Accounting for Effects of Lifetime, Current, and Community Stressors on Depressive Symptoms in Genetics Studies of Depression

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Introduction

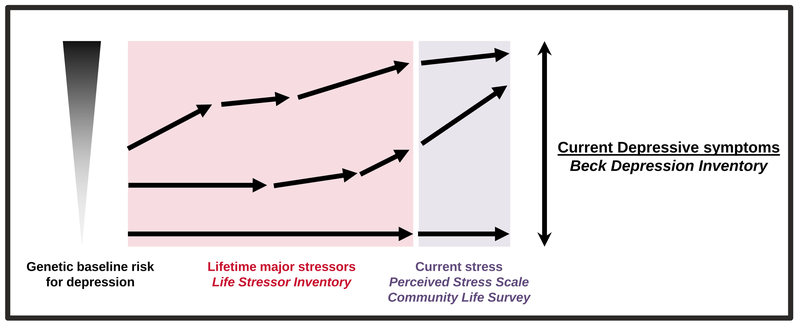
- Depression is a heritable disease, with estimates for h^2 from 8.7% to above 40%, supporting a strong genetic basis but underscoring a complex interaction with a larger proportion of environmental causes. This has led to a stress-diathesis model arguing that environmental impact on depressive symptoms are primarily mediated through induced stress.
- These environmental causes may account for the wide range of heritability estimates or highly variable, difficult to replicate genetic findings. Such environmental stressors are not normally incorporated in most genetic studies of major depression as stress is a multifaceted, complex concept involving, but not limited to, lifetime cumulative stressors, community or culturally specific stressors, and current ongoing stressors. The likely biopsychosocial contributions to depression in humans demand a proper account of such environmental stressors to establish a valid genetic-environmental model for major depression.
- The Old Order Amish and Mennonite (OOA/M) population is a founder population that is an ideal cohort to explore genetic contribution to disease due to relative genetic uniformity and large, well-documented pedigree structures. Another less discussed advantage in studying complex genetic-environmental contributions is that the OOA/M population is also a culture- and community isolate, where some of the environmental stressors maybe be more readily quantified.
- There has been great interest in the search for key markers in genetic predisposition, an effort that is now intensified by continued emergence of massively large phenotype datasets and genome-wide approaches. A limitation in the search for broadly penetrative exposures across the population is lack of ability to examine stressors that are unique to specific cultural groups and communities.
- Here we examined lifetime traumatic events, current state stress, and culturally specific community stressors related to the specific social and religious norms as in the OOA/M, and tested whether these three types of stressors independently contribute to depression, and if so, whether they may impact the heritability estimate of depressive symptoms.

Hypothesis

Major lifetime stressors and current stress environment interact to explain current depressive symptom burden in human populations

Predictions:

1. Longitudinal or lifetime major environmental stressors can quantifiably explain a significant proportion of current depressive symptoms
2. Current environmental stress can quantifiably explain a significant proportion of current depressive symptoms
3. Culturally specific community stress can be measured and reflect and independent contribution of current environment on current depressive symptom burden



Methods

***Subjects*:** Old Order Amish and Mennonites (OOA/M) from Maryland and Pennsylvania with large family pedigrees were recruited as part of the Amish Connectome Project. Subjects included those from families with at least two members having a major DSM-5 disorder, including those with and without diagnoses. Structured Clinical Interview for DSM-IV was completed to verify lifetime and current psychiatric diagnoses.

Stress measures: Current subjective stress level was assessed by the Perceived Stress Scale (PSS); past lifetime traumatic events were accounted by a Lifetime Stressor Inventory (LSI), and finally potential stress from OOA/M specific cultural and religious lifestyle was assess by a Community Life Survey (CLS), a novel 15-item questionnaire developed to evaluate feelings of belonging vs. nonconformity in this community. Examples of questions include "I fit in well with my Plain Church community" and "I feel as though following church and community rules restricts my personal desires and values" with responses given on a 5-point Likert scale from "strongly disagree" to "strongly agree."

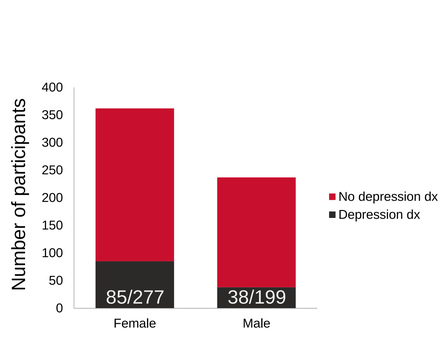
Beck Depression Inventory – Subjects completed the 21-item Beck Depression Inventory questionnaire which rates severity of symptoms over the prior 2 weeks including the date of testing.

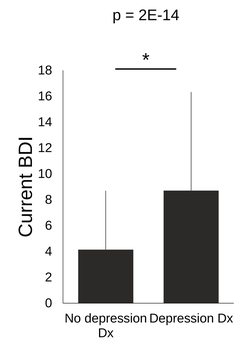
Heritability estimate: The heritability was estimated using the variance components method implemented with SOLAR-Eclipse software (http://www.solar-eclipse-genetics.org). Empiric kinship was generated through quantifying the similarity in the whole-genome among the study participants. SOLAR-Eclipse's heritability calculations are accelerated using the Fast Permutation Heritability Inference (FPHI) approach. Analysis was performed on currently available data from 451 individuals, including patients with mood disorders and their healthy family members. Heritability was calculated for depressive symptoms based on BDI as well as depression diagnosis. Sex and age were used as covariates.

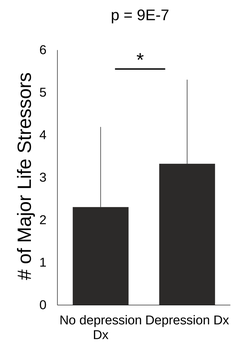
Population sample characteristics & stress measures by diagnosis

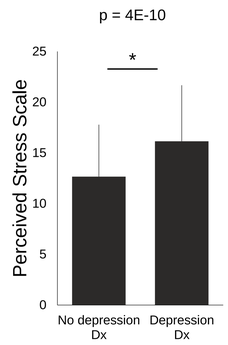
Subject demographic data	
Sex	199 Male, 277 Female
Age	**40.6 ± 18.0 years**
Lifetime diagnosis of depression	123 (25.8%)
BDI > 16	27/476 (5.7%)

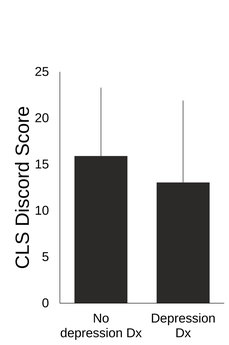
Table (left) summarizes data for number of participants by sex, age, and diagnosis based on SCID, as well as current number of participants with a BDI> 16, a subjective cutoff for current clinical depressive episode. Below graphs summarize demographic data, current BDI, and the three stress measures stratified by diagnosis. There is no significant difference by depression diagnosis in community stress measured by the CLS (p>0.05), but there are significant differences in both current stress and lifetime stress.



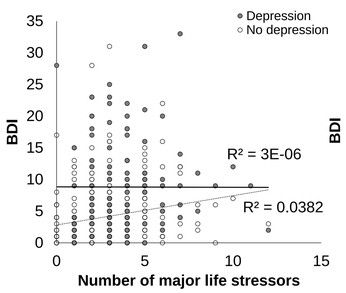


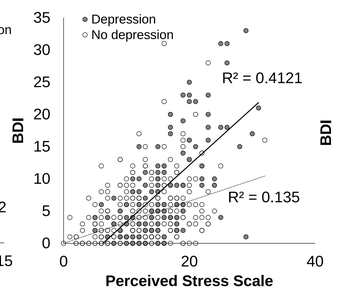


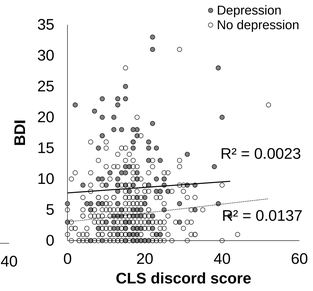




Relationships between stress measures and current depression







Cross-sectional relationships between the three stress measures and current depression symptomatology. There is a significant but weak correlation between number of life stressors and BDI in individuals without a depression diagnosis ($p<0.05$), but not those with a depression diagnosis. Current stress measured by PSS is significantly correlated with BDI in both depression and non-depression individuals, with a significantly stronger relationship in depression (Fisher's r-to-z transformation p = 0.005, z=2.76). For either diagnosis group, there was no significant correlation between community stress measured by CLS and depressive symptoms.

A multiple regression model to explain BDI was performed including each stress measure, sex, and age in both diagnostic groups. In those without a depression diagnosis, partial eta for lifetime stress was 0.14, for PSS was 0.37, for age 0.10 with no other variables significant. For those with a depression diagnosis, partial eta for PSS was 0.67 with no other statistically significant predictor variables.

Heritability of quantitative and categorical depression phenotypes

In this preliminary analysis, heritability for both quantitative and categorical depression were statistically significant. We estimated h^2 of 0.20 ± 0.12 for a categorical diagnosis of major depressive disorder, which is consistent with but on the lower end of SNP- and family-based heritabilities (21-30% to ~40%). We also estimated a heritability for quantitative depression measured by BDI as 0.46 ± 0.11, higher than most depression heritability studies. This supports a role for quantitative depression measures as a phenotype for genetic studies.

Heritability		
	Quantitative Depression (BDI)	Categorical Depression (Diagnosis)
h^2	0.464 ± 0.108	0.201 ± 0.124
p	4.13×10^{-6}	0.042

Conclusions

- Potential OOA/M specific cultural and religious lifestyle stressors did not differ significantly between patients with MDD and non-depressed controls and did not correlate with BDI in either patients with MDD or in the non-MDD control group (all p>0.05).
- Surprisingly, we found that culturally specific community stress measured with a novel questionnaire did not significantly contribute to depressive symptoms in the population.
- In comparison, current stress level as measured by PSS correlated positively with BDI in non-depressed controls as well as depressed subjects (all p<0.01). Number of severe past lifetime stressors also significantly correlated with BDI in non-depressed subjects (p<0.05) but not in those with a depression diagnosis (p>0.05). Together these findings result in a regression model in which lifetime stressors, current stressors and age predict current quantitative depression in those without a depression diagnosis, but only PSS significantly contributes to the model for those with a lifetime depression diagnosis.
- Heritability estimates of depression diagnosis phenotypes as well as BDI in the OOA/M appears consistent with that reported for depression in other populations (e.g. 0.21 to 0.44; Yang et al 2010, Lee et al 2012, Lamers et al 2016). h^2 for quantitative depression was greater than for than diagnosis in this sample, supporting utility as a phenotype for future genetic studies.
- We tested heritability along with three distinct stress measures on depressive symptoms in a unique population isolate. Our results highlight that depression is significantly heritable in this population but environmental contributions in the forms of stressors can also be meaningfully quantified.
- Our findings suggest that accounting for the effects of environmental stressors may increase the precision of heritability estimates of depression and present opportunity for more robust genetic studies.
- This is an ongoing study. We hope to further explore differences between stress-sensitive and stress-independent endophenotypes in depression.

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