Supplemental Online Materials

This supplementary material has been provided by the authors to give readers additional information about their work.

SA1: ***Clinical Assessments***

- *Motor and phonic tics:* The TSAICG Tic and Comorbid Symptom Inventory (TICS) is a modified version of the Schedule for Tourette Syndrome and other Behavioral Syndromes (STOBS) [1] and includes an inventory of >80 motor and phonic tics. Participants were asked whether they had experienced each symptom in the past week, past six months, ever, or never. For analyses, the first three response options were collapsed, and dichotomous data (lifetime presence or absence) were analyzed. Tic frequency and severity TICS items were modified from the Yale Global Tic Severity Scale (YGTSS) [2]. Tic severity was characterized by frequency, intensity, and interference of symptoms. The highest score resulting from summing the modified severity questions is 15. As the TICS was modified during the study period to improve response rates, items not present for all participants were excluded from analysis.
- *Obsessive-compulsive symptoms:* The TICS also includes an obsessive-compulsive symptom (OCD) checklist (>100 items) and questions about OCD severity modified from the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [3, 4]. OCD symptoms were analyzed as lifetime presence or absence. Severity of obsessions and compulsions was characterized jointly (e.g., severity of obsessions and/or compulsions) by time, interference, and distress when symptoms were worst. The highest possible sum score of these items was 12. For Tic and OCD, major category items that subsumed a number of individual symptoms (e.g., "eye movements") were excluded and the individual symptom items were used, as the use of both would result in overlapping data (i.e., participants could endorse the overall category "eye movements" and sub-category item "eye-blinking"). Additionally, vague items (e.g., "other motor tic") and items that were not clearly OC (e.g., "pulls hair out") were excluded. See eTable 1 for a list of included items.
- *ADHD symptoms:* ADHD symptom data were collected using multiple self-report forms across different waves of data collection, including the Conners' Parent Rating Scale [5], Conners' Adult ADHD Rating Scales [6], and the Swanson, Nolan, and Pelham questionnaire [7]. For analyses, symptom questions from each rating scale were mapped onto the 18 DSM-IV-TR ADHD symptoms in a dichotomous fashion (i.e., each symptom was rated present or absent). For example, if the item "Has difficulty sustaining attention in tasks or play activities, more so than his or her friends" on the Conners' Adult ADHD Rating Scales was marked as occurring "often" or "frequently", the DSM-IV-TR symptom "often has difficulty sustaining attention in tasks or play activities" was marked as present. ADHD symptom severity was not examined because these data were not available.
- *Comorbid psychiatric diagnoses:* Additional co-morbid psychiatric diagnoses were assessed through structured interviews. Adults were administered either the Structured Clinical Interview for DSM [SCID-I/NP version 2.0; 8] or the Schedule for Affective Disorders and Schizophrenia-Lifetime Version, Modified for the Study of Anxiety Disorders [SADS-LA; 9]. Children were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Lifetime Version [K-SADS-PL; 10] and Epidemiologic Version [11]. These data were only collected during the first wave of recruitment and were available for ≥19% of participants (see Table 1 in the manuscript). Psychiatric diagnoses other than TS, OCD, and ADHD were combined into categories; mood (depression and bipolar disorder), anxiety (panic, generalized anxiety, social phobia, and separation anxiety),

and disruptive behavior disorders (conduct disorder and oppositional defiant disorder). In order to arrive at a best-estimate set of diagnoses, two clinicians who were not involved in the interview process used DSM-IV-TR criteria to assign diagnoses using all available data (i.e., TICS, structured diagnostic interview data, clinical narrative, and medical records). A consensus diagnosis was achieved after discussion of discrepancies. If a consensus could not be reached, a third clinician's ratings were used to determine diagnostic status.

SA2: Criteria for factor models

The null hypothesis of the traditional chi-square test is that the model is a good fit for the data; a significant result indicates that it is not a good fit for the data. This test has been shown to be sensitive to sample size and should not be used alone. The chi-square difference test compares the fit of two nested models where a significant result indicates the higher order model is a better fit. A RMSEA value of $\leq .05$ suggests that the data fit the model well.

SA3: Polygenic burden analyses

In order to assess the relationship between polygenic risk for TS and phenotypes assessed on the same samples, without risk of over-fitting, we conducted a stratified 11-fold cross-validation study using all individuals with genotype data (4232 TS cases and 8282 controls described previously[12-14]), regardless of whether they had symptom-level phenotype data available. TS cases were first separated into 6 groups based genotyping platforms and population stratification. For one group in which a large number of TS cases were genotyped on the same platform, the samples were further split randomly into 6 groups, resulting in a total of 11 TS case groups. The population- and genotyping platform- matched controls were then split into 11 groups along with each of the cases. Within each group, the same Quality Control (QC) steps were applied, and association tests were performed after adjusting for population stratification. To calculate TS Polygenic Risk Scores (PRS) for each individual within a group, a meta-analysis was performed on the other 10 groups, and both the risk allele and the corresponding effect size on each SNP were extracted from the meta-analysis result. The SNPs were then linkage disequilibrium (LD) pruned ($r^2<0.2$). TS PRS on each individual sample was then calculated as the sum of the number of risk alleles at each locus weighted by the effect size over all LD pruned SNPs with GWAS p-value less than predetermined thresholds ($p<0.01$, 0.1, 0.2, 0.3, 0.4, and 0.5) as described in [15].

The OCD PRS was developed in much the same way, except it was derived from an independent OCD sample and did not require cross-validation. The risk alleles and the corresponding effect sizes were extracted from an OCD GWAS discovery sample (1429 cases, 5083 controls, and 285 trios[16]). OCD PRS were calculated on TS samples at each predetermined GWAS p-value thresholds after LD pruning.

The ADHD PRS was derived in the same way as OCD PRS, except that the discovery sample is an ADHD sample[17], which includes 2064 trios, 896 cases, and 2455 controls.

For each PRS, the phenotype of interest was regressed on PRS of 947 TS cases who have both genotyping data and symptom-level phenotype data. To assess significance of the association, we fit the following linear regression model:

$$Y = \beta_0 + \beta_{PRS}X_{PRS} + \beta_{PC1}X_{PC1} + \ldots \beta_{PC4}X_{PC4} + \beta_{group\_i}X_{group\_i} \quad \text{(full model)}$$

including the top four principal components as covariates to account for any residual confounding by population and site, and an indicator for cross-validation group to account for

group effect and genotyping/imputation platform effect. For OCD PRS and ADHD PRS, the indicator for cross-validation group was changed to the indicator for the genotyping/imputation platform. The percentage of phenotypic variance explained by PRS (i.e. R^2 for PRS) is calculated by subtracting the R^2 of full model by the R^2 of the reduced model:

$$Y = \beta_0 + \beta_{PC1}X_{PC1} + \ldots \beta_{PC4}X_{PC4} + \beta_{group\_i}X_{group\_i}$$ (reduced model).

ST1. Sample size for each analysis

N	Analysis
1191	EFA of original probands
1191	LCA of original probands
3494	LCA of original probands & family members
527	CFA of validation probands
882	LCA of validation probands & family members
3200	Heritability analyses
268	Polygenic burden of factors
294	Polygenic burden of classes

ST2. TICS Inventory Items Included

Tic Items
Blinking: eye blinking
squinting
Eye turn: a quick turn of the eyes
Eye rolling: rolling of the eyes to one side
Eyes wide: opening the eyes wide (briefly)
nose twitching
Tongue biting: biting the tongue
Lip chewing: chewing on lip(s)
licking the lips
lip pouting
teeth bearing
broadening the nostrils (as if smelling something)
smiling
sticking out the tongue
Touch chin: touching the chin to shoulder
Lift chin: lifting the chin up
throwing the head back (as if to get hair out of eyes)
Shoulder jerking: jerking a shoulder
Shoulder shrug: shrugging the shoulders as if to say "I dont know"
poking with fingers
passing hand through hair in a combing-like fashion
counting with fingers for no purpose
Repetitive writing: writing the same letter or word over and over
pulling back on the pencil while writing
kicking
skipping
knee-bending
Flex ankle: flexing or extending the ankle(s)
slower movements (e.g., taking a step forward and 2 steps back)
squatting
deep knee bending
tensing the abdomen
tensing the buttocks
touching
tapping
rude or obscene gestures (copropraxia)
unusual postures (dystonic tics)
bending or gyrating (e.g., bending over)
rotating or spinning
coughing
throat clearing
sniffing
whistling

animal or bird noises
syllables
rude or obscene words or phrases (coprolalia)
words
repeating what someone else said, either sounds, single words or phrases (e.g., repeating what is said on TV) (echolalia)
repeating something s/he said over and over again (palilalia)

OCD sxs

Has to keep a strict timetable or routine for doing ordinary activities
Does thing same way: Has to do things the same way every time
Cleaning compulsions: has compulsions that involve cleaning household items or other inanimate objects
Contamination compulsions: Does other things to prevent or remove contact with contaminants
Checks that did not or will not harm others
Checks no self-harm: Checks that did not or will not harm self
Checks nothing terrible: Checks that nothing terrible did happen or will happen
Checks mistakes: checks that did not make mistakes
Checks things: checks (more than once) on things such as gas (stove, oven, heaters) and electrical (coffee/tea pots, curling iron) appliances, door locks, etc.
Re-reads or re-writes things
Repeat compulsions: Needs to repeat routine activities (like going in and out of a doorway or getting up and down from a chair)
repeating acts
Has counting compulsions
Ordering compulsions: Has ordering or arranging compulsions
Symmetry compulsions: Needs certain things to be symmetrical
Even-up compulsions: Needs to have certain things evened-up
Hoarding compulsions: Has compulsions to hoard or collect things
Mental rituals: Has mental rituals (other than checking or counting) done intentionally to feel better
Needs to tell, ask, or confess things
Need explore: Has experienced a strong need to explore surroundings
Needs to touch, tap, or rub things
Prevent harm compulsions: Takes measures (other than checking) to prevent harm to self or others, or terrible consequences
Has superstitious behaviors
Has silly thoughts that can influence the outcome of some events if does certain things
Fears harming self: Fears that might harm self
Fears harming others: Fears that might harm other people
Violent images: Has violent or horrific images in mind
Fears obscenities: Fears blurting out obscenities
Fears impulse: Fears acting on an unwanted impulse
Fears stealing: Fears will steal things

Fears harm others: Fears that will harm other because not careful enough (like a hit-and-run motor vehicle accident)
Fears responsible something terrible: fears being responsible for something else terrible happening (such as fire or burglary)
Reckless urges: Has experienced unreasonable urges to do sudden and reckless things (behaviors)
Urges destroy: Has experienced unreasonable urges to be destructive
Urges self-injure: Has experienced unreasonable urges to injure self
Urges injure others: Has experienced urges to injure or mutilate others
Urges offend: Has experienced unreasonable urges to offend others
Bodily waste obsessions: Is concerned or disgusted with bodily waste or secretions (like urine, feces, or saliva)
Germ obsessions: Is concerned with dirt or germs
Environmental contaminants obsessions: Is excessively concerned with environmental contaminants (like asbestos, radiation, or toxic waste)
Animal obsessions: Is excessively concerned with animals (like insects)
Sticky obsessions: Is bothered by sticky substances or residues
Contamination obsessions: Is concerned will get ill because of contamination
Sexual obsessions: Has forbidden or upsetting sexual thoughts, images, or impulses
Hoarding obsessions: Has obsessions about hoarding or saving things
Religious obsessions: Is concerned with upsetting thoughts having to do with God, religious teachings or beliefs
Morality obsessions: Is excessively concerned with right or wrong (morality)
Exactness obsession: Has obsessions about exactness
Symmetry obsessions: Has obsessions about symmetry
Lining up obsessions: Often has thoughts about lining things up
Has unreasonable, silly thoughts that may influence the outcome of some events if does certain things
Even-up obsessions: Often has thoughts about evening things up
Remember compulsions: Feels like needs to know or remember certain things
Fears losing things
Lucky numbers: Has lucky or unlucky numbers
Has colors with special significance
Has superstitious fears
Illness obsessions: Is concerned with illness or disease
Is excessively concerned with a part of body or an aspect of appearance

ADHD sxs

No follow through: Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
Trouble organizing: Often has trouble organizing activities.
Forgetful: Is often forgetful in daily activities
No attend detail: Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
Avoids mental effort: Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time

Loses things: Often loses things needed for tasks and activities
Distractible: Is often easily distracted
Trouble attending: Often has trouble keeping attention on tasks or play activities.
No listen: Often does not seem to listen when spoken to directly.
On the go: Is often "on the go" or often acts as if "driven by a motor"
Runs: Often excessively runs about or climbs when and where it is not
Blurts out: Often blurts out answers before questions have been finished
Interrupts: Often interrupts or intrudes on others
Out of seat: Often gets up from seat when remaining in seat is expected
Fidgets: Often fidgets with hands or feet or squirms in seat when sitting still is expected
Trouble waiting: Often has trouble waiting one's turn
Trouble quiet: Often has trouble playing or doing leisure activities quietly
Talks excessively: Often talks excessively

ST3. Fit Statistics for Exploratory Principal Components Models

Model	Number of free parameters	χ^{2a}	df	RMSEA	95% CI
Tic, OCD & ADHD					
Individual models					
1-factor	126	25593.04	7749	0.04	0.04-0.05
2-factor	251	15479.84	7624	0.03	0.03-0.03
3-factor	375	12267.26	7500	0.02	0.02-0.02
4-factor	498	11153.25	7377	0.02	0.02-0.02
5-factor	620	10303.40	7255	0.02	0.02-0.02
6-factor	741	9524.06	7134	0.02	0.02-0.02
7-factor	861	8924.75	7014	0.02	0.01-0.02
8-factor	980	8540.10	6895	0.01	0.01-0.02
Comparisons between adjacent models					
1-factor against 2-factor		3675.40	125		
2-factor against 3-factor		1739.07	124		
3-factor against 4-factor		962.81	123		
4-factor against 5-factor		818.35	122		
5-factor against 6-factor		800.54	121		
6-factor against 7-factor		660.89	120		
7-factor against 8-factor		446.70	119		
Tic & OCD					
Individual models					
1-factor	108	13497.08	5670	0.03	0.03-0.04
2-factor	215	10284.00	5563	0.03	0.03-0.03
3-factor	321	8865.20	5457	0.02	0.02-0.02
4-factor	426	7901.76	5352	0.02	0.02-0.02
5-factor	N/A				
6-factor	633	6761.22	5145	0.02	0.02-0.02
7-factor	735	6412.45	5043	0.02	0.01-0.02
8-factor	836	6126.15	4942	0.01	0.01-0.02
Comparisons between adjacent models					
1-factor against 2-factor		1702.68	107		
2-factor against 3-factor		1148.51	106		
3-factor against 4-factor		792.33	105		
6-factor against 7-factor		391.18	102		
7-factor against 8-factor		347.99	101		

The baseline $\chi 2$ (df) model fit for the baseline model was 52448.415 (7875).

[a] All χ^2 values are significant at $p<.0001$.

RMSEA, root mean square error of approximation

ST4. Correlations between 4 Factors.

	F1 tics	**F2 OCS**	**F3**	**F4 symmetry**
F1	1			
F2	0.31[a]	1		
F3	0.16[a]	0.08	1	
F4	0.30[a]	0.46[a]	0.17[a]	1

[a] indicates significant correlations $p \leq 0.05$

ST5. Fit statistics and class size for LCA solutions

	2 Classes	3 Classes	4 Classes	5 Classes	6 Classes
Probands					
Entropy	0.95	0.94	**0.95**	0.94	0.95
LMR p-value	≤.001	≤.001	**≤.01**	.25	.80
BIC	136888	133976	**132598**	132087	131836
n of LC1	499	345	**191**	261	113
n of LC2	692	402	**243**	264	248
n of LC3		444	**396**	293	232
n of LC4			**361**	128	286
n of LC5				245	177
n of LC6					135
Probands & Family members					
Entropy	0.96	0.95	0.94	**0.95**	0.95
LMR p-value	<0.001	<0.001	0.001	**0.27**	0.70
BIC	306725	296645	290822	**286873**	284800
n of LC1	1467	773	567	**456**	336
n of LC2	2027	1205	970	**541**	589
n of LC3		1516	612	**612**	1175
n of LC4			1345	**604**	578
n of LC5				**1281**	542
n of LC6					274
Replication: Probands & Family members					
Entropy	0.97	0.97	0.96	**0.97**	-
LMR p-value	<0.001	<0.01	0.04	**0.71**	-
BIC	90870	87464	86334	**85608**	-
n of LC1	521	186	251	**356**	-
n of LC2	361	361	190	**114**	-
n of LC3		335	258	**174**	-
n of LC4			183	**169**	-
n of LC5				**169**	-
n of LC6					-

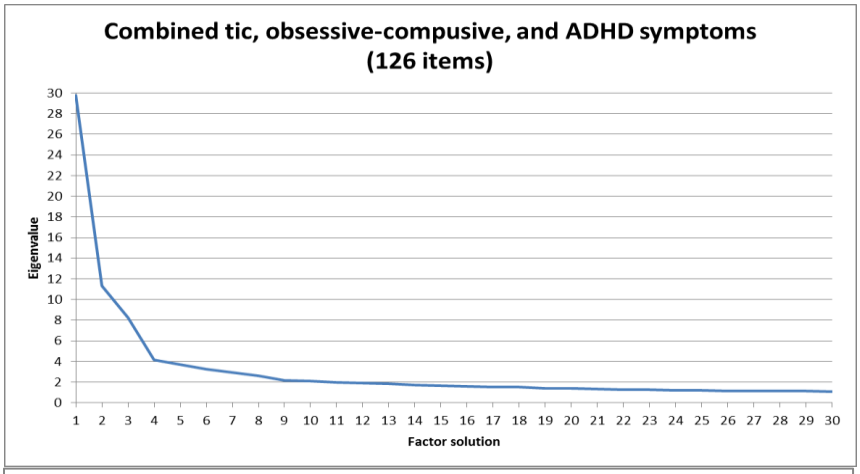
LMR = Lo, Mendel, and Rubin parametric likelihood ratio test
BIC = Bayesian Information Criterion
Note: Bold lettering indicates best fitting solution based on low BIC, significant LMR results, and clinically interpretable classes. The loglikelihood value for the 6-class model using the replication sample data failed to replicate after 640 attempts.

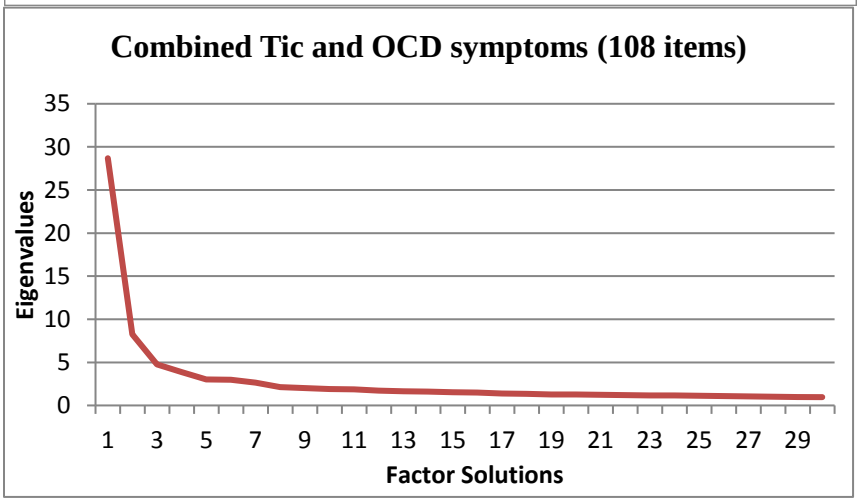
ST6. Polygenic burden analyses of the symmetry and disinhibition endophenotypes.

PRS	GWAS p-value cutoff	Number of SNPs	Symmetry		Disinhibition		Disinhibition regardless of hoarding symptoms	
			R^2	P	R^2	P	R^2	P
TS	P < 0.01	5,756	-0.06%	0.433	-0.05%	0.513	-0.03%	0.621
	P < 0.1	34,702	0.33%	0.074	0.01%	0.803	0.03%	0.593
	P < 0.2	57,942	0.27%	0.107	0.01%	0.806	0.04%	0.521
	P < 0.3	77,267	0.46%	0.036	0.08%	0.391	0.14%	0.257
	P < 0.4	93,706	0.55%	0.022	0.12%	0.295	0.19%	0.183
	P < 0.5	107,559	0.57%	0.020	0.18%	0.194	0.27%	0.109
OCD	P < 0.01	4,871	-0.07%	0.417	0.52%	0.026	0.55%	0.023
	P < 0.1	31,036	-0.03%	0.583	0.46%	0.036	0.56%	0.021
	P < 0.2	52,672	-0.10%	0.335	0.18%	0.186	0.25%	0.125
	P < 0.3	70,463	-0.13%	0.260	0.12%	0.281	0.17%	0.202
	P < 0.4	85,463	-0.10%	0.318	0.17%	0.199	0.22%	0.148
	P < 0.5	98,105	-0.11%	0.307	0.17%	0.198	0.23%	0.138
ADHD	P < 0.01	3,437	-0.19%	0.180	-0.09%	0.355	-0.03%	0.579
	P < 0.1	24,470	0.00%	0.934	0.04%	0.525	0.08%	0.387
	P < 0.2	42,954	0.03%	0.617	0.13%	0.259	0.19%	0.182
	P < 0.3	58,796	-0.04%	0.523	0.10%	0.337	0.13%	0.271
	P < 0.4	72,823	-0.05%	0.511	0.18%	0.194	0.22%	0.146
	P < 0.5	84,975	-0.05%	0.475	0.23%	0.137	0.30%	0.095

R^2 = percentage of phenotypic variance explained in the target sample by the Polygenic Risk Score (PRS) in the TS, OCD or ADHD discovery sample. A negative value indicates a negative correlation between PRS and the target phenotype of interest.
P = the significance level of the correlation between TS, OCD, or ADHD discovery sample PRS and the target phenotype of interest after adjusting for population stratification and any genotyping or imputation platform effects.

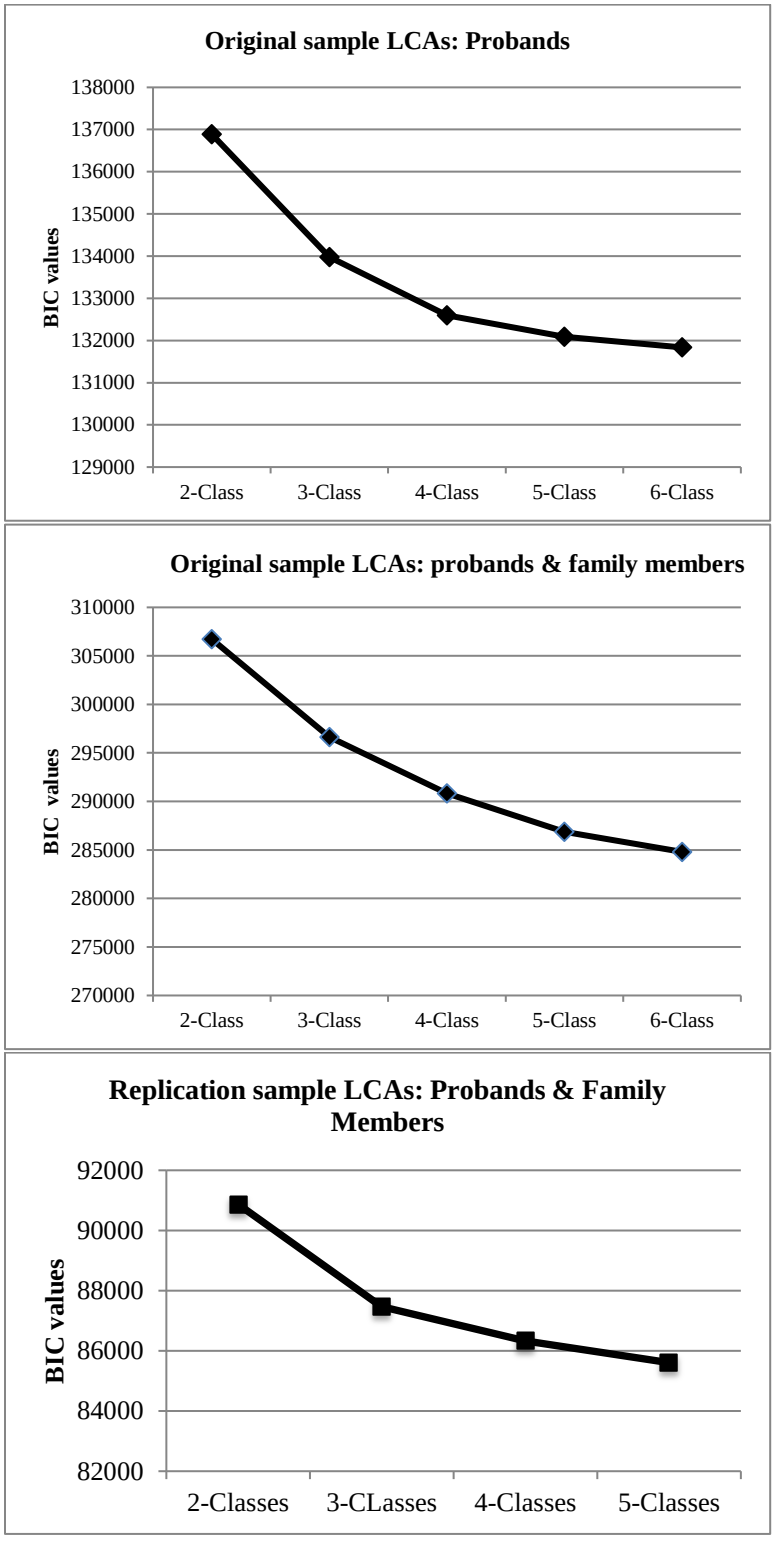
SF1. Scree Plot of Exploratory Principal-Components Analysis among Probands (N=1191)



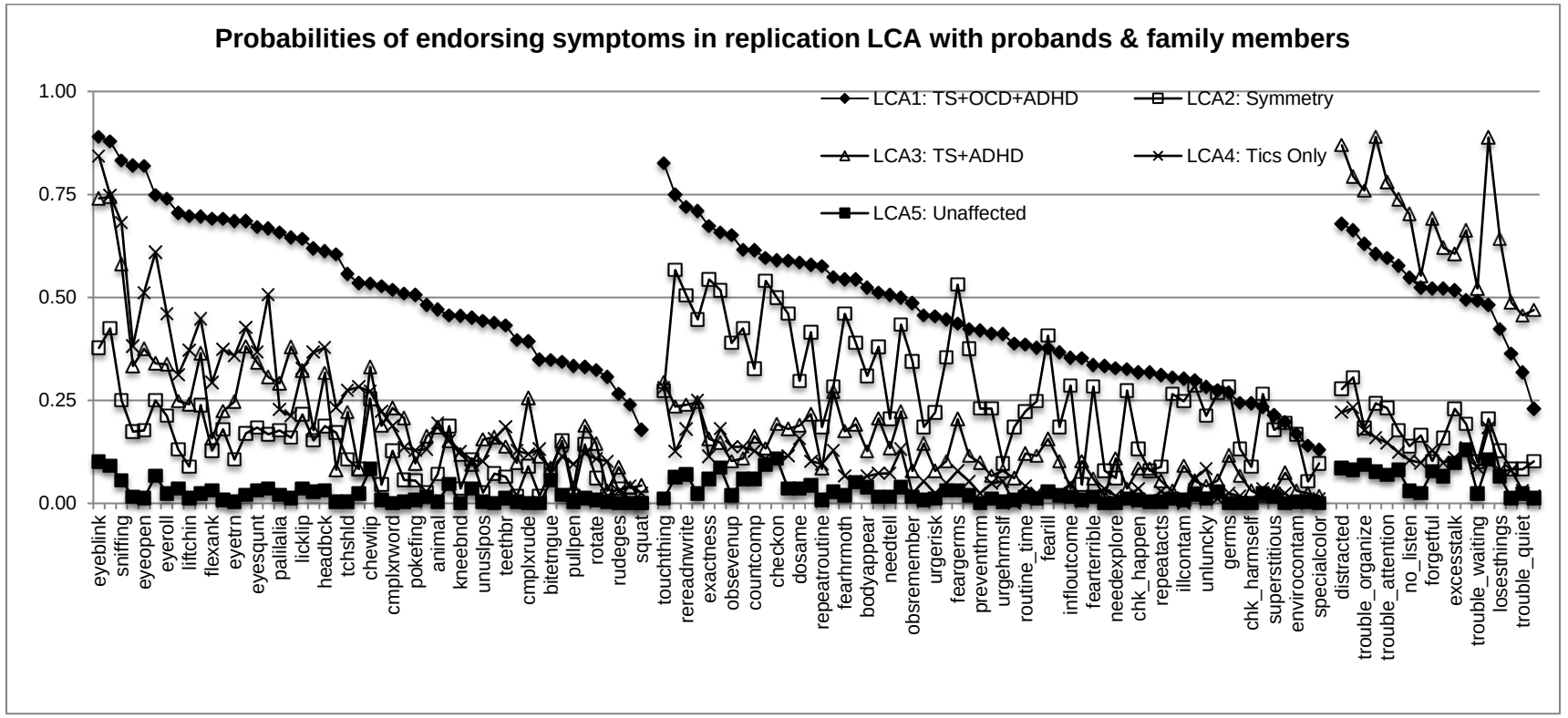


Note: Horizontal axes have been truncated to allow clear visualization of the inflection point ("elbow") of each scree plot.

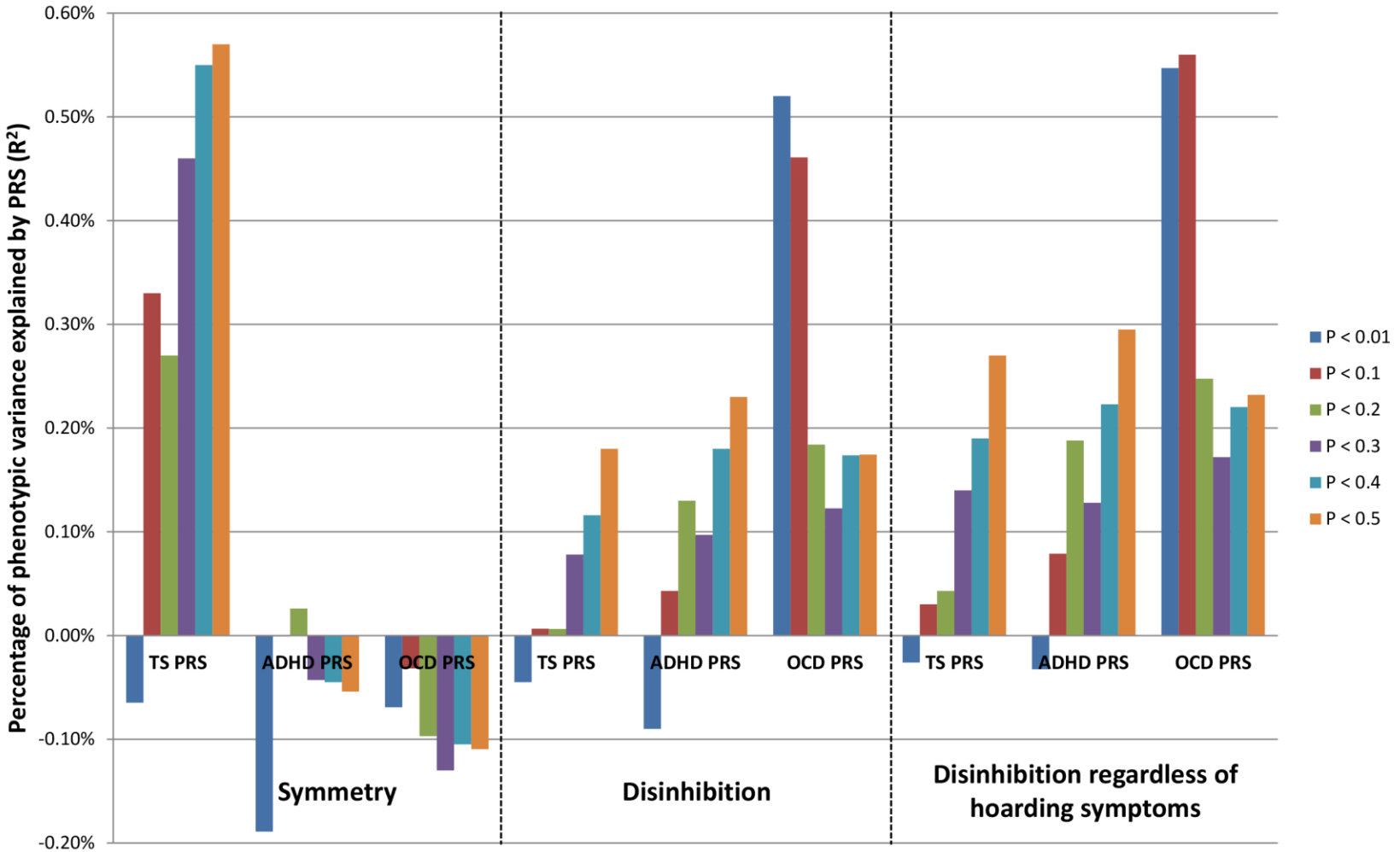
SF2. Graph of Bayesian information criterion (BIC) values for LCA solutions



SF3. Probabilities of endorsing symptoms for LCA classes: replication



SF4. The phenotypic variance of symmetry and disinhibition explained by TS, OCD and ADHD Polygenic Risk Scores (PRS)



The *y* axis represents the percentage of phenotypic variance explained by PRS (i.e. R^2). Negative R^2s indicate negative correlation between the target phenotype of interest and the discovery sample PRS.

SR1: Supplemental References

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