Genetic Overlap Profiles of Cognitive Ability in Psychotic and Affective Illnesses:

Genetic Overlap Profiles of Cognitive Ability in Psychotic and Affective Illnesses: A Multi-Site Study of Multiplex Pedigrees

Emma E. M. Knowles PhD[1,2*], Juan M. Peralta PhD[3], Laura Almasy PhD[4], Vishwajit Nimgaonkar MD PhD[5], Francis J. McMahon MD[6], Andrew M. McIntosh MD[7], Pippa Thomson PhD[8], Samuel R. Mathias PhD[1,2], Ruben C. Gur PhD[9], Joanne E. Curran PhD[3], Henriette Raventós MD[10,11], Javier Contreras MD[10], Assen Jablensky MD[12], Johanna Badcock PhD[13], John Blangero PhD[3], Raquel E. Gur MD[9], David C. Glahn PhD[1,2,14]

[1]Department of Psychiatry, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
[2]Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA.
[3]South Texas Diabetes and Obesity Institute and Department of Human Genetics, University of Texas Rio Grande Valley School of Medicine, Brownsville, TX, USA.
[4] Department of Genetics at University of Pennsylvania and Department of Biomedical and Health Informatics and Lifespan Brain Institute, Department of Child and Adolescent Psychiatry and Behavioral Sciences at Children's Hospital of Philadelphia, PA, USA.
[5]Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Hospital, Pittsburgh, PA, USA; Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA.
[6]Human Genetics Branch, NIMH Intramural Research Program, NIH, DHHS, Bethesda, MD, USA
[7]Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK; Centre for Cognitive Ageing and Cognitive Epidemiology, School of Philosophy, Psychology and Language Sciences, University of Edinburgh, Edinburgh, UK.
[8]Centre for Genomic and Experimental Medicine, Institute for Genetic and Genomic Medicine, University of Edinburgh, Edinburgh, UK.
[9]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
[10]Centro de Investigación en Biología Celular y Molecular y Escuela de Biologia, Universidad de Costa Rica, San Jose, Costa Rica.
[11]Escuela de Biología, Universidad de Costa Rica, San José, Costa Rica.
[12]Centre for Clinical Research in Neuropsychiatry, Division of Psychiatry, Medical School, The University of Western Australia, Perth, Western Australia, Australia.
[13]Perth Voices Clinic, Murdoch, Western Australia, Australia; School of Psychological Science, University of Western Australia, Perth, Western Australia, Australia.
[14]Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital, Hartford, CT, USA.

*Correspondence to Emma E. M. Knowles, Department of Psychiatry, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA. E-mail: emma.knowles@childrens.harvard.edu

Short title: Cognitive Genetic Correlation Profiles in Psychiatric Illness

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Abstract

Background

Cognitive impairment is a key feature of psychiatric illness, making cognition an important tool for exploring of the genetics of illness risk. It remains unclear which measures should be prioritized in pleiotropy-guided research. Here, we generate profiles of genetic overlap between psychotic and affective disorders and cognitive measures in Caucasian and Hispanic groups.

Methods

Data were from four samples of extended pedigrees (N = 3046). Coefficient of relationship analyses were used to estimate genetic overlap between illness risk and cognitive ability. Results were meta-analyzed.

Findings

Psychosis was characterized by cognitive impairments on all measures with a generalized profile of genetic overlap. General cognitive ability shared greatest genetic overlap with psychosis risk (average Endophenotype Ranking Value (*ERV*) across samples from a random-effects meta-analysis = 0.32) followed by Verbal Memory (*ERV* = 0.24), Executive Function (*ERV* = 0.22), and Working Memory (*ERV* = 0.21). For bipolar disorder, there was genetic overlap with Processing Speed (*ERV* = 0.05) and Verbal Memory (*ERV* = 0.11), but these were confined to select samples. Major depression was characterized by enhanced Working and Face Memory performance, as reflected in significant genetic overlap in two samples.

Interpretation

There is substantial genetic overlap between risk for psychosis and a range of cognitive abilities (including general intelligence). Most of these effects are largely stable across of ascertainment strategy and ethnicity. Genetic overlap between affective disorders and cognition, on the other hand, tend to be specific to ascertainment strategy, ethnicity, and cognitive test battery.

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Introduction

Genomic variation substantially impacts risk for developing psychiatric illnesses, with heritability (h^2) estimates in the range of 0.4–0.8 (1). Recently, large-scale consortia have made tremendous strides to assemble large case-control samples (2). However, most of the genetic architecture of psychiatric disorders remains unclear (3). A complementary approach, which may provide additional insight, is to identify behaviors that overlap genetically with risk for psychiatric illness, which may also provide a rubric for prioritization of measures to be included in future research.

Cognitive abilities, which are heritable, have been frequently investigated in terms of their genetic overlap with psychiatric illness (4). However, important questions remain unanswered regarding these relationships. First, why do estimates of genetic overlap between cognitive abilities and psychiatric illness vary so considerably between studies? Prior research on this topic has mostly been conducted using family studies—either classic twin designs or extended pedigree designs—or by leveraging single-nucleotide polymorphism (SNP) data in unrelated individuals. Genetic correlations estimated via twin designs tend to be high (5), leading some to argue that they may be overestimates (6). SNP-based methods were introduced partly due to the perceived drawbacks of twin designs and to squeeze more signal from genome-wide association (GWA) data (7). However, important limitations of the SNP-based approach are that SNPs do not capture the full range of genetic variation (3) and that most approaches do not adequately account for linkage disequilibrium and variation in allele frequency (8). Pedigree designs may be well placed to provide a definitive answer to the degree of genetic overlap between risk for psychiatric illness and cognitive ability because (1) there is less confounding of genetic and shared environmental effects in pedigree than twin designs; (2) pedigree designs do not rely on population-level information regarding LD and allele frequency; and (3) pedigree designs are robust to population stratification (9).

A second question pertains to the use of broad composite measures of cognitive ability rather than specific domains or measures. General cognitive ability, or *g,* is a robust phenotype (10-12). However, *g is* a distillate of what is common across cognitive tests and is insensitive to specific sources of cognitive impairment. This is unlikely to be a problem for studies of psychotic disorders, which are associated with general cognitive impairments (13), but may be problematic for studies of affective disorders, since their cognitive profile is characterized by selective impairments (14). Selection of correct cognitive phenotypes is critical for the detection and interpretation of genetic overlap between psychiatric illnesses and cognition.

A third issue is that prior research efforts are heavily skewed toward psychosis. This is partly because cognitive impairment is considered a core feature of psychosis (13). While impairments are observed for major depression (MD) (15) and bipolar disorder (16), they are less severe. Moreover, gene discovery for affective disorders has lagged behind psychosis. Genome-wide significant hits have recently emerged in large samples for affective disorders, the phenotypic specificity in such large samples tends to be low (17). Extended designs cannot compete with GWA consortia in terms of sample size; however, it is likely that carefully conducted and ascertained pedigree studies will have more reliable and detailed phenotypes.

In the present study, we meta-analyzed four large extended pedigree samples (total N = 3046) to examine the genetic overlap between risk for psychiatric illness and cognitive ability. We generated profiles of genetic overlap, which provide rapid and clear understanding of the

direction and magnitude of pleiotropy between multiple cognitive domains and psychiatric illnesses. The included samples span multiple disorders, international sites, ethnicities, and ascertainment strategies. Using this approach, we attempted to answer the following questions: (1) Are profiles of genetic overlap similar within disorders across sites (and by extension, ethnicities and ascertainment strategies)? (2) Are profiles similar across disorders within/across sites? (3) Are profiles for psychotic and affective disorders similarly generalized, or are there stronger overlaps for specific measures or domains in the latter? The answers provide guidance for future work aiming to more deeply phenotype cognition and psychiatric disorders.

Methods and Materials

Samples

Data comprised four samples (Costa Rican, Mexican American, Pennsylvanian and Western Australian; see *Supplemental Materials* and **Tables S1-4**) with cognitive and genotype data in healthy individuals and individuals with psychotic and affective disorders. Two were of Hispanic ancestry (Costa Rican and Mexican American) and two were European Caucasian (Pennsylvanian and Western Australian). These samples represent the subset of the Whole Genome Sequencing in Psychiatric Disorders (WGSPD) consortium (9) with cognitive data. The total sample size was 3046, including 191, 96, and 771 patients with psychosis, BP, and MD, respectively. Broad diagnostic categories were used in each instance (e.g. psychosis refers to any individual with a schizophrenia, schizoaffective, BP or MD with psychosis diagnosis, and BP refers to any individual with a BP I or BP II diagnosis without psychosis; **Tables S5/6**).

Cognitive Assessments

Cognitive tests varied across samples, but the breadth of assessments permitted evaluation of genetic overlap between measures spanning multiple cognitive domains, plus *g* (see *Supplemental Materials*), with risk for psychiatric illness (**Table S7**).

Phenotypic Effect of Diagnosis on Cognition

Group differences for each diagnosis were calculated for all cognitive measures in each site using standardized mean differences (SMDs) and the absolute values were meta-analyzed using the rma function from the metaphor (18) package in R (19).

Heritability Analysis

Univariate variance components analyses of cognitive measures (including *g*) were performed in SOLAR using genomic relatedness matrices that were empirically estimated (see *Supplemental Materials*) (20). Age, age^2, sex and their interactions were included as covariates.

Coefficient-of-Relatedness Analysis

In samples ascertained for a particular illness it is usually necessary to apply a correction to avoid biasing estimation of h^2. This was not necessary here because we did not explicitly model h^2 of illness risk but instead estimated h^2 of each cognitive measure and included a coefficient of relatedness (CoR) as a covariate. CoR analysis leverages the many coefficients of relationship that exist between individuals in extended pedigrees to explore the genetic relationship between a phenotype and a disease when the disease is not sufficiently common in the sample to estimate its heritability (see *Supplemental Materials*). Here, CoR analysis was applied using cognitive measures as phenotypes and psychosis, BP, and MD as diseases. Age, age^2, sex and their interactions were included as covariates. False discovery rate (FDR) was set at 5% (21).

Profiles of Genetic Overlap

The regression coefficient corresponding to the CoR, denoted by β, can be converted to a mean-based endophenotype ranking value (*ERV*). *ERV* is an index of genetic overlap that varies between 0 and 1, higher values indicate that the endophenotype and the illness have greater genetic overlap (22). First, we graphed β estimates from the above analyses, grouping by disorder across samples. Second, we converted βs to ERVs and pooled them using the metacor function from the meta package in R (23) (see *Supplemental Material*). Finally, we ranked cognitive measures by ERV within site.

Results

Sample Description

Demographics, clinical characteristics, and numbers of kinship pairings (>0.01) available for each diagnosis, are summarized in **Tables S5** and **S6**. Across all samples, mean age = 42.57 years (sd = 16.43) and 54.17% were female.

Phenotypic Effect of Diagnosis on Cognition

Effect sizes for differences in performance on cognitive measures between cases and controls are shown in **Tables S8-10**, which are ordered by ERV.

For psychosis (**Table S8**), cognitive impairments were wide ranging (range of absolute Standardized Mean Difference (SMD) = 0.15-1.20). *g* was ranked in the top-three for all sites, and top in the Pennsylvanian and Western Australian sites. In the Mexican American and Costa Rican samples, the greatest difference for psychosis were the Verbal Memory measure CVLT and Executive Function measure PCET respectively. Meta-analysis of these effects (**Figure S1**) for psychosis indicated that the largest difference observed across sites was for *g* (SMD = 1.02) with consistent effects observable for all measures with the exception of Executive Function, which was subject to heterogeneity.

For BP (**Table S9**) and MD (**Table S10**), a handful of cognitive impairments and improvements were observed (**Figures S2** and **S3** show meta-analyses). For BP, the range of absolute SMDs = 0-1.18. In the Pennsylvanian and Costa Rican samples, the greatest impairments for BP were for the Verbal Memory measure the CVLT. The following improvements were observed for BP cases: Digit Span Backward in the Mexican American sample; Digit Span Forward in the Costa Rican sample; and Emotion Recognition in the Pennsylvanian sample. The phenotypic results for psychosis and BP, in particular in the Western Australian sample, should be interpreted with the caveat that they are based on a small number of cases. These results have been included for the sake of completeness and consistency across disorders.

For MD, small to moderate impairments were observed in most samples (range of absolute SMD = 0.10-0.62). In the Mexican American sample, the largest impairment was for the Digit Span Forward. In the Costa Rican sample, the largest difference was for Facial Memory, where cases outperformed controls. In the Pennsylvanian and Western Australian samples, MD cases exhibited higher scores than controls on all tasks. For the Pennsylvanian sample, the greatest difference was on Facial Memory followed by *g*. For the Western Australian sample, the greatest difference was for Verbal Memory followed by *g* (see *Supplemental Materials* for meta-analyses).

Heritability of Cognitive Measures

Heritability estimates for all tests were small to moderate (**Figure S4**). Tests that were measured across different sites tended to demonstrate similar strength of heritability estimate, suggesting that h^2 is similar across ethnicities and ascertainment.

Coefficient of Relatedness Analysis: Generating Profiles of Genetic Overlap

Significant genetic overlaps, indexed by the *ERV*, were observed between most cognitive abilities and psychosis risk across sites (**Figure 1**). Measures were ranked by *ERV* in each site (**Table S8**). In terms of similarities between sites (and, by extension, ethnicities and ascertainment strategies), the direction of ERV effects were the same irrespective of site, indicating that genetic liability was associated with worse performance on all measures. In all sites, *g* was ranked in the top three. A number of those measures that survived FDR correction (**Figure 2**) were present in at least two sites, including the: the Digit Span Forward; Executive Function measure the PCET; CVLT and RAVLT; Emotion Recognition; Attention measure the CPT. Thus, Verbal Memory and Working Memory ranked highly in samples of differing ethnicity and ascertainment strategies. **Table 1** shows the results of a meta-analysis of *ERV* estimates grouped by domain and ranked by magnitude of effect. The meta-analysis underscored that some domains demonstrated greater genetic overlap with psychosis risk than others (e.g. *g* and Verbal Memory). The *Q*-statistic, an index of heterogeneity of observed effects, is informative here, since a significant *Q*-value indicates that domains were affected differently in different sites. For example, Verbal Memory is ranked second but variation in effect size attributable to heterogeneity was high indicating that similar effects were not observed in all sites. Consistent effects (i.e. with minimal heterogeneity) were observed for *g*, Working Memory and Emotion Identification.

Compared to psychosis, neither risk for BP nor MD demonstrated the same wide-ranging profile genetic overlap with cognition but some specific associations were observed. For BP (**Table S9**; **Figure 3**) performance on the: Semantic Fluency task demonstrated genetic overlap in the Costa Rican and Mexican American samples; the Facial Memory Delayed task in the Costa Rican sample; and on Verbal Memory (CVLT/RAVLT) tasks in the Mexican American, Pennsylvanian and Western Australian samples. In most instances, increased genetic proximity to an individual with BP resulted in a decrement in performance. However, no genetic overlap between BP and any cognitive measure were significant after FDR correction (**Figure 4**).

Risk for MD (**Table S10**) demonstrated genetic overlap with multiple cognitive measures (**Figure 3**), a number of which withstood FDR correction (**Figure 5**), which were specific to particular samples. These included the Facial Memory measures in the Costa Rican and Pennsylvanian samples, where increased genetic proximity to MD improved performance. The same direction of relations was observed for *g* in the Pennsylvanian and Western Australian samples, Spatial Memory (SCAP), and Attention (CPT) in the Pennsylvanian sample, and Verbal Memory (RAVLT) in the Western Australian sample.

Effect of Sex on Genetic Overlap Between Depression and Cognition

At the suggestion of one of the reviewers we explored whether the genetic overlap observed between MD and cognition might vary by sex. We tested the significance of an interaction term between genetic risk for MD (indexed by the CoR utilized in previous analysis) and sex in the univariate polygenic model of each cognitive measure. This analysis was restricted to those measures with ERVs withstanding FDR correction (**Figure 5**). The supplemental material contains the results of these analysis (**Table S11**). Two of the measures, Facial Memory Delayed (β = -

0.65, p = 0.02) in the Costa Rican sample and Attention measure the CPT (β = -0.47, p = 0.04) in the Pennsylvanian sample, demonstrated nominally significant interactions between sex and genetic liability for MD indexed by a CoR, indicating that the relationship between genetic liability for MD and performance on these measures is somewhat stronger in men than in women.

Discussion

We report profiles of genetic overlap, indexed by the *ERV*, between cognitive ability spanning multiple domains and risk for psychiatric illness in four extended-pedigree datasets that span multiple ascertainment strategies, psychiatric illnesses, and ethnicities. This is a comprehensive study of the genetic link between cognition and risk for psychiatric illness in related individuals. Results provide insight at the epidemiological level (i.e. the phenotypic relationship) and are mechanistically informative (i.e. the genetic relationship). Not all findings are novel, however the present manuscript offers a holistic view, allowing a direct comparison of findings across research designs and ethnicities.

While GWA studies have identified numerous genomic loci that contribute to risk for psychotic and affective disorders (24) much of their genetic architectures remain unclear (3). Cognitive endophenotypes have the potential to provide increased understanding of the genetic determinants of the psychiatric illnesses (25, 26). In future research, prioritization of which cognitive measures to include is of utmost importance. Much is known regarding the phenotypic overlap between certain disorders and cognitive measures, however the following question remains unanswered: which measures are most likely to yield further genomic insight into psychiatric illness? This question is particularly important given that efficacious phenotyping is a practical requirement for the type of large-scale data collection necessary for gene identification (27). Despite the established importance of pleiotropy in improving understanding of disease pathogenesis, not to mention its potential for genetic risk profiling, few studies have systematically investigated the extent of pleiotropy between psychiatric disease risk and other complex traits, including cognition (28, 29). The present study attempts to provide a rubric for future studies by creating profiles of genetic overlap between psychotic and affective disorder risk and a wide range of cognitive measures.

In the present study univariate h^2 estimates of cognitive ability are in line with what has previously been reported in the literature. Generally, h^2estimates for *g* are moderate to high, varying between 40-.80 (30), in the present study estimates for *g* were between 0.46-0.67. In the literature the $h^2$of individual cognitive measures vary from low to high, depending on the measure in question, this is also what we observed in the present study (**Table 2**).

Our observed pattern of cognitive impairments in psychosis patients is consistent with previous research (13), with broad ranging decrements in performance across domains. In each site, increased genetic liability for psychosis was associated with lower cognitive performance. While the precise ordering of measures varied between samples, there were similarities, suggesting that some tests were more robustly associated with psychosis liability than others. *g* was in the top-three of measures ranked by degree of genetic overlap (as indexed by the *ERV*). Also, the genetic overlap for Verbal Memory (indexed via the CVLT and the RAVLT) and psychosis liability survived multiple-testing correction in three of the four samples. One of these samples (Costa Rican, of Hispanic ancestry) had a focus on BP in terms of ascertainment strategy, while the other two (Pennsylvanian and Western Australian, of European ancestry) primarily recruited schizophrenia patients. Other overlaps that replicated across sites included Working Memory

measures (Digit Span Forward, Digit Span Backward and Letter Number Sequencing) and the Executive Function measure PCET; similar to the effects observed for Verbal Memory, these effects were observed irrespective of ancestry and psychosis ascertainment.

While the genetic overlap between psychosis risk and cognitive ability is well established, the replication of genetic overlap between psychosis risk and specific cognitive tests across multiple samples of extended pedigrees is novel. Cognitive impairment is a particularly pernicious aspect of psychosis, contributing directly to the social isolation and functional impairments (13); unfortunately, there are no approved treatments for cognitive impairment in psychosis. Isolating the mechanisms by which cognitive impairment arises in psychosis will be important if treatments are to be identified. Our findings highlight that researchers wishing to utilize cognition as an enhancer of genetic signal for psychosis risk *g* is best. However, in a situation where brevity of assessment is key then a focus on some combination of Verbal and Working Memory and Executive Function is key. Pleiotropic discoveries such as this can help inform research that aims to identify shared biological pathways and prioritize probable causal relationships (31). It was surprising that Processing Speed measures (e.g. the Digit Symbol Substitution Task; DSST) did not demonstrate greater genetic overlap with psychosis risk. Numerous meta-analytic studies suggest that processing speed is the single largest cognitive impairment in schizophrenia (32). It is possible that, in the present sample, differences at the phenotypic level between cases and controls on processing-speed performance and psychosis risk were not influenced by the same genetic influences, but rather are influenced by shared environmental or state dependent factors. At the very least, the results of the present study suggest that measures of processing speed might not take precedence over other more highly ranked domains and/or measures in genetic-pleiotropy informed research in the future (33). Importantly, this is not to say that processing speed might not be informative from a clinical standpoint.

Differences in genetic overlap profiles between psychotic and affective disorders might be considered strange given than numerous studies point to overlap in the genetic loci that predispose risk for these disorders (34), the reasoning being that if the genetics of the disorders are similar then the ordering of genetic overlap between cognitive abilities should also be similar. However, differing profiles make sense. First, the genetic correlation between liabilities for psychotic and affective disorders is partial (1, 35), allowing for differences in genetic overlap profiles in cognition. Second, these disorders have a high degree of clinical overlap (36), and any genetic overlap might pertain to this rather than similarities in cognitive impairments per se. Third, specific SNPs that influence cognitive ability in both, for example, bipolar and psychosis, might still be expressed at the phenotypic level in a differing manner (37). Differential phenotypic expression might be tied to molecular mechanisms (e.g. epistasis of non-overlapping genetic influences) or the ways in which such alterations fit within the clinical picture.

An unexpected finding was that MD cases demonstrated elevated performance on some measures and that those differences appeared to be genetically mediated. In two sites (Costa Rican and Pennsylvanian), performance was better in MD cases than in controls on Facial Memory tasks, effects that were matched by positive and significant genetic overlaps. The Facial Memory task presents participants with images of faces with neutral affect, followed by a testing period where the original faces are presented alongside foils, and participants indicate which faces they recognize (38). Facial memory is considered a neurally and cognitively dissociable trait from general cognitive ability (39). The brain has highly specialized regions and networks that are preferentially activated by faces (40, 41). It has been postulated that these

neural underpinnings, which support this specialized ability, are specifically evolved in humans for the purpose of face recognition because it is such a crucial skill for human social interaction (42). We are not the first to find that depressed mood is associated with enhanced face-memory ability. Healthy participants that are induced to feel sad outperform those that feel happy or neutral on Facial Memory tasks (43). One explanation of this apparent advantage in MD cases for Facial Memory is that depressed mood can give rise to attentional biases that benefit the processing of negative stimuli i.e. a mood-congruency bias (44-46). The stimuli in the Face Memory task used in the present study are neutral, which can be interpreted negatively (47). However, a mood-congruency bias is unlikely to explain our results. The presence of a positive genetic overlap in addition to a phenotypic effect strongly suggests that enhanced performance of depressed individuals on the Facial Memory tasks is driven by trait- and not state-dependent mechanisms; that is, a subset of the biological mechanisms which predispose MD risk also mediate performance on these measures. The present work suggests that a circumspect approach to cognitive test selection may be advantageous for MD research, where Facial Memory is a potential endophenotype. Interestingly, despite the increased liability of MD in women (48), and the apparent face memory advantage conferred by being female (49), the link between increased genetic liability for MD and enhanced performance on the Facial Memory task was more pronounced in men in the Costa Rican sample. Thus, in some populations Facial Memory may be a better allied phenotype for MD in men than in women. The present study is not designed to test such hypotheses but generates testable hypotheses pertaining to this issue for future work.

When interpreting the results of the present study, a number of limitations should be considered. First, associations between cognition and, for example, psychosis risk may be confounded by environmental factors (e.g. in the familial environment). Second, we were required to rely on high-level diagnostic categories rather than being able to make inferences based on symptom-level data that would have enabled the demarcation of subgroups of disorders (including age of onset, illness severity and so on). There is growing evidence that fine-grained diagnostic phenotyping in genetics research is crucial for reliability and validity of reported associations (50). Third, this observational study is best described as correlational and as such does not allow us to make causal inferences about the impact of cognitive ability on risk of psychiatric illness. Fourth, the mechanistic insights provided by the present study are limited by the lack of SNP-level information, which might be used to reveal the involvement of specific genes and, by extension, molecular pathways in psychiatric illness risk. Fifth, the phenotypic relationship (i.e. the SMDs between cases and controls on cognitive performance) are, in some cases, based on a small number of cases.

Despite differences in each dataset's design and population, we identified cognitive measures that converge in terms of importance for particular psychiatric disorders from a genetic perspective. Results are important given that efficacious phenotyping is a practical requirement for the type of large-scale data collection necessary for gene identification. Despite the established importance of pleiotropy (overlapping genetic influences on traits) in improving understanding of disease pathogenesis, not to mention its potential for genetic risk profiling, few studies have systematically investigated the extent of pleiotropy between psychiatric disease risk and other complex traits, including cognition. The present study attempts to provide a rubric for future studies by creating profiles of genetic overlap between psychotic and affective disorder risk and a wide range of cognitive measures. Overall, the present study provides future directions for etiological psychiatric research with a genetic focus by highlighting

which cognitive measures are most likely to prove fruitful when paired with psychotic and affective illnesses.

Declaration of Interests

The authors report no biomedical financial interests or potential conflicts of interest.

Figure Legends

Figure 1. mERV β estimates for psychosis (CR = Costa Rican; MA = Mexican American; PA = Pennsylvanian; WA = Western Australian).

Figure 2. Genetic overlap (or *ERV*) profiles for psychosis (*significant after multiple testing correction; CR = Costa Rican; MA = Mexican American; PA = Pennsylvanian; WA = Western Australian).

Figure 3. mERV β estimates for bipolar (BP) and major depressive (MD) disorders (CR = Costa Rican; MA = Mexican American; PA = Pennsylvanian; WA = Western Australian).

Figure 4. Genetic overlap (or *ERV*) profiles for bipolar (BP) and major depressive (MD) disorders (*significant after multiple testing correction; CR = Costa Rican; MA = Mexican American; PA = Pennsylvanian; WA = Western Australian).

Figure 5. Genetic overlap (or *ERV*) profiles for major depressive disorder (*significant after multiple testing correction; CR = Costa Rican; MA = Mexican American; PA = Pennsylvanian; WA = Western Australian).

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