Genetic and Epigenetic Influences on Schizotypal Cognition

by

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Abstract

Genetically-based risk for schizophrenia, a highly polygenic condition, may contribute to a continuum of schizophrenia-related phenotypes between clinical populations and healthy populations. Using data from the literature as well as novel genotype and methylation data, I present evidence that schizophrenia risk alleles influence cognition in non-clinical populations, both individually, and together. Additionally, I find evidence that these alleles may be maintained across evolutionary time due to benefits in terms of enhanced performance in particular cognitive domains. Further, I demonstrate effects of genetic and epigenetic variation in the imprinted gene LRRTM1 on schizotypy and handedness. These results demonstrate that schizophrenia risk alleles influence not only increased disease risk but are also associated with cognitive performance and schizotypal traits in the general population.

Keywords: schizophrenia; schizotypy; risk allele; genetic risk score; cognitive performance; imprinting

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Table of Contents

List of Tables

List of Figures

1. Introduction

The persistence of schizophrenia as a common, widespread, fitness-reducing disorder is paradoxical – how has underlying genetic variation associated with schizophrenia been maintained despite the effects of natural selection? Schizophrenia represents the extreme manifestation of continuously distributed personality and cognitive phenotypes that grade into normality, such that individuals in the non-clinical populations can show schizophrenia-like, or schizotypal, traits (Lenzenweger, 2010). The phenotypic continuum between schizophrenia and schizotypy indicates a shared underlying genetic contribution, and understanding the relationship between genetic and phenotypic variation is important to informing disease etiology (Lenzenweger, 2010) and understanding the connections between schizotypal and normal cognition.

To identify genetic variation contributing to schizophrenia, and likely schizotypy, genome-wide association studies (GWAS) have detected alleles of single nucleotide polymorphisms (SNPs), designated as “risk alleles”, that show significant associations with schizophrenia cases as compared to controls (Purcell et al., 2009). Thousands of such alleles have so far been identified, where each risk allele contributes only slightly in increasing schizophrenia liability (Purcell et al., 2009). While the label of “risk” allele carries a certain negative connotation, studies investigating the cognitive phenotypes of such alleles show a wide range of influences, including both positive and negative effects, and interactive (e.g., gene-by-environment or gene-by-gene) effects, which may also influence phenotypes in non-clinical (“healthy”) populations (Lenzenweger, 2010). Our view takes a wider definition, where “risk” alleles simply influence basic neurodevelopmental, physiological, affective and cognitive processes of the brain in such a way that slightly increases schizophrenia liability (Kendler, 2005). Through this lens, my thesis explores the function of schizophrenia “risk” alleles in a non-clinical population by testing for relationships of genetic and epigenetic variation with measures of schizotypal cognition.

Schizophrenia occurs due to alterations of brain functions that result in symptoms of hallucinations, delusions, disorganized speech and thinking, and dysregulated affect, and it is accompanied by significant reduction in fitness and societal function (Tandon, Keshaven & Nasrallah, 2008). Difficulties in classifying schizophrenia diagnoses and providing effective treatments indicate that there is still much to be learned about the underlying causes of the complex disorder (Tandon, 2012). Indeed, the diagnostic criteria for schizophrenia are continuing to change and are currently shifting away from categorical subtypes to a dimensional approach of diagnosis (American Psychiatric Association, 2013).

Several authors have proposed genetically-based mechanisms by which schizophrenia persistence is plausible, including i) individual alleles have such weak phenotypic effects that they are not selected against and can increase in frequency by drift (Doi et al., 2009); ii) risk alleles were ancestrally adaptive or selectively neutral (Di Rienzo & Hudson, 2005); iii) mutation-selection balance (Keller & Miller, 2006); and iv) epistatic mechanisms, by which interaction (e.g., gene-by-environment or gene-by-gene) is required for a given disease phenotype to be expressed (Nicodemus et al., 2010; Gibson, 2012); however, none of these mechanisms have thus far gained strong support from the literature.

Alternative models posit that natural selection is actively maintaining these alleles due to some net or conditional benefits. Given a continuum of personality variation, schizophrenia represents an extreme manifestation of normal, adaptive dimensions of cognition (Nesse, 2004). Additionally, aspects of schizophrenia and schizotypal cognition may involve trade-offs between different cognitive domains, whereby net benefits outweigh the costs of increased disease liability. The continuum between disease and normality is genetically mediated, but we do not yet know how the underlying genes, singly or in aggregate, influence aspects of cognition in clinical versus non-clinical populations. With newly available GWAS data, we can now test for phenotypic associations with known schizophrenia genes to address this uncertainty.

Due to the inferred shared genetic variation underlying the continuous phenotypic relationship between normality and disease, disease-related genes may exert influence via effects on gene expression levels, mediated by epigenetic mechanisms (e.g., DNA

methylation; El-Osta & Wolffe, 2000). As such, we predict that epigenetic variation may influence schizophrenia-related traits like schizotypy and brain structure (e.g., laterality). LRRTM1 is a specific schizophrenia-associated gene of special interest because it is imprinted and is also associated with handedness (functional asymmetry of the brain) (Francks et al., 2007; Ludwig et al., 2009). Based on this previous work, we now can test for relationships between both SNP variation and CpG island methylation levels in relation to schizotypy and brain asymmetry (handedness). This test can be used to look for evidence supporting continuity between schizophrenia and non-clinical schizotypy based on genetic and epigenetic variation.

My thesis integrates findings from the relevant literature with my own data to obtain a broader view of the functions and effects of schizophrenia risk alleles. In chapter 2, I performed a literature review and applied data from these studies to test predictions from four models of risk allele maintenance, based cognitive performance in patient and control populations. Specifically, my hypotheses predicted that schizophrenia risk alleles may be similar or different in their effects in patient versus control populations and that these effects may be specific to particular cognitive domains. The final two chapters present data collected and analyzed to test for cognitive effects at both the genetic (SNP) and epigenetic (CpG methylation) level. In chapter 3, I test for relationships of schizophrenia risk alleles, individually and together, with cognitive performance and schizotypal personality traits. I use these data to address the hypothesis that genes strongly associated with disease may also influence cognitive variation in a healthy population, such that we might quantify liability to schizophrenia-like cognition with a genetic risk score. Finally, chapter 4 tests how an imprinted gene associated with schizophrenia affects personality and brain structure in a non-clinical population. These chapters help to develop a comprehensive view of the roles that so-called schizophrenia risk alleles play in normal cognition, and generate hypotheses to evaluate the relationships between normal cognitive function and pathological dysfunction.

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2. The effects of schizophrenia risk alleles on cognitive task performance

Emma L. Leach & Bernard J. Crespi

2.1. Abstract

Understanding the causes of the maintenance of genetic variation underlying psychiatric conditions remains an outstanding, unresolved question in human genetics. We reviewed 94 studies that evaluate the effects of schizophrenia risk alleles on cognitive performance in patients with schizophrenia and controls. Four specific hypotheses were tested, that risk alleles: (1) are deleterious, (2) are conditionally beneficial, (3) mediate resilience to schizophrenia risk, and (4) mediate differential sensitivity to epistatic and environmental influences. Most risk alleles showed deleterious effects. However, there was considerable evidence of better performance by risk-allele carriers, compared to non-risk allele carriers, in both patients and controls. Moreover, patients appeared to be especially sensitive to the positive and negative effects of risk alleles, as they showed significantly more reports of differential cognitive performance between carriers versus non-carriers, in comparison to controls. Controls with risk alleles demonstrated relatively better performance on tasks in the cognitive domains involving creativity, fluency and flexibility, and memory than did controls without risk alleles, but this difference was not observed in patients. These results suggest that schizophrenia risk alleles may be maintained, in part, due to positive effects on cognitive performance especially in particular domains, and possibly due to differential sensitivity effects that involve both deleterious and beneficial influences on cognition.

2.2. Introduction

The persistence of highly heritable psychiatric conditions, such as schizophrenia, appears paradoxical due to the power of natural selection against deleterious alleles (Keller & Miller, 2006). Individuals with schizophrenia experience substantial fitness costs through decreased fertility and increased mortality (Tandon, Keshavan & Nasrallah, 2008). Nevertheless, about 1% of people will be affected by schizophrenia in their lifetime. The clinical symptoms of this disorder are also accompanied by significant social, cognitive, and occupational impairments (e.g., van Os & Kapur, 2009), which severely impede affected individuals from participating in society.

Genetic risk for schizophrenia is mediated in part by many alleles, each of small effect (Purcell et al., 2009). Such alleles do not directly affect risk of schizophrenia or its symptoms per se, but instead influence aspects of neurodevelopment, cognition and affect, in the context of alleles at other loci and environmental variation, that together influence expression of this threshold phenotype (Kendler, 2005). Many studies have shown that schizophrenia risk alleles are associated with reduced cognitive task performance in healthy individuals, and in patients with schizophrenia (e.g., Barnett et al., 2007; Tan et al., 2008; Donohoe et al., 2009; Zhang et al., 2010). However, multiple studies have also indicated that carriers of schizophrenia risk alleles show enhanced performance for some tasks, among healthy individuals (Jansen et al., 2009; Jablensky et al., 2011), patients with schizophrenia (Walters et al., 2010), or both (Meyer-Lindenberg et al., 2007; Opgen-Rhein et al., 2008). Understanding the reasons for such diverse results may illuminate how schizophrenia risk alleles influence cognition in healthy individuals and contribute to schizophrenia-related phenotypes and dysfunction, and provide insights into how genetic variation underlying schizophrenia risk is maintained.

Four hypotheses, which are not mutually exclusive, may help to explain patterns of better or worse cognitive performance in healthy individuals, individuals with schizophrenia, or both (Table 2.1).

Table 2.1. Hypotheses and predictions to explain patterns of better versus worse cognitive performance in patients and controls.

Hypothesis	Description	Prediction
1a) Deleterious alleles	Risk alleles are strictly deleterious (e.g., Keller & Miller, 2006).	Individuals carrying risk alleles perform worse on cognitive tasks compared to non-risk allele carriers, regardless of disease status.
1b) Ascertainment bias	Researchers choose cognitive tests for which they expect patients with schizophrenia to perform especially poorly (e.g., Donohoe et al., 2013).	Patients with risk alleles perform worse than those without risk alleles, but no effect will necessarily be seen in control subjects.
2) Conditionally beneficial alleles	Risk allele carriers may show beneficial effects due to pleiotropy, epistasis, or non-linear effects of overall risk allele load on performance (e.g., Nesse, 2004).	All individuals (healthy individuals and patients) carrying risk alleles perform better than non-risk allele carriers.
3) Resilience	Cognitive benefits of risk alleles may be masked by the overall cognitive dysfunction of schizophrenia. Alternatively, healthy risk-allele carriers may possess relatively-beneficial genetic backgrounds that allow expression of positive effects of risk alleles, and reduced risk of schizophrenia (e.g., Masten & Obradovic, 2006).	Healthy risk-allele carriers perform better than non-risk allele carriers, but either no difference or lower performance reported in patients.
4) Sensitivity	Risk alleles increase patient sensitivity to both positive and negative epistatic and environmental influences (e.g., Belsky et al., 2009; Caspi et al., 2010; Pluess & Belsky, 2012).	Patients carrying risk alleles perform better and/or worse than non-risk allele carriers, but no difference observed in healthy individuals.

To evaluate these hypotheses, we performed a comprehensive literature review to compare the performance on neurocognitive tasks of healthy or affected individuals carrying schizophrenia risk alleles at any single polymorphic site ("risk-allele carriers") with that of healthy or affected individuals not having risk alleles ("non-risk carriers"). We present evidence addressing two questions, in the context of evaluating the validity of these four models: (i) to what overall extent do risk-allele carriers perform better or worse on cognitive tasks, for healthy individuals and for individuals with schizophrenia? and (ii) do risk-allele carriers tend to perform better or worse on certain types of cognitive tasks?

2.3. Methods

The goal of this review was to collect all published studies presenting data on the performance of schizophrenia risk-allele carriers on cognitive tasks, as identified by three inclusion criteria: (1) studies based on adult participants who were patients with schizophrenia, unaffected siblings, healthy controls, or any combination of these groups, (2) studies providing results for individual SNPs (rather than haplotypes or variable number tandem repeats, VNTRs), (3) studies identifying the direction of test performance (i.e., “better”, “worse” or “no significant effect” rather than only showing an unspecified “association”). To collect studies, combinations of the search terms “schizophrenia”, “cognitive”, “risk allele”, and “polymorphism” were used in the PubMed database and Google Scholar to initially identify appropriate studies, accessed up to 15 July 2013. We required each gene to be associated with schizophrenia by case-control studies, such that the designated “risk allele” is statistically associated with the patient group. Manual screening of reference lists of the studies returned by the search was then performed to identify additional studies that met the inclusion criteria.

Studies were compiled and the following results were recorded: (1) the name of the gene containing the polymorphism, (2) the SNP name using “rs” identifiers where possible, (3) the risk allele, (4) the name of the cognitive test and the target function of that test (as described in the original study), (5) the performance results of risk-allele carriers, (6) disease status and ethnicity of the participants, and (7) sample size. Results were recorded for patients and controls separately as much as possible, however some studies did not report statistics for these groups individually (e.g., studies testing for a main effect of genotype in a pooled sample). Since results in a pooled sample may be driven by one group or the other, we excluded these results from our analyses. Risk alleles were defined by original association studies where possible, or through the meta-analyses function of the SZgene database. We recorded all data as presented in the reviewed study, such that issues of linkage disequilibrium and correction for multiple testing are addressed by the original authors.

2.3.1. Statistical Analysis

Cognitive tests were grouped into the following broad cognitive domain categories: Attention and Executive function (where the task substantially included both functions); Executive function (where multiple studies specified a task as testing EF explicitly; e.g. Wisconsin Card Sort Test); Creativity, fluency and flexibility; Intelligence; Memory (non-working); and Working memory. Within these categories, risk-allele carrier performance was tallied as “better”, “worse” or “same” (no effect) for patient and control risk allele carriers relative to non-carriers, as reported in the original study. Although some studies include groups of pro-band first degree relatives, we did not include a category for relatives due to small sample size with mainly non-significant results. Fisher’s exact tests were conducted to determine if patients or controls showed significant heterogeneity in performance across cognitive domains, due to small sample sizes for this analysis. Chi-square tests were used when expected cell counts were greater than five.

Where studies performed multiple tests (or subtests) within a single cognitive domain for a single SNP, multiple significant results cannot be considered as statistically independent. To prevent pseudoreplication, we conducted the relevant statistical analyses after excluding all but one test showing each result (as regards statistical significance thresholds), within each specific domain. For example, if I study administered two tests both targeting memory and both show higher performance by risk allele carriers, only one of these results was counted.

Thirty-seven studies reported significantly better or worse performance by risk allele carriers for two or more domains. These 37 studies included 145 reports of significance (out of an overall total of 1,025 significant and non-significant results) that potentially include pseudoreplication across domains, under the supposition that common sources of cognitive variation impact the results of tests across multiple domains. Some of our analyses have assumed that results from different cognitive domains are independent, so if the multiple significant results reported in those studies are indeed due to correlations in performance between different domains, then these results would be subject to some degree of pseudoreplication. Thus, if a study showed multiple reports of significantly better or worse performance or no effect across domains, then data from all but one domain was removed to reduce risk or effects of pseudoreplication.

2.4. Results

Ninety-four studies met the inclusion criteria. Within these 94 studies, 83 SNP loci, from 34 genes, were available for the analysis. The full set of results and study citations are provided in Appendix A (Table A1 and section 2.7.1).

2.4.1. Overall cognitive performance by risk-allele carriers

1) Deleterious allele hypothesis

The Deleterious allele hypothesis predicts that individuals carrying risk alleles will perform worse on cognitive tasks compared to non-risk allele carriers, regardless of disease status.

We found that control individuals with risk alleles performed worse on 67 (13%) of 510 total cognitive tests (with no significant difference for 423 tests, and better performance for 20 tests), and patients with risk alleles performed worse on 52 (18%) of 291 tests (with no significant difference for 214 tests, and better performance for 25 tests) (Table 2.2).

Sixteen (59%) of 27 genes and 25 (38%) of 65 SNPs showed one or more reports of lower performance by risk-allele carriers in controls, as did 16 (67%) of 24 genes and 20 (37%) of 54 SNPs in patients (Table 2.3). Of the 16 genes showing one or more reports of lower performance in controls, 12 (75%) of the genes and 21 (84%) of 25 SNPs were associated with only lower performance (or lower performance and no effect), rather than mixed higher and lower performance, by risk-allele carriers (Table 2.3). Comparably, in patients, 12 (75%) of 16 genes and 18 (90%) of 20 SNPs were associated with lower performance (or lower performance and no effect) by risk-allele carriers. Neither of these comparisons of controls with patients showed significant differences (χ^2 test, $p>0.87$).

2) Conditionally-beneficial allele hypothesis

The Conditionally-beneficial allele hypothesis predicts that risk allele carriers will perform better than non-risk allele carriers.

Our results show that seven (26%) of 27 genes and nine (14%) of 65 SNPs showed better performance by control risk-allele carriers for one or more studies, as did nine (37.5%) of 24 genes and 12 (22%) of 54 SNPs in patients. Of the loci showing one or more reports of better performance, some were associated with only better performance, and some with better performance as well as tests showing no effect. In controls, three (11%) of 27 genes and five (8%) of 65 SNPs were associated with only better performance (or better performance and no effect) by risk-allele carriers. By contrast, in patients five (21%) of 24 genes and 10 (18.5%) of 54 SNPs were associated with higher performance (or higher performance and no effect) by risk-allele carriers, but neither of these comparisons showed significant differences (χ^2 test, p>0.45).

3) Resilience hypothesis

This hypothesis predicts that healthy risk-allele carriers show higher performance, whereas patient risk-allele carriers exhibit worse performance (or no difference from non-risk allele carriers), due to general cognitive impairments (and lower resilience) of patients. By the Resilience hypothesis, controls risk allele carriers with favourable cognitive, environmental or epistatic backgrounds may show performance benefits whereas those without such backgrounds may not, whereas patients are predicted to be cognitively burdened and show no evidence of better performance. Therefore, we tested for significant difference in the number of SNPs showing mixed effects in patients versus controls. For the 25 SNPs associated with one or more reports of lower performance in controls, four (16%) SNPs also showed better performance in at least one study (Table 2.3). Among patients, 20 SNPs were associated with worse performance, and two (10%) of these were associated with better performance in risk-allele carriers in one or more studies. This difference was not statistically significant (Fisher's Exact test, p=0.69).

4) Sensitivity hypothesis

This hypothesis predicts that patients carrying risk alleles are more sensitive than controls to positive or negative genetic and environmental factors associated with liability to schizophrenia. Using overall counts of SNPs associated with cognitive performance, patients (24 (44%) of 54 SNPs) and controls (35 (54%) of 65 SNPs) did not differ in the proportion of SNPs showing no effect on performance (χ^2 test, p=0.66) (Table 2.3).

However, using the overall tally of performance results without reference to genes or SNPs, controls showed a higher proportion of test results (423, 83% of 510) where risk allele status had no significant effect on performance (i.e., no significant difference between carrier and non-carrier performance) relative to patients (214, 74% of 291; χ^2 test, p=0.002; Table 2.2). These results suggest that patients were more sensitive than controls to the cognitive effects of risk alleles.

Table 2.2. Overall cognitive performance results by patient and control risk-allele carriers.

	Better	Worse	Effect (Better + Worse)	No effect (Same)
Controls	20 (23%)	67 (77%)	87 (17%)	423 (83%)
Patients	25 (32%)	52 (68%)	77 (26%)	214 (74%)

Better vs. worse χ^2 test, p=0.237
Effect vs. no effect χ^2 test, p=0.002

Table 2.3. Overall counts of genes and SNPs associated with risk-allele carrier cognitive performance.

	CONTROLS		PATIENTS		POOLED*	
Risk Allele Performance	**Genes**	**SNPs**	**Genes**	**SNPs**	**Genes**	**SNPs**
Better (all studies)	0	1 (1.5%)	0	1 (1.8%)	0	0
Better and no effect	3 (11.1%)	4 (6.2%)	5 (20.8%)	9 (16.7%)	2 (16.7%)	2 (10.0%)
Better and worse	4 (14.8%)	4 (6.2%)	4 (16.7%)	2 (3.7%)	1 (8.3%)	1 (5.0%)
No effect (all studies)	8 (29.6%)	35 (53.8%)	3 (12.5%)	24 (44.4%)	1 (8.3%)	5 (25.0%)
Worse (all studies)	0	2 (3.1%)	0	4 (7.4%)	3 (25.0%)	4 (20.0%)
Worse and no effect	12 (44.4%)	19 (29.2%)	12 (50.0%)	14 (25.9%)	5 (41.7%)	8 (40.0%)
Total reported	27	65	24	54	12	20

*"Pooled" refers to studies for which patient and control data were not presented separately.

2.4.2. Contrasting effects of specific SNPs in patients and controls

Forty SNPs had performance data available for patients and controls analyzed separately (Table 2.4). Of these 40 SNPs, 13 showed no significant effect in both patients and controls, leaving 27 SNPs showing a significant effect on risk allele carrier performance in either patient or control groups, or both. Additionally, there were eight SNPs that had data for patients only, and 14 SNPs had data for controls only; for a total of 49 SNPs. These data were used to evaluate hypotheses regarding performance heterogeneity in control versus patient risk-allele carriers.

1) Deleterious allele hypothesis

The majority of SNPs, 30 (61%) of 49, appeared deleterious in their effects, as they showed lower performance by risk-allele carriers in one or more studies for patients, controls or both (Table 2.4, top five rows). Only three of these SNPs were associated with lower performance in both patients and control risk-allele carriers. Possible evidence of ascertainment bias was found in eight SNPs that showed lower performance in patients, but no effect in controls. The remaining 17 SNPs were only reported for either patients or controls, but not both, so risk allele effects could not be compared between the groups.

2) Conditionally-beneficial allele hypothesis

Six (12%) of 49 SNPs showed better performance by risk-allele carriers in one or more studies for patients, controls, or both, in support of the conditionally-beneficial hypothesis. Only one of these SNPs (DAOA rs1570709) was associated with better performance in both patient and control risk-allele carriers, with the remaining four SNPs only reported in either patients or controls, but not both (Table 2.4).

3) Resilience hypothesis

Six (22%) of 27 SNPs show better performance by control risk-allele carriers and either worse performance or no effect in patient risk-allele carriers, compared to non-carriers. This evidence is consistent with the Resilience hypothesis.

4) Sensitivity hypothesis

Seven (26%) of 27 SNPs showed better performance only in patient risk-allele carriers, compared to non-risk carriers, with controls showing either worse performance or no effect. Eight (30%) of 27 SNPs showed worse performance in patients, but no effect in controls; these overlap with the SNPs discussed above with regard to the Deleterious hypothesis. Taken together, 15 (55.5%) of 27 SNPs supported the Sensitivity hypothesis that patients may be more sensitive to the effects of risk alleles than controls.

Focusing only on SNPs with data for both patients and controls, the Sensitivity hypothesis shows the highest number of SNPs showing the expected patterns of performance (15), followed by the Deleterious/Ascertainment bias hypothesis (13), the Resilience hypothesis (6) and the Conditionally-beneficial hypothesis (1).

Table 2.4. Gene and SNP performance results categorized by the four hypotheses.

Hypothesis	Performance expectations	Genes	SNPs
1) Deleterious alleles	Patients – *lower* & Controls – *lower*	CACNA1C CSMD1 NOS1	rs1006737 rs10503253 rs6490121
	Patients – lower & Controls – NE (Possible ascertainment bias)	AKT1 DISC1 GRIN2B NEUROG1 PRKCA S100B	rs2494732 rs821616 rs220599 rs2344484 rs8074995 rs1051169, rs2839357, rs9722
	Patients – NE & Controls – *lower*	AKT1 DTNBP1	rs1130233 rs1018381
	Patients only – *lower*	DISC1 COMT MTHFR SLC1A2	rs2255340 rs165599, rs737865 rs1801133 rs4354668
	Controls only – *lower*	ANK3 DAO DTNBP1 KCNH2 LIF NRG1 RGS4	rs9804190 rs3918346 rs1047631, rs3213207, rs742105, rs760761 rs3800779, rs929271 NRG433E1006, rs35753505 rs951436, rs951439
2) Conditionally beneficial alleles	Patients – **higher** & Controls – **higher**	DAOA	rs1570709
	Patients only – **higher**	NOS1 CHI3L1 TCF4	G84A rs103998005 rs9960767
	Controls only – **higher**	NRG1 NRGN	rs6994992 rs12807809
3) Resilience	Patients – NE & Controls – **higher**	BDNF DTNBP1	rs6265 rs2619539
	Patients – *lower* & Controls – **higher**	COMT DAOA GRM3	rs4680 rs1421292, rs3918342 rs2189814
4) Sensitivity	Patients – **higher** & Controls – NE	5-HTR2A	rs6313
	Patients – **higher** & Controls – *lower*	DRD4 DTNBP1 NRG3 TCF4 ZNF804A	rs1800955 rs2619522 rs10883866, rs6584400 rs2958182 rs1344706
	Patients – *lower* & Controls – NE	AKT1 DISC1 GRIN2B NEUROG1 PRKCA S100B	rs2494732 rs821616 rs220599 rs2344484 rs8074995 rs1051169, rs2839357, rs9722

2.4.3. Variation among domains of cognitive performance

To evaluate the hypothesis that individuals bearing risk alleles perform better or worse on particular types of cognitive task, the tests used by authors in the reviewed studies were assigned to one of six groups to categorize the cognitive domain assessed, as described above. Results from all studies were then tallied according to the cognitive domain category, to test for differential effects of risk alleles across different domains. Controls showed significant heterogeneity across different domains of test (Fisher's Exact Test, p=0.0007; Table 2.5). Controls thus performed relatively well on tests of Creativity, fluency and flexibility (better on seven (78%) of nine tests) and (non-working) Memory (better on seven (33%) of 21 tests). By contrast, controls showed relatively poor performance on measures of Attention & Executive function, Executive function, Intelligence, and Working memory, with only six (10%) of 57 of these tests (combined across domains) showing better performance among risk-allele carriers. In comparison to controls, patients showed a considerable number of better performance results (25, 37% of 68) but demonstrated no evidence of heterogeneity across cognitive domain categories for better versus worse performance (Fisher's Exact test p=0.69; Table 2.5).

Table 2.5. Performance results tallied by cognitive domain category.

	CONTROLS			PATIENTS		
Original tally	**Better**	**Worse**	**Same**	**Better**	**Worse**	**Same**
Attention & Executive function	**2** (14%)	**12** (86%)	54	**5** (42%)	**7** (58%)	30
Creativity, fluency & flexibility	**7** (78%)	**2** (22%)	23	**2** (40%)	**3** (60%)	17
Executive function	**0** (0%)	**11** (100%)	36	**2** (29%)	**5** (71%)	32
Intelligence	**2** (15%)	**11** (85%)	99	**3** (27%)	**8** (73%)	39
Memory	**7** (33%)	**14** (67%)	128	**5** (28%)	**13** (72%)	58
Working memory	**2** (11%)	**17** (89%)	82	**8** (53%)	**7** (47%)	28
Fisher's Exact test better vs. worse (2x6)	**p=0.0007**			p=0.686		

Next, for each study, we performed a conservative tally by excluding all but one result of each higher, lower, or no effect within each specific domain to prevent pseudoreplication inflating our tally counts (Table 2.6). As with the original tally, controls showed significant

heterogeneity across domains (Fisher's Exact Test, p=0.04) with evidence for relatively better performance on tasks of Creativity, fluency and flexibility (4 of 6 tests) and Memory (4 of 13 tests). There was no further evidence for the sensitivity hypothesis as patients and controls did not differ in the number of tests showing a performance effect versus no effect (Table 2.7; p=0.41).

Table 2.6. Performance results tallied by cognitive domain category using only one Better/Worse/Same result for each domain per SNP was counted in a study.

	CONTROLS			PATIENTS		
Conservative tally	**Better**	**Worse**	**Same**	**Better**	**Worse**	**Same**
Attention & Executive function	**2** (15%)	**11** (85%)	47	**4** (44%)	**5** (56%)	24
Creativity, fluency & flexibility	**4** (67%)	**2** (33%)	19	**2** (40%)	**3** (60%)	16
Executive function	**0** (0%)	**10** (100%)	28	**2** (29%)	**5** (71%)	24
Intelligence	**2** (17%)	**10** (83%)	54	**2** (29%)	**5** (71%)	27
Memory	**4** (31%)	**9** (69%)	42	**3** (25%)	**9** (75%)	30
Working memory	**2** (12.5%)	**14** (87.5%)	49	**4** (40%)	**6** (60%)	19
Fisher's Exact test better vs. worse (2x6)	**p=0.04**			p=0.96		

Table 2.7. Testing for sensitivity, comparing effect versus no effect in patients and controls using conservative tally.

	Effect (Better + Worse)	**No effect (Same)**
Controls	70 (23%)	239 (77%)
Patients	50 (26%)	140 (74%)

χ^2 =6.48, p=0.41

These tests were also conducted after excluding all but one better/worse/no effect result across domains, to prevent pseudoreplication due to possible effects of correlations across cognitive domains (Tables 2.8). By this analysis, the difference between groups in the proportions of no-effect results were not significant (χ^2 test, p=0.27). By condensing many reported “no effect” results and treating them equally, with relatively few condensed better or worse results, we may have introduced bias in our attempt to avoid pseudoreplication. Therefore we tested the total number of “same” (no effect)

counts from both the original tally and adjusted counts were compared, and found no significant difference between original and adjusted patients and control counts (χ^2 test, p=0.89).

Table 2.8. Testing for a sensitivity effect after excluding all but one homogenous result of better/worse/same across domains within a study.

	Better	Worse	Effect (better + worse)	No effect (Same)
Controls	11 (19%)	46 (81%)	57 (35%)	108 (65%)
Patients	12 (32%)	25 (68%)	37 (43%)	50 (57%)

Effect vs. No effect: χ^2=2.76, p=0.27

2.4.4. Effects of sample size on performance

After attempting to reduce potential pseudoreplication by only considering one of each better, worse, or no effect result for each SNP tested in a study, patient sample sizes were significantly smaller than control sample sizes, by t-test (control mean size = 741.32, patient mean size = 277.12; t=4.64, df=271, p=0.0001).

In patients, significantly larger mean sample size for results of no effect were significantly larger than results of lower performance by risk allele carriers, for both original and conservative data (Tukey HSD, p<0.05). In comparison, controls showed significantly smaller mean sample size for higher performance results compared to both lower and no effect in original (ANOVA, p=0.03) but not conservative data (ANOVA, p=0.23).

Our finding of more significant results in patients versus controls is not due increased power of detecting effects in larger sample sizes. Smaller studies might report more false positive results, but replication is required to determine the extent of sample size effects. Our attempt to reduce pseudoreplication seems to help reduce sample size bias in controls and strengthens evidence presented in previous sections using conservative results.

2.4.5. Contrasting effects of SNPs

Thirteen (16%) of the 83 SNPs (in 10 genes) showed both better and worse performance in one or more studies (Appendix A2). There was considerable heterogeneity in the effects of these SNPs on cognitive domains and direction of performance in the healthy and patient groups. For example, DAOA rs1421292 showed differential effects within cognitive domains (e.g., Working memory) between control (better) versus patient (worse) performance; but also within status group (controls) between Working memory (better) versus Executive function (worse). Such findings provide support for the Conditionally-beneficial alleles hypothesis in that some risk alleles show positive effects that appear to involve trade-offs in performance for different cognitive domains.

2.5. Discussion

We report two main findings pertaining to the effects of schizophrenia risk alleles on cognitive task performance, in patients and controls. First, we found some evidence for three of the four hypotheses addressed, suggesting that risk alleles differ in their influences on cognitive phenotypes; and second, controls showed a significant difference between the cognitive domains showing better, compared to worse, performance by risk-allele carriers.

Regarding our hypotheses, the majority of schizophrenia risk alleles showed deleterious effects on cognitive performance, however ascertainment bias due to authors selecting tests where patients are expected to perform poorly is likely to contribute to the perceived deleterious effect to an unknown degree.

There was also considerable evidence of better performance by risk-allele carriers in both patients and controls, for some genes and SNPs. Thus, 26% of genes (and 14% of SNPs) in controls, and 37.5% of genes (and 22% of SNPs) in patients showed one or more reports of better performance by risk-allele carriers. Compared to genes and SNPs that showed one or more reports of better performance (which include those having mixed effects), 11% of genes (8% of SNPs) in controls and 21% of genes (18.5% of SNPs) in patients showed only better performance by risk-allele carriers or a combination of better performance and no significant effect (i.e., no indication of negative

effects). It is important to note, however, that positive effects on cognitive performance do not necessarily translate into positive effects with regard to reduced schizophrenia risk, as over-expression of seemingly-positive effects (e.g., Theory of Mind performance) could manifest as symptoms of schizophrenia (e.g., paranoia). As such, the effects of any given schizophrenia risk allele may be highly conditional on the presence or absence of other alleles mediating aspects of risk and sensitivity (or risk alleles themselves increasing sensitivity) as well as environmental factors such as adversity and stress (van Os, Rutten & Poulton, 2008; Van Winkel et al., 2010).

We found little evidence for the Resilience hypothesis, with only six SNPs showing higher performance in control risk-allele carriers and either lower performance or no difference in patients (Table 2.4). By contrast, we found apparent support for the Sensitivity hypothesis, with a significantly higher proportion of combined positive and negative performance results, and a corresponding lower proportion of non-significant results, in patients relative to controls (Table 2.2), however this finding did not withstand our conservative approach of reducing pseudoreplication.

When we compared performance effects in patients versus controls for individual SNPs, 15 SNPs showed an effect on cognitive performance in patient risk allele carriers, but no effect in controls, supporting the Sensitivity hypothesis (Table 2.4). These findings raise the possibility that genetically-mediated differential sensitivity to epistatic and environmental effects may characterize some risk alleles for schizophrenia. Such effects have been well documented and characterized in studies of other conditions and phenotypes, including depression and stress (Boyce & Ellis, 2005; Belsky et al., 2009; Ellis et al., 2011; Pluess & Belsky, 2012). That sensitivity effects are identified only in patients and not in controls could indicate cognitive differences between the two groups that leave patients more susceptible to risk allele effects.

It is unclear how strongly ascertainment bias (choice of tests based on known relatively-poor performance in schizophrenia) influences the results; such bias may cause more negative effects to be reported in patients versus controls than if tests were chosen independently of known deficits in schizophrenia patients. By contrast, the Sensitivity hypothesis predicts that patients should be relatively sensitive to both positive and negative effects of risk alleles, which is consistent with the results shown in Table 2.2.

While we were not able to quantify evidence of publication bias, inclusion of any additional, unpublished data would increase the number of "no effect" results counted and although our better and worse results would be proportionately fewer, our sensitivity findings would likely remain unchanged.

Next, control risk-allele carriers exhibited relatively more reports of better (versus worse) performance in the domains of Creativity, flexibility and fluency, and (non-working) Memory, and relatively fewer reports of better performance for Attention & Executive function, Executive function, Intelligence, and Working memory. By contrast, patients showed no evidence of such differences across domains in better versus worse performance, although the overall proportion of better performance (compared to worse performance) results did not differ between controls (20 of 87) and patients (25 of 68; χ^2 test, p=0.22).

Enhanced performance on tests of creativity and fluency has been reported in some studies of schizophrenia patients, individuals with high genetic liability for schizophrenia (e.g., first-order relatives of individuals with schizophrenia), and schizotypal individuals (e.g., Barrantes-Vidal, 2004; Tsakanikos & Claridge, 2005; Kyaga et al., 2011). However, many other studies have reported deficits in patients compared to controls, especially on tests that assess aspects of fluency and flexibility (e.g., Yamashita et al., 2005; Wobrock et al., 2009). Schizophrenia, schizophrenia risk, and schizotypy have also been associated with enhanced imagination (reviewed in Nettle, 2001), which may help to explain the apparent pattern of relatively-good performance of controls with risk alleles on tests of non-working memory, given the well-documented neural and cognitive links between memory (as remembering past experiences) and imagination (as simulating possible future experiences) (Addis, Wong & Schacter, 2007; Szpunar, Watson, & McDermott, 2007; Matin et al., 2011; Gaesser, 2012; Schacter et al., 2012). Individuals with schizophrenia also tend to be susceptible to false imagination due to errors in source monitoring, which relies on memory encoding (Keefe et al., 1999; Mammarella et al., 2010). The restriction of apparent enhanced performance on tests of Creativity, fluency and flexibility and non-working Memory to control individuals with risk alleles, but not patients, is consistent with the hypothesis that schizophrenia risk alleles could by maintained by domain-specific cognitive benefits. Maintenance of risk alleles by such mechanisms may involve trade-offs with

performance in other cognitive domains, as well as deleterious effects due to risk of schizophrenia and related disorders.

Additional studies on the cognitive effects of schizophrenia risk alleles would benefit from conducting large numbers of diverse performance tests in healthy populations, using larger numbers of SNPs, to test for differential positive effects on aspects of creativity, memory, imagination, and fluency, as well as for trade-offs of such benefits with task performance in other cognitive domains. In addition, direct tests of the differential sensitivity hypothesis would be useful in the context of schizophrenia risk alleles, given that such differential sensitivity may involve beneficial effects under favourable conditions during development (Ellis et al., 2011; Pluess & Belsky, 2012).

2.6. References

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2.7. Appendix A

Table A1. Data collected from literature searches

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2.7 Appendix A

Table A1. Data collected from literature searches

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
ANK3	rs10994336	No	T (0.07)	Attention & Executive function	Sustained attention	CANTAB (RVIP)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Creativity, Fluency & Flexibility	Planning	Iowa Gambling Task	N.S		Controls [C] - Males only	530	Roussos 2011b
				Creativity, Fluency & Flexibility	Problem solving	CANTAB (Stockings)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Executive function	Interference response	Stroop Interference Task	N.S		Controls [C] - Males only	530	Roussos 2011b
				Executive function	Cognitive flexibility	WCST	N.S		Controls [C] - Males only	530	Roussos 2011b
				Memory	Verbal learning & memory	WMS-R (Word lists)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Working Memory	Spatial working memory	CANTAB (Spatial Task)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Working Memory	Visual working memory	N-back Task	N.S		Controls [C] - Males only	530	Roussos 2011b
	rs9804190	No	C (0.77)	Executive function	Executive function	WCST (Categories)	Lower (0.008)*	Dominant	Controls [C]	513	Roussos 2011a
				Executive function	Executive function	WCST (Total errors)	Lower (0.008)*	Dominant	Controls [C]	513	Roussos 2011a
				Working memory	Working memory	N-back Task (2-back)	Lower (0.003)*	Dominant	Controls [C]	513	Roussos 2011a
				Working memory	Working memory	N-back Task (3-back)	Lower (<0.001)*	Dominant	Controls [C]	513	Roussos 2011a
AKT1	rs1130214	Yes	T (0.30)		Attention and tracking	TMT-A	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Attention & Executive function	Attention	CPT	N.S.		Controls [C]	319	Tan 2008
				Attention & Executive function	Vigilance domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Intelligence	IQ/processing speed	Factor of WAIS-R, VCFT, TMTA&B	N.S.		Controls [C]	319	Tan 2008
				Intelligence	Processing Speed	WAIS-R (Digit symbol)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Visuospatial reasoning	WAIS-R (Block design)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Concepts and abstraction	WAIS-R (Similarities)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Intelligence	WAIS-R (Vocabulary)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Logic & reasoning	WCST (Logical reasoning)	N.S.		Controls [C]	319	Tan 2008
				Executive function	Processing speed domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Reasoning domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Distractibility	Stroop Task	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Strategy shifting	TMT-B	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Perseverative errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Number of categories)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory composite	CVLT tests composite index	Lower (0.0005)	Dominant	Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory	CVLT (Intrusive errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory	CVLT (Recognition index)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Immediate story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Delayed story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal episodic memory	Factor of CVLT and WMS-R	N.S.		Controls [C]	319	Tan 2008
				Memory	Spatial episodic memory	Factor of WMS-R & Judgement of line	N.S.		Controls [C]	319	Tan 2008
				Memory	Visual memory	WMS-R (Visual reproduction)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Working memory	Working memory	N-back task	N.S.		Controls [C]	319	Tan 2008
				Working memory	Attention	WMS-R (Digit span)	N.S.		Controls [C]	319	Tan 2008
				Working memory	Verbal attention	WMS-R (Digit span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Verbal working memory	WMS-R (Digit span backward)	Lower (0.039)	Dominant	Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Visual attention	WMS-R (Visual span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Visual working memory	WMS-R (Visual span backward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Working memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
	rs1130233 (aka rs2498799)	Yes	A (0.25)		Attention and tracking	TMT-A	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Attention & Executive function	Attention	CPT	N.S.		Controls [C]	319	Tan 2008
				Attention & Executive function	Vigilance domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Distractibility	Stroop Task	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Strategy shifting	TMT-B	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Perseverative errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Number of categories)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Logic & reasoning	WCST (Logical reasoning)	N.S.		Controls [C]	319	Tan 2008
				Executive function	Processing speed domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Reasoning domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Intelligence	Concepts and abstraction	WAIS-R (Similarities)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Intelligence	WAIS-R (Vocabulary)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Processing Speed	WAIS-R (Digit symbol)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Visuospatial reasoning	WAIS-R (Block design)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	IQ/processing speed	Factor of WAIS-R, VCFT, TMTA&B	Lower (0.003)*	Dominant	Controls [C]	319	Tan 2008
				Memory	Spatial episodic memory	Factor of WMS-R & Judgement of line	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal memory composite	CVLT tests composite index	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory	CVLT (Intrusive errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory	CVLT (Recognition index)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Immediate story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Delayed story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal episodic memory	Factor of CVLT and WMS-R	N.S.		Controls [C]	319	Tan 2008
				Memory	Visual memory	WMS-R (Visual reproduction)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Working memory	Working memory	N-back task	N.S.		Controls [C]	319	Tan 2008
				Working memory	Attention	WMS-R (Digit span)	N.S.		Controls [C]	319	Tan 2008
				Working memory	Verbal attention	WMS-R (Digit span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Verbal working memory	WMS-R (Digit span backward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Visual attention	WMS-R (Visual span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Visual working memory	WMS-R (Visual span backward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Working memory	Working memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
	rs2494732	Yes	A (0.66)		Attention and tracking	TMT-A	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Attention & Executive function	Attention	CPT	N.S.		Controls [C]	319	Tan 2008
				Attention & Executive function	Attention	CPT-IP	Lower (0.007)	Dominant	Patients [A]	60	Ohi 2011
				Attention & Executive function	Attention	CPT-IP	N.S.		Controls [A]	121	Ohi 2011
				Attention & Executive function	Vigilance domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Distractibility	Stroop Task	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Strategy shifting	TMT-B	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Perseverative errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Executive function	WCST (Number of categories)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Executive function	Logic & reasoning	WCST (Logical reasoning)	N.S.		Controls [C]	319	Tan 2008
				Executive function	Processing speed domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Reasoning domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Intelligence	IQ/processing speed	Factor of WAIS-R, VCFT, TMTA&B	N.S.		Controls [C]	319	Tan 2008
				Intelligence	Concepts and abstraction	WAIS-R (Similarities)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Intelligence	WAIS-R (Vocabulary)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Processing Speed	WAIS-R (Digit symbol)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Intelligence	Visuospatial reasoning	WAIS-R (Block design)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Spatial episodic memory	Factor of WMS-R & Judgement of line	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal memory composite	CVLT tests composite index	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Verbal memory	CVLT (Intrusive errors)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory	CVLT (Recognition index)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Immediate story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal learning & memory	WMS-R (Delayed story recall)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal episodic memory	Factor of CVLT and WMS-R	N.S.		Controls [C]	319	Tan 2008
				Memory	Attention	WMS-R (Attention/concentration)	Lower (0.026)	Dominant	Patients & Controls [A]	94	Ohi 2011
				Memory	Attention	WMS-R (Verbal memory)	N.S.		Patients & Controls [A]	121	Ohi 2011
				Memory	Attention	WMS-R (Visual memory)	N.S.		Patients & Controls [A]	121	Ohi 2011
				Memory	Attention	WMS-R (Delayed recall)	Lower (0.047)	Dominant	Patients & Controls [A]	94	Ohi 2011
				Memory	Attention	WMS-R (General memory)	N.S.		Patients & Controls [A]	121	Ohi 2011
				Memory	Visual memory	WMS-R (Visual reproduction)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal attention	WMS-R (Digit span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal working memory	WMS-R (Digit span backward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Visual attention	WMS-R (Visual span forward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Visual working memory	WMS-R (Visual span backward)	N.S.		Patient & Control Twin Pairs [C]	126	Pietiläinen 2009
				Memory	Verbal memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Working memory	Working memory	N-back task	N.S.		Controls [C]	319	Tan 2008
				Working memory	Attention	WMS-R (Digit span)	N.S.		Controls [C]	319	Tan 2008
				Working memory	Working memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
	rs3730358	Yes	T (0.13)	Attention & Executive function	Attention	CPT	N.S.		Controls [C]	319	Tan 2008
				Attention & Executive function	Vigilance domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Logic & reasoning	WCST (Logical reasoning)	N.S.		Controls [C]	319	Tan 2008
				Executive function	Processing speed domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Reasoning domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Intelligence	IQ/processing speed	Factor of WAIS-R, VCFT, TMTA&B	N.S.		Controls [C]	319	Tan 2008
				Memory	Spatial episodic memory	Factor of WMS-R & Judgement of line	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal episodic memory	Factor of CVLT and WMS-R	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Working memory	Working memory	N-back task	N.S.		Controls [C]	319	Tan 2008
				Working memory	Attention	WMS-R (Digit span)	N.S.		Controls [C]	319	Tan 2008
				Working memory	Working memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
	rs3803300	Yes	A (0.36)	Attention & Executive function	Attention	CPT	N.S.		Controls [C]	319	Tan 2008
				Attention & Executive function	Vigilance domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Logic & reasoning	WCST (Logical reasoning)	N.S.		Controls [C]	319	Tan 2008
				Executive function	Processing speed domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Executive function	Reasoning domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Intelligence	IQ/processing speed	Factor of WAIS-R, VCFT, TMTA&B	N.S.		Controls [C]	319	Tan 2008
				Memory	Spatial episodic memory	Factor of WMS-R & Judgement of line	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal episodic memory	Factor of CVLT and WMS-R	N.S.		Controls [C]	319	Tan 2008
				Memory	Verbal memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
				Working memory	Working memory	N-back task	N.S.		Controls [C]	319	Tan 2008
				Working memory	Attention	WMS-R (Digit span)	N.S.		Controls [C]	319	Tan 2008
				Working memory	Working memory domain	Unspecified, grouped neurocognitive tests	N.S.		Patients [M]	641	Pinheiro 2007
BDNF	rs6265 (val66met)	Yes	G (Val) (0.66)	Executive function	Processing speed	Letter comparison	N.S.		Controls [C]	189	Raz 2009
				Executive function	Processing speed	Pattern comparison	N.S.		Controls [C]	189	Raz 2009
				Executive function	Executive Function	Stroop Task (colour)	not reported		Controls [C]	189	Raz 2009
				Executive function	Executive function	WCST	N.S.		Patients, Siblings & Controls [M]	641	Egan 2003
				Intelligence	Fluid reasoning	Cattell Culture Fair Intelligence Test	not reported		Controls [C]	189	Raz 2009
				Intelligence	Intelligence	WAIS (FSIQ)	N.S.		Controls [A] - Females only	114	Tsai 2004
				Intelligence	Intelligence	WAIS (PIQ)	Higher (0.046)	Recessive	Controls [A] - Females only	114	Tsai 2004

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Intelligence	Intelligence	WAIS (VIQ)	N.S.		Controls [A] - Females only	114	Tsai 2004
				Memory	Episodic memory	CVLT (Immediate recall)	N.S.		Controls [M]	133	Egan 2003
				Memory	Episodic memory	CVLT (Immediate recall)	N.S.		Controls, Patieints & Unaffected siblings [M]	641	Egan 2003
				Memory	Episodic memory	CVLT (Delayed recall)	N.S.		Controls [M]	133	Egan 2003
				Memory	Episodic memory	CVLT (Delayed recall)	N.S.		Controls, Patieints & Unaffected siblings [M]	641	Egan 2003
				Memory	Declarative memory	Declarative memory task	Higher (0.02)	Recessive	Controls [M]	28	Hariri 2003
				Memory	Episodic memory	WMS-R (Immediate recall)	Higher (<0.03)	Dominant	Controls [M]	133	Egan 2003
				Memory	Episodic memory	WMS-R (Immediate recall)	Higher (0.02)	Dominant	Patients & Siblings [M]	641	Egan 2003
				Memory	Episodic memory	WMS-R (Logical memory - Immediate)	N.S.		Patients [C]	92	Dempster 2005
				Memory	Episodic memory	WMS-R (Logical memory - Immediate)	N.S.		Relatives [C]	114	Dempster 2005
				Memory	Episodic memory	WMS-R (Delayed recall)	Higher (0.008)	Dominant	Controls [M]	133	Egan 2003
				Memory	Episodic memory	WMS-R (Delayed recall)	Higher (0.02)	Dominant	Controls, Patieints & Unaffected siblings [M]	641	Egan 2003
				Memory	Episodic memory	WMS-R (Delayed recall)	N.S.		Patients [C]	92	Dempster 2005
				Memory	Episodic memory	WMS-R (Delayed recall)	Higher (0.001)		Unaffected relatives [C]	114	Dempster 2005
				Memory	Episodic memory	WMS-R (Logical memory - Delayed)	N.S.		Patients [C]	92	Dempster 2005
				Memory	Episodic memory	WMS-R (Logical memory - Delayed)	Higher (0.01)		Relatives [C]	114	Dempster 2005
				Memory	Episodic memory	WJPB-R (Memory for names - Immediate)	Higher (<0.07)	Recessive	Controls [C]	189	Raz 2009
				Memory	Episodic memory	WJPB-R (Memory for names - Delayed)	Higher (<0.04)	Recessive	Controls [C]	189	Raz 2009
				Memory	Semantic memory	(unspecified)	N.S.		Controls, Patieints & Unaffected siblings [M]	641	Egan 2003
CACNA1C	rs1006737	No	A (0.30)	Attention & Executive function	Sustained attention	CANTAB (RVIP)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Attention & Executive function	Attention	Attention Network Test (Alerting)	Lower (<0.05)	Dominant	Controls	521	Thimm 2011
				Attention & Executive function	Attention	Attention Network Test (Orienting)	Lower (<0.05)	Dominant	Controls	521	Thimm 2011
				Attention & Executive function	Attention	Attention Network Test (Executive control)	N.S		Controls	521	Thimm 2011
				Creativity, Fluency & Flexibility	Decision making	Iowa Gambling Task	N.S		Controls [C] - Males only	530	Roussos 2011b
				Creativity, Fluency & Flexibility	Problem solving	CANTAB (Stockings)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Creativity, Fluency & Flexibility	Verbal fluency	Lexical fluency task	N.S		Controls [C] - Males only	63	Krug 2010
				Creativity, Fluency & Flexibility	Verbal fluency	Semantic fluency task	Lower (0.021)	Dominant	Controls [C] - Males only	63	Krug 2010
				Executive function	Interference response	Stroop Interference Task	N.S		Controls [C] - Males only	530	Roussos 2011b
				Executive function	Cognitive flexibility	WCST	N.S		Controls [C] - Males only	530	Roussos 2011b
				Executive function		WCST	N.S		Patients [A]	552	Hori 2012
				Executive function		WCST	N.S		Controls [A]	1132	Hori 2012
				Intelligence	Verbal intelligence	WAIS-R (VIQ)	N.S		Controls [C] - Males only	63	Krug 2010
				Intelligence	Processing speed	WAIS-R (Processing speed)	N.S		Patients [A]	552	Hori 2012
				Intelligence	Processing speed	WAIS-R (Processing speed)	N.S		Controls [A]	1132	Hori 2012
				Intelligence	Verbal comprehension	WAIS-R (Verbal comprehension)	N.S		Patients [A]	552	Hori 2012
				Intelligence	Verbal comprehension	WAIS-R (Verbal comprehension)	N.S		Controls [A]	1132	Hori 2012
				Memory	Verbal learning & memory	WMS-R (Word lists)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Memory	Logical memory	WMS-R (Logical memory)	Lower (0.006)	Dominant	Patients [A]	552	Hori 2012
				Memory	Logical memory	WMS-R (Logical memory)	N.S		Controls [A]	1132	Hori 2012
				Memory	Paired-associate memory	WMS-R (Paired-associates)	N.S		Patients [A]	552	Hori 2012
				Memory	Paired-associate memory	WMS-R (Paired-associates)	N.S		Controls [A]	1132	Hori 2012
				Memory	Visual memory	WMS-R (Visual memory)	N.S		Patients [A]	552	Hori 2012
				Memory	Visual memory	WMS-R (Visual memory)	N.S		Controls [A]	1132	Hori 2012
				Working memory	Spatial working memory	CANTAB (Spatial Task)	N.S		Controls [C] - Males only	530	Roussos 2011b
				Working memory	Visual working memory	N-back Task	N.S		Controls [C] - Males only	530	Roussos 2011b
				Working memory	Spatial working memory	Dot Patter Expectancy	Lower (0.048)	Dominant	Patients [A]	104	Zhang 2012
				Working memory	Spatial working memory	Dot Patter Expectancy	Lower (0.032)	Dominant	Controls [A]	396	Zhang 2012
				Working memory	Spatial working memory	N-back Task	Lower (0.03)	Dominant	Patients [A]	318	Zhang 2012
				Working memory	Spatial working memory	N-back Task	Lower (0.014)	Dominant	Controls [A]	401	Zhang 2012
CHI3L1	rs10399805	Yes	C (0.82)	Attention & Executive function	Attentional control	CPT (Distractibility)	N.S.		Patients [C]	237	Yang 2008

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Attention & Executive function	Attentional control	CANTAB (IED)	N.S.		Patients [C]	237	Yang 2008
				Intelligence	General cognitive function	WAIS-R (Vocabulary)	Higher (0.008)	Recessive	Patients [C]	237	Yang 2008
				Intelligence	General cognitive function	WAIS-R (Block design)	N.S.		Patients [C]	237	Yang 2008
				Intelligence	IQ (Premorbid)	Wechsler Test of Adult Reading	Higher (0.007)	Recessive	Patients [C]	237	Yang 2008
				Working memory	Spatial memory	CANTAB (Paired-associates)	N.S.		Patients [C]	237	Yang 2008
				Working memory	Spatial working memory	CANTAB (Spatial working memory)	N.S.		Patients [C]	237	Yang 2008
				Working memory	Verbal episodic memory	WMS-R (Logical memory)	N.S.		Patients [C]	237	Yang 2008
				Working memory	Working memory	WMS-R (Letter-Number Sequencing)	Higher (0.041)	Recessive	Patients [C]	237	Yang 2008
COMT	rs165599	Yes	A (0.65)	Attention & Executive function	Working memory	CPT	Lower (0.039)	Recessive	Patients [C]	325	Diaz-Asper 2008
				Attention & Executive function	Working memory	CPT	Not reported		Siblings & Controls [C]	689	Diaz-Asper 2008
				Attention & Executive function	Working memory	Intra-Extra dimensional set shifting	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Executive function	Working memory	WCST	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Intelligence	Working memory	WAIS-R	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (0-back)	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (1-back)	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (2-back)	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
	rs4680 (Val158Met)	Yes	G (Val) (0.57)	Attention & Executive function	Attention	CPT	N.S.		Patients, siblings & controls [M]	250	Goldberg 2003
				Attention & Executive function	Working memory	CPT	Lower (0.01)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Attention & Executive function	Working memory	CPT	Not reported		Siblings & Controls [C]	689	Diaz-Asper 2008
				Attention & Executive function	Working memory	CPT (AX)	N.S.		Controls [C]	462	MacDonald 2007
				Attention & Executive function	Working memory	Intra-Extra dimensional set shifting	Lower (0.026)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Attention & Executive function	Working memory	Intra-Extra dimensional set shifting	Not reported		Siblings & Controls [C]	689	Diaz-Asper 2008
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C] - Males only	1657	Smyrnis 2007
				Attention & Executive function	Attention	CPT	Not reported		Controls [C]	75	Caldú 2007
				Attention & Executive function	Working memory	CPT-IP (D' indices)	N.S.		Controls [C]	521	Aguilera 2008
				Attention & Executive function	Attention	CPT-IP (D' indices)	N.S.		Controls [C] - Males only	528	Stefanis 2004
				Attention & Executive function	Cognitive stability	Flanker's CPT (Correct trials)	Higher (0.008)	Additive	Patients, relatives & Controls [C]	77	Krabbendam 2006
				Attention & Executive function	Cognitive stability	Flanker's CPT (Reaction time)	N.S.		Patients, relatives & Controls [C]	77	Krabbendam 2006
				Attention & Executive function	Cognitive stability	Flanker's CPT (RT variability)	Lower (0.005)	Additive	Patients, relatives & Controls [C]	77	Krabbendam 2006
				Attention & Executive function	Executive attention	Attention Networking Test	N.S.		Controls	220	Fossella 2002
				Creativity, fluency & flexibility	Organization	Animal naming	N.S.		Patients [M]	58	Bilder 2002
				Creativity, fluency & flexibility	Organization	Controlled word association test	N.S.		Patients [M]	58	Bilder 2002
				Creativity, fluency & flexibility	Cognitive flexibility	Competing Programs Task	Lower (0.004)	Recessive	Patients [M]	26	Nolan 2004
				Creativity, fluency & flexibility	Behavioral flexibility	Change Direction Task (Orienting)	Higher (<0.05)*	Additive	Controls [C]	261	Schulz 2012
				Creativity, fluency & flexibility	Behavioral flexibility	Change Direction Task (Luminance)	N.S.		Controls [C]	261	Schulz 2012
				Creativity, fluency & flexibility	Behavioral flexibility	Change Direction Task (Ori + Lum)	N.S.		Controls [C]	261	Schulz 2012
				Creativity, fluency & flexibility	Attentional control	Change Direction Task (Conflict)	N.S.		Controls [C]	261	Schulz 2012
				Attention & Executive function	Executive control of attention	Attention Network Test (Alerting)	N.S.	Dominant	Patients & Controls [C]	63	Opgen-Rhein 2008a
				Attention & Executive function	Executive control of attention	Attention Network Test (Orienting)	N.S.	Dominant	Patients & Controls [C]	63	Opgen-Rhein 2008a
				Attention & Executive function	Executive control of attention	Attention Network Test (Conflict)	Higher (0.028)	Dominant	Patients & Controls [C]	63	Opgen-Rhein 2008a
	[redacted]				Executive function	Combined CPT-AX and WCST	Lower (<0.02)	Recessive	Patients [C]	106	Galderisi 2005
				Executive function	Executive function	Common Objects Test	N.S.		Controls	473	Starr 2007
				Executive function	Speed of processing	Combined: Pattern comparison and Digit copying	N.S.		Controls [C]	172	Kennedy 2011
				Executive function	Information processing	Paced Auditory Serial Addition Test	Lower (0.041)	Recessive	SPD & Controls [C]	98	Minzenberg 2006
				Executive function	Processing speed	Letter comparison	N.S.		Controls [C]	189	Raz 2009
				Executive function	Processing speed	Pattern comparison	N.S.		Controls [C]	189	Raz 2009
				Executive function	Executive Function	Stroop Task (colour)	N.S.		Controls [C]	189	Raz 2009
				Executive function	Cognitive stability & flexibility	Stroop Task	Lower (0.004)		Patients	67	Rosa 2010
				Executive function	Cognitive stability & flexibility	Stroop Task	Lower (0.05)		Controls	186	Rosa 2010
				Executive function	Processing speed	TMT	N.S.		Patients [C]	66	Szöke 2006

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Executive function	Processing speed	TMT	N.S.		Controls [C]	158	Szöke 2006
				Executive function	Executive function	TMT (time of A-B)	N.S.		Patients	159	Ho 2005
				Executive function	Executive function	TMT (time of A-B)	N.S.		Controls	84	Ho 2005
				[redacted]	Visuoperceptual ability	TMT-A	No effect		Controls [C]	95	Wishart 2011
				[redacted]	Processing speed	TMT-A	Lower (0.01)	Additive	Patients [M]	58	Bilder 2002
				Executive function	Cognitive flexibility	TMT-B	Lower (0.002)	Dominant	Controls [C]	95	Wishart 2011
				Executive function	Processing speed	TMT-B	Lower (0.04)	Additive	Patients [M]	58	Bilder 2002
				Executive function	Executive function	TMT-B	Lower (0.001)	Recessive	Patients	89	Basterra 2012
				Executive function	Executive function	TMT-B	Lower (0.006)	Recessive	Siblings	87	Basterra 2012
				Executive function	Executive function	WCST	N.S.		Patients	159	Ho 2005
				Executive function	Executive function	WCST	N.S.		Controls	84	Ho 2005
				Executive function	Executive function	WCST	N.S.		Controls [C]	521	Aguilera 2008
				Executive function	General executive and Perceptual organization	WCST	N.S.		Patients [M]	58	Bilder 2002
				Executive function	Executive function	WCST	N.S.		Patients [M]	822	[1]Barnett 2007
				Executive function	Executive function	WCST	Lower (0.03)	Dominant	Controls [M] – 10 Samples	1088	[1]Barnett 2007
				Executive function	Executive function	WCST	Lower (0.03)	Additive	Controls [C] – 10 Samples	75	Caldú 2007
				Executive function	Executive function	WCST	N.S.		Controls	318	Nagel 2008
				Executive function	Working memory	WCST	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Executive function	Executive function	Shifting Attention Test (Discovery)	Lower (0.017)	Additive	Controls [C]	172	Kennedy 2011
				Executive function	Executive function	Combined: Tower of Hanoi, Verbal fluency, Working memory	Lower (0.01)	Dominant	Controls [C] - Males only	292	de Frias 2005
				Intelligence	Fluid reasoning	Cattell Culture Fair Intelligence Test	Lower (<0.05)	Dominant	Controls [C]	189	Raz 2009
				Intelligence	Non-verbal reasoning	Raven's progressive matrices	N.S.		Controls	473	Starr 2007
				Intelligence	Reasoning	Raven's Progressive Matrices	N.S.		Controls [C] - Males only	1657	Smyrnis 2007
				Intelligence	Working memory	WAIS-R	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Intelligence	IQ	WAIS-R	N.S.		Patients [C]	175	Egan 2001
				Intelligence	IQ	WAIS-R	N.S.		Controls [C]	55	Egan 2001
				Intelligence	Reasoning	WAIS-R (Arithmetic)	N.S.		Patients [M]	328	Enoch 2009
				Intelligence	Working memory	WAIS-R (Block design)	N.S.		Patients [M]	58	Bilder 2002
				Intelligence	Performance ability	WAIS-R (Block design)	N.S.		Controls [M]	328	Enoch 2009
				Intelligence	Visuo-spatial ability	WAIS (Block design)	Lower (0.03)	Dominant	Controls [C] - Males only	292	de Frias 2005
				Intelligence	Visuo-spatial ability	WAIS (Block design)	N.S.		Controls	473	Starr 2007
				Intelligence	Processing speed	WAIS-R (Digit symbol)	N.S.		Patients [M]	58	Bilder 2002
				Intelligence	Processing speed	WAIS (Digit symbol)	Lower (0.02)	Recessive	Controls	473	Starr 2007
				Intelligence	Working memory	WAIS-R (Digit symbol)	N.S.		Controls [M]	328	Enoch 2009
				Intelligence	Long-term memory	WAIS-R (Information)	Lower (0.014)	Dominant	Controls [M]	328	Enoch 2009
				Intelligence	Attention to detail	WAIS-R (Picture completion)	Lower (0.006)*	Dominant	Controls [M]	328	Enoch 2009
				Intelligence	Concept formation	WAIS-R (Similarities)	N.S.		Controls [M]	328	Enoch 2009
				Intelligence	Intelligence	WAIS-R (Vocabulary)	N.S.		Controls [M]		Bruder 2005
				Intelligence	Intelligence	WAIS-R (Combined: Similarities, Arithmetic, Picture completion, Digit symbol)	N.S.		Patients, siblings & controls [M]	250	Goldberg 2003
				Intelligence	Intelligence	WRAT- Reading (Pronunciation)	N.S.		Patients, siblings & controls [M]	250	Goldberg 2003
				Intelligence	Premorbid IQ	WRAT	N.S.		Patients [C]	175	Egan 2001
				Intelligence	Premorbid IQ	WRAT	N.S.		Controls [C]	55	Egan 2001
				Memory	Verbal learning	California Verbal Learning Test	N.S.		SPD & Controls [C]	98	Minzenberg 2006
				Memory	Verbal declarative memory	Hopkins verbal learning (Total recall)	N.S.		Patients [M]	58	Bilder 2002
				Memory	Verbal declarative memory	Hopkins verbal learning (Delay recall)	Lower (0.05)	Additive	Patients [M]	58	Bilder 2002
				Memory	Verbal declarative memory	RAVLT	N.S.		Controls	473	Starr 2007
				Memory	Visuospatial memory	Spatial Delayed Response Test	N.S.		Controls [M]	402	Bruder 2005

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Episodic memory	Episodic memory tests composite	Lower (0.02)	Dominant	Controls	128	de Frias 2004
				Memory	Semantic memory	Semantic memory tests composite	N.S.		Controls	128	de Frias 2004
				Memory	Episodic memory	WJPB-R (Memory for names - Immediate)	Lower (<0.02)	Dominant	Controls [C]	189	Raz 2009
				Memory	Episodic memory	WJPB-R (Memory for names - Delayed)	Lower (<0.007)	Dominant	Controls [C]	189	Raz 2009
				Memory	Verbal declarative memory	WMS-R (Logical Memory - Immediate)	N.S.		Patients [M]	58	Bilder 2002
				Memory	Verbal declarative memory	WMS-R (Logical Memory - Delayed)	N.S.		Patients [M]	58	Bilder 2002
				Memory	Visual memory	Visual memory recall - Delayed	Lower (0.023)	Recessive	Controls	79	Bates 2003
				Memory	Visual delayed recall	WMS (Visual reproduction)	N.S.		SPD & Controls [C]	98	Minzenberg 2006
				Memory	Organization	WMS-R (Visual reproductions I)	Lower (0.02)	Additive	Patients [M]	58	Bilder 2002
				Memory	Organization	WMS-R (Visual reproductions II)	Lower (0.01)	Additive	Patients [M]	58	Bilder 2002
				Working memory	Visuospatial working memory	Automated Working Memory Assessment battery (Dot Matrix)	Lower (0.036)	Dominant	Controls [C] (Adults)	322	Dumontheil 2011
				Working memory	Visuospatital working memory	DOT	N.S.		SPD & Controls [C]	98	Minzenberg 2006
				Working memory	Working memory	Dot Pattern Expectancy	Lower (0.012)	Recessive	Controls [C]	459	MacDonald 2007
				Working memory	Working memory	Dual Task in Cogscreen	Lower (0.04)	Additive	Controls [C]	172	Kennedy 2011
				Working memory	Organization	Letter-Number Span	N.S.		Patients [M]	58	Bilder 2002
				Working memory	Working memory	N-back Task	N.S.		Controls [M]	402	Bruder 2005
				Working memory	Working memory	N-back Task	N.S.		Controls [C] - Males only	458	Stefanis 2004
				Working memory	Working memory	N-back Task	N.S.		Controls [C] - Males only	1657	Smyrnis 2007
				Working memory	Working memory	N-Back Task (0-Back)	N.S.		Patients, siblings & controls [M]	250	Goldberg 2003
				Working memory	Working memory	N-back Task (0-back)	Lower (0.028)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-Back Task (1-Back)	Lower (0.04)	Additive	Patients, siblings & controls [M]	250	Goldberg 2003
				Working memory	Working memory	N-back Task (1-back)	Lower (0.001)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-Back Task (2-Back)	Lower (0.02)	Additive	Patients, siblings & controls [M]	250	Goldberg 2003
				Working memory	Working memory	N-back Task (2-back)	Lower (0.003)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (3-back)	N.S.		Controls [C]	456	MacDonald 2007
				Working memory	Executive function	Spatial Working Memory Task	N.S.		Controls	318	Nagel 2008
				Working memory	Verbal working memory	Word Serial Position Test	N.S.		Controls [M]	402	Bruder 2005
				Working memory	Verbal working memory	WAIS-R (Letter-Number sequencing)	Lower (0.03)	Recessive	Controls [M]	402	Bruder 2005
				Working memory	Working memory	WAIS-R (Letter-Number sequencing)	Lower (0.046)	Recessive	Controls [C]	521	Aguilera 2008
				Working memory	Working memory	WMS-R (Digit span)	N.S.		Controls [M]	328	Enoch 2009
				Working memory	Working memory	WAIS-R (Digit span backward)	N.S.		Patients	159	Ho 2005
				Working memory	Working memory	WAIS-R (Digit span backward)	N.S.		Controls	84	Ho 2005
				Working memory	Working memory	WMS-R (Visual span backwards)	N.S.		Controls [C]	521	Aguilera 2008
	rs737865			Attention & Executive function	Working memory	CPT	Lower (0.0049)	Recessive	Patients [C]	325	Diaz-Asper 2008
				Attention & Executive function	Working memory	CPT	Not reported		Siblings & Controls [C]	689	Diaz-Asper 2008
				Attention & Executive function	Working memory	Intra-Extra dimensional set shifting	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Executive function	Working memory	WCST	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Intelligence	Working memory	WAIS-R	N.S.		Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (0-back)	Lower (0.0004)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (1-back)	Lower (0.0158)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
				Working memory	Working memory	N-back Task (2-back)	Lower (0.0167)	Recessive	Patients, Siblings & Controls [C]	1014	Diaz-Asper 2008
CSMD1	rs10503253	No	A (0.19)	Attention & Executive function	Attentional control	CPT-IP	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Attention & Executive function	Attentional control	CPT 3-7 version	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (FSIQ)	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (FSIQ)	Lower (0.033)		Patients & Controls [C] (German)	738	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (FSIQ)	N.S.		Patients [C] (German)	205	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (FSIQ)	N.S.		Controls [C] (German)	533	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (PIQ)	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (PIQ)	Lower (0.01)		Patients [C] (German)	205	Donohoe 2013

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Intelligence	General cognitive ability	WAIS-R (PIQ)	N.S.		Controls [C] (German)	533	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (VIQ)	Lower (0.02)		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Intelligence	General cognitive ability	WAIS-R (VIQ)	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Memory	Verbal episodic memory	WMS-R (Logical memory - Immediate)	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Memory	Verbal episodic memory	WMS-R (Logical memory - Immediate)	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Memory	Verbal episodic memory	WMS-R (Logical memory - Delayed)	Lower (0.041)		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Memory	Verbal episodic memory	WMS-R (Logical memory - Delayed)	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Memory	Visual episodic memory	WMS-R (Faces)	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Memory	Visual episodic memory	WMS-R (Visual memory)	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Working memory	Spatial working memory	CANTAB (Spatial working memory)	N.S.		Patients & Controls [C] (Irish)	558	Donohoe 2013
				Working memory	Working memory	N-back Task	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Working memory	Working memory	WAIS-R (Digit span)	N.S.		Patients & Controls [C] (German)	738	Donohoe 2013
				Working memory	Working memory	WMS-R (Spatial span)	Lower (0.015)		Patients & Controls [C] (German)	738	Donohoe 2013
				Working memory	Verbal working memory	WMS-R (Letter-number sequencing)	N.S.		Patients [C] (Irish)	387	Donohoe 2013
				Working memory	Verbal working memory	WMS-R (Letter-number sequencing)	Lower (0.005)		Controls [C] (Irish)	171	Donohoe 2013
DAO (aka DAAO)	rs2111902	Yes	G (0.30)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs3918346	Yes	G (0.76)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-back Task	Lower (0.033)	Recessive	Controls [C] - Males only	2243	Stefanis 2007
	rs3741775	Yes	C (0.57)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
DAOA (G72)	rs1421292 (M24)	No	T (0.49)	Attention & Executive function	Attention and vigilance	CPT (distractibility)	Lower (0.03)	Recessive	Patients [C]	180+	Goldberg 2006
				Attention & Executive function	Attention and vigilance	CPT (distractibility)	Not Reported		Siblings [C]	245+	Goldberg 2006
				Attention & Executive function	Attention and vigilance	CPT (distractibility)	Not Reported		Controls [C]	150+	Goldberg 2006
				Attention & Executive function	Attention	d2-Test	Higher (0.001)	Additive	Controls [C]	423	Jansen 2009
				Creativity, fluency & flexibility	Verbal fluency	Semantic and Lexical Word Generation	N.S.		Controls [C]	423	Jansen 2009
				Creativity, fluency & flexibility	Verbal fluency	Semantic Verbal Fluency Task	N.S.		Controls [C]	96	Krug 2011
				Executive function	Executive function	TMT-B	Lower (0.022)	Additive	Controls[C]	423	Jansen 2009
				Executive function	Scanning and attention	TMT-B	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Executive function	Executive function	WCST	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Intelligence	Intelligence	WAIS-R (Picture completion, Similarities, Digit symbol, & Arithmetic)	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Memory	Episodic Learning	WMS-R (Hard Pairs)	Lower (0.05)	Recessive	Patients [C]	180+	Goldberg 2006
				Memory	Episodic Learning	WMS-R (Hard Pairs)	Not Reported		Siblings [C]	245+	Goldberg 2006
				Memory	Episodic Learning	WMS-R (Hard Pairs)	Not Reported		Controls [C]	150+	Goldberg 2006
				Memory	Verbal Episodic Memory	Memory for Stories	N.S.		Patients & Controls [C]	328	Goldberg 2006
				Working memory	Working memory	N-back Task	Lower (0.05)	Recessive	Patients & Controls [C]	328	Goldberg 2006
				Working memory	Verbal working memory	Letter-Number Span	Higher (0.001)	Additive	Controls [C]	423	Jansen 2009
				Working memory	Spatial working memory	WMS (Spatial Span)	N.S.		Controls [C]	423	Jansen 2009
	rs1570709	No	G (0.27)	Attention & Executive function	Sustained attention	CPT-IP Fast	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Attention & Executive function	Sustained attention	CPT-IP Slow	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Creativity, fluency & flexibility	Semantic fluency	Controlled Word Association Test	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Creativity, fluency & flexibility	Verbal fluency	Verbal Fluency Task	Higher (0.008)	Dominant	Patients [C]	102	Opgen-Rhein 2008b
				Creativity, fluency & flexibility	Verbal fluency	Verbal Fluency Task	Higher (0.008)	Dominant	Controls [C]	94	Opgen-Rhein 2008b
				[redacted]	Executive control	TMT-A	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Executive function	Executive function	TMT-B	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Intelligence	Intelligence	WRAT-R (Reading)	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Memory	Verbal Learning and Memory	CVLT	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
				Working memory	Verbal working memory	WMS-R (Digit Span)	N.S.		Patients & Controls [C]	196	Opgen-Rhein 2008b
	rs2391191	Yes	G (Arg)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007

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	(ARG30LYS) (M15)		(0.62)	Attention & Executive function		CPT (distractibility)	N.S.		Patients & Controls [C]	1185	Donohoe 2007
				Attention & Executive function		CANTAB (IED)	N.S.		Patients & Controls [C]	1185	Donohoe 2007
				Memory	Verbal declarative memory	WMS-R (Logical memory - Immediate)	Lower (0.028)	Dominant	Patients & Controls [C]	1185	Donohoe 2007
				Memory	Verbal declarative memory	WMS-R (Logical memory - Delayed)	Lower (0.015)	Dominant	Patients & Controls [C]	1185	Donohoe 2007
				Memory		CANTAB (Paired associates)	N.S.		Patients & Controls [C]	1185	Donohoe 2007
				Working memory	Working memory	N-back Task	N.S.		Patients & Controls [C]	1185	Donohoe 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs3918342 (M23)**	Yes	T (0.50)	Attention & Executive function	Attention and vigilance	CPT (distractibility)	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Attention & Executive function	Attention	d2-Test	Higher (0.001)	Additive	Controls [C]	423	Jansen 2009
				Creativity, fluency & flexibility	Verbal fluency	Semantic and Lexical Word Generation	N.S.		Controls [C]	423	Jansen 2009
				Creativity, fluency & flexibility	Verbal fluency	Semantic Verbal Fluency Task	N.S.		Controls [C]	96	Krug 2011
				Executive function	Executive function	TMT-B	N.S.		Controls [C]	423	Jansen 2009
				Executive function	Scanning and attention	TMT-B	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Executive function	Executive function	WCST	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Intelligence	Intelligence	WAIS-R (Picture completion, Similarities, Digit symbol, & Arithmetic)	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Memory	Episodic learning	WMS-R (Hard Pairs)	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Memory	Verbal episodic memory	Memory for Stories	N.S.		Patients & Controls [C]	575+	Goldberg 2006
				Working memory	Working memory	N-Back Task	Lower (0.007)	Recessive	Patients [C]	81	Goldberg 2006
				Working memory	Working memory	N-Back Task	Not Reported		Siblings [C]	124	Goldberg 2006
				Working memory	Working memory	N-Back Task	Not Reported		Controls [C]	123	Goldberg 2006
				Working memory	Verbal working memory	Letter-Number Span	Higher (0.002)	Additive	Controls [C]	423	Jansen 2009
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Spatial working memory	WMS (Spatial Span)	N.S.		Controls [C]	423	Jansen 2009
	rs778293	Yes	G (0.40)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
DISC1	rs11122359 (hCV1650723)	Yes	A (0.32)	Attention & Executive function	Visual attention	CPT-IP	N.S.		Patients [M]	250	Burdick 2005
				Creativity, fluency & flexibility	Executive function	Controlled Word Association Test	N.S.		Patients [M]	250	Burdick 2005
				[redacted]	Rapid visual search	TMT-A	N.S.		Patients [M]	250	Burdick 2005
				Executive function	Executive function	TMT-B	N.S.		Patients [M]	250	Burdick 2005
				Intelligence	Premorbid IQ	WRAT-III	N.S.		Patients [M]	250	Burdick 2005
				Memory	Verbal learning	CVLT	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Auditory attention	WMS (Digit span forward)	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Working memory	WMS (Digit span backward)	N.S.		Patients [M]	250	Burdick 2005
	rs2255340 (hCV1650649)	Yes	A (0.25)	Attention & Executive function	Visual attention	CPT-IP	N.S.		Patients [M]	250	Burdick 2005
				Creativity, fluency & flexibility	Executive function	Controlled Word Association Test	N.S.		Patients [M]	250	Burdick 2005
				[redacted]	Rapid visual search	TMT-A	Lower (0.001)	Recessive	Patients [AA]	126	Burdick 2005
					Rapid visual search	TMT-A	N.S.		Patients [C]	124	Burdick 2005
				Executive function	Executive function	TMT-B	N.S.		Patients [M]	250	Burdick 2005
				Intelligence	Premorbid IQ	WRAT-III	N.S.		Patients [M]	250	Burdick 2005
				Memory	Verbal Learning	CVLT	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Auditory attention	WMS (Digit span forward)	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Working memory	WMS (Digit span backward)	Lower (0.002)	Recessive	Patients [AA]	126	Burdick 2005
				Working memory	Working memory	WMS (Digit span backward)	N.S.		Patients [C]	124	Burdick 2005
	rs2738864 (hCV1650650)	Yes	T (0.24)	Attention & Executive function	Visual attention	CPT-IP	N.S.		Patients [M]	250	Burdick 2005
				Creativity, fluency & flexibility	Executive function	Controlled Word Association Test	N.S.		Patients [M]	250	Burdick 2005
				[redacted]	Rapid visual search	TMT-A	N.S.		Patients [M]	250	Burdick 2005
				Executive function	Executive function	TMT-B	N.S.		Patients [M]	250	Burdick 2005
				Intelligence	Premorbid IQ	WRAT-III	N.S.		Patients [M]	250	Burdick 2005

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Verbal Learning	CVLT	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Auditory attention	WMS (Digit span forward)	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Working memory	WMS (Digit span backward)	N.S.		Patients [M]	250	Burdick 2005
	rs701158 (hCV9628138)	No		Attention & Executive function	Visual attention	CPT-IP	N.S.		Patients [M]	250	Burdick 2005
				Creativity, fluency & flexibility	Executive function	Controlled Word Association Test	N.S.		Patients [M]	250	Burdick 2005
				[redacted]	Rapid visual search	TMT-A	N.S.		Patients [M]	250	Burdick 2005
				Executive function	Executive function	TMT-B	N.S.		Patients [M]	250	Burdick 2005
				Intelligence	Premorbid IQ	WRAT-III	N.S.		Patients [M]	250	Burdick 2005
				Memory	Verbal learning	CVLT	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Auditory attention	WMS (Digit span forward)	N.S.		Patients [M]	250	Burdick 2005
				Working memory	Working memory	WMS (Digit span backward)	N.S.		Patients [M]	250	Burdick 2005
	rs821616 (Ser704Cys)	Yes	Ser	Attention & Executive function	Attention	CPT	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Creativity, fluency & flexibility	Letter fluency	Letter fluency	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Executive function	Working memory	WCST (Categories)	Lower (0.04)	Recessive	Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Executive function	Working memory	WCST (Preservative errors)	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Memory	Memory encoding	Encoding & retrieval of novel, complex scenes	N.S.		Controls [C]	80	Di Giorgio 2008
				Memory	Episodic memory	CVLT	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Memory	Episodic memory	WMS-R (Logical memory I)	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
				Memory	Episodic memory	WMS-R (Logical memory II)	Lower (0.02)	Recessive	Patients [C]	252	Callicott 2005
				Memory	Episodic memory	WMS-R (Logical memory II)	Not reported		Parents, Siblings & Controls [C]	917	Callicott 2005
				Working memory	Working memory	N-back (2-back)	Not reported		Patients, Parents, Siblings & Controls [C]	1169	Callicott 2005
DRD4	rs1800955 (521T/C)	Yes	C (0.40)	Attention & Executive function	Executive attention	Attention Networking Test	Lower (0.006)	Additive	Controls	220	Fossella 2002
				Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Patients	150	Alfimova 2007
				Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Relatives	83	Alfimova 2007
				Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Controls	115	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	Higher (0.01)	Recessive	Patients	150	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	N.S.		Relatives	83	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	N.S.		Controls	115	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Patients	150	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Relatives	83	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Controls	115	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Patients	150	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Relatives	83	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Controls	115	Alfimova 2007
	rs936461 (809G/A)	No		Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Patients	150	Alfimova 2007
				Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Relatives	83	Alfimova 2007
				Creativity, fluency & flexibility	Associative processes	Concepts and Syllable Method	N.S.		Controls	115	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	N.S.		Patients	150	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	N.S.		Relatives	83	Alfimova 2007
				Executive function	Attention stability	Semantic verbal fluency and serial counting	N.S.		Controls	115	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Patients	150	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Relatives	83	Alfimova 2007
				Memory	Short-term verbal memory	Word list memorization	N.S.		Controls	115	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Patients	150	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Relatives	83	Alfimova 2007
				Memory	Long-term verbal memory	Pictogram method	N.S.		Controls	115	Alfimova 2007
DTNBP1	rs1011313	Yes	A (0.09)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	5519	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs1018381	Yes	T (0.09)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Attention & Executive function	Attention	d2 test	N.S.		Controls [M]	521	Kircher 2009a
				Creativity, fluency & flexibility	Verbal fluency	Semantic fluency task (Country naming)	N.S.		Controls [M]	521	Kircher 2009a
				Executive function	Psycho-motor speed	TMT-B	N.S.		Controls [M]	521	Kircher 2009a
				Intelligence	Verbal intelligence	Multiple-choice Word Test	N.S.		Controls [M]	521	Kircher 2009a
				Intelligence	Intelligence	Spearman's g/IQ	Lower (0.003)	Dominant	Controls [M] - 8 samples	6017	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Controls	290	Alfimova 2010
				Memory	Episodic memory	Face recognition	N.S.		Controls [C]	84	Thimm 2010
				Working memory	Auditory working memory	Letter-Number Span	N.S.		Controls [M]	521	Kircher 2009a
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Visual working memory	WMS (Spatial Span)	N.S.		Controls [M]	521	Kircher 2009a
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs1047631	Yes	G (0.15)	Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	1159	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	Lower (0.03)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
	rs17470454	Yes	C (0.94)	Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
	rs2005976	Yes	G (0.80)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs2619522	Yes	G (0.21)	Attention & Executive function	Attention	CPT-IP	Lower (0.031)	Recessive	Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Intelligence	Spearman's g/IQ	Lower (0.007)	Dominant	Controls [M] - 6 samples	4793	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Overall productivity)	Lower (<0.01)	Recessive	Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	Higher (<0.05)	Recessive	Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	Lower (<0.05)	Recessive	Controls	290	Alfimova 2010
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	Lower (0.03)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	Lower (0.05)	Dominant	Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
	rs2619538	Yes	T (0.47)	Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	883	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
	rs2619539	Yes	C (0.46)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	2580	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	Higher (0.04)	Dominant	Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory		WMS-R (Attention/Concentration)	N.S.		Patients [A]	70	Hashimoto 2009

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory		WMS-R (Attention/Concentration)	N.S.		Controls [A]	165	Hashimoto 2009
				Memory		WMS-R (Delayed memory)	N.S.		Patients [A]	70	Hashimoto 2009
				Memory		WMS-R (Delayed memory)	N.S.		Controls [A]	165	Hashimoto 2009
				Memory		WMS-R (General memory)	N.S.		Patients [A]	70	Hashimoto 2009
				Memory		WMS-R (General memory)	Lower (0.040)	Recessive	Controls [A]	165	Hashimoto 2009
				Memory		WMS-R (Verbal memory)	N.S.		Patients [A]	70	Hashimoto 2009
				Memory		WMS-R (Verbal memory)	Lower (0.042)	Dominant	Controls [A]	165	Hashimoto 2009
				Memory		WMS-R (Visual memory)	N.S.		Patients [A]	70	Hashimoto 2009
				Memory		WMS-R (Visual memory)	N.S.		Controls [A]	165	Hashimoto 2009
				Working memory		WAIS-R (Digit Span)	N.S.		Patients [A]	70	Hashimoto 2009
				Working memory		WAIS-R (Digit Span)	N.S.		Controls [A]	165	Hashimoto 2009
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs3213207	Yes	C (0.12)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	3273	[2]Zhang 2010
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	Lower (0.04)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs742105	Yes	T (0.47)	Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	Lower (0.01)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Immediate)	Lower (0.01)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
	rs760761	Yes	T (0.22)	Attention & Executive function	Attention	CPT-IP	Lower (0.029)	Dominant	Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	IQ	Raven's Progressive Matrices	Lower (0.041)	Additive	Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M]	4105	[2]Zhang 2010
				Intelligence	Intelligence	WAIS-III (FSIQ)	Lower (0.026)	Dominant	Patients, Siblings & Controls [C]	138	Zinkstok 2007
				Intelligence	Intelligence	WAIS-III (PIQ)	Lower (0.038)	Dominant	Patients, Siblings & Controls [C]	138	Zinkstok 2007
				Intelligence	Intelligence	WAIS-III (VIQ)	Lower (0.049)	Dominant	Patients, Siblings & Controls [C]	138	Zinkstok 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Intelligence	Verbal ability	Mill Hill vocabulary A & B	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid ability	The Cattell Culture Fair	N.S.		Controls [C] (English)	745	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	Cumulative Recall	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Processing speed	Random Letters test	Lower (0.02)	Dominant	Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Semantic memory	N.S.		Controls [C] (English)	745	Luciano 2009

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Verbal declarative memory	Verbal recall (Immediate)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	Verbal declarative memory	Verbal recall (Delayed)	N.S.		Controls [C] (English)	745	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
	rs909706	Yes	T (0.36)	Intelligence	Intelligence	Spearman's g/IQ	N.S.		Controls [M] - 10 samples	2477	[2]Zhang 2010
				Intelligence	Fluid spatial ability	WAIS-III (Block design)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Intelligence	Fluid spatial ability	WAIS-III (Matrix reasoning)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	General memory	WMS-III	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory immediate)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Memory	Verbal declarative memory	WMS-III (Logical memory delayed)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Working memory	Letter-Number Sequencing	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
				Working memory	Spatial memory	WMS-III (Spatial span)	N.S.		Controls [C] (Scottish)	1091	Luciano 2009
GRIN2B	rs12828473	No		Attention & Executive function	Sustained attention	CPT-DS	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-DS	N.S.		Controls [C]	172	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C]	172	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Patients [C]	336	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Patients [C]	336	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Patients [C]	336	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Controls [C]	172	Jablensky 2011
GRIN2B	rs1806201	Yes	T (0.45)	Intelligence	Intelligence	WAIS-R (FSIQ)	N.S.		Controls [A]	112	Tsai 2002
				Intelligence	Intelligence	WAIS-R (PIQ)	N.S.		Controls [A]	112	Tsai 2002
				Intelligence	Intelligence	WAIS-R (PIQ)	N.S.		Controls [A]	112	Tsai 2002
	rs220599	No	T	Attention & Executive function	Sustained attention	CPT-DS	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-DS	N.S.		Controls [C]	172	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C]	172	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Patients [C]	336	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	Lower (<0.05)	Additive	Patients [C]	336	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	Lower (0.02)	Additive	Patients with cognitive deficit [C]	155	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Patients with spared cognition [C]	121	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	Lower (0.008)	Additive	Patients with cognitive deficit [C]	155	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Patients with spared cognition [C]	121	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Controls [C]	172	Jablensky 2011
GRM3	rs2189814	No	C	Attention & Executive function	Sustained attention	CPT-DS	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-DS	N.S.		Controls [C]	172	Jablensky 2011

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C]	172	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Patients [C]	336	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	Lower (0.007)	Additive	Patients with cognitive deficit [C]	155	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Patients with spared cognition [C]	121	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	Higher (6E-5)	Recessive	Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	Lower (0.04)	Additive	Patients with cognitive deficit [C]	155	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Patients with spared cognition [C]	121	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	Higher (5E-5)	Recessive	Controls [C]	172	Jablensky 2011
GRM3	rs6465084	Yes	A (0.76)	Attention & Executive function	Sustained attention	CPT-DS	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-DS	N.S.		Controls [C]	172	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C]	172	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Patients [C]	336	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Patients [C]	336	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Patients [C]	336	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Controls [C]	172	Jablensky 2011
5-HTR2A	rs6311 (A1438G)	Yes	A (0.43)	Memory	Short-term memory	List learning (Overall productivity)	Lower (<0.03)	Recessive	Patients & Controls	695	Alfimova 2010
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Controls	290	Alfimova 2010
	rs6313 (T102C)	Yes	C (0.53)	Attention & Executive function	Sustained attention	CPT-DS	Lower (0.024)*	Dominant	Patients & Siblings [M]	99	Vyas 2012
				Attention & Executive function	Sustained attention	CPT	Lower (0.03)	Hetero-zygote	Patients	82	Ucok 2007
				Creativity, fluency & flexibility	Semantic verbal fluency	Animal naming	Higher (0.005)	Hetero-zygote	Patients [A]	471	Chen 2001
				Creativity, fluency & flexibility	Semantic verbal fluency	Animal naming	N.S.		Controls [A]	523	Chen 2001
				Creativity, fluency & flexibility	Semantic memory	Controlled Word Association Task	N.S.		Patients	269	Golimbet 2006
				Creativity, fluency & flexibility	Semantic memory	Controlled Word Association Task	N.S.		Relatives	141	Golimbet 2006
				Creativity, fluency & flexibility	Semantic memory	Controlled Word Association Task	N.S.		Controls	227	Golimbet 2006
				Executive function	Executive Function	Stroop Task	Not reported		Patients [A]	471	Chen 2001
				Executive function	Executive Function	Stroop Task	Not reported		Controls [A]	523	Chen 2001
				Executive function	Cognitive flexibility	WCST	Lower (0.03)	Hetero-zygote	Patients	82	Ucok 2007
				Memory	Short-term memory	List learning (Overall productivity)	Lower (<0.04)	Recessive	Patients & Controls	695	Alfimova 2010
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Patients	405	Alfimova 2010

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Memory	Short-term memory	List learning (Overall productivity)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Immediate recall)	N.S.		Controls	290	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Patients	405	Alfimova 2010
				Memory	Short-term memory	List learning (Interference)	N.S.		Controls	290	Alfimova 2010
				Memory	Episodic memory	Free recall	Lower (0.008)	Recessive	Patients	269	Golimbet 2006
				Memory	Episodic memory	Free recall	N.S.		Relatives	141	Golimbet 2006
				Memory	Episodic memory	Free recall	N.S.		Controls	227	Golimbet 2006
				Memory	Episodic memory	Pictograms	N.S.		Patients	269	Golimbet 2006
				Memory	Episodic memory	Pictograms	N.S.		Relatives	141	Golimbet 2006
				Memory	Episodic memory	Pictograms	N.S.		Controls	227	Golimbet 2006
				Working memory	Short-term attention	WAIS-R (Digit Forward Span)	N.S.		Patients	82	Ucok 2007
				Working memory	Short-term attention	WAIS-R (Digit Backward Span)	N.S.		Patients	82	Ucok 2007
KCNH2	rs3800779 (M30)	No	T (0.23)	Attention & Executive function	Attention/vigilance	CPT-IP	Lower (0.0079)	Dominant	Controls [A]	191	Hashimoto 2013
				Attention & Executive function	Factor: Attention	N-back-0 + Gordon Distractibility + Gordon Vigilance	N.S.		Controls [C]	230	Huffaker 2009
				Executive function	Processing speed	Category Fluency Test	N.S.		Controls [A]	191	Hashimoto 2013
				Executive function	Reasoning and problem solving	Tower of Hanoi Task	N.S.		Controls [A]	191	Hashimoto 2013
				Executive function	Social cognition	Emotion Recognition Test (FELT)	N.S.		Controls [A]	191	Hashimoto 2013
				Executive function	Factor: Card sorting	WCST	N.S.		Controls [C]	230	Huffaker 2009
				Executive function	Factor: Processing speed	WAIS (IQ) + TMT-A&B + Letter Fluency + Category Fluency	Lower (0.02)	Dominant	Controls [C]	230	Huffaker 2009
				Intelligence	Intelligence	WAIS-R	Lower (0.048)	Dominant	Controls [A]	191	Hashimoto 2013
				Memory	Verbal learning and memory	RAVLT (Immediate Recall)	N.S.		Controls [A]	191	Hashimoto 2013
				Memory	Visual learning and memory	WMS-R (Visual Reproduction I)	N.S.		Controls [A]	191	Hashimoto 2013
				Memory	Factor: Verbal memory	WMS-R (Logical memory, Verbal paired associates) + CVLT	N.S.		Controls [C]	230	Huffaker 2009
				Memory	Factor: Visual memory	WMS-R (Visual reproduction) + Benton line orientation	N.S.		Controls [C]	230	Huffaker 2009
				Working Memory	Working Memory	WMS-R (Digit Span)	Lower (0.0066)	Dominant	Controls [A]	191	Hashimoto 2013
				Working memory	Factor: N-back	N-back Task (1,2, and 3)	N.S.		Controls [C]	230	Huffaker 2009
				Working memory	Factor: Digit span	WMS-R (Digit Span – Forward and Backward)	N.S.		Controls [C]	230	Huffaker 2009
LIF	rs929271	No	T (0.56)	Executive function		WCST	Lower (0.04)	Dominant	Controls [A]	355	Okahisa 2010
				Intelligence	Intelligence	WAIS-R (FSIQ)	N.S.		Controls [A]	355	Okahisa 2010
				Intelligence	Intelligence	WAIS-R (PIQ)	N.S.		Controls [A]	355	Okahisa 2010
				Intelligence	Intelligence	WAIS-R (VIQ)	N.S.		Controls [A]	355	Okahisa 2010
				Memory	Memory	WMS-R (Attention/Concentration)	N.S.		Controls [A]	355	Okahisa 2010
				Memory	Memory	WMS-R (Delayed recall)	N.S.		Controls [A]	355	Okahisa 2010
				Memory	Memory	WMS-R (General memory)	N.S.		Controls [A]	355	Okahisa 2010
				Memory	Memory	WMS-R (Verbal memory)	N.S.		Controls [A]	355	Okahisa 2010
				Memory	Memory	WMS-R (Visual memory)	N.S.		Controls [A]	355	Okahisa 2010
MIR137	rs1625579	No	T (0.81)	Attention & Executive function	Attentional Control	CPT-IP	N.S.		Patients & Controls [C]	570	Cummings 2013
				Attention & Executive function	Attentional Control	CANTAB (IDED)	Lower (0.047)	Dominant	Patients & Controls [C]	570	Cummings 2013
				Executive function	Executive function	Controlled Oral Word Association	N.S.		Patients [C]	617	Green 2012
				Executive function	Executive function	Controlled Oral Word Association	N.S.		Controls [C]	764	Green 2012
				Intelligence	General ability	WAIS-R (FIQ)	N.S.		Patients & Controls [C]	570	Cummings 2013
				Intelligence	General ability	WAIS-R (VIQ)	N.S.		Patients & Controls [C]	570	Cummings 2013
				Intelligence	General ability	WAIS-R (PIQ)	N.S.		Patients & Controls [C]	570	Cummings 2013
				Intelligence	General functioning	Global Assessment of Functioning	N.S.		Patients [C]	617	Green 2012

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Intelligence	General functioning	Global Assessment of Functioning	N.S.		Controls [C]	764	Green 2012
				Intelligence	IQ	Wechsler Test of Adult Reading	N.S.		Patients & Controls [C]	570	Cummings 2013
				Intelligence	Premorbid IQ	Wechsler Test of Adult Reading	N.S.		Patients [C]	617	Green 2012
				Intelligence	Premorbid IQ	Wechsler Test of Adult Reading	N.S.		Controls [C]	764	Green 2012
				Intelligence	Current IQ	Wechsler Abbreviated Scale of Intelligence	N.S.		Patients [C]	617	Green 2012
				Intelligence	Current IQ	Wechsler Abbreviated Scale of Intelligence	N.S.		Controls [C]	764	Green 2012
				Intelligence	Cognitive performance	Repeatable Battery for the Assessment of Neuropsychological Status	N.S.		Patients [C]	617	Green 2012
				Intelligence	Cognitive performance	Repeatable Battery for the Assessment of Neuropsychological Status	N.S.		Controls [C]	764	Green 2012
				Memory	Episodic memory	CANTAB (Paired Associates)	N.S.		Patients & Controls [C]	570	Cummings 2013
				Memory	Episodic memory	WMS-R (Logical memory)	Lower (0.023)	Dominant	Patients & Controls [C]	570	Cummings 2013
				Working memory	Spatial episodic memory	CANTAB (Spatial WM task)	N.S.		Patients & Controls [C]	570	Cummings 2013
				Working memory	Working memory	WAIS (Letter-Number Sequencing)	Lower (0.014)	Dominant	Patients & Controls [C]	570	Cummings 2013
				Working memory	Working memory	WAIS (Letter-Number Sequencing)	N.S.		Patients [C]	617	Green 2012
				Working memory	Working memory	WAIS (Letter-Number Sequencing)	N.S.		Controls [C]	764	Green 2012
				Working memory	Episodic memory	WMS-R (Digit span)	N.S.		Patients & Controls [C]	570	Cummings 2013
MTHFR	rs1801133 (C667T)	Yes	T (0.32)	Creativity, Fluency & Flexibility		Verbal Fluency Test	Lower (0.031)	Recessive	Patients [M]	200	Roffman 2007
				Executive function		WCST	N.S.		Patients [M]	200	Roffman 2007
				Memory		CVLT	N.S.		Patients [M]	200	Roffman 2007
NETO1	rs17086492	No		Attention & Executive function	Attention	CPT-IP	N.S.		Patients [A]	107	Banno 2011
				Attention & Executive function	Attention	CPT-IP	N.S.		Controls [A]	104	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Patients [A]	107	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Controls [A]	104	Banno 2011
	rs17795324	No		Attention & Executive function	Attention	CPT-IP	N.S.		Patients [A]	107	Banno 2011
				Attention & Executive function	Attention	CPT-IP	N.S.		Controls [A]	104	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Patients [A]	107	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Controls [A]	104	Banno 2011
	rs8098760	No		Attention & Executive function	Attention	CPT-IP	N.S.		Patients [A]	107	Banno 2011
				Attention & Executive function	Attention	CPT-IP	N.S.		Controls [A]	104	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Patients [A]	107	Banno 2011
				Executive function	Cognitive flexibility	WCST	N.S.		Controls [A]	104	Banno 2011
NEUROG1	rs2344484	No	C (0.34)	[redacted]	Processing speed/Attention	WAIS-R (Digit span & Digit symbol)+TMT-A&B+Stroop Colour Test	N.S.		Patients [C]	329	Ho 2008
					Language skills	WAIS-R (Vocabulary)+Controlled Word Association + Shipley Institute of Living Scale	Lower (<0.05)	Dominant	Patients [C]	329	Ho 2008
					Problem solving	WCST+Shipley Institute of Living Scale+WAIS-R	N.S.		Patients [C]	329	Ho 2008
				Intelligence	Intelligence	WAIS (FSIQ)	Lower (<0.05)	Dominant	Patients [C]	329	Ho 2008
				Intelligence	Intelligence	WAIS (FSIQ)	N.S.		Controls [C]	162	Ho 2008
				Intelligence	Intelligence	WAIS (PIQ)	N.S.		Patients [C]	329	Ho 2008
				Intelligence	Intelligence	WAIS (PIQ)	N.S.		Controls [C]	162	Ho 2008
				Intelligence	Intelligence	WAIS (VIQ)	Lower (<0.05)	Dominant	Patients [C]	329	Ho 2008
				Intelligence	Intelligence	WAIS (VIQ)	N.S.		Controls [C]	162	Ho 2008
				Memory	Verbal memory	RAVLT+WMS-R (Logical memory immediate & delayed)	Lower (<0.05)	Dominant	Patients [C]	329	Ho 2008
				[redacted]	Visuospatial skills	Rey-Osterrieth Complex Figure Test+WAIS-R (Block design & Object assembly)+Judgement of Line Orientation	Lower (<0.05)	Dominant	Patients [C]	329	Ho 2008
NOS1	G84A (SNP1)	No	A	Attention & Executive function		CPT	Higher (<0.05)	Dominant	Patients [C]	48	Reif 2006
				Executive function		Stroop Colour Word Task	N.S.		Patients [C]	48	Reif 2006

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Executive function		TMT-A&B	N.S.		Patients [C]	48	Reif 2006
				Creativity, fluency & flexibility		Verbal fluency test (Letters and categories)	N.S.		Patients [C]	48	Reif 2006
	rs1047735 (SNP3)	No		Attention & Executive function		CPT	N.S.		Patients [C]	48	Reif 2006
				Executive function		Stroop Colour Word Task	N.S.		Patients [C]	48	Reif 2006
				Executive function		TMT-A&B	N.S.		Patients [C]	48	Reif 2006
				Creativity, fluency & flexibility		Verbal fluency test (Letters and categories)	N.S.		Patients [C]	48	Reif 2006
	rs2133681 (SNP 4)	No		Attention & Executive function		CPT	N.S.		Patients [C]	48	Reif 2006
				Executive function		Stroop Colour Word Task	N.S.		Patients [C]	48	Reif 2006
				Executive function		TMT-A&B	N.S.		Patients [C]	48	Reif 2006
				Creativity, fluency & flexibility		Verbal fluency test (Letters and categories)	N.S.		Patients [C]	48	Reif 2006
	rs6490121	Yes	G (0.34)	Attention & Executive function	Attentional control	CPT	N.S.		Patients & Controls [C] (Irish)	549	Donohoe 2009
				Intelligence	IQ	WAIS (FSIQ)	N.S.		Patients & Controls [C] (Irish)	549	Donohoe 2009
				Intelligence	IQ	WAIS (FSIQ)	Lower (0.001)	Recessive	Patients [C] (German)	232	Donohoe 2009
				Intelligence	IQ	WAIS (FSIQ)	N.S.		Controls [C] (German)	1344	Donohoe 2009
				Intelligence	IQ	WAIS (PIQ)	N.S.		Patients & Controls [C] (Irish)	549	Donohoe 2009
				Intelligence	IQ	WAIS (PIQ)	Lower (0.001)	Recessive	Patients [C] (German)	232	Donohoe 2009
				Intelligence	IQ	WAIS (PIQ)	N.S.		Controls [C] (German)	1344	Donohoe 2009
				Intelligence	IQ	WAIS (VIQ)	Lower (0.04)	Recessive	Patients & Controls [C] (Irish)	549	Donohoe 2009
				Intelligence	IQ	WAIS (VIQ)	N.S.		Patients [C] (Irish)	349	Donohoe 2009
				Intelligence	IQ	WAIS (VIQ)	N.S.		Controls [C] (Irish)	230	Donohoe 2009
				Intelligence	IQ	WAIS (VIQ)	Lower (0.005)	Recessive	Patients [C] (German)	232	Donohoe 2009
				Intelligence	IQ	WAIS (VIQ)	N.S.		Controls [C] (German)	1344	Donohoe 2009
				Memory	Episodic Memory	WMS (Faces)	N.S.		Patients & Controls [C] (Irish)	549	Donohoe 2009
				Memory	Episodic Memory	WMS (Logical Memory)	N.S.		Patients & Controls [C] (Irish)	549	Donohoe 2009
				Working memory	Working memory	CANTAB (Spatial Working Memory)	N.S.		Patients [C] (Irish)	349	Donohoe 2009
				Working memory	Working memory	CANTAB (Spatial Working Memory)	Lower (0.008)	Recessive	Controls [C] (Irish)	230	Donohoe 2009
				Working memory	Working memory	N-back task	Lower (0.007)		Patients & Controls [C] (German)	1576	Donohoe 2009
				Working memory	Working memory	N-back task	N.S.		Patients [C] (German)	232	Donohoe 2009
				Working memory	Working memory	N-back task	N.S.		Controls [C] (German)	1344	Donohoe 2009
				Working memory	Working memory	WMS (Letter-Number Sequencing)	N.S.		Patients [C] (Irish)	349	Donohoe 2009
				Working memory	Working memory	WMS (Letter-Number Sequencing)	Lower (<0.001)	Recessive	Controls [C] (Irish)	230	Donohoe 2009
				Working memory	Working memory	WMS (Combined Digit span and Spatial span)	Lower (0.005)	Recessive	Patients [C] (German)	232	Donohoe 2009
				Working memory	Working memory	WMS (Combined Digit span and Spatial span)	N.S.		Controls [C] (German)	1344	Donohoe 2009
NRG1	rs6994992 (NRG243177)	Yes	T (0.40)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C]	2243	Stefanis 2007
				Creativity, fluency & flexibility	Creativity	Creative Achievement Questionnaire	Higher (0.0002)	Additive	Controls [C] - Academic sample	200	Kéri 2009
				Creativity, fluency & flexibility	Creativity	TTCT (Just Suppose - Flexibility)	Higher (0.006)	Additive	Controls [C] - Academic sample	200	Kéri 2009
				Creativity, fluency & flexibility	Creativity	TTCT (Just Suppose - Fluency)	Higher (0.02)	Additive	Controls [C] - Academic sample	200	Kéri 2009
				Creativity, fluency & flexibility	Creativity	TTCT (Just Suppose - Originality)	Higher (0.05)	Additive	Controls [C] - Academic sample	200	Kéri 2009
				Working memory	Working memory	N-Back Task	Lower (0.040)		Controls [C]	2243	Stefanis 2007
	SNP8NRG433E1006	Yes	G (0.13)	Attention & Executive function	Attention	CPT-IP	Lower (0.048)	Additive	Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-Back Task	Lower (0.044)	Additive	Controls [C] - Males only	2243	Stefanis 2007
	SNP8NRG221132	Yes	G (0.89)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
	rs35753505 (SNP8NRG221533)	Yes	C (0.36)	Attention & Executive function	Attention	d2-Test	N.S.		Controls [C]	429	Kircher 2009b
				Attention & Executive function	Attention	CPT-IP	Lower (0.011)	Recessive	Controls [C] - Males only	2243	Stefanis 2007
				Creativity, fluency & flexibility	Verbal Fluency	Semantic Fluency	Lower (0.034)	Recessive	Controls [C]	429	Kircher 2009b
				Creativity, fluency & flexibility	Verbal Fluency	Lexical Fluency	N.S.		Controls [C]	429	Kircher 2009b
				Working memory	Verbal working memory	Letter-Number Span	N.S.		Controls [C]	429	Kircher 2009b
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Spatial ability	WMS (Spatial Span)	N.S.		Controls [C]	429	Kircher 2009b

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
	SNP8NRG241930	Yes	G (0.65)	Attention & Executive function	Attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2007
				Working memory	Working memory	N-Back Task	N.S.		Controls [C] - Males only	2243	Stefanis 2007
NRG3	rs10883866	No	G (0.11)	Attention & Executive function	Focused sustained attention	CPT-DS	Higher (0.007)	Additive	Patients [C]	411	Morar 2010
				Attention & Executive function		CPT-DS	Lower (0.006)	Additive	Controls [C]	223	Morar 2010
				Attention & Executive function		CPT-IP	N.S.		Patients [C]	411	Morar 2010
				Attention & Executive function		CPT-IP	N.S.		Controls [C]	223	Morar 2010
				Intelligence	IQ	National Adult Reading Test	N.S.		Patients [C]	411	Morar 2010
				Intelligence	IQ	National Adult Reading Test	N.S.		Controls [C]	223	Morar 2010
				Intelligence		Shipley Institute of Living Scale	N.S.		Patients [C]	411	Morar 2010
				Intelligence		Shipley Institute of Living Scale	N.S.		Controls [C]	223	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Immediate recall)	N.S.		Patients [C]	411	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Immediate recall)	N.S.		Controls [C]	223	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Delayed recall)	N.S.		Patients [C]	411	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Delayed recall)	N.S.		Controls [C]	223	Morar 2010
	rs6584400	No	A (0.22)	Attention & Executive function	Focused sustained attention	CPT-DS	Higher (0.025)	Additive	Patients [C]	411	Morar 2010
				Attention & Executive function		CPT-DS	Lower (0.006)	Additive	Controls [C]	223	Morar 2010
				Attention & Executive function		CPT-IP	N.S.		Patients [C]	411	Morar 2010
				Attention & Executive function		CPT-IP	N.S.		Controls [C]	223	Morar 2010
				Intelligence	IQ	National Adult Reading Test	N.S.		Patients [C]	411	Morar 2010
				Intelligence	IQ	National Adult Reading Test	N.S.		Controls [C]	223	Morar 2010
				Intelligence		Shipley Institute of Living Scale	N.S.		Patients [C]	411	Morar 2010
				Intelligence		Shipley Institute of Living Scale	N.S.		Controls [C]	223	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Immediate recall)	N.S.		Patients [C]	411	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Immediate recall)	N.S.		Controls [C]	223	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Delayed recall)	N.S.		Patients [C]	411	Morar 2010
				Memory	Episodic verbal memory	RAVLT (Delayed recall)	N.S.		Controls [C]	223	Morar 2010
NRGN	rs12807809	Yes	T (0.82)	Attention & Executive function	Attention	d2 test	N.S.		Controls [C]	521	Krug 2013
				Creativity, fluency & flexibility	Semantic verbal fluency	Semantic verbal fluency task	Higher (0.046)	Recessive	Controls [C]	521	Krug 2013
				Executive function		TMT-B	N.S.		Controls [C]	521	Krug 2013
				Intelligence	Verbal IQ	Multiple-choice word test	N.S.		Controls [C]	521	Krug 2013
				Working memory		Letter-Number Span	N.S.		Controls [C]	521	Krug 2013
				Working memory		WMS (Spatial span)	N.S.		Controls [C]	521	Krug 2013
PPP1R1B	rs879606 (M04)	No	G (0.85)	Attention & Executive function	Attention	CPT	Higher (0.007)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Creativity, fluency & flexibility	Working memory	Letter Fluency	Higher (0.009)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				[redacted]	Attention	TMT-A	Higher (0.006)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Executive function	Attention	TMT-B	Higher (<0.001)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Executive function	Working memory	WCST (Categories)	Higher (0.034)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Executive function	Working memory	WCST (Preservative errors)	N.S.		Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Intelligence	IQ	WAIS (FSIQ)	Higher (0.013)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Intelligence	General intelligence	WRAT (Reading)	Higher (0.004)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Memory	Episodic Memory	CVLT	N.S.		Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Memory	Episodic Memory	WMS-R (Logical memory)	N.S.		Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Memory	Episodic Memory	WMS-R (Paired associates)	Higher (0.019)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Working memory	Working memory	N-Back task (1-back)	Higher (0.014)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Working memory	Working memory	N-Back task (2-back)	Higher (0.028)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
				Working memory	Working memory	N-Back task (3-back)	Higher (0.018)	Dominant	Patients & Siblings [C] - 257 families		Meyer-Lindenberg
PRKCA	rs8074995	No	A	Attention & Executive function	Sustained attention	CPT-DS	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-DS	N.S.		Controls [C]	172	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Patients [C]	336	Jablensky 2011
				Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C]	172	Jablensky 2011

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Patients with cognitive deficit [C]	155	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	Lower (<0.05)	Additive	Patients with spared cognition [C]	121	Jablensky 2011
				Creativity, fluency & flexibility	Verbal fluency	Controlled Word Association Task	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Premorbid verbal IQ	National Adult Reading Test	N.S.		Controls [C]	172	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Patients [C]	336	Jablensky 2011
				Intelligence	Current IQ	Shipley Institute of Living Scale	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	Lower (0.02)	Additive	Patients with cognitive deficit [C]	155	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Patients with spared cognition [C]	121	Jablensky 2011
				Memory	Verbal memory	RAVLT (immediate recall)	N.S.		Controls [C]	172	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Patients [C]	336	Jablensky 2011
				Memory	Verbal memory	RAVLT (delayed recall)	N.S.		Controls [C]	172	Jablensky 2011
RGS4	rs2661319 (SNP18)	Yes		Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Spatial working memory	Raven Progressive Matrices (S2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Verbal working memory	Raven Progressive Matrices (V2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
	rs951436 (SNP4)	Yes		Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Spatial working memory	Raven Progressive Matrices (S2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Verbal working memory	Raven Progressive Matrices (V2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
	rs951439 (SNP7)	Yes		Attention & Executive function	Sustained attention	CPT-IP	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Spatial working memory	Raven Progressive Matrices (S2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
				Working memory	Verbal working memory	Raven Progressive Matrices (V2B)	N.S.		Controls [C] - Males only	2243	Stefanis 2008
S100B	rs1051169	No	G (0.45)	Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	Lower (0.0008)	Recessive	Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
	rs2839349	No		Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	N.S.		Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
	rs2839357	No	G (0.37)	Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	Lower (0.009)	Recessive	Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
	rs3788266	No		Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	N.S.		Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
	rs881827	No		Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	N.S.		Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
	rs9722	No	A (0.37)	Intelligence	Visuospatial ability	WAIS-RC (Block design)	Lower (0.023)		Patients [A]	304	Zhai 2011
				Intelligence	Visuospatial ability	WAIS-RC (Block design)	N.S.		Controls [A]	196	Zhai 2011
				[redacted]	Spatial ability	Modified Mental Rotation Task	Lower (0.0016)	Recessive	Patients [A]	304	Zhai 2011
					Spatial ability	Modified Mental Rotation Task	N.S.		Controls [A]	196	Zhai 2011
SLC1A2 (EAAT2)	rs4354668	No	G (0.50)	Executive function	Abstract thinking	WCST (Categories)	Lower (0.012)	Dominant	Patients	211	Spangaro 2012
					Visuospatial skills	WCST (Perseverative errors)	N.S.		Patients	211	Spangaro 2012
				Working memory	Working memory	N-back task (1-back)	Lower (0.001)	Dominant	Patients	211	Spangaro 2012
					Working memory	N-back task (2-back)	Lower (0.012)	Dominant	Patients	211	Spangaro 2012
TCF4	rs2958182	No	T (0.89)	Attention & Executive function	Attention	Attention Network Test	Lower (0.043)	Dominant	Controls [A]	402	Zhu 2012

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Attention & Executive function	Attention	Attention Network Test	N.S.		Patients [A]	383	Zhu 2012
				Executive function	Attention	Stroop Task	N.S.		Controls [A]	404	Zhu 2012
				Executive function	Attention	Stroop Task	Higher (0.049)	Dominant	Patients [A]	197	Zhu 2012
				Intelligence	Intelligence	WAIS-RC (Total IQ)	N.S.		Controls [A]	421	Zhu 2012
				Intelligence	Intelligence	WAIS-RC (Total IQ)	Higher (0.013)	Dominant	Patients [A]	526	Zhu 2012
				Working memory	Attention	Dot Patter Expectancy	N.S.		Controls [A]	403	Zhu 2012
				Working memory	Attention	Dot Patter Expectancy	Higher (<0.001)	Dominant	Patients [A]	180	Zhu 2012
				Working memory	Working memory	N-back task	N.S.		Patients & Controls [A]	765	Zhu 2012
				Working memory	Attention	WAIS-RC (Digit span forward)	Lower (0.0012)	Dominant	Controls [A]	421	Zhu 2012
				Working memory	Attention	WAIS-RC (Digit span forward)	N.S.		Patients [A]	526	Zhu 2012
				Working memory	Working memory	WAIS-RC (Digit backward span)	N.S.		Patients & Controls [A]	765	Zhu 2012
	rs9960767	Yes	C (0.07)	Memory	Verbal memory	RAVLT (Delayed recall)	N.S.		Patients [C]	401	Lennertz 2011
				Memory	Verbal memory	RAVLT (Immediate recall)	N.S.		Patients [C]	401	Lennertz 2011
				Memory	Verbal memory	RAVLT (Recognition)	Higher (0.049)	Dominant	Patients [C]	401	Lennertz 2011
				Memory	Verbal memory	RAVLT (Total learning)	N.S.		Patients [C]	401	Lennertz 2011
				Memory	Verbal memory	Intelligence	N.S.		Patients [C]	401	Lennertz 2011
ZNF804A	rs1344706	Yes	T (0.64)	Attention & Executive function	Attention	CPT-IP	N.S.		Patients [C] - Discovery sample	192	Walters 2010
				Attention & Executive function	Attention	CPT-IP	Not Tested		Controls [C] - Discovery sample	0	Walters 2010
				Attention & Executive function	Attention	Attention Network Test (Alerting)	N.S.		Controls [C]	200	Balog 2011
				Attention & Executive function	Attention	Attention Network Test (Orienting)	N.S.		Controls [C]	200	Balog 2011
				Attention & Executive function	Attention	Attention Network Test (Executive control)	Lower (<0.05)	Recessive	Controls [C]	200	Balog 2011
				Attention & Executive function	Executive function	Attention Network Test (Conflict effect)	Lower (0.026)	Dominant	High IQ Patients [A]	238	Chen 2012
				Attention & Executive function	Executive function	Attention Network Test (Conflict ratio)	Lower (0.038)		High IQ Patients [A]	238	Chen 2012
				Attention & Executive function	Executive function	Attention Network Test (Conflict effect)	Higher (0.046)	Dominant	Low IQ Patients [A]	332	Chen 2012
				Attention & Executive function	Executive function	Attention Network Test (Conflict ratio)	Higher (0.034)		Low IQ Patients [A]	332	Chen 2012
				Attention & Executive function	Executive function	Attention Network Test (Conflict effect)	N.S.		Controls [A]	416	Chen 2012
				Attention & Executive function	Executive function	Attention Network Test (Conflict ratio)	N.S.		Controls [A]	416	Chen 2012
				Intelligence	IQ	WAIS-III (Performance IQ)	N.S.		Patients [C] - Discovery sample	288	Walters 2010
				Intelligence	IQ	WAIS-III (Verbal IQ)	N.S.		Controls [C] - Discovery sample	164	Walters 2010
				Intelligence	IQ	WAIS-RC	N.S.		Patients [A]	570	Chen 2012
				Intelligence	IQ	WAIS-RC	N.S.		Controls [A]	448	Chen 2012
				Memory	Episodic memory	WMS-III (Logical memory, delayed)	N.S.		Patients [C] - Discovery sample	283	Walters 2010
				Memory	Episodic memory	WMS-III (Logical memory, delayed)	N.S.		Controls [C] - Discovery sample	160	Walters 2010
				Memory	Episodic memory	WMS-III (Logical memory, immediate)	Higher (0.02)	Additive	Patients [C] - Discovery sample	283	Walters 2010
				Memory	Episodic memory	WMS-III (Logical memory, immediate)	N.S.		Controls [C] - Discovery sample	161	Walters 2010
				Memory	Episodic memory	WMS-R (Logical memory, delayed)	Higher (0.009)	Recessive	Patients [C] - Replication sample	239	Walters 2010
				Memory	Episodic memory	WMS-R (Logical memory, delayed)	N.S.		Controls [C] - Replication sample	376	Walters 2010
				Memory	Episodic memory	WMS-R (Logical memory, immediate)	Higher (0.02)	Recessive	Patients [C] - Replication sample	239	Walters 2010
				Memory	Episodic memory	WMS-R (Logical memory, immediate)	N.S.		Controls [C] - Replication sample	376	Walters 2010
				Working memory	Spatial working memory	CANTAB (Spatial working memory task)	Higher (0.045)	Recessive	Patients [C] - Discovery sample	287	Walters 2010
				Working memory	Spatial working memory	CANTAB (Spatial working memory task)	N.S.		Controls [C] - Discovery sample	153	Walters 2010
				Working memory	Spatial working memory	WAIS-R (Spatial span)	Higher (0.047)	Recessive	Patients [C] - Replication sample	243	Walters 2010
				Working memory	Spatial working memory	WAIS-R (Spatial span)	N.S.		Controls [C] - Replication sample	374	Walters 2010
				Working memory	Verbal working memory	WMS-III (Letter-Number Sequencing)	Higher (0.046)	Recessive	Patients [C] - Discovery sample	276	Walters 2010
				Working memory	Verbal working memory	WMS-III (Letter-Number Sequencing)	N.S.		Controls [C] - Discovery sample	163	Walters 2010
				Working memory	Verbal working memory	WAIS-R (Digit span)	Higher (0.02)		Patients [C] - Replication sample	237	Walters 2010
				Working memory	Verbal working memory	WAIS-R (Digit span)	N.S.		Controls [C] - Replication sample	1836	Walters 2010
				Working memory	Working memory	N-Back Task (1-back)	Lower (0.050)	Dominant	High IQ Patients [A]	238	Chen 2012
				Working memory	Working memory	N-Back Task (2-back)	N.S.		High IQ Patients [A]	238	Chen 2012
				Working memory	Working memory	N-Back Task (1-back)	Higher (0.037)	Dominant	Low IQ Patients [A]	332	Chen 2012

Gene	SNP	Meta-analysis szgene?	Risk Allele (freq.)	Cognitive Domain (Assigned by us)	Function (According to study)	Test (subtest)	Carrier Performance	Model	Group	Sample Size	Reference
				Working memory	Working memory	N-Back Task (2-back)	Higher (0.017)	Dominant	Low IQ Patients [A]	332	Chen 2012
				Working memory	Working memory	N-Back Task (1-back)	N.S.		Controls [A]	414	Chen 2012
				Working memory	Working memory	N-Back Task (2-back)	N.S.		Controls [A]	414	Chen 2012

*Results that remained significant after correction for multiple testing as described by the original authors.

[1]The meta-analysis of COMT genotype in relation to performance on the Wisconsin Card Sort Test (WCST) conducted by Barnett et al. (2007) included 10 studies published prior to 2006 (Egan 2001, Bilder 2002, Joober 2002, Malhotra 2002, Tsai 2003, Rosa 2004, Bruder 2005, Galderisi 2005, Ho 2004, Minzenberg 2006, Rybakowski 2006, Szoke 2006). Therefore we included results for WCST from Barnett et al. (2007) and excluded the other studies, unless they reported results for other cognitive tests (e.g. Bruder et al. 2005).

[2]The meta-analysis of DTNBP1 genotypes in relation to intelligence measures conducted by Zhang et al. (2010) included eight studies published prior to 2010 (Burdick 2006, Hashimoto 2009, Kircher 2009, Luciano 2009, Need 2009, Peters 2008, Stefanis 2007, Zinkstok 2007).

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Aguilera, M., Barrantes-Vidal, N., Arias, B., et al. (2008) Putative role of the COMT gene polymorphism (Val158Met) on verbal working memory functioning in a healthy population. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics, 147B*(6), 898-902.

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Table A2. SNPs showing both higher and lower performance by risk-allele carriers, labelled by cognitive domain and status group.

Gene	SNP	Higher performance	Study	Lower performance	Study
COMT	rs4680	Attention & Executive function	(Pt&C)[1]	Attention & Executive function	(Pt&C)[1][2]
		Attention & Executive function	(Pt&C)[3]		
		Creativity, fluency & flexibility	(C)[4]	Creativity, fluency & flexibility	(C)[5]
				Executive function	(C)[6][7][8][9][10], (Pt)[9][11][12], (Pt&C)[13][14]
				Intelligence	(C)[8][15][16][17]
				Memory	(C)[16][18][19], (Pt)[11]
				Working memory	(C)[20][21][22][23][24], (Pt&C) [2][25]
DAOA	rs1421292	Attention & Executive function	(C)[26]	Attention & Executive function	(Pt)[27]
				Executive function	(C)[26]
				Memory	(Pt)[27]
		Working memory	(C)[26]	Working memory	(Pt&C)[27]
DAOA	rs3918342	Attention & Executive function	(C)[26]		
		Working memory	(C)[26]	Working memory	(Pt)[27]
DRD4	rs1800955			Attention & Executive function	(C)[28]
		Executive function	(Pt)[29]		
DTNBP1	rs2619522			Attention & Executive function	(C)[30][31][32][33]
				Intelligence	
		Memory	(Pt)[30]	Memory	
	rs2619539	Intelligence	(C)[32]		
				Memory	(C)[34]
GRM3	rs2189814	Memory	(C)[35]	Memory	(Pt)[35]
5-HTR2A	rs6313			Attention	(Pt)[36][37]

		Creativity, fluency & flexibility	(Pt)[38]		
				Executive function	(Pt)[36]
				Memory	(Pt)[39], (Pt&C)[30]
NRG1	rs6994992	Creativity, fluency & flexibility	(C)[40]		
				Working memory	(C)[31]
NRG3	rs10883866	Attention & Executive function	(Pt)[41]	Attention & Executive function	(C)[41]
NRG3	rs6584400	Attention & Executive function	(Pt)[41]	Attention & Executive function	(C)[41]
TCF4	rs2958182			Attention & Executive function	(C)[42]
		Executive function	(Pt)[42]		
		Intelligence	(Pt)[42]		
		Memory	(Pt)[42]		
		Working memory	(Pt)[42]	Working memory	(C)[42]
ZNF804A	rs1344706	Attention & Executive function	(Pt)[43]	Attention & Executive function	(C)[44], (Pt)[43]
		Memory	(Pt)[45]		
		Working memory	(Pt)[45]	Working memory	(Pt)[43]

(C)=Controls, (Pt)=Patients, (Pt&C)= Patients and Controls pooled.

[1] Krbbendam 2006, [2] Diaz-Asper 2008, [3] Opgen-Rhein 2008, [4] Schulz 2012, [5] Nolan 2004, [6] Barnett 2007, [7] Caldu 2007, [8] de Frias 2005, [9] Kenndey 2010, [9] Rosa 2010, [10] Wishart 2011, [11] Bilder 2002, [12] Basterra 2011, [13] Galderisi 2005, [14] Minzenberg 2006, [15] Enoch 2009, [16] Raz 2009, [17] Starr 2007, [18] Bates 2003, [19] de Frias 2004, [20] Aguilera 2008, [21] Bruder 2005, [22] Dumontheil 2011, [23] Kennedy 2010, [24] MacDonald 2007, [25] Goldberg 2003, [26] Jansen 2009, [27] Goldberg 2006, [28] Fossella 2002, [29] Alfimova 2007, [30] Alfimova 2010, [31] Stefanis 2007, [32] Luciano 2009, [33] Zhang 2010, [34] Hashimoto 2009, [35] Jablensky 2011, [36] Ucok 2007, [37] Vyas 2013, [38] Chen 2001, [39] Golimbet 2006, [40] Keri 2008, [41] Morar 2010, [42] Zhu 2012, [43] Chen 2012, [44] Balog 2011, [45] Walters 2010

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

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3.1. 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.

3.2. 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.

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. (2013) 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. (2012) 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. (2012), 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 et al. (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 et al., 2007; Vuoksimaa et al., 2010; Suzuki et al., 2011), shows sex differences (e. g., Vuoksimaa et al., 2010), and represents an important, independent component of current psychometric models for intelligence (Johnson and 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.

3.3. Methods

3.3.1. 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.

3.3.2. 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 (Appendix Table B1). 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. (2013; criteria r2>0.8). Therefore we only include one of these SNPs (rs1799913) in our analyses.

3.3.3. 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. (2013), 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 (Appendix Table B1). 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).

3.3.4. 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 and Court, 1998) and to measure spatial skills, we used the mental rotation task (MRT; Peters et al., 1995). For each test, the 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 effect. 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).

3.4. Results

3.4.1. 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 3.1; Appendix Table B2). Neither weighted nor unweighted GRS was significantly correlated with Total Schizotypy or any of the SPQ subscales (all tests $p>0.35$, uncorrected; Appendix B3).

Table 3.1. SNPs nominally significant by ANOVA with scores on higher-level SPQ subscales.

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 ↑ Schizotypy	0.0363* 0.0266*	0.6028 0.5675
RELN	rs262355	↑ Interpersonal ↑ Disorganized	0.0118* 0.0401*	0.4147 0.6028
RGS4	rs2661319	↓ Interpersonal ↓ Cognitive ↓ Schizotypy	0.0162* 0.0125* 0.0155*	0.4147 0.4147 0.4147

Results shown are for all subjects using a dominant inheritance model where risk allele group size N≥10.
*p<0.05

3.4.2. 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 (Appendix B4). Neither weighted nor unweighted GRS was significantly correlated with the Vocabulary score relative to MRT score (all tests p>0.75, uncorrected; Appendix B5).

MRT score was negatively correlated with unweighted GRS in males (r= -0.145, t= -1.999, df=186, p=0.047; Figure 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 (Appendix B6; 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).

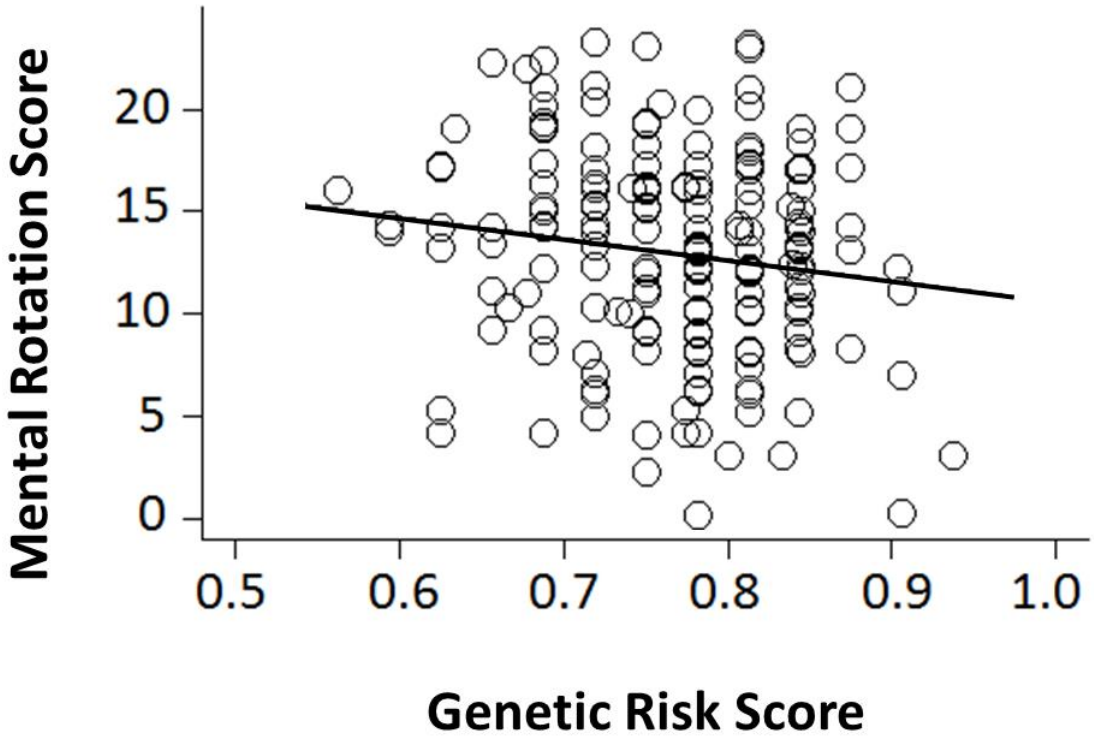

Figure 3.1. Pearson's correlation of unweighted genetic risk score (GRS) with mental rotation test (MRT) performance, for males (r=-0.145, p=0.047).

3.5. Discussion

3.5.1. SPQ - 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 3.1). 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 3.1).

3.5.2. SPQ - Genetic Risk Scores

As also found by Derks et al. (2012) 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 between 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 and 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; Stefanis et al., 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 and D'Esposito, 2011). Epistatic interaction effects between sets of contributing alleles at different loci have also been well documented (e.g., Harrison and 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, page 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.

3.5.3. Cognitive Performance - 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, Raven and Court, 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 with 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.

3.5.4. 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.

3.5.5. 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.

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3.7. Appendix B

Table B1. SNPs and risk alleles used to calculate a genetic risk score.

Gene	SNP	Risk Allele	Odds Ratio
AHI1	rs1154801	C	1.08
AHI1	rs2064430	T	1.13
AKT1	rs3803300	A	1.36
C6orf217	rs10223338	C	1.12
CCKAR	rs1800857	C	1.32
DAOA	rs3916971	C	1.16
DAOA	rs778293	A	1.00
DISC1	rs999710	T	1.07
DRD2	rs6275	T	1.15
DRD2	rs6277	C	1.40
DTNBP1	rs1474605	T	1.08
DTNBP1	rs3213207	T	1.10
GABRB2	rs1816072	C	1.22
GWA_11p14.1	rs1602565	C	1.19
GWA_16p13.12	rs7192086	T	1.12
HIST1H2BJ	rs6913660	C	1.13
HTR2A	rs6311	A	1.21
MDGA1	rs11759115	T	1.19
MDGA1	rs12191311	T	1.18
NOTCH4	rs2071287	G	1.15
NRG1	rs10503929	T	1.12
NRGN	rs12807809	T	1.13
PDE4B	rs910694	T	1.23
PPP3CC	rs10108011	F	1.09
PRSS16	rs13219354	T	1.17
PRSS16	rs6932590	T	1.14
RELN	rs262355	A	1.14
RELN	rs7341475	G	1.12
RGS4	rs2661319	G	1.06
RPP21	rs3130375	C	1.29
TPH1	rs1799913	A	1.17
TPH1	rs1800532	A	1.16
ZNF804A	rs1344706	T	1.12

Table B2. Associations of SPQ subscales with genotype group by ANOVA for both sexes pooled using the dominant inheritance model.

Gene	SNP	Sample	Schizotypy	Disorganized	Cognitive	Interpersonal
AHI1	rs11154801	Dominant Pooled	F=0.121 df=504 p=0.728	F=0.092 df=512 p=0.761	F=0.019 df=509 p=0.891	F=0.515 df=513 p=0.473
AHI1	rs2064430	Dominant Pooled	F=2.029 df=506 p=0.155	F=3.799 df=514 p=0.0518 .	F=0.002 df=511 p=0.965	F=2.775 df=515 p=0.0976 .
AKT1	rs3803300	Dominant Pooled	F=0.15 df=506 p=0.699	F=0.844 df=514 p=0.359	F=3.221 df=511 p=0.0732 .	F=0.687 df=515 p=0.408
C6orf217	rs10223338	Dominant Pooled	F=0.677 df=504 p=0.411	F=0.053 df=512 p=0.818	F=0.812 df=509 p=0.368	F=0.683 df=513 p=0.409
CCKAR	rs1800857	Dominant Pooled	F=0.016 df=506 p=0.901	F=0.221 df=514 p=0.639	F=0.121 df=511 p=0.729	F=0.912 df=515 p=0.34
DAOA	rs3916971	Dominant Pooled	F=0.273 df=505 p=0.602	F=1.713 df=512 p=0.191	F=2.01 df=509 p=0.157	F=0.122 df=514 p=0.727
DAOA	rs778293	Dominant Pooled	F=0.197 df=506 p=0.657	F=1.002 df=514 p=0.317	F=0.571 df=511 p=0.45	F=0.157 df=515 p=0.692
DISC1	rs999710	Dominant Pooled	F=0.13 df=506 p=0.719	F=1.199 df=514 p=0.274	F=0.207 df=511 p=0.649	F=0.479 df=515 p=0.489
DRD2	rs6275	Dominant Pooled	F=0.364 df=506 p=0.546	F=0.553 df=513 p=0.458	F=0.082 df=511 p=0.775	F=0.711 df=514 p=0.399
DRD2	rs6277	Dominant Pooled	F=0.971 df=505 p=0.325	F=1.171 df=513 p=0.28	F=1.484 df=510 p=0.224	F=0.005 df=514 p=0.944
DTNBP1	rs1474605	Dominant Pooled	F=0.74 df=505 p=0.39	F=0.057 df=513 p=0.811	F=1.789 df=510 p=0.182	F=0.049 df=514 p=0.825
DTNBP1	rs3213207	Dominant Pooled	F=0.531 df=481 p=0.467	F=1.61 df=489 p=0.205	F=0.13 df=486 p=0.718	F=1.061 df=490 p=0.304
GABRB2	rs1816072	Dominant Pooled	F=0.923 df=505 p=0.337	F=0.001 df=513 p=0.973	F=2.792 df=510 p=0.0954 .	F=0.201 df=514 p=0.654
GWA_11p14.1	rs1602565	Dominant Pooled	F=0.44 df=506 p=0.508	F=0.093 df=514 p=0.761	F=0.603 df=511 p=0.438	F=0.784 df=515 p=0.376
GWA_16p13.12	rs7192086	Dominant Pooled	F=0.013 df=506 p=0.909	F=0.021 df=514 p=0.885	F=0.115 df=511 p=0.735	F=0.363 df=515 p=0.547
HIST1H2BJ	rs6913660	Dominant Pooled	F=3.043 df=504 p=0.0817 .	F=0.566 df=512 p=0.452	F=6.157 df=509 p=0.0134*	F=0.148 df=513 p=0.701

HTR2A	rs6311	Dominant Pooled	F=0.024 df=505 p=0.877	F=2.156 df=513 p=0.143	F=0.435 df=510 p=0.51	F=0.017 df=514 p=0.897
MDGA1	rs11759115	Dominant Pooled	F=0.18 df=505 p=0.671	F=0.004 df=513 p=0.951	F=1.177 df=510 p=0.279	F=0.134 df=514 p=0.714
MDGA1	rs12191311	Dominant Pooled	F=0.612 df=506 p=0.435	F=0.063 df=514 p=0.802	F=0.348 df=511 p=0.556	F=0.406 df=515 p=0.524
NOTCH4	rs2071287	Dominant Pooled	F=0.757 df=506 p=0.385	F=0.339 df=514 p=0.561	F=0.094 df=511 p=0.76	F=1.395 df=515 p=0.238
NRG1	rs10503929	Dominant Pooled	F=0.346 df=506 p=0.557	F=0.264 df=514 p=0.608	F=3.953 df=511 p=0.0473*	F=0.351 df=515 p=0.554
NRGN	rs12807809	Dominant Pooled	F=0.01 df=505 p=0.922	F=1.875 df=513 p=0.171	F=0.001 df=510 p=0.979	F=0.611 df=514 p=0.435
PDE4B	rs910694	Dominant Pooled	F=3.947 df=504 p=0.0475*	F=3.237 df=512 p=0.0726 .	F=1.382 df=509 p=0.24	F=2.694 df=513 p=0.101
PPP3CC	rs10108011	Dominant Pooled	F=0.323 df=506 p=0.57	F=0.272 df=514 p=0.602	F=2.542 df=511 p=0.112	F=0.039 df=515 p=0.844
PRSS16	rs13219354	Dominant Pooled	F=2.251 df=506 p=0.134	F=0.09 df=514 p=0.764	F=2.818 df=511 p=0.0938 .	F=2.294 df=515 p=0.13
PRSS16	rs6932590	Dominant Pooled	F=4.944 df=498 p=0.0266*	F=1.29 df=506 p=0.257	F=4.405 df=503 p=0.0363*	F=2.235 df=507 p=0.135
RELN	rs262355	Dominant Pooled	F=1.4 df=505 p=0.237	F=4.234 df=513 p=0.0401*	F=0.523 df=510 p=0.47	F=6.383 df=514 p=0.0118*
RELN	rs7341475	Dominant Pooled	F=0.949 df=506 p=0.33	F=1.932 df=514 p=0.165	F=0.647 df=511 p=0.422	F=0.034 df=515 p=0.853
RGS4	rs2661319	Dominant Pooled	F=5.901 df=492 p=0.0155*	F=0.06 df=500 p=0.807	F=6.282 df=497 p=0.0125*	F=5.819 df=501 p=0.0162*
RPP21	rs3130375	Dominant Pooled	F=0.13 df=495 p=0.718	F=0.485 df=503 p=0.487	F=0.79 df=500 p=0.375	F=0.073 df=504 p=0.786
TPH1	rs1799913	Dominant Pooled	F=0.605 df=506 p=0.437	F=1.062 df=514 p=0.303	F=0.0051 df=511 p=0.821	F=1.096 df=515 p=0.296
ZNF804A	rs1344706	Dominant Pooled	F=1.736 df=474 p=0.188	F=1.775 df=482 p=0.183	F=1.501 df=479 p=0.221	F=0.242 df=483 p=0.623

None of the nominally significant associations withstand correction for multiple testing using FDR.
. p<0.1; *p<0.05; **p<0.01

Table B3. Pearson correlations between SPQ-BR subscales and genetic risk scores (GRS).

GRS	Sample	SPQ	Correlation	t-value	df^	p-value
Unweighted	Dominant Both	Interpersonal	0.0409	0.9285	515	0.3536
	Dominant Both	Cognitive	-0.0228	-0.5155	511	0.6064
	Dominant Both	Disorganized	-0.0208	-0.4711	514	0.6378
	Dominant Both	Schizotypy	0.0041	0.0927	506	0.9262
Weighted	Dominant Both	Interpersonal	0.0285	0.6075	453	0.5439
	Dominant Both	Cognitive	-0.0323	-0.6858	449	0.4932
	Dominant Both	Disorganized	-0.0102	-0.2163	451	0.8288
	Dominant Both	Schizotypy	-0.0074	-0.1555	445	0.8765

^degrees of freedom differ between weighted and unweighted GRS samples because individuals with an NA genotype for any of the loci were excluded for the weighted GRS, whereas NA vales did not affect averages for unweighted GRS.

Table B4. Statistical results for comparisons of Vocabulary score with MRT score, in relation to genotype group, by ANOVA.

Gene	SNP	Both	Females	Males
AHI1	rs11154801	F=0.458 df=515 p=0.499	F=0.045 df=327 p=0.833	F=0.011 df=186 p=0.917
AHI1	rs2064430	F=3.471 df=517 p=0.063 .	F=2.563 df=329 p=0.11	F=0.107 df=186 p=0.744
AKT1	rs3803300	F=0.481 df=517 p=0.488	F=1.402 df=329 p=0.237	F=0.419 df=186 p=0.518
C6orf217	rs10223338	F=1.106 df=515 p=0.293	F=0.015 df=328 p=0.904	F=0.804 df=185 p=0.371
CCKAR	rs1800857	F=2.505 df=517 p=0.114	F=0.377 df=329 p=0.539	F=1.267 df=186 p=0.262
DAOA	rs3916971	F=0.705 df=515 p=0.402	F=0.103 df=327 p=0.748	F=1.528 df=186 p=0.218
DAOA	rs778293	F=5.392 df=517 p=0.0206*	F=1.614 df=329 p=0.205	F=1.888 df=186 p=0.171
DISC1	rs999710	F=1.132 df=517 p=0.288	F=0.436 df=329 p=0.51	F=0.929 df=186 p=0.336
DRD2	rs6275	F=0.641 df=516 p=0.424	F=2.145 df=329 p=0.144	F=1.263 df=185 p=0.263
DRD2	rs6277	F=0.314 df=516 p= 0.576	F=0.09 df=328 p=0.764	F=0.782 df=186 p=0.378
DTNBP1	rs1474605	F=4.576 df=516 p=0.0329*	F=0.548 df=328 p=0.46	F=5.629 df=186 p=0.0187*
DTNBP1	rs3213207	F=0 df=492 p=0.989	F=0.313 df=311 p=0.576	F=0.209 df=179 p=0.648
GABRB2	rs1816072	F=0.058 df=516 p=0.810	F=0.021 df=328 p=0.884	F=0.105 df=186 p=0.746
GWA_11p14.1	rs1602565	F=0.800 df=517 p=0.371	F=4.12 df=329 p=0.0432*	F=0.031 df=186 p=0.86
GWA_16p13.12	rs7192086	F=0.021 df=517 p=0.884	F=2.571 df=329 p=0.11	F=0.334 df=186 p=0.564
HIST1H2BJ	rs6913660	F=0.544 df=515 p=0.461	F=0.001 df=327 p=0.978	F=1.536 df=186 p=0.217

HTR2A	rs6311	F=0.177 df=516 p=0.674	F=0.679 df=328 p=0.411	F=0.01 df=186 p=0.92
MDGA1	rs11759115	F=0.37 df=516 p=0.543	F=1.74 df=328 p=0.188	F=0.313 df=186 p=0.576
MDGA1	rs12191311	F=1.826 df=517 p=0.177	F=0.485 df=329 p=0.486	F=2.896 df=186 p=0.0905 .
NOTCH4	rs2071287	F=0.969 df=517 p=0.325	F=0.002 df=329 p=0.965	F=1.902 df=186 p=0.17
NRG1	rs10503929	F=0.026 df=517 p=0.872	F=1.719 df=329 p=0.191	F=1.273 df=186 p=0.261
NRGN	rs12807809	F=1.79 df=516 p=0.182	F=0.24 df=328 p=0.625	F=3.314 df=186 p=0.0703 .
PDE4B	rs910694	F=0.102 df=515 p=0.749	F=0.669 df=328 p=0.414	F=0.048 df=185 p=0.827
PPP3CC	rs10108011	F=1.499 df=517 p=0.221	F=0.184 df=329 p=0.668	F=3.057 df=186 p=0.082 .
PRSS16	rs13219354	F=0.044 df=517 p=0.833	F=0.018 df=329 p=0.894	F=0.084 df=186 p=0.772
PRSS16	rs6932590	F=0.282 df=509 p=0.596	F=0.117 df=324 p=0.732	F=0.775 df=183 p=0.38
RELN	rs262355	F=0.567 df=516 p=0.452	F=0.035 df=329 p=0.851	F=0.945 df=185 p=0.332
RELN	rs7341475	F=0.176 df=517 p=0.675	F=0.451 df=329 p=0.502	F=0.644 df=186 p=0.423
RGS4	rs2661319	F=0.452 df=503 p=0.502	F=0.531 df=322 p=0.467	F=0.131 df=179 p=0.717
RPP21	rs3130375	F=3.85 df=506 p=0.0503 .	F=0.716 df=321 p=0.398	F=3.304 df=183 p=0.0707 .
TPH1	rs1799913	F=0 df=517 p=1	F=0.161 df=329 p=0.688	F=2.036 df=186 p=0.155
ZNF804A	rs1344706	F=6.771 df=485 p=0.00955**	F=4.143 df=307 p=0.0427*	F=1.699 df=176 p=0.194

None of the nominally significant associations withstand correction for multiple testing at the 0.05 level using FDR.

Table B5. Pearson correlations of vocabulary score relative to mental rotation score, and mental rotation score, with genetic risk scores (GRS).

GRS	Sample	Cognitive Task	Correlation	t-value	df^	p-value
Unweighted	Dominant Both	Vocab/MRT	-0.0015	-0.0341	517	0.9728
	Dominant Female	Vocab/MRT	-0.0473	-0.8584	329	0.3913
	Dominant Male	Vocab/MRT	0.0874	1.1964	186	0.2331
Weighted	Dominant Both	Vocab/MRT	-0.0161	-0.3439	454	0.7311
	Dominant Female	Vocab/MRT	-0.0180	-0.3046	286	0.7609
	Dominant Male	Vocab/MRT	0.0500	0.6454	166	0.5195
Unweighted	Dominant Female	MRT	0.0312	0.5658	329	0.5719
	Dominant Male	MRT	-0.1450	-1.9990	186	0.0471
Weighted	Dominant Female	MRT	-0.0093	-0.1574	286	0.8751
	Dominant Male	MRT	-0.0724	-0.2214	166	0.3510

^degrees of freedom differ between weighted and unweighted GRS samples because individuals with an NA genotype for any of the loci were excluded for the weighted GRS, whereas NA vales did not affect averages for unweighted GRS.

Table B6. Male risk allele carriers show lower MRT scores by Wilcoxon sign-rank test for 14 SNPs, W=160, Z=2.43, 2-tailed p=0.015.

SNP	Gene	0	1	Rank	Difference (0-1)	MRT Score with more risk alleles
rs1799913	TPH1	13.98	12.30	1	+1.68	Lower
rs10223338	C6orf217	14.22	12.68	2	+1.54	Lower
rs778293	DAOA	14.13	12.60	3	+1.53	Lower
rs3916971	DAOA	14.04	12.65	4	+1.39	Lower
rs11154801	AHI1	13.91	12.63	5	+1.28	Lower
rs10108011	PPP3CC	13.64	12.40	6	+1.24	Lower
rs1344706	ZNF804A	13.88	12.72	7	+1.16	Lower
rs262355	RELN	13.73	12.63	8	+1.10	Lower
rs6275	DRD2	13.33	12.39	9	+0.94	Lower
rs6311	HTR2A	13.34	12.62	10	+0.72	Lower
rs999710	DISC1	13.30	12.64	11	+0.66	Lower
rs6277	DRD2	13.26	12.70	12	+0.56	Lower
rs1816072	GABRB2	13.08	12.74	13	+0.34	Lower
rs1602565	GWA_11p14.1	12.89	12.64	14	+0.25	Lower
rs910694	PDE4B	12.86	12.92	15	-0.06	Higher
rs7192086	GWA_16p13.12	12.73	12.87	16	-0.14	Higher
rs12191311	MDGA1	12.76	12.90	17	-0.14	Higher
rs6932590	PRSS16	12.73	12.92	18	-0.19	Higher
rs1800857	CCKAR	12.78	13.02	19	-0.24	Higher
rs2661319	RGS4	12.55	13.05	20	-0.50	Higher
rs3803300	AKT1	12.74	13.25	21	-0.51	Higher
rs2071287	NOTCH4	12.32	13.01	22	-0.69	Higher
rs2064430	AHI1	12.22	13.09	23	-0.87	Higher

4. The imprinted gene LRRTM1 mediates schizotypy and handedness in a non-clinical population

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4.1. Abstract

A recent study by Francks and his colleagues (2007) has discovered the imprinted gene LRRTM1 to be associated with schizophrenia and handedness. We investigated if genetic and epigenetic variation in this gene is similarly associated with schizotypy and handedness in a non-clinical population. The schizophrenia risk alleles in three SNPs were each associated with higher Total Schizotypy and the effect appears to be driven by females in the population. These results provide evidence of a shared genetic contribution underlying the continuum between schizophrenia and non-clinical schizotypy. We also report the first finding of epigenetic effects on handedness, whereby relatively higher methylation in a block of CpG sites was correlated with more-mixed handedness, again in females. Our findings indicate that imprinted regions may have important roles in mediating schizotypal personality and brain laterality in non-clinical populations.

4.2. Introduction

4.2.1. Genomic Imprinting

Genomic imprinting occurs when one of two inherited alleles is preferentially expressed due to epigenetic silencing, based on its parent of origin (Wilkinson, Davies & Isles, 2007). Many imprinted genes are known to be expressed in the brain and are considered to be important in neurodevelopment (Davies, Isles & Wilkinson, 2005). In theory, imprinted genes are involved in conflict between the maternal and paternal genomes for resource allocation to offspring (Haig, 1997). As a result, imprinted genes are expected to be involved in physiological and behavioural interactions between the mother and the offspring via influences on cognition, affect, and aspects of personality (Goos & Ragsdale, 2008; Franklin & Mansuy, 2010).

Classic examples illustrating such intragenomic conflict are given by Prader-Willi syndrome, caused by loss of expression for paternally-expressed genes on 15q11-q13, and Angelman syndrome, due to loss of expression for the maternally-expressed imprinted gene UBE3A via maternal deletion, paternal uniparental disomy, or mutation (Malcolm et al., 1991; Kishino, Lalande & Wagstaff, 1997). Thus, Haig and Wharton (2003) described evidence that features of Prader-Willi syndrome, including a placid disposition and poor sucking ability, reflect extreme manifestations of traits that reduce demands on the mother. Conversely, Angelman syndrome reflects extremes of the paternal interest in offspring soliciting additional resources from the mother through increased positive affect (Oliver et al., 2007).

Crespi & Badcock (2008) reviewed physiological and behavioural similarities between Prader-Willi syndrome and psychosis and noted a high incidence of children with Prader-Willi developing affective psychosis in adulthood (Verhoeven et al., 2003; Vogels et al., 2003; 2004; Soni et al., 2007). By contrast, Angelman syndrome showed overlap with several autism-spectrum traits (Crespi & Badcock, 2008) and the UBE3A locus has been associated with autism (Nurmi et al., 2001; Jiang et al., 2004). As such, imprinted genes involved neurodevelopment and cognition also contribute to neuropsychiatric disorders

(Davies, Isles & Wilkinson, 2001; Lin et al., 2012). For example, such is the case for the imprinted gene GABRB2, which known to be associated with schizophrenia (Zhao et al., 2012; Tsang et al., 2013) and shows methylation differences between patients and controls at the schizophrenia-associated SNP rs1816071 (Pun et al., 2011).

Given the continuity between psychiatric disorders and normal cognition, we expect imprinted gene expression to have cognitive effects in non-clinical populations. However, effects of imprinted genes on personality, cognitive function, or other phenotypes have previously been evaluated in non-clinical populations by only a single study. Tsang et al. (2013) investigated SNPs in the imprinted gene GABRB2 and found that rs187269 was associated with increased positive schizophrenia symptom scores (by PANSS; Kay, Fiszbein & Opler, 1987) in patients and also with higher altruistic behaviour (Self-report Altruism scale) in healthy individuals. These findings demonstrate a genetically-mediated continuum of social cognition between patients and controls, and suggest that similar findings may exist for other imprinted genes.

4.2.2. LRRTM1

One of the most interesting brain-expressed imprinted genes is LRRTM1, encoding leucine-rich repeat transmembrane neuronal protein 1, and belonging to a recently described four-member gene family (Laurén et al., 2003). LRRTM1 is known to induce presynaptic differentiation in axons (Linhoff et al., 2009) and interact with the post-synaptic density protein PSD-95 (Bar-shira & Chechik, 2013). This gene is imprinted and paternally expressed (Francks et al., 2007; Ludwig et al., 2009) although no known imprinting control regions (ICR) or differentially methylated regions (DMR) have yet been identified. Thus, Francks et al. (2007) investigated two CpG islands corresponding to the predicted promoter of LRRTM1 but found no differentially methylated regions in a small sample (n=17) of lymphoblast cell lines and post-mortem human brain samples.

Francks et al. (2007) identified a 3-SNP haplotype upstream of LRRTM1 that was significantly associated with schizophrenia and schizoaffective disorder. Most importantly, by testing parent-offspring trios, Francks et al. (2007) demonstrated that this haplotype was paternally inherited to individuals with schizophrenia and schizoaffective

disorder. This finding was replicated by Ludwig et al., (2009) in proband family trios, but the SNPs showed no effect in a schizophrenia case-control sample in this study.

Schizophrenia has been widely associated with reduced cerebral lateralization (meta-analysis by Sommer, Ramsey & Kahn, 2001). Measures of handedness are commonly used as a proxy for cerebral lateralization, with strong hand preference representing greater lateralization and mixed-handedness relating to weak lateralization (Crow, Done & Sacker, 1996; Shin, Sohn & Hallett, 2009). Indeed, there have been widely replicated associations of left and mixed-handedness with both schizophrenia (Orr et al., 1999; Sommer, Ramsey & Kahn, 2001; DeLisi et al., 2002) and schizotypy (Stefanis et al., 2006; Schürhoff et al., 2008; Chapman, Grimshaw & Nicholls, 2011; Barrantes-Vidal et al., 2013). Berlim et al. (2003) hypothesized that handedness, brain asymmetry and schizophrenia share an underlying genetic relationship, but such findings (e.g., Giouzeli et al., 2004; Francks et al., 2007) have yet to be as widely accepted.

The same haplotype originally implicated in schizophrenia was also paternally associated with relative hand skill, assessed by timed peg moving in dyslexic siblings, but not in a set of non-dyslexic twins (Francks et al., 2007). In an attempt to replicate this genetic association with handedness, Ludwig et al. (2009) did not find evidence of associations for any of the risk-haplotype SNPs, but they did identify an association with handedness in dyslexic patients for seven (of 14) other LRRTM1 SNPs. These findings present strong evidence that the LRRTM1 locus influences handedness, at least in dyslexic siblings.

The effects of LRRTM1 SNPs on behaviour in humans are so far unknown, but recent studies have begun to characterize behavioural phenotypes of LRRTM1 knock-out mice. For example, such knock-outs showed reduced locomotor activity, delayed behavioural responses to novel environments, avoidance of large inanimate objects, social discrimination deficits, and spatial memory deficits (Takashima et al., 2011). As well, Voikar et al. (2013) demonstrated that LRRTM1-knockout mice avoided small enclosures, but also showed increased social interaction with an intruder mouse. These behavioural effects in mice suggest that LRRTM1 may influence aspects of cognition

and behaviour in humans as well, with particular regard to psychological traits associated with schizotypy.

The haplotype data from both Francks et al. (2007) and Ludwig et al. (2009) show clear patterns of imprinting, and Francks et al. (2007) provides direct evidence of imprinting in paternal alleles. Thus, LRRTM1's status as an imprinted gene associated to some degree with both handedness and schizophrenia provides an excellent opportunity to test how imprinted genes may influence cognitive and personality traits in a non-clinical population.

In this study, we (1) genotyped three LRRTM1 SNPs, previously linked to schizophrenia and handedness, and (2) analyzed methylation at 19 CpG sites by bisulfite pyrosequencing. We used these genetic and epigenetic data to test for association with measures of Total Schizotypy and handedness. Results from these analyses are useful in addressing the question of the importance of genetic and epigenetic variation in imprinted genes for explaining variation in psychological and related phenotypes.

Based on the findings of Francks et al. (2007) and the replication by Ludwig et al. (2009), we predicted that (1) risk alleles from the previously described haplotype will be associated with higher Total Schizotypy score, (2) individuals with these risk alleles will show a higher incidence of left or mixed handedness, and (3) methylation levels at specific CpG sites or average methylation across all or part of the CpG island will influence Total Schizotypy and handedness.

4.3. Methods

4.3.1. Psychometric measures

We measured Total Schizotypy using the Schizotypal Personality Questionnaire-Brief Revised (SPQ-BR; Cohen et al., 2010). We also used the three subscales from the SPQ: Interpersonal deficits, Cognitive perception, and Disorganization. As we had no *a priori* expectation for associations with the SPQ subscales, we applied Benjamini and Hochberg's False Discovery Rate (FDR; 1995) to reduce the risk of type I error for these

three tests. Handedness was measured with the 32-item Waterloo Handedness Questionnaire (WHQ; Steenhuis & Bryden, 1989). The score for each WHQ item ranges from +2 for strong right, +1 weak right, 0 for ambidextrous or -1 for weak left and -2 for strong left; as such the total scale ranges from +64 to -64. To be consistent with Francks et al. (2007), we used strength of handedness by taking the absolute value of the handedness score such that values near 0 represents mixed-handedess and values near 64 represents strong handedness (right or left). Due to the skewed distribution of absolute handedness, we applied Spearman correlation where applicable (rather than Pearson correlation). Additionally, handedness was assigned as right, left or ambidextrous for specific tests.

4.3.2. Sample

The psychometric measures were tested in questionnaire form for a large sample of Caucasian undergraduate students at both University of Alberta and Simon Fraser University. We collected, extracted and genotyped DNA from 554 individuals (357 females and 197 males) as previously described (Leach, Hurd & Crespi, 2013). A subset of these individuals (29 females and 16 males) was selected for epigenetic data collection. Individuals in the subset were chosen based on handedness such that we attempted to include as many left-handed and ambidextrous individuals as possible. All protocols were carried out according to guidelines established by the ethics boards of both universities.

4.3.3. Genetic Data

We genotyped all three SNPs (rs1007371, rs1446109 and rs723524) from the haplotype previously shown to be associated with handedness and schizophrenia (Francks et al., 2007). These SNPs occur on 2p12 in a region of strong LD, 137kb upstream of LRRTM1 and including the predicted promoter. Genotyping was performed by Genome Québec (Montréal, Canada). We scored genotypes using a recessive inheritance model, based on findings by Francks et al. (2007) where the risk genotype consists of two copies of the minor allele. Unlike Francks et al. (2007) and Ludwig et al. (2009), we did not have

access to parental genotype data, and thus were not able to test directly for parent-of-origin effects.

4.3.4. Epigenetic Data

We selected the larger LRRTM1 CpG island tested by Francks et al. (2007) to test for differences in methylation levels. This 1,169bp CG-rich region is located within the LRRTM1 gene (hg19 assembly, chr2:80,529,678-80,530,846). Since it is accepted that CpG islands are relatively uniformly methylated or unmethylated (Costello et al., 1994; Pieper et al., 1996), we selected a 300bp region, containing 19 CpG sites, assumed to be representative for the larger region.

Bisulfite conversion of ~30ng/ul DNA was performed using the Sigma-Alderich Imprint® DNA Modification Kit (Sigma-Aldrich Co., MO, USA), following the manufacturer's standard protocol. Primers were designed using PyroMark© Assay Design software 2.0 (Qiagen, UK) or manually where CpG density resulted in software error. The PCRs were designed to amplify a 1.5kb region of the CpG island using primers 1-fwd and 3-rev, followed by a nested PCR using 3-fwd and biotinylated 3-rev to amplify a smaller region (Table 4.1). PCR protocols were carried out following the methods of Tost & Gut (2007).

Table 4.1. Primers used for CpG island amplification by nested PCR.

1º PCR primers		Original sequence (5' → 3')	Bisulfite-treated sequence (5' → 3')	Size (bp)	Tm (ºC)	Product size (bp)
1-fwd	F	AGCTGGCAGGGGGCCCCAGAT	AGTTGGTAGGGGGTTTTAGAT	21	53.1	1,090
3-rev	R	GCCTGCTTTCAGATGCTGCC	ACCTACTTTCAAATACTACC	20	46.5	
2º nested PCR primers						
3-fwd	F	GGTGATCTGGTTGGAACTCAG	GGTGATTTGGTTGGAACTTAG	21	51.5	300
3-rev	R	GCCTGCTTTCAGATGCTGCC	/5Biosg/ACCTACTTTCAAATACTACC (biotinylated)	20	46.4	
Sequencing primers						
3d-seq	F	TTGTGATCCAGATAGAGC	TTGTGATTTAGATAGAGT	18	41.3	107
3e-seq	F	CAGGGACAAGCCCAGCAGGC	TAGGGATAAGTTTAGTAGGT	20	46.5	121

DNA methylation was quantified at each CpG site by pyrosequencing using the Pyromark Q24© system (Qiagen, UK) following the manufacturer's standard instructions and the Pyro Q24© CpG 2.0.6 software. The software quantifies the C (methylated) to T (unmethylated) ratio at each CpG site as a percentage and assigns a quality score of blue ('pass'), yellow ('check') or red ('fail'). CpG sites were labelled according to the order they occur in the island. We restricted our analyses to samples that achieved three replicates of either yellow or blue quality, where at least one replicate shows blue quality and averaged across replicates to define methylation levels used in the analyses.

4.3.1. SNP Analyses

We tested for associations between the above measures and risk genotype for each SNP using t-tests. For SNPs with fewer than 10 individuals belonging to one genotype group, we applied non-parametric Mann Whitney-U tests in place of t-tests. Similar to Francks et al. (2007), we tested for associations in a group of males and females pooled. However, due to evidence of sex-dependent imprinting effects at autosomal loci (Hager et al., 2008), we also tested males and females separately.

4.3.2. CpG Island Analyses

Since it is accepted that CpG islands are relatively uniformly methylated or unmethylated (Costello et al., 1994; Pieper et al., 1996), we averaged percent methylation across CpG sites as a proxy for overall methylation level of the island. To compare schizotypy scores to differences in average methylation, we performed a Pearson's product-moment correlation. We also ranked individuals by schizotypy score and split them into two groups of high versus low schizotypy to perform a t-test with average methylation. To test for associations between methylation levels and handedness, we applied Spearman correlations using strength of absolute handedness, as well as ANOVA using categorical handedness (i.e., right vs. left vs. mixed). The same tests were applied to compare schizotypy score with both measures of handedness.

CpG islands tend to be near transcription start sites and are generally unmethylated; high levels of methylation of CpG sites are associated with transcriptional inactivation (Herman et al., 1996; Suzuki & Bird, 2008). Therefore we expect that relatively low methylation levels are representative of the 'normal' state, while significantly higher methylation would indicate a change to reduced expression that could be related to psychological phenotypes. However, data directly testing this expectation are needed.

Based on the results of Wehkalampi et al. (2013) showing lower methylation at an individual CpG site associated with low birth weight, we predict that individual CpG sites in LRRTM1 may similarly influence our phenotypic measures. As such, we tested individual CpG sites for associations with handedness and schizotypy. We also performed principal component analysis (PCA) to reduce the dimensionality of our methylation data and the number of tests, for males and females separately, and pooled. We tested the first two factors (PC1 and PC2) for association with schizotypy and handedness using Pearson's correlations. All statistical analyses we performed using R, version 2.15.1 (R Core Team, 2012).

Table 4.2. Mean and standard deviation of percent methylation across samples for each CpG site.

CpG Site #	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	Avg. methyl
Mean	2.48	5.92	7.49	2.64	2.40	5.98	5.38	2.82	4.06	3.16	5.53	4.94	7.33	4.33	4.72	3.60	4.45	2.61	1.72	4.30
Std. Dev.	2.10	3.96	6.08	1.38	2.33	5.09	3.79	1.62	3.24	2.79	6.45	5.60	7.44	3.11	7.07	1.91	3.61	2.12	2.33	1.96

4.4. Results

4.4.1. SNPs & Schizotypy

Nine (1.6%) of 554 individuals, with males and females pooled, were homozygous for the 2-2-2 risk haplotype identified by Francks et al. (2007). When the sample was split by sex, we found that five (2.5%) of 197 males and four (1.1%) of 357 females carried the risk haplotype. Francks et al. (2007) reported haplotype frequencies ranging between 7.6 and 12.1%, likely because the samples included in their study are enriched for schizophrenia by selecting proband family trios. The frequencies that we report for the three SNPs (rs1007371, rs1446109 and rs723524) appear to be representative of the recessive genotype frequencies in European populations (1%, 1.6% and 4.3%, respectively; dbSNP: Sherry et al., 2001). Two of the three SNPs (rs1007371 & rs1446109) are in complete linkage disequilibrium (r=1) and thus show the same results. In our genotype analyses, we included individuals with the risk genotypes for all three SNPs but also individuals having only one or two of the risk genotypes, such that for some tests a genotype group may have more than 9 individuals.

For both sexes pooled, individuals carrying the risk allele for rs1007371, and for rs1446109, score significantly higher for Total Schizotypy than individuals with the non-risk genotype (risk mean=92.75 (n=8), non-risk mean=80.82; Mann Whitney-U=1203, p=0.033).

In females, all three SNPs are associated with significantly higher scores on both Total Schizotypy and the Interpersonal deficits subscale in risk-allele carriers (MWU test, $p<0.05$). As well, rs1007371 and rs1446109 were both associated with significantly higher scores on the Disorganization subscale (MWU test, p=0.016)(Appendix, Table C2). These associations in females also do not survive correction for multiple testing by FDR (all adjusted p-values > 0.1). No significant association was seen in males between any of the three SNPs and schizotypy score. We found no effect of any of the SNPs on absolute handedness in males and females, pooled or separately.

4.4.2. CpG methylation & Schizotypy

Methylation data was collected for 45 individuals (29 females and 16 males) at 19 CpG sites in the CpG island. Average methylation for all samples, across sites, was 4.30% (standard deviation 1.96%; Table 4.2). Since methylation data for each CpG site was averaged for three pyrosequencing runs, we calculated repeatability for eight of the CpG sites (the CpG78-85 block), which can be measured by comparing within-group variation to between-group variation. Repeatability for each CpG site was acceptably high, ranging from 62-95%, which indicates that between-individual variation is much greater than within-individual variation.

Average methylation and Total Schizotypy showed no association by Pearson's correlation for any of the groups ($p>0.6$). There was no difference in average percent methylation between individuals scoring high versus low on the SPQ (split in half) by Kruskal-Wallis test for males ($p=0.427$) and females ($p=0.723$) separately or pooled ($p=1$).

4.4.3. Methylation & Handedness

Average methylation and absolute handedness showed no association by Spearman correlation for both sexes pooled ($p=0.332$), males ($p=0.196$) or females ($p=0.127$). The 45 individuals with methylation data can be grouped by handedness according to self-report on the questionnaire (Table 4.3) or calculated from the Waterloo Handedness Questionnaire where individuals who score between -29 and +29 are categorized as ambidextrous, and those scoring above or below are categorized as right or left-handed, respectively (Table 4.4). Further, handedness can be grouped into 'weak', with an absolute handedness score ranging 0-29, versus 'strong' (>30). For males and females pooled, no association was found between average methylation and self-report categorical handedness by applying a Kruskal-Wallis test ($p=0.485$). As well, no significant association by Kruskal-Wallis test was found in males and females pooled for handedness categorized by WHQ scores ($p=0.627$) or strength of handedness ($p=0.969$). Due to small sample sizes, this test was not performed for males and females separately.

Table 4.3. Tally of handedness groups, as identified by self-report.

	Right	Left	Amb	
Female	21	3	5	29
Male	13	1	2	16
	34	4	7	n=45

Table 4.4. Tally of handedness groups, categorized based on WHQ score.

	Strong		Mixed	
	Right	**Left**	**Amb**	**Total**
Female	15	1	10	26
Male	9	2	5	16
Total	24	3	15	n=42

NB: Three right-handed females did not have WHQ data available

4.4.4. Handedness & Schizotypy

For both sexes pooled, schizotypy was not associated with self-reported handedness (Kruskal-Wallis test, p=0.844), WHQ categorized handedness (p=0.797), or strength of handedness (p=0.665). Due to small sample sizes, this test was not performed for males and females separately. Similarly, schizotypy was not correlated with absolute handedness (Spearman correlation) for either the pooled sample (p=0.346) or females separately (p=0.612), but males showed a trend-level negative correlation between handedness and schizotypy (rho= -0.432, p=0.095). This negative correlation can be interpreted as more mixed-handed males showing relatively higher schizotypy score.

4.4.5. Individual CpG sites

For 19 CpG sites within our pyrosequenced region, sites closer to each other show more strongly correlated methylation levels than sites farther apart (Mantel test, r=0.277, p=0.01). As well, adjacent CpG sites are more strongly correlated than non-adjacent

sites (t-test, t=4.049, p-value=0.0001). Therefore we expect that CpG sites are not necessarily independent in their effects due to high intercorrelation.

Based on work by Wehkalampi et al. (2013), showing phenotypic association with a single CpG site, we tested all 19 sites individually for correlations with schizotypy and handedness (Appendix, Table C4). We noted three findings of interest. First, higher methylation at CpG69 was associated with significantly lower schizotypy scores in females ($r = -0.54$, $p=0.0027$). Second, CpG75 shows higher methylation associated with both relatively more mixed handedness ($r = -0.52$, $p=0.039$) and higher schizotypy ($r=0.51$, $p=0.043$), in males. Finally, six CpG sites (CpG78-82, 85) in a neighbouring block all showed higher methylation was correlated with relatively more mixed handedness ($p<0.05$; Appendix, Table C4). None of these results withstood correction for 114 tests by FDR (corrected p-values>0.17).

To reduce the dimensionality of our dataset and the number of tests, we applied principal components analysis (PCA) to the CpG methylation data. Together, PC1 and PC2 explained 50% of the variance. PC1 showed strong positive loadings, representing strong inter-correlation between sites, for the block of CpG78-85 sites (Table 4.5). A t-test confirmed that inter-site correlations in the CpG78-85 block were significantly higher (mean r=0.49) than correlations between sites outside the block (mean r=0.29; t=6.24, p=0.0001).

We then used PC1 and PC2 scores for each individual to test for correlations with schizotypy and handedness. PC1 scores were significantly negatively correlated with handedness in females ($p=0.032$) and both sexes pooled ($p=0.026$; Table 4.6). Since the PC1 loadings (Table 4.5) suggest that this inverse relationship between methylation level and strength of handedness is driven by variation in the CpG78-85 block, we performed an additional test of schizotypy and handedness with methylation averaged across only those sites. Average methylation across the CpG78-85 block was negatively correlated with absolute handedness in females ($r = -0.456$, $p=0.019$; Table 4.7), indicating that higher methylation is associated with more mixed handedness. Thus, we have found multiple independent lines of evidence indicating that variation in methylation in the CpG78-85 region is related to strength of handedness in females (or both sexes pooled).

Tests for associations between PC1 and PC2 with schizotypy showed no significant results for males and females both separately and pooled ($p>0.05$). Only our test for both sexes pooled was *a priori*, and tests for males and females separately do not withstand correction for multiple testing (2 tests, $\alpha=0.025$).

Table 4.5. PCA loadings for methylation at CpG sites for males and females pooled.

CpG	PC1	PC2	PC3
67	+0.1551	+0.0842	-0.3968
68	+0.1635	-0.2456	+0.1653
69	+0.0321	-0.4056	+0.0042
70	+0.1536	-0.1069	-0.2950
71	+0.3193	-0.0354	+0.1657
72	+0.1005	-0.3509	+0.0037
73	+0.1196	-0.4830	+0.0107
74	+0.1594	-0.1631	-0.4448
75	+0.2639	+0.0969	-0.1358
76	+0.2030	-0.3910	+0.2278
77	+0.0651	+0.2218	+0.4402
78	+0.2237	-0.0289	+0.4404
79	+0.1425	+0.1948	+0.0945
80	+0.3092	+0.1821	+0.0870
81	+0.2909	+0.1395	-0.1419
82	+0.3362	+0.1030	+0.0055
83	+0.3324	+0.1115	-0.0811
84	+0.2731	-0.0983	-0.0169
85	+0.3301	+0.1917	-0.0330
st. dev.	2.65	1.59	1.32
proportion of variance	0.37	0.13	0.09

Table 4.6. Pearson's correlations of principal component scores with schizotypy and handedness.

	Schizotypy		Absolute Handedness	
	PC1	**PC2**	**PC1**	**PC2**
Pooled	r=0.1113 p=0.5059	r=0.2624 p=0.1115	r= -0.3752 p=0.02636*	r= -0.0495 p=0.7775
Females	r=0.0694 p=0.7474	r= -0.3498 p=0.0938	r= -0.469 p=0.0319*	r=0.07217 p=0.7559
Males	r= -0.1483 p=0.6128	r=0.3369 p=0.2389	r=0.2430 p=0.4026	r= -0.2104 p=0.4702

*p<0.05

Table 4.7. Pearson's correlations of average methylation for the CpG78-85 block with schizotypy and handedness.

	Schizotypy	**Absolute handedness**
Pooled	r=0.0462 p=0.7634	r= -0.2270 p=0.1483
Females	r=0.1230 p=0.5249	r= -0.4562 p=0.0192*
Males	r= -0.0925 p=0.7332	r=0.3413 p=0.1957

*p<0.05

4.5. Discussion

4.5.1. LRRTM1 SNPs

Overall, we found that LRRTM1 genotypes were associated with higher Total Schizotypy for our pooled sample of males and females, with the results apparently driven by SNP effects on schizotypy in females. This result is consistent with our predictions based on findings by Francks et al. (2007) and Ludwig et al. (2009) that SNPs of the risk haplotype are associated with schizophrenia, though these previous studies did not address sex differences. Combined with these previous results of LRRTM1-mediated schizophrenia

risk, these results provide further support for a genetically-based continuum between schizophrenia and non-clinical schizotypy, with three SNPs contributing to a large magnitude of effect.

The relationship of imprinted genes with schizophrenia and schizotypy has been suggested to be mediated by reduced (or 'insecure') psychological attachment of young children to close caregivers (Crespi, 2011). For example, Prader-Willi syndrome is associated with a female bias in imprinted gene expression, and phenotypically shows low demands on the mother (insecure attachment) through a complacent disposition, leading to dysfunctional alterations in social brain development (Haig & Wharton, 2003; Crespi & Badcock, 2008; Crespi, 2011). So too may be the case with LRRTM1, although this hypothesis has yet to be investigated. Associations between insecure attachment and schizophrenia have been previously documented (reviewed by Crespi, 2011). We predict that LRRTM1 risk alleles mediate insecure attachment and resultant higher Total Schizotypy through lower expression of the paternally-inherited LRRTM1 alleles – functionally generating a female bias in imprinted gene expression. As such, we propose the LRRTM1 risk genotype as a potential model for the role of imprinted genes in schizotypy, brain structure and behaviour.

In contrast with schizotypy, we found no effect of LRRTM1 SNP genotypes on handedness, which is consistent with Francks et al.'s (2007) finding for no effect in non-dyslexic twins. Francks et al. (2007) selected a sample of dyslexic twins based on previously reported associations of left-handedness or ambidexterity with dyslexia (Geschwind & Behan 1982), but found no such relationship in their sample and concluded that hand skill could be considered to be normal in the dyslexic group. The corroboration of the LRRTM1-handedness finding in dyslexics by Ludwig et al. (2009) and lack of replication in both Francks et al.'s non-dyslexic twin sample and our non-clinical group, suggest that LRRTM1 SNPs may influence handedness only in dyslexics, apparently thorough some unspecified interaction effect.

4.5.2. LRRTM1 Methylation

We found higher methylation levels to be associated with mixed handedness in both sexes pooled for a block of intercorrelated sites, with the effect apparently driven by the data for females. An epigenetic influence on handedness has not previously been documented. Francks et al. (2007) reported finding no differentially methylated regions in LRRTM1 based on expression levels in lymphoblast and post-mortem samples, and did not test for an association of methylation with schizophrenia or handedness. Our results demonstrate that using average methylation across a CpG island masks the effects of individual sites or groups of sites and as such, it may be important to interrogate smaller windows of sites in future methylation studies.

Based on our expectation that imprinted genes are involved in conflict between paternal and maternal genomes, our findings of higher methylation mediating a schizophrenia-related trait (mixed handedness) are consistent with the idea of reduced expression of the known paternally-inherited copy (Francks et al., 2007). Consequently, reduced expression of LRRTM1 may result in a bias in expression in favour of the maternal genome, and influence neurodevelopment in the direction of functional (handedness via lateralization) and behavioural (schizotypy) traits towards schizophrenia-like phenotypes (Crespi & Badcock, 2008).

The findings described here show that genetic and epigenetic variation in LRRTM1 is related to schizophrenia-associated phenotypes, schizotypy and mixed handedness, in a non-clinical sample. A relationship between these two phenotypes has been consistently documented (Stefanis et al., 2006; Schürhoff et al., 2008; Chapman, Grimshaw & Nicholls, 2011; Barrantes-Vidal et al., 2013; Dinsdale et al., 2013) and our evidence further strengthens the hypothesis that schizophrenia and handedness share common genetic underpinnings (e.g., Giouzeli et al., 2004; Francks et al., 2007). Our results also provide some of the first evidence that genomic imprinting exerts effects on cognition and brain development in non-clinical populations.

4.5.3. Limitations

The main limitations in our study were 1) small sample sizes for some tests, 2) the use of self-report questionnaires, and 3) handedness measures that differed from Francks et al. (2007). The sample size for the methylation study was small, especially for left-handed individuals, and replication is required to confirm our findings. Additionally, our study did not account for parental inheritance patterns, as we did not have access to parental genotypes; however, as the paternal bias of risk SNPs has been previously replicated (Ludwig et al. 2009), we considered this to be sufficient evidence to assume paternal overtransmission to be the mode of LRRTM1 risk SNP inheritance in our study. Lastly, our use of DNA from saliva samples may adversely affect our epigenetic data, as methylation patterns are often tissue-specific. However, Nohesara et al. (2011) successfully detected significant differences in methylation levels from saliva samples between case and control groups, so we conclude differences in cell types are unlikely to adversely affect our results.

Monoallelic expression is similar to imprinting in that only one allele copy is expressed, and the other is silenced using methylation and histone modification. However in monoallelic expression, the distinction between silencing of parental alleles is random and reversible (Gimelbrant et al., 2005). So far, 1% of autosomal genes show monoallelic expression, including genes expressed in the CNS (Gimelbrant et al., 2007; Wang et al., 2007), such as olfactory receptor genes (Chess et al. 1994; Serizawa et al., 2000). While we are not able to distinguish whether methylation differences in our study are due to imprinting or monoallelic expression, previous work by Francks et al. (2007) and Ludwig et al. (2009) shows a parent of origin effects in LRRTM1, indicating that the gene is likely imprinted.

4.5.4. Conclusions

Our findings, considered in conjunction with previous work, indicate that schizophrenia risk alleles in the imprinted gene LRRTM1 are associated with significantly higher Total Schizotypy score. As well, we found an association of higher methylation at a specific CpG region with mixed handedness. This is the first study to test for imprinted effects on

schizotypy and handedness in a non-clinical population, and additional studies of imprinted genes in relation to schizophrenia-related traits will provide useful insights into epigenetic mechanisms involved in schizotypy and schizophrenia.

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4.7. Appendix C

Table C1. P-values for t-tests of SNP genotypes with psychometric measures in both sexes pooled.

Both Sexes Pooled (N=554)	**rs1007371 Recessive (TT)**	**rs1446109 Recessive (GG)**	**rs723524 Recessive (TT)**
Abs. Hand.	0.918	0.918	0.594
Ideas	0.243	0.243	0.269
Constrict	0.392	0.392	0.564
Eccentric	0.144	0.144	0.418
Anxiety	0.469	0.469	0.294
Magic	**0.0278***	**0.0278***	0.161
Speech	0.646	0.646	0.616
Perception	0.51	0.51	0.927
Interpersonal	0.281	0.281	0.359
Cognitive	0.0805 .	0.0805 .	0.257
Disorganized	0.195	0.195	0.407
Schizotypy	**0.032***	**0.032***	0.0642 .

. p<0.1; *p<0.05

Table C2. P-values for t-tests of SNP genotype with psychometric measures in females.

Females (N=357)	**rs1007371 Recessive**	**rs1446109 Recessive**	**rs723524 Recessive**
	(TT)	**(GG)**	**(TT)**
Abs. Hand.	0.915	0.915	0.362
Ideas	0.297	0.297	0.348
Constrict	0.121	0.121	**0.0427***
Eccentric	**0.0329***	**0.0329***	0.121
Anxiety	0.152	0.152	0.115
Magic	0.186	0.186	0.413
Speech	0.0646 .	0.0646 .	0.192
Perception	**0.038***	**0.038***	0.388
Interpersonal	**0.0426***	**0.0426***	**0.0295***
Cognitive	0.064 .	0.064 .	0.254
Disorganized	**0.0155***	**0.0155***	0.0818 .
Schizotypy	**0.0243***	**0.0243***	**0.0276***

. p<0.1; *p<0.05

Table C3. P-values for t-tests of SNP genotype with psychometric measures in males.

Males (N=197)	**rs1007371 Recessive**	**rs1446109 Recessive**	**rs723524 Recessive**
	(TT)	**(GG)**	**(TT)**
Abs. Hand.	0.957	0.957	0.713
Ideas	0.586	0.586	0.583
Constrict	0.618	0.618	0.224
Eccentric	0.816	0.816	0.572
Anxiety	0.666	0.666	0.929
Magic	**0.0378***	**0.0378***	0.127
Speech	0.203	0.203	0.756
Perception	0.207	0.207	0.373
Interpersonal	0.585	0.585	0.391
Cognitive	0.628	0.628	0.65
Disorganized	0.471	0.471	0.572
Schizotypy	0.519	0.519	0.763

. p<0.1; *p<0.05

Table C4. Pearson correlations for square root-transformed methylation at individual CpG sites with schizotypy and handedness.

CpG	Schizotypy			Absolute Handedness		
	Both	Females	Males	Both	Females	Males
67	r=0.134 p=0.379	r=0.282 p=0.138	r= -0.204 p=0.450	r= -0.001 p=0.997	r= -0.051 p=0.803	r=0.216 p=0.421
68	r=0.092 p=0.548	r=0.047 p=0.810	r=0.400 p=0.124	r= -0.232 p=0.140	r= -0.194 p=0.341	r= -0.432 p=0.094
69	r= -0.430 p=0.003**	r= -0.501 p=0.006**	r= -0.068 p=0.804	r=0.193 p=0.221	r=0.241 p=0.235	r=0.047 p=0.863
70	r= -0.109 p=0.475	r= -0.118 p=0.541	r= -0.105 p=0.699	r= -0.070 p=0.659	r= -0.053 p=0.798	r= -0.129 p=0.635
71	r=0.009 p=0.951	r= -0.011 p=0.956	r=0.212 p=0.431	r= -0.302 p=0.052	r= -0.391 p=0.048*	r=0.070 p=0.796
72	r= -0.156 p=0.311	r= -0.217 p=0.258	r= -0.034 p=0.904	r= -0.014 p=0.932	r= -0.116 p=0.572	r=0.322 p=0.241
73	r= -0.186 p=0.257	r= -0.236 p=0.266	r= -0.091 p=0.748	r= -0.054 p=0.753	r= -0.022 p=0.926	r= -0.160 p=0.568
74	r=0.172 p=0.257	r=0.198 p=0.304	r=0.139 p=0.609	r= -0.164 p=0.299	r= -0.150 p=0.463	r= -0.215 p=0.424
75	r=0.160 p=0.292	r=0.198 p=0.303	r=0.599 p=0.014*	r= -0.312 p=0.044*	r= -0.306 p=0.128	r= -0.585 p=0.017*
76	r= -0.147 p=0.336	r= -0.164 p=0.394	r=0.151 p=0.576	r= -0.208 p=0.187	r= -0.229 p=0.260	r=0.009 p=0.974
77	r= -0.279 p=0.063	r= -0.299 p=0.1152	r= -0.172 p=0.525	r= -0.010 p=0.950	r= -0.059 p=0.775	r=0.278 p=0.296
78	r= -0.045 p=0.768	r=0.080 p=0.679	r= -0.210 p=0.434	r= -0.165 p=0.2971	r= -0.490 p=0.011*	r=0.346 p=0.190
79	r=0.083 p=0.587	r=0.199 p=0.300	r= -0.090 p=0.741	r= -0.084 p=0.595	r= -0.410 p=0.038*	r=0.364 p=0.166
80	r=0.012 p=0.937	r=0.096 p=0.618	r= -0.250 p=0.349	r= -0.320 p=0.039*	r= -0.399 p=0.043*	r=0.007 p=0.980
81	r=0.138 p=0.364	r=0.149 p=0.439	r=0.355 p=0.178	r= -0.447 p=0.003**	r= -0.493 p=0.011*	r= -0.116 p=0.670
82	r= -0.101 p=0.510	r= -0.086 p=0.657	r= -0.077 p=0.777	r= -0.369 p=0.016*	r= -0.521 p=0.006**	r=0.229 p=0.393
83	r=0.088 p=0.572	r=0.113 p=0.558	r=0.199 p=0.478	r= -0.304 p=0.053	r= -0.319 p=0.112	r= -0.228 p=0.413
84	r=0.025 p=0.873	r=0.063 p=0.746	r=0.065 p=0.818	r= -0.136 p=0.398	r= -0.150 p=0.465	r= -0.024 p=0.932
85	r=0.152 p=0.325	r=0.173 p=0.369	r=0.403 p=0.136	r= -0.345 p=0.027*	r= -0.406 p=0.040*	r= -0.136 p=0.628

*p<0.05, **p<0.01

None of these remain significant after FDR correction (adjusted p-values >0.17).

5. CONCLUSIONS

Understanding how genetic risk for schizophrenia is related to cognitive function and personality in non-clinical populations has significant implications for how we approach schizophrenia in terms of framing research hypotheses, diagnosis and perhaps even treatment, and how we understand the persistence of this highly-heritable condition. My thesis explored the role of schizophrenia "risk" alleles in terms of cognitive performance and schizotypal personality by testing hypotheses about maintenance in clinical versus non-clinical populations, using data from the literature (chapter 2), tests for genetic (SNP) effects on schizotypy and cognition in a non-clinical population (chapters 3 and 4), and investigating the relationship between an imprinted risk gene and measures of brain structure (asymmetry) and personality (chapter 4). Together, these chapters elucidate schizophrenia gene functions in non-clinical populations, thus providing evidence of the continuum between clinical and non-clinical populations via shared underlying genetic variation.

The evidence reviewed in chapter 2 illustrates that schizophrenia risk alleles are by no means strictly deleterious and instead, may be maintained, in part, due to beneficial effects on cognitive performance in both patients and controls. As well, the nature of these positive effects appears to differ between controls and patients, in that controls may benefit from schizophrenia risk alleles through their effects in particular cognitive domains (i.e., creativity, fluency, and flexibility; memory) whereas patients are more sensitive to cognitive effects of risk alleles both positive and negative. These findings suggest that schizophrenia risk alleles may be maintained in part due to antagonistic pleiotropy involving benefits in particular domains, but costs in others.

Next, chapter 3 results indicate that a measure of overall schizophrenia genetic risk, although not strongly related to levels of schizotypy, does show a combined effect on schizophrenia-related cognition, specifically poorer mental rotation ability in males.

Mental rotation represents a facet of visual-spatial cognition, which is known to be poorer in males with schizophrenia (Jiménez et al., 2010) and is highly heritable (Johnson et al., 2007; Vuoksimaa et al., 2010; Suzuki et al., 2011). These results implicate a broad set of genes associated with visual-spatial skill with a significant summed effect. Since using the same combined genetic score does not predict schizotypy in a linear manner as with mental rotation, the genetic continuum between schizophrenia and schizotypy may not be non-linear due to epistatic interactions (Egan et al., 2001; Meyer-Lindenberg et al., 2007).

Finally, chapter 4 reveals that SNP variation in the imprinted gene LRRTM1 is associated with higher schizotypy and that epigenetic variation mediates mixed handedness. This is the first study to demonstrate an effect of imprinted genes on schizotypy or handedness in a non-clinical population. These findings further support the continuum and highlight that a small number of SNPs (3) in an imprinted gene can have significant effects on schizophrenia and schizotypy.

Overall, we find that schizophrenia risk alleles do influence cognition in non-clinical populations, both individually (Chapter 2) and together (Chapter 3) and that these alleles may be maintained due to benefits in particular domains of cognitive performance. Further, we report a role for an imprinted gene in schizotypy and handedness (Chapter 4) and propose that a maternal imprinting bias may be associated with schizotypy, as predicted by Crespi and Badcock (2008). Finally, the findings of this thesis help to shift the view of “risk” alleles toward a more general interpretation of alleles influencing cognitive and personality variation in non-clinical populations, in addition to slightly increasing liability to schizophrenia.

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