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# Segregating polymorphism in the NMDA receptor gene *GRIN2A*, schizotypy, and mental rotation among healthy individuals

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ABSTRACT

Common alleles associated with psychiatric disorders are often regarded as deleterious genes that influence vulnerability to disease, but they may also be considered as mediators of variation in adaptively structured cognitive phenotypes among healthy individuals. The schizophrenia-associated gene *GRIN2A* (glutamate ionotropic receptor NMDA type subunit 2a) codes for a protein subunit of the NMDA (N-methyl-D-aspartate) receptor that underlies central aspects of human cognition. Pharmacological NMDA blockage recapitulates the major features of schizophrenia in human subjects, and represents a key model for the neurological basis of this disorder. We genotyped two functional *GRIN2A* polymorphisms in a large population of healthy individuals who were scored for schizotypy and mental imagery/manipulation (the mental rotation test). Rare-allele homozygosity of the promoter microsatellite rs3219790 was associated with high total schizotypy (after adjustment for multiple comparisons) and with enhanced mental rotation ability (nominally, but not after adjustment for multiple comparisons), among males. These findings provide preliminary evidence regarding a genetic basis to previous reports of enhanced mental imagery in schizophrenia and schizotypy. The results also suggest that some schizophrenia-related alleles may be subject to cognitive tradeoffs involving both positive and negative effects on psychological phenotypes, which may help to explain the maintenance of psychiatric-disorder risk alleles in human populations.

## 1. Introduction

Mental illnesses are most commonly regarded from medical perspectives as purely deleterious diseases, caused by some combination of deleterious genes and suboptimal environments. This viewpoint contrasts with evolutionary-medical standpoints, which posit that phenotypes and symptoms of mental illnesses can also be considered, to some degree, as maladaptive extremes of usually-beneficial traits or as extremes of tradeoffs or imbalances between cognitive and neurological states (Crespi, 2016). A longstanding example from this perspective is the 'strong imagination' found among many individuals with psychotic and affective (mood-associated) disorders, especially schizophrenia and bipolar disorder (Crespi et al., 2016; Nettle, 2001). Enhanced imagination in this context clearly supports interests and achievements in visual arts, literature, and other imagination-based arenas (e. g., Campbell and Wang, 2012), but mediates the development of psychotic symptoms (hallucinations and delusions) if deviations from reality become too extreme.

Most analyses of the benefits and costs associated with psychiatric conditions have focused at the level of phenotypes, but such traits are expected to evolve genetically.

Recent studies of psychiatric conditions have uncovered large numbers of genome-wide significant common alleles of small effect, which are usually considered as 'risk' alleles for mental diseases. By an evolutionary-genetic perspective, some so-called psychiatric risk alleles and loci may underlie cognitive tradeoffs, such that one allele or genotype is associated with relative benefits in one context, and the alternative allele or genotype with relative benefits in another, different context (e. g., Carter and Nguyen, 2011; Crespi and Go, 2015). Under this paradigm, many common psychiatric-effect alleles underlie psychological phenotypes with both genetically-based benefits (in terms of enhanced abilities for some tasks, or other advantages) and costs (in terms of reduced ability at other tasks, or increased liability to some set of psychiatric disorders).

Examples of psychiatric risk alleles that mediate apparent cognitive-affective tradeoffs include the single nucleotide polymorphism (SNP) rs4680 in the gene *COMT* (catechol-o-methyltransferase), a key determinant of prefrontal dopamine metabolism; for this nonsynonymous

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SNP, Val carriers exhibit reduced cognitive efficiency (prefrontally-modulated executive function) but improved emotion regulation, compared to Met homozygotes (Mier et al., 2010). Similarly, the SNP rs4570625 in the *TPH2* gene (tryptophan hydroxylase 2), which mediates serotoninergic neurotransmission, exhibits evidence of an alternative-genotype based tradeoff of emotionality (neuroticism and negativity) with executive control (Strobel et al., 2007). The general importance of genetically based tradeoffs between different mental phenotypes remains largely unknown, however, because few studies have tested for either positive effects of psychiatric-disease risk alleles in expected contexts, or for multiple effects of such loci that are indicative of their normal roles in healthy individuals. Such studies are important not just to characterize the effects of psychiatric risk alleles, but also to evaluate the degree to which genetically based cognitive and affective tradeoffs underlie human psychological architecture.

Schizophrenia is a paradigmatic polygenic disorder characterized by some mixture of 'positive' (new phenotype) symptoms, such as hallucinations, delusions, and bizarre or disorganized thought and behavior, and 'negative' (reduced phenotype expression) symptoms, including apathy, social withdrawal, reduced speech, anhedonia, diminished emotionality, and impaired attention. The relation of positive to negative symptoms remains unclear, at the levels of genes, neurodevelopment, and neural functions (Frith, 2014). Schizophrenia is considered as a threshold disease phenotype based on present versus absent diagnosis, but its symptoms, and genetic and environmental causes, exhibit continuous variation grading into normality, with 'schizotypy' referring to schizophrenia-associated personality traits and clinical phenotypes expressed at attenuated, non-clinical levels (e. g., Van, 2010).

A key model for studying schizophrenia is based around pharmacological antagonism of the NMDA (N-methyl D-aspartate) receptor, a neural membrane-bound ion channel molecule composed of multiple protein subunits, that is found at high densities throughout the cerebral cortex and hippocampus (Paoletti et al., 2013). Antagonism of this receptor with ketamine, MK-801 or phencyclidine can generate the major symptoms of schizophrenia, in both humans and rodents (Moghaddam and Krystal, 2012). The gene *GRIN2A* (glutamate ionotropic receptor NMDA type subunit 2A, at 16p13.2), which codes for a key subunit of the NMDA receptor, exhibits two genetic elements that show well-replicated associations with schizophrenia risk: (1) the SNP rs9922678 (at position 9946,069 in GRC37/hg19), one of 108 genome wide significant schizophrenia risk loci (Ripke et al., 2014); and (2) the microsatellite rs3219790 at position 10,277,175)(Liu et al., 2015). Length variation in the CA-motif repeat units of this microsatellite marker has been associated with expression levels of *GRIN2A* (Itokawa et al., 2003; Liu et al., 2015) and with schizophrenia risk (Iwayama-Shigeno et al., 2005; Tang et al., 2006; Liu et al., 2015). The microsatellite polymorphism is also associated with several correlates of schizophrenia including liability to bipolar disorder (Itokawa et al., 2003), heroin or alcohol dependence (Domart et al., 2012; Zhao et al., 2013, 2014), and hippocampal and amygdala volumes (Inoue et al., 2010), indicating a range of related functional effects.

The markers rs9922678 and rs3219790 can be considered as well-validated schizophrenia risk loci, with functional connections to the causes and phenotypes of this disorder, but neither has been studied in non-clinical populations to evaluate their psychological and personality-level effects. In this study, we addressed the hypothesis that these schizophrenia risk loci exert effects on two specific psychological phenotypes in healthy populations: (1) schizotypy, and (2) mental rotation, which involves mental imagery, imagination and object-manipulation, and has been demonstrated as enhanced or spared in schizophrenia and high schizotypy by several recent studies (Thakkar and Park, 2012; Benson and Park, 2013; Matthews et al., 2014; Ettinger et al., 2015). Our primary objective is to determine the nature and degree to which these two schizophrenia risk loci mediate joint effects on these phenotypes in normal populations, as predicted from previous work. In particular, based on previous studies at the phenotypic level, we expect positive associations, at the phenotypic and/or genetic levels, between high schizotypy and enhanced mental rotation ability.

## 2. Methods

### 2.1. Participants and ethics

We collected data from 812 undergraduate students (537 females and 275 males). The work was approved by Human Research Ethics at University of Alberta and by the Simon Fraser University Research Ethics Board, and participants provided written informed consent prior to engaging in the study.

### 2.2. Psychological measures

We assessed levels of schizotypy using the Schizotypal Personality Questionnaire-Brief Revised (SPQ-BR) (Callaway et al., 2014). This instrument comprises 32 items using a 5-point Likert scale, with response choices that range from 'strongly disagree' to 'strongly agree'. It includes seven subscales, (1) constricted affect and (2) social anxiety (which make up the 'Interpersonal' subscale); (3) magical thinking, (4) unusual perceptions, and (5) ideas of reference (which make up the 'Cognitive-Perceptual' subscale); (6) eccentric behavior and (7) odd speech (which make up the 'Disorganized' subscale). Total Schizotypy is the sum of all three higher-level subscales, with 'positive' schizotypy including the latter two and 'negative' schizotypy represented by the 'Interpersonal' subscale. SPQ-BR scores can range from 0 to 160, with higher scores indicating higher levels of schizotypy. Scores for one SPQ-BR question were missing due to technical error for 38 samples, and were interpolated from the average of the other questions in the relevant subscale.

We focused in our analyses mainly on Total Schizotypy, as an overall measure of this psychological phenotype; we also report exploratory results for the three higher-level subscales. Cronbach's alpha was 0.72 from the SPQ-BR data.

The mental rotation test, used to evaluate mental imagery/manipulation, requires subjects to rotate a three-dimensional object and choose one figure, out of four possible options, that correctly matches a target object (Vandenburg and Kuse, 1978). A total of 24 object sets are provided, and each correct answer scores one point.

### 2.3. DNA data collection

DNA was collected through salivary samples (which comprise mainly lymphocytes and buccal cells) from mixed Caucasian individuals over two years from the University of Alberta and Simon Fraser University. For genotyping of the microsatellite locus rs3219790, DNA samples were amplified with the primers: Forward: 5 ' GAAGGA AGCATGTGGGAAATGCAG 3′ (fluorescent labeled), and Reverse: 5′ GTTTCTTGCTGGGTACAGTTATCCCCCT 3′). PCR was conducted in a Perkin-Elmer 9700 thermal cycler with stage 1: 95 C for 5 min; stage 2: 30 cycles of 95 °C for 30 s, 56 °C for 30 s, 72 °C for 40 s; and stage 3: 72 °C for 10 min. Amplified samples were genotyped using a LI-COR 4300 Genetic Analyzer apparatus and genotypes were scored for length using GeneImagIR software (Version 3.52, Scanalytics, LI-COR, Inc., Lincoln, NE). Genotyping of the SNP rs9922678 was conducted by Genome Québec (Montréal, Canada) using the Sequenom Mass-ARRAY iPlex platform. Successful call rates were 99.7%, and genotypes at the locus were in Hardy-Weinberg equilibrium ($p > 0.15$). The two markers are in linkage equilibrium (1000 Genomes CEU data, $D' < 0.05$ and $R^2 < 0.02$).

### 2.4. Analyses

The allele frequency distribution for the microsatellite locus