Genetic and Environmental Risk factors associated with Obsessive-Compulsive Disorder and its symptom dimensions: A twin study

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Doctorate in Medicine
Research Line: Clinical and Experimental Neuroscience
Research Group: Psychiatry and Mental Health

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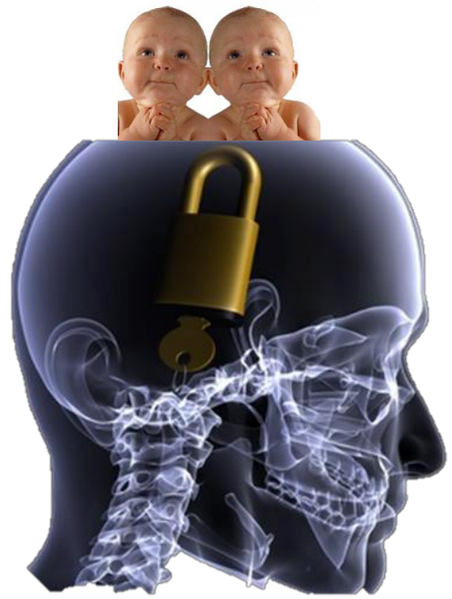

Clara López Solà

Doctoral Thesis

Barcelona University – Faculty of Medicine

Universitat de Barcelona

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DOCTORAL THESIS
CLARA LÓPEZ SOLÀ

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L'ignorance affirme ou nie; Sciences doute
("La ignorancia afirma o niega rotundamente; La ciencia duda"
François Marie Arouet (Voltaire)

It would be possible to describe everything scientifically, but it would make no sense; it would be without meaning, as if you described a Beethoven symphony as a variation of wave pressure.
("Sería posible describir todo científicamente, pero no tendría ningún sentido; Carecería de significado describir la sinfonía de Beethoven como una variación de la presión de la onda auditiva")
Albert Einstein

Professors Ben J. Harrison and José M. Menchón certify that they have supervised and guided the doctoral thesis entitled "**Genetic and Environmental Risk Factors Associated with Obsessive-Compulsive Disorder and its Symptom Dimensions: A twin study**", presented by Clara López Solà. They hereby assert that this doctoral thesis fulfills the requirements to be defended.

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LIST OF ABBREVIATIONS

A	Non-Additive Genetic Factor
ADs	Anxiety Disorders
AIC	Akaike Information Criterion
APA	American Psychiatry Association
ASI	Anxiety Sensitivity Index
ATR	Australian Twin Registry
BDD	Body Dysmorphic Disorder
BDNF	Brain Derived Neurotrophic Factor gene
C	Common Environmental Factor
CI	Confidence Intervals
COMT	Catecholamine-O-methyl-transferase gene
CP	Common Pathway Model
DASS	Depression Anxiety and Stress Scale
DCQ	Dysmorphic Concern Questionnaire
DF	Degrees of Freedom
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DZ	Dizygotic twins
E	Unique Environmental Factor
ED	Excoriation Disorder
EEA	Equal environmental assumption
FKBP5	Gene FK506 Binding Protein 5
GAD	Generalized Anxiety Disorder
GABA	Gamma-Aminobutyric Acid
GWAS	Genome-Wide Association Study
HD	Hoarding Disorder
HRS	Hoarding Rating Scale
ICE FALCON	Inference on causation from examination of familial confounding
IP	Independent Pathway Model
MGH-HPS	Massachusetts General Hospital Hair Pulling Scale
Met	Methionine
-2LL	Minus twice the log-likelihood
MAO-A	Monoamine Oxidase type A
MZ	Monozygotic twins

OC	Obsessive-Compulsive
OCD	Obsessive-Compulsive Disorder
OCI-R	Obsessive-Compulsive Inventory-Revised
OCRDs	Obsessive-Compulsive and Related Disorders
PCA	Principal Component Analysis
PD	Panic Disorder
SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1
SNP	Single Nucleotide Polymorphism
SP	Social Phobia
SPIN	Social Phobia Inventory
SPS	Skin Picking Scale
TTM	Trichotillomania
Val	Valine
WI	Whiteley Index
X^2	Difference in goodness of fit statistic

List of Publications

1. **López-Solà C**, Fontenelle LF, Bui M, Hopper JL, Pantelis C, Yücel M, Menchón JM, Alonso P, Harrison BJ. Etiological Overlap between Obsessive-Compulsive Related and Anxiety Disorder Symptoms: A Multivariate Twin Study. *British J Psychiatry*. 2015; accepted, in-press. **IF: 7.34**

2. **López-Solà C**, Fontenelle LF, Alonso P, Cuadras D, Foley DL, Pantelis C, **et al.** Prevalence and heritability of obsessive-compulsive spectrum and anxiety disorder symptoms: A survey of the Australian Twin Registry. *Am J Med Genet B Neuropsychiatr Genet.* 2014; 165B (4): 314-25. **IF: 3.27**

3. **López-Solà C**, Gutiérrez F, Alonso P, Rosado S, Taberner J, Segalàs C, **et al.** Spanish version of the Dimensional Obsessive-Compulsive Scale (DOCS): Psychometric properties and relation to obsessive beliefs. *Compr Psychiatry.* 2014; 55(1): 206-14**. IF: 2.26**

4. Alonso P, **López-Solà C**, Gratacós M, Fullana MA, Segalàs C, Real E, Cardoner N, Soriano-Mas C, Harrison BJ, Estivill X, Menchón JM. The interaction between Comt and Bdnf variants influences obsessive-compulsive-related dysfunctional beliefs. *J Anxiety Disord*. 2013; 27(3): 321-7. **IF: 2.97**

5. Alonso P, Orbegozo A, Pujol J, **López-Solà C**, Fullana MA, Segalàs C, **et al.** Neural correlates of obsessive-compulsive related dysfunctional beliefs. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; 47C: 25-32. **IF: 4.025**

6. Subirà M, Alonso P, Segalàs C, Real E, **López-Solà C**, Pujol J, **et al.** Brain Structural Alterations in Obsessive-Compulsive Disorder Patients with Autogenous and Reactive Obsessions. *PLoS One.* 2013; 8(9):e75273. **IF: 3.5**

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9. Real E, Gratacòs M, Labad J, Alonso P, Escaramís G, Segalàs C, Subirà M, **López-Solà C**, **et al.** Interaction of SLC1A1 gene variants and life stress on pharmacological resistance in obsessive-compulsive disorder. *Pharmacogenomics J.* 2013; 13(5): 470-5. **IF: 5.513**

10. Alonso P, Gratacós M, Segalàs C, Escaramís G, Real E, Bayés M, Labad J, **López-Solà C**, **et al.** Association between the NMDA glutamate receptor GRIN2B gene and obsessive-compulsive disorder. *J Psychiatry Neurosci.* 2012; 37(4):273-81. **IF: 7.49**

11. Binelli C, Muñiz A, Sanches S, Ortiz A, Navines R, Egmond E, Udina M, Batalla A, **López-Solà C**, Crippa JA, Subirà S, Martín-Santos R. New evidence of heterogeneity in social anxiety disorder: Defining two qualitatively different personality profiles taking into account clinical, environmental and genetic factors. *Eur Psychiatry.* 2015; 30(1):160-5. **IF: 3.21**

Articles Submitted in International Journals:

1. **López-Solà C,** Fontenelle LF, Verhulst B, Neale M, Menchón JM, Alonso P, Harrison BJ. Distinct etiological influences on obsessive-compulsive symptoms dimensions: a multivariate twin study.

2. Davey C, **López-Solà C**, Bui M, Hopper JL, Pantelis C, Fontenelle LF, Harrison, JB. The structure of negative mood states: Twin-study evidence for a causal influence of stress-tension on depression and anxiety.

3. Fusté G, Gil MA, **López-Solà C,** Rosado S, Bonillo A, Pailhez G, Bulbena A, Pérez V, Fullana MA. Psychometric properties of the Spanish version of the Panic Disorder Severity Scale (PDSS).

4. Goldberg X, Soriano-Mas C, Alonso P, Segalàs C, Real E, **López-Solà C**, Subirà M, Via E, Menchón JM, Cardoner N. Predictive value of familial risk, stressful life events and gender on the course of obsessive-compulsive disorder.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1. Obsessive-Compulsive Disorder (OCD). An Introduction to the multidimensional approach.

Obsessive-compulsive disorder (OCD) is a psychiatric illness characterised by recurrent, intrusive thoughts or impulses (obsessions), often accompanied by ritualistic behaviours (compulsions) that are enacted to avoid anxiety or to ameliorate the obsessions. The obsessions are often experienced as involuntary, with patients actively trying to suppress them. However, these compulsive actions are rarely successful in mitigating the obsessive thoughts and, despite full awareness of their futility; patients may repeat them for many hours on end until they "feel done". Varying degrees of sub-threshold symptoms exist in the general population (Fullana et al., 2010). Hence it is important to have diagnostic measures to differentiate between sub-threshold and threshold symptoms. Currently, the frequency, distress and functional impact of a patient's symptomatology serve as the critical basis for a diagnosis of OCD. Epidemiological estimates from 2010 indicate that OCD affects 2-3% of the world's population (Fontenelle, Mendlowicz, & Versiani, 2006; Ruscio, Stein, Chiu, & Kessler, 2010), and is among the top 10 causes of years lived with illness-related disability and 20th among all causes of burden of disease, owing to the extreme financial and social costs (Murray & Lopez, 1996).

The age of onset of OCD is bimodal, i.e., the first average age of onset is around 10 years of age (Flament et al., 1990; Thomsen & Mikkelsen, 1991), whereas the second is during early adulthood, around 20 years of age (Rasmussen & Eisen, 1992). Before puberty there is a peak among male patients (ratios 2-3/1), and during adolescence there is an increase in the number of girls diagnosed with OCD, reaching a 1:1.35 sex ratio in adulthood (Leonard et al., 1992). The onset of OCD is usually gradual and symptom severity fluctuates over time, often in response to stressful life events (Stewart et al., 2004). If untreated, the course of OCD tends to be chronic, with oscillations of major symptoms (Skoog & Skoog, 1999).

OCD frequently leads to isolation, family dysfunction, difficulty forming and maintaining relationships, and unemployment (Murray & Lopez, 1996). It has been

reported that around 90% of OCD patients have at least one other comorbid psychiatric disorder (Angst et al., 2005), such as depression (66%), drug or alcohol abuse (14%), specific phobias (22%), social phobia (18%), panic disorder (12%), general anxiety disorder (30%) eating disorders (17%), body dysmorphic disorder (13%) and Tourette syndrome (7%). There are several explanations for the high rate of co-morbidity: *i)* OCD may increase the vulnerability to other disorders; *ii)* there may be a common etiology between OCD and other such disorders; and/or *iii)* these disorders may be an epiphenomena of the same "latent condition", with the same etiology, but with diverse manifestations due to environmental factors (Nestadt et al., 2009).

Variability in the phenotypic expression of OCD has led to the assumption that it is not only clinically but also genetically heterogeneous, and that different biological and environmental factors probably underlie its ultimate expression. Alternatively stated, this could indicate that specific low-order phenotypes (i.e., hypersensitivity to react in threatening situations, inability to cope in situations of high uncertainty, difficulty in making decisions, etc.) might be more closely related to a particular genetic substrate than the higher-order construct of OCD. A major challenge with regards to the heterogeneity of OCD is that it is likely to obscure the findings of biological and genetic studies. For this reason there is a broad recognition that such studies must address its heterogeneity – either categorically, in terms of studying specific subtypes, or dimensionally, stratifying analyses in terms of the major symptom dimensions of the disorder.

From a categorical point of view, at least four different subtypes of OCD have been described, each with different characteristics: pediatric-onset (Miguel et al., 2005), tic-related (Miguel, Rosario-Campos, Shavitt, Hounie, & Mercadante, 2001), sensory phenomena (Rosario-Campos et al., 2001) and compulsive hoarding phenotypes (Wheaton, Timpano, Lasalle-Ricci, & Murphy, 2008). Accumulated results across studies have revealed that hoarding, as a distinct OCD phenotype has; an earlier age of onset; is more prominent in females; has increased comorbidity with social phobia, personality disorders and pathological grooming behaviours; involves poorer levels of insight and is generally associated with more severe symptoms, specifically symmetry obsessions and ordering, and repeating and counting compulsions (Fontenelle *et al* 2004.; Wheaton *et al.* 2008; Pertusa *et al.* 2010).

From a dimensional point of view, a multidimensional model was proposed by Mataix-Cols (Mataix-Cols, Rosario-Campos, & Leckman, 2005), after early studies by Baer (1994) where OCD was considered a set of overlapping syndromes rather than a unitary entity. Different factor analyses studies have systematically identified at least four OC symptom dimensions; 1) contamination obsessions and washing compulsions; 2) symmetry obsessions and ordering, repeating, and counting compulsions; 3) forbidden thoughts, which contain sexual/religious obsessions, aggressive obsessions and checking compulsions; and 4) hoarding obsessions and compulsions (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008). It has been suggested that some of the etiological factors underpinning these dimensions may be specific to each dimension, whereas other genetic and environmental factors may be common to all of them (Iervolino, Rijsdijk, Cherkas, Fullana, & Mataix-Cols, 2011; van Grootheest, Boomsma, Hettema, & Kendler, 2008).

Categorical and dimensional approaches are both likely to be relevant, although there is strong contemporary interest in the multidimensional OCD approach. The multidimensional OCD approach was broadly applied to validate the method, and to clarify differences in the etiology of the disorder depending on the specific clinical manifestations. Overall, all multidimensional studies showed important value in different areas:

1) Clinical studies, by helping to describe the different phenotypic presentations of the disorder (Leckman et al., 2010; Rosario-Campos et al., 2001);

2) Developmental studies that have found an early emergence of specific behaviours to resemble the symptom dimensions observed in OCD (Evans, Gray, & Leckman, 1999; Zohar & Felz, 2001);

3) Longitudinal studies that confirm the temporal stability of OCD symptom dimensions (Mataix-Cols et al., 2002);

4) Genetic studies where different symptom dimensions showed different patterns of genetic transmission (Iervolino et al., 2011; Katerberg et al., 2010; van Grootheest et al., 2008);

5) Neuroimaging studies which show that OCD symptom dimensions are mediated by partially distinct neural systems (Harrison et al., 2013; Mataix-cols et al., 2004; van den Heuvel et al., 2009; Via et al., 2014); and

6) Treatment studies that indicate different patterns of response to pharmacological and psychological treatments across dimensions (Mataix-Cols, Marks, Greist, Kobak, & Baer, 2002; Rufer, Fricke, Moritz, Kloss, & Hand, 2006).

In addition, OCD symptom dimensions appear to be expressed on a continuum in the general population. This occurs, both in content and in the degree of severity, where individuals at the extreme end of any dimension are more prone to develop or have experienced OCD. The use of a dimensional approach might be helpful in the context of evolutionary perspectives of psychopathology (Leckman, Zhang, Alsobrook, & Pauls, 2001), as it helps to understand the adaptive component associated with a certain degree of specific psychological traits that are also present in the normal population.

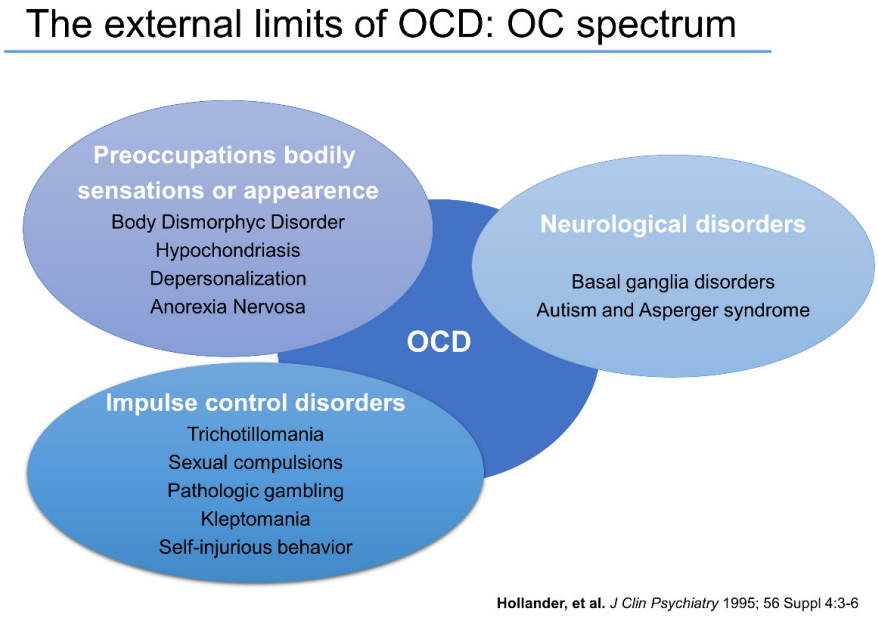
Taking into account this phenotypic heterogeneity should improve understanding of the etiology of OCD and assist in developing more specific, tailored treatments. An important route to disentangling the complex inheritance of OCD may be through the study of normal variation in the quantitative symptoms and major symptom dimensions of OCD.

1.2. Obsessive-Compulsive and Related Disorders (OCRDS)

There has been much debate regarding the optimal diagnostic classification of OCD in relation to the recently published revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Bienvenu et al., 2012; Fineberg, Saxena, Zohar, & Craig, 2007; Hollander, Braun, & Simeon, 2008; Stein et al., 2010; Storch, Abramowitz, & Goodman, 2008). Two decades ago, separate research groups realised that different disorders presented clinical similarities with OCD. For this reason, and to study them further, those disorders were located in the orbit of OCD and were generally named obsessive-compulsive (OC) spectrum disorders (see Figure 1). The constellation of OC-spectrum disorders included three big clusters: *i) Preoccupations focused on bodily sensations or appearance* (body dysmorphic disorder (BDD), hypocondriasis, depersonalization, anorexia nervosa), *ii) Impulse control disorders* (trichotillomania, sexual compulsions, pathologic gambling, kleptomania, self-injurious behaviour, substance abuse disorders), and *iii) Neurological disorders* (basal ganglia disorders such us

Huntington's/Parkinson disease, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, autism) (Hollander & Wong, 1995). However, the notion of "OC-spectrum" group remains controversial.

Figure 1: Obsessive-compulsive Spectrum Disorders.



In DSM-5, OCD has been removed from the broad category of "anxiety disorders" and placed in a separate chapter, called "obsessive-compulsive and related disorders" (OCRDs), which includes the following disorders: BDD, trichotillomania (hair-pulling disorder); as well as excoriation (skin picking) disorder and hoarding disorder (HD) as a new diagnosis. HD is still under scrutiny in this category for revealing clinical and biological features that are not typical in OCD and that could be more related to other pathologies such us social phobia (Mataix-Cols, Billotti, Fernández de la Cruz, & Nordsletten, 2013; Pertusa et al., 2010). However, given the historical link with OCD and Obsessive-Compulsive Personality Disorder, it was suggested to be provisionally listed as an OCRD.

Table 1: Presents the five OCRDs and summarises their main clinical features, epidemiology, age of onset and main psychiatric comorbidities.

Table 1. General Characteristics of Obsessive-Compulsive & Related Disorders at DSM-5.

Diagnoses	Clinical Features (DSM5)	Prevalence	Onset	Comorbidities
Obsessive-Compulsive Disorder (OCD)	Obsessions and compulsions: contamination/washing; aggressive/checking; sexual/religious thoughts; symmetry/ordering; hoarding	2-3% adulthood equal males and females	Bimodal: around 10 and 20 years old	Anxiety disorders, Mood disorders, BDD, hypochondriasis
Body Dysmorphic Disorder (BDD)	Excessive preoccupation with one or more perceived defects in physical appearance	0.7-2.4% equal males and females	Adolescent	Major Depressive Disorder, Substance Use Disorder, Social Phobia and OCD
**Compulsive Hoarding Disorder (HD)*	Difficulty discarding possessions, due to the perceived need to save and distress discarding them, resulting in clutter	0.7-2.2% slightly higher in females	Older adults (around 34 to 60)	Healthy features, Major Depressive Disorder, Anxiety Disorders, Personality Disorders
Excoriation Disorder (ED)	Recurrent skin picking resulting in skin lesions. Preoccupation and/or urges precede the picking, associated with relief or gratification	1.4-5.4% higher in females	Adolescent	OCD, Major Depressive Disorder, BDD and TTM
Hair-Pulling Disorder (TTM)	Compulsive urge to pull one's or own hair leading to noticeable hair loss associated with relief or gratification	1-2% higher in females (ratio 10:1)	Adolescent	Major Depressive Disorder and Excoriation Disorder

*Prevalence, age of onset and comorbidities are still not well known.

The decision to generate a new category for OCD and OCRDs separate from "anxiety disorders" was based on the recognition of specific commonalities between OCD and the OCRDs. Some authors reported that OCRDs share similar phenomenological aspects with OCD, including obsessive thoughts and/or repetitive behaviours that are persistent, resulting in clinically significant anxiety and impairment (Phillips et al., 2010). Moreover, alterations of the serotoninergic, dopamine and glutamate systems have been

broadly implicated across these disorders (Murphy, Timpano, Wheaton, Greenberg, & Miguel, 2010). Molecular genetic studies have supported, in part, a common biological etiology among specific manifestations of the OCD and other OCRDs. For example, animal models have been useful in providing biological models for gene effects and have found the presence of specific genes (Hoxb8 and SAPAP-3) to be associated with repetitive grooming behaviours and increased anxiety (Grados, 2010). Moreover, a recent paper in OCD patients also supports the role for the same gene (SAPAP3) in OCD and trichotillomania (Züchner et al., 2009).

However, it seems that the strongest evidence to support the relationship of OCD with the OCRDs comes from comorbidity and family studies, which have reported higher rates of OCRDs among OCD-affected cases and their relatives (Bienvenu et al., 2012). Nevertheless, familiarity does not prove causality; the question of whether these conditions are etiologically related remains to be conclusively demonstrated, as does the precise nature of this relatedness.

There is now general agreement that overreliance on the current classification systems for psychiatric disorders has hampered research for biologically-based constructs of specific OC symptoms that may be more tightly related to a concrete genetic marker. This approach may help disentangle the complex heterogeneity of OCD. Ideally, this debate will be reconciled by ongoing research regarding the etiology of these disorders in terms of potential shared and distinct risk factors. If the new DSM-5 classification for OCD is accurate, OCD should then be more phenomenologically, etiologically and neurobiologically-related to the other OCRDs. The DSM-5 classification also suggests that OCD shows less overlap with other anxiety disorders, or that anxiety is less relevant to OCD. However, this question remains to be elucidated (Milad et al., 2013; Storch et al., 2008).

1. 3. Obsessive-Compulsive Disorder as an Anxiety Disorder

OCD has been historically classified (DSM-IV) as an anxiety disorder (AD), together with panic disorder (with or without agoraphobia), social phobia, generalized anxiety disorder and post-traumatic stress disorder. This association between OCD and anxiety was made based on different characteristics: 1) core symptoms of OCD are, for some authors, best understood as an escape behaviour from obsessional thoughts that provoke anxiety, and these tend to be similar in nature to avoidance or safety behaviours in AD. Because some patients do not present overt rituals but instead mental compulsions and neutralising behaviours, this is another indicator that repetitive observable behaviours are not the core feature of OCD; 2) the presence of repetitive behaviours is not specific to other OCRDs; they are also present in other ADs (e.g. panic disorder checking their fear bodily sensations), hypochondriasis, certain eating disorders or sexual paraphilias, etc.; 3). Clinical studies have depicted high comorbidity between OCD and other ADs (up to 36%). In fact, comorbidity rates between OCD and other anxiety disorders are considerably higher than the rates for some OCRDs. Only body dysmorphic disorder and hypochondriasis (although it is not characterized among OCRDs) are fairly common among OCD patients; considered by some authors to be anxiety-motivated (Abramowitz & Braddock, 2006; Phillips, McElroy, Hudson, & Pope, 1995; van den Heuvel, Veale, & Stein, 2014); 4), OCD and ADs seem to aggregate strongly in families. Rates of ADs among first-degree relatives of people with OCD are far higher than the rates of OCRDs among relatives of OCD sufferers (Nestadt et al., 2001); and finally 5) psychological treatment for OCD (based on the exposure to threat stimuli) is similar to the one used for other AD, and not to other obsessive-compulsive spectrum disorders, such as inverse habits (Storch et al., 2008).

Table 2: is an adaptation of a table from Stroch et al., 2008 to summarize the phenomenological similarities that exist between OCD and other ADs.

Table 2. OCD and Anxiety Disorders: Phenomenological aspects.

Diagnosis	Fear Evoking Stimuli	Safety behaviours to reduce anxiety
OCD	Intrusive thoughts and related triggers	Avoidance, checking, washing, ordering, cleaning, covert neutralising, asking for reassurance, etc.
Social Phobia (SP)	Social situations, embarrassment, etc.	Avoidance of social situations, speak softly, drinking alcohol, etc.
Panic Disorder & Agoraphobia (PD)	Arousal-related body sensations	Agoraphobic avoidance, sitting down, going to emergency room, drinking water, safety person, etc.
Generalized Anxiety Disorder (GAD)	Images of low-probability catastrophes	Calling loved-ones to verify safety, asking for reassurance, etc.
Specific Phobia	Animals, heights, planes, etc.	Avoidance, drinking alcohol, distraction.

Although some authors recommend that OCD should maintain in the category of ADs with other OC-spectrum disorders such as hypochondriasis (Bienvenu et al., 2012; Stein et al., 2010), the final resolution at DSM-5 (American Psychiatry Association (APA, 2013), was to separate both categories, given the important implications that this decision has on clinical and research practices.

Extensive research is needed to explore the etiological links between OCD and other OCRDs whilst also considering the relationship between OCD and anxiety. These efforts will ultimately help improve future psychiatric classifications of OCD and have strong implications for basic and treatment-oriented research and discovery.

1.4. Twin Studies

1.4.1. The Value of Twin Studies in Psychiatry

Twin studies are considered a key tool in behavioural genetics and related fields. They are used to dissect the nature (genetic) versus nurture (environmental) contributions to individual phenotypes and are one of the best ways of identifying genetic markers relevant to understanding the etiological factors that underlie complex psychopathologies (Plomin, DeFries, McClearn, & Rutter, 1997).

Different research strategies, depending on the question asked, should be used to explore the genetics of mental illness. If we want to answer the question "is the disorder familial?" familial studies should be performed. Twin studies are the first step toward identifying candidate genes in specific pathological conditions related to the general question: "how much do genes (versus environment) contribute to the disorder?". To the specific question "which genes are involved?" linkage and association studies should be performed. Finally if the question is focused on what the genes do, then molecular biology is necessary (Smoller, Block, & Young, 2009).

Univariate twin studies allow one to estimate the "heritability" of a trait or disorder. This provides an index of the proportion of phenotypic variance in a population that is attributable to genetic factors. It is important to recognise that it is a population measure in a specific temporal moment and does not measure what proportion of an individual's disorder is due to genetic factors. The heritability of a disorder can vary in different populations (and different historical contexts) and throughout an individual's life. Heritability can vary from 0 (no contribution of genetic variation to disorder risk) to 100% (entirely due to genetic variation). However, the magnitude of the heritability tells us little to nothing about the potential genetic or environmental association between two or more related pathologies. Multivariate twin studies are more useful for addressing whether co-occurring mental disorders demonstrate overlap in their genetic and environmental risk factors (Neale & Maes, 2001).

1.4.2. Twin Studies in OCD with other Anxiety Disorders

OCD has been confirmed to run in families, with the risk of developing the disorder increasing proportionally to the degree of genetic relatedness with the individual proband (Mataix-Cols et al., 2013). For example, first-degree relatives are at significantly higher risk of developing OCD than second and third degree relatives. Twin studies have supported these findings, indicating that OCD and OC symptoms are moderately heritable in adults (approx. 27-47%) and slightly higher in children (between 45-65%) (van Grootheest, Cath, Beekman, & Boomsma, 2005). Specifically, obsessions seem to be more heritable (around 33%) compared to compulsions (26%) (Jonnal, Gardner, Prescott, & Kendler, 2000). Furthermore, the heritability of OC symptoms appear to be stable over time and fairly equal across genders in non-clinical samples (van Grootheest, Cath, Hottenga, Beekman, & Boomsma, 2009).

There are only two recent studies that look into the heritability of the OC dimensions, both of which utilise adult female twin samples, and which present somewhat contradictory results. Van Grootheest *et al.* (2008) found that contamination showed the lowest percentage of genetic variance common with the rest of OC symptom dimensions, while Iervolino *et al.* (2011) found that the same dimension was the one that shared the highest percentage of common genetic variance with the rest of the dimensions assessed. One possible explanation for these results may be related to the different statistical analyses used in each study (common and independent pathway analyses respectively), and, the different questionnaires used to assess the OC symptom dimensions. However, it seems unlikely that the vastly different results between these studies could be completely attributed to these explanations. Furthermore, only females were assessed in both studies, thus they provide only a partial account of the genetic and environmental structure of OC symptom dimensions, without considering that potential sex differences may exist. Thus, there is a clear need for further studies.

Previous twin studies of OCD, together with other anxiety symptoms and disorders, have confirmed that additive genetic risk factors are important to the etiology of OCD, with the estimated heritability of anxiety disorders, including OCD, ranging between 23% and 40% (Hettema, Prescott, Myers, Neale, & Kendler, 2005; Mosing et al., 2009; Tambs et al., 2009). While it seems that there is a common latent liability (around 54%) to all anxiety

disorders (Tambs et al., 2009), OCD together with specific phobias and social phobia have an important percentage of specific genetic factors (around 40-45%) distinct from the rest of the anxiety disorders. Panic and general anxiety disorder have just a 4% difference in specific genetic factors compared to the rest of anxiety disorders. Moreover, the genetic and environmental risk factors for all anxiety disorders seem to be similar in men and women (Hettema et al., 2005).

1.4.3. Twin Studies in Obsessive-Compulsive and Related Disorders

Little is known about the heritability of the OCRDs due to the lack of twin studies in this area. Heritability rates have been estimated for compulsive hoarding symptoms (50%), body dysmorphic concerns (44%) and skin picking (40%). However, all this evidence has come from a single study of only adult female twins from the "TwinsUK" registry (Iervolino et al., 2009; Monzani et al., 2012; Monzani, Rijsdijk, Cherkas, et al., 2012). Nothing is known about the heritability of hair-pulling disorder.

With regard to multivariate twin studies of the genetic and environmental overlap between OCD and other OCRDs, there are only two studies that have been reported in female twins – again from the TwinsUK study. The first examined the genetic and environmental factors of covariance between OCD and BDD. It found that 64% of the total covariance was explained by shared additive genetic factors and only 36% of the variance was accounted by non-shared environmental factors. More specifically, obsessing and symmetry OC dimensions were the dimensions demonstrating strongest correlations with BDD symptoms: 0.35 and 0.30, respectively (Monzani, Rijsdijk, Iervolino, et al., 2012). A second recent study evaluated OCRD symptoms dimensionally in a normative population of female twins and identified two distinct liability factors: one factor primarily representing OCD symptoms, HD and BDD symptoms; and a second factor representing trichotillomania and skin picking symptoms (Monzani, Rijsdijk, Harris, & Mataix-Cols, 2014). Although further work is needed to support these findings in different populations (including males), these are the first studies showing that there is a common genetic influence among OCRDs, particularly between OCD, BDD and HD.

1.5. Summary

There is an incomplete understanding of the heritability and the specific genetic bases of OCD. It has a complex multifactorial etiology comprising both biological as well as psychosocial components – although these components remain to be clearly elucidated. Moreover, OCD is clinically heterogeneous and it is unknown whether this complex phenotype reflects distinct or partially distinct etiological mechanisms.

Until recently, OCD was designated as an AD due to the similarities in phenomenology, comorbidity and aggregation it has with other families suffering from various ADs. In this context, it was implicitly understood that OCD was sharing common etiological (genetic and environmental) factors with other ADs. However, the idea that disorders not classified in the anxiety group could also be associated with OCD has generated an intense and controversial debate about whether OCD is indeed an AD or, in fact, more closely related to other disorders, with the anxiety merely a consequence of OCD symptoms. Unfortunately, there is a lack of empirical twin studies that have actually directly compared the OCD, OCRDS and ADs. OCD was finally classified into a new category of DSM-5 together with BDD, hoarding disorder, excoriation disorder and hair-pulling disorder with a paucity of evidence for common etiology mechanisms among them. The strongest arguments for this new classification relate to the high rates of comorbidity between OCD and other OCRDs and their family aggregation; however, similar arguments have been proposed by other authors in an attempt to show evidence for the associations between ADs and OCD. This differentiation between ADs vs. OCRDs implies that anxiety is not a primary characteristic of OCD patients, or patients experiencing other OCRDs. This implication is not well supported on empirical grounds and clearly requires further examination.

In summary, prior twin studies indicate that OCD shares genetic factors with ADs and with specific OCRD symptoms, at least in female twins. We are not aware of studies that have systematically evaluated the relationship between all OC symptom dimensions and (1) ADs and (2) OCRD symptoms in the same twin population and assessed at the same period of time. The assessment of a normative population of twin siblings offers the unique opportunity of estimating the heritability and influence of shared and non-shared environmental factors on the prevalence of OCRD symptoms; i.e. if one is able to show that

the correlations between OCD and OCRD symptoms are greater than those between OCD and ADs symptoms in monozygotic (identical) twins, as compared to dizygotic (non-identical) twins, one might argue that the there is greater biological identity between OCD and some conditions of the OCRD rather than ADs.

Because classificatory systems are highly influential in clinical practice and research, it is necessary to clarify whether OCD and other OCRDs have a relationship with other ADs. There are three studies that encompass this thesis's aim of disentangling the proportion of common and specific genetic risk factors for OCD and OC symptom dimensions in comparison with other anxiety and OCRD symptoms. The identification of more stable, comprehensive and homogeneous endophenotypes of analysis in OCD could have a large impact on improving patients' quality of life, helping to develop tailored prevention and treatment programs, and reducing dramatic burden and costs associated with the handling of such a complex and heterogeneous disorder.

CHAPTER 2

GENERAL AIMS AND HYPOTHESES

GENERAL AIMS

The present thesis focuses on clarifying the etiological relationships between OCD, OCRDs and ADs, by way of the twin study approach. The aim of this research was to examine the genetic and environmental factors that may be shared between OCD (and its main obsessive-compulsive symptom dimensions) and other OCRDs and ADs in an adult twin population voluntarily registered with the Australian Twin Registry. Using two different statistical methodologies (classical twin modeling based on structural equation modeling and ICE FALCON analysis to infer causation after controlling for familial confounding), we sought to address the debated question of whether OCD is more etiologically aligned with the symptoms of other OCRDs or ADs.

SPECIFIC AIMS & HYPOTHESES:

Study 1

Aims

- To study, using different *univariate models*, the prevalence and heritability of OCRD and anxiety disorder symptoms together in a twin population, as well as the potential influence of genetic sex differences in explaining these heritability rates.
- To examine hypochondriasis symptoms given parallel debates denoncing its optimal classification in relation to anxiety and OCRDs.

Specific Hypotheses

- Based on previous twin studies, we hypothesise that the prevalence for all of the symptom domains will be higher in ADs versus OCRDs. We expected potential genetic sex differences, particularly in panic disorder symptoms (based on previous biological studies suggesting sex differences in relation to the experience of physical symptoms of panic).

Novelty of the study

- No previous twin study has examined the presence of genetic and environmental sex differences in hoarding disorder, hypochondriasis and BDD together in the same adult twin population.

Study 2

Aims

- To assess the structure of genetic and environmental risk factors for dimensional representations of OCD, other OCRD and AD symptoms using classical *multivariate twin modeling* and controlling by age and gender.
- To study potential causal relationships between OCD and other OCRDs and ADs, eliminating the familial confounding also controlling by age and gender.

Specific Hypothesis

- We hypothesise that if OCD aligns more with certain OCRDs as the new DSM-5 classification proposes, then evidence for strong common genetic liability should be minimal in a multivariate analysis that combines OCRDs with ADs. Also, if this association is evident, then there should be minimal evidence for potential causal influences between OCD and ADs.

Novelty of the study

- No previous twin study has calculated the genetic and environmental risk factors of OCD. Particularly not one that overlaps other ADs at the same time with the new OCRDs in an adult population of males and females. This is also the first twin study to apply ICE FALCON (a causal twin modeling approach) in the mental health field.

Study 3

Aim

- To investigate the structure of genetic and environmental influences between the main obsessive-compulsive symptom dimensions (sexual/religious thoughts, checking, symmetry/ordering and washing) and the symptoms of other OCRDs and ADs, using a *multivariate twin approach*.

Specific hypothesis

- Based on existing neurobiological and clinical (higher comorbidities) evidence, we hypothesized that sexual/religious and harm/checking dimensions might demonstrate greater genetic overlap with other AD symptoms.

Novelty of the study

- This is the first twin study that systematically assesses the genetic and environmental overlap in the four main OC symptom dimensions with other ADs and OCRDs in order to elucidate whether the OC dimensions present different etiological patterns.

CHAPTER 3

METHODS

3. METHODS

All the results presented in the three different papers are based on the same sample. The participants and the specific analysis used in the current thesis are explained in extreme detail in each paper. Here only a brief summary of the material and methods performed to address the proposed aims is presented.

3. 1. Participants

The Australian Twin Registry (ATR) is an organisation that supports medical and scientific studies that involve the participation of twins and/or their relatives. The ATR was established as a national registry with support from the National Health and Medical Research Council (NHMRC) in 1981. Currently it is funded by the federal government through the NHMRC in order to put researchers in touch with twins who might be willing to take part in particular projects. The ATR has been able to play a role in fostering the development of synergistic research programs and has become a model for integrating public health and biomedical research. More than 35,000 pairs of twins are members of the ATR, making it one of the largest volunteer registries of its kind in the world. All requests to carry out research studies with the ATR are carefully reviewed. Approved projects must satisfy ethical guidelines and be of significant value to the area of proposed research.

In our project the ATR selected at random a cohort of up to 7,000 participants (3,500 twin pairs) between 18-45 years (all twin and gender combinations) who were available and willing to be contacted for research. The ATR contacted each member of the pair by email. The survey was sent by an independent link to each participant using the SurveyMonkey website. In the link an ATR cover letter was included as well as a response/consent form and the set of questionnaires. The data collection was opened during approximately 1 year and a half. The PhD candidate was directly involved from the beginning of the project: contacting the ATR for the first time, then applying for the expression of interest to the ATR and modifying the protocol due to the amendments suggested. The candidate was continually in contact with an ATR representative, sending reports every week during the recruitment process with all the twins that answered the survey, and also informing about the incomplete protocols in order to

initiate contact with those subjects in a second round in order to finalise their collaboration.

A total number of 2495 adult twins (1281 monozygotic and 1214 dizygotic) with known zygosity finally respond to the whole survey proposed. The sample was balanced in terms of female (1468) and males (1027) and age (34.5 and 33.4 years in MZ and DZ respectively). Please see *Study 1* "Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety disorder symptoms: A survey of the Australian Twin Registry" in order to read a detail description of the sample recruitment process.

3. 2. Psychometric Measures

We focus on symptoms, rather than discrete diagnoses to evaluate the relationship between OCD, OCRDs, and Anxiety Spectrum Disorders (ASDs). This approach has both clinical and biological relevance. From the clinical point-of-view, it would not be practical to assess each research subject for the presence of a DSM-IV psychiatric disorder. This is also the problem of assessing subjects for the presence of tics. We believe that a clinician is generally needed to provide adequate diagnosis of a tic, as the motor symptom may resemble different extrapyramidal disorders (e.g. dystonias, myoclonus, stereotypies, chorea, etc.). From the biological point-of-view, one needs to take into account that the diagnostic threshold depends on many social, rather than genetic factors.

The twin's survey includes questions about: life-events; personal and family socio-demographic status; personal and family history of psychiatric disorders, including alcohol and drug use/abuse, although these last variables were not included in the final analyses. The questions used are mostly from other Australian and international surveys as well as questions specifically designed for this study. The project does not involve the follow-up of the participants. In total, we requested approximately 20-25 minutes of participants' time to complete a questionnaire-based survey.

The survey is composed by the following questionnaires:

OCRDs self-reported questionnaires:

- Obsessive Compulsive Inventory-Revised (OCI-R): Cut-off >= 21.
    - Subscales (cut-off):
        - Checking (>5)
        - Hoarding (>5)
        - Obsessing (Forbidden thoughts) (>5)
        - Ordering (>7)
        - Washing (>3)

- Hoarding Rating Scale (HRS): Cut-off >=17.
- Dysmorphic Concerns Questionnaire (DCQ): Cut-off >= 11.
- The Skin-Picking Scale (SPS): Cut-off >= 7.
- Whiteley Index, for Hypochondriasis (WI): Cut-off >=9.
- The Massachussets General Hospital- Hair Pulling Scale (MGH-HPS): Cut-off >= 17.

Anxiety Disorders self-reported questionnaires:

- Anxiety Sensitivity Index Revised (ASI-R) for assessing panic symptoms: Cut-off >= 25.
- Social Phobia Inventory (SPIN): Cut-off >= 19
- Depression and Anxiety Stress Scale (DASS-21): Cut-off >= 16 for "stress" subscale which is the subscale more associated with general anxiety symptoms.

Please see *Study 1 (supplementary material)* for more information about the specific questionnaires and material used in the current thesis.

3. 3. Statistical Analysis

Twin designs compare the similarity of monozygotic (MZ) or identical twins with that of dizygotic (DZ) twins. If the correlation in the feature of interest for MZ twins is significantly higher than the correlation for DZ twins, there is evidence for a genetic effect on the characteristic being measured. The twin study partitions phenotypic variance into three components usually expressed as a proportion of phenotypic variance. The first is *heritability,* defined as the proportion of phenotypic variance attributable to the additive effects of genes. Heritability is usually denoted as *h2* or *A* (as additive genetic factor) and is estimated as twice the difference between MZ and DZ correlations. The second component of phenotypic variance is referred to as *common environment (C).* It is the proportion of observed variance attributable to all those environmental variables that twins share and that make twins similar on the trait. Common environment is indexed as twice the DZ correlation minus the MZ correlation. The final variance component is called *unique (or non-shared) environment (E).* It is the proportion of variance attributable to environmental variables that are uniquely experienced by an individual and not shared by members of a twin pair and that make twins uncorrelated for the trait.

The following analyses have been performed in the current thesis. Detailed descriptions of them are provided in the corresponding study:

1. **Univariate twin modeling** analysis looking at the genetic differences between male and females in each symptom dimension: **quantitative and qualitative differences**. Quantitative differences refer to differences in the magnitude of common genetic and environmental influences when comparing MZ male and DZ male with that of MZ female and DZ female. Qualitative differences refer to the estimation of distinct genetic and/or environmental influences for males and females, which is implied if the correlation for DZ opposite-sex is significantly less than the correlation for the same-sex DZ twins. See *Study 1* for more information details.

2. Classical **multivariate twin modeling** analysis to study the common genetic liability between OCD and the anxiety and OCRD symptoms. Common and

independent pathway models were conducted in order to simplify the data. See *Study 2* for more information.

3. **ICE FALCON analysis**: Inference on causation from examination of familial confounding. Those novel analyses were used to assess the potential causal relationship between OCD and the ADs and OCRDS. See *Study 2* and its supplementary material for more information.

4. **Multivariate** twin analysis using **continuous and categorical variables** in the same model and **controlling by age and gender**. Please see *Study 3* for more information.

CHAPTER 4

RESULTS

The present thesis contains the following results:

Paper 1

López-Solà C, Fontenelle LF, Alonso P, Cuadras D, Foley D, Pantelis C, Pujol J, Y.c el M, Cardoner N, Soriano-Mas C, Menchón JM, Harrison BJ.

Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety Disorder Symptoms: A Survey of the Australian Twin Registry.

Paper 2

López-Solà C, Fontenelle LF, Bui M, Hopper JL, Pantelis C, Yücel M, Menchón JM, Alonso P, Harrison BJ.

Etiological Overlap between Obsessive-Compulsive Related and Anxiety Disorder Symptoms: A Multivariate Twin Study.

Paper 3

López-Solà C, Verhulst B Neale M, Fontenelle LF, Pantelis, C, Menchón JM, Alonso P, Harrison BJ.

Distinct etiological influences on obsessive-compulsive symptom dimensions: a multivariate twin study.

Study 1

American Journal of Medical Genetics: Part B

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety Disorder Symptoms: A Survey of the Australian Twin Registry

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While past twin studies indicate moderate levels of heritability of "obsessive-compulsive related" and anxiety disorder symptoms, no single study has reported such estimates in the same twin population nor examined potential genetic sex differences. We assessed symptoms of obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, hypochondriasis, panic disorder, social phobia and generalized anxiety disorder in 2,495 adult twins (1,468 female). Prevalence estimates for the corresponding symptom measures were determined using empirically derived cut-off scores. Twin resemblance was assessed by Pearson correlations and biometrical model-fitting analyses, incorporating sex-specific effects, using OpenMx. Prevalence estimates ranged from 1.6% in the symptoms of generalized anxiety to 16.9% for social phobia. Female twins demonstrated significantly higher prevalence rates across all domains with the exception of obsessive-compulsive symptoms. Additive genetic factors accounted for a moderate proportion of the total liability to each symptom domain. Evidence suggesting qualitative

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genetic sex differences (i.e., distinct genetic influences between genders) was observed for body dysmorphic concern and panic symptoms, while quantitative differences were observed for hoarding and social phobia symptoms, indicating stronger heritability in females. Novel findings in this study include the observation of probable genetic sex differences in liability towards hoarding symptoms and dysmorphic concern, as well as the lack of such differences in hypochondriasis. The trend towards qualitative sex differences in panic symptoms has some intuitive appeal with regard to biological-experimental models of panic.

Key words: obsessive-compulsive related disorders; anxiety disorders; twins; genetic sex differences; heritability

INTRODUCTION

Introduction of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has seen obsessive-compulsive disorder (OCD) reclassified from the anxiety disorders category into a new grouping of "OC-related" disorders, including body dysmorphic disorder, trichotillomania (hair-pulling disorder); as well as excoriation (skin picking) disorder and hoarding disorder as a new diagnosis. Separately, each of these disorders appears to have a clear familial aggregation [Bienvenu et al., 2000; Hettema et al., 2001; Chacon et al., 2007; Pertusa et al., 2008] as well as a higher prevalence rates in females—at least in relation to the anxiety disorders category. Much less is known about the influence of gender on the prevalence and heritability of OC-related disorders and whether there may exist potential genetic sex differences in terms of current estimated heritability rates. Because of the historical link between OCD and other anxiety disorders, there are actually very few studies to have assessed both categories of disorders in the same population at the same period of time. Epidemiological twin studies represent one such example, whereby the majority of published studies correspond to either the former (DSM-IV) conceptualization of anxiety disorders or the recently adopted conceptualization of "OC-related disorders" [Monzani et al., 2014]. Given the ongoing debate that surrounds the DSM-5 revisions, there appears to be merit in the completion of studies that assess both groups of disorders in the same population.

Twin studies represent an important research platform in psychiatry that allows estimation of the relative importance of genetic (i.e., heritable) and environmental influences on complex traits [Neale and Cardon, 1992]. Previous twin studies of anxiety symptoms and disorders have confirmed that additive genetic risk factors are important to their etiology with the estimated heritability of anxiety disorders ranging between 23% and 40% [Hettema et al., 2001; Mosing et al., 2009; Tambs et al., 2009]. With regard to OCD, the heritability of diagnosable cases has been estimated at 29% [Tambs et al., 2009], with higher rates (48%) estimated in relation to the experience of obsessive-compulsive symptoms [Clifford et al., 1984; Iervolino et al., 2011]. In the latter instance, the heritability of obsessive-compulsive symptoms has been reported as stable over time and mostly equivalent across genders in non-clinical samples [van Grootheest et al., 2009]. Regarding "OC-related disorders," heritability rates have also been estimated for compulsive hoarding symptoms (50%), body dysmorphic concern (44%), and skin picking (40%). This latter evidence has been marshalled from a single study of adult female twins from the "TwinsUK" registry [Iervolino et al., 2009; Monzani et al., 2012a,b].

To extend such recent findings, we performed the current study to compare prevalence and heritability rates for OC-related and anxiety disorder symptoms in an adult twin population, including male and female twin pair combinations, and with the intention of testing the influence of gender on estimated heritability. While the "TwinsUK" sample included females twins aged up to 86 years, we restricted the recruitment of twins to between 18 and 45 years; that is, approximating the age range at which the onset of these disorders is most prevalent in the general population [Kessler et al., 2012]. We also extended the current survey to examine hypochondriasis symptoms given parallel debate regarding its optimal classification in relation to anxiety and OC-related disorders [Phillips et al., 2010]. Thus, the primary objective of the current study was to examine the prevalence and heritability of OC-related and anxiety disorder symptoms together in a twin population, as well as the potential influence of genetic sex differences in explaining these heritability rates.

MATERIALS AND METHODS

Participants

Twins were recruited from the Australian Twin Registry (ATR)—a large national voluntary twin registry [overviewed in Hopper et al., 2013]. A total of 6,950 participants (3,475 twin pairs) were emailed by the ATR on our behalf to participate in an online survey of their experience of OC-related and anxiety symptoms. Twins were selected nation-wide according to age (18–45 years), zygosity, and gender combination, and a minimum duration of 6 months since having participated in an ATR-affiliated research study. Twin pairs were randomly selected to receive the study approach email—averaging 112 twin pairs/per week. After 2 weeks, non-responding twins were followed up with a reminder email, followed by a further telephone reminder 2 weeks later. A second phone follow up was performed for all remaining non-responders. This data collection phase ran for approximately 1 year between June 2011 and May 2012 with an overall response rate of 35.9%. We obtained a final sample of 2,495 twins (1,468 females and 1,027 males; Fig. 1).

Psychometric Measures

After providing informed consent and responding to a small number of sociodemographic factors twins completed the following self-report measures in this order: (1) Obsessive Compulsive Inventory-Revised (OCI-R) [Foa et al., 2002]; (2) Hoarding Rating Scale-Self Report (HRS-SR) [Tolin et al., 2010]; (3) Social Phobia Inventory (SPIN) [Connor et al., 2000]; (4) Anxiety Sensitivity Index (ASI) for panic symptoms [Reiss et al., 1986]; (5) Dysmorphic Concern Questionnaire (DCQ) [Oosthuizen et al., 1998]; (6) Skin-Picking Scale (SPS) [Keuthen et al., 2001]; (7) Whiteley Index (WI) to assess hypochondriasis symptoms [Pilowsky, 1967]; (8) Depression, Anxiety, and Stress Scale-21

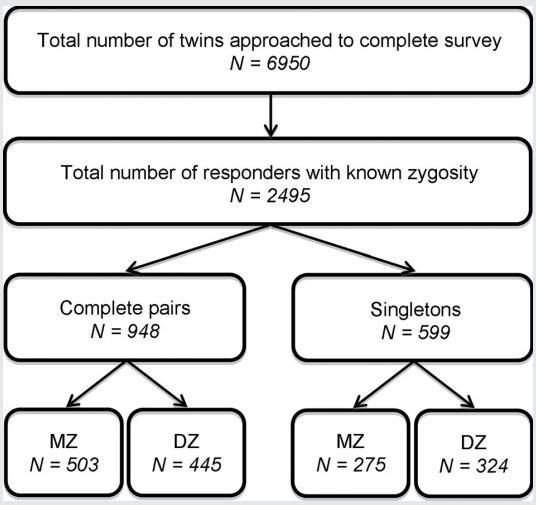

FIG. 1. Flow of the eligible twins through the study. The following zygosity and gender combinations were approached: 795 male monozygotic (MZ) pairs; 666 male dizygotic (DZ) pairs; 755 female MZ pairs; 666 female DZ pairs, and 583 male/female pairs.

(DASS-21) [Antony et al., 1998]; (9) Massachusetts General Hospital-Hair Pulling Scale (MGH-HPS) [O'Sullivan et al., 1995]. The DASS-21 "Stress" subscale was chosen as a proxy measure of generalized anxiety symptoms. This subscale measures persistent arousal, tension, irritability, and tendency to overreact to stressful events. Previous studies endorse its utility differentiating generalized anxiety disorder (GAD) from other anxiety disorders [Brown et al., 1992] as well as being strongly correlated with other measures of worry [Brown et al., 1995]. Cut-off scores were used to classify "clinical levels" of symptom ratings on each scale (see "supplementary online material"). The SPS was completed if participants first answered "yes" to one screening question: "Do you often feel the urge to pick your skin?" Similarly, four screening questions were completed for the MGH-HPS derived from the Structured Clinical Interview for DSM-Research Version (SCID-I/P). These screening questions were included in recognition of the likely low prevalence of symptoms and to reduce the general time burden of the survey as a whole.

Statistical Analysis

Estimation of prevalence. Prevalence estimates for each questionnaire were performed to quantify how many twins scored above the proposed cut-offs on each measure putatively distinguishing between "non-clinical" and "probable clinical" cases. A comparison of the prevalence rates between genders for each measure was evaluated using the Chi-square (χ^2) statistic.

Data normality. All questionnaire responses demonstrated varying degrees of skewness in their distributions. In order to improve the normality of our data Box–Cox transformations were applied [Box and Cox, 1964]. Box–Cox represents a family of power transformations that extend traditional methods in order to identify the optimal normalizing transformation regardless of whether the variable is negatively or positively skewed. In Box–Cox transformation $[y^{\lambda}_{t} = (y^{\lambda} - 1)/\lambda]$ *lambda* (λ) can adopt an almost infinite number of values to calibrate a transformation to be maximally effective in moving a variable toward normality. We therefore estimated the best λ for each variable, separately. Only with regard to the DCQ was the estimated λ statistic equal to 0. In this case, a log transformation was applied to normalize the data. Maximum likelihood model fitting analyses were then conducted on transformed continuous variables.

Estimation of cross-twin–within-trait correlations. The Box–Cox transformed data was used to estimate cross twin—within-trait correlations. Comparing cross-twin (MZ vs. DZ) within-trait correlations provides a first impression of the contribution of genetic and environmental influences on a trait [Neale and Cardon, 1992]. To investigate sex differences, twin correlations were calculated separately for the five zygosity groups: MZ males, DZ males, MZ females, DZ females, and DZ opposite-sex.

Estimation of heritability. All twin analyses were carried out in both genders using the OpenMx package for RStudio ("http://openmx.psyc.virginia.edu/getOpenMx.R"). Structural equation modeling is an analysis tool where putative genetic and environmental influences are modelled to quantify their contribution to the estimated phenotypic variance for each trait measured in a population [Neale and Cardon, 1992]. An individual's phenotype is decomposed into A (*additive genetic factors*), C (*shared environment, shared by twins*), and E (*non-shared environment plus measurement error*). In addition, four models were performed to test for potential sex differences: "qualitative," "quantitative," "scalar," and "null" models. Qualitative sex differences refer to the estimation of distinct genetic and/or environmental influences for males and females, which is implied if the correlation for DZ opposite-sex is significantly less than the correlation for the same-sex DZ twins [Haworth et al., 2008]. In other words, is there evidence of distinct genetic and/or environmental influences on a given trait in males versus females? Quantitative sex differences, by comparison, refer to differences in the magnitude of common genetic and environmental influences when comparing MZ male and DZ male with that of MZ female and DZ female. In other words, is there evidence of stronger heritability of a given trait in males versus females?" In addition, we tested the fit of a "scalar model" whereby the genetic and environmental parameters are constrained to be equal in both sexes but allowing for a different variance in each trait for males and females. Finally, we refer to the "null model" as one that equates the genetic and environmental parameters and phenotypic variance to be equal in both sexes, allowing males and females to differ in their mean scores on each scale. Reduced qualitative and quantitative submodels, where the shared environmental parameter is removed, were tested to explain the observed data most parsimoniously, thus optimizing model fit. The qualitative ACE models were compared with a saturated model imposing equal means and variance restriction across twins and zygosity to maximize information. The Akaike information criterion (AIC) statistic [Akaike, 1987] $[\chi^2 - 2(df)]$ and the difference in the χ^2 value relative to the chance in degrees of

freedom provided an indication of the models' goodness of fit [Neale and Cardon, 1992].

RESULTS

Sociodemographic Measures

Table I provides a comparison of the demographic composition of the MZ and DZ twin pair combinations. A total of 503 MZ and 445 DZ twin pairs as well as 275 MZ and 324 DZ singleton twins completed the survey (1,468 females and 1,027 males). The mean (SD) age was 34.5 (7.8) and 33.9 (8) years for MZ and DZ, respectively. With regard to demographic indices, no significant differences were observed between MZ and DZ twins (Table I).

Estimation of Prevalence

Table II reports the mean scores for each scale in the total sample and the number of twins scoring above the proposed cut-offs on each scale indicating probable "case level" symptoms. Across the entire sample, these prevalence estimates ranged from 1.6% in relation to GAD symptoms (DASS-Stress subscale) to 16.9% in social phobia symptoms. Female twins had a significantly higher prevalence than males across all scales, except for the OCI-R.

Because two cut-off scores have been proposed for the DCQ ($\geq$11 and $\geq$17) and DASS-21 (between 13 and 16, and $\geq$17) scales, we only report prevalence estimates for the highest proposed cut-offs in Table II in order to classify more clinically symptomatic levels. With regard to the DCQ, 8.8% of the entire sample (6.6% female and 2.2% male) scored above the lower proposed cut-off ($\geq$11) while almost 2% of the sample demonstrated probably case-level symptoms when using the higher cut-off ($\geq$17). With regard to the Stress subscale 5.2% (3.8% female and 1.4% male) reported severe symptoms of persistent arousal, tension and irritability (cut-off range 13–16), whereas only 1.6% of the sample reported extremely severe symptoms ($\geq$17) (Fig. 2).

Prevalence estimates for the SPS and MGH-HPS were not as well estimated compared to other measures, primarily due to the use of initial screening questions for these scales. With regard to SPS, only 52 twin pairs (33 MZ and 19 DZ) and 8 MZ and 4 DZ singleton twins screened positive and completed all items, whereas no complete pairs answered the full MGH-HPS. For the SPS, 24% of these participants scored above the proposed cut-off (17.8% females; 6.3% males). Due to the low response rate for skin picking and trichotillomania it was not possible to estimate their heritability in further analyses.

Estimation of Cross-Twin—Within-Trait Correlations

For all measures, cross-twin—within-trait Pearson's correlations for male and female twins were double in magnitude in the MZ compared to DZ pairs (Table III), consistent with a genetic influence across symptom domains. Correlations for opposite-sex DZ twins were similar for same-sex DZ twins in SPIN and

TABLE I. Demographic Characteristics of the Female and Male Twin Sample

Sociodemographic (N = 2,495 twins)	Monozygotic (N = 1,281)	Dizygotic (N = 1,214)	*t*-Student/χ^2 (*P*-value bilateral)
Gender			
Male/male	204 pairs/125 singleton	111 pairs/132 singleton	
Female/female	299 pairs/150 singleton	194 pairs/192 singleton	—
Male/female	—	140 pairs	
Age			
Mean (SD)	34.5 (7.8)	33.9 (8)	1.98 (0.05)
Marital status			
Married/partner (%)	44%	47%	3.15 (0.53)
Girlfriend/boyfriend (%)	12.1%	10.6%	
Divorced/separate (%)	33.7%	33.6%	
Single (%)	10.2%	8.6%	
Widowed (%)	0%	0.1%	
Education			
Primary/secondary school	59.1%	56.2%	3.97 (0.27)
TAFE qualification	28.1%	28.3%	
Undergraduate	7.8%	9.4%	
Post-graduate	4.9%	6.2%	
Employment			
Student (%)	43.6%	39.9%	7.12 (0.21)
Unemployed (%)	8.4%	7%	
Self-employed (%)	18%	19.1%	
Part/time employed (%)	12.5%	14.3%	
Full/time employed (%)	17.6%	19.7%	

OCD, obsessive-compulsive disorder; TAFE, technical and further education.

TABLE II. Means and Standard Deviation (SD) of the Total Scores in Each Scale By Sex and By Zygosity

Variables (cut-off)	Mean (SD) total score				Prevalence						
	Sex		Zygosity		Total Sample (N = 2,495)		Female Twins (N = 1,468)		Male Twins (N = 1,027)		Compare between gender
	Male	Female	MZ	DZ	N	%	N	%	N	%	χ^2 (*P*-value)
OCI-R (≥21)	8.3 (7.8)	8.8 (8.6)	8.6 (8.6)	8.6 (8)	218	8.7	139	9.5	79	7.7	2.4 (0.12)
HRS-RS (≥17)	2.7 (4)	2.8 (4.8)	2.7 (4.5)	2.9 (4.6)	64	2.6	48	3.3	16	1.6	7.1 (0.008)
DCQ (≥17)	3.6 (3.3)	4.9 (4.4)	4.2 (3.9)	4.5 (4.1)	47	1.9	41	2.8	6	0.6	15.95 (<0.001)
WI (≥8)	2.3 (2.4)	2.8 (2.7)	2.6 (2.7)	2.6 (2.6)	170	6.8	116	7.9	54	5.3	6.65 (0.01)
ASI (≥30)	7.3 (7.3)	9.1 (9.4)	8.3 (8.7)	8.5 (8.7)	87	3.5	69	4.7	18	1.8	15.6 (<0.001)
SPIN (≥21)	9.9 (9.7)	12.6 (12.1)	11.5 (11.5)	11.5 (10.9)	421	16.9	298	20.3	123	12	29.8 (<0.001)
DASS.Stress (≥17)	3.3 (3.6)	4.5 (4.3)	4.1 (4.2)	3.9 (3.9)	40	1.6	30	2	10	1	4.39 (0.04)

MZ, monozygotic; DZ, dizygotic; OCI-R, obsessive-compulsive inventory–revised; HRS-SR, hoarding rating scale-self report; DCQ, dysmorphic concern questionnaire; WI, Whiteley index; ASI, anxiety sensitivity index; SPIN, social phobia inventory; DASS.Stress, stress subscale of the depression, anxiety, and stress scale.
Prevalence for total sample and separated by gender of problematic symptoms based on empirically defined cut-off scores on each scale.

hypochondriasis. However, opposite-sex DZ twins correlations were lower compare to same-sex correlations for panic (ASI), obsessive-compulsive (OCI-R), generalized anxiety (Stress subscale), dysmorphic concern (DCQ), and hoarding (HRS-SR) symptoms, suggesting that qualitative sex differences might be expected in the latter domains.

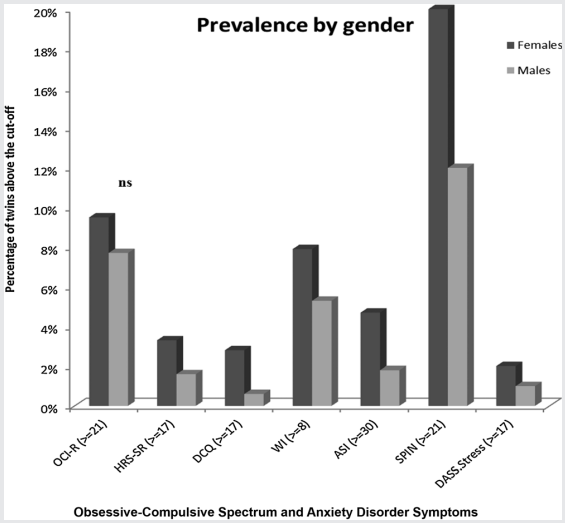

FIG. 2. Percentage of problematic symptoms for male and female based on empirically defined cut-off scores on each scale. OCI-R, Obsessive-Compulsive Inventory–Revised; HRS-SR, Hoarding Rating Scale-Self Report; DCQ, Dysmorphic Concern Questionnaire; WI, Whiteley Index; ASI, Anxiety Sensitivity Index; SPIN, Social Phobia Inventory; DASS.Stress, Depression, Anxiety and Stress Scale-Stress Subscale. ns, Non-significant differences between gender.

Estimation of Heritability

The results of our model-fitting analyses are summarized in Tables IV and V. Consistent with the pattern of observed cross-twin—within-trait correlations, additive genetic factors (A) accounted for a moderate proportion of the total variation in liability to each symptom domain. However, we observed no genetic sex differences in OCI-R, hypochondriasis (WI) and generalized anxiety (DASS-Stress) symptoms. In relation to hypochondriasis and generalized anxiety symptoms, the scalar model demonstrated best fit, indicating a significant difference in phenotypic sex variance.

For OC-related symptoms, we found a tendency for hoarding symptoms (HRS-SR) and DCQ to demonstrate genetic sex differences (Table IV). The quantitative model demonstrated best fit with regard to hoarding after removing the influence of shared environment (C), which significantly improved fit ($P = 0.90$) compared to the quantitative ACE model ($P = 0.63$). Specifically, we identified a tendency towards greater heritability of hoarding symptoms in females (38%) versus males (25%). For DCQ, the qualitative AE model demonstrated best-fit compared to the saturated model, after removing the influence of C ($P = 0.12$). Although this result can only be described as a trend level effect, it was more parsimonious than the full ACE qualitative model ($P = 0.06$). Other reduced models testing quantitative sex differences and non-genetic sex differences did not improve the fit of the data. Therefore, in relation to DCQ, potentially distinct genetic influences occur in this domain between males and females (genetic correlation between both sexes; $rG = 3.58^{-13}$).

In relation to the anxiety traits (Table V), evidence for genetic sex differences was identified in relation to panic (ASI) and social phobia (SPIN) symptoms. For panic symptoms, the qualitative AE model demonstrated best fit when compared with the saturated

TABLE III. Cross-Twin—Within-Trait Correlations for Monozygotic and Dizygotic Twins and Stratified By Sex and Zygosity (n = 2,495 Twins)

Cross-twin-within-trait correlations	MZ (95% CI)	DZ (95% CI)	MZM (95% CI)	DZM (95% CI)	MZF (95% CI)	DZF (95% CI)	DZos (95% CI)
OCI-R	0.41 (0.34, 0.48)	0.17 (0.06, 0.26)	0.40 (0.27, 0.51)	0.16 (−0.03, 0.33)	0.42 (0.32, 0.51)	0.23 (0.09, 0.36)	0.06 (−0.12, 0.23)
HRS-RS	0.33 (0.25, 0.41)	0.15 (0.06, 0.24)	0.25 (0.11, 0.37)	0.14 (−0.05, 0.31)	0.39 (0.29, 0.48)	0.19 (0.05, 0.32)	0.10 (−0.07, 0.27)
DCQ	0.43 (0.36, 0.50)	0.10 (0.006, 0.19)	0.44 (0.32, 0.55)	0.07 (−0.11, 0.25)	0.39 (0.29, 0.49)	0.13 (−0.003, 0.26)	0.03 (−0.14, 0.20)
ASI	0.33 (0.25, 0.40)	0.13 (0.04, 0.22)	0.29 (0.15, 0.41)	0.21 (0.03, 0.38)	0.34 (0.24, 0.43)	0.19 (0.05, 0.32)	0.00 (−0.16, 0.16)
SPIN	0.46 (0.39, 0.52)	0.18 (0.09, 0.27)	0.38 (0.25, 0.49)	0.07 (−0.11, 0.25)	0.49 (0.40, 0.56)	0.24 (0.11, 0.36)	0.16 (−0.01, 0.32)
DASS.Stress	0.36 (0.28, 0.43)	0.16 (0.07, 0.25)	0.32 (0.19, 0.44)	0.21 (0.03, 0.38)	0.35 (0.25, 0.45)	0.16 (0.03, 0.29)	0.10 (−0.06, 0.26)
WI	0.34 (0.26, 0.42)	0.17 (0.08, 0.25)	0.31 (0.18, 0.43)	0.12 (−0.06, 0.30)	0.35 (0.25, 0.44)	0.17 (0.04, 0.31)	0.19 (0.02, 0.34)

MZ, monozygotic; DZ, dizygotic; CI, confidence interval; MZM, monozygotic male twins; DZM, dizygotic male twins; MZF, monozygotic female twins; DZF, dizygotic female twins; DZos, dizygotic opposite-sex twins; OCI-R, obsessive-compulsive inventory—revised; HRS-SR, hoarding rating scale-self report; DCQ, dysmorphic concern questionnaire; ASI, anxiety sensitivity index; SPIN, social phobia inventory; DASS.Stress, stress subscale of the depression, anxiety, and stress scale; WI, Whiteley index.

model ($P = 1$). The full ACE quantitative model did not significantly improve fit ($P = 0.13$), while other submodels showed a significant loss of fit: quantitative AE ($P = 0.09$), scalar ($P = 0.08$), and null ($P = 0.01$). We therefore interpret parameters offered by the qualitative AE model indicating a tendency towards distinct genetic influences between males and females. Finally, for social phobia, females (47%) demonstrated a greater heritability of symptoms compared to males (34%) in the form of a significant quantitative sex difference.

DISCUSSION

This study has examined for the first time the prevalence and heritability of both OC-related and anxiety disorder symptoms in the same twin population of male and female twin pairs. Moreover, this population was particularly well balanced in terms of the age, gender, and sociodemographic characteristics of MZ and DZ twins. As a further novelty, no previous study has investigated the existence of potential genetic sex differences—either due to a lack of male twins or small overall sample size—in relation to hoarding, body-dysmorphic and hypochondriasis symptoms. To summarize, our findings endorse existing evidence for moderate rates of heritability across all of the assessed symptom domains. Significant or trend-level genetic sex differences were detected for hoarding, DCQ, panic, and social phobia symptoms.

Prevalence

Almost nine percent of the overall sample reported OCI-R symptoms that were severe enough to cause distress (OCI-R $\geq$ 21). This is consistent with a recent report of experiencing subclinical OCI-R symptoms (8.3%) in the general population [Adam et al., 2012]. Our estimates support the idea that significant OCI-R symptoms are experienced at a much greater rate in the community than is implied by assessment of diagnostic prevalence alone.

With regard to compulsive hoarding symptoms, we have characterized a similar prevalence rate (2.6%) to the only other twin study utilizing the HRS-SR [2.3%; Iervolino et al., 2009]. For DCQ, we observed a similar prevalence (2%) compared to studies based on the full diagnostic assessment of community-based samples ranging from 0.7% to 2.4% [Faravelli et al., 1997; Otto et al., 2001; Koran et al., 2008].

In relation to anxiety symptoms, 3.5% reported panic-related symptoms, which is consistent with other studies of general community samples reporting a prevalence between 2.5% and 3.4% based on the assessment of diagnostic criteria [Wittchen et al., 2008; Mosing et al., 2009]. In our cohort, social phobia symptoms were slightly higher (16.9%) than in previous epidemiological surveys where diagnostic prevalence rates have been estimated between 7% and 13% [Furmark, 2002; Kessler et al., 2005]. However, as previously emphasized, our study provides symptom-level as opposed to diagnostic-level prevalence estimates. In relation to our measure of generalized anxiety, 5% of individuals reported significant and persistent arousal, tension, and irritability with 1.6% reporting extremely severe of these symptoms that would be considered in the range of other population-based estimates of GAD: 1.9% to 5.1% [Wittchen, 2002]. Lastly, the prevalence of hypochondriasis

TABLE IV. Model-Fitting Analyses to Test Sex Differences for Obsessive-Compulsive Spectrum Traits and their Parameter Estimates

	Model fitting results						Parameters of the models (95% CI)		
							A	C	E
Models (S^2 m/S^2 f)	**−2LL**	**df**	**$\Delta\chi^2$ (Δdf)**	**AIC**	***P***	**Model compared with**	**Male/female**	**Male/female**	**Male/female**
OCI-R (Obsessive-Compulsive Inventory-Revised)									
1. Saturated	7,688	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	7,691	2,486	3.54 (2)	2,719	0.17	1	–	–	–
3. Qualitative ACE (rC = FREE)	7,691	2,486	3.78 (2)	2,719	0.15	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	7,691	2,487	0.24 (1)	2,717	0.63	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	7,698	2,489	6.89 (3)	2,720	0.08	2	–	–	–
6. Scalar (1.3/1.4)	7,694	2,489	2.51 (2)	2,716	0.29	4	–	–	–
7. Null (1.3)	**7,694**	**2,490**	**2.8 (3)**	**2,714**	**0.42**	**4**	**0.39 (0.18–0.45)**	**0.00 (0.00–0.18)**	**0.61 (0.55–0.68)**
HRS-SR (Hoarding Rating Scale–Self Report)									
1. Saturated	4,047	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	4,047	2,486	0.03 (2)	−925	0.99	1	–	–	–
3. Qualitative ACE (rC = FREE)	4,047	2,486	0.07 (2)	−925	0.97	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	4,047	2,487	0.23 (1)	−927	0.63	2	0.07 (0.00–0.23)/0.38 (0.08–0.47)	0.17 (0.05–0.27)/0.00 (0.00–0.25)	0.76 (0.65–0.88)/0.62 (0.53–0.71)
5. Quantitative AE (rG = 0.5; rC = 1)	**4,047**	**2,489**	**0.6 (3)**	**−930**	**0.90**	2	**0.25 (0.13–37)/0.38 (0.29–0.47)**	–/–	**0.75 (0.63–0.87)/0.62 (0.53–0.71)**
6. Scalar (0.3/0.31)	4,050	2,489	2.8 (0)	−928	<0.001	5	–	–	–
7. Null (0.31)	4,050	2,490	3.4 (2)	−929	0.07	5	–	–	–
DCQ (Dysmorphic Concern Questionnaire)									
1. Saturated[a]	1,046	2,477	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	1,063	2,486	16.6 (9)	−3,909	0.06	1	0.42 (0.20–0.52)/0.38 (0.17–0.47)	0.00 (0.00–0.18)/0.00 (0.00–0.17)	0.58 (0.48–0.70)/0.62 (0.53–0.71)
3. Qualitative ACE (rC = FREE)	1,067	2,486	20.8 (9)	−3,905	0.01	1	–	–	–
4. Qualitative AE (rG = FREE)	**1,063**	**2,488**	**16.6(11)**	**−3,913**	**0.12**	**1**	**0.42 (0.30–0.52)/0.38 (0.28–0.47)**	–/–	**0.58 (0.48–0.70)/0.62 (0.53–0.71)**
5. Quantitative ACE (rG = 0.5; rC = 1)	1,066	2,487	3.2 (1)	−3,908	0.07	2	–	–	–
6. Quantitative AE (rG = 0.5; rC = 1)	1,070	2,489	7.06 (1)	−3,908	0.01	4	–	–	–
7. Scalar (0.09/0.10)	1,066	2,489	3.69 (1)	−3,912	0.05	4	–	–	–
8. Null (.09)	1,074	2,490	11.2 (2)	−3,906	<0.001	4	–	–	–
WI (Whiteley Index)									
1.Saturated	4,262	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	4,262	2,486	−0.37 (2)	−710	1	1	–	–	–
3. Qualitative ACE (rC = FREE)	4,262	2,486	−0.37 (2)	−710	1	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	4,262	2,487	0 (1)	−712	1	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	4,262	2,489	0.05(3)	−716	1	2	–	–	–
6. Scalar (0.31/0.35)	**4,262**	**2,489**	**0.2 (2)**	**−716**	**0.90**	**4**	**0.29 (0.06–0.39)**	**0.03 (0.00–0.22)**	**0.68 (0.61–0.76)**
7. Null (0.33)	4,265	2,490	3.1 (3)	−715	0.38	4	0.30 (0.06–0.39)	0.02 (0.00–0.21)	0.68 (0.61–0.76)

S^2 m, predicted variance in males; S^2 f, predicted variance in females; rG, genetic correlation for opposite-sex DZ twins; rC, environmental correlation for opposite-sex twins; −2LL, minus twice the log-likelihood; df, degrees of freedom; $\Delta\chi^2$, difference in goodness-of-fit statistic between the submodel and the specified "model compared with"; Δdf, change in degrees of freedom between the submodel and the specified model; AIC, Akaike information criterion [$\chi^2 - 2(df)$]; *P*, probability; A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects; CI, confidence Interval.

The best fitting models based in AIC are represented in bold text.

[a]Saturated with equal means across zygosity. The rest of the scales are compared with a Saturated with equal means and variance across zygosity.

TABLE V. Model-Fitting Analyses to Test Sex Differences for Anxiety Traits and their Parameter Estimates

	Model fitting results						Parameters of the models (95% CI)		
							A	C	E
Models (S^2 m/S^2 f)	**−2LL**	**df**	**$\Delta\chi^2$ (Δdf)**	**AIC**	***P***	**Model compared with**	**Male/female**	**Male/female**	**Male/female**
ASI (Anxiety Sensitivity Index)									
1.Saturated	7,886	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	7,885	2,486	−0.88 (2)	2,913	1	1	0.27 (0.05–0.41)/0.29 (0.00–0.42)	0.03 (0.00–0.20)/0.04 (0.00–0.31)	0.70 (0.59–0.82)/0.67 (0.58–0.77)
3. Qualitative ACE (rC = FREE)	7,884	2,486	−0.15 (2)	2,912	1	1	–	–	–
4. Qualitative AE (rG = FREE)	**7,885**	**2,488**	**−0.7 (4)**	**2,909**	**1**	**1**	**0.30 (0.18–0.41)/0.34 (0.24–0.42)**	–/–	**0.70 (0.59–0.82)/0.66 (0.58–0.76)**
5. Quantitative ACE (rG = 0.5; rC = 1)	7,887	2,487	2.25 (1)	2,913	0.13	2	0.29 (0.07–0.40)/0.17 (0.00–0.40)	0.00 (0.00–0.16)/0.14 (0.00–0.34)	0.71 (0.60–0.83)/0.69 (0.59–0.80)
6. Quantitative AE (rG = 0.5; rC = 1)	7,888	2,489	2.85 (1)	2,910	0.09	4	0.28 (0.16–0.40)/0.33 (0.23–0.42)	–/–	0.72 (0.60–0.84)/0.67 (0.58–0.76)
7. Scalar (1.3/1.5)	7,888	2,489	3.05 (1)	2,910	0.08	4	–	–	–
8. Null (1.4)	7,894	2,490	9.44 (2)	2,915	0.01	4	–	–	–
SPIN (Social Phobia Inventory)									
1.Saturated	8,803	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	8,804	2,486	1.09 (2)	3,832	0.60	1	–	–	–
3. Qualitative ACE (rC = FREE)	8,804	2,486	1.30 (2)	3,833	0.52	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	8804.4	2,487	0.20 (1)	3,831	0.65	2	0.35 (0.15–0.45)/0.44 (0.17–0.54)	0.00 (0.00–0.14)/0.04 (0.00–0.27)	0.65 (0.55–0.77)/0.53 0.45–0.62)
5. Quantitative AE (rG = 0.5; rC = 1)	**8804.5**	**2,489**	**0.28 (3)**	**3,826**	**0.96**	**2**	**0.34 (0.23–0.45)/0.47 (0.39–0.55)**	–/–	**0.66 (0.55–0.77)/0.53 (0.45–0.61)**
6. Scalar (2.06/2.11)	8,808	2,489	3.63 (0)	3,830	<0.001	5	–	–	–
7. Null (2.09)	8,808	2,490	3.85 (1)	3,828	0.05	5	–	–	–
DASS.Stress (Depression, Anxiety, and Stress Scale—Stress Subscale)									
1.Saturated	6,615	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	6,614	2,486	−0.65 (2)	1,642	1	1	–	–	–
3. Qualitative ACE (rC = FREE)	6,614	2,486	−0.34 (2)	1,642	1	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	6,614	2,487	0.31 (1)	1,640	0.60	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	6614.5	2,489	0.54 (3)	1636.5	0.92	2	–	–	–
6. Scalar (0.80/0.89)	**6614.5**	**2,489**	**−0.07 (0)**	**1636.5**	**1**	**5**	**0.32 (0.09–0.40)**	**0.006 (0.00–0.20)**	**0.67 (0.60–0.75)**
7. Null (0.85)	6,618	2,490	3.73 (1)	1,638	0.05	5	–	–	–

S^2 m, predicted variance in males; S^2 f, predicted variance in females; rG, genetic correlation for opposite-sex DZ twins; rC, environmental correlation for opposite-sex twins; −2LL, minus twice the log-likelihood; df, degrees of freedom; $\Delta\chi^2$, difference in goodness-of-fit statistic between the submodel and the specified "model compared with"; Δdf, change in degrees of freedom between the submodel and the specified model; AIC, Akaike information criterion [$\chi^2 - 2(df)$]; *P*, probability; A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects; CI, confidence Interval.
The best fitting models based in AIC are represented in bold text.

symptoms (6.8%) was similar to that reported in a recent survey of health anxiety in Australia (6%) [Sunderland et al., 2013].

Significantly higher prevalence rates in females compared to males were observed across all measures with the exception of OCI-R symptoms, which taken together is generally consistent with prior studies in community samples [Faravelli et al., 1997; Rief et al., 2006; Koran et al., 2008; Adam et al., 2012; Kessler et al., 2012]. The highest prevalence rate in females was in relation to social phobia, which accords well with previous estimates [Magee et al., 1996; Lampe et al., 2003]. More controversy surrounds hypochondriasis and compulsive hoarding. Epidemiological studies of hypochondriasis are in fact very rare. Two initial studies found no gender differences in hypochondriasis [Gureje et al., 1997; Escobar et al., 1998]. However, a representative study [Rief et al., 2001] noted significantly higher scores in women, but with a small effect size. Least consistent have been gender-based prevalence estimates in compulsive hoarding [Frost et al., 2012]. Two epidemiological studies have reported compulsive hoarding to be more prevalent in males than females [Samuels et al., 2008; Iervolino et al., 2009], although one study [Samuels et al., 2008] did not use a standardized questionnaire to assess hoarding. In the same direction as our results, studies of clinical samples indicate a higher prevalence of compulsive hoarding disorder in females [Steketee and Frost, 2003; Pertusa et al., 2008; Mataix-Cols et al., 2010].

Heritability

Our findings indicate familial aggregation in all symptoms assessed as observed in the pattern of cross-twin—within-trait correlations. The heritability analyses suggest that this familiarity is primarily attributable to genetic factors and not to the shared environment. The results of the twin analyses indicate that genetic factors account for between 30% (i.e., hypochondriasis) and 47% (i.e., social phobia in females), which is consistent with moderate genetic factors contributing to the aetiology of the symptom domains assessed.

The heritability rates for OCI-R symptoms and hypochondriasis appear to be in line with past studies [van Grootheest et al., 2005; Taylor et al., 2006]. Similarly, a recent study of OCI-R symptoms did not report evidence of genetic sex differences [Mataix-Cols et al., 2013]. Ours is the first twin study to suggest no prominent genetic sex differences in relation to hypochondriasis symptoms in adults, extending the only other twin study of hypochondriasis symptoms [Taylor et al., 2006]. For hoarding symptoms we observed a lower heritability rate (38%, female; 25%, males) when compared to the recent study by Iervolino et al. (49% female only). These rates may be explained by the prominent age differences between studies, with the latter study including female twins who were on average two decades older than our current sample, inclusive of elderly twins. When comparing genders, our results indicate a higher heritability of hoarding symptoms in females. This result contrasts with the only other twin study of hoarding symptoms to formally test for genetic sex differences [Ivanov et al., 2013]. In adolescents, Ivanov et al. [2013] reported quantitative sex differences, with genetic influences in boys accounting for considerably more phenotypic variance than in girls (32% vs. 2%). These authors invoked the notion of dynamic developmental genetic and environmental influences operating between adolescence and adulthood in order to explain the low heritability rate observed in young female twins. By adulthood, our results suggest a reversed pattern of heritability, although the actual rates being more similar between females and males. Clearly, further studies are needed to understand how gender impacts on the etiology of hoarding taking into account developmental trajectories.

In relation to DCQ, we observed a similar rate of heritability (42% vs. 44%) to the recent study by Monzani et al. [2012a]. Our results extend their work by indicating a trend towards qualitative sex differences, meaning that different biological risk factors may underlie the manifestation of these symptoms in females and males. The DCQ, as used in our current study, may be considered to represent quite a broad phenotype that captures body image concerns also common to eating disorders, which are more prevalent in females [Smink et al., 2012]. Interestingly, recent studies examining putative biological risk factors for such disorders in twin populations have provided some evidence for distinct developmentally mediated sex liability mechanisms, including levels of prenatal testosterone exposure [Culbert et al., 2008]. It remains untested whether such mechanisms may contribute to sex differences in risk towards body DCQ in addition to eating disorders.

In relation to anxiety symptoms, we found a similar heritability for social phobia symptoms in males compared to a recent study based on the full assessment of DSM criteria (34% vs. 39%) [Mosing et al., 2009]. When compared to studies that have assessed social phobia symptoms using the fear of negative evaluation scale, our heritability estimate is closest with regard to female twins (47% vs. 48%) [Stein et al., 2002]. While some studies have reported no heritable sex differences in fear and phobia (including social phobia) [Hettema et al., 2005; Middeldorp et al., 2005], another study reported that social phobia in males was explained by genetic risk factors and in females by familial-environmental factors [Kendler et al., 2002]. However, two additional twin studies performed separately in males and females reported lower heritability in males (20%) [Kendler et al., 2001] than females (30%) [Kendler et al., 1992a]. This latter pattern is more in agreement with our finding of a quantitative sex difference and with a recent meta-analysis in separation anxiety disorder (associated with social phobia in adulthood [Hofmann et al., 2004]), where genetic risk was reported to be double in females (52%) compared to males (26%) [Scaini et al., 2012].

For panic symptoms, we estimated a similar heritability (30–34%) compared to previous panic disorder-level estimates [33% in Tambs et al., 2009; 38% in Mosing et al., 2009], but a lower rate as compared to a former population-based study of the ASI (45%, 95% CI = 0.33–0.59) [Stein et al., 1999]. This latter difference could be due to the reduced number of male twin pairs in the Stein et al. study, potentially leading to an overestimation of heritability in their case [Van Dam et al., 2009]. Regarding gender, we found a tendency for qualitative differences, which means that a partially different set of genes might mediate the risk towards panic-related symptoms in men and women. Biological sex differences have been recently suggested in experimental studies of physical panic attack symptoms associated with a CO_2 challenge [Nillni et al., 2012]. In this study, sex differences were related to the experience of the physical symptoms of panic rather than its cognitive correlates. Our

results may also be in line with animal studies reporting a role for sex-specific hormones (i.e., progesterone) in the manifestation of anxiety and panic [Smith et al., 2006]. Along these lines, premenstrual distress has been shown to predict higher levels of panic symptoms following a CO_2 challenge [Nillni et al., 2010].

Lastly, our estimated heritability of 32% for the Stress subscale of DASS-21—our proxy measure of GAD symptoms—accords with other studies reporting the heritability of GAD [28–32.5%; Kendler et al., 2007] and when we compare to a more broadly trait of neuroticism [30–50%; Calboli et al., 2010]. A lack of evidence for genetic sex differences has also been previously noted in GAD [Hettema et al., 2005].

Limitations

Although the "dimensional liability" approach adopted here and in other twin studies is a valid and widely employed method in behavioural genetics [Jonnal et al., 2000; Hettema et al., 2001; van Grootheest et al., 2005], it will nonetheless be important to replicate these findings in clinical populations. Secondly, the use of initial screening questions is likely to have precluded our ability to attain a sufficient sample to estimate heritability for skin picking and hair pulling symptoms. However, low response rates may have been anticipated for these domains compared to others, particularly in the case of compulsive hair-pulling symptoms. Thirdly, results from Stress subscale of DASS-21 are interpreted as a proxy measure of GAD symptoms but there is reason to believe it may index a broader vulnerability trait to anxiety and depression—the so-called "general neurotic syndrome" [Henry and Crawford, 2005]. Nevertheless, previous twin studies that have assessed the genetic overlap between GAD and major depressive disorder suggest that both disorders share a strong common genetic liability [Kendler et al., 1992b; Kendler et al., 2007]. Indeed, within our sample there was a strong genetic correlation (r_A) between the Stress and Depression subscales of the DASS-21 $r_A = 0.84$.

While it is difficult to definitively exclude potential sampling biases in relation to surveys such as this [i.e., "accidental sampling method"; Powell, 1997], there are reasons to believe our results are generalizable to the population at large. For example, although our estimate of severe OC-symptoms appears high (8.7%), this rate is reduced to 2.7% when taking into account a personal history of OCD. Importantly, both estimates are consistent with a recent report of the 12-month prevalence of anxiety disorders in the Australian population [McEvoy et al., 2011]. Furthermore, as discussed above, other characteristics of this twin population, such as differences in prevalence of symptoms between genders also appears to be consistent with previous literature.

CONCLUSION

This is the first study to have assessed the prevalence and heritability of OC-related and anxiety symptoms together in an adult twin population. Novel findings include the observation of probable genetic sex differences in liability to hoarding and DCQ symptoms, as well as the lack of such differences in hypochondriasis. The trend towards qualitative sex differences in relation to the heritability of panic symptoms has some intuitive appeal with regard to biological-experimental studies of panic.

Multivariate twin studies will now be important for clarifying the extent to which these symptom domains express common or distinct genetic risk factors. Such studies are likely to be valuable in addressing ongoing debate about the optimal diagnostic classification of OCD in relation to anxiety disorders and the contribution of anxiety more broadly to the etiology of OCD.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Supplementary online material

Obsessive Compulsive Inventory-Revised (Foa et al. 2002)

The OCI-R is an 18-item questionnaire that assesses an individual's level of distress associated with OC symptoms. It evaluates 6 different symptom dimensions: washing, checking, obsessing, hoarding, ordering and neutralising. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely) and with a total overall score ranging from 0 to 72. The OCI-R total score has excellent psychometric properties (Foa *et al.* 2002). A proposed cut-off score of 21 has been suggested to discriminate between non-clinical and clinical levels of OC-symptoms (Foa *et al.* 2002).

Hoarding Rating Scale-Self Report (Tolin et al. 2010)

The HRS-SR is a 5-item questionnaire that assesses distinct components of compulsive hoarding, namely: clutter, difficulty discarding and excessive acquisition, as well as the associated distress and impairment. Each item is measured on a Likert scale ranging from 0 (none) to 8 (extreme), with 4 reflecting "moderate" symptoms. Total score on the HRS-RS range from 0 to 40. The HRS-RS total score has excellent psychometric properties. A cut-off score of 17 discriminates between non-clinical and clinical cases of hoarding (Tolin *et al.* 2010).

Social Phobia Inventory (Connor et al. 2000)

The SPIN is a 17-item inventory that assesses different aspects related to social phobia such as fear, avoidance and physiologic symptoms in different social situations. Each item is measured on a Likert scale ranging from 0 (not at all) to 4 (extremely). Total scores on SPIN ranges from 0 to 68. It has shown excellent internal consistency and good test–retest reliability and convergent and discriminant validity. It distinguishes well between those with social phobia and those with either panic disorder or OCD (Antony *et al.* 2006). A cut-off score of 21 discriminates between non-clinical and clinical cases of social phobia (Osorio *et al.* 2010).

Anxiety Sensitivity Index (Reiss et al. 1986)

The ASI is a 16-item questionnaire that assesses fears related to the experience of anxiety symptoms. Each item is measured on a Likert scale ranging from 0 (no, just a little) to 4 (very much). Total ASI scores range from 0 to 64. It has adequate reliability and validity indices (Reiss *et al.* 1986). ASI has been shown to distinguish between individuals with and without lifetime history of panic attacks, and between individuals experiencing panic attacks versus those with panic disorder (Rector *et al.* 2007). Further, patients with panic disorder were

found to have higher ASI scores than all other anxiety disorders. A cut-off score of 30 has been demonstrated as an indicator of panic disorder (Weems *et al.* 2002).

Dysmorphic Concern Questionnaire (Oosthuizen et al. 1998)

The DCQ is a 7-item questionnaire that assesses the degree of concern with physical appearance and body malfunctioning. Each item is rated on a 4-point Likert scale (0=not at all; 1=like most people; 2= more than other people; 3=much more than other people), with a total score ranging from 0 to 21. It is a reliable and valid measure for the assessment of body dysmorphic symptoms (Oosthuizen *et al.* 1998). Two different cut-off scores (≥ 11 and ≥ 17) have been proposed to discriminate between non-clinical and probable body dsymorphic diagnosis (Mancuso *et al.* 2010; Monzani *et al.* 2012).

Skin-Picking Scale (Keuthen et al. 2001)

The SPS is a 6-item questionnaire that assesses frequency/intensity of urges, time spent picking, interference, distress and avoidance. Each item is measured on a Likert scale ranging from 0 (none) to 4 (extreme), with a total score ranging from 0 to 24. The scale has excellent psychometric properties. A cut-off score of 7 has been proposed to differentiate between self-injurious versus non-self-injurious behaviour (Keuthen *et al.* 2001).

Whiteley Index (Pilowsky 1967)

The WI is a 14-item questionnaire that assesses hypochondriasis symptoms in a binary (Yes/No) format. All items are scored positively, except Item 9 "Is it easy for you to forget about yourself, and think about all sorts of other things?", which is reverse scored. Factor analysis of the WI items yielded 3 principal components ("bodily preoccupation", "disease phobia", "conviction of the presence of disease") (Pilowsky 1967). However, other studies have reported only a one-factor solution in the general population (Speckens *et al.* 1996). The WI has shown satisfactory psychometric properties (Speckens *et al.* 1996). A cut-off score of 8 is considered to distinguish clinical levels of hypochondriasis (Hiller *et al.* 2002).

Depression, Anxiety and Stress Scale-21 (Antony et al. 1998)

The DASS is a 21-item scale designed to assess three domains: Depression, Anxiety and Stress. Each item is rated on a 4-point Likert scale ranging from 0 (did not apply to my study at all) to 3 (applied to my study most of the time). The Stress subscale focuses on persistent arousal, tension, irritability and tendency to overreact to stressful events, with a total score ranging from 0 to 21. A cut-off score between 13 and 16 has been proposed to index severe symptoms (percentiles between 95 and 97), while scores of 17 or above index extremely severe symptoms (percentile 98) (Henry & Crawford 2005).

Massachusetts General Hospital-Hair Pulling Scale (O'Sullivan et al. 1995)

The MGH-HPS is a 7-item instrument that assesses the severity of hair pulling behaviour. Each item ranges from 0 to 4. The scale assesses the "urges" to perform the behaviour (frequency, intensity and ability to control) and three more items related to the behaviour of "hair-pulling" (frequency, resist and control), as well as an item measuring distress. Factor analyses suggest that MGH-HPS consists of two components (Severity/Resistance and Control), with excellent psychometric properties including sensitivity to change in hair-pulling symptoms (O'Sullivan *et al.* 1995).

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Study 2

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Etiological Overlap between Obsessive-Compulsive Related and Anxiety Disorder Symptoms: A Multivariate Twin Study

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Abstract

Background: The etiological boundary between "obsessive-compulsive related disorders" (OCRDs) including obsessive-compulsive disorder (OCD) and anxiety disorders (ADs) is unclear and continues to generate debate.

Aims: To determine the genetic overlap and the pattern of causal relationships among OCRDs and ADs.

Method: Multivariate twin modeling methods and a new regression analysis to infer causation were used, involving 2495 male and female twins.

Results: The amount of common genetic liability observed for OCD symptoms was higher when considering ADs and OCRDs in the model versus modeling OCRD symptoms alone. OCD symptoms emerged as risk factors for the presence of generalized anxiety, panic and hoarding symptoms, whereas social phobia appeared as a risk factor for OCD symptoms.

Conclusions: OCD represents a complex phenotype that includes important shared features with ADs and OCRDs. The novel patterns of risk identified between OCD and AD may help to explain their frequent co-occurrence.

Declaration of interest: None.

Introduction

There has been much debate regarding the optimal diagnostic classification of obsessive-compulsive disorder (OCD) in relation to the recently published revision of the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5*)[1–5]. This revision has seen OCD removed from the broad category of "anxiety disorders (ADs)" and placed at the center of a new separate chapter – "Obsessive-Compulsive and Related Disorders (OCRDs)" – including body dysmorphic disorder (BDD), trichotillomania (hair-pulling disorder), as well as excoriation (skin picking) and hoarding disorder (HD) as new diagnoses. Based upon available evidence, it has been argued that OCD shares a stronger commonality with these disorders in terms of its core phenomenological, neurobiological and treatment characteristics[2,6–9]. However, by implication, the notion that OCD has less in common with ADs or that anxiety is less relevant to OCD remains contested[3].

Multivariate twin studies are particularly well-suited for addressing whether co-occurring mental disorders, such as OCRDs and ADs, demonstrate overlap in their genetic and environmental risk factors[10]. Of the few existing studies to have directly examined OCD with other anxiety disorders in adults, OCD was reported to show the highest percentage of specific genetic risk factors (45%), although OCD and ADs demonstrate a substantial common genetic liability (55%)[11]. In a recent study that evaluated dimensional representations of OCD and OCRD symptoms (i.e., symptoms in a normative twin population), two distinct genetic liability factors were identified: one factor primarily representing OCD symptoms, HD and BDD symptoms; and a second factor representing trichotillomania and skin picking symptoms[12]. In this same cohort it has been reported that 64% of the total covariance between OCD and BDD was explained by shared genetic factors[13]. In summary, prior twin studies suggest that

OCD most likely shares genetic factors with both ADs and certain OCRDs. However, we highlight that no study to date has directly compared OCD to OCRDs *and* AD symptoms in the same twin population assessed at the same period of time. Such comparisons will be important for addressing whether OCD is more or less etiologically aligned with OCRDs versus ADs.

Our primary aim was to therefore more thoroughly assess the structure of genetic and environmental risk factors for dimensional representations of OCD, other OCRD and AD symptoms in an adult twin population using classical multivariate twin modeling. Our second aim was to complement this approach with a recently introduced regression-based twin analysis, which allows inferences to be made about potential causal relationships between predictor and outcome variables[14]. With both approaches we sought to address the debated question of whether OCD symptoms are more or less etiologically aligned with the symptoms of other OCRDs or ADs. If OCD is more aligned with certain OCRDs versus ADs, then evidence for a strong common genetic liability should be minimal in a multivariate analysis that combines OCRD and AD domains. Further, if this "weak" pattern of liability is evident, there should be minimal evidence for potential causal influences between OCD and AD symptoms.

Method

Participants and Measures

A total of 2495 voluntary twin members (18 to 45 years; 34.5 (7.8) and 33.9 (8) in MZ and DZ respectively) of the Australian Twin Registry (ATR) were recruited for this email-based online survey (1281 MZ and 1214 DZ twins). Figure S1 at Supplemental Information provides a schematic overview of the whole sample. All

participants gave informed consent after receiving complete information on the study and before starting to fill the survey. Full recruitment details are provided in López-Solà et al[15]. To address this study's aims, we focused specifically on twins' responses to 6 validated dimensional self-report measures of OCD, OCRD and AD symptoms. To address our particular aims, the inclusion of 3 symptom domains per "diagnostic category" was considered optimal with respect to the planned multivariate model fitting analyses. OCD symptoms were estimated with the Obsessive Compulsive Inventory-Revised (OCI-R)[16]. For OCRDs, we assessed HD symptoms with the Hoarding Rating Scale-Self Report (HRS-SR)[17] and BDD symptoms with the Dysmorphic Concern Questionnaire (DCQ)[18]. For ADs, we assessed social phobia (SP) symptoms with the Social Phobia Inventory (SPIN)[19]; panic disorder (PD) symptoms with the Anxiety Sensitivity Index (ASI)[20]; and generalized anxiety disorder (GAD) symptoms with the "Stress" subscale of the Depression, Anxiety and Stress Scale-21 (DASS-21)[21].

Statistical Analysis

To ensure data normality, all questionnaire responses underwent Box-Cox transformations [$y^{\lambda}_{t}=(y^{\lambda} -1)/ \lambda$][15,22]. To examine the phenotypic structure of OCRD and AD symptoms prior to classical twin modeling analysis, a varimax-rotated principal component analysis (PCA) was performed in SPSS (version 20; SPSS, Inc), adjusting the transformed total scores of each scale for age and gender. To not confound the comparison of the OCD symptoms and HD symptoms measured by the HRS-SR, estimated total scores on the OCI-R excluded twins' responses to the hoarding subscale of this measure (items 1, 7 and 13).

Classical Multivariate Twin Modeling

Structural equation models were conducted on transformed continuous variables fitted by maximum likelihood. Because univariate twin modeling of this data indicated the presence of genetic sex differences[15], all multivariate twin models were performed using standardized residual values for each symptom domain adjusted for age and gender[23]. While controlling for the influence of gender in this manner has been a useful approach in multivariate twin studies, this is not the same as testing for multivariate genetic sex differences in which the variance-covariance structure of the model is allowed to be different for males and females. We chose to control rather than test for multivariate genetic sex differences i) because of an absence of specific hypothesis regarding gender-related multivariate heterogeneity; and ii) due to the acknowledged additional complexity in fitting such models[24].

MZ and DZ cross-twin—within/cross-symptom correlations were estimated for each symptom domain by fitting the data to a constrained saturated model. The structure of genetic and environmental influences on OCRD and AD symptoms was then estimated using classical multivariate twin models[10]. Model 1 corresponded to a fully saturated Cholesky decomposition that estimated 1A (additive genetic), 1C (shared environment), and 1E (non-shared environment) factors for each phenotype, making no assumptions about the nature of their underlying covariance. Model 2 corresponded to an "independent pathway" (IP) model, which seeks to estimate a set of common Ac, Cc, and Ec factors hypothesized to directly influence all phenotypes versus specific As, Cs and Es factors that may explain remaining phenotypic variance. Model 3 corresponded to a "common pathway" (CP) model, which estimated whether the covariance among phenotypes was influenced via one latent factor taking into account the shared contribution of common A, C, and E factors. The Akaike

information criterion (AIC) value was used to provide a measure of the goodness of fit of these models. Reduced submodels were systematically tested to derive the most parsimonious model fitting results. Classical twin modeling was carried out in R (http://www.R-project.org/) using the OpenMx package[25].

Identifying Potential Causal Influences

"Inference on causation from examination of familial confounding" (ICE FALCON) is a regression-based approach for analyzing twin pair data on a continuously or dichotomously distributed outcome and a familial predictor measured for both the twin and his or her co-twin[14]. The underlying statistical model allows one to make inference about (but of course does not "prove") the existence of causal relationships between predictor and outcome variables via the "elimination of familial confounding"[26]. This can also be thought of as using the co-twin as a "negative control". If the predictor is familial — that is, it is strongly correlated in twins — and there is at least in part a causal relationship between the predictor and the outcome, the association between the predictor of twin A with the outcome of twin B will decrease in absolute strength towards the null after including the predictor of twin B in the model[26]. In other words, this model considers the evidence for confounding due to genetic and/or environmental factors shared by both twins (Ac, C and Ec factors) versus non-shared factors (As and Es). Accordingly, when evidence consistent with a "casual" association is identified, the role of subject-specific factors is emphasized, although the relative contribution of specific genetic versus environmental influences is not determined. If the associations between the outcome of twin A and the predictors of both the twin A and co-twin B are the same before and after adjusting for each other, then, under this model, there is no evidence

consistent with a potential causal relationship. On the other hand, if there is a significant attenuation of the cross-trait cross-pair association after conditioning on twin A, there is evidence "consistent with" some causation. In our analyses, we focused on the relationship between OCD symptoms and each of the OCRD and AD symptom domains. A step-by-step explanation of this approach is provided in the Supplemental Information S2.

Results

Correlation and Principal Component Analyses

Moderate-strength phenotypic correlations were observed across all symptom domains. The strongest correlations with OCD were found with AD symptoms; the weakest associations were observed between HD and BDD symptoms, and HD and AD symptoms (0.32-0.37). The pattern of cross-twin cross-trait correlations in MZ compared to DZ twins supports a relevant genetic component to the liability of each domain and their co-occurrence (Table 1). PCA retained one phenotypic factor with an eigenvalue greater than 1 and explaining 55.6% of the total variance. When forcing it to retain 2 factors, the total explained variance increased to 67.8%, and HD symptoms emerged as a distinct factor (see S3 Table in the Supplemental Information).

---Table 1---

Multivariate Twin Modeling

The IP model provided an improved fit, compared to the fully saturated Cholesky with reduced parameters. However, the more restrictive CP model resulted in a

significantly worse fit with an increased AIC value. A series of IP nested sub-models were fitted to test the importance of specific parameters compared with the full-saturated Cholesky and the IP model. In these submodels, the genetic and environmental liabilities were either forced to be entirely common/shared (models 4-6) or entirely independent/specific (models 7-9). Model 4 was the best-fitting such that the covariation between phenotypes was explained by a set of common Ac, Cc and Ec factors, and the remaining variance by As and Es effects specific to each phenotype. Removing the Cs factor did not lead to worse fit, suggesting that these factors were less important in explaining individual differences. Removing As +/- Cs (models 5 and 6) and forcing all genetic risk to be common led to significantly worse fit, suggesting that some of the genetic liability is specific to each phenotype. Models 7 to 9 were forced to have an As, Cs and Es specific to each phenotype, and none of them demonstrated good fit, indicating the existence of common liability to all phenotypes.

---Table 2---

Parameter estimates for the best-fitting model are presented in Table 2 and the independent pathway model in Figure 1(a). Although the Cc factor could not be dropped from the model, it accounted for a minor fraction of the overall variance (0.02%-14%). Figure 1(b) shows that OCD symptoms were the only phenotype to share almost all of its additive genetic influence with the remaining OCRD and AD symptoms, suggesting that OCD symptoms are etiologically related to all of these phenotypes. For HD and BDD symptoms, 55% and 61% of the total genetic variance, respectively, was due to As, suggesting more specific genetic risk factors for these

symptoms versus other AD and/or OCRD symptoms. For these reasons, we conducted a separate multivariate analysis with 2 Ac latent factors: one loading on all symptom domains and another loading only on OCD, HD and BDD symptoms. Similar to the former model, we observed that the majority of the genetic variance for OCD symptoms still loaded onto the first Ac factor sharing genetic effects with other ADs and OCRDs. Only 9% of the total genetic variance of OCD was due to genetic factors shared with other OCRDs. For BDD symptoms 50% of its total genetic variance loaded onto the specific genetic factor (As) while 1.4% loaded onto shared genetic factors with the other OCRDs. 37.5% of the total genetic variance of hoarding symptoms loaded onto shared genetic factors with the other OCRDs, with 31.3% due to specific genetic influences. Results of the 2 factor IP model are provided in Table S4.

---Figure 1---

Potential Causal Influences

As depicted in Figure 2 and Table 3, there was evidence for significant causal influences between OCD and AD symptom domains. Specifically, OCD symptoms demonstrate a significant causal influence on GAD and PD symptoms, respectively ($P < 0.0001$). In other words, it can be inferred that there is a high probability of observing changes in the severity of these latter domains when a person's OCD symptom severity changes, but not nice versa. By comparison, we observed a significant causal influence of SP symptoms on OCD symptoms ($P = 0.03$), suggesting that OCD symptoms themselves show some dependency on SP symptoms.

SP was the only symptom domain to demonstrate a causal influence on OCD symptoms.

Within the OCRD domain, evidence of a significant causal influence of OCD symptoms was observed on HD symptoms ($P = 0.01$), suggesting that any change in OCD symptom severity would predict a corresponding change in HD severity, but not vice versa. There was trend evidence suggesting a causal influence of OCD symptoms on BDD symptoms (P = 0.07), but not vice versa.

---Table 3 & Figure 2---

Discussion

In summary, our results do not support the contention that OCD symptoms are less etiologically aligned with the symptoms of ADs compared to some of the revised *DSM-5* OCRDs. On the basis of classical twin modeling, evidence of a genetic commonality between OCD and AD symptoms was observed, such that the genetic liability to OCD symptoms was better explained when modeling its shared liability with OCRD and AD symptoms compared to when modeling an additional OCRD latent genetic factor. On the basis of causal inference analysis we observed evidence consistent with OCD symptoms being a potential causal risk factor for PD, GAD and HD symptoms, in the sense that having OCD symptoms appears to increase the probability of having PD and GAD symptoms, but not vice versa. By comparison, we observed evidence consistent with SP symptoms being a potential causal risk factor for OCD symptoms. We could reject the alternate (null) hypothesis that there are no direct causal relations.

A Non-Specific Genetic Vulnerability to OCD Symptoms

Our twin modeling results indicate that the genetic liability to OCD symptoms was almost entirely shared with the five other symptom domains. Of these domains, PD, GAD and SP symptoms also demonstrated greater common *vs.* specific genetic liabilities. When taken together with previous twin studies, there is now good evidence to suggest that OCD is influenced by moderately heritable genetic factors that are mostly shared with other OCRDs and ADs[11–13,27,28]. Thus, it stands to reason that this common liability may partly underlie the co-occurrence of these disorders in terms of their high rates of comorbidity[29] and familial aggregation[5,30]. Phenomenologically, in addition to the general characteristic of heightened threat estimation[3], there are other underlying features that link OCD and AD symptoms. For instance, high levels of self-blaming emotions, such as guilt and shame, appear to be shared between OCD and other ADs, including SP[31]. Additionally, although most robustly linked to PD, heightened anxiety sensitivity is observed in patients with OCD, GAD and SP, which may reflect a common cognitive bias towards "over-importance of thoughts" – a recognized dimension of anxiety sensitivity[32,33]. Common deficits of attentional control have also been emphasized in relation to OCD and other ADs, particularly GAD, as a feature that may explain the pervasive negative cognitions (i.e., obsessions, worry) that characterize these disorders[34]. Of course, while such features are not characteristic of all OCD patients, nor patients with other ADs, they nonetheless appear to represent important trans-diagnostic "common threads" that may in part arise from such estimated common liabilities.

OCD and AD Symptoms as Putative Causal Risk Factors

Extending the classical modeling approach, causal pathway modeling has identified novel and potentially important relationships between OCD and AD symptoms. With this approach, the results were more consistent with OCD symptoms being a causal risk factor for PD and GAD symptoms (having OCD symptoms increases the probability of having PD and GAD symptoms, not vice versa), rather than the association between traits being due to unmeasured familial factors such as genes and shared environment. In other studies without twins, OCD checking symptoms – one of the most common OCD symptom dimensions – have been linked to the increased probability of comorbid of PD and GAD diagnoses[35]. It was proposed that an intolerance of uncertainty, which is present in OCD checking symptoms, but more strongly associated with general worry and anxiety, might explain the link between these domains. Thus, one possibility is that intolerance of uncertainty represents an underlying trait dimension through which OCD etiologically enhances the risk to PD and GAD symptoms.

By contrast, SP symptoms emerged as a potential causal risk factor for OCD symptoms, although this was a more moderate finding compared to the estimated strength of the above associations. Nevertheless, adopting similar logic, one possibility is that a relevant underlying trait factor may explain these findings. In the case of SP symptoms, one obvious candidate would be "behavioral inhibition". Although behavioral inhibition has been most strongly characterized a childhood predictor of SP[36], it has also been linked to the development of OCD symptoms in adulthood[37]. Supporting an early etiological link between these domains, mother-reported levels of inhibition/shyness in preschool-aged twins were reported to show substantial overlap with other anxiety-related behaviors, including OCD-like

behaviors[38]. One hypothesis may therefore be that behavioral inhibition, as a core social anxiety trait, partly underlies the development of OCD and potentially represents an important endophenotype related to the co-occurring nature of OCD and ADs.

Relationships for OCRD Symptoms

With respect to the initial multivariate analysis, specific genetic influences were more apparent with regard to HD and BDD symptoms. Considering that no multivariate twin studies have examined them together with AD symptoms, these results are novel. In the recent study of five OCRD domains, OCD and HD symptoms were characterized as sharing more common liability, followed by BDD, then trichotillomania and skin-picking symptoms[12]. In the IP model with two common genetic factors, only a small percentage of the total genetic effect of BDD and OCD symptoms loaded onto the OCRD latent factor, as compared with HD symptoms. The greater loading for HD symptoms may be explained by the following two points: *i)* HD demonstrated a "weak" phenotypic correlation with BDD symptoms – the lowest among all domains assessed (see also reference 12); and *ii)* HD symptoms emerged from the exploratory PCA as a second distinct factor, suggesting it contains some unique variance with regards to the other OCRD domains.

Despite these seemingly complex associations, OCD symptoms were identified as a potential causal risk factor for HD symptoms. Previous twin studies have documented a close association between both symptom domains, with HD symptoms being reported to share a substantial common genetic liability with other major OCD symptom dimensions[39]. Some authors have suggested that the characteristic feature of "indecision" in OCD[40], which is also observed in HD[41,42],

may be a significant risk factor for HD that is genetically transmitted with OCD[42]. Our results potentially add weight to this hypothesis by demonstrating a putative causal link between these symptom domains. Nonetheless, the unique variance estimated for HD symptoms at the multivariate level suggests there are likely to be distinct etiological factors underlying aspects of HD that are not present in OCD, such as the inability to discard.

Limitations

There are certain limitations to this study. Firstly, all symptoms were assessed by self-report measures including the DCQ, DASS-21 "Stress" subscale and ASI, which do not perfectly match the diagnostic criteria for BDD, GAD, and PD. For example, while the ASI has shown validity in distinguishing between individuals experiencing panic attacks versus those with panic disorder[43], it is also predictive of other psychiatric disorder[33]. Secondly, a reliance on self-report limits the generalization of these findings to dimensional representations of symptoms rather than disorders, and does not allow one to rule out whether symptoms may be due to unmeasured third-party factors, such as other mental or medical conditions. Thirdly, it will be important in future multivariate twin studies to assess relationships between OCRDs, ADs and depression, tic and somatoform disorder symptoms, given ongoing interest in clarifying the etiological links between these domains. Indeed, it is highly likely that the etiological "common threads" suggested by the current results will extend beyond the specific OCRD and AD domains studied here. Lastly, extension of the current findings in a prospective longitudinal twin study[44] will be important for validating inferences of direct causal associations between these domains.

In conclusion, the current findings suggest that ongoing etiological (e.g., molecular genetic) and treatment-focused studies of OCD are likely to benefit from the consideration of a more diverse phenotype that represents its important links with some OCRDs (including tic disorders) but also with certain ADs. Parallels can be drawn between this sentiment and recent efforts to identify common molecular genetic risk factors that cut across other major psychiatric diagnoses, including schizophrenia, bipolar disorder and major depression, among others[45,46]. Importantly, if confirmed by future studies, the observed "causal influences" identified here may encourage novel approaches to treatment intervention, with potential to reduce the overall burden of these disorders when co-occurring in individual patients.

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Figure Titles and Legends:

Figure 1.

Title: (a) Independent Pathway (best-fitting) model. (b) The percentage of the variance accounted for by common and specific genetic and non-shared environmental factors.

Legend: **(a)** Ac (symptom-common genetic influence), Cc (symptom-common shared environmental influence) and Ec (symptom-common non-shared environmental influence). OCD, Obsessive-Compulsive Disorder Symptoms; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Symptoms. **(b)** The breakdown of the genetic and non-shared environmental variance into common and specific factors is shown in A (Ac and As) and E (Ec and Es), respectively.

Figure 2.

Title: Causal modeling with ICE FALCON.

Legend: P values refer to the significance of the regression coefficient change between model II to model III. The direction of the arrows indicates the direction of estimated "causality". GAD, Generalized Anxiety Disorder Symptoms; PD, Panic Disorder Symptoms; HD, Hoarding Disorder Symptoms; SP, Social Phobia Symptoms; BDD, Body Dysmorphic Disorder Symptoms. The light and dark coloring symbolize *DSM-5* representations of OCRDs and ADs, respectively.

Table 1. Phenotypic, Cross-Twin Within-Trait (Diagonal) and Cross-Twin Cross-Trait (off-Diagonal) Correlations for MZ and DZ Male and Female Twins

	OCD	HD	BDD	PD	GAD	SP
Phenotypic Correlations (95%CI)						
OCD	1					
HD	.42 (.39; .46)	1				
BDD	.44 (.41; .47)	.32 (.28; .35)	1			
PD	.56 (.54; .59)	.36 (.32; .39)	.48 (.45; .51)	1		
GAD	.55 (.52; .57)	.36 (.32; .39)	.42 (.39; .45)	.56 (.53; .58)	1	
SP	.51 (.48; .54)	.37 (.33; .40)	.48 (.45; .51)	.61 (.59; .64)	.51 (.47; .53)	1
Twin Correlations (95%CI)						
OCD	.38 (.31; .45) .14 (.04; .24)	.20 (.15; .26)	.23 (.17; .29)	.25 (.18; .30)	.28 (.22; .33)	.25 (.19; .31)
HD	.02 (-.05; .09)	.33 (.25; .40) .13 (.04; .22)	.16 (.10; .22)	.16 (.10; .22)	.19 (.13; .25)	.18 (.13; .24)
BDD	.08 (.001; .15)	.03 (-.04; .10)	.40 (.32; .47) .08 (-.02; .17)	.22 (.16; .28)	.19 (.13; .25)	.24 (.18; .30)
PD	.12 (.04; .19)	.05 (-.02; .12)	.07 (-.002; .15)	.30 (.22; .37) .14 (.05; .23)	.24 (.17; .29)	.26 (.20; .32)
GAD	.13 (.05; .20)	.05 (-.02; .12)	.08 (.01; .15)	.11 (.04; .18)	.33 (.25; .40) .17 (.07; .25)	.21 (.15; .27)
SP	.09 (.01; .16)	.06 (-.01; .13)	.06 (-.02; .13)	.16 (.08; .23)	.12 (.04; .18)	.42 (.35; .48) .18 (.08; .26)

Abbreviations: CI, confidence interval; OCD, Obsessive-Compulsive Disorder Symptoms; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms. Cross-Twin cross-trait correlations for MZ are given in the area above the diagonal and for DZ twins in the area below the diagonal.

Table 2. Model-Fitting Results and Standardized Parameters for the Best Fitting Model

Estimated Parameter			Fit Statistic						Comparison of Nested Models		
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	X^2	Δdf	***P* Value**	**Compared with**	ΔX^2 (Δdf)	***P* Value**
1Cholesky Saturated	ACE	ACE	30357.3	14901	555.3	-	-	-	-	-	-
2 IP	ACE	ACE	30397.4	14928	541.4	40.1	27	.05	-	-	-
3 CP	ACE	ACE	30450.1	14938	574.1	92.9	37	<.001	2	10	<.001
4 IP	**ACE**	**AE**	**30397.7**	**14934**	**529.7**	**40.5**	**33**	**.17**	**2**	**6**	**1**
5 IP	ACE	CE	30427.3	14934	559.3	70.1	33	<.001	2	6	<.001
6 IP	ACE	E	30510.3	14940	630.3	153.0	39	<.001	2	12	<.001
7 IP	AE	ACE	30435.3	14934	567.3	78.0	33	<.001	2	6	<.001
8 IP	CE	ACE	30463.8	14934	595.8	106.6	33	<.001	2	6	<.001
9 IP	E	ACE	30557.1	14940	674.1	196.8	39	<.001	2	12	<.001

Standardized Parameters for Best-fitting Model 4 (95% CI)

	Additive Genetic			Shared Environment		Non-shared Environment		
	Common	**Specific**	**Total**	**Common**	**Specific**	**Common**	**Specific**	**Total**
OCD	.37 (.24-44)	.004 (.00-.08)	.37 (.25-.44)	.002 (.00-.10)	-	.25 (.19-.31)	.37 (.33-.42)	.62 (.56-.69)
HD	.15 (.07-.22)	.18 (.12-.24)	.33 (.24-.40)	.006 (.00-.06)	-	.12 (.07-.17)	.55 (.49-.62)	.668 (.60-.74)
BDD	.12 (.03-.22)	.18 (.13-.24)	.30 (.19-.40)	.05 (.00-.13)	-	.22 (.16-.28)	.44 (.39-.50)	.657 (.58-.74)
PD	.15 (.03-.27)	.04 (.00-.08)	.19 (.04-.31)	.09 (.003-.22)	-	.396 (.32-.47)	.33 (.28-.38)	.725 (.65-.80)
GAD	.20 (.09-.28)	.10 (.06-.15)	.30 (.19-.38)	.02 (.00-.11)	-	.28 (.23-.35)	.40 (.35-.45)	.68 (.61-.75)
SP	.13 (.01-.30)	.12 (.05-.18)	.25 (.10-.40)	.14 (.02-.26)	-	.326 (.26-.40)	.29 (.25-.34)	.616 (.55-.69)

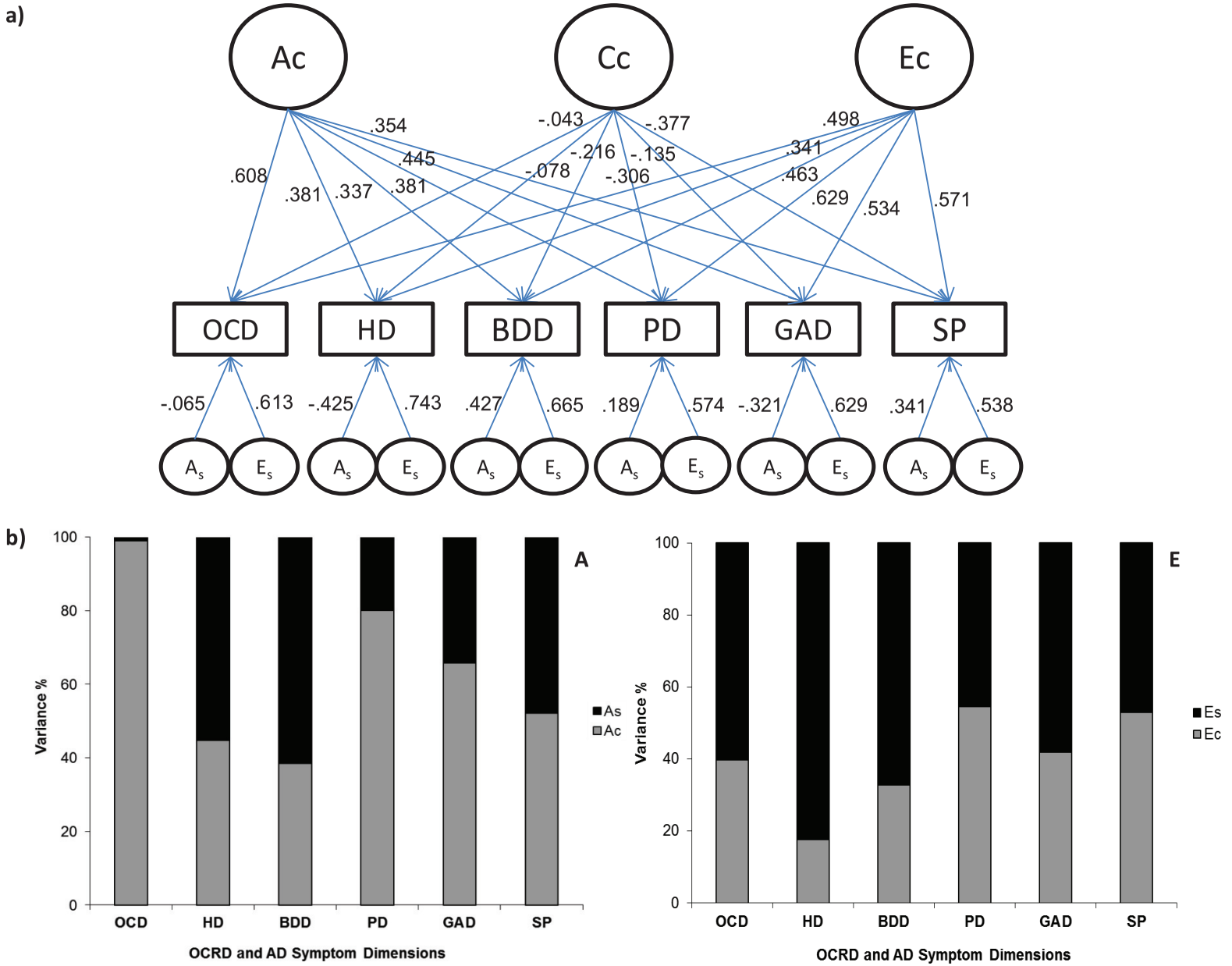
Abbreviations: -2LL, minus twice the log-likelihood; AIC, Akaike information criterion; Δdf, change in degrees of freedom between the sub-model and the full model; ΔX^2, difference in goodness of fit statistic between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CP, common pathway. In boldface type the best-fitting model based on the lower AIC. CI, Confidence Intervals; OCD, Obsessive-Compulsive Disorder Symptoms; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

Table 3. Significance ICE- FALCON after testing the probability for both directions of causation between each pair of symptoms. Regression estimates, standard error (SE), and *P* Value from regression models on monozygotic twin pairs

		Model I			Model II			Model III			Change	
		Estimate	SE	*P* Value	Estimate	SE	*P* Value	Estimate	SE	*P* Value	Absolute (%)	*P* Value (1-side)
[a]**OCD (X)—HD (Y)**	Self	-.438	.030	<.0001				-.430	.030	<.0001		
	Cotwin				-.132	.036	.0002	-.050	.030	.10	-.082 (61)	.01
OCD (X)—BDD(Y)	Self	.440	.029	<.0001				.434	.028	<.0001		
	Cotwin				.122	.036	.0007	.069	.029	.02	-.052 (43)	.07
OCD (X)—PD (Y)	Self	.592	.027	<.0001				.584	.027	<.0001		
	Cotwin				.253	.039	<.0001	.037	.028	.19	-.215 (85.2)	<.0001
OCD (X)—GAD (Y)	Self	.557	.025	<.0001				.539	.027	<.0001		
	Cotwin				.266	.035	<.0001	.081	.027	.003	-.186 (69.7)	.0001
OCD (X)—SP (Y)	Self	.495	.029	<.0001				.493	.029	<.0001		
	Cotwin				.092	.039	.02	.069	.028	.01	-.023 (25)	.33
[a]**HD (X)—OCD (Y)**	Self	-.413	.030	<.0001				-.414	.029	<.0001		
	Cotwin				-.074	.035	.03	-.082	.028	.004	.008 (10.4)	.42
BDD (X)—OCD (Y)	Self	.452	.029	<.0001				.447	.028	<.0001		
	Cotwin				.117	.037	.001	.077	.028	.006	-.040 (34.5)	.16
PD (X)—OCD (Y)	Self	.570	.027	<.0001				.569	.027	<.0001		
	Cotwin				.109	.040	.007	.094	.027	.0005	-.015 (13.7)	.42
GAD (X)—OCD (Y)	Self	.544	.027	<.0001				.534	.027	<.0001		
	Cotwin				.190	.037	<.0001	.118	.027	<.0001	-.072 (37.8)	.11
SP (X)—OCD (Y)	Self	.511	.030	<.0001				.505	.031	<.0001		
	Cotwin				.139	.039	.0004	.047	.030	.11	-.092 (66.2)	.03

Abbreviations: OCD, Obsessive-Compulsive Disorder Symptoms; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms; X, independent variable; Y, outcome variable.

[a]The inverse relationship between OCD and HD was due to the fact that we transformed the raw data using reciprocal function for HD ($1/HD^{0.55}$) and logarithm function for OCD.


a)
Ac
Cc
Ec
.354
-.043
-.377
.498
.608
.381
.337
.445
.381
-.078
-.216
-.306
-.135
.341
.463
.629
.534
.571
OCD
HD
BDD
PD
GAD
SP
-.065
.613
-.425
.743
.427
.665
.189
.574
-.321
.629
.341
.538
As
Es
b)
A
E
Variance %
100
80
60
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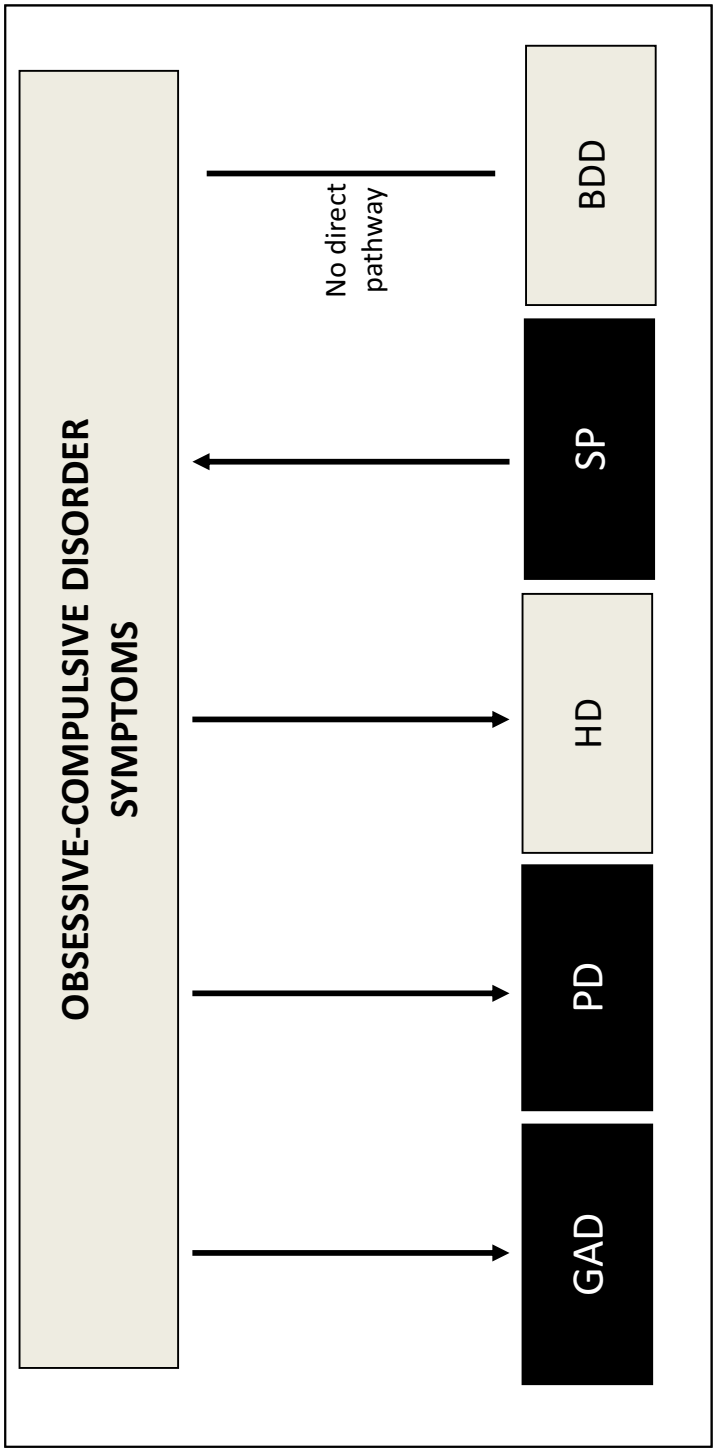
20
0
As
Ac
Es
Ec
OCD
HD
BDD
PD
GAD
SP
OCRD and AD Symptom Dimensions


OBSESSIVE-COMPULSIVE DISORDER SYMPTOMS
No direct pathway
BDD
SP
HD
PD
GAD

Supplemental Information

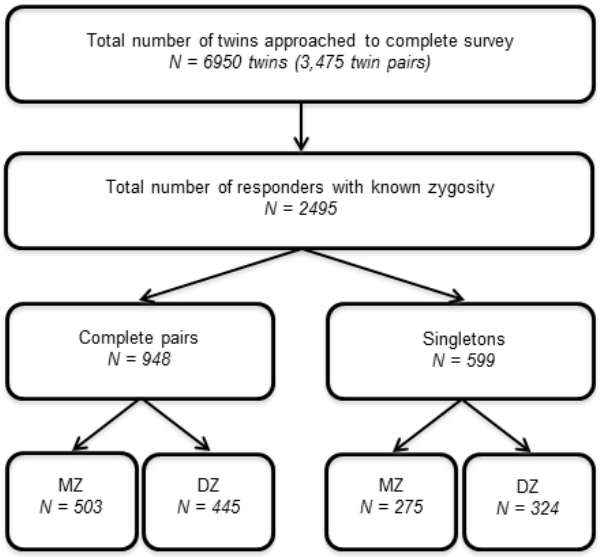
S1. Flowchart of twin recruitment and final sample composition

S2. Expanded description of the ICE FALCON methodology

S3. Principal component analysis (PCA)

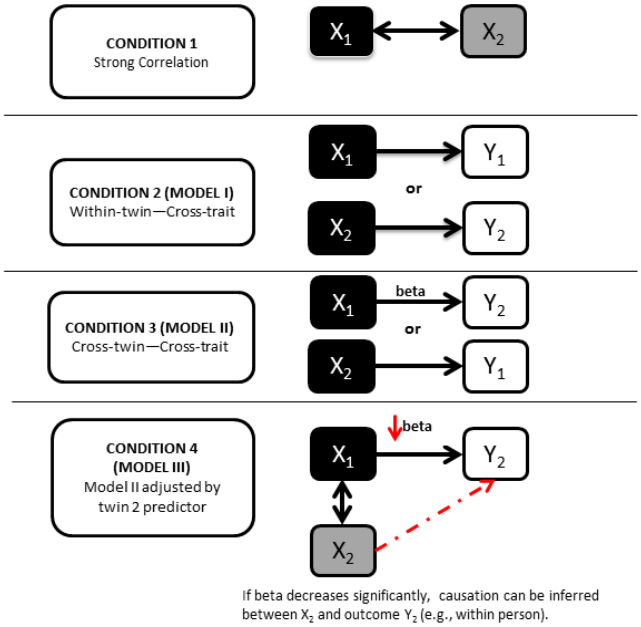
S4. Independent Pathway model with 2 latent common additive genetic factors. Model-fitting results and standardised parameters for the best-fitting model.

S1. Flowchart of twin recruitment and final sample composition



The following zygosity and gender combinations were approached: 795 male monozygotic (MZ) pairs; 666 male dizygotic (DZ) pairs; 755 female MZ pairs; 666 female DZ pairs, and 583 male/female pairs.

S2. Expanded description of the ICE FALCON methodology



The above figure provides a step-by-step explanation of the ICE FALCON regression methodology. X represents the predictor variable and Y the outcome variable. Their numbering represents MZ twin 1 or twin 2.

The following 4 conditions must be satisfied to refute the null hypothesis of no causal influence (X on Y):

Condition 1: The predictor (trait X) or outcome (trait Y) is correlated between the twins of a pair (i.e., between-person correlation).

Condition 2 (Model I): there is an association between the predictor (X) and the outcome (Y) within each twin of a pair (i.e., within person).

Condition 3 (Model II): conditions (1) and (2) must be strong enough to find a detectable and statistically significant "cross-twin cross-trait association"; that suggests that there is a family factor (genetic and/or shared environmental) underneath those two traits.

Condition 4 (Model III): there is a reduction in the magnitude of the cross-twin cross-trait regression (beta) coefficient when modeling the within-person association. If the magnitude of beta significantly *reduces*, "causation" can be inferred because it is the within-person association that is driving this reduction.

Under the null hypothesis, if the regression coefficient for the cross-twin cross-trait association in Model III is the *same* as that of Model II, potential shared genetic and/or environmental mechanisms may be implicated.

In our analyses, the 3 models were adjusted for age and gender. We focused on the question of whether OCD symptoms demonstrated evidence for potential causal relationships with the remaining symptom domains: OCD-HD, OCD-BDD, OCD-PD, OCD-GAD, OCD-SP. "Causality" was tested in both directions, that is, flipping the predictor and outcome variables, which corresponded to a total of 10 (5x2) regression models (Table 3).
An expanded statistical description is provided below.

Description of the Statistical Analysis

Let Y_{ij} denote a outcome of interest, index by *j* = 1, 2 (twin 1 and twin 2, respectively) and *i* = 1,..., *m*, where *m* is the number of twin pairs. Associated with the outcome Y_{ij}, let X_{ij} denote a corresponding predictor, for example OCD as *Y* and HD as *X*. For simplicity let $Y_{i,self} = Y_{i1}$ and $Y_{i,\text{cot}win} = Y_{i2}$, and similarly defined for predictor X_{ij}. Note that the choice of $Y_{i,self}$ and $Y_{i,\text{cot}win}$ is arbitrary – data from both possibilities will be used in the analysis; see below.

The first model expresses the relationship between the expected value (*E*) of an outcome variable and its own predictor to assess the within-person cross-trait association.

$$E(Y_{i,self}) = \alpha + \beta_{self} X_{i,self} \qquad \textbf{Model I}$$
$$E(Y_{i,\text{cot}win}) = \alpha + \beta_{self} X_{i,\text{cot}win}$$

where α is the intercept and β_{self} is the regression coefficient representing the within-person cross-trait association.

The second model expresses the relationship between the expected value of Y_{ij} and its co-twin predictor to assess the cross-twin cross-trait association.

$$E(Y_{i,self}) = \alpha + \beta_{\text{cot}win} X_{i,\text{cot}win} \qquad \textbf{Model II}$$
$$E(Y_{i,\text{cot}win}) = \alpha + \beta_{\text{cot}win} X_{i,self}$$

where $\beta_{\text{cot}win}$ is the regression coefficient representing the cross-twin cross-trait association.

The third model expresses the relationship using both predictors by:

$$E(Y_{i,self}) = \alpha + \beta^{a}_{self} X_{i,self} + \beta^{a}_{\text{cot}win} X_{i,\text{cot}win} \qquad \textbf{Model III}$$
$$E(Y_{i,\text{cot}win}) = \alpha + \beta^{a}_{self} X_{\text{cot}win} + \beta^{a}_{\text{cot}win} X_{i,self}$$

where $\beta^{a}_{\text{cot}win}$ is the regression coefficient representing the effect cross-twin cross-trait association adjusted for its own predictor (β^{a}_{self}).

The above Models can be easily extended to allow for the inclusion of multiple predictors, such as age and gender. Note that the intercept coefficient α is excluded if we use the standardised *Y* and *X* values.

The parameters in Models I-III were estimated using the generalised estimating equations, which take into account the correlation within a twin pair. Under the null hypothesis of no change in regression coefficients for cross-twin cross-trait in Model II and III, i.e $H_0 : \beta_{\text{cot}win} = \beta^{a}_{\text{cot}win}$, we use the t-test: $t = (\beta_{\text{cot}win} - \beta^{a}_{\text{cot}win}) / se(\beta_{\text{cot}win} - \beta^{a}_{\text{cot}win})$, where *se* is the standard error and computes using nonparametric bootstrap method. This involved randomly sampling twin pairs with replacement to obtain the same sample size as the original dataset, then fitting the Models I-III to this new data set to get a new set of estimated parameters. We then repeated the process 1,000 times to yield a sampling distribution of the parameter estimates from which a standard error was estimated by computing the standard deviation. For bootstrap method, we wrote our own programs in R (http://www.R-project.org/). One-sided p-values were derived and considered nominally significant if $p < 0.05$.

S3. Principal component analysis (PCA)

	Factor Matrix	Matrix forced to retain 2 factors	
	Main Factor	**Factor 1**	**Factor 2**
PD	.814	820	**
SP	.789	.785	**
OCD	.786	.678	**
GAD	.765	.734	**
BDD	.697	.718	**
HD	.603	**	.961

The PCA retained 1 phenotypic factor with eigenvalues greater than 1, explaining **55.6%** of the total variance. The PCA were forced to retain 2 phenotypic factor explaining **67.8%** of the total variance.

S4. Independent Pathway model with 2 latent common additive genetic factors. Model-fitting results and standardized parameters for the best-fitting model.

Estimated Parameter			Fit Statistic						
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	***X²***	***Δdf***	***P Value***	**Compared with**
1 Cholesky Saturated	ACE	ACE	30357.25	14901	555.25	-	-	-	-
2 IP	ACE	ACE	30390.99	14925	540.99	33.74	24	.09	1
3 CP	ACE	ACE	30450.46	14938	574.46	93.21	37	<.0001	1
4 IP	**ACE**	**AE**	**30391.40**	**14931**	**529.40**	**.412**	**6**	**.998**	**2**
5 IP	ACE	CE	30414.79	14931	552.79	23.80	6	.0005	2
6 IP	ACE	E	30464.90	14937	590.90	73.91	12	<.0001	2
7 IP	AE	ACE	30424.32	14931	562.32	33.33	6	<.0001	2
8 IP	CE	ACE	30463.84	14934	595.84	72.84	9	<.0001	2
9 IP	E	ACE	30554.06	14940	674.06	163.1	15	<.0001	2

Standardized Parameters for Best-fitting Model 4 (95% CI)

	Additive Genetic Factors				Shared Environmental Factors		Non-Shared Environmental Factors		
	Ac	**Ac2**	**As**	**AT**	**Cc**	**Cs**	**Ec**	**Es**	**ET**
OCD	.23 (.014-.40)	.03 (.00-.14)	.06 (.00-.13)	.32 (.10-.42)	.04 (.00-.22)	-	.27 (.20-.35)	.37 (.32-.42)	.64 (.56-.72)
HD	.11 (.02-.17)	.12 (.02-.28)	.10 (.00-.23)	.32 (.22-.39)	.002 (.00-.07)	-	.13 (.08-.19)	.55 (.49-.61)	.67 (.60-.75)
BDD	.18 (.04-.25)	.005 (.00-.03)	.18 (.12-.23)	.36 (.21-.43)	.0002 (.00-.10)	-	.19 (.14-.27)	.44 (.39-.50)	.63 (.56-.72)
PD	.26 (.08-.33)	-	.04 (.00-.08)	.30 (.11-.37)	.00 (.00-.16)	-	.37 (.30-.45)	.33 (.28-.38)	.70 (.63-.77)
GAD	.21 (.006-.36)	-	.06 (.00-.12)	.27 (.02-.39)	.05 (.00-.26)	-	.28 (.21-.37)	.40 (.35-.45)	.68 (.61-.77)
SP	.30 (.03-.44)	-	.09 (.00-.16)	.39 (.11-.48)	.02 (.00-.24)	-	.29 (.23-.39)	.30 (.25-.34)	.59 (.52-.67)

-2LL, minus twice the log-likelihood; df, degrees of freedom; AIC, Akaike information criterion; X^2, difference in goodness of fit statistic between the sub-model and the full model; Δdf, change in degrees of freedom between the sub-model and the full model; CI, Confidence Intervals; Ac, additive genetic factor common to all disorders; Ac2, additive genetic factor common to Obsessive-Compulsive Related Disorders; As, additive genetic factor specific to each disorder; AT, total additive genetic factor; Cc, shared environmental factor common to all disorders; Cs, shared environmental factor specific to each disorder; Ec, non-shared environmental factor common to all disorders; Es, non-shared environmental factor specific to each disorder; ET, total non-shared environmental factor; IP, independent pathway; CP, common pathway. OCD, Obsessive-Compulsive Disorder Symptoms; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Symptoms.
In boldface type the best-fitting model based on AIC.

Study 3

Under Review

Submitted Manuscripts

Manuscript ID	Manuscript Title	Date Created	Date Submitted	Status
DA-15-196	Distinct etiological influences on obsessive-compulsive symptoms dimensions: a multivariate twin study [View Submission]	16-Apr-2015	16-Apr-2015	ADM: Williams-Klamborowski, Corrie ADM: Roy-Byrne, Peter • Under Review

top

Abstract = 217 words

Manuscript = 3411 words

45 References

5 Tables + 1 Figure

Distinct etiological influences on obsessive-compulsive symptoms dimensions: a multivariate twin study

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Abstract

Background: Obsessive-compulsive disorder (OCD) is characterized by five major dimensions, including contamination/washing, harm/checking, symmetry/ordering, hoarding and forbidden thoughts. How these dimensions may relate etiologically to the symptoms of other obsessive-compulsive related disorders (OCRDs) and anxiety disorders (ADs) is not well known. The aim of this study was to examine the genetic and environmental overlap between each major obsessive-compulsive dimension with the symptoms of other OCRDs and ADs.

Methods: 2495 twins of both sexes, aged between 18 and 45 years, were recruited from the Australian Twin Registry. Measures used: scores on four dimensions (obsessing (forbidden thoughts), washing, checking and ordering) of the Obsessive-Compulsive Inventory–Revised, Dysmorphic Concerns Questionnaire, Hoarding Rating Scale, Anxiety Sensitivity Index, Social Phobia Inventory and Stress subscale of the Depression, Anxiety and Stress Scale. Multivariate twin modelling methods using continuous and categorized variables were performed, also controlling for age and gender.

Results: Our findings suggested that forbidden thoughts and washing demonstrated the strongest genetic overlap with other ADs, while ordering was genetically related to OCRDs. Common genetic influences on checking symptoms were best estimated when modeling OCRDs together with ADs. Common environmental factors of ordering and checking were shared with ADs.

Conclusions: Important shared genetic and environmental risk factors exist between OCD, OCRDs and ADs, but which vary alongside the expression of its major dimensions.

Introduction

There is consistent evidence to suggest that obsessive-compulsive disorder (OCD) encompasses a few consistent and temporally stable symptom dimensions, which may co-exist within an individual patient[1]. These major dimensions typically include: contamination/washing, harm/checking, symmetry/ordering, hoarding, and forbidden (sexual/religious) thoughts[1,2]. Each has been associated with distinct patterns of genetic and environmental influence[3,4]; comorbidity with other psychiatric disorders[5,6]; and treatment responsiveness[7,8]. Neurobiological studies also suggest that these symptom dimensions may, in part, reflect distinct underlying pathophysiological processes[9–11]. For example, elevated amygdala responsiveness to threat – a common finding in other anxiety disorders – is most evident in OCD patients with prominent harm/checking and/or forbidden thoughts[12]. Thus, there is accumulating evidence to suggest that dimension-specific etiological influences contribute to the overall presentation of OCD. Accordingly, it now seems particularly relevant to understand how these dimensions overlap with the symptoms of other anxiety and "OC-related" disorders. Gaining further clarity on this question may ultimately have important implications for the continued refinement of diagnostic and etiological models of OCD.

In a recent population-based twin study of OC-related disorders (OCRDs) and anxiety disorder (ADs) symptoms, we demonstrated that the proportion of common genetic variance in OCD symptoms was higher when modeling with both groups of disorders, compared to when modeling OCRDs alone[13]. In other words, we did not observe a stronger genetic commonality between OCD symptoms and other OCRDs (*hoarding disorder*, *body dysmorphic disorder*) versus OCRDs and ADs (*social phobia, panic disorder and generalized anxiety disorder)* – a distinction that might be expected based on recent conceptualization of OCRDs and ADs[14]. Instead, these results were

more consistent with evidence from past multivariate twin studies, which have indicated OCD is influenced by moderately heritable genetic factors that are mostly shared with other OCRDs[15] and ADs[16].

Considering our recent twin study findings, together with accumulating support for the "multidimensional model of OCD", the aim of the current study was to investigate the structure of genetic and environmental influences between OC symptom dimensions and the symptoms of these five aforementioned OCRDs and ADs. These relationships have yet to be investigated in a multivariate twin study. Nevertheless, on the basis of existing evidence, we anticipated that harm/checking and sexual/religious symptoms, in particular, might demonstrate greater genetic overlap with the symptoms of ADs. This prediction is based on the neurobiological evidence linking these dimensions more closely to ADs[9,11,12], as well as the generally higher rate of comorbidity between these dimensions and other ADs[17].

Material and Methods

Participants and Measures

Participants (aged 18 to 45 years), were recruited from the Australian Twin Registry (ATR) to complete an online survey. The final sample available for the study included 2,495 twins, 1,281 MZ and 1,214 DZ twins (1,027 males and 1,468 females). Briefly, the sample contained 503 MZ pairs, 445 DZ pairs and 599 twins without their cotwins (275 MZ; 324 DZ). All participants provided informed consent. The study was approved by the ATR and the Melbourne Health Human Research Ethics Committee (Victoria, Australia). Full recruitment details are provided in López-Solà et al[18].

OC symptom dimensions were assessed with the Obsessive Compulsive Inventory-Revised (OCI-R)[19]: a widely validated self-report measure of OCD symptoms

for use in general and clinical populations. The OCI-R is an 18-item questionnaire comprising 6 subscales to assess OC symptom dimensions, which are conventionally labeled as (1) "checking" - corresponding to harm-related obsessions and associated checking compulsions; (2) "obsessing" - corresponding to sexual/religious (forbidden/taboo) thoughts; (3) "washing" - corresponding to contaminations fears and associated cleaning compulsions; (4) "ordering" – corresponding to symmetry/order related obsessions and compulsions; (5) "neutralizing" - corresponding to mental (i.e., counting/numeric) compulsions; (6) "hoarding" – corresponding to excessive acquisition/inability to discard. The OCI-R total score and subscales scores have demonstrated excellent psychometric properties, with the exception of the neutralizing subscale[19]. Because, neutralizing does not correspond to the most well-replicated symptom dimensions (in factor analytic studies), it was excluded from our analysis. Hoarding disorder (HD) symptoms were assessed with a specific scale (see below), so the OCI-R hoarding dimension was excluded here. With respect to OCI-R cut-off scores, clinical levels of symptoms are suggested to correspond to scores higher than 3 on the washing subscale, scores higher than 5 on the obsessing and checking subscales, and scores higher than 7 on the ordering subscale[19].

Five validated self-report measures were also used to assess other OCRD and AD symptoms (also detailed in López-Solà *et al.*[18]). For OCRDs, hoarding symptoms were assessed with the Hoarding Rating Scale-Self Report (HRS-SR)[20] and BDD symptoms with the Dysmorphic Concern Questionnaire (DCQ)[21]. For ADs, social phobia (SP) symptoms were assessed with the Social Phobia Inventory (SPIN)[22]; panic disorder (PD) symptoms with the Anxiety Sensitivity Index (ASI)[23]; and generalized anxiety disorder (GAD) symptoms with the "Stress" subscale of the Depression, Anxiety and Stress Scale-21 (DASS-21)[24].

Statistical Analysis

To ensure data normality and to retain the maximum number of variables in their original continuous form, all questionnaire responses underwent Box-Cox transformations [$Y_t = (Y_i^{\lambda} - 1)/ \lambda$][25]. However, four OCI-R subscales could not be normalized using this method and were instead categorized using aforementioned cut-offs scores. Each was transformed into a 3-category variable with 2 thresholds: for example, washing scores from 0 to 2 (category 0) represented non-clinical levels (i.e., no reported distress); scores from 2 to 3 (category 1) represented subclinical levels, and scores above 3 (category 2) were indicative of clinical levels of OCD for this dimension. Because univariate twin modeling of this data indicated the presence of genetic sex differences in some of the scales[18], and because standardized residuals could not be applied to the analysis of OCI-R subscale scores, all multivariate models were performed including age and sex as covariates. To address the study aims, we conducted four multivariate twin models, one for each of the OC-dimensions. Each model therefore contained one ordinal and five continuous variables.

A series of structural equation models were fitted by maximum likelihood. First, we fit a baseline saturated model in which all possible correlations were freely estimated. Next, genetic and environmental variance component models were fitted using classical multivariate twin models[26]. Model 1 is a fully saturated Cholesky decomposition that estimated one additive genetic (1A), one shared environment (1C), and one non-shared environment (1E) factor for each phenotype making no assumptions about the nature of their underlying covariance. Model 2 is an "independent pathway" (IP) model, which estimates a set of common Ac, Cc, and Ec factors to directly influence all phenotypes versus specific As, Cs and Es factors that may explain remaining phenotypic variance. Model 3 corresponds to a "common pathway" (CP)

model, which estimates whether the covariance among phenotypes was influenced via one latent factor taking into account the shared contribution of common A, C, and E factors. The Akaike information criterion (AIC) value was used to measure the relatively goodness of fit of these models; the one with the lowest AIC was taken to be the most parsimonious. Reduced sub-models were systematically tested to derive the most parsimonious model fitting results. For the most parsimonious model, confidence intervals for the factor loadings at the path diagram were calculated to provide the best estimate for each parameter of the model. All analyses were carried out in R (http://www.R-project.org/) using the OpenMx 2.0 package[27].

Results

Best Fitting Models & Estimated Factor Loadings

Table 1 and Figure 1 present results for the most parsimonious model for each of the OC symptom dimensions. Figure 1 also displays the factor loadings (with confidence intervals) for common and specific genetic and environmental influences estimated for each dimension. With reference to Table 1, the four symptom dimensions each demonstrated best fit with the same single factor structure; namely, the independent pathway (IP) model with ACE as common factors and AE as specific factors. Estimates for the best fitting IP model are emphasized in bold text (Table 1). Figure 1 presents the values of the factor loadings for each dimension, indicating a unique pattern of genetic and environmental overlap with ADs and other OCRDs.

---------- *Table 1 & Figure 1* ----------

Figure 1a presents results for checking symptoms and indicates that these symptoms share all genetic factor influences (λ_{gc}= .58) with ADs and OCRDs, while specific genetic factors were zero. This implies that 100% of the genetic variance in checking symptoms is accounted for by the common genetic factor. Shared environmental influences also emerged as relatively important (λ_{cc}=.47) in the expression of checking symptoms.

Figure 1b presents the best fitting model for obsessing symptoms and indicates that these symptoms share higher common genetic factor influences (Ac) (λ_{gc}= .61) with ADs and OCRDs compared to specific genetic influences (As) (λ_{gs}= .27). In other words, 84% of the genetic variance in obsessing symptoms is accounted for by the common genetic factor. Shared environmental influences (Cc) were very low (λ_{cc}=.16) between obsessing symptoms and the other domains, and were not significant.

Figure 1c presents results for washing symptoms, which demonstrated a similar proportion of common (λ_{gc}= .41) and specific genetic influences (λ_{gs}= .47). Accordingly, 43% of the genetic variance in washing symptoms was accounted for by the common genetic factor. Shared environmental influences between washing symptoms and the other domains were very low (λ_{cc}= .17).

Figure 1d presents results for ordering symptoms and indicates that these symptoms have weaker common genetic factor influences (λ_{gc}= .26) with ADs and OCRDs compared to specific genetic influences (λ_{gs}= .52). For ordering symptoms, only 20% of the genetic variance is accounted for by the common genetic factor. Shared environmental influences also emerged as relatively important in the expression of ordering symptoms (λ_{cc}= .37).

Estimated Genetic Influences

In relation to the total genetic variance, standardized parameters for each OC dimension confirmed that obsessing (84%) and checking (100%) showed the highest percentage of common genetic variance with ADs and other OCRDs. Washing (43%) shared almost half of its genetic variance with these domains, while ordering had the lowest percentage of common genetic variance (20%). In order to estimate more precisely the genetic covariance between each OC-dimension and the other symptom domains (ADs and OCRDs, respectively), additional multivariate analyses were performed. The following tables present the results of the most parsimonious model in a different but informative way compare to the results presented above.

Table 2 presents equivalent model estimates results for checking symptoms. Checking demonstrated around 8% of the total variance due to common genetic factors shared with ADs alone. When estimating its overlap with OCRDs alone, the percentage of shared genetic influence was higher (26%), with the strongest association being observed with BDD symptoms. These results can be compared to an estimated shared genetic influence of 34% (λ_{gc}= .58, squared is approximately .34) when the ADs and OCRDs were modeled together. These results suggest that checking shares stronger common genetic influence with ADs *and* OCRDs, although a relatively strong common influence was seen with BDD symptoms. Interestingly, BDD shared 100% of its genetic variance only with checking and not with any other OC symptom dimension.

---------- Table 2 ----------

Results presented at the bottom of Table 3 detail the percentages of common and specific genetic and environmental influence for obsessing symptoms and ADs and,

separately, for obsessing symptoms and OCRDs. For obsessing, 46% of the total variance was due to common genetic influences with ADs alone (100% of its genetic variance), while the specific additive genetic component emerged as non-significant (Table 3). PD and GAD symptoms shared 100% and 66%, respectively, of their genetic variance with obsessing symptoms. When estimating its covariance with OCRDs alone, the percentage of variance due to shared genetic influence decreased to 21%. These results can be compared to an estimated shared genetic influence of 37% when the ADs and OCRDs were modeled together. These results suggest that obsessing symptoms have a stronger common genetic correlation with ADs than with OCRDs symptoms.

---------- Table 3 ----------

Table 4 presents results for the washing symptoms. Washing demonstrated 32% of the total variance due to common genetic factors shared with ADs alone (around 76% of its total genetic variance), while when estimating its covariance with OCRDs alone, the percentage of shared genetic influence was 20%. These results can be compared to an estimated shared genetic influence of 17% of the total variance when the ADs and OCRDs were modeled together. These results suggest that washing symptoms have a stronger common genetic correlation with ADs versus OCRDs symptoms.

---------- Table 4 ----------

Table 5 presents results for ordering symptoms. Ordering demonstrated less than 1% of the total variance due to common genetic factors shared with ADs alone. When estimating its covariance with OCRDs alone, the percentage of shared genetic influence

was higher (18%), but did not surpass the estimate of specific genetic variance (As=24%). These results can be compared to an estimated shared genetic influence of 7% when the ADs and OCRDs were modeled together. These results suggest that ordering has stronger genetic correlation with OCRDs versus ADs symptoms, although it also displays more prominent specific genetic influences.

---------- *Tables 5* ----------

Estimated Environmental Influences

As shown in Tables 3 and 4, only checking and ordering demonstrated relevant findings regarding common environmental influences (zero or close to zero Cc factor loadings were obtained for obsessing and washing; Tables 2 and 5 respectively). Checking had an increased percentage of common environmental influence when assessed with ADs alone (41%) and OCRDs alone (31%), versus the full model with ADs and OCRDs together (22% of the total variance). With respect to ordering, the common environmental factor increased to 39% when assessed in relation to ADs alone, whereas the additive genetic factor (either common or specific) decreased almost to zero. In summary, these results indicate that checking shares common environmental influences with OCRDs and ADs, while ordering shares common environmental influences with ADs alone.

Discussion

The current study supports the idea that OCD is both clinically and etiologically heterogeneous. Three main conclusions can be drawn from its findings. First, obsessing and washing symptoms had the highest genetic correlations with the symptoms of ADs.

Second, ordering was the highest genetic correlation with HD and BDD symptoms, but shared common environmental influences with ADs. Third, common genetic influences on checking symptoms were best estimated when modeling OCRDs (in particular BDD symptoms) together with ADs, rather than when modeling either group alone. In summary, important shared genetic and environmental risk factors exist between OCD, OCRDs and ADs, but which vary alongside the expression of its major symptom dimensions.

Genetic Influences

Checking

Checking symptoms were found to share genetic factors with the symptoms of both ADs and OCRDs, but in particular with BDD. This result did not support the original study prediction that checking would be the OC symptom dimension most closely associated with AD symptoms only. Considering that checking, compared to other symptom dimensions, is predictive of OCD diagnosis as a whole[28], this general pattern of findings is consistent with our previous study where the common genetic liability to OCD symptoms was higher when modeling both ADs and OCRDs compare to either group alone [13]. Separately, checking symptoms have been linked to comorbid ADs[17], as well as BDD [29]. It has been demonstrated that OCD patients with comorbid BDD have increased aggressive/checking, symmetry, and reassurance-seeking severity[29]. BDD patients also demonstrate compulsively checking behaviors[29], which supports the genetic correlation between BDD and checking symptoms observed here. Pathophysiologically, it has been suggested that alterations in ventral visual association pathways, which interface with limbic and striatal brain regions, might explain the tendency for BDD patients to over-attend to imagined or minimal imperfections in their

bodies, particularly the face, and repeatedly check for possible changes in their appearance in order to control their anxiety[30,31].

Obsessing

Obsessing symptom demonstrated the strongest estimated genetic association with ADs. Although we anticipated this relationship as a broad study prediction on the basis of other work by our group[12], it nonetheless appears to be a novel finding. One previous twin study provides indirect support for this finding, having demonstrated genetic overlap between obsessing symptoms (i.e., forbidden thoughts) and neuroticism[32] – the latter being strongly linked to mood and ADs[33]. Obsessing, aggressive and somatic symptoms have also been reported to demonstrate higher rates of comorbidity with ADs (generalized anxiety disorder, panic/agoraphobia and social phobia)[17], which fits with the pattern of findings here. One potential explanation is that obsessive thoughts represent a general cognitive bias towards the anticipation of possible threating events (physical and/or social; self or other-related), akin to cognitive bias that lead to certain behaviors, such as avoiding or reassurance, which are responsible for the maintenance of other ADs.

Washing

Washing was more genetically associated with the symptoms of ADs compared to OCRDs. Clinical and epidemiological studies have reported a consistent association between washing symptoms and comorbid depression and ADs[34], which is consistent with our results. However, other studies have also found an increased presence of comorbid OC spectrum disorders associated to washing symptoms[35]. In the direction of our findings, disgust sensitivity, an emotional state associated with avoidance behavior

of threating/distressing stimuli, plays an important role in washing symptoms[36] and it also seems to be associated to the etiology of other psychiatric disorders such as social phobia and anxiety sensitivity[36]. This negative emotional state could explain in part the genetic overlap found in our study between this OC dimension and other ADs.

Ordering

The genetic correlation of ordering was greater with OCRDs than with ADs. This result is consistent with one recent study of female twin pairs which reported that ordering and obsessing were the OC symptom dimensions most strongly genetically associated with BDD symptoms[37]. Clinical studies have also documented that OCD patients with ordering symptoms display higher comorbidity with OCRDs, such as hoarding disorder[38], and that a substantial proportion of patients with BDD exhibit marked appearance-related symmetry concerns[39].

Ordering also demonstrated a relatively high proportion of specific genetic influences, which is interesting in view of molecular genetic studies that have reported distinct relationships candidate polymorphisms of monoaminergic system genes in OCD patients and in the severity of symmetry/ordering symptoms[40]. Ordering has also been strongly linked to tic-related disorders and to early age at onset of OCD[41]. Thus, it is possible that OCD patients with prominent ordering symptoms, together with these other features, may represent a distinct phenotype of OCD[41].

Environmental Influences

Our results indicated that checking shares common environmental influences with OCRDs and ADs, whereas ordering was more strongly linked with ADs. While the influence of stressful life events is widely recognized as a general etiological factor in

the development of psychiatric disorders[42], few studies have identified which life events may consistently contribute to the manifestation of OCD, ADs and other OCRDs. In one study, perinatal insults were identified as a risk factor to ADs and OCD with prominent ordering symptoms[43] – such factors have not been explored in relation to HD and BDD. Thus, while perinatal events, psychosocial stressors, trauma and inflammatory processes have been linked generally to the development of OCD[44,45], little remains known about their specific contribution to OC symptom dimensions, or other OCRDs.

Limitations

Certain limitations should be acknowledged. Firstly, all symptoms were assessed by self-report measures, which imperfectly align with the diagnostic criteria for ADs and OCRDs. Secondly, despite the good psychometric properties of the OCI-R, it provides only a brief assessment of OC symptom dimensions compared to some other measures that have been developed - especially for clinical use (DY-BOCS). Finally, the OCRD group was not completely assessed due to low response rates for the skin-picking and hair-pulling self-report questionnaires. Those questonnaries were only completed if participants first answered "yes" to some screening questions[18]. Nevertheless, the inclusion of BDD and HD was illuminating, particularly the observed associations between OC symptom dimensions and BDD symptoms. Our results also suggest that HD is genetically quite specific, despite some etiological overlap with obsessing symptoms.

Conclusions

Results from this study support the multidimensional model of OCD. Genetic and environmental influences between OCD and ADs also appear central, not peripheral, to understanding the etiology of OCD. Common genetic factors might reflect specific functional constructs such as responses to fear and anxiety (negative valence system) and/or reward learning and habits processes (positive valance system) rather than corresponding to particular diagnostic domains. Because our results indicate that a high percentage of non-shared environmental factors influence OCRD and AD symptoms, it would be interesting to investigate whether specific events (e.g. perinatal insults) differentially contribute to the development of each one of these conditions. Future twin studies should also examine the genetic association between HD, BDD and specific anxiety phenotypes; including social phobia and panic disorder, as a further test of the etiological validity of the OCRD scheme.

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Table 1. Model-Fitting Results for checking, obsessing, washing and ordering controlled by age and gender.

Models	Estimated Parameter		Fit Statistic						
CHECKING	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	**ΔX^2**	**Δdf**	***P Value***	**Compared with model**
1 Cholesky Saturated	ACE	ACE	26369.5	14889	-3408.49	-	-	-	-
2 IP	ACE	ACE	26424.7	14916	-3407.28	55.2	27	.001	1
3 CP	ACE	ACE	26550.9	14928	-3305.08	181.4	39	<.0001	1
4 IP	**ACE**	**AE**	**26431.1**	**14922**	**-3412.87**	**6.42**	**6**	**.38**	**2**
5 IP	ACE	CE	26457.1	14922	-3386.86	32.42	6	<.0001	2
6 IP	ACE	E	26546.05	14928	-3309.95	121.33	12	<.0001	2
7 IP	AE	ACE	26443.16	14922	-3400.84	18.45	6	.005	2
8 IP	CE	ACE	26462.7	14922	-3381.28	38.01	6	<.0001	2
9 IP	E	ACE	26550.9	14928	-3305.08	126.21	12	<.0001	2
OBSESSING	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	**ΔX^2**	**Δdf**	***P Value***	**Compared with model**
1 Cholesky Saturated	ACE	ACE	26470.77	14889	-3307.23	-	-	-	-
2 IP	ACE	ACE	26501.49	14916	-3330.51	30.72	27	.283	1
3 CP	ACE	ACE	26624.40	14928	-3231.60	153.6	39	<.0001	1
4 IP	**ACE**	**AE**	**26501.96**	**14922**	**-3342.04**	**.475**	**6**	**.998**	**2**
5 IP	ACE	CE	26528.07	14922	-3315.93	26.58	6	.0002	2
6 IP	ACE	E	26612.21	14928	-3243.79	110.72	12	<.0001	2
7 IP	AE	ACE	26526.10	14922	-3317.89	24.62	6	.0004	2
8 IP	CE	ACE	26542.30	14922	-3301.71	40.81	6	<.0001	2
9 IP	E	ACE	26624.40	14928	-3231.60	122.92	12	<.0001	2
WASHING	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	**ΔX^2**	**Δdf**	***P Value***	**Compared with model**
1 Cholesky Saturated	ACE	ACE	26625.44	14889	-3152.56	-	-	-	-
2 IP	ACE	ACE	26646.16	14916	-3185.84	20.72	27	.799	1
3 CP	ACE	ACE	26759.26	14928	-3096.74	133.81	39	<.0001	1
4 IP	**ACE**	**AE**	**26646.16**	**14922**	**-3197.84**	**.0002**	**6**	**1**	**2**
5 IP	ACE	CE	26679.85	14922	-3164.15	33.7	6	<.0001	2
6 IP	ACE	E	26761.82	14928	-3094.18	115.6	12	<.0001	2
7 IP	AE	ACE	26661.07	14922	-3182.93	14.9	6	.02	2
8 IP	CE	ACE	26677.20	14922	-3166.80	31.04	6	<.0001	2
9 IP	E	ACE	26759.26	14928	-3096.74	113.1	12	<.0001	2

ORDERING	Common Factors	Specific Factors	-2LL	*df*	AIC	ΔX^2	Δdf	*P Value*	Compared with model
1 Cholesky Saturated	ACE	ACE	26289.1	14889	-3488.91	-	-	-	-
2 IP	ACE	ACE	26321.4	14916	-3510.63	32.28	27	.22	1
3 CP	ACE	ACE	26439.5	14928	-3416.51	150.39	39	<.0001	1
4 IP	**ACE**	**AE**	**26321.4**	**14922**	**-3522.57**	**.06**	**6**	**.999**	**2**
5 IP	ACE	CE	26348.5	14922	-3495.49	27.14	6	.0001	2
6 IP	ACE	E	26437.7	14928	-3418.32	116.31	12	<.0001	2
7 IP	AE	ACE	26343.9	14922	-3500.10	22.53	6	.0007	2
8 IP	CE	ACE	26358.9	14922	-3485.12	37.5	6	<.0001	2
9 IP	E	ACE	26439.5	14928	-3416.51	118.12	12	<.0001	2

Abbreviations: -2LL, minus twice the log-likelihood; *df*, degrees of freedom; AIC, Akaike information criterion; ΔX^2, difference in goodness of fit statistic between the sub-model and the full model; Δdf, change in degrees of freedom between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CP, common pathway.
In boldface type the best-fitting model based on the lower AIC.

Table 2. Checking Dimension with Anxiety Disorders and Checking Dimension with Obsessive-Compulsive Related Disorders: Best Fitting Models and Standardized Parameters.

	Estimated Parameter		Fit Statistic					
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	X^2	Δdf	***P Value***
			Checking, Social Phobia, Panic and Generalized Anxiety Disorder					
1Cholesky Saturated	ACE	ACE	22792.9	9938	2916.95	-	-	-
2 IP	**ACE**	**AE**	**22800.4**	**9948**	**2904.43**	**7.48**	**10**	**.68**
			Checking, Body Dysmorphic and Hoarding disorder					
1Cholesky Saturated	ACE	ACE	6568.7	7458	-8347.24	-	-	-
2 IP	**ACE**	**AE**	**6569.5**	**7461**	**-8352.51**	**.727**	**3**	**.87**

Standardized Parameters for each Best-fitting Model Number 2 (95% CI)

	Additive Genetic (A)			Shared Environment (C)			Non-shared Environment (E)		
	Common	**Specific**	**Total A**	**Common**	**Specific**	**Total C**	**Common**	**Specific**	**Total E**
SP	.26 (.10-.38)	.14 (.003-.21)	.40 (.25-.47)	.01 (.00-.14)	-	.01 (.00-.14)	.29 (.23-.36)	.29 (.24-.34)	.59 (.52-.65)
PD	.25 (.06-.36)	.02 (.00-.08)	.27 (.10-.36)	.03 (.00-.17)	-	.03 (.00-.17)	.39 (.31-.48)	.31 (.25-.36)	.70 (.63-.78)
GAD	.14 (.02-.26)	.13 (.00-.18)	.27 (.12-.38)	.05 (.00-.17)	-	.05 (.00-.17)	.28 (.21-.36)	.39 (.34-.45)	.68 (.61-.75)
Checking	.08 (.00-.56)	.03 (.00-.36)	.11 (.00-.64)	.41 (.00-.59)	-	.41 (.00-.59)	.14 (.06-.24)	.34 (.23-.47)	.48 (.33-.63)
BDD	.37 (.12-.44)	.00 (.00-.24)	.37 (.29-.44)	.001 (.00-.05)	-	001 (.00-.05)	.06 (.02-.12)	.57 (.50-.65)	.63 (.56-.70)
HD	.06 (.03-.25)	.25 (.005-.32)	.31 (.18-.38)	.0005 (.00-.11)	-	.0005 (.00-.11)	.49 (.25-.75)	.19 (.00-.43)	.68 (.62-.75)
Checking	.26 (.07-.56)	.00 (.00-.18)	.26 (.07-.56)	.31 (.06-.51)	-	.31 (.06-.51)	.15 (.06-.32)	.27 (.13-.41)	.42 (.30-.56)

Abbreviations: -2LL, minus twice the log-likelihood; *df*, degrees of freedom; AIC, Akaike information criterion; X^2, difference in goodness of fit statistic between the sub-model and the full model; Δdf, change in degrees of freedom between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CI, Confidence Intervals; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

At the top of the table is presented the statistics of the best fitting model (number 2 in bold).

At the bottom of the table is presented the standardized parameters for each best-fitting model (checking + ADs and checking + OCRDs). Total A, C and E do not sum to 1 due to rounding. Each parameter can be multiply by 100 to obtain the percentage (e.g. SP shows 40% of Total A, 1% of Total C and 59% of Total E).

Table 3. Obsessing Dimension with Anxiety Disorders and Obsessing Dimension with Obsessive-Compulsive Related Disorders: Best Fitting Models and Standardized Parameters.

	Estimated Parameter		**Fit Statistic**					
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	X^2	Δdf	***P Value***
			Obsessing , Social Phobia, Panic and Generalized Anxiety Disorder					
1Cholesky Saturated	ACE	ACE	22852.2	9938	2976.2	-	-	-
2 IP	**ACE**	**AE**	**22862.6**	**9948**	**2966.6**	**10.41**	**10**	**.41**
			Obsessing , Body Dysmorphic and Hoarding disorder					
1Cholesky Saturated	ACE	ACE	6878.7	7458	-8037.3	-	-	-
2 IP	**ACE**	**AE**	**6878.7**	**7461**	**-8043.3**	**.00003**	**3**	**1**

Standardized Parameters for each Best-fitting Model Number 2 (95% CI)

	Additive Genetic (A)			**Shared Environment (C)**			**Non-shared Environment (E)**		
	Common	**Specific**	**Total A**	**Common**	**Specific**	**Total C**	**Common**	**Specific**	**Total E**
SP	.08 (.00-.24)	.15 (.08-.21)	.24 (.10-.42)	.14 (.008-.26)	-	.14 (.008-.26)	-	.28 (.23-.34)	.62 (.55-.68)
PD	.13 (.02-.30)	.007 (.00 - .06)	.13 (.01 -.30)	.14 (.01-.25)	-	.14 (.01-.25)	.40 (.32-.48)	.33 (.27-.38)	.72 (.65-.79)
GAD	.20 (.07-.40)	.10 (.00 - .15)	.30 (.17-.40)	.03 (.00 - .13)	-	.03 (.00 - .13)	.28 (.22-.35)	.39 (.34-.44)	.67 (.60-.74)
Obsessing	.46 (.15-.60)	.00 (.00 - .00)	.46 (.27-.60)	.01 (.00 - .15)	-	.01 (.00 - .15)	.27 (.18-.38)	.25 (.16-.37)	.52 (.40-.67)
BDD	.18 (.07-.41)	.18 (.00 - .30)	.36 (.26-.43)	.00 (.00 -.07)	-	.00 (.00 -.07)	.22 (.13 -.36)	.41 (.28-.51)	.63 (.56-.71)
HD	.13 (.03-.34)	.16 (.00 -.28)	.29 (.09-.38)	.03 (.00 -.19)	-	.03 (.00 -.19)	.13 (.07-.21)	.56 (.47-.64)	.69 (.61-.76)
Obsessing	.21 (.06-.53)	.25 (.00 -.41)	.46 (.23-.61)	.01 (.00 -.19)	-	.01 (.00 -.19)	.34 (.19-.56)	.18 (.00-.36)	.52 (.39-.68)

Abbreviations: -2LL, minus twice the log-likelihood; *df*, degrees of freedom; AIC, Akaike information criterion; X^2, difference in goodness of fit statistic between the sub-model and the full model; Δdf, change in degrees of freedom between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CI, Confidence Intervals; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

At the top of the table is presented the statistics of the best fitting model (number 2 in bold).

At the bottom of the table is presented the standardized parameters for each best-fitting model (obsessing + ADs and obsessing + OCRDs). Total A, C and E do not sum to 1 due to rounding. Each parameter can be multiply by 100 to obtain the percentage (e.g. SP shows 24% of Total A, 14% of Total C and 62% of Total E).

Table 4. Washing Dimension with Anxiety Disorders and Washing Dimension with Obsessive-Compulsive Related Disorders: Best Fitting Models and Standardized Parameters.

	Estimated Parameter		Fit Statistic					
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	X^2	**Δ*df***	***P Value***
			Washing , Social Phobia, Panic and Generalized Anxiety Disorder					
1Cholesky Saturated	ACE	ACE	23004.4	9938	3128.4	-	-	-
2 IP	**ACE**	**AE**	**23005.6**	**9948**	**3109.6**	**1.23**	**10**	**.999**
			Washing , Body Dysmorphic and Hoarding disorder					
1Cholesky Saturated	ACE	ACE	6841.1	7458	-8074.9	-	-	-
2 IP	**ACE**	**AE**	**6841.1**	**7461**	**-8080.9**	**-.0001**	**3**	**1**

Standardized Parameters for each Best-fitting Model Number 2 (95% CI)

	Additive Genetic (A)			Shared Environment (C)			Non-shared Environment (E)		
	Common	**Specific**	**Total A**	**Common**	**Specific**	**Total C**	**Common**	**Specific**	**Total E**
SP	.19 (.04 - .33)	.16 (.09 - .21)	.35 (.19 - .46)	.06 (.00 - .19)	-	.06 (.00 - .19)	.31 (.25 - .38)	.28 (.24 - .34)	.59 (.53 - .66)
PD	.27 (.09 - .37)	.00 (.00 - .05)	.27 (.09 - .37)	.03 (.00 - .18)	-	.03 (.00 - .18)	.38 (.31 - .46)	.32 (.27 - .36)	.70 (.63 - .77)
GAD	.16 (.05 - .24)	.15 (.10 - .20)	.30 (.18 - .39)	.02 (.00 - .12)	-	.02 (.00 - .12)	.28 (.22 - .35)	.39 (.34 - .45)	.67 (.61 - .75)
Washing	.32 (.05 - .58)	.10 (.00 - .34)	.42 (.11 - .60)	.02 (.00 - .25)	-	.02 (.00 - .25)	14 (.06 -.24)	.43 (.28 - .59)	.56 (.40 - .75)
BDD	.26 (.13 - .43)	.10 (.00 - .24)	.36 (.27 - .43)	-	.00 (.00 -.06)	.00 (.00-.06)	.15 (.06 - .31)	.49 (.33 - .59)	.63 (.57 - .71)
HD	.08 (.03 - .17)	.24 (.04 - .31)	.32 (.12 - .39)	-	.00 (.00 - .15)	.00 (.00-.15)	.20 (.09 - .47)	.48 (.22 - .61)	.68 (.61 - .76)
Washing	.20 (.06 - .42)	.26 (.00 - .45)	.46 (.16 - .62)	-	.00 (.00 - .00)	.00 (.00-.00)	.15 (.05 - .32)	.39 (.22 - .59)	.54 (.38 - .73)

Abbreviations: -2LL, minus twice the log-likelihood; *df*, degrees of freedom; AIC, Akaike information criterion; X^2, difference in goodness of fit statistic between the sub-model and the full model; Δ*df*, change in degrees of freedom between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CI, Confidence Intervals; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

At the top of the table is presented the statistics of the best fitting model (number 2 in bold).

At the bottom of the table is presented the standardized parameters for each best-fitting model (washing + ADs and washing + OCRDs). Total A, C and E do not sum to 1 due to rounding. Each parameter can be multiply by 100 to obtain the percentage (e.g. SP shows 35% of Total A, 6% of Total C and 59% of Total E).

Table 5. Ordering Dimension with Anxiety Disorders and Ordering Dimension with Obsessive-Compulsive Related Disorders: Best Fitting Models and Standardized Parameters.

	Estimated Parameter		**Fit Statistic**					
Model	**Common Factors**	**Specific Factors**	**-2LL**	***df***	**AIC**	X^2	Δdf	***P Value***
			Ordering , Social Phobia, Panic and Generalized Anxiety Disorder					
1Cholesky Saturated	ACE	ACE	22681.7	9938	2805.7	-	-	-
2 IP	**ACE**	**AE**	**22685.3**	**9948**	**2789.3**	**3.66**	**10**	**.96**
			Ordering , Body Dysmorphic and Hoarding disorder					
1Cholesky Saturated	ACE	ACE	7954.6	7458	-6961.4	-	-	-
2 IP	**ACE**	**AE**	**7954.6**	**7461**	**-6967.4**	**.00**	**3**	**1**

Standardized Parameters for each Best-fitting Model Number 2 (95% CI)

	Additive Genetic (A)			**Shared Environment (C)**			**Non-shared Environment (E)**		
	Common	**Specific**	**Total A**	**Common**	**Specific**	**Total C**	**Common**	**Specific**	**Total E**
SP	.21 (.05-.33)	.16 (.09-.21)	.37 (.21-.47)	.04 (.00 -.17)	-	.04 (.00 -.17)	.30 (.24-.37)	.29 (.24-.34)	.59 (.53-.66)
PD	.26 (.08-.36)	.00 (.00-.06)	.26 (.08-.36)	.04 (.00-.18)	-	.04 (.00-.18)	.38 (.31-.46)	.32 (.27-.37)	.70 (.63-.77)
GAD	.10 (.002-.30)	.11 (.00-.17)	.21 (.06-.36)	.10 (.00-.22)	-	.10 (.00-.22)	.30 (.23-.37)	.39 (.33-.45)	.69 (.62-.76)
Ordering	.009 (.00-.30)	.02 (.00-.35)	.02 (.00-.50)	.39 (.02-.53)	-	.39 (.02-.53)	.26 (.13-.40)	.33 (.18-.49)	.59 (.41-.75)
BDD	.23 (.07-.42)	.13 (.00-.27)	.36 (.25-.43)	.003 (.00-.08)	-	.003 (.00-.08)	.15 (.08-.24)	.49 (.39-.57)	.64 (.56-.71)
HD	.11 (.02-.34)	.18 (.00-.30)	.29 (.11-.38)	.02 (.00-.17)	-	.02 (.00-.17)	.20 (.11-.34)	.49 (.35-.59)	.69 (.62-.76)
Ordering	.18 (.03-.46)	.24 (.00-.40)	.42 (.12-.56)	.02 (.00-.25)	-	.02 (.00-.25)	.21 (.10-.36)	.35 (.21-.49)	.56 (.44-.69)

Abbreviations: -2LL, minus twice the log-likelihood; *df*, degrees of freedom; AIC, Akaike information criterion; X^2, difference in goodness of fit statistic between the sub-model and the full model; Δdf, change in degrees of freedom between the sub-model and the full model; A, additive genetic factor; C, shared environmental factor; E, non-shared environmental factor; IP, independent pathway; CI, Confidence Intervals; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

At the top of the table is presented the statistics of the best fitting model (number 2 in bold).

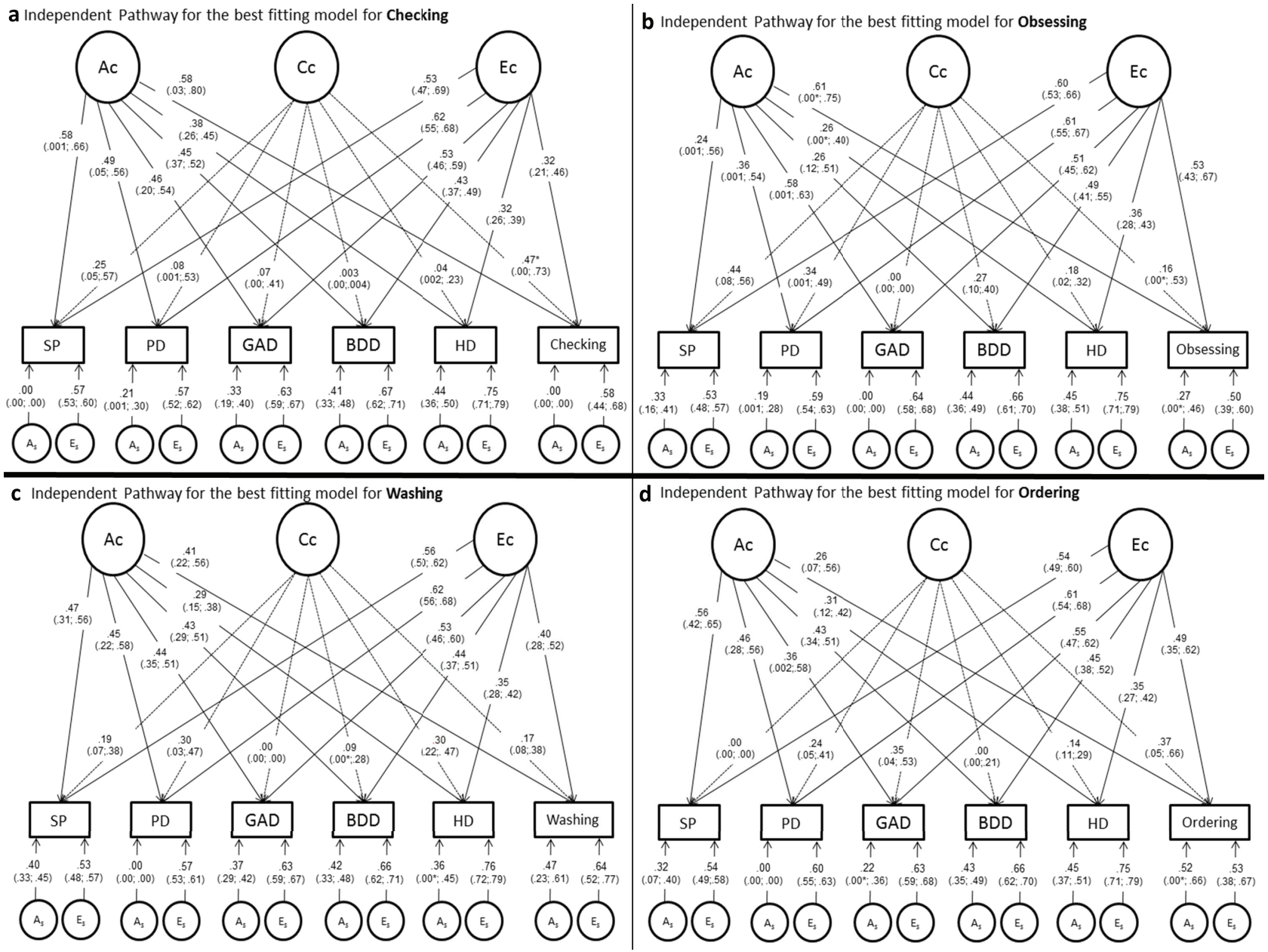
At the bottom of the table is presented the standardized parameters for each best-fitting model (ordering + ADs and ordering + OCRDs). Total A, C and E do not sum to 1 due to rounding. Each parameter can be multiply by 100 to obtain the percentage (e.g. SP shows 37% of Total A, 4% of Total C and 59% of Total E).

Figure 1 Title and Legend:

Title: Path diagrams (standardized factor loadings and confidence intervals) for the best-fitting independent pathway model for each obsessive-compulsive dimension.

Legend: Ac, common additive genetic factor; Cc, common shared environmental factor; Ec, common non-shared environmental factor; As, specific additive genetic factor; Es, specific non-shared environmental factor; HD, Hoarding Disorder Symptoms; BDD, Body Dysmorphic Disorder Symptoms; PD, Panic Disorder Symptoms; GAD, Generalized Anxiety Disorder Symptoms; SP, Social Phobia Disorder Symptoms.

*The lower CI could not be reliably estimate


a Independent Pathway for the best fitting model for Checking
Ac
Cc
Ec
SP
PD
GAD
BDD
HD
Checking
b Independent Pathway for the best fitting model for Obsessing
Obsessing
c Independent Pathway for the best fitting model for Washing
Washing
d Independent Pathway for the best fitting model for Ordering
Ordering

CHAPTER 5

DISCUSSION & CONCLUSIONS

5. DISCUSSION

The present chapter will summarise and present a general discussion of the findings of this thesis. The discussion will focus on implications for future research into the aetiology of OCD particularly with reference to its association with other anxiety disorders and OCRDs. Comments on the general limitations of the thesis and an overall conclusion will also be provided.

5.1. Summary of key findings

Study 1 described the prevalence and the genetic sex differences in the heritability estimates of OCD, OCRDs and ADs. Female twins demonstrated significantly higher prevalence rates across all domains with the exception of OCD. Evidence for distinct genetic influences between genders was observed for BDD and panic disorder symptoms, while a different proportion of genetic factors were observed in relation to hoarding and social phobia symptoms, with stronger heritability in females compared to males. This study is the first to indicate that distinct biological risk factors may influence the manifestation of body-dysmorphic and panic disorder symptoms. Although some previous literature has reported an influence of sex-specific hormones on the physical symptoms of panic, no previous study has reported specific biological sex markers associated with BDD. However, because BDD is a mental disorder focused on a preoccupation with body image, it is not surprising that sex differences may underlie the presentation of the disorder. In relation to OCRDs, we provide novel evidence for the presence of genetic sex differences in BDD and HD symptoms, as well as the lack of such differences in hypochondriasis symptoms.

Study 2 aimed to determine the genetic overlap and the pattern of causal relationships among OCD symptoms and selected OCRD and AD symptoms. The amount of common genetic liability observed for OCD was higher when considering ADs and OCRDs in the model versus modeling OCRD symptoms alone, which indicates that etiological factors for OCD are clearly mixed between the ADs and OCRDs (BDD and HD) – something that it was not observed for any of the other disorders assessed. In parallel, OCD symptoms emerged as risk factors for the

presence of generalised anxiety, panic and hoarding symptoms, whereas social phobia was the only phenotype that appeared to be a risk factor for OCD symptoms. The novel patterns of risk identified between OCD and ADs may help to explain their frequent co-occurrence. For example, certain etiological factors that affect the presence of social phobia symptoms appear to act as potential risk factors for the manifestation of OCD symptoms. At the same time, those etiological factors related to the presence of OCD, become the triggers for the occurrence of future ADs (generalized anxiety and panic symptoms).

Study 3 examined the genetic and environmental overlap between each major obsessive-compulsive symptom dimension (forbidden thoughts (sexual/religious), cleaning/washing, aggressive/checking and symmetry/ordering) with the symptoms of other OCRDs and ADs. This study provides evidence for a strong genetic overlap between forbidden thoughts and washing dimensions and other ADs. Ordering, however, was more strongly genetically related to OCRDs (although at the same time it was the dimension most genetically independent from OCRDs and ADs). Finally, checking was better explained when modeling OCRDs together with ADs, versus OCRDs alone. Nevertheless, it demonstrated a particularly strong genetic correlation with BDD versus HD symptoms.

Overall, important common environmental factors appeared to be shared in ordering and checking with the ADs. This is an appealing result because, although ordering was the most genetically independent OC dimension from other ADs, an important percentage of its variance was due to environmental factors shared with them. In other words, ordering and ADs appear to share family environmental factors such as educational and communicational parental style, parental attachment, school environment (if both twins shared classroom and teachers), friend relationships in some cases, etc. The common environmental factors normally appear to be non-significant when calculating the heritability of specific mental disorders. However, family environmental factors associated with ADs become an important source to be assessed in future twin studies when trying to understand which common environmental factors increase the probability of presenting ordering and checking symptoms.

5.2. General Discussion and Implications for Future Research

The etiological factors of OCD, as well as for ADs and other OCRDs, are multifactorial and indicate a complex interaction of genetic, epigenetic, neurobiological and psychosocial factors. In general, findings from the current thesis improve and complement existing studies and extend our understanding of the pattern of genetic and environmental factors implicated in OCD. Further, they provide a greater insight into the major symptom dimensions of OCD and how they relate to other disorders of high comorbidity.

5.2.1. Implications for Genetic Research in OCD, ADs and OCRDs

The disorders assessed in this thesis showed moderate heritability, a finding that is supported by previous twin studies in psychiatric conditions. In general, it was stronger genetic influences were found in females compared to males (Social Phobia and Hoarding symptoms), and interestingly, this is the first twin study to report that specific genetic influences differ for males and females when presenting BDD and panic disorder symptoms. These patterns of genetic sex differences are in line with the different prevalence rates found between genders. It is well known that women are twice as likely as men to develop anxiety and mood disorders (Milad & Quirk, 2012), thus it is intuitive that certain biological influences should underlie these differences in prevalence rates.

The study of specific genes that confer risk to the OCRDs, such as BDD and HD, has already started as little is known about the genetic factors associated with these conditions. As far as we know, only one molecular genetic study has been performed in patients with BDD, but without attending to the genetic sex differences. This study indicated that one gene related to the GABA system ($GABA_A$-Y^2) could be a potential candidate for the disorder (Richter et al., 2004). Hoarding, as a major dimension of OCD, has been recognised to run in families (Hasler et al., 2007). However, due to its recent inclusion as a disorder in the classificatory systems, no genetic association studies have been completed according to DSM-5 criteria. Our twin study is the first one conducted in adults showing a genetic component in HD

symptoms (not as a dimension of OCD) with a higher genetic loading in females compare to males. Future research is needed to identify the complex gene, environmental and gene-environmental interaction pathways that might explain the clinical manifestation of each OC symptom dimension, HD and BDD.

No genetic sex differences were found in relation to OCD symptoms in our first study, a finding already supported by previous twin studies (Mataix-Cols et al., 2013). The only two GWAS available in OCD (Mattheisen et al., 2014; Stewart et al., 2013a) do not segregate the sample to find specific genes associated with each gender. GWAS studies suggested that genes promoting the differentiation of glutamatergic and GABAerigc synapses could be involved in the pathophysiology of the disorder. However, no single nucleotide polymorphism (SNP) has been identified to be associated with OCD at a significant GWAS level (Mattheisen et al., 2014).

Although we did not find any genetic sex differences in relation to OCD symptoms, several studies have reported gender-related differences in the clinical manifestations of OCD. For example, early age of onset, more tics, poor treatment outcome and sexual/religious symptoms are more prevalent in males (Labad et al., 2005; Labad et al., 2008; Pooley, Fineberg, & Harrison, 2007); whilst females show a higher prevalence of contamination/washing symptoms (Labad et al., 2008). For this reason, different genetic association studies have been performed in order to describe whether specific genes or polymorphisms affect gender differences in the expression of the disorder.

Genetic association studies have revealed that OCD is related to multiple different genes (Taylor, 2012). This is consistent with twin studies showing that an important percentage of additive genetic factors account for the presence of OCD, that is, by multiple genes that gradually increase the probability for developing the disorder. Indeed part of those genetic studies have focused on specific gender differences in neurotransmission. It has been established that high MAO-A enzymatic activity (which decreases the availability of serotonin and other monoamines in the brain), low COMT (Met^{158} allele) activity (which increases dopamine activity) and polymorphisms related to serotonin (5-HTTLPR and HTR2A) are associated with OCD in men (Karayiorgou et al., 1999; Pooley et al., 2007; Taylor, 2012) with higher

scores in OC-related somatic and sensory phenomena symptoms (Katerberg et al., 2009). The genetic sex difference for COMT is consistent with other research in psychiatry showing that COMT expression activity decreases by high oestrogens levels (Kinnear et al., 2001; Taylor, 2012).

Regarding neurotrophins genes, controversial results have been found between brain-derived neurotrophic factor (BDNF), which modulates the serotonin transporter function, and OCD. Some authors did not find any associations between BDNF and OCD (Wendland et al., 2007; Zai et al., 2005), although others did (Alonso et al., 2008; Katerberg et al., 2009). Homozygote females with Met66Met BDNF allele seem to be associated with milder OCD phenotype, while homozygotes for Val66Val BDNF exhibited more severe OCD symptoms (Katerberg et al., 2009). Indeed, in males, Met allele BDNF represents a risk for the development of OCD (Hemmings et al., 2013). Furthermore, BDNF Val66 allele has been associated with sexual/religious obsessions (Katerberg et al., 2009) and in animal models, BDNF homozygotes Met66Met has been implicated in anxiety related behaviours (Chen et al., 2006). In sum, BDNF gene has been implicated in some studies with OCD and the manifestation of forbidden thought symptoms in humans, as well as with anxiety behaviours in animals. Both findings are consistent with our results from *Study 3* where we found a higher genetic overlap between the same OC dimension and other ADs.

Finally, different association genetic studies have linked a glutamate transporter gene (SLC1A1) polymorphism to OCD in males (Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006; Dickel et al., 2006; Stewart et al., 2007). However, a recent meta-analysis did not find a significant association between this glutamate polymorphism and the presence of OCD (Stewart et al., 2013b). More studies with higher samples are needed in order to find potential effects of minor genes in complex psychiatric disorders such as OCD.

Regarding the ADs, the candidate genes most widely studied are genes involving serotonin, norepinephrine, glutamate and dopamine systems, or those related to stress (Olivier et al., 2013; Shimada-Sugimoto et al., 2015). However, genetic studies have produced inconclusive results and GWAS studies, similar to

OCD, have not identified any SNP(s) with a genome-wide significance (Olivier, Vinkers, & Olivier, 2013; Shimada-Sugimoto, Otowa, & Hettema, 2015).

Following on from the genetic sex differences found in our first study, apart from variances in the expression of certain alleles depending on gender, another important source of study is whether or not gonadal hormones (difference between genders) influence the presence of all these related disorders. It is well known that women are more vulnerable to stress and fear/anxiety disorders (Maeng & Milad, 2015) and that fear extinction may be modulated by gonadal hormones (Milad & Quirk, 2012). Indeed, ADs have been associated with difficulties in learning and maintaining fear extinction processes. This may be in line with our female genetic sex differences found in *Study 1* regarding social phobia and panic disorder symptoms. There is an association between normal variation of gonadal hormones, estradiol in particular, and fear inhibition process, where low levels of estradiol, and perhaps progesterone, appear to be related to an impairment in fear extinction in women (Milad et al., 2010; Milad & Quirk, 2012). In contrast, an augmentation of testosterone in male rats facilitates learning inhibitory behaviours, decreases anxiety levels and facilitates conditioned fear extinction (Edinger & Frye, 2007; Frye, Edinger, & Sumida, 2008). In this line, it has been found that some women report an association between the onset and course of their OCD symptoms and fluctuations in the ovarian hormones levels (Labad et al., 2005). Estrogens interact with different neurotransmitter systems (serotonin, adrenergic and cholinergic) (Labad et al., 2005), and for this reason, gonadal hormones in general are important to understand the fluctuations and expression not only for OCD but also for other ADs, such as panic disorder (Cohen, Sichel, Dimmock, & Rosenbaum, 1994a, 1994b) and OCRDs, such as trichotillomania (Keuthen et al., 1997). In OCD, the premenstrual and postpartum periods have been reported to be the more vulnerable episodes for worsening OCD (Labad et al., 2005).

Based on genetic studies on OCD and ADs it can be inferred that a large number of genes with small effects account for the heritability of these phenotypes. In this sense, the genetic liability of OCD and ADs (and probably BDD and HD) are distributed quantitatively rather than qualitatively (Plomin, Haworth, & Davis, 2009). The results from this thesis highlight a more accurate picture of the genetic risk

factors that are shared between OCD and other anxiety and related disorders. This information will help future research by stimulating researchers to focus on clusters rather than on a single individual condition, which in turn will help find the genetic mechanisms that confer increased risk for certain co-occurring psychopathologies (Kendler, Gardner, Gatz, & Pedersen, 2007; Shimada-Sugimoto et al., 2015).

Obsessive-compulsive, anxiety and other OCRD symptoms are distributed dimensionally in the general population. This means that those traits are quantitatively distributed in a continuous manner (with low, medium and high scores), rather than qualitatively present in patients and absent in controls. For this reason, one methodological strategy to increase statistical power in future GWAS studies in OCD, AD and OCRDs would be by studying a large sample of a general, normative population (which may also include a subset of patients) rather than dichotomizing the sample between cases and controls.

The genetic overlap found between OCD and ADs and OCRDs (*Study 2*), highlights the pleiotropic effect of certain genes in the etiology of all these disorders. Due to the high genetic covariance between OCD and certain ADs, it is reasonable to suspect that candidate genes involved in specific ADs could also be identified as risk factors for specific OC dimensions. Specifically for forbidden thoughts and washing symptoms, which are the dimensions more genetically associated to other ADs (*Study 3*). In the same line, and based on our results, specific genes linked to BDD could also be involved in the manifestation of checking symptoms. Different expressions of genes and/or gonadal hormones that are associated with OCD, might be shared between BDD and checking symptoms and, might differ between genders. Future studies would benefit by including samples of the general population and patients with BDD and/or checking symptoms, in order to observer whether a specific genetic and/or hormonal pattern is associated with these two phenotypes.

Besides increasing the understanding of the genes/hormones with common effects on the different pathologies (OCD, ADs and OCRDs), it is important to pay attention to which specific genes/expression of genes and neurobiological factors are relevant for the presence of symmetry/ordering dimension and hoarding disorder. Both phenotypes raised as the most genetically independent variables compared to

other OC dimensions, ADs and BDD. Future genetic studies should address this question by including large samples and taking into account the increased genetic association of hoarding with females (based on the higher genetic component found in *Study 1*) and higher prevalence of tic-related disorders in males (Torresan et al., 2013; Torresan et al., 2009).

Regarding our findings with the ICE FALCON analysis from *Study 2*, future research will benefit from analysing longitudinal twin samples looking at OCD and ADs and OCRDs symptoms in the follow up. Two type of analyses could be performed in this hypothetical sample: first, at an individual level, following patients over time without comparing the differences within and between twin pairs; and second, as a group, comparing whether or not there are differences between MZ and DZ twins. In the first case, it is important to test if there is an increased proportion of subjects with high social phobia symptoms at baseline, who over time, will develop OCD symptoms, compared to those individuals with low or absent social phobia symptoms. The same analogy could be applied to the rest of the causal relationships that emerged with significance in *Study 2* (OCD increasing the risk to present panic, generalized anxiety and hoarding symptoms). If these results were confirmed in a longitudinal study then ICE FALCON findings would be significantly strengthened in terms of inferring causality. Other interesting relevant questions to be investigated include: 1) whether the group of MZ twins present an increased proportion of subjects, compared to the DZ group, with social phobia symptoms that develop OCD in the follow-up. If confirmed, such results would indicate that certain genetic components (compared to the environment) associated with social phobia are playing an important role in increasing the probability of present OCD; 2) whether there are significant differences in environmental factors between the group of MZ and DZ with social phobia that later develop OCD symptoms *versus* the MZ and DZ twins that do not develop OCD symptoms (although having an increased social phobia); and finally 3) whether or not gene-by-environmental interactions explain the causal relationship between social phobia and OCD symptoms, as well as the other causal relationships identified in *Study 2*.

Taken together, twin analyses in this thesis demonstrate that common genetic factors associated with ADs and certain OCRDs play a crucial role in the etiology of

OCD symptoms that vary across its major symptom dimensions. Although our findings suggest the existence of a genetic overlap among different diagnostic entities, this does not guarantee that candidate genes will be easily found for each disorder. Our results support the exploration, in future genetic research, of specific OC symptom dimensions (such as forbidden thoughts and contamination/cleaning symptoms) together with certain ADs. For exploring specific genes associated with checking and ordering it would be appropriate to also assess BDD and HD symptoms respectively (both in patients and the general population). Genetic studies should focus on the identification of pleitropic as well as specific genes conferring risk to OC dimensions in relation to ADs and OCRDs.

5.2.2. Implications for Research on Environmental Risk Factors

At least half, or more than half, of the variance described in each diagnostic domain was explained by non-shared environmental factors (including measurement error). Childhood abuse, neglect and early loss have been consistently associated with an increased risk for anxiety disorders in adulthood (Blanco et al., 2014; Zannas & Binder, 2014). While perinatal events (such as lower birth weight), psychosocial stressors, trauma (such as physical/sexual abuse) and inflammatory processes have been linked generally to the development of OCD (Cath, van Grootheest, Willemsen, van Oppen, & Boomsma, 2008; Lafleur et al., 2011; Vasconcelos et al., 2007), little remains known about their specific contribution to OC symptom dimensions. Only one study has reported that perinatal insults seem to be a risk factor for OCD patients with prominent ordering symptoms (Grisham et al., 2011). Regarding other OCRDs, little is known about HD, although, BBD may be associated with a history of childhood teasing, abuse, and neglect (Buhlmann, Cook, Fama, & Wilhelm, 2007; Buhlmann, Marques, & Wilhelm, 2012; Didie et al., 2006; Neziroglu, Khemlani-Patel, & Yaryura-Tobias, 2006), similar to the factors described above for ADs.

Another main finding emerging from the current thesis is that the majority of the environmental risk factors appear to be specific to each symptom disorder. This suggests that the environmental risk factors that contribute to the risk for developing one specific symptom domain may not confer risk for developing another. Although,

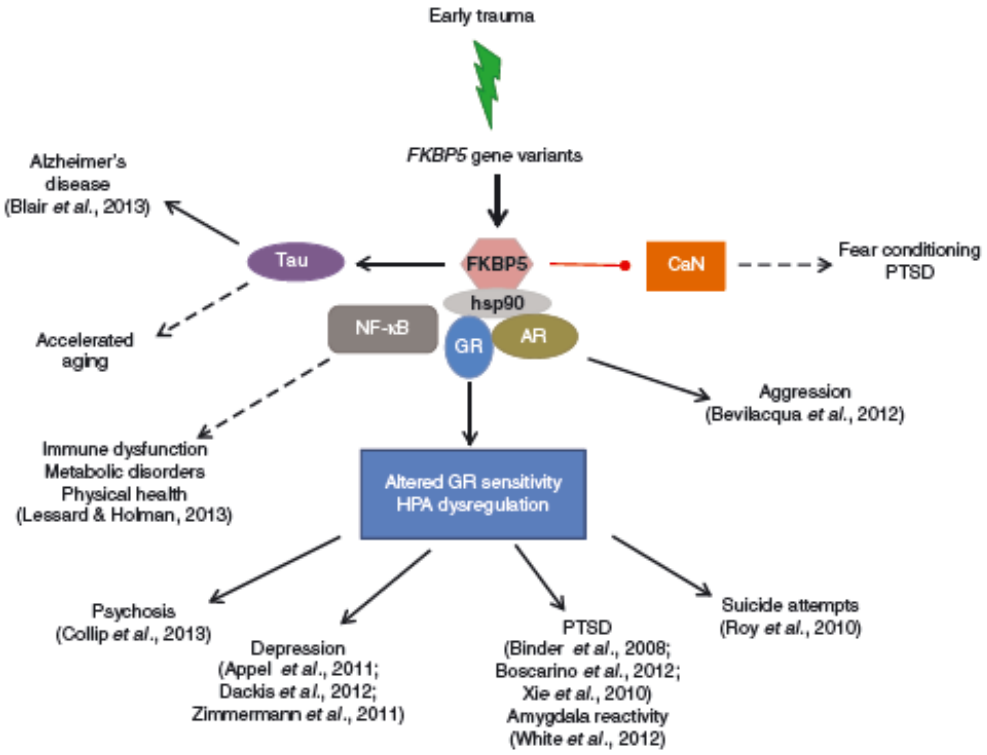
it has been previously described that certain early life stressful events seem to affect the development of OCD, ADs and OCRDs, there is also a crucial role of unique environmental factors in determining whether a person with genetic risk factors would finally develop a mental condition. It is of crucial relevance to address this particular issue in order to know which specific psychosocial stressors, perinatal insults etc. are associated to each condition, as well as to explore the gene-environmental interactions (see the following section 4.2.3).

It is also noteworthy that checking and ordering dimensions share common environmental factors with ADs more than with washing and forbidden thought obsessions. Understanding which environmental factors are associated with certain OC dimensions and ADs will help to develop prevention programs necessary for decreasing the likelihood of comorbid symptom disorders as well as reducing the severity and/or chronicity of them.

5.2.3. Gene-by-Environment Interaction Factors

The results from this thesis are consistent with the "genetic pleiotropic" hypothesis, an occurrence whereby one or more common genes contribute to an important variance of phenotypic expression common among a group of disorders, while specific environmental influences explain most of their differences (Nicolini, Arnold, Nestadt, Lanzagorta, & Kennedy, 2009). For example, variants altering stress sensitivity, such as a gene that regulates the sensitivity of the glucocorticoid receptor (FKBP5), could be a common risk factor behind diverse phenotypic presentations. Understanding how such pleiotropic effects may be mediated is of critical importance and may offer an opportunity for early identification and targeted treatments of individuals at high risk for developing specific psychiatric phenotypes (Zannas & Binder, 2014). See Figure 1 extracted from Zannas & Binder 2014 , which depicts a model of pleiotropy whereby a gene interaction environment at the receptor FKBP5 via intracellular interactions with other molecules goes on to present different somatic and psychiatric conditions.

Figure 1. Model of pleitropy of gene-by-environmental interaction at FKBP5.



Gene-by-environment interaction infers that individuals with different genotypes will have varying responses to the same environmental stimuli due to genetic variation.. More clearly, it means that the "negative" effects of being exposed to specific environmental factors will depend on the genotype of each individual. In other words, the same environmental factor is not expected to have an equal effect on all individuals due to differences in their genotype. However, at the same time, specific genotypes will increase or decrease the probability of a person to be exposed to certain environmental factors (e.g. a behavioural inhibition trait of a person will make more likely to reduce social interactions and subsequently an increased isolation).

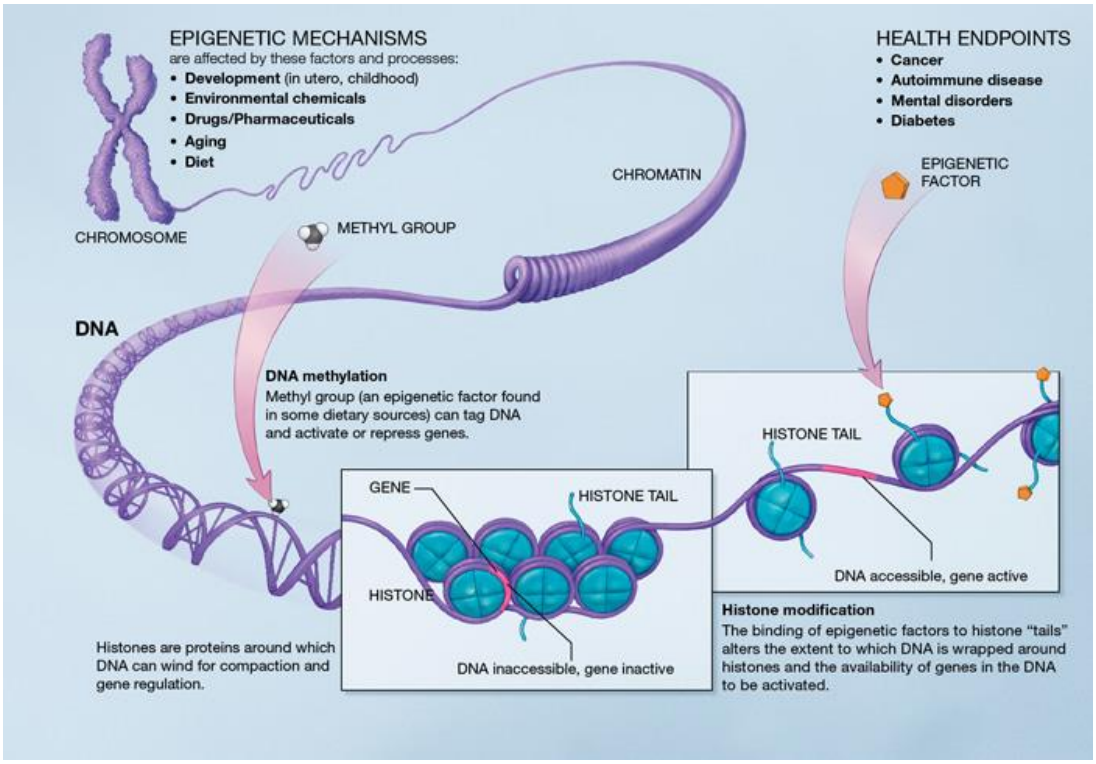
Gene-environmental interactions may induce modifications in the expression of genes. This has been called "epigenetics", which has been related to the development of certain psychiatric disorders. More specifically, Henikoff & Matzke

(1997) defined epigenetics as "*the reversible regulation of gene expression mediated principally through changes in DNA methylation and chromatin structure, occurring independently of the DNA sequence*". However, more recently, it has been demonstrated that changes in the expression or function of genes are potentially heritable through mitosis, but that the transmission is imperfect (Bennett-Baker, Wilkowski, & Burke, 2003). Specific epigenetic factors have not been identified in relation to OCD, BDD and HD. However, future research might be of critical importance with respect to intervention and prevention strategies.

Indeed, DNA methylations, which have been described as one of the major forms of epigenetic modifications, represents the most fundamental link between early life experiences and the risk for psychiatric diseases (Szyf, 2014). The difference between genetic and epigenetic processes is the potential to reverse epigenetic effects by interventions that are either behavioural or pharmacological (Szyf, 2014). Another important aspect of epigenetics is the potential for joining "risky environmental exposures" with specific pathologies in order to design and test prevention therapeutic paradigms. This notion should be addressed by further studies, particularly intervention studies that examine the correlation between therapeutic response and changes in DNA methylation patterns (Szyf, 2014).

For further clarification of how DNA methylation occur see Figure 2 from the National Institutes of Health (http://commonfund.nih.gov/epigenomics/figure.aspx), via Wikimedia Commons, where it explains how epigenetic mechanisms operates.

Figure 2. Epigenetic Mechanisms.



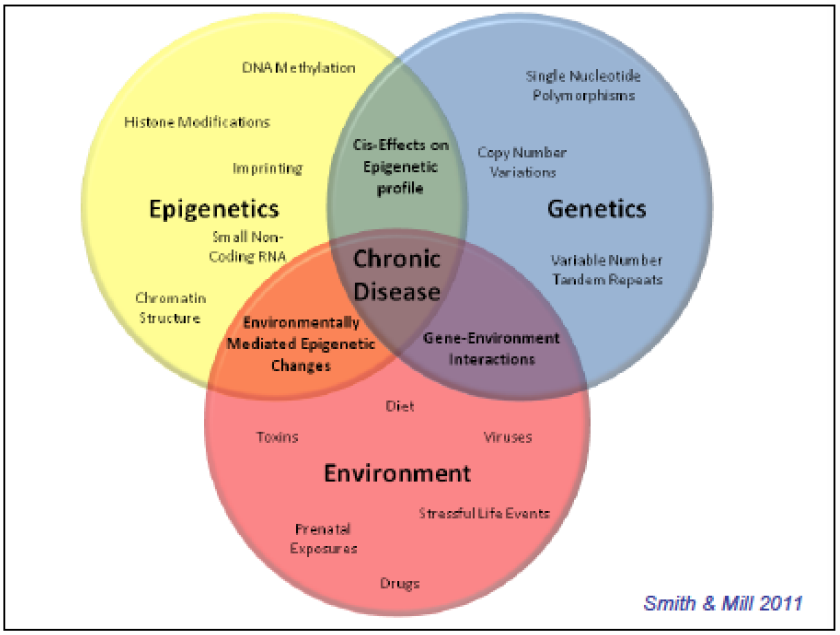
From an epigenetic point of view, the intrauterine environment is considered one of the most relevant places to observe where the first differences in the development of identical twins arise. In fact, epigenetic factors are particularly susceptible to occur during embryogenesis and the perinatal period. Stress in utero has been linked to altered brain plasticity and cognition in humans and animal models (Bock, Wainstock, Braun, & Segal, 2015). There is also evidence that suggests subtle asymmetries within twin pairs (such as weigh at birth). Generally, when favoured for one twin than the other, these asymmetries are associated with medical conditions later in life (Gordon et al., 2012). Specifically it has been found that epigenetic discordant factors in identical twins, which means that although sharing 100% of the genetic factors, the epigenetic mechanisms could differ between both (Gordon et al., 2012). This finding highlights the importance of intrauterine environment in understanding neonatal DNA methylation profiles. Additionally, this study showed that MZ twins sharing only one placenta were more discordant for DNA methylation

than MZ twins with one placenta for each. One explanation made for these surprising results were that MZ twins sharing the placenta are more likely to experience competition for resources and this could increase the greater difference found in their epigenetic factors (Gordon et al., 2012). Moreover, it was postulated that the specific genes of fetuses whose methylation process were associated with low birth weight, were also associated with growth, metabolism and cardiovascular diseases. For this reason, the authors speculated that DNA methylation profiles associated with cardiovascular and metabolic function might be defined in utero (Gordon et al., 2012). It is also well known that different metabolic and cardiovascular diseases are significantly associated with severe mental disorders such as schizophrenia, bipolar disorder and major depression (Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2014; Garcia-Rizo et al., 2013) as well as also to certain ADs (Carroll et al., 2009; Phillips et al., 2009; Player & Peterson, 2011).

Intrauterine environment then is not a common environment factor between twins. Although both twins are gestated at the same time, there are differences that may affect, despite presenting identical genotypes, their genetic expression at birth. Those differences refer to placentation (monochorionic-monoamniotic, monnochorionic-diamniotic and dichorionic-diamniotic); discordant placental weight, discordant placental umbilical cord insertion (resulting in a different fetal blood supply), inter-twin placental proximity, competition for nutrients, etc. (Foley, Neale, & Kendler, 2000; Gordon et al., 2012). All of these factors should be taken into account in future twin studies due to the important role that intrauterine factors may play in the final expression of complex pathologies such as psychiatric disorders.

As illustrated in Figure 3 (see below) it is not only the genetic or environmental components that interact to contribute to disease development, but also the interaction of epigenetic factors, most of them, occurring during the gestational period.

Figure 3. Interaction between genes, environment and epigenetic factors.



5.2.4. Nosological Implications

DSM-IV conceived OCD as an AD, however recent DSM-5 support the segregation between ADs and OCD. This new classification comprehends ADs and OCRDs as underlying different etiological mechanisms. Likewise, from this classification it could be inferred that anxiety is also not an essential part of OCD, or of any other OCRDs. Although the new classification was approved in spite of clear gaps and deficiencies in the scientific literature, recent studies have partially demonstrated that OCD is etiologically related to BDD and to a lesser extent to HD. However, skin picking and trichotillomania do not seem to be highly genetically related to OCD, BDD and HD (Monzani et al., 2014). Moreover, the fact that OCD is genetically related to BDD and HD does not necessary mean that they are not anxiety related as well. The results from this thesis report that OCD and its dimensions comprise other etiological factors apart from the ones associated with BDD and HD, with anxiety (circuit of fear) a core factor For all these reasons, our results support previous proposals that stipulate the importance of keeping ADs and OCRDs together under

the same DSM chapter, and also including other mental conditions such as hypochondriasis (Bienvenu et al., 2012; Stein et al., 2010).

5.2.5. Clinical Implications

Study 1 showed that symptoms of Social Phobia (around 17%) are much more prevalent in the general population than the rest of the ADs and OCRDs symptoms. The second most prevalent symptoms were OCD (8.7%), followed by hypochondriasis (6.8%). Although BDD and HD present prevalence of 2 and 2.6% in the general population, those pathologies may reach high levels of disability, which means that clinicians should screen for these conditions and consider other potential OCRDs and ADs to be present. Moreover, *Study 1* shed light on the idea that different genetic factors may be affecting the presence of BDD symptoms and that hoarding tends to present an increase in genetic aggregation in females more so than males. Gender differences such as hormonal profiles and reproductive circles should be taken into account in clinical practice in order to further future research studies and improve treatment/prevention programs by considering gender as one relevant factor.

Study 2 showed that the presence of OCD should be utilised clinically as a potential indicator and diagnostic tool for the presence of other comorbid conditions which may appear later on in life (such as GAD, PD and HD). In the same line, detecting social phobia could also be a risk factor (and even more if there is a close relative with OCD) for developing OCD. Also, some specific OC dimensions were found to genetically and/or environmentally overlap with the ADs, while others were more related to the OCRDs. These results support the concept that OCD is less etiologically aligned with the OCRDs compared to the ADs. Finally, due to higher genetic commonalities found between ordering symptoms and OCRDs (specifically with hoarding), and based on previous research showing the association between this dimension and tic-related disorders, it would be highly recommended in clinical settings to evaluate the presence of any of these disorders to best determine the severity and prognosis of the patient. In other words, a more holistic clinical approach may facilitate earlier detection and treatment, and potentially help to minimise the risks factors associated with overlapping conditions.

Preventative efforts for individuals at high genetic risk could include, psycho-education about OCD, ADs and other OCRDs; information to parents of the specific environmental risk factors that may increase the risk for developing certain conditions and interventions for patients with OCD and/or their offspring with OCD may also be a useful future clinical tool. Similarly, it would be of clinical relevance to help patients with stress management, social support and to systematically follow them up assessing the interference of OCD in their daily life activities. Specifically, in women with OCD, ADs and OCRDs clinicians should follow any hormonal changes and adapt treatment options to prevent fluctuations in the symptoms. This extensive control during the detection of certain disorders could help to decrease the prevalence and incidence of other related psychiatric conditions.

Hypochondriasis disorder (included in *Study 1*) has not been widely explored as of yet. Hence, there are a myriad of unsolved questions regarding this disorder, for example, whether genetic and environmental factors are related to other ADs more than to the somatoform disorders or, by contrast to OCD and other OCRDs. A recent published revision highlights a phenomenological overlap with both anxiety disorders (e.g., fear, hyper-vigilance to bodily symptoms, and avoidance) and OCRDs (e.g., preoccupation and repetitive behaviours), and argues that hypochondriasis is somewhat different from other somatoform disorders as somatic symptoms do not appear to be a critical characteristic (van den Heuvel et al., 2014). Other studies have also made the link between hypochondriasis and anxiety disorders versus somatoform disorders (Olatunji, Deacon, & Abramowitz, 2009). Neurobiological findings show an overlap of brain structures among hypochondriasis, panic disorder and OCD (van den Heuvel et al., 2011). In this thesis, hypochondriasis symptoms were initially included, however due to the final OCRDs chapter at DSM-5, where hypochondriasis was excluded, we decided to keep it apart from OCRDs group for Study 2 and 3. However, due to its relationship with OCD and other ADs, future research should address whether hypochondriasis is etiologically aligned with specific OC symptom dimensions and/or certain ADs in order to clarify its underlying etiology.

5.3. Limitations

Findings from the current thesis should be interpreted under certain limitations, which have been previously reported in each study at chapter 3. However, here are some limitations that are common in all the analyses performed in this twin study,

Firstly, although skin picking and trichotillomania symptoms were initially assessed, the use of screening questions in the survey to reduce the time of administration was reflected in a decreased number of responders. Second, this is a population based twin study where the main focus of attention was the dimensional representation of different traits in a general population. For this reason, the results are based on self-report measures instead of clinical interviews to obtain full diagnostic criteria. All the questionnaires have been validated for non-clinical samples and also the use of self-report measures is an effective and extensively method employed in behavioural genetics (Neale & Cardon, 1992). Third, twin subjects are a subset of the general population that may not be completely representative due to differences such as pregnancy environment or growing up conditions. Fourth, classical twin method is based on a controversial assumption: identical and same-sex fraternal twin pairs grow up experiencing roughly equal environments. This is known as the "equal-environment assumption" (EEA). However, some authors argue that MZ twins experience much more similar environment than DZ twins. MZ tend to be treated more similar by their parents (equal cloths, etc.) and have more frequent contact than DZ twins, which may impact in the increased correlation found in different measures among MZ vs. DZ twins. On the other hand, MZ twins are sometimes forced to attend separate classes at school and that could increase the variability among MZ twins. Other authors argue that MZ and DZ twins tend to share the same environment: 1) they share the womb at the same time; 2) they are exposed to the same environmental factors; 3) present the same age which means the same cultural/historical moment; and 4) they are raised in the same family. This is a methodological aspect in classical twin modeling analyses that has not yet reached a final agreement. Finally, another limitation of the thesis is that all of the studies are cross-sectional, which means that nothing is known about the stability of those results across the life-span. However, using the ICE-FALCON methodology we can infer causality, and although it is necessary to support those results with longitudinal

studies, this is the first step to explain a possible longitudinal effect in the manifestation of these mental disorders. It would be very interesting in future studies to follow-up this twin sample and observe whether ICE-FALCON results are totally or partially replicated.

5.4. Conclusions

The thesis findings shape a new understanding of the etiology underlying OCD and its major symptom dimensions.

Study 1 provides novel evidence of sex-specificities in the pattern of heritability of the OC-spectrum disorders (hypochondriasis, BDD and hoarding disorder symptoms), and supports moderate heritability for OCD and ADs together when assessed contemporaneously.

Study 2 shows the essential contribution of anxiety to explain OCD's complex etiology. These results concur with findings obtained using the ICE FALCON approach, where the presence of OCD increased an individual's probability to develop PD and GAD symptoms. Additionally, the study shows that suffering social phobia symptoms increases the probability to develop OCD symptoms later in life. Regarding OCRDs, we showed that OCD increases the risk to present hoarding symptoms but the reverse does not hold true. Also, there appears to be no direct association between OCD and BDD symptoms.

Finally, *Study 3* shows that different OC symptom dimensions present different patterns of genetic and environmental associations with ADs and OCRDs, such that: (i) forbidden thoughts and washing OC dimensions share the highest percentage of genetic factors with the ADs; (ii) symmetry/ordering presents the highest specific genetic factors that are not shared with any other AD and OCRD symptoms; (iii) the checking dimension is genetically associated to both OCRDs (specifically BDD) and ADs; (iv) finally, checking and symmetry/ordering shares environmental factors only with ADs.

Overall, OCD shares important genetic factors with symptoms related to the anxiety spectrum and to the OCRDs, but more specifically with BDD symptoms. Shared environmental factors with the ADs have emerged to be relevant, however, just in part of the OCD phenotypes (checking and symmetry/ordering dimensions).

In conclusion, it is necessary to carefully consider the benefits that current diagnostic classifications such as DSM facilitate in the clinical-professional management of OCD patients (clinical realm), whilst also acknowledging the clear limitations engenderred in terms of understanding the disorder's complex etiology (scientific realm). Studies which repeatedly focus on a particular definition of OCD, strictly informed by nosological frameworks of their current time, will ultimately fail in providing a deep understanding of the disorder. In contrast, considering the current thesis results, major scientific and clinical benefit will result from focusing on groups of related symptoms, such as ADs, hypochondria, some OCRDs and tic related-disorders. Also of significance are environmental factors that could be related to the etiology of OCD such as parental communication, family attachment, stressful life events during childhood and adulthood.

In light of this thesis' results, future work using self-report questionnaires should focus on the study of (i) patients with symptoms pertaining to different OCD dimensions combined with other psychiatric disorders associated with OCD (not only included in the OCRDs chapter), (ii) their first-degree relatives and (iii) a general population of MZ and DZ twins. In a related line, it would be of great interest to record clinical symptoms (anxiety, hypochondriasis, BDD, etc.) at two different times of the menstrual cycle in women to assess potential hormonal effects on the expression and relationship between different OCD symptoms. To further understand the stability of those results over the time and the specific contribution of genetic, environmental and epigenetic factors, future longitudinal studies should focus on assessing environmental risk factors and intrauterine environment in the twins' sample. Finally, saliva samples should be collected from patients, relatives and twins to perform subsequent genetic and gene-environmental interaction analyses. Informed by the current thesis, it is the candidate's view that such a study would considerably enhance our current understanding of the causes of OCD.

CHAPTER 6

SUMMARY IN SPANISH

SUMMARY IN SPANISH / RESUMEN EN CASTELLANO

1. INTRODUCCIÓN

1.1. Trastorno Obsesivo-Compulsivo

El trastorno obsesivo-compulsivo (TOC) se caracteriza por pensamientos o imágenes intrusos recurrentes (obsesiones) que van habitualmente acompañados por conductas repetitivas o actos mentales (compulsiones). El trastorno afecta entre un 2-3% de la población mundial y está identificado como uno de los 10 trastornos que provocan más años vividos con discapacidad (Fontenelle et al., 2006; Ruscio et al., 2010).

El TOC presenta, además de la elevada comorbilidad (el 90% de los pacientes padecen al menos otro trastorno psiquiátrico), una gran variabilidad fenotípica lo que ha llevado a pensar que existe no sólo una heterogeneidad clínica sino también genética, y que diferentes factores biológicos y ambientales pueden estar influenciando su expresión clínica. En el año 2005 se propuso un modelo multidimensional (Mataix-cols *et al.* 2005) que consideraba al TOC como un conjunto de síndromes, y donde se definían al menos 4 dimensiones obsesivas: 1) contaminación/limpieza; 2) orden/simetría; 3) pensamientos prohibidos (con contenido sexual/religioso y agressivo)/comprobación; y 4) obsesiones y compulsiones de acumulación (Bloch et al., 2008).

1.2. Trastorno Obsesivo-Compulsivo y Trastornos Relacionados

En la nueva clasificación diagnóstica DSM-5, el TOC fue excluido de la categoría de los trastornos de ansiedad y ubicado en un capítulo aparte titulado "Trastorno Obsesivo-Compulsivo y Trastornos Relacionados" (OCRDs del inglés *Obsessive-Compulsive and Related Disorders)*, incluyendo: el trastorno dismórfico corporal (TDC); la tricotilomanía (TTM); el trastorno por excoriación y el trastorno por acumulación compulsiva.

La decisión de generar una nueva categoría fue basada en las similitudes fenomenológicas (pensamientos obsesivos y conductas repetitivas) (Phillips et al., 2010) y en la alteración de los sistemas serotoninérgicos, dopaminérgicos y glutamatérgicos (Murphy et al., 2010). Sin embargo, la evidencia con mayor soporte científico hasta el momento es la comorbilidad encontrada entre el TOC y los OCRDs, y su agregación familiar (Bienvenu et al., 2012).

Si la nueva clasificación del TOC es precisa, se podría afirmar que el TOC está fenomenológica, etiológica y biológicamente más relacionado con los trastornos OCRDs. De manera implícita se entiende que el TOC estaría menos asociado a los trastornos de ansiedad o que la ansiedad sería un constructo secundario o menos relevante. Sin embargo, esta última cuestión sigue, a día de hoy, estando en duda (Storch et al. 2008; Milad et al 2013). Se necesitan más evidencias científicas que muestren que los factores de riesgo genético y/o ambiental para el TOC se asocian más con los OCRDs y no con los trastornos de ansiedad.

1.3. Estudios de Gemelos en Psiquiatría

Los estudios con gemelos son considerados una de las principales herramientas en la genética de conducta para identificar marcadores genéticos relevantes que subyacen a patologías complejas como los trastornos psiquiátricos.

Los modelos univariados permiten estimar la heredabilidad de un rasgo, o trastorno, que representa la proporción de varianza fenotípica en una población concreta que se puede atribuir a factores genéticos. La heredabilidad de un trastorno puede variar según las poblaciones y a lo largo de la vida de un individuo desde 0 (no hay contribución genética para dicho trastorno) hasta 100% (completamente debido a factores genéticos). Sin embargo, la magnitud de la heredabilidad de un trastorno no proporciona ningún dato sobre la posible asociación genética y/o ambiental que puede existir entre dos o más patologías relacionadas. Los modelos multivariantes son utilizados para resolver la pregunta de si diferentes trastornos que co-ocurren demuestran o no un solapamiento en sus factores de riesgo (Neale & Maes, 2001).

1.3.1. TOC, Trastornos de Ansiedad y Trastornos Relacionados con el Trastorno Obsesivo-Compulsivo (OCRDs)

Los estudios de gemelos han reportado que el TOC y los síntomas obsesivos son hereditarios entre un 27-47% (van Grootheest et al., 2005). Además, la heredabilidad es similar entre hombres y mujeres (van Grootheest et al., 2009).

Existen dos estudios relativamente recientes que miran la heredabilidad de las dimensiones obsesivas en dos muestras de gemelos con mujeres, los cuales presentan resultados contradictorios (Van Grootheest *et al.*, 2008; Ievorlino *et al.*, 2011). Se requieren más estudios para resolver esta contradicción, incluyendo en el muestreo hombres y mujeres conjuntamente.

Los estudios de gemelos han confirmado que existe una carga genética común (alrededor de un 54%) a todos los trastornos de ansiedad incluido el TOC (Tambs et al., 2009). Sin embargo, el TOC junto con las fobias específicas y la fobia social son los que presentan un mayor porcentaje de factores genéticos específicos (aproximadamente un 40%) diferentes al resto de trastornos de ansiedad.

Por otro lado, la heredabilidad ha sido explicada para los síntomas de acumulación compulsiva (50%), TDC (44%) y excoriación (40%). Sin embargo, esta evidencia proviene de un único estudio con mujeres de Reino Unido (Iervolino et al., 2009; Monzani et al., 2012; Monzani, Rijsdijk, Cherkas, et al., 2012).

Únicamente dos trabajos evalúan la genética y el ambiente compartido entre el TOC y otros OCRDs con mujeres. En el primero encuentran que el 64% de la covarianza total entre TOC y TDC era debido a factores genéticos compartidos (Monzani et al., 2012). El segundo estudio evalúa los síntomas de los cinco OCRDs incluidos en el DSM-5 e identifican dos factores independientes de carga genética. El primer factor genético representaba principalmente a los síntomas obsesivos, de acumulación y TDC. Mientras que el segundo factor pesaba sobre tricotilomanía y excoriación (Monzani et al., 2014). Aunque se necesitan más estudios que apoyen estos resultados en una población que incluya a hombres y mujeres, estos son los primeros resultados de gemelos que muestran la existencia de una genética compartida entre el TOC y, sobretodo, síntomas de acumulación y TDC.

1.4. Resumen

Actualmente existe un conocimiento incompleto sobre las bases genéticas del TOC. Ningún estudio de gemelos hasta la fecha ha evaluado sistemáticamente la relación entre todas las dimensiones de síntomas TOC y (1) diferentes trastornos de ansiedad junto con (2) los OCRDs en la misma población de gemelos (hombres y mujeres) y en el mismo espacio temporal. Si se es capaz de demostrar que las correlaciones entre los síntomas obsesivos y los OCRDs son superiores a las encontradas entre el TOC y otros trastornos de ansiedad en gemelos idénticos versus gemelos no idénticos, se podría afirmar que existe una mayor identidad biológica entre el TOC y los OCRDs comparado con los trastornos de ansiedad, validando así la nueva clasificación diagnóstica del DSM-5.

2. OBJETIVOS

Estudio 1:

- Estudiar la prevalencia y la heredabilidad de los síntomas obsesivos, ansiosos y del espectro (incluyendo hipocondría) en una misma población de gemelos en el mismo espacio temporal.
- Analizar si existen diferencias entre hombres y mujeres en la influencia genética y/o ambiental en las dimensiones de síntomas obsesivos, del espectro y ansioso.

Estudio 2:

- Evaluar la estructura de los factores de riesgo genético y ambiental que subyacen al conjunto de síntomas obsesivos, ansiosos y del espectro (OCRDs) utilizando modelos de ecuaciones estructurales multivariantes con gemelos, controlando por edad y género.
- Estudiar las relaciones causales entre los síntomas de TOC, otros trastornos del espectro (OCRDs) y otros trastornos de ansiedad, utilizando una nueva metodología de gemelos (ICE FALCON) y controlando por edad y género.

Estudio 3:

- Investigar la estructura de los factores de riesgo genético y ambiental que subyacen a cada una de las dimensiones obsesivas (pensamientos prohibidos, contaminación, orden/simetría y comprobación), junto con síntomas de los trastornos ansiosos y del espectro obsesivo controlando por edad y género.

3. METODOLOGÍA

Se utilizó una muestra de 2.495 gemelos (1.027 hombres y 1.468 mujeres) de entre 18 y 45 años procedentes del Registro de Gemelos Australiano. Todos ellos respondieron una encuesta online donde se les pedía que contestasen a un conjunto de preguntas sociodemográficas así como varios cuestionarios validados en población general para la valoración de los siguientes síntomas: el OCI-R para los síntomas obsesivos, el HRS para los síntomas de acumulación, el DCQ para los síntomas del TDC, el ASI para síntomas del trastorno de pánico, el SPIN para los síntomas de fobia social, el

DASS (subescala de estrés) para la ansiedad generalizada y la WI para los síntomas de hipocondría. También se incluyó el SPS para los síntomas de excoriación y el MGH-HPS para la valoración de la tricotilomanía (para más información sobre el proceso de reclutamiento de la muestra consultar *Estudio 1).*

Análisis estadístico realizado:

Todos los análisis de la tesis fueron realizados en R. Los modelos de ecuaciones estructurales fueron desarrollados con el paquete estadístico OpenMx2.0. A continuación se nombran los modelos utilizados y el estudio asociado donde se explica detalladamente su procedimiento.

- Modelos Univariados heterogéneos: consultar *Estudio 1*.
  Diferencias de Género: Cualitativas (diferentes factores genéticos afectan a la expresión fenotípica en hombres y mujeres) y cuantitativas (la proporción de factores genéticos implicados en la patología difiere en ambos sexos).
- Análisis Multivariante de gemelos: Consultar *Estudio 2.*
- Análisis para inferir causalidad controlando por variables familiares de confusión (ICE-FALCON): Consultar *Estudio 2* junto con el material suplementario.
- Análisis Multivariante con gemelos en variables continuas y categóricas, controlando por edad y género: Consultar *Estudio 3*.

4. RESULTADOS

Estudio 1: ***"Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety Disorder Symptoms: A survey of the Australian Twin Registry***".

Hallazgos principales:

- La prevalencia de síntomas del espectro obsesivo y ansioso era superior en mujeres, menos en el TOC donde no se encontraron diferencias.
- La heredabilidad de todos los fenotipos estudiados fue moderada entre 47% (fobia social en mujeres) y 25% (síntomas de acumulación en hombres).
- Se encontraron diferencias genéticas cualitativas entre hombres y mujeres en los síntomas de pánico y TDC, mientras que los síntomas de fobia social y acumulación compulsiva mostraron diferencias genéticas cuantitativas, con una mayor carga genética en mujeres respecto a hombres.

- Es la primera vez que se demuestra que los síntomas de acumulación y TDC presentan diferencias genéticas entre hombres y mujeres y la ausencia de tales diferencias en hipocondría.

Estudio 2: "***Etiological Overlap between Obsessive-compulsive related and anxiety disorder Symptoms: A multivariate twin study***"

Hallazgos principales:

- En relación al análisis multivariante clásico con gemelos se observó que el TOC compartía el 100% de su varianza genética en el modelo que incluía los síntomas de ansiedad y los OCRDs. El porcentaje de varianza genética compartida entre TOC y OCRDs, sin síntomas de ansiedad, fue menor. Únicamente un 9% de la varianza genética total de TOC era compartida con síntomas de acumulación y TDC.
- Los modelos de inferencia de causalidad mostraron que la presencia de síntomas obsesivos aumentaba el riesgo a desarrollar síntomas de pánico, ansiedad generalizada y de acumulación compulsiva, y no al revés. Mientras que la presencia de síntomas de fobia social incrementaba la probabilidad de presentar síntomas obsesivos. No se encontró ninguna relación causal entre síntomas TOC y síntomas TDC.

Estudio 3: "***Distinct etiological influences on obsessive-compulsive symptoms dimensions: a multivariate twin study*"**

Hallazgos principales:

- Las dimensiones obsesivas de pensamientos prohibidos y contaminación/ limpieza fueron las que demostraron una mayor carga genética compartida con los trastornos de ansiedad (100% y 76,2% de la varianza genética total).
- La dimensión de orden/simetría demostró compartir más carga genética (42,8% sobre el total de la varianza genética) con los trastornos del espectro obsesivo y no ansioso, todo y que un alto porcentaje de la varianza genética fue debido a factores genéticos específicos (57,2%).
- La varianza genética de la dimensión de comprobación quedaba mejor definida cuando en el modelo estaban incluidos tanto los trastornos de ansiedad como los OCRDs.

- La dimensión de orden/simetría (39% de la varianza total) y comprobación (41% de la varianza total) fueron las únicas que mostraron un elevado porcentaje de factores ambientales compartidos con los trastornos de ansiedad.

5. DISCUSIÓN

5.1. *Implicaciones Generales para Futuros Estudios de Genética*

Los estudios de esta tesis muestran que existe una mayor influencia de los factores genéticos en mujeres con síntomas de fobia social y acumulación, así como diferentes factores genéticos entre hombres y mujeres en la manifestación de síntomas TDC y de pánico. En general, se sabe que las mujeres presentan una probabilidad dos veces mayor que los hombres de padecer trastornos de ansiedad. En este sentido, se podría inferir que influencias biológicas asociadas al género podrían estar afectando al tales diferencias en la prevalencia (Milad & Quirk, 2012).

Los estudios sobre genes específicos asociados a un incremento del riesgo a padecer TDC, acumulación compulsiva o cualquier otro OCRDs están en sus inicios. Hasta la fecha, sólo se ha realizado un estudio en genética molecular en pacientes con TDC, pero sin atender a las diferencias de género (Richter et al., 2004).

A pesar de que en nuestro estudio no encontramos diferencias genéticas de género en el TOC, al igual que otros estudios de gemelos (Mataix-Cols et al., 2013), sí que existen diferencias en la manifestación clínica del trastorno entre hombres y mujeres (Labad et al., 2005; Labad et al., 2008; Pooley et al., 2007). Por este motivo, estudios de asociación genética han examinado si ciertos genes o polimorfismos afectan de manera diferente a hombres y mujeres. En un meta-análisis reciente se observó que el TOC estaba asociado a múltiples genes con "efecto menor", lo que estaría en concordancia con los estudios de gemelos que muestran que una importante proporción de factores genéticos aditivos se van asociando, incrementando así la probabilidad a desarrollar el trastorno (Taylor, 2012). Específicamente, se ha visto que la presencia de una mayor actividad de la enzima MAO-A y una disminución de la actividad de la COMT y el trasportador del glutamato (SLC1A1) se han asociado con la presencia de TOC en hombres (Arnold et al., 2006; Karayiorgou et al., 1999; Katerberg et al., 2009; Pooley et al., 2007; Taylor, 2012; Wu et al., 2012). Por otro lado el gen del BDNF se ha asociado con la presencia de pensamientos prohibidos

(Katerberg et al., 2009) y conductas ansiosas en modelos animales (Chen et al., 2006). Estos últimos resultados concuerdan con los encontrados en el *Estudio 3* donde se observó un aumento de la genética compartida entre la misma dimensión obsesiva y otros trastornos ansiosos.

Por otro lado, los estrógenos interactúan con diferentes sistemas de neurotransmisores (serotonina, adrenalina y colinérgico) y por este motivo se ha estudiado la interacción de las hormonas gonadales en la expresión de síntomas TOC (Labad et al., 2005), de ansiedad como el pánico (Cohen et al., 1994a, 1994b) y de otros trastornos del espectro como la tricotilomanía (Keuthen et al., 1997). Del mismo modo, se sabe que en los trastornos que involucran el circuito del miedo, como los trastornos de ansiedad y recientemente el TOC (Via et al., 2014), podría haber una dificultad en la extinción del miedo condicionado, el cual estaría modulado por las hormonas gonadales (Edinger & Frye, 2007; Frye et al., 2008; Milad & Quirk, 2012). Estos hallazgos irían en la línea de las diferencias genéticas encontradas entre hombres y mujeres en el *Estudio 1*.

En relación a los hallazgos del *Estudio 2*, sería interesante que futuras investigaciones pudieran seguir muestras de gemelos a lo largo del tiempo con el fin de 1) corroborar de manera longitudinal los resultados obtenidos con la metodología ICE FALCON; 2) analizar si existen diferencias en el porcentaje de sujetos que con unos síntomas X acaban desarrollando síntomas propios de la patología Y en MZ y DZ; 3) comparar si existen diferencias en los factores ambientales del grupo que sí desarrolla la patología *vs* los que no la desarrollan; y 4) estudiar si existe una interacción gen-ambiente que pueda explicar el patrón de relaciones causales halladas en el *Estudio 2*.

5.2. Implicaciones para futuros estudios en Factores de Riesgo Ambientales

Al menos la mitad de la varianza de cada diagnóstico evaluado es debido a factores de riesgo ambientales no compartidos (incluyendo el error de medida). Abuso sexual en la infancia, negligencia, pérdida temprana de un miembro importante, procesos inflamatorios, eventos estresantes perinatales (como el bajo peso al nacer), etc. son los factores de riesgo ambientales que se han visto asociados a la presencia de trastornos de ansiedad y TOC en la edad adulta (Blanco et al., 2014; Cath et al., 2008; Lafleur et al., 2011; Vasconcelos et al., 2007; Zannas & Binder, 2014). Sin embargo, poco se sabe sobre los factores ambientales de riesgo específicos para cada una de las

dimensiones obsesivas. Sólo un estudio ha observado que los problemas perinatales parecen ser un factor de riesgo para los síntomas de orden/simetría (Grisham et al., 2011). En relación a los trastornos del espectro obsesivo, el TDC estaría asociado a ciertos factores de riesgo comunes con el TOC y los trastornos de ansiedad como: historia de abuso, negligencia o burlas en la infancia (Buhlmann et al., 2007, 2012; Didie et al., 2006; Neziroglu et al., 2006).

Del *Estudio 2* se desprende que la mayoría de los factores de riesgo ambientales son específicos para cada trastorno evaluado. Por este motivo sería conveniente estudiar dichos factores específicos y así desarrollar programas de prevención y detección precoz de trastornos genéticamente relacionados con el TOC.

5.3. Factores de interacción gen-ambiente

Los resultados de esta tesis son consistentes con la hipótesis sobre "pleitropía" genética, donde múltiples genes contribuyen a explicar una proporción importante de la expresión fenotípica de un grupo de trastornos (Nicolini et al., 2009). La interacción gen-ambiente se refiere a que los efectos de ser expuesto a factores ambientales específicos dependerán del genotipo de cada individuo. Al mismo tiempo, genotipos específicos aumentan o disminuyen la probabilidad de que una persona sea expuesta a cierto tipo de ambientes.

La interacción gen-ambiente puede dar lugar a modificaciones en la expresión de ciertos genes (epigenética). La diferencia principal entre los procesos genéticos y epigenéticos es, en estos últimos, su potencial efecto reversible mediante intervenciones conductuales o farmacológicas (Szyf, 2014). Desde el punto de vista epigenético, el ambiente intrauterino es donde se producen los primeros y más relevantes cambios en la expresión genética. Se ha demostrado la existencia de factores epigenéticos discordantes en gemelos genéticamente idénticos (Gordon et al., 2012). El ambiente intrauterino es por tanto un factor de riesgo ambiental no compartido, a pesar de que ambos gemelos sean gestados en el mismo momento y en el mismo vientre materno, para enfermedades y trastornos mentales en la edad adulta a tener en cuenta en futuros estudios con gemelos.

5.4 Implicaciones Nosológicas y Clínicas

Los resultados de esta tesis explican que el TOC y sus dimensiones de síntomas son etiológicamente un constructo más complejo que el explicado únicamente por los

síntomas del espectro obsesivo, y que su asociación con la ansiedad es crucial para entender su funcionamiento. Nuestros resultados apoyan la visión previa de otros autores que recomendaron mantener juntos bajo el mismo capítulo del DSM los trastornos de ansiedad, el TOC y algunos trastornos del espectro, como la hipocondría y el TDC (Bienvenu et al., 2012; Stein et al., 2010).

Desde el punto de vista clínico, diferencias de género (ej. oscilaciones del ciclo hormonal) deberían tenerse en cuenta en la práctica clínica con el fin de mejorar los programas de tratamiento/prevención. Además, la presencia de TOC debería ser para el clínico un indicador de que esa persona tiene más riesgo de desarrollar otros trastornos de ansiedad (pánico y ansiedad generalizada) así como síntomas de acumulación posterior, con una especial atención si las dimensiones presentadas son de pensamientos prohibidos y limpieza. Esta visión holística de la manifestación de los síntomas obsesivo/ansiosos puede ayudar al diagnóstico precoz de otros trastornos asociados, así como potencialmente ayudar a disminuir los factores de riesgo asociados con grupos de síntomas que frecuentemente co-ocurren. Por otro lado, la prevención dirigida a los padres de niños que presentan riesgo genético para desarrollar el trastorno ayudaría a disminuir la aparición de ciertos trastornos o a controlar el impacto de los mismos en la vida del paciente, mediante programas de psicoeducación sobre los síntomas y factores de riesgo ambiental: estilo educativo, comunicación parental, etc.

Limitaciones

Los síntomas de excoriación y tricotilomanía fueron incluidos en la encuesta inicial, sin embargo la manera de reclutarlos no fue óptima impidiendo recopilar un número suficiente de respuestas finales. Segundo, los resultados están basados en síntomas y no en diagnósticos clínicos. Sin embargo, todos los cuestionarios utilizados han sido previamente validados en población no clínica y además el uso de medidas auto-administradas se recomienda en los análisis de genética de conducta (Neale & Cardon, 1992). Tercero, los gemelos son un tipo de población general que no es del todo representativo. Cuarto, los análisis clásicos de gemelos se basan en diferentes supuestos. Uno de ellos, conocido como "ambiente equivalente", asume que los gemelos MZ y DZ viven compartiendo aproximadamente el mismo tipo de ambiente. Sin embargo, este supuesto ha sido criticado por diferentes autores. Finalmente, todos

los análisis realizados son transversales, lo que significa que se desconoce la estabilidad de los mismos a lo largo del tiempo.

Conclusiones

En conclusión, es necesario poder distinguir entre la utilidad que puede tener la clasificación diagnóstica del TOC para los profesionales clínicos, del impedimento que dicha clasificación puede generar en el estudio de los factores etiológicos subyacentes al trastorno. Para ello, se precisa de una visión más amplia, donde los sistemas de clasificación no actúen de barreras y obstaculicen el desarrollo de su conocimiento. Los estudios científicos que de manera repetida se centran en una definición del TOC guiada por los modelos nosológicos, a menudo cambiantes, fracasarán en el descubrimiento de su etiología. En su lugar, el estudio de grupos de trastornos relacionados como la ansiedad, el TDC o la hipocondría, entre otros, así como factores ambientales traumáticos y no traumáticos sería una aproximación de mayor utilidad a la hora de desgranar cuáles son los factores genéticos y ambientales específicos asociados a la manifestación del trastorno.

CHAPTER 7

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