotor delayed response (ODR) task. The ODR task is fairly different from the traditional stop signal test that assesses response inhibition, making it difficult to compare Rosenberg's results with other studies. Overall, the current findings in this study are consistent with the childhood-onset OCD literature on response inhibition. Discrepancies between pediatric and adult studies may be due to differential progression of brain maturation or cognitive and executive function development (Anderson, 1998).

Working memory. In the present study, groups did not significantly differ on a measure of working memory (SWM), and performance on SWM was not associated with symptom severity in OCD-affected youth. There was a negative association between SWM and age, suggesting that younger subjects within all groups tended to make more errors in their search for tokens than older participants. While no study on endophenotype in OCD has directly assessed working memory using a specific working memory test (only visual memory), one study conducted with OCD-affected youth indicates that probands presented with intact working memory compared to healthy controls on the Spatial Span and N-Back Test (Ornstein et al., 2010). The literature on adults with OCD, however, provides inconsistent support. Purcell et al.

(1998a; 1998b) found significant working memory deficits in OCD patients on the SWM tasks, whereas Barnett et al. (1999), Chamberlain et al. (2004), and Nielen and Den Boer (2003) did not find impairment on the same measure. Similarly, Bannon and colleagues (2006), Barnett et al. (1999), and Moritz et al. (2002) reported that OCD patients presented with intact working memory on other working memory tasks (Auditory/Tracking Dual Task, Self-Ordered Search Task, and Digit Span, respectively).

　　　　Attention. In the present study, attention was assessed using the RVP task, which is a comparable measure to the widely used CPT. No significant difference in performance between groups was found, and there was no relationship between symptom severity and performance on this task. There was a negative association between RVP scores and age and gender, suggesting that younger subjects from all groups had a higher probability of responding both correctly and incorrectly to a sequence of numbers. In particular, males were more likely to respond incorrectly to those sequences than females, pointing to higher levels of impulsivity and lower ability to sustain attention. Similar to the current findings, Viswanath et al. (2009; CPT; TMT) and Rajender et al. (2011; CT; DVT; TT) did not find significant impairment of attention in siblings and first-degree relatives of OCD probands, respectively. Rajender et al. (2011), however, did report attention difficulties in OCD participants in comparison to their first-degree relatives and healthy controls. It is important to note that the task demands of the tests used in Rajender et al.'s study (2011) were fairly different from the RVP test used in the current study, making it difficult to compare the results. Overall, the current findings are similar to the literature in pediatric (Shin et al., 2008) and adult OCD (e.g., Ersche et al., 2012; Rao et al. 2008), which do not provide evidence for impaired attention in OCD.

Visual memory. No evidence for group differences in visual memory measured by the SRM task or a relationship between performance on SRM and symptom severity in OCD-affected youth was found in this study. However, there was a positive association between percentage of correct recall and age, suggesting that the older the subjects in any group, the better their performance on visual memory task. When comparing these findings to similar studies, it is noticeable that visual memory has been mostly assessed using the Rey Complex Figure Test (RCFT), test that combines visual memory and visual-spatial constructional abilities. To a lesser extent, the WMS Visual Memory and Spatial Span subtests have also assessed this domain in the previous literature. Research in endophenotype in OCD provides mixed findings. Viswanath et al. (2009) did not find significant impairment in visual memory (WMS Spatial Span and RCFT) in siblings of OCD probands. On the other hand, deficits in visual memory in OCD probands and siblings (Segalas et al., 2010; RCFT), probands and their parents (Li et al., 2012; WMS Visual Memory), and only probands but not their first-degree relatives (Rajender et al., 2011; RCFT) have been reported. Among the studies with discrepant findings, only Li et al. (2012) used a task other than the RCFT (i.e., WMS Visual Memory). The RCFT test also required visual-constructional ability rather than assessing visual memory by recalling the correct location of a block in a forced-choice paradigm (SRM). In addition, Li et al.'s (2012) sample was comprised of adult probands and their parents, and age (shown to be positively associated with performance on SRM) was not used as a covariate, which could have influenced the results.

Two studies in childhood-onset OCD that indicated impairments in visual memory used the RCFT (Andres et al., 2007; Ornstein et al., 2010). No OCD study conducted with pediatric populations used a similar task to the SRM that would provide more accurate comparison with

the current findings. With regard to the adult literature, using the SRM task, four out of five studies with adult participants identified deficits in visual memory in OCD (Barnett, 1999; Nielen & Den Boer, 2003; Purcell et al. 1998a; 1998b). Although OCD adults were matched for age in these studies, it is possible that differential progression of brain maturation and cognitive and executive function development may have contributed to discrepant findings. Overall, the three OCD endophenotype studies that assessed visual memory deficits in OCD and all the studies conducted with children used a visual memory task that measured both visual memory and visual-spatial constructional abilities and thus assessed a combination of different skills in comparison to the task used in the current study (i.e., SRM).

Summary of discrepant findings across endophenotype studies. There are numerous potential contributors to observed differences between the current and past endophenotype studies. These can be summarized within four main categories: (1) incomplete brain development in the current young sample, (2) failure of some past studies to consider group non-independence in analyses, (3) clinical profile differences between samples, and (4) the lack of 'gold standard' tests across studies to capture EF.

All eight previous studies conducted on endophenotype in OCD used adult samples, who may demonstrate different performance on neurocognitive tests in comparison to youth due to differential progression of brain maturation and cognitive and executive function development (Anderson, 1998). Similarly, all but Viswanath et al.'s (2009), Segalas et al.'s (2010), and de Wit et al.'s (2012) studies used a combination of first-degree relatives in their samples. It is possible that different developmental stages in first-degree relatives and decreased genetic susceptibility may have contributed to discrepant results. While Viswanath et al. (2009) had only unaffected

siblings from families with more than two affected members in their sample, recruitment in this study's sibling group allowed siblings from both multiply- and non-multiply-affected families.

Other OCD endophenotype studies used different analytic methods. While most studies investigated group differences using analysis of variance-based methods (Chamberlain et al., 2007; Li et al., 2012; Rajender et al., 2011; Segalas et al., 2010; Wit et al., 2012), none of these five studies tested family membership as a random factor for inclusion in the statistical model. Cavedini et al.'s study (2010) was the only one to acknowledge the lack of independence between probands and relatives in their sample, using independent t-tests to compare groups with the exception of the OCD and first-degree relatives groups. Cavedini et al.'s findings (2010) were consistent with the current study's results indicating deficits in planning and decision-making and intact cognitive flexibility in OCD-affected individuals and/or sibling participants. All but Segalas et al.'s (2010) and de Wit et al.'s (2012) studies did not include the covariates age and state anxiety and gender (respectively) in their analyses. Although some of the previous OCD endophenotype studies matched their samples for age, IQ, and gender, the present study controlled for the effects of age, gender, IQ, and state anxiety, which demonstrated to be associated with measures of neurocognitive functioning.

The clinical characteristics of the OCD sample (e.g., symptom dimension, medication, comorbidity with other psychiatric disorders) varied across studies. For example, in contrast to the current study's heterogeneous sample, Chamberlain et al. (2007b) and Rajender et al. (2011) only recruited OCD probands with washing/checking symptoms who were free from comorbidities. This particular group of participants may present with distinct neurocognitive correlates. Findings from a neuroimaging study that investigated neural correlates of washing, checking, and hoarding symptom dimensions in OCD indicated that different obsessive-

compulsive symptom dimensions were mediated by distinct components of fronto-striato-thalamic circuits associated with cognitive and emotion processing (Mataix-Cols et al., 2004). Thus, studying unique subgroups separately may provide more consistent findings across studies and, consequently, more robust evidence for endophenotypes candidates (Mataix-Cols et al., 2005).

Finally, given its broad definition, there is no specific consensus on how to operationalize and measure EF processes. Researchers have used similar tests to assess different constructs and, consequently, interpretation of findings has been compromised. For example, previous studies have assessed "mental flexibility" using one of the following tests: WCST, IED, Trail Making, or Stroop. However, most of these tests present with somewhat different demands. Similar to the IED, while the WCST assesses one's ability to develop abstract concepts, to shift and maintain cognitive set, and to utilize environmental feedback (Strauss et al., 2006), the Stroop test requires participants to maintain a goal in mind, while supressing habitual response, where reading ability and knowledge of colours are necessary. It may be that different task demands combined with higher levels of task impurity (EF tasks measure both executive and non-executive processes) may partially explain discrepant research findings, as it is difficult to determine whether the source of failure derives from executive or other functions (Strauss et al., 2006).

Table 15 provides a summary of this study's findings in relation to the OCD endophenotype literature. Overall, the current results are consistent with all the findings reported by Cavedini et al.'s (2010) study that indicated significant group differences in planning and decision-making and intact cognitive flexibility. Cavedini et al. (2010) was the only endophenotype study using OCD, first-degree relatives, and HC subjects that addressed the non-independence of groups.

Table 15. Summary of Current Findings on Neurocognitive Tasks for Youth with OCD, At-Risk Siblings, and Healthy Controls in Comparison to OCD Endophenotype Literature

Current Study's Neurocognitive Domains as a Candidate Endophenotype (measure)	Overall Group Difference in Current Study	Literature with Supporting Findings (measure)	Literature with Contradictory Findings (measure)
Cognitive Flexibility (IED)	Non-significant	Cavedini et al., 2010 (WCST)***; Delorme et al., 2007 (TMT)*; Li et al., 2012 (Stroop; TMT; WCST)***; Viswanath et al., 2009 (WCST)***	Chamberlain et al., 2007b (IED)***; Rajender et al., 2011(WCST)***
Decision-making (IST)	Significant	Cavedini et al., 2010 (IGT)***; Viswanath et al., 2009 (IGT)*	Chamberlain et al., 2007b (CGT)***
Planning (SOC)	Significant	Cavedini et al., 2010 (ToH)***; Delorme et al., 2007 (TOL)*; Li et al., 2012 (ToH)*** Rajender et al., 2011 (TOL time)**	Rajender et al., 2011 (TOL mean moves)***; Viswanath et al., 2009 (TOL)*
Response Inhibition (SST)	Non-significant	de Wit et al., 2012 (SST)*	Chamberlain et al., 2007b (SST)***; de Wit et al., 2012 (SST)** Rajender et al., 2011 (Stroop)***
Working Memory (SWM)	Non-significant	n/a	n/a
Attention (RVP)	Non-significant	Segalas et al., 2010 (WAIS)***; Viswanath et al., 2009 (CPT; TMT)*	Rajender et al., 2011(CT; DVT; TT)**
Visual Memory (SRM)	Non-significant	Viswanath et al., 2009 (WMS; RCFT)*	Li et al., 2012 (WMS)***; Rajender et al., 2011(RCFT)**; Segalas et al., 2010 (RCFT)***
Indirect EF (BRIEF)	Significant	n/a	n/a

n/a: No OCD endophenotype study has assessed this domain individually

Group(s) with significantly different performance (p<0.05): *** Both OCD and relative/SIB; ** Only OCD; * Only relative/SIB.

Indirect assessment of EF impact on daily functioning. To the author's knowledge, no

other study in the OCD literature has assessed parental perspectives of their children's daily

behaviour associated with EF domains. Data from the current study suggest that OCD probands demonstrate significantly greater deficits in EF-related behaviours at home (*BRIEF*), in comparison to their siblings and healthy controls. Siblings and healthy controls did not have a significantly different performance on this indirect measure of EF. One potential explanation for this is as follows: when OCD probands are triggered by intrusive thoughts and compulsive behaviours, they may have more difficulty engaging in age-appropriate behaviours assessed by the *BRIEF*. The following are examples of behaviours described by the *BRIEF* that may present as executive dysfunction in youth with OCD: (a) inhibition: difficulty resisting impulses and considering potential consequences of their actions before acting; (b) shifting: difficulty making transitions, tolerating change, and problem solving with flexibility; (c) emotional control: tendency to have emotional outbursts or frequent mood changes; (d) initiation: difficulty beginning a task or activity without being prompted to do so; (e) working memory: difficulty carrying out multistep activities or following instructions; (f) planning/organization: difficulty planning and organizing approach to problem solving; (g) organization of materials: difficulty organizing, keeping track of, and cleaning up one's belongings, and (i) monitoring: difficulty in regularly checking for mistakes in one's work and in being aware of one's behavior and the impact of this behavior on social interactions (Gioia et al., 2001).

The limited OCD literature examining effects of OCD symptomology on psychosocial, academic, and family functioning among youth provides comparable results to those provided via the *BRIEF* measure in this study. This captures a range of observed behaviour difficulties associated with OCD-affected youths' ability to self-regulate cognitive and social problem solving. Based on previous studies, OCD-identified youth exhibit a variety of functional impairments across diverse settings, often observed as difficulty with concentration on

schoolwork and homework completion (Piacentini et al., 2003), work productivity (APA, 2000), friendships and interpersonal skills (Adams, 2004; Adams & Burke, 1999; Sukhodolsky et al., 2005) and family relationships (Stewart et al., 2011). The current study indicates that executive dysfunction-associated behaviours that negatively impact functioning across environments are more common among OCD-affected youth when compared to their siblings and healthy controls.

Although OCD probands presented with significantly different scores, their overall group estimated mean (t-score=55.89) did not reach clinical significance as determined by the *BRIEF* (i.e., t-scores at or above 65). This suggests that, as a group, youth with OCD did not present with overall clinically significant executive dysfunction [*BRIEF* (gec)], as exhibited in their everyday behaviours. At the individual level, however, several OCD subjects exhibited clinically significant problem behaviours across domains as reported by their parents.

In the present study, OCD probands' scores on the *BRIEF* were significantly worse than those of siblings and healthy controls. Such performance differences between OCD and the other two groups were not found on standardized tests used in the current study, with the exception of the planning domain. Several reasons may account for discrepant performance between the *BRIEF* and direct measures of EF. First, challenges with the direct assessment of EF have been well documented in the literature. These include: inconsistency with the operationalization of the term EF and its domains and assessment, limited numbers of standardized EF measures that are developmentally appropriate for children, low test-retest reliability, concerns with task specificity and impurity, and lack of process-behaviour correspondence (Anderson et al., 2001; Baron, 2004; Strauss et al., 2006). Second, the *BRIEF* measures adults' perception of their child's manifestation of impaired EF rather than directly measuring the child's EF (Maricle & Avirett, 2012). Parents could also have a biased view of their children's daily functioning due to

previous challenges in dealing with their children's OCD. As a result, parents may have over reported on their children's executive dysfunction. Finally, the lack of relationship between indirect and direct measurements of EF could also reflect the lack of ecological validity of objective EF measures (Dawson & Guare, 2004; Lezak et al., 2004). While behavioural rating scales may identify the individual's ability to function with or without distraction or support in their regular environment, direct testing provides information about one's executive functioning under ideal environmental conditions.

Findings from the present study also indicate that there was a negative association between *BRIEF* scores and OCD probands' assessed intelligence (FSIQ). This indicates that the lower the IQ of OCD participants, the more problem behaviours their parents reported. No relationship between symptom severity and *BRIEF* scores was found, suggesting that the reported EF deficit were not merely a result of OCD symptoms. Such lack of association could be due to the different constructs that these measures assessed. While the *CY-BOCS* measured the severity and intensity of obsession and compulsions over the previous week, the *BRIEF* targeted daily behaviours related to self-control and problem-solving skills. In addition, the informants of these measures were not the same. For the *CY-BOCS*, youth's report on the severity of their symptoms were rated by the examiner, whereas parents rated their children's daily functioning on the *BRIEF*.

Based on the aforementioned factors, it appears that in the current study the *BRIEF* provides information about observable executive deficits of daily functioning that may be influenced by youth's manifestation of OCD symptoms. This suggests that when youth with OCD are more vulnerable to environmental triggers, or are actually triggered by obsessions

and/or compulsions, parents tend to perceive their executive function-related behaviours (as assessed by the *BRIEF*) as more impaired than those of siblings and healthy controls.

Implications of the Findings

This study is among the first to investigate neurocognitive deficits as potential candidate endophenotypes in OCD-affected youth, when comparing OCD probands' performance with their unaffected, at-risk siblings and healthy controls. Data from the present study found that both OCD and sibling participants exhibited planning task difficulties that were independent of OCD symptomology, suggesting that planning may be a potential endophenotypic marker in OCD. Providing evidence for potential vulnerability markers for the development of OCD in youth contributes to the very limited body of research in this area (Chamberlain & Menzies, 2013; Freeman et al., 2013).

The following paragraphs discuss the implications of the findings regarding the importance of increased awareness of neurocognitive deficits in OCD as an avenue to improve OCD-affected youth's functioning across settings, to provide information into advancement of treatment interventions, and to assist with future identification of those at risk for developing the disorder.

Improved functioning of youth with OCD. Based on evidence, OCD symptoms have significant impact on family relationships, peer interaction, and academic functioning (Geller et al., 1998; Hollander et al., 1998). While most of the research on general life functioning in youth with OCD has investigated the effects of OCD symptoms on family or psychosocial functioning (Leininger et al., 2007; Piacentini et al., 2003; Stewart et al., 2011; Storch et al., 2006), limited literature has examined reasons why OCD-affected students may exhibit impaired academic functioning (Adams et al., 2007; Parker & Stewart, 1994). Findings from the present study contribute to the limited knowledge regarding the unexplored hypothesis that potential

impairments in neurocognition of childhood-onset OCD could at least partially underlie academic challenges. Because schools may be an optimal setting for detecting OCD and proving early intervention, school personnel can play a key role in recognizing and addressing the presence of OCD symptoms and neurocognitive deficits in academic settings. In particular, via direct and indirect assessment of neurocognitive functioning, a student's strengths and weaknesses could be identified, with subsequent development of school interventions to address potential impairments in academic functioning. Increased awareness of neurocognitive deficits in OCD-affected youth may assist school personnel in developing accommodations and/or modifications to the curriculum, implementing school interventions that target OCD-affected students' unique needs and, consequently, promoting youth's successful outcomes at school.

School psychologists are in a unique, and in many ways ideal, position to facilitate the identification of youth with OCD at schools and to provide appropriate services to support these students academically and behaviourally (Sloman et al., 2007). Among potential strategies that school psychologists can implement in the school setting, increasing school staff and parents' awareness and recognition about OCD symptomology (Leininger et al., 2010) and its impact on school functioning are priorities. School psychologists could help school personnel and parents to understand that students with OCD may present with inattentive, disruptive, or oppositional behaviour that could reflect their struggle with obsessions and compulsions (Jones, Sulkowski, & Wingfield, 2011). Information about the effects of potential neurocognitive deficits on school performance could also provide insight into development of Individual Education Plans (IEPs), adaptations of schoolwork, and implementation of individual interventions targeting academic as well as behaviour functioning. These could include: (a) providing assistance to students to set short-term goals (e.g., select a topic, identify necessary materials, and identify project tasks and

due date), to manage current and future-oriented task demands, and to chart their progress; (b) allowing breaks during tests and extended time for homework and projects; (c) teaching strategies for transitions from one task to another and decision-making skills; and (d) having differential consequences for situations or behaviours affected by OCD symptomology, such as absenteeism, tardiness, or school refusal (Carter et al., 1999; Jones et al., 2011; Kusche & Greenberg, 1994; Leininger et al., 2010).

Findings from the current study highlight the importance of incorporating a multi-level approach within assessment of neurocognitive performance in youth. Gathering information about OCD-affected youth's neurocognitive functioning on performance-based measures and rating scales can increase the understanding about the manifestation of EF processes across environments that require different demands on EF. These data may be helpful for designing interventions targeting individuals' unique needs and tracking both positive and negative behavioural changes in youth's response to intervention. In particular, given the expertise of school psychologists in administering and/or interpreting results derived from both performance measures and rating scales, these professionals could provide guidance to parents, teachers, and mental health clinicians on (a) better understanding youth's EF functioning in relation to everyday home tasks, schooling, and treatment; (b) developing interventions, and (c) progress monitoring changes in behaviour, academic performance, and OCD symptomology in response to school interventions, outside-school CBT treatment, and/or medication (Isiquith et al., 2013; Jones et al., 2011).

Advance in treatment intervention. Identification and increased awareness of neurocognitive deficits in youth with OCD may also provide potential indicators of response to CBT. In a study that examined the impact of neuropsychological function on treatment outcome

in childhood-onset OCD (Flessner et al., 2010), visual-constructional ability, as measured by the RCFT, was predictive of response to treatment among youth receiving CBT alone. In addition, review of childhood-onset OCD CBT studies suggested that treatment approaches could be enhanced by strategies aimed to improve neurocognitive deficits, while addressing symptomology through evidence-based protocols (Freeman et al., 2013). For example, if more studies provide evidence that deficit in planning is an endophenotypic marker in youth with OCD, treatment protocols could include intervention strategies that directly address planning skill development. During treatment sessions, therapists could assist clients to set goals for ERPs and homework, and collaboratively develop a plan to achieve such goals (Guare, 2013). Therapists could coach clients through the development of planning skills, but with success, support would be gradually faded out.

Moreover, increased awareness of neurocognitive deficits in youth with OCD could not only enhance treatment strategies, but also inform clinicians and psychiatrists about the impact of EF deficits on school and home functioning, helping the development of treatment plans. Neurocognitive assessment could be integrated into clinical assessments conducted at hospital-based or community-based OCD programs. Professionals with expertise on neurocognitive deficits in youth and school and home functioning, such as school psychologists, could become part of OCD treatment teams. One of the main goals of including school psychologists in such programs would be to liaise with schools and support families to promote OCD-affected students functioning across environments.

Insight into early identification of OCD. Finally, research supports that OCD is a clinically heterogeneous condition characterized by specific symptom dimensions (Mataix-Cols et al., 2007). Its behavioural presentation may be similar to other psychiatric conditions such as

anxiety disorders, Tourette syndrome, ADHD, depressive and psychotic disorders, and autism (Hollander, Poskar, & Gerard, 2012). And while some of these other disorders also have associated neurocognitive deficits, increased awareness of neurocognitive deficits in OCD may enhance the understanding of the neurobiology and underlying mechanisms associated with OCD (Chamberlain & Menzies, 2013). Having knowledge about neurocognitive impairments in OCD and behaviours associated with executive dysfunction may provide additional information that would help with early identification of those at risk for developing the disorder. Being able to early identify OCD may help individuals from experiencing delay in treatment, prevent or lower distress and impairment, and promote better quality of life and social adjustment including healthier family, school, and social functioning (Bannon, 2003).

Strengths and Limitations

Strengths. The current study is among the first to examine potential neurocognitive markers in OCD-affected youth. This advancement in the OCD endophenotype research is important, as childhood-onset OCD has a higher vulnerability to genetic influence than adult-onset OCD (van Grootheest et al., 2005). Neurocognitive traits have shown to be more closely related to genetic influence than diagnostic classifications. As a result, findings from this study add to the limited body of research aiming to identify genes concerning OCD vulnerability.

The present study addresses ecological validity of EF, or the "functional and predictive relation between the patient's behavior on a set of neuropsychological tests and the patient's behavior in a variety of real-world settings" (Sbordone, 1996, p. 16). The ecological validity construct has been consistently neglected in the empirical literature (Anderson, 2002; Baron, 2003; Dawson & Guare, 2004; Lezak et al., 2004) and, in particular in the OCD literature (Isiquith et al., 2013). Measuring EF through indirect means, via parent rating scales, can provide meaningful information about executive dysfunction in real-life situations, serving as a tool to

measure, understand, and monitor improvements in daily functioning as interventions are implemented.

One of the unique aspects of this study is related to the analytic method used, which addressed previous flaws in the OCD endophenotype literature regarding the assumption of independence of groups (i.e., OCD probands and first-degree relatives). The data in this study accounted for non-independence of groups by testing family as a random factor before analyzing significant group differences. In response to previous critiques of OCD neurocognitive studies (Kuelz et al., 2004), state anxiety was also assessed and included as a covariate in the analysis, in addition to age, FSIQ, and gender.

This study also assessed a wide range of neurocognitive domains that have been hypothesized to be impaired in OCD-affected individuals. Providing additional data on neurocognitive functioning in OCD, especially among youth, adds to the very limited body of research in this area.

In contrast to the few OCD endophenotype studies, the current study included a sibling group, as opposed to relatives from multiple generations. Siblings are at a higher genetic risk for developing OCD (Hanna et al., 2005) and also may be at more similar neurodevelopmental stages in comparison to multiple generation relatives (Viswanath et al., 2009). In the present study, the healthy control group was initially screened for a family history of OCD and Tourette syndrome and assessed for *DSM-IV-TR* Axis I disorders using the *ADIS-P* interview. Such a procedure has not been consistently used in the cognitive and brain literature (Chamberlain & Menzies, 2009). Disconfirming a family history of OCD or Tourette syndrome and lifetime *DSM-IV-TR* Axis I psychiatric disorder, lowered the chances of healthy controls having a genetic

susceptibility for OCD and their neurocognitive performance being impacted by undiagnosed psychiatric problems.

Finally, to translate the current research findings into clinical practice, the author provided families with a written and/or verbal summary of the assessment results. This method proved to be of significant value to the families who reported having gained more information about their children's neurocognitive strengths and weaknesses, and to be better informed about the importance of neurocognition in youth's functioning. This suggests that in both school and research settings examining neurocognitive functioning in OCD-affected youth, reports summarizing the results to parents may be an additional positive intervention.

Limitations. The following paragraphs discuss limitations of the current study with respect to sample characteristics and measures administered.

Sample characteristics. Although comparable to previous OCD neurocognitive studies, sample sizes in the current study were small, limiting the generalizability of the findings and the ability to detect group differences on neurocognitive performance. Healthy control subjects were recruited through poster advertisements and word of mouth, thus not recruited randomly through the general population. Given the challenges of recruiting OCD participants and unaffected siblings, the age range required for inclusion in the study was broad (i.e., between ages 8 and 18 years). Although age was included as a covariate in analyses, pubertal stage, which is marked by hormonal, neuro-maturational, and behaviour changes, was not assessed. As a result, it is possible that brain maturation and EF development may have impacted the participants' performance on the neurocognitive tasks administered (Gur et al., 2012).

The current findings were also limited by other potentially confounding variables, including heterogeneous symptom dimensions, use of psychotropic medications, treatment

history, and comorbid illnesses. OCD probands were not divided into obsessive and compulsive symptom subtypes due to the sample size, which reduced the ability to investigate differences in neurocognitive functioning among OCD subtypes (Shin et al., 2008). Jang et al. (2010) reported that impairments in nonverbal memory and organizational strategies in adults with OCD were associated with the symmetry/ordering dimension and the obsessions/checking dimension, respectively. This implies that distinct symptom dimensions may mediate neurocognitive dysfunction, and potentially significant group differences would be more sensitively captured if OCD probands were divided according to symptom subtype.

Although some of the participants were taking medications at the time of assessment, the effect of medication on neurocognitive test performance was not controlled. Of note, however, none of the subjects were taking medications such as stimulants or cognitive enhancers that are known to improve test performance. According to Chamberlain et al. (2007a), most studies indicate that cognitive impairments persist in OCD probands receiving chronic SSRI treatment. Similarly, Mataix-Cols et al. (2002) reported that SSRIs have no impact on neurocognitive function in OCD. However, other researchers in brain functioning have suggested that medication may alter some structures of the brain and induce cognitive deficits (e.g., reduction in thalamic volume; Rosenberg, Benazon, Gilbert, Sullivan, & Moore, 2000).

The present study did not control for OCD participants' treatment history. The literature regarding the effect of CBT treatment on neurocognitive functioning in OCD is limited and contradictory (Kim et al., 2002; Nielen & Den Boer, 2003; Roh et al., 2005). Some researchers indicate that even though OCD probands have stable neurocognitive deficits, some of these impairments (e.g., visual-spatial memory, verbal fluency) may improve after treatment (Kim et

al., 2002; Roh et al., 2005). Others suggest no changes in cognitive deficits (i.e., planning) following CBT (Nielen & Den Boer, 2003).

Finally, although comorbid illnesses, including bipolar disorder, major depressive disorder, psychosis, substance use, and autism, were defined as exclusion criteria for OCD-affected subjects, OCD probands' comorbidity with other *DSM-IV-TR* Axis I diagnosis (e.g., anxiety disorders, ADHD) was not controlled. Siblings with psychiatric diagnosis (e.g., ADHD, anxiety) were included in the study. Evidence suggests that comorbid disorders, such as ADHD, could impact neurocognitive performance (Barkley, 2003; Brown, 2006).

Measures. While the *CANTAB* tests assessing EF have been validated for use in children, age-standardized norms for this population are limited. In particular, no norms for children are available for the IST and SST tests. As a result, raw scores using age as a covariate were analyzed and the group*age interaction was tested for inclusion in the model. Given time constrains, only one test was administered per neurocognitive domain rather than using multiple tasks. Using more than one measure for each executive process may address issues associated with task impurity (Miyake et al., 2000b).

While the *BRIEF* provided information about parent perceptions of their children's behaviour associated with EF domains and addressed ecological validity, results may represent their unique perspective of a child's behaviour. To identify the best informant regarding a child's psychopathology and behaviour, it is suggested that the child's age (i.e., younger versus older), the problem type (i.e., internalizing versus externalizing), and the setting (i.e., inpatient versus outpatient) be considered (Smith, 2007). For internalizing problems in younger children (i.e., aged 12 years or younger), parents are considered the best informants, followed by the child, and then the teacher. However, for reporting on internalizing problems of older children, the child is

considered the best informant, followed by the parent, and then the teacher. Including multiple observers' perspectives on individuals' everyday behaviour associated with EF domains could also provide a more comprehensive view than a single observer.

Future Directions

Future studies with larger sample sizes are warranted to provide evidence regarding potentially heritable neurocognitive trait markers in childhood-onset OCD. Both OCD probands and unaffected siblings from multiply-affected families should be included in the sample. Specifically, further investigation into possible planning and decision-making deficits in youth with OCD and their siblings is suggested. When developing such studies, researchers may consider recruiting OCD-sibling pairs to better assess differences in neurocognitive performance and to determine if OCD-sibling differences are distinct from OCD-healthy control differences. In addition, most OCD endophenotype studies have violated the assumption of group independence in analysis of variance-based methods. Thus, future studies that examine group differences between OCD, relative, and healthy control subjects should test the random effect for family for inclusion in the model.

Given the high comorbidity between OCD and ADHD, and the hypothesis that comorbid ADHD, Tourette syndrome, and tic disorders may represent distinct familial subtypes (Geller et al., 2012), future studies aimed at improving treatment responses and outcomes may include a measure of attention, such as the RVP, as a covariate to control for the effects of inattention on test performance. Moreover, future studies examining mutually exclusive groups of youth with OCD-only, ADHD-only and OCD+ADHD would help to disentangle potential neurocognitive deficits associated with these commonly comorbid disorders.

To address pubertal influences, future studies may take into account pubertal status when selecting and matching the samples. The Tanner scale has been widely used to describe the onset

and progression of pubertal changes (Marshall & Tanner, 1969; 1970; van Buuren, 2013), where boys and girls rate their developmental stage based on external sex characteristics (i.e., pre-pubertal = Tanner 1, pubertal = Tanner 2-4, and post-pubertal = Tanner 5).

Future studies may also use multiple tasks to assess each EF process. It is suggested that a minimum of two tests per domain be administered (Miyake et al., 2000b). If time constraint for testing is an issue, prioritizing the domains assessed would be essential. It is suggested that further investigation into planning, decision-making, followed by cognitive flexibility, response inhibition, working memory, visual memory, and attention, be investigated. When assessing decision-making in youth with OCD, future studies may also use the children's adapted version of the IGT to allow comparison of findings among other OCD endophenotype adult studies.

To address the mismatch between EF tests used and the constructs that they propose to measure, it would be important for future review papers on neurocognition in OCD to summarize research findings based on a consistent correspondence between EF tests and EF domains. This would improve the comparison and interpretation of research findings. Moreover, there is a need for meta-analysis studies that address neurocognition in childhood-onset OCD. Such studies should consider differences in analytic methods, taking into account the non-independence of groups, covariates used, and tests selected, as well as information about the clinical characteristics of the samples, including OCD subtype, comorbidity, and treatment and medication history.

Finally, no study to date has investigated the impact of neurocognitive functioning on youth with OCD and their academic performance through the use of standardized assessment and rating scales. It is possible that academic difficulty may not be solely linked to OCD symptoms, but also related to neurocognitive deficits in OCD. There is a need to further investigate whether

potential neurocognitive impairment in OCD could be contributing to limited school functioning. Having studies that explore neurocognitive and academic performance in youth with OCD may promote the development of effective interventions that target symptomology, as well as educational and social performance across environments.

Summary and Conclusions

OCD affects 1-3% of the population, occurs in both children and adults, and can be a life-long illness (Weissman et al., 1994). This disorder has complex genetic underpinnings, with a 10-fold increased risk between siblings of OCD-affected youth (Pauls, 2012). Investigating neurocognitive characteristics in clinical populations is a promising method to identify vulnerability markers in psychiatric disorders, and in OCD specifically (Chamberlain & Menzies, 2009). Only eight studies have been published on neurocognitive trait markers in OCD, all conducted with adult samples (Cavedini et al., 2010; Chamberlain et al., 2007b; Delorme et al., 2007; Li et al., 2012; Rajender et al., 2011; Segalas et al., 2010; Viswanathet al., 2009; de Wit et al. 2012). However, childhood-onset OCD is known to have markedly greater genetic influence than that in adulthood (van Grootheest et al., 2005). No study to date has investigated potentially heritable neural correlates of childhood-onset OCD through the assessment of neurocognitive domains. Given the impact that OCD has on family relationships, academic functioning, and peer interaction (Geller et al., 1998; Hollander et al., 1998), increased awareness about potential neurocognitive deficits in OCD-affected youth could provide information into interventions that would improve youth's functioning across environments. In addition, increased knowledge of neurocognitive traits could assist with future identification of those at risk for developing the disorder.

This is among the first studies examining neurocognitive functioning of youth with OCD, in comparison to their unaffected siblings and healthy controls that addressed ecological validity

of the EF performance measures. This study is one of the few to address group independency in its analyses. To accomplish the goals of the study, OCD-affected youth and their siblings were recruited from the Pediatric OCD Program, and healthy control subjects from advertisement posters. Participants were directly assessed using measures of EF (i.e., cognitive flexibility, decision-making, planning, response inhibition, and working memory), attention, visual memory, intelligence, state anxiety, and obsessive and compulsive symptoms severity. An indirect assessment of EF, via parent rating scale, was also performed to provide supplemental information about everyday behaviour associated with EF domains. ANCOVA was used in analyses to examine group effects on the response variables and, mixed model ANCOVA was used, labelling family ID as a random factor, to assess group differences on the response inhibition test.

Through objective assessment of neurocognitive functioning, via standardized testing, overall findings indicated that youth with OCD presented with significant deficits in planning in comparison to healthy controls, but not siblings. Siblings' performance in planning was worse than that of healthy controls, demonstrating a trend towards a deficit, although not reaching statistical significance. Impaired planning was primarily observed in OCD participants followed by siblings. Only siblings' performance in decision-making was significantly different from that of OCD probands and healthy controls, suggesting that siblings tended to gather more information before making a decision, despite being penalized for increased information sampling. There was no evidence to support group differences in the other examined neurocognitive areas (i.e., cognitive flexibility, response inhibition, working memory, sustained attention, and visual memory). Symptom severity was not associated with neurocognitive

performance of OCD-affected youth, whereas higher levels of state anxiety were associated with poorer decision-making across all groups.

Moreover, based on parental report, OCD probands had significantly worse scores on a measure of daily behaviour associated with EF when compared to SIB and HC subjects. This suggests that OCD probands exhibited more problem behaviours in the areas of planning/organization, inhibition, shifting, emotional control, initiation, working memory and organization of materials.

Findings from the current study suggest that planning may be a potential trait marker in OCD, as both OCD and SIB groups had more difficulty executing the planning task than healthy controls, and performance in planning was independent of symptom severity among OCD probands. Planning has been implicated in the search for endophenotype in OCD, and the current results are consistent with prior research conducted with OCD adult participants and their first-degree relatives. The current findings contribute to the limited knowledge regarding the unexplored hypothesis that potential impairments in neurocognition of childhood-onset OCD could at least partially underlie academic challenges. Because schools may be an optimal setting for detecting OCD and proving early intervention, increased awareness of neurocognitive deficits in OCD-affected youth may assist schools in developing and implementing interventions that target OCD-affected students' unique needs and promoting youth's successful outcomes. Increased awareness of neurocognitive deficits in OCD may also provide information into advancement of treatment interventions by including strategies aimed to improve neurocognitive deficits, while addressing symptomology through evidence-based protocols. While some of other neuropsychiatric disorders also have associated neurocognitive deficits, increased awareness of neurocognitive impairments in OCD may enhance the understanding of the neurobiology and

underlying mechanisms associated with OCD. Future studies that explore neurocognitive

functioning in OCD-affected youth are needed to promote the development of effective

interventions that target symptomology, as well as educational and social performance across

environments.

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NEUROCOGNITION IN OCD-AFFECTED YOUTH
TELEPHONE SCREEN FOR SIBLINGS AND HEALTHY CONTROLS (GROUPS 2 AND 3)

Date of Intake: _____   Administered by: _____

Name of child: _____   Name of parent or guardian: _____

Phone number: _____   Email address: _____

How did you hear about this study? _____

How old are you (your child)? _____   DOB: ___/___/___   Gender: Male   Female

[Briefly explain study/confirm consent]

FOR SIBLINGS (Group 2):
1. Have one or more of your child's full biological siblings been diagnosed with OCD?   YES   NO
          Note: IF NO, SUBJECT IS EXCLUDED

FOR HC COHORT (Group 3):
1. Has anyone in your family (first-degree relative) ever been diagnosed with OCD?   YES   NO
          Note: IF YES, SUBJECT IS EXCLUDED

2. Has your child ever been formally diagnosed with a mental health condition (e.g., ADHD, Anxiety, depression)?   YES   NO
          Note: IF YES, SUBJECT IS EXCLUDED

3. Has your child ever experienced OCD or Tourette syndrome?   YES   NO
          Note: IF YES, SUBJECT IS EXCLUDED

FOR ALL SUBJECTS (Group 2 and 3):
1. Does your child currently have a diagnosis of bipolar disorder, major depressive disorder, psychosis, mental retardation, pervasive development disorders, or current or past substance abuse or dependence (including street drugs such as marijuana)?   YES   NO
          Note: IF YES, SUBJECT IS EXCLUDED

A STUDY OF NEUROCOGNITION IN OCD-AFFECTED YOUTH, AT-RISK SIBLINGS AND HEALTHY CONTROLS

Parent Consent Form for OCD-Affected Subjects

Principal Investigator:

S. Evelyn Stewart, MD
Director, OCD Clinic & Translational Research Program, BC Children's Hospital (BCCH)
Associate Professor, Psychiatry, University of British Columbia (UBC)

Co-Investigators:
Juliana Negreiros, MA
UBC School Psychology Doctoral Student, Educational and Counselling Psychology and Special Ed.

Lynn D. Miller, PhD
UBC Associate Professor and Research Supervisor, Educational and Counselling Psychology and Special Ed.

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Noel Gregorowski, MSW, RCSW
Social Worker, OCD Clinic & Translational Research Program, BCCH
Social Worker, Mood & Anxiety Disorder Clinic, BCCH

Introduction:

Your child or youth is being invited to participate in this study (separate consent or assent form) that looks at how neurocognitive abilities of children with obsessive-compulsive disorder (OCD) may be different from those who do not have OCD. This study will also look at whether there are similar neurocognitive characteristics in children with OCD and their siblings that are passed on from parent(s) to child (heritable).

This study is NOT mandatory for your child to participate in an OCD study of our program.

Voluntary Participation:

Your child's participation is entirely voluntary, so it is up to you to decide whether or not to take part in this neurocognitive assessment study. Before you decide, it is important for you to understand what is involved. This consent form will tell you about the assessment process, why it is important to collect neurocognitive data, what will happen to the collected data, and the possible benefits, risks and discomforts. If you wish for your child to participate, you and your child will be invited to sign the consent/assent forms. If your child does decide to take part, s/he is still free to withdraw at any time, without giving any reasons for his/her decision. If you do not wish your child to participate, you do not have to provide any reason for your decision nor will you or your child lose the benefit of any medical care to which you are entitled or may be presently receiving. Please take time to read the following information carefully and to discuss it with your family and doctor before deciding.

Who is conducting the study?

This part of the study is being conducted by Dr. Evelyn Stewart and her team at the OCD Clinic and Translational Research Program ("OCD Program") at BC Children's Hospital (BCCH). Dr. Stewart and her team have no conflicts or potential conflicts of interest with respect to remuneration for conducting or being involved with this study or with the possibility of commercialization of research findings. There is no intention to commercialize. This research is being funded by the Michael Smith Foundation for Health Research (MSFHR) and by start-up funds provided to Dr. Stewart by UBC and PHSA.

Background:

OCD affects 1% to 3% of the population, occurs in both children and adults, and can be a life-long illness. Both genetics and environmental factors contribute to the onset of OCD. Research studies have shown that the disorder is 5–7 times more frequent in first-degree relatives of OCD patients than healthy controls.

Purpose:

Your child is being invited to participate in this effort because s/he has been diagnosed with OCD and it is important to study which neurocognitive abilities may be contributing to OCD as well as better understand the heritability of cognitive traits in OCD. Results from this study may lead to improved OCD treatment approaches.

Who can participate in the study?

This is open to any child or sibling of a child diagnosed with OCD. It is also open to any participants who do not have a family history of OCD (i.e., healthy controls). Participation in this neurocognitive assessment is optional.

Who should not participate in this study?

Those not providing consent should not take part, as well as those with a current diagnosis of major depressive disorder, bipolar disorder, psychosis, mental retardation or pervasive developmental disorder (e.g., autism), and current or past substance dependence/abuse.

Study Procedures:

If you decide for your child to participate in the neurocognitive assessment, you will be asked to complete two questionnaires: one about your child's behaviours observed at home (completion time: 10 to 15 minutes) and another one about your child's background and academic functioning (completion time: 5 minutes). Your child will be asked to complete a very brief questionnaire about his/her feelings before starting the assessment (less than 5 minutes), as well as to answer questions related to verbal knowledge, memory, attention, and problem-solving skills. This can be done during one study visit. This may take 2 to 2.5 hours of your child's time. The assessment will be conducted with your child <u>one time only</u>, if s/he has agreed to participate (on the separate study consent/assent forms).

If your child chooses to participate in the study, a certified school psychologist (Juliana Negreiros) or a trained research assistant will conduct the assessment at an office located at the Child and Family Research Institute (CFRI). If you prefer, there is the option of conducting the assessment in a quiet room at your house. During the assessment, breaks will be provided accordingly to your child's needs.

All data collected will only have unique study code numbers (no personal information, such as names and birthdates, will be used; information will be **"de- identified"**). De- identified data will be securely stored in the BC Mental Health & Addictions Research Institute (BCMHARI) laboratory, Child & Family Research Institute building (CFRI), Vancouver. All data will be kept for a minimum of 5 years from the date of publication and/or presentation of the findings as per the University of British Columbia (UBC) policy. Any study forms that contain personally identifying information of your child (e.g., signed consent forms) will be kept separately from research records in separate locked filing cabinets at BCMHARI. Only Dr. Stewart, her immediate team members, and certain lab/research colleagues will have access to the data. The neurocognitive assessment will be done for research purposes only. Test results from this assessment will <u>not</u> be placed in your child's medical records. If requested, a written report with the results of this assessment will be mailed to your home.

Given the need for large sample sizes to study psychiatric illnesses, your child's de-identified data may potentially be sent to other research labs to study OCD and psychiatric disorders, which will be at the discretion of the study Principal Investigator (PI). No personal identifying information will be forwarded with these samples. You will not have to pay for being in this study, but your child will be compensated in a form of a gift card for taking part.

Potential Risks:

There are no known anticipated risks of the proposed study, although the tests may be considered by some individuals challenging and tiring and, therefore, may result in your child's temporary increase in anxiety level, lack of motivation, or fatigue. Test breaks will be provided accordingly. If at any point your child wishes to discontinue, the assessment will be stopped. In addition, the examiner will monitor your child's reactions and may suspend or ask if s/he would

like to delay or stop the assessment if s/he appears or reports feeling overly anxious, distressed, or tired due to the testing demands.

Although individual neurocognitive results with identifying data will only be verbally reported back to you upon request, there are potential non-physical risks associated with this type of research, such as the possibility of discrimination towards you or your family members by others (such as employers, insurance providers) if discovered that you and/or your family are participating in neurocognitive research involving a psychiatric illness. The risk of such data being released is very small.

Potential Benefits:

There may not be any direct benefits to you from participating in this neurocognitive assessment study. However, if requested, a written report with the results of this assessment will be mailed to your home. This report will be written by a certified school psychologist with extensive experience in reporting back test results to families.

Withdrawing your consent to participate:

Your child's participation in this study is entirely voluntary. If your child takes part in the neurocognitive research study and later decide to withdraw at any time in the future, there will be no penalty or loss of benefits to which you or your child are otherwise entitled, and your and your child's current or future medical care will not be affected. If you wish for your child's test results to be destroyed, you may make this request in writing. If you request destruction/removal of your child's data, any data that may have been sent to an associated lab will also be destroyed (this will be confirmed in writing from each recipient lab).

Compensation for participating in this study:

To compensate your child for completing the neurocognitive assessment, s/he will receive a $25 gift card after the assessment session. Travel or parking expenses will not be reimbursed.

Confidentiality:

Your confidentiality will be respected. However, research records and medical records identifying you may be inspected in the presence of Dr. Stewart or her designate by representatives of the UBC Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your child's identity be removed or released without your consent unless required by law.

Your child will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about your child during the course of this study, so that your child's identity (i.e., your child's name or any other information that could identify your child) as a subject in this study will be kept confidential. A study email account will be created for each child in order to complete an online questionnaire about how the participant feels right before the session. This study email account will contain only your child's study number (with no personal identifiers). This email account will be de-activated once the study is completed. Information that contains your child's identity will remain only with Dr. Stewart and/or designate. The list that matches your child's name to the unique identifier that is used on your research-related information will not be removed or released without your consent unless required by law.

Your child will not be identified by name or initials in any medical journal publications resulting from this research. This research information may also be used for educational purposes (public awareness events, medical conferences, teaching of healthcare professionals) but your child's identity will be kept confidential. Collected data will not be stored with identifying information, and identifying information will not be released or published. Your child's data will be given a unique study number and only this will be on your child's test protocols.

Your child's rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to Dr. Stewart.

Contact for Information about the Study:

If you have any questions or concerns or would like more information about this research at any time during your involvement, you may contact, Dr. Stewart at XXXXX, or Juliana Negreiros or Rhonda Ellwyn at XXXXX

Contact for Concerns about the Rights of Research Subjects:

If you have any concerns about your treatment or rights as a research subject, you may contact the Research Subject Information Line in the UBC Office of Research Services at XXXX

Consent to Participate:
I have read and understood the subject information and consent form for my child to participate in the OCD neurocognition study.
- *I have had sufficient time to consider the information provided and to ask for advice if necessary.*
- *I have had the opportunity to ask questions and have had satisfactory responses to my questions.*
- *I understand that my child's neurocognitive data and information will be kept strictly confidential and that the result will only be used for scientific objectives.*
- *I understand that my child's participation is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without affecting our participation in future studies and without changing the care that my child or I receive.*
- *I understand that I am not waiving any of my child's or my legal rights as a result of signing this consent form.*
- *I understand that there is no guarantee that this study will provide any benefits to my family or myself.*
- *I understand that my child will receive a $30 gift card for completing a neurocognitive assessment.*
- *I have read this form and I freely consent for my child to participate in this study.*
- *I understand that I will receive a dated and signed copy of this form to keep for myself.*

You consent your child to participate in the OCD neurocognition study by signing below.

Printed Name of Parent: _____

_____   _____

Signature of Parent   *Date*

Printed Name of Child: _____

_____
Signature of Research Team Member Obtaining Consent

_____
Date

A STUDY OF NEUROCOGNITION IN OCD-AFFECTED YOUTH, AT-RISK SIBLINGS AND HEALTHY CONTROLS

Assent Form – OCD-Affected Subjects

Invitation

I am being invited to be part of a study that looks at how children who have OCD like me may think or solve problems in a different way than those who do not have OCD. This study will also look at whether there are similar ways of thinking between children with OCD and their siblings that are passed on from parents to kids. This study will try to find out more information about OCD to help children like me. It is up to me if I want to be in this study. No one can make me be part of the study. Even if I agree now to be part of the study, I can change my mind later. No one will be mad at me if I choose not to be part of the study.

Why are we doing this study?

I am being invited to be a part of this study that looks at children's thinking or ways of solving problems and OCD because the OCD clinic staff or my family thinks I have OCD. This condition affects many other children. This study is trying to find out more about OCD so that scientists can learn about how OCD makes me act and feel and what can be done to help me and others like me. Knowing more whether children with OCD think or solve problems in a different way than children without OCD can help scientists develop specific programs to improve these children's way of thinking and how and how they act and feel. Scientists would also like to learn more about how specific ways of thinking or solving problems in people with OCD are different from those of people without OCD and how these problems affect how people with OCD behave or respond to treatment. OCD sometimes gets passed down in families through "genes" that are passed on from parents to kids.

What will happen in this study?

If I agree to be in this study, I will answer a short questionnaire on a computer about how I am feeling before I start the session. To do that, I will have a study email account with no personal information, only my study number. This email account will be de-activated after the study is over. Then, I will do a number of short activities that involve language, memory, attention, and problem-solving skills. The results of these activities will help scientists compare my abilities with those of children without OCD. If I choose to take part in these activities, I will work with a scientist in a quiet room at the Child and Family Research Institute (CFRI) or at my house if my parent prefers for about 2 to 2.5 hours. I will take as many breaks as I need when I feel tired. Being in this study will not make my OCD better, but the results of these activities will help scientists compare my abilities with those of children without OCD.

Who is doing this study?

Dr. Evelyn Stewart and her team from BC Children's Hospital and the University of British Columbia will be doing this study. They will answer any questions I have about the study. I can also call Dr. Stewart at # *XXXXX*, if I am having problems or if there is an emergency and I cannot talk to my parent(s) or another family member. Additional contacts are Juliana Negreiros or Rhonda Ellwyn at XXXXX.

Can anything bad happen to me?

Nothing bad can happen in responding to language, memory, attention, and problem solving questions. During the session, I may feel a bit tired or I may worry that I got a question wrong. I can ask for breaks as many times as I wish. If I do not want to continue doing the activities, I can stop at anytime.

Who will know I am in the study?

Only my doctor and the people who are involved in the study will know I am in it. When the study is finished, the OCD team will write a report about what was learned. This report will not say my name or that I was in the study. They may also share my test results with other scientists who are studying OCD or other mental illness, but my name will not be sent with my test protocols. My parent(s) and I do not have to tell anyone that I am in the study if we do not want to.

Am I going to be compensated to participate in this study?

If I decide to participate in this study, after I complete the testing session, I will receive a $25 gift card. My total time commitment for this study will be 2 to 2.5 hours.

When do I have to decide?

I will have as much time as I want to decide to be part of the study. I have also been asked to talk about my decision with my parent(s).

A STUDY OF NEUROCOGNITION IN OCD-AFFECTED YOUTH, AT-RISK SIBLINGS AND HEALTHY CONTROLS

Assent Form

I have had the opportunity to read this assent form, to ask questions about my participation in this research, and to discuss my participation with my parents/guardians.

All my questions have been answered. I understand that I may withdraw from this research at any time, and that this will not interfere with my future access to health care.

I have received a copy of this assent form.

I assent to participate in this study.

Printed Name of Subject: _____

_____   _____
Signature of Subject   *Date*

A Study of Neurocognition in OCD-affected Youth, At-Risk Siblings, and Healthy Controls

SUMMARY REPORT OF CHILD RESEARCH ASSESSMENT RESULTS

Please note that this is a <u>confidential</u> report that summarizes the assessment results on selected neurocognitive tests and behaviour rating scales. These measures have been administered for <u>research purposes only and should not replace a comprehensive clinical assessment</u> of your child's abilities.

Name: ChildName   Date of Testing:
Parent: Date of Birth:
Examiner: Age at Testing: __ years, __ months

Principal Investigator: Evelyn Stewart, MD

Cautionary Statement: This brief summary of your child's assessment results is based on selected neurocognitive tests administered to your child and behaviour rating scales completed by your child and/or one of (his/her) parents. It is important that the results be considered within the context of a number of other factors, including your child's developmental and medical history and (his/her) current development and functioning. *To avoid misinterpretation, please discuss these results and any questions regarding these findings only with qualified professionals with expertise in child assessment and interpretation of test results*.

SUMMARY OF RESEARCH ASSESSMENT FINDINGS

Purpose of the Study: ChildName participated in a research study examining how neurocognitive abilities of children and youth with Obsessive-Compulsive Disorder (OCD) may be different from those who do not have OCD. This study also looks at whether there are similar neurocognitive characteristics in children and youth with OCD and their siblings that are passed on from parents to their children.

Tests Administered and Rating Scales:
- Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)
- Cambridge Neuropsychological Test Automated Battery (CANTAB) – selected tests
- Behavior Rating Inventory of Executive Function (BRIEF) – Parent Form
- Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) – Severity Rating Scale
- Anxiety Interview Schedule for Parent IV (ADIS-P) – Parent Form

ASSESSMENT RESULTS

Some of the test results are presented as percentile ranks, which indicate a child's standing relative to same-aged children in the test sample (according to US normative data). If your child's score is at the 50th percentile, this means that (he/she) did as well as, or better than, 50%

of same-aged peers. Percentile ranks between 25 and 74 are considered within the Average range. Standard Score (SS) informs if your child fell at, above, or below the Average range compared to other children (his/her) age. The Average range for standard scores is between 90 and 109.

NEUROCOGNITIVE PERFORMANCE

Brief Measure of Intelligence: WASI-II

Cognitive abilities are thought to reflect a child's schooling as well as more general experiences outside of school. The *WASI-II* is a screening measure of intelligence for individuals between ages 6 and 90 years. It is important to recognize that the *WASI-II* measures only a portion of the competencies involved in human intelligence. This cognitive screening is comprised of two composites: The Verbal IQ, which includes the Vocabulary and Similarities subtests, and the Performance IQ, which includes the Matrix Reasoning and Block Design subtests. The Full Scale IQ-4 score was used to estimate ChildName's general level of cognitive functioning based on (his/her) performance across the four subtests.

On the *Verbal IQ* subtests, which measure a child's ability to recall and work with verbal information, such as defining vocabulary words and describing how two objects or ideas are conceptually similar, ChildName performed as well as, or better than, xx% of same-aged peers (xx percentile; SS=xx). (His/her) Verbal IQ score falls in the *xx* range, and this is an area of normative strength for (him/her).

The *Performance IQ* subtests assess a child's ability to analyze and synthesize visual information, such as manipulating patterned blocks to copy designs and using visual reasoning and thinking by choosing one picture from a group of pictures that relates in some way to a series of pictures. ChildName's score on the Performance IQ subtests is in the *xx* range (xx percentile; SS=xx). It is suggested that (he/she) performed as well as, or better than, xx% of same-aged peers on similar tasks.

Option 1: ChildName's *general level of cognitive functioning* (FSIQ-4 score) is in the *xx* range (xx percentile; SS=xx). Overall, it is suggested that the amount and depth of ChildName's general and linguistic knowledge and (his/her) ability to reason using visual stimuli are (below/within/above) age-level expectations.

Option 2: ChildName's *general level of cognitive functioning* (FSIQ-4 score) cannot be interpreted as a single score due to significant discrepancy between (his/her) Verbal and Performance IQ scores. *In summary, the amount and depth of ChildName's linguistic knowledge is an area of normative strength for (his/her), whereas (his/her) ability to analyze and synthesize visual information is within age-level expectations.*

Measure of Executive Function, Visual Memory, and Attention: CANTAB

The *CANTAB* is a set of computerized cognitive tests presented on a high-resolution colour monitor with a touch-sensitive screen. A number of tests from the *CANTAB* battery designed to

measure executive function, visual memory, and attention were administered to your child. Although it is difficult to isolate and measure these constructs separately because executive function processes are intertwined with memory and attention, the description of the results is outlined according to what each test proposed to measure. *Please note that the CANTAB has been mainly used for research purposes, limiting the interpretation of the scores in clinical settings. Due to the very limited normative data for children available, caution in the interpretation of the scores is warranted. Only the tests that had normative data are described below.*

Executive Function has been broadly defined and refers to processes and skills that individuals use to help guide and manage their cognitive, emotional, and behavioural activities, particularly during problem-solving tasks or in adapting to novel situations. Executive function processes and skills are crucial for being productive and independent, for developing and maintaining socially appropriate behaviours and interactions, and for having emotional control and adequate cognitive and academic development. Please see below some of the *CANTAB* tests that were used to assess ChildName's executive function processes:

The *Intra/Extra Dimensional Set Shift* test is a measure of rule acquisition and reversal learning. It assesses one's ability to make visual discrimination and shift attention to novel exemplars according to specific rules. This test is comprised of nine stages and scores are based on the number of errors made through the stages and the number of trials and stages completed. *ChildName's visual discrimination and shifting abilities are within age-level expectations.*

The *Stockings of Cambridge* test assesses one's spatial planning, spatial working memory, and motor control. On this test, an individual is shown two displays containing coloured balls, and asked to use the balls in the lower display to copy the pattern shown in the upper display with the minimum number of moves. *ChildName's planning accuracy is age appropriate.*

The *Spatial Working Memory* test assessed ChildName's ability to retain spatial information and to manipulate remembered items in working memory. It also measured (his/her) ability to reach a goal using heuristic strategy. *No concerns with ChildName's spatial working memory are noted.*

Attention is considered a central component of a neuropsychological assessment. The *Rapid Visual Processing* test was used to measure ChildName's ability to sustain attention. On this test, ChildName was requested to detect target sequences of three digits and to register responses using the press pad. *ChildName's visual sustained attention is in the Average range.*

Spatial memory is related to one's ability to retain spatial information in memory for a few seconds. To assess this domain, the *Spatial Recognition Memory* test was used. On this test, ChildName was required to hold visual stimuli in memory for later recall in a forced-choice paradigm. *No concerns with ChildName's spatial recognition memory are noted.*

Indirect Measure of Executive Functioning (BRIEF- Parent Questionnaire)

The *BRIEF* is a questionnaire that serves as a screening tool for possible executive dysfunctions according to observers' perspectives and provides valuable information about an individual's everyday behaviour associated with eight specific domains of executive function, including shifting, emotional control, inhibition, monitoring, working memory, initiation, planning/organizing, and organizing materials. Based on parent responses, most of ChildName's executive function processes are within age-level expectations. For example, (his/her) ability to inhibit impulsive responses, modulate (his/her) emotions, and plan and organize problem-solving approaches is similar to that of same-aged peers. *Concerns were noted only with regard to* ChildName's *ability to organize (his/her) materials and to hold an amount of information in mind for further processing.*

Measure of Anxiety: ADIS-P

The *ADIS-P* is a semi-structured interview used to assess anxiety disorders in children. ChildName's (mother/father) was administered the *ADIS-P,* and (his/her) responses did not indicate that ChildName meets criteria for any type of anxiety disorder.

Measure of Obsessive and Compulsive Symptom Severity: CY-BOCS

The *CY-BOCS* is a clinician-administered, semi-structured questionnaire of severity of OCD in individuals over the previous week. The *CY-BOCS* is divided into two sections that assess obsessions and compulsions related to frequency, distress, interference, one's ability resist the obsessions, and perceived control over symptoms. Overall, the severity of ChildName's obsessive and compulsive symptoms over the previous week is in the *X* range.
 Option 2: ChildName *did not report experiencing any obsessive or compulsive symptoms over the previous week.*

SUMMARY

Results of the present assessment indicate that ChildName's overall cognitive functioning score, a measure of only a portion of the competencies involved in human intelligence, is in the *xx* range. ChildName's verbal knowledge is (below/within/above) age-level expectations. (his/her) ability to think with visual stimuli is in the xx range. ChildName's executive function processes in all areas assessed (i.e., rule acquisition and reversal learning, spatial working memory, spatial recognition memory, spatial planning, and visual sustained attention) are age appropriate. Similarly, (his/her) parent indicates that ChildName's everyday behaviour associated with specific domains of executive function is within age-level expectations. Results of a parent semi-structured interview used to assess anxiety disorders in children indicate that ChildName (does/ does not) meet the criteria for (any type of anxiety disorder/ xxxx disorder). Finally, the severity of ChildName's obsessive and compulsive symptoms over the previous week is in the *X* range.

It was a pleasure to meet and work with ChildName. We greatly appreciate ChildName and (his/her) family's participation in this study. As previously noted, this research assessment is not meant to substitute for a comprehensive clinical assessment of ChildName's neurocognitive abilities and behaviour functioning. If there are any questions about this summary report or

further questions about the research test findings, please contact Juliana Negreiros at xxxxxx (xxxx), or by email at xxxxxx

Juliana Negreiros, MA
Certified School Psychologist
Co-Investigator of Research Study

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Appendix D: Background and Academic Functioning Questionnaire

OCD Neurocognition Study
Background and Academic Functioning Questionnaire

The following is a brief questionnaire on your child or adolescent's background and current academic functioning at school.

All information will be treated as confidential.

Code Number:_____   Month/Year Birth:_____

Today's date:_____   Child's age:_____

Form Completed by: ❑ Mother   ❑Father   ❑ Other (Please Specify:_____)

BACKGROUND INFORMATION

Biological/Adoptive Mother's Age:_____

Highest Education Completed:_____

Biological/Adoptive Father's Age:_____

Highest Education Completed:_____

Parent's marital status: ❑married/common-law ❑separated ❑divorced ❑widowed ❑other:_____

Primary language spoken in the home: _____

Other languages spoken in the home: _____

Please check the box(es) that best describes the child's ethnicity:

❑ Caucasian   ❑ South Asian   ❑ Aboriginal

❑ Chinese   ❑ South East Asian   ❑ Black

❑ Japanese   ❑ Arab   ❑ Latin American

❑ Korean   ❑ West Asian   ❑ Other:_____

EDUCATION HISTORY
Are there any school personnel currently involved with your child?   ❑ Yes   ❑ No

     If yes, please describe: _____

_____

Is your child in any type of special education program?   ❑ Yes   ❑ No

    If yes, please describe: _____

_____

Has your child ever skipped or repeated a grade in school?   ❑ Yes   ❑ No

    If yes, please describe: _____

_____

Has your child ever received tutoring?   ❑ Yes   ❑ No

    If yes, please describe: _____

_____

Has your child been suspended or expelled from school?   ❑ Yes   ❑ No

    If yes, please describe: _____

_____

Has the school identified any problems with:

Reading	❑ Yes	❑ No	Social Adjustment	❑ Yes	❑ No
Spelling	❑ Yes	❑ No	Behaviour	❑ Yes	❑ No
Math	❑ Yes	❑ No	Attention/Concentration	❑ Yes	❑ No
Writing	❑ Yes	❑ No	Organization	❑ Yes	❑ No

If yes to any of the above, what grade did these problems become noticeable? _____

Appendix E: Intraclass Correlation Coefficient (ICC) Results

Table 16. Intraclass Correlation Coefficient (ICC) Results for Response Variables

Variables	ICC
IED (total error correct)	0.024
IST (total correct fixed)	0.000
IST (total correct decreasing)	0.069
IST (mean box open fixed)	0.000
IST (mean box open decreasing)	0.000
SOC (mean move)	0.012
SOC (mean subsequent thinking)	0.000
SOC (perfect solutions)	0.234
SST (ssrt)	0.579
SWM (between error)	0.339
RVP (a)	0.000
RVP (probability hit)	0.000
RVP (probability false alarm)	0.000
RVP (mean latency)	0.209
SRM (percent correct)	0.339
BRIEF (gec)	0.027

Appendix F: Skewness and Kurtosis Values

Table 17. Skewness and Kurtosis Values for Residuals on Response Variables

Domain	Variable	Skewness	Kurtosis
Cognitive Flexibility	IED (total error correct)	0.472	-0.845
Decision-making	IST (total correct fixed)	-0.800	0.458
	IST (total correct decreasing)	-0.422	-0.054
	IST (mean box open fixed)	0.807	2.059
	IST (mean box open decreasing)	-0.439	-1.01
Planning	SOC (mean move)	0.215	-0.479
	SOC (mean subsequent thinking)	1.056	0.513
	SOC (perfect solutions)	0.082	0.433
Response Inhibition	SST (ssrt)	1.314	2.897
Working Memory	SWM (between error)	0.643	0.847
Attention	RVP (a)	-0.419	-0.636
	RVP (probability hit)	-0.401	-0.786
	RVP (probability false alarm)	2.188	6.720
	RVP (mean latency)	0.573	0.846
Visual Memory	SRM (percent correct)	0.002	-0.821
Indirect EF	*BRIEF* (gec)	0.477	0.475

Appendix G: *BRIEF* scores

Table 18. Performance of OCD-Affected Youth, At-Risk Siblings, and Healthy Controls on *BRIEF* Based on Adjusted Group Means (Standard Error)

Index/Scale	OCD	SIB	HC
Global Executive Composite (GEC)	55.89 (1.68)	45.08 (1.97)	44.74 (1.63)
Metacognition Index (MCI)	55.05 (1.87)	45.71 (2.20)	45.65 (1.82)
Initiate	55.51 (2.25)	47.03 (2.63)	45.53 (2.18)
Working Memory	55.96 (1.82)	46.79 (2.13)	45.64 (1.76)
Plan/Organize	54.57 (1.85)	44.63 (2.20)	46.10 (1.86)
Organization of Materials	54.84 (2.04)	47.54 (2.43)	51.03 (1.94)
Monitor	53.20 (1.96)	46.12 (2.30)	44.99 (1.91)
Behavioral Regulation Index (BRI)	55.53 (1.77)	44.93 (2.07)	43.56 (1.72)
Inhibit	50.52 (1.62)	44.29 (1.92)	43.55 (1.63)
Shift	56.42 (2.03)	47.19 (2.40)	45.35 (2.06)
Emotional Control	57.63 (2.01)	46.51 (2.39)	45.27 (1.90)

Appendix H: *WASI-II* scores

Table 19. Performance of OCD-Affected Youth, At-Risk Siblings, and Healthy Controls on *WASI-II* Based on Unadjusted Index Standard Scores and Subtest T-scores

Index/Subtest	OCD	SIB	HC
Full-Scale IQ	*103*	*105*	*112*
Verbal IQ	*103*	*107*	*114*
Vocabulary	54	54	60
Similarities	50	55	57
Performance IQ	*102*	*102*	*107*
Block Design	49	51	54
Matrix Reasoning	53	52	54

Appendix I: Cohen's d Values for Response Variables

Table 20. Cohen's d Values and 95% Confidence Limits for Response Variables

Domain		OCD vs SIB			OCD vs HC			SIB vs HC		
			CI			CI			CI	
		Cohen's d	lower	upper	Cohen's d	lower	upper	Cohen's d	lower	upper
Cognitive Flexibility	IED (total error correct)	-0.07	-0.65	0.52	-0.1	-0.61	0.41	-0.04	-0.62	0.55
Decision-making	IST (total correct fixed)	-0.34	-0.94	0.25	0.24	-0.27	0.75	0.59	0	1.17
	IST (total correct decreasing)	-0.08	-0.67	0.52	0.36	-0.15	0.88	0.44	-0.15	1.02
	IST (mean box open fixed)	0.09	-0.51	0.68	0.12	-0.39	0.63	0.04	-0.55	0.62
	IST (mean box open decreasing)	-0.69	-1.29	-0.09	0.31	-0.2	0.83	1	0.4	1.48
Planning	SOC (mean move)	-0.17	-0.76	0.42	0.47	-0.04	0.98	0.64	0.05	1.23
	SOC (mean subsequent thinking)	-0.21	-0.8	0.38	-0.38	-0.89	0.13	-0.18	-0.76	0.4
	SOC (perfect solutions)	-0.43	-1.02	0.16	-0.83	-1.29	-0.3	-0.4	-0.98	0.4
Response Inhibition	SST (ssrt)	0.38	-0.21	0.97	0.33	-0.19	0.83	-0.05	-0.64	0.53
Working Memory	SWM (between error)	-0.02	-0.61	0.57	0.32	-0.19	0.83	0.34	-0.24	0.93
Attention	RVP (a)	-0.61	-1.21	-0.02	-0.27	-0.78	0.24	0.35	-0.24	0.93
	RVP (probability hit)	-0.69	-1.28	-0.08	-0.23	-0.74	0.27	0.45	-0.14	1.03
	RVP (probability false alarm)	-0.47	-1.06	0.13	0.14	-0.37	0.64	0.61	0.01	1.19
	RVP (mean latency)	-0.23	-0.82	0.36	0.26	-0.25	0.77	0.49	-0.1	1.07
Visual Memory	SRM (percent correct)	-0.31	-0.9	0.29	-0.54	-1.06	-0.02	-0.23	-0.81	0.35
Indirect EF	*BRIEF* (gec)	1.35	0.71	1.5	1.39	0.83	1.29	0.04	-0.54	0.62