

Common Genetic Variation and Schizophrenia Polygenic Risk Influence Neurocognitive Performance in Young Adulthood

Alex Hatzimanolis,¹ Pallav Bhatnagar,² Anna Moes,² Ruihua Wang,¹ Panos Roussos,^{3,4} Panos Bitsios,⁵ Costas N. Stefanis,⁶ Ann E. Pulver,¹ Dan E. Arking,² Nikolaos Smyrnis,^{6,7} Nicholas C. Stefanis,^{6,7} and Dimitrios Avramopoulos^{1,2*}

¹Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

²McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

³Department of Psychiatry, Friedman Brain Institute and Department of Genetics and Genomics Science, Institute of Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York

⁴James J. Peters Veterans Affairs Medical Center, Bronx, New York, New York

⁵Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, University of Crete, Heraklion, Greece

⁶University Mental Health Research Institute, Athens, Greece

⁷Department of Psychiatry, Eginition Hospital, University of Athens Medical School, Athens, Greece

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Neurocognitive abilities constitute complex traits with considerable heritability. Impaired neurocognition is typically observed in schizophrenia (SZ), whereas convergent evidence has shown shared genetic determinants between neurocognition and SZ. Here, we report a genome-wide association study (GWAS) on neuropsychological and oculomotor traits, linked to SZ, in a general population sample of healthy young males ($n = 1079$). Follow-up genotyping was performed in an identically phenotyped internal sample ($n = 738$) and an independent cohort of young males with comparable neuropsychological measures ($n = 825$). Heritability estimates were determined based on genome-wide single-nucleotide polymorphisms (SNPs) and potential regulatory effects on gene expression were assessed in human brain. Correlations with general cognitive ability and SZ risk polygenic scores were tested utilizing meta-analysis GWAS results by the Cognitive Genomics Consortium (COGENT) and the Psychiatric Genomics Consortium (PGC-SZ). The GWAS results implicated biologically relevant genetic loci encoding protein targets involved in synaptic neurotransmission, although no robust individual replication was

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detected and thus additional validation is required. Secondary permutation-based analysis revealed an excess of strongly associated loci among GWAS top-ranked signals for verbal working memory (WM) and antisaccade intra-subject reaction time variability (empirical $P < 0.001$), suggesting multiple true-positive single-SNP associations. Substantial heritability was observed

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*Correspondence to:

Dimitrios Avramopoulos MD, PhD, Institute of Genetic Medicine and Department of Psychiatry, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB-507, Baltimore, MD 21205. E-mail: adimitr1@jhmi.edu

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for WM performance. Further, sustained attention/vigilance and WM were suggestively correlated with both COGENT and PGC-SZ derived polygenic scores. Overall, these results imply that common genetic variation explains some of the variability in neurocognitive functioning among young adults, particularly WM, and provide supportive evidence that increased SZ genetic risk predicts neurocognitive fluctuations in the general population.

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INTRODUCTION

It is well documented that neurocognition represents a complex heritable phenotypic construct with significant genetic influences across the entire human lifespan [Deary IJ et al., 2012; Plomin R and Deary IJ 2014]. High heritability has been observed in twin-based studies for various neurocognitive traits, including episodic memory, working memory and general cognitive ability [Ando J et al., 2001; Haworth et al., 2010; Owens SF et al., 2011]. Similarly, molecular genetic studies have predicted increased heritability estimates for general cognitive ability in the general population by considering the additive effects of thousands common genetic markers in the human genome [Plomin R et al., 2013; Benyamin B et al., 2014]. Due to the close relationship between neurocognitive deficits and psychiatric illness, nationwide collaborative efforts have joined forces in order to investigate the potential contribution of common genetic variation to neurocognitive performance, which may also lead to the identification of specific genetic loci involved in psychiatric nosology [Donohoe G et al., 2013; Lencz T et al., 2014].

Individuals with schizophrenia (SZ) underperform in a wide range of neuropsychological and neurophysiological tasks compared to the general population, making neurocognitive impairment one of the core features of SZ psychopathology [Kahn RS and Keefe RS 2013]. Substantial evidence indicates that these deficits usually precede the onset of the full-blown clinical presentation of the disease, implying that early cognitive deterioration might represent an important risk factor or prodromal condition of SZ [Kahn RS and Keefe RS 2013; Bora E and Murray RM 2013; Meier MH et al., 2014]. In addition, family studies have shown that the phenotypic relationship between SZ and neurocognition can be attributed to shared genetic effects, which points towards a significant overlap between the underlying genetic factors inducing both cognitive deficits and increased SZ susceptibility [Toulopoulou T et al., 2007, 2010]. This view is further supported by the neurocognitive lag observed among children and adolescents reporting psychotic experiences [Gur RC et al., 2014], which might reflect the common genetically determined neurodevelopmental origin of aberrant neurocognition and psychosis.

Our group and others have previously reported that common SZ risk genetic variants derived from large-scale genome-wide association studies (GWAS), as well as variants within SZ candidate genes

are associated with neurocognitive weaknesses in clinical and non-clinical populations [Burdick KE et al., 2006; Stefanis NC et al., 2007; Greenwood TA et al., 2011; Hatzimanolis A et al., 2012; Walters JT et al., 2013], suggesting that at least some of SZ risk variants might have a significant impact on human cognition. More recently, it has been shown that SZ risk genetic loci, when analyzed as an aggregate polygenic risk score, predict alterations in white matter brain volume, general cognitive ability and working memory related prefrontal brain activation [Terwisscha van Scheltinga AF et al., 2012; McIntosh AM et al., 2013; Kauppi K et al., 2014]. Several neuropsychological and neurophysiological traits have been proposed as putative endophenotypes (or intermediate phenotypes) for SZ, with potential value in genetic studies as an alternative approach to help identify SZ susceptibility loci [Braff DL et al., 2007; Thaker G, 2008; Greenwood TA et al., 2013, Tamminga CA et al., 2014; Ivleva et al., 2014]. The attractiveness of endophenotypes stems from the observation that these traits are heritable, segregate in SZ families and likely possess a less complex genetic architecture [Gottesman II and Gould TD 2003; Cannon TD and Keller MC 2006]. Over the past few years, genome-wide association and linkage studies have identified genetic loci associated with SZ candidate neurocognitive endophenotypes [Almasy L et al., 2008; Greenwood TA et al., 2013; Papassotiropoulos A et al., 2013; Lencz T et al., 2014; Vaidyanathan U et al., 2014].

In the present study, we aimed to uncover through genome-wide association analyses novel common genetic variants associated with candidate endophenotypes for SZ, in healthy young individuals drawn from the general population. Independent replication of the most compelling association results was attempted in two additional samples and plausible functional properties of the associated variants were tested on human brain gene expression. Furthermore, heritability estimates were acquired by assessing the cumulative additive effects of all genome-wide markers. Finally, we generated polygenic risk profile scores based on the results of a general cognitive ability GWAS meta-analysis and the largest to date GWAS meta-analysis for SZ from the Psychiatric Genomics Consortium (PGC-SZ) [Ripke S et al., 2014], and examined their contribution to the endophenotypes under investigation.

MATERIALS AND METHODS

Participants

A detailed description of the Athens Study of Psychosis Proneness and Incidence of Schizophrenia (ASPIS) has been reported previously [Smyrnis N et al., 2007, 2011; Stefanis NC et al., 2007]. Briefly, the ASPIS examined randomly selected young male conscripts aged 18 to 24 years from the Greek Air Force in their first two weeks of admission to the National Air Force Basic Training Center (Tripolis, Greece). All conscripts had received a standardized screening interview by a team of military doctors of different specialties in order to exclude serious medical conditions, including documented diagnosis of psychotic disorders and substance dependence, and individuals with such conditions were not admitted for military training. In all, 2029 eligible individuals provided a mouthwash sample for DNA extraction and completed a battery of computerized tasks measuring different aspects of neuropsychology.

chological and oculomotor performance. Written informed consent was obtained from every individual before participating to the study. The study protocol was approved by the University Mental Health Research Institute (Athens, Greece) and the Johns Hopkins University Institutional Review Boards.

Cognitive and Oculomotor Assessments

Detailed information on the phenotyping procedures of the ASPIS has been described in previous reports [Smyrnis N et al., 2007; Stefanis NC et al., 2007]. We measured sustained attention with the Continuous Performance Task-Identical Pairs version (CPT-IP) and short-term verbal and spatial working memory (WM) with the N-back task (2-back version) [Smyrnis N et al., 2007]. Both accuracy (d' index) and speed of processing (mean reaction time) outcomes were included in the analyses. In accordance with our previous work, we a priori decided to exclude data from further analyses if d' index on CPT-IP and N-back was <0 and if there were ≥ 3 unsuccessful trials (of 5) for verbal and spatial 2-back tasks. Oculomotor performance was tested using standardized tasks measuring antisaccade and smooth eye pursuit eye movements [Smyrnis N et al., 2011; Kattoulas E et al., 2012]. The following oculomotor variables were included in our analyses: antisaccade error rate, median reaction time of correct antisaccades, coefficient of variation of antisaccade reaction time and a principal component analysis (PCA) factor extracting the common variance of smooth eye pursuit gain measures (ratio of eye velocity to target velocity). Reasoning ability (non-verbal IQ) was assessed with the Raven's progressive matrices [Raven J et al., 2004]. A description of the phenotypic outcomes examined in the current study is presented in Table I.

Genotyping and Imputation

We selected for genome-wide genotyping a subsample of 1,216 individuals with the most complete data across all tasks (discovery GWAS sample). Genotyping in the discovery ASPIS sample was conducted on Genome-Wide Human SNP array 6.0 (Affymetrix, Santa Clara, CA) at the Institute of Genetic Medicine, Johns Hopkins University School of Medicine. Appropriate quality control (QC) testing and SNP QC filtering was applied in PLINK [Purcell SM et al., 2007], excluding single-nucleotide polymorphisms (SNPs) with a call rate $<97.5\%$, minor allele frequency $<5\%$ and Hardy-Wienberg equilibrium $P < 0.0001$. Further, we used principal component analysis (PCA) as implemented in EIGENSTRAT [Price AL et al., 2006], to both identify genetic outliers (>6 standard deviations on any of the top ten principal components) and correct for any potential residual population substructure. Batch-related genotyping errors were also ruled out before analyses. Genotype imputation was performed using IMPUTEv2 [Howie BN et al., 2009], with the 1,000 Genomes Project panel as a reference (Phase I, Integrated release, version 3). After rigorous QC and data cleaning processes, a total of 1,079 samples and 5,654,592 high quality autosomal SNPs were available for downstream genome-wide analyses. Further details on genotyping and imputation procedures are provided in the Supplementary material. Follow-up genotyping for top-associated SNPs selected for replication was performed using MassARRAY iPLEX Gold assays (Sequenom, San Diego, CA), following the manufacturer's instructions.

Replication Samples

The remainder ASPIS subsample ($N = 738$) served as an internal validation sample of GWAS results. The only difference between the discovery and replication subsamples is that the former was

TABLE I. Description of the Phenotypic Outcomes Analyzed in the Present Study

Phenotype	Task	Abbreviation	Outcome
Reasoning ability (non-verbal IQ)	Raven's progressive matrices	IQ	Box-cox transformed total score of correct responses
Sustained attention/Vigilance	Continuous Performance Test, Identical Pairs version	CPT	Accuracy index (d'); both correct responses and false alarms are taken into account
		CPT-RT	Mean reaction time for correct responses
Verbal working memory	Verbal N-back [2-back]	VNB	Accuracy index (d'); both correct responses and false alarms are taken into account
		VNB-RT	Mean reaction time for correct responses
Spatial working memory	Spatial N-back [2-back]	SNB	Accuracy index (d'); both correct responses and false alarms are taken into account
		SNB-RT	Mean reaction time for correct responses
Oculomotor functioning	Antisaccade eye movements	AER	Antisaccade error rate
		ART	Mean reaction time for correct antisaccades
		ACV	ART intra-subject coefficient of variation
		SPEM	PCA factor extracting the common variance of all three gain measures (ratio of eye velocity to target velocity)
	Smooth pursuit eye movements (three constant target speeds: 10, 20, and 30 deg/sec)		

selected to have the fewest missing phenotypic data, which we found to correlate with superior performance in most tasks. Additional replication was attempted in the Learning in Genetics of Schizophrenia Spectrum (LOGOS) sample, an independent cohort of healthy young male army conscripts described in detail previously [Roussos P et al., 2011]. The LOGOS acquired the same recruitment procedures as the ASPIS, assessing healthy male conscripts (age range 18–29) at a Greek Army Training Camp (Heraklion, Crete) on several neurocognitive phenotypes that resemble the ones tested in the ASPIS. Available phenotypic scores on sustained attention (RVP; Rapid Visual Information Processing), spatial working memory (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the N-back task were analyzed. As equivalent to the ASPIS phenotypic assessments, we utilized RVP and N-back data on the number of correct responses and reaction time. The total number of errors and a measure of strategy were assessed in the SWM test as outcomes. The LOGOS cohort was genotyped on the HumanOmniExpress array (Illumina, San Diego, CA) applying identical QC metrics.

GWAS Enrichment Analysis

We applied a permutation-based analytical strategy to determine whether our strongest GWAS hits ($P_{\text{GWAS}} < 0.001$) contain true-positive association signals. Specifically, we randomly shuffled the IDs of the individuals included in the GWAS within the file containing the phenotypes and covariates, thus preserving the correlations between covariates and phenotypes and the correlations between genotypes, but randomizing the link between the two. If 100 permutations approached an empirical $P = 0.05$ more permutations, up to 3000, were run as needed to accurately determine lower P -values. Genome-wide analysis was run on each permuted data set with identical parameters as the original run, and all LD-independent ($r^2 < 0.2$) significant SNPs at $P < 0.001$ were extracted and counted. Empirical P -value for signal enrichment was calculated as the fraction of permutations that produced equal or larger number of independent hits than the original data. The most likely number of true signals in each phenotype was calculated as the number of observed signals minus the average number observed across permutations. The number of true signals at 95% confidence was defined as the number of observed signals minus the maximum number observed in less than 5% of permutations.

Human Brain Gene Expression

Postmortem human brain samples were acquired from the Harvard Brain Tissue Resource Center and the National Institute of Child Health and Development (NICHD) Brain and Tissue Bank for Developmental Disorders. In total, we analyzed 162 samples dissected from the superior temporal lobe (Brodmann area 22) and 88 prefrontal cortex samples from healthy donors. Quantitative real-time PCR (qPCR) reactions were performed in triplicate following standard procedures (details in Supplementary material).

Polygenic Score Analysis

Polygenic risk scores (PRS) based on the latest meta-analysis GWAS results on general cognitive ability (Cognitive Genomics

Consortium, COGENT) and SZ (Psychiatric Genomics Consortium, PGC-SZ) [Lencz T et al., 2014; Ripke S et al., 2014] were generated following the procedure described by the International Schizophrenia Consortium [Purcell SM et al., 2009]. SNPs were filtered by applying seven P -value thresholds ($P_T < 0.0001$, $P_T < 0.001$, $P_T < 0.01$, $P_T < 0.05$, $P_T < 0.1$, $P_T < 0.3$, $P_T < 0.5$) to PGC-SZ GWAS summary statistics (discovery sample). General cognitive ability PRSs were generated based on the single P -value threshold ($P_T < 0.001$) that was reported by COGENT. PRS calculation in the ASPIS GWAS subsample (target sample) was performed in PLINK using the “-score” option, after appropriate linkage disequilibrium-based SNP pruning ($r^2 < 0.2$ within a 200 kb window), ensuring that only independent association signals are included. PLINK calculates a weighted risk score for each individual, based on the number of risk alleles that the individual carries at each SNP locus and the natural logarithm of the reported odds ratio for that particular SNP in the reference GWAS (COGENT or PGC-SZ). The sum of single scores across all genotyped SNPs denotes the total PRS for each individual.

Statistical Analyses

To identify genetic outliers (>6 standard deviations on any of the top ten principal components) and correct for any potential residual population substructure, principal component analysis was applied as implemented in EIGENSTRAT [Price AL et al., 2006]. Association testing between phenotypic outcomes and imputed genotype allelic dosages was performed by linear regression under an additive genetic model using SNPTESTv2 [Marchini J and Howie B 2010], adjusting for age, years of education, and the first principal component. Genome-wide Complex Trait Analysis (GCTA) software which implements a restricted maximum likelihood (REML) analysis was used to estimate the proportion of phenotypic variance explained by all genome-wide SNPs (SNP-heritability) [Yang J et al., 2011]. We tested for correlations between phenotypes and polygenic risk scores by linear regression in R (<http://www.r-project.org/>), utilizing the same covariates as above. In this analysis, given the well-documented relationship between poor neurocognitive performance and SZ development by prior studies, one-sided $P < 0.05$ was used to declare significant correlations. Statistical analyses of normalized log-transformed qPCR gene expression measurements were also performed in R, by fitting generalized linear models with age, sex, post-mortem interval, and acquisition site as covariates.

RESULTS

GWAS Results and Replication

Genome-wide association analyses were performed in the discovery ASPIS sample ($N = 1,079$) for the eleven neurocognitive and oculomotor outcomes described in Table I. The corresponding quantile-quantile plots for each outcome showed no inflation of test statistics, with genomic inflation factor values ≤ 1.01 (Figure S1). A single SNP was associated with sustained attention/vigilance task accuracy index (CPT), exceeding the conventional GWAS significance threshold ($rs115501170$ $P = 5.2 \times 10^{-9}$, $\beta = -0.43$), with minor allele carriers exhibiting poorer perfor-

mance. This SNP is located within the first intron of the *CNTNAP5* (contactin associated protein-like 5) gene, which belongs to the neurexin family of neuronal cell-adhesion molecules. However, the above association failed to validate in the remainder ASPIS follow-up sample (1-sided $P=0.183$, $\beta=-0.06$). For replication genotyping, we selected all SNPs with an association $P < 1 \times 10^{-6}$ in the discovery GWAS sample, and those of the SNPs with a $P < 1 \times 10^{-5}$ located within or near genes encoding proteins with a known function implicated in neuropsychiatric disorders by previous studies and thus could be considered as strong candidates. A total of 29 SNPs were tested in the ASPIS follow-up sample ($n=738$), which was ascertained in an identical manner with the discovery sample but genotyped separately. A complete list of the above and all other associated hits at $P < 0.0001$ with any outcome are presented in Supplementary Tables S1, S2. Two SNPs associated with verbal WM performance (VNB, VNB-RT) nominally replicated (1-sided $P < 0.05$), whereas two additional SNPs showed a trend association (1-sided $P < 0.1$). We note that none of the above associations retained significance after correction for the number of SNPs examined. Because of the significantly better performance of the ASPIS discovery sub-sample compared to the replication sub-sample in the majority of tasks (Supplementary Table S3), likely attributable to our selection of individuals with most complete data in the discovery sub-sample, we considered adjusting the analysis for the most significantly different, the Raven's matrices score. We did not observe major changes in the results, yet the P -value for the SNP associated with SNB (rs16823702), reached uncorrected nominal significance ($P=0.049$). Given the strong correlation of SNB with Raven's score however, this should be interpreted with caution. Furthermore, external replication was attempted in the LOGOS cohort ($n=825$) for 13 SNPs (of the 29 SNPs) strongly associated with neuropsychological outcomes in the ASPIS. No evidence for a robust replication was observed in the LOGOS, besides a nominal association between verbal WM reaction time (VNB-RT) and a marker located 134 kb upstream of *LPP* (LIM domain containing preferred translocation partner in lipoma) gene (rs66491174; 1-sided $P=0.02$). The SNPs with a

suggestive association in either of the two replication samples are shown in Table II.

True Signals Among Highly Associated Genetic Loci

We next sought to investigate whether true positive association signals are present among the most strongly associated GWAS loci ($P_{\text{GWAS}} < 0.001$), using permutations as described in the methods. Nine of the 11 sets of association signals corresponding to the 11 phenotypic outcomes showed more signals than the permutation average. For four of these nine sets the number of signals was reached in less than 5% of the permutations, providing 95% confidence that real associations are among them (Table III). The most striking were the signals observed for VNB and ACV providing 418 and 448 signals respectively, which was never observed in 3,000 permuted data sets (empirical $P < 3.3 \times 10^{-4}$). Ninety-five percent of permutations resulted in less than 379 and 387 signals respectively, indicating with 95% confidence that there are at least 39 true signals for VNB (9.3% of signals) and 61 for ACV (13.6% of signals).

SNP-Based Heritability

We estimated the heritability of the examined phenotypes based on genome-wide SNP data (h^2_{SNP}) in unrelated individuals, using an analytic methodology that has been proven successful in prior studies of complex traits [Benyamin B et al., 2013; Lee SH et al., 2013; Robinson EB et al., 2014]. Even though precise h^2_{SNP} estimates could not be obtained, presumably because of the small sample size and the increased standard errors [Visscher PM et al., 2014], we found that a significant proportion of the phenotypic variance for both verbal and spatial WM accuracy (VNB, SNB) can be attributed to common genetic variation ($P=0.0003$ and $P=0.0004$ respectively), with at least 38% of variance explained by all genotyped SNPs. Lower h^2_{SNP} was observed for sustained attention/vigilance ($P=0.03$).

TABLE II. Follow-Up Replication Analysis Results of Single-SNP Associations

Outcome	SNP ID	Discovery GWAS sample			Replication samples				Nearest gene ^c
		Risk Allele ^a	MAF	P_{GWAS}	P_{ASPIS}^b	N	P_{LOGOS}^b	N	
VNB	rs79739201	C	0.16	6.7E-07	0.041	538	0.069 ^d	825	intergenic
VNB- RT	rs815425	G	0.4	7.2E-06	0.043	522	0.361	747	<i>ERC2</i>
VNB- RT	rs66491174	C	0.13	4.7E-07	0.226	523	0.019	732	<i>LPP</i>
SNB	rs16823702	G	0.14	2.9E-06	0.055	588	na	no genotype	<i>GRIK3</i>
AER	rs10168813	C	0.17	6.3E-06	0.080	741	na	no phenotype	<i>BIN1</i>

na, not available.

^aDenotes worse performance (i.e., lower accuracy, higher RT, higher antisaccade error rate).

^bOne-sided replication P -values are shown.

^cWithin range of LD (where any $r^2 > 0.2$ in 1000 genomes project).

^dOpposite direction of SNP effect.

TABLE III. Permutation-Based Enrichment Analysis for GWAS Top-Associated Genetic Loci

Outcome	GWAS dataset	Permuted datasets		P_{emp}	50th PCTL	N_{obs} -50th PCTL	5th PCTL	N_{obs} -5th PCTL
	N_{obs}	N_{exc}/N_{perm}						
IQ	391	11/1000		0.011	343	48	378	13
CPT	338	60/100		ns	342	-	375	-
CPT-RT	349	36/100		ns	340	9	375	-
VNB	418	0/3000		<0.001	344	74	379	39
VNB-RT	323	84/100		ns	347	-	378	-
SNB	370	7/100		ns	343	27	373	-
SNB-RT	354	33/100		ns	345	10	383	-
ERT	357	25/100		ns	343	14	382	-
ART	381	35/1000		0.035	345	36	378	3
ACV	448	0/3000		<0.001	352	96	387	61
SPEM	335	67/100		ns	345	-	382	-

N_{obs} , number of observed loci at GWAS $P < 0.001$.

N_{exc} , number of permutation where the number of loci at $P < 0.001$ exceeded N_{obs} .

N_{perm} , number of permutations performed.

P_{emp} , empirical P -value. Significant enrichment at $P < 0.05$ is shown in bold.

PCTL, percentile, for example 5th PCTL is the number of loci with $P < 0.001$ in 5% of permutations. ns, not significant ($P_{emp} > 0.05$).

Gene Expression Analysis

Three SNPs showing suggestive evidence of replication in the follow-up ASPIS sample are located within brain-expressed genes (*ERC2*, *GRIK3*, *BIN1*) and their protein products are involved in neuronal processes (details in Supplementary material). As GWAS hits are often expression quantitative trait loci (eQTLs) [Nicolae DL et al., 2010], we asked whether this is also true for the above variants. The correlation between genotype and the expression levels of the respective gene transcripts was examined in the temporal lobe ($N = 162$), the prefrontal cortex ($N = 88$), as well as in the combined sample ($N = 250$), adjusting for brain region. In all, no evidence for a significant eQTL was observed (all $P > 0.1$).

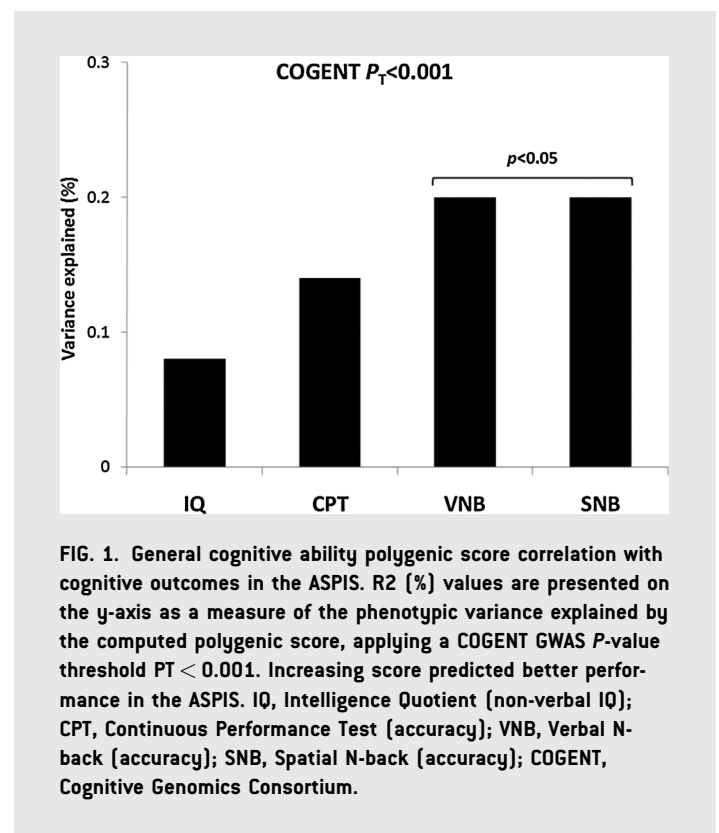
Association With General Cognitive Ability Polygenic Score

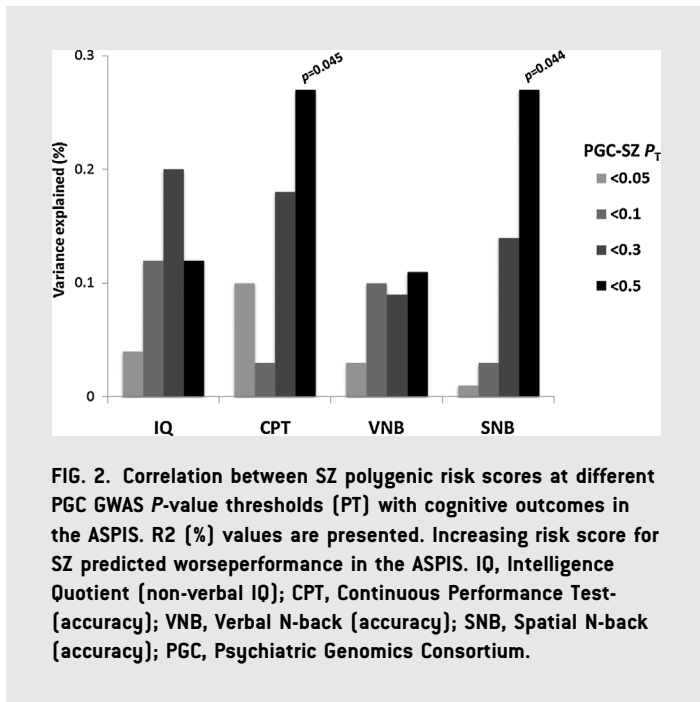
A single PRS was computed based on the reported top-associated SNPs with general cognitive ability by COGENT (COGENT $P_T < 0.001$). We observed a significant correlation (1-sided $P < 0.05$) with verbal and spatial WM accuracy and verbal WM reaction time outcomes (VNB, SNB, VNB-RT) (Fig. 1). A near significant result was noted for sustained attention/vigilance accuracy (CPT $P = 0.051$). Of the top-ranked 1,455 COGENT SNPs with available genotypes in the ASPIS, none reached significance with any of our neurocognitive outcomes after a Bonferroni correction for multiple testing. Similarly, no significant enrichment of nominally associated SNPs was observed, compared to what is expected by chance (binomial test $P > 0.1$).

Polygenic Risk for SZ and Neurocognition

Given the reported shared genetic influences between SZ and neurocognition, we tested the hypothesis that an increased poly-

genic risk score (PRS) for SZ, which defines the aggregate effect of many risk alleles of small effect, would be correlated with poor neurocognitive performance. In Table S3, we show the correlations between the eleven phenotypic outcomes and SZ PRS generated at different PGC GWAS P -value thresholds (P_T). SZ PRS at $P_T < 0.5$





was nominally associated ($P < 0.05$) with both sustained attention/vigilance (CPT) and spatial WM accuracy (SNB) performance (Fig. 2), suggesting a limited but significant genetic overlap with SZ risk loci. A significant correlation was also noted for antisaccade reaction time variability (ACV $P = 0.002$ at $P_T < 0.0001$), however not in the expected direction (high SZ PRS associated with lower variability). Next, we individually tested for association all 128 genome-wide significant SNPs reported by PGC-SZ. After multiple testing corrections, no SNP reached significance with any of the phenotypes, and no excess of single-SNP associations was observed for any of the outcomes (binomial test $P > 0.05$). Nevertheless, nine SNPs were nominally associated with more than one phenotypic outcome in the ASPIS, with SZ risk allele predicting weaker performance (Table IV).

DISCUSSION

The aim of the current study was to evaluate the contribution of common genetic variation to individual neuropsychological and oculomotor performance differences among young adults from the general population, and whether SZ risk loci could predict such differences. We studied traits that represent promising endophenotypes for SZ with presumed less complex biology and influenced by overlapping genetic variation [Braff DL et al., 2007; Glahn DC et al., 2014]. Since compelling evidence has shown that neuro-cognitive disruptions in SZ exist prior to the onset of clinical symptoms [Kahn RS and Keefe RS 2013; Bora E and Murray RM 2013], the discovery of genetic loci implicated in the modulation of cognitive abilities in young adulthood, may shed light into neuronal processes and the underlying molecular mechanisms that, when compromised, increase the risk to develop SZ. Due to the limited power of our discovery sample to detect SNP associations with high confidence, we intended to validate the most promising results in an internal follow-up sample (ASPIS) and an independent sample with almost identical demographic and phenotypic characteristics (LOGOS). Overall, the observed associations replicated weakly and inconsistently; however, given the sample size limitations and the vicinity of genes that are strong functional candidates, these results warrant attention for future genetic and functional studies. The marker showing the strongest association with sustained attention/vigilance, which surpassed genome-wide significance cut-off, is of potential interest since it is located within a brain expressed gene (*CNTNAP5*) previously implicated in neuropsychiatric diseases with known disturbances in sustained attention, that is bipolar disorder, autism and attention-deficit hyperactivity disorder [Djurovic S et al., 2010; Pagnamenta AT et al., 2010; Neale BM et al., 2010]. *CNTNAP5* protein belongs to the neuroligin superfamily of cell-adhesion molecules, which have been shown to constitute key regulators of synapse formation and neurotransmission [Anderson GR et al., 2012; Karayannis T et al., 2014]. Suggestive evidence of association was observed for three additional loci, located within genes whose protein products are involved in glutamatergic signaling (*GRIK3*) and synaptic vesicle

TABLE IV. PGC-SZ Genome-Wide Significant SNPs Nominally Associated With Multiple ASPIS Phenotypes

SNP ID	Location	ASPIS	Best ASPIS	PGC-SZ	Genes in region
		Outcomes	P -value	P -value	
rs12421382	11q22.3	VNB, SNB	7.8E-04 (VNB)	3.7E-08	C11orf87
rs7523273	1q32.2	CPT, ACV	2.0E-02 (CPT)	4.5E-08	CD46, CR1L, CD34
rs6704641	2q33.1	SNB, SPEM	7.5E-03 (SPEM)	8.3E-09	SATB2
rs7819570	8q21.3	SNB-RT, VNB-RT	2.9E-03 (SNB-RT)	1.2E-08	MMP16
rs4129585	8q24.3	CPT-RT, SNB-RT	7.2E-03 (CPT-RT)	1.7E-15	TSNARE1
rs7893279	10p12.31	CPT, VNB	3.4E-02 (CPT)	2.0E-12	CACNB2
rs77502336	11q24.1	IQ, SPEM	4.3E-03 (IQ)	7.5E-09	GRAMD1B
rs2068012	14q12	VNB, SNB	1.9E-02 (VNB)	1.4E-08	PRKD1, MIR548AI

PGC, psychiatric genomics consortium.
Two-sided P -values are shown.

trafficking processes (*ERC2*, *BINI1*). Genetic variation within *GRIK3* has been previously linked to SZ and developmental delay [Djurovic S et al., 2009; Takenouchi T et al., 2014].

Our analyses suggest that while single-SNP effects are small, the aggregate effect of common SNPs (SNP-heritability) can explain a substantial portion of the phenotypic variance for at least two phenotypes, verbal and spatial WM accuracy (N-back task). Of note, this result represents a direct replication of the significant SNP-heritability observed independently for N-back performance in a cohort of healthy young adults [Vogler C et al., 2014]. Moreover, these findings are in agreement with reported heritability estimates of diverse cognitive abilities in children and adolescents using the same genetic approach [Benyamin B et al., 2013; Trzaskowski M et al., 2013; Roninson EB et al., 2014], supporting the contribution of multiple common variants to neurocognitive functioning. Twin and family studies in clinical and non-clinical samples have also revealed a considerable heritability for WM [Greenwood TA et al., 2007; Wilson RS et al., 2011; Goldberg X et al., 2013], as well as a significant genetic relationship between general cognitive ability and aspects of executive function, including WM [Aukes MF et al., 2009; Lee T et al., 2012]. In addition, neuroimaging findings in young twins of the same age range as the participants in the current study, who performed the same WM N-back task, demonstrated an increased heritability for WM-related brain activation [Blokland GA et al., 2011]. Jointly, the above observations underscore the strong influence of genetic components on WM, which has been shown to be a reliable endophenotype for SZ [Horan WP et al., 2008].

While the sample size of the ASPIS did not allow robust genetic associations for individual loci, our permutation analyses detected significantly more associated loci than the null expectation for 4 of the 11 outcomes tested, suggesting that within our strongest signals there are true-positives and allowing an estimate of their minimum number at 95% confidence. Verbal WM and intra-subject reaction time variability in the antisaccade task showed the most promising results, with an estimate of at least 39 and 61 true-positives among the 418 and 448 top-associated signals with $P < 0.001$ respectively, and with such numbers of signals not reached in 3,000 permutations. These results are encouraging for future genome-wide and follow-up studies as they suggest that there are some relatively strong genetic effects influencing these phenotypes and they will likely be among the first to reach genome-wide significance with the inclusion of additional individuals. It is of interest that the intra-subject antisaccade reaction time variability is an oculomotor measure that we have repeatedly found to show different distributions between SZ cases and controls, and therefore may prove a useful SZ endophenotype [Smyrnis N et al., 2009; Theleritis C et al., 2014].

On another front, our results provide independent validation of previously reported GWAS findings on human general cognitive ability. Although we could not replicate individual single-SNP associations, likely due to small effect sizes of the respective variants, the cumulative effect of multiple SNPs, as indexed by the computed polygenic score, shows correlation with WM which is central to general cognitive ability and a key component of the composite phenotypic construct analyzed by COGENT [Lencz T et al., 2014]. Applying the same polygenic strategy, we explored the

extent of the overlapping genetic determinants between neurocognitive performance and SZ risk, if any. To the best of our knowledge, this is the first general population study assessing the contribution of a SZ polygenic risk score derived from the largest to date SZ GWAS meta-analysis [Ripke S et al., 2014], on cognitive and oculomotor performance. We found weak evidence that SZ risk alleles predispose to aberrant sustained attention and spatial WM, at least in young adulthood. We acknowledge that this result could not be considered striking in terms of the obtained statistical evidence in our limited number of individuals; yet it is in agreement with the genetic overlap between neurocognition and SZ observed in twin and family studies [Toulopoulou T et al., 2007, 2010]. Similar findings have also been reported for general cognitive ability by COGENT which studied a much larger sample than the ASPIS, as well as for WM-related prefrontal brain activation in a small cohort of SZ patients and healthy controls [Kauppi K et al., 2014]. We may, therefore, hypothesize that the overlapping variants could modify the function of genes that orchestrate neurodevelopmental processes implicated to both cognitive dysfunction and psychosis (Bora E and Murray RM 2013); however this hypothesis cannot be tested with the existing data. It should be stressed that our results are based on measurements in healthy individuals, thus we cannot rule out a more pronounced effect of PGC-SZ polygenic risk on neurocognitive functioning in a clinical population.

Taken together, our GWAS results reveal associations within or near genes encoding proteins with well-defined neuronal functions and potentially vital involvement in mechanisms shaping human neurocognition, although independent studies will be needed to adequately validate the reported findings. Furthermore, this study underscores the polygenic nature of WM and its genetic relationship with SZ, which even though is of minor magnitude, strengthens the notion that WM may represent a highly suitable phenotype for future collaborative efforts, aiming at the identification and characterization of genetic risk factors that enhance both symptoms of psychopathology and neurocognitive impairment.

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