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Polygenic Risk of Schizophrenia and Cognition in a Population-Based Survey of Older Adults

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Cognitive impairment is a common feature of the major psychotic disorders, with deficits often present in at risk individuals and unaffected first-degree relatives. Previous studies have suggested that polygenic risk scores (PRS) for schizophrenia (SCZ) are associated with cognitive deficits, but there has been little examination of this association in longitudinal datasets, or comparison with other disorders. We used mixed models to study the association between PRS for 4 adult onset psychiatric disorders with cross-sectional cognitive performance and longitudinal cognitive decline in 8616 older adults from the Health and Retirement Study (HRS), followed for an average of 10 years. PRS were computed for SCZ, bipolar disorder (BD), Major Depressive Disorder (MDD), and Alzheimer's disease (ALZ). SCZ PRS associated with decreased cognitive function ($z = -3.00$, $P = .001$, $\Delta R^2 = 0.04\%$), which was largely driven by an association with impaired attention and orientation ($z = -3.33$, $P = 4.3\times10^{-4}$, $\Delta R^2 = 0.08\%$). We found no effect of BD or MDD PRS on cognition, in contrast to a robust effect of the APOE4/TOMM40 locus ($z = -5.05$, $P = 2.2\times10^{-7}$, $\Delta R^2 = 0.36\%$), which was primarily associated with impaired verbal memory ($z = -5.15$, $P = 1.3\times10^{-7}$, $\Delta R^2 = 0.21\%$). APOE4/TOMM40 locus and the ALZ PRS, but not the PRS for SCZ, were associated with greater cognitive decline. In summary, using a large, representative sample of older adults, we found evidence for different degrees of association between polygenic risk for SCZ and genetic risk factors for ALZ on cognitive function and decline, highlighting potential differences in the pathophysiology of cognitive deficits seen in SCZ and ALZ.

Key words: schizophrenia/polygenic risk/cognition/attention/cross-disorder/endophenotype /Alzheimer's/APOE4/bipolar disorder/major depressive disorder

Introduction

Impaired cognitive function is a common feature of the major psychotic disorders, with deficits seen across many cognitive domains.[1] Cognitive impairments are often present prior to the onset of psychotic symptoms, and may manifest, in more attenuated forms, in unaffected relatives of subjects with psychotic disorders.[2–5] As such, cognitive deficits represent classical "endophenotypes,"[6] although the precise nature of the causal relationship between psychosis and impaired cognitive function is still unclear. While cognitive decline is often seen at the time of first diagnosis, it may be confounded by the psychotic symptoms, or by the adverse effects of treatment targeted toward those symptoms. Hence, although cognitive difficulties and psychotic syndromes often co-occur, their etiological relationship remains uncertain.

The major psychotic syndromes, schizophrenia (SCZ) and bipolar disorder (BD), are highly heritable disorders[7] whose genetic architecture is likely to be polygenic, with few, if any, loci of major effect.[8] Similarly, most neurocognitive phenotypes have also been found to be heritable and polygenic in nature.[9] For example, a recent, large scale ($N = 53\ 949$) study of general cognitive ability of adults in middle and older age estimated that up to 29% of the phenotypic variation was attributable to common variation, but found only 3 genome-wide significant loci, despite the large sample size.[10] Among the genome-wide significant findings was the *APOE4/TOMM40* locus, which is a strong risk factor for Alzheimer's Disease (ALZ) and has previously been associated with modest cognitive decline in normal aging.[11,12]

Given the frequent overlap between psychotic disorders and cognitive deficits, there is increasing interest in determining whether the relationship is potentially mediated through a genetic mechanism. Family and twin studies have provided evidence for a modest degree of phenotypic covariance between cognitive function and SCZ that appears primarily attributable to additive genetic effects.[13,14] The familial relationship between cognitive function and other psychiatric disorders, such as BD

and major depression, has been less studied, although a recent Danish Registry based study has suggested that a mild degree of impaired cognitive function may be associated with a family history of a broad range of psychiatric disorders.[15]

With the increasing availability of large genome-wide association study (GWAS) samples it is now possible to use polygenic modeling techniques to examine the extent to which genetic factors associated with a phenotype may influence another independent, or closely allied phenotype.[16] Polygenic scores indexing susceptibility for a specific phenotype can be constructed from a GWAS "training" dataset and tested for an association with a second phenotype in an independent GWAS datasets. The question of whether liability for SCZ, as measured by SCZ polygenic risk scores (PRS), is associated with cognitive function or cognitive decline was initially addressed by McIntosh et al,[17] who found a modest association between PRS constructed from the first Psychiatric GWAS Consortium (PGC-1) meta-analysis of SCZ[18] and cognitive decline between ages 11 and 70. The relationship between the PGC-1 SCZ risk scores and cognitive function was similarly tested by the Cognitive Genomics Consortium (COGENT),[19] which found similar evidence for a negative association (meta-analytic $P = 1.4 \times 10^{-4}$) between the PGC-1 SCZ PRS and overall cognitive function in a combined meta-analysis of 4302 nonpsychiatric control subjects.

Although these studies have provided initial evidence for an association of SCZ risk scores with deficits in cognitive function, they have been limited by relatively small sample sizes for GWAS based analyses, and by the limited consideration of important confounders such as education and depressive symptoms. Moreover, since heritability estimates of cognitive function may vary with age,[20,21] it may be of particular importance to test the genetic influences on cognitive function in older samples. Hence, we sought to revisit the question of whether SCZ PRS are associated with cognitive function or cognitive decline by making use of the more powerful training dataset from the recent PGC-2 meta-analysis of SCZ[22] and the considerable resources of the Health and Retirement Study (HRS), a longitudinal cohort with GWAS and repeated cognitive evaluations available for 8616 middle-aged and older subjects of non-Hispanic Caucasian ancestry.

Materials and Methods

HRS and Inclusion Criteria

The HRS is a longitudinal study investigating the effects of aging and retirement on a representative sample of older Americans.[23] From 1992 onwards, several cohorts have been followed as part of the HRS, with a "core" interview performed every 2 years using a mixed mode design (in-person and telephone interviews) to monitor work, health, social, psychological, family and economic status.[24] More than 26 000 individuals have been studied, with DNA obtained from saliva in 12 507 participants. For the present analysis we selected participants from Waves 3 (1996) through Wave 10 (2010) when the same full-scale "total cognition" measure was consistently administered to the HRS participants. From these waves, we included individuals with: (1) at least 1 cognition measure taken at age 50 or later, (2) self-reported non-Hispanic Caucasian ancestry and (2) available genetic data. A total of 8616 individuals, with 40 257 cognition measures met these criteria.

Cognition Measures

The cognition measure in the HRS ("total cognition") is a customized version of the Telephone Interview for Cognitive Status (TICS).[25] The interview contained 3 phases: (1) a test for immediate recall of 10 nouns, (2) a mental status exam, including a task specific to attention (serial 7s) and a set of tasks for orientation and language (object and president naming, date recitation), and (3) a delayed recall test of the same 10 nouns from the immediate recall test, but given after 5 minutes had elapsed. Total cognition is a summary variable with a range of 0–35 that includes verbal memory (immediate and delayed recall) and mental status (which includes tests for orientation and attention). Our primary analysis focused on the aggregate (total cognition) score; however, we also performed secondary analyses on the attention/orientation and verbal memory subcomponents of the cognition measure to further delineate the effect of PRS on cognition.

Prior studies of the these measures have found that the telephone-administered cognitive battery is highly consistent with face-to-face interviews.[26] The test-retest reliability of the TICS interview has been previously found to be high ($r \geq .9$) in a number of studies of aging and dementia.[25,27]

Genotyping and Data Quality Control

DNA was collected from saliva samples of consenting HRS respondents in 2006 or 2008. DNA from these participants was genotyped by the Center for Inherited Disease Research (CIDR) on the Illumina Human Omni-2.5 Quad array. Quality control has been performed on this data by the original HRS investigators based on the guidelines described by Laurie et al[28] and described in the Quality Control Report for Genotypic Data downloaded from dbGaP. In brief, SNPs were excluded based on the following criteria: (1) minor allele frequency (MAF) = 0 to remove mono-allelic markers; (2) missing call rate ≥ 2%; (3) discordant calls or Mendelian errors in duplicate subjects or family based samples; (4) Hardy-Weinberg equilibrium (HWE) P-value $<10^{-4}$ in European or African samples; (5) sex difference in allelic frequency ≥0.2; (6) sex differences in heterozygosity >0.3; and (7)

MAF < 0.01. As part of the centralized quality control procedures, duplicate and subjects were removed (this information is made available "Sample analysis.csv" file in dbGaP). Based on this information, we excluded 113 subjects found to have been cryptically related. Finally, since training datasets for the polygenic scores were derived from samples primarily of European Ancestry, we restricted our analyses to HRS participants who were of non-Hispanic Caucasian descent ($N = 8616$). We subsequently used the results of the ancestry based principal component analyses to exclude any potential outliers (defined as having a principal component >6 standard deviations from the mean) that may have been misclassified in regard to their ancestry ($N = 59$).

Imputation was originally performed for 12 507 samples using the phase I of the 1000 genomes as a reference dataset. The genotype and imputed data was obtained from dbGAP (accession ID: phs000428.v1.p1) following appropriate IRB approval. The imputed files were initially available in IMPUTE2 format. We extracted markers used in the polygenic scores in each disorder's original training set marker and converted the IMPUTE2 dosage format into a single dosage format for polygenic risk scoring in PLINK1.9.[29]

Polygenic Risk Score

PRS were calculated using the method originally described by the International Schizophrenia Consortium.[30] We obtained summary results of the most recent PGC analyses of SCZ,[22] BD,[31] and Major Depressive Disorder (MDD).[32] These summary statistics were pruned by the original study investigators to exclude markers in linkage disequilibrium. We also obtained the results of a recent meta-analysis of ALZ performed by the IGAP consortium.[33] We subsequently used genotypes from the Caucasian participants of the 1000G project to prune the ALZ training set, removing markers in linkage disequilibrium using PLINK (clumping markers within 500kb and an $r^2 > .25$ of the index SNPs).

PRS for the HRS sample were calculated in PLINK using the imputed HRS data and the relevant training dataset. The logistic regression parameter (β) from the training dataset was used to weight the scoring. We calculated PRS for each individual for each of the 4 disorders at 8 *P*-value thresholds (P_T) in PLINK ($P_T < .5$; $P_T < .4$; $P_T < .3$; $P_T < .2$; $P_T < .1$; $P_T < .05$; $P_T < .01$; $P_T < .001$).

Analysis

To utilize the longitudinal nature of cognition data in the HRS, we used a mixed modeling approach accounting for the repeated measures on each participant. Analyses were performed in STATA 12.1 using the *xtmixed* command. The random-intercept and random slope model included fixed effects terms for age, quadratic age, sex, education, diabetes, stroke, depression and the first 4 ancestry-based principal components. Four principal components were chosen based on evaluation of a scree plot of 10 principal components, which showed minimal changes in eigenvalues starting between the third and fourth principal component. The phenotypic covariates were chosen based on evidence from the literature that they are associated with decreased cognitive function or cognitive decline.[33–36] Depression was measured using an 8-item version of the 20-item CES-D scale, which is widely used in population based studies and has been demonstrated to have high reliability and validity.[37] The CESD-D was also validated in 2 of the HRS waves and was found to have high internal reliability (Cronbach's $\alpha = .81$ and .83).[38] Diabetes and stroke status were operationalized as binary variables based on self-report of these conditions at any time during the study. Educational attainment was operationalized as a class variable (high school incomplete, general educational development [GED], high school graduate, college graduate, graduate degree holder).

Our primary analysis included all subjects of non-Hispanic Caucasian ancestry with at least 1 total cognition variable. As prior studies have shown that the major adult mental disorders are associated with lower cognitive function,[15] we performed polygenic association analyses using 1-sided tests. We fit mixed effect models using the previously described covariates and polygenic scores as fixed effects, while including each individual as a random effect (random intercept). Age and age^2 were included in the model both as fixed and random effects (random slopes). To further characterize the effect of the polygenic scores on cognition, we examined their association with the verbal memory and mental status (attention and language) components of the cognitive exam. The distribution of the primary total cognition and the verbal memory variable were normally distributed, however, the attention and language components of the cognitive measure showed a strong left skew with a prominent ceiling effect (supplementary figure 1).

For polygenic scores that showed a significant main effect in the primary analysis (table 2), we performed an additional analysis to test whether the effect of the polygenic score changes over time, either in a linear or nonlinear (quadratic) pattern. We included interaction terms to test the effect of polygenic score with both age and age^2. A significant interaction term ($P < .05$) was interpreted as evidence to suggest that polygenic scores were associated with differing rates of cognitive decline.

A frequently used metric to measure and compare the effect of PRS on a phenotype of interest is the estimated proportion of phenotypic variance (R^2) explained by the fitted model. The effect of the polygenic score can be estimated by subtracting a model that includes the score to a baseline model that includes all other covariates except for the polygenic score. Although the calculation of R^2 in traditional linear or logistic models is commonplace,

mixed models require methods that account for the correlation of individual data and the presence of hierarchical levels. In our analyses, we have used the Bosker-Snjiders method to estimate R^2 in our multilevel analysis.[39] This method accounts for hierarchical clustering (random intercepts) but does not take into account any potential explanatory effects from random slopes. It should therefore be seen as an approximation of R^2 best used to compare the results within our study, rather than across other studies, which may employ similar but not fully comparable study designs.[40]

Results

Participant Characteristics

A total of 8616 individuals were included in the sample. The average number of total cognition measures per individual was 4.6, providing a total of 40 257 measures to be included in the analysis. The majority of subjects (63.3%) had ≥4 cognition measures (table 1). Subjects tended to be evenly distributed across educational attainment levels. The mean CES-D score in this sample was 0.96 (SD = 1.6), while 21.8% reported a history of diabetes and 11.3% reported at least 1 stroke. Participants had a mean follow-up period of 10.0 years.

SCZ PRS and Cognition

The PRS for SCZ was significantly associated with lower total cognition scores across all training set *P*-value thresholds (supplementary table 1), with the strongest results found using a training set threshold of $P_T = .05$ ($\beta = -.04$, $Z = -3.00$. $P = .001$). The proportion of variance accounted for by the polygenic score (ΔR^2) was 0.04% (table 2). Further analysis of the polygenic association showed that it primarily affected the attention and orientation cognitive measure ($P_T = .05$: $\beta = -.02$, $z = -3.33$, $P = 4.3 \times 10^{-4}$, $\Delta R^2 = 0.08\%$), with relatively smaller effects on the verbal memory components of the cognitive score ($P_T = .05$: $\beta = -.02$, $z = -2.09$, $P = .02$, $\Delta R^2 = 0.02\%$; table 3).

Table 1. Sociodemographic Characteristics of Health and Retirement Study Participants of Individuals With Genotype Data and At Least 1 Total Cognition Measures Taken at Age ≥50[a] ($N = 8616$)

Characteristics	Mean (SD) or *n* (%)	Range
Age at entry (*M*, SD)	60.5 (8.5)	
Women (*N*, %)	4841 (56.2)	
Smoker (*N*, %)	1550 (18.0)	
Stroke (*N*, %)	975 (11.3)	
Diabetes (*N*, %)	1869 (21.7)	
CES-D (*M*, SD)	0.96 (1.6)	0–8
Psychiatric history (*N*, %)	1546 (17.9)	
Education (*N*, %)		
1. Limited HS	1158 (13.4)	1–5
2. GED	365 (4.3)	
3. HS graduate	2896 (33.6)	
4. Some college	2027 (23.5)	
5. College and above	2170 (25.2)	
Years of follow-up (*M*, SD)	10.0 (5.5)	0–14
Measures per person (*M*, SD)	4.6 (2.6)	1–8
% with 1 measure	1807 (21.0)	
% with 2 measures	608 (7.1)	
% with 3 measures	703 (8.1)	
% with ≥4 measures	5498 (63.8)	

Note: *M*, mean; GED, general educational development; HS, high school.

BD and MDD PRS and Cognition

Given the emerging evidence that cognition may be familially related to a broad range of psychiatric disorders, we tested whether polygenic scores derived from the PGC meta-analyses of other adult phenotypes (BD and MDD) were also associated with decline in cognitive function in the HRS. However, we found no significant association between polygenic risk for BD (best $P_T = .001$: $\beta = -.05$, $z = -1.50$, $P = .07$, $\Delta R^2 = 0.01\%$) or MDD (best $P_T = .2$: $\beta = -.000$, $z = -0.07$, $P = .37$, $\Delta R^2 = 0$). These cross-disorder results are shown in table 2.

Alzheimer's PRS, APOE4 Locus, and Cognition

To compare the effect of polygenic scores from the common adult psychiatric disorders to an established neurocognitive disorder with a known genetic risk factor of major effect (*APOE4* allele), we obtained summary data from the IGAP GWAS of ALZ and used it as a training dataset (after appropriate LD pruning) to calculate polygenic scores in the HRS dataset. The *APOE4/TOMM40* risk locus (rs769449) showed a strongly significant association with lower total cognition scores ($\beta = -.36$, $z = -5.05$, $P = 2.3 \times 10^{-7}$, $\Delta R^2 = 0.36\%$). The polygenic score for ALZ was more modestly associated with total cognition ($P_T = .01$: $\beta = -.02$, $z = -1.88$, $P = .03$, $\Delta R^2 = 0.05\%$), suggesting that the association with cognitive impairment is driven primarily by a single

Table 2. Association of Disorder Specific Polygenic Risk Scores With the Total Cognition Measure

	Total Cognition Measure			
Disorder (Training Set *P*-value Threshold)	β	*Z*-score	*P*-value	ΔR^2 (%)
SCZ ($P_T = .05$)	−.04	−3.00	.001	0.04
BD ($P_T = .001$)	−.05	−1.50	.07	0.01
MDD ($P_T = .2$)	−.0005	−0.07	.47	0.00
ALZ ($P_T = .01$)	−.02	−1.88	.03	0.05
APOE/TOMM40 locus	−.36	−5.05	2.2×10^{-7}	0.36

Note: P_T, *P*-value threshold, β, beta-value for fixed effects; ΔR^2, difference in Bosker-Snijders R^2; SCZ, schizophrenia; BD, bipolar disorder; ALZ = Alzheimer's disease.

locus rather than a polygenic component. We further characterized the effect of the *APOE4/TOMM40* locus and the ALZ polygenic score on the attention/orientation and verbal memory subcomponents of total cognition, finding that, in contrast to the results with the SCZ polygenic scores, both the ALZ polygenic score and the *APOE4/TOMM40* locus were more strongly associated with verbal memory components of the cognitive measure (table 3 and figure 1).

Effect of PRS on Decline in Cognition

Using the primary total cognition score, we tested whether the PRS that were significant in table 2 (SCZ, ALZ, and the *APOE4/TOMM40* locus) also showed an association with cognitive decline as subjects aged. We tested for an interaction between polygenic score and age, and found no effect of the SCZ polygenic score (P_T = .05) on cognitive decline (P > .1 for both linear and quadratic interaction terms). However, we found a strong effect of the *APOE4/TOMM40* locus with cognitive decline, with significant interactions seen between the *APOE4/TOMM40* risk locus and both linear ($P = 1.5\times10^{-21}$) and quadratic age ($P = 1.8\times10^{-4}$). The effect of ALZ polygenic score (P_T = .01) cognitive decline was more modest, with a significant interaction seen with linear age (P = .02) but not quadratic age (P = .30).

Discussion

In this study we tested whether polygenic risk for a number of psychiatric disorders was associated with decreased general cognitive function, and whether this effect increased with age. We found that PRS for SCZ was associated with decreased total cognition scores (P = .001, ΔR^2 = 0.04%), and that most of this association was driven by decreased performance on a subcomponent of the cognitive score measuring attention and language ($P = 4.3\times10^{-4}$, ΔR^2 = 0.08%). Not unexpectedly, the extent of the variance in cognition explained by SCZ PRS was modest, especially when compared to the *APOE4/TOMM40* locus, a well know risk factor for ALZ and cognitive decline.[41,42]

Interestingly, the pattern of cognitive deficits affected by the SCZ polygenic risk alleles differed from those of the *APOE4/TOMM40* loci, the former being primarily driven by deficits in mental status (language and attention), with the latter manifesting mostly in verbal

Table 3. Association of Disorder-Specific Polygenic Risk Scores With Mental Status (Attention/Language) and Verbal Memory Components of Total Cognition

Disorder (Training Set *P*-value Threshold)	Attention/Language				Verbal Memory			
	β	*z*	*P*-value	ΔR^2 (%)	β	*z*	*P*-value	ΔR^2 (%)
SCZ (P_T = .05)	−.02	−3.33	4.3×10^{-4}	0.08	−.02	−2.09	.02	0.02
BD (P_T = .001)	−.01	−0.37	.36	0	−.03	−1.32	.09	0.01
MDD (P_T = .2)	.00	−0.21	.42	0	.00	0.25	.60	0
ALZ (P_T = .01)	−.01	−0.97	.17	0.03	−.02	−2.61	.005	0.05
APOE/TOMM40 locus	−.08	−2.52	.0058	0.21	−.25	−5.15	1.3×10^{-7}	0.21

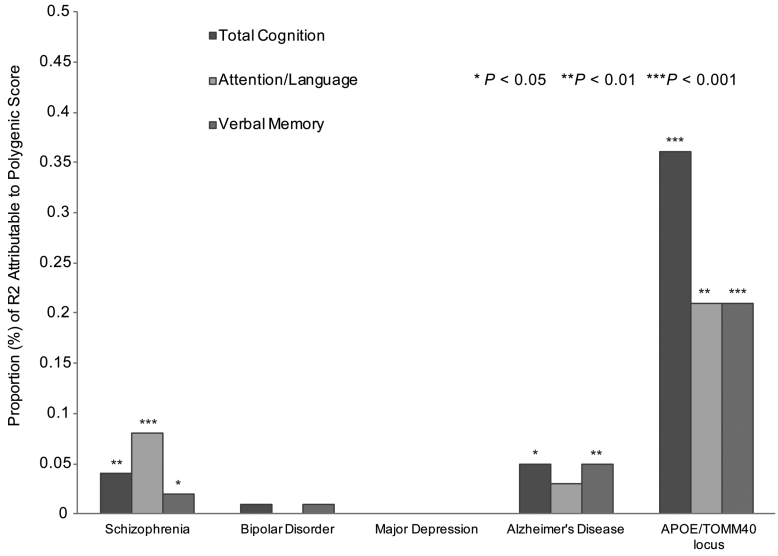

Fig. 1. Cross-disorder polygenic effects on specific cognitive domains.

memory. Verbal memory, language and attention, as measured by the TICS, have been previously found to be heritable,[43] suggesting that this may reflect domain-specific impairments that are related to the differing genetic risk of SCZ risk alleles and *APOE4*. An additional difference between the effects of the SCZ polygenic score and the *APOE4* locus was the lack of effect on cognitive decline seen in the former and the prominent effect seen in the latter. These results are consistent with a modest but "static" effect of SCZ risk alleles on overall cognition, in contrast to the deteriorating, age related effect of the major risk locus of Alzheimer's disorder. As such, these results are broadly consistent with these disorders being traditionally considered as neurodevelopmental vs neurodegenerative disorders.

In contrast to SCZ, we did not find an association between polygenic risk for BD or MDD and total cognition (figure 1). This is perhaps not surprising, given that the cognitive deficits seen in these disorders is milder than in SCZ.[4,44,45] However, one important consideration is that the primary meta-analyses of these disorders used in the polygenic training sets were smaller in sample size than that of SCZ, and were likely less predictive.

While PRS from the most recent PGC2 meta-analysis were found to explain 7%–18% of the phenotypic variance of SCZ case status in independent samples,[22,46] the proportion of variance explained by polygenic scores when applied to alternative phenotypes, particularly in unselected participants, has been much smaller and more consistent with the findings of our study (supplementary table 2).[17,19,47,48] Indeed, our findings were consistent with the modest effects found by the recent COGENT study,[19] where pseudo-R^2 values in the individual studies ranged from 0% to 2%. McIntosh et al[17] also found a small but significant effect of SCZ polygenic risk on both cognitive decline and ability in the Lothian Birth Cohort ($R^2 <$ 1%). Moreover, while most studies of the effect of polygenic risk on cognition have so far focused on generalized measures of cognitive function,[17,19] a recent study of the effects of polygenic risk for SCZ on cognitive performance also found evidence for varying associations with differing cognitive phenotypes.[48] Consistent with our results, the 2 cognitive phenotypes that showed significant associations with the SCZ polygenic score were measures of attention and spatial working memory.

The significant but modest association of polygenic scores with cognition suggests that other factors beyond common variation are likely to be associated with the cognitive impairment seen in SCZ. However, one important limitation of currently available GWAS data is that they do not fully account for all the heritability attributed to common variation.[49] As GWAS meta-analyses increase in sample size, this gap, which has been termed "hidden" heritability, will lessen and the ensuing polygenic scores will become more predictive.[50] Polygenic scores also do not reflect the contribution of rare variation and copy-number variants, which play an important role in neurodevelopmental disorders with intellectual disability,[51,52] although their role in cognitive function in the general population is unclear. In addition, polygenic scores, by definition, do not index any significant environmental factors involved in general cognition and cognitive decline. In this study, we have controlled for the role of education, but did not specifically evaluate the role of additional environmental factors, such as life stressors,[53] physical activity,[54] occupational activity,[55] and social engagement,[56] all of which have been previously shown to have associations with cognition in later life.

Several additional limitations of our study should be taken into consideration. First, although the HRS sample was designed to specifically test cognition in later life, its large ascertainment and longitudinal nature necessitated the use of an abbreviated cognitive measure designed to be administrable by lay interviewers over the telephone. This could introduce potential bias if subjects with higher rates of cognitive or mental disorders are less likely to respond to the study surveys. Although such a bias could lead to a loss of power, it is likely to be limited given the high rates of study participation (>80%) and reinterview participation (>90%) seen across all of the HRS data collection waves.[57] Second, while previous studies have demonstrated performance on the TICS to be both heritable and a well validated dementia-screening tool,[43,58,59] it is less comprehensive than more traditional neurocognitive batteries and may have limited power to detect associations seen primarily with specific cognitive domains. However, the consistency of our findings with the prior literature provides reassurance that the cognitive measurement was sufficiently robust. Third, the HRS sample was comprised entirely of older individuals, which may limit the generalization of our results to a younger population, although it may also hold the advantage of testing cognition during an age range when it is highly heritable.[20] Finally, the greater medical comorbidity in the elderly could have confounded our results, particularly since common disorders such as stroke and diabetes may also be associated with lower cognitive function. However, in our primary analyses, we included both stroke and diabetes as time-dependent covariates. Moreover, in an additional sensitivity analyses, we excluded subjects with a history of stroke of diabetes and found reassuringly similar results (supplementary table 3).

In sum, we found an association between increased polygenetic risk of SCZ and a modest decline in overall cognitive performance in older adults. Moreover, we provide initial evidence that this decline may be domain-specific and potentially distinguishable from the cognitive deficits associated with the *APOE4* risk loci. As such, our findings are consistent with a modest degree of shared genetic risk between SCZ and overall cognition, but they also point to the importance of measuring domain specific cognitive phenotypes to help delineate the specific type of deficits associated with of SCZ.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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