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The polygenic risk for obsessive-compulsive disorder is associated with the personality trait harm avoidance

Bey K, Weinhold L, Grützmann R, Heinzel S, Kaufmann C, Klawohn J, Riesel A, Lennertz L, Schmid M, Ramirez A, Kathmann N, Wagner M. The polygenic risk for obsessive-compulsive disorder is associated with the personality trait harm avoidance.

Objective: Obsessive-compulsive disorder (OCD) is a complex psychiatric disorder with a substantial genetic contribution. While the specific variants underlying OCD's heritability are still unknown, findings from genome-wide association studies (GWAS) corroborate the importance of common SNPs explaining the phenotypic variance in OCD. Investigating associations between the genetic liability for OCD, as reflected by a polygenic risk score (PRS), and potential endophenotypes of the disorder, such as the personality trait harm avoidance, may aid the understanding of functional pathways from genes to diagnostic phenotypes.
Methods: We derived PRS for OCD at several P-value thresholds based on the latest Psychiatric Genomics Consortium OCD GWAS (2688 cases, 7037 controls) in an independent sample of OCD patients ($n = 180$), their unaffected first-degree relatives ($n = 108$) and healthy controls ($n = 200$). Using linear regression, we tested whether these PRS are associated with the personality trait harm avoidance.
Results: Results showed that OCD PRS significantly predicted OCD status, with patients having the highest scores and relatives having intermediate scores. Furthermore, the genetic risk for OCD was associated with harm avoidance across the entire sample, and among OCD patients. As indicated by mediation analyses, harm avoidance mediated the association between the OCD PRS and OCD caseness. These results were observed at multiple P-value thresholds and persisted after the exclusion of patients with a current comorbid major depressive or anxiety disorder.
Conclusion: Our findings support the polygenic nature of OCD and further validate harm avoidance as a candidate endophenotype and diathesis of OCD.

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Significant outcomes

- Polygenic risk scores for OCD are associated with the personality trait harm avoidance.
- The findings support the polygenic nature of OCD and further validate harm avoidance as a candidate endophenotype and diathesis of OCD.

Limitation

- The sample sizes of the discovery and target samples are relatively small.
- The association between the polygenic risk score for OCD and harm avoidance did not remain significant when unaffected first-degree relatives and controls were analyzed separately.

Introduction

Obsessive-compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (intrusive unwanted thoughts or images) and/or compulsions (ritualized repetitive behaviors), which affects 1–3% of the population worldwide (1). OCD is familial, with first-degree relatives having an approximately five-fold increased risk of also being affected by the disease (2–4). Twin studies of OCD and OCD-related traits estimated a heritability of around 27–47% in adults, and 45–65% in children (5–7). Though recent evidence supports the involvement of rare and de novo variants (8–10), a major proportion of OCD's heritability appears to stem from common genetic variants (minor allele frequency (MAF) > 5%), with an estimated single nucleotide polymorphism (SNP)-based heritability of 28–42% (11, 12). In fact, around 65% of OCD's SNP-based heritability is accounted for by SNPs with a MAF $\geq 40\%$ (12). Thus, the majority of the genetic variability underlying the heritability estimates from family studies in OCD seems to be captured by GWAS. Yet, the specific variants underlying the disorder are largely unknown, as no genome-wide significant associations have been found so far in case–control GWAS, possibly because of the limited sample size of these analyses (combined 2688 cases, 7037 controls) (12–14). Investigating endophenotypes, which are heritable, quantitative traits associated with the disease and observed in unaffected relatives of patients, may aid the understanding of functional pathways from genes to diagnostic phenotypes (15). Since endophenotypes are supposed to share underlying genetic factors with the clinical disorder, they should be associated with specific genetic risk variants for the disease (16) and thus represent genetically driven vulnerability factors.

One of the best-validated candidate endophenotypes of OCD is the personality trait harm avoidance. Conceptualized as a temperament dimension in Cloninger's biosocial model of personality, harm avoidance is defined as an automatic tendency to respond intensely to aversive stimuli (17). People scoring high on this trait are characterized by excessive worrying, fear of uncertainty, shyness and fatigability. With heritability estimates ranging from 42% to 57%, harm avoidance has a strong genetic contribution (18–20) and is highly stable throughout life (21). In line with Cloninger's and Svrakic's proposal that individual configurations in personality structure influence the risk of psychopathology (17), high levels of harm avoidance have repeatedly been associated with various psychiatric disorders, including OCD (22–24). Within the framework of the Core Dimensions Model of OCD, harm avoidance is considered one of two central motivators underlying the disorder (25). Most notably, increased levels of harm avoidance have also been observed in unaffected first-degree relatives of OCD patients (26–28). This suggests that harm avoidance may partially mediate the genetic risk for OCD, but this hypothesis has not been tested using molecular genetic methods, so far.

To assess the association between the genetic underpinnings of OCD and a potential endophenotype, polygenic risk scores (PRS) can be employed, which represent the combined effect of a large number of SNPs (29). Based on the summary statistics of an independent GWAS, various PRS can be calculated by including SNPs with a P-value smaller than a predefined threshold of significance. As almost all of OCD's heritability is explained by variance in common SNPs, PRS based on common variants are a valid approach to capture the genetic liability for this disease.

Several studies have investigated the relationship between endophenotypes and PRS for psychiatric disorders other than OCD, supporting the assumption that common genetic variants associated with a specific disorder also predict cognitive performance, psychological trait measures as well as brain structure and function (30–34). In a large population-based sample, Taylor et al. found that genetic factors associated with psychiatric disorders, including OCD, are related to subclinical traits throughout the general population (35). Furthermore, a PRS for OCD predicted obsessive-compulsive symptoms in a population-based twin-family sample (36). However, the specific association between relevant endophenotypes of OCD and OCD-derived PRS has not been examined systematically.

Aims of the study

In the present study, we aimed to investigate whether the genetic risk for OCD, as defined by a PRS derived from GWAS data on OCD, is associated with the personality trait harm avoidance in a sample of OCD patients, their unaffected first-degree relatives and healthy control subjects. The examination of relatives of OCD patients has the advantage that these subjects have a higher genetic load than controls but are not afflicted by the confounds of the disease itself (32). Our sample thus allowed for the validation of harm avoidance as an endophenotype at both the phenotypic and the genetic level. To account for the phenotypic heterogeneity of OCD, age of onset and symptom

Table 1. Demographic and clinical characteristics of OCD patients, unaffected first-degree relatives and healthy control subjects

	OCD patients	Unaffected first-degree relatives	Healthy control subjects	Statistic	P
N	180	108	200		
Mean age, years (SD)	33.18 (10.66)	47.19 (13.91)	34.77 (12.67)	$F(2, 485) = 49.27$	<0.001
Gender, % male	41.7	33.3	36.5	$X^2(2) = 3.33$	0.19
Education (SD)[†]	4.97 (1.85)	4.76 (2.01)	5.22 (1.58)	$X^2(2) = 3.30$	0.19
Mean harm avoidance score (SD)	22.18 (6.99)	14.85 (6.31)	10.74 (5.32)	$F(2, 485) = 163.34$	< 0.001
Mean OCI-R score (SD)	27.26 (11.72)	6.83 (6.64)	4.63 (4.54)	$F(2, 485) = 398.46$	< 0.001
Mean obsessing subscale (SD)	6.92 (3.33)	1.10 (1.52)	0.64 (1.15)	$F(2, 485) = 414.75$	< 0.001
Mean ordering subscale (SD)	4.58 (3.43)	1.92 (2.23)	1.32 (1.57)	$F(2, 485) = 83.69$	< 0.001
Mean Y-BOCS score (SD)[‡]	22.22 (6.71)				
Mean age of onset (SD)[‡]	21.23 (10.73)				

OCD, obsessive-compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

[†]Education was assessed on a scale from 1 to 7.

[‡]Y-BOCS and age of onset were only applicable in patients.

dimensions were considered as potential modulation factors.

Methods and Materials

Sample and clinical assessment

The sample consisted of 180 patients with OCD, 200 healthy comparison subjects and 108 unaffected first-degree relatives of OCD patients, who participated in the EPOC (Endophenotypes of OCD) study (26, 37). Sample characteristics are presented in Table 1. OCD patients and relatives were recruited via the outpatient clinics at the Department of Psychology of Humboldt-Universität zu Berlin and at the Department of Psychiatry and Psychotherapy of the University Hospital Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements. All participants were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV (SCID-I) (38, 39). To establish cross-site reliability of clinical ratings, all instructions were standardized and raters completed assessments of four training videos. Patients and relatives were only included if they were (i) free of past or present psychotic, bipolar or substance-related disorders; (ii) did not take neuroleptic medication for the previous four weeks; and (iii) did not use benzodiazepines in the prior two weeks. Additionally, healthy controls were excluded if they (i) took any psychoactive medication in the previous three months; (ii) had a current Axis I disorder; (iii) had a lifetime diagnosis of OCD or tic disorder; or (iv) had a family history of OCD. All relatives were free of past or present OCD.

Consistent with the concept of endophenotypes being state-independent, OCD patients varied with respect to cognitive behavioral and medical treatment (see Table S1). Ninety OCD patients were medicated with selective serotonin reuptake inhibitors (SSRIs) and/or other antidepressants in the previous four weeks. Furthermore, the majority of patients had one or more comorbid Axis I disorders, with major depression being the most common comorbidity ($n = 41$ current episode, $n = 69$ remitted). A total of $n = 34$ had a current comorbid anxiety disorder, that is, panic disorder with/without agoraphobia, agoraphobia, social phobia, specific phobia, or generalized anxiety disorder, as assessed by the SCID-I interview.

Written informed consent was obtained and participants were compensated for their time. The study was in accordance with the revised Declaration of Helsinki and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Hospital Bonn.

Measures

Harm avoidance was assessed using the German version of the Temperament and Character Inventory (TCI) (40, 41). For each subject, a sum score was computed based on the 35 binary items of the harm avoidance scale. Cronbach's α of the global scale was $\alpha = 0.92$, indicating high internal consistency. The severity of OCD symptoms was evaluated with the German versions of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (42, 43) and the Obsessive-Compulsive Inventory-Revised (OCI-R), which comprises five subscales, that is, washing, obsessing, ordering, neutralizing and hoarding (44, 45). Here, we specifically focused on the obsessing and ordering subscales, since the former has been strongly and uniquely linked to harm avoidance, while the latter is proposed to be unrelated to harm avoidance (46, 47). Internal consistencies were $\alpha = 0.86$ for the Y-BOCS total score,

$\alpha = 0.93$ for the OCI-R sum score, $\alpha = 0.92$ for the obsessing subscale, and $\alpha = 0.89$ for the ordering subscale.

Genotyping

DNA was obtained from blood ($n = 458$) or saliva ($n = 30$) using standard procedures. DNA samples were genotyped with the Infinium Global Screening Array (Illumina) according to the manufacturer's instructions. Data were uploaded in the GenomeStudio 2.0 software and genotypes were exported in PLINK format. We applied standard quality control procedures, phasing and imputation (HRC, Michigan Imputation server), and adjustments for population structure as described in the Supplementary Material.

Polygenic risk scores

Summary statistics from the most recent Psychiatric Genomics Consortium (PGC) GWAS for OCD (48), which included 2688 cases and 7037 controls, were used as a discovery sample. Using PLINK (49), polygenic scores were calculated for each individual in our target sample from the number of risk alleles carried for each selected SNP (imputed dosage, respectively), weighted by the log (OR) provided by the PGC GWAS, and averaged across all SNPs. In accordance with practice guidelines for PRS analysis (50), SNPs were selected using different significance thresholds ($P_T = 0.01$, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1; see Table S2 for the number of SNPs included at each threshold). This resulted in eight continuous PRS that reflect the genetic risk for OCD at different P_T thresholds for each individual in our target sample based on the GWAS results of the discovery sample. PRS were standardized to have a mean of 0 and an SD of 1.

Statistical analyses

To assess group differences in OCD polygenic scores, ordinal logistic regression models with group as outcome variable (OCD > relatives > controls) were fitted to the data. Linear regression analyses were performed to test whether the OCD polygenic scores predicted levels of harm avoidance. Normal distribution of residual errors was verified for all linear regressions. We also tested whether the association between the PRS and OCD case/control status was mediated by harm avoidance using mediation analysis in PROCESS (51). PROCESS is a well-established computational tool that uses ordinary least squares regression (and logistic regression for dichotomous

dependent variables, respectively) to estimate the parameters of each of the equations in a prespecified model. Here, the PRS was defined as the independent variable (X), OCD casesness was the dependent variable (Y) and harm avoidance was the mediator (M; model 4 in PROCESS). To assess mediation, we verified the direct effect of the PRS on OCD caseness using logistic regression and employed bootstrapping with 10 000 samples to compute confidence intervals (CI) and inferential statistics of the indirect effect of the PRS on OCD caseness via harm avoidance. In all analyses, the first two population structure principal components were included as covariates to control for population stratification. The selection of covariates was based on visual inspection of cluster plots obtained from principal component analysis of the genetic data. Because the sample included related individuals, heteroscedasticity-consistent standard errors were used to account for effects of clustering within families (HC3; Davidson-MacKinnon) (52). The models assessing harm avoidance were first run across all subjects and were then stratified by group (OCD patient, unaffected relative, healthy control).

Analogue linear regression analyses were conducted to explore associations between OCD polygenic scores, symptom severity (Y-BOCS) and age of onset. As male gender has repeatedly been related to an earlier age of onset (53), regression analyses of OCD onset were stratified by gender.

To account for the observation that OCD symptom dimensions have been differentially linked to harm avoidance (46, 47), we performed median splits in OCD patients based on obsessing and ordering dimensions respectively. Linear regression analyses as described above were re-run including OCD patients with obsessing scores ≥ 7 ($n = 100$) and ordering scores ≥ 4 ($n = 100$), respectively, as assessed by OCI-R. Notably, the resulting subsamples of OCD patients did not exhibit reductions in mean values or variability of harm avoidance scores ($M = 23.30$, SD = 6.58 for patients scoring high on obsessing, and $M = 23.73$, SD = 6.87 for patients scoring high on ordering) as compared to the full OCD sample ($M = 22.18$, SD = 6.99).

In the results section, we report the change in R^2 between a model only including the covariates and a model including covariates plus the PRS. Group differences in harm avoidance were assessed using analysis of variance (ANOVA) with F-tests and post hoc Tukey's tests. Partial eta squared (η_p^2) was used to calculate effect sizes in ANOVA. A P-value of < 0.05 was considered significant. Descriptive statistics and distributions of PRS and harm avoidance scores as well as zero-order

correlations can be found in the Supplement (Table S3 and S4; Figures S1–S4).

Results

Harm avoidance significantly differed between groups ($F(2, 485) = 163.34$, $P < 0.001$, $\eta_p^2 = 0.40$), with OCD patients showing the highest ($P < 0.001$ compared to controls) and relatives exhibiting intermediate scores ($P < 0.001$ compared to controls).

OCD PRS derived from PGC OCD data were significantly associated with OCD status (max $\Delta R^2 = 0.031$, $P < 0.001$ at $P_T = 0.3$), with patients having the highest scores and relatives having intermediate scores (Table 2; Table S5 for more details; Fig. 1).

OCD PRS were associated with higher levels of harm avoidance across all subjects (max $\Delta R^2 = 0.020$, $P = 0.0017$ at $P_T = 0.3$; Table 3; Table S6 for more details). This effect was especially pronounced in OCD patients (max $\beta = 0.15$, $P = 0.021$ at $P_T = 0.1$; Table S7), while no significant associations were observed in unaffected relatives and controls. These results were observed at multiple P_T-value thresholds.

As indicated by mediation analyses, there was a significant indirect effect of the PRS on OCD caseness via harm avoidance at all P_T (Table 4). The association between the PRS and OCD caseness did not remain significant when harm avoidance was included in the model (Table 4; Figure S4), supporting the assumption of a full mediation.

Analyses in OCD patients scoring high on the obsessing dimension yielded larger effects for the associations between PRS and harm avoidance than in the full OCD sample (max $\beta = 0.19$, $P = 0.006$ at $P_T = 0.3$; Table S8). Analyses in OCD patients scoring high on the ordering dimension, on the contrary, yielded less significant results (max $\beta = 0.17$, $P = 0.037$ at $P_T = 0.1$; Table S9).
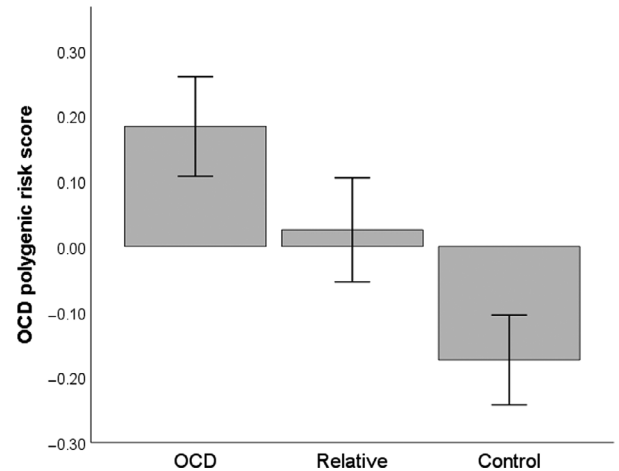

Fig. 1. Association between OCD polygenic risk scores (z-scores) and group (OCD patients, unaffected first-degree relatives, control subjects) at $P_T = 0.3$. Error bars indicate standard errors.

Table 3. Association between OCD polygenic risk scores at different P_T thresholds and harm avoidance across the entire sample. The change in R^2 between a model only including the covariates and a model including covariates plus the polygenic score is reported

P_T	ΔR^2	Model P	OCD polygenic risk score P
0.01	0.009	0.15	0.038
0.05	0.014	0.057	0.011
0.1	0.019	0.019	0.0028
0.2	0.018	0.022	0.0032
0.3	0.020	0.013	0.0017
0.4	0.017	0.019	0.0030
0.5	0.013	0.049	0.0093
1	0.010	0.094	0.021

Examining relatives and controls who reported a subclinical obsessing score > 0 ($n = 53$ and $n = 66$, respectively) yielded suggestive associations between PRS and harm avoidance, as we report in the Supplement (Table S10). No significant associations were found in relatives and controls scoring > 0 on the ordering dimension ($n = 70$ and $n = 107$ respectively). Notably, there were no significant associations between the OCD PRS and OCD symptom dimension scores as assessed by OCI-R subscales among OCD patients (Table S11).

Since gender differences have been reported for some aspects of OCD (45), we explored the association between OCD PRS and age of onset in gender-stratified samples. OCD PRS at higher P_T thresholds ($P_T \geq 0.4$) were significantly associated with an earlier age of OCD onset in male patients (max $\beta = -0.20$, $P = 0.036$ at $P_T = 0.5$; Table S12), whereas this comparison was non-significant in female patients.

Table 2. Association between OCD polygenic risk scores at different P_T thresholds and group (OCD patients, unaffected first-degree relatives, control subjects). The change in Nagelkerke pseudo-R^2 between a model only including the covariates and a model including covariates plus the polygenic score is reported, which represents the additional proportion of variance explained by the polygenic risk score

P_T	ΔR^2	Model P	OCD polygenic risk score P
0.01	0.011	0.17	0.032
0.05	0.025	0.010	0.001
0.1	0.029	0.004	< 0.001
0.2	0.030	0.004	< 0.001
0.3	0.031	0.003	< 0.001
0.4	0.028	0.005	< 0.001
0.5	0.022	0.017	0.002
1	0.019	0.032	0.003

Table 4. Mediation analysis with OCD polygenic risk score (PRS) as independent variable (X), OCD caseness as dependent variable (Y) and harm avoidance as mediator (M) at different P_T thresholds of the PRS. Effect sizes for caseness prediction are expressed in a log-odds metric. Results for indirect effects are based on 10 000 bootstrapping samples. Confidence intervals excluding 0 indicate significant effects

Model P_T	Direct effect of X on Y before mediation		Direct effect of X on Y after mediation		Direct effect of X on M before mediation		Indirect effect of X on Y mediated via M		Direct effect of M on Y adjusted for X	
	Effect size (SE)	P	Effect size (SE)	P	Effect size (SE)	P	Effect size (SE)	95% CI	Effect size (SE)	P
0.01	0.24 (0.11)	0.027	0.07 (0.15)	0.62	0.15 (0.05)	0.005	0.33 (0.12)	[0.10, 0.59]	2.17 (0.22)	<0.001
0.05	0.35 (0.11)	0.001	0.23 (0.15)	0.13	0.17 (0.06)	0.002	0.37 (0.13)	[0.14, 0.64]	2.16 (0.21)	<0.001
0.1	0.38 (0.11)	0.001	0.20 (0.15)	0.18	0.20 (0.05)	<0.001	0.43 (0.13)	[0.20, 0.69]	2.15 (0.21)	<0.001
0.2	0.37 (0.11)	0.001	0.21 (0.15)	0.16	0.19 (0.05)	<0.001	0.40 (0.12)	[0.18, 0.66]	2.15 (0.21)	<0.001
0.3	0.37 (0.11)	0.001	0.21 (0.15)	0.15	0.19 (0.05)	<0.001	0.41 (0.12)	[0.18, 0.66]	2.15 (0.21)	<0.001
0.4	0.35 (0.11)	0.001	0.19 (0.15)	0.19	0.18 (0.05)	<0.001	0.38 (0.12)	[0.17, 0.64]	2.15 (0.21)	<0.001
0.5	0.31 (0.11)	0.004	0.18 (0.15)	0.21	0.16 (0.05)	0.003	0.34 (0.12)	[0.11, 0.58]	2.16 (0.21)	<0.001
1	0.29 (0.11)	0.007	0.17 (0.15)	0.24	0.14 (0.05)	0.006	0.31 (0.12)	[0.09, 0.56]	2.16 (0.21)	<0.001

To account for the impact of group differences in age, all main analyses were re-run with age as a covariate. Effect sizes remained similar when age was included in the models. Results also persisted after the exclusion of patients with a current comorbid major depressive disorder or any current comorbid anxiety disorder (see Supplement). We did not observe any significant associations between OCD PRS and Y-BOCS severity scores among OCD patients.

Discussion

The present study investigated whether PRS for OCD are associated with the personality trait harm avoidance, which is a promising candidate endophenotype for OCD, in a sample of OCD patients, their unaffected first-degree relatives and healthy controls. Supporting the validity of the current PGC OCD PRS for out-of-sample predictions, OCD patients had significantly higher scores than controls, while unaffected relatives showed intermediate scores. Furthermore, we observed a significant association between OCD PRS and harm avoidance throughout the entire sample and among OCD patients. Mediation analyses indicated that the association between the PRS and OCD caseness was fully mediated by harm avoidance. These results were observed at multiple P-value thresholds.

Our findings support the notion that genetic variants modulating the susceptibility to OCD are also contributing to harm avoidance, a personality trait found to be increased in OCD patients. In line with these results, shared heritability analyses (54) have revealed a strong and significant genetic correlation between OCD and neuroticism, a construct closely linked to harm avoidance (40, 55). Importantly, our findings were obtained using genetic variants which did not reach genome-wide

significance in previous GWAS of OCD, supporting the polygenic nature of both OCD and harm avoidance. Previous GWAS specifically analyzing harm avoidance did not identify any genome-wide significant signals (56–58) so that similar to OCD, a large number of variants appears to contribute to the genetic component of this trait via small effect sizes. This notion is further supported by our observation that effect sizes were largest for the PRS with a moderate P-value threshold of 0.3, which appears to achieve a good balance between capturing a wide range of SNPs with small genetic contributions and containing noise that inevitably increases with more liberal P-value thresholds.

Strikingly, the correlation between the OCD PRS and OCD caseness did not remain significant when harm avoidance was entered into the model as a mediator, suggesting that a substantial amount of the shared variance between the genetic liability for OCD and the diagnostic phenotype is accounted for by harm avoidance. We acknowledge that some researchers take the position that mediation analysis should not be conducted with cross-sectional data, and we concede that based on our approach, we cannot infer that associations were present before manifestation of the disorder. However, PRS are unchanged from birth throughout the subjects' lifetime and can hence be interpreted as antecedent predictors of personality traits and psychopathology. Harm avoidance is also highly stable across lifetime (21) and even remains increased in remitted OCD patients compared to healthy controls (59), supporting its trait nature. The notion that high levels of harm avoidance may be driven by genetic factors is further supported by findings of increased levels of harm avoidance in unaffected first-degree relatives of OCD patients (26–28). In sum, a specific genetic disposition may result in an increased tendency to respond intensely to aversive stimuli and in

interaction with negative life events or early childhood trauma, this vulnerability may contribute to the development of OCD (26).

The observation that harm avoidance mediates the association between OCD PRS and OCD diagnosis highlights the significance of anxiety proneness as a key vulnerability factor for the disease and supports the traditional classification of OCD as an anxiety-related disorder. The Research Domaine Criteria (RDoC) perspective posits that biologically informed investigations of endophenotypes will contribute to a more precise classification of syndromes, the identification of functional pathways and improved treatment options (60). In this regard, our study places harm avoidance on the functional pathway between genetic liability and obsessive-compulsive disorder.

Considering potential physiological pathways, both OCD and harm avoidance are associated with overlapping aberrations in the functional connectivity of large-scale brain networks (61–64). Furthermore, patients with OCD robustly exhibit an increased error-related negativity (ERN), which is a neural indicator of error monitoring established by the anterior cingulate cortex (ACC). An increased ERN has repeatedly been observed in unaffected relatives of OCD patients (65) and has also been found to be linked to harm avoidance in a subgroup of the present sample (66). Future investigations should examine whether these overlapping brain correlates of harm avoidance and OCD are driven by the same genetic liability.

We addressed the issue of phenotypic heterogeneity in OCD by re-running analyses in OCD patients that scored high on two specific symptom dimensions, that is, obsessing and ordering. Consistent with the notion that obsessing is strongly linked to harm avoidance (46, 47), we found associations between OCD PRS and harm avoidance to be more pronounced in patients with higher obsessing symptoms than in the full sample. Conversely, associations were less pronounced and only marginally significant in patients with higher ordering symptoms, which is in line with the observation that this symptom dimension is less strongly linked to harm avoidance (46, 47). These findings suggest that harm avoidance may be a particularly promising endophenotype for the obsessing subtype of OCD. Preliminary evidence from relatives and controls exhibiting subclinical obsessing symptoms also supports this notion. While associations between PRS and harm avoidance did not reach significance in the full relatives and controls samples, explorative analyses in healthy subjects scoring > 0 on the obsessing subscale of the OCI-R revealed positive correlations between PRS and

harm avoidance. However, these findings should be interpreted with caution, given the reductions in sample size.

Despite previous reports of distinct genetic contributions (67, 68), we did not observe any significant associations between the OCD PRS and symptom dimensions as assessed by OCI-R subscales. This suggests that the relationship between general OCD risk alleles and specific symptom dimensions is not quantitative but may rather be characterized by qualitative differences, that is, specific sets of SNPs or VNTR being linked to specific symptom dimensions (e.g., 69, 70). A general PRS for OCD lumps all of these hypothetical dimension-specific SNPs together, so that a lack of an association is not surprising. A recent GWAS of obsessive-compulsive symptom dimensions also supports the notion that divergent genes and pathways may be involved in the expression of different symptom dimensions, although no genome-wide significant SNPs have been found, so far (71).

Further examining the heterogeneity in OCD, we analyzed associations between OCD PRS and age of onset. Early age of OCD onset has been related to male gender, tic disorders, other comorbidities and higher familiarity (53, 72), suggesting distinct etiological pathways. Whereas the odds ratio of familial recurrence in adult-onset OCD is approximately 5, it ranges from 12 to 30 for childhood-onset OCD (2–4). Here, we observed that in male patients, a higher OCD PRS was significantly associated with an earlier age of onset, supporting the assumption of an increased genetic contribution in early-onset OCD among male patients. However, effect sizes were small and given the reduction of test power in the stratified sample, we cannot draw definitive conclusion from these observations.

Notably, OCD symptom severity as assessed by Y-BOCS was not significantly associated with a higher genetic risk for OCD. Considering the state character of symptom severity and the fact that OCD patients were assessed at different stages of the disorder and treatment, respectively, this finding appears plausible. Future studies examining associations between symptom severity and OCD PRS may record peak symptom severity or conduct clinical interviews before or after a standardized treatment. Recently, Alemany-Navarro et al. found that an OCD PRS was associated with basal and post-Y-BOCS scores in a sample of 103 patients, but did not predict treatment response to pharmacotherapy (73). The overall Y-BOCS in our study was in-between the pre- and post-therapy Y-BOCS reported by Alemany-Navaro et al. and showed similar variance. However, Alemany-

Navaro et al. calculated their PRS using an own independent sample of 302 cases and 484 controls rather than using the larger PGC database. Pooling data from well-phenotyped samples and using ever more precise PRS derived from large GWAS will reveal whether symptom severity and treatment response are influenced by the same genes that are related to disease liability.

While several studies have investigated the relationship between potential endophenotypes and PRS for schizophrenia, studies on OCD are scarce. To our knowledge, the present study is the first one to specifically examine the predictive power of OCD PRS for a candidate endophenotype. Our findings show that results from GWAS are valid and transferable to an independent sample despite the absence of genome-wide significant hits. A major strength of the present study is the inclusion of unaffected first-degree relatives, who have an increased polygenic risk load but are not afflicted by the confounds of the disease itself. Another strength is the homogeneity of methods and endophenotype assessment. All samples were genotyped at the same laboratory using the same platform. Processing of the genetic data, quality control, and imputation were completed in a uniform way.

The study is not without limitations. First, although the PGC sample that we used to derive the PRS is the largest sample currently available, it is still comparatively small and its power is hence limited. Notwithstanding, the group differences observed between OCD patients, unaffected relatives and controls support the validity of the PGC GWAS and of the PRS based on these data. Second, the discovery sample is also relatively small, which may have contributed to inflations of explained variance (50). Still, our sample comes with the advantage of thorough and homogeneous phenotyping, which becomes more and more difficult at larger sample sizes. Finding balance between increasing sample size and maintaining good phenotype quality is one of the key endeavors for current genetic research. Third, the association between OCD PRS and harm avoidance is not completely independent of covarying group differences in harm avoidance and polygenic scores. As these group differences are presumably inherent, we considered OCD status a moderator rather than a covariate (74) and ran stratified analyses to assess effects in each of the three groups. While the association persisted in the group of OCD patients, it did not reach significance in relatives and controls, respectively, likely due to reductions in variance and test power. Notably, OCD patients also exhibited larger mean values, which may suggest that the genetic liability has a higher penetrance for higher levels of harm avoidance. Moreover, we found evidence that the association between PRS and harm avoidance was linked to obsessing symptoms. This may have also contributed to the lack of significant effects in relatives and controls, as these subjects scored comparatively low on the obsessing dimension in terms of subclinical symptoms. Fourth, the association between a genetic disposition and harm avoidance is likely not specific to OCD. Since OCD has a large genetic overlap with other psychiatric disorders (54), and harm avoidance has also been linked to anxiety and depression (46, 75), our findings may capture a transdiagnostic vulnerability for psychiatric disorders. Still, associations between OCD PRS and harm avoidance remained significant when patients with comorbid depression or anxiety disorders were removed, demonstrating that the effect was not driven by these comorbidities. Future studies may include clinical comparison groups to further examine transdiagnostic effects. Fifth, any PRS only captures additive effects of potential risk alleles and does not account for epistasis effects. Furthermore, PRS do not account for the impact of rare and de novo variants, which have also been implicated in OCD (8–10). Finally, our cross-sectional study design precludes definite inferences about causality.

In conclusion, our results support the validity of harm avoidance as an endophenotype of OCD and point to common genetic underpinnings. Harm avoidance appears to mediate the familial risk for OCD, representing a central vulnerability factor in the etiology of the disease. Moreover, we found that in male OCD patients, the OCD PRS was significantly associated with an earlier age of onset, providing further evidence for an increased genetic contribution in male early-onset OCD.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Peer Review

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Data Availability Statement

Data from the PGC OCD sample can be retrieved from: https://www.med.unc.edu/pgc/download-results/ocd/. Data from the EPOC sample will be made available upon request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distributions of PRS at eight different P_T thresholds across the entire sample.

Figure S2. Distributions of OCD polygenic risk scores at $P_T = 0.3$ in OCD patients, unaffected first-degree relatives and controls.

Figure S3. Distributions of harm avoidance sum scores in OCD patients, unaffected first-degree relatives and healthy controls.

Figure S4. The association between the polygenic risk for OCD and OCD caseness is mediated by the personality trait harm avoidance.

Table S1. Treatment status of OCD patients.

Table S2. Number of SNPs included in each polygenic risk score at the different P_T thresholds.

Table S3. Means and SDs of z-standardized PRS in OCD patients, unaffected relatives and controls.

Table S4. Zero-order correlations between harm avoidance and PRS across the entire samples and stratified by group.

Table S5. Ordinal regression models displaying the association between PRS at different p_T thresholds and OCD status (OCD = 1, relative = 2, control = 3; N = 488; extension of Table 2).

Table S6. Regression models displaying the association between harm avoidance and PRS at different p_T thresholds across the entire sample. ($N = 488$; extension of Table 3).

Table S7. Association between OCD polygenic risk scores at different P_T thresholds and harm avoidance in OCD patients.

Table S8. Association between OCD polygenic risk scores at different P_T thresholds and harm avoidance in OCD patients scoring high on the obsessing dimension.

Table S9. Association between OCD polygenic risk scores at different P_T thresholds and harm avoidance in OCD patients scoring high on the ordering dimension.

Table S10. Zero-order correlations between harm avoidance and PRS across the combined and stratified relatives and controls samples, only including subjects who reported an obsessing score > 0 on the OCI-R.

Table S11. Associations between OCD polygenic risk scores and OCI-R symptom dimensions among OCD patients.

Table S12. Association between OCD polygenic risk scores at different P_T thresholds and age of onset in male OCD patients.

Table S13. Association between OCD polygenic risk scores and group (OCD patients, unaffected first-degree relatives, control subjects) when age was included as a covariate.

Table S14. Association between OCD polygenic risk scores and harm avoidance across the entire sample when age was included as a covariate.

Table S15. Association between OCD polygenic risk scores and harm avoidance in OCD patients when age was included as a covariate.

Table S16. Association between OCD polygenic risk scores and non-depressive harm avoidance in OCD patients.

Table S17. Association between OCD polygenic risk scores and harm avoidance in OCD patients after the exclusion of patients with any current comorbid anxiety disorder.

Table S18. Association between OCD polygenic risk scores at different P_T thresholds and trait anxiety in OCD patients.