The Structure of Genetic and Environmental Risk Factors for Dimensional Representations of DSM-5 Obsessive-Compulsive Spectrum Disorders

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IMPORTANCE The new DSM-5 “Obsessive-Compulsive and Related Disorders” chapter contains a series of conditions thought to be etiologically related to obsessive-compulsive disorder (OCD). However, the evidence to support this relatedness remains incomplete.

OBJECTIVE To estimate the degree to which genetic and environmental risk factors are shared and/or unique to dimensionally scored OCD, body dysmorphic disorder (BDD), hoarding disorder (HD), trichotillomania (hair-pulling disorder) (TTM), and excoriation (skin-picking) disorder (SPD).

DESIGN, SETTING, AND PARTICIPANTS Multivariate twin modeling methods involving 5409 female members of the TwinsUK adult population-based twin register.

MAIN OUTCOMES AND MEASURES Scores on the Obsessive-Compulsive Inventory-Revised, the Dysmorphic Concern Questionnaire, the Hoarding Rating Scale, the Massachusetts General Hospital Hairpulling Scale, and the Skin Picking Scale.

RESULTS A 2-latent factor common pathway model fitted the data best; the first latent factor loaded on all 5 phenotypes, particularly on OCD, BDD, and HD. A second factor loaded exclusively on TTM and SPD. Disorder-specific genetic (for OCD, BDD, and HD only) and particularly nonshared environmental risk factors were also evident. Shared environmental influences were negligible.

CONCLUSIONS AND RELEVANCE Obsessive-compulsive and related disorders may be influenced by 2 distinct liability factors rather than a single liability factor. One of these factors was common to all disorders, and another was exclusive to TTM and SPD. Disorder-specific genetic factors unique to OCD, BDD, and HD were also apparent, whereas TTM and SPD were largely influenced by the same latent genetic factor. Environmental influences were largely disorder specific. The results help explain the apparent similarities as well as some important differences between the disorders included in the new Obsessive-Compulsive and Related Disorders chapter.
The DSM-5 includes a new “Obsessive-Compulsive and Related Disorders” (OCRDs) chapter, comprising a series of mental disorders thought to be phenomenologically and etiologically related to obsessive-compulsive disorder (OCD). The disorders classified alongside OCD are body dysmorphic disorder (BDD), hoarding disorder (HD), trichotillomania (hair-pulling disorder) (TTM), and excoriation (skin-picking) disorder (SPD). Body dysmorphic disorder and TTM were previously classified in other sections of the DSM-IV, whereas HD and SPD are new to the nomenclature. There are similarities as well as differences across the OCRDs on a number of diagnostic validators, including symptomatology, patterns of comorbidity, familiality, brain circuitry, and treatment response. However, the removal of OCD from the anxiety disorders grouping and the inclusion of TTM and SPD in the new OCRDs chapter are somewhat controversial. Fundamentally, whether these conditions are etiologically related still remains to be conclusively demonstrated, as is the precise nature of such relatedness.

Perhaps the strongest evidence to support the relatedness of the OCRDs originates from controlled family studies, which have consistently reported higher rates of OCRDs in relatives of OCD probands compared with relatives of matched controls. However, family studies cannot address whether OCRDs run in families due to shared genetic risk factors, shared environmental risk factors, or both. Multivariate twin studies are better suited to examine the structure of genetic and environmental risk factors associated with the co-occurrence of various mental disorders. Such studies have, for instance, helped clarify the etiologic structure of personality disorders and other common psychiatric disorders. Using self-report questionnaires, one previous twin study suggested that the association between OCD and BDD symptoms is likely to be explained by genetic influences largely common to both disorders. However, no twin study has included all OCRDs in the same analysis; therefore, the extent to which OCRDs share genetic and environmental risk factors remains unknown.

The present twin study aims to clarify the structure of genetic and environmental risk factors for dimensional representations of DSM-5 OCRDs in a large community sample of adult female twins. On the basis of previous family and twin studies, we predicted that the liability to individual OCRDs would be largely influenced by genetic and nonshared environmental factors, while shared environmental effects would be negligible. Furthermore, consistent with the new DSM-5 classification, we expected the covariance between the OCRDs to be largely explained by a single latent phenotypic construct conferring risk to all disorders, as well as disorder-specific genetic and environmental influences.

### Methods

#### Participants

Participants were monozygotic (MZ) and dizygotic (DZ) twins from the TwinsUK adult twin register (www.twinsuk.ac.uk). The register is a volunteer, general population sample of approximately 10,000 white adult twins aged 16 to 90 years. The sample is comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics. Zygosity was determined using the Peas in a Pod Questionnaire and further established via DNA confirmation methods in uncertain cases. The study was approved by the St Thomas’ Hospital Research Ethics Committee, and all participants provided written informed consent.

Five dimensional self-report measures of OCRDs were sent to all active twins in the register in different waves of data collection. Response rates ranged between 49.1% (BDD) and 63.3% (TTM and SPD). The sample consisted of 6310 individual twins who completed at least one of the questionnaires (2752 complete and 806 incomplete pairs). Male twins (n = 666), DZ opposite-sex twins (n = 122), and twins for whom co-twin sex (n = 96) or zygosity (n = 23) was unknown were excluded since the small number of cases in these categories did not allow sufficient power to investigate sex differences. Twin analyses were carried out on a final sample of female twins (N = 5409), including 3042 MZ and 2367 DZ female twins.

#### Measures

The Obsessive-Compulsive Inventory–Revised, a widely used, 18-item measure of distress associated with various OCD symptoms, has strong reliability, validity, and clinical utility; correlates strongly with other measures of OCD; and discriminates well between OCD and other anxiety disorders. A cutoff score of 21 discriminates patients with OCD from nonpatients, with a sensitivity of 78.2% and a specificity of 65.0%. In the current study, the hoarding subscale was excluded from the total score, and Cronbach α was 0.87.

The Dysmorphic Concern Questionnaire is a 7-item self-report questionnaire assessing the extent of concern with one’s own physical appearance and body malfunction (eg, body odor). Its items measure a broad dimensional construct closely related, but not limited to, BDD. The scale has strong psychometric properties; correlates well with other measures of BDD symptoms, including the BDD version of the Yale-Brown Obsessive Compulsive Scale; and discriminates patients from controls. An empirically derived cutoff score of 11 is indicative of a likely BDD diagnosis, with a sensitivity of 89.1% and a specificity of 94.7%. Cronbach α was 0.85.

The Hoarding Rating Scale is a 5-item self-report questionnaire measuring clutter, difficulty discarding, excessive acquisition, distress, and impairment. The scale is psychometrically sound, with much empirical support for its reliability, validity, and clinical utility. Scores above 17 discriminate between hoarding and nonhoarding cases, with a sensitivity and a specificity of 95%. Cronbach α was 0.86.

The Massachusetts General Hospital Hairpulling Scale, a 7-item self-report instrument assessing the severity of hair pulling, measures the frequency, intensity, and control over urges to pull hair, as well as the frequency, distress, resistance, and control over hair-pulling behaviors. To our knowledge, no studies have identified cutoff scores, but the scale has good internal consistency, test-retest reliability, and strong convergent and divergent validity. Cronbach α was 0.93.

The Skin Picking Scale, a 6-item self-report instrument, assesses the extent and severity of skin-picking behavior, in-
including the frequency and intensity of urges, frequency of skin-picking behavior, and the associated interference, distress, and avoidance. The scale has excellent psychometric properties, supporting its reliability and validity. A cutoff value of 7 differentiates between self-injurious and non–self-injurious skin pickers, with a sensitivity of 96.4% and a specificity of 92.2%. In the current study, Cronbach α was 0.78.

Statistical Analysis
Univariate twin analyses seek to decompose phenotypic variance into 3 factors: A (additive genetic; ie, the proportion of phenotypic variation attributed to genetic factors), C (common or shared environment; ie, environmental effects shared by twins), and E (unique environment; ie, environmental effects unique to each twin, plus measurement error). In multivariate twin analyses, the covariance between multiple phenotypes is partitioned in much the same way.

Three models are commonly tested in multivariate twin analyses. The Cholesky decomposition estimates as many A, C, and E factors as phenotypes under study, making no assumptions regarding the genetic and environmental structure underlying their covariance. The independent pathway (IP) model estimates a set of common genetic and environmental factors hypothesized to directly influence all phenotypes. Finally, the common pathway (CP) model, nested within the IP model, assumes that genetic and environmental factors act via 1 or more latent factors to influence all phenotypes. Both the IP and CP models allow specific genetic and environmental influences to account for the remaining disorder-specific variance. Both models can be extended to have multiple genetic and environmental factors, albeit with additional constraints to identify the model. The Akaike information criterion value provides an indication of the goodness of fit of these models. To explain the pattern of covariance using as few parameters as possible, researchers commonly test reduced submodels against the best-fitting full model.

Since the data were substantially skewed, we used liability-threshold modeling. This approach is well suited to the study of continuously distributed traits. Consistent with previous studies by our group, scores on each scale were categorized using 3 thresholds, ranging from 0 (ie, no symptoms) to 3 (ie, clinically significant symptoms, with scores above empirically derived cutoffs for each measure) (eTable 1 in the Supplement).

Twin analyses were carried out using Mx (http://www.vcu.edu/mx/). Data were first fitted to a saturated Cholesky ACE model. Varimax- and oblimin-rotated principal component analyses of the total scores on the self-report measures of OCRDs were carried out in SPSS (version 20; SPSS, Inc) to examine their phenotypic structure. On the basis of these results, we tested an IP model containing the resulting genetic, shared environmental, and unique environmental factors common to all disorders, as well as disorder-specific factors. This model was then compared with a CP model, in which the common influences acted via latent phenotypic factors. Goodness of fit was established by likelihood ratio and the Akaike information criterion. Reduced submodels were then tested; the difference in the χ² value relative to the change in degrees of freedom provided an indication of the goodness of fit of the simplified models.

Results
Polychoric Correlations and Principal Component Analyses
Phenotypic correlations (with 95% CIs) are presented in Table 1. As expected, we found moderate phenotypic associations across all variables; the stronger associations were between OCD, BDD, and HD on one hand and TTM and SPD on the other. Cross-twin within-trait and cross-twin cross-trait correlations for MZ and DZ twins are also depicted in Table 1. The pattern of correlations (ie, strongest in MZ vs DZ pairs) suggests a

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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OCD</th>
<th>BDD</th>
<th>HD</th>
<th>TTM</th>
<th>SPD</th>
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<tr>
<td>Phenotypic correlations</td>
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<tr>
<td>OCD</td>
<td>1</td>
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<tr>
<td>BDD</td>
<td>0.36</td>
<td>1</td>
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<tr>
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<td>0.49</td>
<td>0.28</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTM</td>
<td>0.17</td>
<td>0.11</td>
<td>0.14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SPD</td>
<td>0.25</td>
<td>0.18</td>
<td>0.24</td>
<td>0.30</td>
<td>1</td>
</tr>
<tr>
<td>Twin correlations*</td>
<td></td>
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<tr>
<td>OCD</td>
<td>0.52 (MZ)</td>
<td>0.23</td>
<td>0.34</td>
<td>0.19</td>
<td>0.09</td>
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<tr>
<td></td>
<td>0.21 (DZ)</td>
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<tr>
<td>BDD</td>
<td>0.10</td>
<td>0.45 (MZ)</td>
<td>0.16</td>
<td>0.17</td>
<td>0.17</td>
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<td></td>
<td></td>
<td>0.19 (DZ)</td>
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<tr>
<td>HD</td>
<td>0.15</td>
<td>0.12</td>
<td>0.55 (MZ)</td>
<td>0.20</td>
<td>0.15</td>
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<td></td>
<td></td>
<td></td>
<td>0.29 (DZ)</td>
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<tr>
<td>TTM</td>
<td>0.10</td>
<td>0.13</td>
<td>0.10</td>
<td>0.20 (MZ)</td>
<td>0.24</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10 (DZ)</td>
<td></td>
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<tr>
<td>SPD</td>
<td>0.05</td>
<td>0.07</td>
<td>0.03</td>
<td>0.10</td>
<td>0.28 (MZ)</td>
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<td>0.13 (DZ)</td>
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</table>

Abbreviations: BDD, body dysmorphic disorder; DZ, dizygotic; HD, hoarding disorder; MZ, monozygotic; OCD, obsessive-compulsive disorder; SPD, skin-picking disorder; TTM, trichotillomania.

* Cross-twin within-trait (diagonal) and cross-twin cross-trait (off-diagonal) correlations.

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meaningful genetic contribution to the liability of each trait and to their co-occurrence. The moderate MZ correlations are indicative of unique environmental influences.

The principal component analyses retained 2 phenotypic factors with eigenvalues greater than 1, explaining 54.7% of the total variance (Table 2 in the Supplement). Factor 1 included OCD, BDD, and HD, while factor 2 included TTM and SPD.

**Model Fitting**

For model-fitting results, see Table 2. The 2-factor CP model (model 3), with a first latent factor loading on all variables and a second one constrained to load on TTM and SPD only, provided a better fit to the data than the 2-factor IP (model 2), as indicated by a more negative Akaike information criterion value. To explain the data using as few parameters as possible, we fitted nested submodels 4 through 6. A CP model with only 1 common latent factor (model 4) produced a significantly worse fit, indicating the significant contribution of the second phenotypic latent factor in explaining common variance. Dropping disorder-specific genetic factors (model 6) also resulted in a poorer fit, providing evidence of their contribution in the liability to OCRD traits. A better fit was obtained by dropping all shared environmental parameters (model 5). Finally, we reduced model 5 by setting the contributions of specific genetic influences for TTM and SPD to 0, without loss of fit.

According to the best-fitting model (model 7), the covariance between the 5 OCD-related phenotypes was best explained by a 2-latent factor structure. The first factor loaded highly on all variables, particularly on OCD (0.76), HD (0.63), and BDD (0.47), while a second latent factor loaded on TTM and SPD. Both latent factors were strongly influenced by genetic factors (0.63–0.74). Disorder-specific genetic factors moderately contributed to the risk for OCD, BDD, and HD symp-

toms but not for TTM and SPD, suggesting the genetic influences on these 2 phenotypes are mostly shared. Unique environmental risk factors (including measurement error) appeared to be mostly disorder specific, with estimates ranging between 0.31 (OCD) and 0.55 (TTM). Finally, shared environmental factors played a marginal role. Parameter estimates under the best-fitting model (model 7) are shown in Figure 1 and Table 3. Figure 2 depicts the proportion of genetic and unique environmental variance shared among the OCRDs vs disorder specific.

**Discussion**

The new DSM-5 OCRDs chapter includes a series of disorders thought to be etiologically related to OCD. However, the evidence to support this relatedness is incomplete and, perhaps unsurprisingly, the field has yet to universally agree with the amalgamation of some of these disorders. We used multivariate twin models to clarify the degree to which genetic and environmental risk factors are shared and/or unique to the 5 OCRDs. We draw the following main conclusions.

**OCRDs Are Moderately Heritable**

As predicted, the heritability of all OCRD symptoms was moderate, ranging from 31.6% (TTM) to 51.1% (HD); nonshared environment (plus measurement error) accounted for the remaining variance, while shared environmental factors appeared to be negligible. In the only previous TTM study, which included 34 twin pairs recruited from a patient organization (the Trichotillomania Learning Centre), heritability estimates ranged between 0.76 and 0.78.7 To our knowledge, ours is the first study to estimate the contribution of genetic and environmental risk factors to TTM symptoms in a large
community twin sample, resulting in substantially lower heritability estimates (32%). These discrepancies are likely attributable to the substantial methodologic differences between the 2 studies (ie, volunteers from a patient organization vs a population-based twin sample).

### Two, Rather Than One, Common Liability Factors

The pattern of co-occurrence between OCRDs was better explained by 2 common liability factors rather than a single liability factor. Both latent factors were substantially heritable, with approximately one-third of the variance explained by each.
attributable to nonshared environment (plus measurement error).

The first latent factor had substantial loadings on all OCRDs. Largely influenced by genes (63.3%; 95% CI, 59%-66%), this factor could be conceptualized as a nonspecific genetic vulnerability conferring risk to all OCRDs and possibly explaining the phenomenologic similarities, patterns of comorbidity, and familiality described in the OCRD literature. While all 5 OCRDs loaded on this common "OCRD latent factor," the strongest loadings were for OCD, BDD, and HD, the so-called cognitive OCRDs. By contrast, TTM and SPD, sometimes referred to as "body-focused repetitive behavioral disorders," because they lack a prominent cognitive component, had substantially lower loadings on this factor.

Disorder-specific genetic influences were also evident for OCD, BDD, and HD. The implication for molecular genetic studies is that, in addition to generalist "pleitropic" genes conferring risk to all OCRDs, it is likely that there will be a set of disorder-specific genes for OCD, BDD, and HD. While the search for OCD-related genes is well under way with the recent publication of the first genome-wide association study, gene-searching efforts in the remaining OCRDs lag considerably behind. Recruiting and combining sufficiently large samples of individuals with all OCRDs rather than conducting separate studies for each OCRD may potentially facilitate the search for common and disorder-specific genes for these disorders. In this regard, the new OCRDs chapter could potentially stimulate such endeavors.

The second latent factor, which was also strongly genetically influenced (73.7%; 95% CI, 30%-99%), loaded exclusively on TTM and SPD, suggesting a set of genetic influences exclusive to these 2 disorders. In clinical samples, there is a high degree of symptom overlap and comorbidity among TTM, SPD, and other body-focused repetitive behaviors (eg, nail biting, thumb sucking, and knuckle cracking). Some authors have suggested that TTM and SPD are strongly etiologically related. Our finding that all genetic variance of the second latent factor is shared between TTM and SPD would in fact suggest that these disorders might represent alternative phenotypic expressions of the same condition, with most differences being attributable to environmental risk factors unique to each disorder (see below). The implication for molecular genetic studies is that the same genes will likely confer risk to both TTM and SPD (and possibly other body-focused repetitive behaviors) and that these genes will be distinct from those conferring general risk to OCRDs. Gene-searching efforts in TTM and SPD are still in their infancy, but some promising susceptibility genes have been identified, such as SAPAP3.

The bifactorial etiologic architecture of OCRDs has not been previously reported, to our knowledge, and may help explain both the apparent similarities and differences between the "cognitive" and the "body-focused repetitive" OCRDs. Indeed, while there are some similarities between these disorders, there are also important differences in terms of symptomatology (eg, absence of obsessions and gratification or pleasure after the repetitive behavior in some patients with TTM and SPD), sex distribution (TTM and SPD more frequent in females), and treatment response (poor or incomplete response to selective serotonin reuptake inhibitors and preferential response to habit-reversal therapy in TTM and SPD).

Future twin studies should examine the overlap between OCRDs and other phenotypes, such as anxiety and mood disorders, since some of the "generalist" genes, conferring risk to all OCRDs, may also be shared with other emotional disorders. This work may shed further light on the somewhat controversial removal of OCD from the anxiety disorders grouping in the DSM-5.

Disorder-Specific Environmental Factors
Most unique environmental risk factors appear to be disorder specific. The implication for future research is that the identification of environmental risk factors that contribute to developing one particular OCRD may not necessarily confer risk to acquiring another. Research in this area is sparse and methodologically questionable, with some inconsistent evidence for perinatal complications, traumatic life events, and streptococcal infections as potential nonspecific environmental risk factors for various OCRDs. Disorder-specific environmental risk factors are yet to be identified, but some research suggests that appearance-related teasing may be important in BDD, while trauma-related loss may be highly relevant in HD. Further longitudinal, population-based research is clearly needed to identify specific environmental factors conferring risk to each of the OCRDs. This will be equally if not more im-
important than gene-searching efforts since environmental factors are potentially amenable to prevention and early intervention. Similarly, the identification of gene-environment correlations and gene × environment interactions will remain a major goal for the future.

Limitations

Twin analyses were limited to adult female white twins; future studies should include male participants and extend to younger cohorts. Symptoms of OCRDs were measured using self-report questionnaires primarily validated on DSM-IV diagnostic criteria, although their items map reasonably well onto the new DSM-5 criteria. Of all applied measures, the Dystrophic Concern Questionnaire shows a less perfect match with DSM-5 BDD criteria; it includes items on bodily function and thus measures a closely related, but somewhat broader, construct. Using self-report questionnaires, we were also unable to determine whether OCRDs were attributable to other mental or medical conditions. Future studies including psychiatric diagnostic interviews for DSM-5 OCRDs are strongly encouraged. Finally, findings need to be interpreted in view of the general limitations of the twin design, particularly the equal environment assumption.57

In conclusion, OCRDs have a complex etiologic architecture consisting of 2 latent liability factors largely under genetic control. One of these factors was common to all disorders, and another was exclusive to TTM and SPD. Disorder-specific genetic factors unique to OCD, BDD, and HD were also apparent, whereas environmental influences were largely disorder specific. The results help explain the apparent similarities as well as some important differences between the disorders included in the new OCRDs chapter. Further research is needed to identify common as well as disorder-specific genes and nonshared environmental risk factors that increase the susceptibility to these disabling conditions, as well as their likely interaction.

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Study concept and design: Monzani, Harris, Mataix-Cols.

Acquisition of data: Harris.

Analysis and interpretation of data: Monzani, Rijsdijk, Mataix-Cols.

Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Monzani, Rijsdijk. Obtained funding: Mataix-Cols.

Administrative, technical, or material support: Harris.

Study supervision: Rijsdijk, Mataix-Cols.

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