Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2020: 142: 326–336
All rights reserved
DOI: 10.1111/acps.13226

ACTA PSYCHIATRICA SCANDINAVICA

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.

K. Bey[1,2], L. Weinhold[3], R. Grützmann[4], S. Heinzel[4,5], C. Kaufmann[4], J. Klawohn[4], A. Riesel[4,6], L. Lennertz[1], M. Schmid[3], A. Ramirez[1,7,8], N. Kathmann[4], M. Wagner[1,2,9]

[1]Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, [2]German Center for Neurodegenerative Diseases (DZNE), Bonn, [3]Department of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, [4]Department of Psychology, Humboldt-Universität zu Berlin, Berlin, [5]Clinical Psychology and Psychotherapy, Freie Universität Berlin, Berlin, [6]Department of Psychology, University of Hamburg, Hamburg, [7]Institute of Human Genetics, University Hospital Bonn, Bonn, [8]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, and [9]Department for Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany

Key words: obsessive-compulsive disorder; OCD; polygenic risk score; PRS; harm avoidance

Katharina Bey, Department of Psychiatry and Psychotherapy, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany. Email: katharina.bey@ukbonn.de

Accepted for publication August 9, 2020

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 fivefold 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).

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

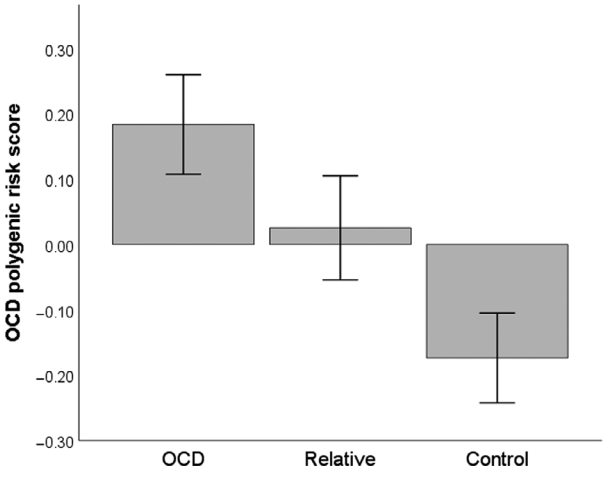

Fig. 1. Association between OCD polygenic risk scores (*z*-scores) and group (OCD patients, unaffected first-degree relatives, control subjects) at $P_T = 0.3$. Error bars indicate standard errors.

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 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	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	
P_T	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.

Acknowledgements

The present study was funded by the Deutsche Forschungsgemeinschaft (DFG; KA815/6-1, WA731/10-1 and WA731/15-1). We sincerely thank all research assistants and subjects who participated in the study. Open access funding enabled and organized by Projekt DEAL.

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

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13226.

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.

References

1. Weissman MM, Bland RC, Canino GJ et al. The cross national epidemiology of obsessive-compulsive disorder. J Clin Psychiatry 1994;**55**(3 Suppl.):5–10.
2. Grabe HJ, Ruhrmann S, Ettelt S et al. Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. Am J Psychiatry 2006;**163**:1986–1992.
3. Nestadt G, Samuels J, Riddle M et al. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 2000;**57**:358–363.
4. Pauls DL, Alsobrook JP II, Goodman W et al. A family study of obsessive-compulsive disorder. Am J Psychiatry 1995;**152**:76–84.
5. Mataix-Cols D, Boman M, Monzani B et al. Population-based, multigenerational family clustering study of obsessive-compulsive disorder. JAMA Psychiatry 2013;**70**:709–717.
6. Nicolini H, Arnold P, Nestadt G et al. Overview of genetics and obsessive–compulsive disorder. Psychiatry Res 2009;**170**:7–14.
7. Van Grootheest DS, Bartels M, Van Beijsterveldt CE et al. Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. J Am Acad Child Adolesc Psychiatry 2008;**47**:1182–1188.
8. Cappi C, Brentani H, Lima L et al. Whole-exome sequencing in obsessive-compulsive disorder identifies rare mutations in immunological and neurodevelopmental pathways. Transl Psychiatry 2016;**6**:e764.
9. Cappi C, Oliphant ME, Péter Z et al. De novo damaging DNA coding mutations are associated with obsessive-compulsive disorder and overlap with tourette's disorder and autism. Biol Psychiatry 2019;**87**:1035–1044.
10. Halvorsen M, Samuels JF, Wang Y et al. Rare and de novo variants in obsessive compulsive disorder. Eur Neuropsychopharmacol 2019;**29**:S860–S861.
11. Guo W, Samuels JF, Wang Y et al. Polygenic risk score and heritability estimates reveals a genetic relationship between ASD and OCD. Eur Neuropsychopharmacol 2017;**27**:657–666.
12. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. Mol Psychiatry 2018;**23**:1181.
13. Mattheisen M, Samuels JF, Wang Y et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry 2015;**20**:337–344.
14. Stewart SE, Yu D, Scharf JM et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry 2013;**18**:788–798.
15. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;**160**:636–645.
16. Iacono WG, Malone SM, Vrieze SI. Endophenotype best practices. Int J Psychophysiol 2017;**111**:115–144.
17. Cloninger CR, Svrakic DM. Integrative psychobiological approach to psychiatric assessment and treatment. Psychiatry 1997;**60**:120–141.
18. Garcia D, Lundström S, Brändström S et al. Temperament and Character in the Child and Adolescent Twin Study in Sweden (CATSS): comparison to the general population, and genetic structure analysis. PLoS One 2013;**8**:e70475.
19. Gillespie NA, Cloninger CR, Heath AC et al. The genetic and environmental relationship between Cloninger's dimensions of temperament and character. Pers Individ Dif 2003;**35**:1931–1946.
20. Keller MC, Coventry WL, Heath AC et al. Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. Behav Genet 2005;**35**:707–721.
21. Josefsson K, Jokela M, Cloninger CR et al. Maturity and change in personality: developmental trends of temperament and character in adulthood. Dev Psychopathol 2013;**25**:713–727.
22. Fossey MD, Roy-Byrne PP, Cowley DS et al. Personality assessment using the Tridimensional Personality Questionnaire (TPQ) in patients with panic disorder and generalized anxiety disorder. Biol Psychiatry 1989;**25**:10–13.
23. Kim SJ, Kang JI, Kim CH. Temperament and character in subjects with obsessive-compulsive disorder. Compr Psychiatry 2009;**50**:567–572.
24. Richter MA, Summerfeldt LJ, Joffe RT et al. The Tridimensional Personality Questionnaire in obsessive-compulsive disorder. Psychiatry Res 1996;**65**:185–188.
25. Summerfeldt LJ, Kloosterman PH, Antony MM, Swinson RP. Examining an obsessive-compulsive core dimensions model: Structural validity of harm avoidance and incompleteness. J Obsessive Compuls Relat Disord 2014;**3**:83–94.
26. Bey K, Lennertz L, Riesel A et al. Harm avoidance and childhood adversities in patients with obsessive-compulsive disorder and their unaffected first-degree relatives. Acta Psychiatr Scand 2017;**135**:328–338.
27. Calvo R, Lázaro L, Castro-Fornieles J et al. Obsessive-compulsive personality disorder traits and personality dimensions in parents of children with obsessive-compulsive disorder. Eur Psychiatry 2009;**24**:201–206.
28. Ettelt S, Grabe HJ, Ruhrmann S et al. Harm avoidance in subjects with obsessive-compulsive disorder and their families. J Affect Disord 2008;**107**:265–269.
29. International Schizophrenia Consortium, Purcell SM, Wray NR et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009;**460**:748–752.
30. Burton CL, Wright L, Shan J et al. SWAN scale for ADHD trait-based genetic research: a validity and polygenic risk study. J Child Psychol Psychiatry 2019;**60**:988–997.
31. Liu M, Malone SM, Vaidyanathan U et al. Psychophysiological endophenotypes to characterize mechanisms of known schizophrenia genetic loci. Psychol Med 2017;**47**:1116–1125.
32. Ranlund S, Calafato S, Thygesen JH et al. A polygenic risk score analysis of psychosis endophenotypes across brain functional, structural, and cognitive domains. Am J Medical Genet B Neuropsychiatr Genet 2018;**177**:21–34.
33. Wang SH, Hsiao PC, Yeh LL et al. Polygenic risk for schizophrenia and neurocognitive performance in patients with schizophrenia. Genes Brain Behav 2018;**17**:49–55.
34. Yüksel D, Dietsche B, Forstner AJ et al. Polygenic risk for depression and the neural correlates of working memory in healthy subjects. Prog Neuropsychopharmacol Biol Psychiatry 2017;**79**:67–76.
35. Taylor MJ, Martin J, Lu Y et al. Association of genetic risk factors for psychiatric disorders and traits of these

disorders in a Swedish population twin sample. JAMA Psychiatry 2019;**76**:280–289.
36. Den Braber A, Zilhao NR, Fedko IO et al. Obsessive–compulsive symptoms in a large population-based twin-family sample are predicted by clinically based polygenic scores and by genome-wide SNPs. Transl Psychiatry 2016;**6**:e731.
37. Bey K, Lennertz L, Grützmann R et al. Impaired antisaccades in obsessive-compulsive disorder: Evidence from meta-analysis and a large empirical study. Front Psychiatry 2018;**9**:284.
38. First MB, Spitzer RL, Gibbon M et al. User's guide for the Structured Clinical Interview for DSM-IV axis I Disorders SCID-I: clinician version. Arlington: American Psychiatric Association Publishing; 1997.
39. Wittchen HU, Zaudig M, Fydrich T. SKID. Strukturiertes klinisches Interview für DSM-IV. Achse I und II. Handanweisung [Structured Clinical Interview for DSM-IV. Axis I and II. Manual]. Göttingen, Germany: Hogrefe; 1997.
40. Cloninger CR, Przybeck TR, Svrakic DM et al. The Temperament and Character Inventory (TCI): A guide to its development and use. Washington: Center for Psychobiology of Personality; 1994.
41. Richter J, Eisemann M, Richter G. German version of the temperament and character inventory. Zeitschrift für Klinische Psychologie-Forschung und Praxis 2000;**29**: 117–126.
42. Goodman WK, Price LH, Rasmussen SA et al. The Yale brown obsessive compulsive scale: II. Validity. Arch Gen Psychiatry 1989;**46**:1012–1016.
43. Hand I, Büttner-Westphal H. Die Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen. Verhaltenstherapie 1991;**1**:223–225.
44. Foa EB, Huppert JD, Leiberg S et al. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess 2002;**14**:485–496.
45. Gönner S, Leonhart R, Ecker W. The obsessive–compulsive inventory-revised (OCI-R): validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. J Anxiety Disord 2008;**22**:734–749.
46. Cervin M, Perrin S, Olsson E et al. Incompleteness, harm avoidance, and disgust: a comparison of youth with OCD, anxiety disorders, and no psychiatric disorder. J Anxiety Disord 2020;**69**:102175.
47. Ecker W, Gönner S. Incompleteness and harm avoidance in OCD symptom dimensions. Behav Res Ther 2008;**46**:895–904.
48. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS); 2018; OCD_Aug2017; Retrieved from https://www.med.unc.edu/pgc/download-results/ocd/
49. Purcell S, Neale B, Todd-Brown K et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;**81**:559–575.
50. Choi SW, Mak TSH, O'Reilly P. A guide to performing Polygenic Risk Score analyses. BioRxiv 2018. https://doi.org/10.1101/416545.
51. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York: Guilford Publications; 2017.
52. Hayes AF, Cai L. Using heteroskedasticity-consistent standard error estimators in OLS regression: An introduction and software implementation. Behav Res Methods 2007;**39**:709–722.
53. Taylor S. Early versus late onset obsessive–compulsive disorder: evidence for distinct subtypes. Clin Psychol Rev 2011;**31**:1083–1100.
54. Brainstorm Consortium, Anttila V, Bulik-Sullivan B et al. Analysis of shared heritability in common disorders of the brain. Science 2018;**360**:eaap8757.
55. Aluja A, Blanch A. The five and seven factors personality models: differences and similitude between the TCI-R, NEO-FFI-R and ZKPQ-50-CC. Span J Psychol 2011;**14**:659–666.
56. Service SK, Verweij KJH, Lahti J et al. A genome-wide meta-analysis of association studies of Cloninger's Temperament Scales. Transl Psychiatry 2012;**2**:e116.
57. Verweij KJ, Zietsch BP, Medland SE et al. A genome-wide association study of Cloninger's temperament scales: implications for the evolutionary genetics of personality. Biol Psychol 2010;**85**:306–317.
58. Wang KS, Liu X, Aragam N et al. Polymorphisms in ABLIM1 are associated with personality traits and alcohol dependence. J Mol Neurosci 2012;**46**:265–271.
59. Lyoo IK, Yoon T, Kang DH et al. Patterns of changes in temperament and character inventory scales in subjects with obsessive–compulsive disorder following a 4-month treatment. Acta Psychiatr Scand 2003;**107**:298–304.
60. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med 2013;**11**:126.
61. Beucke JC, Sepulcre J, Eldaief MC et al. Default mode network subsystem alterations in obsessive–compulsive disorder. Br J Psychiatry 2014;**205**:376–382.
62. Gürsel DA, Avram M, Sorg C et al. Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. Neurosci Biobehav Rev 2018;**87**:151–160.
63. Huggins AA, Belleau EL, Miskovich TA et al. Moderating effects of harm avoidance on resting-state functional connectivity of the anterior insula. Front Hum Neurosci 2018;**12**:447.
64. Jiang R, Calhoun VD, Zuo N et al. Connectome-based individualized prediction of temperament trait scores. NeuroImage 2018;**183**:366–374.
65. Riesel A. The erring brain: Error-related negativity as an endophenotype for OCD—A review and meta-analysis. Psychophysiology 2019;**56**:e13348.
66. Riesel A, Klawohn J, Grützmann R et al. Error-related brain activity as a transdiagnostic endophenotype for obsessive-compulsive disorder, anxiety and substance use disorder. Psychol Med 2019;**49**:1207–1217.
67. Hasler G, LaSalle-Ricci VH, Ronquillo JG et al. Obsessive–compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. Psychiatry Res 2005;**135**:121–132.
68. López-Solà C, Fontenelle LF, Verhulst B et al. Distinct etiological influences on obsessive–compulsive symptom dimensions: A multivariate twin study. Depress Anxiety 2016;**33**:179–191.
69. Taj MJRJ, Ganesh S, Shukla T et al. BDNF gene and obsessive compulsive disorder risk, symptom dimensions and treatment response. Asian J Psychiatry 2017;**38**:65–69.
70. Viswanath B, Purushottam M, Kandavel T et al. DRD4 gene and obsessive compulsive disorder: do symptom dimensions have specific genetic correlates? Prog Neuropsychopharmacol Biol Psychiatry 2013;**41**:18–23.
71. Alemany-Navarro M, Cruz R, Real E et al. Looking into the genetic bases of OCD dimensions: a pilot genome-wide association study. Transl Psychiatry 2020;**10**:1–16.

72. Pauls DL, Abramovitch A, Rauch SL et al. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci 2014;**15**:410–424.
73. Alemany-Navarro M, Costas J, Real E et al. Do polygenic risk and stressful life events predict pharmacological treatment response in obsessive compulsive disorder? A gene–environment interaction approach. Transl Psychiatry 2019;**9**:70.
74. Miller GA, Chapman JP. Misunderstanding analysis of covariance. J Abnorm Psychol 2001;**110**:40.
75. Kampman O, Viikki M, Järventausta K et al. Meta-analysis of anxiety disorders and temperament. Neuropsychobiology 2014;**69**:175–186.

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.