Using genome-wide approaches to understand the genetic etiology of suicide-related behaviors and substance use disorders

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Why genetics?

• Scientific impact: a better understanding of genetic risk, in conjunction with socio-environmental factors → identification of at-risk groups

• Societal impact: a better understanding of genetic and biological mechanisms → reduce stigma around suicide
Background

- Suicidal thoughts and behaviors are transdiagnostic, heterogeneous, and partly heritable
- Linear spectrum of liability?
Background

• Suicidal thoughts and behaviors are transdiagnostic, heterogeneous, and partly heritable

• Linear spectrum of liability?

“The genetic and environmental etiologies of suicide attempt and death are partially overlapping, exhibit modest sex differences, and shift across the life course”
–Edwards et al., 2021

“While suicide attempt and suicide death are substantially genetically correlated, a model that proposes that they reflect quantitatively different degrees of severity on the same continuum of liability can be ruled out”
–Kendler et al., 2020

Kendler et al., 2020. American Journal of Psychiatry
Outline of today’s talk

1. How does genetic predisposition for depression, risk-taking, and cognitive function relate to different suicidal thoughts and behaviors?
2. What are the genetic relationships between suicidal thoughts and behaviors themselves, and substance use disorders?
3. Current directions:
   - Cross-disorder analysis of problematic alcohol use, depression, and suicide attempt
   - Multi-PRS models predicting detailed suicide-related phenotypes

Overarching goal: use genome-wide data to better understand genetic etiology of suicide.
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How do depression, risk-taking, and cognitive function relate to suicidal thoughts and behaviors?
Methods: target sample

• We tested whether polygenic scores for depression, risk-taking, and cognitive performance are associated with suicidal thoughts and behaviors and NSSI in a high-risk sample \((N = 10,843)\)

• **Target sample:** Collaborative Study on the Genetics of Alcoholism (COGA)
  - Case families ascertained for high prevalence of alcohol use disorders
  - Some families have high prevalence of other psychiatric disorders as well

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>African-ancestry N reporting ‘yes’ (% of analytic N)</th>
<th>European-ancestry N reporting ‘yes’ (% of analytic N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation</td>
<td>880 (32.8%)</td>
<td>2,990 (41.5%)</td>
</tr>
<tr>
<td>Persistent ideation (7 consecutive days, in those reporting any ideation)</td>
<td>249 (28.3%)</td>
<td>943 (31.6%)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>300 (11.2%)</td>
<td>776 (10.8%)</td>
</tr>
<tr>
<td>Non-suicidal self-injury</td>
<td>149 (6.0%)</td>
<td>548 (8.7%)</td>
</tr>
</tbody>
</table>
Methods: GWAS for creating polygenic scores

<table>
<thead>
<tr>
<th>GWAS Phenotype (EA)</th>
<th>GWAS Phenotype (AA)</th>
<th>Sample Size (EA)</th>
<th>Sample Size (AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-harm (UK Biobank)</td>
<td>NA</td>
<td>(N_{\text{cases}} = 5,099)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N_{\text{controls}} = 112,634)</td>
<td></td>
</tr>
<tr>
<td>Depression meta-analysis (Howard et al., 2019)</td>
<td>Generalized Anxiety Scores (Levey et al., 2020)</td>
<td>(N_{\text{cases}} = 170,756)</td>
<td>(N = 24,448)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N_{\text{controls}} = 329,443)</td>
<td></td>
</tr>
<tr>
<td>Risk-taking behaviors (Linner et al., 2019)</td>
<td>Self-reported risk taker (Pan UKB)</td>
<td>(N = 315,894)</td>
<td>(N = 6,101)</td>
</tr>
<tr>
<td>Cognitive performance meta-analysis (Lee et al., 2018)</td>
<td>Fluid intelligence sum score (Pan UKB)</td>
<td>(N = 257,828)</td>
<td>(N = 3,280)</td>
</tr>
</tbody>
</table>
Methods: Polygenic score creation

• We used PRS-CS (Ge et al. 2019) and PRS-CSx (‘meta’ option) to create polygenic scores (PGS) in the COGA sample
• Logistic mixed effect regression models controlled for sex, age, array type, AUD case or control family background, and 10 genetic ancestry principal components as fixed effects, and for family ID as a random intercept
<table>
<thead>
<tr>
<th>Outcome</th>
<th>PGS</th>
<th>Beta</th>
<th>SE</th>
<th>FDR q value</th>
<th>$R^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation</td>
<td>Self-harm</td>
<td>0.097</td>
<td>0.027</td>
<td>5.15E−04*</td>
<td>0.24</td>
</tr>
<tr>
<td>Persistent ideation</td>
<td>Self-harm</td>
<td>0.128</td>
<td>0.038</td>
<td>0.001*</td>
<td>0.39</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>Self-harm</td>
<td>0.178</td>
<td>0.041</td>
<td>5.29E−05*</td>
<td>0.68</td>
</tr>
<tr>
<td>NSSI</td>
<td>Self-harm</td>
<td>0.162</td>
<td>0.051</td>
<td>0.002*</td>
<td>0.50</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Depression</td>
<td>0.278</td>
<td>0.028</td>
<td>3.41E−22*</td>
<td>1.96</td>
</tr>
<tr>
<td>Persistent ideation</td>
<td>Depression</td>
<td>0.264</td>
<td>0.040</td>
<td>2.18E−10*</td>
<td>1.73</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>Depression</td>
<td>0.339</td>
<td>0.043</td>
<td>4.38E−14*</td>
<td>2.49</td>
</tr>
<tr>
<td>NSSI</td>
<td>Depression</td>
<td>0.167</td>
<td>0.054</td>
<td>0.002*</td>
<td>0.58</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Risky behaviors</td>
<td>0.124</td>
<td>0.037</td>
<td>3.00E−05*</td>
<td>0.40</td>
</tr>
<tr>
<td>Persistent ideation</td>
<td>Risky behaviors</td>
<td>0.152</td>
<td>0.042</td>
<td>1.01E−04*</td>
<td>0.62</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>Risky behaviors</td>
<td>0.152</td>
<td>0.052</td>
<td>8.01E−04*</td>
<td>0.30</td>
</tr>
<tr>
<td>NSSI</td>
<td>Risky behaviors</td>
<td>0.152</td>
<td>0.052</td>
<td>8.01E−04*</td>
<td>0.30</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Cognitive performance</td>
<td>0.027</td>
<td>0.027</td>
<td>0.360</td>
<td>0.02</td>
</tr>
<tr>
<td>Persistent ideation</td>
<td>Cognitive performance</td>
<td>0.026</td>
<td>0.039</td>
<td>0.545</td>
<td>0.01</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>Cognitive performance</td>
<td>−0.159</td>
<td>0.042</td>
<td>3.76E−04*</td>
<td>0.57</td>
</tr>
<tr>
<td>NSSI</td>
<td>Cognitive performance</td>
<td>0.006</td>
<td>0.052</td>
<td>0.911</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Not significant when controlling for DSM-IV alcohol dependence and abuse symptom count!

Starred rows indicate significance after multiple testing corrections (FDR < 0.05). COGA, Collaborative Study on the Genetics of Alcoholism; NSSI, nonsuicidal self-injury; PGS, polygenic score.
Summary & limitations

• Genetic liability for depression broadly associated with suicidal thoughts & behaviors

• Genetic predisposition for decreased cognitive performance only associated with increased risk of suicide attempts

• No significant PGS associations in the African-ancestry subset of COGA, most likely due to smaller discovery GWAS sample sizes – need larger discovery GWAS in non-European ancestry populations

• PGS not predictive on an individual level
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Background

• It is well established that SUDs load onto common factor
• Genetics of suicide-related behaviors less well-characterized

Hatoum et al. 2021. Neuropsychopharmacology
Strawbridge et al. 2019 EBioMedicine
## Methods

- LD score regression
  - Genetic correlations
- Genomic structural equation modeling (gSEM)
  - Genetic factor structure

### Phenotype Table

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>PMID</th>
<th>Sample Size</th>
<th>SNP-heritability (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAU</td>
<td>32451486</td>
<td>N = 435,563</td>
<td>0.07 (0.004)</td>
</tr>
<tr>
<td>CUD</td>
<td>33096046</td>
<td>N = 358,534; N_cases = 14,808</td>
<td>0.12 (0.011)</td>
</tr>
<tr>
<td>OUD</td>
<td>32492095</td>
<td>N = 82,707; N_cases = 10,544</td>
<td>0.11 (0.018)</td>
</tr>
<tr>
<td>FTND</td>
<td>33144568</td>
<td>N = 46,213</td>
<td>0.09 (0.012)</td>
</tr>
<tr>
<td>Death by suicide</td>
<td>32998551</td>
<td>N = 18,223; N_cases = 3,413</td>
<td>0.25 (0.04)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>30116032</td>
<td>N = 50,264; N_cases = 6,024</td>
<td>0.05 (0.009)</td>
</tr>
<tr>
<td>Ever self-harmed</td>
<td>PMID not available</td>
<td>N = 117,733; N_cases = 5,099</td>
<td>0.05 (0.028)</td>
</tr>
<tr>
<td>Depression</td>
<td>30718901</td>
<td>N = 500,199; N_cases = 170,756</td>
<td>0.09 (0.003)</td>
</tr>
<tr>
<td>Risk tolerance</td>
<td>30643258</td>
<td>N = 466,571</td>
<td>0.05 (0.001)</td>
</tr>
</tbody>
</table>

Bulik-Sullivan et al., 2015. *Nature Genetics*
Grotzinger et al., 2019. *Nature Human Behavior*
Genetic correlations

All significant with FDR < 5%

Strong positive correlations among SUDs
Genetic correlations

All significant with FDR < 5%

Strong positive correlations among SUDs

Strong positive correlations among suicide-related behaviors
Genetic correlations

All significant with FDR < 5%

Strong positive correlations among SUDs

Strong positive correlations among suicide-related behaviors

Strong positive correlations among SUDs and suicide-related behaviors + comparable to correlations among depression and suicide-related behaviors
Common SUD and specific suicide-related behaviors model with covariates

**Depression** was most strongly associated with ever self-harmed and least strongly associated with suicide death. ($\chi^2_{\text{diff}}(2) = 13.28, p = 0.001$)

Associations between **risk tolerance** and suicide-related behaviors are somewhat less variable. ($\chi^2_{\text{diff}}(2) = 5.17, p = .08$)

Model fit statistics:
$X^2 = 11.16, \text{df} = 11, p_{X^2} = 0.43$
AIC = 79.16
CFI = 0.9999
SRMR = 0.0464

Even accounting for depression and risk tolerance, suicide-related behaviors are significantly correlated with **SUD factor**
Summary & limitations

• We found significant correlations between SUDs and suicide-related behaviors, accounting for depression and risk tolerance.

• Interestingly, correlations b/w SUDs and suicide phenotypes rival correlations between depression and suicide.

• Limited data on death by suicide and non-suicidal self-injury.

• Genetic correlations, but no evidence of causality; larger studies (or alternative designs) needed.
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Zooming in on alcohol use, depression, and suicide attempt

in prep; Sarah Colbert will be presenting at RSA annual meeting in June 2022
In follow-up models,
• self-harm ideation, depression, and suicide attempt PRS remained associated with suicidal ideation in multi-PRS model
• self-harm ideation, depression, suicide attempt, and suicide death PRS remained associated with suicide attempt

*manuscript in prep*
Summary

• Suicidal thoughts and behaviors are genetically complex

• Embracing that complexity will lead to better research and better outcomes

• By incorporating this complexity into undergraduate education, we aim to reduce stigma
Thanks

• My AFSP mentor, Dr. Arpana Agrawal
• Collaborators: Sarah Colbert, Alexander Hatoum, Anna Docherty, Hilary Coon, Elliot Nelson, COGA collaborators, PGC-SUD working group
• All the generous participants in these studies
• Past and current funding support from AFSP, BBRF, NIAAA, NIDA, and NIMH

Washington University School of Medicine in St. Louis

PGC
Psychiatric Genomics Consortium

American Foundation for Suicide Prevention

Brain and Behavior Research Foundation

NIH
National Institute of Mental Health

NIH
National Institute on Alcohol Abuse and Alcoholism

NIH
National Institute on Drug Abuse