

Shared genetic etiology between obsessive-compulsive disorder, obsessive-compulsive symptoms in the population, and insulin signaling

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INTRODUCTION

- **Obsessive Compulsive Disorder (OCD)** can be understood as the upper extreme of an underlying genetic liability and behavioural continuum of **obsessive-compulsive symptoms (OCS)** in the general population [1,2].
- **Insulin signaling** has been implicated in OCD through genetic and epidemiological studies [3-5].
- Here, we aimed to assess the genetic overlap between OCD, OCS in the population, and central/nervous system (CNS) and peripheral insulin signaling.

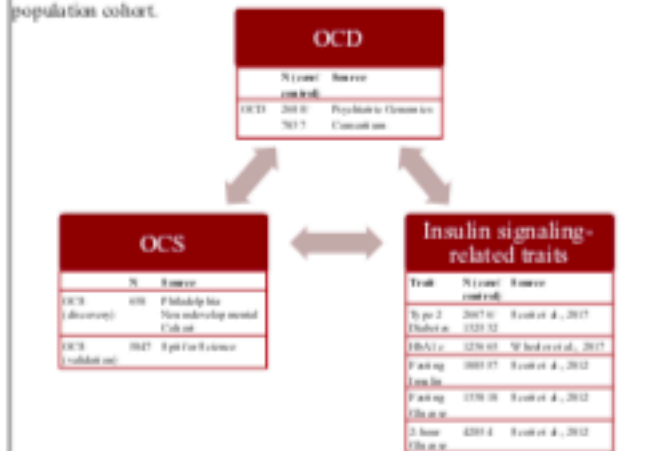
METHODS

OCS in the general population

We analyzed OCS measured in the population-based Philadelphia Neurodevelopmental Cohort (PNC), by conducting:
 → Factor analysis of 22 OCD-related questions from GO-ASSESS, a computerized version of the K-SADS
 → Genome-wide association analysis of the total OCS score and six OCS factors

Shared genetic etiology analyses

We performed polygenic risk score (PRS) - based analyses in PRSice [6] to assess genetic sharing between clinical OCD, OCS, and five peripheral insulin signaling-related traits. We validated our findings in the independent, Spitz for Science population cohort.

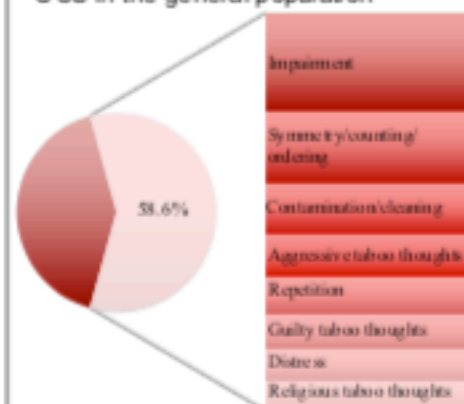


Gene-set analysis

We performed gene-set analysis with a set of 51 autosomal OCD-linked genes centered around CNS insulin-regulated synaptic function [3] using the Multitasker Analysis of GenoMic Annotation (MAGMA) software [7].

RESULTS

OCS in the general population



Factor analysis of the total score on 22 OCD-related questions. Eight factors constitute the best fitting model, explaining 58.6% of variance.

Gene-set analysis

MAGMA-based gene-set analysis with a set of OCD-linked genes centered around CNS insulin-regulated synaptic function revealed a significant association with 'symmetry/counting/ordering' ($P=4.08E-07$).

Within the significant gene-set, none of the individual genes showed gene-wide association.

Summary of findings

- (1) We found genetic sharing between OCD and the OCS factor 'guilty taboo thoughts', which we were able to expand by showing genetic sharing between OCD and OCS factors 'contamination/cleaning' and 'symmetry/counting/ordering' in the larger Spitz for Science cohort.
- (2) We found significant association between a set of OCD genes centered around CNS insulin-regulated synaptic function and 'symmetry/counting/ordering'.
- (3) We identified genetic sharing between Type 2 Diabetes (T2D) and 'aggressive taboo thoughts' (in PNC), as well as 'contamination/cleaning' (in Spitz for Science). For two out of the four T2D blood markers (Fasting Insulin and 2-hour Glucose), we also identified a shared genetic etiology with OCD.

CONCLUSIONS

Our findings suggest genetic sharing between clinical OCD and specific OCS in the general population. Our results also imply that altered insulin signaling, as relevant to Type 2 Diabetes, is involved in different aspects of obsessive-compulsive behaviours and clinical OCD. This may open up a new field of brain-based insulin-related disorders.

Shared genetic etiology analyses

	OCD	Type 2 Diabetes	HbA1c	Fasting Insulin	Fasting Glucose	2-hour Glucose
Total OCS score	4.79E-08	3.36E-01	7.64E-02	3.74E-01	4.16E-01	4.72E-01
	0.04%	0.28%	1.00%	0.19%	0.10%	0.02%
Impairment	2.61E-08	4.10E-01	2.28E-01	4.10E-01	4.10E-01	3.53E-01
	0.51%	0.11%	0.58%	0.11%	0.12%	0.22%
Symmetry/counting/ordering	3.53E-08	2.56E-01	4.10E-01	4.72E-01	2.80E-01	4.10E-01
	0.23%	0.53%	0.11%	0.04%	0.39%	0.11%
Contamination/cleaning	1.12E-08	3.53E-01	3.21E-01	4.47E-01	2.28E-01	2.71E-02
	0.85%	0.24%	0.33%	0.07%	0.58%	0.49%
Aggressive taboo thoughts	2.28E-08	5.95E-03	7.99E-02	4.66E-01	2.71E-01	2.28E-01
	0.46%	1.84%	0.97%	0.06%	0.49%	0.59%
Guilty taboo thoughts	2.52E-03	1.89E-01	4.03E-01	2.61E-01	3.21E-01	9.74E-02
	2.28%	0.68%	0.15%	0.52%	0.33%	0.90%
Distress	4.05E-08	4.72E-01	4.07E-01	2.80E-01	3.53E-01	3.53E-01
	0.13%	0.02%	0.13%	0.43%	0.23%	0.25%
OCD	NA	2.80E-01	4.15E-01	7.67E-05	3.53E-01	4.75E-03
	NA	0.03%	0.01%	0.26%	0.02%	0.14%
Symmetry/counting/ordering _{PNC}	2.42E-05	3.39E-01	2.71E-01	3.71E-01	2.47E-01	4.45E-01
	0.49%	0.03%	0.04%	0.02%	0.04%	0.01%
Contamination/cleaning _{PNC}	4.07E-03	1.59E-03	1.68E-01	4.37E-01	4.36E-01	3.76E-01
	0.23%	0.28%	0.05%	0.01%	0.01%	0.02%

Note: The table presents the Bonferroni-Holm adjusted P-values of the best SNP-P-value thresholding with the variance explained for each of the sample pairs from PRS-based analyses in PRSice. Significant findings are indicated in bold. Abbreviations: PNC - Philadelphia Neurodevelopmental Cohort, PGC - Psychiatric Genomics Consortium, TOCS - Toronto Obsessive-Compulsive Scale

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