Investigating divergent and convergent pathways in Major Depressive Disorder through Coordinated Epistasis

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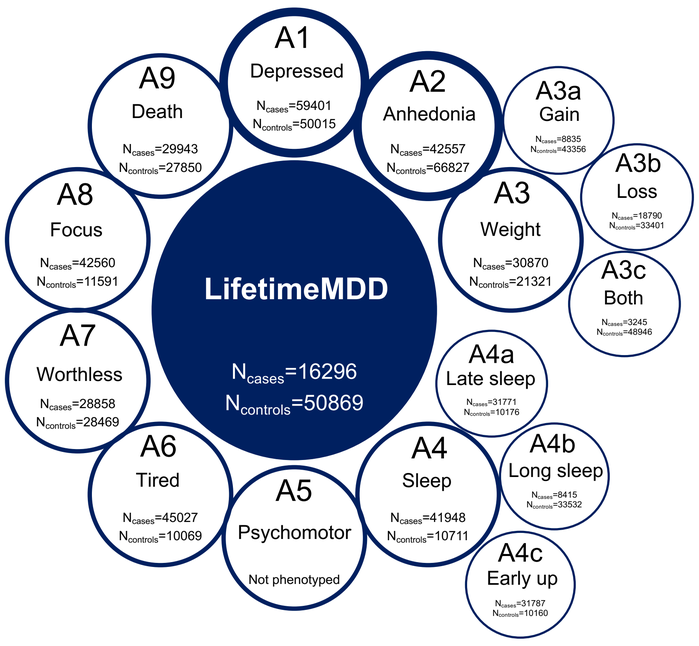
SUMMARY

There is mounting evidence that Major Depressive Disorder (MDD) is likely the common outcome of diverse and potentially interacting pathways. However, these subtypes are yet to be robustly demonstrated[1,2]. Taking advantage of the polygenic nature of MDD, we study MDD subtypes through a new statistical framework called Coordinated Epistasis (CE)[3]. The CE framework tests for polygenic interactions between polygenic risk scores (PRS) generated from partitions of the genome, which act as proxies for bona fide biological pathways leading to disease. The closer the the proxies to bona fide biological pathways leading to MDD, the better powered the CE test is; the distribution of interaction effect directions between proxy pathways further indicate the nature of CE in MDD. Using data from the UKBiobank[4] we identify significant CE in both MDD and its worst-episode symptoms, as well as significant CE between worst-episode symptoms in their effect on MDD. We thereby agnostically and conclusively demonstrate the presence of heterogenous pathways leading to MDD. We further perform SNP-PRS interaction tests between pairs of significantly interacting PRS (each a proxy pathway), and identify genetic loci driving their interactions. For the first time, we demonstrate the existence of robust epistasis in MDD and its symptoms at the locus level. Overall, our results indicate there are synergistic and antagonistic polygenic epistasis in MDD and its symptoms, increasing our understanding of the polygenic etiology underlying MDD.

DATA

Major Depressive Disorder (MDD) and its symptoms in UKBiobank. MDD in UKBiobank is defined by DSM-V criteria[5] using its worst-episode and current symptoms collected through the Online Mental Health Questionnaire (MHQ). For analyses of individual symptoms we only extract worst-episode symptoms collected through the CIDI-SF.



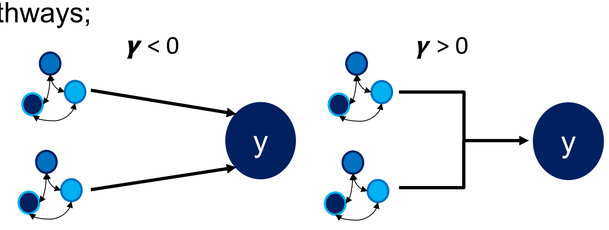
METHODS

UKBiobank dataset of individuals' genotypes and phenotypes is split into 10 sets of train-test pairs. This allows for **10-fold cross validation.** GWAS is performed on each training set to estimate individual variant effect sizes. **Polygenic Risk Scores (PRS)** are constructed using GWAS summary statistics per chromosome in the training sets and genotypes on the test sets[6]. CE is then performed through testing for interaction effects between PRS from a) all even-chromosomes and all odd-chromosomes (**Even-Odd**), as shown:

$$H_0 : log(y) \sim covariates + \alpha_e \mathrm{PRS}_e + \alpha_o \mathrm{PRS}_o$$

$$H_1 : log(y) \sim covariates + \alpha_e PRS_e + \alpha_o PRS_o + \boldsymbol{\gamma}_{eo} PRS_e * PRS_o$$

where a positive interaction effect $\boldsymbol{\gamma}$ implies synergistic pathways, while a negative $\boldsymbol{\gamma}$ implies antagonistic pathways;



and b) across PRS from all chromosome pairs in a **joint F-test.** To test the distribution of interaction effects genome-wide, we performed **100 random splits** of the genome with 11 chromosomes per partition, and obtained a distribution of CE γ across all 100 splits.

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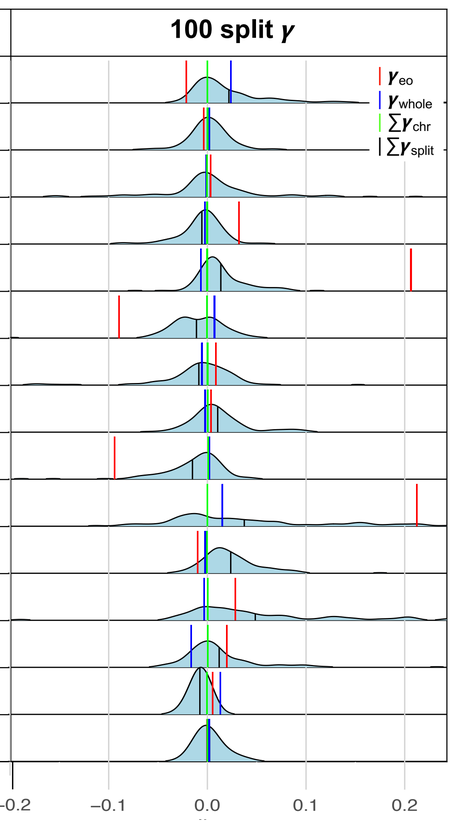
RESULTS

Significant Even-Odd CE in MDD in UKBiobank (γ_{eo} = -2.1E-02 P=3.0E-02). Joint F-test across all chromosome-specific PRS gives consistent findings with an increase in power ($\sum\gamma_{chr}$ **= -4.01E-05, P= 1.1E-11**). Replication analysis using GWAS summary statistics from external cohorts to construct PRS in UKBiobank show consistent results, validating significant CE in MDD. However, $\sum\gamma_{chr}$ are inconsistent between cohorts.

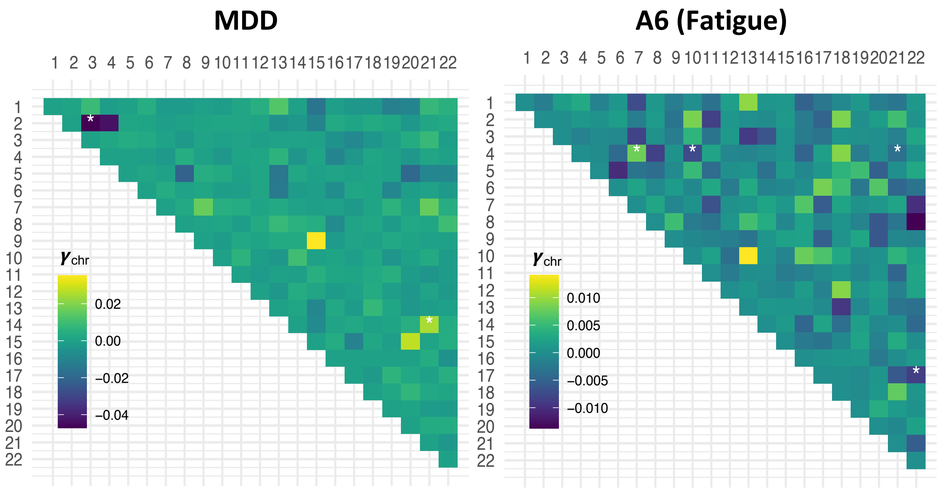
	$\sum\gamma_{chr}$	$P_{F\text{-}test}$
UKBiobank	-4.0E-05	1.1E-11
iPSYCH	5.6E-04	1.8E-15
PGC29	6.1E-05	1.3E-02
23andMe	-1.4E-04	5.7E-49

Even-Odd CE γ and per-chromosome PRS CE $\sum\gamma_{chr}$ estimates insufficiently represent the complexity of interactions effects in MDD. To capture this complexity more accurately, we **performed CE on 100 random genome splits**. Each random genome split resulted in a γ estimate; we show the distribution of γ in the plot below for MDD and all its worst-episode symptoms. In addition, we performed a self-PRS interaction test, testing for interaction between the whole-genome PRS from MDD with itself (γ_{whole} = 2.4E-02, P= 9.0E-07). This reduces power, and γ_{whole} is not always representative of the distributions of γ obtained from the 100 random splits. However, they capture the median γ better than the Even-Odd test γ_{eo}. This is true for MDD and all its worst-episode symptoms, as shown in the figure below.

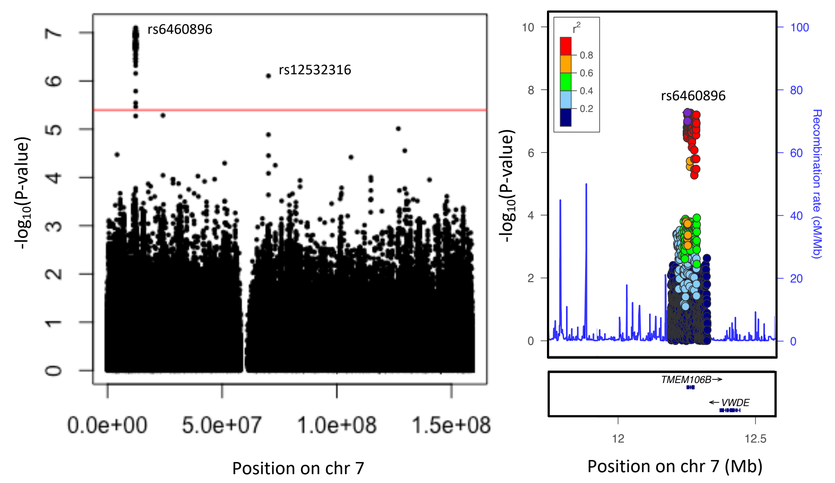
	P_{eo}	$P_{F\text{-}test}$	P_{whole}	100 split γ
MDD	3.0e-02	1.1E-11	8.9E-07	
A9	8.1E-01	4.2E-06	7.7E-01	
A8	6.8E-01	7.0E-11	9.0E-01	
A7	6.7e-02	2.8E-06	6.3E-01	
A6	2.8e-02	6.2E-07	6.2E-01	
A4c	1.6E-01	8.8E-03	3.2E-01	
A4b	6.6E-01	2.1E-04	4.1E-01	
A4a	7.4E-01	2.0E-02	7.3E-01	
A4	7.0e-02	5.1E-07	6.8E-01	
A3c	1.1e-02	2.2E-06	4.6E-01	
A3b	1.9e-01	6.7E-04	5.4E-01	
A3a	1.7E-01	5.1E-08	8.4E-01	
A3	6.3e-02	8.1E-04	2.9E-02	
A2	5.3E-01	2.5E-08	4.4E-04	
A1	9.8E-02	1.6E-14	6.1E-01	



2 Significant γ's between chromosome pairs in the joint F-test on chromosome specific PRS at FDR 10% for MDD: chr2-chr3 (γ_{chr} = -4.7E-02, P=5.9E-04) and chr14-chr21 (γ_{chr} = 2.4E-02, P=5.4E-04). The same level of resolution is obtained for symptoms that have significant joint F-test CE, for example: A6 (fatigue) ($\sum\gamma_{chr}$ = -1.7E-04, P= 6.2E-07) shows four significantly interacting chromosome pairs at FDR 10%. This includes chr4-chr7(γ_{chr} =8.0E-03, P=1.6E-03), chr4-chr10 (γ_{chr} =-7.5E-03, P=1.4E-04), chr4-chr21 (γ_{chr} =-3.5E-03, P=1.2E-03) and chr17-chr22 (γ_{chr} =-8.6E-03, P=6.2E-04).

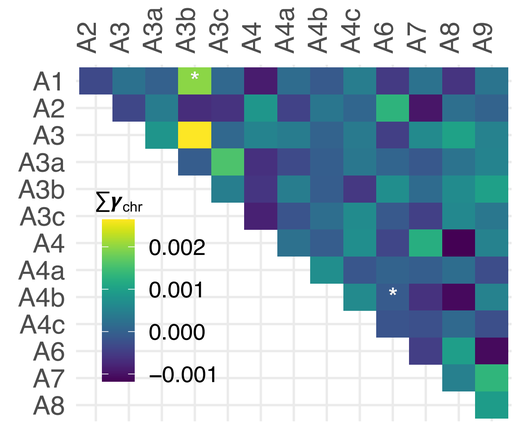


Further resolution of CE latent pathways can be obtained through SNP-PRS interactions on significant chromosome pairs from joint F-test. For example, for the chr4-chr7 interaction in A6 (fatigue), SNP-PRS interaction test between PRS trained on chr4 and SNPs on chr7 shows two hits on chr7 at chr-wide significance: rs6460896 (P = 1.0E-07) and rs12532316 (P = 7.9E-07). Notably, the former is within the *TMEM106B* gene, previously found in MDD GWAS.[2,7,8] This indicates that interacting pathways leading to A6 (fatigue) may be etiologically integral to MDD.



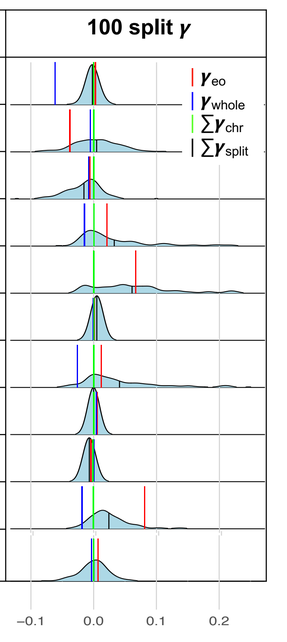
Significant CE between symptom pairs in their effects on MDD: A1-A3b ($\sum\gamma_{chr}$=2.0E-03,P = 1.1E-03), and A4b-A6 ($\sum\gamma_{chr}$=-9.6E-05, P = 1.8E-03).

When jointly fitting these chromosome-PRS against each other for predicting MDD, demonstrating that symptom pathways may interact in their effect on MDD. Interaction of symptoms may help delineate subtypes of MDD.



Coordinated Epistasis detected in clinically defined MDD subtypes, however not in neuroticism score, smoking and addiction. Though power for Even-Odd test, F-test and self-PRS are varying, MDD subtypes (peripartum, non-peripartum, melancholic, non-melancholic and early-onset) all show significant CE, demonstrating interactions between pathways leading to MDD subtypes. Lack of interactions in other traits show that CE can be used to distinguish between different architectures, traits or diseases.

	P_{eo}	$P_{F\text{-}test}$	P_{whole}	100 split γ
T2D	2.7E-02	6.0E-01	1.7E-69	
Peripartum	1.8E-01	6.7E-04	7.2E-01	
Nonperipartum	6.2E-01	6.0E-04	1.2E-01	
Nonmelancholic	2.1E-02	1.4E-13	1.4E-04	
Nonearlyonset	6.7E-02	1.1E-02	9.9E-01	
Neuroticismscore	8.7E-01	3.8E-01	8.1E-01	
Melancholic	3.3E-01	2.5E-09	1.3E-04	
Eversmoked	5.6E-03	6.0E-01	3.6E-02	
Educationage	3.5E-01	6.0E-01	9.6E-01	
Earlyonset	8.1E-02	2.2E-09	1.3E-04	
Addicted	6.8E-01	2.0E-01	4.1E-01	



DISCUSSION

We show, for the first time using an agnostic statistical framework, that there are interacting pathways in MDD and its worst-episode symptoms. Pathways leading to symptoms interact with each other when conferring risk to MDD. Further, we show that the CE framework narrows down the search space for locus level interactions, through initial detection of chr-pair interactions. Our locus-level findings give further insight into the underlying biology of these genome-wide CE interactions.

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