NEURAL CORRELATES OF PERINATAL OBSESSIVE-COMPULSIVE DISORDER

THE NEURAL CORRELATES OF PERINATAL OCD: AN EXPLORATORY INVESTIGATION INTO SEROTONIN RISK GENES AND CORTICAL MORPHOLOGY

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Lay Abstract

Women are at greater risk for the development of mental illness in the time surrounding pregnancy and postpartum, known as the perinatal period. In the case of perinatal obsessive-compulsive disorder (OCD), mothers may experience unique worries in regard to their parenting or fears that their baby may be harmed. While these worries are common, they can become disruptive when persistent and impact the mother's mood and ability to bond with the infant. Our current understanding of OCD includes the influence of genetic factors and brain changes, but little is understood about what factors may increase risk for OCD in the perinatal period. In this thesis, we aimed to review whether certain alterations within DNA segments, known as gene variants, may be linked to the development of OCD in females and if these gene changes, as well as differences in brain structures in postpartum mothers, are associated with OCD symptoms during the perinatal period. The genes we examined are important for regulating a chemical signaling substance in the brain known as serotonin. Based on our results, we did not find a relationship between serotonin gene variants and OCD symptoms in perinatal women. We also found no differences when comparing the cortical brain structures between mothers with OCD and healthy mothers; however, we observed that measures of surface area across several cortical brain regions were related to symptom worsening from pregnancy to postpartum, and also with symptom severity in postpartum mothers with OCD. These results suggest that there are widespread brain changes during the postpartum period that may increase a mother's risk for developing OCD. Overall, the work in this thesis provides the first glimpse into potential risk factors for perinatal OCD.

Abstract

Introduction: Obsessive-compulsive disorder (OCD) is a complex disorder that is associated with significantly impaired functioning. The current prevailing model of OCD implicates dysfunction of the serotonergic neurotransmitter system and fronto-striatal neural networks, but challenges in replicating findings within OCD samples are often attributed to clinical heterogeneity. OCD symptoms that develop or worsen within the perinatal period appears to reflect a distinct subtype of the disorder, but the genetic and neurobiological factors that contributes to its presentation in women is poorly understood. In this dissertation, we aimed to review the literature on the genetic architecture of OCD, identify potential gene candidates for perinatal OCD and analyze one serotonin system gene according to OCD and possible subtypes using meta-analytic techniques. Based on these findings, we then tested the association of serotonergic candidate gene polymorphisms with the presence of infant-related obsessive-compulsive symptoms (OCS). Lastly, we investigated the cortical morphological features associated with perinatal OCD and OCS symptom severity in postpartum mothers.

Results: From prior reports in the literature and our own meta-analytic investigation, polymorphic variants in genes coding for the serotonergic transporter and serotonin 2A receptor subtype (*SLC6A4* and *HTR2A*, respectively) appear to be candidates for perinatal OCD due to their association in female samples. However, upon investigation in our perinatal sample (n=107), we found no evidence to support the association of the 5-HTTLPR polymorphism of *SLC6A4* with perinatal-related OCS, but larger samples are needed to confirm this finding. Due to technical challenges, the *HTR2A* polymorphism

remains to be tested. Our novel whole-brain explorations revealed distinct cortical morphology associated with symptom worsening across the perinatal period, irrespective of diagnosis. Cortical parameters were not able to differentiate mothers with and without OCD; however, OCD mothers displayed positive correlations between cortical surface area and symptom severity in widespread regions, including the frontal, parietal, temporal and occipital cortex.

***Conclusions*:** Overall, this body of work aimed to fill the gap in the literature by exploring the possible genetic and cortical correlates of perinatal-related OCS and OCD. While 5-HTTLPR or *HTR2A* are candidates for perinatal OCD, it is not yet clear whether they increase susceptibility for the development of infant-related OCS in the perinatal period. Distinct cortical alterations in surface area appeared alongside OCS exacerbation in the postpartum period in regions that extend beyond the frontoparietal network. This suggests that additional neural networks may be contributing to symptom severity and that the cortical plasticity that occurs across the perinatal period may predispose women for risk of OCD. Future studies should continue to use a multiple perspective approach, that utilizes genetic and neurobiological techniques, in order to provide greater insight into the etiology of perinatal OCD.

Key words:

Obsessive-compulsive disorder; perinatal period; sex differences; genetic association; serotonin transporter; serotonin receptor 2A; structural imaging; cortical morphology

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List of Abbreviations

5-HT_{2A} – postsynaptic serotonin 2A receptor

5-HTTLPR – serotonin transporter linked polymorphic region

5'UTR – five prime untranslated region

ACC – anterior cingulate cortex

B_0 - an externally applied constant and homogeneous magnetic field

CIDI-Venus – Composite International Diagnostic Interview for Women

COMT - catechol-O-methyltransferase

CPAD – current or past anxiety and/or depressive disorder

CpG – cytosine nucleotide followed by guanine nucleotide in a DNA sequence

CSA – cortical surface area

CSF – cerebrospinal fluid

CT – cortical thickness

CTQ – Childhood Trauma Questionnaire

DL – Dersimonian and Laird method

DNA - deoxyribonucleic acid

DSM – Diagnostic and Statistical Manual of Mental Disorder

ECA – Epidemiologic Catchment Area study

ENIGMA - Enhancing Neuro-Imaging Genetics through Meta-Analysis collaborative network

EO – early onset

EPDS – Edinburgh Postnatal Depression Scale

ERE – estrogen response element

GABA - γ-aminobutyric acid

GWAS – genome wide association study

HC – healthy control

HKSJ - Hartung-Knapp-Sidik-Jonkman method

HPA - hypothalamus-pituitary-adrenal

HTR2A – serotonin receptor 2A gene

HWE – Hardy-Weinberg equilibrium

LMM – linear mixed model

LO – late onset

MAO-A – monoamine oxidase-A

MRI – magnetic resonance imaging

mRNA – messenger ribonucleic acid

NCS-R – US National Comorbidity Survey Replication study

OCD – obsessive-compulsive disorder

OCDB – Obsessive-compulsive Disorder Database

OCRD – obsessive-compulsive and related disorders

OCS – obsessive-compulsive symptoms

OFC – orbitofrontal cortex

PCR – polymerase chain reaction

PET - positron emission tomography

POCS - Perinatal Obsessive-Compulsive Scale

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSQI - Pittsburgh Sleep Quality Index

Q-Genie - Quality of Genetic Association Studies tool

REML - restricted maximum likelihood

RF – radio frequency

RFLP – restriction fragment length polymorphism

SBM – surface-based morphometry

SERT - serotonin transporter

SJHH – St. Joseph's Healthcare Hamilton

SLC6A4 - solute carrier family 6 member 4 / serotonin transporter gene

SNP - single nucleotide polymorphism

SPECT – single-photon emission computerized tomography

SNRI - serotonin and noradrenaline reuptake inhibitors

SSRI - selective serotonin reuptake inhibitor

STAI - Spielberger State Trait Anxiety Inventory

T – Tesla

TS - Tourette's syndrome

TDT - transmission-disequilibrium test

VBM - voxel-based morphometry

VNTR – variable number tandem repeat

WHCC – Women's Health Concerns Clinic

Y-BOCS - Yale-Brown Obsessive-Compulsive Scale

Declaration of Academic Achievement

Chapter 1

This chapter contains material taken from the **published** book chapter entitled "Obsessive–compulsive and related disorders" from ***Handbook of Clinical Neurology*** (Volume 175) composed by G.F. Mattina and A. Slyepchenko, with assistance from M. Steiner. The material that appears in this dissertation is taken from the subsection on Obsessive-Compulsive Disorder.

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Chapter 2

G.F. Mattina and M. Steiner formulated the research question, identified relevant literature, assessed the quality of studies, and interpreted findings. G.F. Mattina summarized the evidence and composed the manuscript. M. Steiner assisted in the manuscript composition.

This chapter in its entirety has been **published** in ***Progress in Neuro-Psychopharmacology and Biological Psychiatry***.

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Chapter 3

G.F. Mattina and M. Steiner formulated the research question, identified relevant literature using a systematic approach, and independently assessed the quality of studies. G.F. Mattina additionally completed data extraction, data analysis and composed the manuscript. Z. Samaan provided statistical guidance and assisted in the manuscript composition. G.B. Hall and M. Steiner assisted in the manuscript composition.
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Chapter 4

G.F. Mattina contributed to the formulation of research questions, project design, completed participant recruitment and assessment, data collection, genotyping and statistical analysis, and composed the chapter. L. Mak contributed to the initial project design, formulation of research questions, participant recruitment and data collection. She had completed genotyping of the 5-HTTLPR using a different protocol and data analysis on a subsample of the participants, but these previous versions of the results were not

reported in this chapter. Z. Samaan provided statistical guidance and assisted in the manuscript composition. G.B. Hall contributed to the chapter composition. M. Steiner contributed to the formulation of initial research questions, initial study design, the data analysis plan and contributed to the chapter composition.

Chapter 5

G.F. Mattina contributed to the formulation of research questions, project design, completed participant recruitment and assessment, data collection, image processing and statistical analysis, and composed the chapter. J.S. Soh assisted in neuroimage processing and cortical data analysis. L. Mak contributed to the initial project design, participant recruitment and data collection. Z. Samaan provided assisted in the manuscript composition. M. Steiner contributed to the formulation of initial research questions, initial study design and contributed to the chapter composition. G.B. Hall contributed to the formulation of research questions, the data analysis plan and contributed to the chapter composition.

Chapter 1: Introduction

This chapter contains material taken from the following book section that has been **published** in *Handbook of Clinical Neurology: Sex Differences in Neurology and Psychiatry, 175*, Mattina, G.F., Slyepchenko, A., & Steiner, M., Obsessive-Compulsive and Related Disorders, 369-86, Copyright Elsevier, 2020.

1.1 General Introduction

The perinatal period is a reproductive life event that is accompanied by a multitude of changes, including physiological, behavioural and cognitive changes that are necessary for the survival and well-being of both the mother and infant. Unsurprisingly, dysfunctional alterations within these systems lead to the development or exacerbation of psychopathologies in mothers, making the time surrounding pregnancy and postpartum an important period of concern within women's mental health. Advancement of methodological techniques that investigate biological features specific to the individual, including DNA genotyping and neuroimaging of the brain, have provided avenues for the identification and quantification of potential risk factors or biological markers that are associated with disorders in a relatively non-invasive manner. In light of these advances, more is being uncovered about the etiology of disorders that perturb women's health during periods of vulnerability.

Of these disorders, obsessive-compulsive disorder (OCD) during the perinatal period has received relatively less attention, despite the significant adversities it places on mothers and their families. Perinatal OCD presents with a distinct clinical picture from

OCD outside the perinatal period, which will be discussed at length in a later section. Currently, the underlying biological correlates of its occurrence are unknown.

Combining a multiple perspective approach, that utilizes genetic and neurobiological techniques, will allow greater insight into the complexities of perinatal OCD. The general aims of this body of work were to examine the current literature on the genetic architecture of OCD and identify potential gene candidates related to OCD in females (Chapter 2), analyze the association of a serotonin candidate gene in relation to OCD and its subtypes by pooling data from the literature using meta-analytic techniques (Chapter 3), explore the association of serotonergic candidate genes with the presence of clinical infant-related obsessive-compulsive symptoms (OCS) and examine whether genotype status was a significant predictor of symptom severity in women across the perinatal period (Chapter 4), and to investigate the cortical features associated with OCD and OCS symptom severity within the 1st year postpartum (Chapter 5). In sum, this research aims to fill a number of the gaps regarding the biological correlates of perinatal OCD by identifying potential genetic risk factors and neurological factors that may be contributing to the pathophysiology of OCS and OCD during the perinatal period.

1.2 Obsessive-Compulsive Disorder

OCD is a debilitating mental disorder that involves the presence of obsessions and/or compulsions. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), obsessions are recurrent and persistent thoughts, urges, or images that the individual attempts to ignore or suppress, whereas compulsions are repetitive behaviours or mental acts that the individual performs to prevent or reduce

feelings of anxiety or distress (American Psychiatric Association, 2013). Symptoms associated with the disorder can be clustered into four clinical dimensions: (1) responsibility obsessions and checking rituals, (2) contamination obsessions and decontamination rituals, (3) symmetry obsessions and ordering/arranging rituals, and (4) violent, sexual and religious obsessions and mental and reassurance-seeking rituals (Abramowitz, Deacon, et al., 2010). Hoarding, a symptom initially categorized as a major dimension of OCD, has since been recognized as its own separate disorder based on evidence indicating differences in cognitive and behavioural processing, course of illness, neurobiological basis and treatment response (Mataix-Cols et al., 2010).

OCD is a complex, heterogenous disorder that follows a chronic course, and is associated with significantly impaired functioning and decreased quality of life (Eisen et al., 2006). This disorder is characterized by the presence of obsessions and/or compulsions, where the individual experiences thoughts, images and urges that are intrusive, and performs ritualistic or repetitive behaviours that are aimed at reducing distress (American Psychiatric Association, 2013). Even though intrusive thoughts are fairly common and prevalent in the general population (Rachman, 2014), these may become maladaptive when they are unwanted, disruptive and occur frequently. Obsessions or compulsions must occupy more than 1 hour a day or cause significant impairment, must not be attributable to substances or another medical condition, and cannot be better explained by another mental disorder. Individuals with OCD often spend an excessive amount of time focusing on their symptoms (roughly 5.9 hours for obsessions and 4.6 hours for compulsions, per day) (Ruscio, Stein, Chiu, & Kessler,

2010), which leads to significant impairments in quality of life (Eisen et al., 2006; I. S. Fontenelle et al., 2010).

The heterogeneity within clinical presentations of OCD is often acknowledged as a limitation and may explain inconsistencies found within the literature. Efforts are being made towards identifying more homogenous subtypes within OCD that will aid our understanding of the etiology of the disorder and provide advancements towards personalized treatment.

1.3 Sex Differences in OCD

1.3.1 Epidemiology and Course of Illness

Globally, OCD affects approximately 1-3% of the population (L. F. Fontenelle, Mendlowicz, & Versiani, 2006; Sasson et al., 1997). Analysis of a subsample of epidemiological data collected from the United States revealed lifetime prevalence of OCD to be around 2.3%, with lower 12-month estimates observed in adults at 1.2% (Ruscio et al., 2010). When comparing adult OCD prevalence by sex, there appears to be an equal distribution between males and females (Kolada, Bland, & Newman, 1994), although some report a slightly higher lifetime prevalence in females (Fineberg et al., 2013; Karno, Golding, Sorenson, & Burnam, 1988; Torres et al., 2016; Weissman, Bland, Canino, Greenwald, & et al, 1994). On the other hand, pediatric OCD samples have consistently reported a higher preponderance of males (Hanna, 1995; Mancebo et al., 2008; Masi et al., 2010). In adults, a higher prevalence of males have been found among those with an earlier onset in some (L. F. Fontenelle, Mendlowicz, Marques, & Versiani,

2003; Mahajan, Chopra, & Mahajan, 2014), but not all studies (Rosario-Campos et al., 2001).

Prevalence in treatment-seeking individuals is substantially lower, suggesting that OCD may be underdiagnosed and undertreated (Veldhuis et al., 2012). Feelings of shame, lack of insight into symptoms and available healthcare services are all barriers to treatment noted for individuals with OCD (García-Soriano, Rufer, Delsignore, & Weidt, 2014). Approximately 10% to 62% of patients seek treatment (García-Soriano et al., 2014), and diagnosis is often delayed, with many reporting an untreated illness duration lasting around 7 years (Dell'Osso et al., 2019). Among patients seeking treatment, OCD was found to be more prevalent in females (Veldhuis et al., 2012). A greater delay in treatment-seeking has been reported in females (Mahajan et al., 2014), but this finding may be culturally driven as others have reported no sex differences (Belloch, Valle, Morillo, Carrió, & Cabedo, 2009; Mayerovitch et al., 2003) or have found that females tend to seek help earlier (Stengler et al., 2013).

Symptoms of OCD generally emerge in childhood/adolescence and early adulthood, with peak incidence rates occurring around age 19-20, with few novel onset cases appearing in the mid-30s or later (Fineberg et al., 2013; Ruscio et al., 2010). Phenotypic differences have supported the classification of OCD onset into two separate subtypes: early onset, appearing in childhood and adolescence around age 11, and late onset, appearing in young adulthood or later around 23 years of age (L. F. Fontenelle et al., 2003; Taylor, 2011a). Those with an earlier onset are more likely to be male and have increased familial risk, experience greater severity and higher frequency of OCS, and

have comorbid tics or comorbidity with other obsessive-compulsive related disorders (OCRDs) (Taylor, 2011a; Torresan et al., 2009). Furthermore, neural differences based on age of onset were recently shown, with early onset cases exhibiting larger brain volumes of precentral, orbitofrontal, middle frontal, and middle temporal gyri, in relation to those with late onset (T. Kim et al., 2020). However, more research into the neurobiological mechanisms underlying early vs. late onset OCD are needed.

OCD is a condition that may follow a chronic, fluctuating pattern of symptom exacerbation or an episodic course, where individuals experience periods of symptom-free intervals (Ravizza, Maina, & Bogetto, 1997). Notably, studies have reported that males with earlier OCD onset were more likely to experience a chronic course, while females were more likely to have an episodic course (Bogetto, Venturello, Albert, Maina, & Ravizza, 1999), but these findings have been mixed (Garcia et al., 2009; Tükel et al., 2007). In one of the longest longitudinal studies completed to date, adult patients with OCD were followed across 40 years and males who developed OCD before age 20 experienced worse prognosis than females or those with a later age of onset (Skoog & Skoog, 1999). In pediatric samples, an earlier onset age was associated with a longer persistence of the condition (Stewart et al., 2004). These findings suggest greater chronicity associated with early onset OCD, especially in males. However, it is important to note that longitudinal studies assessing OCD course from childhood and adolescence have been primarily comprised of male samples and may underestimate the chronicity females with early OCD onset experience.

Diminished quality of life has been repeatedly reported in OCD (Moritz, 2008), with individuals experiencing worse social functioning compared to other psychiatric conditions, such as major depressive disorder and schizophrenia (Kugler et al., 2013). Furthermore, quality of life is markedly impacted in children with OCD, with greater reduction observed in those with any comorbidity as compared to OCD alone (Weidle, Jozefiak, Ivarsson, & Thomsen, 2014).

Subclinical OCS have been reported in similar rates between adult males and females (Fineberg et al., 2013; Grabe et al., 2000), though some inconsistencies have been reported (Olatunji, Sawchuk, Arrindell, & Lohr, 2005). There is a higher degree of inconsistency in pediatric populations: some studies have found higher prevalence of subclinical symptoms among males (Alvarenga et al., 2016; Canals, Hernández-Martínez, Cosi, & Voltas, 2012), whereas others report increased rates for females (Politis et al., 2017; Vivan et al., 2014).

In those seeking treatment, sex has been identified as a predictor of clinical course, where females experienced remission earlier than males, but overall remission rates did not differ between sex in a 5-year period (Eisen et al., 2010, 2013). Those with poor insight into their symptoms, as defined as the ability for an individual to recognize the irrational nature of their obsessions and compulsions, have a worse prognosis since they are less likely to seek or adhere to treatment and may be misdiagnosed with a psychotic disorder (Kashyap, Kumar, Kandavel, & Reddy, 2014). One study reported that females experienced greater insight than males (Mahajan et al., 2014), but prior studies failed to find sex differences according to level of insight (Catapano et al., 2010; Cherian

et al., 2012; Lochner et al., 2004). There is supporting clinical evidence that OCD with poor insight may represent a possible subtype (de Avila et al., 2019), but the neurobiological substrates have yet to be robustly demonstrated.

1.3.2 Symptomatology

Sex differences concerning symptom type have been reported in a large number of studies; however, there is much heterogeneity (Hasler et al., 2005; Hunt, 2020; Karadaĝ, Oguzhanoglu, Özdel, Ateşci, & Amuk, 2006). One of the most persistent findings among OCD samples is the increased frequency of contamination and cleaning symptoms observed in females (Cherian et al., 2014; Denys, De Geus, Van Megen, & Westenberg, 2004; Labad et al., 2008; Y. Li, Marques, Hinton, Wang, & Xiao, 2009; Masi et al., 2010; Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999; Torresan et al., 2013; Tükel, Polat, Genç, Bozkurt, & Atli, 2004). Similarly, subclinical contamination fears are more frequent in adult females sampled from the general population (Olatunji et al., 2005). Alternatively, males with OCD often present with a higher prevalence of forbidden thoughts (i.e. aggressive, sexual or religious obsessions) and related checking compulsions (Cherian et al., 2014; Hunt, 2020; Labad et al., 2008; Lochner et al., 2004; Mataix-Cols, Nakatani, Micali, & Heyman, 2008; Sobin et al., 1999), as well as symptoms related to symmetry and ordering (Karadaĝ et al., 2006; Leckman et al., 1997; Y. Li et al., 2009; Masi et al., 2010; Mataix-Cols et al., 1999). Differences in presentation within pediatric samples have also been reported, with males experiencing increased contamination obsessions (Masi et al., 2010). These associations have been documented

worldwide and are likely tied to biological, psychosocial and cultural factors that influence males and females separately.

A recent study failed to detect any notable symptom differences between males and females in a community sample with elevated OCS severity (Raines et al., 2018), suggesting that sex differences may be more prominent in individuals with clinically severe manifestations.

Indeed, sex differences have emerged when comparing symptom severity in clinically defined samples. Males with OCD are more likely to display increased symptom severity, with females reporting fewer symptoms and better global functioning compared to their male counterparts (L. F. Fontenelle, Marques, & Versiani, 2002). However, these findings have not been consistent (Lochner et al., 2004; Sobin et al., 1999; Torresan et al., 2009). Another study found that females with OCD experience higher OCS severity, and higher levels of depressive and anxiety symptoms (Torresan et al., 2013). The association between males and increased symptom severity observed in the literature may be attributable to onset timing and illness duration, as discussed above (Rosario-Campos et al., 2001; Sobin, Blundell, & Karayiorgou, 2000).

Sex has also been found to influence the relationship between primary symptom type and illness course in females only. Females with obsessions dealing with aggressive, sexual or religious content described an episodic course, while females with primary symmetry or cleaning symptoms were more likely to endorse a chronic course (Kichuk et al., 2013).

1.3.3 Comorbidity

High rates of comorbidity have consistently been reported among OCD samples, with rates as high as 90% or 92% reported in large, national samples (de Mathis et al., 2013; Ruscio et al., 2010). Comorbidity with other psychiatric disorders results in a more complicated clinical picture, associated with a worse prognosis and treatment difficulties (Pallanti, Grassi, Sarrecchia, Cantisani, & Pellegrini, 2011). The most common comorbid conditions reported in OCD include anxiety disorders, mood disorders, impulse-control disorders and substance use disorders (Ruscio et al., 2010). Higher rates of comorbidity with tics or Tourette's disorder (TD), as well as bipolar disorders, alcohol and substance use disorders, have been repeatedly observed in males with OCD (Angst et al., 2005; Karadaĝ et al., 2006; Mataix-Cols et al., 1999; Sobin et al., 1999; Torres et al., 2016; Torresan et al., 2013), whereas higher rates of anxiety disorders, eating disorders and post-traumatic stress disorder are more prevalent in females (Angst et al., 2005; Grabe et al., 2001; Lochner et al., 2004; Torresan et al., 2013). Females with OCD are more likely to experience comorbid depressive disorders (Cherian et al., 2014; Karadaĝ et al., 2006), though findings have been inconsistent (Torresan et al., 2013).

A recent nationwide registry-based study conducted in Finland reported slightly lower comorbidity rates of 73% in those with OCD, with similar sex differences observed (Rintala et al., 2017). Regarding comorbidity with OCRD in a small sample of OCD patients, 20% met criteria for at least one OCRD and there was a slightly higher proportion of males in this group (Öcal, Özdel, Şafak, Karnaz, & Kisa, 2019), yet body-focused compulsive disorders, such as trichotillomania (hair pulling) and excoriation

(skin picking) that involve repetitive "self-grooming" behaviours that can result in physical damage of the body, were found to be more frequent in females with OCD (Torresan et al., 2013). Most studies have shown that comorbidity was associated with worse functioning, greater levels of distress and suicidality (Angst et al., 2005; Cherian et al., 2014). Furthermore, higher suicidal risk has been reported in females with OCD (Cherian et al., 2014), but this difference has not always been found (Torresan et al., 2013).

1.4 Sex Differences in OCD Risk Factors

1.4.1 Genetic Vulnerability

The genetic influences contributing to sex differences in OCD have yet to be elucidated, despite the strong evidence that OCD is a familial disorder based on family and twin studies (Nestadt et al., 2000; Pauls, 2010). Genetic factors may play a greater role in males, as OCD among males with an earlier onset have higher familial loading (Pauls, 2010); however, studies in adult and adolescent twins have shown small to no sex differences in heritability (Van Grootheest et al., 2007, 2008).

Meta-analytic analyses of candidate gene studies on serotonergic genes have found support for associations with genes coding for serotonin transporter (*SLC6A4*) and serotonin receptor 2A (*HTR2A*), which have been found to be associated with - and specific to - OCD (Taylor, 2013, 2016), with recent findings from meta-analyses supporting a possible female-specific association with risk alleles (Mak, Streiner, & Steiner, 2015; Mattina, Samaan, Hall, & Steiner, 2020). Several other genes and variants

have been found to have sex-specific associations with OCD (see Chapter 2 for a review of recent studies).

Recently, a genome wide association study was conducted, where strong genetic similarities between males and females with OCD were found, except for the *GRID2* (glutamate ionotropic receptor delta type subunit 2) and *GPR135* (G protein-coupled receptor 135) genes that were significantly associated with OCD females, and not males (Khramtsova et al., 2019). Due to the small or moderate effect sizes that polymorphic variants contribute to OCD, pooled results and those obtained from large data sets hold substantial promise for the future identification of sex-specific genes of OCD.

1.4.2 Neurobiological Factors

Findings from neuroimaging studies have provided substantial evidence of abnormal functioning in frontal-subcortical circuits of OCD patients that supports the current working model that the cortico-striatal-thalamic-cortico (CSTC) circuit is implicated in the disorder (Pauls, Abramovitch, Rauch, & Geller, 2014).

Less is understood about the potential sex differences in the neurobiology of OCD, as the majority of investigations have had predominantly male samples. Among opposite sex twin pairs, sex differences in gray matter volume has been observed (den Braber, de Geus, Boomsma, & van ’t Ent, 2013). Specifically, males showed an enlarged right temporal gyrus, whereas females had a larger right precuneus. Pediatric samples have shown smaller pituitary volume in boys with OCD, as compared to neurotypical control boys (MacMaster et al., 2006). Among studies assessing white matter structure, widespread reductions in total white matter have been reported in females with OCD

(Jenike et al., 1996), and larger midsagittal corpus callosum area was observed in OCD males, as compared to control males (Park et al., 2011). These studies suggest that males and females may possess different altered neural structures that are involved in OCD pathophysiology, but more studies aimed at examining common and sex-related differences in the neurobiological substrates of OCD are needed.

1.4.3 Exposure to Stressful Life Events and Trauma

The majority of literature supports an association between trauma exposure and development in OCD, predominantly in females (L. F. Fontenelle, Cocchi, Harrison, Miguel, & Torres, 2011); however, some studies report similar trauma exposure across all individuals with OCD (Torresan et al., 2013).

Several reports have shown that females with OCD were more likely to experience a stressful event preceding illness onset (Real et al., 2011, 2016), that trauma was associated with a more rapid development of symptoms (as opposed to gradual), an episodic course and more severe symptoms, when compared to males (Bogetto et al., 1999; M. L. Miller & Brock, 2017). Associations between OCS and exposure to trauma have been documented in community samples of adolescents, which are especially evident in females (Barzilay et al., 2019). It has been hypothesized that perinatal trauma or early life brain injury may play a role in the etiology of early onset OCD in males (Hibbard, Uysal, Kepler, Bogdany, & Silver, 1998; Lensi et al., 1996; Noshirvani, Kasvikis, Marks, Tsakiris, & Monteiro, 1991); however, some studies were unable to find sex differences in exposures to head injuries related to OCD (Lochner et al., 2004). These

results suggest that environmental stressors play a greater causal role and may act as triggers for OCD onset in females.

Childhood trauma, especially sexual abuse, is associated with a six-fold increased likelihood of developing OCD in females, as compared to non-abused females (Saunders, Villeponteaux, Lipovsky, Kilpatrick, & Veronen, 1992). Greater exposure to childhood emotional neglect has also been reported in an all-female OCD sample (Lochner et al., 2002), whereas another study found higher rates in OCD males (Lochner et al., 2004).

It is likely that an interaction between stressful life events and sex steroids, such as estrogens and progestogens, contributes to the emergence of OCD in females. In line with this, giving birth has been found to be a unique stressor for females (Maina, Albert, Bogetto, Vaschetto, & Ravizza, 1999; Torresan et al., 2013; Williams & Koran, 1997), suggesting that females are more vulnerable to OCD onset during reproductive-related events.

1.4.4 Reproductive Life Events

According to findings from previous studies, a subset of females may be more vulnerable to hormonal changes that accompany reproductive events and are associated with development or exacerbation of OCD. Interestingly, the bimodal incidence rate pattern described earlier in this chapter coincides with two major reproductive life events: pubertal onset and reproductive years, with peak incidence rates in females observed from ages 20 to 29 (Veldhuis et al., 2012).

Numerous reports have noted OCD onset or exacerbation in females during reproductive life events, such as menarche, pregnancy/postpartum and menopause.

Within the general community, OCD onset has been reported among 0.5-1% of females during pregnancy, 2.3-2.9% during postpartum, and 0.7% in menopause (Fairbrother, Janssen, Antony, Tucker, & Young, 2016; Uguz, Gezginc, et al., 2007; Uguz, Sahingoz, Gezginc, & Karatayli, 2010; Zambaldi et al., 2009). Initial symptom onset during reproductive events is more frequently reported in diagnosed OCD cases, with 13-22% of females experiencing onset in the year following menarche, 2-15.4% in pregnancy, 4.7-14.1% in postpartum, and 2-10.5% in menopause (Forray, Focseneanu, Pittman, McDougle, & Epperson, 2010; Guglielmi et al., 2014; Labad et al., 2010, 2005; Uguz et al., 2010).

Females with pre-existing OCD commonly report symptom exacerbation during reproductive life events, with 20-49.7% of female experiencing symptom worsening during the premenstruum, 8-34.1% during pregnancy, 46.6-50% in postpartum period, and 8-47% during the menopausal transition (Forray et al., 2010; Guglielmi et al., 2014; Labad et al., 2005; L. Moreira et al., 2013; Uguz, Kaya, Gezginc, Kayhan, & Cicek, 2011; Vulink, Denys, Bus, & Westenberg, 2006). Notably, females were more likely to experience symptom worsening in the postpartum period if they experienced exacerbation in a preceding postnatal period (Guglielmi et al., 2014), which underscores the risk females with perinatal onset experience in subsequent pregnancies and importance of discussing past reproductive history in clinical settings. Females with OCD who experience onset or symptom worsening in the perinatal period have reported greater premenstrual worsening of symptoms, compared to females who developed OCD outside of the perinatal period (Forray et al., 2010; Labad et al., 2005).

1.5 Obsessive-Compulsive Disorder in the Perinatal Period

Literature on perinatal disorders has focused primarily on depression or psychosis, with perinatal OCD often overlooked. Evolutionary perspectives highlight the potential benefits of perinatal OCD, as there is an adaptive advantage conferred to the infant with the emergence of parental behaviours regarding protection and safety concerns (Feygin, Swain, & Leckman, 2006). However, clinical levels of OCD in the perinatal period cause significant distress and may lead to adverse consequences for the mother and infant, making recognition and treatment of this disorder imperative.

1.5.1 Prevalence and Comorbidity

Within the perinatal period, OCD prevalence ranges between 0.2-3.5% in pregnancy, with rates as high as 9% reported in the postpartum period (McGuinness, Blissett, & Jones, 2011). When investigating incidence rates across pregnancy, the highest rates were found in the 2nd trimester, whereas the lowest rates were observed in the 3rd trimester (Kaya, Uguz, Şahingöz, & Gezginc, 2015). As described previously, symptom exacerbation during the perinatal period is frequently reported in women with OCD (Guglielmi et al., 2014), supporting a close connection between perinatal events and OCS symptoms.

When compared to the general population, females are nearly 1.5 and 2 times more likely to develop OCD during pregnancy and the postpartum period, respectively (Russell, Fawcett, & Mazmanian, 2013). Similar to the general OCD population, females with perinatal OCD also report high levels of comorbid depressive episodes (Zambaldi et al., 2009) and anxiety disorders (Kaya et al., 2015), with generalized anxiety disorder

being the most prevalent. Notably, higher rates of obsessions and compulsions are commonly endorsed by women with postpartum depression (Wisner, Peindl, Gigliotti, & Hanusa, 1999), especially regarding obsessive thoughts of infant-related harm (Jennings, Ross, Popper, & Elmore, 1999); however, the exact rates of comorbidity in perinatal samples are unknown.

1.5.2 Clinical Course and Symptomatology

Perinatal OCD is associated with a distinct clinical course and symptomatology. Postpartum-onset OCD is often characterized by a rapid onset in the early postnatal days after childbirth, which is in contrast to the gradual development that is typically reported in OCD (L. M. Arnold, 1999; Sichel, Cohen, Dimmock, & Rosenbaum, 1993). Symptom persistence in the early postnatal period is likely (Yakut, Uguz, Aydogan, Bayman, & Gezginc, 2019), with one prospective study reporting symptom persistence at 6 months postpartum in approximately half of the females who screened positive for OCD symptoms at 2 weeks postpartum (E. S. Miller, Chu, Gollan, & Gossett, 2013).

Intrusive thoughts are commonly experienced in mothers, especially in first-time parents (Abramowitz, Schwartz, Moore, & Luenzmann, 2003; Fairbrother & Abramowitz, 2007), with one study finding that nearly half of postpartum females experienced subclinical obsessions or compulsions (E. S. Miller et al., 2013). Notably, these worries are not exclusive to OCD, as women with major depressive disorder and postpartum-onset depressive episodes also endorse obsessional thoughts during this time (Wisner et al., 1999).

Postpartum mothers with OCD often endorse aggressive and contamination obsessions, and cleaning/washing and checking compulsions, which are frequently driven by fears of their baby being harmed (Zambaldi et al., 2009). More recently, a meta-analytic review highlighted the distinct clinical features associated with perinatal OCD, with postpartum OCD women displaying more aggressive obsessions related to the infant and fewer washing/cleaning compulsions, as compared to pregnancy or outside the perinatal period (Starcevic, Eslick, Viswasam, & Berle, 2020).

Among new mothers, approximately 70-100% report thoughts of harm coming to the baby, either intentionally or accidentally (Abramowitz, Khandker, Nelson, Deacon, & Rygwall, 2006; Abramowitz, Nelson, Rygwall, & Khandker, 2007; Brok et al., 2017; Fairbrother & Woody, 2008). Commonly, mothers with perinatal OCD describe symptoms that are aimed at preventing a feared catastrophic outcome, which may manifest as situational avoidance (e.g. holding the baby) due to these fears (Fairbrother & Abramowitz, 2007). As a result, these unique symptoms have long-term adverse consequences on the entire family, especially the mother-infant relationship (Brandes, Soares, & Cohen, 2004; Challacombe et al., 2016); however, there is no evidence to suggest that the manifestation of these symptoms represents any real risk of infant-harming behaviours occurring (Fairbrother & Woody, 2008).

1.5.3 Gonadal Hormones

Fluctuations in gonadal hormones across the perinatal period are likely contributing to the increased risk for the development of OCS in women. Across gestation, estradiol and progesterone levels steadily increase, which is followed by a

sudden drop in the days after delivery (Nott, Franklin, Armitage, & Gelder, 1976). Estrogen and progesterone appear to play a protective role against OCS (Karpinski, Mattina, & Steiner, 2017), which may help to explain why OCD incidence rates across the perinatal period are lowest in the third trimester when estradiol and progesterone levels are high, and highest in the postpartum period when these hormone levels are low (Kaya et al., 2015). Further evidence of this link comes from preclinical studies, where administration of estradiol alone or the combination of estradiol and progesterone were found to decrease repetitive behaviours in a rat model of OCD (Fernández-Guasti, Agrati, Reyes, & Ferreira, 2006; Flaisher-Grinberg et al., 2009). Despite this clear relationship, the mechanism by which estrogen and progesterone influence OCD risk in the perinatal period is unknown.

Another hormone that undergoes fluctuation in the perinatal period is oxytocin. Delivery and breastfeeding in the postpartum period is accompanied by increases in oxytocin, a hormone important for maternal behaviour and mother-child bonding (Feldman, 2012; Gimpl & Fahrenholz, 2001). It is possible that exposure to elevated levels of oxytocin in the postpartum may increase risk for the development or worsening of OCS in some women. Several studies have found increased oxytocin levels in the cerebrospinal fluid of OCD patients (Leckman et al., 1994; Marazziti et al., 2015), providing indirect evidence that oxytocin is another hormone likely involved in the etiology of perinatal OCD.

1.6 Genetics of Obsessive-Compulsive Disorder

1.6.1 Family and Twin Studies

According to family and twin studies, there is substantial support for the genetic transmission of OCD; however, the mode of transmission is complex and likely involves the contribution of several genes and interactions with the environment. Due to the heterogeneity associated with OCD, gene by environment interactions have been challenging to study and may explain why genetic investigations often ignore the role of the environment (Grisham, Anderson, & Sachdev, 2008).

Within families, it has been shown that individuals with OCD are more likely to have a first-degree relative with the disorder or subthreshold OCS, as compared to healthy controls (Hanna, Himle, Curtis, & Gillespie, 2005; Nestadt et al., 2000; Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995). One such study determined that the lifetime prevalence for OCD in the relatives of OCD probands was approximately 5 times greater than relatives of controls (10% vs 1.9%, respectively) (Pauls et al., 1995). After pooling the data from five studies, Hettema et al. reported an odds ratio (OR) of 4.0, suggesting a 4-fold increase in the association of OCD among probands and their relatives (Hettema, Neale, & Kendler, 2001). Furthermore, probands with early onset OCD (do Rosario-Campos et al., 2005) or those with symmetry/ordering symptoms (Hanna et al., 2005) appear to be more familial, suggesting that etiologically homogeneous subgroups likely exist within OCD.

Twins studies have been valuable in discerning genetic and environmental contributions towards OCD. Genetic contributions, assessed by concordance rates, have

revealed higher rates of OCD among monozygotic twins (80-87%) than dizygotic twin-pairs (47-50%) (Carey & Gottesman, 1981). In a different twin-pair study, heritability estimates of obsessional trait and symptoms were 47%, suggesting that just under half of the phenotypic variation was influenced by genetic factors (Clifford, Murray, & Fulker, 1984). Twin studies in children have estimated the heritability of OCS to be between 45-65% (Eley et al., 2003; Hudziak et al., 2004), with a recent review estimating 27-47% heritability in adults (van Grootheest, Cath, Beekman, & Boomsma, 2005). Despite the evidence supporting the heritability of OCD, no studies have investigated the genetic factors related to perinatal OCS or OCD.

1.6.2 Genetic Association Studies

Genetic association studies have sought to better understand the genetic etiology of OCD by exploring specific candidate genes in relation to the disorder. These studies primarily investigate single nucleotide polymorphisms (SNPs) of genes that are chosen based on the current understanding of the physiology and dysfunction associated with the phenotype of interest. In the case of OCD, serotonergic system genes have received a lot of attention (Sinopoli, Burton, Kronenberg, & Arnold, 2017); however, replication across studies has been challenging, which is likely a result of the heterogeneity among the OCD groups sampled. A summary of recent reports investigating several neurotransmitter system genes in relation to OCD and its subtypes is provided in Chapter 2.

1.7 Serotonin and OCD

1.7.1 Serotonergic Hypothesis

The serotonin hypothesis of OCD emerged after it was observed that clomipramine, a tricyclic antidepressant that inhibits serotonin reuptake, and selective serotonin reuptake inhibitors (SSRIs) were effective in treating the disorder (DeVeaugh-Geiss et al., 1991; Pigott & Seay, 1999). This has led many to place serotonergic dysfunction at the center of the pathogenesis of OCD. To this day, SSRIs remain as the first-line pharmacological treatment choice for OCD, with the recommended duration and dosage being higher for treatment of OCD than for other disorders, such as major depressive disorder (Koran, Hanna, Hollander, Nestadt, & Simpson, 2007).

Serotonin is a key regulator of several essential behavioural and physiological functions, including emotion (mood, anxiety and fear), cognition, aggression, pain, sleep, sexual behaviour, motor activity, and other autonomic processes (Olivier, 2015). Within the brain, the raphe nuclei are responsible for the synthesis of serotonin from the amino acid tryptophan and its release, with neuronal projections that extensively innervate cortical and subcortical areas (Charnay & Léger, 2010).

Studies that measured serotonin metabolite levels in cerebrospinal fluid of individuals with OCD (Kruesi et al., 1990) and the changes in serotonin levels following treatment response (Flament, Rapoport, Murphy, Berg, & Lake, 1987) provided some support for the serotonergic hypothesis, yet some OCD patients do not adequately respond to pharmacotherapies targeting the serotonin system. The clinical heterogeneity associated with OCD may help to explain this discrepancy and finding more

homogeneous subgroups could aid efforts in understanding the neurobiological mechanisms underlying the disorder.

In the case of perinatal onset OCD, changes in estrogen and progesterone during pregnancy and in the postpartum period may lead to the development of OCS through their effects on the serotonergic system. Studies from preclinical models suggest that estradiol and progesterone increase serotonergic neurotransmission by regulating the expression of proteins that are involved in the activation or termination of the serotonergic response (Bethea, Lu, Gundlah, & Streicher, 2002; Hernández-Hernández, Martínez-Mota, Herrera-Pérez, & Jiménez-Rubio, 2018), though these effects may differ according to the protein type and brain region studied (Barth, Villringer, & Sacher, 2015). This perspective provides a potential cellular mechanism from which hormonal fluctuations may impact various cognitive and mood processes. However, the development of OCD and its associated complexity cannot be fully explained by serotonin dysfunction (Pauls et al., 2014).

1.7.2 Serotonin Transporter and Serotonin 2A Receptor

The serotonin transporter (SERT) and serotonin 2A ($5\text{-}HT_{2A}$) receptor subtype play integral roles in functional regulation and intracellular signalling of the serotonin neurotransmitter. Dysfunction of the serotonergic system is thought to underlie several psychopathologies, with SERT being a primary target of pharmacological interventions for OCD and other affective disorders.

Expressed on the presynaptic neuron and axons, SERT is involved in the reuptake and removal of serotonin in the synaptic cleft and is the central mechanism underlying

termination of serotonin neurotransmission (Tao-Cheng & Zhou, 1999; F. C. Zhou, Tao-Cheng, Segu, Patel, & Wang, 1998). Highest density of SERT in the human brain is found in the superior and inferior raphe nuclei, followed by the hypothalamus, thalamus, and substantia nigra, with lower quantities found in the amygdala, hippocampus, prefrontal and other cortical areas (Cortés, Soriano, Pazos, Probst, & Palacios, 1988; Laruelle, Vanisberg, & Maloteaux, 1988).

The 5-HT_{2A} receptor is a G-protein coupled receptor type that is also distributed widely across the cortices in the brain and is found on a variety of cell types, including pyramidal neurons, interneurons, and glial cells (Burnet, Eastwood, Lacey, & Harrison, 1995; Pazos, Probst, & Palacios, 1987; Quirion, Richard, & Dam, 1985; Willins, Deutch, & Roth, 1997). Activation of the 5-HT_{2A} receptors leads to the initiation of a signal transduction pathway that is responsible for regulating a number of cellular processes and functions (Julius, Huang, Livelli, Axel, & Jessell, 1990), including the release of calcium from intracellular stores and activation of protein kinase C (Hoyer et al., 1994; Raymond et al., 2001; Watts, 1998). Increased calcium and activated protein kinase C may then lead to modulation of SERT distribution and subsequently alter serotonin reuptake ability (Qian et al., 1997). Furthermore, the 5-HT_{2A} receptor has known interactions with dopamine, γ-aminobutyric acid (GABA), glutamate and norepinephrine function (Aghajanian & Marek, 1999; Fink & Göthert, 2007), suggesting that multiple neurotransmitter systems are influenced. Considering the high density of 5-HT_{2A} receptors and SERT in cortical areas, it has been hypothesized that they may play a role

in mediating cognitive functions and emotions (Hensler, 2012), which is often impaired in individuals with OCD (Snyder, Kaiser, Warren, & Heller, 2015).

1.7.3 SLC6A4 and HTR2A

The SERT and 5-HT_{2A} receptor proteins are encoded by the *SLC6A4* and *HTR2A* genes, respectively. *SLC6A4* is found on chromosome 17q11.1-q12 and has been extensively studied in relation to multiple psychiatric disorders (Margoob & Mushtaq, 2011). Found within the promoter region of this gene, the serotonin transporter linked polymorphic region (5-HTTLPR) is a 44-base pair insertion/deletion polymorphism that results in either the short (S) allele or long (L) allele, with the S allele demonstrating reduced transcription of SERT (Heils et al., 1996; Lesch et al., 1996). A nearby variation (rs25531) was discovered that altered the functional activity of the L allele, whereby a change from an adenosine (L_A) to guanine (L_G) nucleotide within the extra repeats results in the L_G allele displaying similar transcriptional activity as the S allele (Hu et al., 2006). Prior to this discovery, studies assessing 5-HTTLPR in relation to OCD only considered it as bi-allelic (L vs. S), which has likely contributed to the inconsistencies across findings.

Unlike 5-HTTLPR, *HTR2A* has received less attention in the context of OCD but has also been linked to other psychopathologies (Serretti, Drago, & De Ronchi, 2007). *HTR2A* is found on chromosome 13q14-21, and two of the most commonly studied polymorphisms are G-1438A (rs6311), located upstream of the promoter, and T102C (rs6313), located in the first exon of the gene (Spurlock et al., 1998). These SNPs exist in almost complete linkage disequilibrium, whereby presence of the A allele of rs6311 almost always co-occurs with the T allele of rs6313 (Bray, Buckland, Hall, Owen, &

O'Donovan, 2004; R. M. Smith et al., 2013). The association of *HTR2A* polymorphisms with OCD is analyzed and described in further detail in Chapter 3.

1.7.4 Serotonergic Polymorphisms, Behavioural Outcomes and Allelic Frequencies

In healthy samples, the 5-HTTLPR variant has been linked to different behavioural phenotypes, whereby the S allele carriers often display increased anxiety and depressive symptoms, as well as other traits related to neuroticism, including hopelessness, feelings of guilt, and aggression (Gonda et al., 2009; Schinka, Busch, & Robichaux-Keene, 2004). Similarly, variants of *HTR2A* have been investigated in several psychiatric disorders, including schizophrenia, depressive disorders, eating disorders, and anxiety disorders, with generally mixed outcomes (Serretti et al., 2007).

The S allele appears to confer greater risk for the development of mood symptoms following exposure to early life stress, suggesting that the 5-HTTLPR may moderate the effects of stressful life events (Caspi et al., 2003). More recently, the S allele was demonstrated to be a marker of differential susceptibility for psychiatric illnesses, such that some individuals with the S allele may be more sensitive to adverse and positive environments (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Others failed to find any relationship between 5-HTTLPR, adverse events and development of clinical symptoms (Fergusson, Horwood, Miller, & Kennedy, 2011). When considering sex, the S allele was found to increase risk for affective symptoms in women, especially when coupled with stressful life events (Gressier, Calati, & Serretti, 2016). Overall, these findings suggest that the 5-HTTLPR may increase general risk for psychopathology that may be modified by sex and stressful environmental exposures.

Across ethnic groups, the frequency of the minor S allele of the 5-HTTLPR varies, with the highest frequency found in Indigenous Nations (64-66%), intermediate levels found in Caucasians (35-40%) and lowest in Black or African Americans (25%), whereas frequency of the L_G allele is lowest in Indigenous Nations (1%), with higher rates observed in Caucasians (9-15%) and the highest in Black or African Americans (24%) (Hu et al., 2006; Wendland, Martin, Kruse, Lesch, & Murphy, 2006). For the G-1438A (or T102C) polymorphism of *HTR2A*, frequency of the A (or T) allele appears highest in Egyptians, East and West Asians (43-61%) (Hamdy et al., 2002; Y.-H. Liu & Zhang, 2013; Sina, Ahmadiani, Asadi, & Shams, 2018; Tot, Erdal, Yazici, Yazici, & Metin, 2003), with similar rates found among Caucasians, Hispanics and Black or African Americans (34-50%) (Hamdy et al., 2002; Saiz et al., 2008; Walitza et al., 2002). Currently, the lack of diversity in most genetic association studies conducted to date is a serious problem, as it prevents a full comprehension on the genetic architecture underlying disease and the ability to generalize results to the global population (Sirugo, Williams, & Tishkoff, 2019). Furthermore, ethnic differences across studies may partly help explain the inconsistency across studies investigating 5-HTTLPR or *HTR2A* polymorphisms with OCD.

1.8 Neurobiological Model of Obsessive-Compulsive Disorder

Neuroimaging literature has revealed a substantial amount of evidence for altered brain functioning in OCD, which has improved our understanding of the neural correlates of OCD. Specifically, abnormal functioning in patients with OCD has been detected in fronto-subcortical brain circuits that are involved in executive functioning processes and

emotional regulation, and are inclusive of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), caudate nuclei, and the thalamus (Saxena & Rauch, 2000). Positron emission tomography (PET) studies have also demonstrated increased glucose metabolism in the OFC and caudate regions relative to controls (Whiteside, Port, & Abramowitz, 2004), and studies utilizing single photon emission computed tomography (SPECT) have revealed increased cerebral blood flow to the medial frontal cortex (Machlin et al., 1991).

Following treatment with either medication or cognitive behavioural therapies, the functional activities of these areas are seen to normalize and no longer differ from healthy controls (Saxena & Rauch, 2000; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). A recent review of PET and SPECT studies completed on OCD patients before and after treatment found that symptom improvement post-treatment was associated with decreased blood flow or glucose metabolism in the caudate, OFC and thalamus, providing indirect evidence that hyperactivity within these regions is associated with OCD (van der Straten, Denys, & van Wingen, 2017).

A functional magnetic resonance imaging (fMRI) study confirmed abnormal functional connectivity (i.e. coordinated activity) involving the ventral striatum and OFC that was related to overall severity of the disorder (Harrison et al., 2013). Additionally, these researchers were able to detect distinct relationships between some symptom dimensions and striatal functional connectivity, with aggression symptoms correlated with ventral striatum, amygdala and ventromedial frontal cortex activity, and sexual/religious symptoms correlated with ventral striatal-insular connectivity (Harrison

et al., 2013). In addition to providing more evidence that supports disrupted functioning in OCD individuals, these results also suggest that some symptom dimensions of OCD may have discrete neural correlates.

1.8.1 Cortico-Striato-Thalamo-Cortical Circuit

Based on the neural regions identified from neuroimaging studies, there is sufficient evidence pointing towards involvement of the cortico-striato-thalamo-cortical (CSTC) circuit, also known as the fronto-striatal circuit (Saxena & Rauch, 2000). This circuit includes both a direct and indirect pathway that is comprised of excitatory and inhibitory projections. Starting from the cortex, the direct pathway projects from the OFC and ACC to the striatum via excitatory glutamatergic signaling. Striatal activation then inhibits activity of the globus pallidus interna and substantia nigra via inhibitory GABA signaling, which results in activation of the thalamus leading back to excitation of the cortex as part of a positive-feedback loop. The indirect pathway follows similar circuitry, with a slight deviation where activation of the striatum leads to inhibition of the globus pallidus interna, resulting in reduced inhibition of the subthalamic nucleus. The subthalamic nucleus is then able to increase activity of the globus pallidus interna and substantia nigra, which has inhibitory influences over the thalamus, resulting in decreased cortical activation (negative-feedback loop). The prevailing model proposes that individuals with OCD experience greater excitation via the direct pathway, leading to an imbalance in the CSTC circuit that may explain why OCD patients experience difficulties in disengaging from cognitive and behavioural functions (Pauls et al., 2014; Saxena & Rauch, 2000).

When considering the influence of neurotransmitter systems on the CSTC circuit, altered serotonergic functioning in OCD is likely contributing to the imbalance that favours the direct pathway. As part of a neurotransmitter signaling cascade, the absence of sufficient serotonin and signaling via the 5-HT_{2A} receptors found on dopaminergic neurons leads to increased dopaminergic activity, which may then stimulate greater GABA release and inhibitory effects from the striatum onto the globus pallidus interna and substantia nigra, thus eliciting greater cortical activation via the direct pathway (Karpinski et al., 2017).

While there is a lot of supporting evidence for the CSTC model of OCD, confounding factors, such as symptom type, comorbidity, medication use, age of onset and illness duration, may influence results and make comparisons across studies difficult. More recently, neural networks outside the CSTC circuit have been implicated in OCD, that include the parietal cortex, limbic regions and the cerebellum (Hazari, Narayanaswamy, & Venkatasubramanian, 2019; Milad & Rauch, 2012), suggesting that the disorder may arise from widespread dysfunction and dysconnectivity of multiple neural regions.

1.8.2 Brain Morphometry and Magnetic Resonance Imaging

Brain morphometry is an important area of interest within neuroimaging that concerns the measurement of brain structures and the changes that take place across development, aging and with disease. It allows for researchers to quantify structural measures of the brain and relate it to specific behavioural phenotypes. Some of the more popular methodological approaches within the study of brain morphometry include voxel-

based morphometry (VBM), surface-based morphometry (SBM), and diffusion tensor imaging (DTI), which measures the diffusivity of water molecules across white matter fibre tracts. VBM and SBM are applied to T_1-weighted anatomical images acquired from magnetic resonance imaging (MRI).

Structural MRI is an imaging technique that is non-invasive and produces 3-dimensional images of internal body structures, making it a useful tool for analyzing the anatomy and structures within the brain. MRIs are able to generate detailed images using a combination of magnetic fields and radio waves to discern between different tissue types by utilizing the magnetic properties of hydrogen atoms found in water and fat to generate the detailed images (Berger, 2002; Logothetis, 2008). The hydrogen atom contains a single positively charged proton that spins on its own axis and will be randomly oriented at any given time. When entering an MRI scanner, a strong magnetic field is applied (known as B_0 and measured in Tesla) that causes a proportion of the hydrogen nuclei to become aligned with the magnetic field in either the parallel or antiparallel direction of B_0, while maintaining their spin (Berger, 2002; Logothetis, 2008). Overall, there are slightly more hydrogen nuclei in parallel alignment that generates a magnetization vector that is also oriented parallel to the axis of B_0. Additionally, the strength of B_0 also influences the speed at which hydrogen protons spin, known as the precessional or Larmor frequency, which is 127.74 MHz at 3 Tesla (Logothetis, 2008). When a radio frequency (RF) pulse is applied that is at the same rate as the Larmor frequency, the magnetic vector of the proton is deflected into the transverse plane as the protons move out of alignment with B_0, due to being in a state of resonance (Berger,

2002; Logothetis, 2008). When the RF pulse stops, the magnetization vector aligns back with the B_0 field, known as returning to rest or relaxation. This return in orientation causes a signal in the form of a radio wave to be emitted and is collected by receiver coils (Logothetis, 2008). The first relaxation time (known as T_1) is the time it takes protons to realign in parallel with B_0 (Berger, 2002). Time to relaxation is different across tissue types (e.g. gray matter, white matter, cerebrospinal fluid (CSF) and blood) and it is this disparity that is used to generate the composite images that can then be analyzed (Logothetis, 2008). Regions with higher fat content have shorter T_1 times and will appear brighter in images, whereas areas with low to no fat content (such as CSF) will appear darker.

1.8.3 Cortical Thickness and Cortical Surface Area

Most of the studies performed on OCD patients have been conducted predominantly with VBM approaches; however, surface-based measures can provide additional information about brain structure by generating detailed cortical maps that are able to delineate and differentiate between measures of cortical surface area (CSA) and cortical thickness (CT), which are distinct properties.

Studies investigating the development of the cortical cytoarchitecture across species have provided support for the radial unit hypothesis (Rakic, 1988, 2007), which views the cortex as a system of connected ontogenetic columns that contain neurons that, “act as a basic functional unit subserving a set of common static and dynamic cortical operations” (Rakic, 2008). While CSA has shown considerable expansion across evolution, CT has remained relatively stable, suggesting that these cortical measures are

distinct from one other. In support of this view, twin studies have shown that CSA and CT are highly heritable, with minimal genetic overlap (Panizzon et al., 2009). It is thought that the CSA reflects the number and spacing of columns in a distinct brain region, whereas CT is a reflection of the number and size of cells within a column (Casanova & Tillquist, 2008; Rakic, 1988).

1.8.4 Structural Morphology of OCD

Compelling evidence from meta-analyses display gray matter and white matter structural abnormalities within the key regions of the CSTC associated with OCD (Piras, Piras, Caltagirone, & Spalletta, 2013; Piras et al., 2015). More specifically, studies assessing structural volume using a whole-brain VBM approach have consistently highlighted alterations of the orbitofrontal, cingulate, thalamic and temporolimbic regions (temporal cortex, amygdala, hippocampus, hypothalamus and insula) in OCD (Piras et al., 2015); however, the direction of these changes were variable across studies, which is likely attributed to the heterogeneity across OCD samples and differences in the methodologies used.

Findings from a large-scale meta- and mega-analysis conducted by the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) working group reported cortical abnormalities, specifically lower surface area of the transverse temporal and inferior parietal cortex, associated with OCD in adults (Boedhoe et al., 2018). The ENGIMA group also found that medication use in patients was associated with thinner cortices detected in frontal, temporal, parietal and occipital cortices.

SBM approaches into the cortical parameters associated with OCD have revealed lower CSA of the superior and inferior parietal and occipital regions, with no differences found in CT (Rus et al., 2017). Overall, these studies provide evidence for the presence of widespread cortical abnormalities associated with OCD, but structural investigation into specific subgroups of OCD is needed in order to identify which neural regions are associated with specific clinical presentation.

1.8.5 Neuroimaging in Perinatal OCD

Neuroimaging studies conducted on perinatal samples are scarce. A preliminary study examining stress hormone dysregulation and altered brain functioning patterns in a postpartum population found that women with postpartum OCD had significantly elevated basal salivary cortisol levels and greater activation of the OFC and temporal cortex in response to a stress task, as compared to healthy postpartum women (Lord, Steiner, Soares, Carew, & Hall, 2012). Despite these interesting preliminary results, no other studies to date have examined functional or structural neuroimaging in postpartum women with OCS or OCD.

1.9 Integrative Model

Investigations into complex psychiatric disorders requires a combination of different scientific approaches in order to better elucidate the pathophysiology. An integrative model of OCD has been proposed regarding the contributions of genetic, environmental, and neurobiological factors leading to the expression of OCD (Pauls et al., 2014). According to this model, environmental factors such as stress, trauma, and perinatal events can act as triggers in individuals with genetic vulnerability, leading to the

modification of serotonergic and additional neurotransmitter systems via epigenetic mechanisms. Altered neurotransmission, which may be coupled with neuroanatomical changes and aberrant functional connectivity, contributes to the imbalance between the direct and indirect pathways of the CSTC circuit, resulting in cognitive, mood and behavioural outcomes that are characteristic of OCD.

These biological factors have yet to be investigated in the context of perinatal OCD, where pregnancy and childbirth appear to trigger symptom onset in a subset of vulnerable women (Forray et al., 2010). When considering that genetic vulnerability associated with OCD may be sex-specific, it is therefore possible that certain genes may confer greater risk to women, due to fluctuations in gonadal hormones. Furthermore, the perinatal period is associated with structural and functional reorganization that occurs in the brain (Hoekzema et al., 2017; Oatridge et al., 2002), which may help to explain the heightened susceptibility for the development of infant-specific OCS during this time. In healthy mothers, structural volume increases in limbic, reward and sensory processing regions have been found in the early postpartum period when caregiving behaviours are established (P. Kim, Strathearn, & Swain, 2016). To date, no studies have looked at the cortical morphology associated with perinatal OCD. With growing awareness of the adversities mothers with clinical OCS and OCD face, these investigations into the underpinnings of perinatal OCD are necessary.

1.10 Research Aims

To date, no studies have taken a genetic and neuroimaging approach to better understand the pathophysiology of perinatal OCD. Despite mounting evidence to suggest

that perinatal OCD may reflect a distinct subtype, little research has been devoted to better understand whether this unique clinical presentation is due to a difference in the biological underpinnings. Understanding whether genetic or neurobiological factors contribute to risk or resilience in this population may help shape future methods of identification and treatment, in order to enhance preventative measures and response outcomes in mothers.

Our research intends to highlight gaps in our understanding of the genetics and cortical morphology underlying OCS and OCD and the importance of considering sex as a clinical variable when investigating the disorder. Based on what is known in the literature, a network of genes likely contributes to the etiology of OCD, with SERT and 5-HT_{2A} receptor genes (*SLC6A4* and *HTR2A*, respectively) acting as prominent candidates for perinatal-related OCD. Furthermore, cortical abnormalities in surface area and thickness measures in widespread brain areas may be found in relation to postpartum OCD and symptom severity, as it has been observed in the general population.

Overall, the general research aim of this body of work was to examine *SLC6A4* and *HTR2A* polymorphisms and the cortical morphological profile as it relates to perinatal OCS in mothers, in order to explore the potential role these genes and neural systems play in the disorder. Having a better understanding of perinatal OCD will help to one day improve the lives of women at risk for the development or exacerbation of perinatal-related OCS.

1.11 Specific Objectives

The specific objectives of this thesis are described below:

1. Review the literature on the genetic architecture of OCD, highlight inconsistencies in findings, emphasize the importance of considering sex and age of onset as clinical variables and identify possible candidate genes that are of interest in the context of perinatal OCD (Chapter 2);
2. Analyze the existing literature to determine whether the serotonin receptor 2A gene (*HTR2A*) is associated with OCD and its subtypes, according to sex and age of onset, using two different meta-analytic techniques (Chapter 3);
3. Explore the genetic association of the serotonin transporter polymorphism (5-HTTLPR) and *HTR2A* G-1438A polymorphism with the presence or absence of infant-related OCS during the perinatal period, determine whether symptom severity differs significantly by genotype and whether genotype status is a predictor of symptom severity across the perinatal period (Chapter 4);
4. Investigate cortical thickness and cortical surface area parameters associated with OCD and symptom severity in mothers during the postpartum period, as well as other perinatal-related factors that may contribute to postpartum OCD, including anxiety and depressive symptoms, sleep quality and past exposure to childhood maltreatment (Chapter 5).

Lastly, Chapter 6 provides a discussion on the overall findings and significance of this body of work, as well as the limitations, and concludes with future directions.

Chapter 2: The need for inclusion of sex and age of onset variables in genetic association studies of obsessive-compulsive disorder: Overview

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Abstract

Obsessive–compulsive disorder (OCD) is a heterogeneous mental disorder that significantly impairs an individual's functioning. The candidate gene approach has proven to be a useful tool in investigating potential risk genes for OCD, but genetic studies have been largely inconclusive. Etiologically distinct forms of obsessive–compulsive disorder based on sex and age of onset have been identified, yet many genetic studies fail to examine the association by these subtypes. Due to the sexually dimorphic nature of the disorder, positive associations have been found with OCD in males only, suggesting the potential for identifying risk genes that contribute to OCD in women, such as perinatal OCD. This review includes a brief overview of the disorder and its subtypes, with a current update on candidate genes that may contribute to OCD using single nucleotide polymorphisms (SNPs) and genome wide association studies (GWAS).

Keywords: Obsessive–compulsive disorder, Genetic association studies, Distinct subtypes, Perinatal period

2.1 Introduction

2.1.1 Obsessive-Compulsive Disorder

OCD is a debilitating mental disorder that involves the presence of obsessions and/or compulsions. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), obsessions are recurrent and persistent thoughts, urges, or images that the individual attempts to ignore or suppress, whereas compulsions are repetitive behaviors or mental acts that the individual performs to prevent or reduce feelings of anxiety or distress (American Psychiatric Association, 2013). Symptoms associated with the disorder can be clustered into four clinical dimensions: (1) responsibility obsessions and checking rituals, (2) contamination obsessions and decontamination rituals, (3) symmetry obsessions and ordering/arranging rituals, and (4) violent, sexual and religious obsessions and mental and reassurance-seeking rituals (Abramowitz et al., 2010). Hoarding, a symptom initially categorized as a major dimension of OCD, has since been recognized as its own separate disorder based on evidence indicating differences in cognitive and behavioral processing, course of illness, neurobiological basis and treatment response (Mataix-Cols et al., 2010).

2.1.2 Prevalence

Epidemiological studies conducted in several countries report lifetime prevalence of OCD in the general population to be between 1 and 3% (Fontenelle et al., 2006, Kessler et al., 2005, Ruscio et al., 2010). The Epidemiologic Catchment Area (ECA) study was the first to conduct a comprehensive report on the prevalence of OCD and other mental disorders in the US. Data collected for the study from 1980 to 1985, using

the Diagnostic Interview Schedule (DIS) (Robins et al., 1981), reported a lifetime OCD prevalence of 2.6%, with prolonged illness duration (mean = 7.2 years) and occurring more commonly in women aged 18–44 (Robins and Regier, 1991). Recent estimations of prevalence from the US National Comorbidity Survey Replication (NCS-R) report a lifetime OCD prevalence of 1.6% (Kessler et al., 2005). A later assessment of OCD in a random subsample of the NCS-R population found a lifetime prevalence of 2.3%, with the highest proportions found in the 18–29 and 30–44 age groups (Ruscio et al., 2010). The increased prevalence during childbearing years may reflect the increased incidence of OCD that occurs during pregnancy and postpartum in women. OCD prevalence in pregnancy ranges between 0.2–3.5%, and prevalence in the postpartum ranges between 2.7–9% (McGuinness et al., 2011), however, studies examining this reproductive period in women are limited and may not be reflective of all ethnicities.

2.1.3 Age of Onset and Sex

A bimodal distribution of OCD based on age of onset has been consistently described, with early onset (mean onset = 11 years) and late onset (mean onset = 23 years) (Taylor, 2011a). Upon closer examination of these subgroups, a greater proportion of pediatric cases of OCD occur in boys, whereas data in adults have shown a preponderance of females in late onset cases in some, but not all studies (Fontenelle et al., 2006, de Mathis et al., 2011). According to the ECA study, 49% of individuals with OCD experienced symptom emergence in childhood or adolescence, whereas approximately 40% experienced onset between ages 20–40 (Robins and Regier, 1991). OCD onset distribution across ages for both sexes in the NCS-R subsample has shown that males

have a greater proportion of cases observed during the early onset period (before age 10), which is followed by a rapid increase in female cases through adolescence and early adulthood, with an overall average age of onset occurring around 19.5 years of age (Ruscio et al., 2010). Studies examining cases of OCD in line with female reproductive milestones have found that women who have been pregnant have a later age of onset (mean = 20.2 years), whereas women who have never been pregnant have an earlier onset (mean = 13.3 years) (Williams and Koran, 1997). An earlier study examining childbirth status on OCD onset found that women who had given birth experienced a later age of onset (22–24 and 29–32 years), compared to nulliparous women who first experienced symptoms early on (13–15 years) (Neziroglu et al., 1992). Taken together, these results provide evidence for the existence of distinct forms of OCD based on differences in age of onset and sex.

2.2 Genetics of OCD

The etiology of OCD has yet to be clearly understood. It has been suggested that the disorder arises from a complex interaction between a multitude of genetic and environmental factors (Taylor et al., 2010). Family association studies have demonstrated a heritability factor of OCD, as individuals with the disorder are more likely to have a first degree relative with OCD (Hettema et al., 2001). Further support is based on twin studies: a meta-analysis of 14 studies revealed that 40% of phenotypic variance of OCD was accounted for by additive genetic variance (Taylor, 2011b). Additional studies employing the Genome-wide Complex Trait Analysis (GCTA) program that quantify the variance in OCD susceptibility that can be explained by all detected single nucleotide

polymorphisms (SNPs) have demonstrated a heritability point estimate of 0.37 for OCD (Davis et al., 2013). These studies demonstrate the potential role genetic factors may have in contributing to the etiological basis of OCD.

It is highly likely that multiple susceptibility genes contribute to the genetic inheritance of OCD. There is evidence of altered neurotransmission of both the serotonergic and dopaminergic systems in individuals with OCD, as well as evidence for catecholamine enzymes, growth factors and glutamate playing a role in the disorder (Pauls et al., 2014). As a result, polymorphisms of genes within these systems have been predominantly tested in genetic studies examining OCD, which has led to the publication of several meta-analyses (Taylor, 2013, Stewart et al., 2013a, Walitza et al., 2014, Mak et al., 2015, Wang et al., 2015, Taylor, 2015). A brief overview of inconsistent findings from genetic association studies that have examined variations in genes involved in the abovementioned systems in relation to OCD are reviewed, with descriptive characteristics and results summarized in Table 1.

Current treatment for the disorder favors selective serotonin reuptake inhibitors (SSRIs) to target serotonergic dysfunction associated with the OCD (Soomro et al., 2008). Meta-analytic data of 8 studies demonstrated a significant association of the gene coding for the serotonin 2A (5-HT_{2A}) receptor, *HTR2A*, with OCD (Taylor, 2013). 5-HT_{2A} receptors are distributed in central and peripheral tissue, and its activation leads to several downstream processes, such as the regulation of serotonin transporter (SERT) expression (Qian et al., 1997, Raymond et al., 2001). Despite the significant result found in the meta-analysis, genetic association studies examining polymorphisms within the

HTR2A gene have been inconclusive. An initial positive finding of the association of the *HTR2A* SNP G-1438A was suggestive of a sexually dimorphic effect on OCD, as the association was only found in a sample of women who had (on average) an early age of onset (Enoch et al., 2001). There are mixed results in replication studies, with some unable to find any significant association (Hemmings, 2006, Saiz et al., 2008), and others finding an association in those with early onset OCD (Walitza et al., 2012).

SSRIs target the serotonin transporter, making the serotonin transporter linked polymorphic region (5-HTTLPR), found in the serotonin transporter gene *SLC6A4*, a candidate polymorphism for OCD. The 5-HTTLPR is a tri-allelic variation composed of either the short (S) allele or long (L) allele, which exists in two active forms, L_A and L_G, due to a nearby variation that influences transcription (Hu et al., 2006). The L_G allele behaves similarly to the S allele, resulting in reduced transcriptional efficiency of the 5-HTT gene, leading to decreased expression of the transporter and subsequently, a decrease in serotonin re-uptake (Caspi et al., 2010). Hu et al. were the first team of researchers to demonstrate the tri-allelic functionality of 5-HTTLPR and a significant association of the L_A allele with OCD (Hu et al., 2006). The 5-HTTLPR was found to be significantly associated with OCD in a comprehensive meta-analysis (Taylor, 2013), as well as in a more recent meta-analysis only examining early onset OCD (Walitza et al., 2014). Another meta-analysis conducted of 13 studies found no significant association between 5-HTTLPR allele status and OCD, however, a trend for the S-allele was detected overall in females only when stratified by sex (Mak et al., 2015). A recent study examining a different variant in the *SLC6A4* gene found an association of the rs16965628

SNP with OCD, which did not differ by sex (Cengiz et al., 2015). Another study examining regions of the *SLC6A4* gene found the genotype 9/10 of the intron 2 variable number tandem repeat (VNTR) to be significantly associated with OCD in females, but there was no association with 5-HTTLPR (Voyiaziakis et al., 2011).

Dopamine has been shown to be important in frontostriatal circuits, specifically in the modulation of cognitive flexibility, which is impaired in individuals with OCD (Chamberlain et al., 2006). Animal studies have shown that administration of dopamine agonists that act to increase dopaminergic activity results in stereotyped behaviors, whereas dopamine antagonists decrease these behaviors in deer mice, a strain of mice associated with naturally occurring repetitive behaviors (Hoffman, 2011). Additionally, Tourette's syndrome (TS) is associated with dopaminergic dysfunction, providing indirect evidence for the role of dopamine in OCD, since these disorders are commonly comorbid and may share common genetic factors (Lochner et al., 2005). Genetic association studies examining dopamine receptors 2 and 4 (*DRD2* and *DRD4*) have been found to be significantly associated with OCD (Denys et al., 2006, Billett et al., 1998), but results are mixed (Nicolini et al., 1996, Hemmings et al., 2003). Demonstrating the importance of analysis stratification by sex and age of onset, a study examining the *DRD2* TaqI A variant found a significant association of the A2 allele with OCD in males only and an association of the A2A2 genotype was found in OCD patients with early-onset (defined as 15 years of age or younger) (Denys et al., 2006). Furthermore, in examination of the *DRD4* 48 bp VNTR, a study recently found association of allele 7 (repeat 7) with OCD in females, and the association of allele 2 with symmetry symptom dimension (Taj M J et

al., 2013), which has been linked to OCD previously (Millet et al., 2003). In addition to these genes, trends have been described in a meta-analysis for two other genes in the dopamine system: dopamine transporter gene, *DAT1*, and dopamine receptor D3, *DRD3* (Taylor, 2013), despite the largely negative results reported by others (Billett et al., 1998, Walitza et al., 2008, Zhang et al., 2015a, Liu et al., 2011).

Studies examining polymorphisms within catecholamine modulation genes, monoamine oxidase-A (*MAO-A*) and catechol-O-methyltransferase (*COMT*), have found largely positive associations with OCD predominantly in men (Karayiorgou et al., 1999). *MAO-A* gene is found on the X chromosome and codes for one form of the monoamine oxidase enzyme that is involved in the metabolism of serotonin, dopamine, epinephrine and norepinephrine (Weyler et al., 1990). The EcoRV (C1460T) variant of *MAO-A* significantly differs between OCD patients and controls in a sex-specific manner, with an increased frequency of the low activity C allele detected in females, and male OCD patients having an increased frequency of the high activity T allele (Camarena et al., 2001, Lochner et al., 2004). The T allele of a different variant in the *MAO-A* gene, found in exon 8 (T941G), was associated with OCD in males only (Karayiorgou et al., 1999), further providing evidence of the sexually dimorphic nature of the *MAO-A* gene. *COMT* gene is found on chromosome 22 and codes for the enzyme that metabolizes dopamine, epinephrine and norepinephrine (Lotta et al., 1995). The low-activity allele (L-allele/Met) of the Val158Met polymorphism of *COMT* has been shown to be significantly associated with OCD in males only (Karayiorgou et al., 1999, Denys et al., 2006). The association of *COMT* with OCD in males was also confirmed in a meta-analysis (Pooley et al., 2007),

despite some negative results (Sampaio et al., 2015). Overall, results from *MAO-A* and *COMT* association studies suggest that certain genes act in a sexually-dimorphic manner and may contribute as genetic risk factors of OCD.

Glutamate is the primary excitatory neurotransmitter in the brain and abnormalities in the glutamatergic system have been suggested to contribute to OCD through its actions in the cortico-striato-thalamo-cortical circuit (Pauls et al., 2014). Variants in a number of genes in the glutamatergic system have been associated with OCD risk. Associations were found with the *SLC1A1* gene, which codes for a glutamate transporter (Pittenger et al., 2011). However, the association of *SLC1A1* has been prominent in males and not females in the majority of studies, suggesting a possible sex-specific association of this gene (Arnold et al., 2006, Dickel et al., 2006, Stewart et al., 2007a). *GRIN2B*, a gene coding for the NR2B glutamate receptor subunit, has not been examined as extensively as *SLC1A1*, but association of a *GRIN2B* variant with OCD was found in a preliminary study (Arnold et al., 2004). This association was not replicated in a following study, however, a different variant of *GRIN2B* was associated with certain obsessive–compulsive symptoms in males only (Alonso et al., 2012). Despite these promising findings, not all studies have been able to detect significance with either of these variants in *GRIN2B* with OCD (Liu et al., 2012). Animal studies have implicated postsynaptic synapse-associated protein 90 (SAP90)/postsynaptic density-95 (PSD95)-associated protein 3 (*SAPAP3*, also known as *DLGAP3*) gene in OCD, with *SAPAP3*-knockout mice displaying compulsive grooming behavior (Welch et al., 2007). SAPAP3 is part of a family of scaffolding proteins that is highly expressed at glutamatergic

synapses (Scannevin and Huganir, 2000). Genetic association studies have found nominally significant association of *SAPAP3* variants with grooming disorders such as pathological nail biting, skin picking and/or trichotillomania, which are related forms of OCD (Bienvenu et al., 2009), and rare variants of *SAPAP3* have been identified in individuals with co-occurring OCD and trichotillomania (Züchner et al., 2009). Through examining OCD by age of onset, a team of researchers found that a haplotype of *SAPAP3* variants was significantly associated with early onset OCD (Boardman et al., 2011). Another gene of the glutamatergic system that has been associated with OCD is the glutamate kainate receptor, *GRIK2*, however, replication issues exist (Delorme et al., 2004, Sampaio et al., 2011).

Furthermore, polymorphisms in other candidate genes, such as 5-HT receptor type 1β (*HTR1β*) (Mundo et al., 2000, Mundo et al., 2002, Mas et al., 2014), tryptophan hydroxylase 2 (*TPH2*) (Mössner et al., 2006, Mas et al., 2013), glutamate decarboxylase 2 (*GAD2*) (Mas et al., 2014), brain-derived neurotrophic factor (*BDNF*) (Hall et al., 2003, Liu et al., 2015), neurotrophin-2 receptor gene (*NTRK2*) (Alonso et al., 2008a), neurotrophin-3 receptor gene (*NTRK3*), specifically with the hoarding phenotype (Alonso et al., 2008b, Muinos-Gimeno et al., 2009), myelin oligodendrocyte glycoprotein (*MOG*), a component of myelination in the central nervous system (Zai et al., 2004), oligo-dendrocyte lineage transcription factor 2 (*OLIG2*) (Stewart et al., 2007b, Zhang et al., 2015b), and gamma-amino-butyric acid type B receptor 1 (*GABBR1*) (Zai et al., 2005), have been implicated in OCD, but results are generally mixed (Hemmings et al., 2003, Mössner et al., 2005, Atmaca et al., 2010, Mas et al., 2013).

It is important to note that finding a significant association in genetic association tests may be interpreted in a number of ways. As described by Lewis and Knight (Lewis and Knight, 2012), a positive association found with the SNP genotyped may reflect (1) a true, causal relationship where the variant is directly responsible for conferring risk, (2) an indirect association, where the SNP is in linkage disequilibrium with the true variant, or (3) a false-positive result, in which case the result was due to chance or confounding variables. In addition, there are some factors to consider when a negative result is found in a genetic association study. If a study design does not contain sufficient power or large enough sample size, a gene contributing a small effect of increasing risk will be difficult or impossible to detect. Underpowered genetic association studies may cause part of disparity seen in the OCD literature.

These limitations are improved upon through aggregated meta-analytic data of genetic association studies. Meta-analyses are highly beneficial tools which afford higher statistical power and better illustrate genetic underpinnings of various disorders. As previously described, four genes (*HTR2A, 5-HTTLPR, COMT* and *MAO-A*) have been shown to be significantly associated with OCD through a comprehensive meta-analysis (Taylor, 2013), with three genes (*HTR2A, 5-HTTLPR* and *COMT*) having been shown to be specific to OCD as compared to other psychiatric disorders in a recent meta-analysis (Taylor, 2015).

Genome-wide association studies (GWAS), an approach that examines genetic variants across the entire genome, have been conducted in order to further elucidate the genetic basis of OCD. The International OCD Foundation Genetics Collaborative

(IOCDF-GC) reported a significant association with a variant near the *BTBD3* gene, which exceeded genome-wide significance in the parent-offspring trio sample but not in the total sample (Stewart et al., 2013b). Despite no other SNPs exceeding genome-wide threshold for significance, variants that had the lowest p-value and may be associated with OCD include the *DLGAP1* gene and a variant near the *FAIM2* gene. A recent case–control study further examined the association between *DLGAP1* and OCD, finding a significant association with cleaning and contamination symptoms when stratified by symptom phenotypes (Li et al., 2015).

Another collaborative project, the OCD Collaborative Genetics Association Study (OCGAS), examined early onset OCD and was unable to detect a SNP that reached genome-wide significance, but identified the strongest association for a variant near the *PTPRD* gene, followed by a SNP near the cadherin genes, *CDH9* and *CDH10* (Mattheisen et al., 2015). Evidence was also detected for the association of *GRIK2* and a SNP in the region surrounding the *DLGAP1* gene. The results from the GWAS studies suggest that the genes identified are candidate genes for OCD.

When examining OCD and TS, variants that contribute to gene expression in the parietal cortex and cerebellum, analyzed by expression quantitative trait loci (eQTLs), were found to significantly contribute to the heritability for both disorders (Davis et al., 2013). Despite distinct genetic architecture between the disorders, the genetic correlation was 0.41, suggesting a degree of shared heritability. A separate GWAS study conducted on OCD and TS also found variants strongly associated with brain eQTLs (Yu et al., 2015). When examining the polygenic risk score, a significant polygenic component was

found for OCD, but not for TS, further providing evidence of distinct genetic architectures. Additionally, results from these studies suggest that OCD comorbid with TS or tics may reflect a genetically distinct form that is associated with altered susceptibility.

2.3 Gonadal Hormones and OCD

Despite clear evidence of distinct forms of OCD based on sex and age of onset, the mechanisms by which these OCD subtypes differ is unclear. In consideration of genetic factors that contribute to the development of OCD, a strong role for gonadal hormone influences is plausible.

Following the average age of menarche, a rapid rise of OCD onset cases has been detected in females (Ruscio et al., 2010), suggesting a possible triggering effect resulting from changes in estrogen. In line with this theory, increased vulnerability of OCD onset or exacerbation for females coincides with reproductive events associated with alterations of estrogen, such as pregnancy/postpartum and menopause (Guglielmi et al., 2014), further supporting the possible role of gonadal hormones in OCD.

Estrogens are known to impact neurotransmitter systems implicated in OCD, such as serotonin, dopamine, and glutamate (McEwen and Alves, 1999). A case–control study examining estrogen receptor alpha and beta gene, *ESR1* and *ESR2* respectively, found a significant association of a *ESR1* haplotype (that is associated with higher alpha receptor expression) in OCD patients with contamination and cleaning symptoms (Alonso et al., 2011). Testosterone levels have been linked to impulsivity and aggression, which may be related to the increased prevalence of aggressive symptoms detected in males with OCD

(de Mathis et al., 2011). However, one study examining levels of testosterone in OCD patients found lower levels in male OCD patients compared to healthy control males, with no differences reported between females (Erbay and Kartalci, 2015).

Activated estrogen receptors function as transcription factors that bind DNA sequences at promoter regions of target genes called estrogen response elements (EREs), subsequently regulating gene transcription (Driscoll et al., 1998). Estrogen has been shown to regulate levels of TPH2, the rate limiting enzyme in serotonin synthesis (Hiroi and Handa, 2013), GAD2, an enzyme responsible for GABA synthesis (Hudgens et al., 2009), MAO-B, an enzyme that degrades dopamine (Zhang et al., 2006), BDNF (Sohrabji et al., 1995) and COMT (Kinnear et al., 2001) through interaction with EREs found on these genes. It may be hypothesized that while variations in genes that code for neurotransmitter systems, growth factors and catecholamines increase risk susceptibility for OCD, estrogen may partially account for sex and age of onset differences through transcriptional modulation of associated genes.

Animal studies have provided additional insight into estrogen effects on compulsive-like behavior. Male mice deficient in estrogen present with compulsive-like symptoms, whereas female mice deficient of estrogen do not develop any behaviors, suggesting a sex-specific interaction between estrogen and compulsive behaviors (Hill et al., 2007). However, lever-pressing responses in adult female rats have been found to fluctuate in correspondence to their estrous cycle (Flaisher-Grinberg et al., 2009), suggesting that changes in estradiol may be responsible for the increased risk women have for OCD during the perinatal period.

2.4 Perinatal Period and OCD

The perinatal period represents a reproductive milestone that has been shown to be associated with increased vulnerability to psychiatric disorders (Altshuler et al., 1998, Steiner et al., 2003, Payne et al., 2009, Guglielmi et al., 2014). Significant attention has been placed on examining postpartum depression, with less research focused on perinatal onset OCD. Stressful life events, such as pregnancy and delivery, have been described as triggers of OCD (Maina et al., 1999). Among women with children, pregnancy was associated with OCD onset more than any other life event (Neziroglu et al., 1992). In addition to the increased prevalence rates of OCD found in women in the perinatal period, reports also describe symptom exacerbation in women with pre-existing OCD during pregnancy and postpartum (Williams and Koran, 1997, Labad et al., 2005, Forray et al., 2010). Worsening of obsessive–compulsive symptoms has been reliably linked to female reproductive events. A recent study found that OCD exacerbation during the perinatal period was a risk factor for symptom exacerbation in a subsequent pregnancy, which may reflect an underlying biological mechanism in this unique population (Guglielmi et al., 2014).

The perinatal period has been shown to influence the type of obsessional thoughts and compulsive behaviors in OCD and nonclinical samples, for both mothers and fathers with newborns (Abramowitz et al., 2003a). Novel symptoms of OCD are likely to emerge that are based upon the well-being of the child (Abramowitz et al., 2003b). Specifically, thoughts of harm coming to the infant are more likely to manifest in the postpartum (Sichel et al., 1993, Arnold, 1999), whereas contamination obsessions are more prevalent

in pregnancy (Forray et al., 2010). Aggressive obsessive–compulsive symptoms are also common in postpartum women with and without depression (Wisner et al., 1999), suggesting that women have increased risk of OCD or obsessive–compulsive symptoms in the postpartum period. Despite mounting evidence to suggest that perinatal onset OCD may reflect a distinct subtype, little research has been devoted to better understand whether this is due to a difference in the biological basis.

2.5 Conclusions

There is substantial evidence pointing towards etiologically distinct forms of OCD based on sex differences and age of onset. The OCD literature reflects differences associated with distinct subtypes, yet some genetic studies fail to report certain demographic characteristics or examine the impact sex or age of onset may have, despite the heterogeneous nature of the OCD population examined. Additional subtypes that have been suggested are based on symptom clustering, treatment response, presence of tics and history of streptococcal infection (Hollander et al., 2009). There is some evidence suggesting that postpartum OCD may reflect a distinct subtype (McGuinness et al., 2011). As a result of the heterogeneous nature of the disorder, genes that may be involved in one specific subtype of OCD may be different in another. However, with more subtypes included in analyses, an even larger sample size will be needed in order to achieve sufficient power to detect any true effects of genes contributing to the pathophysiology of the disorder. Large scale studies utilizing known variables that affect OCD etiology are needed and will allow thorough insight into the potential role candidate genes may have on the disorder.

The results from genetic association studies of OCD demonstrate that certain genes are likely to confer greater susceptibility to men, which in turn suggests the potential for identifying genetic variants that may increase susceptibility in women, specifically in the case of perinatal onset OCD. Sex differences in genetic susceptibility have been reliably evident, with polymorphisms involved in the glutamate transporter gene, *SLC1A1*, and those in catecholamine modulation, specifically *MAO-A* and *COMT*, having been found to be associated with OCD only in males. Association of susceptibility genes with female OCD is unclear given the current literature. More research must be conducted in examining candidate genes of OCD by sex and other subtypes in order to better understand the potential role these genes and neurobiological systems play in the disorder.

2.6 References

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Table 1: Descriptive characteristics of genetic studies of OCD featured in the review

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
HTR1β	(Mundo et al., 2000)	67 families (27:40)	N/A	15.2 ± 8	G861C	G allele p = 0.006 (n=32)
	(Mundo et al., 2002)	121 families [a] (58:99)	N/A	13.6 ± 8.2	G861C	G allele p = 0.023
					T371G	NS
	(Hemmings et al., 2003)	71	129	---	G861C	NS
	(Mas et al., 2014)	75 families (41:34)	N/A	M 11.67 ± 2.9 (n = 47) F 12.03 ± 3.2 (n = 37)	rs2000292	A allele (EO) p = 0.0001 (males only) p = 0.0006
HTR2A	(Enoch et al., 2001)	101 (53:48)	138 (61:77)	M 13.1 ± 7.2 F 14.8 ± 9.0	G-1438A	A allele (females only) p = 0.015
	(Hemmings, 2006)	132 (71:61)	218 (56:162)	14 (median)	G-1438A	NS
	(Saiz et al., 2008)	99 (46:53)	420 (216:204)	---	G-1438A	NS
	(Walitza et al., 2012)	136 (77:59)	106 (65:41)	11.1 ± 3.2	G-1438A	A allele (EO) p = 0.007
SLC6A4	(Hu et al., 2006)	169 (97:72)	253 (137:116)	---	5-HTTLPR	L_A allele p = 0.036
	(Voyiaziakis et al., 2011)	459 families	N/A	< 18	5-HTTLPR	NS
					Intron 2 VNTR	Alleles 9/10 (females only) p = 0.0069
	(Cengiz et al., 2015)	80 (32:48)	100 (39:61)	---	rs16965628	G allele p = 0.005
TPH2	(Mössner et al., 2006)	71 families (41:30)	N/A	11.73 ± 2.9	rs4570625/ rs4565946 haplotype	G/C (EO) p = 0.035
	(Mas et al., 2013)	74 (39:35)	91 (30:61)	≤ 18	rs10748185	A allele (EO) p = 0.007

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
DRD2	(Nicolini et al., 1996)	67 (29:38)	54 (34:20)	22.6 ± 9.1	TaqI A	NS
	(Denys et al., 2006)	139 (51:88)	133 (67:66)	17.7 ± 8.3	TaqI A	A2 allele (males only) p = 0.02
DRD3	(Billett et al., 1998)	103 (50:53)	103 (50:53)	18.5	rs6280	NS
	(Liu et al., 2011)	103 families	N/A	EO ≤16 (n = 37) LO >16 (n = 66)	rs6280	NS
DRD4	(Billett et al., 1998)	118 (55:63)	118 (55:63)	18.5	48 bp VNTR	Allele 2 (protective) p = 0.021
	(Millet et al., 2003)	55 families (32:23)	N/A	12.9 ± 6	48 bp VNTR	Allele 2 (protective) p = 0.016
	(Hemmings et al., 2003)	71	129	---	48 bp VNTR	NS
	(Taj M J et al., 2013)	173 (119:54)	201 (126:75)	20.7 ± 8	48 bp VNTR	Allele 7 (females only) p = 0.02
DAT1	(Walitza et al., 2008)	69 families (40:29)	N/A	11.7 ± 2.9	40 bp VNTR	NS
	(Zhang et al., 2015)	305 (151:154)	435 (203:232)	---	40 bp VNTR	NS
MAO-A	(Karayiorgou et al., 1999)	103 families (47:56)	N/A	14.4 ± 8.6	T941G	G allele (males only) p = 0.0186
	(Camarena et al., 2001)	122 (63:59)	124 (60:64)	M 19.5 ± 8 F 23.4 ± 8.8	EcoRV C1460T	T allele (males only) p = 0.0053
		51 families (32:19)	N/A	---	EcoRV C1460T	C allele (females only) p = 0.022
	(Lochner et al., 2004)	Afrikaner 79 (37:42)	Afrikaner 99 (20:79)	---	EcoRV C1460T	NS

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
MAO-A	(Lochner et al., 2004)	Caucasian 95 (52:43)	Caucasian 94 (21:73)	---	EcoRV C1460T	C allele (females only) p = 0.009 T allele (males only) p = 0.008
COMT	(Karayiorgou et al., 1999)	103 families (47:56)	N/A	14.4 ± 8.6	Val158Met	L allele (males only) p = 0.0079
	(Denys et al., 2006)	155 (56:99)	150 (79:71)	17.7 ± 8.3	Val158Met	L allele (males only) p = 0.035
	(Sampaio et al., 2015)	783 families	N/A	---	Val158Met	NS
SLC1A1	(Arnold et al., 2006)	157 probands (60:97) 49 affected relatives (15:34)	270 unaffected family members	14.4 ± 9.2	rs301434/ rs3087879 haplotype	C/G (males only) p = 0.001 T/C (protective) (males only) p = 0.002
	(Dickel et al., 2006)	20 families (31 probands)	N/A	< 18	rs3780412	A allele (males only) p = 0.002
					rs301430	C allele p = 0.03
					rs301430/ rs301979 haplotype	T/C (protective) (males only) p = 0.003
	(Stewart et al., 2007a)	66 families (47:19)	N/A	7.9 ± 5.9	rs2228622	A allele (males only) p = 0.045
					rs3780412	C allele (males only) p = 0.045
					rs12682807/ rs2072657/ rs301430 haplotype	A/T/T (males only) p = 0.0031
GRIN2B	(Arnold et al., 2004)	130 families (51:79)	N/A	---	T5072G	T allele p = 0.014

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
GRIN2B	(Arnold et al., 2004)	130 families (51:79)	N/A	---	T5072G/ T5988C haplotype	G/T p = 0.002
	(Alonso et al., 2012)	225 (116:109)	279 (161:118)	C/C Sx 18.8 ± 8.5 No C/C Sx 20.6 ± 8	rs1805476	T allele (males only) (C/C Sx only) p = 0.002
	(Liu et al., 2012)	206 (131:75)	413 (254:159)	---	rs1805476	NS
					T5072G	NS
SAPAP 3	(Bienvenu et al., 2009)	383 families	N/A	< 18	rs6662980	G allele (GD only) p < 0.05
	(Boardman et al.)	172 (85:87)	153 (63:90)	15 (median)	rs11583978/ rs7541937/ rs6662980/ rs4652867 haplotype	A/T/A/T (EO) p = 0.036
GRIK2	(Delorme et al., 2004)	156 (85:71)	141 (87:54)	---	M867I	NS
		124 families	N/A		M867I	I allele (protective) p < 0.03
	(Sampaio et al., 2011)	47 families [b] (32:15)	N/A	---	M867I	NS
					rs1556995	A allele p = 0.03
					rs1556995/ rs1417182 haplotype	G/C (protective) p = 0.01
GAD2	(Mas et al., 2014)	75 families (41:34)	N/A	M 11.67 ± 2.9 (n = 47) F 12.03 ± 3.2 (n = 37)	rs8190748	A allele p = 0.0001 (females only) p = 0.0006 (males only) p = 0.01
					rs992990	C allele p = 0.0002 (males only) p = 0.01

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
BDNF	(Hall et al., 2003)	164 families (78:86)	N/A	EO <18 (n = 120) LO ≥18 (n = 44)	Val66Met	Val66 allele (EO) p = 0.001
	(Mössner et al., 2005)	67 families (36:31)	N/A	11.52 ± 3	Val66Met	NS
	(Liu et al., 2015)	321 (176:145)	426 (238:188)	EO <18 (n = 135) LO >18 (n = 186)	Val66Met	Val66 allele (females only) p = 0.00
NTRK2	(Alonso et al., 2008a)	215 (103:112)	342 (202:140)	19.5 ± 8.3	rs2378672	A allele (females only) p < 0.0009
NTRK3	(Alonso et al., 2008b)	120 (64:56) Hoarding subset 36	342 (202:140)	Hoarders 18 ± 7.1 Non-hoarders 20.5 ± 8.5	rs7176429	GT Heterozygote (hoarding only) p < 0.0004
	(Muinos-Gimeno et al., 2009)	153 (85:68) Hoarding subset 47	324 (187:137)	---	rs28521337	C allele (protective) (hoarding only) p < 0.005
MOG	(Zai et al., 2004)	160 families	N/A	14.7 ± 9 (n = 121)	MOG4 (TAAA repeat)	Allele 2 (459 bp allele) p = 0.022
	(Atmaca et al., 2010)	30 (16:14)	30 (16:14)	---	G511C	NS
OLIG2	(Stewart et al., 2007b)	41 families (28:13)	N/A	10.5	rs762178	G allele p < 0.001
					rs1059004	A allele p = 0.005
					rs9653711	C allele p = 0.004
	(Mas et al., 2013)	74 (39:35)	91 (30:61)	≤ 18	rs762178 rs1059004 rs9653711	NS NS NS
	(Zhang et al., 2015)	400 (243:157)	459 (276:183)	20.24 ± 10.31	rs762178	A allele (EO) p = 0.013 (females only) p = 0.032

Gene	Reference	OCD sample (M:F)	Control sample (M:F)	Mean age of onset ± SD	SNP	Results
OLIG2	(Zhang et al., 2015)			EO <18 (n = 233) LO ≥18 (n = 167)	rs1059004 rs9653711	C allele (EO) p = 0.039 G allele (EO) p = 0.039
GABBR1	(Zai et al., 2005)	159 families	N/A	14.7 ± 9 (n = 121)	A-7265G	A allele p = 0.006
DLGAP1	(Li et al., 2015)	320 (178:142)	431 (239:192)	EO (n = 154) LO (n = 166)	rs11081062	T allele (C/C Sx only) p < 0.05
ESR1	(Alonso et al., 2011)	229 (120:109)	279 (161:118)	19.7 ± 8.2	rs34535804/ rs488133 /rs9478245/ rs2234693/ rs9340799 haplotype	A/C/C/C/G (protective) (C/C Sx only) p = 0.02

Abbreviations. OCD: obsessive-compulsive disorder; SD: standard deviation; GD: grooming disorder (nail biting, skin picking or trichotillomania); M: male; F: female; EO: early onset; LO: late onset; N/A: not applicable; NS: not significant; VNTR: variable number tandem repeat; C/C Sx: contamination obsessions/cleaning compulsions symptoms.

Dashes indicate unreported values.

"Protective" represents allele(s) with decreased transmission in family-based transmission disequilibrium tests or allele(s) that are associated with lower risk.

[a] includes 67 families from Mundo et al. (2000)

[b] includes 21 families from Delorme et al. (2004) (Note: a secondary analysis was conducted without the overlapping sample, and results remained significant)

Chapter 3: The association of HTR2A polymorphisms with obsessive-compulsive disorder and its subtypes: A meta-analysis

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Abstract

Background: Genetic risk factors that contribute to obsessive-compulsive disorder (OCD) have yet to be elucidated. Historically, serotonergic dysfunction has been implicated. Evidence from the literature points towards the serotonin receptor 2A gene (HTR2A) as a primary candidate. Our meta-analysis investigated whether polymorphisms in HTR2A are associated with OCD or its subtypes, based on sex and age of onset.

Methods: Studies employing case-control or family-based designs were systematically searched, and those meeting eligibility underwent quality assessment, resulting in 18 studies. A random-effects meta-analysis using standard inverse-variance weighting to compute odds ratio (OR) was conducted. To examine sensitivity, results were also obtained using a more conservative statistical method.

Results: Three HTR2A variants were identified: T102C, G-1438A, and C516T. T102C and G-1438A were analyzed together due to strong linkage disequilibrium, where the 102T allele co-occurs with -1438A allele. Results reported as OR [95%CI] showed that the T/A allele were significantly associated with OCD, 1.14 [1.01, 1.29]. After stratification, results remained significant for females, 1.20 [1.00, 1.45], and early-onset OCD, 1.27 [1.02, 1.58], but not males, 1.06 [0.91, 1.23]. No associations were found for late-onset OCD, 0.98 [0.70, 1.37], or C516T, 1.22 [0.14, 10.37], but conclusions cannot be drawn from two studies.

Limitations: Associations no longer reached significance with the conservative statistical approach. HTR2A alone cannot explain OCD complexity and limited samples reporting genetic data according to subtypes.

Conclusions: These results suggest a possible association of HTR2A polymorphisms with OCD, but further investigations considering sex and age of onset with larger samples is needed.

Keywords: Obsessive-compulsive disorder; Serotonin receptor 2A; HTR2A; Genetic association; Sex differences; Age of onset

3.1 Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder characterized by the presence of unwanted and intrusive thoughts, images or urges (obsessions) and/or repetitive behaviours (compulsions) which are performed as attempts to neutralize the obsessions. Affecting approximately 1-3% of the population (Fontenelle et al., 2006; Ruscio et al., 2010), OCD is a chronic disorder impacting patients' quality of life (Abramowitz et al., 2009; Kugler et al., 2013).

OCD is thought to arise from a multitude of factors, which include genetic, neurobiological, cognitive and environmental influences (Pauls et al., 2014). Despite the well-established moderate heritability associated with OCD (Grabe et al., 2006; Nestadt et al., 2000; Taylor, 2011a; Van Grootheest et al., 2007), the genetic etiology of the disorder has yet to be elucidated. Association studies have shown inconsistent findings in identifying specific risk genes (Nestadt et al., 2010; Pato et al., 2002; Pauls, 2010). The heterogeneity associated with OCD is often a cited challenge in the literature and may explain such discrepant results. Awareness of these limitations is growing, and the field is moving toward identifying homogenous subtypes within OCD (de Mathis et al., 2011; Lochner et al., 2008; Raines et al., 2018; Taylor, 2011b). This approach, which groups or classifies OCD individuals according to different clinical presentations, will increase the power to detect and determine the factors contributing to the disorder and lead to opportunities for therapeutic advances. Evidence from candidate gene studies and genome wide association studies (GWAS) suggests that distinct genetic vulnerabilities may be linked to specific OCD subtypes based on sex, age of onset, family history of OCD,

presence of psychiatric comorbidities, and by symptom clustering (Mattina and Steiner, 2016).

Polymorphic variants within the genes involved in serotonergic transmission, specifically serotonin 2A (5-HT_{2A}) receptor and serotonin transporter (SERT), have been the most commonly studied in OCD and findings from candidate gene studies provide supporting evidence that these serotonin gene variants may be associated with the disorder (Sinopoli et al., 2017). Prior meta-analyses have demonstrated that polymorphisms within the 5-HT_{2A} receptor gene (*HTR2A*) and SERT gene (*SLC6A4*) are associated with OCD (Taylor, 2013) and specific to this disorder, when compared against several other psychiatric disorders (Taylor, 2016). Unlike the 5-HTTLPR polymorphism in the *SLC6A4* gene that has undergone considerable investigation (Mak et al., 2015), the functional influence of genetic variations within the *HTR2A* gene on 5-HT2A receptors, serotonergic signaling and its involvement in OCD is less clear.

The *HTR2A* gene codes for a G-protein coupled receptor and is found on chromosome 13q14-21. It spans approximately 66 kb and consists of 7 exons, some of which were recently described (Ruble et al., 2016). The gene has been described as having two alternative promoters, a silencer element and four transcription initiation sites (Myers et al., 2007; Zhu et al., 1995).

Two of the most widely studied *HTR2A* polymorphisms within the OCD literature are G-1438A (rs6311) and T102C (rs6313). These polymorphisms have been found to be in almost complete linkage disequilibrium with each other in various ethnic and clinical populations (Bray et al., 2004; Gomes et al., 2018; Gray et al., 2018; Segman et al., 2001;

Smith et al., 2013; Spurlock et al., 1998). T102C is a synonymous/silent single nucleotide polymorphism (SNP) found within the first exon, whereas G-1438A is a SNP located upstream of the promoter region of *HTR2A* (Spurlock et al., 1998). The functional consequence of these polymorphisms is unclear (Parsons et al., 2004; Smith et al., 2013).

Based on the emergence of recent publications utilizing larger cohort sizes, a meta-analytic investigation that considers etiologically distinct OCD subtypes is warranted. This review will investigate whether *HTR2A* polymorphisms are associated with OCD and its subtypes according to sex and age of onset. A meta-analysis was conducted using a standard statistical approach that has been used in the field previously (Taylor, 2016, 2013) in order to assess case-control association studies and family-based transmission-disequilibrium tests (TDT) examining polymorphisms in this gene in relation to OCD, with subgroup meta-analyses performed according to OCD groups stratified by sex or age of onset (early vs. late onset). Following the conventional statistical approach, we repeated the analyses using a more conservative method to explore sensitivity and test the robustness of our model. Lastly, the literature concerning the functional impact of the *HTR2A* SNPs examined in our meta-analyses is reviewed and the clinical relevance of our results are briefly discussed.

3.2 Methods

Published studies or grey literature, such as dissertations, from inception up to December 2019 were identified in PubMed, MEDLINE, PsycINFO, Embase, DisGeNET (version 3.0; Bauer-Mehren et al., 2010), and OCD Database (OCDB; Privitera et al., 2015). A detailed search strategy describing terms used for each database can be found in

Supplementary Table 1. The meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Article screening and data abstraction were performed in duplicate independently by two authors (G.M. and M.S.) and disagreements were resolved by consensus. Articles meeting initial screen requirements were translated if the full text was not available in English.

Studies met criteria for inclusion if they employed a case-control or family-based design, where cases or probands met DSM-III, DSM-III-R, DSM-IV or DSM-5 diagnostic criteria for OCD and sufficient information regarding the *HTR2A* genotype or allelic frequencies in the sample was available. For a list of studies excluded after full-text review with the rational provided, see Supplementary Table 2. An exception was made for two papers published by Walitza et al.'s research group where their later publication included a subsumed sample of OCD cases from their earlier publication (Walitza et al., 2012, 2002). Since each study contained different samples of healthy controls, both studies were included in the quantitative analyses but only genetic information from the novel OCD cases (n=81) were extracted from their later publication (Walitza et al., 2012).

All studies meeting inclusion underwent quality assessment using the Quality of Genetic Association Studies (Q-Genie) tool (Sohani et al., 2015) by two raters (G.M. & M.S.). The Q-Genie tool provides an estimate of the methodological quality of published genetic association studies and is freely available for download from <http://fhs.mcmaster.ca.libaccess.lib.mcmaster.ca/pgp/links.html>. Ratings were provided independently, and disagreements were resolved by consensus. Only papers achieving an

overall score of moderate or good quality, as outlined in the suggested scoring instructions, met full inclusion criteria and were included in the meta-analysis. Inter-rater agreement on Q-Genie scores was measured using quadratic weighted Cohen's kappa (Cohen's κ_W).

Subgroup analyses were performed for investigating the association of *HTR2A* gene with OCD by sex (male vs. female) and age of onset (early vs. late onset), as the literature supports the existence of distinct forms of OCD based on these groups (Mattina and Steiner, 2016). Early onset was described as OCD onset during childhood/adolescence up to and including 18 years of age, whereas late onset was described as occurring in adults older than 18 years of age. These cut-off scores were chosen based on reported data. An exception was made for one paper (Liu et al., 2013) where the researchers defined late onset OCD as onset after 16 years of age. Additional information regarding the procuring of genetic data according to sex and age of onset can be found in the Supplementary Information file.

Statistical analyses were conducted in the R software (version 3.6.2)(R Core Team, 2019). The 'metafor' package (Viechtbauer, 2010) was used to combine case-control and family-based studies to conduct a random-effects meta-analysis, which was chosen due to the etiological and clinical heterogeneity associated with OCD populations (McKay et al., 2004). Measures of individual odds ratio (OR) were conducted using inverse variance weighting, and statistical pooling of data was conducted when there were two or more data sets meeting criteria. Between-study heterogeneity, known as tau-squared (τ^2), was estimated using the Dersimonian and Laird method (DL), which is a

standard practice and one of the most widely used random-effects model approaches (DerSimonian and Laird, 1986). Statistical heterogeneity of ORs across studies was measured using Cochran's Q statistic (Cochran, 1954), reported as a chi-square statistic χ^2, and the Higgins and Thompson's I^2 statistic (Higgins and Thompson, 2002). The potential of publication bias was assessed using the trim-and-fill method and L_0 estimator (Duval and Tweedie, 2000a, 2000b), which identifies funnel plot asymmetry and provides an adjusted model based on the estimated number of missing studies. Correlation between individual Q-Genie item scores and effect size of studies included in our primary meta-analysis was analyzed using the nonparametric Kendall's rank correlation coefficient (Kendall's τ_b), to determine whether methodological quality is associated with effect size outcome. Lastly, to test the robustness of our model results obtained under the DL method, a more conservative meta-analytical approach was also performed. The same models were analyzed using the restricted maximum likelihood (REML) estimator and confidence intervals and p-values were obtained using the method proposed by Hartung and Knapp (Hartung and Knapp, 2001a, 2001b), as well as by Sidik and Jonkman (Sidik and Jonkman, 2003, 2002), and will be referred to as the Hartung-Knapp-Sidik-Jonkman (HKSJ) method. HKSJ method was chosen for our sensitivity analysis because it has been shown to result in more adequate type I error rates, as compared to the DL method (IntHout et al., 2014; Rubio-Aparicio et al., 2018).

3.3 Results

The PRISMA flow chart detailing the review process is found in Fig. 1. From 180 papers screened, a total of 19 studies met initial inclusion criteria and underwent quality

assessment. There was strong inter-rater reliability and agreement between the two raters on Q-Genie scores (quadratic Cohen's κ_W=0.824, p<0.001). Low scores on Q-Genie questions were generally attributed to a lack of disclosure on the rationale of chosen gene, the genotyping methods used, potential sources of biases, having inadequate sample sizes and failure to control for confounders (see Supplementary Table 3 for averaged scores). From the 19 papers assessed, one paper (Enoch et al., 1998) was excluded based on an overall poor quality rating, reducing the total number of included studies to 18.

Three single nucleotide polymorphisms (SNPs) within the *HTR2A* gene were investigated in association with OCD in more than one paper: T102C (rs6313), G-1438A (rs6311), and C516T (rs6305). The T102C and G-1438A polymorphisms of the *HTR2A* gene have been described to be in almost complete linkage disequilibrium, with the 102 T allele co-occurring with the -1438 A allele (Spurlock et al., 1998). As a result, information from both G-1438A and T102C variants were combined and analyzed together in the meta-analysis to afford greater statistical power. Results of C516T polymorphism were analyzed separately, as there is no known linkage disequilibrium of this variant with the other two SNPs.

A total of six studies investigated both T102C and G-1438A variants in their sample and from these studies, only two confirmed complete linkage disequilibrium (Mas et al., 2014; Saiz et al., 2008). For the studies where both SNPs were examined in the same population and a complete linkage disequilibrium was not found (Gomes et al., 2018; Hemmings, 2006; Sina et al., 2018; Tot et al., 2003), allele frequencies from the G-1438A variant were extracted, unless a larger sample was reported for the T102C variant.

3.3.1 Sample Characteristics

Demographics and clinical characteristics for OCD cases and controls (where applicable), as well as the *HTR2A* association results, for each of the studies meeting qualitative inclusion criteria can be found in Tables 1 and 2. The mean number of OCD cases across studies was approximately 102 (range 35-293), while the mean number of healthy controls was approximately 184 (range 30-420) and all control samples met Hardy-Weinberg Equilibrium (HWE).

Case-control was the most widely used design, with only three studies employing a family-based design. Ethnic groups varied across studies and included populations with ancestry from Asia, Eastern and Western Europe, Middle East, North and South America, and Southern Africa. One study (Frisch et al., 2000) investigated populations of two distinct ethnic groups, Ashkenazi or Non-Ashkenazi Jewish origin; thus, each ethnic group was included separately in the meta-analysis.

3.3.2 Primary Meta-Analysis

After combining the data for both G-1438A and T102C polymorphisms, the risk allele (either A or T allele, respectively) was found to be significantly associated with OCD, OR [95%CI]=1.14 [1.01, 1.29], z(18)=2.08, p=0.038 (see Fig. 2A). Cochran's Q, $\chi^2(18)=34.3$, p=0.01, suggests presence of study heterogeneity, which can further be interpreted by the I^2 statistic, 46%, indicating moderate heterogeneity. Funnel plot asymmetry was evaluated and the trim-and-fill method imputed 3 additional missing studies (see Fig. 2B), which provided the following adjusted model results: OR [95%CI]=1.08 [0.95, 1.23], p=0.26. Therefore, this method suggests the presence of

positive publication bias; however, funnel plot asymmetry may also be confounded by study heterogeneity, as it is not possible to disentangle the two (Shi and Lin, 2019). Kendall's τ_b revealed no significant correlations between quality scores, as measured using the Q-Genie tool, and the associated effect size for our included studies (all $p>0.05$, see Supplementary Table 3 for exact values). When applying the HKSJ method to test the robustness of these results, the association no longer remained significant due to widened 95% confidence intervals: OR[95%CI]=1.14 [0.99, 1.31], p=0.059.

Despite only two case-control studies having investigated the C516T in relation with OCD, analyses were also completed to determine whether this *HTR2A* variant may be a promising candidate for future studies. Pooled data from two studies revealed a non-significant association, OR [95%CI]=1.22 [0.14, 10.37], z(1)=0.18, p=0.86 (see Fig. 3). Considerably high levels of heterogeneity were observed across these two studies, Cochran's Q, $\chi^2(1)=6.8$, p=0.009, and $I^2=85\%$. Funnel plot asymmetry could not be assessed using the trim-and-fill method due to the small number of included studies. Furthermore, the results remained non-significant when the HKSJ method was applied, p=0.89.

3.3.3 Secondary Meta-Analysis

Subgroup analyses were performed to investigate the association of *HTR2A* polymorphisms according to OCD subtypes based on sex and age of onset and were limited to the rs6311 and rs6313 *HTR2A* variants due to data availability.

When stratified by sex, the *HTR2A* risk allele (A or T of rs6311 or rs6313, respectively) was significantly associated with OCD in females, OR [95%CI]=1.20 [1.00,

1.45], z(11)=1.97, p=0.049, but not for OCD in males, OR [95%CI]=1.06 [0.91, 1.23], z(11)=0.74, p=0.46 (see Fig. 4). Little to no heterogeneity was found in the male subgroup, Cochran's Q, $\chi^2(11)=11.1$, p=0.4, and $I^2=1\%$). Heterogeneity was present in the female subgroup, according to Cochran's Q, $\chi^2(11)=17.2$, p=0.1, and $I^2=36\%$, suggesting low to moderate heterogeneity. Observed funnel plot asymmetry suggests that publication bias was present in both subgroups. Within the female subgroup, 4 missing studies were imputed and the adjusted model resulted in OR [95%CI]=1.02 [0.82, 1.26], p=0.89, whereas 3 studies were imputed in the male subgroup and the adjusted results were OR [95%CI]=0.99 [0.84, 1.16], p=0.87 (see Supplementary Fig. 1 for funnel plots). Model results obtained using the conservative HKSJ approach no longer reached significance for the female subgroup, OR [95%CI]=1.21 [0.99, 1.48], p=0.065, and were also not significant for the male subgroup, OR [95%CI]=1.06 [0.90, 1.26], p=0.45.

When stratified by age of onset, a significant association was found for those with early onset OCD and the A or T risk allele of rs6311/rs6313, OR [95%CI]=1.27 [1.02, 1.58], z(6)=2.16, p=0.03 (see Fig. 5). This was not the case for those with late onset OCD, OR [95%CI]=0.98 [0.70, 1.37], z(1)=-0.11, p=0.92, but only two studies reported genetic data for adult onset cases, and so these results must be interpreted with caution. The trim-and-fill method could not be applied to the late onset OCD subsample as there was not enough data available; however, results for the early onset stratified group suggest no presence of publication bias as there were no estimated missing studies (see Supplementary Fig. 2 for funnel plot). Heterogeneity was present in both groups, with early onset studies showing low to moderate degree of heterogeneity (Cochran's Q,

$\chi^2(6)=9.75$, p=0.1, and $I^2=38\%$), whereas greater heterogeneity was present in the late onset studies (Cochran's Q, $\chi^2(1)=2.4$, p=0.1, and $I^2=58\%$). Similar to the sex stratified group, results were not significant after applying the HKSJ method for both the early onset, OR[95%CI]=1.27 [0.96, 1.68], p=0.08, and late onset OCD subgroup, OR[95%CI]=0.98 [0.11, 8.70], p=0.9.

3.4 Discussion

In reviewing the literature for genetic association studies of the *HTR2A* polymorphisms with OCD, three SNPs were identified as having been investigated in two or more papers. Individual studies investigating G-1438A, T102C and C516T variants of the *HTR2A* gene in relation to OCD were remarkably inconclusive, and our study aimed to provide some resolve using meta-analytic approaches. Our results demonstrate that the A allele from G-1438A and/or T allele from T102C polymorphisms of *HTR2A* were found to be associated with OCD when using the standard meta-analytic approach. This finding lends support to the involvement of serotonin regulation genes in OCD and implies that 5-HT_{2A} receptors may play a role in the pathophysiology of the disorder. However, when a more conservative method was applied, this association no longer remained significant. The wider confidence intervals obtained with the HKSJ approach suggests a higher degree of uncertainty in the relationship; yet the overall effect remains in the same direction. Based on these results, the true effect size of our model is expected to occur between 0 and 1.3. Considering the small effect size that the *HTR2A* T102C and G-1438A polymorphisms may have on OCD or its subtypes, the clinical importance of this gene remains to be established and future studies should use a polygenic or

multifactorial approach in order to better understand which genetic or environmental factors contribute to disease risk.

Prior meta-analytic investigations using the DL approach found significant associations with G-1438A/T102C polymorphisms with OCD (Taylor, 2016, 2013), which we were able to replicate with a larger number of studies when using the same statistical method. Several concerns have been communicated about the DL method, including inflated type I error rates, which was shown to be pronounced in cases where few studies were included and moderate to large between-study heterogeneity was present (Hartung, 1999; Hartung and Knapp, 2001c; Hartung and Makambi, 2003; Makambi, 2004). In simulation studies, the HKSJ method was shown to have improved error rates when directly compared to the standard DL method (IntHout et al., 2014; Thorlund et al., 2011). Nevertheless, concerns with the HKSJ approach remain and recommendations for the use of the standard method in conjunction with the HKSJ method have been advocated (Jackson et al., 2017). Therefore, our findings suggest that the relationship between G-1438A/T102C polymorphisms with OCD may be more complex than previously described and obtaining a larger sample size is crucial for reaching any definitive conclusion.

When stratifying the OCD sample by sex and age of onset, the association of the A and/or T allele from G-1438A/T102C polymorphisms remained for females and those with early onset OCD, but the results from our sensitivity analysis suggest greater uncertainty as these associations no longer reached significance when HKSJ method was applied. No significant associations were observed for males or late onset OCD when

using the standard or conservative approach. More data is required to determine whether OCD individuals with a later age of onset have any association with *HTR2A* polymorphisms, as only two studies reported genetic data according to a later age of onset and standard meta-analytic techniques have been shown to be inadequate when few studies (k=2) are included (Seide et al., 2019). Likewise, the limited number of studies investigating the C516T variant in relation to OCD make it difficult to draw any conclusions and further investigation into this polymorphism is necessary.

Within the OCD literature, individuals with an earlier age of onset are more likely to be males, have greater OCD severity, have comorbidities with tics, other obsessive-compulsive like disorders and personality disorders, and have a first-degree relative with OCD (Taylor, 2011b). Since early onset cases appear to be more familial than those with a later age of onset, it may be the case that genetic factors play a greater role in this subtype.

Sex-specific associations with serotonergic polymorphisms may occur as a result of an interaction between gonadal hormones and serotonergic receptor availability. Higher binding potential of 5-HT_{2A} receptors in male frontal and cingulate cortices have been found (Biver et al., 1996), and hormonal changes in women may influence 5-HT_{2A} receptor density, as postmenopausal women demonstrated increased 5-HT_{2A} receptor binding potential in widespread areas of the cerebral cortex following progesterone and estradiol administration (Moses et al., 2000). Remarkably, women are more likely to develop OCD or experience symptom exacerbation around times of hormonal change, including pregnancy and postpartum (Forray et al., 2010; Russell et al., 2013), further

lending support to sex-specific subtypes of OCD. Since the functional consequence of the *HTR2A* polymorphisms have yet to be fully elucidated, their role in OCD development according to sex and age of onset requires further investigation.

3.4.1 T102C

The T102C variant (rs6313) is a silent polymorphism located in exon 1 of *HTR2A* that is defined by a T to C transition at position 102. Nicolini et al. were the first team to investigate the rs6313 SNP in relation to OCD, reporting null findings (Nicolini et al., 1996). The majority of follow-up studies investigating this variant with OCD were unable to find an association (Frisch et al., 2000; Hemmings, 2006; Jung et al., 2006; Mas et al., 2014; Saiz et al., 2008). In one study of OCD cases, the TT genotype was found at a higher rate in patients with severe obsessive-compulsive symptoms, as compared to those with moderate symptoms (Tot et al., 2003). Therefore, there is some evidence that the T allele of rs6313 may be associated with OCD, especially in those experiencing more severe symptoms.

3.4.2 G-1438A

The G-1438A polymorphism is found upstream of two alternative *HTR2A* promoters (Norton and Owen, 2005). Enoch et al. were the first to examine the rs6311 SNP and found an increase in the frequency of the A allele in patients with OCD, as compared to controls (Enoch et al., 1998). A replication study led by the same researchers confirmed the original findings; however, when stratified by sex, the A allele association was sustained for women only (Enoch et al., 2001).

Follow-up attempts to replicate this association led to mixed results. Several studies reported finding an association with the A allele of rs6311 in children and adolescents with OCD (Walitza et al., 2012, 2002), where one family-based study of early onset OCD found nominally significant association of the A allele with OCD cases comorbid for tics, which disappeared following multiple testing corrections (Dickel et al., 2007). Conflicting evidence from another family-based study showed higher transmission of the A allele in those with late onset OCD and males (Liu et al., 2011). Furthermore, a case-control study found an almost significant association of the G allele in OCD patients with early onset and a positive family history of OCD (Denys et al., 2006). When considering sex and symptom severity, one study demonstrated that the GG genotype was more frequent in OCD females, and the AA genotype was found at a higher rate in patients with severe OCD symptoms (Tot et al., 2003); however, these results may only be reflective of late onset cases. Taken together, there appears to be involvement of the G-1438A polymorphism with OCD, which may be specific to unique OCD subtypes. The overall inconclusive nature of the findings from both G-1438A and T102C candidate gene studies are likely attributable to the heterogeneity of the samples assessed.

3.4.3 Functional Consequence of T102C and G-1438A Polymorphisms

Understanding the influence rs6311 and rs6313 has on the *HTR2A* gene, its associated protein and distribution of 5-HT_{2A} receptors, is important for identifying the role these polymorphisms may play in the development, prognosis and treatment of OCD. Research over the last two decades investigating the functional consequence of both SNPs on *HTR2A* mRNA and protein expression has led to equivocal results. Investigations

using post-mortem brain samples in healthy controls and those with psychiatric disease, such as schizophrenia and suicide victims, found associations with the T allele of T102C polymorphism with higher expression of total *HTR2A* mRNA, 5-HT_{2A} receptor protein levels, and increased 5-HT_{2A} binding in various cortical tissues (Polesskaya and Sokolov, 2002; Turecki et al., 1999). In contrast, other studies were unable to find any effect of the T102C or G-1438A allele status on 5-HT_{2A} receptor densities in frontal cortex tissue (Hrdina and Du, 2001; Kouzmenko et al., 1999, 1997). Failure in replicating findings may be a result of the methodological techniques used or type of tissue sampled.

One investigation using reporter gene assays to examine *HTR2A* promoter activity according to the G-1438A polymorphism in three different cell lines found that the A allele was associated with increased promoter activity, especially when in the presence of a downstream SV40 enhancer element (Parsons et al., 2004). Conversely, rs6311 was recently shown to modulate expression of an extended 5'untranslated region (5'UTR) mRNA isoform, whereby the A allele decreases usage of an upstream transcription start site and results in reduced expression of the long 5'UTR (Smith et al., 2013). The long 5'UTR mRNA transcript has more efficient translation compared to the short 5'UTR; therefore, these results suggest that the rs6311 A allele may lead to decreased protein production (Smith et al., 2013). The same research group later went on to demonstrate that, (1) rs6311 doesn't appear to influence expression of the primary mRNA isoform that does not contain the extended 5'UTR, (2) E47, EGr3, SMAD3 and NF1 are candidate transcription factors that bind the DNA region containing rs6311 and (3) rs6311 may influence alternative splicing (Ruble et al., 2016).

Epigenetic modifications, such as changes to DNA methylation, may help explain allele-specific expression differences in regulating *HTR2A*. Specifically, presence of the C allele of rs6313 and G allele of rs6311 creates two additional CpG sites (Polesskaya et al., 2006). In post-mortem samples, increased methylation of the promoter CpG site when the G allele is present was found to be associated with greater *HTR2A* mRNA expression (Polesskaya et al., 2006). Conversely, when the A allele of rs6311 is present, a binding site for transcription factors Th1/E47 is generated, which may alter *HTR2A* expression (Falkenberg et al., 2011; Smith et al., 2008). The functional impact of these modifications remains to be studied in OCD.

Further investigation is needed to determine how rs6311 or rs6313 regulates *HTR2A* expression and serotonin signalling in the context of OCD, as differential methylation, transcription factor activity, transcription start site usage and their influence on *HTR2A* mRNA isoforms may help explain inconsistent findings across findings.

3.4.4 C516T (rs6305)

The other *HTR2A* polymorphism that has been investigated in OCD is the C516T (rs6305) variant, a silent variant located in exon 2 of the *HTR2A* gene (Davies et al., 2006). Unlike the other two SNPs previously described, the C516T variant has not been extensively examined in the OCD population. Meira-Lima et al. were the first research group to find a relationship between rs6305 with OCD patients in a Brazilian sample, whereby a strong association of the C allele in OCD patients was reported (Meira-Lima et al., 2004). Despite this promising finding, another research group found no significant association with either alleles in the same ethnic population (Corregiari et al., 2012). It

may be the case that the low frequency of the C allele contributed to the initial positive result. Based on the small number of studies and sample sizes, no conclusion can be made and further examination of the C516T variant in larger OCD samples and other ethnic groups is needed.

3.4.5 Clinical Relevance

At the moment, there is insufficient evidence to support the association of *HTR2A* polymorphisms with OCD and genetic screening using *HTR2A* or other candidate genes for the prediction, diagnosis or treatment for those with OCD is not possible. Nevertheless, 5-HT_{2A} receptors may be a potential pharmacological target in OCD. Atypical antipsychotics have high affinity for 5-HT_{2A} receptors and have been found to be effective in treating some treatment-resistant OCD patients when given in conjunction with a selective serotonin reuptake inhibitor (SSRI) (Dold et al., 2013; Erzegovesi et al., 2005; Hollander et al., 2003; Pignon et al., 2017). On the other hand, atypical antipsychotics have been shown to induce or exacerbate obsessive-compulsive symptoms in patients with other mood disorders, such as schizophrenia (Dodt et al., 1997; Fonseka et al., 2014; Poyurovsky et al., 1996), suggesting different involvement of 5-HT_{2A} in the emergence of obsessive-compulsive symptoms across psychiatric disorders.

Even though it is still unclear as to what SSRI target is mediating therapeutic effects in OCD patients, intervention with SSRIs continues to be the first-line treatment choice in this disorder (Hirschtritt et al., 2017). Several reports have examined the relationship between *HTR2A* variants with SSRI treatment response in OCD samples with unclear results. One study found higher frequency of the rs6311 A allele in sertraline non-

responders (Liu et al., 2013) and another found that SSRI responders had a greater frequency of the rs6311 and rs6313 AC haplotype (Sina et al., 2018), whereas others were unable to find any relationship of these SNPs with SSRI response (Corregiari et al., 2012; Tot et al., 2003). In another report, the CC genotype of C516T was found to occur more frequently in the non-responders group for several SSRI types (Corregiari et al., 2012). Overall, pharmacogenetic research on *HTR2A* polymorphisms is limited and inconclusive.

3.4.6 Limitations

Serotonergic dysfunction and the *HTR2A* gene alone are not able to explain the complexity of OCD. Rather, it is likely that the clinical phenotype results from the combined effect of multiple genes, as well as environmental and epigenetic factors. Other neurotransmitter systems, such as dopamine, glutamate and γ-aminobutyric acid (GABA), and their polymorphisms have been implicated in OCD (Bozorgmehr et al., 2017). These systems and genes interact with the serotonergic system, forming a complex network. Indeed, 5-HT_{2A} receptors have been shown to alter dopaminergic transmission, as well as affecting GABA and norepinephrine release (Fink and Göthert, 2007). Although it is not clear which neurotransmitter system or genes play the greatest role in the etiology of OCD, attempts to understand the function of individual genes and their interconnected pathways will further our understanding of OCD pathogenesis.

The general inconsistencies observed for *HTR2A* polymorphisms in the OCD literature may be due to the fact that the ORs associated are small and therefore, differences in statistical power across studies may result in altered findings. It is possible

that we were not able to find consistent associations with *HTR2A* in our stratified analyses due to the limited samples reporting genetic data according to sex and age of onset; thus, results must be interpreted with caution. Stratification of the OCD group according to other clinical factors, such as presence of comorbidity, symptom type or severity, and familial forms of OCD, was not possible in our analyses due to limited data. Future studies should be encouraged to collect, include and report OCD clinical variables in connection with genetic data to allow for greater pooling of homogeneous data.

To stratify the OCD sample into early vs. late age of onset groups, we defined 18 years of age as the cut-off according to the criteria employed in one study (Dickel et al., 2007), yet empirical evidence defines 21 years of age as the optimal cut-off between early and late OCD onset (Taylor, 2011b). Clinical differences have been shown to emerge around the ages of 10 and 17 (de Mathis et al., 2008), suggesting that multiple cut-off points might exist to provide greater homogeneity. It may be the case that using different age of onset cut-offs in our analyses would have affected our results. Additionally, data reliability must also be considered in this context as age of onset is typically collected through retrospective recall and is vulnerable to bias.

Several notable strengths of our analyses included the use of a quality assessment tool and the procuring of primary data by sex and age of onset variables. By identifying and removing papers of poor quality, the Q-Genie tool limits biases and threats to validity associated with pooling results from genetic association studies. It remains to be stated that the results of our primary meta-analysis model remained significant when including the study that received a poor-quality rating (see Supplementary Fig. 3 for the forest plot).

Notably, inclusion of this study altered the results obtained from our sensitivity analysis, such that the overall effect became significant when using the HKSJ approach: OR [95%CI]=1.15 [1.01, 1.31], t(19)=2.26, p=0.036. Therefore, these results highlight the importance of assessing study quality prior to data pooling and calls upon the need for more studies with sufficient methodological quality in order to resolve any uncertainty surrounding the association between *HTR2A* polymorphisms and OCD.

Another strength was the implementation of a different meta-analytic approach as part of our sensitivity analysis. Here we were able to show that the DL and HKSJ techniques resulted in slightly different outcomes, yet the direction of the true effect was similar. As can be expected, greater uncertainty was reported when a more conservative approach (HKSJ) was used. Regardless of the method used, extreme caution and consideration is needed when the number of included studies is small.

3.5 Conclusions

This is the most recent and comprehensive analysis of *HTR2A* polymorphisms associated with OCD by sex and age of onset. Our meta-analytic results suggest a possible association of the A and T allele of G-1438A and T102C, respectively, with the development of OCD, but no conclusions can be drawn at this point in time. Our results point towards a possible sex-specific association with females and those with early onset OCD; however, larger samples are needed for improve the validity of our results. Currently, there is not enough evidence to decipher whether the rs6305 (C516T) may be associated with OCD. The functional consequences of these polymorphisms are unclear, and more research is warranted to elucidate their role in OCD. Future studies

investigating the pathophysiology of the disorder should take into consideration important clinical variables that reduce OCD heterogeneity. Given the disorder's complexity, a multifactorial approach is necessary for providing greater insight into the genetic basis and etiology of OCD.

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Table 1: Demographics and clinical characteristics of studies included in qualitative analysis.

Study	De-sign	Ethnicity	OCD Sample N (M:F)	Control Sample N (M:F)[a]	OCD Group Age (M ± SD)	Control Group Age (M ± SD)	Age of Onset (M ± SD)	Y-BOCS Total (M ± SD)	OCD Family History N (%)	Tic Comor-bidity N (%)
(Corregiari et al., 2012)	CC	Brazilian	60 (36:24)	30 (18:12)	37.13 ± 10.07	37.10 ± 9.56	16.52 ± 7.95	32.72 ± 4.75	N/A	N/A
(Denys et al., 2006)	CC	Caucasian (Nether-lands)	156 (56:100)	134 (N/A)	36.6 ± 11.5	N/A	17.7 ± 8.3	24.9 ± 5.7	43 (28)	9 (6)
(Dickel et al., 2007)	FB	N/A (USA)	Group 1: 28 (N/A)		N/A		N/A	N/A	N/A	N/A
			Group 2: 26 (11:15)		28.4 ± 17.5		8 ± 3.7	N/A	N/A	11 (42)
(Enoch et al., 1998)	CC	N/A (USA)	62 (N/A)	144 (N/A)	N/A	N/A	N/A	N/A	N/A	N/A
(Enoch et al., 2001)	CC	Caucasian (North America)	101 (53:48)	138 (61:77)	40.65 ± 10.57	41.72 ± 12.85	13.91 ± 8.1	N/A	N/A	N/A
(Frisch et al., 2000)	CC	Ashkenazi Jews	39 (12:18)	112 (58:54)	N/A	N/A	N/A	N/A	N/A	None
		Non-Ashkenazi Jews	35 (12:23)	60 (16:44)	N/A	N/A	N/A	N/A	N/A	None
(Gomes et al., 2018)	CC	Brazilian	203 (99:104)	205 (78:127)	37.79 ± 13.28	32.37 ± 13.45	14.81 ± 7.44	N/A	N/A	N/A
(Hemmings, 2006)	CC	Afrikaner	132 (71:61)	218 (56:162)	27[b]	36[b]	14[c], 15[d]	21[a]	20 (25)	18 (14.2)
(Jung et al., 2006)	CC	Korean	103 (69:34)	157 (83:74)	28.62 ± 9.59	24.1 ± 2	19.35 ± 8.28	N/A	N/A	N/A
(Liu et al., 2011)	FB	Han Chinese	103 (62:41)		N/A		N/A	N/A	N/A	N/A

Study	De-sign	Ethnicity	OCD Sample N (M:F)	Control Sample N (M:F)[a]	OCD Group Age (M ± SD)	Control Group Age (M ± SD)	Age of Onset (M ± SD)	Y-BOCS Total (M ± SD)	OCD Family History N (%)	Tic Comor-bidity N (%)
(Liu et al., 2013)	CC	Han Chinese	127 (75:52)	224 (119:105)	31.67 ± 13.28	32.48 ± 10.51	N/A	N/A	N/A	N/A
(Mas et al., 2014)	FB	Spanish Caucasian	84 (47:37)		14.95 ± 2.57		11.83 ± 3.09	16.74 ± 8.74	47 (56)	5 (5.9)
(Meira-Lima et al., 2004)	CC	Brazilian (Caucasian)	79 (44:35)	202 (102:100)	33.6 ± 10	33.9 ± 9	N/A	N/A	N/A	N/A
(Nicolini et al., 1996)	CC	Mexican	67 (29:26)	54 (34:20)	32.3 ± 10.8	36.4 ± 11.4	N/A	N/A	N/A	N/A
(Saiz et al., 2008)	CC	Spanish Caucasian	99 (46:53)	420 (216:204)	37.1 ± 12.1	40.6 ± 11.3	N/A	N/A	N/A	N/A
(Sina et al., 2018)	CC	Iranian	293 (89:204)	245 (N/A)	35.03 ± 10.34	N/A	24.73 ± 10.77	20 ± 8.63	233 (79.5)	N/A
(Tot et al., 2003)	CC	Turkish	58 (20:38)	83 (42:41)	30 ± 9	27 ± 5	21 ± 7	20.4 ± 6.6	27 (47)	8 (14)
(Walitza et al., 2002)	CC	German	55 (29:26)	223 (108:115)	12.11 ± 2.11	25.2	N/A	N/A	N/A	3 (5)
(Walitza et al., 2012)	CC	German	136 (77:59)	106 (65:41)	13 ± 2.9	11.6 ± 2.6	11.1 ± 3.2	N/A	N/A	13 (9.6)

Notes: CC = case-control; FB = family-based; N/A = information not available or reported.

[a] Family-based studies do not contain a control sample.

[b] median

[c] median (males)

[d] median (females)

Table 2: Results of studies included in meta-analyses.

Study	Diagnostic Criteria	Assessment Method Used	SNP	Study Result	Notes	Q-Genie Score
(Corregiari et al., 2012)	DSM-IV	Y-BOCS	T102C C516T	p = 0.007, T allele p = 0.18	OCD group did not meet Hardy-Weinberg equilibrium.	Moderate
(Denys et al., 2006)	DSM-IV	MINI, Y-BOCS	G-1438A	p = 0.78	G allele and G/G genotype frequencies were higher in those with positive OCD family history and those with an early onset.	Moderate
(Dickel et al., 2007)	Group 1: DSM-III-R Group 2: DSM-IV	SCID, K-SADS-E-5, Y-BOCS	G-1438A	p = 0.14	Only consisted of early onset probands.	Good
(Enoch et al., 1998)	DSM-II-R	SCID	G-1438A	p < 0.05[a], A allele	Article is a short research letter.	Poor[b]
(Enoch et al., 2001)	DSM-III-R	SCID-I, SADS-L	G-1438A	p = 0.015, A allele	Association with A allele was only found for females.	Good
(Frisch et al., 2000)	DSM-IV	SADS-L, SCID-P	T102C	NS[a]	Results were NS for both samples of Ashkenazi Jews and Non-Ashkenazi Jews.	Good
(Gomes et al., 2018)	DSM-IV-TR	MINI, OCI-R	G-1438A T102C	p = 0.39 p = 0.88	G-1438A and T102C were not in complete linkage disequilibrium.	Good
(Hemmings, 2006)	DSM-IV	SCID-I, Y-BOCS, DY-BOCS	G-1438A T102C	p = 0.93 OR [95%CI] = 1.03 [0.71, 1.50] p = 0.86 OR [95%CI] = 0.96 [0.66, 1.38]	G-1438A and T102C were not in complete linkage disequilibrium.	Good

Study	Diagnostic Criteria	Assessment Method Used	SNP	Study Result	Notes	Q-Genie Score
(Jung et al., 2006)	DSM-IV	SCID-I, Y-BOCS	T102C	p = 0.21		Good
(Liu et al., 2011)	DSM-IV	Y-BOCS	G-1438A	p = 0.034, A allele	After subgroup analyses, transmission disequilibrium of A allele was found for the late-onset group and for males.	Good
(Liu et al., 2013)	DSM-IV	Y-BOCS	G-1438A	p = 0.03, A allele	Subgroup analyses revealed significant association of A allele with females and those with early-onset cases.	Good
(Mas et al., 2014)	DSM-IV	K-SADS-PL (Spanish version), CY-BOCS	G-1438A and T102C	p = 0.54	G-1438A and T102C were in complete linkage disequilibrium. Only consisted of early onset probands.	Good
(Meira-Lima et al., 2004)	DSM-IV	SCID, Y-BOCS	T102C C516T	p = 0.5 p < 0.001, C allele	Low C allele frequency of C516T.	Good
(Nicolini et al., 1996)	DSM-III-R	DIS (Spanish version), Y-BOCS	T102C	p = 0.24		Good
(Saiz et al., 2008)	DSM-IV	MINI (Spanish version)	G-1438A and T102C	p = 0.36	G-1438A and T102C were in complete linkage disequilibrium.	Good
(Sina et al., 2018)	DSM-IV-TR	Y-BOCS	G-1438A T102C	p = 0.031[c] p = 0.18	G-1438A and T102C were not in complete linkage disequilibrium. CC genotype was associated with familial form of OCD in females only.	Good
(Tot et al., 2003)	DSM-IV	SCID-I, Y-BOCS	G-1438A T102C	p = 0.85 p = 0.30	G-1438A and T102C were not in complete linkage disequilibrium. A/A and T/T genotype frequencies were	Good

Study	Diagnostic Criteria	Assessment Method Used	SNP	Study Result	Notes	Q-Genie Score
					higher in patients with more severe OCD.	
(Walitza et al., 2002)	DSM-IV	Y-BOCS, CY-BOCS, Kinder-DIPS (parent and children version)	G-1438A	p = 0.046, A allele	OCD group consisted of children with OCD. Control group consisted of university students.	Good
(Walitza et al., 2012)	DSM-IV	ICD-10, CY-BOCS, Kinder-DIPS (parent and children version)	G-1438A	p = 0.03[d] and p = 0.007[e], A allele	Population includes same OCD sample as 2002 paper. Therefore, only new OCD cases and controls were extracted and used in the meta-analysis. OCD and controls consisted of children.	Good

Notes: CY-BOCS = Children Y-BOCS; DIS = Diagnostic Interview Schedule; DSM = Diagnostic and Statistical Manual of Mental Disorders; DY-BOCS = Dimensional Y-BOCS; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; Kinder-DIPS = Diagnostic Interview for Mental Disorders in Childhood and Adolescence; K-SADS-E-5 = Schedule for Affective Disorders and Schizophrenia for School Age Children - Epidemiologic Version-5; K-SADS-PL = K-SADS - Present and Lifetime Version; MINI = Mini-International Neuropsychiatric Interview; NS = not significant; OCI-R = Obsessive-Compulsive Inventory - Revised; OR = Odds Ratio; Q-Genie = Quality of Genetic Association Studies; SADS-L = Schedule for Affective Disorders and Schizophrenia - Life-time Version; SCID = Structured Clinical Interview for DSM-IV; SCID-I = SCID Axis I Disorders; SCID-P = SCID Patient Version; Y-BOCS = Yale-Brown Obsessive Compulsive Scale

[a] Exact p-values were not reported.

[b] Studies rated as "poor" Q-Genie quality were not included in the meta-analysis.

[c] Not significant following Bonferroni correction

[d] p-value obtained when only new OCD cases were analyzed

[e] p-value obtained when the total sample (new and old OCD cases) was analyzed

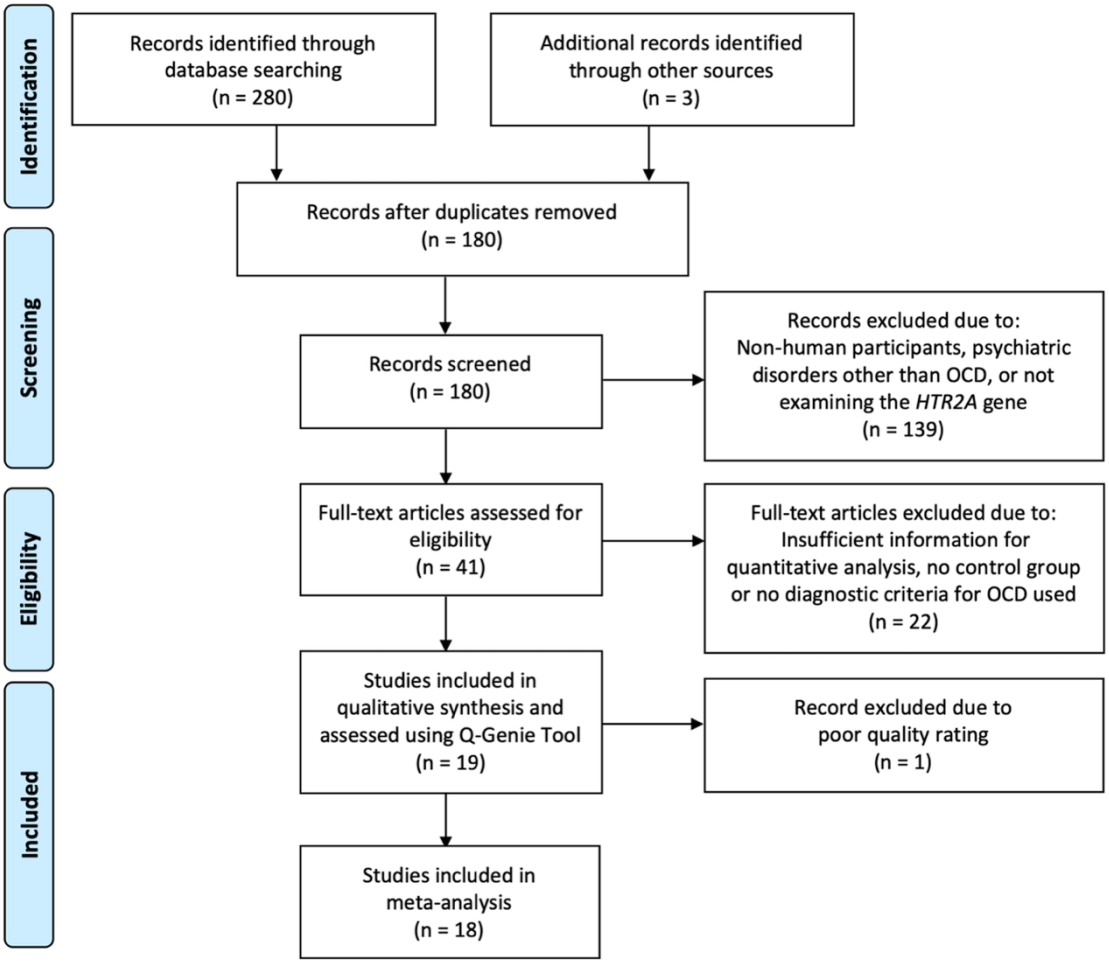


Fig. 1. PRISMA flow chart detailing the systematic literature search process

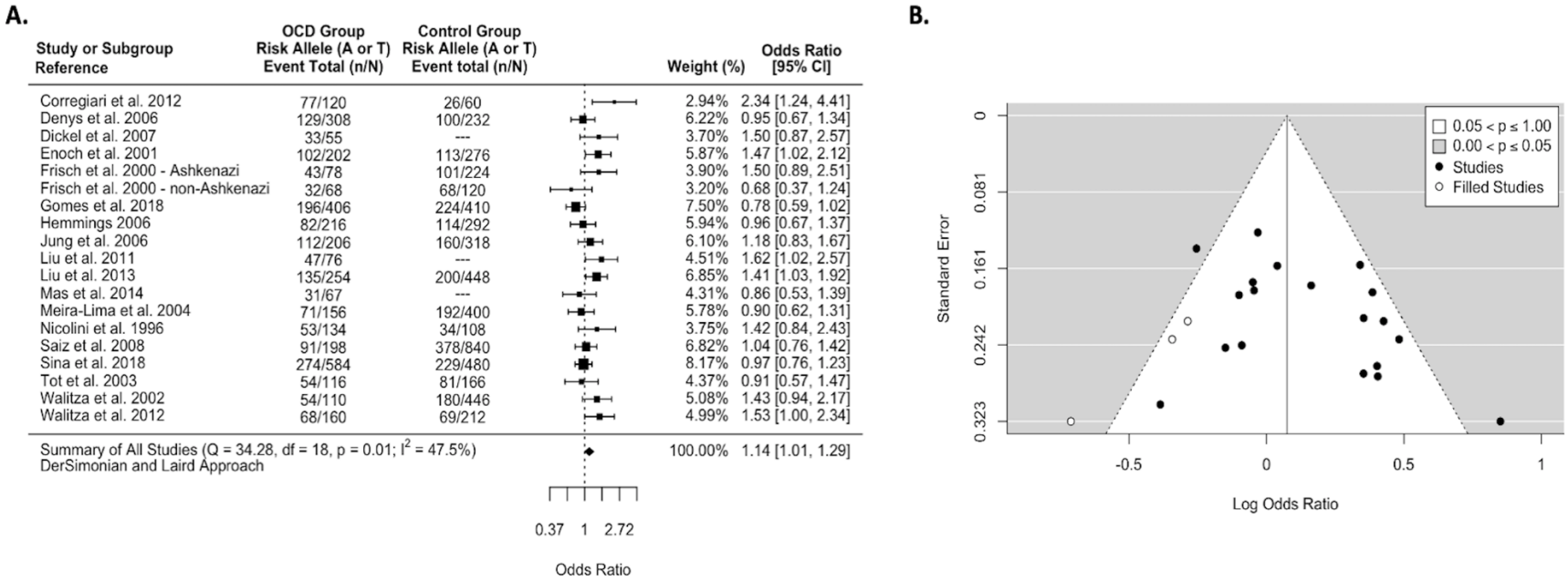


Fig. 2. Analysis of the included samples that investigated the association of HTR2A G-1438A (rs6311) and T102C (rs6313) polymorphisms combined with obsessive-compulsive disorder (OCD). The risk allele was defined as either the A or T allele of rs6311 or rs6313, respectively. A. Forest plot depicts the odds ratio (OR), with the 95th percentile confidence intervals reported (p=0.038). Event total was defined as frequency of risk alleles in a sample, over the total allele frequencies in that sample and is reported separately for OCD cases and controls. "---" indicates family-based study with no control group. B. Funnel plot depicts the standard error according to the log odds ratio for each study included in the meta-analysis and the estimated missing studies (indicated by the filled studies) as determined by the trim-and-fill method.

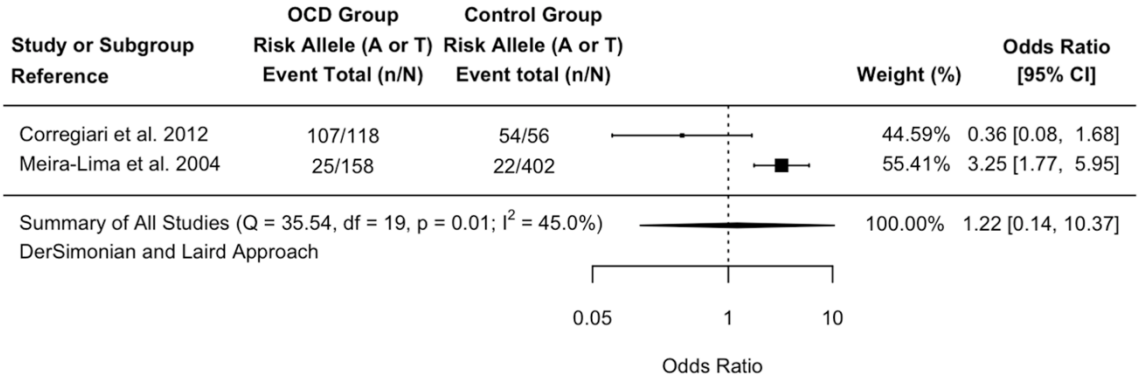


Fig. 3. Forest plot depicts the odds ratio (OR), with the 95th percentile confidence intervals reported (p=0.86) for the investigation of the association of obsessive-compulsive disorder (OCD) with the *HTR2A* C516T (rs6305) polymorphism. The risk allele was defined as the C allele of C516T. Event total was defined as frequency of risk alleles in a sample, over the total allele frequencies in that sample and is reported separately for OCD cases and controls.

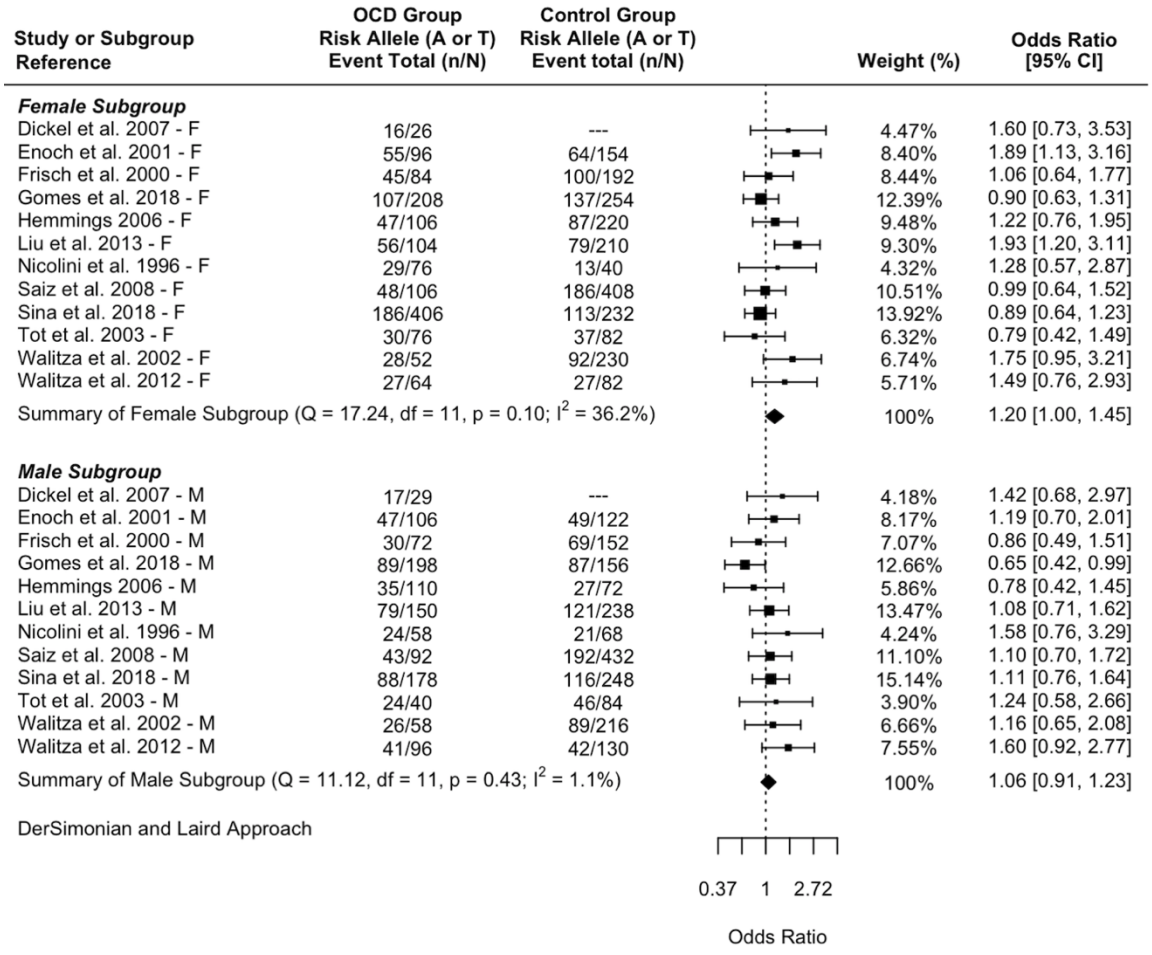


Fig. 4. Forest plot depicts the odds ratio (OR) for the obsessive-compulsive disorder (OCD) stratified groups according to sex (female subgroup p=0.049, male subgroup p>0.05), with the 95th percentile confidence intervals reported. The risk allele was defined as either the A or T allele of G-1438A (rs6311) or T102C (rs6313), respectively. Event total was defined as frequency of risk alleles in a sample, over the total allele frequencies in that sample. "—" indicates family-based study with no control group.

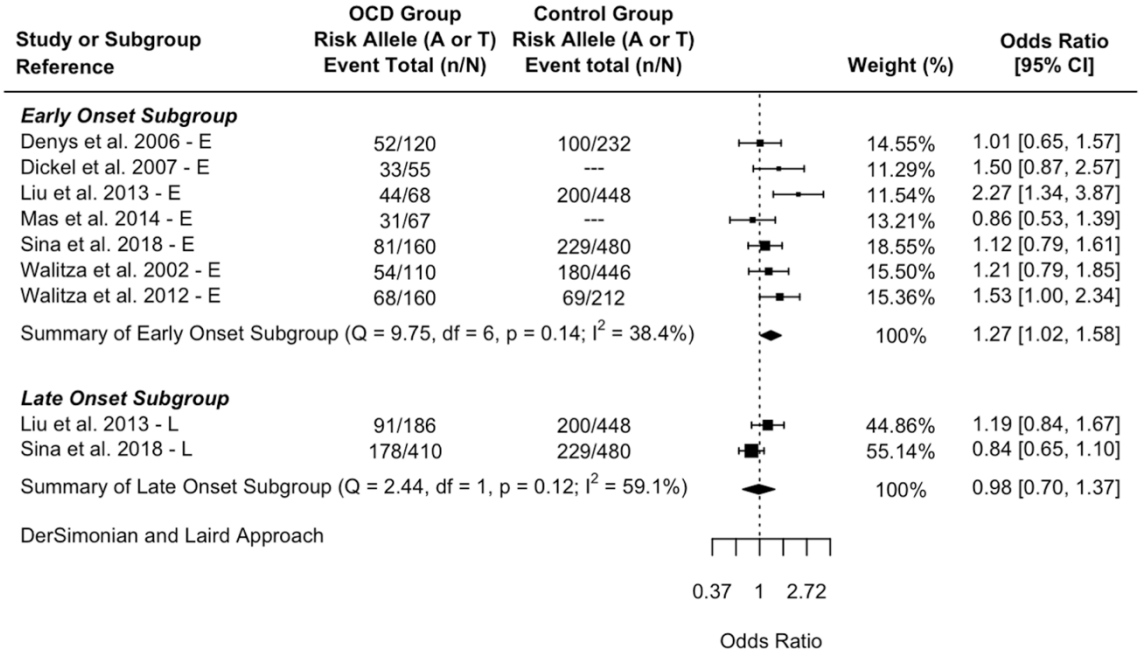


Fig. 5. Forest plot depicts the odds ratio (OR) for the OCD stratified groups according to age of onset (early onset subgroup p=0.031, late onset subgroup p>0.05), with the 95th percentile confidence intervals reported. The risk allele was defined as either the A or T allele of G-1438A (rs6311) or T102C (rs6313), respectively. Event total was defined as frequency of risk alleles in a sample, over the total allele frequencies in that sample. "—" indicates family-based study with no control group.

3.8 Supplementary Material

3.8.1 Subgroup Analyses

For the subgroup analyses completed according to sex and age of onset (early vs. late onset), inclusion of studies was limited based on reported data. In cases where genotype or allele information was not provided by these subgroups in the published text, the corresponding author was contacted in order to determine data availability and to request permission for its use.

Within the published manuscripts, a total of seven studies reported genotype or allele frequencies for the serotonin receptor 2A gene (*HTR2A*) polymorphisms separately for males and females, and only one study reported genetic information separately for early and late onset cases. However, five studies only included OCD cases that were of childhood/adolescence age, which is indicative of early onset cases.

After attempts to contact author(s), additional genetic information for the *HTR2A* variants was collected for five more studies according to sex, males and females separately (Frisch et al., 2000; Nicolini et al., 1996; Saiz et al., 2008; Tot et al., 2003; Walitza et al., 2012) and we received data from one study with the associated age of onset (Sina et al., 2018). In many cases, primary data was unavailable or contact with author(s) was not possible. In sum, genetic information according to sex was available from a total of 12 studies, data for early onset OCD was available from 7 studies, and data for late onset OCD was available from only 2 studies.

3.8.2 Statistical Calculations

All statistical analyses were performed in R using the 'metafor' package (version 2.4-0) that is freely available at <https://cran.r-project.org/web/packages/metafor/index.html>. For more information on how our analyses were conducted, please see the affiliated paper written by the package developer for detailed descriptions and examples (Viechtbauer, 2010). We also recommend the following papers for additional information on understanding meta-analysis outcomes (Andrade, 2015; Szumilas, 2010).

Supplementary Table 1: Detailed search strategy for studies up to December 2019

Database	Search Term	# of Articles
PubMed	(("Obsessive-Compulsive Disorder"[Mesh]) AND "Receptor, Serotonin, 5-HT2A"[Mesh]) AND ("Polymorphism, Genetic"[Mesh] OR "Genetic Association Studies"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh])	15
MEDLINE (via Ovid)	((obsessive-compulsive disorder or ocd or obsessive-compulsive or obsessive compulsive or obsessive or compulsive) and (serotonin receptor 2A or 5-HT2A or HTR2A or 5-HT receptor 2A or 5HT2A) and (polymorphism or SNP or gene variant or genetic association))	37
Embase	((obsessive-compulsive disorder or ocd or obsessive-compulsive or obsessive compulsive or obsessive or compulsive) and (serotonin receptor 2A or 5-HT2A or HTR2A or 5-HT receptor 2A or 5HT2A) and (polymorphism or SNP or gene variant or genetic association))	68
PsycINFO (via Proquest)	(obsessive-compulsive disorder or ocd or obsessive-compulsive or obsessive compulsive or obsessive or compulsive) and (serotonin receptor 2A or 5-HT2A or HTR2A or 5-HT receptor 2A or 5HT2A) and (polymorphism or SNP or gene variant or genetic association)	25
DisGeNET (Bauer-Mehren et al., 2010)	(obsessive-compulsive disorder) and (HTR2A)	17
OCD Database (Privitera et al., 2015)	(HTR2A)	118

Supplementary Table 2: Summary of studies excluded

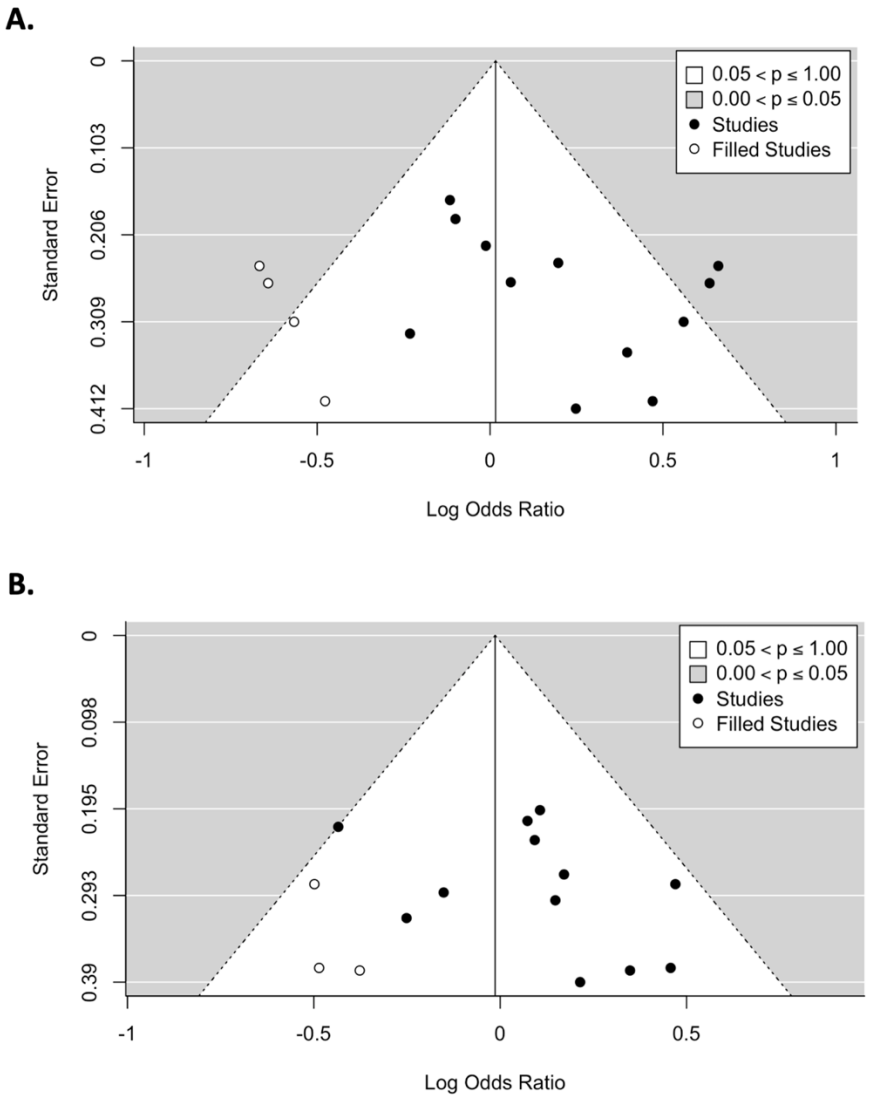
Study	Reason for Exclusion
(Denys et al., 2007)	No control group.
(Fonseca et al., 2017)	Conference abstract.
(Gomes et al., 2018a)	Corrigendum to 2018 paper – updated reported values were used in the meta-analysis.
(Gratacòs et al., 2009)	Did not examine HTR2A polymorphisms in OCD group.
(Grünblatt et al., 2011)	Conference abstract. Findings were later published in Walitza et al. 2012.
(Grünblatt et al., 2014)	No control group.
(Hemmings et al., 2003)	Group was subsumed in Hemmings 2006 thesis dissertation.
(Huang et al., 2001)	Abstract describes cases as individuals with Tourette's, with a subsample comprised with comorbid OCD. Unable to access the full-text article.
(Lee et al., 2007)	No control group.
(Mas et al., 2013)	Insufficient information (no allele/genotype frequencies provided for HTR2A variants according to OCD cases and controls). Author (Mas) confirmed that the OCD group was subsumed in Mas et al. 2014 paper.
(Miguita et al., 2011)	No control group.
(Plana et al., 2019)	No control group.
(Sinopoli et al., 2019)	Insufficient information (no allele/genotype frequencies provided for HTR2A variants according to OCD cases and controls).
(Tot et al., 2002a)	Conference abstract. Findings were later published in Tot et al. 2003.
(Tot et al., 2002b)	Conference abstract. Findings were later published in Tot et al. 2003.
(Wang et al., 2006)	Did not use DSM criteria to diagnose OCD.
(Zai et al., 2017)	Conference abstract.
(Zai et al., 2015)	No control group.
(Zai et al., 2016)	Conference abstract.
(Zai et al., 2013)	Conference abstract. No control group.
(Zai et al., 2014)	Conference abstract. No control group.
(Zhang et al., 2004)	Unable to access full-text article.

Supplementary Table 3: Quality assessment of studies meeting inclusion criteria using Q-Genie tool

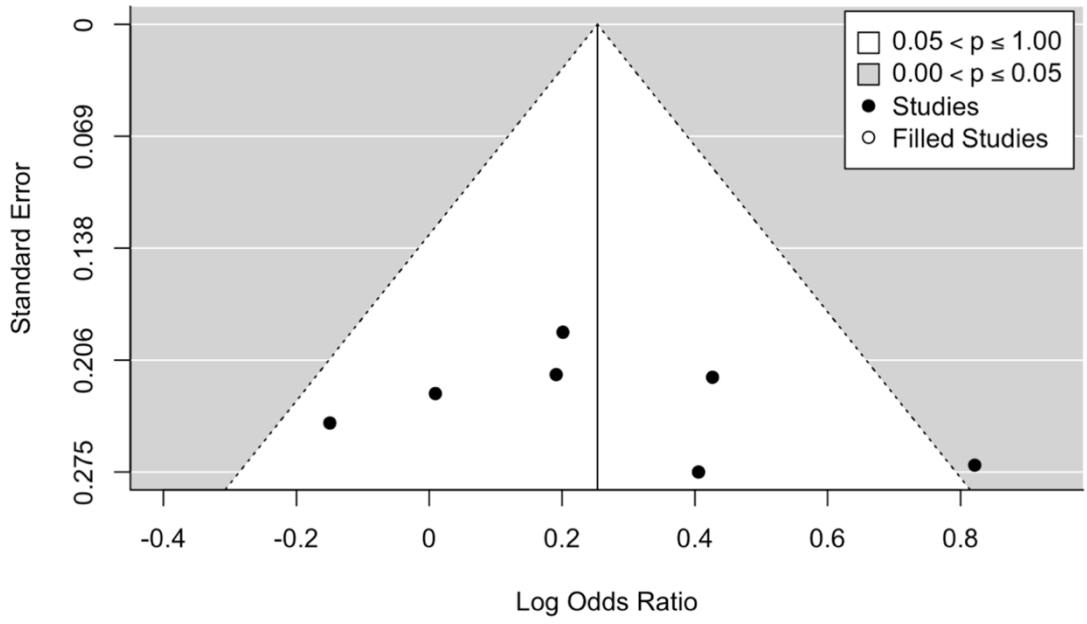
Reference	Averaged Q-Genie Response											Total Score	Rating
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11		
(Corregiari et al., 2012)	2.5	3.5	5	3	2	3	1.5	5.5	3.5	3	4.5	37	Moderate
(Denys et al., 2006)	5.5	5.5	4	3	2.5	3	2	3.5	2.5	4	2.5	38	Moderate
(Dickel et al., 2007)[a]	7	6	NA	6	2.5	2.5	1.5	6	2.5	3.5	3.5	41	Good
(Enoch et al., 1998)	4.5	4.5	3	1.5	1	1	1.5	3.5	1	1.5	2	25	Poor
(Enoch et al., 2001)	7	6.5	6.5	3	1	3.5	1.5	4.5	3	4	5.5	46	Good
(Frisch et al., 2000)	6	7	7	6.5	1.5	5.5	1.5	4	4	5.5	6.5	55	Good
(Gomes et al., 2018b)	7	6.5	6.5	5.5	1	1.5	3.5	4	4.5	4.5	6.5	51	Good
(Hemmings, 2006)	7	7	3	6.5	4	6	1.5	7	3	3.5	6.5	55	Good
(Jung et al., 2006)	5	5.5	4	5.5	1	4.5	1.5	4.5	4	5.5	6.5	47.5	Good
(Liu et al., 2011)[a]	7	6.5	NA	6.5	1	2	1.5	3.5	4.5	4.5	6	43	Good
(Liu et al., 2013)	6.5	6	5.5	5.5	1.5	2	2	5	5.5	5	6	50.5	Good
(Mas et al., 2014)[a]	6.5	6.5	NA	4	2	3.5	3	5.5	4	5	6	46	Good
(Meira-Lima et al., 2004)	4	7	5.5	6.5	1	5.5	2.5	6.5	6	4.5	6.5	55.5	Good
(Nicolini et al., 1996)	3.5	5.5	3.5	6.5	1	5.5	1.5	2	4	6.5	6.5	46	Good
(Saiz et al., 2008)	7	5.5	5.5	6.5	1	6	5.5	7	5	4	6.5	59.5	Good
(Sina et al., 2018)	7	6.5	4	6.5	1	3.5	4.5	7	6.5	5	6.5	58	Good
(Tot et al., 2003)	7	6	6.5	6.5	4.5	1	1.5	7	6	7	6.5	59.5	Good
(Walitza et al., 2002)	7	6.5	6.5	5.5	1	4.5	4	5	5.5	5	6.5	57	Good
(Walitza et al., 2012)	7	6.5	7	5.5	1	5.5	5.5	6	6	6	6.5	62.5	Good
Kendall's τ_b (p-value)	0.006 (0.97)	-0.21 (0.23)	0.02 (0.9)	-0.15 (0.39)	-0.12 (0.5)	-0.04 (0.79)	-0.2 (0.27)	-0.09 (0.6)	-0.11 (0.53)	-0.13 (0.43)	-0.26 (0.15)	-0.2 (0.23)	

Notes: NA = not applicable for studies with no control group; Q-Genie = Quality of Genetic Association Studies.

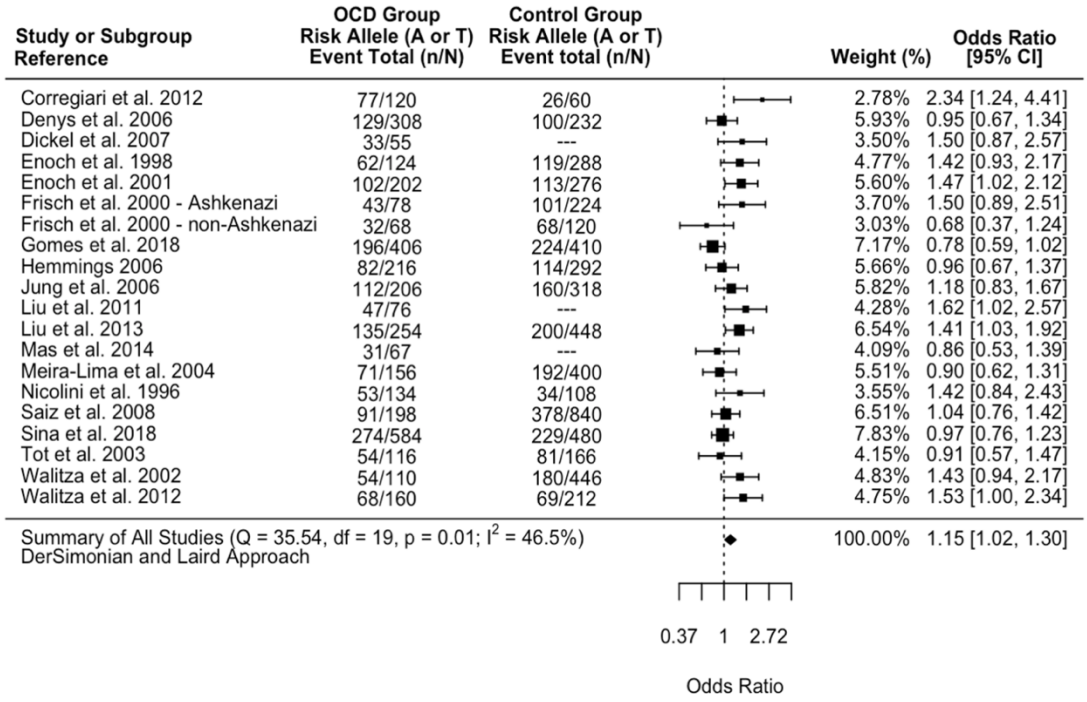
[a] Family-based studies with no control group.



Supplementary Figure 1. Funnel plots depict the standard error according to the log odds ratio for the stratified groups according to sex, for **A.** females and **B.** males. Each filled point represents a study included in the analyses, that investigated the association of the combined *HTR2A* polymorphisms (G-1438A and T102C) with obsessive-compulsive disorder according to subtypes based on sex. Estimated missing studies are indicated by open points (filled studies) as determined by the trim-and-fill method.



Supplementary Figure 2. Funnel plot depicts the standard error according to the log odds ratio. Each point represents a study included in the analyses, that investigated the association of the combined *HTR2A* polymorphisms (G-1438A and T102C) with early onset (≤ 18 years of age) obsessive-compulsive disorder. No missing studies were estimated according to the trim-and-fill method.



Supplementary Figure 3. Meta-analysis results obtained using the Dersimonian and Laird method when including Enoch et al. 1998 paper, which was originally excluded due to an overall poor-quality rating. Forest plot depicts the odds ratio (OR), with the 95th percentile confidence intervals reported. Data from G-1438A (rs6311) and T102C (rs6313) were combined due to strong linkage disequilibrium. The risk allele was defined as either the A or T allele of rs6311 or rs6313, respectively. Event total was defined as frequency of risk alleles in a sample, over the total allele frequencies in that sample and is reported separately for OCD cases and controls. The overall model is significant, z(19)= 2.30, *p=0.021*. "---" indicates family-based study with no control group.

3.8.3 Supplementary References

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Chapter 4: An exploratory investigation into serotonergic candidate genes associated with perinatal-related obsessive-compulsive symptoms in mothers across pregnancy and postpartum

Abstract

Background: Women are at increased risk for developing obsessive-compulsive symptoms (OCS) in the perinatal period, with distressing intrusive thoughts often emerging that are focused on parenting and the infant's well-being. To date, no studies have examined the genetic determinants underlying perinatal-related OCS in mothers. We explored whether single nucleotide polymorphisms in serotonergic candidate genes, *SLC6A4* and *HTR2A*, are associated with clinical levels of perinatal OCS.

Methods: A total of 107 women were enrolled in the study during their 2nd or 3rd trimester of pregnancy, with 62 women returning for a second visit within the 1st year postpartum. The 5-HTTLPR of *SLC6A4* and G-1438A of *HTR2A* were genotyped using polymerase chain reaction with restriction fragment length polymorphism. Technical challenges with *HTR2A* genotyping led to unreliable results, consequently, only results from 5-HTTLPR genotyping are reported. The Perinatal Obsessive-Compulsive Scale (POCS) was completed at each visit and used to categorize women into low (n=73) or high (n=34) OCS symptom groups based on a 12-point cut-off. Linear mixed models were applied to investigate the effects of the 5-HTTLPR genotype, maternal status (pregnancy vs. postpartum), and their interaction on perinatal-related OCS severity, while controlling for age, diagnosis and parity.

Results: There was no association between 5-HTTLPR allele (L_A or S/L_G) or genotype frequencies with high POCS severity scores in pregnancy or postpartum (all $p>0.05$). When considering different models of genetic inheritance (additive/dominant/recessive), none were significant (all $p>0.05$). Linear mixed models confirmed no effect of genotype ($\chi^2(2)=5.04$, $p=0.081$), time ($\chi^2(1)=0.0075$, $p=0.93$) or their interaction ($\chi^2(2)=2.71$, $p=0.26$) on predicting POCS scores. Diagnosis significantly influenced POCS scores ($\chi^2(2)=41.15$, $p < 0.00001$), such that mothers with pre-existing OCD had higher scores. There was no effect of age or parity ($p=0.14$ and $p=0.87$, respectively).

Conclusions: This is the first reported genetic association study to explore whether serotonergic risk genes confer susceptibility for the development and worsening of OCS in women during the perinatal period. We found no evidence that the 5-HTTLPR was associated with the unique perinatal-related symptoms, but replication in larger samples is warranted, with *HTR2A* polymorphisms remaining to be tested.

4.1 Introduction

Obsessive-compulsive disorder (OCD) is a chronic psychiatric illness that affects an estimated 1-3% of the global population (Angst et al., 2004; L. F. Fontenelle et al., 2006; Kessler et al., 2005; Sasson et al., 1997) and is associated with an increased health burden and mortality risk (Meier et al., 2016). The most prominent features associated with this disorder are the presence of recurrent thoughts, images or urges, and/or repetitive behaviours or rituals that are performed as attempts to alleviate anxiety (American Psychiatric Association, 2013). The disability associated with OCD is compounded by increased rates of comorbidity with other mood and affective disorders (Pallanti et al., 2011) and delayed treatment seeking, with reports suggesting an untreated illness duration of approximately 7 years (Dell'Osso et al., 2019).

The current first-line pharmacological treatment for OCD are the selective serotonin reuptake inhibitors (SSRIs) (Koran et al., 2007). These medications act on the serotonergic system to modulate neurotransmission and increase serotonin availability at the level of the synapse. When left untreated for more than 2 years, individuals with OCD tend to experience a poorer response to treatment (Dell'Osso, Buoli, Hollander, & Altamura, 2010), warranting the need for greater prevention and prompt identification for individuals at risk.

Although there have been considerable difficulties in identifying factors that contribute to the etiology of OCD, substantial evidence points towards genetic influences. Family and twin studies have shown that OCD is familial and heritable (Grabe et al., 2006; Nestadt et al., 2000; Taylor, 2011b), yet no specific genes have been consistently

identified from candidate gene and genome-wide approaches (Mattina & Steiner, 2016). To date, genes from the serotonergic system have received a great deal of attention (Sinopoli et al., 2017), which is in part due to the efficacy of SSRIs on treating OCD (Soomro, Altman, Rajagopal, & Oakley-Browne, 2008). From these studies, two primary candidates have emerged: the solute carrier family 6 member 4 gene (*SLC6A4*) and the serotonin receptor 2A gene (*HTR2A*).

The *SLC6A4* gene is found on chromosome 17q11.1-q12 and encodes the serotonin transporter protein (SERT) (Heils et al., 1995). SERT is a monoamine transporter protein that plays a critical role in the regulation of serotonergic neurotransmission by mediating serotonin uptake from the synaptic cleft back into the presynaptic neuron (Tao-Cheng & Zhou, 1999; F. C. Zhou et al., 1998).

The serotonin transporter linked polymorphic region (5-HTTLPR; rs4795541), which exists within the promoter of *SLC6A4,* is one of the most widely studied variants across psychopathologies. The 5-HTTLPR is a 44-base pair insertion/deletion polymorphism that contains 20-23 base pair tandem repeats of GC-rich elements (Heils et al., 1996). It is comprised of the short (S) allele with 14 repeats or the long (L) allele with 16 repeats (Caspi et al., 2003). This difference in length between the S and L allele affects the expression of SERT, whereby the S allele has reduced transcriptional efficiency and results in decreased SERT protein expression and lower serotonin reuptake (Lesch et al., 1996). At the level of the synapse, the S allele would result in slower recycling of serotonin due to less efficient transporter function, causing an overall reduction in the circulating levels of serotonin at target synapses (Heils et al., 1996; Jasinska, Lowry, &

Burmeister, 2012). Among neuroimaging investigations, the effects of 5-HTTLPR on SERT expression within the human brain have yielded inconsistent findings, with some confirming an association between S allele carriers and reduced SERT relative to L allele homozygotes (Heinz et al., 2000; Kalbitzer et al., 2009; Praschak-Rieder et al., 2007; Reimold, Smolka, Schumann, et al., 2007), and others finding no change in SERT expression according to the 5-HTTLPR genotype status (Parsey et al., 2006; Shioe et al., 2003).

It was later discovered that a nearby variation (rs25531) in the L allele of 5-HTTLPR results in an adenosine (L_A) to guanine (L_G) change occurring at the sixth nucleotide within the first of the two extra repeats, such that the L_G form has similar transcriptional activity to the S allele, resulting in reduced SERT mRNA and protein (Bradley, Dodelzon, Sandhu, & Philibert, 2005; Hu et al., 2006, 2005; Wendland et al., 2006). Therefore, studies that failed to consider this additional polymorphism and the tri-allelic nature of 5-HTTLPR require caution in its interpretation and may partly explain the discrepancies across studies.

The *HTR2A* gene is found on chromosome 13q14-21 and encodes the serotonin 2A ($5\text{-}HT_{2A}$) receptor, a G-protein coupled receptor type that is responsible for the regulation of a number of cellular signaling cascades (Raote, Bhattacharya, & Panicker, 2007). Notably, the $5\text{-}HT_{2A}$ receptors mediate serotonergic-induced excitation in many cortical pyramidal cells, with effects on glutamate and γ-aminobutyric acid (GABA) neurons (G. J. Marek, 2010). Furthermore, their activation can lead to downstream modulation of SERT distribution (Qian et al., 1997).

The two single nucleotide polymorphisms (SNPs) in *HTR2A* that have been repeatedly investigated in OCD are G-1438A (rs6311) and T102C (rs6313), which are in nearly complete linkage disequilibrium (Bray et al., 2004; R. M. Smith et al., 2013). G-1438A is located upstream of the promoter, whereas T102C is a silent polymorphism found in the first exon of the gene (Spurlock et al., 1998). The functional consequence of these variants is unclear, with conflicting reports suggesting that the A allele may be associated with increased or decreased promoter activity, thereby influencing 5-HT_{2A} protein production (Parsons, D'Souza, Arranz, Kerwin, & Makoff, 2004; R. M. Smith et al., 2013). More research is needed to determine the mechanisms from which these polymorphisms may influence *HTR2A* and 5-HT_{2A} receptor protein expression, and the resulting effect on serotonergic neurotransmission.

As promising as both of these serotonergic candidate genes are in the context of OCD, studies assessing the 5-HTTLPR and G-1438A polymorphisms in OCD samples have found largely mixed results (Sinopoli et al., 2017). Despite challenges with replication, several meta-analytic investigations have demonstrated that these polymorphisms within *SLC6A4* and *HTR2A* genes are associated with OCD (Grünblatt et al., 2018; Taylor, 2013, 2016). Specifically, the L_A allele of 5-HTTLPR was found to confer greater risk for OCD, as well as the A allele of G-1438A (or T allele of T102C) from *HTR2A*. Interestingly, the association of *HTR2A* with OCD appears to be specific to females (Mattina et al., 2020), with another meta-analysis finding a trending association of the S allele of 5-HTTLPR (treated as bi-allelic) with OCD in females (Mak et al.,

2015). Taken together, these investigations suggest that these candidate serotonergic genes may confer greater risk to women in a sex-dependent manner.

Females experience a slightly higher lifetime prevalence of OCD as compared to males (Torres et al., 2006), with the majority of onset cases occurring in late adolescence and early adulthood (Ruscio et al., 2010). Notably, OCD onset in females commonly coincides with reproductive years, with peak incidence rates occurring in females aged 20 to 29 years (Kessler et al., 2005; Veldhuis et al., 2012). The perinatal period poses significant risk for women to develop psychiatric disorders, including OCD. Indeed, women are approximately 1.5 to 2 times more likely to experience OCD during pregnancy and postpartum, as compared to the general non-perinatal female population (Russell et al., 2013). Furthermore, women with pre-existing OCD are more likely to experience symptom exacerbation during the perinatal period (Forray et al., 2010; Guglielmi et al., 2014; Labad et al., 2010, 2005; Uguz et al., 2011; Vulink et al., 2006). Obsessive-compulsive symptoms (OCS) are also more commonly endorsed in the postpartum period by women with depression, along with comorbid anxiety (E. S. Miller, Hoxha, Wisner, & Gossett, 2015).

Obsessive intrusions and doubts regarding the baby and caregiving activities are relatively common in parents with and without psychiatric illness (Abramowitz et al., 2006; Abramowitz, Schwartz, & Moore, 2003; Fairbrother & Woody, 2008), especially during the early postpartum period (Brok et al., 2017). Approximately 11% of mothers followed prospectively over the postpartum period endorsed OCS at 2 weeks and 6 months postpartum, which was higher than that of anxiety symptoms (E. S. Miller et al.,

2013). While it is largely advantageous for mothers to attend to the safety and protection of their child, unwanted thoughts of harm (either accidental or intentional) can cause substantial distress and may predispose women to develop clinical symptoms, i.e. perinatal OCD (Abramowitz, Schwartz, & Moore, 2003; Fairbrother & Woody, 2008).

The risk factors associated with the development of OCS in the perinatal period are not well known, but there is some evidence suggesting that maternal age and delivery method, specifically younger maternal age and delivery by caesarean section, are associated with increased OCS (House et al., 2016). Furthermore, presence of an anxiety or depressive disorder in the perinatal period may be a risk factor for the development of perinatal OCS (Abramowitz, Schwartz, Moore, et al., 2003; Kaya et al., 2015; E. S. Miller et al., 2013). As a result, it is imperative that risk factors for the development or exacerbation of perinatal OCD in mothers during the perinatal period are identified in order to guide preventative strategies or treatment for those that are most at risk.

To date, no studies have looked at the genetic determinants underlying perinatal-related OCS in mothers. The purpose of the present study was to examine whether the 5-HTTLPR and G-1438A polymorphic variants of *SLC6A4* and *HTR2A* serotonergic genes, respectively, were associated with the presence or absence of clinical OCS in women during pregnancy or within the 1st year postpartum. In this preliminary investigation, our objectives were principally to explore this genotype-phenotype relationship and determine whether genotype or allele status was associated with infant-focused symptoms under several classical genetic models, including additive, dominant and recessive modes of inheritance. Furthermore, we were interested in determining whether there were

differences in severity scores according to genotype status, and whether these polymorphisms predicted OCS severity scores across the perinatal period.

4.2 Methods

4.2.1 Participants

Participants were mainly comprised of an outpatient sample of treatment-seeking women presenting with diverse mood symptoms at the Women's Health Concerns Clinic (WHCC) at St. Joseph's Healthcare Hamilton (SJHH). Recruitment also occurred via flyer advertisements in the Hamilton area, including midwifery and physician clinics, as well as online (i.e. Kijiji). Prior to study enrollment, participants were screened for the presence of any psychiatric disorder or neurologic condition. Women were eligible to participate in the observational study if they were pregnant, above 18 years of age and proficient in English. Potential participants were excluded if they had experienced a head trauma or injury in the last 10 years, perinatal complications, were in poor physical health, or had a psychiatric diagnosis other than OCD, an anxiety disorder or a depressive disorder. Women with anxiety or depressive disorders were eligible to participate because this clinical sample is more likely to endorse infant-related OCS during the perinatal period (Wisner et al., 1999). Diagnosis and identification of comorbidities were completed by an experienced SJHH psychiatrist and confirmed with the composite international diagnostic interview for women (CIDI-VENUS) (Martini, Wittchen, Soares, Rieder, & Steiner, 2009) based on criteria from the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV-TR) (American Psychiatric Association, 2000). Due to the nature of this clinical sample, treatment status was not part of the exclusion

criteria. This study was approved by the Hamilton Integrated Research Ethics Board (Project # 10-3338) and all participants provided written informed consent.

4.2.2 Study Design and Clinical Scales

Participants were asked to complete two study-related visits over the course of the perinatal period: the first visit took place during the 2nd-3rd trimester of pregnancy and a follow-up visit took place in the first year postpartum. During the first visit, participants underwent venipuncture for the purposes of collecting blood specimen to be used for the genotyping analysis. To assess the characteristics and severity of OCS, the Perinatal Obsessive-Compulsive Scale (POCS) (Lord, Rieder, Hall, Soares, & Steiner, 2011) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) self-report questionnaires were used and completed at both time points.

The POCS measures the content, severity, and onset of intrusive thoughts and repetitive behaviours that mothers may experience (Lord et al., 2011). The symptoms assessed are unique to the perinatal period and are primarily focused on the newborn's health and wellbeing. Symptoms on the checklist include excessive maternal behaviours (e.g. immoderate researching about pregnancy, repeatedly checking on the baby or cleaning the baby's environment), disturbing thoughts of accidentally or intentionally harming the infant, doubts about mothering and reassurance seeking behaviours. Overall severity scores range from 0-40, with recent investigations into its psychometric properties revealing good internal consistency and test-retest reliability in perinatal samples (Rowa et al., 2020). Results from this validation study demonstrated a cut-off score of 11.5 associated with 84.7% sensitivity and 63.0% specificity. Furthermore, it was

found that this scale has an accuracy of 68.2% in distinguishing between those with and without an OCD diagnosis during the perinatal period. Lastly, scores on the POCS were found to be significantly different than scores obtained with the Y-BOCS, suggesting that the POCS scale is likely more sensitive to perinatal-related symptoms that are not represented in the Y-BOCS.

The Y-BOCS is considered a 'gold standard' assessment tool for measuring the content and severity of OCS (Goodman et al., 1989). The self-report paper-and-pencil version was used (Baer, Brown-Beasley, Sorce, & Henriques, 1993), and it has shown excellent internal consistency and test-retest reliability (Steketee, Frost, & Bogart, 1996). Unlike the POCS, the Y-BOCS does not contain any prompts for the consideration of perinatal-related symptoms. Total severity scores on this scale also range from 0-40, with recent empirical evidence providing the following symptom severity ranges in adults: 0-13 'mild symptoms', 14-25 'moderate symptoms', 26-34 'moderate-severe', and 35-40 'severe' (Storch et al., 2015). Since these scales appear to measure distinct OCS content, both scales were included, with severity scores on the POCS being our main outcome of interest.

4.2.3 Genotyping

Venous blood collected in EDTA vacuum tubes during the antenatal visit was immediately frozen and stored at -80°C. Genomic DNA was extracted from whole blood using the QIAamp DNA blood mini-kit (QIAGEN 51106, Toronto, ON) and DNA concentration (ng/μL) was determined using the NanoDrop 2000c. Genotyping for the 5-HTTLPR and *HTR2A* G-1438A polymorphisms was conducted using polymerase chain

reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques. Genotyping was conducted in small batches (n=8 samples) as blood samples were collected over the course of the study, with the same protocol performed across batches.

4.2.4 5-HTTLPR

To assess the polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*), the following forward (5'-GGCGTTGCCGCTCTGATGC-3') and reverse (5'-GAGGGACTGAGCTGGACAACCAC-3') primers were used to amplify the 44-bp deletion/insertion fragments, resulting in either the S allele or L allele (Lesch et al., 1996). The 25 µL amplification mixture consisted of 100 ng genomic DNA, 0.5 µL of forward and reverse primers (each), 10 mM of deoxynucleoside triphosphates (dNTP) mix (Invitrogen 18427-088, Burlington, ON), 5 µL of 5X Platinum II PCR Buffer, 5 µL Platinum GC-rich enhancer and 0.2 µL Platinum II Taq Hot-Start DNA Polymerase (Invitrogen 14966-005). Conditions for cycling were the following: initial denaturation at 94°C for 2 minutes, followed by 40 cycles of denaturation at 94°C for 15 seconds, annealing at 55°C for 15 seconds, and extension at 68°C for 30 seconds.

Visualization of the 5-HTTLPR allele bands was completed in a two-step process. First, 13 µL of the PCR product underwent electrophoresis on a 1.5% agarose gel supplemented with 5 µL of SyberSafe (Invitrogen S33102) at 50V for 90 minutes. Resulting band patterns are visible at 528-bp and 484-bp for the L and S allele, respectively (see Figure 1).

In order to identify the L_A and L_G alleles (rs25531), the remaining 12 µL of the PCR product was then incubated with 0.1 µL of the restriction enzyme MSPI (New

England Biolabs R0106S, Whitby, ON) and 1.3 µL of CutSmart Buffer (New England Biolabs B7204S) for 3 hours at 37°C (Praschak-Rieder et al., 2007). The cut product was run on a 4-20% gradient polyacrylamide gel (Invitrogen EC6225BOX) in a vertical XCell SureLock gel box at 14 mA for 60 minutes using the VWR AccuPower model 500 electrophoresis power supply. Afterwards, the gel was immersed in a solution containing 100 mL water and 10 µL of SyberSafe for 3 hours. Visualization of the agarose and polyacrylamide gel took place using the Bio-Rad Chemidoc ultraviolet transilluminator system. The cut PCR product generates bands visible at 340-bp for the L_A allele, 166+174-bp for the L_G allele and 297-bp for the S allele (see Figure 2).

4.2.5 G-1438A

The G-1438A (rs6311) polymorphism located in the promoter of the *HTR2A* gene was genotyped using similar PCR protocol as the 5-HTTLPR. Technical challenges with genotyping this polymorphism and optimization of the protocol resulted in poor band visualization and unreliable results. A description of the PCR protocol, including optimization strategy attempts and challenges, can be found in the Appendix. As a result, the *HTR2A* data will not be otherwise described in this report.

4.2.6 Statistical Analysis

Participants were grouped according to presence or absence of clinical perinatal-related OCS, as measured using the POCS. Women with a total score of 12 or higher were grouped and classified under the “high POCS” category, and those scoring less than 12 were categorized as “low POCS.” All analyses were completed using the R Statistical Software version 4.0.1. (R Core Team, 2019). Differences in continuous variables

between groups were assessed by Welch's *t*-test or Mann-Whitney *U* test, depending on the equality of variances and normality of distribution. Normality and homogeneity of variance were assessed using Shapiro-Wilk test and Levene's test, respectively. Categorical data was assessed using chi-square (χ^2) test or Fisher's exact test in cases where individual counts were below 5. Odds ratios (ORs) with 95% confidence intervals (95%CI) were computed to estimate effect size.

Due to the tri-allelic nature of the 5-HTTLPR, the following genetic association tests were performed by combining the S and L_G alleles (which will be referred to collectively as the S allele) due to similar lower levels of transcriptional activity, as compared to the L_A allele (referred to as the L allele in our results) (Hu et al., 2006). Tests for the Hardy–Weinberg Equilibrium (HWE) were performed by means of χ^2 test in the whole population, and according to POCS symptom group status.

Since the underlying genetic model is unknown, we conducted exploratory analyses under several inheritance models: the dominant inheritance model, where it is hypothesized that S allele carriers have increased likelihood of experiencing perinatal OCS (LL vs. LS+SS); the recessive inheritance model, where it is hypothesized that both S allele copies are needed to have a greater probability of experiencing clinical symptoms (LL+LS vs. SS); and the additive (codominant) inheritance model, where it is hypothesized that the S allele confers risk that is 1-fold in the LS heterozygotes and 2-fold in the SS homozygotes. The genotype frequencies under the dominant and recessive models were assessed using χ^2 statistics, whereas the Cochran-Armitage trend test for genotype frequencies was used for the additive model. As the analyses are exploratory in

nature, the results were left unadjusted for multiple comparisons, with the significance level α of all tests set to 5% ($p<0.05$).

Differences in symptom severity, as measured by the POCS and Y-BOCS, according to genotype across the entire sample irrespective of group were assessed with Kruskal-Wallis *H* test (non-parametric) for the pregnancy and postpartum visits separately. Furthermore, linear mixed modeling was performed on the subgroup of mothers who completed both visits to investigate the influence of 5-HTTLPR genotype (LL vs. LS vs. SS) over time (pregnancy vs. postpartum) on perinatal-related obsessive-compulsive scores. The linear mixed model was fitted using restricted maximum likelihood (REML) and included main and interaction effects of 5-HTTLPR and time, as well as diagnosis (healthy controls (HC) vs. OCD vs. non-OCD clinical (i.e. anxiety and/or depressive disorder only)) and parity as predictors of total symptom severity on the POCS, with age controlled for. To test the significance of each variable, a likelihood ratio test was applied, whereby the full model was compared to a reduced model that targeted each variable. For instance, to test the significance of the effect of 5-HTTLPR genotype, we compared the full model to a reduced model that did not contain genotype yet retained the remaining variables. Since a smaller proportion of women completed the study and were seen for a total of two visits, we were unable to estimate random slopes for this model; therefore, a random intercept model with fixed slopes was used. Significance of models was determined using the likelihood ratio test.

A post-hoc power analysis was carried out for the 5-HTTLPR using the software program Quanto (Gauderman, 2002) based on our sample size. These calculations were

completed under a log additive inheritance model with an unmatched case to control ratio of 1:2 and an 11% population risk based on estimates from the literature (E. S. Miller et al., 2013).

4.3 Results

A total of 107 pregnant women completed the first visit in pregnancy. Our sample was primarily Caucasian of European descent (86.9%), followed by West Asian (4.7%), African American or Black (2.8%), East Asian (1.9%), Hispanic (1.9%), South Asian (1.9%), and one biracial woman. The participants were between the ages of 18 and 41 (mean ± SD: 31.08 ± 4.44) and between 16 and 40 weeks in gestation (32.41 ± 4.25).

According to the clinical scores obtained in pregnancy, 34 women were classified as having a high POCS score and 73 with low POCS, based on the defined cut-off. Demographic information according to symptom severity group is summarized in Table 1. Demographic variables appeared well-matched between groups, with the exception that women in the high POCS group had greater family history of any psychiatric disorder (χ^2=7.28, p=0.007), were more likely to be taking psychotropic medications (χ^2=13.23, p=0.0003), especially SSRIs (χ^2=8.59, p=0.003), had a greater proportion of diagnosed OCD cases (p<0.0001) and comorbidities (χ^2=41.16, p<0.0001). During pregnancy, mean scores on the POCS for women in the high POCS group was 18.18 ± 5.41 and for women in the low POCS group was 3.29 ± 3.28. Unsurprisingly, women who scored higher on the POCS also scored higher on the Y-BOCS (15.12 ± 6.34), as compared to those with lower POCS scores (Y-BOCS: 3.12 ± 4.92).

Women completing the second visit returned during 11 and 40 weeks postpartum (18.66 ± 7.29). A high attrition rate was observed (42%), with 45 women dropping out of the study after the first visit. There were no significant demographic or clinical differences observed between completers and drop-outs (see Table 2). For five participants, POCS severity status changed from pregnancy to postpartum, with 3 women changed from low to high POCS, with the opposite occurring for 2 women. During postpartum, women in the high POCS group had mean POCS scores of 18.09 ± 5.25, while those in the low POCS group had mean scores of 4 ± 3.57. Similar to pregnancy, postpartum mothers in the high POCS group had higher Y-BOCS scores (14.82 ± 5.8), compared to women in low POCS group (Y-BOCS: 3.7 ± 4.63).

All 107 samples were successfully genotyped for the 5-HTTLPR. A total of 50 (46.7%) samples were re-genotyped with a 100% concordance rate observed. The genotype frequency distribution did not significantly differ from HWE in the entire sample (p=0.17), or in the high POCS and low POCS subjects (p=0.45 and p=0.33, respectively).

The allelic and genotypic frequencies for the 5-HTTLPR according to group status at both time points can be found in Table 3, and a boxplot summary of the POCS total scores in pregnancy and postpartum according to the 5-HTTLPR genotype status can be found in Figure 3. There was no association observed according to genotype (χ^2=0.29, p=0.87) or allele frequency (χ^2=0.29, p=0.59, OR [95%CI] =1.17 [0.63, 2.17]) in pregnancy, or in the postpartum period (genotype χ^2=1.75, p=0.42; allele χ^2=1.82, p=0.18, OR [95%CI] =1.66 [0.74, 3.75]). Furthermore, there was no significant difference in the

5-HTTLPR genotype frequencies between the high and low POCS groups under any inheritance model in pregnancy (additive model p=0.62; dominant model p=0.60; recessive model p=0.74) or postpartum (additive model p=0.19; dominant model p=0.24; recessive model p=0.32). There was no difference in mean symptom severity scores, as measured on the POCS and Y-BOCS, according to the *5-HTTLPR* genotype, in pregnancy or postpartum (all p>0.05, see Table 4).

Results from the full linear mixed model, which included each predictor variable, can be found on Table 5. To test the significance of each predictor, the full model was compared to a reduced model that did not contain the variable of interest, as described earlier in the Methods section. Through these comparisons, genotype was not found to be a significant predictor for POCS severity scores, $\chi^2(2)=5.04$, p=0.081. There was no effect of maternal status, $\chi^2(1)=0.0075$, p=0.93, age, $\chi^2(1)=2.15$, p = 0.14, or parity, $\chi^2(1)=0.027$, p = 0.87, on POCS scores. Furthermore, there was no significant interaction between genotype and time, $\chi^2(2)=2.71$, p=0.26. Psychiatric diagnosis as obtained during pregnancy appeared to influence POCS scores, $\chi^2(2)=41.15$, p < 0.00001, such that an OCD diagnosis increased perinatal-related symptom severity score by 16.75 ± 2.50 (SE), 95%CI [12.06, 21.44] and a non-OCD diagnosis increased severity by 5.06 ± 2.10 (SE), 95%CI [1.11, 9.00], when compared to healthy controls.

Post-hoc power calculations of *5-HTTLPR* for our sample size (n=34 cases) revealed 8.3% power to detect two-sided p-value significance of 0.05. Due to our modest sample, our study did not have enough power to detect genetic effects.

4.4 Discussion

This is the first investigation in the extant literature exploring serotonin genetic variants as a potential risk factor associated with the onset and exacerbation of infant-related OCS in women during the perinatal period. Overall, there were no significant associations of 5-HTTLPR allele or genotype status with presence of clinical perinatal OCS. In the absence of data regarding the genetic model of inheritance, we explored additive, dominant and recessive inheritance models and found that the 5-HTTLPR was not associated with infant-focused OCS in pregnancy or during the postpartum under any model. This finding was also confirmed in our linear mixed model analyses where 5-HTTLPR genotype status was not found to be predictive of perinatal symptom severity scores. Therefore, the current study does not support involvement of the 5-HTTLPR in the genetic basis of perinatal-related OCS; however, we did not have sufficient power to detect genetic effects given the limited size of our sample. Despite these null findings, research studies utilizing larger samples are needed in order to reach any conclusions. We were unable to genotype the *HTR2A* rs6311 polymorphism due to technical challenges and limitations. Thus, *HTR2A* has yet to be investigated in relation to perinatal OCS.

Consistent with prior literature, our linear mixed model results confirmed that women with pre-existing OCD were most likely to develop and have worse infant-related symptoms, as compared to women with no OCD diagnosis (Abramowitz, Schwartz, & Moore, 2003; Abramowitz, Schwartz, Moore, et al., 2003; Forray et al., 2010; Labad et al., 2005; Williams & Koran, 1997). Furthermore, our results showed that women diagnosed with an anxiety and/or depressive disorder had higher severity scores on the

POCS, albeit not to the same degree as women with pre-existing OCD. This is in-line with evidence from the literature that shows that presence of an anxiety disorder at the time of pregnancy is predictive of perinatal-onset OCD (Kaya et al., 2015), and that women with anxiety and depressive symptoms in the early postpartum period are more likely to have concurrent OCS in the postpartum period (E. S. Miller et al., 2013).

Notably, we did not see any influence of maternal status (pregnancy vs. postpartum visit) on symptom severity scores. Generally, the postpartum period is associated with symptom worsening in those with OCD (Labad et al., 2005), but others also failed to note any significant changes in OCS severity in adult women with OCD across the perinatal period (House et al., 2016). Within our study, we found relatively stable symptom severity across the perinatal period, which may be a result of the clinically diverse sample studied that included women undergoing treatment and/or therapy.

We found no evidence for the effects of age or parity on the severity of perinatal-related OCS. These results appear to parallel those previously reported in the literature, where a study by House et al. failed to detect any relationship between parity and OCS severity in a sample of perinatal women with OCD (House et al., 2016). Contrary to our results, they found that maternal age was a significant predictor of illness severity, with increased age at the time of delivery predicting decreased scores on the Y-BOCS (House et al., 2016). The authors from this study speculate that increased maternal age may be a reflection of a longer duration of treatment, which may be in-line with the findings from another study where OCD was found to improve after several decades (Skoog & Skoog,

1999). Reasons why we did not find age to be a predictor of symptom severity may be due to the fact that our study was comprised of a clinically diverse sample, with women experiencing a range of anxiety, depressive and OCS. Furthermore, our study focused primarily on infant-related symptoms. Unlike the Y-BOCS, the POCS has not been extensively utilized in perinatal research, despite its unique features that identify and measure OCS content that is specific to the perinatal period. Therefore, differences in sample and symptom content may explain the discrepancy across studies.

While it can be expected that first-time mothers may have additional worries related to childbirth, the transition to motherhood and new care-giving responsibilities, one study comparing primiparous and multiparous mothers' postpartum experiences found that both groups frequently reported concerns regarding the health and wellbeing of the baby (Affonso, Mayberry, & Sheptak, 1988). This may explain why parity was not significantly associated with symptom severity across the perinatal period.

Within our study, women classified in the high POCS severity group appear to represent a more clinical sample, as can be evidenced by greater psychotropic medication use, OCD diagnoses and comorbidities. Since our sample was primarily comprised of outpatients experiencing OCS within the mild to moderate severity range, our results may not be reflective of those with more severe OCS. Only one participant in our study scored above 30 on the POCS, which is indicative of severe perinatal OCS. It should be noted that the majority of the literature investigating genetic determinants of OCD tends to exclusively study individuals with severe symptoms of OCD (i.e. scoring above 30 on the Y-BOCS). It is possible that we could not detect any genetic influences on the expression

of infant-related OCS due to the fact that we did not compare clinically severe extremes to healthy controls.

4.4.1 5-HTTLPR and HTR2A

The functional effects of 5-HTTLPR have been reliable within *in vitro* studies, whereby the S or L_G allele is associated with reduced transcription of SERT and decreased serotonin reuptake (Greenberg et al., 1999; Hu et al., 2006; Lesch et al., 1996; Wankerl et al., 2014). On the other hand, *in vivo* studies utilizing positron emission tomography (PET) or single photon emission computed tomography (SPECT) techniques in Caucasian and European samples have been inconclusive regarding the effects of 5-HTTLPR on SERT binding in the human brain (Fisher et al., 2017; Murthy et al., 2010; Praschak-Rieder et al., 2007; van Dyck et al., 2004). Furthermore, additional SNPs have been reported in the *SLC6A4* gene that may influence transcriptional activity, but these are more challenging to study due to the fact that they are rare and would require larger samples (Martin, Cleak, Willis-Owen, Flint, & Shifman, 2007; Ozaki et al., 2003; Wendland, Moya, et al., 2007).

The functional consequence of G-1438A polymorphism on HTR2A gene transcription and receptor protein expression remain unclear. Despite some evidence suggesting that the A allele may be associated with altered transcriptional activity (Parsons et al., 2004; R. M. Smith et al., 2013), results from a PET study failed to demonstrate an association between *HTR2A* polymorphism and 5-HT_{2A} receptor binding (Erritzoe et al., 2009). More recently, 5-HTTLPR and *HTR2A* (G-1438A) variants were

not found to be predictive of 5-HT_{2A} receptor binding across the neocortex *in vivo* (Spies et al., 2020).

While some studies reported that the L_A allele of 5-HTTLPR confers increased genetic susceptibility to OCD (Hu et al., 2006; Walitza et al., 2014), other investigations failed to detect any significant association with either allele (Rocha, Marco, Romano-Silva, & Corrêa, 2009; Tibrewal et al., 2010; Voyiaziakis et al., 2011; Wendland, Kruse, Cromer, Cromer, & Murphy, 2007). Multiple meta-analyses investigating 5-HTTLPR with OCD have been conducted, with some reporting an association with the S allele (Lin, 2007), the L_A allele (Taylor, 2013, 2016; Walitza et al., 2014), or finding no significant association with either (Bloch et al., 2008; Mak et al., 2015). Lack of conclusive findings may be a result of the inclusion of studies that failed to consider rs25531, the tri-allelic nature of 5-HTTLPR, differences in the ethnicity of the sample investigated and the clinical heterogeneity associated with OCD. In contrast, the results from the meta-analyses completed on *HTR2A* have all implicated the A allele from G-1438A (or T from T102C) polymorphism with OCD (Mattina et al., 2020; Taylor, 2013, 2016).

4.4.2 Perinatal OCD, Stress and Sex Hormones

Interactions between the environment and genetic predisposition may help to explain the increased incidence rates of OCS during the perinatal period. Pregnancy, childbirth and the postpartum period may be perceived as stressful events that trigger the development of obsessions and compulsions in some women. When investigating precipitating factors for the development of OCD, women with the disorder were more

likely to report childbirth and obstetric complications within the year preceding onset, as compared to healthy women (Maina et al., 1999). Furthermore, this sample of women with postpartum OCD reported higher frequency of aggressive infant-related symptoms. In another study, pregnancy was associated with OCD onset more than any other life event among women with children (Neziroglu, Anemone, & Yaryura-Tobias, 1992). Considering that childbirth may be an unpleasant and stressful experience for some women, one study found that mothers who delivered via Caesarian section had higher OCS severity scores than those who delivered vaginally (House et al., 2016), which may be a reflection of greater stress associated with a more invasive delivery procedure. Studies in non-perinatal samples also point towards an association between stressful life events and OCD onset in females (Real et al., 2011, 2016). Furthermore, there is evidence suggesting that those with the S allele of 5-HTTLPR tend to develop poor reactions to stress and are less emotionally resilient when faced with adverse events (Gonda et al., 2009; Stein, Campbell-Sills, & Gelernter, 2009). Therefore, genetic risk coupled with environmental stress may lead to the emergence of OCS in mothers.

In addition to the unique stressors experienced in the perinatal period, fluctuating levels of gonadal hormones may also trigger OCD onset and exacerbation in women. Across pregnancy, levels of estradiol and progesterone steadily increase until childbirth, after which a rapid and significant decline in both hormones occur in the days after delivery (Nott et al., 1976). Estrogen and progesterone appear to have a protective role against OCD symptoms, which may help to explain why OCD incidence rates across the perinatal period are lowest in the third trimester and higher in the early postpartum period

(Kaya et al., 2015). Further evidence of this link comes from preclinical studies, where administration of estradiol alone or the combination of estradiol and progesterone were found to decrease repetitive behaviours in a rat model of OCD (Fernández-Guasti et al., 2006; Flaisher-Grinberg et al., 2009).

Estradiol and progesterone have modulatory actions on serotonergic transmission, whereby they commonly lead to increased serotonin release and signaling (Karpinski et al., 2017). Estrogens act on estrogen receptors alpha (ERα) and beta (ERβ) that are found throughout the brain, with high densities in the amygdala, hypothalamus and other limbic areas (Osterlund & Hurd, 2001). In the presence of progesterone, high levels of estradiol leads to the downregulation of ERα and the upregulation of ERβ (Cheng et al., 2005), which is associated with an increase in 5-HT_{2A} receptors (Kugaya et al., 2003; Moses-Kolko et al., 2003; Moses et al., 2000; Ostlund, Keller, & Hurd, 2003). Therefore, it is possible that OCS onset and exacerbation in the perinatal period may be triggered by gonadal hormone fluctuations through their modifying actions on the serotonergic system, but this has yet to be directly investigated.

Another hormone of interest in perinatal OCD is oxytocin due to its involvement in labour, delivery, lactation and mother-infant bonding, but evidence for its associations with OCD remains limited. Oxytocin has an inhibitory effect on serotonergic neurotransmission (Mottolese, Redouté, Costes, Le Bars, & Sirigu, 2014) and high levels of oxytocin have been reported in the plasma of individuals with OCD in some (Leckman et al., 1994; Marazziti et al., 2015), but not all studies (Altemus et al., 1999). Furthermore, positive correlations between oxytocin levels and obsessive-compulsive

severity scores were found in patients responsive to either SSRI or a tricyclic antidepressant (Humble, Uvnäs-Moberg, Engström, & Bejerot, 2013). In our sample, when comparing breastfeeding status among the subsample of postpartum women (n=62) according to high or low POCS score classification, the results were non-significant (p=0.84). Despite not finding any difference between breastfeeding status on infant-related symptom severity, results from the literature suggests that oxytocin may contribute to the onset or worsening of OCS in the postpartum period, but more evidence is needed.

4.4.3 Limitations

The main limitation of this study was the small sample size. Our results suggested that there is no association between the 5-HTTLPR with the presence of perinatal-related OCS; however, we did not have sufficient power to detect genetic effects given our limited size of participants. The recruitment method was designed to optimize access to a pregnant sample of women exhibiting a wide range of clinical symptoms. Since the majority of participants in our study were sampled from an outpatient population, the results obtained may only reflect those of help-seeking females. We were not able to account for differences according to ethnicity, comorbidity, and medication use, which are factors that may influence the genetic association results.

Furthermore, a higher attrition rate was experienced with a considerable proportion of women dropping out of the study following the pregnancy visit, limiting our ability to investigate clinical variables in the postpartum period and changes over time. Notably, there were no demographic or clinical differences according to completer status.

A small number of mothers experienced a change in their POCS group status from pregnancy to postpartum, but owing to the limited sample size, we were not able to investigate potential factors that may have been related to these changes. Future explorations with larger samples, perhaps via multi-site collaborations, are needed to confirm our genetic findings and their effects on the clinical trajectory across the perinatal period.

While no studies have investigated the genetic influence of candidate serotonergic genes on the development and severity of infant-related OCS in the perinatal period, it is unlikely that a single gene contributes to this phenotype. Evidence from the literature suggests that OCD is polygenic, i.e. influenced by multiple genes exerting small effects (Pauls et al., 2014). As a result, genes from outside the serotonergic system (e.g. dopamine, glutamate, GABA) may contribute risk, and possible genotype x environment interactions should also be considered.

As a relatively understudied clinical presentation, future studies should continue to examine the underlying genetic predisposition associated with perinatal-related OCS and OCD. Recruitment of larger samples is necessary for identifying risk genes and determining the role that endocrine and environmental factors may play in contributing to the complex pathogenesis of perinatal OCD.

4.5 Conclusions

Our study failed to detect any association of the 5-HTTLPR with moderate symptoms of infant-related OCS in a perinatal sample; however, replication in a larger sample is needed before any conclusions can be made. Due to challenges in genotyping

the G-1438A variant, the *HTR2A* gene still remains to be tested in the context of perinatal OCS. Mothers with pre-existing OCD, as well as those with anxiety or major depressive disorders, were more likely to experience greater severity and impairment of infant-related symptoms, as compared to healthy mothers. Investigating genetic and other factors related to the emergence and worsening of OCS in the perinatal period is necessary for our understanding of the etiology of perinatal OCD, with the goal of one day translating this knowledge into healthcare practices that promote the health, safety and well-being of mothers and their infants.

4.6 Acknowledgements

We would like to thank Lauren Mak, Anastasiya Slyepchenko, and Calan Savoy and for their assistance in participant recruitment. A special thank you to Marg Coote and Lauren Mak for their assistance on DNA extraction, and to Jodi Gilchrist for their assistance with trouble-shooting challenges related to genotyping the 5-HTTLPR and *HT2A* polymorphism.

Table 1: Demographics for pregnant women (n=107) according to perinatal-related obsessive-compulsive symptom severity.

	High POCS (n=34)	**Low POCS (n=73)**	**p-value**
Mean ± SD			
Age	30.53 ± 5.54	31.34 ± 3.84	0.44 [a]
Education (years)	16.35 ± 2.81	17.51 ± 3.18	0.078 [b]
Weeks pregnant	32.56 ± 4.59	32.34 ± 4.11	0.62 [b]
Expected parity (including current pregnancy)	1.76 ± 1.13	1.58 ± 0.80	0.60 [b]
n (%)			
Family history of OCD	2 (5.9%)	2 (2.7%)	0.59 [c]
Family history of any psychiatric dx	27 (79.4%)	38 (52.1%)	**0.007** [d]
Smoking status (yes)	3 (8.8%)	2 (2.7%)	0.32 [c]
Currently taking psychotropic medication(s)	17 (50%)	12 (16.4%)	**0.0003** [d]
Psychotropic Medication			
Anticonvulsant	2 (5.9%)	0	0.10 [c]
Atypical antipsychotic	3 (8.8%)	1 (1.4%)	0.09 [c]
Benzodiazepine	2 (5.9%)	3 (4.1%)	0.65 [c]
SARI	1 (2.9%)	0	0.32 [c]
SNRI	3 (8.8%)	2 (2.7%)	0.32 [c]
SSRI	11 (32.4%)	7 (9.6%)	**0.003** [d]
Combination of 2 or more	4 (11.8%)	1 (1.4%)	**0.034** [c]
Marital Status			
Married	21 (61.8%)	58 (79.5%)	0.053 [d]
Common-law	7 (20.6%)	10 (13.7%)	0.36 [d]
Single	5 (14.7%)	5 (6.8%)	0.28 [c]
Widowed	1 (2.9%)	0	0.32 [c]
Employment			
Full-time	19 (55.9%)	34 (46.6%)	0.37 [d]
Part-time	3 (8.8%)	20 (27.4%)	**0.042** [c]
None	11 (32.4%)	19 (26%)	0.50 [d]
Did not disclose	1 (2.9%)	0	0.32 [c]
Current Primary Diagnosis			
Anxiety disorder	7 (20.6%)	13 (17.8%)	0.73 [d]
Major depressive disorder	2 (5.9%)	1 (1.4%)	0.24 [c]
Obsessive-compulsive disorder	20 (58.8%)	2 (2.7%)	**< 0.0001** [c]
None	5 (14.7%)	59 (80.0%)	**< 0.0001** [c]

	High POCS (n=34)	**Low POCS (n=73)**	**p-value**
n (%)			
Comorbidity Within Clinical Sample			
None (only primary diagnosis)	7 (20.6%)	9 (12.3%)	0.26 [d]
1 or more comorbid disorders	22 (64.7%)	5 (6.8%)	**< 0.0001** [d]

Notes: Women scoring 12 or higher on the Perinatal Obsessive-Compulsive Scale (POCS) total severity scale comprise the "high POCS" group, whereas women scoring below 12 were in the "low POCS" group.

Dx = diagnosis; SARI = serotonin antagonist and reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

[a] Welch's t-test (independent samples with unequal variances)

[b] Mann-Whitney U test (non-parametric independent samples)

[c] Fisher's exact test

[d] Chi-square test

Table 2: Demographics and behavioural characteristics for entire pregnant sample (n=107) according to completer/drop-out status.

	Completers (n=62)	**Drop-out (n=45)**	**p-value**
Mean ± SD			
Age	30.84 ± 3.89	31.42 ± 5.13	0.52 [a]
Education (years)	17.18 ± 3.08	17.09 ± 3.16	0.94 [b]
Weeks pregnant	31.87 ± 4.93	33.16 ± 2.97	0.30 [b]
Expected parity (including current pregnancy)	1.5 ± 0.7	1.82 ± 1.13	0.18 [b]
n (%)			
Family history of OCD	2 (3.2%)	2 (4.4%)	1 [c]
Family history of any psychiatric dx	41 (66.1%)	25 (55.5%)	0.36 [d]
Current smokers	2 (3.2%)	3 (6.7%)	0.65 [d]
Currently taking psychotropic medications	18 (29.0%)	11 (24.4%)	0.60 [d]
Psychotropic Medication Use			
Anticonvulsant	2 (3.2%)	0	0.51 [c]
Atypical antipsychotic	3 (4.8%)	1 (2.2%)	0.64 [c]
Benzodiazepine	3 (4.8%)	2 (4.4%)	1 [c]
SARI	0	1 (2.2%)	0.42 [c]
SNRI	5 (8.1%)	0	0.072 [c]
SSRI	9 (14.5%)	9 (20%)	0.45 [d]
Combination of 2 or more	4 (6.5%)	1 (2.2%)	0.40 [c]
None	44 (71.0%)	34 (75.6%)	0.60 [d]
Marital Status			
Married	49 (79.0%)	30 (66.7%)	0.22 [d]
Common-law	9 (14.5%)	8 (17.8%)	0.85 [d]
Single	4 (6.5%)	6 (13.3%)	0.32 [c]
Widowed	0	1 (2.2%)	0.42 [c]
Employment			
Full-time	33 (53.2%)	20 (44.4%)	0.48 [d]
Part-time	10 (16.1%)	13 (28.9%)	0.18 [d]
None	19 (30.6%)	11 (24.4%)	0.63 [d]
Did not disclose	0	1 (2.2%)	0.42 [c]
Current Diagnosis			
Anxiety disorder	20 (32.3%)	15 (33.3%)	0.91 [d]
Major depressive disorder	7 (11.3%)	3 (6.7%)	0.51 [c]
Obsessive-compulsive disorder	13 (21.0%)	9 (20%)	0.90 [d]
None	37 (60.0%)	27 (60%)	0.97 [d]

	Completers (n=62)	**Drop-out (n=45)**	**p-value**
n (%)			
Comorbidity			
None (only primary diagnosis)	9 (14.5%)	7 (15.6%)	0.88 [d]
1 or more comorbid disorders	16 (25.8%)	11 (24.4%)	0.87 [d]
Mean ± SD			
POCS			
Total	8.95 ± 8.58	6.73 ± 7.17	0.18 [b]
Y-BOCS			
Total	7.61 ± 7.85	6 ± 7.66	0.27 [b]
n (%)			
Number of women in high POCS group	21 (33.9%)	13 (28.9%)	0.58 [d]
Number of women in low POCS group	41 (66.1%)	32 (71.1%)	0.58 [d]

Notes: Dx= diagnosis; POCS = Perinatal Obsessive-Compulsive Scale; SARI = serotonin antagonist and reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

[a] Welch's t-test (independent samples with unequal variances)

[b] Mann-Whitney U test (non-parametric independent samples)

[c] Fisher's exact test

[d] Chi-square test

Table 3: Genotype and allele distribution of the 5-HTTLPR polymorphisms in women with and without perinatal-related obsessive-compulsive symptoms, in pregnancy and postpartum, under different genetic inheritance models.

	Pregnancy (n=107)						**Postpartum (n=62)**					
5-HTTLPR	High POCS		Low POCS		χ^2	p-value	High POCS		Low POCS		χ^2	p-value
	n	%	n	%			n	%	n	%		
Genotype												
LL	9	26.5	16	21.9	0.29	0.87	6	27.3	6	15	1.75	0.42
LS	14	41.2	31	42.5			10	45.4	18	45		
SS	11	32.3	26	35.6			6	27.3	16	40		
Allele												
L	32	47.1	63	43.2	0.29	0.59	22	50	30	37.5	1.82	0.18
S	36	52.9	83	56.8			22	50	50	62.5		
Dominant inheritance												
LL	9	26.5	16	21.9	0.27	0.60	6	27.3	6	15	1.37	0.24
LS+SS	25	73.5	57	78.1			16	72.7	34	85		
Recessive inheritance												
LL+LS	23	67.6	47	64.4	0.11	0.74	16	72.7	24	60	1.0	0.32
SS	11	32.4	26	35.6			6	27.3	16	40		

Notes: POCS = Perinatal Obsessive-Compulsive Scale

Table 4: Severity of OCD according to *5-HTTLPR* genotype status in pregnancy and postpartum.

	Pregnancy			Postpartum		
5-HTTLPR Genotype	n	POCS (mean ± SD)	Y-BOCS (mean ± SD)	n	POCS (mean ± SD)	Y-BOCS (mean ± SD)
LL	25	8.68 ± 8.03	6.36 ± 7.11	12	11.5 ± 9.34	7.33 ± 5.71
LS	45	9 ± 8.70	7.09 ± 7.90	28	8.89 ± 8.80	7.68 ± 8.13
SS	37	6.38 ± 7.16	7.14 ± 8.22	22	7.77 ± 5.90	7.77 ± 7.40
Kruskal-Wallis test		$\chi^2 = 2.95$ $p = 0.23$	$\chi^2 = 0.15$ $p = 0.93$		$\chi^2 = 1.21$ $p = 0.55$	$\chi^2 = 0.10$ $p = 0.95$

Notes: POCS = Perinatal Obsessive-Compulsive Scale.

Table 5: Results of the linear mixed model examining 5-HTTLPR genotype, maternal status (pregnancy vs. postpartum), and their interaction, as well as age, diagnosis and parity predictors on POCS severity scores.

Predictor	β (SE)	t-value	p-value*
5-HTTLPR Genotype [a]			
LS	-1.41 (2.37)	-0.60	0.55
SS	-4.26 (2.30)	-1.85	0.068
Maternal Status [b]			
Postpartum	1.25 (1.28)	0.98	0.33
LS:Postpartum	-2.18	-1.43	0.16
SS:Postpartum	-0.61	-0.39	0.70
Age	-0.30 (0.21)	-1.39	0.17
Diagnosis [c]			
OCD	16.75 (2.50)	6.70	**1.18e-08**
Non-OCD [d]	5.06 (2.10)	2.41	**0.02**
Parity	-0.19 (1.21)	-0.16	0.88

Notes: OCD = Obsessive-Compulsive Disorder; POCS = Perinatal Obsessive-Compulsive Scale.

* p-values obtained using the Satterthwaite approximation method

[a] Reference genotype is LL

[b] Reference maternal status is pregnant

[c] Reference diagnosis is healthy control

[d] Non-OCD diagnosis includes women with anxiety and/or depressive disorder only

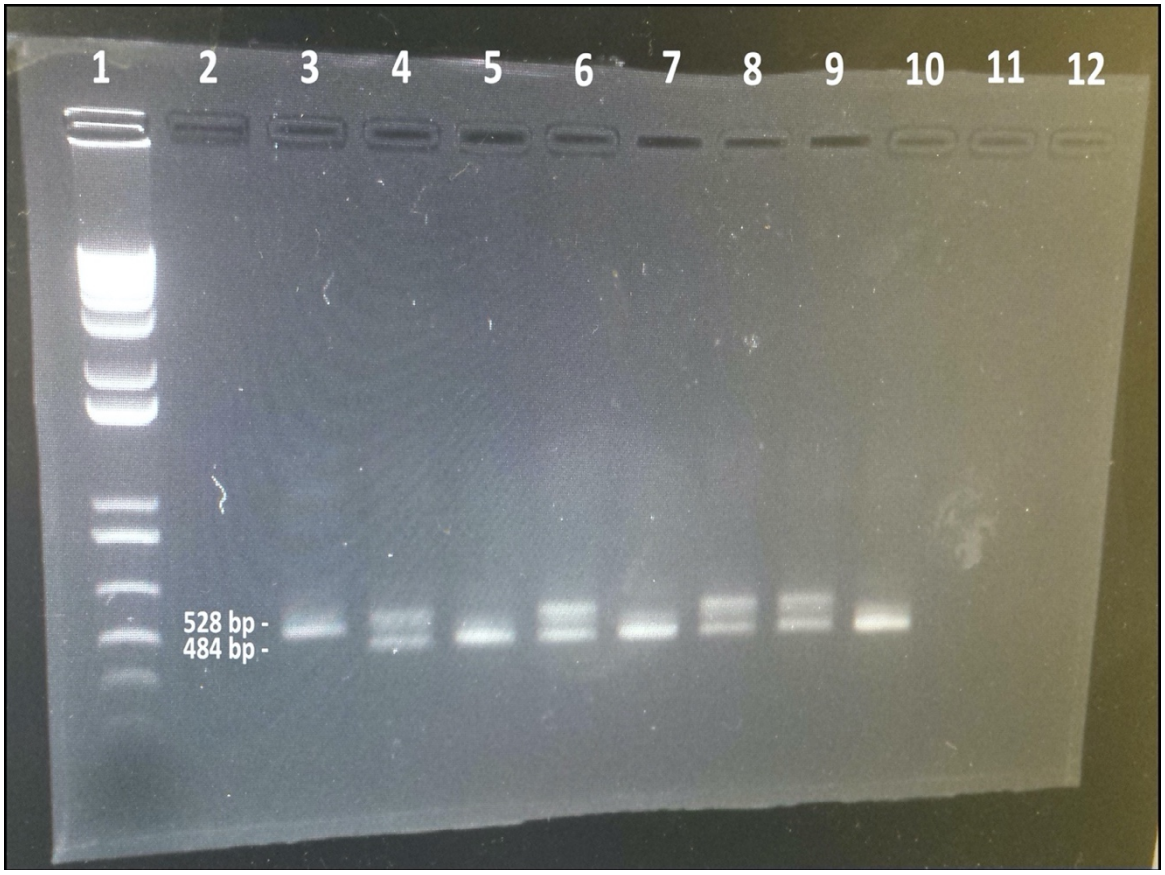


Figure 1. Amplified PCR products of 5-HTTLPR indicating presence of L (528 bp) or S (484 bp) allele on 1.5% agarose gel. Lane 1: 1 kb plus DNA ladder; Lanes 2 and 11: empty; Lane 3: L/L genotype; Lanes 4, 6, 8 and 9: L/S genotype; Lanes 5, 7 and 10: S/S genotype; Lane 12: H_2O control.

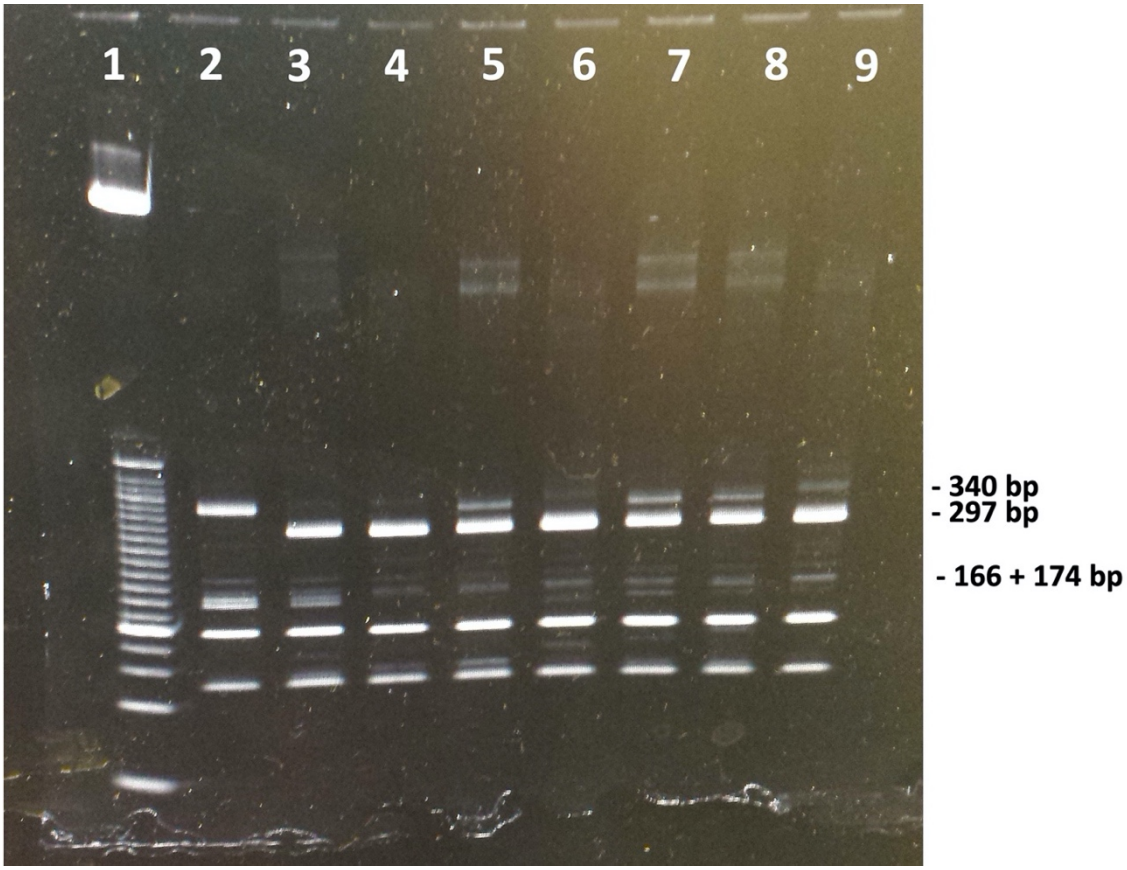


Figure 2. PCR-RFLP products of 5-HTTLPR visualized on 4-20% gradient polyacrylamide gel after digest with MSPI. The following alleles were visualized by their corresponding band length: L_A (340 bp), L_G (166+174 bp) or S (297 bp) allele. Lane 1: 25 bp DNA ladder; Lane 2: L_A/L_G genotype; Lane 3: L_G/S genotype, Lanes 4, 6 and 9: S/S genotype; Lanes 5, 7 and 8: L_A/S genotype.

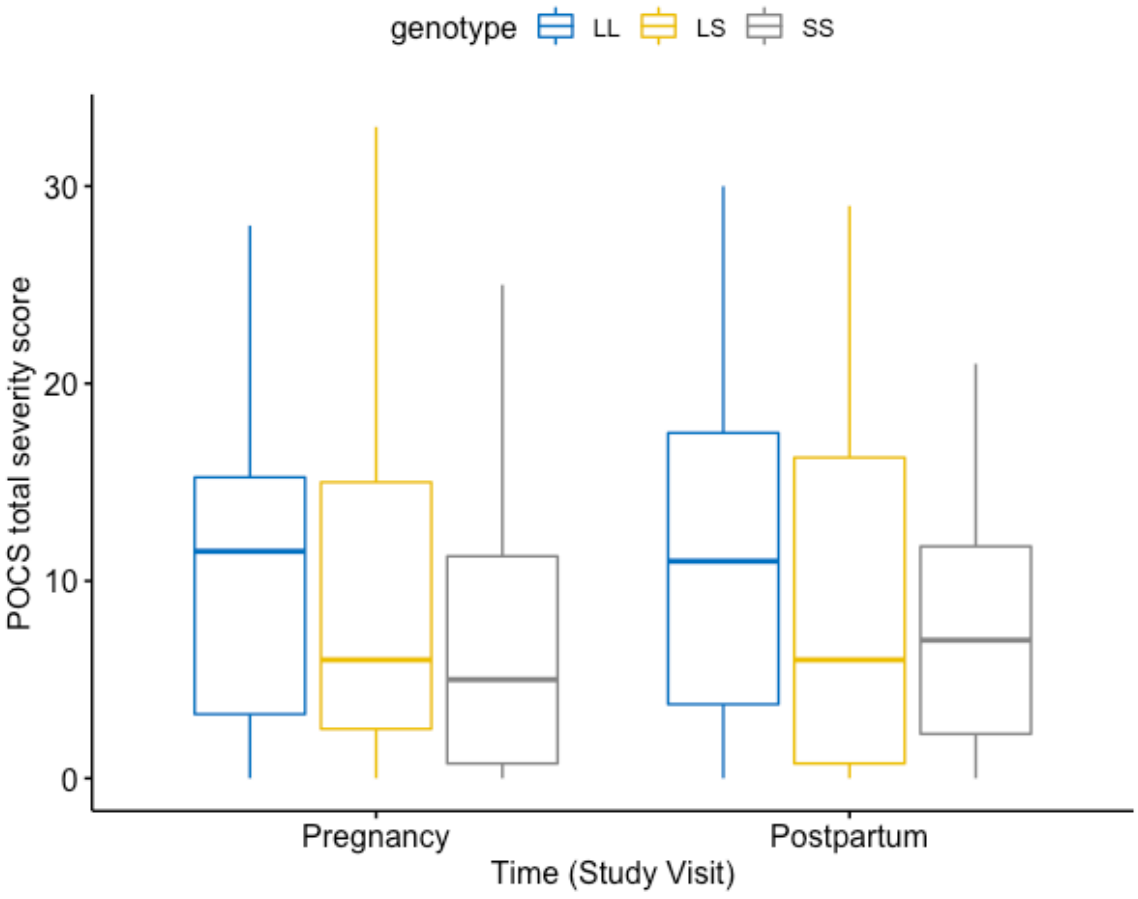


Figure 3. Boxplots depicting perinatal-related obsessive-compulsive symptom severity (POCS total scores) at different time points in the perinatal period according to the *5-HTTLPR* genotype status in the subsample of women that completed the study (n=62).

4.7 Appendix

HTR2A G-1438A PCR Protocol

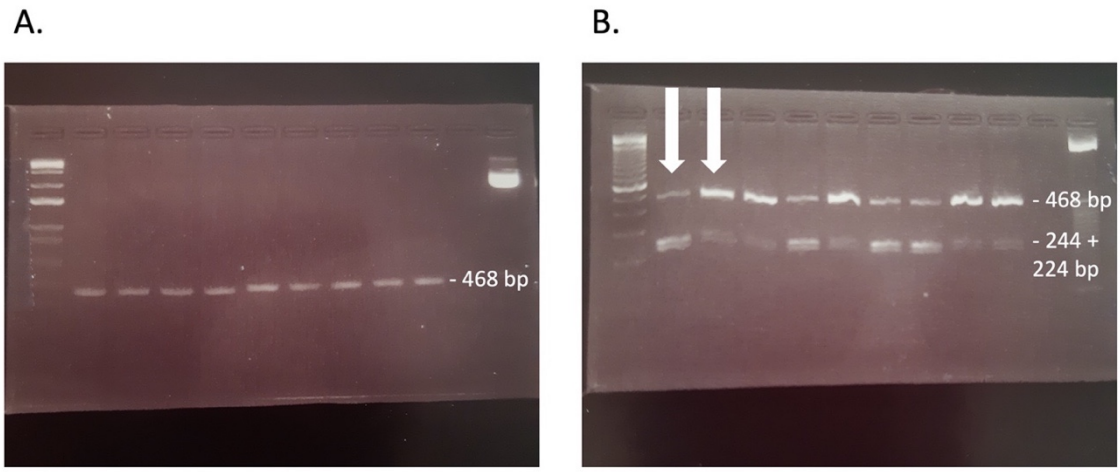
Briefly, the 468-bp fragment was amplified using the forward (5'-AACCAACTTATTTCCTACCA-3') and reverse (5'-AAGCTGCAAGGTAGCAACAG-3') primers. The 25 µL amplification mixture was identical to the one described for *5-HTTLPR*, with the exception that the GC-rich enhancer was not incorporated. The same PCR cycling conditions were also used. 12 µL of PCR product underwent immediate gel electrophoresis at 50V for 90 minutes on a 2% agarose gel in order to visualize and confirm the presence of the 468-bp band (see Appendix Figure 1A). The remaining 13 µL of PCR product was digested with MSPI restriction enzyme using the same conditions described for *5-HTTLPR* in order to differentiate between the G and A allele. The cut products underwent gel electrophoresis on a 2.5% agarose gel at 50V for 90 minutes. All gels were visualized using the same UV transilluminator system, with bands visible at 224+244-bp for the G allele and 468-bp for the A allele.

Using the abovementioned protocol, band visualization was challenging. Notably, it was unclear why differences in intensities were noted for individuals displaying the same alleles and genotype (see arrows on Appendix Figure 1B). Furthermore, all randomly genotyped samples (from ~ 30 individuals) contained the same G/A heterozygous genotype, which prompted further examination and protocol optimization attempts.

As part of the optimization attempts, we altered the following: composition of the agarose gel (tested 2.5 and 3% agarose), DNA concentration (doubled at 200 ng), PCR

annealing and extension temperatures, extension time, number of PCR cycles, and MSPI digest time, in addition to ordering new Taq polymerase and MSPI enzymes. From these attempts, we found no discernable differences or even worse visualization.

Due to failure in obtaining positive controls, we were unable to complete genotyping of the *HTR2A* and plan to continue this endeavor in the future once we are able to secure positive controls (i.e. samples known with having the G/G, G/A, and A/A genotypes) and will look into other genotyping methods (i.e. quantitative PCR with fluorescent-labelled probes).



Appendix Figure 1. PCR-RFLP products of *HTR2A* rs6311 (G-1438A). **A.** Uncut amplified PCR product (468 bp) visible on 2% agarose gel. First and last lanes contained 1 kb plus DNA ladder and 25 bp DNA ladder, respectively. **B.** Cut products following digest with MSPI on 3% agarose gel, indicating presence of A (468 bp) or G (244+224 bp) allele. All samples were heterozygous G/A. First and last lanes contained 100 bp DNA ladder and 25 bp DNA ladder, respectively. White arrows indicate difference in band intensities, despite identical genotypes.

Chapter 5: Cortical Markers Associated with Obsessive-Compulsive Symptom Worsening and Clinical Severity in Postpartum Mothers: An Exploratory Investigation

Abstract

Background: Women are at increased risk for the development and exacerbation of obsessive-compulsive disorder (OCD) in the perinatal period. Notably, unique symptoms surrounding the wellbeing of the newborn commonly emerge. Despite evidence of structural brain alterations associated with OCD, no studies have examined cortical characteristics associated with perinatal OCD and symptom severity in women during the postpartum period.

Methods: A total of 62 women completed two study visits: one in the 2nd to 3rd trimester of pregnancy and one in postpartum as part of a longitudinal study. The sample was comprised of 13 healthy controls and 49 psychiatric outpatients, of whom 13 met DSM-IV criteria for OCD. Several self-report clinical scales were completed at both time points, including the Perinatal Obsessive-Compulsive Scale (POCS), and participants underwent a 3T structural magnetic resonance imaging (MRI) scan in the postpartum visit. Whole brain surface-based analyses of cortical thickness (CT) and surface area (CSA) were completed using the automated FreeSurfer software to compare group differences and correlate gray matter parameters to symptom severity for the whole sample and stratified groups. Analyses were corrected for multiple testing using Monte Carlo simulations.

Results: There were no observable differences in cortical parameters across diagnostic groups. Greater worsening of obsessive-compulsive and trait anxiety symptoms across the perinatal period was associated with increased CSA of the left precuneus, in addition to other regions in the parietal, temporal, and occipital cortex. After group stratification, postpartum mothers with OCD exhibited CSA measures that were positively correlated with symptom severity, with the left inferior temporal, superior parietal and precentral gyrus, and the right precuneus associated with baby-focused obsessive-compulsive symptom severity (all corrected cluster-wise $p<0.01$). There was no association between CT and symptom severity.

Limitations: Comorbidity, psychotropic medication use, symptom heterogeneity and sample size.

Conclusions: To our knowledge, this is the first study to assess cortical morphology related to perinatal OCD in a postpartum sample. These findings suggest that multiple neural networks likely contribute to OCD and anxiety symptom exacerbation in the perinatal period.

5.1 Introduction

The perinatal period reflects a critical reproductive milestone for females that is marked by profound physiological changes. These biological adaptations are necessary for meeting the demands of the developing fetus or newborn but place a significant proportion of mothers at increased risk for the development or exacerbation of affective disorders (Fairbrother, Young, Janssen, Antony, & Tucker, 2015; Howard et al., 2014). Obsessive-compulsive disorder (OCD) during the perinatal period affects a significant proportion of females at rates higher than what is observed in the general population (1-3%), with some epidemiological studies reporting prevalence as high as 9% in postpartum samples (Uguz, Akman, Kaya, & Cilli, 2007; Wenzel, Haugen, Jackson, & Brendle, 2005; Zambaldi et al., 2009). Furthermore, among OCD samples, symptom onset during pregnancy or postpartum has been reported in 2–15.4% of women, whereas exacerbation during the perinatal period occurs more frequently (8-50%) in women with pre-existing OCD (Forray et al., 2010; Guglielmi et al., 2014; Labad et al., 2010, 2005; Uguz et al., 2011; Vulink et al., 2006). Unlike postpartum depression, perinatal OCD may be an underdiagnosed and undertreated disorder, as evidenced by the poor identification of these symptoms in healthcare settings (Mulcahy, Rees, Galbally, & Anderson, 2020). When left untreated, perinatal OCD is associated with symptom persistence and reduced quality of life due to detrimental effects on physical and psychological wellbeing, as well as social relationships (Gezginç et al., 2008; E. S. Miller et al., 2013).

Within clinical samples, obsessive-compulsive symptoms (OCS) are more frequently described among women with perinatal depression or anxiety (Abramowitz,

Meltzer-Brody, et al., 2010; E. S. Miller et al., 2013; Wisner et al., 1999). Notably, the emergence of perinatal-related symptoms is a risk factor for the development of OCD. When severe, such symptoms are distressing, disruptive, and have serious negative consequences on the mother-infant relationship (Abramowitz, Schwartz, & Moore, 2003; L. M. Arnold, 1999; Challacombe et al., 2016; Fairbrother & Woody, 2008). As a result, early identification and treatment is necessary to mitigate the adverse effects perinatal OCD has on the mother, baby and family.

While numerous investigations into risk factors and biological correlates of OCD in the general population have been conducted, little is understood about what factors contribute to perinatal OCD. Mounting evidence of structural and functional abnormalities in several neural circuits, such as the cortico-striato-thalamo-cortical (CSTC) circuit, have been documented in OCD samples (Menzies et al., 2008; Pauls et al., 2014). Commonly, results from functional neuroimaging studies (fMRI) have pointed towards increased resting-state functional connectivity of regions within the CSTC system (Beucke et al., 2013; Calzà et al., 2019; Harrison et al., 2009; Jung et al., 2013; Sakai et al., 2011). Prior work examining the cortical structure of OCD samples has frequently implicated widespread abnormalities in regions such as the dorsomedial and dorsolateral prefrontal, orbitofrontal, temporal, parietal and anterior cingulate cortices (Fan et al., 2013; Nakamae et al., 2012; Piras et al., 2015; Radua & Mataix-Cols, 2009; Rotge et al., 2010; Venkatasubramanian et al., 2012). In the largest mega-analysis completed to date, the Enhancing NeuroImaging and Genetics by Meta-Analysis (ENIGMA) consortium pooled cortical morphometric data from 1905 OCD cases and

1760 healthy controls finding lower surface area of the transverse temporal cortex and a thinner inferior parietal cortex in OCD cases (Boedhoe et al., 2018). Similarly, decreased cortical thickness in the parietal and temporal areas, as well as the right dorsolateral prefrontal cortex and left posterior cingulate cortex, was reported in a prior multi-site mega-analysis (Fouche et al., 2017). Taken together, these results suggest that wide-spread brain regions within and outside of the conventional CSTC model are involved in OCD and highlights the potential for cortical markers to act as biomarkers for the disorder.

Literature on the neural correlates of perinatal OCD is extremely scarce, with only one imaging study conducted that investigated the brain activation patterns associated with psychosocial stress in a postpartum sample (Lord et al., 2012). To date, no studies have looked at gray matter morphology within a postpartum sample with OCD.

This study aims to fill knowledge gaps by exploring cortical features associated with OCD and clinical symptom severity in the postpartum period. We applied surface-based morphometry across the whole brain in order to explore possible variations in cortical thickness (CT) and cortical surface area (CSA) in postpartum women related to OCD diagnosis and symptom severity, as well as other factors that may contribute to postpartum OCD, including anxiety and depressive symptoms, sleep quality and past exposure to childhood maltreatment.

5.2 Methods

5.2.1 Participants

Of 107 women initially recruited during pregnancy, a subsample of 62 women were followed into the postpartum period as part of a longitudinal study conducted from 2013-2017. This subsample of women included healthy controls and women presenting with a spectrum of obsessive-compulsive or anxiety symptoms. Participants were primarily recruited through the Women's Health Concerns Clinic (WHCC) at St. Joseph's Healthcare Hamilton (SJHH) and by flyer advertisements in the Hamilton area, including midwifery and physician clinics. The SJHH outpatient clinic specializes in the assessment and treatment of psychiatric symptoms in females during reproductive events

All participants were screened on the presence of any psychiatric or neurologic disorders and MRI contraindications. Eligibility criteria for all participants included being 18 years of age or older and able to communicate in English. For women meeting a primary diagnosis of OCD, as assessed by a SJHH experienced psychiatrist, exclusion criteria consisted of the following: (1) comorbid current diagnosis of any Axis I psychiatric disorder, other than an anxiety disorder or major depressive disorder, as confirmed with the composite international diagnostic interview for women (CIDI-Venus) (Martini et al., 2009); (2) any serious head trauma or injury within the last 10 years; and (3) any significant perinatal complications or physical conditions. Due to the challenges in recruiting a perinatal sample with OCD, participants with comorbid anxiety and/or major depressive disorders and those receiving pharmacological treatment or psychotherapy for their psychiatric symptoms were not excluded. Healthy controls were

defined using the same aforementioned inclusion and exclusion criteria, with the exception that they could not have any current or past history of a psychiatric illness, including alcohol or substance abuse. In addition to the OCD and HC samples, a third group was recruited that consisted of participants who had a current or past history of an anxiety and/or depressive disorder, and the same exclusion criteria outlined above was applied. The study was approved by the Hamilton Integrated Research Ethics Board (Project # 10-3338) and all participants provided written informed consent.

5.2.2 Study Design

After obtaining consent, women participated in two study-related visits. The first visit took place during the 2nd or 3rd trimester of pregnancy. At this time, clinical diagnoses and psychiatric history were established with a fully structured psychiatric interview (CIDI-Venus), based on criteria from the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV), and each participant completed several self-report clinical scales. The second visit took place between 2-10 months postpartum, where the participants returned to recomplete the clinical scales and a magnetic resonance imaging (MRI) scan on the same day. Women who were lost to follow-up and did not complete the postpartum visit (n=45, from the initial 107 recruited) are not included in the current report (see Chapter 4: Table 2 and Appendix Table 1 for demographic and clinical differences between completers and drop-outs).

5.2.3 Clinical Measures

The following paper-and-pencil self-report measures were completed at both visits, in pregnancy and postpartum, and assessed the presence and severity of clinically relevant behavioural symptoms in the perinatal period:

Perinatal Obsessive-Compulsive Scale (POCS) (Lord et al., 2011). The POCS assesses the content and severity of perinatal-specific OCS that are primarily focused on the baby's well-being, health and environment. Several examples of symptoms listed in the POCS include: '*Recurrent doubts about mothering*', '*Your baby being contaminated (by germs)*', '*Repeatedly washing and cleaning your baby's environment*', '*Your baby being harmed or dying in an accident*', '*Repeatedly checking the baby while he/she is asleep*.' Preliminary investigations into its psychometric properties revealed strong support for its reliability and validity in perinatal populations (Rowa et al., 2020).

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989)**.** Considered a 'gold standard' assessment tool in clinical and research settings, the Y-BOCS is a validated measure for assessing severity of OCS. The self-report version that was used has been shown to have excellent internal consistency and test-retest reliability (Baer et al., 1993; Steketee et al., 1996). Despite the symptom checklist containing areas for participants to list 'Other' obsessive or compulsive symptoms not mentioned, the Y-BOCS does not contain any language or prompts related to unique perinatal-focused symptoms. The following empirically derived score ranges indicate the severity of OCS: 0-13 'mild symptoms', 14-25 'moderate symptoms', 26-34 'moderate-severe', and 35-40 'severe' (Storch et al., 2015).

Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987). This 10-item scale is one of the most widely used assessments for identifying depressive symptoms and its associated severity within perinatal samples. Scores ≥ 15 and ≥ 13 indicate presence of perinatal depression in antenatal and postpartum periods, respectively (D. Murray & Cox, 1990; L. Murray & Carothers, 1990).

Spielberger State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970). Not specific to the perinatal period, the STAI measures general anxiety and distinguishes between two different forms: (1) state anxiety (STAI-S), a transient measure of current anxiety level, and (2) trait anxiety (STAI-T), a measure of the general tendency to be anxious. Cut-off scores > 40 on the state and trait subscales corresponded to the highest sensitivity and reliability estimates for antenatal anxiety in pregnant samples (Grant, McMahon, & Austin, 2008).

In addition to the above clinical scales, the *Childhood Trauma Questionnaire* (CTQ) (Bernstein et al., 2003) was completed during the pregnancy visit to retrospectively determine exposure to childhood maltreatment measured across 5 different subscales: physical abuse, emotional abuse, emotional neglect, sexual abuse and physical neglect. In order to assess overall sleep quality in the postpartum period, the *Pittsburgh Sleep Quality Index* (PSQI) (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) was administered during the second study visit.

5.2.4 MRI Data Acquisition

Images were acquired using a GE short-bore 3-Tesla MRI scanner with an 8-channel phased array head coil (General Electric Healthcare). A T_1-weighted 3-

dimensional (3D) axial magnetization-prepared rapid acquisition with gradient echo (MPRAGE) anatomic scan was performed with the following parameters: repetition time [TR] 9 ms, echo time [TE] 3.2 ms, flip angle 12°, field of view [FOV] 240 mm, slice thickness 2.0 mm, 140–168 slices, acquisition matrix size 320 × 192.

5.2.5 Image Processing and Surface-Based Morphometry

The FreeSurfer software suite for brain imaging analysis (version 6.0; http://surfer.nmr.mgh.harvard.edu/)(Fischl, 2012) was used to calculate measures of cortical thickness (CT) and cortical surface area (CSA), which have been shown to have a number of advantages over other voxel-based morphometry approaches, including the ability to differentiate between gray matter parameters (e.g. CT and CSA), greater anatomical alignment precision, greater spatial subvoxel accuracy, greater reproducibility of thickness measures, and less susceptibility to noise and partial volume effects (Clarkson et al., 2011). The surface-based analysis pipeline used to generate cortical surface models for each participant has been described elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Fischl et al., 2002, 2004; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). Briefly, the FreeSurfer processing includes motion correction, transformation to Talaraich space, intensity normalization, skull stripping, hemisphere separation, labeling, segmenting and connecting white matter surfaces, tessellation of the gray matter/white matter boundary, and topological correction. As part of a deformation procedure, the tessellated triangle mesh surfaces are used to identify the boundaries between gray matter/white matter and pial/cerebrospinal fluid surfaces. For each vertex, CT is defined as the shortest distance between the white

and pial surface, measured in millimeters (mm), and CSA is defined as the average area of the triangles at the vertex, measured in millimeters squared (mm^2). The surfaces and measures of CT and CSA are then inflated and registered to a spherical MNI atlas based on characteristic folding patterns, to allow for visualization across the entire cortical surface. The cortical surface maps obtained for each participant were visually inspected to confirm proper segmentation. Prior to conducting vertex specific general linear model (GLM), a 10 mm (full-width at half-maximum) Gaussian kernel was applied to smooth maps. Individual participant data was then transformed to an average surface that is optimally aligned according to sulcal and gyral features to match cortical locations across participants.

5.2.6 Statistical Analysis

Differences in demographic and clinical variables between the OCD, current or past anxiety/depression (CPAD), and healthy control (HC) groups were assessed by performing one-way analysis of variance (ANOVA) tests with post-hoc Tukey's HSD test (parametric) or Kruskal-Wallis *H* test with post-hoc Dunn's multiple comparison test using Bonferroni adjustment (non-parametric) for continuous data. Categorical data were assessed using Fisher's exact test with Bonferroni correction. Change over time in severity scores on the behavioural data, as measured by the various self-report clinical scales, from pregnancy to the postpartum period was assessed using paired sample *t*-test (parametric) and Wilcoxon signed-rank test for paired samples (non-parametric). Normality and homogeneity of variance assumptions were checked using Shapiro-Wilk test and Levene's test, respectively. In case of a non-normal distribution, transformations

were applied to the data if possible. Statistical analyses were completed using R Statistical Software version 4.0.1. (R Core Team, 2019).

Between- and within-group comparisons of whole-brain gray matter characteristics (CT and CSA measures) were analyzed using FreeSurfer's QDEC statistical interface. GLM analysis was used to determine whether CT and CSA measures differed according to diagnosis (OCD vs. HC; Anxiety (current or past) vs. HC; Depression (current or past) vs. HC), with age and weeks postpartum included as covariates. Furthermore, exploratory GLMs were fitted, assessing CT and CSA measures according to symptom severity on each of the separate clinical scales (POCS, Y-BOCS, EPDS, STAI-S and STAI-T) and other measures (PSQI, CTQ) were completed across the entire postpartum sample and in the OCD subgroup, using the same covariates described above. Due to the high rates of comorbid anxiety in the OCD sample, we also completed these analyses in the subgroup of mothers with a current anxiety disorder, in order to compare findings and determine whether similar or different associations were found across diagnostic groups. Furthermore, to assess the possible effect of medication use on cortical parameters, we performed separate GLM analyses to test if there were any differences in gray matter thickness or surface area between medicated and unmedicated mothers, with age and weeks postpartum as covariates.

Monte Carlo-simulation correction (10,000 iterations) was applied to all GLM results to account for multiple comparisons across the whole brain, with a cluster-wise p-value threshold set to 0.01 to remain conservative due to the exploratory nature of the analysis.

5.3 Results

5.3.1 Demographic and Clinical Characteristics

A total of 62 outpatient (n=49) and healthy control (n=13) women participated in the study and completed the MRI scan in the postpartum period. Within the outpatient sample, 13 met DSM-IV criteria for OCD, with the remainder (n=36) representing mothers who had a current or past history of any anxiety and/or depressive disorder (CPAD). Within the OCD group, 77% (n=10) had a comorbid diagnosis, with Generalized Anxiety Disorder being the most common. Age when OCS symptoms first emerged ranged from 7 to 29 years of age (mean ± SD=14.61 ± 6.12) in the OCD group.

Demographic and clinical characteristics according to diagnostic group are summarized in Table 1. The participants were aged 20 to 40 years and completed the postpartum visit between 11 to 40 weeks postpartum. Demographics were well-matched across the three groups, with the exception that HC mothers were younger than CPAD mothers ($F_{2,59} = 3.54$, adjusted p=0.03). When examining the postpartum clinical data, women with OCD were more likely to be taking psychotropic medications and had significantly higher severity scores on the POCS, Y-BOCS, STAI state and trait, and EPDS clinical scales, as well as greater exposure to childhood maltreatment, specifically on the emotional abuse subscale of the CTQ (all adjusted $p<0.02$), when compared to the HC group. When compared to the CPAD group, women with OCD scored higher scores on POCS, Y-BOCS, STAI-T, and EPDS (all adjusted $p<0.005$). The only statistical differences noted between the CPAD and HC group was on the STAI state and trait subscales (adjusted $p<0.001$), with greater anxiety measures reported in the CPAD group.

Additionally, OCD mothers reported worse sleep quality as assessed on the PSQI as compared to the other groups ($F_{2,59}$ = 8.73, adjusted p<0.005).

Change in clinical severity scores across the behavioural measures from pregnancy to postpartum for each group is depicted in Table 2. Women in the OCD group experienced a decrease in severity on the POCS total score (t=2.23, p=0.045) and EPDS total (t=3.22, p=0.005) across the perinatal period. In the CPAD group, women experienced a decrease in the EPDS total (t=3.76, p=0.0006), whereas no significant changes were observed for the HC group.

5.3.2 Cortical Surface-Based Analysis

5.3.2.1 By Diagnosis

When comparing the mothers with OCD (n=13) to the HC (n=13) mothers, there were no significant differences noted in either CT or CSA measures across the whole brain. Furthermore, when comparing women with current or past history of an anxiety disorder (n=36) or women with current or past history of major depressive disorders (n=43) to women in the HC group, no significant differences in any cortical measure was observed.

5.3.2.2 Whole Group Analysis

When correlating symptom severity with measures of CT or CSA across the entire sample irrespective of diagnosis (n=62), there were no significant associations found for any obsessive-compulsive (POCS or Y-BOCS), anxiety (STAI-S or -T) or depressive symptoms (EPDS). Additionally, there were no associations with childhood maltreatment (CTQ) or sleep quality (PSQI) with any cortical measure.

When examining change in scores from pregnancy to postpartum in the entire sample, there were no associations found with measures of CT. On the other hand, measures of CSA was found to be significantly correlated with change in scores on several clinical scales. Greater CSA was associated with greater symptom worsening on the following questionnaires: POCS total severity (ΔPOCS) in the left precuneus and fusiform, Y-BOCS total severity (ΔY-BOCS) in the right lateral occipital region, and trait anxiety severity (ΔSTAI-T) in the left precuneus and right superior parietal region (see Table 3). There were no associations with CSA and symptom change in the other anxiety or depression clinical scales.

5.3.2.3 OCD Subgroup Analysis

Within the sample of mothers with OCD, there were no significant associations of any clinical measures with CT estimates. However, several significant positive correlations were observed for CSA measures. Specifically, when looking at postpartum-related OCS, greater CSA was associated with total POCS severity score in the left inferior temporal, superior parietal and precentral regions and the right precuneus (see Table 4). When examining general OCS, greater CSA was positively associated with the Y-BOCS in the left fusiform and superior temporal areas, and right superior frontal region. Measures of STAI-T were positively associated with CSA estimates in the right lateral orbitofrontal cortex (OFC). No associations were found with CSA and STAI state, EPDS, CTQ or PSQI scores.

When examining change in score across the perinatal period, no associations were found for CT, but a greater increased change in Y-BOCS symptom severity scores (ΔY-

BOCS) from pregnancy to postpartum was associated with greater CSA in the left lingual and rostral middle frontal areas, and the right lateral occipital. Furthermore, increased change in trait anxiety scores (Δ STAI-T) in the postpartum period was associated with greater CSA in the left pericalcarine and right lingual and rostral middle frontal regions. There were no associations observed for CSA and changes in the other clinical measures across the perinatal period.

5.3.2.4 Current Anxiety Subgroup Analysis

When examining the relationship between CT and CSA estimates with clinical scales in women with current anxiety (n=20), which included several (n=9) women from the OCD group, no significant associations were observed with any clinical, childhood or sleep measure.

5.3.2.5 Psychotropic Medication Use

In the whole-brain analysis, there were no group differences observed when comparing cortical measures between mothers taking psychotropic medication and unmedicated mothers.

5.4 Discussion

To our knowledge, this is the first study assessing cortical measures in a postpartum sample related to OCD and perinatal OCS. Our exploratory investigation using whole brain analyses revealed no significant differences in CT or CSA between diagnostic groups. Furthermore, when looking at symptom severity across the entire sample irrespective of diagnosis, there were no associations of CT or CSA measures related to postpartum obsessive-compulsive, depressive or anxiety symptom severity, as

well as sleep quality or exposure to childhood maltreatment. However, we found that greater CSA of areas within the ventral temporal, lateral occipital, superior and posterior parietal regions associated were associated with the greater worsening of clinical symptoms from pregnancy to postpartum. Specifically, greater CSA of the left precuneus and fusiform was positively associated with perinatal-related OCS worsening, while greater CSA of the right lateral occipital region was associated with worsened OCS that are not specific to the perinatal period. There were no associations with change in depressive symptoms, but greater CSA of the left precuneus and right superior parietal region was associated with worse trait anxiety. Comparisons of mothers taking psychotropic medication to those that were unmedicated revealed no differences in CT or CSA measures across the whole brain.

Analyses completed on the subsample of women diagnosed with OCD during pregnancy revealed several significant findings related to clinical severity. In mothers with OCD, symptom severity according to POCS, Y-BOCS and STAI-T clinical scales was positively associated with gray matter surface area. Particularly, greater CSA in the following regions was associated with the following symptoms: (1) total scores on the POCS were linked to temporal, parietal and frontal regions, (2) total scores were linked to the Y-BOCS in temporal and frontal areas, and (3) STAI-T scores were linked to the right lateral OFC. Furthermore, greater worsening of scores from pregnancy to postpartum on the Y-BOCS and STAI-T were the only clinical scales associated with greater CSA, in occipital and frontal regions. No significant associations were observed for gray matter thickness measures in any analyses within this sample.

Given that OCD patients experience a high prevalence of comorbid anxiety, we ran similar GLM analyses on the sample of mothers with a current diagnosis of an anxiety disorder, yet results revealed no relationships between any cortical and behavioural measures in this subgroup. These findings imply that the significant associations observed in the OCD subgroup are likely not a consequence of comorbid anxiety and may be specific to perinatal OCD. Notably, trait anxiety in the OCD group, but not the current anxiety group, was associated with surface area measures in the right lateral OFC, suggesting that mothers with OCD may be more vulnerable to cortical alterations in the postpartum period related to their tendency to be anxious. We were unable to run analyses examining mothers with a current depressive disorder due to the limited number in our sample (n=2).

We did not find any significant associations of cortical measures with depressive symptoms, sleep quality or exposure to childhood maltreatment in the whole group or OCD subgroup. The literature provides some supporting evidence that early adverse experiences (L. F. Fontenelle et al., 2011; Saunders et al., 1992) and sleep disturbance (Sharma, 2019) may increase risk for OCD in females. Furthermore, major depression is a frequently comorbid condition in OCD samples and is a predictor of poor quality of life outcomes in OCD samples (Karadağ et al., 2006; Masellis, Rector, & Richter, 2003). It is not yet clear whether these comorbid behavioural symptoms and early life exposures play an important role in the etiology of perinatal OCD, warranting investigation in subsequent studies.

5.4.1 Cortical Morphometry in OCD

As this is the first study exploring cortical structure of postpartum women in relation to OCS, we can only compare our findings to those of the general OCD population. Several of the cortical areas that were found linked to clinical symptom severity in our postpartum sample are regions that have previously been implicated in OCD samples. In particular, one recent study conducted using the same surface-based approach identified differences in the surface area of the rostral middle frontal, superior parietal, precuneus, and lateral occipital regions associated with OCD (Rus et al., 2017). This overlap provides promising evidence that these regions are implicated in the pathophysiology of the disorder; however, their results depicted decreased surface area measures, whereas our results reflected increased surface area that was not associated with diagnosis, but rather clinical severity. Moreover, additional investigations comparing CSA of OCD to healthy controls have reported decreases in surface area (Boedhoe et al., 2018; Venkatasubramanian et al., 2012) or no difference (Fan et al., 2013). It should be noted that investigations into OCD using the surface-based analysis approach have expanded in the last decade but remain rather scarce.

Our inability to find any notable differences of cortical thickness measures in our perinatal sample are consistent with a few studies conducted on the general OCD population (S. G. Kim, Jung, Kim, Jang, & Kwon, 2013; Rus et al., 2017), but are in disagreement with the remaining literature that has either reported cortical thinning (Boedhoe et al., 2018; Fullana et al., 2014; Kühn et al., 2013; W. Liu et al., 2019; Peng, Xu, et al., 2014; Shin et al., 2007; Venkatasubramanian et al., 2012; C. Zhou et al., 2018),

or increases in thickness of frontal, temporal, parietal and occipital regions associated with OCD (Fan et al., 2013; Narayan et al., 2008; Wagner et al., 2019).

These inconsistencies in cortical markers associated with OCD across reports is likely due to differences in the clinical characteristics of the samples. Considering that our sample was entirely comprised of postpartum mothers, our findings must be interpreted in the context of perinatal OCD and are likely not representative of the general OCD population.

It is important to note that thickness and surface area reflect distinct cortical characteristics, with evidence from ontogenetic studies suggesting that CSA is influenced by the number and spacing of neuronal columns, whereas CT is influenced by the number of cells within a column (Casanova & Tillquist, 2008; Rakic, 1988). Additionally, a relationship between CSA and the underlying myelin white matter was recently shown, which was not related to CT (Cafiero, Brauer, Anwander, & Friederici, 2019). Therefore, it is possible that changes in surface area may be a reflection of altered cortical and functional connections between regions associated with psychopathology.

5.4.2 Relating Structural Alterations to Functional Implications

Our results demonstrated widespread cortical alterations associated with perinatal obsessive-compulsive and anxiety symptoms within the entire postpartum sample. Only a handful of prior studies found a relationship between cortical measures and OCD clinical severity (Fan et al., 2013; Kühn et al., 2013; Venkatasubramanian et al., 2012; C. Zhou et al., 2018), but reproducibility of these findings remains a serious problem. In our sample, greater worsening of these symptoms from pregnancy to postpartum was associated with

changes to the CSA of parietal, temporal and occipital regions. In particular, the surface area of the left precuneus was positively correlated with symptom exacerbation on both the POCS and STAI-T clinical scales.

The precuneus, located in the medial portion of the posterior parietal lobe, has extensive cortico-cortical connections with the dorsolateral prefrontal cortex, premotor cortex and the anterior cingulate cortex and is involved in several motor and cognitive functions, such as spatial mapping and guided motor responses, episodic memory retrieval, mental imagery, self-awareness and consciousness (Cavanna & Trimble, 2006; S. Zhang & Li, 2012). In typical postpartum-related brain changes, the precuneus was found to undergo structural changes, albeit in mixed directions over time (P. Kim, Dufford, & Tribble, 2018; K. Zhang, Wang, Zhang, Du, & Chen, 2020).

Although the precuneus is infrequently discussed in the context of neurobiological models of OCD, decreases in surface area, thickness and volume have been consistently reported in OCD patients (Fouche et al., 2017; Rus et al., 2017; Soriano-Mas et al., 2007). When considering OCD symptomatology, one study found a positive correlation between harm/checking OCS and left precuneus volume (van den Heuvel et al., 2009), suggesting that the precuneus may have a symptom-specific dependent relationship. This is further evidenced by symptom provocation studies, where precuneus activation has been reported in OCD samples (Rotge et al., 2008).

The precuneus is part of the default mode network (DMN), which is the neural network most active during resting states (Utevsky, Smith, & Huettel, 2014). Evidence from functional connectivity studies demonstrates altered relationships between the DMN

and the fronto-parietal network (FPN), involved in cognitive attention and control (S. Marek & Dosenbach, 2018), in OCD patients that was coupled with hyper-connectivity of the posterior cingulate cortex/precuneus with the anterior insula seed of the FPN (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). Altered functional connectivity of the precuneus may help explain why individuals with OCD experience difficulties in disengaging from internally driven thoughts when trying to complete tasks that require providing attention to the external environmental (Stern et al., 2012). In the case of perinatal OCD, mothers experiencing intrusive thoughts likely experience added challenges and greater anxiety related to tending to the needs of their newborn. Our structural findings suggest that the precuneus may be related to symptom exacerbation across the perinatal period and investigations into its functional connectivity is needed to better understand its role in infant-specific OCS and perinatal OCD.

The left fusiform was another cortical structure associated with change in perinatal-related OCS in our whole sample. Functionally, the fusiform is involved in perception and processing of visual information, such as the recognition of faces, colour, objects, bodies and words (Weiner & Zilles, 2016). Within the OCD literature, enhanced functional connectivity of the fusiform has been shown during task-related paradigms, such as an emotional face-processing task and in symptom provocation studies (Cardoner et al., 2011; Gonçalves et al., 2016). In postpartum studies, the fusiform is preferentially activated when viewing photos of their own baby (Swain, Leckman, Mayes, Feldman, & Schultz, 2006) and in response to own infant cries (Laurent & Ablow, 2012). From these studies, the fusiform appears to be related to normative parental response and may be

dysfunctional in OCD, thereby making it a region of interest in mothers with perinatal-related OCS.

Alterations to the right lateral occipital and right superior parietal areas appeared when examining symptom worsening of general OCS and trait anxiety, respectively, in the entire sample. These regions are functionally related to visual and sensory processing, including object and face recognition, spatial orientation and attention (Johns, 2014; Malach et al., 1995; Nagy, Greenlee, & Kovács, 2012). The functional consequence of these cortical alterations in the perinatal period are not clear but suggest that parieto-occipital areas are involved in OCS and trait anxiety symptom exacerbation.

When looking at associations with clinical severity scores in the OCD group, postpartum mothers showed greater surface area of extensive regions in the frontal, parietal, temporal and occipital cortex associated with clinical severity on the POCS, Y-BOCS and STAI-T. Specifically, the left inferior temporal, superior parietal, and precentral, and right precuneus regions were associated with the severity of unique OCS directed towards the well-being of the baby. Overall, these regions are involved in higher order cognitive functioning, visual processing, attention, task-switching and inhibitory control (Cavanna & Trimble, 2006; Conway, 2018; C. S. R. Li, Huang, Constable, & Sinha, 2006; Vandenberghe, Molenberghs, & Gillebert, 2012).

As part of the ventral visual stream, the inferior temporal area is involved in the visual processing of objects, faces and scenes (i.e. a collection of objects or shapes that contain a spatial layout)(Conway, 2018). Investigations into the functional connectivity of the inferior temporal region in OCD revealed decreased local connectivity when at rest, as

compared to healthy controls (Yang et al., 2019). In a sample of healthy first-time mothers, the inferior temporal gyri and several other cortical areas showed greater activity when viewing images of their own baby's face, as compared to unknown infants (Strathearn, Li, Fonagy, & Montague, 2008). Although its relationship to perinatal OCD is not yet clear, the inferior temporal area appears to play a role in responding to one's own infant and may be dysregulated in OCD.

The superior parietal cortex is important for several neuropsychological functions, including visuospatial attention and orientation, task switching, planning and response inhibition (Vandenberghe et al., 2012), many of which are impaired in OCD patients (Abramovitch, Dar, Schweiger, & Hermesh, 2011; Gruner & Pittenger, 2017; Penadés et al., 2007). Structural and functional abnormalities within the parietal region have been reported in OCD samples (Mataix-Cols et al., 2004; Peng, Xu, et al., 2014; Valente et al., 2005; Yang et al., 2019), in addition to disrupted white matter integrity (Peng, Shi, et al., 2014). Alterations to the parietal cortex may help to explain the cognitive inflexibility associated with OCD. During the postpartum period, mothers are required to adapt and respond to changing infant cues, and in the context of perinatal OCD, they may experience a greater difficulty dismissing internal fears and inhibiting repetitive behaviours. Therefore, changes to the cortical structure of the superior parietal cortex may help to explain cognitive dysfunctions experienced by OCD mothers.

The precentral gyrus is involved with inhibitory control processes and is part of the sensorimotor network, which was found to be associated with less global functional connectivity in OCD patients while at rest (Cui et al., 2020). Furthermore, heightened

activity of this region in OCD samples has been reported when participating in a variation on the go/no-go task (Morein-Zamir et al., 2016). Alterations to the sensorimotor network may help explain why OCD patients have difficulty suppressing intrusive obsessions or repetitive behaviours. In the context of maternal responses, this brain region shows heightened activity when healthy mothers view their own infant as compared to other infants (Noriuchi, Kikuchi, & Senoo, 2008). Together, there is evidence to support that the structural changes to the precentral gyrus may be involved with impaired inhibitory responses and maternal behaviours in perinatal OCD.

Change in symptom severity on the Y-BOCS and STAI-T across the perinatal period in mothers with OCD was found to be positively correlated with surface area of frontal, occipito-temporal and temporal regions. Notably, CSA of the lingual and rostral middle frontal regions were found to be associated with symptom worsening for both general OCS and trait anxiety. The lingual gyrus is functionally associated with visual imagery and processing emotional visual stimuli (Kosslyn, Ganis, & Thompson, 2001; Lang et al., 1998). In OCD samples, the lingual gyrus has been found to have decreased resting-state functional connectivity with the postcentral gyrus and other subcortical limbic regions (amygdala, hippocampus) (Göttlich, Krämer, Kordon, Hohagen, & Zurowski, 2014; P. S. Moreira et al., 2017), and reduced activity during a symptom-provocation paradigm (Mataix-Cols et al., 2004). These functional studies suggest that the lingual gyrus may be implicated in OCD, and its role in processing emotional visual stimuli may therefore have implications for the perinatal period.

The rostral middle frontal area, a subdivision of the dorsolateral prefrontal cortex (DLPFC), is another brain region tied to emotional perception and regulation (Phillips, Drevets, Rauch, & Lane, 2003), as well as higher-order executive functioning processes, such as working memory, attention and planning (E. K. Miller & Cohen, 2001). Hyperactivity of this frontal region in OCD samples has been observed in several studies at rest (Millet et al., 2013) and during neuropsychological testing (Nakao et al., 2009). Furthermore, one investigation found that gray matter indices of the rostral middle frontal region were associated with clinical scores in OCD patients (Venkatasubramanian et al., 2012), but differences in methodology and the heterogeneity within OCD samples (including symptom type, comorbid diagnoses, and medication use) make comparisons across studies difficult.

5.4.3 Brain Plasticity Associated with Motherhood and Sex Hormones

Structural and functional changes in the maternal brain across the perinatal period are thought to be influenced by endocrine and environmental factors. These changes likely prepare the mother for their new role as a parent that requires them to care for and focus on the needs of their baby. Several reports have described unique brain plasticity associated with reproductive events, where extensive gray matter reductions have been observed across pregnancy in first-time mothers (Hoekzema et al., 2017), with mothers exhibiting an overall decrease in brain size during pregnancy that was later found to be reversed by 6 months postpartum (Oatridge et al., 2002). Of the few studies assessing gray matter changes in humans across the perinatal period, results generally show reductions in gray matter volume during pregnancy, followed by increases in gray matter

volume and thickness within the postpartum period (Barba-Müller, Craddock, Carmona, & Hoekzema, 2019; P. Kim et al., 2018, 2010). Therefore, the reproductive events of pregnancy and postpartum appear to elicit different effects on cortical structure and it may be the case that perinatal-related neural plasticity contributes to increased vulnerability of psychopathologies in mothers.

The exact mechanisms that underlie CSA expansion in motherhood and across the lifespan are not understood, but in the context of OCD, it is likely tied to aberrant functional activity of similar brain regions. It is currently unclear whether cortical alterations play a causal role in influencing functional activity or are a consequence of dysfunction within the CSTC and FPN. Regardless of the directionality, neural changes during the transition to motherhood in women with and without OCD appears to constitute a period for symptom emergence and exacerbation.

A maternal neural network consisting of the precuneus, medial frontal, anterior cingulate, and OFC was identified from a multitude of studies assessing maternal responses to infant cues (Gholampour, Riem, & van den Heuvel, 2020). Considering that unique OCS emerge that are focused on the infant in postpartum OCD, it is unsurprising then that the same regions involved in maternal behaviours are the same ones affected in perinatal OCD. Based on the cognitive behavioural model of OCD during the perinatal period proposed by Fairbrother and Abramowitz (Fairbrother & Abramowitz, 2007), parents experience a shift in their sense of responsibility and how threats are perceived. This cognitive shift, accompanied by dysregulated changes to the maternal neural network, can lead mothers to overestimate probability of harm associated with the

misinterpretation of intrusive thoughts. Although these neural changes appear to promote maternal behaviours and positive interactions with their infants that are imperative for child development, it is not yet clear how it becomes dysfunctional in the case of postpartum OCD.

5.4.4 Limitations

There are several limitations that must be noted, with the main limitation being the small sample size. Despite employing recruitment strategies that maximized access to a perinatal population, there were challenges finding women that met OCD criteria and with having participants return for the MRI scan in the postpartum period. Furthermore, our sample was primarily comprised of out-patient mothers seeking and receiving treatment for a combination of obsessive-compulsive, anxiety and depressive symptoms. As a result, comorbidity and medication use was not an exclusion and we were unable to control for these confounding effects owing to the small sample size. When comparing mothers taking psychotropic medication to those without, we found no differences in CSA or CT measures, but a prior mega-analysis found alterations in cortical thickness associated with medication status in adult OCD samples (Boedhoe et al., 2018), providing further evidence that psychotropic medications influence brain plasticity. Additionally, the severity of symptoms experienced in our clinical sample were largely considered in the mild to moderate range and would not be reflective of mothers with clinically severe OCD. Given these characteristics and size of our sample, we were underpowered to detect any cortical differences in thickness or surface area according to diagnosis.

Due to the cross-sectional nature of the neuroimaging component of this study, it cannot be determined whether clinical symptoms precede or follows the cortical structure alterations we observed. Since measures of CSA are susceptible to change across the lifespan (Raznahan et al., 2011; Storsve et al., 2014), it can be speculated that symptom severity, as well as onset and duration of OCD, can affect the cortical parameters measured in this study. Despite there being no proven risks to pregnant women or their developing fetus, we restricted MRI scans to the postpartum period because of ethical considerations. Future longitudinal investigations examining neural correlates prior to and following OCS exacerbation, especially as it relates to the perinatal period, are imperative to better capture changes in cortical structure associated with psychopathology.

5.5 Conclusions

The present study is the first to examine the cortical morphology associated with perinatal-related OCS severity and OCD in mothers. Our whole-brain explorations revealed that gray matter surface area appears to be altered in relation to greater OCS worsening across the perinatal period, and also with other dimensions of clinical severity in postpartum mothers with OCD. Regions in the frontal, parietal, temporal and occipital lobe were affected and may be related to functional impairments in attention, cognitive functioning, emotion regulation, response inhibition, visuospatial perception, and the processing of sounds and visual stimuli. Taken together, these findings suggest that widespread neural changes during the postpartum period may predispose mothers for risk of psychopathology. This novel contribution highlights a need for replication in larger samples and to assess the functional correlates of postpartum OCD. Furthermore, future

work employing a longitudinal design across the perinatal period are needed in order to determine the degree of cortical plasticity during this transitional period and whether cortical measures act as a risk marker for the development or worsening of OCS in women.

5.6 Acknowledgements

We would like to thank Calan Savoy and Anastasiya Slyepchenko for their assistance in participant recruitment. A special thank you to JeeSu Suh for assisting with the cortical analysis.

Table 1: Demographics and behavioural characteristics for postpartum women (n=62) according to diagnosis group

	Obsessive-Compulsive Disorder (OCD) (n=13)	**Current or Past Anxiety and/or Depression (CPAD) (n=36)**	**Healthy Controls (HC) (n=13)**	**p-value**
Mean ± SD				
Age	31.46 ± 4.07	31.5 ± 3.51	28.38 ± 4.03	**0.033** [a] (CPAD and HC)
Education (years)	17.15 ± 2.94	16.92 ± 3.28	17.92 ± 2.72	0.48 [b]
Weeks Postpartum	20.23 ± 8.73	19.17 ± 7.26	15.69 ± 5.22	0.2 [b]
Parity	1.77 ± 0.93	1.53 ± 0.65	1.15 ± 0.38	0.084 [b]
n (%)				
Family History of OCD	0	2 (5.6%)	0	1 [c]
Family History of Any Psychiatric Diagnosis	10 (76.9%)	25 (69.4%)	5 (38.5%)	0.094 [c]
Smoking Status (yes)	2 (15.4%)	2 (5.6%)	0	0.37 [c]
Breastfeeding Status (yes)	7 (53.8%)	30 (83.3%)	9 (69.2%)	0.11 [c]
Resumed Menstruation (yes)	7 (53.8%)	8 (22.2%)	4 (30.8%)	0.14 [c]
Psychotropic medication use (yes)	9 (69.2%)	11 (30.6%)	1 (7.7%)	**0.011** [c] (OCD and HC)
Psychotropic Medication				
Anticonvulsant	1 (7.7%)	0	0	0.42 [c]
Atypical Antipsychotic	0	1 (2.8%)	0	1 [c]
SNRI	1 (7.7%)	2 (5.6%)	0	1 [c]
SSRI	3 (23.1%)	7 (19.4%)	1 (7.7%)	0.73 [c]
Combination of 2 or more	4 (30.8%)	1 (2.8%)	0	**0.043** [c] (OCD and CPAD)
Marital Status				
Married	8 (61.5%)	30 (83.3%)	11 (84.6%)	0.26 [c]
Common-law	4 (30.8%)	4 (11.1%)	1 (7.7%)	0.21 [c]
Single	1 (7.7%)	2 (5.6%)	1 (7.7%)	1 [c]

	Obsessive-Compulsive Disorder (OCD) (n=13)	**Current or Past Anxiety and/or Depression (CPAD) (n=36)**	**Healthy Controls (HC) (n=13)**	**p-value**
n (%)				
Employment				
Full-time	9 (69.2%)	19 (52.8%)	5 (38.5%)	0.3 [c]
Part-time	1 (7.7%)	4 (11.1%)	5 (38.5%)	0.058 [c]
None	3 (23.1%)	13 (36.1%)	3 (23.1%)	0.6 [c]
Mean ± SD				
CTQ				
Total	43.31 ± 14.24	36.75 ± 9.02	31.85 ± 7.8	**0.018** [a,d] (OCD and HC)
Emotional Abuse	13.46 ± 6.32	8.67 ± 3.06	7.38 ± 2.93	**0.007** [b] (OCD and HC)
Physical Abuse	6.38 ± 2.33	6.53 ± 2.14	5.23 ± 0.6	0.075 [b]
Sexual Abuse	5 ± 0	6.14 ± 3.75	6.23 ± 4.44	0.26 [b]
Emotional Neglect	11.15 ± 5.13	9.11 ± 3.09	7.46 ± 3.23	0.052 [b]
Physical Neglect	7.31 ± 2.32	6.31 ± 1.95	5.54 ± 1.13	0.065 [b]
POCS				
Total	17.08 ± 5.81	8.03 ± 7.33	3.62 ± 5.36	**<0.001** [b] (OCD and HC; OCD and CPAD)
Y-BOCS				
Total	16.92 ± 4.86	6.03 ± 6.25	2.85 ± 3.31	**<0.001** [b] (OCD and HC; OCD and CPAD)
STAI				
State Anxiety Subscale	46 ± 13.16	35.56 ± 10.87	25.85 ± 8.17	**<0.001** [b] (OCD and HC; CPAD and HC)
Trait Anxiety Subscale	53 ± 10.5	40.03 ± 11.95	28.15 ± 8.73	**<0.001** [b] (OCD and HC; OCD and CPAD; CPAD and HC)

	Obsessive-Compulsive Disorder (OCD) (n=13)	Current or Past Anxiety and/or Depression (CPAD) (n=36)	Healthy Controls (HC) (n=13)	p-value
EPDS				
Total	12.88 ± 4.28	6.58 ± 3.92	3.77 ± 3.75	**<0.001** [a,d] (OCD and HC; OCD and CPAD)
PSQI				
Total	11.46 ± 4.39	7.03 ± 3.58	5.23 ± 3.88	**<0.005** [a,d] (OCD and HC; OCD and CPAD)

Notes: CTQ = Childhood Trauma Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; POCS = Perinatal Obsessive-Compulsive Scale; PSQI = Pittsburgh Sleep Quality Index; STAI = State-Trait Anxiety Inventory; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

[a] One-way ANOVA and post-hoc Tukey HSD test (adjusted p-values)

[b] Kruskal-Wallis test and post-hoc multiple comparison test (adjusted p-values)

[c] Fisher's exact test with Bonferroni correction (adjusted p-values)

[d] Box-Cox transformed data

Table 2: Behavioural characteristics in the entire sample (n=62) across the perinatal period according to diagnosis group.

	Pregnant	Postpartum	p-value
Obsessive-Compulsive Disorder (n=13)			
POCS			
Total	20.31 ± 7.13	17.08 ± 5.81	**0.045** [a]
Y-BOCS			
Total	18.77 ± 4.55	16.92 ± 4.86	0.21 [a]
STAI			
State Anxiety Subscale	49.62 ± 12.13	46 ± 13.16	0.38 [a]
Trait Anxiety Subscale	56.85 ± 9	53 ± 10.5	0.21 [a]
EPDS			
Total	15.54 ± 4.01	12.88 ± 4.28	**0.005** [a]
Current or Past Anxiety and/or Depressive Disorder (n=36)			
POCS			
Total	7.11 ± 6.17	8.03 ± 7.33	0.26 [b]
Y-BOCS			
Total	5.69 ± 5.68	6.03 ± 6.25	0.72 [b]
STAI			
State Anxiety Subscale	37.19 ± 11.02	35.56 ± 10.87	0.21 [a,c]
Trait Anxiety Subscale	42.28 ± 11.94	40.03 ± 11.95	0.09 [a]
EPDS			
Total	8.81 ± 4.92	6.58 ± 3.92	**<0.001** [a]
Healthy controls (n=13)			
POCS			
Total	2.69 ± 4.5	3.62 ± 5.36	0.15 [b]
Y-BOCS			
Total	1.77 ± 3.92	2.85 ± 3.31	0.26 [b]
STAI			
State Anxiety Subscale	25.31 ± 5.81	25.85 ± 8.17	1 [b]
Trait Anxiety Subscale	27.69 ± 6.79	28.15 ± 8.73	0.91 [b]
EPDS			
Total	3.39 ± 3.95	3.77 ± 3.75	0.60 [b]

Notes: EPDS = Edinburgh Postnatal Depression Scale; POCS = Perinatal Obsessive-Compulsive Scale; STAI = State-Trait Anxiety Inventory; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

[a] Paired sample t-test

[b] Wilcoxon signed-rank test (paired samples)

[c] Reciprocal (1/X) transformed data

Table 3: Cortical regions associated with greater cortical surface area according to increased change in postpartum severity scores across the entire sample.

Clinical Scale	Cluster	Max	Annotation	Size (mm^2)	Tal(X)	Tal(Y)	Tal(Z)	Cluster-wise p-value (CWP)
Δ POCS	Left Hemisphere							
		5.52	Precuneus	1925.52	-8.9	-46.7	64.1	0.0001
		3.87	Fusiform	1247.23	-33.5	-66.5	-9.5	0.0011
Δ YBOCS	Right Hemisphere							
		2.97	Lateral Occipital	928.67	31.6	-83.5	16.4	0.0087
Δ STAI trait	Left Hemisphere							
		4.95	Precuneus	1183.2	-16.7	-41.1	51.7	0.0015
	Right Hemisphere							
		4.25	Superior Parietal	967.99	8.1	-83.1	30.9	0.0072

Notes: Max indicates the maximum -log(p) among the vertices in the cluster. Annotation is the location according to the Desikan-Killiany cortical atlas. Tal(XYZ) refers to the Talairach (MNI305) coordinate of the peak vertex. Change in scores were obtained by subtracting pregnancy from postpartum scores.

Table 4: Cortical regions associated with greater cortical surface area according to postpartum symptom severity scores within the OCD group.

Clinical Scale	Cluster	Max	Annotation	Size (mm^2)	Tal(X)	Tal(Y)	Tal(Z)	Cluster-wise p-value (CWP)
POCS	Left Hemisphere							
		4.19	Inferior Temporal	3550.12	-44.5	-45.7	-8.8	0.0001
		4.11	Superior Parietal	1957.86	-28.5	-57.0	42.3	0.0001
		4.76	Precentral	747.52	-55.4	4.8	9.6	0.0065
	Right Hemisphere							
		5.18	Precuneus	1500.92	17.1	-53.7	12.5	0.0001
Y-BOCS	Left Hemisphere							
		4.27	Fusiform	1556.76	-33.5	-74.6	-6.6	0.0001
		2.91	Superior Temporal	778.92	-50.9	-17.3	-6.4	0.0076
	Right Hemisphere							
		3.44	Superior Frontal	1573.31	7.8	45.4	21.5	0.0001
STAI trait	Right Hemisphere							
		3.05	Lateral Orbitofrontal	993.53	15.6	48.3	-15.9	0.0023

Notes: Max indicates the maximum -log(p) among the vertices in the cluster. Annotation is the location according to the Desikan-Killiany cortical atlas. Tal(XYZ) refers to the Talairach (MNI305) coordinate of the peak vertex. Change in scores were obtained by subtracting pregnancy from postpartum scores.

Table 5: Cortical regions associated with greater cortical surface area according to increased change in postpartum severity scores within the OCD subsample.

Clinical Scale	Cluster	Max	Annotation	Size (mm^2)	Tal(X)	Tal(Y)	Tal(Z)	Cluster-wise p-value (CWP)
Δ Y-BOCS	Left Hemisphere							
		6.12	Lingual	3238.82	-7.1	-77.0	6.7	0.0001
		4.57	Rostral Middle Frontal	1055.35	-35.2	51.8	-3.2	0.0011
	Right Hemisphere							
		3.33	Lateral Occipital	2342.50	13.9	-92.7	-2.8	0.0001
Δ STAI trait	Left Hemisphere							
		3.83	Pericalcarine	783.56	-13.6	-71.3	6.0	0.0076
	Right Hemisphere							
		3.56	Lingual	1164.62	16.0	-48.7	-1.2	0.0008
		3.71	Rostral Middle Frontal	1134.60	22.1	53.6	-13.7	0.001

Notes: Max indicates the maximum -log(p) among the vertices in the cluster. Annotation is the location according to the Desikan-Killiany cortical atlas. Tal(XYZ) refers to the Talairach (MNI305) coordinate of the peak vertex. Change in scores were obtained by subtracting pregnancy from postpartum scores.

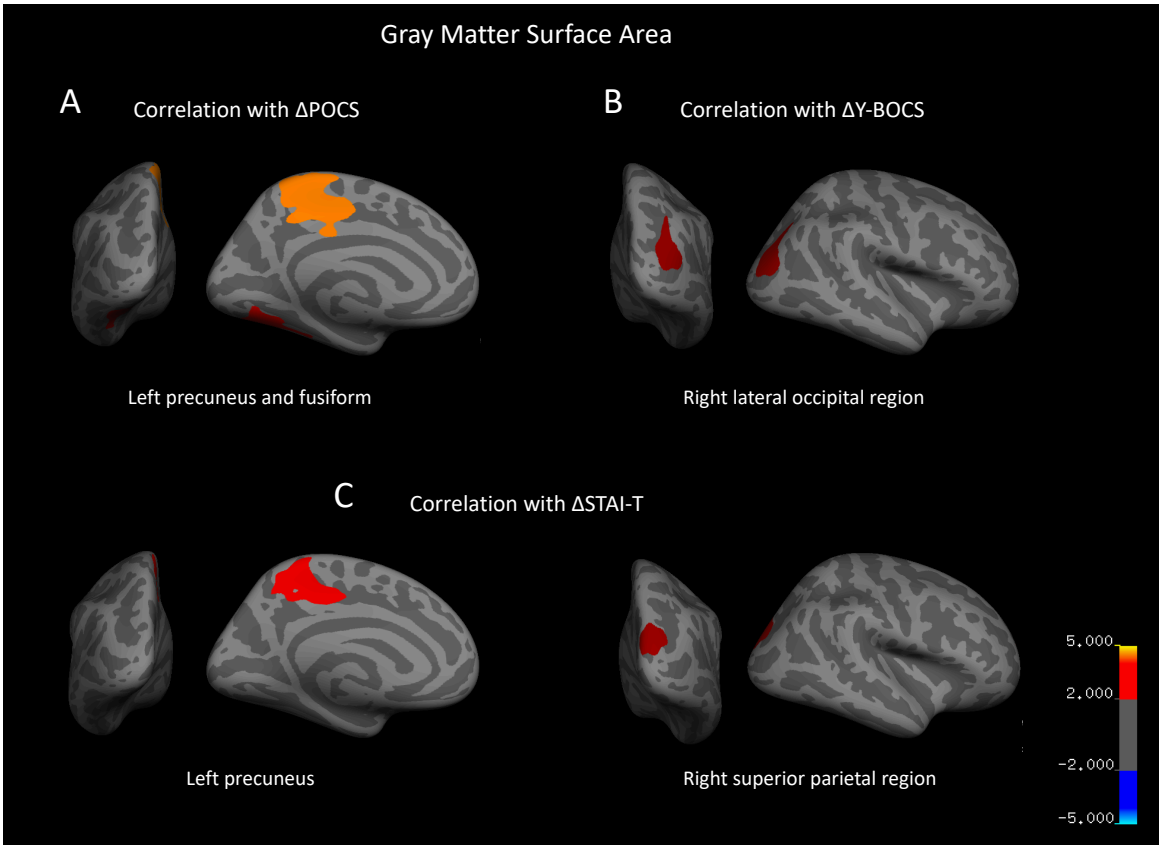


Figure 1. Surface area of cortical regions that were positively correlated with worsening of symptoms from pregnancy to postpartum in the entire sample (n=62). (**A**) Significant clusters in the left precuneus and fusiform were associated with change in scores on the Perinatal Obsessive-Compulsive Scale (ΔPOCS) and are displayed from posterior and medial views. (**B**) Significant cluster in the right lateral occipital region was associated with change in scores on the Yale-Brown Obsessive-Compulsive Scale (ΔY-BOCS) and is displayed from posterior and lateral views. (**C**) Significant clusters in the left precuneus and right superior parietal region were associated with change in scores on the State-Trait Anxiety Inventory measuring trait anxiety (ΔSTAI-T) and are displayed in left posterior and medial, and right posterior and lateral views. Scale bar shows max -log(p) values, following corrections for multiple comparisons using Monte Carlo simulations ($p<0.01$).

5.7 Appendix

Appendix Table 1: Behavioural characteristics for entire pregnant sample (n=107) according to completer/drop-out status.

	Completers (n=62)	**Drop-out (n=45)**	**p-value ***
Mean ± SD			
CTQ			
Total	37.1 ± 10.62	34.09 ± 12.21	**0.024**
Emotional Abuse	9.4 ± 4.43	7.87 ± 4.32	**0.0051**
Physical Abuse	6.22 ± 2.01	6.13 ± 3.22	0.29
Sexual Abuse	5.92 ± 3.49	5.82 ± 3.03	0.97
Emotional Neglect	9.19 ± 3.76	8.27 ± 3.71	0.10
Physical Neglect	6.35 ± 1.96	6 ± 2.18	0.21
POCS			
Total	8.95 ± 8.58	6.73 ± 7.17	0.18
Y-BOCS			
Total	7.61 ± 7.85	6 ± 7.66	0.27
STAI			
State Anxiety Subscale	37.31 ± 12.97	35.96 ± 11.56	0.66
Trait Anxiety Subscale	42.62 ± 13.89	40.71 ± 13.47	0.60
EPDS			
Total	9.08 ± 6	8.38 ± 6.15	0.46

Notes: CTQ = Childhood Trauma Questionnaire; EPDS = Edinburgh Postnatal Depression Scale; POCS = Perinatal Obsessive-Compulsive Scale; STAI = State-Trait Anxiety Inventory; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

* All p-values obtained from Mann-Whitney U test (non-parametric independent samples)

Chapter 6: Discussion

6.1 Summary of Findings

OCD and obsessive-compulsive symptoms that develop or worsen during the perinatal period can cause significant distress and functional impairment that may negatively influence the mother-infant relationship (Challacombe et al., 2016). While perinatal OCD appears to have a distinct clinical course and unique symptomatology (McGuinness et al., 2011), the risk factors contributing to its presentation are poorly understood. A combination of genetic, neurobiological and environmental influences are likely involved in OCD (Pauls et al., 2014); therefore, investigations using a multiple-perspective approach will allow greater insights into the pathophysiology of perinatal OCD. Advancements in technology have facilitated the study of specific genes or whole genome sequences related to OCD, as well as the neural structure and function of the brain in patients with the disorder through neuroimaging procedures. While the serotonergic neurotransmitter system and brain regions involved in the CSTC circuit have been consistently implicated in OCD through candidate gene association studies and neuroimaging investigations (Pauls et al., 2014), the substrates underlying perinatal OCD have not been explored in prior studies. This exploratory body of work aimed to fill this gap in the literature and explore the possible genetic and cortical correlates of perinatal-specific OCS and OCD, in order to provide a foundation of preliminary work from which future studies can continue to build from.

Chapter 2 presented an overview of the genetics of OCD that described investigations into multiple neurotransmitter system genes and the replication challenges

that exist within the literature. Importantly, prior studies may have failed to consider differences in the clinical presentation of OCD according to sex and age of onset, as part of their investigations. Due to the heterogeneous nature of OCD and its complex pattern of inheritance, results from genetic association studies have been largely inconsistent and no single gene has been reliably associated with the disorder. Pooled data from meta-analyses support the involvement of two serotonergic genes in OCD (Taylor, 2013, 2016), specifically the serotonin transporter gene (*SLC6A4*) and the serotonin receptor 2A gene (*HTR2A*). Furthermore, the 5-HTTLPR polymorphism that exists within *SLC6A4* may be specific to females (Mak et al., 2015), whereas polymorphisms within *HTR2A* remain to be tested according to OCD subtypes based on sex and age of onset. While it has yet to be established whether these genes confer greater susceptibility in a sex-specific manner, *SLC6A4* and *HTR2A* are promising candidates for the study of perinatal OCD.

Based on the findings from the literature review, a systematic and meta-analytic approach was then taken to investigate the association of *HTR2A* polymorphisms with OCD and its subtypes in Chapter 3. Using a the Dersimonian and Laird approach, we found evidence that the A allele of G-1438A (or T of T102C) SNP of *HTR2A* was associated with OCD and remained significant in a female sample and those with early onset. When checking the robustness of our analysis, the results of our meta-analysis no longer reached significance when using a more conservative approach, suggesting that larger samples are needed to confirm the association with the true effect size existing

somewhere between 0 and 1.3. The functional consequence of these polymorphisms were reviewed, however their role in OCD requires clarification and further examination.

In Chapter 4, we explored the possible association of the 5-HTTLPR genotype and allele (L_A vs. S/L_G) frequencies with the presence or absence of clinical perinatal-specific OCS in women followed from pregnancy to postpartum and found no evidence for association of the 5-HTTLPR with perinatal OCS in our sample. The 5-HTTLPR genotype failed to be a significant predictor of symptom severity, and there was no interaction effect or main effect of maternal status (pregnant vs. postpartum) on this relationship. However, having a diagnosis of OCD, as assessed in pregnancy, was associated with increased OCS severity scores as measured on the POCS. These results confirmed that women with pre-existing OCD are more likely to develop unique, infant-related OCS and experience greater disturbance in these symptoms as compared to non-OCD perinatal samples. Due to technical challenges with genotyping *HTR2A*, the G-1438A polymorphism remains to be tested in relation to perinatal OCS. To our knowledge, this is the first study to investigate the genetic contributions of 5-HTTLPR to perinatal-related OCS in a sample entirely comprised of perinatal women.

In Chapter 5, we present a preliminary study assessing the relationship between CT and CSA measures and perinatal psychiatric symptoms, including perinatal-related OCS, mood and anxiety symptoms, in a clinically diverse postpartum sample. There were no significant differences in either cortical measure that discerned each diagnostic group (OCD, CPAD) from healthy controls. Furthermore, we found no correlation between CSA and CT parameters with postpartum symptom severity scores across the entire

postpartum sample irrespective of diagnosis. When examining the change in scores across the perinatal period in the entire sample, greater worsening of obsessive-compulsive and trait anxiety symptoms from pregnancy to postpartum was positively correlated with surface area of the ventral temporal, lateral occipital, superior and posterior parietal regions, while no associations were found with CT measures. Specifically, gray matter surface area of the left precuneus and fusiform were correlated with change in infant-related OCS, CSA of the right lateral occipital was correlated with change in OCS not specific to the perinatal period, and CSA of the left precuneus and right superior parietal region was correlated with change in trait anxiety scores, where change in scores were obtained by subtracting the pregnancy scores from those obtained in the postpartum. Following sample stratification, postpartum mothers diagnosed with OCD in pregnancy exhibited correlations between CSA of brain regions within the frontal, temporal and parietal cortices with obsessive-compulsive and trait anxiety symptom severity scores. Once again, no significant associations were detected for gray matter thickness in the OCD subgroup. Notably, we found no relation between depressive symptom severity, sleep quality or exposure to childhood trauma with any cortical measure.

6.2 Significance and General Discussion

Overall, this body of work attempted to identify and characterize potential genetic risk factors and neurobiological correlates associated with the unique presentation of perinatal OCS and OCD. Despite the increased awareness that women are more susceptible to some psychopathologies during the perinatal period (Vesga-López et al., 2008), OCD in pregnancy or postpartum has received less attention as compared to that of

depression or psychosis. The phenomenology of perinatal OCD is vastly different from OCD that arises outside of this reproductive life event (McGuinness et al., 2011); however, it is not yet clear whether etiologically distinct factors contribute to perinatal OCD as the number of investigations are rather limited. Having a greater understanding of the factors which influence perinatal onset or exacerbation of OCS will provide potential targets for the prevention, identification and treatment of OCD in women.

Through an evolutionary perspective, it can be argued that obsessive and compulsive behaviours were advantageous in helping individuals prepare and avoid future risk (Saad, 2006), but when dysregulated, such as in the case of perinatal OCD, such behaviours cause distress and functional impairment that negatively impacts the mother and her relationships, especially the mother-infant bond (Challacombe et al., 2016). Several models have been proposed to explain the development of OCD, including the cognitive behavioural model and neurobiological model, that can be extended to perinatal OCD.

As mentioned previously, mothers are likely to experience distressing intrusive thoughts regarding their baby (Abramowitz et al., 2003a), but it's not yet clear what predisposes some to developing OCD. Cognitive-behavioural models suggest that these fleeting intrusive thoughts can reach clinical levels if they are interpreted as meaningful due to the content and frequency at which these thoughts occur (Abramowitz et al., 2006; Abramowitz, Schwartz, & Moore, 2003; Salkovskis, 1999). Negative interpretations of these thoughts may lead to exaggerated responsibility beliefs that their actions (or lack thereof) can result in their infant being harmed, thereby reinforcing the obsessions

(Barrett, Wroe, & Challacombe, 2016). However, it is important to note that these obsessions, even when aggressive in nature, do not reflect the actual desires of the individuals and are not predictive of harming behaviour (Fairbrother & Woody, 2008).

The neurobiological model of OCD takes an integrative approach that incorporates genetic risk factors, environmental exposures and abnormal neural structure and circuitry, to explain the emergence of the clinical behaviour (Pauls et al., 2014). Despite the supporting evidence for this model that comes from genetic and neuroimaging studies that have shown that OCD is heritable and has a complex genetic architecture (Mattina & Steiner, 2016) and is associated with altered neural structure and functional connectivity (Saxena & Rauch, 2000), similar approaches had not been conducted in the context of perinatal OCD. Notably, there have been no prior studies that have examined the genetic factors of perinatal OCS, and only one neuroimaging study to date has investigated a postpartum sample of OCD mothers, where stress reactivity was the key outcome measured (Lord et al., 2012). As a result, the findings from this dissertation provide novel examinations into two genetic candidates from the serotonergic system and the cortical morphological profile associated with perinatal-related OCS and OCD.

Chapters 2 and 3 highlight the importance of reporting and investigating genetic associations according to clinical or demographic variables of interest in OCD, such as sex and age of onset. The etiological heterogeneity associated with OCD has made research into the genetic determinants of the disorder challenging. As such, it is imperative that efforts are made to identify more homogeneous subgroups within the disorder. Understanding the clinical trajectories and vulnerabilities of different subgroups

of individuals with OCD may provide important prevention and intervention targets for clinicians, as well as biological and clinical markers, which may be distinct depending on the subgroup of the disorder.

In addition to sex and age of onset, additional variables that should be considered include differences based on symptom type, illness course or duration, comorbid conditions (e.g. OCD with tics) and response to treatment. A growing number of studies are applying a dimensional approach towards investigating the etiological factors of OCD, with many neuroimaging studies finding distinct and overlapping neural systems that underlie different OCS dimensions (Alvarenga et al., 2012; Harrison et al., 2013; Mataix-Cols et al., 2004; van den Heuvel et al., 2009). Thus far, grouping individuals by co-occurring symptoms appears to be beneficial towards revealing the neurological correlates of the disorder.

While distinct clinical features appear to separate perinatal-onset OCD in females from OCD that occurs outside the perinatal period, evidence of sex differences in the genetics of OCD remain conflicting. More recently, the first GWAS reporting on the sex-specific genetic architecture of OCD found similarities between males and females, with the exception of two genes (*GRID2* and *GPR135*) that were specific to OCD in females only (Khramtsova et al., 2019). While preliminary, these findings hold promise for the detection of sex-specific genetic influences in OCD that may contribute to the prominent clinical disparities observed between males and females with the disorder. Our review of the literature acknowledged genetic associations that may be specific to OCD in sex-dependent manner. From this work, we identified the 5-HTTLPR polymorphism of

SLC6A4 and the G-1438A polymorphisms of *HTR2A* as promising gene candidates for OCD. We reported supporting evidence that these serotonergic polymorphisms may be associated with OCD in females, warranting their investigation in the context of perinatal OCS.

To date, candidate gene studies have yet to reliably find a gene that confers risk to OCD, suggesting that this disorder has a complex genetic architecture that cannot be attributed to the effects of a single gene. Instead, it is likely that there are multiple genes across different functional domains, including genes that affect development, connectivity and neurotransmission, that each contribute a small effect (Nestadt, Grados, & Samuels, 2010). As such, testing in large samples and the pooling of data through meta-analytic techniques will aid efforts in establishing the genetics of OCD, but it is important that the quality of studies are assessed in any systematic review and potential risk of bias, such as publication bias, is considered. Furthermore, GWAS will continue to be a useful approach in identifying genetic contributions outside of hypothesis-driven gene explorations; however, recent studies have not been successful in finding a SNP that reaches genome-wide significance in OCD (P. D. Arnold et al., 2018; Mattheisen et al., 2015; Stewart et al., 2013).

In the case of perinatal-related OCS, we found no evidence for an association with 5-HTTLPR or in the ability of 5-HTTLPR to predict symptom severity, as described in Chapter 4. From these results, we are not able to conclude whether 5-HTTLPR plays an important role in the development of infant-related symptoms that are specific to the perinatal period; therefore, continued investigations in larger samples are needed.

The 5-HTTLPR polymorphism has undergone extensive investigation in relation to multiple psychiatric disorders and has been linked to different behavioural phenotypes (Margoob & Mushtaq, 2011). Notably, S allele carriers often display increased anxiety and depressive symptoms, as well as other traits related to neuroticism, including hopelessness, feelings of guilt, and aggression (Gonda et al., 2009; Schinka et al., 2004). Similarly, variants of *HTR2A* gene have been investigated in several psychiatric disorders, including schizophrenia, depressive disorders, eating disorders, and anxiety disorders, with mixed outcomes (Serretti et al., 2007). While less is known about the risk A allele of the G-1438A variant, it has been linked to impulsive behaviours in non-clinical samples (Nomura et al., 2006), which is a behavioural trait that may be heightened in some OCD patients (Boisseau et al., 2012).

Given that the 5-HTTLPR has been associated with many behavioural traits, it is possible that this serotonergic polymorphism increases a general susceptibility for psychopathology, in a manner that is not specific to OCD. Prior work has shown that S allele carriers are at greater risk for postpartum depression in the early postnatal period (McEvoy, Osborne, Nanavati, & Payne, 2017), though results are inconsistent. Few studies have examined the comorbidity between perinatal OCD and depression, but research in non-perinatal samples suggest that the co-occurrence of OCS and depressive symptoms may be due to shared genetic factors (Bolhuis et al., 2014). This genetic overlap across different behaviours suggests that genetic pleiotropy may be possible, whereby one gene variant contributes to multiple phenotypic traits (Gratten & Visscher, 2016).

Furthermore, environmental influences, such as stress, appear to moderate the relationship between 5-HTTLPR and behaviour. The S allele of 5-HTTLPR has been found to increase risk for affective symptoms in females, especially when coupled with a stressful life event (Gressier et al., 2016). The perinatal period can be a source of stress for some women and additional stressors, such as obstetric complications, have been linked to greater rates of perinatal OCD in some (Maina et al., 1999; Zambaldi et al., 2009), but not all samples (Forray et al., 2010; Labad et al., 2005).

As a result of this relationship between stress and OCD onset, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis may also be contributing to the etiology of perinatal OCD. Higher levels of basal salivary cortisol, the major end product of the HPA axis in response to stress, was reported in postpartum women with OCD in one study, as compared to postpartum healthy controls, but no differences between groups were noted in cortisol production in response to a physical stressor (Lord et al., 2011). Conversely, a different study found no difference in serum cortisol in postpartum women according to whether they endorsed perinatal OCS or not (Labad et al., 2011); however, they did find that mothers with intrusive thoughts on infant-related harm displayed higher levels of adrenocorticotropic hormone, which is produced by the pituitary gland and acts on the adrenal cortex to stimulate release of cortisol. Furthermore, cortisol has known influences on serotonin synthesis pathway, whereby cortisol induces tryptophan 2,3-dioxygenase (Ren & Correia, 2000), which is an enzyme that metabolizes L-tryptophan, the essential amino acid required for serotonin synthesis. Therefore, cortisol can lead to decreased L-tryptophan availability, thus decreasing the rate of serotonin synthesis. While it has yet to

be determined if dysregulation of the HPA axis is associated with the development of perinatal OCD, the maternal HPA axis undergoes significant change across pregnancy and postpartum (Duthie & Reynolds, 2013) and altered functioning of the HPA axis has been linked to other perinatal psychopathologies, such as postpartum depression (Glynn, Davis, & Sandman, 2013).

Epigenetic modifications offer another plausible mechanism through which environmental factors may interact with genetic variations to modify risk for perinatal OCD. Epigenetics refers to the heritable yet dynamic processes that lead to alterations in gene expression but do no change the underlying DNA sequence. These modifications include DNA methylation and histone modification (Jaenisch & Bird, 2003). Recent evidence has shown that DNA methylation levels of the *SLC6A4* (SERT) promoter were increased in the saliva of pediatric OCD samples, but not in adult OCD patients (Grünblatt et al., 2018). To date, no studies have looked at epigenetic modifications related to OCD in women, or during the perinatal period. It deserves to be noted that epigenetic modifications influence the endocrine system, and in turn, gonadal hormones such as estrogen can influence the expression genes that code for epigenetic-modifying proteins (X. Zhang & Ho, 2011), suggesting the existence of a complicated interaction between the endocrine system, environmental influences and genetics. As this is an emerging field, little is currently understood about the role epigenetic modifications play in OCD, however this holds a lot of future promise for research endeavours.

The effects of estradiol and progesterone on SERT expression are not consistent across studies, with some reporting increased (Charoenphandhu, Teerapornpuntakit,

Nuntapornsak, Krishnamra, & Charoenphandhu, 2011; L. J. Smith, Henderson, Abell, & Bethea, 2004), decreased (Bethea, Gundlah, & Mirkes, 2000; Pecins-Thompson, Brown, & Bethea, 1998) or no change on SERT expression (Chavez et al., 2010) following administration. These findings from animal studies appear to be dependent on the brain region examined and the duration of administration. In humans, indirect evidence for an influence of estradiol on SERT availability comes from an observation in healthy females where pharmacologically induced ovarian hormone fluctuation led to the emergence of depressive symptoms that was associated with increased SERT binding and decreased levels of estradiol (Frokjaer et al., 2015). These findings from animal and clinical studies provide evidence of a complex interaction between gonadal hormones and serotonergic system that may underlie perinatal OCD, with the effects of 5-HTTLPR and *HTR2A* polymorphisms on these interactions not well understood.

Findings from imaging studies provide further support for the investigation of *SLC6A4* and *HTR2A* as ideal gene candidates in OCD. Overall, studies assessing the SERT and 5-HT_{2A} receptor availability and binding in drug-naïve OCD patients using PET or SPECT imaging techniques have been inconclusive. Several studies found reduced SERT availability in the midbrain, brainstem, thalamus, hypothalamus, insula and orbitofrontal cortex of OCD patients (Hesse et al., 2005; Matsumoto et al., 2010; Pogarell et al., 2003; Reimold et al., 2011; Reimold, Smolka, Zimmer, et al., 2007; Stengler-Wenzke, Müller, Angermeyer, Sabri, & Hesse, 2004; Zitterl et al., 2007). Later onset of OCD, in adulthood after the age of 18, was also associated with reduced SERT binding in the amygdala, anterior cingulate, nucleus accumbens and striatum (Hesse et al.,

2011). In contrast, others found increased SERT density in the midbrain and pons (Pogarell et al., 2003) or were not able to detect any difference in SERT availability between OCD patients and healthy controls (Simpson et al., 2003); however, differences in the type and specificity of the radioactive tracer used may partly explain the discrepancy. The literature on 5-HT_{2A} receptors demonstrates increased 5-HT_{2A} receptor binding in the caudate nuclei (Adams et al., 2005), and reduced availability in frontal polar, dorsolateral, medial frontal, parietal and temporal associative cortex of drug-naïve OCD patients (Perani et al., 2008), with some finding no difference (Simpson et al., 2011). These findings illustrate that the expression of proteins involved in serotonergic neurotransmission, specifically SERT and 5-HT_{2A} receptor, across cortical and subcortical regions are altered in OCD patients.

Chapter 5 provided the first exploratory investigation into the neurological substrates of perinatal OCD and symptom severity by assessing measures of CSA and CT in a clinically diverse sample of postpartum mothers. This preliminary work identified associations between perinatal symptom worsening of unique infant-focused OCS with measures of gray matter surface area of regions involved with attention and perceptual processes in postpartum mothers. Furthermore, in mothers with OCD, clinical symptom severity for obsessive-compulsive symptoms and trait anxiety was related to increased surface areas of regions in the frontal, temporal, parietal, premotor and occipital cortex. These findings are in line with current neurobiological models of OCD that implicate dysfunction of several neural circuits associated with loss of attention and inhibitory

control, as well as cognitive dysfunction. The reproducibility of these findings will need to be determined in future work with larger samples.

The existing literature on the cortical morphological profile of OCD in the general population provide supporting evidence for widespread cortical alterations, with the majority of studies reporting decreased CSA and CT in frontal, temporal and parietal areas, as it relates to heathy controls (Boedhoe et al., 2018; Rus et al., 2017). Our results were unable to confirm these findings in a postpartum sample, however our sample sizes for OCD and healthy control mothers were limited. Based on our findings, CSA appeared to be a marker associated with clinical severity in postpartum women with OCD and OCS worsening across the perinatal period in postpartum women, irrespective of diagnosis. Therefore, CSA may be a potential marker for OCS severity in postpartum mothers, but more research is warranted.

Although we were able to parallel some of our findings to those observed in structural and functional studies in OCD, the differences across study designs, statistical approach used, and sample characteristics make drawing comparisons challenging. Prior investigations have typically focused on comorbidity-free, medication naïve OCD samples in men and women outside of reproductive events using either surface-based, voxel-based, or region of interest approaches. Therefore, the inconsistencies across results are likely due to these confounding factors.

As it currently stands, it is unclear how structural alterations in perinatal OCD may relate to functional change. Based on the aberrant functional activity consistently reported in OCD (Saxena & Rauch, 2000), we can speculate that our findings of increased

surface area associated with postpartum OCD severity may be related to hyper-connectivity and dysfunction of these brain regions. It may be the case that maternal cortical plasticity in the perinatal period in women that are at risk for psychopathology contributes to the abnormal threat detection and harm avoidance behaviours associated with perinatal OCD.

There is a great deal of overlap in the findings across structural and functional studies that implicate the CSTC circuit and more widespread neural networks in OCD (Saxena & Rauch, 2000) that may lead to impairments in regulating cognitive, behavioural and emotional processes. Currently, it is not yet known whether structural alterations, such as changes to CSA or CT, result in aberrant neural activity, or if structural alterations occur as part of a compensatory mechanism intended to manage OCS symptoms and inefficiency within the CSTC circuit (de Vries et al., 2014). Furthermore, it is unclear whether the structural and functional changes in the brain are a consequence of or have a causal role in OCD.

Among the findings reported in Chapter 5, we were not able to detect any association with CT. Recently, a relationship between gray and white matter was found, where CSA, but not thickness, was associated with white matter myelin content in children across development (3 – 7 years of age) (Cafiero et al., 2019). In this study, Cafiero et al. observed increased CSA associated with age in frontal, temporal and parietal regions that strongly overlapped with age-related changes in myelin of the same brain regions. One theory proposes that tension along the white matter fibers drive cortical folding and gyrification (van Essen, 1997), which in turn may influence cortical

surface expansion. According to this perspective, changes in CSA may reflect underlying functional connectivity alterations implicated in perinatal OCD.

Notably, cortical alterations are not specific to the perinatal period, as gray matter reductions have also been observed in pubertal male and female children (Peper, Hulshoff Pol, Crone, & van Honk, 2011), suggesting that changes in sex hormones may play an important role in gray matter restructuring. Evidence in support of this view has been found in females aged 10 to 15 years, where higher levels of estradiol were associated with decreased gray matter volume in several frontal, parietal and temporal regions (Peper et al., 2009).

Given that gonadal hormones contribute to sex-specific changes in cortical organization across puberty (Herting, Gautam, Spielberg, Dahl, & Sowell, 2015), cortical restructuring and plasticity in the perinatal period could be a result of changes in estrogens and progesterone. Estrogens and progesterone are known to exhibit modulatory effects on several neurotransmitter systems, with general findings pointing towards these hormones having a protective role against obsessive-compulsive symptoms (Karpinski et al., 2017). In the perinatal period, levels of estradiol and progesterone steadily rise across gestation and is followed by a dramatic drop and decline in levels with childbirth (Nott et al., 1976), which may trigger OCD onset or symptom exacerbation. Based on our research design, we were not able to directly test the influence of gonadal hormones on the cortical profiles observed in our sample; however, it is possible that changes in estrogen and progesterone may play a role in cortical restructuring and the development of infant-related OCS during the perinatal period.

Based on all of our findings and what is currently known in the literature, we speculate that perinatal OCD and the unique infant-focused symptoms that arise during this time are a result of a combination of influences, including increased genetic susceptibility, altered neurotransmission, and neural alterations that may be triggered from hormonal fluctuation. More specifically, we theorize that alterations in serotonergic functioning may be involved in perinatal OCD and occurs due to interactions between serotonergic gene variants (such as 5-HTTLPR of *SLC6A4* and G-1438A of *HTR2A*) and changes in estradiol and progesterone in the perinatal period, which may be further influenced by the effects of cortisol as well. These changes not only result in altered neurotransmission of serotonin, but likely that of additional neurotransmitter systems, such as dopamine, glutamate and GABA. These effects in turn influence cortical structure within the maternal brain in regions that are responsible for a wide variety of processes, including attention, cognitive functioning, emotion regulation, and response inhibition, thus leading to the functional impairments commonly associated with OCD. While more research is needed to test the above hypothesis, this work provides a possible framework from which future studies can continue to investigate the risk factors and neurobiological correlates underlying perinatal OCD.

6.3 Limitations

Earlier chapters in the dissertation included the strengths and limitations for each individual study. This section will focus on the general limitations, as summarized below.

One of the main limitations noted within our studies is the small sample size. Despite higher prevalence of OCD in females that have been reported during the perinatal

period (McGuinness et al., 2011), recruitment of women presenting with clinical levels of OCS in pregnancy posed a challenge, as did the high attrition rates observed across the perinatal period. While we were unable to detect any significant clinical differences between women who completed the longitudinal study and those that dropped out after the first visit, it may be possible that perinatal/obstetric complications or changes in mood and behavioural symptoms influenced their participation in the study.

The majority of participants were recruited from an outpatient clinic that specializes in treating mood and affective symptoms in women across reproductive life events. As a result, a significant proportion of our participants were therefore receiving treatment with psychotropic medication and/or receiving psychotherapeutic treatment throughout the study. Therefore, our findings reflect that of a help-seeking, clinically diverse population, with the majority of women endorsing OCS symptoms within the mild to moderate range. Studies conducted on OCD samples generally focus on treatment-naïve, clinically severe cases that present with no other comorbidities. Comorbid clinical presentations are common in individuals with OCD, with higher rates of depressive disorders and anxiety disorders observed in females (Rintala et al., 2017). While such studies are informative, the characteristics of these samples do not represent the complex clinical picture individuals with OCD often present with to healthcare professionals.

One disadvantage to a small sample includes not having enough statistical power to detect associations in some analyses. Furthermore, it limits the ability to control for other confounding factors that likely influence OCS, such as medication use and

comorbidity. When stratifying our pregnant sample into high and low POCS severity group, women in the high POCS group were more likely to be taking psychotropic medications. In Chapter 5, we considered the effects of medication use on cortical morphology and found no differences in CSA or CT measures between mothers taking psychotropic medications and those not on medications. Furthermore, we found no difference in the proportion of women taking psychotropic medications during pregnancy, as compared to the postpartum (both 29%). An additional limitation in our study is that we did not assess if participants had undergone any form of psychotherapy prior to or during their time in the study. Prior evidence supports the improvement of perinatal OCS following an intensive form of cognitive behavioural therapy in the postpartum period (Challacombe & Salkovskis, 2011).

Since we did not reassess diagnosis in the postpartum period, we were not able to capture possible changes in diagnostic states in our longitudinal study. Furthermore, this limited our ability to capture unique incidences of postpartum onset OCD in our sample. Despite the risk of those with anxiety and depressive disorders to developing OCD due to the high comorbidity shared between these disorders (Carter, Pollock, Suvak, & Pauls, 2004; Tükel, Polat, OÖzdemir, Aksuüt, & Tuürksoy, 2002), all of our OCD cases were pre-existing and therefore the results of this study more accurately reflect perinatal symptom exacerbation, rather than onset.

Another potential limitation of the study is the possibility that mothers did not fully disclose their infant-related symptoms, due to the distressing nature of the symptoms. While self-report scales are inherent to bias, the POCS questionnaire is unique

in that the items contained are specific and target a wide-range of perinatal-related symptoms. It is a very useful tool for measuring the presence, content, severity and interference of infant-related symptoms in women in both clinical and research settings (Lord et al., 2011). Therefore, our utilization of the POCS likely mitigated barriers of with symptom reporting.

As discussed earlier in Chapter 4, we did not find any effects of parity on predicting OCS severity across the perinatal period. Prior research on women with OCD who experienced symptom exacerbation during the perinatal period found that they were more likely to experience symptom worsening in or after subsequent pregnancies (Guglielmi et al., 2014). Regrettably, we did not capture data on our participants' history of OCS across past reproductive events, which serves as another limitation. Therefore, it's not yet clear from the literature whether new mothers are more at risk to experience infant-related OCS than mothers who had prior experience with childbirth and caring for their infant, but findings from our study suggests that parity does not influence severity.

Lastly, an unfortunate limitation of our study described in Chapter 4 is that we were unable to successfully genotype the *HTR2A* G-1438A (rs6311) polymorphism. Results obtained of the rs6311 polymorphism were unreliable due to poor band visualization. While the genotyping protocol using restricted fragment length polymorphism is an older technique, visualization of 5-HTTLPR did not present with similar problems, suggesting that further optimization was needed for visualizing the *HTR2A* polymorphism. Alternative PCR based genotyping methods can be considered and include the use of real-time PCR with Taqman SNP genotyping assays, where distinct

fluorescent probes are used to detect and tag the alleles of interest. As a result, polymorphisms within the *HTR2A* should be tested in the future, and larger samples are needed to better inform the genetics of perinatal OCS.

6.4 Future Directions

Due to the preliminary nature of our explorations, the work presented throughout the thesis provides a starting point from which future investigations may expand upon. Most importantly, any future study that aims to investigate the etiological factors of OCD should consider sex as a variable within analyses in order to reduce clinical heterogeneity and identify possible risk factors for perinatal OCD. While sex differences in the clinical presentation of OCD is fairly evident, more work is needed to determine if OCD during the perinatal period represents a valid and distinct subtype.

Of importance is the need for replication of our findings in larger samples, as this is the first known report on the genetic contributions of 5-HTTLPR towards the presence of perinatal OCS and on the relationship between gray matter measures and clinical severity in postpartum samples with OCD. Furthermore, future investigations into the association of *HTR2A* or other candidate gene polymorphisms with OCD should be conducted on large samples and reported in relation to various clinical factors that may be associated with distinct OCD subtypes (i.e. by sex, age of onset, symptom type, etc.). Given that the *HTR2A* polymorphisms appeared to be associated with OCD in a sex-dependent manner, studies should continue to examine whether this gene is associated with OCD, particularly in females.

Since multiple neurotransmitter genes likely contribute to OCD, genes outside the serotonin system warrant investigation in relation to perinatal-onset OCD. Findings from a recent GWAS study point towards the future investigation of two genes that were significantly associated with OCD in females only: *GRID2*, a gene that codes for a glutamate receptor channel delta 2 subunit, and *GPR135*, a G protein-coupled receptor 135 (Khramtsova et al., 2019). While little is understood about *GPR135*, there is an emerging interest in the glutamate system genes, which include *SLC1A1* glutamate transporter gene and *DLGAP* (*SAPAP*-related) genes involved in synaptic functioning, as dysregulation of this system may be implicated in OCD (Rajendram, Kronenberg, Burton, & Arnold, 2017).

In addition to the importance of identifying genes that may confer risk for the development of perinatal OCD or symptom exacerbation, understanding the functional consequence of these genetic polymorphisms on neurotransmission is equally critical. Gene expression studies that quantify mRNA in brain tissue will improve our understanding of how genetic polymorphisms influence gene transcription across different neural regions. Moreover, analyses on DNA methylation and histone modification will uncover how these genes are being regulated by epigenetic mechanisms in relation to OCD risk.

While the examination of cortical structure prior to and following OCS onset or exacerbation in the perinatal period would clarify whether cortical alterations have a causal role or occur as a consequence of psychopathology, challenges in predicting the timing of symptom onset or exacerbation limits the feasibility of this type of

investigation. Instead, a more practical investigation might examine the cortical alterations of women in the postpartum period across diagnostic groups in order to characterize the clinical trajectories that lead to perinatal OCS worsening and changes in the maternal cortical structure.

Since little is known about the neural correlates of perinatal OCD, future investigations should look towards examining functional connectivity that may be affected in mothers with OCS and OCD in the postpartum period. In the only postpartum OCD neuroimaging study published to date, Lord et al. found that the OFC and temporal cortices were significantly activated in response to psychosocial stress in mothers with OCD, as compared to healthy postpartum controls (Lord et al., 2012). Resting state and other task-based approaches will be beneficial in determining whether aberrant functional connectivity in multiple neural networks, such as the default mode network and fronto-parietal network, are associated with postpartum OCD and if there is an overlap with the structural findings that we reported in Chapter 5. Furthermore, a longitudinal imaging study across the postpartum period would prove to be worthwhile for characterizing structural and functional neural alterations in the CTSC circuit across this period of time of neural plasticity in mothers.

It would be interesting to see if genetic or cortical markers could predict treatment responses in women with perinatal OCD. When investigating the clinical utility of 5-HTTLPR and *HTR2A* polymorphisms, there is insufficient evidence that genotype or allele status of either variant influences treatment outcomes in general OCD samples (Billett et al., 1997; Denys, Van Nieuwerburgh, Deforce, & Westenberg, 2007; Di Bella,

Erzegovesi, Cavallini, & Bellodi, 2002; Miguita, Cordeiro, Shavitt, Miguel, & Vallada, 2011). Notably, no study has investigated serotonergic function, including SERT and 5-HT_{2A} receptor availability, in perinatal samples with OCD and the potential effects it may have on treatment. Therefore, it is imperative that efforts are being made towards improving early identification and treatment of OCD, especially as it relates to mothers during the perinatal period.

With advancements in the field of genetics and neuroimaging, many studies are now turning towards the use of neuroimaging techniques to explore the influence of genetic variants on brain structure and function, which is known as imaging genetics (Bigos & Weinberger, 2010). This approach is useful for characterizing the functional effects that specific candidate genes may have on neural networks that regulate behaviour. Few explorations have been conducted in OCD samples (Grünblatt, Hauser, & Walitza, 2014), with preliminary reports suggesting that the 5-HTTLPR variant influences SERT availability in the midbrain (Hesse et al., 2011), gray matter volume in the right frontal pole (Honda et al., 2017), and volume of the OFC (Atmaca et al., 2011). The OFC is one of the main targets of serotonergic projecting neurons from the raphe nucleus (Roberts, 2011) and is a key structure implicated in the CSTC circuit and OCD, as described earlier. These preliminary reports prompt further investigation into 5-HTTLPR and its influence on cortical structures in OCD and perinatal samples with OCS.

Lastly, an integrative approach that collects and combines clinical, biological, and subjective measures can be applied to machine learning techniques to predict behavioural outcomes, such as perinatal OCS. As such, subsequent studies would benefit from

integrating genetic and neuroimaging techniques in order to identify risk factors or targets for therapeutics in OCD and its subtypes.

6.5 Conclusions

The collection of work contained within this thesis demonstrates support for the existence of etiologically distinct forms of OCD, based on sex and age of onset. In particular, we focused on perinatal OCD and its clinical presentation, which may represent a more homogeneous subgroup. We found evidence that polymorphic variants in genes pertaining to the serotonin system may be specific to OCD in females; however, we could not conclude whether the serotonin transporter polymorphism, 5-HTTLPR, was associated with the unique emergence of infant-related OCS in women across the perinatal period. Replication in larger samples is warranted, in addition to investigating the serotonin 2A receptor gene, *HTR2A*, with perinatal OCS. Novel whole-brain explorations in a sample of clinically diverse postpartum mothers revealed associations between gray matter surface area measures and greater OCS worsening from pregnancy to postpartum, as well as correlations between the surface area of frontal, parietal and temporal cortices with clinical severity in mothers with OCD. These findings suggest that widespread neural changes during the postpartum period may predispose women for risk of psychopathology. Due to the distressing nature and adverse consequences of OCD in the perinatal period, it is imperative that research continues to identify risk factors that contribute to its pathophysiology in women.

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