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Schizotypy, cognitive performance, and genetic risk for schizophrenia in a non-clinical population

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ABSTRACT

Schizophrenia risk alleles are expected to mediate effects on cognitive task performance, and aspects of personality including schizotypy, in nonclinical populations. We investigated how 32 of the best-validated schizophrenia risk alleles, singly and as summed genetic risk, were related to measures of schizotypal personality and measures of two aspects of cognitive performance, verbal skills (vocabulary) and visual-spatial skills (mental rotation), in healthy individuals. Summed genetic risk score was not associated with levels of total schizotypy or its three main subscales. Similarly, genotypic variation at none of the individual risk loci was related to cognitive performance measures, after correction for multiple tests. Higher overall genetic risk score was, however, associated with lower performance on the mental rotation test in males, with a broad set of loci contributing to this effect. These results imply that there is a lack of linear, genetically-based continuity connecting schizotypal cognition with the expression of schizophrenia itself, and indicate that, for males, higher genetic risk of schizophrenia exerts negative effects on visual-spatial skills, as measured by mental rotation.

1. Introduction

Risk alleles for schizophrenia influence the expression of this disorder via effects on aspects of neurodevelopment, neurological mechanisms, cognitive and affective functions, and personality variation (Kendler, 2005). Within the past several years, a large set of well-validated, common schizophrenia risk alleles has been identified (Allen et al., 2008). These findings provide the first opportunities to ascertain how schizophrenia risk alleles, singly and together, mediate schizotypy-related phenotypes and aspects of cognitive performance in non-clinical populations. Such studies are important because they elucidate how genetic and phenotypic variation within non-clinical populations is related to risk of psychiatric conditions, which provides insights into both normal cognitive-affective architecture and its dysregulation in disease.

An emerging body of literature shows that individual schizophrenia risk alleles, despite small odds ratios, show notable effects on levels and patterns of schizotypy and cognitive performance in healthy controls. Several studies have documented associations of schizotypy with schizophrenia risk alleles in healthy populations, using the Schizotypal Personality Questionnaire (SPQ; Cohen, Matthews, Najolia, & Brown, 2010). Thus, Yasuda et al. (2011) showed that individuals carrying the risk allele in the ZNF804A gene showed higher Total Schizotypy, as well as higher Disorganization. Similarly, Ohi et al. (2012) found that healthy carriers of the p250GAP gene risk allele showed higher Total Schizotypy, and higher scores for the Interpersonal factor. In contrast to these positive associations of schizotypy with schizophrenia risk alleles, Stefanis et al. (2008) reported that healthy male carriers of an RGS4 gene risk allele scored lower on the Interpersonal subscale. As well, Kircher et al. (2009) reported lower scores on Total Schizotypy and the Interpersonal Deficit subscale in healthy carriers of a DTNBP1 risk allele. Stefanis et al. (2007) likewise showed that risk alleles of two DTNBP1 SNPs were associated with lower Positive and Paranoid schizotypy scores. The causes for these divergent results among studies remain unclear, but they may be related to differences between schizophrenia risk SNPs in how they mediate aspects of schizophrenia-related cognition and personality.

With regard to cognitive tasks, most studies have shown that schizophrenia risk alleles are associated with reduced performance in healthy individuals (e.g., Tan et al., 2008; Zhang, Burdick, Lencz, & Malhotra, 2010), but multiple studies have indicated that healthy carriers of schizophrenia risk alleles show enhanced performance for some abilities (e.g., Jablensky et al., 2011; Jansen et al., 2009). Reasons for such enhanced performance remain uncertain, although they may be associated with the types of cognitive tests used, differences among populations studied, and variation among SNPs in their effects.

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Overall effects of genetic risk for schizophrenia on schizotypy and task performance, as compared to effects of individual SNPS, can be quantified by summing across risk alleles carried by an individual. Walton et al. (in press) calculated genetic risk scores (GRS) using 41 SNPs in 34 genes from the SZGene database 'Top Results' list (Allen et al., 2008) and found associations of GRS with prefrontal brain activity, though not performance, during a working memory task. Derks et al. (in press) reported that GRS, calculated using genome-wide genotype data, significantly differentiated case versus control status, but they found no association between GRS and any of five psychosis dimensions within each status group. These results raise the question of why genetic risk scores should predict schizophrenia presence or absence, but not dimensional schizotypy in healthy populations, given that we expect continuous underlying genetic liability and expression of subclinical schizophrenia-related phenotypes (Lenzenweger, 2010).

To elucidate the effects of schizophrenia risk SNPs and cumulative genetic risk on measures of schizotypy and domains of cognitive performance, we genotyped a large non-clinical population sample for 32 schizophrenia-associated SNPs ('Top Results' risk SNPs, Allen et al., 2008). We used these data to evaluate three hypotheses concerning associations of GRS, or GRS and individual risk loci, with measures of personality and cognitive performance.

First, we attempted to replicate the counter-intuitive findings of Derks et al. (in press), that schizotypy scores are unrelated to genetic risk of schizophrenia in non-clinical populations. In doing so, we predicted *a priori* that GRS would not predict total schizotypy, or scores on its three major subscales, as measured by the SPQ (Cohen et al., 2010). We also conducted *a posteriori* analyses (with corrections for multiple testing, as described below) for associations of individual loci with these measures of schizotypy.

Second, based on results from Jiménez, Mancini-Marïe, Lakis, Rinaldi, and Mendrek (2010), who found that healthy males performed significantly better on a mental rotation task than did males with schizophrenia, but that no such difference existed for females, we predicted *a priori* that males, but not females, with higher overall genetic risk of schizophrenia would exhibit lower mental rotation scores. These predictions are predicated on the observations that mental rotation ability is highly heritable (Johnson, Nijenhuis, & Bouchard, 2007; Vuoksimaa et al., 2010; Suzuki, Shikishima, & Ando, 2011), shows sex differences (e.g., Vuoksimaa et al., 2010), and represents an important, independent component of current psychometric models for intelligence (Johnson & Bouchard, 2005; Johnson et al., 2007).

Third, a study by Kravariti et al. (2006) documented a strong association of low visual-spatial skills, relative to verbal skills, with pedigree-based genetic risk of schizophrenia (for males and females pooled). Based on these results, we predicted *a priori* that individuals with higher overall genetic risk (as measured by the GRS), would exhibit lower performance on a measure of visual-spatial skills, relative to their performance on a verbal skills test, as described below.

2. Materials and methods

2.1. Sample

Questionnaire data and saliva samples for DNA extraction were collected from 519 Caucasian undergraduate students (331 females and 188 males) at both University of Alberta and Simon Fraser University. All protocols were carried out according to guidelines established by ethics boards of both universities.

2.2. Genetic data

We extracted genomic DNA from mouthwash samples provided by each participant. For genotyping, we selected 33 common SNPs (minor allele frequency > 0.1) from the 24 top-ranked genes listed by the Schizophrenia Gene (SZGene) database (Allen et al., 2008) in February 2012 (Supplementary Table S1). We included SNPs from the following genes: AHI1 (rs1154801, rs2064430), AKT1 (rs3803300), C6orf217 (rs10223338), CCKAR (rs1800857), DAOA (rs3916971, rs778293), DISC1 (rs999710), DRD2 (rs6275, rs6277), DTNBP1 (rs1474605, rs3213207), GABRB2 (rs1816072), GWA_11p14.1 (rs1602565), GWA_16p13.12 (rs7192086), HIST1H2BJ (rs6913660), HTR2A (rs6311), MDGA1 (rs11759115, rs12191311), NOTCH4 (rs2071287), NRG1 (rs10503929), NRGN (rs12807809), PDE4B (rs910694), PPP3CC (rs10108011), PRSS16 (rs13219354, rs6932590), RELN (rs262355, rs7341475), RGS4 (rs2661319), RPP21 (rs3130375), TPH1 (rs1799913, rs1800532), and ZNF804A (rs1344706).

Genotyping was performed by Genome Québec (Montréal, Canada). We scored genotypes using a dominant inheritance model; individuals carrying one or more risk alleles were compared to individuals carrying no copies of the risk allele. Two SNPs from the TPH1 gene (rs1799913 and rs1800532) are in strong linkage disequilibrium ($r = 1$), as is also shown in Walton et al. (in press); criteria $r^2 > 0.8$. Therefore we only include one of these SNPs (rs1799913) in our analyses.

2.3. Genetic risk score calculations

We calculated both a weighted and unweighted version of the GRS. The weighted GRS used the same formula as in Walton et al. (in press), using the log of the odds ratio of an allele for each SNP, multiplied by the number of risk alleles and summed for all loci. Odds ratios in Caucasian populations were taken from SZGene.org (Allen et al., 2008); if Caucasian ORs were unavailable, then the total OR for all populations was used (Supplementary Table S1). For the unweighted GRS, we averaged the number of risk alleles across all loci, treating all SNPs equally. The weighted GRS is calculated under the assumption that ORs are accurately estimated, and that SNPs with higher ORs contribute more to genetic risk of the schizophrenia phenotype than those with low ORs. By contrast, the unweighted GRS assumes no difference in amount of risk associated with individual SNPs. For consistency with recent applications of GRS calculation in the literature (Falcone et al., 2012; Piccolo et al., 2009), we include both weighted and unweighted GRS measures. All statistical analyses were performed using R version 2.15.1 (R Core Team, 2012).

2.4. Psychometric measures

We measured schizotypy using the Schizotypal Personality Questionnaire-Brief Revised (SPQ-BR; Cohen et al., 2010). We tested *a priori* for associations of Total Schizotypy, and its three major subscales (Interpersonal, Cognitive-Perceptual, and Disorganization) with genetic risk scores using Pearson product-moment correlations. *A posteriori* tests were conducted for associations of Total Schizotypy and its subscales with individual schizophrenia risk SNPs, using *t*-tests. Overall, 32 SNPs were tested for association with four schizotypy measures, yielding 128 tests; we adjusted for multiple tests using a False Discovery Rate (FDR) set at 0.05 (Benjamini & Hochberg, 1995). All statistical analyses using SPQ scores were performed on the total sample of individuals, with males and females pooled together.

To assess verbal skills, we used the Mill Hill Vocabulary Scale from the Raven Progressive Matrices (Raven, Raven, & Court, 1998) and to measure spatial skills, we used the mental rotation task (MRT; Peters et al., 1995). For each test, number of questions correctly answered yielded scores. We tested for an association of genetic risk scores with Vocabulary score, relative to MRT score, using the Pearson product-moment correlation, with the sexes

pooled. To generate the measure of relative performance, we normalized scores for each test via dividing by the maximum possible score and then dividing normalized Vocabulary score by normalized MRT score. This test was conducted on both sexes pooled (as an *a priori* test, as done by Kravariti et al., 2006), and also on males and females separately (as an *a posteriori* test using FDR correction as described above), to account for any sex differences in test performances. We also tested for associations of Vocabulary score, relative to MRT score, with individual schizophrenia risk SNPs using *t*-tests; these tests were also subjected to correction for multiple comparisons (as described above).

We tested for associations of genetic risk scores with MRT scores using Pearson product-moment correlations. Based on our *a priori* expectation of an effect for males but not for females, we analyzed males and females separately. We also used a Wilcoxon signed-rank test to quantify the magnitude and direction of individual SNPs contributions to the summed genetic effect. This analysis allows us to determine if any GRS–MRT association was driven by relatively few SNPs of strong affect, versus many SNPs of weak affect. We also tested for associations of MRT with individual schizophrenia risk SNPs using *t*-tests; these tests were subjected to correction for multiple comparisons using False Discovery Rate adjustments, set at the 0.05 level (Benjamini & Hochberg, 1995).

3. Results

3.1. Schizotypy

Of the 32 SNPs, six (19%) showed nominal (uncorrected) *t*-test significance with one or more of the higher-level subscales of the SPQ, but none of these tests survived adjustment for multiple testing (Table 1; Supplementary Table S2). Neither weighted nor unweighted GRS was significantly correlated with Total Schizotypy or any of the SPQ subscales (all tests $p > 0.35$, uncorrected; Supplementary Table S3).

3.2. Cognitive tasks

Of the 32 SNPs, three (9%) showed nominal (uncorrected) significance for Vocabulary score relative to MRT score, but none of these tests survived adjustment for multiple testing (Supplementary Table S4). Neither weighted nor unweighted GRS was significantly correlated with the Vocabulary score relative to MRT score (all tests $p > 0.75$, uncorrected; Supplementary Table S5).

MRT score was negatively correlated with unweighted GRS in males ($r = -0.145$, $t = -1.999$, df = 186, $p = 0.047$; Fig. 1), indicating that males with more risk alleles performed significantly worse on the mental rotation task. Overall, risk-allele carriers showed lower mean MRT performance for 14 (61%) of 23 SNPs, with the overall sign and magnitude of these mean differences significant by a Wilcoxon sign-rank test (Supplementary Table S6; $W = 160$, $Z = 2.43$, 2-tailed $p = 0.015$). The high proportion of SNPs showing this difference indicates that a broad range of the risk alleles contributed to the association, rather than just a small subset. Females did not show a correlation between unweighted MRT and GRS ($r = 0.031$, $t = 0.566$, df = 329, $p = 0.572$), nor a difference in MRT performance by a Wilcoxon sign-rank test ($W = 24$, $z = 0.32$, 2-tailed $p = 0.75$).

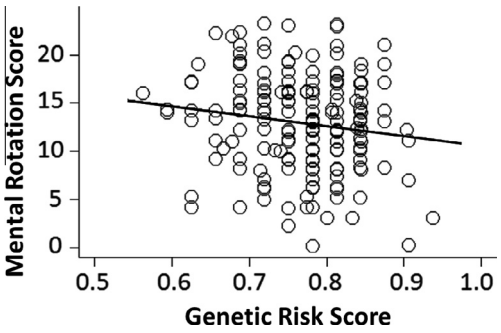

Fig. 1. Pearson's correlation of unweighted genetic risk score (GRS) with mental rotation test (MRT) performance, for males ($r = -0.145$, $p = 0.047$).

4. Discussion

4.1. SPQ

4.1.1. Individual SNPs

Overall, we found an absence of evidence for positive associations of individual schizophrenia risk alleles with Total Schizotypy, or scores on any of the three main subscales (Table 1). As regards overlap of our results with previous tests, Stefanis et al. (2008) reported that healthy male carriers of the rs2661319 (RGS4) risk allele scored lower on the Interpersonal subscale. We also found lower Interpersonal scores associated with this risk allele, as well as lower scores on Cognitive-Perceptual and Total Schizotypy, prior to correction for multiple testing (Table 1).

4.1.2. Genetic risk scores

As also found by Derks et al. (in press) using a larger set of schizophrenia risk alleles, our data clearly demonstrate that genetic risk scores do not predict Total Schizotypy or scores on any of the three major schizotypy subscales. These findings appear counterintuitive, given a general expectation that alleles contributing to schizophrenia risk should also contribute to schizotypal traits along a continuum (Lenzenweger, 2010).

Four important considerations from previous work caution against expectations of simple, positive linear relationships be-

Table 1
SNPs nominally significant by ANOVA with scores on higher-level SPQ subscales. Results shown are for all subjects using a dominant inheritance model where risk allele group size $N \geqslant 10$.

Gene	SNP	Risk allele carrier performance	*p*-Value	FDR-adjusted *p*-value
HIST1H2BJ	rs6913660	↑ Cognitive	0.0134*	0.4147
NRG1	rs10503929	↑ Cognitive	0.0473*	0.6028
PDE4B	rs910694	↓ Schizotypy	0.0475*	0.6028
PRSS16	rs6932590	↑ Cognitive	0.0363*	0.6028
		↑ Schizotypy	0.0266*	0.5675
RELN	rs262355	↑ Interpersonal	0.0118*	0.4147
		↑ Disorganized	0.0401*	0.6028
RGS4	rs2661319	↓ Interpersonal	0.0162*	0.4147
		↓ Cognitive	0.0125*	0.4147
		↓ Schizotypy	0.0155*	0.4147

* $p < 0.05$.

tween schizophrenia risk alleles and schizotypy. First, although full siblings and parents of patients with schizophrenia tend to show higher levels of schizotypal traits (e.g., Tarbox & Pogue-Geile, 2011) such findings may not be directly relevant to non-clinical populations since these populations are expected to exhibit much lower overall genetic loadings for schizophrenia risk alleles than do first-degree relatives.

Second, individual schizophrenia risk alleles do not show consistent positive, or negative, effects on schizotypy in non-clinical populations across previous studies (Kircher et al., 2009; Stefanis et al., 2007, 2008; Yasuda et al., 2011), nor do our results show any such patterns. As a result, there is no necessary expectation from studies of individual SNPs that summed genetic risk scores should be positively associated with levels of schizotypy.

Third, the relationship between schizophrenia risk alleles and schizophrenia-associated phenotypes may be strongly non-linear, as documented in some previous analyses. For example, non-linear effects have been observed in the COMT 'inverted-U' dose–response of dopamine signalling in prefrontal cortex, a system strongly implicated in schizophrenia risk (Egan et al., 2001; Meyer-Lindenberg et al., 2007) and in cognitive control generally (Cools & D'Esposito, 2011). Epistatic interaction effects between sets of contributing alleles at different loci have also been well documented (e.g., Harrison & Owen, 2003; Nicodemus et al., 2007), and may contribute to non-linearity for larger sets of summed multi-locus effects.

Finally, non-clinical individuals may vary in resilience to the effects of schizophrenia risk alleles (Lenzenweger, 2010, p. 149), such that summed genetic risk derived from case–control comparisons would not necessarily predict levels of schizotypy. Individual variation in resilience would presumably be affected by genetic and environmental factors, which are not accounted for in the analyses conducted here. Determining what factors, if any, protect against deleterious impacts of schizophrenia risk alleles, or personality-level effects of such alleles, represents an important direction for future research.

4.2. Cognitive performance

4.2.1. Genetic risk scores

We found no associations of genetic risk for schizophrenia with verbal relative to visual-spatial performance, for individual SNPs or GRS. These findings contradict the results of Kravariti et al. (2006), who demonstrated that higher pedigree-based genetic risk of schizophrenia, among non-clinical individuals of both sexes, was strongly associated with lower visual-spatial skills relative to verbal skills; Purcell, Lewine, Caudle, and Price (1998) similarly showed that males with schizophrenia exhibited higher verbal IQ relative to performance IQ. Both Kravariti et al. (2006) and Purcell et al. (1998) quantified verbal skills and visual-spatial skills using the Wechsler Adult Intelligence Scale – Revised (WAIS – R; Wechsler, 1981), whereas we applied a Vocabulary Scale from the Raven Progressive Matrices (Raven et al., 1998). Differences between our results and previous findings could be related to differences in the tests used to evaluate verbal and visual-spatial abilities; differences in the populations analyzed, and lower genetic loadings for schizophrenia in our population.

Consistent with the results of Jiménez et al. (2010), and the high heritability of mental rotation ability (Johnson et al., 2007; Vuoksimaa et al., 2010; Suzuki et al., 2011), we found a relationship between higher overall genetic risk of schizophrenia (as measured by the unweighted GRS) and lower performance on the mental rotation test in males, but not in females. Moreover, a notable proportion (61%) of schizophrenia risk alleles contributed to the pattern found in males. Such correlations of schizophrenia genetic risk scores with indices of cognitive task performance have not been previously reported, and may provide useful insights into the collective effects of schizophrenia risk alleles in non-clinical populations, and the mechanisms whereby increased genetic risk translates into expression of psychiatric disease. Our findings thus suggest that reduced visual-spatial skills in schizophrenia may have a polygenic basis that also mediates variation in visual-spatial abilities among non-clinical individuals. Replication of these results will be important given that significance was at the 0.05 level, and the effect size was small (with only about 2% of variance in MRT explained by GRS). Studies involving a broader set of visual-spatial tests, and a larger set of schizophrenia-risk alleles, are required to comprehensively evaluate the hypothesis.

4.2.2. Conclusions

Our findings, considered in conjunction with previous work, suggest that schizophrenia risk alleles, singly or combined, have low predictive power as regards associations with schizotypy in non-clinical populations. By contrast, in our study, genetic risk score negatively predicted mental rotation ability in males, and a substantial proportion of the risk alleles influenced expression of this phenotype. Additional studies on the cognitive and personality correlates of schizophrenia risk alleles in non-clinical populations should provide useful insights into the functional effects of such allelic variation.

4.3. Limitations

The primary limitations of our study include: (1) the use of undergraduate populations, which may not be representative of larger-scale populations, (2) the use of only 32 schizophrenia risk loci, rather than a larger set, and (3) deployment of only two cognitive tests, which reduces the generality of interpretation.

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Contributors

Crespi and Hurd designed the study and wrote the protocol. Hurd collected questionnaire data and mouthwash samples. Leach undertook the statistical analyses. Leach and Crespi managed literature searches and wrote the manuscript draft. All authors contributed to, and approved, the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.paid.2013.03.010.

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