PSYCHIATRY GENETICS

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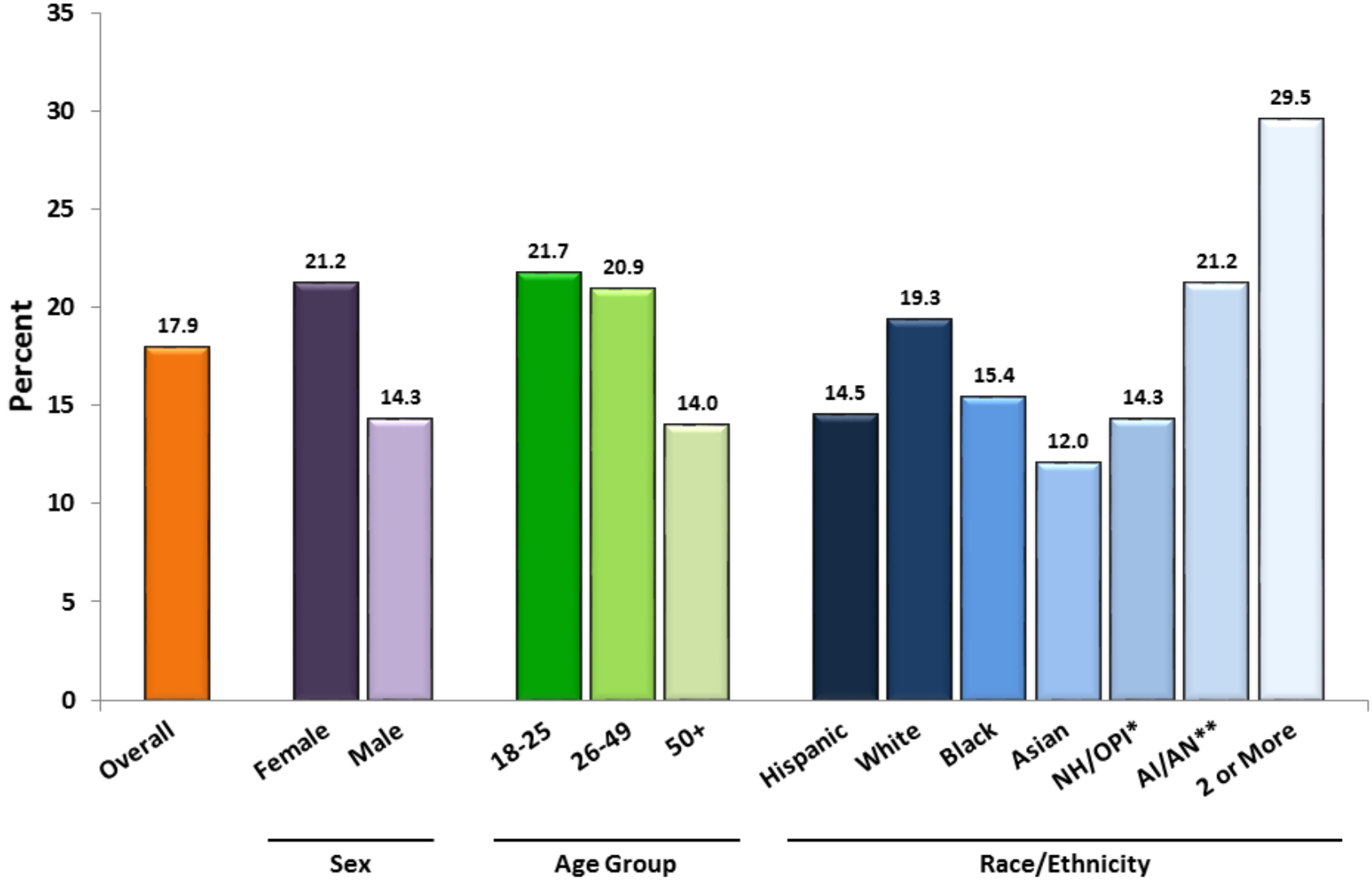
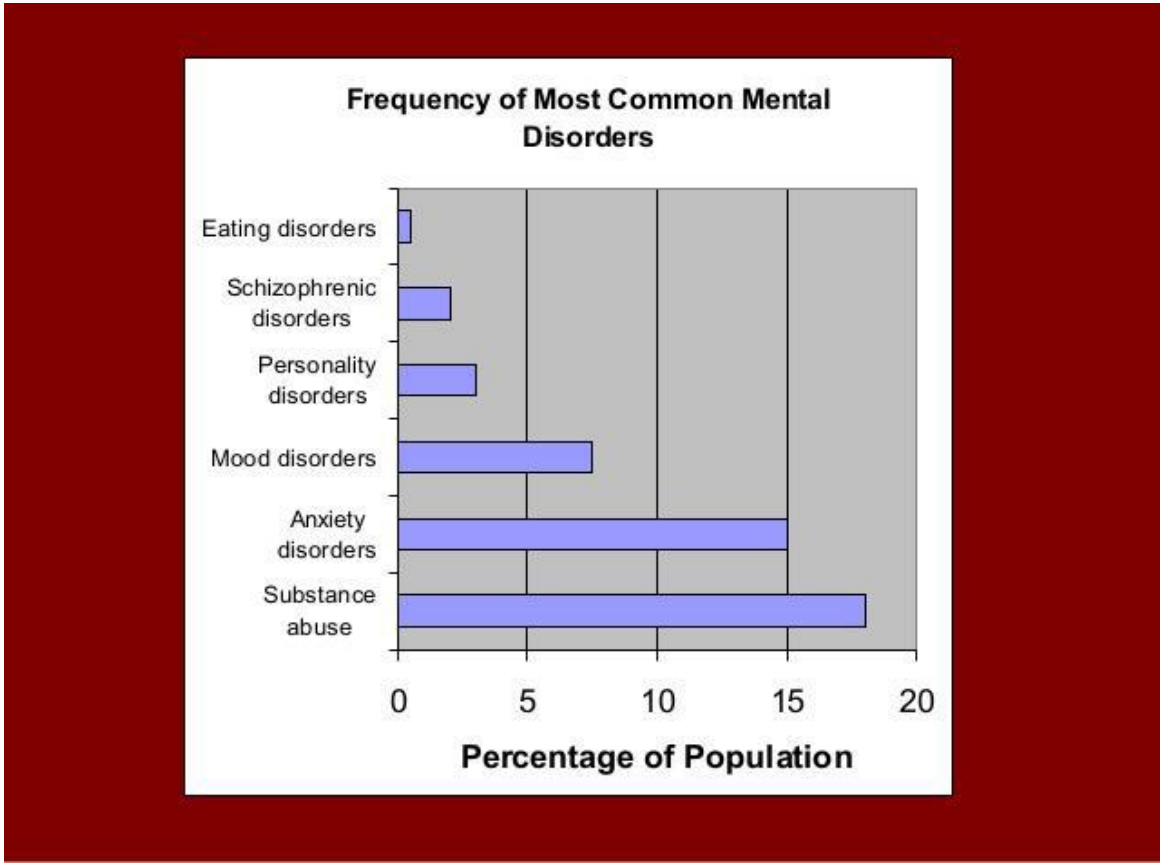
Prevalence of Any Mental Illness Among U.S. Adults (2015)



Data courtesy of SAMHSA

*NH/OPI = Native Hawaiian/Other Pacific Islander
**AI/AN = American Indian/Alaska Native


Frequency of Most Common Mental Disorders
Eating disorders
Schizophrenic disorders
Personality disorders
Mood disorders
Anxiety disorders
Substance abuse
0
5
10
15
20
Percentage of Population

Genetics and cerebral structure

- Netrin 1 receptor gene DCC at 18q21.2
- Axon guidance (white matter)
- Midline commissure tracts
- Role in early organization of neuronal circuits
- Maturation of mesolimbic DOPAminergic connections to the prefrontal cortex during adolescence
- Preferential expression in first fetal trimester
- NOX4 (NADPH Oxidase 4)
- Superoxide production
- Neural stem cell growth

Genes and cerebral structure

- DRD2 gene has been linked to differences in structural connectivity between the basal ganglia structure with the frontal cortices.
- Particularly, anterior cingulate cortex, frontal cortex and cortex brain regions.
- DRD2 is also associated with mood modulation and emotion processing
- Dopamine 2 receptor
- RBFOZ1 (RNA Binding Fox-1 Homolog 1) at 16p13.3
- NMDA receptor 1 and voltage-gated calcium channels

Genes and cerebral structure

- CELF4 gene at 18q12.2 plays a key role in coordinating the synaptic function in excitatory neurons with dynamic changes in expression during brain development
- ELAVL2 potentially aids in the regulation of gene expression pathways in human neurodevelopment
- LIN28B regulates cell pluripotency and developmental timing
- Mediates Lethal-7 miRNA in inflammation and immune response

Genetics and cerebral structure

- 7q34 SNP between MRPS33 (mitochondrial ribosomal protein S33) and BRAF
- Promotes BRAF (and MAPK signaling)
- Postsynaptic responses of hippocampal neurons
- Promotes KDM7A (lysine demethylase 7A)
- Central role in nervous system and midbrain development

Genes and cerebral structure

- MEF2C
- Regulation of synaptic function
- VRK2 and RSRC1 also
- TCF4 is involved in the synaptic plasticity and the excitability of prefrontal neurons
- CHD13 and ASTN2 involved with cell adhesion
- DRD and ANNK1

Genetics and cerebral structure

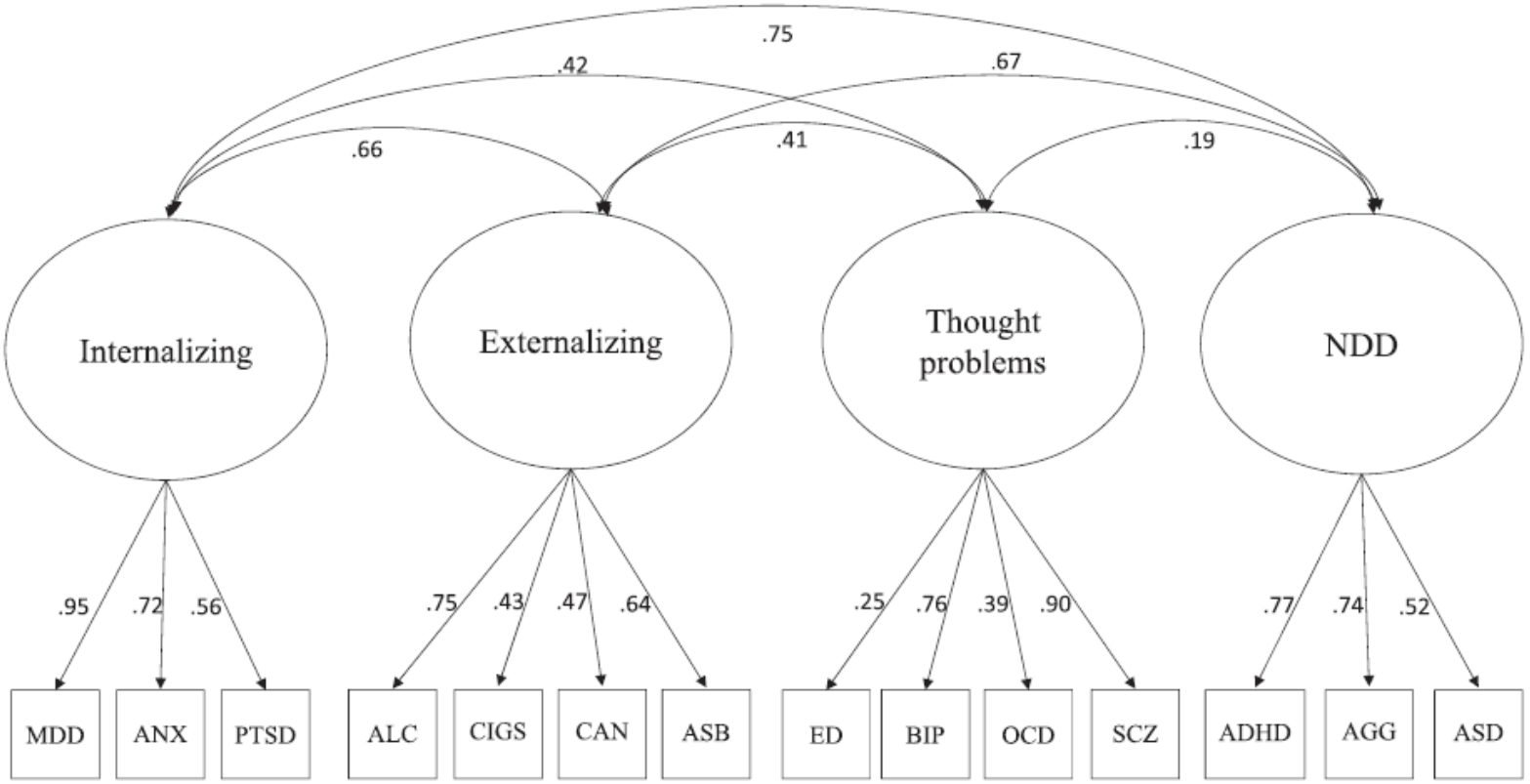
- Pleiotropic genes over-represented in frontal cortex
- Mainly expressed in neurons
- Not expressed in glial cells
- Non-pleiotropic genes enriched in occipital cortex

Table 3 Genetic correlations among the fourteen psychiatric disorders and related traits

	AGG	ADHD	ASD	CIGS	CAN	ALC	ASB	ANX	MDD	PTSD	BIP	OCD	SCZ	ED
AGG	1													
ADHD	0.77	1												
ASD	0.49	0.37	1											
CIGS	0.52	0.41	0.07	1										
CAN	0.81	0.42	0.03	0.12	1									
ALC	0.12	0.41	0.02	0.33	0.12	1								
ASB	0.24	0.52	0.21	0.20	0.41	0.59	1							
ANX	0.67	0.30	0.28	0.09	0.35	0.54	0.42	1						
MDD	0.46	0.56	0.44	0.16	0.23	0.44	0.55	0.89	1					
PTSD	0.40	0.52	0.24	0.44	0.41	0.33	0.36	0.09	0.49	1				
BIP	0.11	0.12	0.13	0.20	0.34	0.24	0.11	0.18	0.33	0.07	1			
OCD	0.38	–0.16	0.12	–0.05	0.25	–0.27	–0.05	0.30	0.30	0.42	0.32	1		
SCZ	0.04	0.12	0.21	0.11	0.07	0.09	0.09	0.26	0.37	0.18	0.68	0.33	1	
ED	–0.20	–0.26	–0.08	–0.12	0.04	–0.10	–0.10	0.09	0.20	–0.02	0.18	0.50	0.23	1

AGG – aggression, ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, CIGS – number of cigarettes smoked per day, CAN – cannabis dependence, ALC – alcohol dependence, ASB – antisocial behavior, ANX – anxiety disorders, MDD – major depressive disorder, PTSD – post-traumatic stress disorders, BIP – bipolar disorder, OCD – obsessive-compulsive disorder, SCZ – schizophrenia, ED – eating disorders. Borders denote correlations among disorders within each higher-order dimension.

Waldman, ID, Poore, HE, Luningham, JM, Yang, J, Testing structural models of psychopathology at the genomic level, World Psychiatry 2020;19:350–359



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	EXT	INT	TP	NDD
Antisocial behavior	.64 (.14)***			
Tobacco use	.43 (.09)***			
Alcohol dependence	.75 (.13)***			
Cannabis dependence	.47 (.16)**			
PTSD		.56 (.09)***		
MDD		.95 (.10)***		
Anxiety disorders		.72 (.09)***		
Eating disorders			.25 (.05)***	
Schizophrenia			.90 (.05)***	
Bipolar disorder			.76 (.04)***	
OCD			.39 (.05)***	
ASD				.52 (.05)***
Aggression				.74 (.12)***
ADHD				.77 (.06)***
EXT	–			
INT	.66 (.14)***	–		
TP	.41 (.08)***	.42 (.05)***	–	
NDD	.67 (.15)***	.75 (.09)***	.19 (.04)***	–

ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, MDD – major depressive disorder, PTSD – post-traumatic stress disorders, OCD – obsessive-compulsive disorder, EXT – externalizing factor, INT – internalizing factor, TP – thought problems factor, NDD – neurodevelopmental disorders factor

*p<0.05, **p<0.01, ***p< 0.001

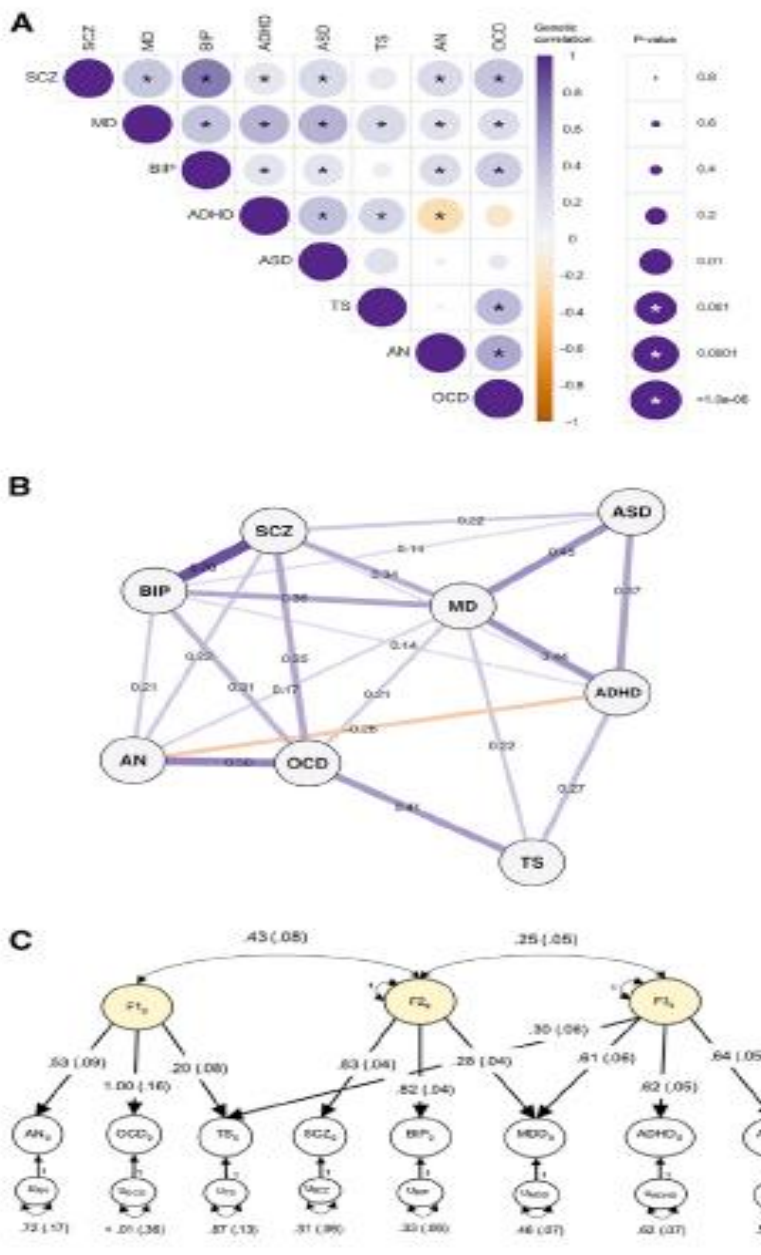
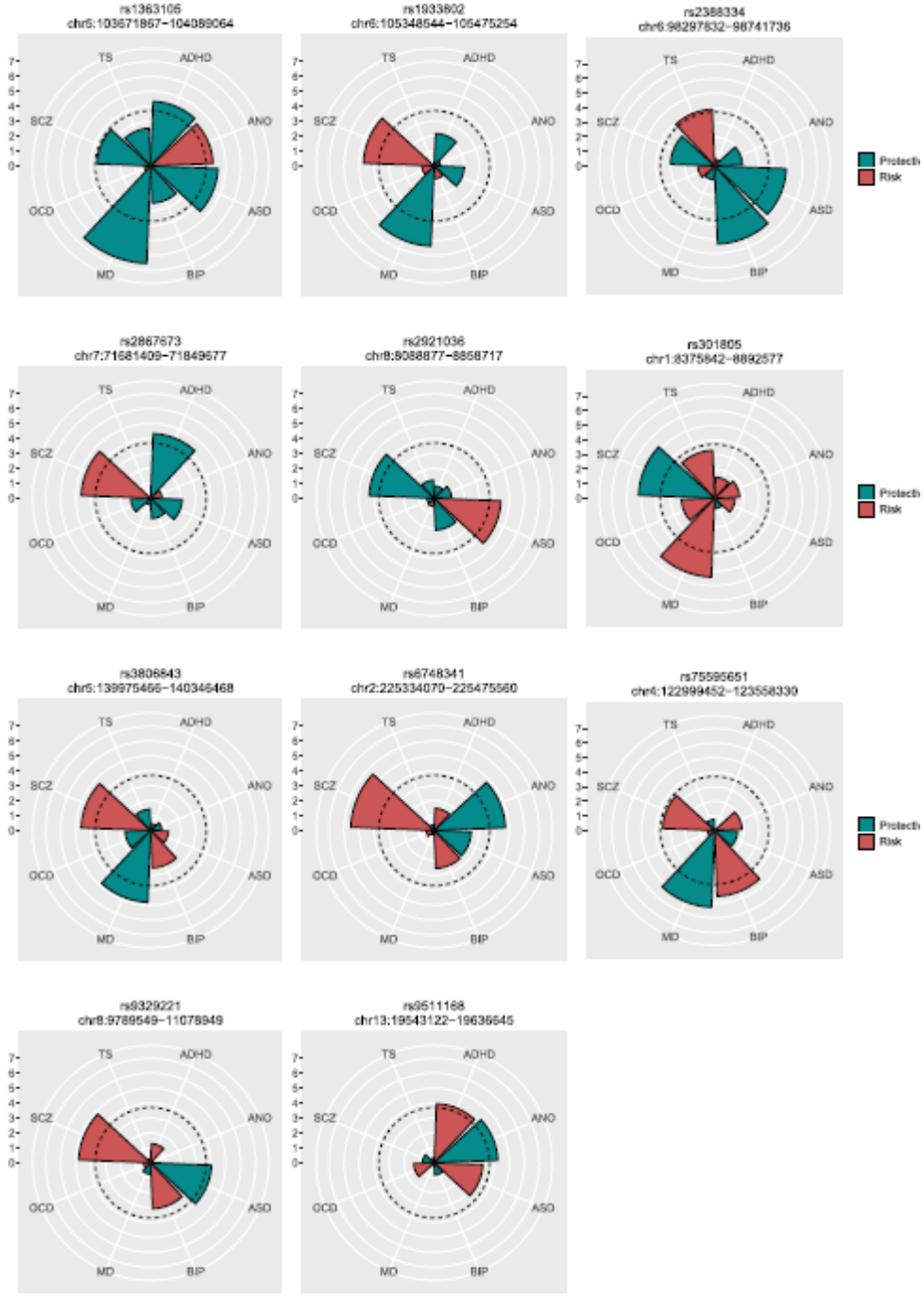
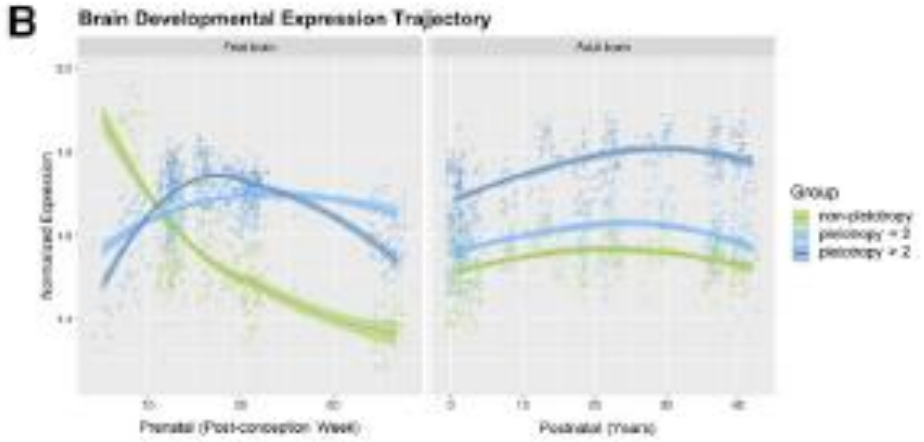


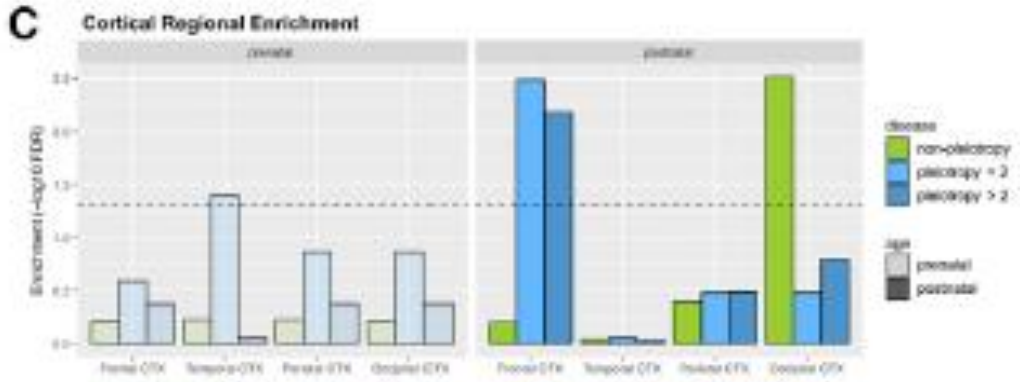
Figure 1. Genetic Relationships between Eight Psychiatric Disorders

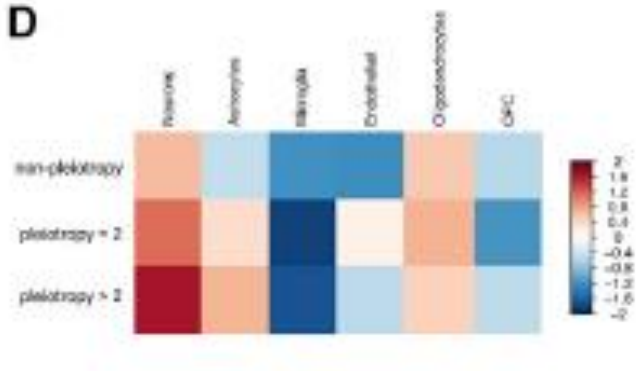
Cross-Disorder Group of the Psychiatric Genomics Consortium, Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders, Cell 179 (2019), 1469–1482 Figure 1 https://doi.org/10.1016/j.cell.2019.11.020



Cross-Disorder Group of the Psychiatric Genomics Consortium, Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms
across Eight Psychiatric Disorders, Cell 179 (2019), 1469–1482 Figure 4
https://doi.org/10.1016/j.cell.2019.11.020







Cross-Disorder Group of the Psychiatric
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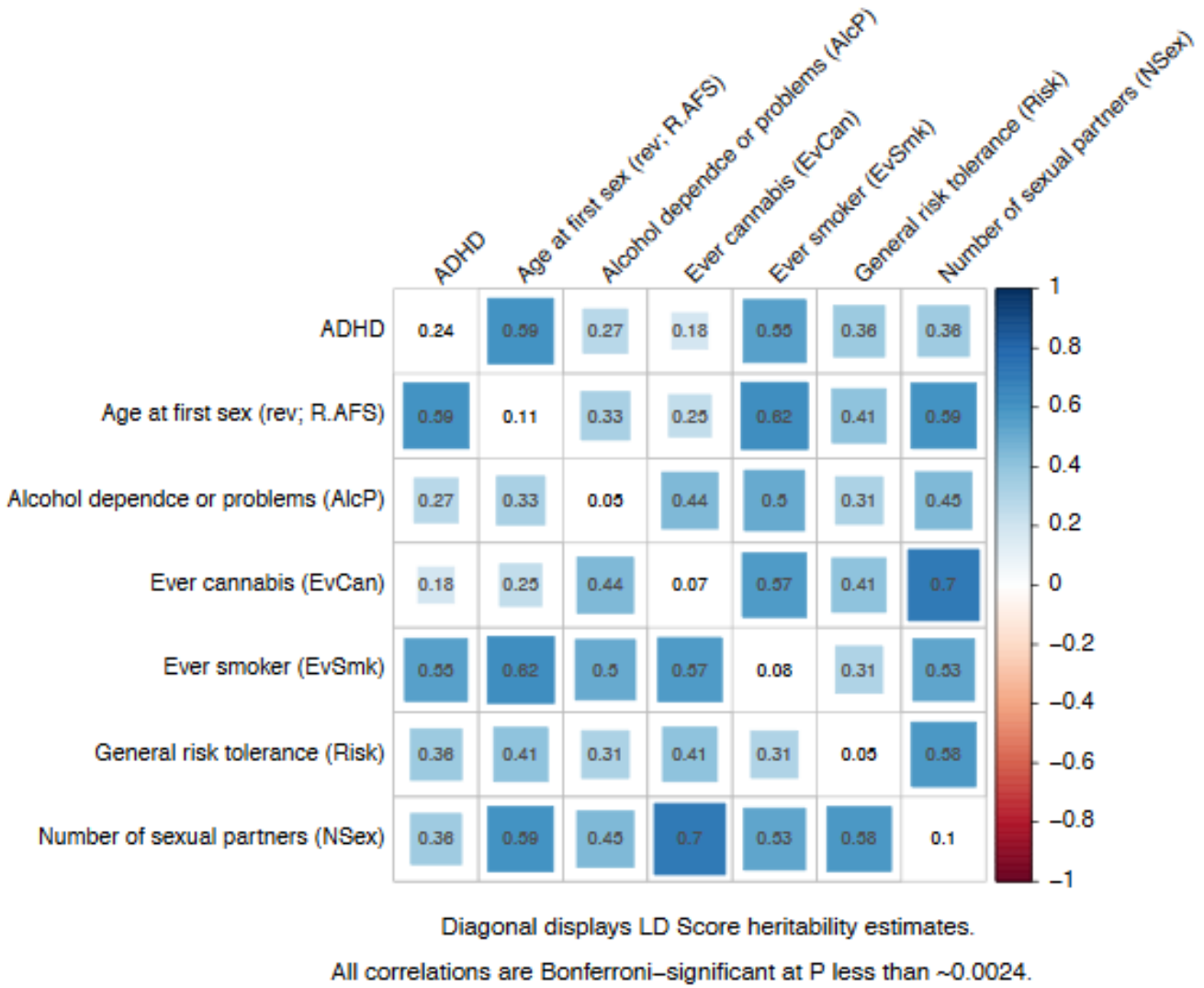
across Eight Psychiatric Disorders, Cell 179 (2019), 1469–1482
Figure 5
https://doi.org/10.1016/j.cell.2019.11.020

a **LD Score regression genetic correlations and heritabilities.**



Diagonal displays LD Score heritability estimates.

All correlations are Bonferroni–significant at P less than ~0.0024.

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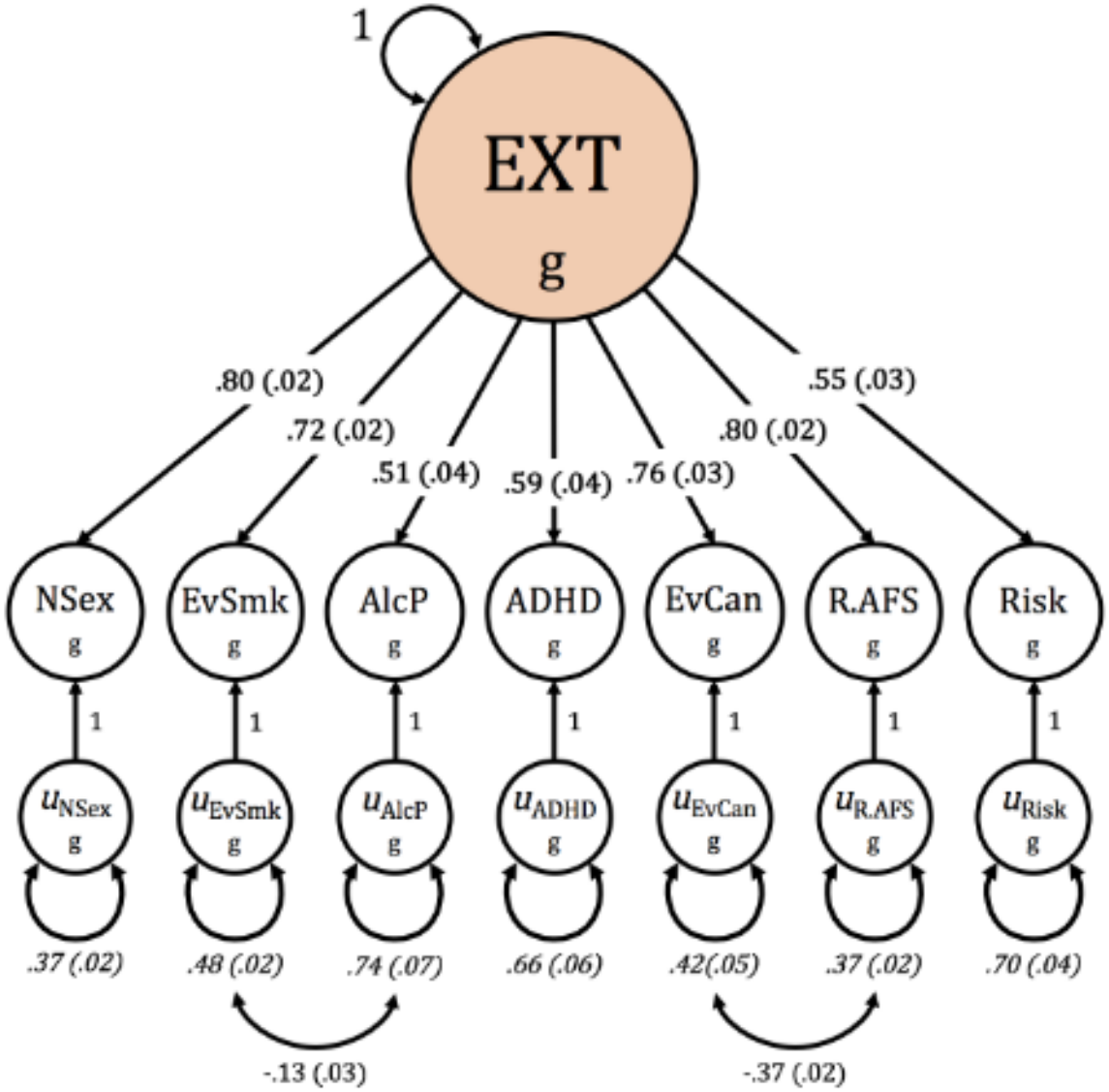
b



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Relationships

- Thought problems factor
- Eating disorders and Obsessive compulsive disorder (OCD) as well as bipolar disorder (BP) and schizophrenia (SCZ) load together
- Neurodevelopmental disorders (NDD) factor
- Autism spectrum disorder (ASD) and Attention deficit hyperactivity disorder (ADHD) load together
- Internalizing disorders
- Major depression disorder (MDD)
- Does not load with BP and SCZ.

Relationships

- Significant genetic correlations for MDD with neuroticism, anorexia nervosa (AN), ADHD, AS, SCZ, BP, OCD, and Tourette's.
- Unidirectional effect of neuroticism on depression
- Early onset depression associated with genetic risk for ADHD and neurodevelopmental phenotypes (ASD)

Role of genes

- SNP within MRSA opposing effects on AS and SCZ
- SNP within KIA1109 opposing effects on MDD and BPD
- SORCS3 cross-disorder locus in fetal development

Role of genes

- RBFOZ1
- Not associated with AN
- Implicated in aggressive behaviors
- NOX4
- Associated with SCA, BPD, MDD, AS, AN

Role of genes

- Neurodevelopmental disorders (NDD)
- Deletions in the region surrounding CELF4 (18q.12.2) are associated with ASD and developmental and behavioral disorders.
- ELAVL2 potentially aids in the regulation of gene expression pathways in human neurodevelopment
- LIN28B associated with earlier age at menarche as well as with smoking

Role of genes

- MEF2C
- Associated with SCZ and MDD
- VRK2 and RSRC1 also
- CHD13 and ASTN2
- DRD and ANNK1 as well
- ADHD associated with MDD in adolescence

Role of genes

- OCD and compulsion symptoms:
- KIT, GRID2, WDR7, and ADCK1
- BD and SCZ associations appear to be independent at 3 of the 8 shared loci:
- NCAN, TRANK1 and 7q22.3:105
- No genome-wide significant BD locus overlapped with those identified for MDD
- BD1 and SCZ
- BD2 and MDD