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ABSTRACT

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Harmonized phenotypes for internalizing problems and ADHD

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The aim of this study is to harmonize questionnaire item data with an objective of having one phenotype, that is comparable across various cohorts. Our focus is on internalizing problems and ADHD symptoms. We used a total of 1330, 10-year-old children data available in the Western Australian Pregnancy Cohort study (RAINE) dataset, with complete data on the Child Behaviour Checklist (CBCL) and the Strength and Difficulties Questionnaire (SDQ). We carried out a varimax factor analysis on all items to identify relevant dimensions. We found two dimensions ('emotional problems' and 'ADHD') with high CBCL and SDQ loadings. We carried out an Item Response Theory (IRT) analysis using a Generalized Partial Credit Model to investigate the psychometric quality of these two dimensions. The results showed that particular subsets of CBCL and SDQ items can be used together but also separately to measure emotional problems and ADHD. We recommend to use these sets of items, rather than the original subscales, in order to work with commensurate phenotypes across various research groups.

A multi-polygenic score approach to the prediction of harmonized aggression

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Aggressive behavior is a substantially heritable trait with genetic influences explaining 40–80% of the variance across childhood (Porsch et al. 2016) and accounting for most stability of aggression over time. However, molecular genetic research on aggression is still in an early stage and prediction models incorporating polygenic epidemiological approaches are lacking. Here we employed a multi-polygenic score approach to the prediction of aggression in a sample of 21,000 individuals of European ancestry participating in the ACTION consortium (Aggression in Children: Unraveling gene–environment interplay to inform Treatment and InterventiON strategies). Participants are members of four prospective twin cohorts—Twins Early Development Study, Netherlands Twin Register, Childhood and Adolescent Twin Study of Sweden, and FinnTwin12 study. We harmonized phenotypic data in these four cohorts to create harmonized measures of aggression at ages 9–10; 12; 14–15 and 16–18. These measures were then averaged across ages to create a unique measure of 'broad aggression' that we analyzed in prediction models. After harmonizing genomic data, we constructed genome-wide polygenic scores (GPS) for 250 behavioral, anthropometric, mental health- and cognition-related traits from publicly available GWAS summary statistics. Preliminary results indicate a SNP heritability of 4.6% for broad aggression, setting a low ceiling for polygenic risk prediction in the overall sample of 21,000. Polygenic prediction models performed in the TEDS cohort (N $\sim$ 4000) show significant associations of $\sim$ 40 GPS–top GPS for importance were educational attainment (−), ADHD (+), mood swings (+), tobacco smoking (+) and maternal smoking around birth (+)—predicting a total of 2.08% of the variance in broad aggression. We are currently exploring age and gender differences and we will extend our analyses to the overall sample of unrelated individuals (N $\sim$ 11,370) as well as the full sample of N $\sim$ 21,000, which includes related individuals. Intriguingly, these preliminary results point to a shared genetic architecture between broad aggression and several psychiatric and health-related traits. Furthermore, they hold promise for a practical application of polygenic scores in the prediction of aggressive behaviors, especially once we break through the low SNP heritability ceiling.

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Genomic prediction of cognitive traits in childhood and adolescence

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Methodological advances in the flourishing field of polygenic epidemiology, coupled with constantly increasing sample sizes in genome-wide association studies (GWAS), call for a practical application of current state-of-the-art methodologies to complex trait prediction. Here we set out to test the extent to which we can maximize prediction accuracy of cognitive and educationally relevant traits in a sample of 7026 individuals representative of the UK population. We are developing our prediction models in the Twin Early Development Study (TEDS), a large longitudinal study involving 16,810 pairs of twins born in England and Wales between 1994 and 1996, with DNA data available for 10,346 samples (including 3320 dizygotic twin pairs and 7026 unrelated individuals). Our current analyses focus on a TEDS subsample with genome-wide genotyping and measures of general cognitive ability (*g*) and educational achievement at ages 12 and 16. As a first step, we tested associations between g and educational achievement versus polygenic scores constructed using the latest GWAS summary statistics of *g* (IQ3: Savage et al. 2018) and educational achievement (EA3: Lee et al. 2018). IQ3 predicted up to 4% of the variance in *g* at age 12 (N = 3271) and 5% at age 16 (N = 1923). EA3 predicted 5.6% of the variance in educational achievement at age 12 (N = 2587) and 12.6% at age 16 (N = 4922). These results set the lower bound for polygenic score prediction of cognitive related traits and serve as a benchmark against which we compare different prediction models. We are building our models by leveraging several large publicly available GWAS summary statistics and testing different multivariate GWAS methods and polygenic score approaches with the aim of maximizing variance predicted in *g* and educational achievement. We will report on the most predictive combination of modelling approaches to trait prediction.

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How parents facilitate the educational achievement of their children: an adoption study

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Unlike most behavioral phenotypes, educational achievement is substantially influenced by environmental factors shared by siblings reared in the same home. For example, shared environmental factors have been estimated to account for 30% or more of the variance in educational attainment (Branigan et al. 2013). This strong evidence of shared environmental influence raises the question of what parents do to foster the educational attainment of the children they rear. Resolving this question is, however, difficult in intact nuclear families where environmental and genetic effects may be confounded by passive gene–environment correlational processes. As an alternative, we use data on adoptive families from the Sibling Interaction and Behavior Study (SIBS) in an attempt to identify specific factors contributing to the shared environmental influence on educational attainment. SIBS is a longitudinal study of 409 adoptive and 208 non-adoptive families and includes 1232 offspring and their rearing parents. SIBS offspring participants have been assessed up to three times, at an average (SD) age of 14.9 (1.9) at intake, 18.3 (2.1) at follow-up 1, and 22.4 (1.9) at follow-up 2. Rate of participation was 94% at the first and 92% at the second follow-up. SIBS participants are currently completing a third follow-up assessment, although data from that follow-up will not be used in this presentation. We investigated the following, not necessarily independent, mechanisms by which highly educated parents might foster the educational achievement of the children they rear (c.f., McGue et al. 2017): (1) by creating rearing environments that support the development of the cognitive and non-cognitive skills underlying academic achievement; (2) by contributing financially to the education of their children; (3) by establishing high academic expectations; (4) by helping their children complete academic tasks (e.g., homework, tutoring); (5) by providing a structured, non-chaotic home environment; and (6) by living in safe neighborhoods with good schools. We concluded that there is no single major way by which parents foster the academic achievement of their children. Perhaps the nature of the shared environmental influence on educational attainment is not altogether unlike the genetic influence, with multiple minor contributing factors.

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Genetic overlap between ADHD and externalizing, internalizing and neurodevelopmental disorder symptoms: a systematic review and meta-analysis

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder (Wilens, Biederman & Spencer 2002) and affects approximately 5% of children (Polanczyk, de Lima, Horta, Biederman & Rohde 2007). About half of those diagnosed in childhood continue to have the diagnosis and symptoms in adulthood (Kessler et al. 2006). The co-occurrence of ADHD with other psychiatric disorder symptoms (Burt et al. 2001; Cole et al. 2009; Polderman et al. 2014) has been suggested to be partly explained by a shared genetic vulnerability (Polderman et al. 2014). However, the strength of the genetic overlap is currently unclear. Also, no study has examined whether the genetic correlations differs between age groups (childhood versus adulthood), by rater (self-report, other informant, combined (parent-teacher, parent-twin, teacher-twin)), or by type of psychiatric disorder symptoms (externalizing, internalizing, neurodevelopmental). To address this gap, we conducted a systematic literature search to identify relevant twin studies, in PubMed, PsycINFO, and EMBASE. A total of 31 articles were identified and included in the present study. The pooled estimates showed that the comorbidity between ADHD and diverse psychiatric disorder symptoms were explained by shared genetic effects $rg = 0.50$ (0.43–0.56). A similar shared genetic overlap between ADHD and psychiatric

disorder symptoms was observed in both childhood $rg = 0.51$ (0.42–0.61) and adulthood $rg = 0.47$ (0.40–0.53). Similar results were also found for self-reports $rg = 0.49$ (0.42–0.55), other informants $rg = 0.50$ (0.40–0.60), and combined raters $rg = 0.51$ (0.30–0.69). Further, the strength of the genetic correlations of ADHD with the externalizing $rg = 0.49$ (0.39–0.59), internalizing $rg = 0.55$ (0.40–0.68) and neurodevelopmental $rg = 0.47$ (0.40–0.53) spectrums were similar in magnitude. These findings emphasize the presence of a shared genetic liability between ADHD and externalizing, internalizing and neurodevelopmental disorder symptoms, independent of age and rater.

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Type 2 diabetes in the Washington State Twin Registry

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Background: Once considered a disease of older age, type 2 diabetes (T2D) is now prevalent across both younger and older age and all demographic groups in the US. The reasons for this prevalent health problem span biologic to policy-level factors. In adults 45 years and older, the DISCOTWIN consortium showed a moderate to high contribution of genetic factors in structural equation modelling of T2D in twins from European and Australian cohorts, with a pooled heritability estimate of 72%. The purpose of this study was to investigate the contributions of genetic and environmental factors from structural equation modeling of T2D in twins 45 years and older in a US twin cohort and compare the estimates with those reported in the DISCOTWIN consortium, and to determine how these factors differ in older and younger (above and below 45 years) US twins.
Methods: Data was obtained from 6881 same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs from the Washington State Twin Registry that responded to the question "Has a doctor ever diagnosed you with (type 2) diabetes?" Twins missing a response were excluded. In 43% of the sample, diabetes type was not specified, whereas in the remainder the question specifically queried on type 2 diabetes. We combined responses to both questions to ascertain T2D prevalence because T2D accounts for 90% of all diabetes cases in the Registry. Twin similarity in T2D among those over and under 45 was analyzed using both tetrachoric correlations and structural equation modeling. Twin pairs discordant for being above and below 45 years were excluded, unless the younger twin was within 6 months of turning 45, in which case they were included in the above 45 group.
Results: There were 4187 pairs (70% MZ, 64% female) under and 2694 pairs (64% MZ, 64% female) over 45 in the sample. Overall, 9.3% of MZs over 45 and 1.6% of MZs under 45 were discordant for T2D. In both MZ and DZ twins discordant for T2D, the twin with T2D had a significantly higher BMI than the nonaffected cotwin. Correlations were higher in MZ ($r_{MZ} = 0.75$, 95% CI 0.68–0.81) than DZ ($r_{DZ} = 0.51$, 95% CI 0.38–0.62) pairs over 45. However, differences in the MZ-DZ correlations were attenuated in twin pairs under 45 ($r_{MZ} = 0.65$, 95% CI 0.45–0.79; $r_{DZ} = 0.67$, 95% CI 0.46–0.80). In twins over 45, the best fitting model only included additive genetics and unique environment, with a heritability of 77%, consistent with the DISCOTWIN findings. However, in twins under 45, the best fitting model included only the shared and unique environment, with the shared environment contributing 66% of the variance.
Conclusion: Consistent with findings from European and Australian twin cohorts, heredity is the strongest influence on T2D in US twins over 45. On the other hand, the shared environment is the strongest influence on T2D in US twins under 45.

First genetic variants for eudaimonia and the genetic overlap with hedonia

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Whether hedonia or eudaimonia are two distinguishable forms of well-being is a topic of ongoing debate. To shed light on the relation between the two, large-scale available molecular genetic data were leveraged to gain more insight into the genetic architecture of the overlap between hedonic and eudaimonic well-being. Hence, we conducted the first genome-wide association studies (GWAS) of eudaimonic well-being ($N = \sim 108$ K) and linked it to a GWAS of hedonic well-being ($N = \sim 222$ K). We identified the first two genome-wide significant independent loci for eudaimonic well-being and 6 independent loci for hedonic well-being. Joint analyses revealed a moderate phenotypic correlation ($R = .53$), but a high genetic correlation ($r_g = 0.78$) between eudaimonic and hedonic well-being. For both traits we identified enrichment in the frontal cortex -and cingulate cortex as well as the cerebellum to be top ranked. Bi-directional Mendelian Randomization analyses using two-sample MR indicated some evidence for a causal relationship from hedonic well-being to eudaimonic well-being whereas no evidence was found for the reverse. Additionally, genetic correlations patterns with a range of positive and negative related phenotypes were largely similar for hedonic- and eudaimonic well-being. Our results reveal a large genetic overlap between hedonia and eudaimonia.

Stress vulnerability effects on gene–environment correlation over time

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People select environments nonrandomly, in part because people match to environments based on their enduring genetic predispositions and existing environmental access. Previous research has demonstrated how person-environment matching processes can be parameterized in longitudinal twin studies (Beam, Turkheimer. *Dev Psychopathol* 2013;25:7–16; de Kort, Dolan, Boomsma. *Neth J Psychol* 2012; 67:81–90). These studies have shown that gene–environment correlation can be estimated to quantify the strength of the match between people and their environments over time. Using a reciprocal effects framework (Bronfenbrenner, Ceci. *Psychol Rev* 1994;101:568–86; Dickens, Flynn. *Psychol Rev* 2001;108:346–69), people actively seek out and are reinforced by their subsequent environmental exposure based on their genetic and environmentally influenced behavior. One statistical consequence of this process is that gene–environment correlation increases over time. Yet, whether stress conditions affect the degree to which people pursue environments that are a stronger match for them has not been explored. In this study, we test the hypothesis that person-environment matching is stronger in high stress vulnerability periods compared to low stress vulnerability periods. We present a longitudinal twin study of positive affect (PA) and negative affect (NA) using a sample of normal menstrual cycling MZ and DZ female twin pairs from the Michigan State University Twin Registry (Klump et al. *Twin Res* 2006, 9:971–977) across 25 days of the menstrual cycle (MZ pairs = 250; DZ pairs = 191). We used a genetic simplex model that allows for estimation of gene–environment correlation parameters over 25 days. Specifically, the parameter allows for the accrual of within-family gene–environment correlation (rGE) in DZ twins, which is used to test whether gene–environment correlation is stronger during high stress vulnerability periods versus low stress vulnerable periods. High stress vulnerability period was defined as the second half (luteal phase) of the menstrual cycle while low stress vulnerability was defined as the first half (follicular phase) of the cycle. We observed no systematic rGE pattern during the first-half of these twins' menstrual cycles whereas rGE for both PA and NA increased steadily during the luteal phase. Additionally, we note that heritability of PA and NA increased slightly during this same period. Persistence of nonshared environmental effects were not observed. We conclude with a discussion about why gene–environment correlation is stronger during high stress vulnerability periods compared to low stress vulnerability periods.

Heritability of sleep duration from early adolescence to young adulthood

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Purpose: Many individuals fail to get the recommended amount of sleep per night, despite the fact that sleep duration is associated with physical and psychological health. While many characteristics of sleep are heritable, there are discrepancies in heritability estimates for sleep duration as age, sample size, and measures of sleep duration vary (h^2 = 0.00–0.52; Barclay et al. 2010, Sletten et al. 2013). Sleep pressure and duration change throughout development, with adolescence showing particular growth. The purpose of this study is to assess the heritability of weekday and weekend sleep duration for in a longitudinal sample of adolescents as they mature into young adults.
Methods: Participants included 857 same-sex twins from the Longitudinal Twin Sample at the University of Colorado Boulder (54%MZ; 51% female). They were primarily Caucasian (86.6%), and born between 1986 and 1990. Sleep duration was assessed at 4 time-points spanning adolescence through early adulthood for both weekday and weekend sleep (W1: mean age 13.12 (SD = 1.82), W2: M = 17.26 (SD = 0.64), W3: M = 21.07 (SD = 2.02), W4: 22.28 (SD = 1.28)). Participants were asked, "About how many hours of sleep do you usually get each week night?" followed by "How about on weekend nights?" Answer options included: < = 5, 6, 7, 8, 9, 10, 11+, or, would rather not answer.
Analyses: The present study investigated: (1) the heritability of weekday and weekend sleep duration at each time-point using univariate (AE) twin models; (2) whether was there significant stability throughout development or if unique genetic influences come online; and (3) to what degree did weekday and weekend sleep share genetic effects using a series of Cholesky decompositions.
Results: Mean sleep durations decreased over time, with shorter average weekday sleep durations compared to weekend sleep. Heritability estimates for weekday sleep ranged from h^2 = 0.15 (age 21) to h^2 = 0.43 (age 23), and weekend sleep ranged from h^2 = 0.13 (age 12) to h^2 = 0.38 (age 17). Overall heritability increased as individuals aged. We examined genetic stability across time and found evidence for shared genetic variation between earlier sleep and later sleep: at ages 12–17 (r_A = 0.61, SE = 0.13) and 21–23 (r_A = 0.99, SE = 0.01) for weekday sleep and from 17 to 21 (r_A = 0.46, SE = 0.17) and 21 to 23 (r_A = 0.61, SE = 0.16) for weekend sleep. Lastly, we asked whether the same or different genetic variation contributed to weekday and weekend sleep within time-points, and we found shared genetic variation at all time-points ranging from r_A = 0.44 to 0.92.
Conclusion: Weekday and weekend sleep duration are moderately heritable from adolescence to young adulthood, and at least some of the same additive genetic variation contributes to heritability both across time and across weekday and weekend sleep.

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Shared genetic and environmental effects on social support, stress, and depression in Adult African American Twins

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Introduction: Prior twin studies suggest that various types of social support (SS) are genetically influenced (h^2_{ss} up to 75% depending on the measure)[1]. One possible explanation for the observed heritability of SS is that the observed additive genetic contributions reflect effects on associated psycholopathology(ies) that might not have been measured/modeled (i.e., gene–environment correlation effects; e.g., personality traits). Given that it is still relatively unknown how SS affects depression and stress-related behaviors in African Americans, the present study examined the co-heritability of stress, depression, and perceived quantity and quality of emotional and instrumental support.

Methods: Data were collected from adult African American twins (MZ pairs = 102 and DZ pairs = 179 from 396 families; 41% male) who reported on SS provided by their friends and/or family over the preceding year. Participants described the quantity and quality of support in two distinct areas: (1) emotional support (i.e., activities such as being comforted when upset), and (2) instrumental support (i.e., receiving assistance in the form of advice, transportation, or money when needed). Additionally, an abbreviated 11-item Center for Epidemiological Studies-Depression (CES-D) scale was used to evaluate their depression over the past week, and the Perceived Stress Scale (PSS) was completed to measure participants' appraisal of stress over the past month. Univariate twin models were run to determine the role of additive genetic (A), non-additive genetic (D), or common/shared environment (C) effects, and non-shared environmental effects (E). Bivariate twin analyses examined the relationship between instrumental SS and depression, as well as instrumental SS and stress. All models were run using Mplus (version 8) and controlled for variation in age and gender.
Results: The estimated broad-sense heritability differed across depression, perceived stress, and both indices of social support. AE models best described depression, perceived stress, and quantity/quality of instrumental support. The best fitting models were: (1) AE effects on perceived stress ($a^2 = 0.22$) and depression ($a^2 = 0.47$), (2) CE effects on the quality and quantity of emotional support ($c^2 = 0.18$ and $c^2 = 0.19$, respectively), and (3) AE effects on the quality and quantity of instrumental support ($a^2 = 0.23$ and $a^2 = 0.17$, respectively). Bivariate AE models testing the genetic and non-shared environmental covariance between depression and both types of instrumental social support indicated moderate genetic overlap ($rA_{DEPRESSION-QUALITY} = -0.64$, $\Delta\chi^2_{rA-DEPRESSION-QUALITY}$ 1.852, $\Delta df = 1$, $p = 0.17$, $\Delta BIC = -0.61$; $rA_{DEPRESSION-QUANTITY} = 0.79$, $\Delta\chi^2_{rA-DEPRESSION-QUANTITY} = 0.73$, $\Delta df = 1$, $p = 0.39$, $\Delta BIC = -1.74$). Similarly, additive genetic effects on perceived stress were common with instrumental quality ($rA_{STRESS-QUANTITY} = -0.74$, $\Delta\chi^2_{rA-STRESS-QUALITY} = 1.79$, $\Delta df = 1$, $p = 0.18$, $\Delta BIC = -0.68$) and with instrumental quantity ($rA_{STRESS-QUANTITY} = 0.65$, $\Delta\chi^2_{rA-STRESS-QUANTITY} = 0.134$, $\Delta df = 1$, $p = 0.71$, $\Delta BIC = -2.33$).
Discussion: The current study provides novel insight into the relationship between stress, depression, and social support in African Americans. Moreover, the possibility of a gene–environmental correlation (evocative/active) suggests cautionary use of social support indices as moderator variables of risk for depression and stress.

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Polymorphisms in dopaminergic genes predict proactive inhibition in a Go/No Go task

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Efficient avoidance of actions that have been rendered inappropriate or maladaptive by altered environmental demands is a critical neurocognitive mechanism. Disturbed response inhibition is seen in many neurodegenerative pathologies, and is a putative early indicator endophenotype for some psychiatric disorders. One of the processes that contribute to response inhibition is the deliberate slowing of reaction time following an error, or where cessation of a prepotent response might become necessary. This process is referred to as proactive inhibition. The Go/No–Go paradigm (e.g., the Sustained Attention to Response Task) allows us to distinguish proactive inhibition (slowing of response speed following an error to improve the likelihood of successful inhibition on future no-go trials) from reactive inhibition (withholding a prepotent response on no-go trials). We isolated post-error slowing (PES), an error-correction mechanism that approximates proactive inhibition, to reconcile the inconsistencies in the literature as to whether proactive inhibition relies on the indirect basal ganglia pathway and DRD2 receptors, or the hyperdirect pathway and DRD1 receptors. We investigated whether PES is better predicted by SNPs associated with enhanced dopamine D1 versus D2 neurotransmission (rs686/A at DRD1 is associated with increased expression of the DRD1 gene, and rs1800497/C at DRD2/ANKK1 is associated with increased D2 receptor density) in 260 healthy individuals. We report a main effect of rs686 and polygenic interaction derived from an unweighted genetic risk score (rs686 and rs1800497) that each indicate a genetic predisposition toward higher dopamine D1 neurotransmission increases proactive inhibition. This suggests that PES requires activation of the hyperdirect pathway.

Polygenic influences on clinical features of schizophrenia in diverse populations

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Schizophrenia is a common complex psychiatric syndrome that is clinically heterogeneous. Individual presentations embrace diverse constellations of positive, negative, and affective symptoms, and patients vary with respect to onset, course and outcome, and response to treatment. Despite considerable advances in our understanding of the multifactorial architecture of schizophrenia, research on clinical features of schizophrenia has seen considerably less progress, largely owing to comparably much smaller sample sizes. We extend previous findings from the Psychiatric Genomics Consortium (PGC) Schizophrenia Phenotype Working Group, Bipolar Disorder Working Group, and Cross-Disorder Group to the Genomic Psychiatry Cohort (GPC) studies of schizophrenia and bipolar disorder. Subsequent mega-analyses combine available clinical data on substance use, age-of-onset, and symptom dimensions from the PGC and GPC in what represent the largest such studies to date, and the first to incorporate large numbers of cases with African (N = 6152) or Latino (N = 1234) ancestry. We consider the evidence of associations between symptom level items and both specific variants and aggregate genetic factors, as well as pleiotropic polygenic effects. The largest of these studies, of age-of-onset of psychotic symptoms, attained a combined discovery sample size of over 20,000 schizophrenia cases of European, African, and Latino ancestry.

Prediction of aggression by ADHD subscales in children and adults

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Based on Bayesian machine learning analysis performed in the MATRICS consortium, in clinical adolescent ADHD and population cohorts, differential associations between aggression and hyperactivity and between aggression and inattention were suggested. We

aimed to replicate these findings in the large population based Netherlands Twin Register in childhood (age 7–16 years) and in adulthood, employing both cross-sectional and longitudinal designs. In children and in adults outcome and predictor variables were assessed by comparable instruments. Aggression was assessed by the Achenbach System of Empirically Based Assessment (ASEBA) age-appropriate inventories, namely the Child behavior Check List (CBCL), the Youth or the Adult Self Report (YSR/ASR). Hyperactivity and inattention were assessed by the Conners Parent Rating Scale-Revised: Short version (CPRS-R:S) and the Adult ADHD Rating Scales (CAARS). Based on linear regression analyses in which hyperactivity and inattention predicted aggression, we observed different results in children and in adults in a series of cross-sectional and longitudinal analyses. In children, hyperactivity was a stronger predictor of aggression than inattention. However, in adults, inattention was the stronger predictor. As data were collected in twin families, we next will estimate the extent to which genetic correlations between aggression and these ADHD subscales explain the observed associations. ACTION (Aggression in Children: Unraveling gene–environment interplay to inform Treatment and InterventiON strategies) and MATRICS (Multidisciplinary Approaches to Translational Research In Conduct Syndromes) are supported by funding from the European Union Seventh Framework Program (FP7/2007–2013).

Quantitative reconcilliation of GWAS and candidate gene findings: measurement error, nonlinearity, and artifactual results

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Candidate gene and genome-wide investigations of complex traits and related endophenotypes are both fundamentally concerned with elucidating the biological pathways underlying individual differences in behavior. However, these two methods have produced disparate literatures and have often reached contradictory conclusions about the genetic architectures of target traits. Previous attempts at reconciling these discrepancies have been largely theoretical, and both methods continue to gain popularity in the broader social sciences. In contrast, the present research uses rigorous quantitative methods to evaluate plausible explanations for the current disagreement in the literature: poor measurement, coarse phenotyping, and simplistic models in genome-wide studies versus publication bias, methodological errors, and non-replication in candidate gene work. Particularly, we investigate the extent to which the above arguments might explain previously published results, relying on both analytic results and reanalysis of genome-wide association study results. We aim to aid investigators in parsing the fragmented empirical literature and in selecting future lines of inquiry likely to advance our understanding of genetic architecture.

Examining the relevance of candidate genes for major depression

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Major Depressive Disorder (MDD) is substantially heritable, but its genetic architecture is complex, and identifying specific molecular genetic polymorphisms underlying MDD susceptibility has been difficult, even compared to other complex psychiatric disorders. Whether or not the candidate gene approach has aided our understanding of MDD, particularly in the context of genome-wide association study results, is controversial and polarizing among behavioral scientists. The current research, comprising the most comprehensive and well-powered investigation of candidate polymorphism, candidate gene, and candidate gene-by-environment interaction hypotheses in MDD to date, is in direct response to this ongoing controversy. We focus on three lines of inquiry concerning how these polymorphisms may impact MDD liability:

1. additive effects of the most commonly studied polymorphisms;
2. moderation of polymorphism effects by environmental exposure;
3. additive effects at the whole gene level.

We first empirically identified the 18 most commonly studied candidate genes in MDD research between 1991 and 2016 from the corpus of scientific publications indexed in the PubMed database. Within these regions, we determined the most commonly studied variants and their canonical risk alleles. Using data from the UK Biobank initial touchscreen interview and online mental health follow-up, we examined multiple measures of MDD (e.g., lifetime diagnostic status, symptom severity among individuals reporting mood disturbances, lifetime number of depressive episodes), employing multiple statistical frameworks and, in interaction analyses, considering multiple indices of environmental exposure. Our results aim to directly address the following question: do the large datasets of the whole-genome data era lend any support to previous canonical candidate gene hypotheses?

The genetics of depression: exploring the role of traumatic environments

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Exploring both the environmental and genetic risk factors for depression is essential if geneticists and epidemiologists can contribute to the improvements in healthcare for depression. In UK Biobank there are $\sim$ 157k people who have completed a standardised questionnaire on common mental disorders that included 26 childhood and adult trauma items. We compared the shared aetiology between depression and a range of phenotypes, contrasting individuals reporting trauma exposure with those who did not (final sample size range: 24,094–92,957). Depression was heritable in participants reporting trauma exposure and in unexposed individuals, and the genetic correlation between depression in participants reporting trauma exposure and in unexposed individuals was substantial. Genetic correlations between depression and psychiatric traits were strong regardless of reported trauma exposure, whereas genetic correlations between depression and body mass index (and related phenotypes) were observed only in trauma exposed individuals. The homogeneity of genetic correlations in trauma unexposed depression and lack of correlation with BMI echoes earlier ideas of endogenous depression.

Genetic and environmental associations between objective sleep and weight indicators in 8-year-old twins

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Previous research has established associations between sleep and weight indictors (e.g., body mass index [BMI]; Gregory et al. 2006). For example, twin studies suggest that sleep indicators may be as high as 70% heritable, and BMI between 60 and 70% heritable in middle childhood (Fernandez et al. 2012; Maes et al. 1997). One adult twin study found that associations between self-reported sleep duration and BMI may be accounted for by environmental effects rather than shared genetics (Watson et al. 2010). However, it is unclear whether objective sleep indicators (sleep duration, efficiency) are associated with objective weight indicators in children (BMI, waist circumference, and percent body fat), and the extent to which these associations may be genetic or environmental. The sample included 203 twin pairs (28.6% MZ, 37.6% same-sex DZ, 33.5% opposite-sex DZ; 54.4% Caucasian, 26.1% Hispanic; M_{age} = 8.5 years) drawn from the Arizona Twin Project (Lemery-Chalfant et al. 2013). Objective sleep indicators were collected using wrist-based accelerometers (Ambulatory Monitoring Inc.). Weight and percent body fat measurements were collected at home visits using a Tanita scale with bioelectrical impedance, and waist circumference was collected using Gulick tape measures. BMI was computed using height and weight, accounting for age and sex. Bivariate models were fit in OpenMx after regressing out the effects of age and sex. Phenotypic correlations between sleep duration/efficiency and weight ranged from .18 to .23. Heritability for sleep ranged from .47 to .50, and from .90 to .91 for weight indicators. Thus, the best fitting model for all bivariate models was an ACE-AE model, with no reduction in model fit. Covariance between sleep duration and all weight indicators were primarily accounted for by shared additive genetic factors. For sleep duration models, shared additive genetics accounted for 8% of the variance in BMI, 7% of the variance in waist circumference, and 11% of the variance in percent body fat. In sleep efficiency models, shared additive genetics accounted for 9% of the variance in BMI, 8% of the variance in waist circumference, and 10% of the variance in percent body fat. Future studies should test possible environmental moderators of genetic associations between sleep and weight.

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Genetic contributions to suicidal ideation and neurocognitive functioning

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Despite the challenges associated with conducting large scale genetic studies of suicide, researchers have used twin and family studies to identify heritability estimates ranging from 17 to 55% for suicide-related phenotypes (e.g., attempts, ideation, behavior, etc.). These studies are often conducted in adult samples and findings are fragmented across a wide range of operational definitions of suicide, including ideation with or without a plan, non-fatal attempts with low or high lethality, and death by suicide. Several researchers have promoted the adoption of endophenotypes in an effort to focus genetic research on traits that are more proximal to genes and the underlying biology of disease. Mann et al. (2009) proposed several endophenotypes for studying suicidal behavior, including neurocognitive function. The present study investigated: (1) the heritability of suicide phenotypes within a sample of adolescents and (2) the genetic correlation of suicide across four domains of neurocognitive functioning (memory, executive, social cognition, and complex cognition) phenotypes among adolescents.

Genome-wide data (N = 3564 unrelated individuals of European Ancestry, aged 8–21, 49.7% male) were drawn from the Philadelphia Neurodevelopment Cohort and imputed (5,360,405 biallelic single nucleotide polymorphisms [SNPs] after imputation and quality control). Participants completed a clinical assessment of psychopathology symptoms based on the Kiddie-Schedule for Affective Disorders and Schizophrenia as well as a computerized neurocognitive battery (CNB) that assessed speed and accuracy across several domains. Factor analysis of the CNB items yielded four domains (i.e., memory, executive, social cognition, and complex cognition). Suicidal Ideation (SI) was operationalized as having endorsed one or more questions involving current or lifetime thoughts about death/dying or killing self. Genomic-relatedness-matrix restricted maximum likelihood estimation was used to determine the proportion of variance in suicide and neurocognitive phenotypes attributable to additive genetic variance (h^2_{SNP}) and bivariate models were used to estimate the genetic correlation between traits (r_G). Genome-wide association (GWA) analyses were performed with adjustments for multiple testing to identify significant markers associated with each phenotype. All traits were adjusted for gender and age. Nearly 17% of adolescents in the sample reported SI, including current (3.21%) and lifetime thoughts about death or dying (13.83%) and thoughts about killing themselves (7.54%). The SNP-heritability estimate for SI was 11% (SE = 8%) and was nominally significant ($p = 0.086$). SNP-heritability estimates for the neurocognitive domains were all significant and ranged from 13 to 25%, with 13% (SE = 8%, $p = 0.032$) for social cognition, 17% (SE = 8%, $p = 0.013$) for memory, 24% (SE = 8%, $p < 0.001$) for complex cognition, and 25% (SE = 8%, $p < 0.001$) for executive. Bivariate analyses indicated a nominally significant r_G between SI and memory ($r_G = 0.68$, SE = 0.57, $p = 0.07$). No single marker for any phenotype was significant at the GWA level of $p < 10^{-8}$. Consistent with previous genetic research, neurocognitive phenotypes were heritable. Endorsement of SI had a small, nominally significant SNP-heritability estimate that was genetically correlated with memory. Implications and future directions for genetic studies of SI are discussed.

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Considering the multiverse of gene–environment interplay

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Development is complicated. Phenotypes are influenced by genetic variants, environmental experiences, and complex interconnections between these factors dynamically across the lifespan. In contrast, behavior genetic decompositions give estimates of isolated and static genetic and environmental variance. Some empirical studies track how genetic and environmental influences shift across development or operate differently across context. However, even the best attempts at empirically delineating gene–environment interplay represent vast oversimplifications of the dynamic and interactive processes that likely operate to some extent. These models necessarily rely on sets of assumptions, the reasonableness of which may be either known or unknown. Potential models of parallel, sequential, and reciprocal processes of gene–environment correlation and gene–environment interaction are nearly unlimited, and vastly under-determined when considering the available data. Here, we articulate a framework for evaluating how these complex developmental processes might combine to produce results obtained under standard behavior genetic methods. It is relatively easy to identify the effect of one processes, such as active gene–environment correlation leading to genetic variance in a twin model, but it is much more difficult to say how this process plays out in relation to gene–environment interactions and how these effects might wax and wane across the lifespan. A solution to this problem will allow us to answer important questions: (1) Given a set of observed empirical trends (e.g., genetic and environmental variance estimates, stability estimates, and how they shift across the lifespan), which combinations of additive, interactive, and dynamic processes are plausible and which can be ruled out?; and (2) When does the dynamic, highly interactive nature of development ensure that the 'gloomy prospect' of unsystematic and non-replicable genetic associations with a phenotype becomes an unavoidable certainty?

Direct and indirect pathways to middle childhood anxiety symptoms: the role of inherited risk, early childhood characteristics, and negative parenting

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Hostile parenting in early childhood has been linked to increased child anxiety in the developmental literature. However, some genetically informed studies have shown that the covariation between negative parenting and child anxiety is largely attributable to heritable influences. Thus, hostile parenting and child anxiety may be associated via gene–environment correlation (*r*GE). To rule out the presence of passive *r*GE, the present study examines whether hostile parenting during the preschool period is linked to increased middle childhood anxiety symptoms assessed via a diagnostic interview in a sample of parents and their adopted children. The present study examines data from the Early Growth and Development Study (Leve et al. 2013), a longitudinal parent–offspring adoption study ($N = 561$ children). Inherited vulnerability for psychopathology was indexed using a composite score created from structured diagnostic interviews administered to birth parents that capture lifetime internalizing, externalizing, and substance abuse symptoms. Toddler anxiety symptoms were assessed via adoptive parent report of the Internalizing T-Score on the Child Behavior Checklist at age 27 months and parents' reports were averaged. Adoptive parents reported on their own hostile parenting when children were age 4.5 years using the Iowa Family Interaction Rating Scales. Middle childhood (M age = 7.37 years) generalized anxiety symptoms were assessed via the preschool age psychiatric assessment (PAPA), a clinical interview administered to one adoptive parent per family. Structural equation models exhibited good model fit [c^2 (2) = 0.01, p = *ns*; RMSEA = .00; CFI = 1.00; SRMR = .001] and indicated that toddler anxiety symptoms were directly related to middle childhood anxiety symptoms ($\beta = .17$, $p < 0.01$) and indirectly via hostile parenting at 4.5 years ($\beta = .06$, 95% CI [0.02, 0.10]). Inherited vulnerability for psychopathology was related to toddler anxiety symptoms ($\beta = .12$, $p < 0.01$) but was not related to hostile parenting or middle childhood anxiety symptoms. Together, results suggest that middle childhood anxiety symptoms have early developmental origins and evoke hostile parenting, which in turn leads to increased anxiety symptoms.

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A novel family-based model to evaluate the role of mitochondrial DNA in neuropsychiatric phenotypes

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Mitochondrial DNA is distinct from nuclear DNA in two key ways: it is passed exclusively through the maternal line, and is passed essential intact from mothers to their children (i.e., it recombines with copies of itself). As such, all offspring that are biologically related through their mothers have identical mitochondrial DNA. This includes all full siblings, maternal half-siblings, and cousins who are related through their mothers, but not paternal half-siblings or cousins who are related through their fathers. We argue that this unique inheritance pattern can be exploited to quantify the effects of mitochondrial DNA on phenotypes. Such work would be critically important, not only for clarifying the presence or absence of mtDNA effects, but also because it would establish a clear prior for subsequent molecular genetic studies (as twin studies did for nuclear DNA). We will evaluate the utility of our new family-based model several ways: first, we will conduct a series of simulation studies in a variety of family structures to ensure that our model identifies the effects as intended. Second, we will run a series of power analyses, again in a variety of family structures, to get a sense of the samples sizes necessary to detect mtDNA. Third, we will run the model in two children-of-twin samples, each with roughly 1000 twin pairs and their children. We also hope to run the model in a large population-based registry (active discussions are underway). Implications from our results, and complications to be considered in the future, will be discussed.

One reason children in the same family are so different: parental difference in phenotype

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Based on evidence from twin and adoption studies, children raised in the same family show little resemblance in cognitive ability, personality, or psychopathology after accounting for genetic effects, indicating that relevant environmental factors result in differentiation rather than convergence within sibling pairs (Plomin and Daniels 1987). One potential factor underlying sibling differentiation is parental difference in phenotype. Using scores from the BFI-S, a short version of the Big Five Inventory completed by parents and twins in the German study 'TwinLife', we assessed whether parents who were more different from one another in their personality ratings had twin children who also were more different from one another. Parental personality difference significantly predicted within-pair personality difference in both DZ and MZ young adult twins; the same pattern emerged but was not significant in the adolescent twin cohort. The pattern was not evident for other traits; parental difference in height and weight did not predict twin difference.

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Extracting stability increases the SNP heritability of emotional problems in young people

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Twin studies have shown that emotional problems (anxiety and depression) in childhood and adolescence are moderately heritable ($\sim$ 20–50%). In contrast, DNA-based 'SNP heritability' estimates are generally $< 15\%$ and non-significant. One notable feature of emotional problems is that they can be somewhat transient, but the moderate stability seen across time and across raters is predominantly influenced by stable genetic influences. This suggests that by capturing what is in common across time and across raters, we might be more likely to tap into any underlying genetic vulnerability. We therefore hypothesised that a phenotype capturing the pervasive stability of emotional problems would show higher heritability. We fitted single-factor latent trait models using 12 emotional problems measures across ages 7, 12 and 16, rated by parents, teachers, and children themselves in the Twins Early Development Study sample. Twin and SNP heritability estimates for stable emotional problems (N = 6110 pairs and unrelated individuals, respectively) were compared to those for individual measures. Twin heritability increased from 45% on average for individual measures to 76% (se = 0.023) by focusing on stable trait variance. SNP heritability rose from 5% on average (n.s.) to 14% (se = 0.049; p = 0.002). Polygenic scores for both adult anxiety and depression significantly predicted variance in stable emotional problems (0.4%; p = 0.0001). The variance explained was twice that in most individual measures. Stable emotional problems also showed significant genetic correlation with adult depression and anxiety (average = 52%). These results demonstrate the value of examining stable emotional problems in gene-finding and prediction studies. We suggest that future genomic studies of emotional problems could benefit from adopting a lifelong approach, using measures of adult case/control status as well as childhood dimensions. We are currently testing whether these findings replicate in two other samples (NTR and TCHAD).

Investigating the causal relationships between mental and physical health outcomes using Mendelian randomization

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Mendelian randomization (MR) is a statistical genetics approach that allows inferring causal relationships between human traits and health outcomes using genetic variants as instrumental variables. Specifically, 2-sample MR analysis utilizes genetic effects on the exposure and the outcome to infer the exposure-outcome causal relationship. The effects of genetic variants on the exposure and the outcome can be estimated with standard genetic association analysis and are often available from existing genome-wide association studies (GWAS). With publicly available GWAS summary results for a wide range of human traits, 2-sample MR analysis enabled us to comprehensively investigate the causal relationships between human traits and health outcomes. Here, we utilized 95 publicly available GWAS summary results and UK Biobank to investigate the causal relationships between human traits and mental and physical health outcomes. We focused on the causal relationship between psychiatric disorders and physical health outcomes, including schizophrenia, bipolar disorder, major depression, autism spectrum disorder, autoimmune disorders, coronary artery disease, diabetes, etc. We also investigated the effects of complex traits, such as height, BMI, blood lipids, brain imaging, personality, on health outcomes. Multiple methods were used to detect and control for potential pleiotropic biases in the MR analysis, including modified Q and Q′ test, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test, Multivariable MR, MR-Egger regression, weighted median-based MR estimator, and weighted mode-based MR estimator. We also conducted bi-directional MR analysis to elucidate the causal relationship for given pairs of traits and health outcomes. Our analysis highlighted the complex causal relationships between mental and physical health outcomes.

Higher genetic risk for schizophrenia is associated with living in more densely populated areas

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Social stress in urban life has been proposed as an environmental risk factor associated with the increased prevalence of schizophrenia in

urban compared to rural areas. However, the potential genetic contributions to this relationship have been largely ignored. We used data of genotyped adults from four independent non clinical cohorts. Analyses performed in the discovery cohort (QIMR, Australia, N = 15,544) were replicated in participants from the UKB (United Kingdom, N = 456,426), the NTR (The Netherlands, N = 16,434) and QSKIN (Australia, N = 15,726). We found higher genetic loading for schizophrenia in participants living in more densely populated areas. Mendelian Randomization suggested that high schizophrenia genetic risk is a causal factor in choosing to live in denser areas; these results were only significant in the UKB, our largest cohort. Our study investigates the association between genetic risk for schizophrenia and characteristics of where people live using data from 504,130 participants from three different countries. Our results support the hypothesis of selective migration to more urban environments by people at higher genetic risk for schizophrenia and suggest a need to refine the social stress model for schizophrenia by including genetic influences on where people choose to live.

GWAS meta-analysis of nausea and vomiting during pregnancy

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Nausea and vomiting during pregnancy (NVP) is an extremely common condition in pregnancy (70% prevalence) that may affect the psychosocial functioning of affected women. There is an increased prevalence of major depressive disorder prior to pregnancy among women with severe NVP and NVP is a risk factor of postnatal depression. There is evidence from different methodological approaches that NVP is highly heritable. The NVP Genetics Consortium is a collaborative project that aims to identify the causes of NVP. One of the goals is to identify novel genetic variants associated with NVP by carrying out a genome-wide association study (GWAS) meta-analysis on the presence of NVP.

These analyses include data from 27,631 women from participating cohorts (QIMR, Australia; MTR, Spain; ALSPAC, United Kingdom; EGCUT, Estonia). Each cohort ran GWAS for NVP severity (with the exception of EGcut which analysed HG case status) including age and age2 at time of interview, and the first four ancestry principal components as covariates. Meta-analysis is currently underpowered (we are awaiting data from two additional large samples). Within the current results we see a suggestive intronic signal (1e−07) with CERS6 (2q24.3) a gene that is implicated in weight gain and glucose intolerance (in mice). We also see a suggestive intronic signal (7e−07) within SLC39A12 (10p12.33) a Zinc transporter implicated in carbohydrate and lipid metabolism. These results are an important first step toward understanding which genes are associated with NVP. Future directions involve a larger meta-analysis and use of multivariate GWAS to investigate the potential genetic variants influencing NVP and other phenotypes.

Socioeconomic status and adolescent alcohol involvement: evidence for a gene–environment interaction

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Adolescent alcohol use patterns stem from both genetic and environmental influences. In addition to these factors contributing additively to risk for use, genetic and environmental factors interact with each other to inhibit or exacerbate risk (Young-Wolff et al. 2011). Socioeconomic status (SES) is one environmental factor that might interact with genetic risk for alcohol use. Two theories exist for understanding how SES might interact with genetic risk: (1) the social control model (Shanahan and Hofer 2005) and (2) the diathesis stress model (South et al. 2015). Evidence for these two competing theories is complicated by the fact that an agreed upon definition of SES has not been reached, and many studies conceptualize the term using only social status or financial status indicators. The current study examined indicators of both family social status and financial resources as potential moderators of genetic and environmental influences on alcohol involvement among adolescents using data from the 1962 National Merit Twin Study. 839 same sex adolescent twin pairs (509 monozygotic and 330 dizygotic) from the 1962 National Merit Twin Study completed a questionnaire containing items assessing alcohol involvement. Twins were approximately 17 years old at the time of participation. Parents provided reports of family income and educational attainment. Results provided evidence for moderation of genetic and environmental influences on alcohol involvement by family income. For twins with the lowest levels of family income, genetic influences accounted for 50% of the variance in alcohol involvement, compared to just 2% of the variance among those at the highest level of income. Shared environmental influences accounted for 67% of the variation among twins at the highest levels of family income compared to 26% among twins at the lowest level of income. Despite a lack of significance, analyses did show that genetic and shared environmental influences varied across average parental education levels, particularly for females. These findings suggest etiological influences on alcohol involvement vary as a function of an adolescent's socioeconomic status. Implications and limitations are discussed.

The genomics of neonatal abstinence syndrome

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An epidemic of neonatal abstinence syndrome (NAS) currently exists due to dramatic increases in prenatal opioid exposure. Significant variability has been observed in the development and severity of NAS among neonates exposed to prenatal opioids. This suggests that genetic factors may be playing a significant role. This has prompted case control studies that have examined the association of several single nucleotide polymorphisms (SNPs) in genes known to be involved in opioid metabolism and addiction with length of hospitalization, need for pharmacologic treatment, and total days of opioid treatment in neonates with NAS (1). Previous studies in small cohorts have demonstrated an association with genetic variants in the *OPRM1, COMT, and PNOC* genes with a shorter length of hospital stay and less need for treatment in neonates exposed to opioids in utero (2, 3). We recently conducted a multisite randomized controlled trial examining the most common pharmacologic treatments in infants with NAS. If parents refused the treatment portion, they could still consent to data collection and buccal swabs for genomic analyses in infants. A total of 262 infants had adequate samples and data available. Isolated DNA was tested on the Illumina Omni Array with 2.5 million SNPs involving addiction, psychiatric diseases, opioid metabolism. Once we filtered out markers defying Hardy Weinberg equilibrium or those unable to be precisely mapped, 1.3 million markers remained for testing. While 24,000 SNPs met genome-wide significance at $p < 0.05$ with false discovery rates of 5%, 29 SNPs

met significance using 1%, and 9 SNPs met significance using a cutoff of 5×10^{-5}. While analysis of individual SNPs was important, a focus on biologic plausibility through pathway analysis was considered to be more robust. KEGG and PANTHER pathway analyses found genes involved with drug detoxification, inflammation, and antioxidant capacity to be associated with the development and severity of NAS. Genes associated with GABAnergic synapses, morphine and nicotine addiction, endocannabinoid signaling, opioid proenkephalin pathways, enkephalin release, and histamine signaling and release were also found to have important associations. Preliminary data indicate that genetic factors are associated with NAS. However, larger scale trials with a nationwide biobank will be needed to establish more definitive associations in order to implement a more targeted and Precision Medicine approach to NAS.

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Genome-wide investigation of alcohol response: a meta-analytic review

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Heritability estimates from twin and family studies suggest that approximately 50% of the variation related to the development of alcohol use disorder (AUD) can be attributed to genetic influences (Verhulst et al. 2015). Nonetheless, molecular genetic efforts attempting to identify individual variants that confer risk for the development of AUD have yielded few replicable results suggesting that large sample sizes achievable through meta-analysis will be required to identify robust associations. An additional challenge in the genetic study of complex traits such as AUD is the substantial phenotypic heterogeneity found within the AUD diagnosis. One strategy for addressing this heterogeneity is the examination of AUD endophenotypes that focus on specific subfacets of AUD (Gottesman and Gould 2003). One well-established AUD endophenotype is level of response (LR) to alcohol. LR is the extent to which a specific dosage of alcohol produces the responses typically associated with alcohol consumption (Schuckit 1980). One widely-used retrospective measure of LR to alcohol is the Self-Rating of the Effects of Alcohol questionnaire (SRE; Schuckit et al. 1997). Notably, previous molecular genetic studies of LR, including studies of the SRE, have reported associations with multiple variants and genes of interest; however, these studies have also resulted in inconsistent findings (e.g., Joslyn et al. 2010). The current study is an initial effort to extend results from previous molecular genetic studies of LR to alcohol by conducting a meta-analysis of two genome-wide association studies (GWAS) of SRE participant reports of their first five drinking episodes (*SRE First 5*). GWAS were carried out examining common variants (MAF > 0.05) for each sample using a linear mixed model approach to account for familial relatedness and population substructure. Results were then meta-analyzed using a weighted inverse-variance fixed-effects model in METAL (Willer et al. 2010) yielding a final sample size of $N = 1568$. Notably, no individual variants in either of the respective samples, or the combined meta-analysis of the two samples, reached genome-wide significance. The top single-variant association across samples was found in an intergenic region located near the *CD5L* gene (rs12086663, $p = 6.28 \times 10^{-7}$) located on chromosome 1. An additional finding of interest emerged in an intronic region of *SYNE1* located on chromosome 6 (rs4472361, $p = 2.64 \times 10^{-6}$) that has previously been implicated with alcohol dependence and alcohol and tobacco co-use outcomes (e.g., Edenberg et al. 2010; Otto et al. 2017). These findings suggest that, similar to other complex traits, larger sample sizes will be required to achieve adequate power to examine the genetic influences contributing to LR to alcohol. Importantly, the current study represents initial findings from a larger meta-analytic effort aimed toward achieving sufficient power to identify individual genetic variants that contribute to alcohol response outcomes and AUD more broadly.

Does warm parenting mitigate birth risk effects on conduct problems? An MZ twin differences study

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Can an emotionally warm and supportive post-natal environment mitigate the effects of low birth weight (BW) and premature birth on conduct problems (CP) in childhood (Aarnoudse et al. 2009)? There is evidence from correlational studies and at least one intervention that the answer is 'yes', via enrichment of psychosocial and learning experiences that support optimal development (e.g., Bagner et al. 2010). However, the prior work has not controlled for genetic factors, even though it is known that BW is heritable (Lunde et al. 2007) and parenting reflects, in part, child evocative gene–environment effects (Wang et al. 2017). To address this gap, we used an identical twin differences design and hypothesized that: (1) the combination of low birth weight (relative to co-twin) and short gestation would most strongly predict CP (relative to co-twin); and (2) this effect would be strongest when parental warmth was lowest, and weakest at the highest levels of parental warmth. The sample included 114 MZ twin pairs, assessed three times (5-7 years; composite scores analyzed) for parent-rated CP and observer-rated parental warmth. The full regression model predicting MZ difference in CP was significant, F (7, 107) = 3.258, $p = 0.004$, $R^2 = .18$. The hypothesized two-way ($\beta = .23$) and three-way ($\beta = -.33$) interactions were significant. Post-hoc probing revealed that the anticipated BW-by-gestation interaction effect was weakest at high warmth, and strongest at low warmth. It was among the lower warmth households that we found the combination of low BW and earlier birth to most strongly predict higher CP (relative to co-twin). The findings indicate that future research should examine the interaction of BW and gestation length when predicting outcomes. More importantly, the results lend further credence to the emerging literature suggesting that enriched post-natal parenting environments can mitigate deleterious effects of birth risks on behavioral adjustment outcomes.

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Monozygotic twin similarities for AD biomarkers: the Twin60+ study

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Background: Limited information is yet available on the genetic architecture of Alzheimer's Disease (AD) biomarkers in non-demented subjects. In 2014 we started the EMIF-AD Twin60+ study in which we collected an extensive set of AD amyloid and neuronal injury biomarkers in 98 cognitively healthy elderly monozygotic twin pairs from the Netherlands Twin Register. We aim to assess the predictive value of early AD biomarkers in this healthy group and to determine the resemblance in monozygotic twins, especially by multivariate modeling to get insight into the etiology of comorbidity among markers. Here we present the first results of our study on the monozygotic twin similarity for a range of these biomarkers.
Methods: Twin correlations were calculated for continuous data obtained for amyloid pathology as assessed on [^{18}F] Flutemetamol positron emission tomography (PET) scans and in cerebrospinal fluid (CSF), hippocampal volume and cortical thinning as estimated using Freesurfer, functional connectivity on resting state networks as measured with functional magnetic resonance imaging (fMRI), white matter hyperintensities, structural gray matter connectivity constructed from structural MRI and memory tests.
Results: We found moderate to high correlations in monozygotic twins (58% female, average age 70.2 $\pm$ 7.3), with correlations of 0.54 for amyloid pathology measured on PET and in CSF, 0.78 for hippocampal volume, 0.54 for cortical thickness, 0.41 for resting state network connectivity, 0.76 for white matter hyperintensities, 0.67 for structural gray matter connectivity and 0.52 for memory tests.
Conclusions: Even after more than 60 years of life, there are substantial similarities in monozygotic twins for amyloid and neuronal injury markers. This indicates that genetic factors are likely to play an important role in AD pathophysiology. However, resemblance is less than 100% indicating a role for non-genetic factors as well. Next steps include the study of non-genetic risk factors, including epigenetics, lifestyle, vascular comorbidity and inflammation status. These mechanisms may explain the difference in AD markers within monozygotic twin pairs. Unraveling the mechanisms underlying monozygotic twin differences, may eventually lead to the discovery of early treatment targets and preventative strategies for AD. This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking EMIF grant agreement n°115,372.

G×E in health and well-being

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From theoretical, evolutionary, and experimental non-human genetic perspectives, gene–environment interactions (G×E) are expected to influence human behavioral outcomes. Existing approaches to modeling G×E, however, take narrowly defined approaches to selecting genes, environments, outcomes, and models, rather than seeking to develop a bird's-eye view of patterns of G×E influence. Such an omnibus perspective proved useful to developing an understanding the typical structure of genetic main effects, demonstrating that, across phenotypes: main effects are numerous and individually small; and phenotypic correlation implies genetic correlation, whereby variants identified as associated with one outcome can be used as reliable indicators of others. We can ask similar questions in a G×E space. That is, what is the likely distribution of G×E influences, in terms of both effect sizes and effect shapes; and to what extent are sources of G×E outcome-specific versus general. This project explores patterns of G×E across a variety of health-relevant outcomes (subjective well-being, neuroticism, tobacco use, and body mass index) by educational attainment (as an indicator of resource stability versus uncertainty). Patterns of heritability and prediction are compared to understand the distribution and consistency of G×E shape, structure, and size across phenotypes and modeling approaches. Estimation of effects in both twin samples and among unrelated individuals provides unique information that allows us to restrict the universe of likely effects embedded within the larger pattern of observed data. Results suggest potential for the development of higher-order theories of G×E that can be applied broadly to complex mental and physical health outcomes.

Couples' drinking and perceived spousal support: contextual influences of regional socioeconomic status

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Assortative mating for alcohol use is significant, and couples who report greater discrepancy in alcohol consumption also report greater marital dissatisfaction. Previous research has not investigated how regional and SES differences can shape associations between drinking and spousal support. This study examined the effects of individual drinking (ID), spousal drinking (SD) and regional socioeconomic status (RSES) on individual differences in spousal support. We hypothesized that lower RSES and higher discrepancy between ID and SD predicts less perceived spousal support. Participants were adults from two Australia Twin Registry cohorts. RSES was assessed using postal-code area level Index of Relative Socio-economic Advantage and Disadvantage scores. Linear mixed effect models adjusting for zygosity indicated a three-way interaction between ID, SD, and RSES for women ($\beta = -0.07$, $p < 0.05$ (-0.11 to -0.03 [NG1])). In other words, discordant drinking effects (e.g., how ID moderated the association between SD) on spousal support were evident in low RSES areas. In contrast, regardless of the discordance between couples, higher levels of SD negatively affected social support in high RSES areas; there was no effect of discordance when

SD was high, and a positive effect of discordance when SD was low. Sex-limited biometric genetic twin models were fitted to further explore associations between ID, SD and RSES. Associations between ID and SD were best explained by shared genetic risks for men (rG = 0.88, $p < 0.05$). For women, ID-SD associations were best explained by common (rC = 0.77, $p < 0.05$) and unique (rE = 0.37, $p < 0.05$) environmental risks. For women, associations between ID and RSES were explained by shared genetic risks (rG = 0.93, $p < 0.05$), there was no shared risk between ID and RSES for men. The [NG2] association between SD and RSES was explained by shared unique (rE = 0.61, $p < 0.05$) and common (rC = 0.49, $p < 0.05$) environment risk for men. There was no shared risk between SD and RSES for women. There was a shared genetic risk between SD and spouse support for women (rG = − 0.98, $p < 0.05$), and a shared common environment association for men (rC = 0.97, $p < 0.05$). The current study indicates how RSES relate to spousal support via its effect on SD and ID. In particular, RSES appears to play a role in how much alcohol discrepancy relates to spouse support. Also for women, similarity in couples' drinking is more environmentally driven. This suggests that assortative mating related to alcohol use, at least for women, may not play a role in associations between RSES, alcohol use discrepancy and spousal support. However, shared genetic risk does influence how ID, SD, and RSES interactively relate to spousal support in two specific ways, particularly in the shared genetic risk between one's drinking and regional SES, as well as the risk between how much their partner drinks and how much they perceive their partner's support.

Genetics, cybernetics, and human agency

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Cybernetics, the study of goal-directed, adaptive, information processing systems that self-regulate via feedback, can serve as a bridge from genetics to an understanding of human agency that is mechanistic but can also encompass the phenomenology of free will. In this talk, I lay out an argument for this approach, describe a cybernetic theory of individual differences (DeYoung 2015), and apply it briefly to understanding mental illness (DeYoung and Krueger, in press). Gray (2004) has argued that cybernetics is necessary for a mechanistic understanding of living things because the laws that govern biological systems are not reducible to the laws of physics. As physical objects, organisms obviously obey the laws of physics, but under physical law any base pair can be adjacent to any other in DNA. Evolutionary theory can describe the historical process that leads to the structure of a particular organism, but cybernetics describes law-like regularities in the structure of all organisms because cybernetic systems are exactly what evolution necessarily produces, as organisms pursue strategies that increase the likelihood of reproduction. A basic tenet of cybernetics is that the concept of "agency" is applicable specifically and exclusively to cybernetic systems. As complex cybernetic systems, human beings are unusual in their ability to adopt an extraordinarily broad range of goals. Most species are genetically constrained to pursue a very particular set of goals relevant to survival and reproduction, whereas human beings, though obviously subject to evolutionary pressures, have evolved capacities for exploration and abstraction that both allow and require us to choose many of our goals, leading to the flexibility of human agency with which philosophers are often concerned. We relate differences in agency across situations and individuals both to the likelihood of the individual's choosing differently under similar conditions and to the integration of the various goals that the individual pursues. This cybernetic perspective can reconcile and improve on two competing types of account in the philosophical literature on agency, which have been described as "control" theories and "self-expression" theories (Sripada 2016).

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Using the genetic architecture of externalizing disorders to aid in gene identification

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Twin and family studies have unambiguously demonstrated a shared genetic architecture across disorders and traits characterized by behavioral disinhibition and impulsivity. The underlying latent factor has been called Externalizing, and is highly heritable. Externalizing is a core feature of many psychiatric and substance use disorders, and encompasses multiple clinical diagnoses across development, including attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder, antisocial personality disorder, alcohol use disorders, and other substance use disorders, as well as personality traits and behaviors characterized by under-control. Capitalizing on the known genetic overlap, we have launched a new consortium that will employ genome-wide association studies (GWAS) of externalizing phenotypes, with the goal of identifying genes involved in the shared underlying liability to Externalizing versus genes unique to specific phenotypes, and boosting statistical power for GWAS of specific externalizing phenotypes that are currently available in only relatively small samples. We apply Genomic SEM, a new multivariate method, which applies structural equation modeling to summary statistics from genetically correlated traits. With the method we perform exploratory and confirmatory factor analyses, allowing for sample overlap. Our initial analyses include GWAS summary statistics for addictive behaviors ($N \sim 157{,}000$), ADHD ($N \sim 53{,}000$), alcohol consumption ($N \sim 414{,}000$), antisocial behavior ($n \sim 16{,}000$), childhood aggression ($N \sim 19{,}000$), lifetime cannabis use ($N \sim 32{,}000$), and several risk behaviors ($N \sim 370{,}000$–$405{,}000$). We present results from the initial analyses of these phenotypes and our planned future directions. We conclude with details about the Externalizing Consortium, in order to invite groups to participate in the next wave of analyses.

The need for racial/ethnic diversity in genetics research, and how we make that happen

Danielle Dick, Virginia Commonwealth University

The vast majority of genetics research has been conducted in populations of European descent. This is true of both twin-family studies, as well as gene identification efforts. Recently, there has been growing recognition of the need to increase diverse representation in genetic studies, to ensure that all groups equally benefit from scientific advances. However, recruiting racial/ethnic minority groups into genetic studies can be challenging, for a number of reasons. In this presentation, we will present our efforts to create a more inclusive genetically-informed study through the Spit for Science project. We discuss the interesting and important questions that can be addressed by studying more diverse samples. Finally, we review why understanding pathways of risk and resilience in our increasingly diverse world will be critical to improving human health and well-being, and the role that behavior geneticists can play in that effort.

Inaccurate perceptions of emotional faces elicit bullying via gene–environment correlations

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A number of factors may increase the vulnerability of a child to be victimized by other children. One risk factor is child genotype, acting indirectly through temperament or other behaviors that may evoke bullying from others (DiLalla and John 2014, Genetic influences on victimization during preschool play with unfamiliar peers. Merrill-Palmer Quarterly, 60, 168–192). A possible set of evocative behaviors might be child emotion skills, including the ability to accurately portray emotions as well as to accurately read others' emotions. In this study of multiples aged 6–16 years old, children were assessed for accuracy of expressed emotion (EE) by being photographed while being told to display certain emotions (happy, sad, fearful, or angry). Six different unbiased raters viewed the photographs in random order and rated which emotion they thought was being portrayed. Children also were assessed for accuracy of emotion recognition (ER) on the DANVA (Nowicki 2005, The manual for the Diagnostic Analyses of Nonverbal Accuracy (DANVA) tests. Atlanta, GA: Emory University) by watching children's faces on a computer and rating each for happy, sad, fearful, or angry. Genetic risk scores for angry and fearful EE and ER errors were calculated as a function of co-twin's errors (top 33%) and zygosity (if co-twin scored in the bottom 33% for accuracy and was an MZ, risk = 4; if co-twin scored in the bottom 33% for accuracy and was a DZ, risk = 3; if co-twin scored in the top 67% and was DZ, risk = 2; if co-twin scored in the top 67% and was MZ, risk = 1). Children completed a victimization questionnaire administered by a tester in the lab. Mixed model multilevel linear regression results showed that children who were poor at making recognizably angry faces were less likely to be victimized ($p = 0.029$), but this relationship was an effect of between-family factors ($p = 0.040$) and causality could not be determined. Also, children who were poor at recognizing fearful faces were more likely to be victimized ($p = 0.021$), and this was due to a significant interaction between ER and zygosity ($p = 0.002$) and therefore shared genes. Finally, a significant gene–environment correlation was evident; children with a genetic risk for not recognizing other children's faces as angry when those children were intending to convey that emotion were significantly more likely to be in an environment characterized by peer bullying ($r = .27$, $p = 0.026$). These results suggest that girls who do not realize that their peers are feeling angry are likely to elicit bullying from their peers, perhaps because by mis-interpreting their peers' expressions they are responding incorrectly and inappropriately to negative situations. Interestingly, this did not hold for boys, suggesting that facial expressions may be less important as eliciting stimuli for them in social situations.

Genetic instrumental variable (GIV) regression: explaining socioeconomic and health outcomes in non-experimental data

Thomas Diprete, Columbia University; Casper Burik, Vrije Universiteit Amsterdam; Philipp Koellinger, Vrije Universiteit Amsterdam

Abstract: Identifying causal effects in non-experimental data is an enduring challenge. One proposed solution that recently gained popularity is the idea to use genes as instrumental variables (i.e. Mendelian Randomization—MR). However, this approach is problematic because many variables of interest are genetically correlated, which implies the possibility that many genes could affect both the exposure and the outcome directly or via unobserved confounding factors. Thus, pleiotropic effects of genes are themselves a source of bias in nonexperimental data that would also undermine the ability of MR to correct for endogeneity bias from non-genetic sources. Here, we propose an alternative approach, GIV regression that provides estimates for the effect of an exposure on an outcome in the presence of pleiotropy. As a valuable byproduct, GIV regression also provides accurate estimates of the chip heritability of the outcome variable. GIV regression uses polygenic scores (PGS) for the outcome of interest which can be constructed from genome-wide association study (GWAS) results. By splitting the GWAS sample for the outcome into non-overlapping subsamples, we obtain multiple indicators of the outcome PGS that can be used as instruments for each other, and, in combination with other methods such as sibling fixed effects, can address endogeneity bias from both pleiotropy and the environment. In two empirical applications, we demonstrate that our approach produces reasonable estimates of the chip heritability of educational attainment (EA) and show that standard regression and MR provide upwardly biased estimates of the effect of body height on EA.

Tens of thousands of associations but no causal mechanisms revealed: mismatches between GWAS and developmental molecular biology

Stephen Downes, University of Utah

Lowe and Reddy conclude: "As of February 2015, genome-wide association studies (GWAS) and other studies had demonstrated the association of more than 15,000 SNPs with a complex disease or trait (Welter et al. 2014). However, the mechanisms underlying these associations remain largely undefined. More generally, the underlying architecture of complex diseases and traits remains poorly defined." Here I consider whether we should be surprised at the disparity between apparent successes of GWAS (and other related techniques) and lack of success at isolating underlying genetic mechanisms for the relevant traits. I argue that we should not be surprised and proceed by examining the mismatch in methods and assumptions between GWAS and related techniques on the one hand and developmental molecular biology on the other. I argue that Richard Lewontin's (1974) conclusions about mismatches between high heritability measures and claims about genetic causation can be applied here. I support my claim that Lewontin's arguments are relevant to this issue by looking at a few detailed examples of contrasting genetic approaches to human traits.

Are neuroticism, depressive rumination, and anger rumination genetically distinct?

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Anger and depressive rumination—patterns of repetitive, self-focused thought in response to either anger or sadness—are transdiagnostic risk factors of psychopathology. Previous research has identified these two clinically relevant ruminative subtypes as phenotypically overlapping yet distinct constructs. Additional work has emphasized how these two ruminative subtypes have predictive value distinct from neuroticism, a personality trait that has strong relations with psychopathology and is often associated with rumination. However, no research has directly examined whether rumination is genetically distinct from neuroticism. Thus, the present study investigated the extent to which anger rumination, depressive rumination, and neuroticism share genetic and environmental influences. These analyses were conducted on 877 individuals from 439 same-sex twin pairs in the Colorado Longitudinal Twin Study. Seven subscales were taken from three rumination questionnaires administered at age 23 and used to create depressive and anger rumination latent variables. Neuroticism subscales from shortened versions of the Eysenck Personality Questionnaire administered at ages 16 and 21 were used to create a neuroticism latent variable. Multivariate Cholesky decompositions indicated common genetic and environmental influences on neuroticism, depressive rumination, and anger rumination. Genetic influences specific to rumination explained 20% of the variance of anger rumination and 7% of the variance of depressive rumination, although they were not statistically significant. Furthermore, depressive rumination had specific nonshared environmental influences after controlling for neuroticism and anger rumination, and anger rumination had specific nonshared environmental influences after controlling for neuroticism and depressive rumination. These results indicate that rumination is influenced by the same genetic variance as neuroticism, but both subtypes of rumination are distinguished by nonshared environmental influences. Building on these analyses, we plan to also examine whether the specific nonshared environmental influences and perhaps additive genetic variance on rumination predict internalizing and externalizing psychopathology. Our findings point to the importance of examining rumination as a multifaceted construct and deepen current understanding of the separability of rumination and neuroticism. Taken together, these findings suggest that a comprehensive understanding of these transdiagnostic risk factors must include an examination of both genetic and environmental influences.

TWINStudy of environment, lifestyle behaviors, and health

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The role of built (BE) and social environments in supporting healthy lifestyles has received increased attention over the last decade as research and prevention paradigms have shifted from a focus on individual-level behaviour change to macro-level influences embedded within social-ecological models that affect population health. The TWINS Cohort was set up to link biological and survey data with BE and social environment exposures developed from geocoded residential addresses of adult twins in the Washington State Twin Registry (WSTR). Twin studies enable the detection of environmental effects on health while reducing the structural confounding and biases inherent in studying unrelated individuals who have not been randomly assigned to different environments, as would happen in a randomized controlled trial, which in the case of the BE is neither practical nor ethical under free-living conditions. Twins are thus used as quasi-experimental controls for shared genetic and environmental effect confounds that cannot be held constant via random assignment. We specifically use the twin design to identify causal associations among unique environmental exposures, lifestyle behaviours, and a broad array of physical and mental health outcomes. Subsamples from the TWINS Cohort can be recruited based on select characteristics of interest for detailed, in-person studies. The present study reports on an ongoing prospective sub-cohort of TWINS in which identical (MZ) twins reared together, but who now live apart as adults, wear accelerometers and GPS data loggers for 1–2 weeks to measure objective physical activity levels within a real-time and space continuum. The purpose of this prospective study is to investigate cross-sectional and longitudinal associations between the walkability of the home neighbourhood BE and objective walking and moderate-to-vigorous physical activity (MVPA) levels (minutes per week in activity "bouts") controlling for genetic and shared environmental influences. The commercially available Walk Score® index is used to derive a continuous walkability score normalized on a scale of 0–100, with 100 being the most "walkable" neighbourhood. We quantify both walking and MVPA levels inside and outside of empirically defined neighborhoods using the *Life Log* framework our group previously developed. The home neighborhood BE is quantified within circular buffers of different sizes (e.g., 833 m, 1666 m) and types (Euclidean versus network-based) and is conceptualized using two different definitions based on the location of GPS data points beginning, ending, and/or traversing the pre-defined buffers. In one analysis from this sub-cohort (n = 106 individual MZs), objectively measured walking bouts were related to neighborhood walkability, controlling for twin pair ID (random factor), sex, age, BMI, and income ($p < 0.01$). The findings held regardless of buffer size or type (all $p < 0.05$). In ongoing analysis of this sub-cohort, 144 MZ pairs have thus far completed baseline and 15 MZ pairs 3-year follow-up assessments. Mean walking levels within the neighborhood are 60–84 min per week, while MVPA levels within the neighborhood are 35–63 min per week, depending on buffer size and neighborhood definition. Ultimately, this study will determine longitudinal, causal associations between changes in the BE on lifestyle behaviors and health.

Genes, exposure to adversity, and sensitive periods in risk for depression

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Across multiple disciplines, there is a long-standing belief that there are developmental windows when experience can have lasting effects in shaping behavior, health, and ultimately risk for disease. During

these "sensitive periods," experience may become biologically embedded due to occurring at a stage in development when the foundation of organs, tissues, and physiological systems is established. For example, an exposure coinciding with peak periods of brain plasticity may shape brain circuitry and function more than the same exposure occurring earlier or later in development. Although sensitive periods shaping risk for depression are not yet identified, they likely arise through a complex orchestration of genes and experience. With respect to genes, preclinical studies in animals have identified specific genes involved in regulating the timing and duration of sensitive periods. For instance, studies using mouse knock-in genetic models in the visual system have shown that increased *Bdnf* expression can initiate a sensitive period, whereas disruptions to *Gad2* delay sensitive period onset. With respect to experience, epidemiological studies are beginning to implicate specific age stages when the effect of adversity, including exposure to child maltreatment, is more potent in conferring risk for depression. Building from these two lines of evidence, the goal of the current study was to examine the role of sensitive period-regulating genes, alone and in interaction with exposure to adversity, on risk for depression. To accomplish this goal, we: (1) performed gene-level and gene-set-level analyses using data from the Psychiatric Genomics Consortium (PGC) to evaluate the effect on risk for major depressive disorder (MDD) of 53 genes shown in animal studies to regulate sensitive periods; (2) evaluated the developmental expression patterns of these sensitive period-regulating genes by analyzing data from BrainSpan, a transcriptional atlas of 57 healthy, post-mortem donors (ages 5.7 weeks post-conception to 82 years); and (3) tested for gene-by-development interplay by analyzing the combined effect of common variants in these sensitive period genes and timing of exposure to adversity within a population-based study of children (n = 6255). Results indicated that as a set, genes regulating the opening of sensitive periods were most associated with MDD risk; this included genes regulating neurogenesis (*BDNF, NTRK2*) and gaba-ergic neurotransmission (*GABBR1, GABRA1, GABRA2*). Genes implicated in MDD risk were also developmentally regulated. That is, age was significantly associated with expression levels in about half of the 15 MDD-implicated genes, explaining up to 56% of the variation in gene-level expression. Among genes associated with MDD, 75% (6 of 8) had a nadir of expression between ages 1 and 5. Gene-by-development interplay analyses revealed a significant main environmental effect of adversity exposure between ages 1 and 5 years ($\beta = 0.85$, 95% CI 0.57–1.12, p-value = .007), but no genetic main effect or gene-by-development interaction effect. These results indicate that genes involved in regulating sensitive periods may be implicated in depression vulnerability and be differentially expressed across the lifecourse, but that larger studies will be needed to identify developmental G×E effects.

Parental prenatal depression and offspring ADHD: a genetically informed intergenerational study

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Maternal prenatal depression has been associated with elevated levels of ADHD symptoms in offspring. This association could reflect detrimental effects of in-utero exposure to depression, but it could also be due to common genetic influences underlying depression and ADHD. The primary aim of the present study was to investigate whether an effect of maternal prenatal depression could be demonstrated while controlling for intergenerational transmission of genetic risk. In this study we use a children-of-twin design based on 17,070 sibling pairs, their partners and their children participating in the Norwegian Mother and Child Cohort Study. Self-ratings of prenatal depression were obtained from both mothers and fathers using the Symptom Checklist in week 17 and 30 during pregnancy. Maternal ratings of ADHD symptoms using Conner's Parent Rating Scale were obtained when the children were 5 years of age. Results will be presented at the conference.

A major role for common genetic variation in anxiety disorders

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Anxiety disorders are common, complex psychiatric disorders with twin heritabilities of 30–60%. Selecting from 126,443 individuals in the UK Biobank, we conducted a genome-wide association study of self-reported "Any anxiety disorder" (cases n = 21,108). As a secondary phenotype we also defined severe levels of current generalised anxiety symptoms ("Current anxiety symptoms"; cases n = 19,012). We had three sources of data for replication analyses. First, we identified cases who met criteria for self-rated lifetime assessment of probable generalised anxiety disorder, who were not also identified as meet our "Any anxiety disorder" criteria, thus these definitions were independent of one another ("Probable GAD"; cases n = 4345). Second, we utilised the published summary statistics from the ANGST consortium (cases n = 3695). Finally, we analysed anxiety cases defined using the same criteria as for our "Any anxiety disorder" definition from the iPSYCH consortium (cases n = 2829). Findings from these three sets of participants were considered individually, and were then meta-analysed together to create a combined replication sample. This was then meta-analysed with our "discovery", the UK Biobank "Any anxiety disorders" cases. The liability scale common variant heritability estimate for "Any anxiety disorder" was 31.1%, and for the total combined sample meta-analysis was 13.8%. Three novel genome-wide significant loci were identified including an intergenic region on chromosome 9 that has previously been associated with neuroticism. Genetic correlations between different anxiety definitions and levels of severity both within and across samples were very high. Anxiety phenotypes also showed significant genetic correlations with depression and insomnia as well as coronary artery disease, mirroring findings from epidemiological studies. We conclude that common genetic variation underlies a substantive proportion of the genetic architecture underlying anxiety.

Financial strain moderates genetic influences on self-reported health: support for social compensation model

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The existence of genetic influences on both health and SES attainment suggests that GE interplay plays a role in SES-health associations. Adverse environments raise the risk of disease for everyone, but various models of GE interplay predict that some genotypes are more vulnerable to adversity than others (diathesis-stress), enriched environments prevent the expression of an underlying genetic vulnerability (social compensation), or genetic factors are minimized in adverse environments and maximized in favorable ones (social enhancement). Differential susceptibility models propose that specific genotypes might be more responsive to the social environment at both positive and negative extremes. Nine of the 15 twin studies of adult development and aging that are part of the IGEMS consortium included items assessing financial strain as well as subjective health, representing 10,756 individuals. The sample was 55% women, included 3185 MZ twins and 5228 DZ twins, and age ranged from 24 to 98. A factor model was used to create a harmonized measure of financial strain across studies and items: extent to which money covers needs, difficulty in paying monthly bills, economic situation compared to others, and whether there is money for extras. Twin analysis of genetic and environmental variance for self-rated health incorporating age and financial strain as continuous moderators and sex as a dichotomous moderator indicated significant financial strain moderation of genetic influences on self-rated health. Genetic variance increased as financial strain increased, matching the predictions of the diathesis-stress and social comparison models for components of variance.

Genetic and environmental contributions to stability and change in callous-unemotional behaviors across the preschool years

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Behavioral genetic research on callous-unemotional behaviors (CU) in children shows that CU is genetically influenced as early as 2 years of age, and that there are genetic contributions to stability and change in toddlerhood and in middle to older childhood (M. Flom & K. J. Saudino, 2016, Dev Psychopathol, 29, 1227–1234; N. M. G. Fontaine et al. 2010, J Am Acad Child Adolesc Psychiatry, 49, 656–664; E. Viding & E. J. McCrory, 2012, Dev Psychopathol, 24, 969–983). Nothing, however, is known about the underlying etiology of development across the preschool years, when children undergo vast changes in moral and socio-emotional development. The present study expands upon previous work by using a new Boston University Twin Project cohort of 300 twin pairs at ages 3, 4, and 5 years (MZ = 123; DZ = 187). CU was assessed using the parent-reported Child Behavior Checklist 1.5–5 (T. M. Achenbach & L. A. Rescorla, 2000), and demonstrated moderate stability across age (r ranging from .44 to .52). Consistent with previous work at different ages, model-fitting analyses revealed little differential heritability across age (age 3 h^2 = .64 [.55–.72]; age 4 = .64 [.54–.71]; age 5 = .58 [.46–.67]), with nonshared environmental influences explaining remaining variance. Genetic correlations between age 3 and later ages were substantial (age 3 and age 4 r_g = .74 [.65–.82]; age 3 and age 5 r_g = .72 [.62–.82]), and continuity across these intervals was due solely to genetic effects. In contrast, the genetic correlation between CU at ages 4 and 5 was lower, and there were both genetic and nonshared environmental contributions to stability (r_g = .54 [.44–.64]; r_e = .43 [.30–.53]). Although there is substantial genetic covariation from 3 years on, there was also considerable novel genetic variance coming online. Age-specific genetic effects accounted for roughly 70% of the genetic variance in CU at ages 4 and 5. Nonshared environmental effects were primarily age-specific, though modest continuity across ages 4 and 5 explained 10% of the overall nonshared environmental effects at age 5. As with research in toddlers and older children, these results confirm that CU is genetically influenced in preschoolers, with genetic factors contributing to both change and stability and nonshared environmental factors primarily influencing change. The minimal, but significant, contribution of the nonshared environment to stability between CU at ages 4 and 5 is different from past research, and may represent small carry-over effects of unique peer or teacher influences that begin emerging at age 4, as more children in our sample enter preschool.

Genetic and environmental relations of executive functions to antisocial personality disorder symptoms and psychopathy

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Executive functions (EFs) are high-level cognitive abilities that help regulate thoughts and actions during goal-directed behavior. EF deficits, measured with laboratory cognitive or neuropsychological tasks, have been associated with multiple types of psychopathology, including internalizing and externalizing disorders. With respect to externalizing, meta-analytic findings suggest that antisocial behavior, broadly defined, and psychopathy are associated with lower performance on a range of EF tasks. The generality of the findings suggest that these behaviors may relate to a Common EF factor that captures covariance across multiple correlated but separable EFs and is thought to capture differences in goal implementation abilities. However, it is unclear whether this common factor accounts for all of the EF variance in antisocial behavior and psychopathy, or if they also relate to factors that capture abilities specific to particular EFs, such as updating working memory and shifting mental sets. Moreover, findings that antisocial behavior and lower cognitive ability are particularly associated with the psychopathy dimension reflecting social deviance and impulsivity (i.e., secondary psychopathy), compared to the dimension reflecting emotional-interpersonal functioning (i.e., primary psychopathy), raise the possibility that EF relates primarily to secondary psychopathy. We examined these possibilities with data from the Colorado Longitudinal Twin Study. At age 23, this sample (N = 765) completed measures of psychopathy, antisocial personality disorder symptoms (ASPDsx), and nine laboratory tasks tapping multiple EF latent variables—a Common EF factor, which is isomorphic with individual differences in response inhibition, as well as factors specific to updating working memory (Updating-Specific) and shifting mental sets (Shifting-Specific). Phenotypically, higher ASPDsx and secondary psychopathy, but not primary psychopathy, were associated with lower Common EF. Moreover, both primary and secondary psychopathy negatively correlated with Updating-Specific ability, which was unrelated to ASPDsx. Twin models indicated that the association between secondary psychopathy and ASPDsx was due to both genetic and nonshared environmental influences; however, Common EF's association with ASPDsx was primarily genetic,

whereas its association with secondary psychopathy was primarily environmental. These results indicate that the interrelations among EFs, psychopathy, and ASPD symptoms are multifaceted and may reflect different etiological pathways.

Adolescent-limited cannabis use and developmental delay

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Persistent heavy cannabis use in adolescence has been linked to a number of adverse outcomes in adult transitions, especially in the domains of educational attainment and career development. Given demonstrated risks of persistent adolescent use, the question of potential mitigating or rescuing factors arises. There is some previous work on the impact of cessation after adolescence; however, much of this work focuses on cessation or decrease in use much after the end of adolescence, usually focusing around the age of 25 or later. This study examines the cessation of use at or after the age of 20, with the aim of evaluating the effect of cessation directly after adolescence. We use data drawn from longitudinal studies at the University of Colorado through the Center for Antisocial Drug Dependence. These studies include twin samples, family samples, and individuals recruited from treatment and juvenile justice facilities, aiming to incorporate both community and clinical samples for a broad look at the impacts of adolescent cannabis use. Several use groups have been defined from these samples, including persistent (almost daily or more use before and after the age of 20), adolescent-limited (weekly or more frequent use before the age of 20; monthly or less frequent use after the age of 20), abstainer (no initiation before or after 20), late-bloomer (initiation only after the age of 20), and chippers (less than weekly use before and after the age of 20). We present results on adult transition variables such as highest level of education, number years of education, finishing high school, finishing university or trade school, finishing post-undergraduate education, still in school, ever employed, job type, income, income source, fulltime employment, relationship status, relationship satisfaction, and number of children, controlling for covariates such as age, sex, other drug and substance use, arrest and imprisonment, and pregnancy.

Behavioral approaches to probe value-based choice in genetic mouse models for neuropsychiatric disease

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Goal-directed behaviors are interrelated neural functions that organize animal behavior with respect to the surrounding environment. In humans, abnormalities in goal-directed function greatly impair situational adaptability and are frequently associated with neuropsychiatric disease. Mice, by virtue of numerous genetic tools, provide a unique opportunity to explore the molecular underpinnings of core neural circuits mediating goal-directed dysfunction. Towards this end, we generated dynamic operant foraging tasks that assess the selection of actions according to relative benefits and costs. We have modeled benefit as varying volumes of liquid reward and cost as increasing operant response schedules. After demonstrating that wildtype mice sensitively respond to both parameters, we explored how disease-associated mutations in the Neurexin1α synaptic adhesion molecule might compromise this function. Neurexin1α has a central role in organizing central synapses and is a significant genetic risk factor for schizophrenia, autism spectrum disorder and Tourette's syndrome. We find that Neurexin1α mutant mice can acquire operant responding similarly to wildtype mice and exhibit normal flexibility during un-cued contingency changes. However, Neurexin1α mutants exhibit robust deficits in value-based choice. Specifically, mutant mice show significantly less bias towards higher benefit (larger reward volume) choices than wildtypes while also showing less bias towards lower effort (shorter operant schedule) choices. Furthermore, we observed blunted local modulation of response vigor by recent outcome in mutants. Overall, these data are consistent with perturbations either of neural systems for value representation or action selection according to outcome value, a focus of our ongoing work.

Inhibitory control and attention deficit hyperactivity disorder (ADHD) in childhood: evidence from two multi-method, longitudinal twin studies

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In childhood, low levels of inhibitory control (IC) are associated with externalizing behavior problems and Attention Deficit Hyperactivity Disorder (ADHD). Multiple twin studies indicate that IC is genetically influenced, however; findings depend somewhat on the age of the participants and the assessment methodology (Gagne and Saudino 2010, 2016; Gagne and Goldsmith 2011). For example, two of these studies show evidence for shared environmental influences and non-significant genetic influences on lab-based assessments of IC at age 3. However, parent-ratings of IC show a much more stable and consistent etiology and developmental trajectory. Genetic and environmental covariance between IC and externalizing behavior problems has also been noted in toddlers (Gagne, Saudino & Asherson 2011) and school age children (Lemery-Chalfant, Doelger, Goldsmith 2008). We investigated the development and etiology of IC and ADHD behavior problems and symptoms from a multi-method perspective in two independent twin samples. Using both datasets allows us the ability to examine IC development and behavioral maladjustment within early childhood and longitudinally from toddlerhood, through school transition, to early adolescence. Participants included 300 twin pairs (half MZ), 2 and 3 years of age, from the Boston University Twin Project (BUTP) and between 143 and 237 MZ and 237–401 DZ twin pairs (samples sizes differ) at 2.5 years, early school age, and early adolescence from the Wisconsin Twin Project (WTP). In the BUTP, parents rated IC and externalizing and ADHD behavior problems, and a lab-based assessment of IC was collected at both ages. In the WTP, mothers rated IC in todderhood and first grade, and ADHD symptoms in first grade and early adolescence. In first grade, an observational measure of IC similar to that used in the BUTP was obtained. Phenotypic correlations between IC and behavior problems and ADHD symptoms ranged from − .10 to − .68. MZ correlations exceeded DZ correlations for most traits, indicating genetic influences. In addition, MZ cross-twin, cross-trait twin correlations between IC and ADHD generally exceeded DZ correlations indicating significant genetic covariance between IC and ADHD across age. Initial bivariate Cholesky decompositions of

BUTP age 2 IC (both parent- and lab-assessed) and ADHD behavior problems, WTP parent-rated toddler IC and first grade ADHD, and WTP parent-rated first grade IC and early adolescent ADHD yielded genetic and nonshared environmental variances and covariances. Toddler IC was phenotypically and etiologically associated with concurrent ADHD behavior problems and ADHD in first grade, as was first grade IC and early adolescent ADHD. Based on these findings, early IC can be considered a genetic risk factor for later ADHD symptoms. Future genetic analyses will include IC and ADHD behavior problems data from the BUTP at age 3, and laboratory-based behavioral assessments of IC and measures of home environment from WTP in early school age.

AC'RE model: estimating rearing effects without twins raised apart

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Studies of twins reared-apart and -together can untangle environmental effects further than classic designs. These reared-apart studies can partition the shared environment into the narrower rearing environment—common only to twins reared together, and the broader correlated environment—common to twins irrespective of rearing. Twins reared apart, however, are rare and arise from extraordinary circumstances. As a result, these studies have small samples that are unlikely to be representative or ethically replicated. In the current study, we address those limitations with an extended family design based on ordinary kinship categories: siblings, cousins, parent–child, and aunt-nibling. Similar to the twins reared-apart and -together, the shared environment can be partitioned into a narrow rearing environment (r) that siblings share and a broader correlated environment (c') that the extended family share. We call this model the AC'RE model. We illustrate this design, using data from the National Longitudinal Surveys of Youth (NLSY). The NLSY is multigenerational study and is based on a nationally representative household probability sample from the United States. Recently developed kinship links have produced over 42,000 kinship pairs (Rodgers et al. 2016); we use 36,370 of them across the following groups: Monozygotic Twins (n = 29 pairs) Full Siblings (9688) Parent–Child (11,477) Half Siblings (3390) Aunt-Nibling (7511) Cousins reared together (96) Cousins reared apart (4179) We estimated the heritability of self-reported adult height (standardized within gender, grouped by minority status), using the AC'RE model. Estimates varied by minority status. For minorities, a^2 was 80% (95% confidence interval [68, 93]), c'^2 4.6% (95% CI [.3, 14]), r^2 .3% (95% CI [0, 10]), and e^2 was 15% (95% CI [8.7, 24]). For non-minorities, a^2 was 88% (95% CI [81, 96]), c'^2 0% (95% CI [0, 1]), r^2 .3% (95% CI [0.8]), and e^2 was 11% (95% CI [5.4, 19]). The model fit very well; RMSEA was .016 (90% CI [0, .02]), TLI and CFI > .99, and SRMR was .034. Estimates were consistent with the literature and suggest that shared-environmental sources of height among minorities arise from outside the home rather than from within it. We will highlight other applications of the AC'RE model, note the differing interpretations of the rearing environment, and discuss the challenges associated with modeling intergenerational effects.

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Interplay of a country's income inequality in childhood and adult depressive symptoms

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The purpose of the study was to test the relationship between inequality of income distribution within one's country during childhood and depressive symptoms in adulthood, using both level of depressive symptom scores and the relative contribution of genes and environment to depressive symptom scores. Inequality of income distribution was operationalized as the percent of the nation's income controlled by the top 1% of the population when the individual was age 10. Our hypothesis was that the level of inequality to which a person was exposed during key development growth periods would moderate genetic influences on depressive symptoms in adulthood. Participants included 32,502 individuals from 13 IGEMS consortium twin studies in Denmark, Sweden, Finland, Australia, and the U.S. who completed a self-reported assessment of depressive symptoms as an adult. In pooled analyses, controlling for sex, age, and age-squared at which the depressive symptoms scale was completed, higher depressive symptom scores were observed in those who grew up in a society with a higher Top 1% index, that is, where income inequality was greater. Using a modified twin correlation model, we found that raw variance in depressive symptom scores was markedly higher for those who grew up in more unequal time-periods. Furthermore, twin correlations were moderated by inequality, with faster divergence of DZ similarity across the Top 1% compared to MZ similarity. This pattern implies increasing genetic effects with greater inequality, consistent with a diathesis-stress model. At lower inequality, there was a smaller relative contribution of genetic influences to depressive symptom scores, and a greater relative contribution of shared environment. At higher inequality, there was a larger relative contribution of genetic influences to depressive symptom scores, and a minimal contribution of shared environment. In summary, growing up in a more unequal society—where families experience wage stagnation, spiraling healthcare costs, and a sense of disenfranchisement and social isolation—potentiates genetic risk for depressive symptoms as an adult. Those growing up in a more equal society are more protected in adulthood from depressive symptoms.

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Genetic overlap between ADHD and ASD: a review of the evidence from twin and family studies

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Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are highly heritable neurodevelopmental disorders that frequently co-occur. Family studies have shown that relatives of individuals with ASD have an increased risk of receiving a diagnosis of ADHD (1–3) and that the magnitude of the risk is higher in relatives who are more genetically related (3). This implies that ADHD and ASD might be influenced by partially shared familial factors that are likely to be of genetic origin. This hypothesis is corroborated by twin studies, which have consistently found moderate genetic correlations between continuous traits of ADHD and ASD in the general population (4–7). In addition, because ADHD and ASD are

considered heterogeneous disorders, researchers have relied on twin studies to examine associations among ADHD and ASD subscales. These studies have found that in children there were stronger phenotypic and genetic correlations between all ADHD subscales and ASD subscales related to communication and social difficulties (5–6). However, in adults, there was a stronger association between all ADHD subscales and ASD subscale related to restricted and repetitive behaviors (7). In this review, we are going to summarize the evidence from family and twin studies regarding the possible genetic overlap between ADHD and ASD. We will compare results from studies using data on clinical diagnoses and traits continuously measured in the population in childhood, adolescence, and adulthood. Furthermore, we will investigate how the magnitude of the correlations between ADHD and ASD subscales may differ by age.

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Gene × SES interaction and age-related increases in the heritability of cognitive ability

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Background: The proportion of variance in cognitive ability due to genetic factors fluctuates across both age and environmental context. Numerous behavior genetics studies have demonstrated that the heritability of cognitive ability increases substantially as age rises. Gene × socioeconomic status (SES) interaction has also been observed in most U.S. samples, where individuals reared in higher SES environments show greater heritability of cognitive ability than lower SES peers. To date, these phenomena have been studied largely in isolation from each other, and the specific mechanisms that underlie them remain poorly understood. In this study, we propose that both G × SES interaction and age-related increases in the heritability of cognitive performance are driven by the same process: divergence in dizygotic (DZ) twins. Using longitudinal cognitive data from middle childhood and early adolescence, we tested whether (1) DZ twins become more phenotypically distinct more quickly than monozygotic twins with rising age, resulting in increased heritability; and (2) the rate of this divergence is modified by SES.

Methods: Hollingshead SES and longitudinal WISC data were drawn from the Louisville Twin Study (LTS). Data collection for the LTS ran from 1957 until the late 1990s, generating arguably the most comprehensive twin data on childhood cognitive development ever assembled. Twin pairs were all from the Louisville, Kentucky area, and were included in the current analyses if cognitive and SES data at ages 7, 8, 9, 12, and/or 15 years were available for both twins. We analyzed data from 566 twin pairs in total (282 monozygotic (MZ), 284 DZ; 236 same sex female, 210 same sex male, 120 opposite sex). 80.04% of the sample participated in data collection at three or more ages. We modeled divergence with a latent growth curve (LGC) model. Latent intercept and slope factors were created for the between-pair and within-pair variances in cognitive ability. Divergence was quantified by the within-pair slope and the within-pair covariance between intercept and slope. We tested whether these parameters differed between MZ and DZ twins. To test whether the magnitude of within-family divergence in cognitive ability varied as a function of SES, we compared the − 2 log likelihoods of four models. The first included the base LGC model plus linear main effects of SES on between- and within-pair intercept and slope factors, moderation of the within-pair slope variance, and moderation of the covariance between the within-pair intercept and slope factors. In the second model, the moderation of the within-pair slope variance was constrained to 0. In the third model, moderation of the within-pair intercept and slope correlation was constrained to 0. Finally, in the fourth model, the moderation of both the within-pair slope variance and the covariance of the within-pair intercept and slope were constrained to 0. All twin analyses were performed using OpenMx with full information maximum likelihood estimation and NPSOL optimization.

The genetic and environmental structure of psychopathology spectra in middle childhood

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In recent years, there has been a renewed interest in understanding the causes of psychiatric comorbidity, and several studies have re-examined dimensionality using hierarchical or bi-factor modeling techniques. Previous reports from child and adolescence samples indicate that early psychopathology can be conceptualized through two dimensional spectra: internalizing and externalizing risk. Evidence for a higher order general factor that accounts for comorbidity across the two specific spectra has also been found. Childhood and adolescence comprises several developmental stages where rapid changes can occur. A current limitation in understanding the structure of childhood psychopathology is that samples incorporating broad age spans are most common. Clearly defined age ranges are needed to understand the nature of comorbidity because factors leading to co-occurrence may differ throughout the lifespan. Although efforts have been made to assess associations between psychopathology spectra and personality, to the best of our knowledge, no studies have systematically incorporated normal personality traits into these models. Understanding the genetic and environmental structure of childhood

psychopathology is important both for general knowledge and for designing intervention strategies. In this study, we aim to investigate the joint structure of common psychopathology symptoms (e.g. anxiety, depression, conduct disorder, and ADHD) and normal personality traits in children from a twin-sibling subsample of the Norwegian Mother and Child Cohort Study. Preliminary results will be presented at the conference.

Nurturing our better nature: epistemic integrity as a foundation for autonomous living

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Do we bear responsibility for our beliefs and attitudes? Answering this question is especially important in today's "post-truth" cultural climate. In particular, can we choose to cultivate an active, truth-oriented approach to our thinking and belief formation, even if we do not directly control the content of our beliefs as such? A growing body of work on epistemic responsibility and doxastic voluntarism contends that we both *can* and *should* choose to control our thinking (Audi 2001; Paul 2015). Some philosophers have even argued that this freedom over our thought processes is the source and prerequisite of our moral agency (Clifford 1877; Salmieri and Bayer 2014). After all, if we cannot choose how—and whether—to think, how responsible can we be for the actions we take on the basis of our thinking (or non-thinking)? Yet many scholars have challenged this notion of metacognitive agency, often pointing to cases in which our thinking appears to be constrained by factors outside our control. Two common sources of evidence against the robust agentic view are (1) genetic findings for the heritability of agency-relevant traits, such as intelligence and self-control (see Bouchard 2004); and (2) mental health disorders such as addiction, which have a biological basis and purportedly rob their victims of the ability to do or think otherwise (e.g., Levy 2011). This project marshals theory and evidence from both behavior genetics and clinical psychology/psychiatry to sketch out a proposed mechanism by which even the most genetically vulnerable individuals can choose to change how they think. First, we present both published and original findings suggesting that deliberative thinking is less genetically constrained than other psychological traits—including intelligence, self-control, and addictive tendencies—and that thinking style, in turn, can predict how addictive tendencies develop over time. Second, we review clinical and experimental evidence that individuals with addictions and other psychiatric disorders retain at least some agency over their thought processes. Taken together, this research points to a promising new pathway for increasing our moral agency: by internalizing the moral-epistemic norm that *good living depends on active, honest thinking*. Drawing on philosophical and empirical research on moral norms, we posit that baking this norm into one's self-concept should make its value chronically salient and accessible, even when conflicting urges are present. This idea has important implications for how we understand and measure moral-epistemic agency, even in the most "volitionally-impaired" individuals.

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Gene × environment interaction on developmental outcomes in Germany: what is the environment that matters?

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A common a priori assumption of research on Gene × Environment interaction is that a high socioeconomic status (SES) is a good proxy for favorable home environments, given the well-documented relation between socioeconomic advantage and positive consequences for adults and children. With respect to the question whether SES moderates the heritable potential of developmental outcomes (e.g., cognitive abilities), this underlying tenet seems to be appropriate for samples from the United States, but not for samples from other Western nations. Given this, other factors of the home environment might be better indicators of a supportive or adverse rearing environment, especially in countries with less SES disparities. Here, the family stress model (Conger and Elder 1994) can serve as a theoretical framework for the search for the family mechanisms that may moderate the heritability of developmental outcomes. The present study examines different factors of the family environment (i.e., maternal/paternal parenting style, family chaos), as moderators of the heritability of developmental outcomes, i.e., cognitive abilities, internalizing and externalizing behavior. We use data from cohorts 2 and 3 of the German twin family study 'TwinLife' (913 MZ and 1,165 DZ twins), and apply the modified twin-correlation model to investigate the G × E interactions. Results are discussed in light of recent literature on the G×E interplay, and with regard to developmental processes.

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Heritability and genetic correlations of cortical thickness and surface area, and their association with cognitive ability and psychiatric diseases

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The expansion of the human cerebral cortex relative to other non-human primates is thought to underlie our uniquely human cognitive capabilities. Deviations in the morphology of specific cortical regions are correlated with various cognitive abilities and psychiatric disorders. Results from family studies have indicated a genetic relationship between some differences in the cortex certain psychiatric disorders. Using the results from GWAS meta-analyses of the thickness and surface area of cortical regions derived from structural magnetic resonance imaging (MRI) scans from ~ 35,000 individuals, we applied LDscore regression to estimate the heritability of and the genetic correlations among cortical regions. Using partitioned heritability, we assessed differential enrichment patterns between total surface area and average thickness. Genetic correlations between

cortical regions and cognitive ability and psychiatric disorders were estimated using summary statistics from large published GWAS. Results from the meta-analyses demonstrate that common variation substantially influences the architecture of the human cortex (h^2_{SNP} = 0.33 for total surface area and h^2_{SNP} = 0.25 for average thickness). A modest negative genetic correlation ($RG = -.32$, $p = 3.9 \times 10^{-11}$) supports findings from twin studies that genetic influences on thickness and surface area are largely independent. We identified significant enrichment for loci influencing total surface area in regulatory regions of the developing fetal brain, specifically in the progenitor associated germinal zone. For average thickness, heritability was significantly enriched in adult brain. This provides support for the radial unit hypothesis in humans and implies that common genetic variation impacts progenitor associated gene regulation during fetal development to influence post-natal surface area. Examining the 34 specific regions of the cortex, heritability was greater for surface area (h^2_{SNP} 0.09–0.31) than for thickness (h^2_{SNP} 0.01–0.16). Consistent with findings from twin studies, genetic correlations within a region were typically negative, with the exception of structures in the occipital lobe. Between the surface area regions, genetic correlations of adjacent regions were typically positive and particularly strong among the structures in the occipital lobe. There were fewer significant genetic correlations between thickness measures of cortical regions and most were strongly negative. These bivariate findings will be compared and contrasted with results from clustering and factoring of areal heritability. In addition, significant positive genetic correlations were observed between total surface area and IQ, educational attainment, and Parkinson's disease, while negative genetic correlations were observed with neuroticism, depression, attention deficit hyperactivity disorder, and insomnia. In contrast, no significant genetic correlations were observed between average thickness and any disorders. This contrasts with the findings of phenotypic correlations between cortical thickness and various psychiatric disorders and psychological traits. Genetic correlations of specific regions were observed for IQ, educational attainment, neuroticism, depression, epilepsy, and schizophrenia and results will be discussed.

Investigating the genetic and phenotypic relationship between anxiety and nausea and vomiting during pregnancy

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Nausea and vomiting during pregnancy is very common. Many women who are pregnant experience some symptoms of nausea or vomiting and about a third experience moderate to severe symptoms. The impact of symptoms is wide-ranging and can be substantial, including weight loss, disrupted routines, and impeded ability to work and/or care for children. Severe cases may result in hospitalisation. Women with severe symptoms also have a higher incidence of anxiety and depression. It is unclear if anxiety precedes symptoms of nausea and vomiting or is a consequence. Anxiety and severity of nausea and vomiting are both moderately heritable. We tested if a genetic predisposition to anxiety was associated with more severe nausea and vomiting during pregnancy. As a comparison, we also tested if a predisposition to depression was associated with more severe nausea and vomiting during pregnancy. Participants were 1440 parous women reporting on the severity of nausea and vomiting experienced during their most affected pregnancy. Severity of nausea and vomiting was measured on a 5-point scale, from "None" to "It really disrupted my daily routine. I lost weight. I was prescribed medication or put on a drip/feeding tube." Genetic predisposition for anxiety and depression was measured with polygenic risk scores (PRS). For anxiety the PRS loadings were from the summary statistics of a GWAS on anxiety, conducted on 37,215 cases and 120,151 controls from the UK Biobank. For depression the PRS loadings were from the summary statistics of the second depression GWAS from the Psychiatric Genetics Consortium, conducted on 135,458 cases and 344,901 controls. A genetic predisposition to depression did predict more severe nausea and vomiting during pregnancy; it explained $\sim$ 0.5% of the variation in severity of nausea and vomiting during pregnancy. There was a suggestive association of a genetic predisposition to anxiety with severity of nausea and vomiting in pregnancy. However, this did not survive multiple testing, and the PRS lost precision with increasing p-threshold. This provides support for the hypothesis that genetic factors that predispose a person to depression also contribute to the severity of nausea and vomiting experienced during pregnancy. The GWAS used for the loadings in the calculation of the anxiety PRS was much smaller in size than that of depression. It may be that with a larger, more powerful anxiety GWAS the precision of the anxiety PRS will improve the PRS for anxiety and lead to more stable results for anxiety.

The influence of positive emotionality, social competence, and parental warmth on psychological adjustment: a genetically informed design

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Children who are socially competent during early childhood are less likely to show elevated levels of internalizing and externalizing behaviors in middle childhood, which decreases subsequent mental health risk. It is likely that child characteristics related to social competence and rearing environment work together to influence the development of internalizing and externalizing behaviors. Toddler positive emotionality and parental warmth are two factors that have been directly linked to child social competence during early and middle childhood. It is possible that heritable influences on child positive emotionality may evoke parental warmth (child-driven effect), which may indirectly promote the development of social competence. This study uses a longitudinal parent–offspring adoption design (N = 561, Early Growth and Development Study) to examine how heritable (birth parent temperament) and environmental (adoptive parent warmth) factors contribute to positive emotionality during early childhood, the development of social competence during early and middle childhood, and internalizing and externalizing behaviors during middle childhood. Birth mother agreeableness was indexed heritable influences as part of a birth parent temperament factor measured with the Adult Temperament Questionnaire, Temperament and Character Inventory, and Harter Adult Self-Perception Profile. Adoptive parents reported on toddler positive emotionality with the Toddler Behavior Assessment Questionnaire at 18 months. Warmth from adoptive mother and father was assessed with self-reports on the Iowa Family Interaction Rating Scales at 4.5 and 6 years. Parents reported on child social competence using the Social Skills Rating System at 4.5 and 6 years. Internalizing and externalizing behaviors were assessed at 7 years with mother, father and teacher report on the

Child Behavior Checklist. Findings indicated heritable effects of birth mother agreeableness on child social competence ($b = .14$, $p < 0.01$) at 4.5 years, but not on positive emotionality at 18 months ($b = -.02$, *ns*). Toddler positive emotionality elicits maternal ($b = .31$, $p < 0.01$) and paternal ($b = .27$, $p < .01$) warmth and was associated with child social competence ($b = .14$, $p < .01$) at 4.5 years. While there was stability in maternal warmth ($b = .76$, $p < .01$), paternal warmth ($b = .68$, $p < .01$), and social competence ($b = .77$, $p < .01$), there was no evocative effect from child social competence at 4.5 years to maternal ($b = -.02$, $p = 0.75$) or paternal ($b = .09$, $p = 0.07$) warmth at 6 years. Parental warmth at 4.5 years was also not associated with social competence at 6 years. Maternal warmth ($b = -0.11$, $p < 0.05$; $b = -0.15$, $p < 0.01$, respectively) and social competence ($b = -0.33$, $b = -0.40$, $p < .01$, respectively) at 6 years were associated with reduced internalizing and externalizing behaviors at 7 years, with internalizing and externalizing behaviors being moderately correlated ($R = .53$, $p < 0.01$). Heritable characteristics and toddler positive emotionality increased parental warmth and social competence during early childhood. Children who were socially competent during middle childhood were less likely to show high levels of internalizing and externalizing behaviors in middle childhood, with a similar pattern of findings for parental warmth. Additional analyses will examine possible evocative *r*GE influences on child behavior problems.

Using genomic SEM for multivariate GWAS discovery

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A powerful application of Genomic Structural Equation Modeling (Genomic SEM) is to specify a model in which the SNP effects occur at the level of a latent genetic factor defined by several phenotypes. This allows researchers to identify variants with effects on general dimensions of cross-trait liability (i.e., multivariate GWAS), boost power for discovery, and calculate more predictive polygenic scores. When certain SNPs only influence a subset of genetically correlated traits, a key assumption of the model is violated. With this in mind, we develop a test of heterogeneity that can be used to evaluate the extent to which the effect of a given SNP operates through a common pathway(s) model. SNPs with high heterogeneity estimates can be flagged as likely to confer disproportionate or specific liability toward individual traits or disorders, can be removed when constructing polygenic risk scores, or studied specifically to understand the nature of heterogeneity. These heterogeneity estimates act as safeguards against false inference when considering a locus specific to one trait in its effect on a set of correlated traits. As an example of this approach, we conduct a joint analysis of GWAS summary statistics from five genetically correlated psychiatric case-control traits: schizophrenia, bipolar disorder, major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and anxiety. We model genetic covariances among the traits using a general factor of psychopathology (*p*), for which we identify 27 independent SNPs not previously identified in the univariate GWASs, 5 of which can be validated based on previous outside GWASs. Polygenic scores derived using this *p*-factor consistently outperform polygenic scores derived from GWASs of the individual traits in out-of-sample prediction of psychiatric symptoms. As a tool for discovery and validation, Genomic SEM is both flexible and allows for continuous innovations in how multivariate genetic architecture is modeled.

Using genomic SEM for GWAS of latent phenotypes

Andrew Grotzinger, University of Texas at Austin; K. Paige Harden, University of Texas at Austin; Michel Nivard, Department of Biological Psychology, VU University; Elliot M. Tucker-Drob, University of Texas at Austin

Genome wide association studies are conventionally conducted using a "massively univariate" approach in which a regression effect is estimated for each individual SNP on a single measured phenotype. A long history of research in psychometrics and quantitative genetics indicates that many different cognitive, behavioral, and psychiatric phenotypes are genetically correlated. For both theoretical and practical reasons, cross-cutting dimensions of genetic liability across phenotypes (e.g. general intelligence, externalizing psychopathology) may be more appropriate targets for GWAS than the individual phenotypes themselves (e.g. numerical reasoning, vocabulary knowledge, working memory; conduct disorder, alcohol use, sexual risk taking). Here we demonstrate how Genomic SEM can be used to conduct GWAS of latent dimensions of cross-cutting genetic liability. Genomic SEM is freely available to users as a package in R.

Novel insight into the epigenomic signature of regular smoking using serum cotinine

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Owing to the adverse health effects of nicotine and tobacco, understanding the consequences and mechanisms involved in nicotine exposure are crucial. Exposure to tobacco smoke associates extensively with DNA methylation alterations, providing a plausible link between smoking and adverse health effects. As self-reported smoking may be erroneous due to misreporting (recall bias or under reporting), we utilized cotinine, the primary metabolite of nicotine and a reliable biomarker of nicotine exposure, to identify DNA methylation alterations associated with smoking. We performed an epigenome-wide association study of serum cotinine levels among regular (current daily) smokers in the Finnish Twin Cohort (N = 310) and identified DNA methylation at 50 CpG sites significantly (FDR P-value < 0.05) associated with cotinine levels. Seventeen of these associations were novel and reside in smoking-related genes such as *THSD4, LSM6*, and *CACNA2D4*. As cotinine levels are influenced not only by nicotine intake but also by the rate of cotinine formation and removal, primarily mediated by *CYP2A6*, we performed secondary analyses accounting for such influence with a genetic risk score for *CYP2A6*, and identified five additional novel associations. We further investigated the role of genetic variants in the highlighted genes. We observed 124 *cis* and 3898 *trans* methylation quantitative trait loci (meQTLs), among which 19 meQTLs also directly associated with cotinine levels. Based on these findings we performed causal inference test at the 19 meQTLs and observed a trend (P-value < 0.05) for mediation by DNA methylation at seven CpG sites. This suggests that

methylation at these CpG sites may be on the causal pathway between underlying genotype and nicotine exposure (intake) and not directly altered due to nicotine exposure. In conclusion, using a reliable biomarker of nicotine exposure, we replicated and identified novel epigenetic associations in nicotine exposure pertinent genes. We also demonstrate evidence of an interplay between the epigenome and the genome, and propose that DNA methylation alteration at a small proportion of the highlighted CpG sites may be a molecular mediator for the effects of underlying genotype and not a consequence of smoking.

Genetic and environmental influences on verbal fluency in middle age: a new framework

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Neuropsychological measures of verbal fluency are some of the most widely used tests for detecting age-related cognitive decline and dementia. Although substantial evidence suggests that phonemic and semantic fluency measures are differentially associated with neuropsychiatric conditions and other cognitive functions, few studies have examined the shared/unique variance between these aspects of fluency, especially using genetically-informative studies. We present a novel two-factor model of verbal fluency, describe its genetic/environmental architecture, and evaluate multiple hypotheses regarding the relevance of these fluency abilities to cognition and aging. 1464 middle-aged male twins from the Vietnam Era Twin Study of Aging (VETSA) completed letter (F-A-S) and category (animals, boys' names, fruits/furniture) fluency tests at up to two time-points (mean age 56 at baseline, and 62 years at follow-up). The best-fitting model at both waves comprised two factors. A General Fluency latent factor predicted variation in all letter and category subtests and a Semantic-Specific latent factor accounted for additional variation in category fluency not already captured by the common factor. Both factors were explained primarily by genetic influences at both waves (a^2 = .56–.76) as well as nonshared environmental influences (e^2 = .24–.44), but not at all by shared environmental influences (c^2 = .00). There was considerable stability of individual differences over 6 years (r = .90 for General Fluency, r = .81 for Semantic-Specific), especially for genetic influences (r_g = .99 and 1.0, respectively). Additionally, there was evidence for mean-level decline in General Fluency (d = − .22) but not Semantic-Specific Fluency (d = − .01). Further analyses of the first wave data revealed that the General Fluency factor was associated with vocabulary (β = .26), executive functions (β = .24), and working memory (β = .23), whereas the Semantic-Specific factor was strongly associated with episodic memory (β = .60). The Semantic-Specific factor at age 56 also predicted change of variance in episodic memory at age 62 and predicted conversion to amnestic mild cognitive impairment (OR = 2.00) controlling for episodic memory. The results provide a new framework for viewing verbal fluency as a combination of general and semantic-specific processes, both of which have unique genetic underpinnings and differential relations with other cognitive variables. Semantic fluency is particularly impaired in Alzheimer's disease. Therefore, the role of the heritable Semantic-Specific factor may be particularly important in future efforts to understand transitions to mild cognitive impairment and Alzheimer's disease.

How your parents influence your well-being—genetic and environmental pathways for parenting styles

Elisabeth Hahn, Saarland University; Juliana Gottschling, Saarland University; Julia Iser, Saarland University; Frank Spinath, Saarland University

Subjective well-being is influenced by a multitude of factors often assigned to either nature or nurture. Traditionally considered as shared environment, parenting style—the perceived emotional climate—was shown to be a meaningful predictor for several developmental outcomes of children including overall well-being. However, the characterization of parenting as pure environmental has been challenged since studies consistently revealed genetic contributions to parenting as evidence of genotype-environment correlation. Moreover, different perspectives on parenting showed differential effects in terms of predictive power and the relative contribution of genetics. Therefore, the present study investigates the predictive power of parenting styles for satisfaction with life in the developmental stages from early adolescence to early adulthood. We used data from the German twin family study TwinLife (N = 3078 twin families) where twins aged 11, 17 and 23 years rated their satisfaction and the perceived maternal and paternal parenting behavior. Analyses revealed consistent positive effects across cohorts for maternal and paternal emotional warmth. Also, differential effects for other parenting styles depending on the developmental stage were found. To investigate whether parenting contributes to differences between family members rather than similarities, we further applied a twin difference model to specify whether differences in parenting can directly predict differences in life satisfaction controlled for genetic and family similarities. In addition, we tested for moderating effects of e.g., socio-economic family characteristics to capture the effect of cultural disadvantages or privileges. Results are discussed with respect to genetic as well as environmental transmission pathways for parenting influencing well-being in offspring.

Structural equation modeling: what is it for and why is it useful for genetics?

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The development of statistical methods for estimating genetic correlations from genome-wide association study (GWAS) summary statistics have produced ever-expanding "atlases" of genetic correlations among traits. As a result, widespread pleiotropy is now taken to be the rule rather than the exception for complex human phenotypes. *Structural equation modeling* (SEM) is a statistical framework for testing hypotheses about the data-generating processes that give rise to observed patterns of variation and covariation. In this talk, I review the utility of SEM—what is it typically used for and why it is useful for answering questions in genetics? Paying particular attention to the role of *latent variables*, I describe classes of problems typically addressed by SEM, such as assessing convergent and discriminant validity and ameliorating the consequences of imperfect measurement. As applied to genetic correlations among traits, these classic "psychometric" problems are, in fact, critical to our understanding of genetic architecture. Moreover, many psychological, behavioral, and disease phenotypes of interest to researchers in complex trait genetics were developed as latent constructs in an SEM framework and do not correspond neatly to a single, univariate measurement. Several previous methods have been developed to capitalize on genetic

associations among traits to, *e.g.*, boost statistical power for genetic discovery, but these methods have assumptions that can limit their applicability. Thus, there is a lacuna in the methodological landscape, one that we aim to fill with the method we introduce in this symposium—genomic structural equation modeling.

"Don't feed the bugbears": moving beyond imagined evils in debates about GWAS of complex human outcomes

K. Paige Harden, University of Texas at Austin

Genome-wide association studies (GWAS) have now begun to identify specific genetic variants that collectively account for non-negligible variance in complex human outcomes, such as educational attainment, reproductive behavior, and mental disease. Like heritability estimates from twin studies, these genetic associations raise empirical questions regarding the biological, psychological, and social mechanisms that link differing gene sequences to diverging life pathways. Searching for mechanisms is necessarily intertwined with resolving questions that interface with both philosophy of science and science communication, such as, what evidence is sufficient to characterize a phenotype as "genetic"? However, progress in understanding the mechanisms linking genetic discoveries and complex phenotypes is impeded by common philosophical bugbears. Bugbears are folklore creatures that are used to scare disobedient children; following Dennett (1984/2015), I use the term here to refer to moral, political, and/or philosophical fears that color scientists' and non-scientists' interpretations of GWAS results. I describe common bugbears that lurk in scientific debates about the value of GWAS discovery and in public debates about the value and meaning of genetic research, including the threat of losing control and the threat of being held responsible. I further suggest that focus on these common fears have blinded both scientists and non-scientists to other, potentially undesirable social outcomes that could stem from a misinterpretation of genetic research. I conclude by describing how the search for mechanisms will be aided by no longer feeding the bugbears.

Electrophysiological endophenotypes and polygenic risk scores for substance misuse

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Recent work from the GWAS and Sequencing Consortium of Alcohol and Nicotine (GSCAN) has identified over 500 genetic variants associated with several substance misuse phenotypes. We previously evaluated the genetic basis of 17 endophenotypes, including antisaccade, P300 amplitude, and resting EEG power, that have been identified as relevant to problematic substance use behaviors and externalizing spectrum psychopathology. GWAS of these endophenotypes was performed using a community-based sample of over 4900 individuals, comprising adolescent twins and their biological parents, and the results were published as a special issue in Psychophysiology (Iacono 2014). In a recent report, our group tested whether genetic variants relevant to schizophrenia were associated with individual differences in these psychophysiological endophenotypes (Liu et al. 2017). This exploratory study did not find a significant association between polygenic risk scores for schizophrenia and any of the 17 endophenotypes. However, because there is strong theoretical and empirical evidence that these endophenotypes are relevant to biological and cognitive systems implicated in externalizing and addictive behaviors, we hypothesized that these endophenotypes would relate to genetic variants associated with substance misuse/externalizing behaviors. The current project will focus on testing the association between these externalizing-related endophenotypes (P300 amplitude, resting EEG power, antisaccade performance) and a polygenic risk score for alcohol use (number of drinks per week; derived from the GSCAN study findings) in a community-based sample of over 4900 individuals genotyped on the Illumina 600W-Quad array. Results will have implications for the utility of psychophysiological endophenotypes to characterize the genetically-mediated neurophysiological systems implicated in externalizing and problematic substance use behaviors.

Inferring psychological traits using functional MRI connectivity in genetic studies

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Early magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) studies in behavioral genetics sought associations between brain-based phenotypes and psychological traits of interest. While the association patterns themselves were a step forward in the literature, integrating more complex fMRI procedures could improve our capability and utility to conduct gene-finding studies of cognitive/behavioral outcomes, even expanding beyond measured phenotypes. "Connectivity-Based Predictive Modeling" (CBPM) is an approach for creating brain-based measures of a psychological variable. In this approach, individual associations across the human functional connectome are used to construct a single score that predicts a behavioral trait. Once a score is estimated, other fMRI samples that did not measure the behavioral trait can use the brain as a proxy measure for that behavior. While these approaches are becoming popular in the MRI literature, they have not been used for genetic studies to date. Further, aspects of their functionality may be improved by using genetically informative samples. This study is the first to conduct a GWAS of a CBPM variable, validating the procedure for future use. In addition, we use twin data to improve the utility of this approach, possibly increasing the power to detect genetic effects. To this end, we use general intelligence as a practical example phenotype and a training sample 232 individual twin pairs from the Colorado Longitudinal Twin Study (LTS), a matched test sample of 199 twins from the LTS to test the properties of the out of sample predictions of the trained model, and a test sample $\sim$ 8500 individuals from the UKBiobank to test the effectiveness of these phenotype techniques for GWAS. We found that the standard CBPM of intelligence was significantly predictive within the train sample and in the out of sample test set. The CBPM estimated with only phenotypic information was not significantly heritable in the test set. Heritability of the CBPM was significantly improved by incorporating information from twin models into the training procedure. Finally, using a LD score, we found that our CBPM estimated in the UKBiobank was significantly genetically correlated with intelligence. All effect sizes fell within the moderate range. Further steps should be taken to improve model prediction, matching between samples and integration

of multimodal brain imaging data. This approach holds the possibility for integrating information from twin and fMRI studies into a broader statistical genetics literature.

Familial co-aggregation of attention-deficit/hyperactivity disorder and autoimmune diseases

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Introduction: The etiology of attention-deficit/hyperactivity disorder (ADHD) remains largely unknown. In later years, ADHD has been associated with several autoimmune diseases (AD) and traits, potentially reflecting common underlying mechanisms. Still, most studies have investigated intraindividual relationships that reveal little regarding etiology. In addition, some of the findings in previous studies have not been replicated in independent samples.To further elucidate the relationship between autoimmunity and ADHD, we conducted a familial co-aggregation study using Swedish population-wide national registers.
Materials and methods: We linked several Swedish population-wide national registries to define a birth cohort with their biological relatives and to identify the individuals who had been diagnosed with ADHD and ADs of interest. The base cohort included more than 5 million individuals born between 1960 and 2010. Logistic regression was used to investigate the associations between different ADs and ADHD, both within individuals, and across biological family members of differing relatedness.
Results: In the preliminary analyses, ADHD was in intraindividual models associated with several relatively common ADs with odds ratios (OR) in the range of 1.1–1.7, including, but not limited to celiac disease (OR 1.19, 95% confidence interval 1.12–1.28), psoriasis (OR 1.48, 95% CI 1.41–1.55), Sjögren's disease (OR 1.64; 95% CI 1.27–2.12), and type 1 diabetes mellitus (OR 1.32, 95% CI 1.24–1.41). Moreover, results supporting familial co-aggregation, with attenuation of the association estimates with decreasing relatedness, were noted for several offspring ADHD—relative AD-relationships. For example ADHD was more strongly associated with psoriasis in full siblings (OR 1.26, 95% CI 1.20–1.32) than full cousins (OR 1.07, 95% CI 1.04–1.09). Though this was not the case for all ADHD-AD associations.
Discussion and conclusion: Our study supports some of the previous findings on the intraindividual associations between ADHD and ADs, and also indicate that there could be common underlying genetic architecture between ADHD and some of the ADs. However, the absence of clear familial co-aggregation for many ADHD-AD associations dissuades us from stating general conclusions regarding common genetic risk factors between ADHD and ADs. (We aim to present replication of some our findings with the use of similar Norwegian register data).

Comparing the genetic architecture of childhood aggression across socioeconomic strata in the Netherlands and the United Kingdom

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The aim of the present study was to examine whether the genetic architecture of childhood aggression varies across socioeconomic strata in the Netherlands and the United Kingdom. We analyzed data from 7-year-old twins from the Netherlands Twin Register (N = 24,112) and the Twins Early Development Study (N = 19,644). The results revealed a moderation effect of socioeconomic status (SES) on the contribution of genetic and environmental factors to individual differences in childhood aggression. The heritability was higher, the contribution of the shared environment was lower, and the contribution of the nonshared environment was higher, for children from high SES families, compared to children from low or medium SES families. The pattern was similar for Dutch and UK families. We discuss the importance of these findings for prevention and intervention goals.

Animal models of addiction-prone and—protected behavioral phenotypes

Nathan Holtz, University of Washington; Marilyn Carroll, University of Minnesota, Twin Cities

Animal models have employed selection or selective breeding practices based on phenotypic traits related to substance use disorders, enhancing our understanding of the role genes play in the vulnerability to such compulsive behaviors. Rodent models, in particular, have shown that some behavioral traits are under strong genetic influence and positively associated with drug intake, similar to human populations. For instance, rats that are selected or selectively bred for high impulsivity, sweet preference or emotional reactivity consume greater quantities of addictive drugs compared to rats with low measurements on these behaviors. This presentation will review a number of rat models of phenotypic vulnerability to and protection from drug abuse. It will compare and contrast these models and evaluate whether they provide evidence for one or multiple addiction-prone phenotypes, and assess the potential utility of these models in predicting clinical outcomes in treating substance use disorders. Research supported by NIDA Grants R01 DA02486 and P50 DA033942 (MC).

Cocaine'omics: genome-wide and transcriptome-wide associations with cocaine use and dependence, a GWAS follow-up study

Spencer Huggett, University of Colorado Boulder, Institute for Behavioral Genetics; Michael Stallings, University of Colorado Boulder, Institute for Behavioral Genetics

We investigated the genetic and transcriptional landscape of cocaine dependence (CD) and chronic cocaine use. We performed and integrated popular genome-wide and transcriptome-wide analyses using

data from the largest genome wide association study (GWAS) on CD to date (Gelernter et al. 2014), 3176 European Americans (EAs), and human post-mortem brain tissue from seven cocaine users and eight drug free controls. First, linkage disequilibrium (LD) score regression analyses was performed and detected a significant genomic heritability of 28% (*s.e* = 0.14) for CD and gene-based association tests found three novel genes underlying this heritability: the *C1QL2, KCTD20* and *STK38* genes. Tissue specificity analyses indicated robust enrichment in numerous brain regions, including the hippocampus, sub > adj = 2.02e−06. Therefore using RNA-sequencing (RNA-seq) analyses we performed differential expression and weighted gene covariance network analyses (WGCNA) on post-mortem hippocampal brain tissue from Zhou et al. 2011. Differentially expressed genes or transcripts between chronic cocaine users versus drug free controls were enriched for genes associated with CD ($p < 0.05$), OR = 1.34, $p = 0.031$, and were used to find various potential therapeutic compounds for cocaine use/toxicity. Lastly, we found that *KCTD20* was a central part of a hippocampal gene network strongly associated with cocaine use and thus, might be contributing to the genetic liability of CD by disrupting intricate gene networks in the brain. Overall, our study elucidates the biological architecture of cocaine use/dependence, proposes various novel therapeutic compounds for cocaine use and includes an alternative framework to validate/provide biological meaning to genome-wide findings.

Cocaine'omics: the genetic and neurological basis of cocaine use and dependence

Spencer Huggett, University of Colorado Boulder, Institute for Behavioral Genetics; Michael Stallings, University of Colorado Boulder, Institute for Behavioral Genetics

We investigated the genetic and neurological landscape of cocaine dependence (CD) and chronic cocaine use. We performed and integrated popular genome-wide and transcriptome-wide analyses using data from the largest genome wide association study (GWAS) on CD to date (Gelernter et al. 2014), 3370 African Americans (AAs), and human post-mortem brain tissue from 19 cocaine users (all diagnosed with cocaine use disorder) and 17 cocaine free controls. First, we performed a MAGMA gene-based association test and found that the Nicotinamide adenine dinucleotide ubiquinone oxidoreductase subunit Beta 9 (*NDUFB9*) gene was significantly associated with the genetic predisposition to CD, # SNPs = 174, $Z = 4.7917$, $p = 8.267e{-}07$. Subsequently, we used single cell RNA-sequencing (scRNA-seq) analyses and conducted differential expression and weighted gene covariance network analyses (WGCNA) on post-mortem dorsal-lateral Pre-frontal Cortex neurons from Ribeiro et al. (2017). We detected 133 differentially expressed genes/transcripts between chronic cocaine users versus controls, none of which were genome-wide significant findings from GWAS/gene-based association tests (*NDUFB9, FAM53B, C1ql2, KCTD20*; $_{all}$ *FDR-BH* > 0.34). Using all genes, we created 12 WGCNA networks, which were validated using an external sample of post-mortem brains from cocaine users and controls (Zhou et al. 2011). We found that the blue WGCNA network (# genes = 2735) was most robustly associated with cocaine use and contained two of the genome-wide findings (*NDUFB9, C1ql2*) associated with CD via gene-based association tests from AAs and European Americans. The blue gene network was most enriched for KEGG pathways likely involved in the pathophysiology of cocaine use (i.e. GABAergic/Glutamaterigic/Dopamanergic Synapse, cAMP/Ca+ signaling, Alcoholism, Nicotine/Morphine/Cocaine Addiction $_{all}$ *FDR-BH* < 0.05). All together, our study elucidates the biological architecture of cocaine use/dependence, proposes an alternative framework to validate/provide biological meaning to genome-wide findings and suggests that one way that the genes predisposing individuals to CD might be disrupting gene networks among the brains of cocaine users.

Multivariate GWAMA in over 500k observations on aggressive behavior and ADHD symptoms

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We present the results of a multivariate genome-wide association (GWA) study of the developmental genetic etiology of aggressive behavior (AGG) and attention-deficit/hyperactivity disorder (ADHD). The project involves a collaboration among more than 20 international cohorts from Europe, Australia, New-Zealand and the USA. The cohorts are characterized by rich phenotyping in children and adolescents, including repeated measures at different ages and assessment by multiple informants and multiple instruments. In total, the meta-analysis included ~ 526,000 observations and over 250 GWA studies. The data includes longitudinal measures of AGG and ADHD in children and adolescents aged 3–18 years, assessed by multiple informants (mother, father, teacher, and self) and multiple instruments. First, a series of univariate GWA studies was performed for every available combination of age, informant and instrument within cohort. This resulted in 1–52 analyses per cohort, with sample sizes ranging between 309 and 10,812. Next, results were pooled into age-by-informant combinations (e.g. mother-rated aged 3–5, teacher-rated 8–11, etc.) that resulted in an excess of 10,000 independent observations, and then meta-analyzed. Genetic correlations between the age-by-informant meta-analyses, both within and across AGG and ADHD, were estimated with LD Score Regression. We then performed a multivariate meta-regression analysis across all GWA studies, correcting for dependency due to repeated measurements of the participants. We obtained an average SNP-heritability of 6.1% and 7.2% for AGG and ADHD, respectively, across the age-by-informant meta-analyses. After meta-analysis across age, genetic correlations between mother- and teacher-ratings was 0.54 for AGG and 0.51 for ADHD. Interestingly, the genetic correlation between teacher-ratings and self-report approached zero for both traits. Genetic correlation within rater, across phenotype ranged from 0.58 to 0.7. The multivariate meta-analysis across rater and phenotype revealed no significant loci for AGG/ADHD. Our study includes multiple international cohorts (ABCD, Add Health, ALSPAC,

BREATHE, CATSS, Dunedin Study, E-RISK, FINNTWIN, GENR, GINI/LISA, IBG, INMA, MOBA, MSUTR, MTFS, MUSP, NFBC 1966/1986, NTR, QIMR, RAINE, Richmond State University, TCHAD, TEDS, TRAILS, Understanding Society, YFS).

Detection and interpretation of psychiatric pleiotropy

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Co-occurrence of psychiatric symptoms such as depression, substance use, and psychosis is a pervasive phenomenon. Spectrum models of psychopathology hypothesize that this co-occurrence is related to shared liability among different forms of psychopathology and a substantial part of this liability is attributable to genetic influence. Twin and genome-wide association studies (GWAS) have suggested the existence of a close genetic relationship among psychiatric disorders. However, to date, no systematic search of genetic variants shared across these disorders has been conducted. The present study aimed to identify, characterize, and interpret pleiotropic variants associated with multiple psychiatric and related behavioral phenotypes. We applied a multivariate Bayesian test developed by Pickrell (2016) to GWAS summary statistics of 16 psychiatric and psychological traits that have been associated with externalizing, internalizing, and thought disorder (N = 16,731 $\sim$ 1.2 million depending on the phenotype), as well as summary statistics of heights and BMI as control traits (N = 575,442). We used these variants to identify traits that have common genetic causes and conducted a functional interpretation to give insights as to shared etiology of psychiatric disorders. Finally, evidence for the causal relationship between pairs of traits was evaluated based on patterns of correlation between genetic variants associated with each trait.

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Associating psychiatric polygenic risk scores with neurodevelopmental disorders in a clinical child and adolescent sample

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Objective: Psychiatric disorders like attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia (SCZ) are highly heritable and influenced by many single nucleotide polymorphisms (SNPs). One way to explore the influence of common genetic variation is the use of polygenic risk scores (PRS), an individual's genetic risk for a disorder. We aim to identify associations of genetic risk for ADHD, ASD and SCZ, with neurodevelopmental disorders (NDD) in a clinical child and adolescent population.
Methods: We derived PRS for ADHD, ASD and SCZ using the latest GWAS results, and tested for an association in a sample (1) with a single diagnosis of ADHD (N = 280), (2) with a single diagnosis of ASD (N = 295), and (3) combining the first two samples, thus subjects with either ASD or ADHD, plus children with both diagnoses (NDD, N = 688). With logistic regression analyses we explored associations between each clinical sample and a sample of healthy controls (N = 957). Follow-up analyses exploring the associations further were performed by means of linear regression analyses of the syndrome scales of the child behavioral checklist (CBCL) in each clinical sample.
Results: Our results showed a significant association of the ADHD PRS with ADHD ($p = 7.2 \times 10^{-5}$, OR 1.37), and with NDD ($p = 1.44 \times 10^{-4}$, OR 1.32), but not with ASD status ($p = 5.04 \times 10^{-2}$, OR 1.23). No associations with the ASD and SCZ PRS were observed. Follow-up analyses with the ADHD PRS and CBCL syndrome-scales showed in the ADHD sample associations with anxious/depressed (Beta = 0.119, $p = 0.035$) and a trend towards aggressive behavior (Beta = 0.111, $p = 0.054$). In the NDD sample an association with attention problems (Beta = 0.093, $p = 0.035$) and aggressive behavior (Beta = 0.107, $p = 0.015$) was observed.
Conclusion: The genetic risk of ADHD is significantly associated with ADHD in a clinical child and adolescent sample. The signal can be traced back to attention problems and aggressive behavior in the complete NDD sample but replication in larger samples is needed to confirm these results.

Development, G×E interactions, and the challenges of causation

Jonathan Kaplan, Oregon State University

Consider the following scenario. We identify some behavioral trait. We determine that it has reasonably high heritability. GCTA (or other similar techniques) confirm that more similar genomes tend to be more similar phenotypically (though the "molecular" heritability estimate isn't identical). GWAS studies find a number of more or less replicable 'hits,' that together explain a small fraction of the variance (much smaller than the heritability). Variation in the trait between populations is significant—often as large as or larger than the within-population individual variation addressed by the aforementioned studies. Finally, on reflection it seems likely that the trait in question is wrapped up with particular social practices; perhaps it is because of the kind of social practices we engage in that the trait exists as a trait, or perhaps our social practices make it a trait that we can sensibly name and measure. Now consider the question: what causes the heritable variation in the trait that we observe? Even in the case of variation within populations—the heritable variation that is associated with genetic differences, where GWAS studies find a number of SNPs, etc.—the question turns out to be more difficult to answer coherently than one might have guessed. In this talk, I'll develop an example (based loosely on a thought experiment of James Flynn) that shows the ways in which a trait's heritability may be produced by the kind of gene × environment interaction/correlation that makes identify something as a cause seem challenging. How common such interactions may be, and to what extent they are responsible for some of the patterns seen in behavior genetics research, will likely remain open questions for some time. But exploring the possible ways in which the developmental pathway taken can be influenced by genetic differences can reveal the ways in which environmental differences can be both driven by, and drivers of, phenotypic outcomes.

Forced migration due to war suppresses genetic influences on cigarette smoking

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Background: Stressful life events associated with forced migration and war increase vulnerability for adverse health consequences, including health-related behaviors. Due to WWII Finland lost 10% its land area to the Soviet Union in 1944, and the entire population (420,000 persons) of Ceded Karelia was settled in the rest of Finland after the war. We studied how war experiences, especially forced migration, are associated with subsequent cigarette smoking within the nationwide Finnish Adult Twin Cohort.
Methods: Altogether 12,933 twin individuals born before 1945 replied to a questionnaire in 1975 of the Finnish Twin Cohort (89% response rate) and were included in the present analysis. The exposure (forced migration due to war, categorized as 'no', 'once', '2+') used following measures: the municipality of birth and whether the respondent had moved municipality ever and if so, for what reason (10 options, including war). For a subset, we had a PRS for smoking initiation from GSCAN (gscan.sph.umich.edu) omitting Finnish data. As a measure of the validity of the item, we found that of the respondents born in Ceded Karelia 83% replied that they had had to move due to war, with the corresponding percentages varying from 5 to 20% in other provinces (due to fighting in border areas and bombings of urban areas). Detailed smoking questions were used to create the smoking status variable: 'ever smoker' versus 'never smoker' with an ever smoker defined as a person who has smoked more than 100 cigarettes lifetime. Logistic regression with correction for sampling of twins as twin pairs was used for analyses of individuals, while twin tetrachoric correlations were computed to assess similarity within pairs.
Results: Those who had experienced forced migration due to World War II showed higher likelihood of being ever smoker (age, sex, education, and birth area adjusted Odds Ratio 1.70, 95% Confidence Interval 1.43–2.02; $p < 0.001$) than those without forced migration experience. Adjustment for smoking initiation PRS did not attenuate this. For pairwise analyses, we focus on male twin pairs as smoking rates were low in women. Among male pairs with no forced migration experience (71.6% ever smokers), the correlation for being an ever smoker was in MZ pairs 0.83 (standard error (se) 0.021, N = 1162 pairs) and in DZ pairs 0.55 (se 0.026, 2640 pairs); a finding consistent with genetic influences on smoking. Among pairs in which both twins experienced forced migration (78.7% ever smokers), the MZ correlation (r = .71, se 0.09, 138 pairs) and the DZ correlation (r = .79, se 0.05, 306 pairs) were very similar and indicate absence of genetic effects. The average age in 1975 was 44.6 years in the non-exposed pairs and 46.7 in the exposed group, some 30 years after the end of the war.
Conclusions: Forced migration experience as a stressful life event seems to increase vulnerability for use of addictive substances, such as cigarette smoking, and suppresses familial/ genetic influences on the liability to initiate smoking. Forced migration due to war represents a true environmental influence that the twins were not able to control.

Genome-wide study identifies ~ 600 loci associated with risk tolerance and risky behaviors

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Risk tolerance—defined as the willingness to take risks, typically to obtain some reward—varies substantially across humans and has been actively studied in the behavioral and social sciences. An individual's risk tolerance may vary across domains, but survey-based measures of *general* risk tolerance (e.g., "Would you describe yourself as someone who takes risks?") have been found to be good all-around predictors of risky behaviors such as portfolio allocation, smoking, and starting one's own business. In a combined sample of more than one million individuals, we conducted genome-wide association studies (GWAS) of general risk tolerance, adventurousness, and risky behaviors in the driving, drinking, smoking, and sexual domains. We identified ~ 600 approximately independent genetic loci associated with at least one of our phenotypes, including 124 with general risk tolerance. We report evidence of substantial shared genetic influences across general risk tolerance and risky behaviors: 72 of the 124 general risk tolerance loci contain a lead SNP for at least one of our other GWAS, and general risk tolerance is moderately to strongly genetically correlated ($|r_g| \sim 0.25$–0.50) with a range of risky behaviors. A polygenic score of general risk tolerance explains up to 1.6% of the variation in general risk tolerance in independent datasets. The score is also predictive of a suite of real-world measures of risky behaviors in the health, financial, career, and other domains. Our bioinformatics analyses point to the role of gene expression in brain regions that have been identified by neuroscientific studies on decision-making, notably the prefrontal cortex, basal ganglia, and midbrain. Our analyses failed to find evidence for the five main biological pathways that had been previously hypothesized to influence risk tolerance—the steroid hormone cortisol, the monoamines dopamine and serotonin, and the steroid sex hormones estrogen and testosterone. Instead, our analyses implicate genes involved in glutamatergic and GABAergic neurotransmission, which were heretofore not generally believed to play a role in risk tolerance.

Best practices and proper interpretation of SNP-heritability estimates

Matthew Keller, University of Colorado Boulder; Luke Evans, University of Colorado Boulder

Multiple methods have been developed to estimate narrow-sense heritability using single nucleotide polymorphisms in unrelated individuals ("SNP-heritability"). However, a comprehensive evaluation of these methods has not yet been performed, leading to confusion and discrepancy in the literature. We present the most thorough and realistic comparison of these methods to date using thousands of real whole genome sequences to simulate genotypic and phenotypic data under various scenarios. We show that SNP-heritability estimates can be highly sensitive to assumptions about the frequencies, effect sizes, and levels of linkage disequilibrium of underlying causal variants. We introduce a novel procedure (LDMS-I) that leads to estimates that are less sensitive to these assumptions across a wide range of genetic architectures and possible confounding factors. Our findings provide guidance for best practices and proper interpretation of published estimates.

Genetic and phenotypic associations between political ideology and fertility

Yuri Kim, University of Minnesota, Twin Cities; James Lee, University of Minnesota Twin Cities

Much secondary literature has reported a positive correlation between conservatism and fertility, but there only exists a small empirical basis for this finding. Using data from the General Social Survey, we

again see this trend of conservatism correlating with increased number of children; this association motivates our endeavor to understand the sources of the relationship. In the present work, we study the relationship between traditionalism and fertility. Traditionalism is a measure of the adherence to traditional customs or beliefs, a construct closely related to social conservatism. Fertility is defined as the number of children ever born. The phenotypic data comes from the Minnesota Center for Twin and Family Research; the genetic data from the human reproductive behavior (fertility) GWAS (Barban et al. 2016). We attempted to predict traditionalism with a fertility polygenic score (PGS). However, the PGS analysis was insignificant. The null result is possibly due to the insufficient sample sizes of the GWAS and validation samples resulting in small statistical power. Fertility is highly polygenic trait: because most other traits or behaviors influence fertility, it is likely shaped by a manifold of genetic variants.

Social defeat-induced depressive-like behavioral disorders in Drosophila males

Yong-Kyu Kim, University of Georgia; Matthew Romaine, University of Georgia; Haini Cai, University of Georgia; Ping Shen, University of Georgia

Traumatic and stressful experiences are among the major causes of psychiatric disorders such as post-traumatic symptom disorders (PTSD) and depression. However, our understanding of the molecular and neural bases of the stress state and the chronic manifestations of mental illness as well as effective treatments are largely lacking. Aggression is prevalent in the animal kingdom and is influenced by genes and environment as well as G×E interaction (reviewed in Kim 2016). Here, we investigated if repeated fighting encounters would induce an internal state that could affect the expression of subsequent behavior. We trained wild-type males to become winners or losers, by repeatedly pairing them with hypo- or hyper-aggressive opponents, respectively. Kim et al. (2018) observed that chronic losers tend to lose subsequent fights, while chronic winners tend to win them. Moreover, the effect of chronic losing experience generalized to other behaviors, such as gap-crossing and courtship, and the depressive-like behaviors were transmitted to F1 male offspring. We found that two conserved neuropeptide Y (NPY)-like neuropeptide F (NPF) and dopamine (DA) systems play central roles in the development of depression-like brain state. Furthermore, olfactory conditioning experiments showed that winning is perceived as rewarding, while losing is perceived as aversive. We showed that the activities of the PPL1-γ1pedc dopaminergic neuron and the MBON-γ1pedc $> \alpha/\beta$ mushroom body output neuron were required for aversion to an olfactory cue associated with losing fights. Currently we are studying the mechanisms of transgenerational epigenetic inheritance of aversive paternal losing experience. Subsequently, we will identify major neural chemicals and gene activities that could be of general importance in stress responses and coping mechanisms among diverse animals. The knowledge gained from these studies could be potentially useful for the development of new concepts and more effective treatments of stressful experience-induced psychiatric disorders.

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The importance of diversity in genetic research on aging: when less is just less

Jonathan W. King, Division of Behavioral and Social Research, National Institute on Aging/NIH

Genetic and genomic research on psychological, behavioral, and interpersonal processes is an integral part of many research projects funded by the National Institute on Aging (NIA). In the Division of Behavioral and Social research we are especially interested in areas that include the genetics and genomics of social behavior and social environments; understanding genetic and genomic influences linking social, psychological, and behavioral processes with health and well-being over the life course; and understanding the social and environmental contexts in which genetic and genomic factors are expressed and influence social, psychological, and behavioral aspects of aging. Increasingly, we would like to support the work of researchers who propose to use genetically informative methods to examine important health disparities in outcomes of interest to the institute, notably Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD). Unfortunately, just as landmark advances in the analysis of genome-wide association studies (GWAS) give us tools that could be used to inform disparities research, it has also become clear that we currently quite simply lack sufficient genotype data from non-European populations to generate GWAS summary statistics to calculate even the simplest polygenic scores valid in such populations (e.g., Martin et al. 2017), thus potentially magnifying the research disparity that already exists. The frank necessity to fix this situation is well-understood by funding agencies, and, hopefully, will be mitigated in the near future. This talk will thus in some sense provide some sense of urgency as well as the context for the following presentations by Drs. Melissa Munn-Chernoff, Danielle Dick, and Alicia Martin, who will describe their work focused on the identification of individual differences in health behaviors and the study of health disparities across multiple populations.

Can the causal contingent common-pathway model of substance-use initiation and disorder be applied to genotyped samples of unrelated participants? Results of a Monte Carlo simulation

Robert Kirkpatrick, Virginia Commonwealth University; Michael Neale, Virginia Commonwealth University

When applied to the classical twin design, the causal contingent common-pathway (CCC) model (Kendler et al. 1999, *Psychological Medicine* 29; Kendler 2001, *Arch Gen Psychiatry* 58) estimates genetic and environmental contributions to risk of substance-use initiation and substance-use disorder, taking into account the fact that initiation is a necessary precondition for substance-use disorder. Theoretically, the CCC model could also be applied to genotyped samples of unrelated participants, via genomic-relatedness-matrix restricted maximum likelihood (GREML). To assess whether such an analysis is realistic in practice, we present results from Monte Carlo simulations in which the CCC model is fitted in OpenMx to simulated genotypic and phenotypic datasets. In order to avoid calculating intractably high-dimensional multivariate-normal probability integrals, these simulations treated initiation as though it were a continuous variable (even though it was in fact a dichotomous threshold trait) and transformed its heritability estimates from the observed scale to the liability scale (Dempster and Lerner 1950, *Genetics* 35). Results clearly showed that this approximation made the causal path from initiation to exposure virtually empirically unidentified, even in very large samples of simulated twin pairs.

Alternatives approaches were discussed, such as initiation variables with more than one level of initiation, and imputation of latent liability for initiation (Hayeck et al. 2015, *AJHG* 96; Weissbrod et al. 2015, *Nature Methods* 12).

Psychological features of Russian women with different diplotypes of HTR2A, COMT, BDNF genes

Ekaterina Kovsh, Southern Federal University, Academy of psychology and Educational sciences; Elena Vorobyeva, Don State Technical University; Pavel Ermakov, Southern Federal University, Academy of psychology and Educational sciences

Introduction: This article is devoted to research the level and types of aggression, expressiveness of legitimized aggression (LA), conflict-handling behavior, level of the personality anxiety, level of depression and formal-dynamic properties of individuality (temperamental characteristics) of Russian women-carriers of different HTR2A, COMT, BDNF genes diplotypes. These genes are associated with neurotransmitters systems, neuroplasticity and it is important—to discover their correlations with the psychological characteristics; it was the aim of our research. The hypothesis of research: different combinations of genotypes of neurotransmitters systems and neuroplasticity genes (HTR2A, COMT, BDNF), probably, associated with the various psychological characteristics of women.
Materials and methods: Genetic stage: buccal epithelium sampling, PCR ("BiReT", Russia). Psychological stage: Buss–Durkee Hostility Inventory, Thomas conflict-handling behavior Inventory, Questionnaire of formal-dynamic individuality properties, Beck Depression Inventory, State-Trait Anxiety Inventory, legitimized aggression Inventory. Observers: 68 Russian women. Explored diplotypes: BDNF Val/Val + COMT Val/Met + TR2 A/G + TR3 T/C (№1), BDNF Val/Val + COMT Val/Val + TR2 A/G + TR3 T/C (№2), BDNF Val/Val + COMT Val/Met + TR2 A/A + TR3 T/T (№3), BDNF Val/Met + Val/Met + TR2 G/G + TR3 C/C (№4). Statistical data processing: factorial ANOVA, $p \leq 0.05$.
Results: Based on the analysis, we find the psychological characteristics of Russian women with different diplotypes of the genes studied. Carriers of diplotype №1 have the following features: a significantly lower level of offense (M = 2.7, p = 0.03), a low level of preference for avoidance conflict strategies (M = 3.8, p = 0.03), a low level of LA (M = 56.6, p = 0.02), including—in politics (M = 32.1, p = 0.03) and in personal experience (M = 24.3, p = 0.006). Members of this group have a high level of personal anxiety (M = 50, p = 0.02). Women with a diplotype №2 have opposite characteristics: a higher level of offense (M = 5.2, p = 0.03), avoidance of conflict (M = 6.8, p = 0.04); high integral index of LA (M = 82, p = 0.02), including—in politics (M = 49.4, p = 0.03), in personal experience (M = 39, p = 0.006), in sports (M = 15.6, p = 0.03). Girls with this diplotype have lower motor mobility (M = 23.2, p = 0.01) and motor speed (M = 28.6, p = 0.01), but more high level of communicative emotionality (M = 38.2, p = 0.03). Russian women with diplotype №3 have a higher level of inclination to cooperate in the conflict (M = 7, p = 0.03), low integral level of LA (M = 56.4, p = 0.02), including LA in politics (M = 33.6, p = 0.04) and in sports (M = 9.6, p = 0.04). The high motor mobility (M = 33.3, p = 0.01) and the low level of communicative plasticity (M = 26.3, p = 0.05) can be individually attributed to the formal-dynamic properties of this women. Women with diplotype №4 have a high level of inclination to cooperate in the conflict (M = 7, p = 0.04), compared with the carriers of other diplotypes. A higher level of avoidance of conflict is inherent in women with diplotype (M = 6.9, p = 0.03). The formal-dynamic properties of this women: high level of communicative plasticity (M = 32, p = 0.05), high motor speed (M = 36.6, p = 0.01). There were no significant differences in the level of depression in the study sample.
Conclusion: Based on the results obtained, we can conclude that the hypothesis was confirmed.

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Association of COMT and MAOA genes with psychological features of Caucasian women

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The study of the genes influence on the psychological characteristics of different ethnic groups representatives has a particular importance in view of the possibility of assessing the gene–environment interaction. This study examines the influence of factors "heredity—the genes of the monoaminergic system MAOA and COMT" and "nationality" on the psychological characteristics of women with Balkars, Kabardians, Karachai nationalities, living in the Caucasus.
Observers: 143 women.
Methods: (1) Testing: Buss-Durkee hosting Inventory, Thomas test, "LA-44", V.M. Rusalov Inventory "IFDFI", Oryol test. (2) PCR.
Results: The combination of factors "COMT gene*nationality" has the greatest influence on the level of indirect aggression (p = 0.04), preference for conflict cooperation strategy (CiC) (p = 0.02), as well as the tendency to legitimize aggression (LA) in personal experience (p = 0.03) The combination of factors "MAOA gene*COMT gene" is associated with the adaptation strategy in conflict (p = 0.03).
Results: The combination of factors "MAOA gene*nationality" has the greatest impact on the level of negativity (p = 0.01) and guilt (p = 0.04), LA in upbringing (p = 0.003), as well as a tendency to deviant behavior (DB, p = 0.02). The combination of factors "gene COMT*gene MAOA*nationality" affects the severity of guilt (p = 0.02). At the same time, the presence of identical diplotypes manifests itself differently in the psychological characteristics of Caucasian women. High-activity Val/Val COMT + 3.5/4 MAOA diplotype associated: **In Kabardians**: with an average level of guilt (M = 65.3, p = 0.02) and an integral index of LA; tendency to CiC. (M = 6.4, p = 0.003), a high tendency to various forms of DB. **In Balkars**: with a low level of resentment (M = 37.4, p = 0.03), communicative (M = 20.9, p = 0.04), emotional (M = 20.5, p = 0.01) plasticity, intellectual (M = 22.4, 0.02) and motor (M = 23.1, p = 0.04) speed; low preference for competition strategies (M = 2.4, p = 0.02) and CiC (M = 3.2, p = 0.02); high suspicion (M = 62.3, p = 0.02). ***Met/Met COMT + 3.5/4 MAOA diplotype associated***: **In Kabardians**: with a higher tendency to LA, including—in the media (M = 38.22, p = 0.05), to competition (M = 6, p = 0.01) and CIC (M = 5.1, p = 0.03); with an average level of motor speed (M = 32, p = 0.02). ***Diplotype Val/Met COMT + 3.5/4 MAOA associated***: **In Kabardians**: low resentment (M = 41.4, p = 0.03) and susceptibility to various forms of DB; high levels of suspicion (M = 60.2, p = 0.02), communicative ergicity (M = 41.8, p = 0.002), the average level of LA, and intelligent (M = 29.8, p = 0.02), communicative (M = 30, p = 0.02), emotional (M = 29, p = 0.03) plasticity; with the average level of the motor (M = 31.4, p = 0.05), intellectual (M = 31.3, p = 0.02), communicative (M = 31.6, p = 0.02) speed. **In Balkars**: with a low level of suspicion (M = 46.2, p = 0.02), a high level of guilt (M = 80.3, p = 0.02), a strategy of CIC (M = 5.9, p = 0.009); with an average integral level

of LA (M = 58.1, p = 0.01), a low tendency to various forms of DB; weak nervous system: low rates of speed, plasticity, ergicity, emotionality. **In Karachai**: with low level of resentment (M = 36.8, p = 0.03), suspicion (M = 44, p = 0.02), hostility (M = 3.4, p = 0.02); propensity to CIC (M = 5.9, p = 0.009); with low level of PA in mass media (M = 26.2, p = 0.05), high propensity to addictive behavior (M = 7, p = 0.04), low emotional plasticity (M = 22.7, p = 0.04).
Conclusion: Thus, the presence of the same diplotypes manifests itself differently in the psychological characteristics of Caucasian women with different nationalities.

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An early risk indicator of Alzheimer's disease (AD): AD polygenic risk score is associated with a psychophysiological index of cognitive effort in cognitively normal adults

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Background: The pupillary dilation response during cognitive tasks is a validated index of cognitive effort. Given the same score, requiring greater effort suggests being closer to the point when compensatory capacity will be exceeded. We previously showed that adults with single-domain amnestic MCI showed greater pupil dilation during digit span tasks than cognitively normal (CN) individuals despite equivalent task performance (Granholm EL, Panizzon MS, Elman JA, Jak AJ, Hauger RL, Bondi MW, Lyons MJ, Franz CE, Kremen WS [2017] Pupillary responses as a biomarker of early risk for Alzheimer's disease. J Alzheimers Dis 56(4):1419–1428). We have also shown that higher Alzheimer's disease polygenic risk scores (AD-PRSs) were associated with significantly increased odds of having MCI in adults who were only in their 50 s (Logue MW, Panizzon MS, Elman JA, Gillespie NA, Hatton SN, Gustavson DE, Andreassen OA, Dale AM, Franz CE, Lyons MJ, Neale MC, Reynolds CA., Tu XM, Kremen WS [2018] Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50 s. Mol Psychiatry Epub ahead of print). To validate pupillary responses as a psychophysiological biomarker of early risk for AD, here we tested whether the AD-PRS was associated with pupil dilation during digit span tasks in rigorously-defined CN individuals.
Methods: Participants were in wave 2 of the Vietnam Era Twin Study of Aging (VETSA). With a neuropsychological test battery comprising 18 tests covering 6 cognitive domains, CN was defined as having no domains below the impairment threshold. We tested 576 CN participants on digit spans at low (3-digit), moderate (6-digit), and high (9-digit) cognitive loads while pupillary changes were recorded. Mean age = 62 years; range = 56–66. The AD-PRS was developed from the International Genomics of Alzheimer's Project (IGAP) database. We used the single nucleotide polymorphism (SNP) p-value threshold that best differentiated CN versus MCI in our study and CN versus AD in prior studies. We controlled for the first 3 principal components (to account for ethnic stratification), age, anticholingeric medications, and clustered twin data.
Results: Higher AD-PRSs were not associated with digit span performance, but they were associated with significantly greater pupil dilation at the high cognitive load. Results held up after excluding *APOE*-related SNPs from the AD-PRS.
Conclusions: Increased pupil dilation at high cognitive loads indicates increased compensatory effort in late middle-aged adults with normal neuropsychological function. The significant association with genetic risk based on the AD-PRS supports task-related pupillary response as a psychophysiological biomarker of early risk for AD. Further support stems from the fact that this pupillary response is largely driven by the locus coeruleus, the earliest sites of tau deposition in the brain. Both the AD-PRS and pupillary responses are non-invasive indicators that may augment prediction of increased risk for AD while people are still relatively young. Importantly, this analysis included only CN individuals. Thus, these are non-invasive indicators that may aid in identifying people at increased risk even before neuropsychological performance becomes impaired.

A likelihood implementation for censored data; an implementation of the tobit model in a likelihood setting

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Disorders are often conceptualized as the extreme end of continuous traits, eg in ADHD (1). However, many scales used to capture the traits focuses only on one part of the distribution—the negative symptoms. Thus, the distribution of the resulting scale contains a lot of "non-endorsers", ie zeros—sometimes this is referred as the scale being zero-inflated. However, given the plausible belief that the scale is not capturing the entire variation of the trait, calling it left-censored is more appropriate. When analyzing this data, under assumption of a missing part of the distribution, and normality assumption, a so-called tobit transformation may be used (2). Another option is the polychoric correlation, or ordered probit model when referring to single outcomes, but has costs with regards to precision of estimates (2). To our knowledge, no description of straight-forward and easily implemented approaches to incorporate censored variables in a likelihood setting in structural equation models has been published. Thus, we suggest a general method to incorporate censored variables in quantitative genetic analyses in a likelihood setting, by deriving a re-statement of the likelihood through conditional probabilities. The re-statement of likelihood can be used for any type of structural equation model, including univariate and multivariate heritability models, where variables analyzed may be continuous, ordered categorical, or censored, or any combination thereof. Further, we will address the best normalizing transform in censored data within the Box-Cox-family of transformations. We will investigate the properties (ie, bias, precision, and power) in a series of simulations, and apply the method to estimate heritability of ADHD using the A-TAC questionnaire assessed in Swedish twins. We will also highlight the symmetric problem of right-censored data, such as survival data (i.e., time of an event happening), via a heritability analysis of time to cause-specific death in prostate cancer (3).

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Genetic effects shared between schizophrenia and cognition: changes across age of risk

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Neurodevelopmental models seeking to explain schizophrenia's peak age of onset in the twenties may be heuristically divided into "early" and "late" models[1], with "early" models proposing that schizophrenia-specific brain effects occur perinatally but remain clinically latent until they are revealed by normative brain changes during young adulthood[2] and "late" models hypothesizing that schizophrenia-specific brain effects, such as excessive synaptic pruning, occur during young adulthood[3]. Given schizophrenia's high heritability ($h^2 = .80$)[4], early neurodevelopmental models thus predict that schizophrenia genetic effects should be present during childhood[2], whereas late neurodevelopmental models suggest that schizophrenia genetic effects should increase during adulthood nearer to the peak age of onset[3]. Cognition is genetically correlated with schizophrenia and thus this correlation may serve as a proxy index of some schizophrenia genetic effects among non-schizophrenia individuals. The present study thus sought to examine whether the genetic correlation between schizophrenia and cognition increases from ages prior to the peak age of onset of schizophrenia to ages after the peak, as predicted by "late" developmental hypotheses. To address this question, 636 relatives from 43 multiplex, extended pedigrees (15–87 years old) and 135 unrelated controls underwent diagnostic interview and cognition assessment. Epidemiological studies of population incidences identify the peak age of schizophrenia onset at approximately 23 years[5]. Therefore, non-schizophrenia relatives and control participants were stratified into two risk groups based on their ages relative to the putative trajectory of schizophrenia genetic risk effects: pre-peak (younger than 23 years) and post-peak (older than 23 years). Quantitative genetic analyses were conducted using maximum-likelihood variance decomposition methods in SOLAR[6]. Exploratory factor analysis conducted on the eleven cognitive assessments (Penn Computerized Neurocognitive Battery, Trail Making Test, and California Verbal Learning Test) yielded a single general cognition factor. General cognition was heritable in both the pre-peak ($h^2 = 1.00$, $p = 0.008$) and the post-peak periods ($h^2 = 0.49$, $p < 0.001$) and the genetic correlation between the risk periods was high (RG = 1.00, p = 0.002), suggesting that similar overall genetic factors influence general cognition across risk periods. The genetic correlations between schizophrenia and general cognition for was moderate and not significant (RG = − 0.32, p = 0.070) in the pre-peak period. Importantly, the genetic correlation between schizophrenia and cognition was significant and significantly higher in the post-peak (RG = − 0.58, $p < 0.001$) than in the pre-peak period (Fisher's z = 2.62, p = 0.004), suggesting that pleiotropic effects between schizophrenia and cognition increase during and continue after the peak age of onset of schizophrenia. These findings are consistent with late neurodevelopmental models of schizophrenia in which schizophrenia peak age of onset arises at least partly due to the late expression during young adulthood of schizophrenia risk variants and suggest the importance of examining whether specific schizophrenia genetic risk variants modulate their effects across development.

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Associations between subjective well-being polygenic scores and personality, mental health and behavioral outcomes in young adults

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Subjective well-being is associated with a variety of better psychosocial and health outcomes. Twin studies suggest that subjective well-being is heritable and genetically correlated with depression and personality traits such as neuroticism. We examined whether genome-wide polygenic scores for subjective well-being predict phenotypic measures for subjective well-being, personality traits, and mental/behavioral health outcomes in a sample of young adults. Our sample included 2451 European-American college students (58% female, age range 18–25) collected as part of the Spit for Science study (S4S). Phenotypic subjective well-being was measured using the Mental Health Continuum Short Form. Our personality traits included the Big Five domains. Mental and behavioral health outcomes included depressive symptoms, anxiety symptoms (assessed by the Symptom Checklist-90), alcohol consumption, and criterion counts for DSM-5 alcohol use disorder. Subjective well-being polygenic scores (SWB-PGS) were calculated using genome-wide association weights from the Social Science Genetic Association Consortium. We used regression models to examine whether SWB-PGS were associated with phenotypic subjective well-being, personality, mental health and behavioral outcomes. Covariates included age, sex, and three genetic ancestry principal components. We found evidence that higher SWB-PGS predicted higher subjective well-being in S4S (effect size $\sim$ 1%). In addition, SWB-PGS were associated with neuroticism (beta = − .04, $p = 0.03$), but not associated with the other domains of personality. Higher SWB-PGS also predicted lower levels of depressive symptoms (beta = − .09, $p < 0.01$) and anxiety symptoms (beta = − .09, $p < 0.01$). Finally, SWB-PGS were not associated with alcohol consumption, associations with alcohol use disorder criterion count were just above the traditional threshold (beta = − .04, $p = 0.07$). Together, our results show that higher SWB-PGS predicted higher levels of subjective well-being and lower levels of neuroticism and mental health problems in an independent, college sample.

Behavior, epigenetics, and the inescapable problem of animal constraint

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Seminal work beginning over 50 years ago compared rats living inside standard laboratory cages with rats living as pets or under more complex environmental conditions in larger cages. These comparisons found that freer rats were better at solving problems and had

heavier brains. Environmental complexity in those early experiments involved provisioning rats with both *spatial* heterogeneity (objects in the cages) and *temporal* variety (daily access to reconfigured mazes). Common "enrichment" protocols now typically involve modest changes to the cage interior and more available space. Experimental use of these protocols often shows that "enrichment" vastly increases the complexity of cellular and capillary architecture and enhances resilience to the deleterious neurological effects of genetic, surgical, and chemical manipulations, often via epigenetic mechanisms. Stepping back for a moment, we see that the term "enrichment" is a misnomer. For a mouse, the ratio between the footprint of a standard cage and the area of its natural home range is about 1–280,000. For a rhesus macaque, this ratio is about 1–7 million. Laboratory animals can be highly responsive to drugs that turn out not to be effective in human trials. The paucity of environmental stimulation inside the cage can lead to unwanted artifacts and contribute to undue sensitivity to uncontrollable variables. Very likely, our standard cage conditions (and likely as well our various 'enriched' conditions) impose boredom on our non-human animal subjects, starving them of the spatial and temporal environmental complexity necessary for their brains to fully function and develop; they lack the freedom to make choices, to learn from trial and error, and to experience on a daily basis the consequences of their decisions. We have made great strides in understanding behavior genetics through studies of animals in cages. The time has come to move forward. The next generation of non-human animal studies should employ semi-natural conditions where subjects have ongoing freedom to make decisions, face manageable challenges, and endure the robust variety of cognitive and affective experiences we know is necessary for healthy brain development and function. By so doing, behavioral models will achieve greater relevance to our understanding of human health and disability.

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Differences in DNA methylation profiles from lifetime and symptom-based major depression measures

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Background: Results from recent, high-powered DNA methylation (DNAm) studies have underscored the potential for EWAS to yield robust, credible findings that identify genomic regions associated with complex trait pathophysiology or risk liability; however, issues of replicability have prompted researchers to identify practices that may be contributing to non-overlapping results. Covariates such as cell-type heterogeneity and substance use have received the most attention, but the impact of phenotype measurement and definition has been understudied. For example, EWAS of major depression (MD) have relied on depressive symptom (DSx) scores and MD case status to identify genomic regions associated with depression, but the question of whether these two broad depressive phenotypes both tap into the same latent construct is unresolved.
Objective: Evaluating the similarity of DNAm patterns associated with both DSx and MD case status using the same sample may provide evidence regarding the relationship between self-reported DSx and phenotype based on a clinical diagnosis.
Method: A co-twin control design was leveraged to assess genome-wide DNAm in N = 75 monozygotic twin pairs (N = 150 twins; ages 15–20 years; 73% female). Data from the Infinium HumanMethylation450 Beadchip was processed in the R environment using BioConductor packages. All samples passed rigorous quality control metrics, and poorly performing probes were identified and removed. Phenotypic data related to psychopathology, substance use, and demographic information were collected electronically using self-report questionnaires. DSx were measured using the Short Mood and Feelings Questionnaire, which is validated for use in both juvenile and adult populations. Early-onset MD case status was assessed using an extended version of the self-report Composite International Diagnostic Interview-Short Form (CIDI-SF). Linear regression methods were used to identify DNAm sites associated with an MD phenotype.
Results: One hundred thirty-six sites were differentially methylated by early-onset MD case status (1% false discovery rate). These sites mapped onto 84 genes, and enrichment analysis revealed a significant portion of these genes were associated with neuro-related functions, such as axon projection, neural differentiation, and synaptic signaling. No significant results were identified in the quantitative DSx analyses. Association sign tests revealed that only a minority of probes significant in the MD case analysis had the same direction of effect compared to DSx (4/136).
Conclusions: Significant differences in DNAm exist by early-onset MD case status. DSx and MD case status yielded exceptionally different results, which supports the notion that DSx and MD case status are disparate phenotypes and that poor replicability may be tied to this problem.

Genetic risk of insomnia in children and adolescents and later aggression

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Sleep quality problems in children and adolescents have been widely linked to risk indicators of later emotional and behavioural difficulties and highlight the importance of resolving sleep problems in young persons. Parental reports of their children sleeping less than the recommended number of hours of sleep for age, overtiredness and insomnia, have also been shown to predict higher ratings of aggression later in life. Whilst associations of the characteristics of sleep quality problems in child and adolescent development, and later emotional and behavioural difficulties have been found, little research has been undertaken to consider the specific link between sleep quality problems such as insomnia and aggression. Method Using data collected in wellbeing and health studies from Queensland Institute of Medical Research (QIMR; Brisbane, Australia) on N $\sim$ 1500 individuals, we evaluated phenotypic results and associations for sleep quality problems including insomnia from the Insomnia Severity Index, Pittsburgh Sleep Quality Index and the Quick Inventory of Depressive Symptomatology Insomnia and Hypersomnia Scale, and Aggression from the Buss–Perry Aggression Scale. We used polygenic risk scores from the latest genome-wide association study on insomnia in order to test whether the genetic risk for insomnia in young persons predicted aggression or any of its components. Results will be discussed. Expected Conclusions: Genetic links between insomnia and aggression would inform prevention and early treatment and interventions.

Genetic influences on socio-cultural sensitivity: moderation of effects of the family check-up intervention on symptoms of child psychopathology

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From the cultural genomics theoretical perspective, there is no one "best" genotype, as the best genotype varies as a function of the environment. A genotype that provides an advantage in one environment may be disadvantageous in another, with natural selection maintaining genetic variation when there is high variability in environments, as is the case for the human population today. Consistent with Differential Susceptibility Theory (Belsky and Pluess 2009), individuals can vary in their sensitivity to socio-cultural conditions, including intervention, for reasons including their genotype. Consequently, understanding genetic influences on intervention response is critical. We tested an interaction between a polygenic environmental susceptibility score based on identical twin differences (Keers et al. 2016) and the Family Check-Up intervention, which focuses on improving positive parent management skills (Dishion and Stormshak 2007). Participants were a high risk, culturally diverse sample of children and their families drawn from the Early Steps Multisite randomized prevention trial and followed longitudinally (N = 731; 13% Latino, 28% African American, 50% European American, 13% biracial, and 9% other groups). Families were randomly assigned (but gender balanced) to the control or intervention condition after the baseline assessment at child age 2 years. The polygenic susceptibility scores contained 2372 SNPs for a $p = 0.05$ threshold based on Keers and colleagues' (2016) GWAS, and 4606 SNPs for $p = 0.10$. Covariates included age, gender, income, study site, and the first two of 20 ancestry principal components, examining main effects and two-way interactions (Keller 2014). Symptoms of internalizing psychopathology were assessed through child report on the Diagnostic Interview Schedule for Children (DISC-IV) structured clinical interview conducted in the home when the children were 10 years of age. As hypothesized, polygenic susceptibility moderated the effects of the intervention on children's symptoms of internalizing psychopathology, such that children who were genetically susceptible to the socio-cultural environment and randomly assigned to the intervention group had fewer symptoms than children assigned to the control condition. A significant difference in self-reported DISC-IV internalizing symptoms emerged between the intervention and control groups for those 0.493 standard deviations above the mean on polygenic susceptibility, or approximately 25% of the sample. With genetically informative designs, we can elucidate individual and socio-cultural differences in treatment response and individualize psychosocial interventions, reducing the burden of child psychopathology and maximizing wellbeing for children growing up in a wide range of physical environments and cultures.

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Heritability of screen time in the ABCD study

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The Adolescent Brain Cognitive Development Study (ABCD) is a longitudinal study of brain development and child health in the United States. About 4500 subjects were included in the first wave of data collection. Released data on 96 SNPs, family membership, and age at testing were used to identify 105 MZ twin pairs and 133 DZ twin pairs. All subjects were born in the years 2005 through 2008, and were interviewed between the month of their ninth birthday and their eleventh birthday. As markers of the beginning of the era of near ubiquitous Internet-enabled computing devices, the iPhone was released in June, 2007 and the iPad in April, 2010. That means the subjects in ABCD were some of the first to have modern, pocket computing devices widely available from early childhood. The mean self reported, non-school related screen time is 24.69 (SD = 19.38) hours per week for boys and 19.41 (SD = 17.49) for girls. Twin modeling shows for males $V_A = 0.26$, $V_C = 0.32$, $V_E = 0.42$ and for females $V_A = 0.50$, $V_C = 0.06$, $V_E = 0.45$.

Using a siblings reared apart and together design to study associations between parenting and child behavior problems

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There is a large body of research documenting the association between parenting practices and child behavior problems. A range of mechanisms have been posited for this association, including shared genetic factors (passive gene–environment correlation), child evocative effects on parenting, and child modeling of parental behavior. Genetically-sensitive studies are uniquely suited to separate genetic and environmental factors that underlie associations between parenting practices and child problems, and intervention studies are uniquely suited to isolate malleable environmental influences on child problems. However, the principles underlying these two paradigms are seldom used in concert with one another, hampering the identification of malleable mechanisms for intervention research. The purpose of this study was to address this gap through the use of a natural experimental design facilitated by an adoption-sibling study. We expected to replicate the well-known association between parenting practices and child behavior problems, to demonstrate that this correlation remains significant in unrelated adoptive parent–child dyads (e.g., passive gene–environment correlation alone cannot explain the association), and to replicate prior studies indicating that child behavior problems are partially heritable using a sibling analysis. Participants were drawn from the Early Growth and Development Study, a prospective adoption-sibling study that includes over 500 adoptees who were placed with genetically unrelated adoptive families at birth, and their siblings who either resided in the same home as the adoptee or who had been reared apart since birth. In addition, in some families, there were additional children in

the birth parent home who were not genetically related to the adoptee. Thus, the design includes siblings living in the same or different homes since birth who are either genetically-related or genetically unrelated (N = 1285 children, M age = 11.35 yrs, SD = 4.3 years). Mothers completed the Strengths and Difficulties Questionnaire (total behavior problem scale) individually about each of her children and also reported her warm and harsh parenting to each child using the Iowa Family Interaction Rating Scales. Cross-sectional analyses indicated a positive association between child behavior problems and harsh parenting (R = .47) and a negative association between child behavior problems and warm parenting ($R = -.19$) that was similar when the parent was genetically-related (R = .41 for hostility and $R = -.17$ for warmth) or unrelated to the child (R = .51 for hostility and $R = -.19$ for warmth; all p's $< .01$ after correcting for multiple testing), suggesting negligible effects of passive gene–environment correlation. Sibling models controlling for age and sex indicated significant heritable (.34) and nonshared environmental variance components (.60) of child behavior problems. Regression analyses predicting parental hostility indicated a significant effect of genetic relatedness of child to parent in the adoptive home, where mothers reported less hostility to children who were genetically related to them, and more hostility toward their adoptee. Results were discussed in terms of the ability of natural experimental designs to provide insights into environmental mechanisms and intervention targets.

NR3C1 methylation is associated with internalizing symptoms in middle childhood

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Behavioral problems in childhood are often the earliest and most reliable predictors of developing a psychiatric disorder (Roza et al. 2003). Internalizing problems are associated with both mood and anxiety disorders, which share high-comorbidity rates and a common dysregulated hypothalamic–pituitary–adrenal (HPA) axis endophenotype (Tandon et al. 2009). A large body of research suggests early adverse experiences may shape mental health related physiology and behavior through altering methylation of the *NR3C1*gene (Palma-Gudiel et al. 2015). The *NR3C1* gene codes for the glucocorticoid receptor, a central component in HPA axis regulation. However, much of this research did not control for genetic influences on methylation levels. Therefore we used a monozygotic (MZ) twin design to control for genetic effects. First, we used mixed-model regression analyses to investigate the hypothesis that *NR3C1* methylation is associated with internalizing behavior. Next, we used linear regression to test the hypothesis that MZ differences in internalizing is associated with MZ difference in gene methylation. Our sample included 96 monozygotic twins (48 families; 51% male; 50% Non-Hispanic White, 14.6% Hispanic/Latinx, 8.3% African American, 4.2%Asian American), mean age = 8.5 years, drawn from the Arizona Twin Project (Lemery-Chalfant et al. 2013). We collected buccal cell samples and conducted primary caregiver interviews to assess internalizing symptoms (MacArthur Health and Behavioral Questionnaire [HBQ]) during home visits. DNA methylation was quantified using the Infinium Methylation EPIC Bead Chip. We included 33 CpGswithin *NR3C1* promoter regions to extract the first principal component after removing all sites with a $< .3$ loading (18 CpG sites remained; variance explained 35.17%, all sites loaded from .31 to .81). Results indicated *NR3C1* methylation was a significant predictor of internalizing symptoms ($b = -0.056$, p = 0.012), however MZ differences in internalizing were not significantly related to MZ differences in methylation. These results suggest that dynamic methylation of the *NR3C1* gene may be an endophenotype related to internalizing behavior. However, this association maybe genetically driven more than environmentally driven. These results implicate DNA methylation as a possible molecular marker related to children's mental health and risk for psychiatric disorders.

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Associations between dopaminergic gene methylation and executive performance in a childhood MZ twin difference design

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Specific allele types of dopaminergic genes have been associated with cognitive function. However, an emerging body of empirical research suggests that environmental factors are also influencing complex phenotypes by affecting the epigenome. We used a monozygotic (MZ) twin difference design to assess if between-twin differences in methylation of CpG sites near dopaminergic genes predicted differences in cognitive performance of 48 MZ twin pairs (51% male; 50% Non-Hispanic White, 14.6% Hispanic/Latinx, 8.3% African American, 4.2% Asian American), mean age = 8.5 years, drawn from the Arizona Twin Project (Lemery-Chalfant et al. 2013). Comparing MZ twins allowed us to assess if environmentally driven differences in methylation affected phenotypes while controlling for the influence of genotype on methylation status. We collected buccal cell samples and conducted cognitive and memory tasks during home visits. DNA methylation was quantified using the Infinium MethylationEPIC BeadChip. Executive attention was assessed with the Flanker Task (Linear Integration Speed Accuracy Score [LISAS] for congruent and incongruent trials). Short-term and working memory were assessed with Digit Span (Total Forward [TF] and Backward [TB]). Since the number of CpGs near each gene ranged from 20 to 41, we used PCA to extract the first component after removing all sites with a $< .3$ loading (variance explained ranged from 45.12 to 70.15%). Next, we computed MZ difference scores from components and task performance for linear regression analysis controlling for sex. We found MZ co-twin differences in *DRD4* (b = 0.359, p = 0.019) and *DBH* (b = 0.298, p = 0.045) methylation predicted differences in short-term memory. MZ differences in DBH (b = 0.311, p = 0.046) and trending for COMT (b = 0.277, p = 0.076) predicted differences in response inhibition. Lastly, differences in DAT1 trended

towards predicting differences in executive attention ($b = 0.284$, $p = 0.073$). Taken together, findings suggest methylation status of dopaminergic genes may influence cognitive functions in a dissociable manner. Our results highlight the importance of the epigenome and environment, over and above the influence of genotype, in supporting complex cognitive functions.

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An experimental study reveals that the FTO gene and gender modify peer influence on body mass index

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Research has shown that friends' obesity statuses are correlated. However, it is difficult in observational data to test whether peer influence on obesity is causal. We conducted an experimental study of randomly-assigned college roommates to investigate peer influence on body mass index (BMI). We examined whether the *FTO* (fat mass and obesity associated) gene and gender modify peer influence. We found that women inheriting two risk alleles for obesity weigh about three pounds less if randomly assigned a frequently-exercising roommate than if randomly assigned a non-frequently-exercising roommate. This effect size is equivalent to about 60% of the *FTO* gene effect. Both women and men inheriting two risk alleles exercise more often if randomly assigned a frequently-exercising roommate. However, for men this increase in physical activity does not lead to a decrease in BMI, probably because men's exercise motivation is often muscle building while women's motivation is often weight control.

An examination of the influence of early childhood care on academic achievement using quantile regression

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Purpose: Early childhood education and care (ECEC) receives widespread support in the public domain; however, previous studies of ECEC have revealed mixed results. In some cases ECEC attendance is positively associated with academic outcomes (e.g. Fox & Geddes, 2016), and in others ECEC attendance appears ineffective or negative (e.g. Coley et al. 2015) in terms of later academic achievement. The mixed evidence surrounding ECEC suggests the need for further investigation into its influence on educational achievement. The present study addressed this need by examining whether ECEC attendance influenced later school achievement not just at the means, but at multiple points along the distributions of achievement in a large sample of Australian twins spanning 3rd through 9th grade. Furthermore, this study examined whether ECEC attendance moderated the heritability and/or shared environmental influences of school achievement across the distributions of achievement.

Methods: Participants were obtained from the Longitudinal Twin Study of NAPLAN (n = 1517; 667 MZ, 850 DZ). Early childhood education and care attendance was measured as hours of attendance per week. Quantile regression was used to examine the influence of ECEC attendance across the distribution of reading in 3rd, 5th, 7th, and 9th grades. Next, a genetically-sensitive extension of quantile regression (see Logan et al. 2012) was conducted to examine ECEC attendance as a moderating influence on the heritability and shared-environmental influences of school achievement across the distributions of achievement. *Results and Discussion*: Results indicated a slightly negative, though mostly non-significant influence of ECEC attendance across the distributions of reading for all grade levels after controlling for ECEC type (e.g. family-day care, formal ECEC setting), father's education level, and total number of months attending ECEC. Additionally, results indicated that heritability estimates were higher, and shared environmental estimates were lower, with ECEC attendance included as a moderator in 3rd grade, with these trends disappearing by 5th grade. These results suggest that, although ECEC attendance does account for a small portion of the shared environmental influence on reading in 3rd grade, these influences appear to have no significant short-term or long-term sway on reading for Australian students. Additional results for numeracy and writing in 3rd, 5th, 7th, and 9th grades will be presented and discussed.

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Modeling child body mass index Z-score variation from age 2 to 12 years associated with heritable and rearing environmental factors using multilevel model with heterogeneous variance

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Many children follow predictable growth curves for BMI, showing consistent z-scores over time. However, some children show high BMI instability. The current study explored whether variability in children's BMI-z scores over time reflects the impact of heritable and environmental factors that may constrain or predict instability in BMI z-scores over time. Consistent with current obesity theories, we hypothesized that children with higher heritable risk for obesity may demonstrate higher and more stable BMIs relative to peers who are not at risk. We also hypothesized that parent behaviors that encourage children to use external cues to regulate eating would lead to less stable BMI z-scores over time: children who are not taught to rely on internal cues of hunger and satiety may have more difficulty maintaining a stable BMI z-score. Participants were drawn data from the Early Growth and Development Study, a prospective adoption study that includes 561 adoptees who were placed with nongenetically related adoptive families close to birth. Child BMI was obtained via adoptive parents' (AP) reports and extracted from medical records. Child BMI z-score adjusted for sex and age was calculated based on the US CDC 2000 norms (Kuczmarski et al. 2002). On average, there were 9 BMI assessments per child (range = 1–51), and assessments spanned from age 2 to 12 years. Birth mother and birth father (birth parents: BP) BMIs were self-reported 6 times from post-partum

5 months to 9 years, and used to compute birth mother and birth father's average BMIs. BP average BMIs were used to index heritable influences on BMI. At child age 4.5 years, adoptive mothers (AMs) reported on how much they controlled their children's eating (food restriction, pressure to eat) vs. permitted them to regulate their own eating. Analyses were conducted using a multilevel model with heterogeneous variance, in which within-person variances were modeled as a function of heritable and environmental factors. Both heritable and rearing environmental factors were associated with mean levels and variability in child BMI z-score. Consistent with hypotheses, children whose BP have higher BMIs also have higher BMI z-scores (birth mother: ß = .03, $p < 0.01$, and birth father: ß = .03, $p = 0.04$) and more stable BMI z-scores from early childhood to early adolescence (birth mother: $\chi^2 = 13.18$, $df = 1$, $p < 0.01$; birth father: $\chi^2 = 3.12$, $df = 1$, $p = 0.07$). AMs' external regulation of eating was related to more variability in child BMI z-scores over time. Although food restriction was not associated with mean levels of BMI z-scores, it was positively associated with variability in child BMI z-scores ($\chi^2 = 17.11$, $df = 1$, $p < 0.01$); pressure to eat was negatively associated with mean levels of BMI z-scores (ß = − .28, $p < 0.01$) and positively associated with variability in BMI z-scores ($\chi^2 = 11.98$, $df = 1$, $p < 0.01$). Therefore, more stable BMIs were observed for children at heritable risk for higher BMIs and for parents who do not externally regulate children's eating.

Meta-analysis of genome-wide association study of 1.2 million people finds novel signals in alcohol and nicotine use

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Alcohol and nicotine use are leading causes of preventable deaths in the US. Past twin and family studies have shown moderate heritability and genome-wide analyses have found a handful of replicable genes (eg. CYP2A6 and cigarettes per day). However, there are still many variants that may be important to addiction but not yet found due to their small effect sizes. To discover and better understand the biological mechanisms of addiction, GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) conducted a large meta-analysis across 29 cohorts in over 1 million people for 5 substance use related phenotypes. We targeted four phenotypes related to nicotine use: age of initiation of regular smoking (AgeSmk, N = 234,398), initiation of regular smoking (SmkInit, N = 1,232,091), cigarettes per day (CigDay, N = 337,334), smoking cessation (SmkCess, N = 547,219) and one related to alcohol use: drinks per week (DrnkWk, N = 941,280). We report to have found 564 independently associated variants in 405 loci for these 5 phenotypes. Amongst those, we replicated many previous findings such as the aforementioned CYP2A6 for CigDay and ADH1B for DrnkWk. Pleiotropy was also observed with ∼ 47% of our tested loci implicated in 2 or more phenotypes and 3 of those implicated in all 5 phenotypes. Single nucleotide polymorphism (SNP) based heritability estimated ranged from 4% (DrnkWk) to 8% (CigDay). Genetic correlation analysis shows the four smoking phenotypes are more genetically correlated with each other and most behavioral, psychiatric, substance use and medical phenotypes. DrnkWk is only correlated with SmkInit as compared to the other smoking phenotypes and weakly correlated with most of the other phenotypes. In conclusion, we conducted the largest addiction genome-wide meta-analysis to date and have found numerous loci in different biological pathways. By studying all 5 phenotypes simultaneously, we hope to shed light on the biological mechanisms that are not only specific to each phenotype, but also reflect a general risk for substance use and addiction.

Phenotype harmonization: balancing between psychometric ideals and empirical data reality in the ACTION consortium

Gitta Lubke, University of Notre Dame; Justin Luningham, University of Notre Dame

Behavioral phenotypes are usually measured with different questionnaires across cohorts. Since different items tap into different aspects of a behavior, the aggregation of whatever items are available in each cohort can introduce considerable noise in the phenotype measure across cohorts. This in turn leads to loss of power in subsequent genetic analyses. Psychometric phenotype harmonization has been shown to improve power but faces the challenge of severe structural missingness at the item level since any given cohort usually only has item level data on one of the questionnaires used by the different cohorts. The missingness can be dealt with either by imputation or by the collection of an additional small phenotypic "reference panel" which provides data on all items. The various additional challenges of psychometric phenotype harmonization are discussed using our recent harmonization of the aggression phenotype in the ACTION consortium as an example.

Genetic and environmental contributions to overt aggression harmonized across multiple studies, nations, and raters in the ACTION consortium

Justin Luningham, University of Notre Dame; Meike Bartels, Vrije Universiteit Amsterdam; Dorret Boomsma, Vrije Universiteit Amsterdam; Gitta Lubke, University of Notre Dame; ACTION Consortium

Aggression in children is highly predictive of problems later in life, including delinquency, interpersonal relationship difficulties, and depression, among other maladjustments (Brame, Nagin, & Tremblay, 2001; Provencal, Booij, & Tremblay, 2015). The ACTION Consortium is a collaboration of several large-scale, prospective longitudinal studies of childhood aggression and its comorbidities (Boomsma, 2015; Bartels et al. under review). As in most behavioral consortia, there is a moderate degree of measurement heterogeneity across studies in ACTION. To assess aggression in children, cohorts in ACTION used different questionnaires, collected data from different raters, and obtained scores for children at different ages. In this talk, we present a modeling strategy for creating a harmonized aggression phenotype score for school-aged children. Aggression was modeled across five cohorts from Scandinavia, the Netherlands, and the UK using mother and father reports for children aged 7–12 years. Creating a harmonized phenotype score with a multirater bi-factor model allowed for genetic structural equation models to be fitted to the combined data across the consortium. The increased sample size due to pooling across cohorts (42,468 twin pairs) permitted us to investigate complex models for twin data, including quantitative and qualitative sex-limitation models and sibling interaction effects. Results indicated that opposite sex twin pairs were better modeled as having unique path coefficients for shared and non-shared environmental components compared to their same-sex counterparts. Heritability estimates were generally higher for males (∼ 62%) than females (∼ 50%), and these estimates were slightly lower than initial estimates within two large individual cohorts (Bartels et al. under review). This difference could be due to a negative sibling interaction effect found in female same-sex pairs and opposite sex pairs.

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Modeling the association of school achievement and criminal behavior in Swedish twins, full and half siblings, and cousins using SEM and co-relative designs

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Using Swedish nationwide registry data, we compared testing the contribution of genetic and environmental risk factors to the association of school achievement and criminal behavior by structural equation modeling and by co-relative control designs. School achievement data were obtained from conscription registries while criminal behavior was derived from criminal records. Twin, full sibling, half sibling, and cousin pairs born between 1960 and 1990 were obtained from the national twin and genealogical registers. Genetic structural equation modeling and logistic regression were applied to the population-based data, using OpenMx and R. The focus of SEM modeling was more empirically driven by fitting all possible identified bivariate models including up to three parameters accounting covariance from additive genetic, shared environmental and unique environmental sources and reciprocal causal paths, with simultaneous testing for qualitative and quantitative sex differences. Analyses were done separately for twin pairs only, including twins & full siblings, adding half sibling, testing just full and half siblings and finally combining twins, full & half sibs and cousins to evaluate the power of alternative designs. Furthermore, we tested the information gained from SEM modeling compared to using discordant co-relative designs.

'Same but different': associations between multiple aspects of self-regulation, cognition and academic abilities

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Self-regulation (SR) refers to the ability to control both behaviors and internal states against a backdrop of conflicting or distracting situations, drives, or impulses. In the cognitive psychology tradition, SR is commonly measured with performance-based tests of executive functioning, whereas in the personality psychology tradition, SR is usually assessed with report-based measures of impulse control, effortful control and temperament. The goal of this project was (1) to comprehensively examine the structure of associations between multiple SR constructs stemming from the cognitive and personality psychology traditions; (2) to estimate how these constructs, individually and collectively, relate to mathematics and reading abilities beyond psychometric measures of processing speed and fluid intelligence; and (3) to estimate extent to which genetic and environmental factors mediated the observed associations. Data were available for 1019 child participants from the Texas Twin Project (M age = 10.79, *Range* = 7.8–15.5). Results highlighted the differentiation among cognitive and personality aspects of SR, both at observed and genetic levels. After accounting for processing speed and fluid intelligence, EF remained a significant predictor of reading and mathematics abilities. Educationally relevant measures of personality—particularly an openness factor representing curiosity and self-concept—incrementally contributed to individual differences in reading ability. Collectively, measures of cognition, SR and other educationally relevant aspects of personality accounted for the entirety of genetic variance in mathematics and reading ability. The current findings point to the important independent role that each construct plays in academic settings.

Genome-wide association study of mania and psychosis reveals complex relationships between psychiatric disorders and their cardinal symptoms

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Recent advances in psychiatric genetics have provided novel insight into the etiology of serious mental illnesses, such as bipolar disorder and schizophrenia. However, few studies have investigated the genetic architecture of specific symptoms of serious mental illness. To address this dearth of research, we conducted a series of genome-wide association studies (GWAS) of continuous indices of mania ($N \sim 220$ k) and psychosis ($N \sim 140$ k) in the general population, constructed with Item Response Theory (IRT) scaling. We found complex patterns of genetic overlap between specific symptoms, psychiatric disorders, and related social, behavioral, and cognitive traits. Most notably, we observed high genetic correlations among many pairs of psychiatric symptoms ($r_g \sim .60$ to .90), but only moderate genetic correlations between bipolar disorder and schizophrenia and their cardinal symptoms ($r_g \sim .30$ to .40). To further probe the relationship between continuous symptom variation and psychiatric diagnoses, we applied a new method, Genomic SEM, to explore the multivariate genetic architecture of psychiatric symptoms (mania, psychosis, irritability, and depression) and their corresponding disorders (bipolar disorder, schizophrenia, and major depressive disorder). Finally, we conducted a series of polygenic prediction and bioinformatics analyses to interrogate shared and dissociable genetic risk for various forms of psychopathology. In doing so, we use a variety of methods to investigate sources of heterogeneity within psychiatric genetics.

Psychosocial exposures and well-being: concurrent and longitudinal overlap before and after accounting for gene–environment correlation

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There has been a proliferation of studies on the correlates of hedonic well-being, and several psychosocial variables have been identified as risk and protective factors. However, individuals are not randomly exposed to psychosocial variables. Instead, individuals select into and evoke responses from psychosocial variables based on their genetic predispositions (i.e. active and evocative gene–environment correlation). Consequently, overlap between psychosocial exposures and hedonic well-being may not reflect environmental influence alone. Rather, if individuals are assorted into exposures based partly on their genetic predispositions, then associations between psychosocial exposures and hedonic well-being may be undergirded by both genetic and environmental factors. The aims of the present study were as follows: (1) Using a large population-representative sample of adults, estimate the degree of concurrent and longitudinal overlap between psychosocial exposures measured at midlife and hedonic well-being measured at midlife and later adulthood. (2) Using a subsample of identical and fraternal twins, test for the presence of heritable variation in psychosocial exposures- i.e. test for gene–environment correlation. (3) After accounting for gene–environment correlation, estimate the degree of overlap between psychosocial exposures and hedonic well-being. The sample included adults ($N > 7000$; mean age $\sim$ 45 years) and a subsample of twins ($N > 1800$) who took part in the National Survey of Midlife Development in the United States (MIDUS). Data collection first took place between 1995 and 1996. The second wave of the study took place a decade later, between 2004 and 2006 (N = 4963). Retention rates for the full sample and twin subsample were high ($\sim$ 70% and 78%, respectively). Hedonic well-being was measured using self-reports of positive affect, negative affect, and general life satisfaction. Twelve psychosocial variables were also measured using self-reports: maternal affection, paternal affection, maternal discipline, paternal discipline, family strain, family support, friendship strain, friendship support, spouse stain, spouse support, positive work-to-family spillover, and negative work-to-family spillover. Results of bivariate confirmatory factor analysis models found small-to-moderate overlap (mean $R = .21$, range = .07–.52) between psychosocial exposures measured at midlife and hedonic well-being measured at midlife and later adulthood. In addition, quantitative genetic models provided evidence that psychosocial exposures were heritable (mean $h^2 = .34$, range = .18–.58); After accounting for these genetic confounds, the degree of overlap between psychosocial exposures and hedonic well-being was negligible-to-small (mean $R = .10$, range = $-$ .03 to .28). Thus, the present study showed that associations between psychosocial exposures and hedonic well-being reflect, in part, overlapping genetic predispositions. Nevertheless, with the exceptions of maternal and paternal discipline, even after accounting for gene–environmental correlation, the associations between psychosocial exposures and hedonic well-being remained significantly different than zero. This provided evidence for a quasi-causal effect of psychosocial exposures on hedonic well-being, albeit of small magnitude.

Copy number variation and neurodevelopmental problems in females and males in the general population

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Neurodevelopmental problems (NPs) are childhood phenotypes that are more common in males. Conversely, anxiety and depression (which are frequently comorbid with NPs) are more common in females. Rare copy number variants (CNVs) have been implicated in clinically-defined NPs. Here, we aimed to characterise the relationship between rare CNVs with NPs and anxiety/depression in a childhood population sample. Additionally, we examined whether sex-specific CNV effects underlie the sex bias of these disorders. We analysed a sample of N = 12,982 children, of whom 5.3% had narrowly-defined NPs (clinically-diagnosed), 20.9% had broadly-defined NPs (based on validated screening measures, but no diagnosis) and 3.0% had clinically-diagnosed anxiety or depression. Rare (<1% frequency) CNVs were categorised by size (medium: 100–500 kb or large: $>$ 500 kb), type (duplication or deletion) and putative relevance to NPs (affecting previously implicated loci or evolutionarily-constrained genes). We tested for associations between the different CNV categories with NPs and anxiety/depression, followed by examination of sex-specific effects. Medium deletions (OR (CI) = 1.18 (1.05–1.33), p = 0.0053) and large duplications (OR (CI) = 1.45 (1.19–1.75), p = 0.00017) were associated with broadly-defined NPs. Large deletions (OR (CI) = 1.85 (1.14–3.01), p = 0.013) were associated with narrowly-defined NPs. The effect sizes increased for large NP-relevant CNVs (broadly-defined: OR (CI) = 1.60 (1.06–2.42), p = 0.025; narrowly-defined: OR (CI) = 3.64 (2.16–6.13), p = 1.2E$-$6). No sex differences in CNV burden were found in individuals with NPs ($p > 0.05$). In individuals diagnosed with anxiety or depression, females were more likely to have large CNVs (OR (CI) = 3.75 (1.45–9.68), p = 0.0064). Rare CNVs are significantly associated with both narrowly- and broadly-defined NPs in a general population sample of children. Our results also suggest that large, rare CNVs may show sex-specific phenotypic effects.

GWAS for anorexia nervosa finds 6 loci and suggests it is both a psychiatric and metabolic disease

Nick Martin, Queensland Institute of Medical Research

Characterized primarily by extremely low BMI, anorexia nervosa (AN) is a complex, serious, and commonly misunderstood illness. Predominantly, but not exclusively affecting women, mortality from the illness and from suicide are markedly elevated, and outcomes remain unacceptably poor. AN is under-researched—no medications exist that are effective or target the core biology of the illness. Average twin-based heritability estimates are 50–60%, and genomic discovery in AN is just beginning. We conducted a genome-wide association study (GWAS) meta-analysis (15,807 cases and 50,411 controls) based on clinical, population-based, and volunteer cohorts and identified six independent genome-wide significant loci. Our analyses reveal high genetic correlations with obsessive–compulsive disorder (OCD), major depressive disorder (MDD), and anxiety disorders. However, we also observed strong negative genetic correlations between AN and fasting insulin levels, body fat percentage, and BMI as well as a strong positive genetic correlation between AN and high-density lipoprotein (HDL) cholesterol. These results may suggest that AN should be reconceptualised as both a psychiatric and metabolic disorder, though direction of causation also needs consideration.

Genetic risk prediction across diverse populations

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The vast majority of GWAS are performed in individuals of European descent. The applicability of these genetic findings to non-European populations varies with genetic divergence, differences in LD and allele frequencies, and genetic architecture. Human history provide a critical lens into complex trait studies, including the generalizability of genetic risk prediction to understudied populations. By simulating genetic data that models human history, we have shown that genetic risk predicted using European summary statistics transfers poorly to non-European populations. We have also empirically evaluated genetic risk prediction across populations using results from the Psychiatric Genetics Consortium. We find that East Asian schizophrenia risk is better predicted by summary statistics from East Asian cohorts (13k cases and 16k controls) than from $\sim$ threefold larger European cohorts (37k cases and 113k controls, Nagelkerke's $R^2 = .104$ versus .066). To improve cross-population genetic risk prediction, we are developing novel statistical methods to improve prediction accuracy across populations, such as when GWAS summary statistics are available from multiple populations. This method models LD structure in each respective population to better approximate causal effect sizes used in prediction. Our work cautions that findings from large-scale GWAS may have limited generalizability across populations with standard approaches, highlighting the need to include more diverse individuals in medical genomics.

Genome-wide association study of anxiety and stress-related disorders in the iPSYCH cohort

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Anxiety and stress-related disorders (ASRD) are among the most common mental disorders with the majority of patients suffering from additional disorders. Family and twin studies indicate that genetic and environmental factors are underlying their etiology. As ASRD are likely to configure various expressions of abnormalities in the basic stress-response system, we conducted a genome-wide association study including 12,655 cases with various anxiety and stress-related diagnoses and 19,225 controls. Standard association analyses were performed supplemented by a framework of sensitivity analyses. Variants in *PDE4B* showed consistent association with ASRD across a wide range of our analyses. In mice models, alternations in *PDE4B* expression were observed in those mice displaying anxious behavior after exposure to chronic stress. We also showed that 28% of the variance in ASRD was accounted for by common variants and that the genetic signature of ASRD overlapped with psychiatric traits, educational outcomes, obesity-related phenotypes, smoking, and reproductive success.

Three legs of the missing heritability problem

Lucas Matthews, University of Virginia; Eric Turkheimer, University of Virginia

In 2008 Maher coined 'the missing heritability problem' (MHP), an issue about conflicting results from classical, 'quantitative' genetics and molecular genetics. For any trait, decades of classical genetics had inspired optimism that molecular investigations would lead to the discovery of single genes of large effect for nearly all behavioral traits, but to date none have been found. A second aspect of the MHP was the expectation that molecular genetic information would confer newfound genomic predictive ability – still not true, as the best way to predict one's height or IQ is to average that of their parents. A variety of explanations for missing heritability are now on offer; nearly all of them focus on closing the gap between quantitative and molecular estimates of heritability, which we call the *heritability gap*. Although we acknowledge the importance of reconciling conflicting heritability estimates, here we argue that the hunt for heritability overlooks the real problem of heritability, as it is only the first leg of a tripartite problem. In addition to the *heritability gap*, there is the challenge of accurately predicting phenotype from genotype, which we call the *prediction gap*. The third leg of the MHP is the *mechanism gap*, which involves elucidating meaningful causal-mechanical stories that link small genotypic differences (e.g., SNPs) to complex behavioral differences. The MHP remains alive and well until the three legs are resolved for any given behavioral trait.

Maternal prenatal depression as a risk factor for early-life psychopathology in offspring: results from a genetically-informative, population-based sample

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Background: Maternal prenatal depression is a known risk factor for early-life psychopathology among offspring. However, it is necessary to distinguish between potential mechanisms by which this risk may be transmitted to properly understand the clinical and epidemiological implications of this link.
Objective: To test the relative importance of passive genetic transmission, direct exposure, and indirect exposure in the association between maternal prenatal depression and later internalizing and externalizing psychopathology.
Design: Structural equation modelling of phenotypic data and genetically-informative relationships the families of participants in the Norwegian Mother and Child Birth Cohort Study (MoBa).
Setting: The MoBa sample was recruited at routine ultrasound examinations offered to all pregnant women in Norway, between July 1999 and December 2008.
Participants: The total MoBa sample includes $>$ 114,500 children, $>$ 95,000 mothers, and $>$ 75,000 fathers. The analytic sub-sample of MoBa used in the current study comprises 33,580 mothers and 27,459 children.
Main outcomes and measures: We used mothers' self-reported depressive symptoms during pregnancy, as captured by the Symptom Checklist (SCL), and their reports of symptoms of psychopathology in their offspring during the first few years of life (measured at 18, 36 and 60 months using the Child Behavior Checklist [CBCL]).
Results: Maternal prenatal depression was found to be associated with both internalizing and externalizing problems in early childhood primarily via intergenerationally-shared genetic factors. For internalizing problems, phenotypic transmission also contributed significantly to the association, but was found to be explained by exposure to concurrent maternal depression, rather than by direct exposure.
Conclusions and relevance: Associations between maternal prenatal depression and offspring behavioral outcomes in early childhood are

likely to be at least partially explained by shared genes. This genetic confounding should be considered when attempting to quantify risks posed by in utero exposure to maternal depression.

Genome-wide association study of diet composition identifies 21 loci and uncovers associations with health and behavior

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The effect of diet coposition on weight, health, and longevity has been an important topic in epidemiology for decades. Yet, measuring diet composition accurately and identifying its causal effects remains a notoriously difficult task, and despite the lack of strong empirical evidence, different dietary guidelines have been published—with their focus recently shifting from recommending low-fat to low-carbohydrate (and in particular, low-sugar) diets. One aspect that is still largely missing from the literature are insights into the genetic architecture of diet composition and how it relates to lifestyle behaviors such as physical activity and health outcomes such as BMI, diabetes, and cardiovascular disease. Unobserved genetic effects could confound the observed phenotypic relationships between dietary intake and health, and insights into the genetic architecture of diet composition could help to model the effects of diet intake on health more accurately. Therefore, we conducted the largest genome-wide association study (GWAS) on diet composition to date. In particular, our measure of diet composition was represented by four phenotypes, which broadly represented energy intake from fat, protein, carbohydrate, and sugar. These phenotypes were corrected for total caloric intake in a non-linear fashion, and were created on the basis of self-report questionnaire data on hundreds of food items in 18 different genotyped samples. With a combined maximum total sample size of $N \sim 265$k for fat, protein and carbohydrate, and $N \sim 234$k for sugar, we discover 21 unique independent loci across phenotypes, revealing surprising genetic associations with health outcomes and indicators of socioeconomic status and lifestyle. Finally, we find that the genetic signal for all diet composition phenotypes is particularly driven by SNPs expressed in the brain.

Examining the genetic relationship between nausea and vomiting in pregnancy, anxiety and depression

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Nausea and vomiting in pregnancy (NVP) is an extremely common condition in pregnancy with global prevalence of 70%. NVP can progress to hyperemesis gravidarium, present in 1% pregnancies, defined as persistent and excessive vomiting, with dehydration, ketonuria and $> 5\%$ bodyweight loss. NVP may affect the psychosocial functioning of affected women. There is an increased prevalence of major depressive disorder and anxiety prior to pregnancy among women with severe NVP and NVP is a risk factor of post-natal depression. The relationship between NVP, depression and anxiety is compatible with a shared liability arising from shared genetic factors. The aim of this study is to test this hypothesis by estimating the genetic correlations between this conditions. The NVP Genetics Consortium is a collaborative project that aims to identify the causes of NVP and hyperemesisgravidarum and the factors explaining the relationship of NVP with psychiatric traits. We have conducted a GWAS meta-analysis on 27,631 women from participating cohorts (QIMR, Australia; MTR, Spain; ALSPAC, United Kingdom; EGCUT, Estonia), which is currently underpowered. We used LD-score to estimate the genetic correlations between NVP (results from the NVP Consortium), depression (MDD, results of the Psychiatric Genomics Consortium Major Depressive Disorder 2018) and anxiety (ANX, ANGST consortium 2016). Additionally, we estimated rg with post-traumatic stress disorder (PTSD, Psychiatric Genomics Consortium 2017) and schizophrenia (SCZ, Psychiatric Genomics Consortium2014). MDD and ANX may share genetic risk, with variants increasing the severity of NVP increasing the risk for MDD (rg = 0.28, p = 0.08) and ANX (rg = 0.27, p = 0.06). NVP does not seem to be genetically related to SCZ (rg = − 0.03, p = 0.70) or PTSD (rg = − 0.39, p = 0.23). The identification of genetic variants having a pleiotropic effect in NVP and depression will clarify the mechanism by which these traits co-occur, and help identify biological pathways that can inform new treatments. This information may also allow medical professionals to assess the need for increased monitoring of NVP in pregnant women with a history of depression.

What can GWAS tell us about the genetic architecture of the human cortex: results from the ENIGMA consortium GWAS meta-analyses of cortical thickness and surface area

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While cortical thickness and surface area are both strongly heritable, the two processes are genetically independent and there is little known about the loci influencing these morphological characteristics. We will present results from GWAS meta-analyses of the thickness and surface area of cortical regions of interest derived from magnetic resonance imaging (MRI) scans from a meta-analysis of $\sim$ 35,000 individuals. Across cohorts, structural T1-weighted MRI brain scans were analysed locally using harmonized analysis and quality-control protocols. Cortical parcellations were performed with freely available and validated segmentation software. Cortical measurements were averaged across the hemispheres resulting in the average thickness and surface area of 34 Gy matter regions. We also analyzed two summary measures, average cortical thickness across regions and total surface area. Corrections for the summary measures were included in the regional measures to account for the omnibus effects of brain size. Results from the meta-analyses demonstrate that common variation substantially influences the architecture of the human cortex and supports the findings from twin studies that genetic influences on thickness and surface area are largely orthogonal. Across phenotypes we find over 270 regions P = 5e−08 with over 95 surviving correction for multiple testing. Unlike our previous work on the subcortical structures, we find the effects of genetic variants often

to impact a number of neighboring regions, reflecting the influence of areal patterning factors during human cortical development. Key findings and the distributions of effect sizes will be discussed.

The genetic and environmental associations between sleep and impulsivity in middle childhood

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Objective: Prior research has established a link between temperament and sleep among children, such that poor sleep (e.g. shorter duration) has been associated with problems in emotion regulation (El Sheikh and Buckhalt 2005). Specifically, impulsivity has been associated with shorter sleep durations among children (Gruber et al. 2012). Additionally, sleep and temperament in childhood are both heritable. This study examined (1) the heritability of several objective sleep indicators (i.e., duration, efficiency) and temperament and (2) the heritability of the association between objective sleep and impulsivity among twins in middle childhood.
Methods: A subset of 203 families (28.6% MZ, 37.9% same-sex DZ, 33.5% opposite-sex DZ twins) from the Arizona Twin Project (Lemery-Chalfant et al. 2013) were included in this study. Twins ($M = 8.50$, $SD = 0.52$; 49.5% male; 54.1% Caucasian, 26.3% Hispanic) wore an actigraph watch on their non-dominant wrist for seven consecutive days to assess their sleep. Primary caregivers (94.8% mothers) completed questions related to their twins' temperament. Prior to model fitting in OpenMx, effects for age and sex were regressed out from all variables.
Results: Based on phenotypic correlations impulsivity was the dimension of temperament most strongly related to objective sleep. Specifically, impulsivity was correlated with sleep duration ($R = -.21$, $p < 0.001$) and sleep efficiency ($R = -.17$, $p = 0.001$). Univariate ACE models indicated sleep duration and efficiency were each moderately heritable, with 50% of the variance in duration and 47% of variance in efficiency accounted for by additive genetic factors. Additionally, an ADE model was the best fitting model for impulsivity and indicated a strong additive genetic component (77%). Bivariate model fitting indicated and AE–AE model was the best fitting model between duration and impulsivity ($\Delta AIC = 2.55$, $\Delta df = 4$, $p = 0.24$) in which the E21 path was also dropped. This model indicated the shared additive genetic correlation between duration and impulsivity was 0.24. Similarly, an AE–AE (dropping E21) model was also the best fitting model between efficiency and impulsivity ($\Delta AIC = 1.66$, $\Delta df = 4$, $p = 0.17$); the additive genetic correlation was 0.23.
Conclusions: Findings suggest the link between sleep and impulsivity is genetic; therefore interventions may need to target sleep and impulsivity among children separately given the unique environmental contributions to each. Future work should (1) consider moderators of the associations between sleep and impulsivity, (2) investigate these associations in other developmental periods, such as adolescence, to determine if additive genetic factors remain a significant influence on sleep and impulsivity associations, and (3) investigate driving factors of the shared genetic associations and potential causal links.

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Differential patterns of genetic overlap between inattention and four neurocognitive factors

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Purpose: Twin and family studies indicate that individual differences in inattention and neurocognitive functioning are heritable, ranging from 50 to 80% across adolescence. There is also evidence for moderate genetic overlap (64%) between inattention and at least one aspect of neurocognitive functioning, reaction time variability. Adolescence is a period of rapid growth in neurocognitive functioning, yet a comprehensive understanding of the patterns of genetic overlap between inattention and multiple aspects of neurocognitive functioning during this period of development is lacking. The present study investigated: (1) the heritability of inattention and four aspects of neurocognitive functioning (memory, social cognition, executive function, complex cognition) based on additive genome-wide effects; and (2) the degree to which genetic effects are shared between inattention and each of the four aspects of neurocognitive functioning.
Participants and Measures: Genome-wide data were drawn from 3563 unrelated children and adolescents (ages 8–21 years) of European Ancestry enrolled in the Philadelphia Neurodevelopmental Cohort and imputed. 5,360,405 biallelic single nucleotide polymorphisms [SNPs] were retained following imputation and quality control. Participants (for children ages 18+) or their parents (for participants ages 8–17) reported on six inattention questions drawn from the Kiddie Schedule for Affective Disorders and Schizophrenia (adapted) interview, and completed a computerized neurocognitive battery consisting of nine tasks measuring efficiency (response speed, accuracy) across the four neurocognitive domains.
Approach: Factor analysis of the six symptoms of inattention revealed a single dimension of inattention. Confirmatory factor analysis of the neurobehavioral data replicated the four-factor solution previously demonstrated in Moore et al. 2015. Genomic-relatedness-matrix restricted maximum likelihood estimation (GREML) was used to determine the proportion of variance in each phenotype attributable to additive genetic variance. Bivariate GREML was used to examine the genetic correlations (r_{G-SNP}) between inattention and each neurocognitive domain. Genome-wide association (GWA) analyses (adjusted for multiple testing) were performed to identify genetic variants associated with inattention and each neurocognitive trait.
Results: Common SNPs explained 20% (SE = .08, $p < 0.01$) of individual differences in inattention; 17% (SE = .08, $p < 0.05$) in memory, 13% (SE = .08, $p < 0.05$) in social cognition, 25% (SE = .08, $p < 0.01$) in executive function, and 24% (SE = .08, $p < 0.01$) in complex cognition. Bivariate analyses indicated that genetic overlap between inattention and social cognition was high (r_{G-SNP} = .67, SE = .37, $p < 0.01$), whereas the genetic correlations between inattention and the other neurocognitive domains were nonsignificant. No single genetic variant for any trait was significant at the GWA level of $p < 10^{-8}$. *Conclusions*: Modest genetic influences on individual differences in inattention and neurobehavior were observed. Common additive genetic effects explained the overlap between inattention and social cognition. That is, the same genes that influence

inattention also contribute to more efficient social cognition. Potential reasons for this overlap and implications will be discussed.

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Genetic loci associated with voluntary ethanol consumption and preference in diversity outbred mice

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Background: This study aims to identify genetic contributions to voluntary ethanol consumption variability in mice. Intermittent Ethanol Access (alternating periods of free access to ethanol, and forced abstinence) has been shown to produce progressively increasing ethanol consumption in mice, and models the repeated, intermittent, and increasing alcohol consumption that often leads to dependence in humans. In order to identify Quantitative Trait Loci (QTL) at higher mapping resolution, allelic variation, and trait variability than previous studies, we used Diversity Outbred (DO) mice for this study.
Methods: DO mice (n = 539, post-QC) were exposed to 3 24 h periods of three-bottle choice (15% and 30% ethanol, and water) per week, for 4 weeks, without any prior ethanol exposure. Genotyping was performed on gigaMUGA arrays, and imputation and analysis were performed using the qtl2 R package. We conducted QTL analysis for first and last week mean 30% ethanol choice ($mL_{30\%EtOH}/mL_{TotalEtOH}$) and total ethanol consumption (g_{EtOH}/kg_{mouse}) and preference ($mL_{EtOH}/mL_{TotalFluid}$).
Results: On average, mice consumed 6.07 g/kg and 7.66 g/kg ethanol, had preference levels of 23.83% and 27.48%, and 30% EtOH choice levels of 4.27% and 4.09%, during the first and last weeks of ethanol access, respectively. Paired t-tests revealed significant differences between first- and last-week phenotypes ($t = 6.34$, $p = 4.631*10^{-10}$ for consumption; $t = 4.12$, $p = 4.400*10^{-5}$ for preference; $t = -2.01$, $p = 0.045$ for 30% EtOH choice). QTL analysis revealed 3 genome-wide significant loci, and several suggestive loci (LOD > 6). The significant locus for last-week mean ethanol consumption (LOD = 8.22) was found at 8.41 Mb Chr4, with a 95% Bayesian support interval of 1.05 Mb. This region contained genes *Car8, Rab2a, Chd7*, and *Clvs1*, all of which are expressed most highly in mouse cerebellum. The significant locus for first week mean total ethanol preference (LOD = 7.52) was found at 79.35 Mb on Chr12, with a support interval of 1.82 Mb. This region contains several genes, with the peak signal lying just upstream of *Rad51b*, which is expressed most highly in mouse central nervous system and liver and is involved in DNA repair. Finally, the significant locus for last week mean 30% EtOH choice (LOD = 8.63) was found at 108.23 Mb on Chr3, with a support interval of 3.77 Mb, across a gene-rich region. Support intervals for significant and suggestive signals did not overlap between first- and last-week phenotypes. Ongoing analyses involve narrowing candidate gene lists within the support intervals of significant regions, by finding loci with genotypic patterns across founders that follow the pattern of founder haplotype effects at each QTL.
Conclusion: This study identified several novel genetic loci, with unprecedentedly narrow support intervals, for voluntary ethanol consumption and preference, and choice for higher-concentration ethanol, by examining a genetically and phenotypically highly diverse mouse population. Results suggest that different genetic mechanisms drive these behaviors during the initial period of ethanol exposure versus post-long-term exposure, also evidenced by the mean differences between first- and last-week phenotypes. Preliminary assessment of candidate genes indicate that the liver and CNS may both be involved during ethanol access initiation, whereas specifically the cerebellum may be more involved after long-term consumption.

Cross-species alcohol dependence-associated gene networks: co-analysis of mouse brain gene expression and human genome-wide association data

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Background: The heritability of Alcohol Dependence (AD) has been estimated to be roughly 50% by twin studies and 30% by whole-genome SNP-based studies (Prescott and Kendler 1999; Mbarek et al. 2015). However, genome-wide association studies (GWAS) have yet to account for a large proportion of this heritability, and they lack the ability to provide insight into functional pathways. However, gene co-expression networks can be used to leverage GWAS results and provide functional information. Controlled experiments have identified significantly ethanol-responsive gene networks in mouse brain. Direct integration of human GWAS and protein–protein interaction (PPI) data with mouse gene expression data has the potential to identify novel associated gene networks and the mechanistic frameworks through which they function.
Methods: The present analysis used Edge-Weighted dense module searching for Genome Wide Association Studies (EW-dmGWAS) to co-analyze GWAS data from the Irish Affected Sib-Pair Study of Alcohol Dependence (IASPSAD), human PPI data, and acute-ethanol-exposed mouse gene expression data, to identify and prioritize ethanol-regulated gene networks (i.e. modules) with respect to AD risk contribution. Expression data was obtained from the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC), due to their role in reward pathways, and previous findings of significantly ethanol-regulated networks in these regions. Largely overlapping modules from the EW-dmGWAS output were then merged to form Mega Modules (MMs). To validate our results, we tested modules for overrepresentation of genes with nominal GWAS p-values ($p < 0.001$) from an alternative GWAS dataset (Avon Longitudinal Study of Parents and Children; ALSPAC). To determine functional relatedness of genes within significantly over-represented modules, we analyzed their functional enrichment using ToppGene.
Results: After correction for multiple testing, there were 276, 171, and 314 significant MMs for the VTA, NAc, and PFC, respectively. One significant MM from each brain region was significantly overrepresented with ALSPAC-nominally significant genes. Top functional enrichment categories for these MMs included: ubiquitination, and ligase activity for the VTA MM; telomere maintenance and syndecan-mediated signaling for the NAc MM; and chromatin organization, immune response, and NFKB and Wnt signaling pathways for the PFC MM.
Discussion: The results indicate that integration of mouse gene expression data and human genetic data via EW-dmGWAS allows identification of novel alcohol-associated gene networks in the VTA, PFC, and NAc with overrepresentation of nominally associated genes from an independent GWAS dataset. This suggests that IASPSAD and ALSPAC have identified different AD-associated genes that are contained in the same ethanol-responsive networks in these three

brain regions. Functional enrichment results suggest that these networks potentially play a role in several brain region-specific pathways involved in gene and protein regulation, cell signaling, and immune response. The exact mechanisms through which these pathways are related to alcohol dependence will be explored in future studies.

Sex differences in associations between personality polygenic risk scores and hazardous alcohol use

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Prior twin research has indicated that, on average, 40% of observed variation in personality traits can be explained by additive genetic influence. Additionally, twin and molecular genetic studies have also suggested that specific personality traits found to be associated with hazardous alcohol use or the development of alcohol use disorders (AUD) may represent tractable endophenotypes for investigating the shared underlying etiology between psychiatric disorders. Specifically, characteristics of personality including impulsivity, risk-taking, sensation-seeking as well as neuroticism, extraversion and low conscientiousness have been identified in research examining the relations between individual personality traits and hazardous binge drinking phenotypes. However, these associations have been shown be moderated by several factors including drinking motives, alcohol expectancies and sex. Expanding on prior research, the present study examined potential sex differences in the associations between cumulative genetic influence for risk-taking and the Big Five personality traits (openness to experience, conscientiousness, extraversion, agreeableness and neuroticism) and hazardous alcohol use quantified by lifetime maximum drinks in 24-h, DSM-5 AUD symptom count, alcohol-induced blackout, and drinking to intoxication 2–3 times per week. GWAS summary data from the UK Biobank project and the Genetics of Personality Consortium were used to calculate polygenic risk scores (PRSs) for risk-taking, and the Big Five personality traits, respectively. PRSs were calculated in an independent Caucasian sample of 1685 related individuals (62.6% female) collected as part of the UCSF Family Alcoholism Study. Genotype data were obtained from low-coverage whole genome sequencing and a linear mixed modeling approach was used to predict alcohol use phenotypes from personality PRSs for the total sample and for males and females separately. Ancestry estimates derived from principal components analysis were included as covariates to account for population sub-structure. For the overall sample, risk-taking PRSs at a range of variant inclusion significance thresholds ($p < 0.50$-<.10) were significantly associated with drinking to intoxication 2–3 times per week and experiencing 3 or more lifetime alcohol-induced blackouts, neuroticism PRSs ($p < 0.50$-<.10) were significantly associated with maximum number of drinks in 24-h, and extraversion PRSs ($p < 0.50$-<.20) showed a significant negative association with 3 or more lifetime alcohol-induced blackouts such that those with lower extraversion risk scores were more likely to have experienced 3 or more blackouts. When modeled separately based on sex, associations between risk-taking PRSs and regular drinking to intoxication and extraversion PRSs and blackouts were significant in females, while only the association between risk-taking PRSs and blackouts were significant in males. Additionally, significant interactions between risk-taking PRSs and sex were observed for the prediction of both maximum number of drinks ($p < 0.05$) and having 3 or more blackouts (p <.50-<.20), and a significant interaction between extraversion PRSs at the $p < 0.001$ threshold and sex suggested that males with higher extraversion scores were more likely to have experienced 3 or more blackouts while the opposite was true for female individuals. These findings extend previous research by suggesting that associations between genetic influences on personality and problematic alcohol use may be sex and phenotype-specific.

Etiologic contributions to callous-unemotional traits and emotion recognition in children, adolescents, and young adults

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Abnormal emotional experience has long been considered a hallmark of psychopathy.[1] One way psychopathic emotional deficits manifest is as an impaired ability to recognize the emotions of others, particularly the negatively valenced emotions of fear and sadness.[2] Although 'psychopathic' is not a label applied to children, callous-unemotional (CU) traits in childhood represent the core emotional deficit of adult psychopathy.[3] Children with high levels of CU traits also appear to have impaired recognition of emotions[2] similar to those seen in adult psychopaths. However, no studies to date have investigated the genetic and environmental contributions to the relationship between CU traits and emotion recognition in children.

Methods: Data were drawn from two community-based twin samples of 9–20 year olds. The combined analytic sample consisted of 1214 individuals (607 twin pairs; 54.0% female, mean age = 14.1 years). CU traits were examined via subscale scores (callous-uncaring and unemotional) on the inventory of callous–unemotional traits. Emotion recognition was examined via participant's unbiased hit-rate (UBHR) on the facial expression labeling task (FELT). Pearson's product-moment correlations were used to examine the phenotypic relationships between ICU subscales and UBHR for the emotions of anger, happiness, sadness, fear, surprise, and disgust. Furthermore, etiologic associations were examined via biometrical structural equation modeling where the genetic, common environmental, and unique environmental correlations between phenotypes were computed. Lastly, the proportion of the phenotypic association attributable to these etiologic sources was calculated. All analyses were performed in R using OpenMx.

Results: The callous-uncaring subscale was modestly but significantly negatively correlated with recognition of happiness ($r = -0.06$, $p \leq 0.01$), sadness ($r = -0.12$, $p \leq 0.001$), fear ($r = -0.08$, $p \leq 0.05$), surprise ($r = -0.07$, $p \leq 0.05$), and disgust ($r = -0.10$, $p \leq 0.01$). Conversely, the unemotional subscale was significantly positively correlated with recognition of surprise ($r = .07$, $p \leq 0.05$) and disgust ($r = .10$, $p \leq 0.01$). There were no significant genetic correlations between the unemotional subscale and any FELT emotion. However, there were significant genetic correlations between the callous-uncaring ICU dimension and UBHR for sadness ($rA = -0.41$, $p \leq 0.05$), and fear ($rA = -0.33$, $p \leq 0.05$). Transformation of these genetic correlations revealed that the phenotypic correlation between callous-uncaring and the recognition of sadness and fear are due entirely to genetic effects. There were no significant common or unique environmental correlations between either ICU subscale and any FELT emotion.

Discussion: The callous-uncaring ICU subscale, a core component of adult psychopathy, is associated with an overall impaired ability to recognize emotions. However, the genetic relationship underpinning

this relationship is specific to the emotions of fear and sadness, which are the most common emotion recognition deficits seen in adult psychopaths.

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Associations between loneliness, social isolation and mortality in older twins: familial confounding?

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Loneliness and social isolation are established risk factors for mortality among older adults. It is however poorly understood whether loneliness and social isolation have differential predictive value on mortality and whether these observed associations are causal or due to confounding familial factors. The aim of the present study was to: (1) replicate previous findings of a relationship between loneliness, social isolation and mortality in a large genetically informative sample of aging twins; (2) establish potential differential associations between loneliness and social isolation, respectively, with mortality; and (3) establish whether such relationships are consistent with a causal hypothesis utilizing the co-twin control design. Data on more than 40,000 twin individuals from the IGEMS consortium were used including participants aged 41–108 years at baseline. Information about perceived feelings of loneliness, social isolation (i.e. living alone), as well as on relevant covariates including self-rated health, multimorbidity, smoking status, alcohol use, depression, and education was used. Data were linked to the respective Cause of Death registry to get information about date and cause of death with a follow-up time of more than 16 years. Survival analysis and the co-twin control design were applied to address the three aims. Findings and implications will be discussed. This work is supported by the NIH grant AG037985.

Genetic influences on musical specialization: a twin study on choice of instrument and music genre

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Though several studies show that genetic factors influence individual differences in musical engagement, aptitude and achievement, no study to date has investigated whether specialization among musically active individuals in terms of choice of instrument and genre is heritable. Using a large twin cohort, we explored whether individual differences in instrument choice, instrument category and the type of music individuals engage in can entirely be explained by the environment or are partly due to genetic influences. About 10,000 Swedish twins answered an extensive questionnaire about music related traits, including information on the instrument and genre they played. Of those, 1259 same-sex twin pairs both reported to either play an instrument or sing. We calculated the odds ratios (ORs) for concordance in music choices (if both twins played) as compared between identical and non-identical twin pairs, with significant ORs indicating that identical twins are more likely to engage in the same type of music-related behavior compared to non-identical twins. Results showed that for almost all music related variables, the odds were significantly higher for identical twins to play the same musical instrument or music genre, suggesting significant genetic influences on such music specialization. Possible interpretations and implications of the findings are discussed.

Genetic factors in the neuro-development of negative urgency: findings from a community dwelling sample

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Background: Negative urgency (NegUrg) refers to impulsive behaviors aimed at avoiding negative emotions. It has been described as a predisposing factor in psychopathology, with a moderate degree of heritability. This study investigates the genetic, neuroanatomic, cognitive, and social-emotional underpinnings of NegUrg.
Methods: The present project examines data from 225 healthy participants, age 7–21, from the Pediatric Imaging, Neurocognition, and Genetics (PING) study. Study sample was split into subsets for model building and cross-validation (training sample, 80%) and external validation of the final model (test sample, 20%). Across three models, best subset or least absolute shrinkage and selection operator (LASSO) regression was performed to predict scores on the Negative Urgency subscale of the Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency (UPPS-P) Behavior Scale. Mean square error (MSE) and r^2 values were evaluated as indices of model fit. Model I contained 14 variables derived from sociodemographic information, neuromedical history, cognitive, and socio-emotional data. Model II included cortical thickness measures of ten regions of interest (from five homologous pairs) in the cingulate and orbitofrontal cortices. Model III focused on genetic contributions to NegUrg, investigating 265 single nucleotide polymorphisms (SNPs) from nine candidate genes associated with dopaminergic and serotonergic transmission and metabolism, language development, and psychopathology.
Results: LASSO regression performed for Model I yielded seven significant predictors for NegUrg, including age, gender, household income, behavior problems, maternal alcohol use during pregnancy, negative affect, and anxiety. Fit indices for the training sample (MSE = 0.35, R^2 = 0.25) and the test sample (MSE = 0.35, r^2 = 0.30) were comparable, indicating appropriate model fit. Best subset regression results for Model II indicated that three right cingulate regions (i.e., rostral anterior, caudal anterior, and posterior cingulate cortices) were significant predictors of NegUrg. Model fit indices were, again, comparable across study samples (training sample: MSE = 0.41, R^2 = 0.04; test sample: MSE = 0.47, R^2 = 0.05). For Model III, the LASSO regression retained three SNPs from two candidate genes (*CADM2* and *SLC6A4*) to predict NegUrg. Fit indices supported the validity of this model as well (training sample: MSE = 0.43, R^2 = 0.16; test sample: MSE = 0.38, R^2 = 0.11).
Conclusions: The results of this study provide a construct and criterion validation of the UPPS-P Negative Urgency Scale. The principal findings were that individual differences in sociodemographic factors, as well as psychological, genetic, and neuroanatomical variables

related to emotional regulation (as opposed to cognitive control) contribute to NegUrg from childhood to early adulthood. Of particular interest, we provide evidence of associations between NegUrg and candidate genes *CADM2* and *SLC6A4*. *CADM2* is involved in synaptic organization, is robustly expressed in the anterior cingulate, and has been previously linked to hyperactivity and impulsivity in children. *SLC6A4* is a serotonin transporter, particularly expressed in corticolimbic regions, with a role in emotion processing and emotion-driven behavior. Taken together, we provide support for a genetic basis to NegUrg that is in line with both the sociodemographic and neuroanatomical findings of the construct.

Racial and ethnic differences in the genetic risk of eating disorder phenotypes

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Eating disorders affect individuals of all racial and ethnic groups, yet inclusion of individuals with diverse backgrounds in research is limited, especially within a genetics framework. Twin studies that include European Americans and African Americans have examined the eating disorder symptoms of binge eating and purging, reporting statistically similar heritability estimates for both groups. Additional research examining genetic correlations between eating disorder symptoms and other psychiatric and substance use disorders suggest potential differences in these estimates between groups. Existing genome-wide association studies of eating disorder phenotypes only include European Americans, yet samples from other racial/ethnic groups are currently being added to these studies. The inclusion of diverse racial/ethnic samples in genetic research on eating disorders and their symptoms will be essential for elucidating genetic and environmental risk on these pernicious disorders.

Life event severity moderates genetic influences on cognitive function

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Life events represent discrete and observable social and/or environmental changes that can be threatening and result in some level of stress. Greater reports of life events are associated with poorer cognitive function and this association may differ depending on the severity of the life event (i.e., the extent to which an event has a negative impact on the individual). Given genetic influences contribute to cognitive function and some evidence suggesting life events may show heritable influences, we tested GE interplay in the life event severity-cognition relationship using an extended univariate model accounting for self- and cotwin- reports of life event stress. Our analytic sample consisted of 5090 twins (2166 MZ, 2924 DZ; age range: 25–99; 49% female) from six studies of the IGEMS consortium. Participants indicated whether they experienced a common set of five life events across studies (death of a spouse, divorce, retirement, death of a friend, and death of a child) and they completed a range of cognitive assessments. Life events were weighted by the average severity ratings obtained from an independent sample. Severity scores for each life event were on a four-point scale from "no effect" to "a strong effect"; the average total severity was 2.35 (SD = 2.34; Median = 1.84). The MZ twin correlation of weighted life events was .58 ($p < .0001$) and the DZ twin correlation was .53 ($p < .0001$) suggesting environmental influences. Further, severity weighted life event scores were associated with poorer cognitive performance in all tasks (Rs $-$ .37 to $-$ .03, ps $< .002$). We tested for moderation of life event severity on genetic and environmental influences on cognitive function, while accounting for age moderation. More severe life events were associated with reduced additive genetic variance and amplified environmental influences on verbal and speed of processing abilities—a similar, but not statistically significant, pattern was found for spatial abilities. Moreover, non-shared environmental variance decreased with more severe life events. Life events counts were associated with increases in both additive genetic and environmental variance, in comparison. Results demonstrate that severity weighted and life event counts may influence the etiology of cognitive function differently.

Age of onset and clinical severity, cognitive functioning, and community functioning in schizophrenia: a multiplex extended pedigree study

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Schizophrenia has substantial variation in symptom severity, cognitive deficits, and overall functioning. Age of onset is a consistent predictor of this variation and yet the causes of this association are still unknown. We employed a multiplex, extended pedigree study to examine within schizophrenia the heritability of age of onset and its prediction of symptom severity, cognition, and functioning. Our primary aim was to determine the causes of this relationship—specifically, to assess whether genetic effects on age of onset are shared with those that influence outcome. We also examined the degree to which genetic effects on age of onset in schizophrenia might influence functioning in relatives with major depression or those with no psychiatric diagnosis, thus assessing whether or not those genetic factors are diagnostically specific or transdiagnostic. This study is, to the best of our knowledge, the first to examine the potential shared genetic effects between age of onset and relevant outcome measures and to examine their diagnostic specificity. The sample (total N = 771) consisted of 43 extended pedigrees (N = 636 relatives, including N = 110 with major depression, N = 256 with no psychiatric diagnosis) with at least two first-degree relatives diagnosed with schizophrenia (N = 103) and 135 matched controls. All participants completed a demographic and symptom interview as well as a cognitive battery with 11 tasks. Factor analyses were conducted separately on the 11 cognitive measures and the four community functioning measures and single factor solutions were considered appropriate for both cognition and community functioning. Within schizophrenia, earlier age of onset significantly predicted increased severity of negative (r = $-$ 0.196, p = 0.003) and positive (r = $-$ 0.228, p = 0.045) symptoms, poorer cognition (r = .295, p = 0.030), and poorer community functioning (r = .318, p = 0.008). Age of onset of schizophrenia was modestly heritable, although not significant ($h^2 = 0.198$, $p = 0.277$). Negative symptoms ($h^2 = 0.977$, $p < 0.001$), positive symptoms ($h^2 = 0.853$, $p = 0.003$), and cognition ($h^2 = 0.835$, $p = 0.013$) were all significantly heritable, and community functioning was not ($h^2 = 0.320$, $p = 0.182$). Notably, the genetic correlation between age of onset of schizophrenia and negative symptoms was significant ($R_G = -1.0$, p = 0.007), indicating pleiotropy, while the genetic correlations between age of onset and positive symptoms, community functioning, and cognitive

functioning were high (i.e., R_Gs = 1.0 or − 1.0) but not statistically significant (*p*s = 0.139–0.590). Genetic correlations between age of onset in schizophrenia and community or cognitive functioning in depressed or non-diagnosed relatives were not significant, thus not supporting transdiagnostic age of onset genetic effects.

Strengthening causal inference via genetically informative studies

Michael Neale, Virginia Commonwealth University

For many health-related phenotypes, randomized control trials are impractical or unethical, so alternative methods of causal inference are needed. Historically, longitudinal observational studies appear to have been the most popular, but more recently other research designs and analytical methods have been pursued. Two more recent approaches are of interest to the behavior geneticist: the use of data collected from relatives such as twins, and Mendelian randomization. The latter is an application of a mediation model for three variables, typically a genetic variant, an intermediate trait believed to be directly caused by it, and an outcome variable whose causal relationship to the intermediate trait is of interest. Each method relies on assumptions, some of which may be difficult to test directly. In this talk, I discuss the three approaches individually, and the potential for combinations of them to provide tests of key assumptions, and to yield actionable information on causal processes. The further potential for multivariate methods, such as network modeling via partial correlation or structural equation modeling is also considered.

The influence of familial risk, cannabis use, and depression on college student academic success

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Background: Shared genetic underpinnings may partially account for the observed comorbidity between cannabis use and depression. Both cannabis and depression also impact cognitive functioning, and are associated with poorer academic outcomes for college students. In the current study, we examined the degree to which familial risk for drug problems and depression or anxiety increase the risk of cannabis use and depression and impact academic outcomes.
Methods: Participants included 9886 freshman students from the Spit for Science (S4S) study. S4S is a longitudinal study of genetic and environmental influences on substance use and emotional health outcomes in college students. Familial risk scores were estimated using self-reported family history (FH) of drug problems and FH of depression or anxiety. We hypothesized that: (1) FH of drug use predicts both higher lifetime cannabis use and depression; (2) FH of depression-anxiety predicts both depression and cannabis use; and (3) cannabis use and depression predict lower GPA. Structural equation modeling was implemented in OpenMx to estimate the direct and indirect effects of FH of drug use and FH of depression/anxiety on cannabis use, depression, and freshman year GPA.
Results: We observed significant direct effects of familial risk of drug use on cannabis use ($\beta = 0.155$, [0.123, 0.187]) and GPA ($\beta = -0.062$, [0.092, − 0.033]), but not depression. We also observed significant direct effects of familial risk of depression-anxiety on depression ($\beta = 0.388$, [0.356, 0.420]), cannabis use ($\beta = 0.217$, [0.184, 0.250]), and GPA ($\beta = 0.059$, [0.024, 0.093]). Cannabis use was negatively associated with GPA ($\beta = -0.187$, [− 0.213, − 0.161]), but there was no direct effect of depression on GPA. Further, FH of drug use was indirectly associated with lower GPA via cannabis use ($\beta = -0.029$, [− 0.037, − 0.022]), and FH of depression-anxiety was indirectly associated with lower GPA via cannabis use ($\beta = -0.041$, [− 0.050, − 0.033]).
Conclusions: Our findings support our hypotheses that FH of drug use is associated with greater cannabis use, greater depressive symptoms, and lower GPA both directly, and indirectly through cannabis use. However, while FH of depression-anxiety was associated with greater depressive symptoms and cannabis use, we observed no indirect effect of depression on GPA. We plan to expand upon these analyses to include polygenic scores for depression and cannabis use. These findings contribute to understanding of the genetic relationship between cannabis use and depression, while also investigating the potential impact of these factors on college student performance.

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Genetic path modeling using genomic structural equation modeling

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The ability to model complex and multivariate relationships between variables and indicators has been the enduring allure of structural equation modeling (SEM). Our tool genomic structural equation model offers the same ability to model complex and multivariate relationships between traits, based on the summary statistics generated by genome wide association studies (GWAS). We use genomic structural equation modeling to study whether 1. Educational attainment (EA) mediates the relationship between attention deficit hyperactivity disorder (ADHD) and unhealthy or risky behaviors (smoking behaviors, drinking, speeding, eating related behaviors). Our analysis are based on the latest GWAS and our technique is robust for the fact that these GWAS have considerable sample overlap. We further explore whether ADHD liability is a common cause which contribute between the strong genetic relationship between EA and age at death. To test the causal directions implied in these models we introduce genetic instruments (both individual SNPs, and polygenic instruments based on concurrently modeling 10–75 SNPs). Our results imply the relationship between ADHD and unhealthy or risky behaviors is mediated by EA, suggesting an educational pathway for intervention. We contrast and compare our findings with those based on pairwise and multivariable Mendelian randomization (MR). Results obtained with genomic SEM are consistent with results obtained using genomic SEM, but the ability to

account for sample overlap, and the ability to include any number of variables, and thus known confounders, in the model are advantages over MR. Our conditional analysis of the relationship between EA and mortality reveals that this relationship is weakened substantially when both traits are conditioned on ADHD liability, suggesting ADHD liability as a common cause for the two traits.

Maternal smoking during pregnancy and DNA methylation disruption in toddlers

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Background: Cigarette smoking has been linked to significant and long-term epigenetic alterations (Joubert et al. 2016; Fa et al. 2016). Smoking-related changes in DNA methylation have been detected in somatic tissues of smokers and former smokers, in the placenta of smoking mothers and in fetal and neonatal tissues. These alterations in methylation patterns can lead to destabilization of genome activity in differentiated embryonic tissues causing irreversible disturbances in the development programme. This study aims to investigate the long-term epigenetic effects of fetal and tobacco smoke exposure in early childhood. Here we present the preliminary results based on a small cohort study.
Methods: Genome-wide DNA methylation profiling was performed using Illumina Infinium HumanMethylation450 array that targets over 450,000 CpG sites. DNA methylation of blood samples from 56 children were analyzed: 28 children with a history of maternal smoking during pregnancy (M_{age} = 21 ± 9 months) and 28 children of non-smoking mothers (M_{age} = 23 ± 10 months).
Results: Due to small sample size, no significant intergroup differences in DNA methylation were found after multiple testing correction. However, approximately 10% (~ 48k of 450k) of CpG sites showed a nominally significant ($p < 0.05$) methylation difference between the comparison groups; a decrease in global methylation in the toddlers with a history of maternal smoking was observed. Children with a history of exposure were reliably distinguished from controls based on methylation profiles of the top 527 CpGs ($p_{nominal} < 10^{-3}$). In accordance with the genome annotation, these CpGs were related to 400 genes. Pathway enrichment analysis showed that these differentially methylated genes were predominantly involved in the control of the development and differentiation of cells, including neurons. In addition, changes in the methylation level of several genes controlling muscarinic and nicotinic acetylcholine signaling pathways were found, that, in turn, can be attributed to direct impacts of maternal smoking on the regulation of specific biological pathways in children's genomes.
Conclusions: Maternal smoking during pregnancy can cause significant and long-term epigenetic changes in newborns. These changes are of a twofold nature—gene-specific and global methylation alterations; they include both the changes related to the direct genomic response to tobacco smoke components and the genome-wide methylation changes that may affect cascade regulation of child development.
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Apgar score and heritability in twins

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The Apgar score is one of the first measures by which a newborn is evaluated. Introduced by Virginia Apgar in 1952, it is widely used for reporting the status of the infant and response to resuscitation immediately after birth, usually on several assessment points. The advantage of this screening tool is a standardized assessment, which is included in many national guidelines and World Health Organization policy (WHO 2013). Apgar scores are affected by many environmental factors (socioeconomic, demographic, medical), but less is known about genetic effects. Some authors estimated correlation coefficients for the Apgar scores of first and second born in monozygotic and dizygotic twin pairs, but studies are very limited (Riese 1990; Franchi-Pinto et al. 1999), thus, the research question remains: what are the contributions of genetic and environmental factors on variation in the early health indicators of new-born twins as measured by Apgar scores? The aim of this study is to estimate heritability of Apgar score using classical twin modeling in a large cohort. The data on Apgar score and prenatal parameters in twins came from a longitudinal study in which twin families were volunteer members of the Netherlands Twin Register (NTR) established by the Department of Biological Psychology, Vrije Universiteit in Amsterdam. The NTR recruits families with twins a few months after birth. The study sample comprised 15,124 twins that were born from 2005 to 2015. All cases without zygosity, with the time difference between birth of first and second twin more than 24 h, or missing data were excluded. A sample of 5205 twin pairs was included in the analysis: 1773 monozygotic (MZ) and 3432 dizygotic (DZ) pairs. Of these, information on the Apgar score measured on 1 min after birth was available for 5089 pairs, on 5 min—for 4860 pairs, on 10 min—for 468 pairs. The status of the newborn twins changed significantly in the first minutes after birth: the frequency of high Apgar score increases from 16.6% at 1st minute to 72% at 5th minute. The Apgar scores measured at 1-, 5-, 10-min after birth were correlated between first and second born in both MZ and DZ pairs. Zygosity did not have a significant main effect on Apgar scores. The heritability of the Apgar score was 8–9%. The combined influence of environmental factors shared by twins was 51–52%. Birth order, sex and perinatal characteristics (gestational age, fetal presentation at birth, mode of delivery, birth weight and time between birth of first and second born) all had significant effect on Apgar scores.

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A repository of polygenic scores

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An important output of genome-wide association studies are summary statistics from which it is possible to construct *polygenic score (PGS)*: indices of SNPs that aggregate their explanatory power. Because PGSs are far more predictive of the phenotype than individual SNPs, they can be used in many analyses that would be underpowered if conducted using individual SNPs. For example, researchers have used polygenic scores as a measure of G in studies of gene-by-environment interactions. Going forward, sufficiently predictive polygenic scores may also prove valuable for targeting interventions (e.g., those most at risk of future Alzheimer's disease) or as a control variable in evaluations of randomized experiments. The construction of PGSs with substantial predictive power has been enabled primarily by larger discovery samples. In the coming years, it is likely that the number of traits for which we can construct accurate PGSs will increase substantially. However, researchers who wish to use PGSs in their research continue to face a number of obstacles: (i) there are restrictions on the summary statistics that can be made publicly available and as a result, PGSs based on publicly available summary statistics are often less predictive than PGSs that could be constructed in principle (ii) from public summary statistics, it requires some effort to construct PGSs (especially for researchers doing this for the first time or researchers who wish to apply sophisticated methodologies), (iii) publicly available summary statistics may not be based on analyses of samples that are fully independent of the cohort for which the investigator wishes to construct polygenic scores, and (iv) because different researchers construct PGSs using different methodologies, it is hard to compare and interpret results from different studies. In this project, we aim to construct polygenic scores for a range of traits in some social-science data sets using a uniform methodology, and make the scores publicly available via mechanisms agreed upon by the cohort representatives. Since PGSs themselves are not SNP-level summary statistics, they can be disseminated more easily than the weights themselves. Directly sharing the polygenic scores (as opposed to just SNP-level summary statistics) may also contribute to progress by reducing barriers to entry for researchers interested in working with PGSs (especially researchers new to the field).

Bootstrap confidence interval methods for DeFries–Fulker models

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DeFries–Fulker (DF) analysis is a regression model used in behavior genetics (DeFries and Fulker 1985) to estimate ACE (and other) models. It is appealing for its simplicity, however it violates certain regression principles including homogeneity of variances and independence of errors. These violations make calculation of standard errors and confidence intervals problematic. Methods have been developed to account for this (Kohler and Rodgers 2001), although the research on these methods is sparse. The univariate bootstrap is a relatively recently developed version of the bootstrap (Lee and Rodgers 1998), one that resamples from the marginal univariate distributions rather than the bivariate/multivariate data space. Currently, research on the univariate bootstrap has largely focused on individual bivariate correlations, however the univariate bootstrap represents a unique means of obtaining confidence intervals for DF models (one that is presaged by suggestions from previous DF research; e.g., Cherny, Cardon, Fulker, & DeFries, 1992). This project presents the results of a simulation study examining various methods for obtaining confidence intervals for DF model parameters, including standard confidence intervals, robust Huber–White confidence intervals, and confidence intervals from traditional and univariate bootstrapping. Results for both normal and highly skewed data are presented. It is predicted that the univariate bootstrap may potentially improve on both parametric methods and other bootstrap procedures.

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Causes of individual differences in health-related quality of life according to the EQ-5D questionnaire: a twin tale of two countries

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The EQ-5D is among the most widely used questionnaires for measuring subjective health-related quality of life (HRQOL). Its descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The score on the five dimensions can be combined into a single summary index (SSI), representing the social value of EQ-5D health states. Additionally, the questionnaire includes a visual analogue scale (VAS), measuring the subjective health perception of the respondent. However, little is known about genetic and environmental influences on individual differences in the five health dimensions and the two scales (VAS and SSI) comprising the questionnaire. The present study aimed to explore causes of variation in the EQ-5D in two large population based twin samples in Sweden and Spain with a combined sample of more than 20,000 twin individuals. Results showed that although there were slight cohort-related differences on the phenotypic level, heritability estimates were comparable across countries and dimensions, ranging between .27 and .43; which is within the range of previously reported estimates for similar constructs from other HRQOL/QOL questionnaires or self-rated health analyses. While heritability of self-rated health, assessed through the visual analogue scale (VAS), was very similar in both samples, there was some indication for a somewhat lower heritability for the single summary index (SSI), representing the social value of EQ-5D health states, in the Spanish sample (27%) as compared to the Swedish sample (43%). Possible implications and potential explanations for the present findings are discussed in detail.

A general psychopathology factor (P factor) in adolescence: a test of hierarchical structure, heritability, and associations with parental psychopathology

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An emerging literature challenges traditional dimensional approaches to the study of psychopathology, bolstering evidence of a general (P) factor underlying symptomology across the internalizing and externalizing broad-band domains (Caspi et al. 2014). However, important developmental considerations necessitate further research testing this hierarchical structure in younger populations before generalizations can be made. Adolescence, in particular, is a significant risk period for the onset of psychopathology, warranting further attention (Costello, Copeland, & Angold, 2011). The current study tested competing structural models of psychopathology in a sample of adolescent twin pairs from the Wisconsin Twin Project, allowing for estimation of the heritability of the general P factor. Lastly, associations with parental psychopathology were considered. It was hypothesized that the bifactor model would exhibit the best fit to the data and that the general P factor would be highly heritable. Five hundred five adolescent twin pairs (mean age 13.23 years) and their parents completed independent diagnostic interviews (DISC and CIDI, respectively), providing self-reports of symptomology across several DSM-IV disorders. Two-factor oblique, bifactor, and 1-factor models were tested utilizing adolescent symptom counts. The bifactor model exhibited the best fit to the data (χ^2 (25) = 114.007, RMSEA = .059, CFI = .966, TL I = .938). An AE model was the best fit to the P factor, with 56% of the variance explained by additive genetic factors. Lastly, mixed model regression analyses were conducted to test for associations between parental diagnoses and adolescents' general liability to psychopathology. Paternal depression and both paternal and maternal anxiety were significantly associated with adolescent P factor scores (β = .21 (.08), $p < 0.05$, β = .11 (.05), $p < 0.05$, and β = .17 (.07), $p < 0.05$, respectively). Conversely, parental alcohol dependence/abuse (a proxy for parental externalizing) was not associated with adolescent P factor scores. These findings provide evidence of a moderately heritable general P factor underlying adolescent psychopathology. Additionally, significant associations with parental psychopathology provide external validation of the adolescent bifactor model. Future directions include modeling the hierarchical structure of parental psychopathology and testing whether the intergenerational transmission of psychopathology is sufficiently explained at the level of the P factor. Lastly, application of the nuclear twin-family design can elucidate whether conferral of genetic risk sufficiently explains the intergenerational transmission of this general liability to psychopathology or whether environmental transmission effects exert additional influence. These findings stand to make a significant contribution to science, as the traditional nosological approaches to classification of psychopathology, which have so long informed our research and treatment, are called into question.

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Effects of rare DNA sequence variation in genes and regions susceptible to DNA methylation on alcohol and tobacco use phenotypes

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Alcohol and tobacco use and dependence are moderately heritable phenotypes (Verhulst et al. 2015) with complex genetic architecture. The majority of observed associations for common variants have been located outside of genes (Finucane et al. 2015; Maurano et al. 2012), such as regulatory regions marked by open chromatin (i.e., DNase I hypersensitive sites) and regions susceptible to epigenetic processes like DNA methylation (i.e., CpG islands). The few studies relating low-frequency and rare variants to alcohol and tobacco use, in contrast, have been restricted to regions that code for proteins (Otto et al. 2017; Vrieze et al. 2014), given their putatively functional role and the high costs associated with sequencing. However, these studies have yielded limited success in identifying significant associations, and top variants have very small effect. Less is known about the effects of rare non-coding regulatory variation, despite the high proportion of heritability thought to be explained by the effects of common variants in these regions. Given the large number of rare variants located outside of genes, and a less than complete understanding of their function, the current study aims to evaluate methods of prioritizing and grouping rare sequence variation within gene and non-coding regulatory regions in studies of alcohol and tobacco use and dependence. Low-coverage whole genome sequencing data was obtained from 1889 individuals as part of the UCSF Family Study of alcohol dependence (Vieten et al. 2004). The Combined Annotation-Dependent Depletion (CADD; Kircher et al. 2014) bioinformatics tool was used to compute a single measure of deleteriousness (i.e., scaled C-scores) for variants with minor allele frequency (MAF) < 5% located within independent CpG islands and a 2 kb surrounding "shore" region of DNA (N = 17,304 CpG islands). Set-based tests of rare CpG island/shore variants with alcohol and tobacco use phenotypes were conducted using the SKAT-O test (Lee et al. 2012), applying C-scores as variant weights within a set to allow for adjustments based on the relative deleteriousness of each variant. After correction for multiple testing, a limited number of rare variant CpG island sets were significantly associated with alcohol and tobacco use phenotypes. A subset of the top associations were located near genes previously identified in molecular genetic and epigenetic studies of these traits. These included a suggestive association of average cigarettes smoked per day with rare variants in a CpG island on chromosome 13, the latter of which overlapped with a loci identified as a differentially methylated region in previous studies of smoking phenotypes (Allione et al. 2016; Ambatipudi et al. 2016). Results from genome-wide hypothesis-free tests of rare variant sets using a sliding genomic window approach will be used to validate the possible enrichment of association signals from these regions susceptible to DNA methylation. Pre-processing and quality control of DNA methylation is currently being conducted in order to test for differential DNA methylation and potential epigenetic mediation of DNA sequence variation in the context of these traits. Future work will extend these approaches to other types of regulatory elements and in replication samples.

The relationship between smoking, years of education, and cognitive functioning in mid- and late-life: a co-twin control study

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Smoking and its influence on health is well known but the relation of smoking oncognitive functioning is less understood, with inconsistent findings as to impacts on cognitive functioning in late adulthood. This paper will explore these relations to determine if smoking does impact cognitive performance, and if educational level moderates these effects. To address these questions, the current study will use data collected and harmonized by the international IGEMS (Interplay of Genes and Environment across Multiple Studies; Mage = 68.4 years) consortium. Measures included pack years, years of education, and cognitive ability assessments in twins from three countries (Sweden, Denmark, and the USA): digits backwards, digits forward, symbol digit, block design, and synonyms. Negative associations were found between pack years and most cognitive tasks, with significant negative effects for symbol digit, the digit span tasks, and block design, although magnitudes differed by sex for symbol digit. Only the Symbol Digit task showed evidence for an interaction between smoking and years of education at the individual level but these effects were reversed across sex, with males showing apositive interaction. To examine potential causal relationships between pack years and cognitive performance, a co-twin control (CTC) design was used, adjusting for age, study, and cognitive impairment. Pack years was found to negatively impact symbol digit and block design within the CTC approach with no significant differences across sex in comparing within-pair twin effects among discordant twins. Effect sizes were larger for the dizygotic than monozygotic twins, but these effects were not significantly different across zygosity. Overall, smoking exposure shows supportive evidence of an environmental stressor that negatively impacts the more fluid associated cognitive tasks.

Integrative prioritization of genomic loci for alcohol use disorders

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Alcohol use disorder (AUD) is a persistent disease (10%) with a polygenic architecture that complicates the localization and identification of susceptibility loci. Prior studies suggest that AUD related phenotypes, such as dependence and vulnerability are genetically influenced (h^2 = 40–60%), but no single gene or robust set of gene have been identified. The integration of gene expression and functional experimentation evidence across species may facilitate human-based association analyses. Typically, applications of experimental results from humans and model-organisms in human genetic association analyses have been limited to post-genomewide association study screens of only the most-highly associated variants, which often fail to replicate. The present study investigates how highly connected genes related to specific features of AUD (e.g., craving and withdrawal) that are linked by their association to alcohol-related behaviors and processes in humans, Drosophila, mice and rats, contribute to individual differences in alcohol dependence severity (AD) in humans. We examine a new pipeline to assess the ability of genes identified from expression-QTL (eQTL) studies in model-organisms to prioritize genes for AD. eQTL-based gene sets were derived from the GeneWeaver, an Ontological Discovery Environment. Over 14,000 genes were initially identified, ranked, and systematically examined as joint predictors of alcohol dependence in several human studies (i.e., COGA, SAGE, and Australian GWAS) to identify sets of SNPs in an subset of genes that are highly connected to AD. In addition, we apply a novel Bayesian Hierarchical Model with annotation-specific effect-size priors to identify loci with the strongest enrichment for causality.

The family check-up intervention attenuates the link between polygenic risk and trajectories of aggression across middle childhood

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Childhood aggression is normative and typically declines with age, but when it persists it may be due to a combination of early environmental and genetic influences. A few early interventions have shown to moderate the effect of single genes on childhood externalizing behavior (Bakermans-Kranenburg & van IJzendoorn, 2015). However, no study has tested the buffering effect of an intervention on a polygenic risk score (PRS) in predicting trajectories of middle childhood aggression. The present study examined how polygenic risk for childhood aggression influenced trajectories of aggression across middle childhood, and differences based on intervention condition. Participants were from a longitudinal randomized prevention trial (family check-up; FCU) designed to improve parenting ($N_{intervention}$ = 252; $N_{control}$ = 250), and consisted of 49% female, 45% Caucasian, 31% African American, 12% Hispanic, 10% Biracial, 2% Other. Parents reported on their child's aggression from ages 5-9 using Achenbach's CBCL. SNPs for the current PRS were drawn from a meta-GWAS of childhood aggression (Pappa et al. 2016), and filtered using gene-set enrichment analyses to retain functional SNPs at a $p < .05$ cutoff. A latent growth curve model was estimated for aggression from 5 to 9 years of age, with the effect of the PRS included on intercept and slope, and PRS differences examined by intervention condition. Analyses controlled for child age, sex, ethnicity, demographic risk factors and ancestry using principal components analysis. An initial unconstrained model (RMSEA = .06, CFI/TLI = .99) with decreasing slope of aggression (to reflect decreasing mean levels from ages 5-9) had significant mean and variance of the intercept and slope ($ps < .001$). Next, the PRS and covariates were entered as predictors of the intercept and slope. The PRS was significantly associated with the slope ($B = -.32$, $p = .004$). In a multigroup model split by control/intervention condition the PRS was significantly associated with the slope in the control group ($B = -.48$, $p = .001$) but not the intervention group ($b = -.10$, $p = .60$; $X^2_{difference}$ (1) = 4.75, $p = .029$). Results indicate the FCU attenuated the link between polygenic risk for aggression and trajectories of aggression from 5 to 9 years of age, although replication is needed. This research highlights the utility of employing a polygenic and functionally-informed approach to indexing genetic risk. Importantly, results suggest that early intervention is effective in reducing trajectories of problem behavior among children at genetic risk.

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Translating knowledge of genetic risk into prevention of speech and language disorders: a pilot study in infants with classic galactosemia

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Many children experience severe difficulty learning to produce speech sounds well enough to be understood and to express their thoughts in words and sentences. These disorders, called speech sound disorder and language impairment, respectively, are debilitating in terms of social and educational development. Typically, these disorders cannot be diagnosed until children are old enough to show overt signs, between ages 2 and 4 years. Twin, adoption, and familial aggregation studies have shown that speech and language disorders have a genetic etiology. In those cases where genes and regions of interest have been found, it should be possible in principle to identify infants at risk and to develop earliest and preventative interventions for them. Our study is the first to leverage knowledge of a genetic etiology towards testing a protocol of preventative measures called Babble Boot Camp. Infants with classic galactosemia (CG) are at high risk for severe speech and language disorders. Even during the prespeech stages (cooing, babble), they show very delayed development. In addition, infants with CG are at risk for cognitive delays. The Babble Boot Camp is implemented via parent training by an experienced pediatric speech-language pathologist during infant ages 2 to 24 months. In weekly online meetings, parents learn strategies to foster and support earliest signals of communication (cooing, babble, turn-taking), expand the child's vocabulary, and increase the child's sentence length and complexity. Outcome measures include amount of pre-speech vocalizations, number of words understood and produced, general communication competence, cognitive development, and parent and child quality of life. The first cohort of children with CG and a control infant with CG recently turned a year old. The children in the treatment cohort show age-appropriate amounts of speech-like vocalizations, communication behaviors, and emergence of first words, whereas the control infant produces substantially fewer vocalizations and does not yet produce words. A surprising indirect outcome was the fact that the infants in the treatment group showed age-appropriate cognitive development whereas the control infant's cognitive development was borderline. Together, these results are consistent with a beneficial direct effect of earliest intervention on speech and language development and a beneficial indirect effect on cognitive development. We continue to enroll families and collect data towards validating these early results. Future studies should investigate the effects of the Babble Boot Camp on children's and parents' quality of life and the effectiveness of the Babble Boot Camp in children with other types of genetic risk for speech and language disorders.

Rare LAMA5 variant is the likely cause of a severe speech and reading disorder in a de novo case

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Childhood apraxia of speech (CAS) is a rare and severe form of speech sound disorder that is frequently comorbid with dyslexia. There is evidence that CAS has a genetic etiology, but causal DNA variations have only been identified in a few cases. Here, we describe a child age 9 years with CAS and extremely poor reading and spelling abilities; there was no family history of speech or language disorder. The phenotype was further characterized by poor fine and gross motor coordination and poor motor speech control, especially regarding integrating complex motor commands. Together, these traits are consistent with cerebellar dysfunction. Exome sequences were obtained for the child and both biological parents. Exomes were annotated with VEP and filtered with Gemini. De novo variant analysis yielded three validated variants. Of these, most likely to be pathogenic is an extremely rare missense variant in the *LAMA5* gene at bp position 60,921,247. This variant is not reported in dbSNP and is predicted to be deleterious (scaled CADD = 22.7). *LAMA5* is associated with encoding of the vertebrate laminin alpha chains. A homozygous sequence variant in *LAMA5* has been associated with a failure of neuromuscular transmission and central nervous system (CNS) manifestations. *LAMA5* is highly expressed in the cerebellum (median RPKM = 41.2). In addition, 19 validated X-linked recessive variants were found. Of these, one is rare, predicted to be deleterious (CADD = 22.7), and situated in a gene involved in neurogenesis, which is *NLGN4X*. Of 85 validated autosomal recessive variants, one is a splice variant in *VWA3B*, which has been associated with cerebellar ataxia and intellectual disability. Together, these results are consistent with a monogenic or possibly polygenic etiology of CAS that is expressed in the cerebellum and has downstream effects on abilities under cerebellar control, including conversational speech, motor speech control, reading, and fine and gross motor control. Future studies should extend these findings by evaluating cerebellar structures and functions using MRI technology.

Genetic overlap and causality among major depressive disorder, alcohol dependence, and alcohol consumption: findings from the Psychiatric Genomics Consortium

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Major depressive disorder (MDD) and alcohol dependence (AD) are common psychiatric disorders, contribute substantially to global morbidity, and often co-occur in the same individual. Epidemiological studies report that individuals with MDD are at increased risk for AD and vice versa. Leading hypotheses suggest these associations may be due to shared risk factors (e.g., genetic, environmental) or causal processes of one disorder leading to the other, such as the self-medication hypothesis. However, the mechanisms at the basis of the MDD-AD dual diagnosis, contemporaneously, or across the lifetime, remain unclear. Twin studies show genetic factors influence individual differences in susceptibility to MDD, AD, and alcohol consumption, with heritabilities on the order of 0.37, 0.49, and 0.43 respectively. Large-scale genome-wide association studies (GWAS) have identified putative risk variants for MDD, AD, and alcohol consumption quantity (AC-Quantity) and, like other complex diseases, have revealed polygenic architectures with multiple loci of small effect. Bivariate twin studies report moderate shared genetic liability between MDD and AD, estimating the genetic correlation from 0.3 to 0.6. However, questions remain whether these traits show genetic correlation because of shared genetic effects independently on each trait (i.e., pleiotropy) or because of causal processes indexed by genetic instruments. Here, we leverage summary statistics from genome-wide findings to estimate genetic correlations between MDD, AD, AC-Quantity, and alcohol consumption frequency (AC-

Frequency). We obtained GWAS summary statistics of MDD and AD from the Psychiatric Genomics Consortium and conducted GWAS of alcohol consumption measures in the recently released UK biobank data. Further, we investigate support for causal mechanisms via two-sample Mendelian randomization (MR). Our results are consistent with twin studies, as MDD and AD showed moderate overlap of genetic risk factors ($rg_{MDD\text{-}AD} = +0.47$, $p = 6.6 \times 10^{-10}$). A significant genetic correlation between AC-Quantity and AC-Frequency was observed ($rg = +0.52$, $p = 1.3 \times 10^{-149}$), but MDD showed significant correlations with these traits in opposite directions ($rg_{MDD\text{-}ACQ} = +0.14$, $p = 2.9 \times 10^{-7}$; $rg_{MDD\text{-}ACF} = -0.17$, $p = 1.5 \times 10^{-10}$). The high genetic correlation between AD and AC-Quantity ($rg_{AD\text{-}AC\text{-}Quantity} = 0.75$, $p = 1.8 \times 10^{-14}$) suggests that these phenotypes capture overlapping constructs and that quantity of consumption is an indicator of problematic alcohol use. The MR analysis indicated that most of these correlations are best explained by shared genetic mechanisms, but a strong causal relationship is present between MDD and AD as individuals with a lifetime MDD diagnosis have a 32% increased risk of having a lifetime AD diagnosis (beta = 0.28, $p = 1.29 \times 10^{-6}$). Results indicate that comorbidity among MDD, AD, and alcohol consumption are partially due to shared genetic liability, and partially to causal mechanisms of MDD predisposing to AD. The current findings have important implications for both MDD and AD treatment and prevention efforts as well as understanding mechanisms involved in the etiology of psychiatric comorbidities.

A meta-analysis of the association of oxytocin receptor gene (OXTR) polymorphisms with aggression and antisocial behavior

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Increasing evidence suggests that oxytocin and the Oxytocin Receptor Gene (*OXTR*) influence social cognition and behavior in humans and animals. *OXTR* has been investigated in relation to antisocial behavior and aggression, but studies of which SNPs in *OXTR* influence antisocial behavior and aggression and the magnitude of these associations have yielded inconsistent findings. The present meta-analysis (number of studies = 11, number of samples = 14), based on a total sample of 11,479 individuals, examined the overall effects and consistency of associations between six variants in OXTR and antisocial behavior. Evidence of significant heterogeneity was found for each SNP analyzed, thus the results of random-effects models are presented. Random effects models identified significant associations between rs237887 (r = .06, p = .002) and antisocial behavior. The small number of studies available for analyses of each SNP precluded examination of the specific moderator variables that accounted for heterogeneity. Sensitivity analyses suggest that the results of these analyses were robust to exclusion of each individual study and publication bias. Despite several limitations, this meta-analysis is the first to systematically examine the effects of *OXTR* polymorphisms on aggression and antisocial behavior and suggests that, despite heterogeneity across studies, there is some consistent evidence that *OXTR* is significantly associated with antisocial behavior and aggression.

Genetic and environmental contributions to alcohol reduction attempts

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Alcohol use disorders remain one of the most undertreated mental health outcomes (Cohen, Feinn, Arias and Kranzler, 2007). The greatest burden of alcohol use is in developed countries; these nations account for half of all alcohol-related harm. Despite the significant personal and societal consequences associated with alcohol use and problems, the prevalence of high risk drinking and DSM-IV alcohol use disorder increased between 2001 and 2013 in American adults (Grant et al. 2017). Mild alcohol use often remits without treatment. However, increasingly severe forms go undiagnosed or untreated (Connor, Haber and Hall, 2016). Accordingly, it is important to understand what factors contribute to alcohol reduction attempts. In this study, we examine genetic and environmental contributions involved in lifetime alcohol reduction attempt and test the extent to which those factors are shared with alcohol problems. A prospective cohort sample of 2605 (N = 2573 complete pairs) young adult twin pairs from FinnTwin16-25 study was assessed for lifetime alcohol initiation, lifetime maximum alcohol use, and lifetime attempt to reduce or avoid alcohol. A multi-stage modeling approach, also known as the causal-common-contingent (CCC) model was used to determine the extent to which genetic and environmental influences were shared between alcohol problems and any lifetime alcohol reduction attempt while adjusting for the influence of alcohol initiation. Approximately 88% of participants reported some lifetime alcohol use. Additionally, 40% of participants who had initiated alcohol use reported making a lifetime attempt to reduce alcohol use. Additive genetic and unique environmental effects specific to alcohol reduction significantly accounted for the total variance. Further, among participants who initiated alcohol, there was a significant association between lifetime maximum alcohol use and lifetime alcohol reduction ($r = 0.39$, $p < 0.05$). Portions of the shared environmental variance in alcohol reduction was shared with alcohol initiation (10%) and lifetime maximum alcohol use (89%). Further, small portions of the additive genetic variance in alcohol reduction was shared between lifetime maximum alcohol use (3%) and alcohol initiation (2%). Estimates of genetic and environmental influences were consistent across sex. These results emphasize the role of genetic and environmental influences shared between alcohol use and alcohol reduction attempts. These results also highlight how individualized approaches focused on both biological and environmental influences during young adulthood can improve attempts to reduce alcohol consumption.

Examining the role of the parent and child in positive youth development: an adoption study

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Prior work has suggested that parenting directly impacts the development of character behaviors (i.e. cooperativeness) particularly in adolescence; however, the majority of this work fails to consider how the child impacts interactions with their parents, which in turn impacts the development of their character. Previous genetic work has found that adolescents' character behaviors elicit negativity and

positivity from their parents, but this work hasn't been explored as thoroughly in early childhood. One possible eliciting behavior in early childhood is callous-unemotional behaviors, the antithesis of character behaviors, which has been shown to elicit negative parenting practices. Using data from the Early Growth and Development Study, a parent–offspring adoption sample ($N = 561$), we examined genetic (birth parent (BP) agreeableness) and rearing environmental (adoptive parent positive reinforcement and corporal punishment) influences, as well as child evocative effects (callous-unemotional behaviors) on adopted child cooperativeness in middle childhood. BP agreeableness was assessed using self-reports on the Adult Temperament Questionnaire, and the Harter Adult Self-Perception Profile. Adoptive parent parenting was assessed using self-report on the Alabama positive reinforcement and corporal punishment subscales at child age 4.5 years. Adopted child's callous-unemotional behavior, social competence, and cooperativeness were assessed using parent reports on the Child Behavior Checklist (CBCL) and the Preschool Socioaffective Profile at 27 months, and the Junior TCI at 8 years, respectively. The current study examined adoptive parent positive reinforcement and corporal punishment in separate regression models. Model fit was acceptable for both models, (χ^2 (9) = 21.63, RMSEA = .06, CFI = .96, SRMR = .03; χ^2 (9) = 8.01, RMSEA = .00, CFI = 1.00, SRMR = .02). Findings indicated that BP agreeableness was positively associated with adopted child cooperativeness ($\beta = .09$, $p < .001$) and negatively associated with child callous-unemotional behavior ($\beta = -.07$, $p < .05$), suggesting genetic influences. Child social competence was also positively associated with child cooperativeness ($\beta = .27$, $p < .001$), but child callous-unemotional behavior was not. Child social competence was positively associated with both adoptive mother and father positive reinforcement ($\beta = .18$, $p < .001$; $\beta = .16$, $p < .01$), but child callous-unemotional behaviors were not associated with parent positive reinforcement. Adoptive parents' positive reinforcement was not associated with child cooperativeness in middle childhood. Both child social competence and callous-unemotional behaviors were not associated with adoptive parents' corporal punishment at 4.5 years. Adoptive mother corporal punishment was negatively associated with child cooperativeness in middle childhood ($\beta = -.17$, $p < .05$), but not adoptive father corporal punishment. There were no significant indirect effects that indicated genetically-influenced child evocative child effects. These findings suggest that genetic and environmental influences uniquely impact child cooperativeness in middle childhood. Due to the importance of child social competence for later cooperativeness, future research might consider examining the effects of early parenting on children's early social competence in order to increase later character development.

Genetic and environmental influences on executive functioning in middle childhood: the role of early adversity

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Stressful early family experiences (e.g., unsupportive parenting) are associated with risk for later maladjustment across domains, including executive functioning (EF; Repetti et al. 2002). However, it is unknown whether family adversity in toddlerhood impacts the heritability of EF in middle childhood. We examined whether early adversity at 30-months moderated the heritability of common and individual components of EF at 8 years. Common EF is highly heritable (Engelhardt et al. 2015), with little room for environmental input. Therefore, we hypothesized that early adversity would not moderate the common EF factor, but instead moderate individual EF components. The sample included 208 twin pairs from the Arizona Twin Project (Lemery-Chalfant et al. 2013). Early adversity, assessed at 30 months of age, included parenting daily hassles, low perceived MOS social support, punitive punishment (parental responses to child misbehavior), home chaos (Confusion, Hubbub, and Order Scale), CES-D maternal depression, and low maternal emotional availability. EF at 8 years included the eriksen flanker task, continuous performance task, digit span forward and backward, and parent-reported attentional focusing and inhibitory control (Temperament in Middle Childhood Questionnaire). For both early adversity and EF, the first principal components were extracted as composites. Genetic analyses were tested on the common EF composite as well as each individual task using umx (Bates et al. 2017).

Univariate models revealed genetic influences on all individual measures and common EF, with broad sense heritability from .22 (digit span backwards) to .61 (parent-reported inhibitory control). Shared environmental influences were found for the Flanker Task (.13) and parent-reported inhibitory control (.24), and E was moderate to high (.40–.73) for all measures except parent-report inhibitory control (.15) and attentional focusing (.31). Moderation of heritability was not observed in the individual tasks, but for common EF, A and E were moderated ($\Delta\chi^2(1) = 3.75$, p = .053), such that A was highest and E was lowest at higher levels of early adversity. At the mean of adversity, A explains 52% of the variance (31% at − 1 SD, 77% at + 1 SD) and E explains 41% of the variance (84% at − 1 SD, 13% at +1 SD). It is possible that in low stress homes, children may have more access to individualized resources that promote EF development.

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Genetic and environmental influence on the human functional connectome: evidence from studies of twins and unrelated individuals

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Functional connections refer to intrinsically correlated activity between brain regions when individuals are not engaged in a particular task (i.e., measured during the "resting state"). Individual differences in the strength of functional connections predict psychological function, but the sources of connectivity strength differences are unknown. Historical attempts to estimate the genetic etiology of functional connectivity have focused on large-scale brain networks—obscuring possible heterogeneity among small network

subcomponents. Detailed mapping of genetic and environmental influences on the functional connectome is made possible by using twin modelling methodology and SNP-based methods using genotype data from unrelated individuals. In this presentation, we present genetic and environmental maps at a finer-grained level of detail than prior work, which is a crucial step toward developing intermediate phenotypes between genes and clinical diagnoses or cognitive abilities. We analyze resting-state functional MRI data from two adult twin samples—198 twins from the Colorado Longitudinal Twin Sample and 422 twins from the Human Connectome Project—and from approximately 8300 unrelated individuals from the UK Biobank dataset to examine genetic and environmental influence on all pairwise functional connections between 264 brain regions ($\sim$ 35,000 functional connections; twin samples) or 51 brain regions ($\sim$ 1500 functional connections; UK Biobank). Genetic analyses conducted on each connection were run as structural equation models in R through the OpenMx and UMX packages for twin samples, or using GCTA software for UK Biobank data. Results of twin and GCTA models were similar and suggest non-shared environmental influence was high across the entire connectome, with moderate heritability in approximately half of all connections. The highest heritability estimates were found for connections involving default, attention, and frontoparietal areas. Twin models revealed shared environmental influences were weak to moderate across the entire connectome, with the highest estimates for connections between subcomponents of the default network. The pattern of genetic influence across the connectome is related to a priori notions of functional brain networks, with some evidence of similar levels of genetic and environmental influence among regions of the same network. However, we also found substantial evidence of heterogeneity based on the distribution of heritability estimates. Additionally, a hierarchical clustering analysis of the genetic influence patterns of all regions revealed that the brain's genetic organization is diverse and not as one would expect based solely on community structure evident in non-genetically informative data. We found regions clustered into two to three groups, a level more superordinate to the 7–20 classically defined resting-state networks. Notably, there was a mixed sensory/attention cluster and a cluster of higher-level cognitive regions including default and frontoparietal areas. In conclusion, our analyses reveal a novel genetic taxonomy of brain regions and suggest genetic risk factors may be limited to a subset of the connectome.

Longitudinal associations of APOE and general cognitive ability in CATSLife

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The genetic risk variant *APOE* ε4 predicts cognitive aging and dementia risk yet its role in early life cognitive growth and functioning is not understood. We assessed the possible association of *APOE* genotypes and cognitive performance from mid-childhood to mid-adulthood in the ongoing Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife) study, with three to four decades of participant data available from two foundational studies, the Colorado Adoption Project (CAP) and Longitudinal Twin Study (LTS). *APOE* ε4 was a significant predictor of lower Full-Scale, Performance, and Verbal IQ scores, compared to ε33 individuals, in longitudinal analyses from the year 7-, 12- and 16-year assessments (7–18 years, N = 1321). Results suggested Full scale IQ scores were lower for each ε4 allele, compared to *APOE* ε33 (adjusted $p < 0.01$). Moreover, the ε4 effects for Full-scale IQ were more evident in females (adjusted $p < 0.02$) compared to males. Consistent effects were observed for Verbal and Performance IQ. Up to eight assessments between 9 and 46 years (N = 1380) were available for two episodic memory tasks (names and faces, picture memory), and a general cognitive ability (GCA) factor formed from the colorado perceptual speed (CPS), ETS Card Rotations, the Wechsler Similarities subtest, and the paired-associates names and faces measures. Nonlinear logistic growth models were fitted to explore individual differences in the amount of gain to the upper performance asymptote, age at maximum acceleration at inflection point, and rate of change. Initial results did not suggest differential growth by *APOE* for memory or a general cognitive ability (GCA) factor that was dominated by processing speed. Although results of these initial analyses suggest that *APOE* ε4 genotypes may not influence growth patterns, they may be associated with lower cognitive ability as early as middle childhood, particularly for Performance and Full-scale IQ and to a lesser extent for Verbal IQ. *APOE* may show stronger effects on performance and full-scale IQ in women than men, consistent with emerging evidence of a differential risk of Mild Cognitive Impairment and Alzheimer's disease.

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DNA provides the best child-specific prediction of educational achievement from birth

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Individual differences in educational achievement are highly heritable (60%) throughout the school years, and this high heritability is largely explained by genetically influenced cognitive and non-cognitive factors (Krapohl et al. 2014). The best early predictor of academic achievement is family socioeconomic status (SES), with children from poorer SES families doing worse at school compared to children from higher SES families (Bradley and Corwyn 2002). However, this prediction is the same for all children within a household, yet academic achievement often differs between family members. Intelligence (*g*) is by far the best individual-specific predictor of educational achievement, both contemporaneously and longitudinally. However, intelligence as measured in infancy or early childhood is not as reliable and explains less than 3% of the variance in exam grades at the end of compulsory education. Conversely, we have previously shown that we can predict up to 9% of the variance in exam performance at age 16 using a single polygenic score derived by aggregating the effects of educational attainment-associated DNA variants identified through a discovery genome-wide association (GWA) study (Okbay et al. 2016; Selzam et al. 2016). Importantly, this DNA predictor is individual specific (unlike family SES) and it is available at birth or even prenatally (unlike *g*). Here, we use the UK representative Twins Early Development Study (TEDS) sample of over 4000 unrelated individuals to explore the variance explained in exam scores (GCSE) at the end of compulsory education by *g* across development (from age 2 to 16). We compared these estimates to the variance explained by DNA (polygenic score) using the summary statistics from a 2018 educational attainment GWA with a sample of 1.1 million participants (Lee et al. 2018). We will also explore the variance explained by genome-wide polygenic score (GPS) and *g* across development when controlling for SES. Our preliminary findings show that DNA provides the best child-specific prediction of

school achievement available at birth, explaining over 14% of the variance. Until age 7, the prediction from DNA is stronger than from IQ and from previous educational achievement. DNA has slightly more predictive power than family SES measured at birth; importantly, DNA explains additional variance in exam grades when family SES is controlled. This prediction from DNA will improve with more powerful GWA studies and using multi-polygenic score approaches. Eventually, it will be possible to identify children who are likely to have difficulties at school, which will foster hope for early intervention.

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A genetically-informed study of neighborhoods and health: results from the MIDUS twin sample

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People living in adverse neighborhoods, i.e., those that are low income or perceived as unsafe, have poor health (Robinette, Charles, Almeida, Gruenewald. *Health and Place* 2016;41:110–118). Despite a large literature attesting to the neighborhood-health link, however, general inability to randomly assign people to various neighborhoods causal inference (Diez Roux, Mair. *Ann. N.Y. Acad. Sci* 2010;1186:125–145). Using a large sample of adult twins from the Midlife in the United States Study II (MIDUSII), we examined whether neighborhood income and neighborhood safety concerns influence health after adjusting for genetic and environmental selection effects that may have biased previous investigations. Health was assessed with a composite measure of multi-system physiological risk (Gruenewald et al. *Soc Sci Med* 2012;74:75–83), with higher scores representing more physiological dysregulation and risk for future chronic health problems. Neighborhood income was collected from the 2000 United States decennial census, and respondents self-reported neighborhood safety concerns. We used structural equation modeling to fit biometric regressions (Neale and Maes 2004) to a genetically informed sample of 686 pairs of twins (MZF = 140, MZM = 128, DZF = 152, DZM = 89, and DZOS = 177) in the MIDUSII. Controlling for additive genetic and shared environmental processes, results indicated that higher neighborhood safety perceptions were associated with less physiological risk among women but not men. Our findings suggest a possible causal role of neighborhood features for a measure of physiological risk that is associated with the development of disease. Efforts to increase neighborhood safety, perhaps through increased street lighting or neighborhood watch programs, may improve community-level health.

Responding to a 100-year-old challenge from fisher: a biometrical analysis of adult height in the NLSY data using only cousin pairs

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One hundred years ago, Fisher (1918) published a paper that highlighted that genetic researchers should be especially interested in cousin pairs. We have the potential using the NLSY data to respond to a 100-year-old challenge issued by Fisher: "… the hypothesis of cumulative Mendelian factors seems to fit the facts very accurately. The only marked discrepancy from existing published work lies in the correlation for first cousins…but until we have a record of complete cousinships measured accurately and without selection, it will not be possible to obtain satisfactory numerical evidence on this question" (p. 168). Like Fisher, we have observed the "cousin anomaly" in the NLSY cousin data. Further, the NLSY data approximate Fisher's "complete cousinships measured accurately and without selection."

In the current study, we compute kinship correlations, and estimate ACE models, to directly address Fisher's question, and also indirectly expand it to include several different questions: Are cousins anomalous in the kinship relatedness on a highly reliable phenotype, height (Fisher's challenge)? What is the biometrical status of other cousin categories besides full cousins? Can we conduct a genetically-informed biometrical study with sufficient power using only cousin categories? If so, what results do we obtain?

Recently developed kinship links in the NLSY79 and NLSY-Children have produced thousands of cousin pairs. A few cousin studies exist in the literature, but none (to our knowledge) have used biometric modeling of only cousin categories. Using cousins is challenging, partly because different cousin categories are so similar in their average (segregating) genetic relatedness; large samples are required to have enough statistical power. Alternatively, a highly reliable phenotype can also contribute. We use height as the phenotype in the current study, along with an impressively large sample of cousins. Table 4 in Rodgers et al. (2016) lists and describes nine cousin categories in the NLSY-Children data.

We used full cousins (R =.125, N = 4179) and half cousins (R = .0625, N = 548), and estimated an ACE model of self-reported height (after age 17, standardized within gender); we set the C parameter to .80 (compared to the usual 1.0 for those raised in the same house). Kinship correlations were r =.17 for full cousins, and r =.10 for half cousins. The ACE estimates were $a^2 = .92$, $c^2 = .07$, $e^2 = .01$; these are very close to traditional estimates of height heritability and c^2.

We will engage additional biometrical analyses to investigate NLSY cousin pairs, partly for substantive interest, but also as proof-in-principle of the value of the NLSY cousin data, and to help address Fisher's challenge.

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Do environmentally-induced psychotic experiences exist in adolescence?

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Background: Psychotic experiences (PEs) refer to traits in the general population, such as paranoia, that at the extreme are characteristic of disorders such as schizophrenia. PEs are common in teenagers and are modestly heritable. Mechanistic studies demonstrate that PEs can be

induced by certain activities and environmental contexts, such as smoking cannabis or by reducing someone's relative height in social situations. Our aim was to compare the degree of genetic and environmental influences on PEs in 16-year-old twins who were more and less exposed to multiple environmental risk factors.
Methods: Participants in the Twins Early Development Study (TEDS), a community sample, reported on PEs (paranoia, hallucinations, cognitive disorganization, grandiosity, anhedonia) at age 16 and the twins' parents reported on the twins' negative symptoms (N = 4542 pairs). An environmental composite was created, based on risk factors including cannabis use, tobacco use, dependent stressful life events and bullying victimization. Twin pairs were categorized as 'more exposed' if either or both twins had experienced at least three exposures and as 'less exposed' if both twins experienced fewer than three 'environmental' exposures. Univariate heterogeneity twin models and Purcell moderation models were run to test for differences in the heritability of PEs in the exposure groups. As an internal control, analyses were re-run on height and autistic traits, for which no differences between exposure groups were predicted. Finally, a univariate liability threshold model was run on the environmental composite.
Results: Heterogeneity twin models showed that heritability could not be equated in the more and less exposed groups for four of the six PE subscales. These four PEs—paranoia, hallucinations, cognitive disorganization and anhedonia –were on average 50% less heritable in the more exposed than the less exposed group (mean heritability = 21% versus 42%, respectively). Lower heritability in the more exposed group was not explained by higher measurement error (assessed using Cronbach's alphas). Purcell moderation models concurred in showing a pattern of reduced heritability in the exposed group. Significant differences in heritability contingent on exposure were not present for the control variables (autistic traits and height), suggesting the effect was not general to other variables. Negative symptoms was the only subscale that showed the opposite pattern, with significantly higher heritability in the more exposed group. The environmental composite showed significant heritability (46%) and significant shared and nonshared environmental influences (both 27%).
Discussion: These results suggest that psychotic experiences are less heritable when reported by adolescents in the community who have experienced multiple environmental risks. PEs may sometimes result from social environments and these PEs may differ in etiology from PEs that form part of a more heritable neurodevelopmental/neuropsychiatric pathway. If further work supports it, this hypothesized distinction could be useful for both gene-discovery work and for early intervention approaches. It is unlikely that "environmentally-induced" PEs are completely independent of genetic effects, since exposure to environmental risk factors is in itself partly heritable through gene–environment correlation. Future steps include testing for differential genome-wide polygenic score prediction of PEs contingent on environmental exposure.

The impact of cannabis use on intelligence and executive functioning

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Changes in the legalization of cannabis use have been widespread across the United States, accompanied by increased rates of use. This has led to a recent increase in concern that cannabis use has a negative impact on cognitive functioning. Most studies assessing this association have reported that persistent cannabis users who initiate use at earlier ages have a greater decline in IQ across time compared to those who occasionally use cannabis or initiate use at later ages. However, there are many potential confounders that may account for the association between cannabis use and decline in cognitive functioning (e.g., SES). Studies examining twin pairs who are discordant on the degree of cannabis use control for potential confounding caused by common genetic and family environmental factors that may influence both cannabis use and cognitive functioning. Such studies have consistently found that cannabis use does not cause cognitive decline. The current study assessed within and between-families, in a sample of twins, the association between multiple measures of cannabis use and cognitive functioning. This study extends previous twin studies on this topic by using multiple measures of cannabis use (age of initiation and frequency of use in addition to disorder diagnosis) and factor scores of multiple executive functions (EFs; including a common factor and factors specific to updating working memory and shifting mental sets). Given the previous research results among twins, we hypothesized that cannabis use is not associated with individual differences in cognitive function. Analyses included about 750 individuals including about 380 twin pairs and about 10 individuals without co-twin data, depending on the models, from the Colorado Longitudinal Twin Study. Multilevel models were used to estimate the between-family and within-family associations between cannabis use (frequency, cannabis use disorder diagnosis, and age of initiation) and cognitive functioning (IQ and EFs) at ages 17 and 23, controlling for IQ measured prior to cannabis initiation (ages 7–12). Results indicated that cannabis use is significantly associated with measures of IQ and EF between families and within families. Specifically, between-families, twin pairs with younger age of initiation, greater frequency of cannabis use, and more severe cannabis use disorder diagnosis had lower IQ scores. Within-families, but not between-families, the twin with a greater frequency of cannabis use and more severe cannabis use disorder diagnosis had lower common EF. Next, we conducted the same analyses while also controlling for other substance use variables (i.e., alcohol, nicotine, and other drugs). The between-family and within-family cannabis associations were no longer significant or only marginally significant. Our results suggest that cannabis use is associated with concurrent IQ and EFs, even after controlling for IQ differences prior to cannabis initiation. However, most of these associations are not significant within families, suggesting familial confounding, and these between-family and within-family effects may be due to other substances that are used more frequently by individuals who use cannabis. These results are inconsistent with a simple causal model in which cannabis use causes declines in IQ or EF.

Co-twin control models: assessing bias from measured and unmeasured confounders

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Genetically informative research designs are becoming increasingly popular as a way to strengthen causal inference with their ability to control for genetic and shared environmental confounding. Co-twin control (CTC) models, a special case of these designs using twin samples, decompose the overall effect of an exposure on an outcome into a within and between twin pair term. Ideally, the within twin pair

term would serve as an estimate of the exposure effect controlling for genetic and shared environmental factors, but it is often confounded by factors not shared within a twin pair. Previous simulation work has shown that if twins are less similar on a non-shared confounder than they are on an exposure, the within twin pair estimate will be a biased estimate of the exposure effect, even more biased than the individual, unpaired estimate[1]. The current study uses simulation and analytical derivations to show that incorporating a covariate related to the non-shared confounder in CTC models can reduce this bias in many cases. Additionally, the form of covariate inclusion is compared between adjustment for only one's own covariate value and adjustment for the deviation of one's own value from the covariate twin pair mean. Results show that both ways of covariate adjustment demonstrate comparable results in terms of bias when the covariate is a weak measure of the non-shared confounder. When the covariate is a stronger measure of the non-shared confounder, adjusting only for one's own covariate value can reduce bias more than including the twin pair mean in all cases except when the twin pair correlation in the non-shared confounder is zero.

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Genetic influences of schizophrenia and intelligence independently associate with general cognitive function in middle-aged adults

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A hallmark symptom of schizophrenia is cognitive impairment, which is also observed in first-degree relatives of schizophrenia patients. Schizophrenia and cognition have independent genetic loci associated with them. We tested whether: (i) polygenic scores of risk for schizophrenia predict general cognitive function in an adult male twin sample, and (ii) the association is independent of a polygenic score for intelligence. We used a mixed effect linear regression to account for non-independence of twins and zygosity via random effects, and covaried for genome-based ancestry in addition to health and lifestyle influences known to affect cognitive performance via fixed effects. Higher schizophrenia risk scores were associated with lower levels of cognitive function across a variety of assessments which were aggregated via principal components analysis into an index of general cognitive function. We found that the schizophrenia and intelligence polygenic scores were both significantly associated with general cognition. These results suggest that the common variants identified in genome-wide association studies for schizophrenia are associated with lower general cognition and that this effect is independent of common variants previously associated with intelligence.

How genes and the environment influence executive cognitive functions in inbred strains of mice

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Deficits in working memory and attention are endophenotypes of major mental disorders, including schizophrenia and mood disorders. Such executive cognitive dysfunctions can also be triggered by early life stress (ELS) exposure of laboratory mice. However, the emergence of such deficits depends upon their genetic background. For example, while the stress susceptible strain Balb/c exhibits spatial working memory and extradimensional attention set-shifting deficits after ELS (infant maternal separation for 3 h daily from postnatal age P2 until P15), the more resilient strain C57Bl/6 does not exhibit such deficits. In addition to genetic factors that differentially modulate the stress susceptibility in these two strains, our studies showed that the emergence of cognitive deficits in Balb/c mice is linked to an ELS-triggered epigenetic response, namely reduced activity of histone deacetylase 1 (HDAC1) and increased histone H4K12 acetylation at promotors of distinct plasticity-associated genes that are known to modulate cognitive task performance. As a result, cognitive test exposure triggers enhanced recruitment of RNA polymerase II to these promotors and, thereby, abnormally increases test-induced transcription of genes that influence cognitive task performance negatively. This epigenetic mark of ELS exposure is transmitted to the first progeny of Balb/c mothers, and the male and female progeny (although not exposed to ELS) exhibits the same epigenetic and cognitive abnormalities. Our studies showed that this transmission is germ-line independent and triggered by maternal behavior[1]. Moreover, this trans-generational effect exerted by ELS Balb/c mothers on the cognitive phenotypes of their offspring also extends to different genetic backgrounds. F1 C57Bl/6 × Balb/c hybrid mice that were raised by Balb/c mothers during ELS exposure develop the same cognitive phenotypes found in Balb/c mice[2], and C57Bl/6 foster pups develop deficits in attention-set-shifting (but not working memory)[3]. In all strains of pups, reduced promotor-associated HDAC1 activity is a common underlying mechanism for these deficits, but the genes affected differ: While in Balb/c mice, test-induced overexpression of brain-derived neurotrophic factor (Bdnf) transcript variant 3 is responsible for the emergence of cognitive deficits, foster C57Bl/6 mice exhibit normal Bdnf expression but increased test-induced expression of the early growth response gene 2 (Egr 2), and F1 hybrid mice exhibit both increased Bdnf and Egr 2 expression[2,3]. These findings indicate that the magnitude of ELS effects on pups depend upon their genetic background and their environment (maternal care). Nevertheless, a pharmacological intervention that lowered the levels of acH4K12 during adolescent development (P35 to P59) in ELS Balb/c mice significantly improved their cognitive functions, and abolished the trans-generational propagation of such deficits[1].

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Twins switched-at-birth: chronology, life histories and research findings

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Monozygotic (MZ) twins reared apart from birth are a rare natural experiment, allowing unique insights into genetic and environmental factors underlying behavior. Accidentally switched MZ twins are an even rarer subgroup of separated twins with only nine documented

cases world-wide. This presentation will review the complete chronology (1941–1988), life histories and research findings from these cases, as well as the psychological and legal implications posed by these unusual situations. The material is based on information gathered personally from the twins and/or their families in eight of the nine cases. Particular attention will be given to the most recent switched twins, which involved a double exchange: the switching of one newborn MZ male twin from two different pairs, born in Colombia, South America in 1988. This event generated a series of genetically and environmentally informative kinships–some familiar, but some unique. Familiar sibling sets are the two MZA twin pairs raised in dramatically different environments. The unique sibling pairs consist of (a) two virtual twin pairs (same-age unrelated siblings) who believed they were dizygotic (DZ) twins and who were raised as such; and (b) two pairs of "replicas" (unrelated siblings who were not reared together, but who genetically replicate the unrelated reared-together pairs; comparing the replicas with the virtual twins yields a measure of shared environmental influence). Selected findings on physical measures, health characteristics, mental abilities and epigenetic profiles are published (Segal and Montoya 2018), but new findings in these areas will be presented, supplemented by photographic material from Colombia. The nine switched-at-birth MZ twin pairs variously come from Switzerland (n = 1), Puerto Rico (n = 2), Canada (n = 1), Poland, (n = 1) the Canary Islands (Gran Canaria; n = 2) and now Colombia (n = 2). Five pairs are male and four pairs are female. The ages at which the truth about their birth was discovered range from 18 months to 28 years. Despite the extremely different environments in which some of the co-twins were raised, some striking similarities in their behavioral and medical characteristics were observed. At the same time, differences in mental abilities and other behavioral traits were expressed that were possibly tied to events in their respective life histories. An epigenetic analysis of the Colombian twins and a biological sister (who was raised with one brother, but apart from the other), found that the pairs of genetic relatives were most alike with one exception, possibly associated with prenatal factors (Segal, Montoya, Loke &; Craig, 2017). The various cases can be viewed against the backdrop of extant findings from MZ and DZ twins raised apart and together, but each individual switched-at-birth pair should be evaluated with caution.

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The role of the child in teacher-child relationships: evocative gene–environment correlation

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Children's close and conflictual relationships with their teachers have profound impacts on their school success and social and emotional outcomes. The field has focused on teacher influences on student outcomes, with few studies addressing the role of the child. Children's negative emotionality has been linked to numerous behavioral outcomes, highlighting emotionality as a crucial aspect for successful adjustment. Our goal was to examine how early childhood negative emotion expression impacted later teacher-child relationships, and if a part of this association was explained by birth parent (BP) temperament (heritable influences). Using data from the Early Growth and Development Study ($N = 561$), we examined heritable (BP temperament) influences on children's sadness and anger at 4.5 years and how heritable influences may evoke close or conflictual relationships with teachers at child age 7 years via children's negative emotion expression. To capture the possible heritable influences of BPs, we used factor analyses to develop latent temperament factors for BPs. We factor analyzed BP self-report on the Adult Temperament Questionnaire, Temperament Character Inventory, and the Harter Adult Self-Perception Scale in early childhood. Four factors were extracted: negative affect versus self-control, agreeableness versus disagreeableness, high versus low orienting sensitivity, and high versus low behavioral activation. Teacher-child relationships were assessed with teacher-report of the Student–Teacher Relationship Scale at child age 7 years. Child sadness and anger was assessed using parent-report on the Child Behavior Questionnaire at child age 4.5 years. Child behavior problems was assessed using parent-report on the Child Behavior Checklist at age 11 years. We examined child sadness and anger at age 4.5 years predicting teachers' report of their close and conflictual relationships at age 7 and parent report of child behavior problems at age 11. The model fit was acceptable (χ^2 (25) = 42.44, RMSEA = .04, CFI = .95, SRMR = .03). Results indicated that high child sadness was associated with a closer but not conflictual teacher-child relationship ($\beta = .17$, $p < .05$) and more internalizing behavior problems ($\beta = .22$, $p < .01$). Child anger was not associated with teacher-child closeness or conflict but was associated with internalizing ($\beta = .21$, $p < .01$) and externalizing problem behavior ($\beta = .31$, $p < .01$). Conflictual teacher-child relationships was positively associated with children's externalizing problems ($\beta = .16$, $p < .05$). Higher BP control was associated with more child sadness ($\beta = .12$, $p < .05$) and internalizing behavior problems ($\beta = -.12$, $p < .05$). Higher BP behavioral activation was associated with more child sadness ($\beta = .08$, $p < .05$) and anger ($\beta = .09$, $p < .01$). However, the indirect effects of BP temperament to child sadness to teacher-child closeness to internalizing problem behavior was not significant. These findings suggest that children's negative emotion expression can elicit specific teacher–child relationships. However, it is unclear if the child evocative effect on teachers is influenced by these heritable influences on child anger and sadness. The current study helps us better understand how and by what mechanisms children affect their learning.

Genetic and environmental influences on psychopathy: a meta-analysis of twin studies

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Psychopathy is a multidimensional syndrome that is characterized by affective (e.g. callousness, shallow affect) and interpersonal (e.g., arrogance, manipulative) deficits and is associated with persistent antisocial behavior across the lifespan. Importantly, psychopathic personality traits are distinguished from psychopathic behavior. It is theorized that these dimensions have distinct etiologies such that affective-interpersonal deficits are largely genetic in origin while associated behaviors are due to both genetic and environmental influences, but these etiological distinctions remain largely untested. Prior meta-analyses investigating the etiology of psychopathy have been limited by a focus on behavioral features of psychopathy, rather than the personality deficits that distinguish it from other forms of

externalizing behavior. Fortunately, behavioral genetic literature on psychopathy has expanded greatly in the past decade and now includes numerous studies of both personality deficits and pathological behaviors. Therefore, the current meta-analysis aimed to investigate the origins of personality and behavioral features of psychopathy by examining the type and magnitude of genetic and environmental influences on each. A comprehensive literature search yielded 52 twin studies of psychopathic traits. Of these, 16 unique samples were retained for analysis. In general, AE models provided the best fit to the data, indicating that additive genetic and unique environmental factors, but not common environmental factors, accounted for the variance in psychopathy factors and their subfacets. However, moderation analyses indicated that there are significant sex and age differences in their etiologies. Genetic factors explained a greater proportion of variance in females than males across psychopathic traits. Additionally, common environmental factors are an important source of variance in childhood and adolescence for the affective/interpersonal factor, but not in adulthood or for the socially deviant factor. These findings suggest that psychopathic dimensions may not have such distinct etiologies as previously theorized or that etiological differences depend on moderating factors, such as developmental stage.

Highly efficient multivariate GREML

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Genomic-relatedness-matrix restricted maximum-likelihood (GREML) estimation of a bivariate linear mixed model (LMM) is often used for estimating the genetic correlation and covariance between traits. An extension of such bivariate GREML methods is a multivariate approach. Instead of estimating multivariate LMMs, researchers often estimate pairwise bivariate LMMs for each combination of two phenotypes within a set of phenotypes. This practice for inferring genetic covariance between multiple traits can pose a problem, since the resulting (combined) covariance matrix is not necessarily positive (semi)-definite. To overcome this problem, we present a multivariate GREML (MGREML) estimation method. This method consists of an iterative procedure, based on a Newton–Raphson algorithm, to obtain consistent estimates of the parameters of a multivariate SNP-based LMM for balanced data on P phenotypes, hence, observed in the same set of N individuals. We provide a parametrization of the LMM, such that resulting estimates of the $P \times P$ genetic and environment covariance matrices are positive (semi)-definite, irrespective of starting values and updates of the estimates throughout the iterations. Provided one has access to the eigendecomposition of the genomic-relatedness matrix, we are able, from there on, to reduce the computational complexity of MGREML estimation from the order NP^3 to an order of $N(P)^3$. Therefore, the MGREML estimation method we propose can be applied to a large set of phenotypes and individuals, provided the data are balanced.

Low frequency genetic variation in the TP53 locus has large effects on head circumference and intracranial volume

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Background: Craniofacial development involves complex growth and differentiation of hard and soft tissues, characterised by cephalocaudal and allometric patterns, and gives rise to the closely related traits of head circumference (HC) and intracranial volume (ICV). Previous studies have identified genetic variants influencing infant HC, but the role of low-frequent and common variation contributing to childhood and final HC is not well understood, nor the nature of genetic determinants that contribute to an underlying joint skeletal and brain-related phenotype (final craniofacial dimension).
Participants and methods: Here we carry out a genome-wide analysis of final HC and final craniofacial dimension studying 11 population based cohorts with either whole genome sequencing information (n = 1762; UK10K consortium), genotype imputation to a joint UK10K/1KG panel (n = 8285) or genotype imputation to the Haplotype Reference Consortium (HRC) panel (n = 8834). All participants were aged 5.5 years or older and of European ancestry, as near final HC is largely determined by the age of 6 years. The entire HC meta-analysis included 18,881 participants, with a replication in a further independent sample of 973 adults, aged 18–85 years. Joint analysis of HC and ICV (craniofacial dimension) included 26,577 additional participants aged 9-98 years from the CHARGE / ENIGMA consortia with a total sample size of 45,458.
Results: We identified and replicated evidence for genetic association between both final HC and final craniofacial dimension and a novel region on chromosome 17p13.1, implicating low frequency variants within *TP53*. For final HC, the strongest evidence for association was observed at rs35850753 (EAF = 0.02; $p = 2 \times 10^{-10}$), while final craniofacial dimension, based on the joint analysis of HC and ICV, was most strongly associated with rs78378222 (EAF = 0.02; $p = 9 \times 10^{-13}$). Both variants are in partial linkage disequilibrium, and their effect sizes are substantially larger than any previously

reported GWAS signals for either HC or ICV alone. Specifically, they reach nearly a fifth and quarter of a SD unit change in final craniofacial dimension and final HC per rare effect allele respectively, an effect that is observable from mid-childhood onwards, but not in infancy. In addition, we identified eight further loci affecting final craniofacial dimension. The genetic variance composition of HC showed considerable genetic stability between infancy and mid-adolescence, with genetic factors operating at the age of 1.5 years explaining 63.1%(SE = 0.09%) of the genetic variance at age 15 years. However, we also observed evidence for some developmental changes in the underlying genetic architecture.
Discussion: *TP53* encodes the p53 protein, which has anti-proliferative functions, and both rs35850753 and rs78378222 have been robustly linked to neuroblastoma. There is furthermore support from animal and tissue models for a role of TP53 in early neurological patterning, especially neural crest development involving epithelial–mesenchymal transition (EMT), where epithelial cells are converted into individual migratory cells, as well as neural tube closure and early brain development. Together, our findings thus support a role for TP53 transcripts in human craniofacial development and contribute to an improved understanding of the dynamic nature of genetic architectures throughout human growth and development.

Maternal opioid analgesic use during pregnancy and offspring neurodevelopmental problems

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The use of prescription opioid analgesic (POA) medications during pregnancy is increasing.[1] Studies have linked maternal POAs during pregnancy to adverse birth outcomes in offspring (e.g., preterm birth).[2] However, research on later childhood outcomes is lacking. Because pregnant women are typically excluded from randomized clinical trials of medications, researchers must use observational methods to study prenatal POA exposure. Research suggests that maternal POA use during pregnancy is correlated with environmental risk factors[3] and genetic liability for neurodevelopmental problems.[4] Therefore, to rigorously evaluate associations between prenatal POA exposure and two neurodevelopmental problems—autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD)—we used records of POA prescriptions filled by pregnant women and observational methods that help account for genetic and environmental factors that differ between exposed and unexposed offspring. We studied 840,659 singleton offspring born 2006 to 2013. First, we assessed associations between pregnancy, maternal, paternal, and other familial and socioeconomic factors and POA exposure. Second, we estimated associations between POA exposure and the neurodevelopmental problems while controlling for numerous measured characteristics associated with POA exposure. Third, we compared risk of the outcomes among differentially exposed siblings while adjusting for measured characteristics that may vary among siblings. By design, sibling comparisons account for all unmeasured genetic and environmental factors that make sibling similar, including influences from maternal conditions that are stable across pregnancies. We used Cox proportional hazard regression to account for right censoring of the outcomes. For sibling-comparisons, we fit fixed-effect models using stratified Cox regression. Numerous risk factors were associated with POA exposure (e.g., maternal smoking during pregnancy odds ratio [OR] 2.03, 95% confidence interval[CI] 1.96–2.10, prenatal exposure to other psychoactive medications OR 2.80, 95% CI 2.68–2.92). After adjustment for measured covariates, POA exposure was associated with risk of ASD (hazard ratio [HR] = 1.49, 95% CI 1.28–1.74) and ADHD (HR = 1.99, 95% CI 1.71–2.31). The associations remained elevated in sibling comparison models, though CIs were wider (ASD HR = 1.45, 95% CI 0.71–2.95; ADHD HR = 2.34, 95% CI 0.98–5.56). In sum, our results showed that (a) several risk factors were associated with POA use during pregnancy, indicating that exposed and unexposed offspring differ on several important background characteristics, (b) the associations between POA exposure and ASD and ADHD were independent of several measured risk factors, and (c) these associations remained elevated in siblings comparisons models, indicating that associations may be independent of unmeasured genetic and environmental factors that make siblings similar. However, given that CIs in sibling comparisons were wide, future studies using larger samples will need to replicate these results. Additionally, given that all observational methods have strengths and weaknesses and control for different sets of confounding factors, future research will also need to use other observational methods to further test the role of confounding factors, such as paternal POA use during the pregnancy period as a negative control for the exposure and maternal use of other pain medications during pregnancy as active comparators.

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Using a siblings reared apart and together design to parse genetic vs. environmental influences on children's body mass index

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Childhood obesity is associated with adverse outcomes that can persist into adulthood, including continued obesity, type 2 diabetes, and hypertension. Understanding the underlying mechanisms that contribute to childhood obesity is critical for prevention efforts. Research has identified both genetic and environmental influences on children's risk for obesity, although most existing work confounds genetic background with rearing environment when comparing genetically-related individuals who are living in the same home (e.g., traditional family studies). Novel approaches such as the children of twins design and discordant twin design provide unique methods for examining shared environmental and genetic influences on child obesity, but have design-specific limitations related to shared rearing environment of family members. To address these confounds, the present study uses biological and adoptive parents and their children to examine how the rearing environment and genetics may contribute to the body mass indices (BMI) among siblings reared apart and together. The study sample was drawn from the Early Growth and Development Study and includes 899 linked children with different levels of relatedness (unrelated siblings, half-siblings, full siblings) residing in the same home or different homes. Parent-reported height, weight, age, and child sex were used to calculate BMI scores for all children using the US CDC 2000 norms. We used age-adjusted

Z-score estimates of BMI for children ages 2–20. The complex nature of the study design with many multi-level connections among participants—both in relatedness and shared environment—provides a unique opportunity to employ a novel statistical approach—a profiled restricted maximum likelihood model (pREML) with pairwise relatedness and environmental matrices to partition variance into that which can be explained by genetic background (V_A), shared environment (V_C), and residual variance (V_E). Heritability was estimated as the proportion of variation in BMI that can be explained by genetic factors over the total variation in BMI. We observed a heritability estimate of 0.63 for BMI in this dataset, and an effect of shared environment of 0.26. The obtained heritability estimate of 0.63 falls in the middle range for other genetic studies that have used more traditional twin methods (e.g., range 0.40–0.85; Feng 2016), suggesting that prior studies of genetically-related children reared together may underestimate the role of shared and unique environment on child BMI, or may include the effects of non-additive genetic factors in the heritability estimate. The results of this study confirm the unique influence of genetics while simultaneously highlighting the important role that the rearing environment can have on childhood weight status.

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Common genetic influences on autism spectrum disorders and sleep disturbances: evidence from a nationwide twin sample

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Autism spectrum disorders (ASD) are frequently comorbid with other conditions. Sleep disorders, such as insomnia and parasomnia, are common comorbidities with ASD; as many as 80% of individuals with ASD either report disturbed sleep or clinically significant sleep problems. It is now relatively well known that ASD shares genetic causes with many other conditions with which it is frequently comorbid; whether ASD and sleep disorders are also associated with similar genetic factors is largely unknown. We therefore aimed to test whether ASD and sleep disorders are associated with similar genetic influences to one another. From 27,350 pairs of twins in the Swedish Twin Register born between 1973 and 2009, we identified 672 individuals with a diagnosis of ASD recorded in nationwide health registries. We also identified 2400 individuals with a recorded diagnosis of a sleep disorder or prescriptions of sleep medications recorded in the Swedish Prescribed Drug Register. The association between these disorders was tested using bivariate liability threshold twin models. Both ASD and sleep disorders are also strongly associated with anxiety and depression, and we hence repeated the analyses while controlling for the effects of comorbid anxiety disorders and depression. There was a significant association between ASD and sleep disorders ($\beta = 2.40$, SE = 0.12, odds ratio = 10.98 [8.70–13.78]). ASD and sleep disorders were, individually, under strong genetic influence, with respective heritability estimates of 92% and 65%. There was a moderate phenotypic correlation of .46 (95% confidence intervals = .38–.50). The genetic correlation was also moderate in magnitude ($r_a = .46$, 95% CI .41–.52), as was the nonshared environmental correlation ($r_e = .67$, 95% CI = .44–.84). Shared genetic influences accounted for 76% of the phenotypic correlation between ASD and sleep disorders. Adjusting for anxiety and depression resulted in a reduction in the magnitude of the phenotypic correlation to .29 (95% CI .27–.37). Similarly, the genetic correlation decreased to .26 (95% CI .17–.29) and the nonshared environmental correlation decreased to .55 (95% CI .31–.71). Of note, however, significant associations remained between ASD and sleep disorders even after adjustments for anxiety and depression. These results thus suggest that the genetic pleiotropy seen in relation to ASD and other outcomes, such as ADHD, extends to sleep disorders. Some of this association is accounted for by the strong overlap seen between these disorders individually and anxiety and depression, stressing the need to account for anxiety and depression when studying the association between ASD and sleep disorders in genetic studies. On the other hand, a certain degree of the association between these phenotypes is independent of anxiety and depression, indicating that at least some of the genetic causes of ASD are the same as those that lead to sleep disorders. Ongoing analyses are now investigating these associations longitudinally, and using polygenic risk scores.

Fitting structural equation models to GWAS-derived genetic covariance matrices

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Genome-wide association studies (GWASs) are rapidly identifying loci affecting multiple phenotypes. Moreover, using cross-trait versions of methods such as genomic-relatedness-based restricted maximum-likelihood (GREML) and LD-score regression (LDSC) researchers have identified genetic correlations between diverse behavioral, cognitive, psychiatric, and medical traits. These analyses are suggestive of constellations of phenotypes affected by shared sources of genetic liability, but they do not permit the causes of the observed genetic correlations to be investigated systematically. Here we introduce Genomic Structural Equation Modeling (Genomic SEM), a new method for modeling the multivariate genetic architecture of constellations of traits. Genomic SEM formally models the genetic covariance structure of GWAS summary statistics from samples of varying and potentially unknown degrees of overlap. We validate key properties of Genomic SEM with simulation and illustrate the flexibility and utility of Genomic SEM with several analyses of real summary data.

Multiple processes underlie twin correlations for skewed BMI

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Body Mass Index (BMI), like most human phenotypes, is substantially heritable. However, BMI is not normally distributed; the skew appears to be structural, and increases as a function of age. Moreover, twin correlations for BMI frequently violate the assumptions of the most common variety of the classical twin model, with the MZ twin correlation greater than twice the DZ correlation. This study aimed to decompose twin correlations for BMI using more general skew-t distributions. Same sex MZ and DZ twin pairs ($N = 7086$) from the community-based Washington State Twin Registry were included. We used latent profile analysis (LPA) to decompose twin correlations for BMI into multiple mixture distributions. LPA was performed using the default normal mixture distribution and the skew-t mixture

distribution. Similar analyses were performed for height as a comparison. Our analyses were then replicated in an independent dataset. A two-class solution under the skew-t mixture distribution fit the BMI distribution for both genders. The first class consists of a relatively normally distributed, highly heritable BMI with a mean in the normal range. The second class is a positively skewed BMI in the overweight and obese range, with lower twin correlations, especially in DZ. In contrast, height is normally distributed, highly heritable, and is well-fit by a single latent class. The finding was then replicated in an independent dataset consisting of 13,553 (5965 MZ, 7588 DZ) same-sex male twin pairs from the National Academy of Sciences-National Research Council Twin Registry. Results in the replication dataset were highly similar. Our findings suggest that two distinct processes underlie the skew of the BMI distribution, only one of which fits the conventional model of heritable variance resulting from independent assortment of a large number of loci. The second latent profile, highly skewed with a mean in the overweight to obese range, lower MZ correlations and DZ correlations close to zero, is consistent with reciprocal phenotype-environment processes in which small initial differences within pairs are magnified by non-random exposure to subsequent environments. The contrast between height and weight is in accord with subjective psychological experience: both are under obvious genetic influence, but BMI is also subject to behavioral control, and thus to complex person-environment interactions, whereas height is not. Dual process models of this kind have potential relevance to a wide variety of psychopathological phenotypes that plausibly consist of a heritable, normally distributed trait in the normal range, and a positively skewed pathological upper tail. In traits of this kind, the psychopathology is located in one distribution but not the other. The goal of treatment programs for BMI or drinking is not to produce teetotalers or people who are as thin as possible, but rather to prevent individuals from drifting into the skewed upper tail.

Multi-ancestry meta-analysis and LD score regression

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Although large strides have been made in genome-wide association studies (GWASs) and polygenic prediction for individuals of European ancestry, these activities have lagged behind for non-European samples. Unfortunately, existing methods for meta-analysis do not account for cross-ancestry differences in genetic architecture and linkage disequilibrium (LD), making it impossible to share information from existing, European-based GWAS summary statistics to GWAS summary statistics from cohorts of non-European descent. In this paper, we develop a principled method, multi-ancestry meta-analysis (MAMA), that meta-analyzes GWAS summary statistics based on samples of different ancestries accounting for differences in LD pattern and genetic architecture. This method increases the precision of GWAS effect-size estimates for both ancestries, improving polygenic prediction and elucidating biological pathways. A key component of MAMA is an extension of LD score regression which accounts for LD differences across populations. Using our extension of LD score regression, we can estimate the genetic correlation of phenotypes measured in different ancestry groups. We illustrate the improved precision of effect size estimates and increase predictive accuracy of polygenic scores when using MAMA in simulation and in applications to a number of anthropometric and psychiatric phenotypes.

Understanding the genetic architecture of language- and literacy-related abilities during mid-childhood and adolescence: evidence for genetically shared factors with early vocabulary

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Background: Mastering language skills is an important milestone and influences children's cognitive development during later life. The heritability of language abilities increases during child and adolescent development, as shown by longitudinal twin studies in 2 to 12-year old twins. Moreover, language- and literacy-related abilities (LRAs) in mid-childhood are highly genetically correlated with each other. However, knowledge about early genetic predictors of language and literacy skills is scarce. Here, we apply genetic-relationship-matrix structural equation modelling (GSEM), a multivariate analysis framework in unrelated individuals, to model genetically shared factors between early vocabulary and multiple LRAs during mid-childhood and adolescence.
Methods: Expressive and receptive vocabulary at 38 months, as well as thirteen LRAs related to reading, spelling, phonemic awareness, listening comprehension, non-word repetition and verbal intelligence (7–13 years) were studied in children from a UK birth cohort (ALSPAC; $N \leq 6092$). GSEM based on Cholesky decomposition was applied to investigate developmental genetic architectures using rank-transformed measures. Due to computational constraints, 13 GSEM models each consisting of the two early vocabulary measures and one mid-childhood LRA were defined. Path coefficients across multiple GSEM models were combined using random-effects meta-regression. In addition, we estimated the factorial co-heritability as the proportion of genetic variance explained by a genetic factor with respect to the total genetic variance of a trait.
Results: Across all Cholesky models, we observed one shared genetic factor between both vocabulary measures, with up to 0.75(SE = 0.25) of the genetic variance in early receptive vocabulary being accounted for by genetic variance in expressive vocabulary. This common factor explained $\sim$ 8.5% phenotypic variation in receptive vocabulary (standardised path coefficient: $-$ 0.29 (SE = 0.08)). A second genetic factor that was unique to early receptive vocabulary accounted for $\sim$ 3.8% of phenotypic variation (standardised path coefficient: 0.20 (SE = 0.04)). The early common genetic factor also predicted $\sim$8.6% phenotypic variation in verbal intelligence scores (standardised path coefficient: $-$ 0.29 (SE = 0.10)). However, there was little evidence that this factor contributed to phenotypic variation in other LRAs. The second genetic factor, unique to early receptive vocabulary, explained genetic variance for many literacy, but not language-related abilities. Specifically, it accounted for $\sim$ 43% of phenotypic variance in pooled reading-related abilities, with little evidence for heterogeneity (pooled standardised path coefficient: 0.66 (SE = 0.03), $p_{het} = 0.93$). This captured the majority of the total genetic variance for reading-related measures during mid-childhood and adolescence (factorial co-heritability for e.g. reading accuracy and comprehension age 7: 0.94 (SE = 0.08)). There was no evidence for genetic factors that are specific for mid-childhood LRAs, across any of the models studied.
Discussion: Genetic variation in literacy-related abilities during mid-childhood can be fully accounted for by genetic factors influencing

receptive, but not expressive vocabulary, at the age of 38 months. In contrast, genetic variation in verbal intelligence is predicted by genetic factors influencing both early expressive and receptive vocabulary. Our findings suggest that genetically predictable biological mechanisms affecting LRAs during mid-childhood and adolescence emerge already at an early age.

Type I error rates in multivariate behavioral genetic models

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Numerical Type I error rates for certain commonly used multivariate twin models do not align with theoretical Type I error rates. This issue can have profound implications for hypothesis testing and statistical inference. Here we present two simulation studies to compare the Type I error rates for commonly used parameterizations of multivariate twin models. In particular, both the Cholesky decomposition and correlated factors models show markedly reduced power to reject the null hypothesis when it is false. By contrast, a model where the covariance matrices for additive genetic, common environment and specific environment variance components are estimated directly and without constraints yields Type I error rates that are consistent with expectations derived from hypothesis testing theory. The loss of power is considerable and increases with the number of observed variables. It appears that each model implied boundary, whether explicit or implicit, increases the discrepancy between the numerical and theoretical Type I error rates. Furthermore, imposing boundary conditions truncates the sampling distribution, and induces bias in the expected parameters. Implications for published research and limitations associated with directly estimating the relevant covariance matrices are discussed.

Exploring the tradeoff between phenotypic specificity and sample size

Brad Verhulst, Michigan State University

In psychiatric genetics with genome-wide data we are forced to make a trade-off between well characterized phenotypes and large sample sizes. Well characterized phenotypes have less measurement error, and accordingly provide a higher signal to noise ratio in genomic analyses. Due to the effort required to assess a well characterized phenotype, fewer observations can be collected for the same amount of effort/money. By contrast, if we relax the phenotypic specificity we can much more economically collect data, but the signal to noise ratio will be lower. Relaxing phenotypic specificity induces phenotypic heterogeneity. The ultimate question, therefore, is what is the optimal tradeoff in terms of statistical power between well characterized phenotypes and large sample sizes? Embedded within this research question is a series of hypotheses: (a) what factors increase the statistical power in heterogeneous phenotypes and how much heterogeneity is tolerable within genome-wide association studies (GWAS), (b) how much additional power is provided by well characterized phenotypes (e.g. where is the tipping point viz. lower sample size), and (c) what meta-analytical or multivariate analytical? factors can be leveraged to enhance the power to detect significant genetic associations with varying levels of phenotypic specificity. These hypotheses will be tested using a series of simulation studies.

Results from the largest GWAS of lifetime cannabis use (N = 184,765): new risk loci, genetic overlap with mental health, and a causal influence of schizophrenia on cannabis use

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Cannabis use is a heritable trait that has been associated with adverse mental health outcomes. To identify genetic risk variants, we performed the largest genome-wide association study for lifetime cannabis use (N = 184,765) to date. We identified 8 independent SNPs in 6 regions, with all measured variants combined explaining 11% of the variance. Gene-based tests revealed 35 significant genes in 16 regions and S-PrediXcan analyses identified 21 genes with different expression levels between cannabis users versus non-users. The most significant and consistent finding over the different analyses was CADM2, which has previously associated with substance use and risk-taking phenotypes. Significant genetic correlations were found with 14 of 25 tested substance use and mental health traits, including smoking, alcohol use, risk-taking, schizophrenia, and bipolar disorder. Mendelian randomisation analysis provided evidence for a causal positive influence of schizophrenia risk on lifetime cannabis use.

Birth cohort effects on the quantity and heritability of alcohol consumption in adulthood: a Finnish longitudinal twin study

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Aims: To explore the importance of birth cohort for alcohol consumption and abstinence over the life course, and to study differences between birth cohorts in genetic and environmental sources of variation in adult alcohol use.
Design: The Older Finnish Twin Cohort longitudinal survey study 1975–2011. Setting: Same-sex twins from the general population of Finland.
Participants: A total of 26 121 individuals aged 18–95 (full twin pairs at baseline n =11 608).
Measurements: Longitudinal survey data on monthly alcohol consumption, collected in 1975, 1981, 1990, and 2011.
Findings: Hierarchical growth curve models indicated that mean levels of alcohol consumption were the highest in more recent birth cohorts, and alcohol use declined due to aging in earlier-born cohorts. Abstaining was less common in every successive cohort. Aging was associated with increasing abstinence only in the earliest cohorts. Birth cohort differences in the genetic and environmental components of variance in alcohol consumption were found: heritability was 21% (95% CI 0–56%) in an earlier-born cohort of women (born 1901–1920; mean age 62.8, SD = 5.3) and 51% (95% CI 36–56%) in a more recent cohort (born 1945–1957; mean age 60.2, SD = 3.7) at the age of 54–74. For men, heritability was 39% (95% CI 27–45%) in both cohorts. In alcohol abstinence, environmental influences shared between co-twins explained a large proportion of the variation in the earlier-born cohort (43%, 95% CI 23–63%), whereas non-shared environmental (54%, 95% CI 39–72%) and additive genetic

influences (40%, 95% CI 13–61%) were more important among more recent cohorts of men and women.
Conclusion: In Finland, the quantity of alcohol consumption as well as its heritability in adulthood have increased in more recent birth cohorts, suggesting genetic influences have been moderated by changes in environmental conditions.

Shared environmental sources of the variation in non-verbal intelligence are largely twin-specific: the study of twin and sibling pairs from Russia

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Our previous research on Russian adolescent twins revealed a substantial shared environmental variation in the individual differences in the non-verbal ability (65%, Malykh et al. 2016), unlike the other behavior genetic research of cognitive abilities (30%, Polderman et al. 2015). The current study aimed to estimate the role of twin-specific shared environmental effects by comparing twin and sibling pairs. The sample included 730 twin pairs (305 MZ, 425 DZ, mean age 13 years, SD = 2.9 years) and 154 sibling pairs (139 full sibling, 15 half sibling, mean age 11 years, SD = 3.2 years). The mean age difference in sibling pairs was 4.4 years. The non-verbal ability was assessed by means of Raven's Progressive Matrices. The twin-sibling model included the age variable to filter out the age-related variation. The MZ and DZ twins showed substantially higher similarity in cognitive ability than full and half siblings (r = 0.78 and 0.67 versus 0.20 and 0.23) which indexes the twin-specific shared environment. The total estimate of the shared environmental effects was 73%, the rest of the phenotypic variance accounted for non-shared environment (27%). Half of the shared environmental variance was twin-specific (34% of the total variance). The age had statistically significant effect in the twin-sibling model ($\beta = 1.36$, $p < 0.05$). Our results suggest that the large part of the shared environmental effects of the non-verbal intelligence is twin-specific. This matches the twin-sibling research on the child twins (Koeppen-Schomerus et al. 2003). We suggest that the twin-specific environmental effects observed in our study stem from the school environment. Unlike siblings, twins undergo the school program synchronically and often attend the same class. Therefore the twins share more environmental variation than siblings. As an additional analysis we computed the similarity in the two groups of full siblings divided by the median age difference 4 years. The siblings with closer age exhibited higher similarity in the level of cognitive ability than the siblings of dissimilar age (r = 0.44 and − 0.07).

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Linking human and animal addiction genetics—a role for human genetic association studies

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The historical direction of cross-species genetic translation has been from model organism to human. Biological mechanisms with clear genetic influence on a behavioral phenotype are discovered and validated in mice, for example, but that same gene in humans typically does not harbor variation of relevance to the behavior in humans. On the other hand, the vast majority of genetic variants associated with behavioral traits in humans often have no obvious functional relationship to the behavior in question. I will describe a program of research on the human side, where through a community effort we have discovered hundreds of genetic loci associated with alcohol and nicotine use in humans and are now attempting to use deep whole genome sequencing to fine map these loci to discover rare variants with potentially large effect. However, no matter how large the genetic association study or how deep the sequencing, it remains extremely difficult to characterize the functional consequence and mechanism of action, of the associated variants, whether at the cellular, physiological, or behavioral level. I will recommend that one solution is greater collaboration with scientists investigating behavioral genetics in animal models. Substance use may represent an especially fertile testing ground for such collaborations, given the apparent phenotypic similarity between human and animal substance use and addiction.

Reconceptualizing psychopathology for genetic studies using hierarchical dimensional structural models: the example of externalizing and AVPR1a

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Recent trends in the psychopathology literature have reconceptualized psychopathology in terms of transdiagnostic or hierarchical dimensional perspectives. Despite these trends, the modal phenotypes used in psychiatric genetic studies (e.g., in GWASs of psychiatric disorders conducted through the Psychiatric Genetics Consortium) are single, specific psychiatric diagnoses. In this paper, I explore different conceptualizations of a higher-order Externalizing symptom dimension, as well as different analytic methods used to characterize this dimension, in its association with the Arginine Vasopressin 1a receptor gene (*AVPR1a*). I contrasted different models for characterizing the Externalizing symptom dimension with each other, as well as with models of its constituent diagnoses and symptom dimensions. In phenotypic analyses, data were available on parent ratings of DSM-IV symptoms of attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) from $\sim$ 2800 children whereas in genetic analyses data were available from $\sim$ 600 children, all aged 6–16 years old. In analyses of genetic association six SNPs in *AVPR1a* were used to characterize the gene in a series of gene-based tests. Comparisons of these phenotypic models used the percentage of variance explained and the relative fit of the alternative models to adjudicate among them. Results of these analyses highlight the benefits of construing psychopathology in terms of hierarchical dimensional models, as well as which conceptualizations and analytic methods are optimal.

Genome-wide meta-analysis of > 14,000 alcohol dependent individuals highlights psychiatric comorbidities

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Excessive alcohol use is a leading contributor to morbidity and mortality. Of those who drink alcohol, 12% meet criteria for alcohol dependence (AD), a serious psychiatric disorder characterized by tolerance, loss of control over drinking, and excessive consumption despite negative consequences. AD is heritable and previous studies have implicated functional variants in *ADH1B* [1, 2], but relatively little is known about the full polygenic architecture of AD. We performed genome-wide meta-analysis of 14,904 individuals with AD and 37,944 controls from 28 case/control and family-based studies, stratified by genetic ancestry (European, N = 46,568; African; N = 6280). AD cases were defined using DSM-IV criteria, primarily from structured interviews. Controls were screened for AD and alcohol abuse where possible. Strict quality control, imputation, and GWAS were performed for each cohort, with family-based studies analyzed using generalized estimating equations or logistic mixed models to control for family structure as appropriate. One locus, covering *ADH1B*, shows significant association with AD, with independent variants observed in European (rs1229984; p = 9.8E−13) and African ancestries (rs2066702; p = 2.2E−9), replicating previous findings [1] and providing the strongest evidence to date for rs2066702. A variety of trans-ethnic meta-analysis models yield nearly identical results. The different lead variants are consistent with differences in allele frequency between ancestries; both are functional missense variants in *ADH1B* that affect the efficiency of oxidizing ethanol. Conditional analysis, along with GTEx gene expression data, suggests that there may be additional independent effects in the locus similarly associated with *ADH1B* activity. We observe substantial genome-wide polygenicity in both African and European ancestry samples (European h^2_g = .09, p = 8.0E−7). There was no substantial heterogeneity within or between ancestry, by study design (case/control versus family-based), or across the full meta-analysis. Using polygenic scores, we evaluate the variance explained for AD diagnosis and symptom counts in external cohorts. Comparing the meta-analysis of AD in European ancestry samples to related traits identified significant genetic correlation with several psychiatric disorders, including depression (rg = .57, p = 3.0E−4), ADHD (rg = .44, p = 4.2E−6), and schizophrenia (rg = .36, p = 3.2E−11). We also observe noteworthy genetic correlations with use of cannabis (rg = .79, p = 2.5E−4) and cigarettes (rg = .71, p = 1.3E−7), as well as the age of having a first child (rg = − .63, p = 2.0E−9) and educational attainment (rg = −.42, p = 6.8E−9). We then evaluate whether these correlations are reflected by associations of AD with the transmission of polygenic risk within families. Notably, genetic correlations are meaningfully less than 1 with GWAS of alcohol consumption from UK Biobank [3] (rg = .37; p = 5.2E−5) and GWAS of the Alcohol Use Disorders Identification Test in 23andMe [4] (rg = .08, p = .65). This suggests genetics of AD does not solely reflect very high risk for alcohol consumption, but also involves other factors, such as loss of control over intake. Potential differences between the genetic etiology of AD and the genetics of alcohol consumption in the population will be an important focus for future research.

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Redefining phenotypes to advance psychiatric genetics: implications from hierarchical taxonomy of psychopathology

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Abstract: Genetic discovery in psychiatry is hindered by suboptimal phenotypic definitions, including diagnostic unreliability, comorbidity among disorders, and heterogeneity within them. The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium proposed a data-driven, dimensional classification system for a wide range of psychiatric disorders—based on a comprehensive review of existing nosologic and psychometric research—that addresses many shortcomings of traditional diagnoses[1,2]. The system promises to be a useful guide for psychiatric geneticists, who require valid and reliable phenotypes to maximize precision and statistical power in the search for genetic vulnerabilities to mental illness. Conversely, genetic findings are a crucial external validator of psychiatric nosology. The current presentation addresses both issues. First, I will present a review of how the HiTOP model dovetails with our existing understanding of the genetic architecture of psychopathology that emerged from a large body of family and twin studies. I will also discuss the convergence between the HiTOP model and findings from recent molecular genetic studies of psychopathology, such as cross-disorder SNP-based genetic correlations and polygenic risk scores, which inform genetic architecture and indicate broad genetic pleiotropy[3]. Second, I will discuss how the HiTOP model can inform future psychiatric genetic research by providing quantitative, hierarchically organized and easily implementable phenotypes. Specifically, genes are expected to operate at different levels of the HiTOP hierarchy, with some highly pleiotropic genes influencing higher-order psychopathology (e.g. the general factor[4,5]), whereas other genes confer specific risk for individual spectra (e.g. internalizing), subfactors (e.g. fear disorders), or narrow symptoms (e.g. mood instability). I will highlight molecular genetic studies that have successfully redefined phenotypes to enhance precision and statistical power. Finally, I will suggest how to integrate the HiTOP approach into future molecular genetic research, including quantitative and hierarchical assessment tools for future data-collection, and tips for phenotypic analyses. *Keywords*: behavior genetics, comorbidity, general factor, molecular genetics, pleiotropy, taxonomy.

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The interface between personality and psychopathology among youth: a multivariate behavior genetic investigation

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Although numerous models explaining the interface between personality and psychopathology have been put forth in the literature, one prominent model posits shared etiological mechanisms between personality and psychopathology (see Krueger and Tackett, 2003, for a review). It is now relatively well-demonstrated that neuroticism (or negative emotionality) in particular shows robust phenotypic and genotypic relations with internalizing and externalizing psychopathology, as well as a general psychopathology factor (e.g., Tackett et al. 2013). At the same time, the extent to which other personality traits, such as extraversion, agreeableness, and conscientiousness, map onto the structure of psychopathology phenotypically and genotypically has received less attention. Similarly, our knowledge regarding the extent to which early forms of personality and psychopathology share common etiological mechanisms is limited. We analyzed data from a representative twin sample (N = 507) of youth aged 6 to 16 (51% female) to make inroads into these questions. Extending previous research using this sample, which supported a five-factor model of personality in youth (Watts, Poore, Lilienfeld, & Waldman, 2017). we will first present analyses examining the extent to which five-factor model personality traits are associated with higher-order dimensions of psychopathology. We will then present multivariate behavior genetic analyses that examine the shared etiological influences between these same five-factor model personality traits and higher-order psychopathology dimensions, which we will test using both independent and common pathway models. Taken together, our findings may bear important implications for reconceptualizing the linkages between personality and psychopathology.

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Results from the largest genetic study of sexual orientation

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Homosexual behavior in humans is genetically influenced (Långström et al. 2010), yet solid evidence about the genetic determinants of sexual orientation is lacking. In this study, we report current results from the largest genetic study of sexual orientation to date by focusing on two main phenotypes: non-heterosexual behavior (NHB), defined as having had at least one same-sex partner (N = 28,486 cases and 469,427 controls) and number of sexual partners (NSP) in heterosexual individuals (N = 362,993). Data in this study are meta-analyzed and come from the UK Biobank and 23andMe. We identify four and 41 loci significantly ($P < 5 \times 10^{-8}$) associated with NHB and NSP, respectively. Interestingly, twelve loci were sex-differentiated, and the genetic correlation between males and females was significantly less than one ($r_g = 0.67$, $P = 4 \times 10^{-14}$ for NHB). By studying the association between significant loci and more than 2500 GWAS results we highlight pleiotropic effects with smoking behavior and hormone-related phenotypes like balding. Genetic correlations indicate a shared genetic component between NHB and risk-taking ($P = 5.1 \times 10^{-9}$) and substance use (e.g., cannabis use, $P = 3.6 \times 10^{-6}$). Using polygenic scoring analyses, we replicate our results in an external study of adolescents, the National Longitudinal Study of Adolescent to Adult Health (Add Health), and in an external sample of homosexual and heterosexual men, the Molecular Genetic Study of Sexual Orientation (MGSOSO). Overall, our results provide the first well-powered genetic insights into this complex, heritable behavioral phenotype.

Gene–environment interplay and music ability

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Although genes (G) and the environment (E) have both been shown to be important for individual differences in expertise related traits, e.g. music achievement, still little is known about the GE interaction

underlying expertise. Here we explored whether musical enrichment of the childhood environment moderates individual differences in music achievement in adulthood. Particularly, we tested whether a musically enriched environment reduces genetic influences on music achievement, as has commonly been proposed. Music achievement was measured in 5260 Swedish twin pairs using the Creative Achievement Questionnaire. As an indicator of musical enrichment a principal component was derived based on: the number of records in the family home, individuals in the environment playing an instrument, visited concerts, and music education before the age of 12. Moderation of the childhood musical environment on the mean level of music achievement and on the underlying genetic and environmental influences was evaluated. We also tested for sex differences. Results showed a positive association between musical enrichment of the childhood environment and music achievement in adulthood. Further, total variance in music achievement increased as a function of musical enrichment, which was explained by a relative increase in genetic influences on music achievement. Estimates of genetic and environmental influences as well as the magnitude of the moderation of the musically enriched environment on these estimates differed for males and females. These findings suggest that contrary to past believes, a musically enriched childhood environment amplifies differences in music achievement, which is largely driven by an increase in genetic factors.

The relationship between callous-unemotional behaviors and social fear: a cross-lagged analysis

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The Relationship Between Callous-Unemotional Behaviors and Social Fear: A Cross-Lagged Analysis Dorothy A. White, Megan Flom, Julia Mancini, Jody M. Ganiban, Kimberly J. Saudino Callous-unemotional behaviors (CU) (e.g., low empathy and callous treatment of others) are an early risk factor for severe conduct problems. The temperament characteristic "social fear" may protect children from developing CU behaviors by rendering children more aware of social cues and inhibiting behavior during unfamiliar social situations. To date, few studies have examined the associations between CU and social fear (SF) in toddlerhood. The current study examined their association by using a cross-lagged twin design to examine the stability, change, and reciprocal influences of these constructs from ages 2 to 3 years, and the extent to which genetic and environmental factors contribute to observed associations. Participants included 314 same-sex twin pairs from the Boston University Twin Project (N_{MZ} = 144, N_{DZ} = 168) assessed at ages 2 and 3. CU was assessed via an empirically validated five-item subset of the Child Behavior Checklist Ages 1½–5 (parent report). SF was assessed via the Social Fear subscale of the Toddler Behavior Assessment Questionnaire (parent report), a measure of child temperament. CU showed moderate genetic influences at ages 2 (A^2 = .54) and 3 (A^2 = .31). Shared and nonshared environmental influences were observed at ages 2 (C^2 = .17; E^2 = .29) and nonshared at age 3 (C^2 = .09; E^2 = .41). SF showed shared and nonshared environmental influences at ages 2 (C^2 = .24; E^2 = .24) and 3 (C^2 = .07; E^2 = .31). Genetic influences on SF were significant at age 2 (A^2 = .52) and at 3 (A^2 = .35). The phenotypic associations between CU and SF at ages 2 and 3 were respectively R = .47 and R = .22. This relationship was explained by genetic and environmental factors. SF and CU were correlated across age (SF R = .55, CU R = .49). Both SF and CU were moderately stable over time (β_{CU} = .43, β_{SF} = .52). SF at age 2 significantly predicted CU at age 3 (β_{21} = − .13), and this association was primarily driven by genetic factors. CU did not predict SF over time. These findings suggest higher social fear predicts less callous-unemotional behaviors over time, and that a common set of genes explain this relationship. It is possible that higher social fear makes some toddlers more aware of social cues and, perhaps, more sensitive to social consequences of CU behaviors. Genetic influences may be driving this relationship. This finding shows promise for early intervention in CU.

Out of control: the association between family conflict and low self-control in adolescence

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Low self-control in adolescence is predictive of psychological and physiological problems across the lifespan (Moffitt 2011, *Proceedings of the National Academy of Sciences*. 108(7), 2693–2698). The aim of the present research was to investigate the relation between family conflict and low self-control in adolescence with a genetically sensitive design (> 9000 Dutch twins, aged 14). Applying the direction of causation model (Duffy and Martin, 1994, *Genetic Epidemiology*. 11(6), 483–502), we compared models examining several possible explanations for their association including reciprocal causation, unidirectional causation from family conflict to low self-control, unidirectional causation from low self-control to family conflict, and common genetic susceptibility. Considering the robust phenotypic correlation between family conflict and low self-control, the higher heritability of self-control (50% − 60%, Willems, 2018, *Behavior Genetics*, 48(2), 135–146) as compared to family conflict (30%–40%, van der Aa et al. 2010, *Twin Research and Human Genetics*, 13(2), 143–162.), and the application of measurement models, we are confident for the model to work well. Comparing competing models through AIC weights (Wagenmakers and Farrell 2004, *Psychonomic bulletin & review*. 11(1), 192–196), our results suggest that an unidirectional causal pathway model where family conflict leads to low self-control in adolescence, with genetic factors also playing a role in explaining the association, fits the data best. This finding implies that adolescents experiencing family conflict are at risk to show hampered self-control capacities, with family conflict being a robust predictor of low self-control through common genetic factors but also through direct causal influences.

Free will, determinism, and intuitive judgments about the heritability of behavior

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The fact that genes and environment contribute differentially to variation in human behaviors, traits and attitudes is central to the field of behavior genetics. To the public, perceptions about these differential contributions may affect ideas about human agency. Intriguingly, the relationship between our intuitions about free will and knowledge about the heritability of human traits has remained largely unstudied. For example, a deterministic universe would have

the same logical implications for free will regardless of whether genes or environment are more responsible for determining our behavior. And yet it seems plausible that people might have different intuitions about how these types of causal factors are related to the concept of free will. This suggests that a behavioral genetic approach is uniquely equipped to answer an important question in this vein: How do attitudes about free will and determinism relate to what people believe about the genetic and environmental contributions to behavior? We surveyed two independent samples (N = 301 and N = 740) to assess beliefs about free will and determinism (Paulhus and Carey 2011; Nadelhoffer 2014), as well as political orientation, religiosity, and the relative contribution of genes and environment to 21 human traits (Carver et al. 2017). We find that beliefs about the heritability of these traits cluster into four distinct groups, loosely defined as physical, psychiatric, psychological and lifestyle traits, which differentially predict both beliefs about human agency and political orientation. Despite apparent ideological influences on these beliefs, the correspondence between lay judgments of heritabilities and published estimates is large ($R = .77$). Belief in genetic determinism emerges as a modest significant predictor of accuracy in these judgments. Additionally, level of education, gender, and number of children all positively predict accuracy, with educated mothers of multiple children emerging as particularly accurate in their judgments of the heritabilities of these traits.

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Early cannabis use and young adult sleep duration: a biometrically informed design

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Early cannabis use is linked to cognitive and neuroanatomical outcomes and has become a focus of developmental substance use research. Sleep is an important factor across development that plays a crucial role in the regulation of emotions, attention, and numerous other outcomes. Sleep disturbances and substance use may be related through several different mechanisms, but this relationship has rarely been investigated using a genetically informed design. In this study we tested the hypothesis that age of first regular cannabis use is associated with adult sleep duration, and disentangled the genetic and/or environmental influences underlying this relationship in a sample of young adult twins (n = 1656). Phenotypically we found that early regular cannabis use was associated with decreased adult sleep duration for both weekdays ($\beta = .16$, $p = 0.000916$) and weekends ($\beta = .19$, $p = 0.0000688$) controlling for gender, current cannabis use, current alcohol use, and depression. We extended these analyses by performing univariate twin modeling which suggested additive genetic contributions for age of first regular use ($a^2 = 51\%$, $p = .0004$) and adult weekend sleep duration ($a^2 = 20\%$, 0.04044). Furthermore, we fit bivariate Cholesky decomposition models to dissect the nature of the association between age of first regular cannabis use and adult sleep duration and found a significant additive genetic overlap between age of first regular cannabis use and weekend sleep ($a = .14$, $p = 0.0020$). Lastly, our best fitting model was a directional causal model which yielded a significant path between early cannabis initiation and adult sleep duration on the weekends ($\beta = .11$, $p = 0.0006$). Results from these analyses are consistent with a casual model and provide evidence for a novel association between early regular cannabis use and adult sleep duration. These combined results lead us to propose a model where additive genetics play a significant role in the initiation of early cannabis use which in turn affects sleep duration in later life. Findings may have important implications for early substance use and developmental research.

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Discovering rare variants associated with substance use in 65,000 deep whole genome sequences in the Trans-Omics for Precision Medicine (TOPMed) Program

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Smoking is a moderately heritable behavior that is one of the leading preventable causes of death in the United States. Genome wide association studies have discovered hundreds of common variants associated with tobacco use in individuals of European ancestry, but similar associations have not been studied in non-European populations. Low frequency variants are expected to affect smoking risk, but any such rare variants are yet to be identified, likely due in part to low statistical power of existing studies.

As a part of the Trans-Omics for Precision Medicine Whole Genome Sequencing Program (TOPMed), we seek to identify novel associations between rare variants and four measures of smoking behavior in a multi-ethnic sample. Two of these phenotypes relate to the initiation of smoking, capturing whether an individual has ever smoked regularly in their life and the age at which they began smoking regularly. We also measured smoking cessation through a comparison of current and former smokers. Finally, the heaviness of tobacco use among smokers is measured with the number of cigarettes smoked per day. At the time of writing, the TOPMed project has called genotypes from 65,000 individuals with $\times$ 30 whole genome sequences. A subset of 45,000 individuals from this data freeze have one or more smoking phenotypes. We will present results for all four of our smoking phenotypes, including single variant tests on up to 582,000,000 variants and gene based tests on rare nonsynonymous and loss of function variants. To date, we have conducted single variant association tests for cigarettes smoked per day with 154,176,919 variants with minor allele count $>$ 10 using whole genome sequences from 10,444 individuals. This preliminary meta-

analysis showed no significant associations between any variants and cigarettes smoked per day, suggesting that additional samples will be required to make discoveries for this and other complex substance use phenotypes. We will present updated results from single variant tests and gene based tests on much larger samples, up to the full sample of 45,000 with one or more smoking phenotypes. Our power to detect effects will increase as the remainder of our sample is analyzed and as the data available to us through TOPMed continues to grow with the release of new data freezes.

Assortative mating and intergenerational transmission of ADHD

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ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning. Previous twin and family studies have shown moderate estimates of heritability for adult ADHD and high estimates of heritability of child ADHD. However, there is to date comparatively little knowledge on to what extent assortative mating on adult ADHD traits could change the genetic variation in the offspring generation. By using the Intergenerational Transmission of Risk (IToR) study, a twin-family subsample of the Norwegian Mother and Child Cohort study, we will estimate the extent of assortative mating in adult ADHD. What is more, we will estimate the impact of assortative mating on, one, the heritability of adult ADHD, two, the heritability of child ADHD, and, three, the genetic transmission of adult ADHD to child ADHD. To estimate such parameters, we will apply an extended children of twin model on the IToR dataset comprising a large number of sibling/twinfamilies. If there is a strong assortative mating on adult ADHD, this could alter the prevalence and heritability in the offspring generation. What is more, the results will inform on the biological underpinnings of the similar phenomena of adult and child ADHD.

Genetics of ADHD dimensions. Genome-wide association analyses of inattention and hyperactivity/impulsivity

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Attention deficit hyperactivity disorder (ADHD) is a common and highly heritable childhood onset psychiatric condition, presenting multidimensional clinical picture, with two main symptom dimensions being inattention and/or hyperactivity/impulsivity. As ADHD persists into adulthood (in up to $\sim$ 80% of the cases), hyperactive-impulsive symptoms tend to decline, whereas inattentive symptoms are more stable. Furthermore, the various combinations of symptom dimensions are associated with different clinical features (e.g. co-morbidities) and treatment outcomes of ADHD. So far, the biology underlying symptomatology of ADHD is far from understood. In this study, we aim at genome-wide exploration of genetics of ADHD dimensions and their genetic correlation with a variety of common phenotypes, reflecting ADHD co-morbidities and quality of life. We are performing genome-wide meta-analyses on a sample of 37,771 children. The ADHD dimensions are measured by calculating a score summarizing child's hyperactive and inattentive behaviours based on established questionnaires (SWAN, SNAP, A-TAC, DAWBA and Conners' Rating Scale). Each score from each measurement tool was first analysed individually, followed by fixed effect meta-analyses to combine the resulting data. The genetic correlations and heritability were estimated using LD score regression. Our preliminary results indicate that both hyperactivity and inattention have small heritability attributable to common variants (h2 = 0.054 [SE = 0.023] for inattention and h2 = 0.083 [SE = 0.022] for hyperactivity). Nonetheless, genetically, these dimensions reveal high correlation with ADHD diagnosis (r2 = 0.89 [SE = 0.12, p = 1.46E−13] between ADHD diagnosis and hyperactivity; r2 = 0.93 [SE = 0.18, p = 3.50E−07] between ADHD diagnosis and inattention). The genetic correlation between inattention and hyperactivity is estimated to be 0.55 (SE = 0.15, p = 0.0003). Evaluation of genetic correlations between the two examined ADHD dimensions and common neuropsychiatric disorders, autoimmune disorders, measures of cognition and anthropometric measures reveals that, on average, inattention shows higher correlation than hyperactivity. The individual genome-wide meta-analyses of each dimension did not reveal a genome-wide significant association in our preliminary analyses of 24,770 children (we will present the results from the full sample of 37,771 children). The exploration of how ADHD dimensions in childhood relate/lead to ADHD diagnosis and common ADHD co-morbidities/co-occurring phenotypes will aid our understanding of biological processes behind ADHD symptomatology and, potentially, lead to better diagnosis, treatment and prevention options for this disorder.

Measurement invariance and predictive validity of behavioral disinhibition in two twin samples

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Objective: Behavioral disinhibition is a highly heritable premorbid risk factor for drug use, including marijuana. We sought to model behavioral disinhibition as a latent factor and examine its heritability, factor structure, and predictive validity. It is unknown how behavioral disinhibition may be related to marijuana use trajectory. We sought to address this question using two longitudinal genetically informative samples.
Methods: We evaluated the factor structure and biometric variance decomposition of ADHD, Alcohol Dependence, and Conduct Disorder symptom counts in adolescence in two independent twin samples, one from Colorado (N = 2333) and one from Minnesota (N = 3630), with highly similar birth years and assessment waves. Next, we evaluated the relationship between adolescent behavioral disinhibition and marijuana use frequency in early adulthood (mean age = 26.2, SD = 2.5). Finally, we will evaluate marijuana use trajectories across adolescence and young adulthood and their relationship with behavioral disinhibition. To evaluate trajectories, we will run a growth model in which the observed variables will be marijuana use frequency. We will fix the factor loadings for the intercept and we will use a definition variable (participant age) as the factor loadings for the slope. We will evaluate differences in slope and intercept between states and we will examine the correlation between adolescent behavioral disinhibition and slope and intercept in each state.
Results: A single factor model fit the adolescent symptom counts well, under strong measurement invariance (χ^2 = 5.11, df = 6, p = .53). Adolescent behavioral disinhibition was associated with young adult marijuana use frequency to the same extent in both states (CO r = .31, 95% CI [.24, .38], MN r =.36, 95% CI [.30, .42], χ^2 = 2.10, df = 4, p =.71; Constrained Model AIC = − 9553.7, Base Model AIC = − 9547.8; Constrained Model BIC = − 129,950.7, Base Model BIC = − 129,920.8). Analyses evaluating marijuana use trajectories are underway.
Conclusions: The factor structure of behavioral disinhibition was highly similar between these two independently conducted studies. The large samples sizes mean that these analyses were well powered to detect differences in the latent factor and its predictive ability. The lack of significant differences between states means that behavioral disinhibition is a robust and replicable factor. The heritability of behavioral disinhibition and factor loadings for all observed variables are the same in each state. Adolescent behavioral disinhibition was positively associated with later marijuana use to the same degree in each cohort. Because adolescent behavioral disinhibition is the same in both states, future analyses can utilize this factor in predicting other adult outcomes associated with externalizing behaviors. Iacono, Malone, and McGue (2008) proposed that a common genetic vulnerability to behavioral disinhibition underlies the co-occurrence of substance use disorders and externalizing psychopathology. Our replication of this factor across states supports this and sets the stage for further research on specific factors to drug use development and expression of this underlying vulnerability over time.

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Signatures of negative selection in the genetic architecture of human complex traits

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Methods such as LD-score regression and GREML typically assume a fixed relationship between allele frequency and effect size of single-nucleotide polymorphisms (SNPs), whereby rarer variants have larger effects than common variants, to exactly such an extent that each causal variant contributes by the same amount to phenotypic variance, regardless of allele frequency. However, the strength of the relation between allele frequency and effect size may differ across traits. Estimates of this relationship give us a clue about the effect selection has had on the frequency of trait-affecting variants. Therefore, such estimates may yield new insight into the genetic architecture of complex human traits, and can help to guide future GWAS efforts. To enable estimation of this relationship, we provide a Bayesian linear mixed model. This model allows us to simultaneously estimate SNP heritability and polygenicity (i.e. the proportion of SNPs with non-zero effects) as well as the strength of the relationship between effect size and allele frequency, for complex human traits. This method uses genome-wide SNP data on unrelated individuals. An application to data from the UK Biobank on 28 complex traits shows that, on average, 6% of the SNPs have non-zero effects. On average, these SNPs in total explain 22% of the phenotypic variance. For 23 traits, we find significant signatures of natural selection in the genetic architecture. Amongst others, these traits include reproductive and anthropometric traits, as well as biologically more distal outcomes such as educational attainment. As we illustrate using forward simulations, these estimates are compatible with negative selection, where deleterious variants are kept at low frequencies. We, therefore, conclude that negative selection has acted across the genome, affecting the allele frequencies of variants associated with a wide range of complex human traits.

Genetic and environmental influences on achievement goals shift with age

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As students move through the educational system, endorsement of achievement motivation tends to decline, which could have socioeconomic ramifications. In particular, students' achievement goal orientation (AGO), including motivation to learn for the sake of learning (i.e., mastery goal orientation), to learn for the sake of demonstrating proficiency to others (i.e., performance approach goal orientation), and to prevent showing incompetence on tasks (i.e., performance avoidance goal orientation), predicts academic outcomes. Concerningly, both mastery goal orientation and performance approach goal orientation decline substantially as students mature. Little is known concerning whether these mean-level trends are coupled with shifts in the genetic and environmental influences on motivation. It is possible that students are differentially sensitive to their genetically influenced psychological characteristics or aspects of

their environment during the early school years compared to later. Using a cross-sectional, diverse population-based sample of twin pairs (N = 734 pairs, ages approximately 8–18 years), we estimated age-trends in genetic and environmental influences on the above three domains of AGO. We replicate mean-level decreases in mean-levels of AGO. Turning toward variance, we find fairly similar levels of genetic and environmental influences on performance orientations across the age range. In contrast, genetic influences on mastery goal orientation are minimal at early ages, increase substantially through 11th grade, and then decrease fairly quickly over the final year of formal education. The peak in genetic variance during 11th grade corresponds to a period that is known for heightened pressure to graduate and prepare for the post-high school (e.g., college) transition. We track this trend in relation to child personality, cognitive ability, and inputs from peers, parents, and teachers. Our results demonstrate the developmental complexity of child academic motivation.