



## Sex-stratified gene-by-environment genome-wide interaction study of trauma, posttraumatic-stress, and suicidality

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### ABSTRACT

Epidemiologic studies recognize that trauma and posttraumatic stress are associated with heightened suicidal behavior severity, yet examination of these associations from a genetic perspective is limited. We performed a multivariate gene-by-environment genome-wide interaction study (GEWIS) of suicidality in 123,633 individuals using a covariance matrix based on 26 environments related to traumatic experiences, posttraumatic stress, social support, and socioeconomic status. We discovered five suicidality risk loci, including the male-associated rs2367967 (CWC22), which replicated in an independent cohort. All GEWIS-significant loci exhibited interaction effects where at least 5% of the sample had environmental profiles conferring opposite SNP effects from the majority. We identified PTSD as a primary driving environment for GxE at suicidality risk loci. The male suicidality GEWIS was enriched for three middle-temporal-gyrus inhibitory neuron transcriptomic profiles: *SCUBE*- and *PVALB*-expressing cells ( $\beta = 0.028$ ,  $p = 3.74 \times 10^{-4}$ ), *OPRM1*-expressing cells ( $\beta = 0.030$ ,  $p = 0.001$ ), and *SPAG17*-expressing cells ( $\beta = 0.029$ ,  $p = 9.80 \times 10^{-4}$ ). Combined with gene-based analyses (*CNTN5*  $p_{\text{association}} = 2.38 \times 10^{-9}$ ,  $p_{\text{interaction}} = 1.51 \times 10^{-3}$ ; *PSMD14*  $p_{\text{association}} = 2.04 \times 10^{-7}$ ,  $p_{\text{interaction}} = 7.76 \times 10^{-6}$ ; *HEPACAM*  $p_{\text{association}} = 2.43 \times 10^{-6}$ ,  $p_{\text{interaction}} = 3.82 \times 10^{-7}$ ) including information about brain chromatin interaction profiles (*UBE2E3* in male neuron  $p = 1.07 \times 10^{-5}$ ), our GEWIS points to extracellular matrix biology and synaptic plasticity as biological interactors with the effects of potentially modifiable lifetime traumatic experiences on genetic risk for suicidality. Characterization of molecular basis for the effects of traumatic experience and posttraumatic stress on risk of suicidal behaviors may help to identify novel targets for which more effective treatments can be developed for use in high-risk populations.

### 1. Introduction

Suicide is a critical public health concern with nearly 45,000 people dying by suicide per year in the United States alone (Hedegaard et al.,

2020). Over 70% of these individuals had a prior diagnosed mental disorder (Krysinska and Lester, 2010). Genome-wide studies have estimated the single nucleotide polymorphism (SNP)-based heritability ( $h^2$ ) of death by suicide at 25–48% (Docherty et al., 2019; Otsuka et al.,

**Abbreviations:** GEWIS, gene-by-environment genome-wide interaction study; MICE, Multivariate Imputation via Chained Equations; StructLMM, Structured Linear Mixed Model; MAGMA, Multi-marker Analysis of GenoMic Annotation; FUMA, Functional Mapping and Annotation of Genome-Wide Association Studies; BF, Bayes factor; EE, Environmental enrichment; ECM, Extracellular matrix.

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2019). Recent large-scale studies have focused on understanding the genetic risk for thoughts and behaviors leading up to the commission of acts to end one's life: ideation (Kimbrel et al., 2018), planning, and attempt (Levey et al., 2019). In this study we use the term suicidality to collectively refer to these thoughts and behaviors (Strawbridge et al., 2019).

Suicidality is interpersonally and situationally complex; and 33–98% of individuals exhibiting non-fatal suicidal behaviors have a prior psychiatric diagnosis (Krysinaka and Lester, 2010). With  $\sim 7.6\% h^2$ , a recent large-scale GWAS detected several genome-wide significant (GWS) loci for suicidality (Strawbridge et al., 2019). Under the stress-diathesis model, suicide and its preceding thoughts and behaviors are the result of interaction between a stressor, environment, or state-of-being and a susceptibility to suicidal behaviors. It remains unclear which stressors are most important in influencing suicidality risk for this stress-diathesis model (van Heeringen and Mann, 2014). Epidemiologic studies associate trauma and posttraumatic stress (PTS) with heightened suicidal behavior severity (LeBouthillier et al., 2015), yet examination of these associations from a genetic perspective is limited.

Gene-by-environment (GxE) interaction studies historically rely on *a priori* hypotheses regarding SNP or gene effects on a phenotype given specific environmental conditions (Van der Auwera et al., 2018). Large-scale genetic studies fail to support historical candidate genes and GxE interactions (Border et al., 2019). Genome-wide gene-by-environment interaction studies (GEWIS) are an advantageous alternative approach capable of detecting GxE at risk loci across the genome without relying on *a priori* hypotheses and while assessing interactions with multiple, potentially phenotypically and/or genetically correlated, environmental factors (Moore et al., 2019).

The goal of this study was to identify GxE between traumatic experiences, PTS, social support, and socioeconomic status, and suicidality risk loci. We performed a multivariate GEWIS of a derived ordinal suicidality phenotype in 123,633 participants (Strawbridge et al., 2019) (55.9% female) from the UK Biobank (UKB) using a linear mixed model to investigate a covariance matrix based on 26 environments. Motivated by robust evidence that males and females experience traumatic events differently, we aimed to uncover GxE in sex-stratified analyses. Using the computational tool StructLMM (Moore et al., 2019), we performed a series of follow-up analyses to describe GxE at these detected loci and previously described suicidality risk loci in relation to environmental profiles in the UKB.

## 2. Materials and methods

### 2.1. Discovery cohort

The UK Biobank (UKB) is a large population cohort comprised of nearly 502,000 participants. UKB participants range in age from 37 to 73 years at time of recruitment and represent a general sampling of the UK population with no enrichment for specific disorders. Assessments included physical health, anthropometric measurements, and socio-demographic characteristics. By August 2017, 157,366 participants in the UK Biobank completed an ancillary online mental health questionnaire (Davis et al., 2020) covering topics of self-reported mental health and well-being.

From the UKB mental health questionnaire, we defined a suicidality phenotype for 123,633 individuals described below and following the sample inclusion pipeline of Strawbridge et al. (Strawbridge et al., 2019) plus selection of traumatic event and trauma response endorsements. The total sample included 123,633 UKB participants. Of these, 84,196 (52.7% female) were coded as “no suicidality” controls (rank = 0), 21,176 (60.7% female) as “thought life not worth living” (rank = 1), 13,078 (63.6% female) as “contemplated self-harm or suicide” (rank = 2), 2487 (70.7% female) as “deliberate self-harm” (rank = 3), and 2696 (68.1% female) as “attempted suicide” (rank = 4). Complete cohort description is provided in Supplementary Materials and Methods.

UKB genetic data were filtered to include SNPs with imputation score  $>0.8$ , minor allele frequency  $>0.01$ , Hardy-Weinberg Equilibrium *p*-values  $>1 \times 10^{-6}$ , and missingness  $>0.1$ .

### 2.2. Environments

To study the effects of traumatic events, responses to trauma, and diagnosis of posttraumatic stress disorder (PTSD) we included 26 environments from the UKB mental health questionnaire (Tables S1 and S2). (Nievergelt et al., 2018) These relate to traumatic events, PTS, social support, and socioeconomic status. Detailed descriptions of each environment are described in Supplementary Materials and Methods. Environments were imputed using the MICE (Multivariate Imputation via Chained Equations) (van Buuren and Groothuis-Oudshoorn, 2011) package in R using ten iterations of 5 multiple imputations (see Supplementary Materials and Methods). Imputation quality was evaluated by comparing the relative change in standard error (dSE) between original unimputed and imputed data (He et al., 2010).

### 2.3. Neuroimaging data

UKB neuroimaging data (Field IDs 25005 through 25920) represent magnetic resonance imaging (MRI) data for 32,915–39,755 suicidality study participants (mean *N* per neuroimaging trait = 37,799). Neuroimaging data include T1-weighted structural MRI, T2-weighted MRI, diffusion MRI, resting functional MRI, task functional MRI, and susceptibility weighted MRI.

Neuroimaging phenotypes were associated with suicidality in the full cohort and in sex-stratified analyses. Linear models were covaried for age, sex, genotype batch, and ten principal components of ancestry. For each significantly associated neuroimaging phenotype, we tested for evidence of GxE with respect to suicidality risk loci including the same set of environments and covariates as the main analysis (Materials and Methods Section 2.4).

### 2.4. Gene-by-environment genome-wide interaction analyses (GEWIS) using StructLMM

GEWIS was performed using StructLMM (Moore et al., 2019), a linear mixed-model approach to efficiently detect interactions between loci and one or more potentially correlated environments. Here we evaluated whether traumatic events, response to trauma, PTSD, or socioeconomic status individually and collectively interact with respect to risk for suicidality. GEWIS was performed using age, genotyping batch, and 10 principal components of ancestry as covariates. For the full sample combining males and females, sex was included as a covariate.

Marginal log likelihoods (log (Bayes factor (*BF*))) between the full model and the reduced model with environments removed were used to identify which environments are most relevant for the detected locus interaction effects. To prioritize sets of environments that drive GxE and to account for observed correlation between environments, we performed a greedy backwards elimination procedure prioritizing sequential removal of the strongest individual environments until the change in log marginal likelihood ( $\Delta \log (BF) < 1$  (Moore et al., 2019)).

Allele effects were predicted in 50% of the UKB participants using a model trained with the remaining 50% of the sample based on the best linear unbiased predictor (BLUP) (Moore et al., 2019) method accounting for potentially different relative importance of each environment.

### 2.5. Functional annotation

Association results from GEWIS were mapped to genes using MAGMA (Multi-marker Analysis of GenoMic Annotation) (de Leeuw et al., 2015) implemented in FUMA v1.3.6a (Functional Mapping and Annotation of Genome-Wide Association Studies) (Watanabe et al.,

2017, 2019) based on positional mapping of each variant to genes in a 2 kb window upstream and downstream of the variant (i.e., 4 kb window size) (Watanabe et al., 2017, 2019). We evaluated enrichment of gene-ontology, tissue-transcriptomic (see Supplementary Materials and Methods), and cell-type transcriptomic profiles. Enrichments, gene-based tests, and expression quantitative locus (eQTL) tests were adjusted for multiple testing using a false discovery rate (FDR) of 5%. By FUMA default, chromatin interaction tests were adjusted for multiple testing using an FDR  $q < 1 \times 10^{-6}$ . Functional insights of brain-tissue enrichments were further tested using Hi-C coupled MAGMA (H-MAGMA) (Sey et al., 2020). Further annotation of sex-stratified gene sets was performed using the ShinyGO platform (v0.61). (Ge and Jung, 2018).

## 2.6. Replication

We replicated the GxE effects of genomic risk regions discovered by GEWIS using the Yale-Penn cohort. Mapping of each UKB suicidality phenotype into Yale-Penn and selection of environments (Table S3) is described in Supplementary Materials and Methods).

Replication was performed for all five GEWIS-discovered genomic risk regions in the UKB. Where Yale-Penn did not contain suitable information for the genomic risk region, we performed GEWIS for the first 75 SNPs up and downstream of the region. For example, the chromosome 9 genomic risk region tests 150 SNPs from chr9:137112902-chr9:13749377.

## 3. Results

### 3.1. Cohort and phenotype summary

After sample and variant quality control we analyzed 7,284,651 SNPs for suicidality (Strawbridge et al., 2019) GxE effects in 123,633 participants (55.9% female) of European ancestry from the UKB (Fig. 1). (Strawbridge et al., 2019)

For 24 out of 26 environments (described in Tables S1 and S2), less than 10% of participants required imputation. Two environments, “felt irritable or had angry outbursts in past month” and “felt distant from other people in past month,” had missing information for 68,972 and 68,699 individuals, respectively. After imputation of all 26 environments with MICE, there was a relative decrease in standard error estimates indicating that the data were reliably imputed (Figs. S1 and S2, Tables S1 and S2) (van Buuren and Groothuis-Oudshoorn, 2011; He et al., 2010). After multiple testing correction ( $FDR < 5\%$ ), all environments were associated with suicidality in males, females, and the full cohort in generalized linear models (Fig. 2 and S3). Genetic correlations recapitulated phenotype correlations (Supplementary Results Cohort and Phenotype Summary).

### 3.2. Risk locus discovery using multivariable GEWIS

The discovery GEWIS of 126,633 individuals revealed one risk locus in association and interaction tests whose lead SNP was rs12589041 ( $p_{\text{association}} (p_a) = 2.43 \times 10^{-8}$ ,  $p_{\text{interaction}} (p_{\text{int}}) = 2.04 \times 10^{-9}$ ; Table 1 & Fig. S4). In sex-stratified GEWIS we discovered 1 significant risk locus for suicidality in females (rs118118557  $p_a = 2.37 \times 10^{-8}$ ,  $p_{\text{int}} = 1.14 \times 10^{-7}$ ; Fig. S5) and three LD independent risk loci for suicidality in males (rs2367967  $p_a = 2.47 \times 10^{-9}$ ,  $p_{\text{int}} = 5.91 \times 10^{-10}$ , rs72619337  $p_a = 1.08 \times 10^{-8}$ ,  $p_{\text{int}} = 1.63 \times 10^{-9}$ ; and rs6854286  $p_a = 1.98 \times 10^{-8}$ ,  $p_{\text{int}} = 9.41 \times 10^{-9}$ ; Fig. S6). The rs118118557 risk locus detected in females positionally mapped to the transcription start site of CHST14 and the rs2367967 locus discovered in males positionally mapped to the CWC22 locus. The male-specific genomic risk locus mapping to CWC22 replicated ( $N = 1936$  males; rs2367967, Yale-Penn  $p_a = 0.019$ ,  $p_{\text{int}} = 0.099$ ; Tables S4–8; Supplementary Results: Locus Replication in Yale-Penn using Multivariable GEWIS).

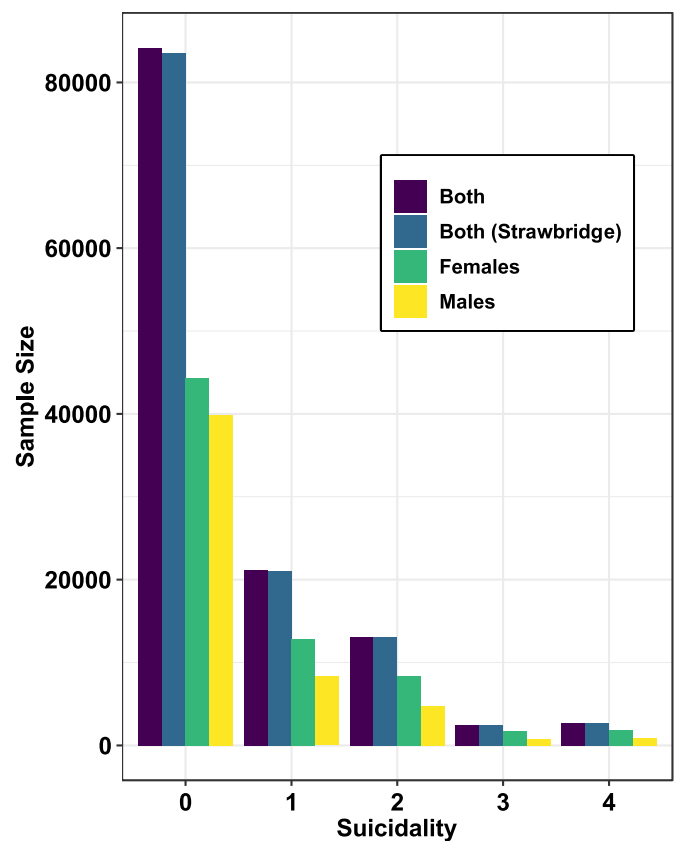


Fig. 1. Sample sizes used in this GEWIS of suicidality by sex and in the full cohort and those used in the GWAS by Strawbridge et al. (Strawbridge et al., 2019) Suicidality is coded as follows: 0 = no suicidality controls, 1 = “thought life not worth living,” 2 = “contemplated self-harm or suicide,” 3 = “deliberate self-harm,” and 4 = “attempted suicide.”

### 3.3. Comparing GWAS vs. multivariable GEWIS

In multivariable GEWIS interaction tests, Strawbridge, et al. (Strawbridge et al., 2019) GWAS loci showed nominally significant GxE interactions with the covariance matrix tested (rs62535711  $p_{\text{int}} = 6.76 \times 10^{-5}$ ; rs598046  $p_{\text{int}} = 2.00 \times 10^{-6}$ ; rs7989250  $p_{\text{int}} = 0.023$ ). In the multivariable GEWIS association tests, rs598046 also was associated with suicidality ( $p_a = 0.020$ ) (Table S9). Because of the GxE effects at these loci (Strawbridge et al., 2019), we included them in the subsequent GxE characterization analyses. The effects of loci identified in our multivariate GEWIS were not detected in Strawbridge et al. (Strawbridge et al., 2019) (Table S10).

### 3.4. Environmental risk factors

All GEWIS-discovered loci showed compelling evidence for interaction with PTSD and/or a quantitative PTSD risk score (the PTSD Checklist 6-item subset, PCL-6) (Figs. 3 and S7 and Supplementary Results: Genetic Variance Explained by GxE). GxE for rs12589041 in both sexes had  $\log(\text{Bayes factor (BF)}) = 9.97$  for PTSD and  $\log(\text{BF}) = 9.59$  for PCL-6; GxE for rs118118557 in females had  $\log(\text{BF}) = 8.82$  for PTSD and  $\log(\text{BF}) = 8.86$  for PCL-6; in males, GxE at rs2367967 had  $\log(\text{BF}) = 5.27$  for PTSD and  $\log(\text{BF}) = 6.56$  for PCL-6, GxE at rs6854286 had  $\log(\text{BF}) = 10.41$  for PTSD and  $\log(\text{BF}) = 5.31$  for PCL-6, and GxE at rs72619337 had  $\log(\text{BF}) = 8.04$  for PTSD and  $\log(\text{BF}) = 10.57$  for PCL-6.

Consistent with Moore et al. (Moore et al., 2019), we identified many environments driving the detected GxE interactions (Fig. 3) but also observed distinct GxE architectures per SNP after greedy backwards

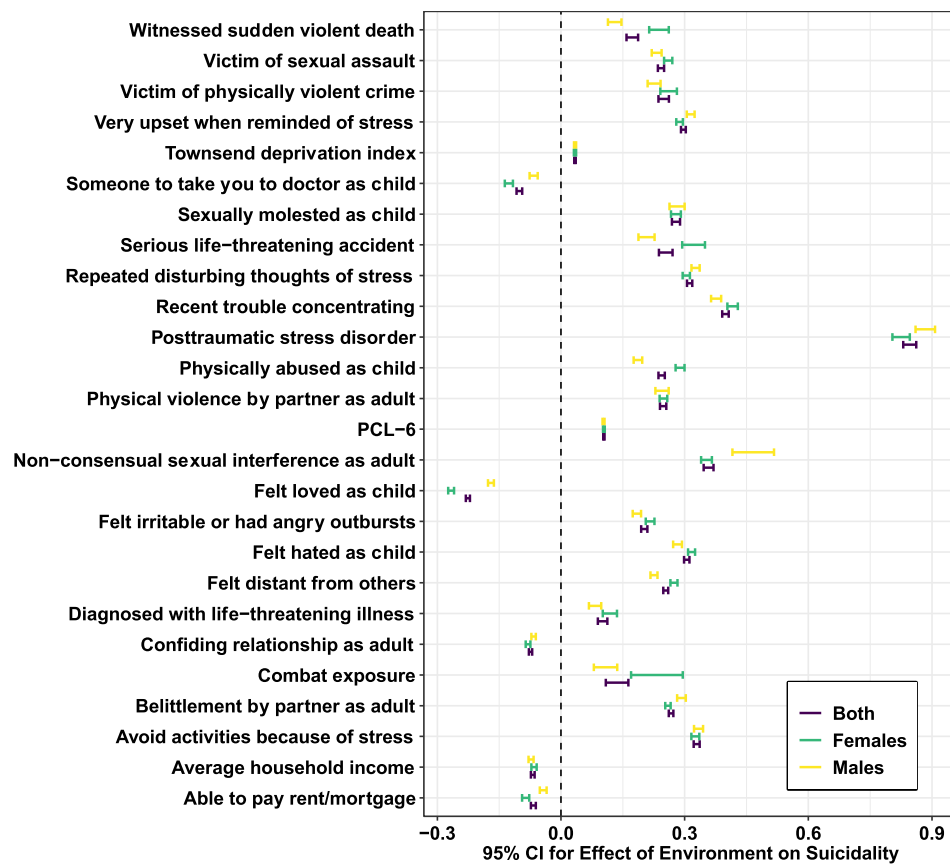


Fig. 2. Association between suicidality and 26 environments related to traumatic experiences, responses to trauma, posttraumatic stress, social support, and socioeconomic status. Shown are 95% confidence intervals surrounding point estimates from a generalized linear model of suicidality adjusting for age, sex, genotyping batch, and ten principal components of ancestry.

Table 1

Lead SNP information for five risk loci, including tested alleles (A1) and their frequencies (AF) in UKB, detected in a GEWIS of suicidality.

RSID	Sex	Chr	Position	$P_{association}$	$P_{interaction}$	AF (A1)	Nearest Gene
rs12589041	Both	14	71172013	$2.43 \times 10^{-8}$	$2.04 \times 10^{-9}$	0.25 (G)	RP6-65G23.1
rs118118557	Female	15	40762879	$2.37 \times 10^{-8}$	$1.14 \times 10^{-7}$	0.01 (G)	CHST14
rs2367967	Male	2	180948951	$2.47 \times 10^{-9}$	$5.91 \times 10^{-10}$	0.32 (G)	CWC22
rs6854286	Male	4	12652325	$1.98 \times 10^{-8}$	$9.41 \times 10^{-8}$	0.37 (C)	RP11-145E17.2
rs72619337	Male	9	137175269	$1.08 \times 10^{-8}$	$1.63 \times 10^{-9}$	0.03 (G)	RP11-352E6.1

elimination procedures. All driving environment sets contained PCL-6 and/or PTSD. In females, two additional environments drove GxE at rs118118557: UKB Field ID 20498 *felt very upset when reminded of stressful experience in past month* log (BF) = 9.82 and UKB Field ID 20495: *avoided activities or situations because of previous stressful experience in past month* log (BF) = 9.39. Implicated driving environments in males include UKB Field ID 20523: *physical violence by partner or ex-partner as an adult* (log (BF) = 10.34 at rs2367967), UKB Field ID 20487: *felt hated by family member as a child* (log (BF) = 6.42 at rs6854286), and UKB Field ID 20497: *repeated disturbing thoughts of stressful experience in past month* (i. e., re-experiencing; log (BF) = 8.47 at rs72619337).

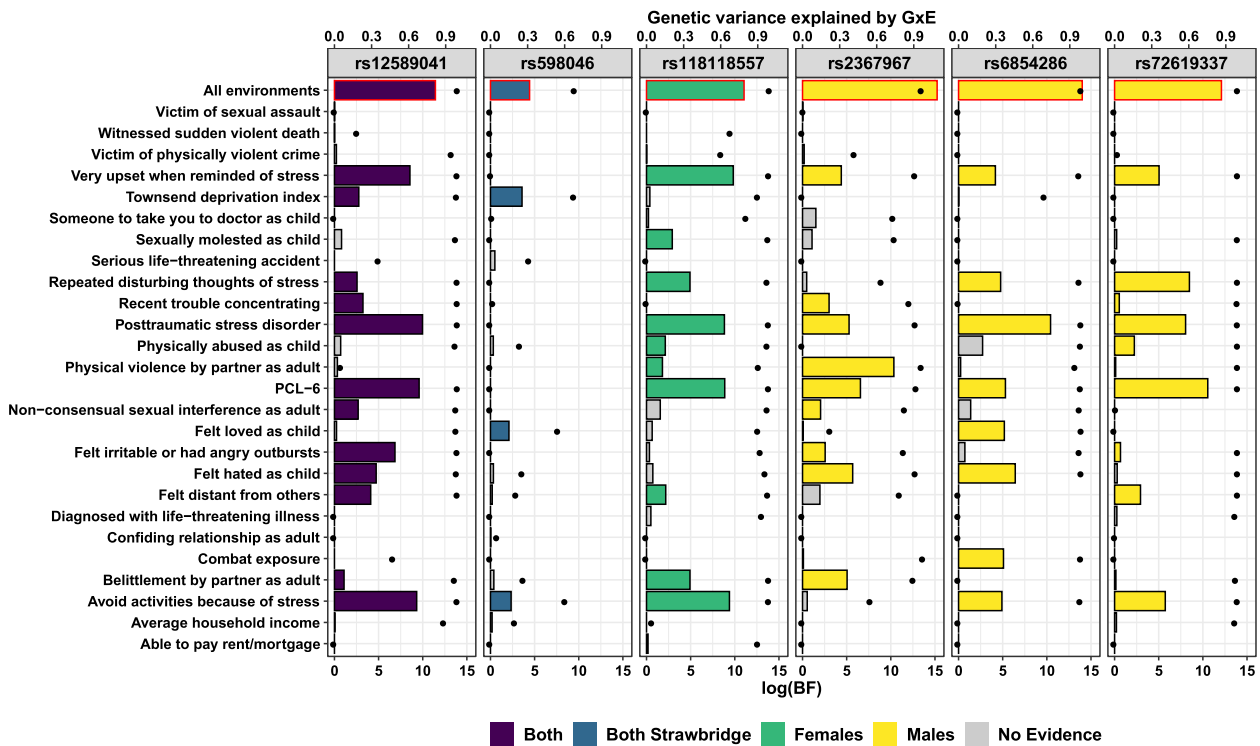
One suicidality risk locus from Strawbridge et al. (Strawbridge et al., 2019) showed evidence of GxE interaction with the environments evaluated in this study (rs598046 full model log (BF) = 4.43; rs62535711 full model log (BF) = 0; and rs7989250 full model log (BF) = 0). The GxE at rs598046 (CNTN5 intronic variant) was driven primarily by UKB Field ID 189: *Townsend deprivation index at recruitment* (log (BF) = 3.58, Fig. S7).

### 3.5. Effect size predictions

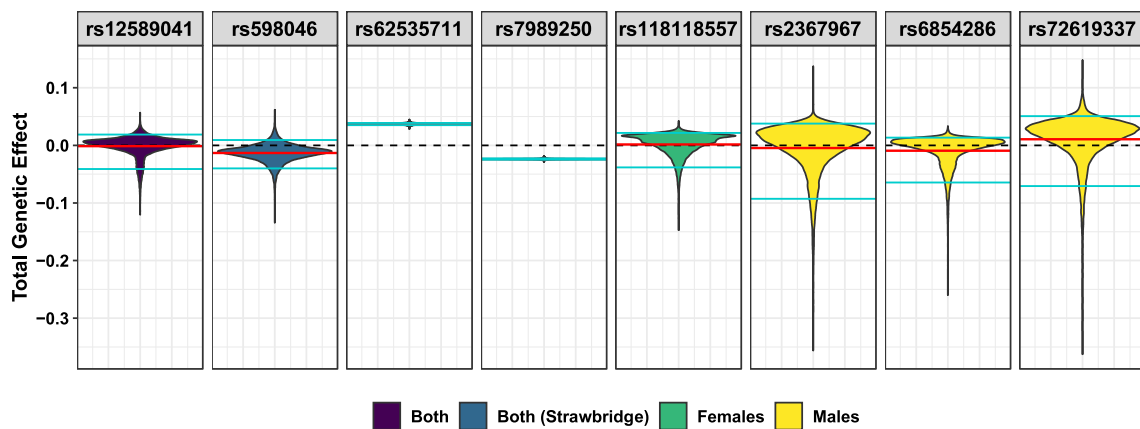
All five suicidality risk loci discovered by GEWIS exhibited qualitative interactive effects in which the effect of each SNP on suicidality switches direction depending on an individual's environmental profile (Fig. 4). Two loci exhibited positive persistent genetic effects on suicidality: rs118118557 in females ( $\beta = 1.39 \times 10^{-3}$ ) and rs72619337 in males ( $\beta = 0.011$ ) and three loci exhibited negative persistent genetic effects: rs12589041 in the full cohort ( $\beta = -1.49 \times 10^{-3}$ ), rs2367967 in males ( $\beta = -4.62 \times 10^{-3}$ ), and rs6854286 in males ( $\beta = -9.35 \times 10^{-3}$ ).

Effect sizes for the loci that Strawbridge et al. (Strawbridge et al., 2019) detected by GWAS should show effects on suicidality unbiased by GxE effects. GEWIS persistent genetic effects for rs62535711 ( $\beta_{GEWIS} = 0.037$ ,  $\beta_{Strawbridge} = 0.105$ ,  $p_{diff} = 1.70 \times 10^{-4}$ ) and rs7989250 ( $\beta_{GEWIS} = -0.024$ ,  $\beta_{Strawbridge} = -0.052$ ,  $p_{diff} = 0.002$ ) were consistent, yet significantly smaller, estimates compared to GWAS. The locus rs598046 (CNTN5) demonstrated qualitative interactive effects with a persistent genetic effect significantly different than, and in the opposite direction from, that reported by Strawbridge et al. (Strawbridge et al., 2019) ( $\beta_{GEWIS} = -0.013$ ,  $\beta_{Strawbridge} = 0.053$ ,  $p_{diff} = 1.84 \times 10^{-13}$ , Fig. 4).





**Fig. 3.** Individual relevance of the environment included in the covariance matrix used to detect gene-by-environment (GxE) interactions with suicidality. Each bar represents the log marginal likelihood (log (Bayes factor (*BF*))) of models for the indicated environment relative to models lacking that environment. Black data points indicate the genetic variance explained by GxE at each locus for the indicated environment. Bars outlined in red highlight the full GxE model at each locus; colored bars indicate environments with positive evidence for their contribution as part of a driving set of environments underlying the detected GxE (Fig. S7). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 4.** Predicted genetic effects of GEWIS loci for suicidality. Violin plots of the distribution of estimated allelic effect sizes at each locus in 61,816 unrelated individuals (“Both”), 27,256 unrelated males, and 34,560 unrelated females of European ancestry given full models of traumatic events and posttraumatic stress environments. Persistent genetic effect estimates are shown in solid red lines; zero effect is shown in black dashed lines; cyan lines indicate the top and bottom 5% of each distribution. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.6. Neuroimaging

We investigated potential neurobiological underpinnings of the detected GxE relationships by testing each GEWIS locus for GxE effects in brain phenotypes from UKB (872 brain-imaging phenotypes;  $N \leq 39,755$ ). After multiple testing correction per sex ( $FDR < 5\%$ ), we detected 285 neuroimaging correlates of suicidality in the full cohort, 189 in females, and 33 in males (Tables S11–13). We detected nominally significant GxE-adjusted neuroimaging associations at *rs12589041* in the full sample putatively implicating various regions of the brain

involved in memory (e.g., T1-weighted MRI volume of hippocampus (left)  $p_a = 0.037$ ), emotions (e.g., T1-weighted MRI volume of grey matter in amygdala (left)  $p_a = 0.040$ ), and goal-oriented behaviors (e.g., diffusion MRI weighted-mean fractional anisotropy in tract inferior fronto-occipital fasciculus (right)  $p_a = 0.049$ ) (Tables S14–16).

3.7. Gene-based association tests

*HEPACAM* ( $z_a = 4.36$ ,  $p_a = 6.44 \times 10^{-6}$ ,  $z_{int} = 4.62$ ,  $p_{int} = 1.93 \times 10^{-6}$ ) was the only gene associated with suicidality in association and

interaction tests ( $FDR\ q < 0.05$ ; Table S17). Three additional genes were associated with suicidality after multiple testing correction ( $FDR\ q < 0.05$ ) in either association or interaction tests ( $CNTN5$  ( $z_a = 5.30$ ,  $p_a = 5.85 \times 10^{-8}$ ,  $z_{int} = 2.99$ ,  $p_{int} = 1.66 \times 10^{-4}$ ),  $PSMD14$  ( $z_a = 4.68$ ,  $p_a = 1.44 \times 10^{-6}$ ,  $z_{int} = 3.96$ ,  $p_{int} = 3.74 \times 10^{-5}$ ), and  $HEPN1$  ( $z_a = 4.20$ ,  $p_a = 1.35 \times 10^{-5}$ ,  $z_{int} = 4.52$ ,  $p_{int} = 3.05 \times 10^{-6}$ )). After multiple testing correction, there were no genes surviving multiple testing correction in the sex-stratified analyses.

We detected 9 Hi-C coupled gene-neuron associations in male suicidality GEWIS (Table S18). Two of these have been previously associated with psychopathology:  $UBE2E3$ -neuron ( $z_a = 4.25$ ,  $p_a = 1.07 \times 10^{-5}$ ,  $z_{int} = 4.42$ ,  $p_{int} = 4.89 \times 10^{-6}$ ) previously associated with bipolar disorder, smoking behavior, and hurt (McCarthy et al., 2014) feelings;  $MORC3$ -neuron ( $z_a = 4.16$ ,  $p_a = 1.58 \times 10^{-5}$ ,  $z_{int} = 4.42$ ,  $p_{int} = 4.99 \times 10^{-6}$ ) previously associated with frequency of tiredness and depressive symptoms; and  $DOP1B$ -neuron ( $z_a = 4.16$ ,  $p_a = 1.58 \times 10^{-5}$ ,  $z_{int} = 4.42$ ,  $p_{int} = 4.99 \times 10^{-6}$ ) previously implicated in neurological disorders and dystonias (Al-Mubarak et al., 2020).

### 3.8. Functional annotation and regulatory effects

The GEWIS association test in males was enriched for the gene set mature B-cell differentiation ( $FDR\ q = 0.027$ ) (Table S19). Three middle temporal gyrus (MTG) cell-type transcriptomic profiles were enriched in the GEWIS of suicidality in males ( $FDR\ q < 0.05$ ; Table S20): (1)  $SCUBE3$ - and  $PVALB$ -expressing inhibitory neurons from MTG layers 2–5 (association tests:  $\beta = 0.028$ ,  $FDR\ q = 0.028$ ; interaction tests:  $\beta = 0.018$ ,  $FDR\ q = 0.049$ ), (2)  $OPRM1$ -expressing neurons from MTG layers 1–4 ( $\beta = 0.030$ ,  $FDR\ q = 0.049$ ), and (3)  $SPAG17$ -expressing inhibitory neurons from MTG layers 2–4 ( $\beta = 0.029$ ,  $FDR\ q = 0.049$ ).

In the full UKB sample, the genomic risk locus containing  $rs12589041$  was a PsychENCODE eQTL for  $TTC9$  ( $FDR\ q = 0.026$ ) but did not exhibit brain-associated chromatin interactions (Fig. S8 and Table S21). In females, the genomic risk locus containing  $rs118118557$  exhibited significant chromatin interactions in fetal and adult cortex, the most significant of which involved the genomic region containing  $CCDC32$  (fetal cortex  $FDR\ q = 2.61 \times 10^{-35}$ ; adult cortex  $FDR\ q = 1.25 \times 10^{-46}$ ; Fig. S9 and Table S22). In males, two SNPs in the genomic risk locus containing  $rs2367967$  were PsychENCODE eQTLs for  $UBE2E3$  ( $FDR\ q = 0.044$  and  $0.046$ ; Fig. S10 and Table S23). This same genomic risk locus exhibited significant chromatin interactions with the region of chromosome 2 containing  $NEUROD1$  and  $CERKL$  (dorsolateral prefrontal cortex cells  $FDR\ q = 6.75 \times 10^{-10}$ ),  $ITGA4$  (neural progenitor cells  $FDR\ q = 6.31 \times 10^{-7}$ ), and  $ZFN385B$  (neural progenitor cells  $FDR\ q = 4.07 \times 10^{-19}$ ; Fig. S10 and Table S24). In males, the genomic risk locus containing  $rs6854286$  exhibited chromatin interaction with the chromosome 2 region encoding  $HS3ST1$  (neural progenitor cells  $FDR\ q = 1.18 \times 10^{-7}$ ; Fig. S11 and Table S24).

## 4. Discussion

We conducted a comprehensive analysis of suicidality describing (i) five GEWIS risk loci with interaction and association effects with specific environments including sex-stratified GxE effects, (ii) environments with strong evidence as drivers of GxE interactions at these loci, (iii) replication of locus-suicidality associations in an independent dataset, (iv) description of GxE effects that may have confounded prior large-scale studies of suicidality, and (v) annotation of genome-wide suicidality genetic architecture uncovering relevant neuronal cell types and brain-circuitry. In aggregate, these data identify the extracellular matrix (ECM) as a molecular target for suicidality that interacts with traumatic experiences and PTS.

Of the five suicidality risk loci discovered by GEWIS, two mapped to genic regions:  $rs118118557$  mapped to  $CHST14$  and  $rs2367967$  mapped to  $CWC22$ .  $CHST14$  encodes carbohydrate sulfotransferase 14 and is responsible for sulfation of *N*-acetylgalactosine residues of dermatan

sulfate in the ECM (Kosho et al., 2014). ECM in the brain plays a major role in the storage of information through learning and thus, ECM maintenance, regulation, and composition are reportedly highly relevant for disorders related to, or exacerbated by, prior experiences including traumatic events (Bach et al., 2019). Describing the GxE at the  $CHST14$  SNP  $rs118118557$  demonstrated interaction with physically and sexually violent experiences in childhood and adulthood (Moore et al., 2019). This relationship suggests that synaptic plasticity mechanisms are possible targets for treating suicidality and perhaps psychiatric disorders with a strong influence from memories of prior experiences (Whitlock et al., 2006). Although they do not survive multiple testing correction, our neuroimaging-based analyses seem to point to brain regions involved in emotion and memory processing such as hippocampus, amygdala, and the inferior fronto-occipital fasciculus (Chaaya et al., 2018). Based on this preliminary evidence, we hypothesize that one possible suicidality therapeutic target is decentering, the capacity to observe items arising in the mind (e.g., thoughts, feelings, memories, or bodily sensations) with physiological distance, heightened self-awareness, and perspective thinking (Fresco et al., 2017). One successful example of decentering is the application of mindfulness in controlling symptoms of anxiety, depression, and PTSD (Boyd et al., 2018; Parmentier et al., 2019). More statistically powerful follow-up studies are required to confirm our suggestive results and test further our hypothesis.

$CWC22$  encodes the “ $CWC22$  spliceosome associated protein homolog” protein, which is the only protein-coding component of the large (127 kb) Rd2 segmental duplication.  $CWC22$  is one of the protein-coding regions of the genome that is most often duplicated (Pezer et al., 2015).  $CWC22$  and the Rd2 segmental duplication have previously been implicated in brain microstructural changes in response to environmental factors such as social engagement (Dause and Kirby, 2019), which has memory-inducing effects on the ECM (Koskinen et al., 2019). Environmental enrichment (EE) describes exposure to situations that facilitate enhanced sensory, cognitive, and motor stimulation and is known to affect synaptic plasticity in humans (Dause and Kirby, 2019). EE approaches have shown favorable clinical outcomes with respect to developmental disorders (Woo et al., 2015) and stroke (McDonald et al., 2018); we hypothesize that this association between  $CWC22$  and suicidality suggests that such a noninvasive, non-pharmacological, and personalizable treatment strategy such as EE may effectively mitigate the effects of genetic liability to suicidality.

Using gene-based association testing, we discovered four genes associated with suicidality:  $HEPACAM$  (hepatocyte cell adhesion molecule),  $HEPN1$  ( $HEPACAM$  Opposite Strand 1),  $PSMD14$  (26S proteasome non-ATPase regulatory subunit 14), and  $CNTN5$  (contactin-5).  $HEPACAM$  encodes  $GlialCAM$ , which is responsible for promoting interactions between ECM components and glia (Moh et al., 2009). Though previously associated with psychiatric disorders, detection of  $HEPN1$  is likely attributed to colocalization of  $HEPN1$  and  $HEPACAM$  (Chung Moh et al., 2005). The ubiquitin-proteasome system, of which the  $PSMD14$  gene product is a component, plays a critical role in the expression of ECM-associated genes (Ramos de Carvalho et al., 2018).  $CNTN5$  was previously detected by GWAS of suicidality also performed in the UKB – a finding that is consistent, but not wholly independent from the information included herein. Its product, contactin-5 is part of the glycosylphosphatidylinositol-bound protein family that has often been implicated in autism spectrum disorder (Sharom and Lehto, 2002). Contactin-5 is secreted into the ECM, where it facilitates the formation and growth of neuronal projections (Mercati et al., 2013). Strawbridge et al. (Strawbridge et al., 2019), described the  $rs598046$  risk locus, mapped to  $CNTN5$ , as conferring increased risk for suicidality ( $\beta = 0.053$ ) (Strawbridge et al., 2019). However, using GEWIS, we observed significant interaction effects at  $rs598046$ . With respect to *Townsend deprivation index*,  $rs598046$  conferred increased and decreased suicidality risk. The confounding nature of socioeconomic status has been observed extensively in GWAS of psychiatric disorders including PTS

and PTSD (Wendt et al., 2020) and it is therefore unsurprising to observe similar effects by GEWIS. This finding highlights the importance GxE characterization of GWAS risk loci to adequately evaluate the effects of environmental heterogeneity, especially via socioeconomic status.

Detected via functional annotation of the suicidality GEWIS in males only, we recapitulate two cell types previously implicated in suicidal behaviors: *SPAG17*-expressing and *OPRM1*-expressing inhibitory neurons from the middle temporal gyrus (Hodge et al., 2019). *SPAG17* (sperm-associated antigen 17) was previously identified by whole exome sequencing of suicide deaths as a locus enriched for rare variants (Tombacz et al., 2017). *OPRM1* encodes the mu-opioid receptor 1 and has garnered considerable attention in candidate gene and large-scale genetic studies of several psychiatric disorders and suicidal ideation (Nobile et al., 2019) and suicidal behavior (Arias et al., 2012). We also detected inhibitory neurons from layers 2–5 of the middle temporal gyrus expressing both *SCUBE3* and *PVALB*. *PVALB* encodes parvalbumin, a calcium-binding protein that supports neuroplasticity and other functional properties of fast-spiking interneurons in cortical and subcortical regions; in humans, pathology in parvalbumin neurons was implicated in schizophrenia (Dienel and Lewis, 2019) and depression (Fogaca and Duman, 2019). The *OPRM1*, *SCUBE3*, and *SPAG17* cell-type transcriptomic enrichments converged with nominally significant Hi-C chromatin-informed gene-based association thereby reinforcing their importance with respect to suicidality and pinpointing possible cellular and developmental trajectories of particular relevance. These findings highlight genetic and biological overlap between suicidality and key genetic targets for other psychiatric disorders, especially those exacerbated by adverse prior experiences, and suggests that there are pervasive environmental interaction effects underlying genetic risk for the trait.

Several regulatory interactions were detected that further implicate the ECM and synaptic plasticity in the GxE effect of PTS and genetic risk for suicidality. Reduced *TTC9* (tetratricopeptide repeat domain 9) expression was associated with higher anxiety-like behaviors (Nepon et al., 2010) and regulatory pathways implicated in adult neuroplasticity and serotonin signaling. *NEUROD1* (neuronal differentiation 1) is a potent transcription factor capable of controlling neuronal fate under some circumstances. For example, *NEUROD1* alone was capable of converting reactive glia into functional neurons *in vivo* (Guo et al., 2014). *NEUROD1* activates neuronal development genes through acetylation and its transient activity during development was sufficient for long-term epigenetic memory (Pataskar et al., 2016). *HS3ST1* encodes heparan sulfate 3-O-sulfotransferase 1, which is responsible for sulfation of heparan in the ECM. Heparan sulfate has been previously implicated in ECM contributions to schizophrenia and bipolar disorder (Woo et al., 2017). Finally, *UBE2E3* was detected via eQTL and chromatin interaction mapping in FUMA and Hi-C coupled gene-based association in the neuron. This ubiquitin-conjugating enzyme participates in efficient degradation of DNA binding-proteins in the frontal lobe whose accumulation contributes to neurodegeneration and associated psychopathologies (Rabinovici and Miller, 2010). These findings reinforce suicidality as a trans-diagnostic psychiatric trait (Strawbridge et al., 2019), demonstrating substantial overlap between regulatory effects across disorders including major depressive disorder (Mullins et al., 2019), schizophrenia, and bipolar disorder.

Convergent evidence that ECM biology underlies suicidality is intriguing given recent evidence that ECM is involved in memory retention and synaptic plasticity following traumatic experiences (Bach et al., 2019). Rather than identifying a single environment or state-of-being that interact with the loci discovered herein, we uncover patterns of highly correlated environments that contributed to a locus' effect on suicidality. Many of the environments that we studied are modifiable, lending additional evidence that an EE approach may mitigate suicidality risk. For example, attachment style (e.g., an individual's perception and expectations of the availability and/or responsiveness of meaningful others during times of stress (Mikulincer and Shaver, 2012)) is a potentially modifiable risk factor for PTS, PTSD,

and suicidality. A secure attachment style is clinically a protective factor for PTSD (Woodhouse et al., 2015) but also protects against PTSD polygenic risk (Tamman et al., 2020). Possible future directions for this work include the investigation of relationships between attachment style and social support, PTS, and longitudinal reports of suicidal behaviors. Future work may also consider how these factors influence the putatively informative brain regions identified herein with well-characterized roles in memory and emotion. Based on the present findings, we hypothesize that future studies can be most impactful if focused on the longitudinal effects of traumatic events identified by our sex stratified analyses (e.g., male suicidality genetic risk and specific incidence traumas such sexual violence by partner in adulthood).

Our study detected novel biological underpinnings of suicidality but has limitations. First, replication of GEWIS was limited to independent samples with comparable environments. Indeed, our replication with the Yale-Penn cohort lacked 1-to-1 matched environments; however, we successfully included variables from Yale-Penn that capture the same domains of environment or state-of-being: traumatic experiences, PTS, social support, and socioeconomic status. The highly correlated nature of these environments suggests that GxE tests in Yale-Penn should be well suited to detect comparable association and interaction effects. Second, our findings rely on self-reported thoughts and behaviors of suicide and may suffer from reporting biases due to stigma associated with these responses. Third, these data reflect European-ancestry risks for suicidality that require dedicated investigation in other ancestries. Finally, although Struct-LMM is a powerful tool for GEWIS locus discovery, additional work is required to understand best practices for validating GEWIS functional annotations using dynamic SNP effect estimates in place of static GWAS effect sizes.

## 5. Conclusions

We identified interactions between suicidality risk variants and potentially modifiable environments that point to the ECM as a possible source of suicidality risk in relation to learned behavior following traumatic experiences across the lifespan. There were shared genetic effects between the identified loci and brain circuitry associated with planning behaviors and cell types that contribute to synaptic plasticity and axonal innervation. Characterization of the molecular basis for the effects of traumatic experience and PTS on the risk of suicidal behaviors may help to identify novel targets for which more effective treatments can be developed for use in high-risk populations.

## CRedit authorship contribution statement

**Frank R. Wendt:** Conceptualization, Data curation, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Gita A. Pathak:** Data curation, Writing - review & editing. **Daniel F. Levey:** Data curation, Writing - review & editing. **Yaira Z. Nuñez:** Data curation, Writing - review & editing. **Cassie Overstreet:** Data curation, Writing - review & editing. **Chelsea Tyrrell:** Data curation, Writing - review & editing. **Keyrun Adhikari:** Software, Writing - review & editing. **Flavio De Angelis:** Writing - review & editing. **Daniel S. Tylee:** Writing - review & editing. **Aranyak Goswami:** Writing - review & editing. **John H. Krystal:** Writing - review & editing. **Chadi G. Abdallah:** Writing - review & editing. **Murray B. Stein:** Writing - review & editing. **Henry R. Kranzler:** Writing - review & editing. **Joel Gelernter:** Writing - review & editing, Resources, Funding acquisition. **Renato Polimanti:** Conceptualization, Resources, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing.

## Declaration of competing interest

Dr. Krystal reports compensation as the Editor of Biological Psychiatry. He also serves on the Scientific Advisory Boards for Bioasis Technologies, Inc., Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc.



(Clinical Advisory Board), Cadent Therapeutics (Clinical Advisory Board), PsychoGenics, Inc, Stanley Center for Psychiatric research at the Broad Institute of MIT and Harvard and the Lohocla Research Corporation. He owns stock in ArRETT Neuroscience, Inc., Biohaven Pharmaceuticals, Sage Pharmaceuticals, and Spring Care, Inc. and stock options in Biohaven Pharmaceuticals Medical Sciences, BlackThorn Therapeutics, Inc. and Storm Biosciences, Inc. He is a co-inventor on multiple patents as listed below: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5,447,948. September 5, 1995, (2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard—Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8,778,979 B2 Patent Issue Date: July 15, 2014. US Patent Application No. 15/695,164: Filing Date: May 09, 2017, (3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C.—Intranasal Administration of Ketamine to Treat Depression United States Application No. 14/197,767 filed on March 5, 2014; United States application or Patent Cooperation Treaty (PCT) International application No. 14/306,382 filed on June 17, 2014, (4) Zarate, C, Charney, DS, Manji, HK, Mathew, Sanjay J, Krystal, JH, Department of Veterans Affairs “Methods for Treating Suicidal Ideation”, Patent Application No. 14/197.767 filed on March 5, 2014 by Yale University Office of Cooperative Research, (5) Arias A, Petrakis I, Krystal JH.—Composition and methods to treat addiction. Provisional Use Patent Application no.61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research, (6) Chekroud, A., Gueorguieva, R., & Krystal, JH. “Treatment Selection for Major Depressive Disorder” [filing date June 3, 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University, (7) Gihyun, Yoon, Petrakis I, Krystal JH—Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U. S. Provisional Patent Application No. 62/444,552, filed on January 10, 2017 by Yale University Office of Cooperative Research OCR 7088 US01, (8) Abdallah, C, Krystal, JH, Duman, R, Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases. U.S. Provisional Patent Application No. 047162–7177P1 (00754) filed on August 20, 2018 by Yale University Office of Cooperative Research OCR 7451 US01. Dr. Kranzler is a member of the American Society of Clinical Psychopharmacology’s Alcohol Clinical Trials Initiative, which for the past three years was supported by AbbVie, Alkermes, Amygdala Neurosciences, Arbor, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, and Pfizer. Dr. Kranzler is paid for his editorial work on the journal *Alcoholism: Clinical and Experimental Research*. Drs. Kranzler and Gelernter are named as inventors on PCT patent application #15/878,640 entitled: “Genotype-guided dosing of opioid agonists,” filed January 24, 2018. Dr. Murray Stein is paid for his editorial work on the journals *Biological Psychiatry* and *Depression and Anxiety*, and the health professional reference *Up-To-Date*. Drs. Polimanti and Gelernter are paid for their editorial work on the journal *Complex Psychiatry*. The other authors declare no competing interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yjnstr.2021.100309>.

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## Data sharing

All data discussed in this study are provided in the article and in the Supplementary Material.

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